Scope, limitations and mechanistic analysis of the HyperBTM-catalyzed acylative kinetic resolution of tertiary heterocyclic alcohols

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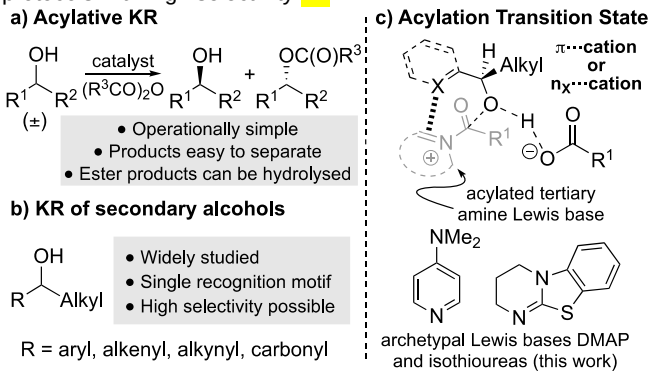
Abstract: The full scope and limitations of the catalytic acylative kinetic resolution of a range of tertiary heterocyclic alcohols (78 examples, *s* up to > 200) is reported under operationally-simple conditions, using low loadings of a commercially-available Lewis basic isothiourea catalyst, HyperBTM (generally 1 mol%). The protocol is highly effective for the kinetic resolution of 3-substituted 3-hydroxyoxindole and α-substituted α-hydroxylactam derivatives bearing up to three potential recognition motifs at the stereogenic tertiary carbinol centre. The full power of this methodology has been showcased through the synthesis of highly enantioenriched biologically-active target compounds in both enantiomeric forms. To provide further insight into the reaction mechanism, a detailed kinetic analysis of this Lewis base-catalyzed acylation of tertiary alcohols is reported using the VTNA method.

1. Introduction

Catalytic kinetic resolution (KR) is a widely-used and effective approach for the separation of racemic mixtures into their constituent enantiomers.[1] In such processes, a chiral catalyst promotes the reaction of one substrate enantiomer with a larger rate constant compared with its antipode.[2] The most commonly-applied metric to assess the efficiency of a KR is the selectivity factor (*s*), which is defined as the rate constant for the reaction of the fast-reacting enantiomer divided by the rate constant for the slow-reacting enantiomer (Equation 1).[3] Experimentally, *s* is most conveniently calculated using the reaction conversion (c) and the % enantiomeric excess (ee) of either the recovered substrate or isolated product (Equation 1). A value of $s > 20$ is often regarded as the benchmark for an efficient KR process, as this allows highly enantiomerically-enriched material to be isolated in both enantiomeric series in close to the theoretical maximum 50% yield.

$$s = \frac{k_{fast}}{k_{slow}} = \frac{\ln[(1-c)(1-ee_{substrate})]}{\ln[(1-c)(1+ee_{substrate})]} = \frac{\ln[1-c(1+ee_{product})]}{\ln[1-c(1-ee_{product})]} \quad (1)$$

The KR of racemic alcohols is both academically and industrially relevant, and, as such, an enormous range of strategies and catalysts has been developed for these processes. Catalytic acylative KR represents a particularly attractive strategy for the KR of alcohols due to the operational simplicity, and the ease of separation of the enantiomerically-enriched alcohol and ester products.[4] Furthermore, the isolated ester products are often readily hydrolyzed, providing facile access to both enantiomers of the alcohol substrate (Scheme 1a). The catalytic acylative KR of *secondary alcohols* using nitrogen-centred Lewis base catalysis has been widely studied (Scheme 1b), with enantiodiscrimination typically dictated by the relative ability of the two non-hydrogen substituents at the stereogenic carbinol centre to stabilize the catalytically-generated chiral *N*-acyl transfer reagent. Therefore, the alcohol substrate often contains *one* electron-rich sp^2/sp-hybridized substituent (e.g. aryl, alkenyl, alkynyl, carbonyl), which acts as a recognition motif by engaging in a stabilizing π•••cation or n_X•••cation interaction with the cationic *N*-acyl-catalyst intermediate;[5] and *one* non-stabilizing sp^3-hybridized alkyl substituent, which is differentiated from the hydrogen atom based on steric effects (Scheme 1c). The large difference in the ability of the carbinol substituents to stabilize the cationic *N*-acyl intermediate can result in effective KR protocols with high selectivity.[6,7]



Scheme 1. Lewis base-catalyzed acylative KR of *secondary alcohols.*

One of the remaining challenges within this field is the development of effective methods for the catalytic acylative KR of *tertiary alcohols*.[8] Such processes are challenging as: 1) acylation is inherently difficult due to the hindered nature of the alcohol; and 2) the catalyst is required to discriminate between enantiomers bearing three non-hydrogen substituents at the

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carbinol centre (Figure 1a). There is therefore the possibility of having up to three competing recognition motifs for the catalytic *N*-acyl intermediate, which can result in poor selectivity. For example, a tertiary carbinol centre may bear three sp^2-hybridized substituents (e.g. aryl, alkenyl, and carbonyl) that could each stabilize a cationic intermediate. This situation results in six possible competing acylation transition state combinations that lead to the preferential acylation of either substrate enantiomer (Figure 1b).

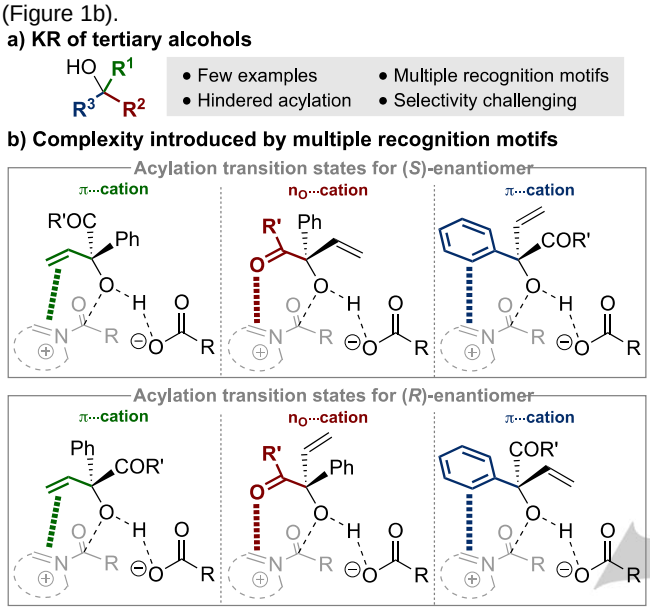
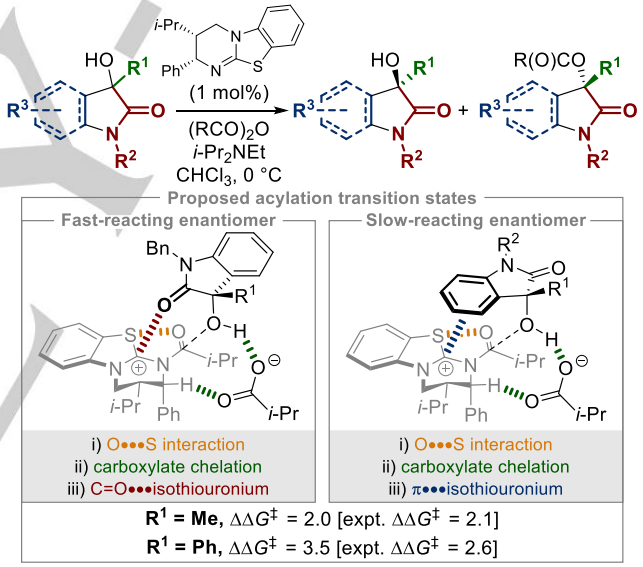


Figure 1. Lewis base-catalyzed acylative KR of *tertiary alcohols* bearing multiple recognition motifs.

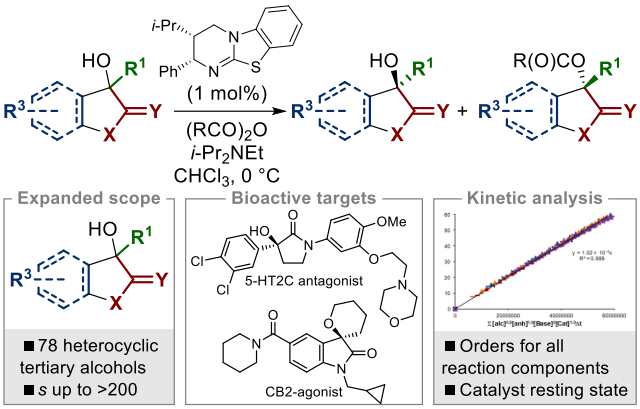
Due to the associated challenges, only four methods for the non-enzymatic catalytic acylative KR of tertiary alcohols have been reported to date.[9–13] Seminal work from Miller introduced a biomimetic strategy using a pentapeptide catalyst for the acylative KR of acyclic tertiary aminoalcohol substrates ($s \leq 50$).[9] Subsequently, Zhao,[10] ourselves,[11] and Suga[12] have reported the acylative KR of 3-hydroxy-3-substituted oxindole derivatives using chiral N-heterocyclic carbene, isothiourea, and DMAP catalysts, respectively.

