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C=O...Isothiouonium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolution of Tertiary Heterocyclic Alcohols

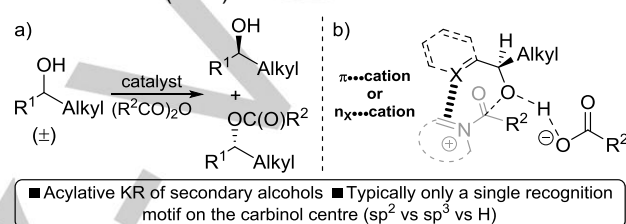
Mark D. Greenhalgh,^[a] Samuel M. Smith,^[a] Daniel M. Walden,^[b] James E. Taylor,^[a] Zamira Brice,^[a] Emily R. T. Robinson,^[a] Charlene Fallan,^[a] David B. Cordes,^[a] Alexandra M. Z. Slawin,^[a] H. Camille Richardson,^[b] Markas A. Grove,^[b] Paul Ha-Yeon Cheong*^[b] and Andrew D. Smith*^[a]

Abstract: A combination of experimental and computational studies have identified a C=O...isothiouonium interaction as key to efficient enantiodiscrimination in the kinetic resolution of tertiary heterocyclic alcohols bearing up to three recognition motifs at the stereogenic carbinol center. This discrimination was exploited in the isothiurea-catalyzed acylative kinetic resolution of tertiary heterocyclic alcohols (38 examples, *s* up to > 200). The reaction proceeds at low catalyst loadings (generally 1 mol%) using isobutyric anhydride as the acylating agent under mild conditions.

The catalytic kinetic resolution (KR) of racemates offers an effective approach to the separation of enantiomers,^[1,2] with an enormous range of processes and catalysts developed for applications in academia and industry.^[3] Among the most popular methods is the acylative KR of alcohols,^[4] as this approach allows simple separation of the enantiomerically-enriched alcohol and ester products. Within this area, the use of small molecule Lewis base catalysts is well developed for the catalytic acylative KR of *secondary alcohols* (Scheme 1a).^[1,4] In such processes, enantiodiscrimination is dictated by the relative ability of the two non-hydrogen substituents at the stereogenic carbinol center to stabilize the catalytic cationic acyl transfer intermediate. Therefore, a common prerequisite for the selective KR of an alcohol substrate is the presence of one electron-rich sp²-hybridized substituent (e.g. aryl, carbonyl), which acts as a cation recognition motif,^[5] and one non-stabilizing sp³-hybridized alkyl substituent (Scheme 1b).

Lewis basic isothiurea catalysts, first developed for acyl transfer reactions by Birman^[6] and Okamoto,^[7] have emerged as exceptional catalysts for the acylative KR of secondary alcohols^[8] and desymmetrization of diols,^[9] amongst other applications.^[10] The high selectivity factors (*s*) obtained for the KR of secondary alcohols are attributed to the presence of an effective recognition motif on the racemic alcohol, allowing one antipode to react preferentially with a chiral acyl isothiuronium intermediate. Established recognition motifs in isothiurea-catalyzed KR include aryl,^[6,8a-c,h,i] heteroaryl,^[8e] alkenyl,^[8a,h] alkynyl,^[8a,h] C=O,^[8d,f] and P=O^[8g] substituents. Consequently, high selectivity is only commonly observed for stereogenic

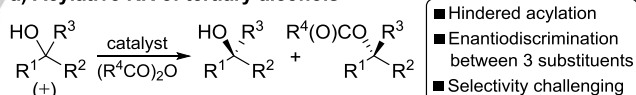
carbinols bearing *one* of these motifs in combination with an alkyl substituent and a hydrogen atom.^[11] An unmet challenge within acylative KR is the ability to resolve alcohols bearing multiple recognition motifs, with the relative strength of the different interactions only poorly understood. For example, the KR of ethyl mandelate, which contains two recognition motifs (π -system and carbonyl), is ineffective with only very low selectivity factors obtained (*s* < 2).^[8c]



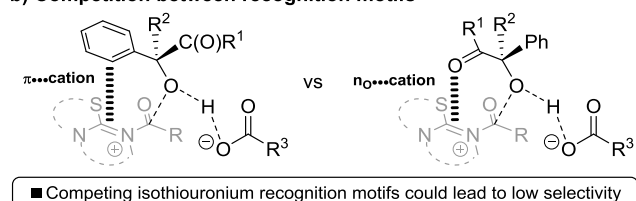
Scheme 1. Lewis base-catalyzed acylative KR of *secondary alcohols*.

