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PAPER

Structure-enantioselectivity effects in 3,4-dihydropyrimido[2,1-*b*]-benzothiazole-based isothioureas as enantioselective acylation catalysts†

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The catalytic activity and enantioselectivity in the kinetic resolution of (±)-1-naphthylethanol with a range of structurally related 3,4-dihydropyrimido[2,1-*b*]benzothiazole-based catalysts is examined. Of the isothiourea catalysts screened, (2*S*,3*R*)-2-phenyl-3-isopropyl substitution proved optimal, giving good levels of selectivity in the kinetic resolution of a number of secondary alcohols (*S* values up to >100 at ~50% conversion). Low catalyst loadings (0.10–0.25 mol%) of the optimal isothiourea can be used to generate enantiopure alcohols (>99% ee) in good yields.

Introduction

In recent years a range of synthetic small molecule catalysts have been developed that promote efficient kinetic resolution of racemic alcohols *via* derivatisation with anhydrides and related electrophiles.[1] Among these catalysts, those based upon the parent archetypal DMAP or PPY scaffolds are among the most common, with catalysts **1**, **2** and **3**, developed by Fu,[2] Spivey[3] and Campbell[4] respectively, representative of the aminopyridine class (Fig. 1).[5] A number of alternative catalyst architectures have also been introduced, such as proline-derived diamine **4** used by Oriyama,[6] peptides such as **5** introduced by Miller,[7] and chiral phosphine **6** utilised by Vedejs.[8,9]

Building upon this success, Birman and co-workers have elegantly shown that amidines and isothioureas can efficiently promote a range of alcohol acylation protocols. In this area, Birman first introduced a range of dihydroimidazo[1,2-*a*]pyridine (DHIP) derivatives (such as CF_3-PIP **7** and Cl-PIQ **8**) for kinetic resolutions,[10] before showing that isothioureas such as commercially available tetramisole **9** and its benzannulated analogue (benzotetramisole, BTM) **10** could promote efficient kinetic resolution[11] and desymmetrisation reactions.[12] Independent studies by Okamoto and Birman showed that achiral 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (DHPB) **11** was an efficient catalyst for *O*-acylation,[13] with subsequent work by Birman utilising homobenzotetramisole (HBTM) **12** for the kinetic resolution of aryl-cycloalkanols[14] and α-aryl, α-aryloxy and α-arylthioalkanoic acids (Fig. 2).[15] The high levels of selectivity observed with

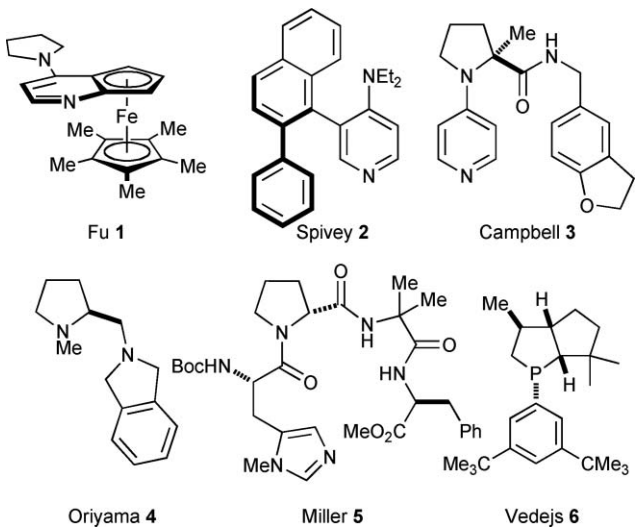

Fig. 1 Selected small molecule catalysts for the kinetic resolution of alcohols.

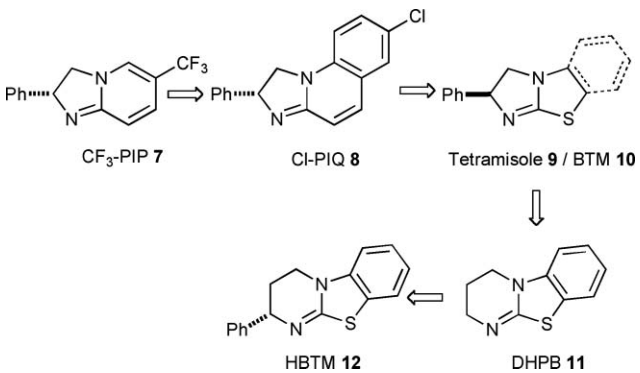

Fig. 2 Amidines and isothiourea catalysts for alcohol acylation.

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† Electronic supplementary information (ESI) available: Experimental procedures, HPLC data and spectroscopic data for all new products is available. See DOI: 10.1039/c0ob00515k

these isothiourea catalysts in kinetic resolution reactions has prompted the use of BTM for the kinetic resolution of 2-hydroxyalkanoates,[16] 2,2,2-trifluoro-1-arylethanols,[17] and tetramisole derivatives for the resolution of carboxylic acids.[18]

As part of our interest in the development of synthetic methods employing Lewis bases[19] as catalysts,[20] we have employed isothiourea DHPB **11** as an efficient achiral catalyst for the Steglich rearrangement of oxazolyl carbonates.[21] Our further recent studies have shown that enantiomerically pure isothioureas such as HBTM **12**, as well as alternative 3,4-dihydropyrimido[2,1-*b*]benzothiazole-based isothioureas **13** and **14**, are efficient asymmetric catalysts of this reaction, giving *C*-carboxyazlactones in high ee. Notably, variation in catalytic activity with the stereodirecting unit of the isothiourea was observed in this model study, with isothiourea **13** giving the highest enantioselectivity at rt, but proving less catalytically active than either HBTM **12** or **14** (Fig. 3).[22]

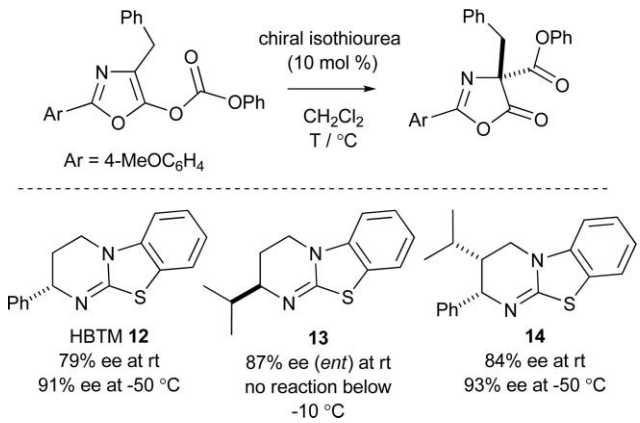


Fig. 3 Previous work: isothiourea mediated *O*- to *C*-carboxyl transfer.

Building upon these precedents, we were intrigued to probe the effect of integrating alternative stereodirecting groups within the tetrahydropyrimidine unit of isothioureas such as HBTM, and to examine the consequence of these changes upon the efficiency and stereoselectivity of kinetic resolution reactions. Birman and co-workers have conducted an analogous study within the DHIP structural class, with a C(2)-aryl substituent shown to be essential for high levels of stereocontrol.[10c] While this work was ongoing, Birman and co-workers showed that the incorporation of a methyl group within the HBTM-skeleton had a dramatic effect upon both catalytic activity and stereoselectivity in kinetic resolutions of aryl-cycloalkanols,[23] with catalyst **15** (HBTM 2) proving optimal (Fig. 4).

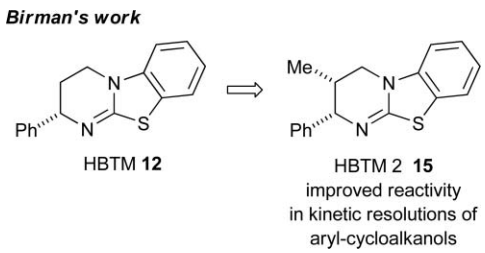


Fig. 4 Evolution of HBTM.

We delineate herein our complementary studies within this area, focusing on the effects upon catalytic efficiency and selectivity with variation in stereodirecting unit within a series of isothiourea derivatives of generic structure **16** (Fig. 5). The utility of the optimal catalyst identified from these studies is subsequently used to promote the kinetic resolution of a number of simple aryl-alkyl alcohols.

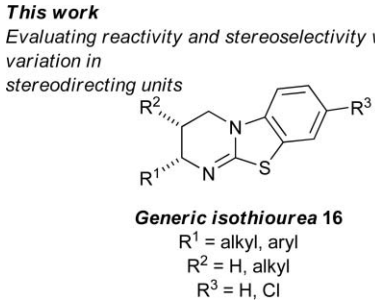


Fig. 5 Probing structure-enantioselectivity relationships using isothioureas in the kinetic resolution of alcohols.

Results and Discussion

Synthesis of isothiourea catalysts

The preparation of a series of bespoke isothiourea catalysts that varied in the nature of the stereodirecting group(s), substitution pattern and conformational constraints within the catalyst framework required synthetic routes to the corresponding enantiomerically pure γ-amino alcohols. γ-Amino alcohol **21** was prepared following the literature procedure from methionine,[24] while alcohols **22–24** were synthesised by reduction of the corresponding enantiomerically pure β-amino acids **18–20** respectively, which are commercially available[25] or made following literature procedures.[26] Reduction of diastereo- and enantiomerically pure β-amino aldehydes **25** and **26**, readily available following List's proline-catalysed asymmetric Mannich protocol on multi-gram scale, gave alcohols **28** and **29**.[27] Deprotection of **27**, prepared following Gellman's asymmetric aminomethylation procedure, gave alcohol **30** (Fig. 6).[28]

Commercially available (*S*)-3-amino-3-phenylpropan-1-ol hydrochloride, and the synthesised γ-amino alcohols **21–24**, **28–30** were each condensed with 2-chlorobenzothiazole to give **31–39**, with subsequent cyclisation giving the desired isothioureas. To probe the effect of a substituent upon the benzothiazole ring, amino alcohol **28** was condensed with 2,6-dichlorobenzothiazole and cyclised to give isothiourea **43** (Table 1).