In our initial communication,[11] the KR of a range of 3-hydroxy-3-substituted oxindole derivatives was demonstrated using low loadings of an isothiourea catalyst (1 mol%), providing selectivities of up to 200 (Scheme 2). In this methodology substrates were resolved containing up to three potential recognition motifs present at the tertiary alcohol centre (e.g. R^1 = aryl, alkenyl, etc.). To provide insight into the origin of this high selectivity, the structural features of catalyst-substrate recognition were explored using computations and compared to experimental results. Acylation transition structures for each enantiomer of two substrates (R^1 = Ph, Me; R^2 = Bn) were computed[14] using M06-2X/6-31G(d) with polarized continuum model (PCM) implicit solvent model for chloroform.[15] Energy refinements were computed at M06-2X/6-311++G(2df,p)[16] level of theory also in PCM (chloroform). The computed transition structure energy differences between the fast- and slow-reacting enantiomers were consistent with experimental selectivity as derived from the observed *s* values (Scheme 2). The lowest energy transition structures for the acylation of each enantiomer contained three key interactions (Scheme 2). i) Both acylation transition states exhibited an S•••O chalcogen bonding[17–19] interaction that locks the conformation of the acylated catalyst; ii) chelation of the substrate and catalyst by the carboxylate counterion through hydrogen bonding. iii) The transition structures for the acylation of each enantiomer, however, differed in the stabilization of the isothiouronium ion. While the transition structure for the slow-reacting enantiomer contained a π•••isothiouronium interaction, transition structure for the fast-reacting enantiomer contained a C=O•••isothiouronium interaction. It was therefore suggested that this C=O•••isothiouronium interaction was the key stabilizing interaction that drives the high enantiodiscrimination observed (Scheme 2). Based on this proposed model, we have since extended our methodology to the KR of acyclic tertiary α-hydroxy ester substrates under slightly modified conditions.[20] We have also demonstrated the KR of both cyclic and acyclic tertiary alcohols in continuous flow using a polymer-supported variant of the HyperBTM isothiourea catalyst.[20,21]



Scheme 2. Lewis base-catalyzed methods for acylative KR of *tertiary alcohols*.

Herein we report a comprehensive study of this isothiourea-catalyzed KR methodology, including detailed reaction optimization; expanded scope and limitations for the KR 3-hydroxyoxindole derivatives (53 examples, *s* up to 200); and a range of α-substituted α-hydroxylactam derivatives (25 examples, *s* up to 200) (Scheme 3). These classes of tertiary alcohol are prevalent throughout nature and display a range of biological activities,[22] and therefore the utility of this methodology to access both enantiomers of bioactive target compounds has been demonstrated. The mechanism of this KR is also further investigated through the kinetic analysis of the reaction under catalytically-relevant conditions using variable time normalization graphical analysis (VTNA).[23] To the best of our knowledge, this is the first time that such an analysis has been applied to the acylative KR of tertiary alcohols.



Scheme 3. This manuscript: extension, application, and mechanistic analysis of isothiourea-catalyzed acylative KR of heterocyclic tertiary alcohols.

2. Results and Discussion

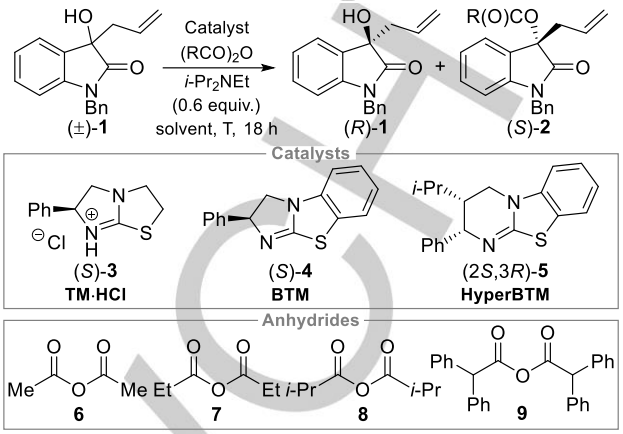
2.1. Kinetic resolution of 3-hydroxyoxindole derivatives

2.1.1. Reaction optimization

Initial studies aimed to identify conditions for the KR of 3-allyl-3-hydroxyoxindole **1**, which bears two potential recognition motifs at the tertiary carbinol centre: an aryl π-system and a carbonyl (Table 1). The use of acetic anhydride **6** as the acylating agent and either (*S*)-tetramisole·HCl **3** or (*S*)-benzotetramisole **4** (BTM) as catalyst (10 mol%) with *i*-Pr_2NEt as base (0.6 equiv.) resulted in disappointing conversion and low selectivity (s < 2, entries 1–2). However, using just 1 mol% loading of commerically-available (2*S*,3*R*)-HyperBTM **5**[24] gave improved conversion and promising selectivity (s = 8, entry 3). Lowering the reaction temperature and increasing the steric bulk of the acylating agent significantly increased the selectivity, with s = 100 obtained using isobutyric anhydride **8** at 0 °C (entries 4–7). The absolute configuration of the recovered alcohol (93:7 er) was assigned as (*R*)-**1** through comparison of its specific rotation with literature.[25] The KR protocol using (2*S*,3*R*)-**5** and isobutyric anhydride **8** was also effective at room temperature, and in the absence of *i*-Pr_2NEt (s = 80–90, entries 8–9), however the selectivity was slightly lower compared with the optimal conditions (entry 6). While the KR in $CHCl_3$ at 0 °C gave the highest selectivity, the use of industrially-preferable solvents[26] including acetates, dimethyl carbonate and toluene at room temperature also provided synthetically-useful levels of selectivity (s = 34–41, entries 10–12).

The validity of using equation 1 to calculate s was assessed for the KR of (±)-**1** at room temperature by monitoring the enantiomeric enrichment of the recovered alcohol and ester product over time.[3] Linear regression analysis was performed for a room temperature KR by plotting $\ln[(1-c)(1-ee_{substrate})]$ vs $\ln[(1-c)(1+ee_{substrate})]$ (Figure 2a). This resulted in high linearity, demonstrating s to be independent of reaction conversion, and validating its use as a metric to describe the efficiency of the KR. The reproducibility of the KR was investigated by performing 12 repeat reactions (Figure 2b). Comparable results were obtained in each case, with the use of equation 1 providing reaction conversions in the range of 45–48% and s values of 97–106.

Table 1: Reaction optimization for the KR of 3-hydroxyoxidindoles



Entry	Cat (mol%)	$(RCO)_2O$ (equiv.)	Solvent	T	c (%)	s
1[a]	(*S*)-**3** (10)	**6** (0.55)	$CHCl_3$	r.t.	37	1
2	(*S*)-**4** (10)	**6** (0.55)	$CHCl_3$	r.t.	41	2
3	(2*S*,3*R*)-**5** (1)	**6** (0.55)	$CHCl_3$	r.t.	53	8
4	(2*S*,3*R*)-**5** (1)	**6** (0.55)	$CHCl_3$	0 °C	53	9
5	(2*S*,3*R*)-**5** (1)	**7** (0.55)	$CHCl_3$	0 °C	42	19
6	(2*S*,3*R*)-**5** (1)	**8** (0.7)	$CHCl_3$	0 °C	47	100
7	(2*S*,3*R*)-**5** (1)	**9** (0.7)	$CHCl_3$	0 °C	47	60
8	(2*S*,3*R*)-**5** (1)	**8** (0.7)	$CHCl_3$	r.t.	53	90
9[b]	(2*S*,3*R*)-**5** (1)	**8** (0.7)	$CHCl_3$	0 °C	37	80
10	(2*S*,3*R*)-**5** (1)	**8** (0.7)	EtOAc	r.t.	53	34
11	(2*S*,3*R*)-**5** (1)	**8** (0.7)	*i*-PrOAc	r.t.	56	30
12	(2*S*,3*R*)-**5** (1)	**8** (0.7)	$(MeO)_2CO$	r.t.	53	36
13	(2*S*,3*R*)-**5** (1)	**8** (0.7)	PhMe	r.t.	56	41

Conversion (c) and er determined by HPLC analysis using a chiral stationary phase. s calculated using equation 1 and rounded according to ref. [3]. Optimization performed using (±)-**1** (0.2 mmol), anhydride (0.11 mmol), catalyst **3**-**5** (0.002 mmol). [a] (*S*)-**1** obtained as the major enantiomer of recovered alcohol. [b] no *i*-Pr_2NEt used.