In this context, this work investigates such cases through the isothiurea-catalyzed acylative KR of *tertiary alcohols* (Scheme 2a). The efficient KR (*s* > 20) of tertiary alcohols is particularly challenging as: 1) they are difficult to acylate due to their hindered nature; and 2) the catalyst must distinguish between three substituents at the reactive carbinol center. The presence of multiple recognition motifs (e.g. aryl and carbonyl) provides an additional challenge, as the acylation of both substrate enantiomers may be promoted by different carbinol substituents, resulting in poor selectivity (Scheme 2b).

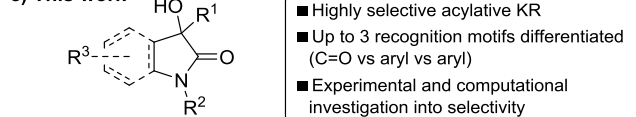
a) Acylative KR of tertiary alcohols



b) Competition between recognition motifs



c) This work



Scheme 2. KR of *tertiary alcohols*.

For the KR of tertiary alcohols, the situation is further complicated if three recognition motifs are present, with potential for competition between six stabilized transition states for acylation (three for each substrate enantiomer). As such, only two non-enzymatic acylative KR of tertiary alcohols have been reported to date, using either a bespoke pentapeptide catalyst or

[a] Dr M. D. Greenhalgh, S. M. Smith, Dr J. E. Taylor, Z. Brice, E. R. T. Robinson, Dr C. Fallan, Dr D. B. Cordes, Prof. A. M. Z. Slawin, Prof. A. D. Smith

EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST (UK)

E-mail: ads10@st-andrews.ac.uk

[b] D. M. Walden, H. C. Richardson, M. A. Grove, Prof. P. H.-Y. Cheong

Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, OR 97331 (USA)

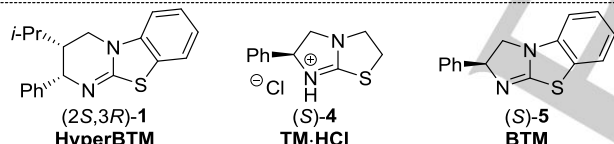
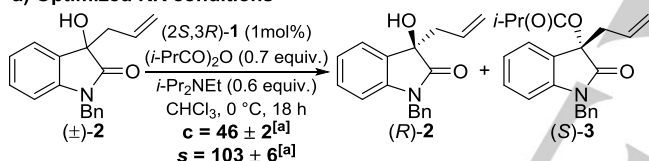
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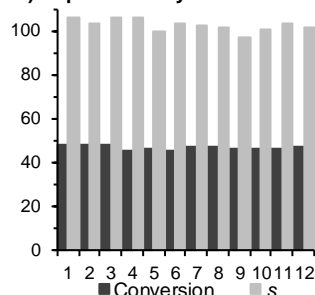
through oxidative NHC catalysis.^[12] In both cases high catalyst loadings (10 mol%) are required. Herein, the isothiourea-catalyzed acylative KR of tertiary 3-hydroxyoxindole and 3-hydroxypyrrolidin-2-one derivatives,^[13] in which either two or three of the carbinol substituents can potentially act as a recognition motif, is investigated (Scheme 2c). The key structural features of catalyst-substrate recognition that allow effective enantiodiscrimination are explored both experimentally and computationally.

Optimization studies focused on the KR of 3-allyl-3-hydroxyoxindole **2**, which bears two potential recognition motifs at the tertiary carbinol center: an aryl π -system and a carbonyl. A highly efficient KR process was identified ($s > 100$) using isothiourea catalyst HyperBTM **1** (1 mol%) and isobutyric anhydride in CHCl_3 at 0 °C (Figure 1a).^[14,15] The use of less sterically-hindered anhydrides provided lower selectivity factors, whilst alternative isothiourea catalysts, tetramisole **4** and benzotetramisole **5**, were ineffective in terms of both conversion and selectivity ($s < 2$).^[14] Industrially-preferable solvents [EtOAc, *i*-PrOAc, $(\text{MeO})_2\text{CO}$, PhMe] also provided synthetically-useful levels of selectivity ($s = 34\text{--}41$),^[14,16] albeit lower than those obtained in CHCl_3 . The robustness of the process was demonstrated through 12 repeat reactions, in which comparable conversions and selectivities were obtained in each case (Figure 1b). Monitoring the temporal change in er of alcohol and ester in a KR at r.t. and applying a linear regression analysis confirmed s was independent of conversion, thus validating its use as a descriptor for the efficiency of the process (Figure 1c).^[1b,14,17]