Model studies: structure-enantioselectivity relationships in the kinetic resolution of (±)-1-naphthylethanol with isothioureas

The reactivity and stereoselectivity of these 3,4-dihydropyrimido[2,1-*b*]benzothiazole-based isothioureas in kinetic resolutions was next evaluated in order to probe the effects of variation in stereodirecting unit within these systems. As a model system, the resolution of (±)-1-naphthylethanol **46** with propionic anhydride (0.5 eq) in $CHCl_3$ using $(i\text{-Pr})_2NEt$ (0.6 eq) as an auxiliary base was studied (Table 2).[29] As a benchmark standard, isothiourea HBTM **12** (0.75 mol%) was

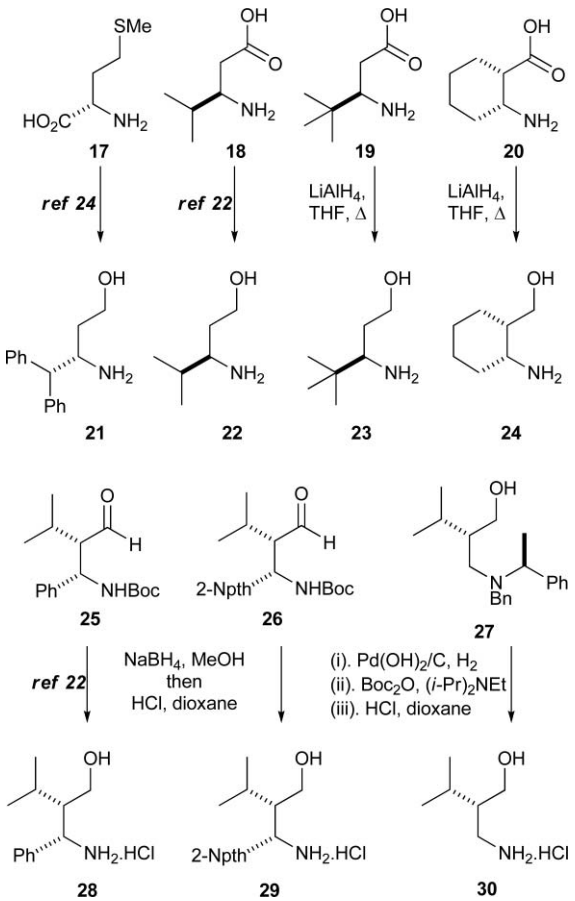
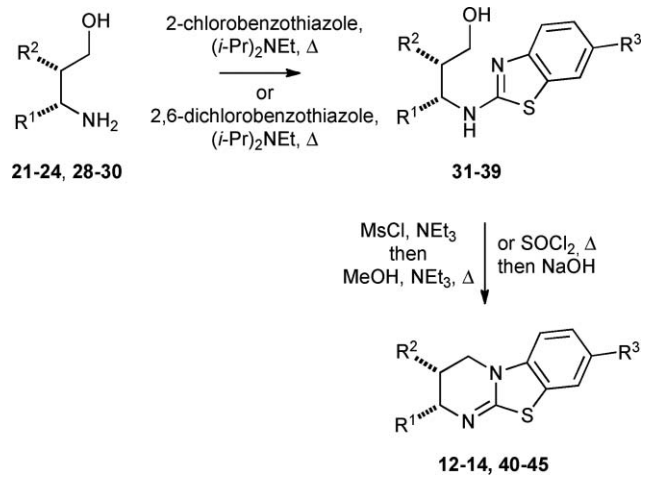


Fig. 6 Synthesis of enantiomerically pure γ-amino alcohols.

used, giving good levels of conversion within 1 h and good levels of stereoselectivity (S = 18). C(2)-Benzhydryl ($CHPh_2$) substituted isothiourea **40** showed only modest catalytic activity at 0.75 mol% loading (<10% conversion to propionate **47** within 1 h), requiring extended reaction times and increased catalyst loading for acceptable reaction conversions, although delivering approximately equivalent levels of stereoselectivity to HBTM **12** (S~20, entries 2–4). Similarly, C(2)-isopropyl and C(2)-*tert*-butyl substituted isothioureas **13** and **41** required extended reaction times at 2.5 mol% loading to give good product conversions, albeit with only modest enantioselectivity (S = 12 and 8 respectively, entries 5–6). C(3)-*i*-Pr substituted isothourea **45** showed only modest catalytic activity and enantioselectivity in this process (entry 7), although increased reaction rates were observed using 2,3-disubstituted isothioureas **14** and **42–44**, with good conversion (47–50%) reached within 1 h at rt using 0.75 mol% of the respective isothiourea. Among these disubstituted isothioureas, the highest enantioselectivity was observed using isothiourea **14** (S = 30, entry 9) containing an additional *cis*-*i*-Pr substituent in comparison to HBTM **12**, consistent with Birman's work with HBTM-2 **15**. Reduced stereoselectivity was observed using the constrained tetracyclic isothiourea **42** or the C(2)-2-naphthyl substituted isothiourea **44** (entries 8 and 11). The incorporation of a Cl-substituent into the benzothiazole ring had a negligible effect, with isothiourea **43** giving approximately equivalent stereoselectivity to its parent catalyst **14** (entry 10). Taken together, these structure–activity studies indicate that

Table 1 Synthesis of isothioureas

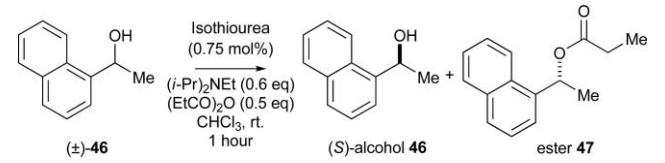


Entry	R^1	R^2	R^3	Alcohol (yield)	Isothiourea (yield)
1	Ph	H	H	**31** (80%)	**12** (61%)
2	$CHPh_2$	H	H	**32** (62%)	**40** (74%)
3	*i*-Pr	H	H	**33** (60%)	**13** (97%)
4	*t*-Bu	H	H	**34** (51%)	**41** (78%)
5	$CH_2CH_2CH_2CH_2$		H	**35** (61%)	**42** (quant)
6	Ph	*i*-Pr	H	**36** (86%)	**14** (83%)
7	Ph	*i*-Pr	Cl	**37** (79%)	**43** (81%)
8	2-Naphthyl	*i*-Pr	H	**38** (85%)	**44** (88%)
9	H	*i*-Pr	H	**39** (59%)	**45** (51%)

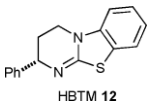
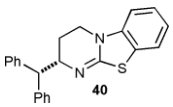
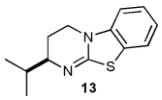
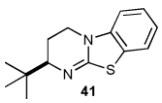
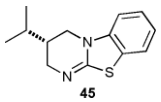
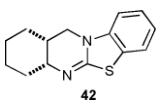
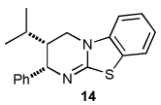
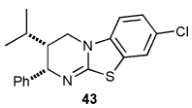
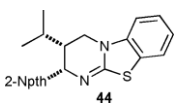
the incorporation of an α-branched sterically encumbered C(2)-alkyl stereodirecting unit (as in isothioureas **13**, **40** and **41**) is detrimental to catalyst activity (in comparison to HBTM **12** or **14**) for this kinetic resolution, although isothiourea **40** shows equivalent enantioselectivity to HBTM **12**. 2,3-Disubstitution of the isothiourea leads to improved catalytic activity, with a C(2)-phenyl unit within the tetrahydropyrimidine structure leading to high enantioselectivity and reactivity. Interestingly, this contrasts the trends in stereoselectivity observed in our previous studies on *O*- to *C*-carboxyl transfer reactions of oxazolyl carbonates, where isothiourea C(2)-*i*-Pr **13** gave the highest enantioselectivity at rt,[22] but is consistent with Birman's previous structural investigations upon the DHIP class of Lewis bases in kinetic resolution reactions.[10c] In direct comparison to HBTM **12**, isothiourea **14**, containing an additional C(3)-*i*-Pr unit gives enhanced selectivity; as C(3)-*i*-Pr isothiourea **45** gives poor enantioselectivity and catalytic activity, the 2,3-disubstitution within **14** appears to exert a synergistic effect upon the enantioselectivity in this process.