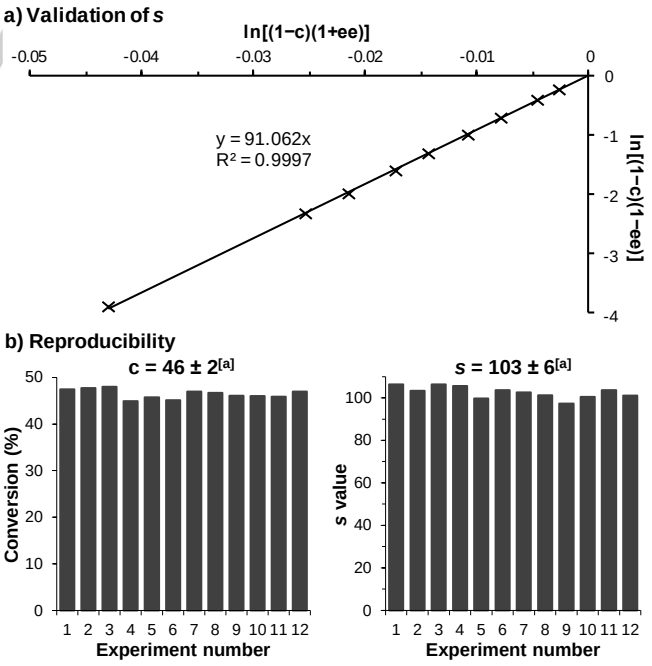


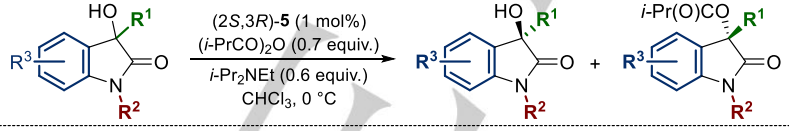
Figure 2. **a)** Linear regression analysis of the KR of (±)-**1** at room temperature by determination of the temporal er of **1** and **2**. **b)** Twelve repeat KRs of (±)-**1**

at 0 °C. [a] Mean value of twelve repeat reactions, with errors given as two standard deviations of the mean.

2.1.2. Reaction scope: 3-Alkyl substituted 3-hydroxyoxindoles

The generality of the method for the KR of 3-alkyl substituted 3-hydroxyoxindoles, bearing one sp^3 and two sp^2 substituents at the tertiary carbinol centre, was investigated first (Table 2). 3-Alkyl-substituted alcohols bearing a range of *N*-substituents [benzyl, allyl, methyl, *para*-methoxybenzyl (PMB) and *tert*-butyloxycarbonyl (Boc)] were successfully resolved with high *s* values obtained in each case (**10**–**14**; *s* = 39–140). Alcohol **15**, bearing a 3-trifluoromethyl substituent, was resolved with moderate selectivity under the standard conditions;[27] however, high selectivity was achieved upon lowering the reaction temperature to −40 °C (*s* = 32). Increasing the size of the 3-alkyl substituent was tolerated for 3-ethyl- and 3-isopropyl derivatives **16** and **17**; however, 3-*tert*-butyl-substituted derivative **18** was not acylated using either isobutyric or acetic anhydride. Alcohols bearing functionalized substituents were investigated next. Alcohols **20** and **21**, bearing Lewis basic ester and amide substituents that could act as competitive recognition motifs, were resolved with good selectivity (*s* = 19 and 26). In contrast, the attempted acylative KR of ketone-substituted alcohol **22** did not give any ester, with dehydration taking place to give the highly-conjugated enone instead. The alcohol substrate **22** was recovered in 60% yield and 56:44 er, indicating the operation of a chiroablative KR with only low selectivity (*s* = 2). Nitrile-containing 3-hydroxyoxindole derivatives **23** and **24**, which are intermediates in the synthesis of bioactive pyrrolidinoindoline alkaloid natural products, CPC-1 and flustraminol-B,[28,29] were successfully resolved (both *s* = 30). For these substrates, improved *s* values were obtained in the absence of *i*-Pr_2NEt and with the addition of isobutyric acid. This effect can be attributed to suppression of an unselective base-promoted acylation, identified by control studies (Table S4).[27] The difference in reactivity between ketone-substituted alcohol **22** and the structurally-related ester **20**, amide **21**, and nitrile-containing substrates **23** and **24**, can presumably be rationalized by a difference in pK_a, with acetophenone derivatives typically 5-8 pK_a units more acidic than the corresponding esters, amides and nitriles.[30] Finally, the effect of substitution within the benzenoid core of the oxindole was investigated using a 3-methyl and *N*-benzyl substituent as standard. Incorporation of a 4-chloro substituent (**25**) resulted in high selectivity (*s* = 80), although higher catalyst loading and an extended reaction time was required for good conversion, presumably due to increased steric hindrance. Substitution at the 5-position within alcohols **26**–**28** led to lower *s* values (*s* = 21–34), with the electron-withdrawing 5-bromo substituent having the most pronounced effect (*s* = 21). Finally, tertiary alcohols **29** and **30** bearing 6- and 7-chloro substituents were resolved with excellent selectivity (*s* = 120 and 44, respectively).

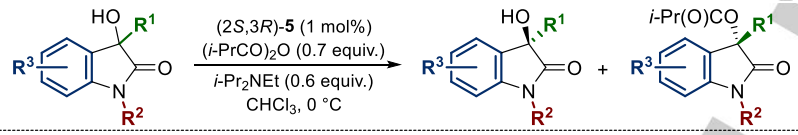
Table 2: Scope: 3-Alkyl-3-hydroxyoxindole derivatives (sp^2 vs sp^2 vs sp^3)