a) Optimized KR conditions



b) Reproducibility^[b]



c) Validation of $s^{[c]}$

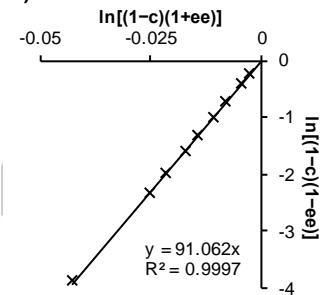
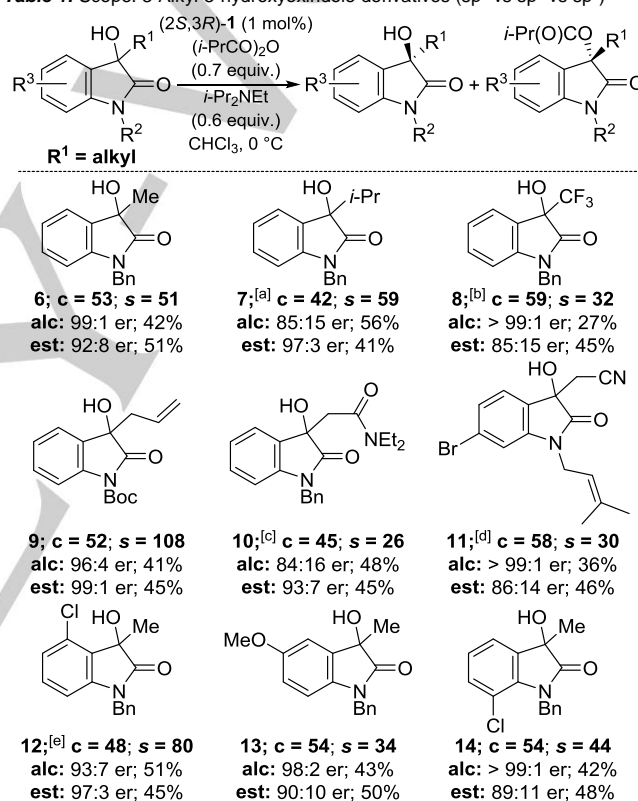


Figure 1. KR of 3-hydroxyoxindole $(\pm)\text{-2}$. Conversion (c) determined by chiral HPLC analysis. s calculated using equations given in ref. 2. [a] Mean of 12 repeat reactions (see part b); errors given as 2 standard deviations of mean. [b] 12 repeat KR of $(\pm)\text{-2}$ at 0 °C. [c] Linear regression analysis of the KR of $(\pm)\text{-2}$ at r.t. by determination of temporal alcohol and ester er data.

The scope and limitations of the KR process was first evaluated for a range of 3-alkyl-substituted 3-hydroxyoxindole derivatives, through variation of the 3-alkyl-, *N*- and benzenoid ring substituents (Table 1). Simple alkyl chains, including an α -branched *i*-Pr and perfluorinated CF_3 group, were well tolerated (**6–9**, $s = 32\text{--}108$), as were a range of *N*-substituents, including benzyl, allyl, and *tert*-butyloxycarbonyl (Boc). Alcohols **10** and **11** bearing Lewis basic amide and nitrile substituents, which could

potentially act as competitive recognition motifs, were also resolved with good selectivity ($s = 26$ and 30). Nitrile-containing 3-hydroxyoxindole derivatives, including **11**, are intermediates in the synthesis of bioactive pyrrolidinoindoline alkaloid natural products, such as CPC-1 and flustraminol-B.^[18] For the KR of this substrate, improved selectivity factors were obtained in the presence of isobutyric acid and without *i*-Pr₂NEt as a surrogate base. This effect can be attributed to suppression of a non-selective base-promoted background acylation, identified by control studies (Table S5).^[14] Substitution around the benzenoid ring in every position with both electron-donating and withdrawing groups was also tolerated, albeit with substitution in the 4-position leading to reduced reactivity, presumably due to increased steric hindrance. For the KR of **12** a higher catalyst loading of 10 mol% was therefore required. A current limitation of this method is that exceptionally sterically-hindered 3-*tert*-butyl-substituted derivatives were unreactive.