Further reaction optimisation studies used the most effective isothiourea (2*S*,3*R*)-**14** and focused upon solvent and temperature variation (Table 3). At 0 °C, good reaction conversion was observed within 1 h, with best selectivity observed in either toluene (S = 34) or $CHCl_3$ (S = 36) rather than CH_2Cl_2 or THF (entries 2–5). In toluene and $CHCl_3$ the kinetic resolution could be performed at –40 °C, giving ~40% conversion within 1 h but with similar levels of enantioselectivity to that observed at 0 °C (entries 7–8). Further reduction in catalyst loading to 0.1 mol% proved possible, giving 36% conversion at 0 °C within 1 h, although further reduction in catalyst loading gave only modest product conversion (entries 9–11). Alternatively, using 0.6 eq of propionic anhydride and a

Table 2 Model studies for the kinetic resolution of (±)-1-naphthylethanol



(±)-**46** (*S*)-alcohol **46** ester **47**

Entry	Isothiourea	$ee_{alcohol}$(%)[a]	ee_{ester}(%)[a]	*c* (%)[b]	*S*
1	 HBTM **12**	57	81	41	18
2	 **40**	8	87	8	26
3[c]		22	84	20	19
4[c,d]		70	86	20	19
5[c,e]	 **13**	60 (*ent*)	72 (*ent*)	45	12
6[c,e]	 **41**	54 (*ent*)	67 (*ent*)	45	8
7	 **45**	5	15	27	1.3
8	 **42**	70	69	50	11
9	 **14**	84	84	50	30
10	 **43**	75	86	47	28
11	 **44**	73	79	48	19

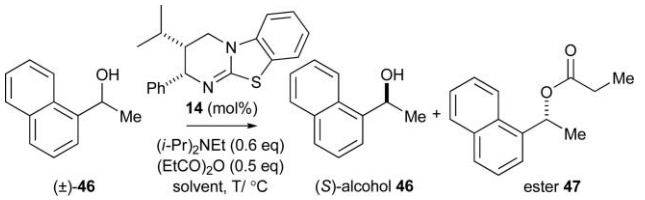
[a] Determined by chiral HPLC analysis. [b] Reaction conversion was determined using $c_{HPLC} = 100 \times ee_{alcohol}/(ee_{ester} + ee_{alcohol})$.[30] [c] Isothiourea loading of 2.5 mol%. [d] Reaction time 63 h. [e] Reaction time 44 h.

catalytic amount of Hünig's base (0.75 mol%), the resolution of (±)-**46** could be effected using only 0.05 mol% of isothiourea **14**, giving ~5% conversion to propionate **47** within 28 h at rt (entry 12).

Reaction generality – kinetic resolutions of model secondary alcohols

Further studies probed the utility of isothiourea **14** (0.75 mol%) to catalyse the kinetic resolution of a series of model secondary aryl-alkyl alcohols in $CHCl_3$ (Table 4). Good conversion (34–50%) to the corresponding ester was observed within 1 h for all substrates, with (±)-2-naphthylethanol **48** resolved with high selectivity at either rt or –20 °C (entries 3–4). (±)-Arylethanols **49–51** were competently resolved (entries 5–10), with resolution of (±)-**52** proceeding with high selectivity ($S > 100$, entries 11–12). The (±)-cinnamyl and (±)-propargylic alcohols **53** and **54** were also resolved with lower, but still acceptable, levels of enantiodiscrimination ($S > 17$, entries 13–17).

Table 3 Optimisation studies: kinetic resolution of (±)-1-naphthylethanol



(±)-**46** (*S*)-alcohol **46** ester **47**

Entry	**14** (mol%)	*T*/°C	solvent	$ee_{alcohol}$(%)[a]	ee_{ester}(%)[a]	*c* (%)[b]	*S*
1	0.75	rt	$CHCl_3$	84	84	50	30
2	0.75	0	$CHCl_3$	86	86	50	36
3	0.75	0	PhMe	80	85	48	34
4	0.75	0	CH_2Cl_2	77	80	49	20
5	0.75	0	THF	74	84	47	24
6	0.75	–20	$CHCl_3$	87	86	50	40
7	0.75	–40	$CHCl_3$	53	90	37	33
8	0.75	–40	PhMe	57	91	39	38
9	0.25	0	$CHCl_3$	77	87	47	33
10	0.10	0	$CHCl_3$	49	88	36	24
11	0.025	0	$CHCl_3$	10	86	10	21
12[c]	0.05	rt	$CHCl_3$	92	76	55	23

[a] Determined by chiral HPLC analysis. [b] Reaction conversion was determined using $c_{HPLC} = 100 \times ee_{alcohol}/(ee_{ester} + ee_{alcohol})$.[30] [c] Reaction conditions: isothiourea **14** (0.05 mol%), $(EtCO)_2O$ (0.6 eq), *i*-Pr_2NEt (0.75 mol%), alcohol (±)-**46** (1 mmol), 28 h, rt; purification gave alcohol (*S*)-**46** in 39% yield (92% ee) and ester **47** in 40% yield (76% ee).

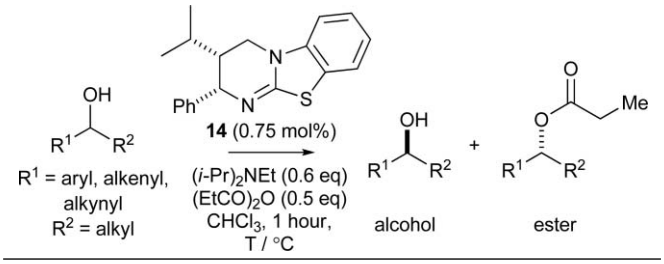
Comparison of 3,4-dihydropyrimido[2,1-*b*]benzothiazole-based isothiourea catalysts

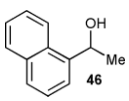
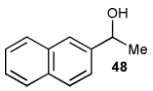
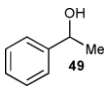
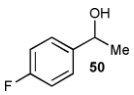
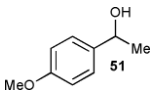
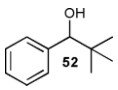
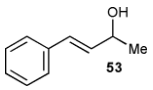
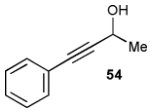
Having shown that isothiourea **14** is able to operate in kinetic resolution reactions at relatively low catalyst loadings, a direct assessment of its reactivity and stereoselectivity in comparison with the literature studies of the related 3,4-dihydropyrimido[2,1-*b*]benzothiazole-based catalysts HBTM **12** and HBTM 2 **15** was carried out. In our hands, employing **14** as the acylation catalyst under the experimental conditions employed by Birman for the kinetic resolution of (±)-2-naphthylethanol **48** using HBTM **12**, and propargylic alcohol **54** using HBTM 2 **15**, indicated that isothiourea **14** gave comparable reactivity but improved selectivity to the literature in both cases (Tables 5 and 6). Although the levels of asymmetric induction using isothiourea **14** are useful in these reactions, BTM **10** has been shown to catalyse highly enantioselective kinetic resolutions of (±)-**48** ($S = 108$)[11a] and (±)-**54** ($S = 31$)[11c] using 4 mol% of the acylation catalyst using related reaction conditions.

Model for asymmetric induction

The high levels of enantiodiscrimination observed in these kinetic resolutions, with a consistent preference for the (*R*)-enantiomer of the racemate to undergo esterification, resulting in isolation

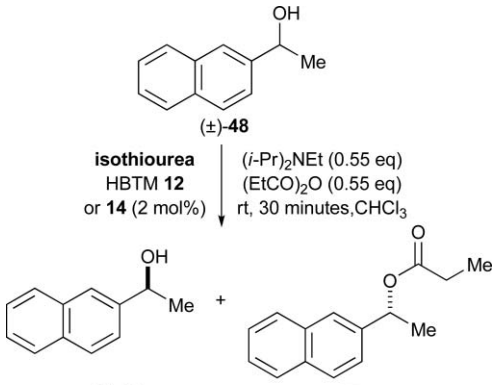
Table 4 Kinetic resolutions using isothiourea **14**

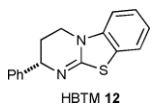
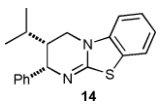


Entry	substrate	T/°C	$ee_{alcohol}$(%)[a]	ee_{ester}(%)[a]	c (%)[b]	S
1	 **46**	rt	84	84	50	30
2		–40	57	91	39	38
3	 **48**	rt	81	91	47	55
4		–20	71	94	43	65
5	 **49**	rt	77	84	52	14
6		0	75	87	46	35
7	 **50**	rt	78	71	52	14
8		0	74	76	45	17
9	 **51**	rt	65	84	44	23
10		0	47	89	34	35
11	 **52**	rt	82	96	46	>100
12		0	98	99	50	>100
13	 **53**	rt	70	65	52	10
14		0	73	83	47	22
15	 **54**	rt	50	67	42	9
16		0	55	83	40	18
17		–20	43	84	34	17

[a] Determined by chiral HPLC analysis. [b] Reaction conversion was determined using $c_{HPLC} = 100 \times ee_{alcohol}/(ee_{ester} + ee_{alcohol})$.[30]

Table 5 Comparison of HBTM **12** and isothiourea **14** for the kinetic resolution of (±)-**48**



Entry	Isothiourea	$ee_{alcohol}$(%)	ee_{ester}(%)	c (%)	S
1	 HBTM **12**	76[a]	83[a]	48[a]	25[a]
2	 **14**	88[b]	91[b]	50[c]	67

[a] Literature values taken from reference 14; [b] Determined by chiral HPLC analysis. [c] Reaction conversion was determined using $c_{HPLC} = 100 \times ee_{alcohol}/(ee_{ester} + ee_{alcohol})$.[30]

of the resolved enantioenriched (*S*)-alcohol, is consistent with the following simplistic model. Based upon a combination of previous modelling studies from Birman and Houk on the origin of CF_3-PIP catalysed kinetic resolutions,[31] and our own modelling studies upon the behaviour of HBTM in asymmetric Steglich reactions,[22] we postulate that the *N*-acylated catalyst preferentially adopts a conformation that places the adjacent Ph substituent in a pseudoaxial position in order to minimise 1,2-strain.[32] In this intermediate, the *N*-propionyl group is assumed to lie preferentially approximately co-planar with the isothiourea heterocycle, with the *syn*-rotamer (C=O group *syn* to C=N) preferred.[22,31] Preferential reaction of the (*R*)-enantiomer of the alcohol, presumably with the propionate counterion hydrogen bonded to the hydroxyl of the substrate following the calculations of Mayr and co-workers,[33] is favoured due to π–π and/or cation-π interactions of the π-system of the alcohol with the acetylated isothiouronium catalyst intermediate (shown in Fig. 7 for the kinetic resolution of (±)-1-naphthylethanol for simplicity).[34] Although this model accounts for the sense of asymmetric induction in these kinetic resolutions, the apparent beneficial effect of the adjacent C(3)-*i*-Pr substituent within isothiourea **14** is not immediately clear, although we currently speculate this substituent acts as a conformational lock within the *N*-acyl intermediate. Computational analysis is underway to probe the origin of this effect.