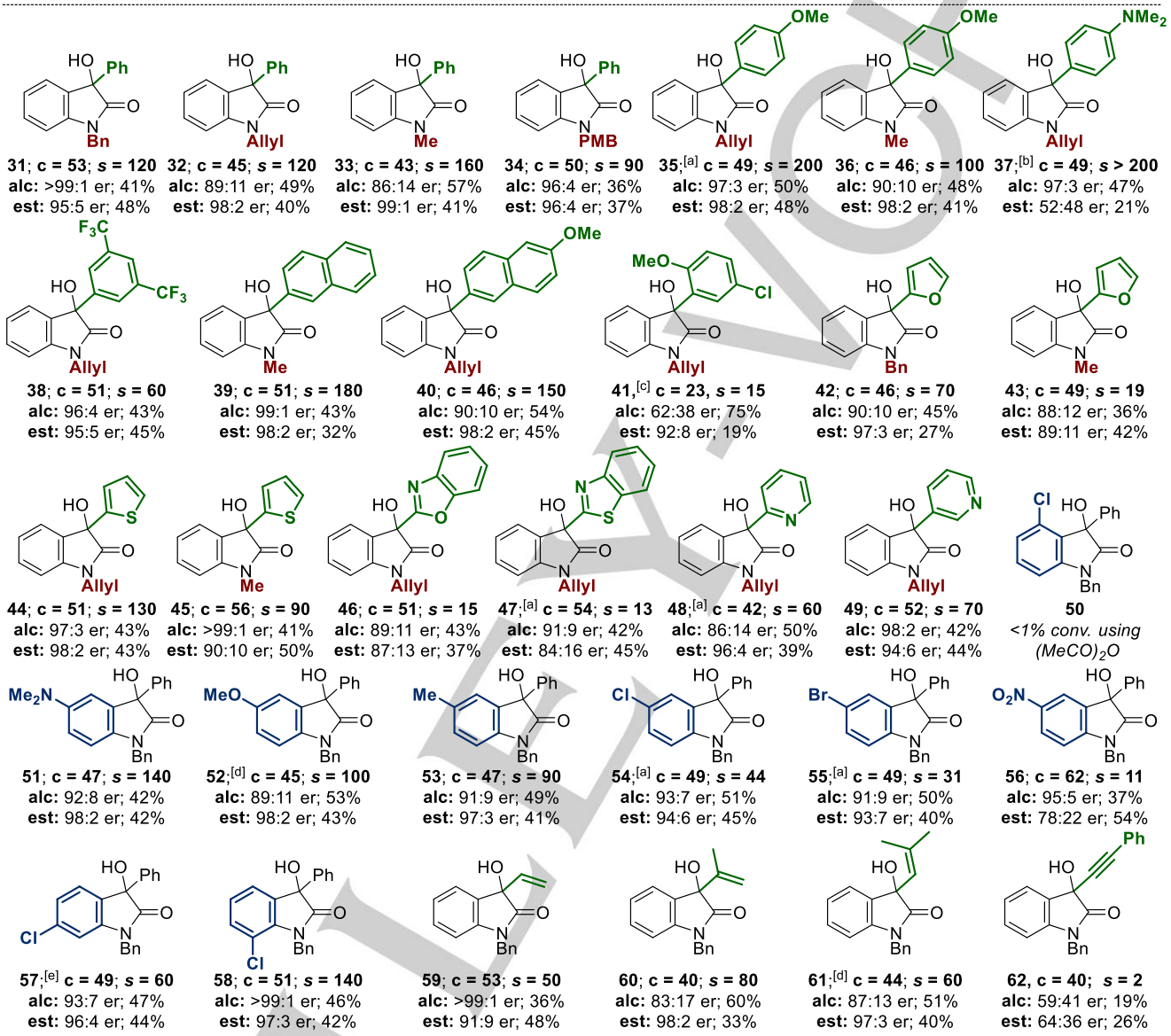


10; **c = 53**; ***s* = 50** **alc:** 99:1 er; 42% **est:** 92:8 er; 51%	**11**; **c = 42**; ***s* = 140** **alc:** 85:15 er; 49% **est:** 99:1 er; 42%	**12**; **c = 52**; ***s* = 39** **alc:** 96:4 er; 36% **est:** 92:8 er; 48%	**13**; **c = 49**; ***s* = 50** **alc:** 94:6 er; 43% **est:** 96:4 er; 49%	**14**; **c = 52**; ***s* = 110** **alc:** 96:4 er; 41% **est:** 99:1 er; 45%	**15**;[a] **c = 59**; ***s* = 32** **alc:** >99:1 er; 27% **est:** 85:15 er; 45%	**16**; **c = 51**; ***s* = 47** **alc:** 95:5 er; 44% **est:** 94:6 er; 46%
17;[b] **c = 42**; ***s* = 60** **alc:** 85:15 er; 56% **est:** 97:3 er; 41%	**18** *<1% conv. using* $(MeCO)_2O$	**19**; **c = 51**; ***s* = 21** **alc:** 91:9 er; 45% **est:** 89:11 er; 45%	**20**; **c = 59**; ***s* = 19** **alc:** 98:2 er; 31% **est:** 83:17 er; 44%	**21**;[c] **c = 45**; ***s* = 26** **alc:** 84:16 er; 48% **est:** 93:7 er; 45%	**22**; **c ≈ 35**; ***s* = 2** **alc:** 56:44 er; 60% **est:** —[d]	**23**;[e] **c = 59**; ***s* = 30** **alc:** >99:1 er; 35% **est:** 84:16 er; 52%
24;[e] **c = 58**; ***s* = 30** **alc:** >99:1 er; 36% **est:** 86:14 er; 46%	**25**;[f] **c = 48**; ***s* = 80** **alc:** 93:7 er; 51% **est:** 97:3 er; 45%	**26**; **c = 54**; ***s* = 34** **alc:** 98:2 er; 43% **est:** 90:10 er; 50%	**27**; **c = 52**; ***s* = 30** **alc:** 94:6 er; 42% **est:** 91:9 er; 40%	**28**; **c = 54**; ***s* = 21** **alc:** 94:6 er; 45% **est:** 88:12 er; 47%	**29**; **c = 52**; ***s* = 120** **alc:** >99:1 er; 45% **est:** 96:4 er; 46%	**30**; **c = 54**; ***s* = 44** **alc:** >99:1 er; 42% **est:** 89:11 er; 48%

Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1 and rounded according to ref. [3]. Reactions performed on a 0.3 to 1.0 mmol scale of (±) substrate alcohol. See SI for reaction concentration and time. [a] −40 °C. [b] 2 mol% (2*S*,3*R*)-**5**. [c] 5 mol% (2*S*,3*R*)-**5**. [d] No ester isolated. Enone product, derived from dehydration, isolated in 31%. [e] 0.6 equiv. $(i\text{-PrCO})_2O$, 0.5 equiv. *i*-$PrCO_2H$, no *i*-Pr_2NEt used. [f] 10 mol% (2*S*,3*R*)-**5**.

Table 3: Scope: 3-Aryl-, 3-alkenyl- and 3-alkynyl-3-hydroxyoxindole derivatives (sp^2 vs sp^2 vs sp^2/sp)





31; **c = 53**; ***s* = 120**
alc: >99:1 er; 41%
est: 95:5 er; 48%

32; **c = 45**; ***s* = 120**
alc: 89:11 er; 49%
est: 98:2 er; 40%

33; **c = 43**; ***s* = 160**
alc: 86:14 er; 57%
est: 99:1 er; 41%

34; **c = 50**; ***s* = 90**
alc: 96:4 er; 36%
est: 96:4 er; 37%

35;[a] **c = 49**; ***s* = 200**
alc: 97:3 er; 50%
est: 98:2 er; 48%

36; **c = 46**; ***s* = 100**
alc: 90:10 er; 48%
est: 98:2 er; 41%

37;[b] **c = 49**; ***s* > 200**
alc: 97:3 er; 47%
est: 52:48 er; 21%

38; **c = 51**; ***s* = 60**
alc: 96:4 er; 43%
est: 95:5 er; 45%

39; **c = 51**; ***s* = 180**
alc: 99:1 er; 43%
est: 98:2 er; 32%

40; **c = 46**; ***s* = 150**
alc: 90:10 er; 54%
est: 98:2 er; 45%

41,[c] **c = 23**, ***s* = 15**
alc: 62:38 er; 75%
est: 92:8 er; 19%

42; **c = 46**; ***s* = 70**
alc: 90:10 er; 45%
est: 97:3 er; 27%

43; **c = 49**; ***s* = 19**
alc: 88:12 er; 36%
est: 89:11 er; 42%

44; **c = 51**; ***s* = 130**
alc: 97:3 er; 43%
est: 98:2 er; 43%

45; **c = 56**; ***s* = 90**
alc: >99:1 er; 41%
est: 90:10 er; 50%

46; **c = 51**; ***s* = 15**
alc: 89:11 er; 43%
est: 87:13 er; 37%

47;[a] **c = 54**; ***s* = 13**
alc: 91:9 er; 42%
est: 84:16 er; 45%

48;[a] **c = 42**; ***s* = 60**
alc: 86:14 er; 50%
est: 96:4 er; 39%

49; **c = 52**; ***s* = 70**
alc: 98:2 er; 42%
est: 94:6 er; 44%

50
<1% conv. using $(MeCO)_2O$

51; **c = 47**; ***s* = 140**
alc: 92:8 er; 42%
est: 98:2 er; 42%

52;[d] **c = 45**; ***s* = 100**
alc: 89:11 er; 53%
est: 98:2 er; 43%

53; **c = 47**; ***s* = 90**
alc: 91:9 er; 49%
est: 97:3 er; 41%

54;[a] **c = 49**; ***s* = 44**
alc: 93:7 er; 51%
est: 94:6 er; 45%

55;[a] **c = 49**; ***s* = 31**
alc: 91:9 er; 50%
est: 93:7 er; 40%

56; **c = 62**; ***s* = 11**
alc: 95:5 er; 37%
est: 78:22 er; 54%

57;[e] **c = 49**; ***s* = 60**
alc: 93:7 er; 47%
est: 96:4 er; 44%

58; **c = 51**; ***s* = 140**
alc: >99:1 er; 46%
est: 97:3 er; 42%

59; **c = 53**; ***s* = 50**
alc: >99:1 er; 36%
est: 91:9 er; 48%

60; **c = 40**; ***s* = 80**
alc: 83:17 er; 60%
est: 98:2 er; 33%

61;[d] **c = 44**; ***s* = 60**
alc: 87:13 er; 51%
est: 97:3 er; 40%

62, c = 40; *s* = 2
alc: 59:41 er; 19%
est: 64:36 er; 26%

Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1 and rounded according to ref. [3]. Reactions performed on a 0.3 to 1.0 mmol scale of (±) substrate alcohol. See SI for reaction concentration and time. [a] 2 mol% (2*S*,3*R*)-**5**. [b] 10 mol% (2*S*,3*R*)-**5**, c determined by ^{1}H NMR. [c] 10 mol% (2*S*,3*R*)-**5**, reflux. [d] 5 mol% (2*S*,3*R*)-**5**. [e] DMF in place of $CHCl_3$.

2.1.3. Reaction scope: 3-Aryl- and 3-alkenyl-substituted 3-hydroxyoxindoles

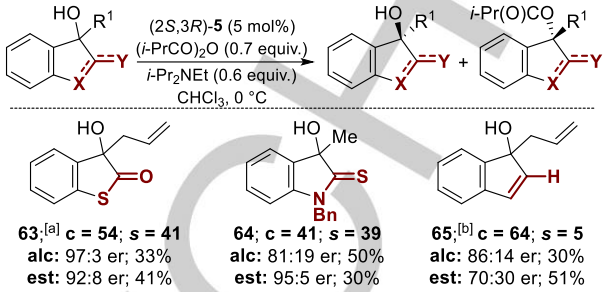
To further challenge the enantiodiscrimination capability of (2*S*,3*R*)-**5**, the KR of 3-aryl-, heteroaryl- and alkenyl-substituted derivatives was investigated, in which all three carbinol substituents could potentially act as competitive recognition motifs (two π-systems and a carbonyl) (Table 3). Notably, 3-phenyl-substituted derivatives **31**–**34** were resolved with very high selectivity (*s* = 90–160), indicating exceptional enantiodiscrimination by the isothiourea catalyst. In this series, the absolute configurations were confirmed by X-ray crystallographic analysis of recovered (*R*)-**31**, with all other examples assigned by analogy.[31] The resolution of oxindole derivatives **35**–**40** bearing both electron-donating and electron-withdrawing aromatic groups at the 3-position also gave excellent selectivity (*s* = 60–200). Interestingly, the resolution of 4-*N*,*N*-dimethylaminophenyl-substituted alcohol **37** allowed for the isolation of enantiomerically-enriched (*R*)-**37** (97:3 er) at 49% conversion; however the isobutyric ester was obtained as a