Table 1: Scope: 3-Alkyl-3-hydroxyoxindole derivatives (sp^2 vs sp^2 vs sp^3)

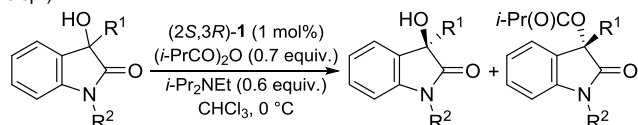


Conversion (c) and er determined by chiral HPLC analysis. s calculated using equations given in ref. 2. See SI for reaction concentration and time. [a] 2 mol% $(2S,3R)\text{-1}$. [b] -40°C . [c] 5 mol% $(2S,3R)\text{-1}$. [d] 0.6 equiv. $(i\text{-PrCO})_2\text{O}$, 0.5 equiv. $i\text{-PrCO}_2\text{H}$, no $i\text{-Pr}_2\text{NEt}$ used. [e] 10 mol% $(2S,3R)\text{-1}$.

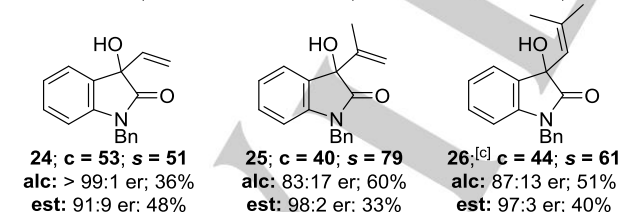
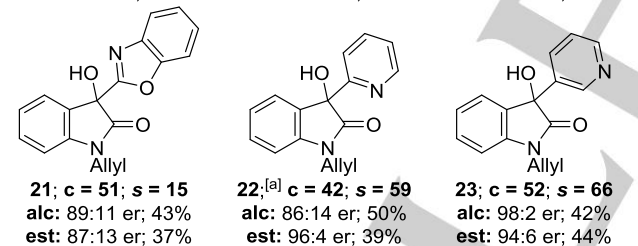
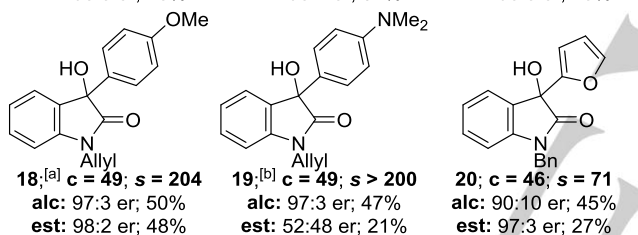
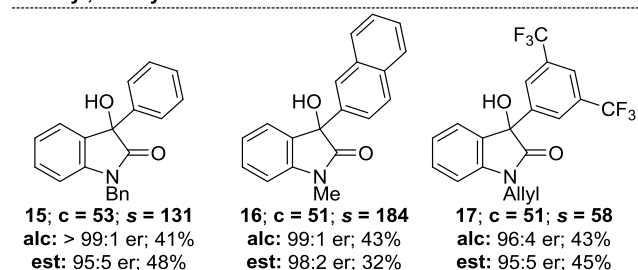
The developed method was next challenged in the KR of 3-aryl-substituted 3-hydroxyoxindole derivatives, in which all three carbinol substituents could act as competitive recognition motifs (two aryl π -systems and a carbonyl) (Table 2). Notably, these derivatives were resolved with excellent selectivity (s up to > 200), indicating exceptional enantiodiscrimination by the isothiourea catalyst. The resolution of oxindole derivatives **15–18** bearing phenyl, naphthyl, an electron-withdrawing 3,5- CF_3 -aryl and an electron-donating anisole at the 3-position gave excellent selectivity ($s = 58\text{--}204$).^[19] The resolution of 4-*N,N*-dimethylaminophenyl-substituted alcohol **19** allowed the isolation of highly enantiomerically-enriched (*R*)-**19** (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 NMe₂ group. Various heteroaromatic substituents were also successfully incorporated including furan, benzoxazole, and Brønsted and Lewis basic pyridine groups (**20–23**, *s* = 15–71). The method was equally applicable for the KR of 3-alkenyl-substituted 3-hydroxyoxindole derivatives **24–26**, in which the catalyst was again capable of differentiating between three potential recognition motifs at the carbinol stereocenter. Excellent selectivity factors were obtained in each case (*s* = 51–79), however incorporation of an alkyne substituent at the tertiary alcohol center (sp² vs sp² vs sp) resulted in very low selectivity (*s* = 2).^[14]