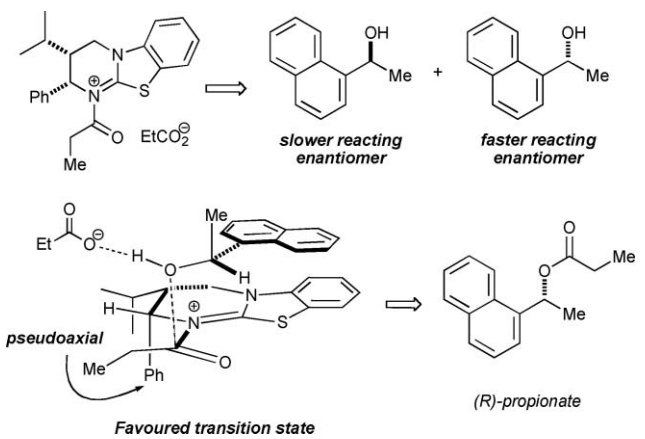
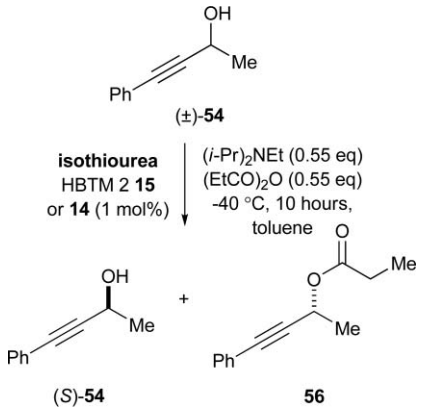
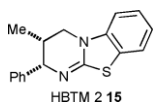
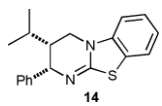


Fig. 7 Simplistic model for enantiodiscrimination in the kinetic resolution of secondary alcohols using catalyst **14**.

Table 6 Comparison of HBTM 2 **15** and isothiourea **14** for the kinetic resolution of (±)-**54**



Entry	Isothiourea	$ee_{alcohol}$(%)	ee_{ester}(%)	*c* (%)	*S*
1	 HBTM 2 **15**	86[a]	76[a]	53[a]	21[a]
2	 **14**	99[b]	76[b]	55[c]	39

[a] Literature values taken from reference 23; [b] Determined by chiral HPLC analysis. [c] Reaction conversion was determined using $c_{HPLC} = 100 \times ee_{alcohol}/(ee_{ester} + ee_{alcohol})$.[30]

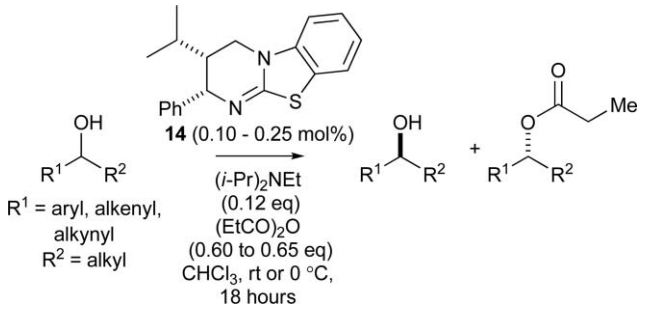
Preparative scale kinetic resolutions of secondary alcohols

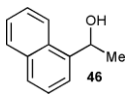
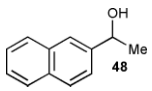
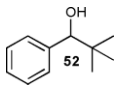
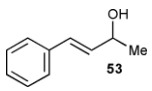
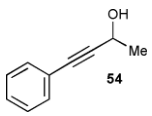
To further demonstrate the synthetic utility of isothiourea catalyst **14**, its ability to deliver alcohols of high enantiopurity in a selection of kinetic resolution reactions at *low catalyst loadings* (0.10–0.25 mol%) on a ~3 mmol scale was investigated. Based upon the selectivity factors observed in the reactions above, judicious choice of propionic anhydride stoichiometry (0.60–0.65 eq) allowed the reactions to proceed to 50–63% conversion. In each case the resolved alcohols and the corresponding esters were isolated by chromatography, giving the alcohols in 24–44% isolated yield and 95%->99% ee (Table 7).

Conclusion

In conclusion, we have demonstrated that variation of the stereodirecting group and conformational constraints within the tetrahydropyrimidine skeleton of a series of chiral isothioureas leads to dramatic changes in catalytic efficiency and stereoselectivity in the kinetic resolution of secondary alcohols. (2*S*,3*R*)-2-Phenyl-3-isopropyl substituted isothiourea **14** proved optimal of those tested in this study, allowing low catalyst loadings (<1 mol%) to be used to generate good reaction conversion within 1 h with good enantioselectivities (*S* up to >100) for a series of aryl-alkyl alcohols. The application of isothiourea **14** to prepare alcohols with ees of up to >99% has also been demonstrated utilising low catalyst loadings (0.10–0.25 mol%). Current studies are focused upon developing alternative applications of enantiomerically pure isothioureas in asymmetric catalysis.

Table 7 Preparative scale resolutions using isothiourea **14**



Entry	substrate	$ee_{alcohol}$ (%)[a]	Yield (%)	ee_{ester} (%)[a]	Yield (%)	*c* (%)[b]	*S*
1[c]	 **46**	>99	30	74	50	57	35
2[c]	 **48**	>99	30	67	50	60	30
3[d]	 **52**	>99	44	99	44	50	>100
4[c]	 **53**	95	24	66	54	59	17
5[c]	 **54**	>99	27	57	44	63	18

[a] Determined by chiral HPLC analysis. [b] eaction conversion was determined using $c_{HPLC} = 100 \times ee_{alcohol}/(ee_{ester} + ee_{alcohol})$.[30] [c] Isothiourea loading of 0.10 mol% and reaction temperature rt. [d] Isothiourea loading of 0.25 mol% and reaction temperature 0 °C.

Experimental

For general experimental details see ESI.† The ESI also contains spectroscopic and HPLC data for isothioureas **12**, **13**, **40–45**, products **29–35**, resolved alcohols **46** and **48–54** as well as the corresponding propionate esters. The ee for catalysts **40** and **45** has been unambigously determined by chiral HPLC analysis while the ee for catalysts **41–44** is assumed to be >98%.

Preparation of isothioureas: Preparation of (*R*)-3-amino-4,4-dimethylpentanol 23

$LiAlH_4$ (2.0 M in THF, 5.20 mL, 10.3 mmol, 3.0 eq) was added dropwise to a solution of (3*R*)-3-amino-4,4-dimethylpentanoic acid **19**[25] (500 mg, 3.44 mmol, 1.0 eq) in dry THF (10 mL) at 0 °C. The reaction mixture was then refluxed for 2 h, cooled to 0 °C and quenched by dropwise addition of H_2O. The mixture was filtered through Celite® and concentrated under vacuum to give **23** as a white solid (330 mg, 73%); mp 70–74 °C; $[\alpha]_D^{20}$ +1.5 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 3400–2700, 3348, 2955; δ_H (400 MHz;

$CDCl_3$) 0.86 (9H, s), 1.32–1.42 (1H, m), 1.64–1.70 (1H, m), 2.51 (1H, dd, *J* 11.3, 2.1), 2.81 (2H, br s) 3.76–3.86 (1H, m), 3.84 (1H, dt, *J* 10.4, 4.0); δ_C (75 MHz, $CDCl_3$) 25.9, 31.7, 34.7, 63.0, 63.8; *m/z* (ES^+) 132 ($[M+H]^+$, 29%), 97.1 ($[M–NH_2–OH]^+$, 100%).

Preparation of ((1*S*,2*R*)-2-aminocyclohexyl)methanol 24

An oven-dried three-necked flask equipped with a magnetic stirrer, a condenser and a nitrogen-inlet tube was flushed with N_2 and charged with THF (10 mL) and $LiAlH_4$ (2.0 M in THF, 5.24 mL, 10.5 mmol, 1.5 eq). The reaction mixture was cooled to 0 °C and **20** (1.00 g, 6.99 mmol, 1.0 eq)[26] was added in portions. After the addition was complete the ice bath was removed and the mixture was warmed to rt and refluxed overnight. The mixture was cooled again to 0 °C and diluted with Et_2O (8 mL). The reaction was quenched with H_2O (0.40 mL), 15% aq. NaOH (0.40 mL), and H_2O (1.19 mL). The mixture was stirred vigorously for 30 min and the white precipitate was filtered. The filter cake was washed with Et_2O and the organic filtrates combined, dried (Na_2SO_4), and concentrated *in vacuo* to give **24** (689 mg, 76%) as a colourless oil;[35] $[\alpha]_D^{20}$ −14.0 (*c* 0.5 in CH_2Cl_2);[36] δ_H (400 MHz, $CDCl_3$) 1.22–1.37 (2H, m), 1.39–1.49 (2H, m), 1.51–1.64 (4H, m), 1.67–1.78 (1H, m), 3.27 (1H, dd, *J* 8.1, 3.8), 3.72 (1H, dd, *J* 11.0, 3.5), 3.80 (1H, dd, *J* 11.1, 6.7).