racemate (52:48 er). This phenomenon is attributed to racemization of the ester by reversible ionization promoted by the presence of the electron-donating *N*,*N*-dimethylamino group. The KR of alcohol **41** bearing a sterically demanding *ortho*-substituted aryl group was ineffective under the standard reaction conditions; however, increasing the catalyst loading to 10 mol% and heating at reflux for 48 h provided moderate selectivity (*s* = 15) albeit with only 23% conversion. Various heteroaromatic substituents were also successfully incorporated. The KR of furanyl- and thienyl-substituted alcohols **42**–**45** gave good to excellent selectivity factors (*s* = 19–130), while alcohols **46** and **47** containing benzoxazole and benzothiazole groups were also successfully resolved (*s* = 15 and 13). Notably, alcohols **48** and **49** bearing Brønsted and Lewis basic pyridyl groups were resolved with excellent levels of selectivity (*s* = 60 and 70). The effect of substitution within the benzenoid ring of the oxindole core was then investigated using a 3-phenyl and *N*-benzyl substituent as standard. In contrast to the 3-methyl-substituted analogue **25**, incorporation of a 4-chloro substituent (**50**) was not tolerated in this series, presumably due to inhibitory steric hindrance. A series of 3-phenyl-3-hydroxyoxindole derivatives **51**–**56** with electronically-differentiated substituents at the 5-position were all successfully resolved. The presence of electron-donating groups (5-dimethylamino **51**, 5-methoxy **52** and 5-methyl **53**) allowed resolution with high selectivity (*s* = 90–140), whereas alcohols **54**–**56** bearing electron-withdrawing halogen and nitro groups were resolved with lower selectivity (*s* = 11–44). 6-Chloro-substituted oxindole **57** was completely insoluble in chloroform; however, the resolution could be affected with high selectivity when performed in DMF (*s* = 60). 7-Chloro-substituted substrate **58** was only sparingly soluble in chloroform but was still resolved with excellent selectivity following an extended reaction time (*s* = 140). The method proved equally applicable for the KR of 3-alkenyl-substituted 3-hydroxyoxidinole derivatives **59**–**61.** The catalyst was again capable of differentiating between three potential recognition motifs at the carbinol stereocentre and excellent selectivity factors were obtained in each case (*s* = 50–80). In contrast, incorporation of an alkyne substituent at the tertiary alcohol centre (sp^2 vs sp^2 vs sp) resulted in very low selectivity (**62**, *s* = 2), representing a current limitation of the methodology.

2.1.4. Reaction scope: Core structure variations

The substrate scope of this KR process demonstrates that good selectivities can be achieved for oxindole derivatives bearing a range of C(3) substituents, indicating that this substituent is unlikely to act as a dominant recognition motif in this resolution. To provide further insight, the core heterocyclic structure was systematically varied to probe the effect of the carbonyl group and benzannulation (Tables 4 and 5). Benzothiophenone derivative **63**, in which the lactam nitrogen is replaced with sulfur, and indoline-2-thione derivative **64**, in which the carbonyl oxygen is replaced with sulfur, were both resolved with excellent selectivity (*s* = 41 and 39). The effect of removing the carbonyl was simulated using indenol **65**. No acylation was observed using isobutyric anhydride, while using acetic anhydride gave a selectivity factor of just 5. These results are consistent with the carbonyl playing a significant role in facilitating both reactivity and enantiodiscrimination in this process.

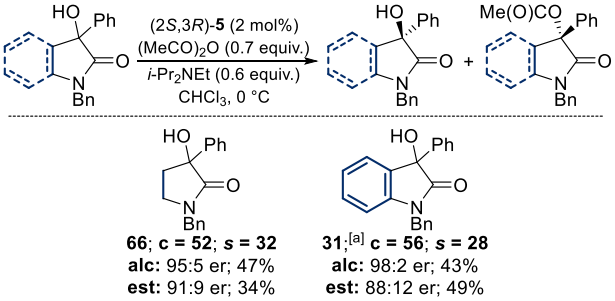
Table 4: Structural variations I: effect of carbonyl



Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1. See SI for reaction concentration and time. [a] 1 mol% (2*S*,3*R*)-**5**. [b] using $(MeCO)_2O$ in place of $(i\text{-PrCO})_2O$.

Next, the significance of benzannulation was investigated. α-Hydroxy-γ-lactam **66**, which lacks the benzannulation present in all other substrates, was unreactive using isobutyric anhydride; however, the use of acetic anhydride allowed resolution of **66** with good selectivity (*s* = 32). Under analogous conditions, benzannulated analogue **31** was resolved with comparable selectivity (*s* = 28). Single crystal X-ray analysis of enantiomerically-pure α-hydroxy-γ-lactam **66** confirmed the same sense of enantiodiscrimination for both substrates.[32] The lack of acylation of **66** using isobutyric anhydride suggests that benzannulation may favour acylation, possibly due to a reduction in steric hindrance α- to the reactive carbinol centre, while the similar *s* values obtained for the resolution of **66** and **31** using acetic anhydride is consistent with benzannulation having minimal effect on selectivity. The results presented in Tables 4 and 5 are consistent with the previously-reported computational work that found the carbonyl group is the dominant recognition motif required for this KR process.

Table 5: Structural variations II: effect of benzannulation



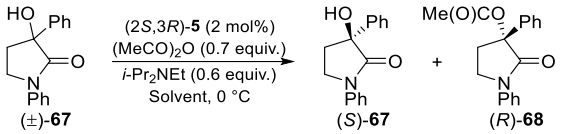
Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1. See SI for reaction concentration and time. [a] 0.6 equiv. of $(MeCO)_2O$.

2.2. Kinetic resolution of 3-hydroxypyrrolidinone derivatives

2.2.1. Reaction optimization

α-Substituted-α-hydroxylactams form the core structure of several natural products and possess a range of biological activities; however, there are few general methods for their enantioselective synthesis.[33] The KR of this substrate class was

Table 6: Reaction optimization for the KR of 3-hydroxypyrrolidinones



Entry	Solvent	c (%)	**67** er	**68** er	*s*
1	$CHCl_3$	51	95:5	93:7	40
2	Et_2O	43	86:14	97:3	60
3	*t*-AmylOH	25	66:34	97:3	41
4	$(MeO)_2CO$	50	95:5	95:5	50
5	EtOAc	48	94:6	98:2	110
6	PhMe	44	88:12	99:1	180

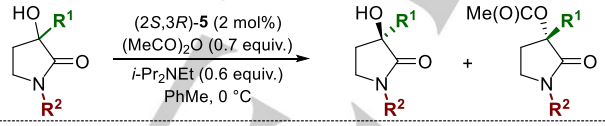
Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1 and rounded according to ref. [3].