Table 2: Scope: 3-Aryl- and alkenyl-3-hydroxyoxindole derivatives (sp² vs sp² vs sp²).



R¹ = aryl, alkenyl

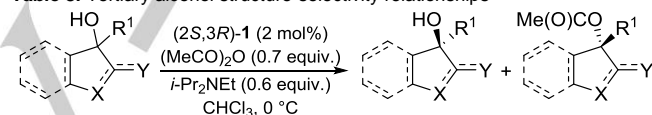


Conversion (**c**) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 2. See SI for reaction concentration and time. [a] 2 mol% (2*S*,3*R*)-1. [b] 10 mol% (2*S*,3*R*)-1. Conversion determined by ¹H NMR spectroscopy. [c] 5 mol% (2*S*,3*R*)-1.

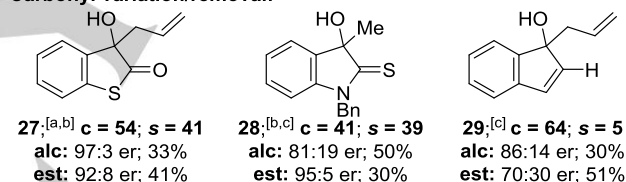
The broad substrate scope of this KR process had demonstrated good selectivities for a range of C(3) substituents, indicating that this substituent was unlikely to act as a dominant recognition motif in this resolution. To provide further insight, the core heterocyclic structure was systematically varied to probe the effect of the carbonyl group and benzannulation (Table 3). Benzothiophenone derivative **27**, in which the lactam nitrogen is replaced with sulfur, and indoline-2-thione derivative **28**, in which

the carbonyl oxygen is replaced with sulfur, were both resolved with excellent selectivity (*s* = 41 and 39 respectively). The effect of removing the carbonyl completely was simulated using indenol derivative **29**. No acylation was observed using isobutyric anhydride, while using acetic anhydride gave a selectivity factor of just 5. This is consistent with the carbonyl moiety playing a significant role in facilitating both reactivity and enantiodiscrimination. α-Hydroxy-γ-lactam **30**, which lacks the benzannulation present in all other substrates, was unreactive using isobutyric anhydride, however, the use of acetic anhydride allowed resolution of **30** with excellent selectivity (*s* = 105), indicating that benzannulation has minimal effect on selectivity.^[20,21] α-Substituted-α-hydroxylactams possess a range of biological activities; however there are few general methods for their enantioselective synthesis.^[22] The KR of this substrate class was therefore further investigated. The KR of γ-lactams **31–33**, bearing electron-donating, electron-withdrawing and heteroatomic substituents at the tertiary alcohol center was achieved with excellent selectivity (*s* = 99–201). The scope was further expanded to include β-lactam and δ-lactam derivatives **34** and **35**. A reaction temperature of 90 °C was required for the acylation of δ-lactam **35**; however even at this temperature an impressive *s* of 25 was obtained.

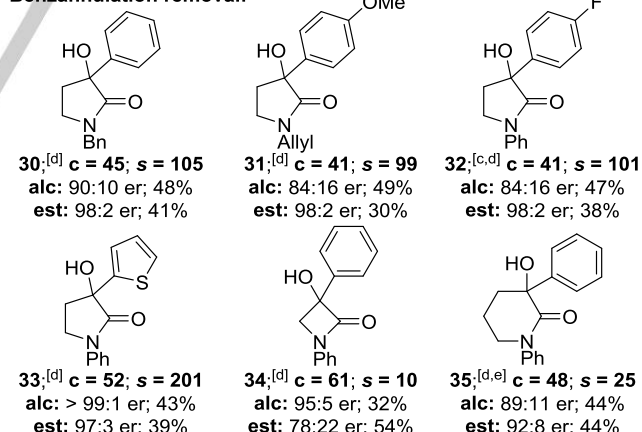
Table 3: Tertiary alcohol structure-selectivity relationships