Preparation of (1*S*,2*S*)-2-(hydroxymethyl)-3-methyl-1-(naphthalen-2-yl)butan-1-aminium chloride 29

26[27] (5.80 g, 17.0 mmol, 1.0 eq) was dissolved in MeOH (133 mL). $NaBH_4$ (964 mg, 25.5 mmol, 1.5 eq) was added portion-wise and the reaction mixture was allowed to stir for 2 h. The mixture was quenched with sat. aq. $NaHCO_3$ and MeOH was removed *in vacuo*. The product was extracted with CH_2Cl_2 (×3) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *tert*-butyl (1*S*,2*S*)-2-(hydroxymethyl)-3-methyl-1-(naphthalen-2yl)butylcarbamate **57** (5.75 g, 99%) as a white solid; mp 124-126 °C; $[\alpha]_D^{20}$ −48.0 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr) 3308, 2964, 1677, 1545; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.9), 1.03 (3H, d, *J* 6.4), 1.44 (9H, s), 1.68–1.84 (1H, m), 1.97 (1H, br s), 2.31 (1H, br s), 3.53 (1H, dd, *J* 11.1, 9.0), 3.70 (1H, br d, *J* 9.2), 5.21 (1H, br s), 5.82 (1H, br s), 7.43–7.51 (3H, m), 7.77 (1H, s), 7.79–7.85 (3H, m); δ_C (100 MHz, $CDCl_3$) 19.3, 22.8, 26.6, 28.5, 51.3, 55.3, 61.1, 79.8, 125.3, 125.8, 125.9, 126.2, 127.7, 128.0, 128.3, 132.7, 133.3, 138.8, 155.9; *m/z* (NSI^+) 344 ($[M+H]^+$, 75%); HRMS (NSI^+) $C_{21}H_{30}NO_3^+$, ($[M+H]^+$) requires 344.2220; found 344.2226 (+1.7 ppm). HCl (4.0 M in dioxane, 45.9 mL, 184 mmol, 12.6 eq) was added to **57** (5.00 g, 14.6 mmol, 1.0 eq) and stirred at rt for 4 h. The reaction mixture was concentrated *in vacuo* to afford **29** (3.68 g, 90%) as a white solid; mp 190–196 °C; $[\alpha]_D^{20}$ −36.0 (*c* 0.5 in MeOH); ν_{max} (KBr) 3273, 2875, 2163, 1602; δ_H (400 MHz, CD_3OD) 0.84 (3H, d, *J* 5.8), 1.18 (3H, d, *J* 4.2), 1.54–1.69 (1H, m), 2.09–2.21 (1H, m), 3.54 (1H, t, *J* 10.1), 3.73–3.82 (1H, m), 4.77 (1H, s), 7.54 (2H, d, *J* 3.2), 7.66 (1H, d, *J* 5.1), 7.87–8.01 (3H, m), 8.05 (1H, s); δ_C (100 MHz, CD_3OD) 19.7, 22.5, 28.1, 49.8, 58.5, 61.4, 126.4, 127.8, 127.9, 128.7, 128.9, 129.2, 129.7, 133.3, 134.5, 134.8; *m/z* (NSI^+) 244 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{16}H_{22}NO^+$, ($[M]^+$) requires 244.1696; found 244.1698 (+0.9 ppm).

Preparation (*S*)-2-(aminomethyl)-3-methylbutan-1-ol hydrochloride 30

A stirred solution of alcohol **27** (709 mg, 2.30 mmol, 1.0 eq) in MeOH (11 mL), distilled H_2O (1 mL) and acetic acid (1 mL) was degassed for 30 min before 20% palladium hydroxide on carbon (272 mg) was added. The resulting suspension was stirred for 3 days under 1 atm of hydrogen. The reaction mixture was then diluted with CH_2Cl_2 (8 mL) and Boc_2O (608 mg, 2.74 mmol, 1.2 eq) was added followed by *i*-Pr_2NEt (0.97 mL, 5.47 mmol, 2.4 eq). The mixture was stirred overnight then filtered through Celite® and washed with MeOH. The solvent was then removed *in vacuo* to afford a colourless liquid. After partitioning between CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ (20 mL) the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give alcohol (*S*)-*tert*-butyl-2-(hydroxymethyl)-3-methylbutylcarbamate **63** (457 mg, 92%) as a pale yellow solid; mp 57–59 °C; {lit.[28] mp 68–69 °C}; $[\alpha]_D^{20}$ +8.6 (*c* 0.8 in MeOH); {lit.[28] $[\alpha]_D^{20}$ +11.4 (*c* 0.5 in MeOH)}; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.8), 0.94 (3H, d, *J* 6.8), 1.25–1.34 (1H, m), 1.44 (9H, s), 1.58–1.69 (1H, m), 3.13–3.23 (1H, m), 3.33–3.41 (1H, m), 3.51 (1H, ABX, J_{BA} 11.7, J_{BX} 7.0), 3.68 (1H, ABX, J_{AB} 11.7, J_{AX} 4.0), 4.82 (1H, s). A solution of HCl (4.0 M in dioxane, 5.80 mL, 23.0 mmol, 11.8 eq) was added to alcohol (*S*)-**63** (423 mg, 1.95 mmol, 1.0 eq) and stirred at rt for 4 h. The reaction was concentrated and dried *in vacuo* to afford amino alcohol (*S*)-**30** (248 mg, 83%) as a colourless oil; $[\alpha]_D^{20}$ −4.7 (*c* 0.5 in MeOH); ν_{max} (film) 3385, 2926; δ_H (400 MHz, CD_3OD) 0.96 (6H, d, *J* 6.7), 1.67–1.80 (2H, m), 2.98–3.10 (2H, m), 3.63 (1H, dd, *J* 10.5, 8.5), 3.81 (1H, dd, *J* 10.5, 3.4); δ_C (75 MHz, CD_3OD) 19.8, 20.0, 28.5, 42.5, 45.3, 63.9; *m/z* (ES^+) 118 ([M], 100%); HRMS (ES^+) $C_6H_{16}NO$, ([M]) requires 118.1232; found 118.1236 (+3.6 ppm).

Preparation of (*S*)-3-(benzo[*d*]thiazol-2-ylamino)-4,4-diphenylbutan-1-ol 32

A mixture of (*S*)-3-amino-4,4-diphenylbutan-1-ol[24] (500 mg, 2.07 mmol, 1.0 eq), 2-chlorobenzothiazole (0.28 mL, 2.28 mmol, 1.1 eq) and *i*-Pr_2NEt (0.72 mL, 4.14 mmol, 2.0 eq) was heated at 135 °C in a sealed tube for 40 h. After cooling to 40 °C, CH_2Cl_2 (4 mL) was added and the reaction mixture was cooled to rt. The crude product was transferred to a flask and concentrated *in vacuo*. The residue was purified *via* flash column chromatography (silica; 99 : 1 to 98 : 2 CH_2Cl_2–MeOH) to give **32** (480 mg, 62%) as a yellow solid; mp 170–172 °C; $[\alpha]_D^{20}$ −110.1 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3449, 3024, 1570, 1546, 1529; δ_H (400 MHz, $CDCl_3$) 1.39 (1H, t, *J* 12.6), 1.90–1.98 (1H, m), 3.51–3.63 (2H, m), 4.02 (1H, d, *J* 9.3), 4.84 (1H, br s), 5.08 (1H, br s), 7.07 (1H, t, *J* 7.6), 7.12–7.19 (2H, m), 7.19–7.30 (9H, m), 7.47 (1H, d, *J* 7.9), 7.52 (1H, d, *J* 8.1); δ_C (100 MHz, $CDCl_3$) 38.4, 54.2, 57.6, 58.1, 119.2, 120.9, 122.3, 126.2, 127.0, 127.1, 128.3, 128.4, 129.0 (2×), 130.2, 141.5, 142.1, 151.5, 167.5; *m/z* (CI^+) 375 ($[M+H]^+$, 100%), 207 ($[M–Ph_2CH]^+$, 13%); HRMS (CI^+) $C_{23}H_{23}N_2OS^+$, ($[M+H]^+$) requires 375.1531; found, 375.1526 (−1.4 ppm).

Preparation of (*R*)-3-(benzothiazol-2-ylamino)-3-*tert*-butylpropanol 34

A pressure tube charged with amino alcohol (*R*)-3-amino-4,4-dimethylpentanol **23** (360 mg, 2.74 mmol, 1.0 eq),

2-chlorobenzothiazole (0.37 mL, 3.01 mmol, 1.1 eq) and *i*-Pr_2NEt (1.42 mL, 8.22 mmol, 3.0 eq) was flushed with N_2 several times, then heated at 130 °C for 3 days. After cooling to 40 °C, the reaction mixture was treated with CH_2Cl_2 (3 mL) then further cooled to rt. The diluted reaction mixture was applied directly to a chromatographic column (silica; 1 : 1 : 98 *i*-PrOH/NEt_3/hexanes) to give **34** as a white solid (374 mg, 51%), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 10 : 90 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 6.3 min (*R*), 8.6 min (*S*)} to have >99% ee; mp 160–164 °C; $[\alpha]_D^{20}$ −78.7 (*c* 0.3 in $CHCl_3$); ν_{max} (KBr) 3291–2700, 2960, 1542; δ_H (300 MHz; $CDCl_3$) 1.02 (9H, s), 1.88 (1H, ddt, *J* 14.1, 11.7, 2.6), 2.07 (1H, dddd, *J* 13.8, 10.9, 5.6, 2.8), 3.73–3.59 (2H, m), 4.01 (1H, ddd, *J* 11.8, 9.5, 2.4), 4.49 (1H, br s), 4.87 (1H, br d, *J* 9.0), 7.08 (1H, td, *J* 7.7, 1.1), 7.28 (1H, td, *J* 7.2, 1.2), 7.49 (1H, dd, *J* 8.1, 0.7), 7.54 (1H, dd, *J* 8.0, 0.9); δ_C (75 MHz, $CDCl_3$) 26.8, 33.5, 34.6, 58.7, 60.7, 118.9, 120.8, 122.0, 126.1, 130.0, 151.7, 168.1; *m/z* (ES^+) 265 ($[M+H]^+$, 100%); HMRS (ES^+) $C_{14}H_{21}N_2OS^+$, ($[M+H]^+$) requires 265.1369; found 265.1372 (+1.1 ppm).