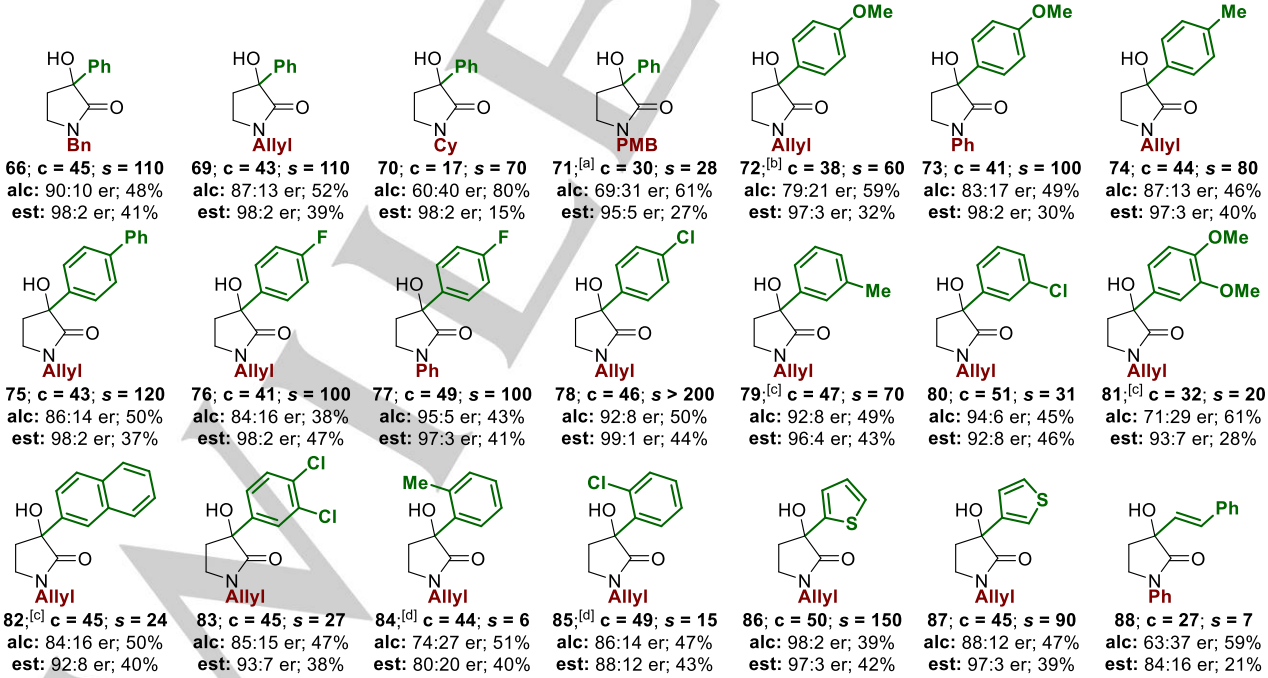
therefore considered of interest for further investigation. Optimization studies were conducted using 3-phenyl-3-hydroxypyrrolidinone derivative **67**, with (2*S*,3*R*)-HyperBTM **5** as catalyst and acetic anhydride as acyl donor (Table 6). The choice of solvent had a significant effect on the efficiency of the KR. In chloroform, similar conversion and selectivity were obtained to that observed for *N*-benzyl analogue **66** (entry 1, *s* = 40), while improved selectivity was obtained in Et_2O (entry 2, *s* = 60). The KR was then investigated in more industrially-preferable solvents.[26] The use of *tert*-amyl alcohol or dimethyl carbonate led to similar selectivities (entries 3–4, *s* = 41–50), while significantly higher selectivities were obtained using either ethyl acetate (entry 5, *s* = 110) or toluene (entry 6, *s* = 180). The use of either (*S*)-TM·HCl **3** or (*S*)-BTM **4** as catalyst provided only very low conversion and selectivity, whilst the use of more sterically-demanding anhydrides, such as propionic or isobutyric anhydride, led to lower conversion.[27]

2.2.2. Reaction scope: 3-Aryl- and alkenyl-substituted 3-hydroxypyrrolidinone derivatives

Using the optimized conditions, the KR of a range of 3-aryl-, 3-heteroaryl- and 3-alkenyl-substituted pyrrolidinone derivatives was investigated (Table 7). 3-Phenyl-substituted derivatives **66, 69–71**, bearing a range of N-substituents were resolved with good to high selectivity (*s* = 28–110). The introduction of *para*-electron-donating and electron-withdrawing groups on the 3-aryl substituent were tolerated, with alcohols **72–78** all resolved with excellent selectivity (*s* = 60–200). The introduction of both electron-donating and electron-withdrawing groups at the *meta*-position was also tolerated, although slightly lower selectivity factors were obtained (**79–83**, *s* = 20–70). The use of more highly electron-withdrawing substituents could not be investigated due to a limitation of the synthetic route used to access the substrates.[27] In keeping with the KR of 3-hydroxyoxindole derivatives, the introduction of an *ortho*-substituted aryl group resulted in significantly diminished

Table 7: Scope: 3-Aryl- and 3-alkenyl-3-hydroxypyrrolidinone derivatives (sp^3 vs sp^2 vs sp^2)





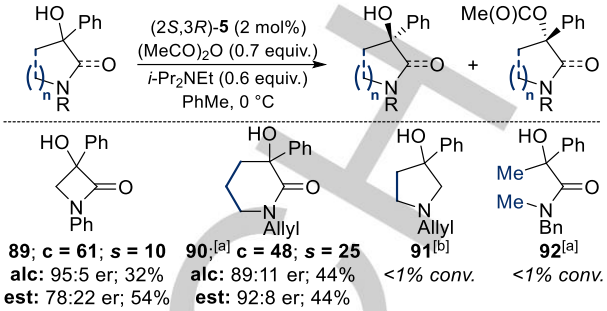
Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1 and rounded according to ref. [3]. Reactions performed on a 0.3 to 1.0 mmol scale of (±) substrate alcohol. See SI for reaction concentration and time. [a] $CHCl_3$ in place of PhMe. [b] 5 mol% (2*S*,3*R*)-**5**. [c] 5 mol% (2*S*,3*R*)-**5**, 0.9 equiv. $(MeCO)_2O$. [d] 20 mol% (2*S*,3*R*)-**5**, 1.5 equiv. $(MeCO)_2O$, 1.5 equiv. *i*-Pr_2NEt, 90 °C.

reactivity. For the KR of alcohols **84** and **85**, increased catalyst loading (20 mol%) and a high reaction temperature (90 °C) were required for good conversion (44–49%). *ortho*-Tolyl-substituted alcohol **84** was only resolved with low selectivity under these conditions (*s* = 6); however, *ortho*-chlorophenyl derivative **85** underwent resolution with synthetically-useful selectivity (*s* = 15). The KR of thienyl-substituted derivatives **86** and **87** was also achieved with excellent selectivity (*s* = 90–160). Finally, the KR of 3-alkenyl-substituted 3-hydroxypyrrolidinone derivative **88** was investigated but, under the standard reaction conditions, relatively low conversion and selectivity was obtained (c = 27%, *s* = 7). A limitation of the synthetic route used to access these substrates meant that the KR of substrates bearing 3-alkyl substituents could not be investigated.[25]

2.2.3. Reaction scope: Structural variations

To provide further insight into the operation of this KR, variations to the 3-hydroxypyrrolidinone core structure were investigated (Table 8). Initially, the effect of the lactam ring size was probed. α-Hydroxy-β-lactam derivative **89** underwent facile acylation and provided a useful level of selectivity (*s* = 10). In contrast, the ring-expanded analogue, α-hydroxy-δ-lactam **90**, was unreactive under the standard conditions. A catalyst loading of 20 mol% and reaction temperature of 90 °C was required for acylation, although even at this temperature an impressive *s* value of 25 was obtained. Under analogous conditions, 3-hydroxypyrrolidinone derivative **69** underwent KR with comparable selectivity (*s* = 26).[27] The importance of the carbonyl moiety was next investigated using tertiary alcohol **91**. No acylation was observed, even when increased catalyst loading (10 mol%) and reaction temperatures (90 °C) were used. This is in line with the structural variations performed on the oxindole series and our previous computational analysis, which show the importance of the carbonyl functionality for reactivity and selectivity. Finally, the significance of the cyclic structure was probed using acyclic amide **92**. No acylation was observed even at high catalyst loading and reaction temperature, demonstrating the importance of the cyclic structure. We have since shown that acyclic tertiary α-hydroxy secondary amides are resolved with relatively low selectivity (*s* < 7), while acyclic tertiary α-hydroxy esters can be resolved efficiently, with *s* values of up to 140.[20]

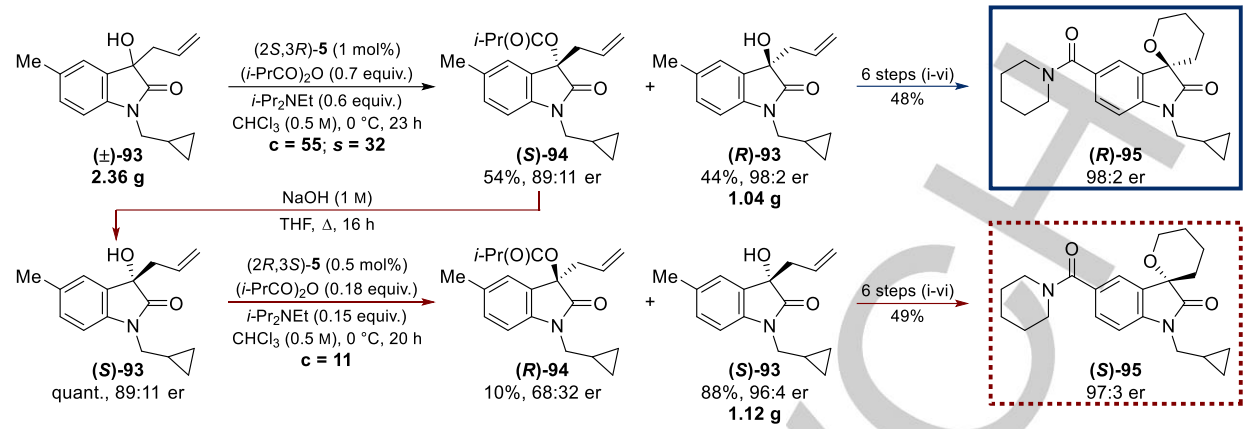
Table 8: Structural variations



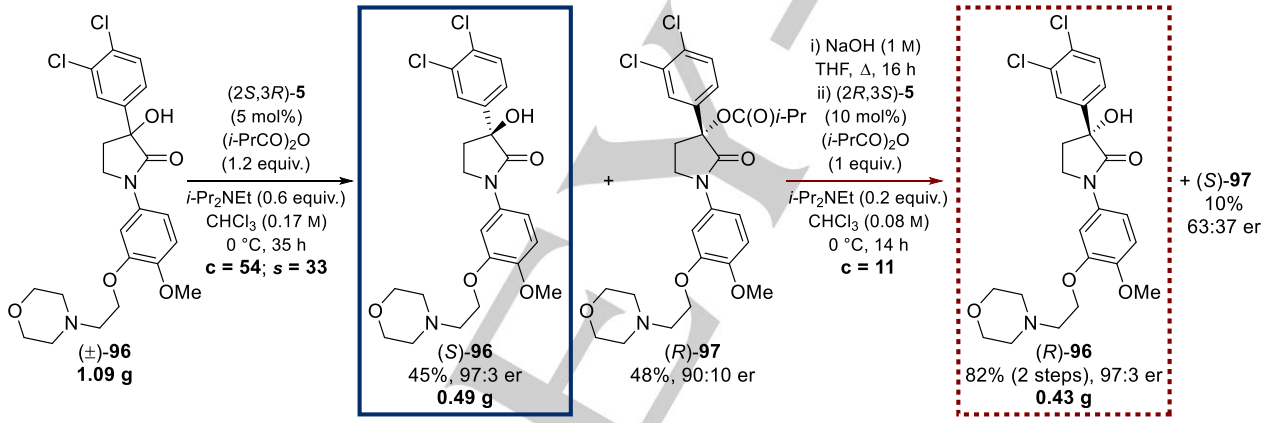
Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1. See SI for reaction concentration and time. [a] 20 mol% (2*S*,3*R*)-**5**, 90 °C. [b] 10 mol% (2*S*,3*R*)-**5**, 90 °C.

2.3. Application for the preparation of bioactive compounds

Having developed an efficient protocol for the acylative KR of a range of tertiary heterocyclic alcohols, application to the synthesis of bioactive target compounds was demonstrated (Schemes 4 and 5). By taking advantage of the non-destructive nature of acylative KR, both enantiomers of the target compounds were accessed in highly enantiomerically-enriched form. First, an early-stage KR approach was used for the synthesis of spirocyclic CB2 cannabinoid receptor agonist **95** (Scheme 4).[34] The multigram-scale KR of 3-allyl-3-hydroxyoxindole alcohol (±)-**93** under the standard conditions using (2*S*,3*R*)-HyperBTM-**5** gave (*R*)-**93** in 44% yield with excellent enantioenrichment (98:2 er). The recovered (*S*)-isobutyrate ester (*S*)-**94** (54% yield, 89:11 er) was hydrolyzed to provide the (*S*)-alcohol (*S*)-**93** in quantitative yield. The enantiopurity of (*S*)-**93** (89:11 er) was enhanced by performing a second KR. In this case, enantiomeric (2*R*,3*S*)-HyperBTM-**5**[22] was used to acylate the remaining (*R*)-enantiomer of the alcohol selectively, requiring only 11% conversion to obtain highly enantiomerically-enriched (*S*)-**93** (96:4 er). The two enantiomers of **93** were subsequently transformed in six steps to give both enantiomers of CB2 agonist **95** without any erosion in enantiopurity.[27,35] This method compares favourably with the original synthesis of **95** in which (±)-**95** was obtained in 4% yield, with separation of the enantiomers achieved by preparative chiral HPLC.[34a] Next, the late-stage KR of a bioactive compound was demonstrated using 5-HT2C antagonist **96** (Scheme 5).[22b] Racemic bioactive target (±)-**96** was synthesized in five steps from commercially-available reagents in 64% yield.[27] Gram-scale KR using 5 mol% (2*S*,3*R*)-HyperBTM **5** gave (*S*)-**96** in 45% yield and 97:3 er. As previously, the enantiomeric purity of the recovered isobutyrate ester (*R*)-**97** (90:10 er) was enhanced through hydrolysis and a further KR using (2*R*,3*S*)-HyperBTM **5**, to provide (*R*)-**96** in 97:3 er. Overall, both (*S*)- and (*R*)-**96** were isolated in highly enantioenriched form in a combined 84% yield from (±)-**96**, showcasing the highly powerful and efficient nature of the developed KR methodology.



Scheme 4. Early-stage KR for the synthesis of both enantiomers of CB2-agonist **95**. Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1. i) *n*-Bu_4NI (1 mol%), allyl bromide (1.6 equiv.), NaOH (aq), CH_2Cl_2, r.t., 20 h, 89–92%; ii) Grubbs catalyst I (1 mol%), PhMe, 110 °C, 2 h, 85–92%; iii) Pd/C (1 mol%), H_2 (1 atm.), MeOH, r.t., 2 h, 98%; iv) $Ce(NH_4)_2(NO_3)_6$ (4 equiv.), MeOH/MeCN (2:1), r.t., 5 min, 71–73%; v) $NaClO_2$ (2 equiv.), $NaH_2PO_4{\cdot}2H_2O$ (4 equiv.), 2-methyl-2-butene (4 equiv.), *t*-BuOH/H_2O (1:1), 0 °C→r.t., 4 h, 90–91%; vi) CDI (2 equiv.), piperidine (4 equiv.), THF, 0 °C→r.t., 7 h, 92–98%.



Scheme 5. Late-stage KR for the synthesis of both enantiomers of 5-HT2C antagonist **96.** Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equation 1,

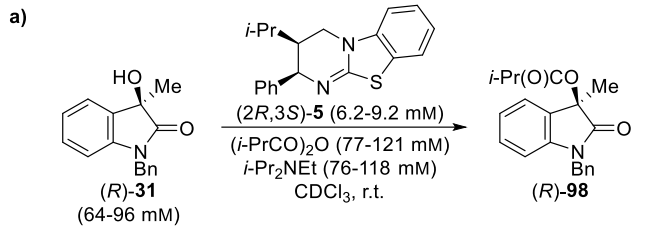
2.4. Experimental mechanistic studies

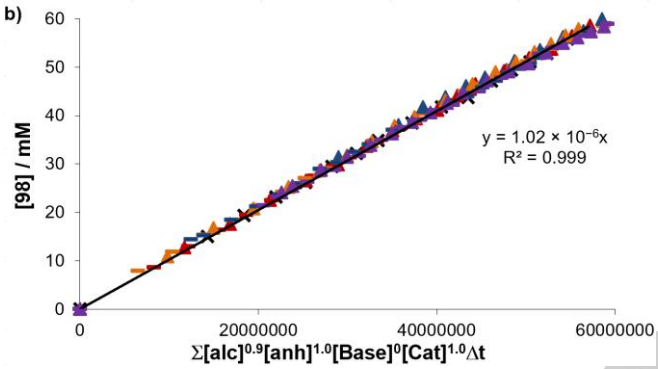
2.4.1. Kinetic analysis

Kinetic analyses have previously been reported for tertiary amine-catalyzed acylation of secondary alcohols using DMAP, chiral DMAP derivatives, and the isothiourea HBTM.[36] These analyses were performed either under pseudo-first order conditions or using reaction progress kinetic analysis (RPKA).[37] In each case, acyl transfer was first order in catalyst and zeroth order in the auxiliary base (NEt_3 or *i*-Pr_2NEt). Zipse[36a] and Rychnovsky[36c] reported the acyl transfer was also first order in both alcohol and anhydride, using DMAP and HBTM, respectively. In contrast, Dinér found that using a planar-chiral DMAP derivative gave orders for the alcohol and anhydride as fractional values (0.8 and 0.7 respectively).[36b] These fractional orders were rationalized by a steady-state approximation, in which the free catalyst exists in equilibrium with the acylated catalyst.

To gain insight into the mechanism of the acylative KR of a tertiary alcohol substrate promoted by HyperBTM **5**, a kinetic analysis was performed to obtain orders for each reaction component. *In situ* ^1H NMR spectroscopic analysis was used to determine temporal concentrations of each component, and the variable time normalization graphical analysis method developed by Burés was used to determine reaction orders.[23] This method was chosen as full-time course data is used, reaction orders are determined under catalytically relevant conditions (i.e. not under pseudo-first order conditions), and less data manipulation is required than for RPKA.[37,23b] Kinetic analysis was performed using (2*R*,3*S*)-HyperBTM **5** and the fast-reacting (*R*)-enantiomer of 1-benzyl-3-hydroxy-3-methylindolin-2-one **31** (> 99:1 er) to simplify the kinetic scenario. Nine reactions were performed with three different starting concentrations of alcohol (*R*)-**31**, isobutyric anhydride, *i*-Pr_2NEt and (2*R*,3*S*)-HyperBTM **5** (Figure 3a). A plot of concentration of ester formation against a

normalized time axis of Σ[**alc**]$^{\alpha}$[**anh**]$^{\beta}$[**base**]$^{\gamma}$[**cat**]$^{\delta}\Delta$t (where α, β, γ and δ represent the respective reaction orders of each component) allowed graphical interrogation of the kinetic profiles (Figure 3b). Systematically varying α, β, γ, and δ provided optimal overlay and linearity for α = 0.9, β = 1.0, γ = 0, and δ = 1.0, indicating the reaction is first order in anhydride and catalyst, zeroth order in base, and a fractional order of 0.9 in alcohol.