Preparation of ((1*S*,2*R*)-2-(benzo[*d*]thiazol-2-ylamino)cyclohexyl)-methanol 35

24 (400 mg, 3.10 mmol, 1.0 eq), 2-chlorobenzothiazole (0.45 mL, 3.41 mmol, 1.1 eq), *i*-Pr_2NEt (1.08 mL, 6.20 mmol, 2.0 eq) and MeCN (3 mL) were placed in a sealed microwave tube. The reaction mixture was heated to 145 °C for 1 h in a microwave reactor. The mixture was transferred to a flask and concentrated *in vacuo*. Purification of the residue *via* automated flash column chromatography (silica; NEt_3/*i*-PrOH/isohexane) gave **35** (496 mg, 61%) as a white solid;[37] mp 154–164 °C; $[\alpha]_D^{20}$ +92.0 (*c* 0.3 in CH_2Cl_2); ν_{max} (KBr) 3254, 2925, 1531; δ_H (400 MHz, $CDCl_3$) 1.00–1.13 (1H, m), 1.32–1.45 (3H, m), 1.66–1.80 (3H, m), 1.81–1.91 (1H, m), 1.92–1.99 (1H, m), 3.31 (1H, t, *J* 11.3), 3.39 (1H, dd, *J* 11.9, 4.7), 4.54 (1H, br s), 5.30–5.45 (1H, m), 5.67 (1H, br s), 7.06–7.11 (1H, m), 7.27 (1H, ddd, *J* 8.2, 7.2, 1.1), 7.48 (1H, ddd, *J* 8.1, 1.1, 0.5), 7.50–7.54 (1H, m); δ_C (100 MHz, $CDCl_3$) 21.1, 23.6, 25.2, 31.0, 44.2, 50.7, 63.7, 119.0, 120.8, 122.2, 126.2, 130.0, 151.5, 167.5; *m/z* (ES^+) 263 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{14}H_{19}N_2OS^+$, ($[M+H]^+$) requires 263.1213; found 263.1213 (−0.1 ppm).

Preparation of (2*S*,3*R*)-2-(((6-chlorobenzo[d]thiazol-2-yl)amino)(phenyl)methyl)-3-methylbutan-1-ol 37

28 (500 mg, 2.17 mmol, 1.0 eq), 2,6-dichlorobenzothiazole (488 mg, 2.39 mmol, 1.1 eq), *i*-Pr_2NEt (1.13 mL, 6.52 mmol, 3.0 eq) and MeCN (2 mL) were placed in a sealed microwave tube. The reaction mixture was heated to 145 °C for 1 h in a microwave reactor. The reaction was transferred to a flask and concentrated *in vacuo*. Purification of the residue *via* automated flash column chromatography (silica; NEt_3/*i*-PrOH/isohexane) gave **37** (618 mg, 79%) as a white solid; mp 56–62 °C; $[\alpha]_D^{20}$ −84.0 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr) 3290, 2960, 1599, 1543; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.8), 1.15 (3H, d, *J* 6.7), 1.67 (1H, dq, *J* 13.4, 6.7), 2.18 (1H, ddt, *J* 10.0, 6.9, 3.6), 3.68 (1H, t, *J* 10.4), 3.91 (1H, dd, *J* 10.8, 3.7), 4.90 (1H, d, *J* 3.8), 7.21 (1H, dd, *J* 8.6, 2.0), 7.26–7.38 (4H, m), 7.47 (1H, d, *J* 2.1), 7.49–7.54 (2H, m); δ_C (100 MHz, $CDCl_3$) 19.8, 22.7, 27.0, 51.0, 60.6, 62.3, 118.8, 120.7, 126.6, 126.7, 127.9, 128.2, 128.6, 130.9, 138.7, 149.6, 168.3; *m/z* (ES^+) 361 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{19}H_2ClN_2OS^+$, ($[M+H]^+$) requires 361.1136; found 361.1137 (+0.2 ppm).

Preparation of (*S*)-2-((*S*)-(benzo[*d*]thiazol-2-ylamino)(naphthalen-2-yl)methyl)-3-methylbutan-1-ol 38

A pressure tube charged with **29** (400 mg, 1.43 mmol, 1.0 eq) was flushed with Ar several times. *i*-Pr_2NEt (0.97 mL, 5.57 mmol, 3.9 eq) was added, the reaction mixture was heated to 135 °C and 2-chlorobenzothiazole (0.21 mL, 1.57 mmol, 1.1 eq) was added. After 3 days and cooling to rt CH_2Cl_2 was added and the mixture was transferred to a flask and concentrated *in vacuo*. The residue was purified *via* flash column chromatography (silica; 2 : 98 EtOH–CH_2Cl_2) to give **38** (458 mg, 85%) as an orange solid; mp 80–86 °C; $[\alpha]_D^{20}$ −74.0 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr) 3296, 2959, 1600, 1545; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d *J* 6.8), 1.18 (3H, d, *J* 6.7), 1.70 (1H, dq, *J* 13.6, 6.8), 2.28 (1H, ddt, *J* 10.2, 6.9, 3.6), 3.75 (1H, t, *J* 10.5), 3.97 (1H, dd, *J* 10.8, 3.9), 5.08 (1H, d, *J* 3.8), 6.96–7.03 (1H, m), 7.18–7.24 (1H, m), 7.38–7.44 (3H, m), 7.48 (1H, d, *J* 7.8), 7.70 (1H, dd, *J* 8.5, 1.5), 7.77 (3H, dd, *J* 8.8, 4.7), 7.95 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.8, 22.8, 27.0, 51.1, 60.6, 62.4, 118.2, 121.0, 121.4, 126.0, 126.1, 126.1, 126.3, 127.4, 127.7, 128.1, 128.4, 129.8, 133.0, 133.2, 136.6, 151.2, 168.4; *m/z* (NSI^+) 377 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{23}H_{25}N_2OS^+$, ($[M+H]^+$) requires 377.1682; found 377.1683 (+0.2 ppm).

Preparation of (*S*)-2-((*S*)-benzo[*d*]thiazol-2-ylamino)methyl)-3-methylbutan-1-ol 39

A sealed tube was charged with amino alcohol (*S*)-**30** (240 mg, 1.57 mmol, 1.0 eq) and *i*-Pr_2NEt (1.09 mL, 6.28 mmol, 4.0 eq). The reaction mixture was heated to 135 °C and 2-chlorobenzothiazole (0.21 mL, 1.73 mmol, 1.1 eq) was added. The mixture was left at 135 °C for 3 days then allowed to cool to rt. The mixture was diluted with CH_2Cl_2 (2 mL) and purified *via* column chromatography (0 : 100 to 2 : 98 EtOH–CH_2Cl_2) to give the alcohol (*S*)-**39** (233 mg, 59%) as a white solid; mp 126–128 °C; $[\alpha]_D^{20}$ +28.1 (*c* 0.6 in $CHCl_3$); ν_{max} (KBr) 3252, 2952, 1581; δ_H (300 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8), 1.00 (3H, d, *J* 6.8), 1.51 (1H, app tq, *J* 7.2, 3.7), 1.75 (1H, dq, *J* 14.0, 7.2), 3.57–3.63 (2H, m), 3.74–3.80 (2H, m), 4.28 (1H, br s), 5.47 (1H, s), 7.08 (1H, app dt, *J* 7.6, 1.0), 7.25–7.31 (1H, m), 7.49–7.56 (2H, m); δ_C (75 MHz, $CDCl_3$) 20.4, 28.1, 44.8, 48.2, 62.0, 118.8, 121.8, 122.6, 126.9, 131.1, 153.0, 169.6; *m/z* (ES^+) 251 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{13}H_{19}N_2OS^+$, ($[M+H]^+$) requires 251.1218; found 251.1218 (−0.1 ppm).

Preparation of (*S*)-2-benzhydryl-3,4-dihydro-2*H*-pyrimido[2,1-*b*]-benzothiazole 40

Et_3N (0.50 mL, 3.60 mmol, 3.0 eq) was added to a solution of (*S*)-3-(benzo[*d*]thiazol-2-ylamino)-4,4-diphenylbutan-1-ol **32** (450 mg, 1.20 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) at 0 °C under N_2, followed by methanesulfonyl chloride (0.10 mL, 1.32 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 1 h and was then allowed to warm to rt. Once a few drops of MeOH had been added to quench excess methanesulfonyl chloride, Et_3N (2 mL) was added and the mixture refluxed for 16 h. After cooling to rt, water was added and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified

via flash column chromatography (silica; 99 : 1 to 95 : 5 CH_2Cl_2–MeOH) to give **40** as a yellow solid (310 mg, 74%), which was shown by chiral HPLC {Daicel CHIRALCEL AD-H, 4.6 mm × 250 mm, 30 : 70 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 14.0 min (*R*), 24.2 min (*S*)} to have >99% ee; mp 176–177 °C; $[\alpha]_D^{20}$ +54.4 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 2925, 1624, 1586; δ_H (300 MHz, $CDCl_3$) 1.59 (1H, dtd, *J* 13.8, 8.6, 5.3), 1.82 (1H, app dq, *J* 13.6, 4.4), 3.53–3.71 (2H, m), 3.88 (1H, d, *J* 9.5), 4.26 (1H, td, *J* 8.9, 4.0), 6.61 (1H, dd, *J* 7.9, 0.5), 6.87 (1H, td, *J* 7.6, 1.1), 7.06–7.27 (10H, m), 7.33 (2H, dd, *J* 8.1, 1.0); δ_C (100 MHz, $CDCl_3$) 23.7, 41.0, 57.6, 57.7, 107.3, 121.6, 121.8, 122.9, 125.8, 126.3, 126.5, 128.4, 128.5, 128.7, 128.9, 140.8, 142.8, 143.6, 157.1; *m/z* (ES^+) 357 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{23}H_{21}N_2S^+$, ($[M+H]^+$) requires 357.1420; found 357.1420 (0.0 ppm).

Preparation of (*R*)-2-*tert*-butyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*]-benzothiazole 41

Et_3N (0.71 mL, 5.10 mmol, 3.0 eq) was added to a solution of (*R*)-3-(benzothiazol-2-ylamino)-3-*tert*-butylpropanol **34** (450 mg, 1.70 mmol, 1.0 eq) in CH_2Cl_2 (18 mL) at 0 °C under N_2 atmosphere, followed by methanesulfonyl chloride (0.26 mL, 3.40 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 1 h and was then allowed to warm to rt. Once MeOH (0.5 mL) had been added to quench excess methanesulfonyl chloride, Et_3N (1.8 mL) was added and the mixture refluxed for 16 h. After cooling to rt, H_2O was added and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* flash column chromatography (silica; 2 : 1 : 97 *i*-PrOH/NEt_3/hexanes) to give **41** (325 mg, 78%) as a white solid; mp 114–116 °C; $[\alpha]_D^{20}$ –148.7 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 2948, 1625; δ_H (300 MHz; $CDCl_3$) 0.99 (9H, s), 1.58–1.72 (1H, m), 2.08 (1H, dddd, *J* 13.2, 4.8, 3.3, 1.2), 3.08 (1H, dd, *J* 11.1, 3.3), 3.62 (1H, dt, *J* 11.4, 1.8), 3.84 (1H, ddd, *J* 11.4, 5.7, 2.1), 6.68 (1H, app d, *J* 7.5), 6.95 (1H, dt, *J* 7.7, 0.9), 7.16 (1H, dt, *J* 7.8, 1.2), 7.26 (1H, dd, *J* 7.6, 1.2); δ_C (75 MHz, $CDCl_3$) 20.5, 26.6, 34.4, 42.0, 64.6, 107.1, 121.3, 121.8, 122.7, 125.7, 141.0, 156.4; *m/z* (ES^+) 247 ($[M+H]^+$, 100%); HMRS (ES^+) $C_{14}H_{19}N_2S^+$, ($[M+H]^+$) requires 247.1263; found 247.1265 (+0.6 ppm).

Preparation of (6a*R*,10a*R*)-(7,8,9,10,10a,11)-hexahydro-6a*H*-benzothiazolo[2,3-*b*]quinazoline 42

Thionyl chloride (0.12 mL, 1.66 mmol, 2.2 eq) was added to a stirred solution of **35** (198 mg, 0.756 mmol, 1.0 eq) in PhMe (3 mL) and the reaction mixture was heated at 120 °C. Once complete the mixture was allowed to cool to rt and MeOH was added. After evaporation of the solvent, 10% aq. NaOH was added to the residue followed by extraction with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford **42** (186 mg, quantitative yield) as a brown solid; mp 100–102 °C; $[\alpha]_D^{20}$ +146.0 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr) 2932, 2848, 1615; δ_H (400 MHz, $CDCl_3$) 1.25–1.67 (7H, m), 1.72–1.82 (1H, m), 2.01 (1H, tt, *J* 8.8, 4.3), 3.46 (1H, dd, *J* 11.4, 4.4), 3.55–3.60 (1H, m), 3.65 (1H, dd, *J* 11.4, 5.0), 6.62 (1H, d, *J* 8.0), 6.89 (1H, td, *J* 7.6, 1.0), 7.09 (1H, td, *J* 7.8, 1.1), 7.18 (1H, dd, *J* 7.8, 0.9); δ_C (100 MHz, $CDCl_3$) 21.9, 24.6, 26.6, 30.6, 32.3, 46.4, 54.6, 107.2 121.5, 121.8, 122.8, 125.8, 141.1, 156.5; *m/z* (ESI^+) 245 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}N_2S^+$, ($[M+H]^+$) requires 245.1107; found 245.1108 (+0.3 ppm).

Preparation of (2*S*,3*R*)-8-chloro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole 43

Thionyl chloride (0.11 mL, 1.52 mmol, 2.2 eq) was added to a stirred solution of **37** (250 mg, 0.693 mmol, 1.0 eq) in PhMe (3 mL) and the reaction mixture was heated at 120 °C. Once complete, the mixture was allowed to cool to rt and MeOH was added. After evaporation of the solvent, 10% aq. NaOH was added to the residue followed by extraction with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford **43** (192 mg, 81%) as a gold solid; mp 140–144 °C; $[\alpha]_D^{20}$ +194.0 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr) 2959, 2864, 1629; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.7), 1.05 (3H, d, *J* 6.5), 1.16–1.28 (1H, m), 1.88 (1H, ddt, *J* 11.2, 9.3, 4.7), 3.28 (1H, t, *J* 11.5), 3.78 (1H, ddd, *J* 11.7, 5.2, 1.6), 4.84–4.87 (1H, m), 6.67 (1H, d, *J* 8.5), 7.07–7.14 (3H, m), 7.16–7.26 (4H, m); δ_C (100 MHz, $CDCl_3$) 20.0, 22.1, 26.9, 40.8, 42.2, 60.9, 108.5, 121.9, 124.8, 126.1, 127.4, 127.5, 128.0, 128.5, 139.2, 140.2, 158.3; *m/z* (NSI^+) 343 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{19}H_{20}ClN_2S^+$, ($[M+H]^+$) requires 343.1030; found 343.1034 (+1.1 ppm).

Preparation of (2*S*,3*R*)-3-isopropyl-2-(2-naphthyl)-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole 44

Thionyl chloride (0.20 mL, 2.79 mmol, 2.1 eq) was added to a stirred solution of **38** (500 mg, 1.33 mmol, 1.0 eq) in PhMe (6 mL) and the reaction mixture was heated at 120 °C. Once complete, the mixture was allowed to cool to rt and MeOH was added. After evaporation of the solvent, 10% aq. NaOH was added to the residue followed by extraction with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford **44** (420 mg, 88%) as a brown solid; mp 108–112 °C; $[\alpha]_D^{20}$ +250.0 (*c* 0.5 in CH_2Cl_2); ν_{max} (KBr) 3057, 2959, 1624, 1587; δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.7), 1.09 (3H, d, *J* 6.5), 1.22–1.34 (1H, m), 1.97 (1H, ddt, *J* 10.7, 9.3, 4.7), 3.37 (1H, t, *J* 11.4), 3.84 (1H, ddd, *J* 11.7, 5.3, 1.6), 5.03 (1H, dd, *J* 4.3, 1.1), 6.77 (1H, d, 7.7), 6.99 (1H, td, *J* 7.7, 1.0), 7.15–7.21 (1H, m), 7.26 (1H, dd, *J* 8.5, 1.8), 7.29 (1H, dd, *J* 7.7, 1.0), 7.35–7.39 (2H, m), 7.62 (1H, s), 7.69–7.75 (3H, m); δ_C (100 MHz, $CDCl_3$) 20.1, 22.3, 27.1, 41.2, 42.2, 61.5, 107.8, 122.1, 122.1, 123.3, 125.8, 126.1, 126.1, 126.1, 126.2, 127.0, 127.6, 128.1, 132.8, 133.4, 138.2, 140.8, 158.7; *m/z* (NSI^+) 359 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{23}H_{23}N_2S^+$, ($[M+H]^+$) requires 359.1576; found 359.1574 (–0.7 ppm).

Preparation of (*S*)-3-isopropyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole 45

A flask was charged with alcohol (*S*)-**39** (233 mg, 0.930 mmol, 1.0 eq), thionyl chloride (0.150 mL, 2.05 mmol, 2.2 eq) and toluene (5 mL). The reaction mixture was refluxed for 6 h, cooled to rt and concentrated *in vacuo*. The residue was dissolved in MeOH (9 mL), KOH (131 mg, 2.33 mmol, 2.5 eq) was added and the mixture was refluxed for 3 h. After cooling to rt, H_2O (9 mL) was added and the product extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. (*S*)-**45** was

obtained as a brown oil (110 mg, 51%), which was shown by chiral HPLC {Daicel CHIRALCEL AD-H, 4.6 mm × 250 mm, 20 : 80 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 7.6 (*R*), 9.0 (*S*)} to have >98% ee; $[\alpha]_D^{20}$ −64.0 (*c* 0.6 in $CHCl_3$); ν_{max} (KBr) 2961,1631; δ_H (300 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.3), 1.04 (3H, d, *J* 6.3), 1.65–1.79 (2H, m), 3.22 (1H, ABX, J_{AB} 14.8, J_{BX} 10.2), 3.36 (1H, app t, *J* 10.7), 3.67–3.71 (1H, m), 3.82–3.86 (1H, m), 6.75 (1H, d, *J* 8.0), 6.98 (1H, app. t, *J* 7.6), 7.18 (1H, app t, *J* 7.6), 7.26–7.27 (1H, m); δ_C (75 MHz, $CDCl_3$) 157.7, 140.8, 125.8, 122.7, 121.8, 121.6, 107.2, 49.4, 45.1, 35.9, 29.2, 20.2, 20.0; *m/z* (ES^+) 233 ([M+H], 100%); HRMS (ES^+) $C_{13}H_{17}N_2S$, ([M+H]) requires 233.1112; found 233.1105 (−3.2 ppm).