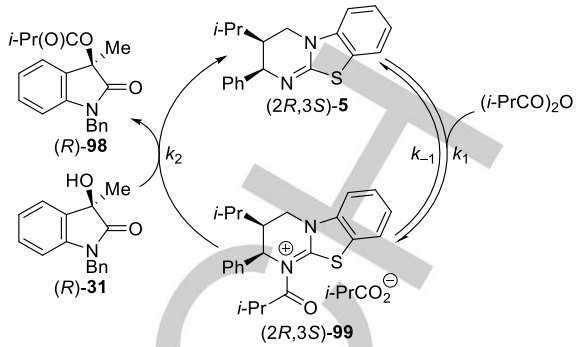




Key	[Alc] (mM)	[anh] (mM)	[base] (mM)	[cat] (mM)
×	80	96	103	7.7
▲	96	93	101	7.7
–	64	93	103	8.0
▲	80	121	99	7.7
–	80	77	101	7.6
▲	80	99	118	7.6
–	80	97	76	7.6
▲	80	92	102	9.2
–	80	93	102	6.2

Figure 3. Kinetic analysis of the (2*R*,3*S*)-**5**-catalyzed acylation of (*R*)-**31** using variable time normalization kinetic analysis.

A fractional order of 0.9 in alcohol indicates that the alcohol appears in both the numerator and denominator of the rate equation.[37,27] Although reasonable overlay and linearity is also obtained when the order in alcohol is set to 1.0, a fractional order in alcohol is expected according to a steady state approximation in which the concentration of the acyl isothiouronium intermediate remains low, resulting in the total concentration of catalyst being approximately equal to the concentration of free isothiourea throughout the reaction course (Scheme 6). In this kinetic scenario the alcohol appears in both the numerator and denominator of the rate equation and is consistent with a fractional order in alcohol of less than one (Equation 2).

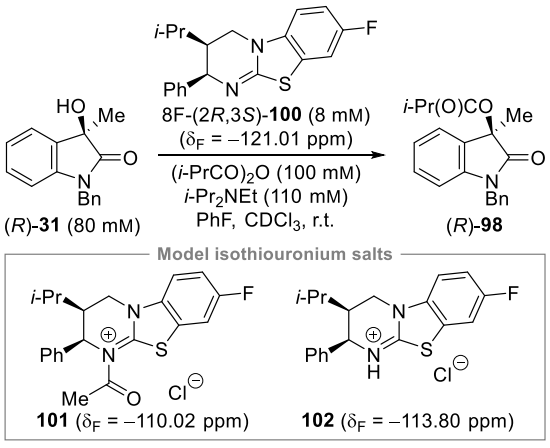


when $[Cat]_{total} \approx [(2R,3S)\text{-}\mathbf{5}]$:

$$\frac{d[(R)\text{-}\mathbf{98}]}{dt} = \frac{k_1 k_2 [\mathbf{anh}][(R)\text{-}\mathbf{31}][(2R,3S)\text{-}\mathbf{5}]}{k_{-1} + k_2[(R)\text{-}\mathbf{31}]} \qquad (2)$$

Scheme 6. Simplified schematic representation of the (2*R*,3*S*)-**5**-catalyzed acylation of (*R*)-**31**, and rate expression for the formation of (*R*)-**31** using a steady-state approximation where $[Cat]_{total} \approx [(2R,3S)\text{-}\mathbf{5}]$.

Catalyst speciation was investigated experimentally by performing the acylation of (*R*)-**31** using a fluorine-tagged analogue of the catalyst, 8F-(2*R*,3*S*)-HyperBTM **100**[38] [δ_F = −121.01 ppm ($CDCl_3$)], and following reaction progress by single-scan *in situ* ^{19}F NMR spectroscopic analysis (Scheme 7). Model isothiouronium chloride salts **101** [δ_F = −110.02 ppm ($CDCl_3$)] and **102** [δ_F = −113.80 ppm ($CDCl_3$)] were prepared through reaction of **100** with acetyl chloride and HCl, respectively, to aid *in situ* identification of potential catalyst-derived intermediates or by-products.[27] Over the time course of the reaction, the free isothiourea was found as the major observable species (~8.0 mM), with the only other observable catalyst-derived species [δ_F = −112.05 ppm ($CDCl_3$)] present in very low concentration (< 0.05 mM). The difference in chemical shift between this species and the model *N*-acyl isothiouronium makes identification inconclusive; however, the extremely low concentration of this species is consistent with the kinetic analysis, in which catalyst speciation is dominated by the free isothiourea.



Scheme 7. 8F-(2*R*,3*S*)-**100**-catalyzed acylation of (*R*)-**31**.

Conclusions

In conclusion, the full scope and limitations of the catalytic acylative kinetic resolution of a range of tertiary heterocyclic alcohols (78 examples, *s* up to > 200) is reported. This protocol is highly effective for the kinetic resolution of 3-substituted 3-hydroxyoxindole and α-substituted α-hydroxylactam derivatives. This methodology has been showcased through the synthesis of both enantiomeric forms of highly enantioenriched biologically-active target compounds. A detailed kinetic analysis of this Lewis base-catalyzed acylation has provided insight into the reaction mechanism. Ongoing work from within our laboratory is focused on demonstrating further applications of chiral isothioureas in enantioselective catalysis and specifically their use in challenging kinetic resolution processes.

Experimental Section

General procedure for the acylative kinetic resolution of tertiary alcohols using isothioureas and acid anhydrides
An isothiourea catalyst (1-10 mol%) was added to a solution of alcohol (1 equiv.) in the required solvent. The reaction was adjusted to the required temperature and anhydride (0.7 equiv.) and *i*-Pr_2NEt (0.6 equiv.) were added. The reaction mixture was stirred for the required time. On completion, the mixture was diluted with EtOAc (20 mL) and washed sequentially with 1 M HCl (2 × 10 mL) and sat. aq. $NaHCO_3$ (2 × 10 mL), brine (10 mL) dried ($MgSO_4$), filtered and concentrated *in vacuo*. The alcohol and ester were separated by flash column chromatography and analyzed by chiral HPLC.

Representative Example:
According to the general procedure, 3-allyl-1-benzyl-3-hydroxyindolin-2-one **1** (112 mg, 0.4 mmol), isobutyric anhydride (46 µL, 0.7 mmol), (2*S*,3*R*)-HyperBTM **5** (1.2 mg, 0.004 mmol, 1 mol%) and *i*-Pr_2NEt (42 µL, 0.6 mmol) were reacted in $CHCl_3$ (2.4 mL) at 0 °C for 21 h to give the crude products, which were purified by Biotage® Isolera 4 chromatography (eluent: 0%→35% EtOAc in hexane) to give 3-allyl-1-benzyl-3-hydroxyindolin-2-one **1** (58 mg, 0.21 mmol, 52%) and 3-allyl-1-benzyl-2-oxoindolin-3-yl isobutyrate **2** (58 mg, 0.17 mmol, 42%).
(*R*)-3-Allyl-1-benzyl-3-hydroxyindolin-2-one 1: $[\alpha]_D^{20}$ +13 (*c* 1.0, $CHCl_3$) {Lit.[23] (90% ee) $[\alpha]_D^{27}$ +8.5 (*c* 1.0, $CHCl_3$)}; **Chiral HPLC analysis** Chiralcel OD-H (98:2 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (*R*): 31.4 min, t_R (*S*): 37.6 min, 93.8:6.2 (*R*:*S*) er.
(*S*)-3-Allyl-1-benzyl-2-oxoindolin-3-yl isobutyrate 2: $[\alpha]_D^{20}$ +20 (*c* 1.0, $CHCl_3$); **Chiral HPLC analysis** Chiralcel OD-H (98:2 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (*R*): 8.0 min, t_R (*S*): 9.8 min, 97.4:2.6 (*S*:*R*) er.

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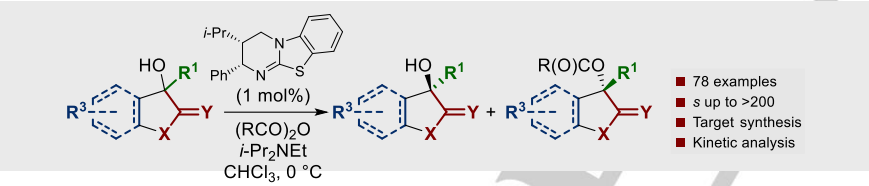

The isothiourea HyperBTM catalyzes the acylative kinetic resolution of a wide range of tertiary heterocyclic alcohols under mild conditions with high selectivity. The synthetic utility of the methodology has been demonstrated with the preparation of two bioactive targets. Kinetic analysis reveals a fractional reaction order with respect to the alcohol concentration.

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Scope, limitations and mechanistic analysis of the HyperBTM-catalyzed acylative kinetic resolution of tertiary heterocyclic alcohols