General procedure for the kinetic resolution of secondary alcohols (Table 4)

The requisite secondary alcohol (1.00 mmol, 1.0 eq) was added to 0.5 mL of the stirred catalyst stock solution (see below for preparation) at the required temperature. Once the reaction mixture was homogenous, propionic anhydride (0.60 mL, 0.500 mmol, 0.5 eq) was added and timing was initiated. After 1 h, MeOH (2 mL) was added and the mixture was diluted with EtOAc. The mixture was washed with 1.0 M aq. HCl, sat. aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue *via* flash column chromatography {silica; 5 : 95 EtOAc/hexanes (entries 3–6 and 13–17; Table 4) 2 : 98 EtOAc/hexanes (entries 1,2 and 7–12, Table 4)} gave the corresponding alcohol and ester. The alcohols were directly analysed by chiral HPLC. The esters were derivatised (see below for derivatisation procedures) and then analysed by chiral HPLC. All propionate esters have previously been characterised in the literature, except (*R*)-1-(4-fluorophenyl)ethyl propionate **59**.

Preparation of catalyst stock solution

Chiral isothiourea **14** (3 mol%), *i*-Pr_2NEt (0.42 mL, 2.40 mmol, 2.4 eq) and the requisite solvent (1 mL) were placed in a 2 mL volumetric flask. Once the mixture was homogeneous the requisite solvent was added until the total volume of the mixture had reached 2 mL.

Derivatisation procedures DMAP-catalysed esterification of alcohols (entries 3 and 4; Table 4)

A flask was charged with DMAP (0.7 mg, 0.00600 mmol, 10 mol%), CH_2Cl_2 (0.2 mL) and alcohol **48** (11 mg, 0.0660 mmol, 1.0 eq). Once homogeneous, propionic anhydride (0.10 mL, 0.0850 mmol, 1.3 eq) was added and the reaction mixture was stirred for 3 h at rt. The mixture was then diluted with EtOAc, washed with 1.0 M aq. HCl and sat. aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo.* The corresponding esters were then analysed by chiral HPLC.

KOH hydrolysis of ester (entries 5–10, 13–17; Table 4)

To a solution of the requisite ester in MeOH was added aq. 2.0 M KOH. The reaction mixture was stirred for 2 h at 65 °C then extracted with EtOAc (×2) and concentrated *in vacuo*. The alcohols obtained were then analysed by chiral HPLC.

$LiAlH_4$ reduction of ester (entries 11 and 12; Table 4)

To a solution of the propionate ester of **52** (40 mg, 0.180 mmol, 1.0 eq) in anhydrous Et_2O (2.5 mL) was added $LiAlH_4$ (2.0 M in hexanes, 0.14 mL, 0.290 mmol, 1.6 eq). The reaction mixture was stirred at rt for 2 h then quenched with MeOH. The resulting mixture was filtered through a cotton wool bud, dried (Na_2SO_4) and concentrated *in vacuo* to furnish the corresponding alcohols.

Characterisation data for (*R*)-1-(4-fluorophenyl)ethyl propionate 59

76% ee; $[\alpha]_D^{20}$ +76.4 (*c* 0.3 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 1.13 (3H, t, *J* 7.6), 1.51 (3H, d, *J* 6.6), 2.33 (2H, qd, *J* 7.6, 1.5), 5.86 (1H, q, *J* 6.6), 6.99-7.05 (2H, m), 7.26-7.34 (2H, m); δ_C (75 MHz, $CDCl_3$), 9.7, 22.9, 28.5, 72.1, 115.9 (d, *J* 21.5), 128.5 (d, *J* 8.2), 138.3, 161.3 (d, *J* 166.1), 174.3; ν_{max} (film) 2983, 1735; *m/z* (EI^+) 196 ($[M]^+$, 12%), 123 ($[M–CO_2Et]^+$, 100%); HRMS (ES^+) $C_{11}H_{17}FNO_2$ ($[M+NH_4]^+$) requires 214.1238; found 214.1239 (+0.5 ppm).

General procedure for the preparative scale kinetic resolution of secondary alcohols (Table 7)

The requisite secondary alcohol (1.0 eq) was added to 2 mL of the stirred stock solution of catalyst **14** at the required temperature. Once the reaction mixture was homogenous, propionic anhydride (0.6 eq) was added and timing was initiated. After the specified time, MeOH (5 mL) was added and the mixture was diluted with EtOAc. The mixture was washed with 1.0 M aq. HCl, sat. aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue *via* flash column chromatography gave the corresponding alcohol and ester.

Preparative scale kinetic resolution of 1-(naphtalen-1-yl)ethanol 46

Following the general procedure, alcohol **46** (500 mg, 2.90 mmol, 1.0 eq) and 2 mL of the catalyst stock solution {**14** (4.4 mg, 0.0140 mmol, 0.5 mol%) and *i*-Pr_2NEt (0.30 mL, 1.74 mmol, 0.6 eq) in $CHCl_3$ (10 mL)} were stirred and propionic anhydride (0.22 mL, 1.74 mmol, 0.6 eq) was added. The reaction was stirred at rt for 18 h. Purification *via* flash column chromatography gave the alcohol as a beige solid (144 mg, 30%, >99% ee) and the ester as a pale yellow oil (333 mg, 50%, 74% ee). The alcohol and ester were directly analysed by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 10 : 90 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of alcohol enantiomers: 16.1 min (*R*), 9.9 min (*S*) and ester enantiomers 4.8 min (*R*), 5.9 min (*S*)}.

Preparative scale resolution of 1-(naphtalen-2-yl)ethanol 48

Following the general procedure, alcohol **48** (500 mg, 2.90 mmol, 1.0 eq) and 2 mL of catalyst stock solution {**14** (4.4 mg, 0.0140 mmol, 0.5 mol%), *i*-Pr_2NEt (0.30 mL, 1.74 mmol, 0.6 eq) in $CHCl_3$ (10 mL)} were stirred and propionic anhydride (0.22 mL, 1.74 mmol, 0.6 eq) was added. The reaction was stirred at rt for 18 h. Purification *via* flash column chromatography gave the alcohol as a white powder (154 mg, 30%, >99% ee) and the ester as brown oil (332 mg, 50%, 67% ee). The alcohol was derivatised and analysed by chiral HPLC {Daicel CHIRALCEL OD-H,

4.6 mm × 250 mm, 1 : 99 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 7.2 min (*R*), 8.7 min (*S*)}.

Preparative scale resolution of 2,2-dimethyl-1-phenylpropan-1-ol 52

Following the general procedure, alcohol **52** (500 mg, 3.05 mmol, 1.0 eq) and 5 mL of the catalyst stock solution {**14** (4.7 mg, 0.0150 mmol, 0.5 mol%), *i*-Pr_2NEt (0.31 mL, 1.83 mmol, 0.6 eq) in $CHCl_3$ (10 mL)} were stirred and propionic anhydride (0.25 mL, 1.98 mmol, 0.65 eq) was added. The reaction was stirred at 0 °C for 60 h. Purification *via* flash column chromatography gave the alcohol as a white powder (220 mg, 44%, >99% ee) and the ester as a pale yellow oil (298 mg, 44%, 99% ee) The ester was hydrolysed and analysed by chiral HPLC analysis {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 15 : 85 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 5.9 min (*R*), 4.7 min (*S*)}.

Preparative scale resolution of (*E*)-4-phenylbut-3-en-2-ol 53

Following the general procedure, alcohol **53** (500 mg, 3.37 mmol, 1.0 eq) and 2 mL of the catalyst stock solution {**14** (5.2 mg, 0.0170 mmol, 0.5 mol%), *i*-Pr_2NEt (0.34 mL, 2.02 mmol, 0.6 eq) in $CHCl_3$ (10 mL)} were stirred and propionic anhydride (0.26 mL, 2.02 mmol, 0.6 eq) was added. The reaction was stirred at rt for 24 h. Purification *via* flash column chromatography gave the alcohol as a colourless oil (120 mg, 24%, 95% ee) and the ester as a pale yellow oil (354 mg, 54%, 66% ee) The ester was hydrolysed and analysed by chiral HPLC analysis {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 10 : 90 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 10.1 min (*R*), 15.3 min (*S*)}.

Preparative scale resolution of 4-phenylbut-3-yn-2-ol 54

Following the general procedure, alcohol **54** (500 mg, 3.42 mmol, 1.0 eq) and 2 mL of the catalyst stock solution {**14** (5.2 mg, 0.0170 mmol, 0.5 mol%), *i*-Pr_2NEt (0.34 mL, 2.02 mmol, 0.6 eq) in $CHCl_3$ (10 mL)} were stirred and propionic anhydride (0.26 mL, 2.05 mmol, 0.6 eq) was added. The reaction was stirred at 0 °C for 18 h. Purification *via* flash column chromatography gave the alcohol as a colourless oil (134 mg, 27%, >99% ee) and the ester as a pale yellow oil (300 mg, 44%, 57% ee) The ester was hydrolysed and analysed by chiral HPLC analysis {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 15 : 85 *i*-PrOH/hexane, 1 mL min^{-1}, retention times of enantiomers: 5.9 min (*R*), 11.3 min (*S*)}.

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