Carbonyl variation/removal:



Benzannulation removal:



Conversion (**c**) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 2. See SI for reaction concentration and time. [a] 5 mol% (2*S*,3*R*)-1. [a] 1 mol% (2*S*,3*R*)-1. [b] (i-PrCO)₂O. [c] 5 mol% (2*S*,3*R*)-1. [d] PhMe used as solvent. [e] 20 mol% (2*S*,3*R*)-1, 90 °C.

Computational studies on the KR of 3-methyl- and 3-phenyl-3-hydroxyoxindole derivatives **6** and **15** were used to further elucidate the mechanism and origin of enantiodiscrimination in this KR process.^[23] The stereodetermining acylation transition states were calculated following the established Lewis base-promoted acylative pathway described by Zipse and Spivey.^[24] The lowest energy diastereomeric transition state structures (TSs) for the acylation of the (*S*)-enantiomer ((*S*)-TS-II) and (*R*)-enantiomer ((*R*)-TS-II) of each substrate are shown in Figure

2.^[14] Significantly, the conformation of the acylation TSs of the (S)- and (R)-enantiomers are independent of the alcohol substrate, demonstrating a general model can be proposed. The predicted $\Delta\Delta G^\ddagger$ of 2.0 kcal/mol for the KR of **6** is in good agreement with the experimental selectivity factor of 51 ($\Delta\Delta G^\ddagger = 2.1$ kcal/mol). The increased value of $\Delta\Delta G^\ddagger$ calculated for the KR of 3-phenyl-3-hydroxyoxindole **15** (3.5 kcal/mol) is in qualitative agreement with experiment (2.6 kcal/mol), albeit the magnitude of this $\Delta\Delta G^\ddagger$ is slightly overestimated.^[25]

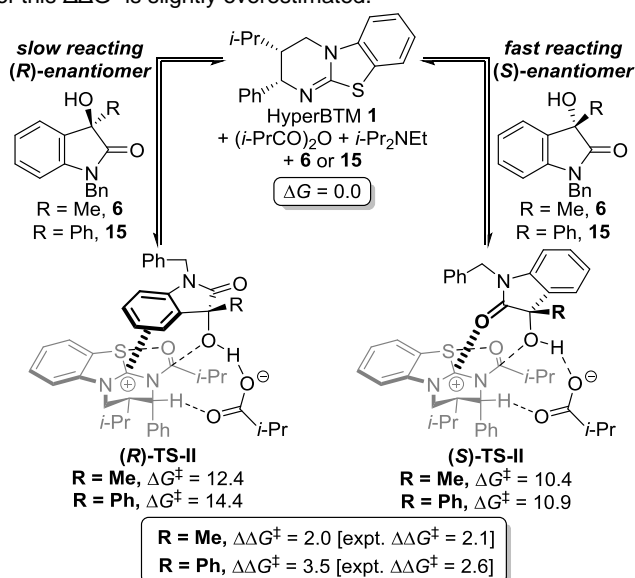


Figure 2. Computed TSs for the acylation of (R)- and (S)-**6** and **15**. Energies given in kcal/mol.

We hypothesize that three critical interactions govern enantiodiscrimination:

i) S \cdots O Interaction: The most stable conformation of acylated HyperBTM exhibits *syn*-coplanarity of the 1,5-O and S atoms. This arrangement is favored by 6.5 kcal/mol over the *anti* conformation (Figure S4).^[14,26] With the acyl group held rigid a single prochiral face is exposed, with the opposite face blocked by the stereodirecting Ph group of the catalyst.

ii) Chelation by isobutyrate: The isobutyrate counterion simultaneously deprotonates the alcohol and engages in a non-classical H-bond to the catalyst ⁺NC-H group.^[24,27]

iii) Isothiouonium interaction: The diastereomeric TSs for the acylation of both enantiomers of the alcohol share the S \cdots O interaction and the two-point isobutyrate binding. NBO analyses show that the isothiouonium carbon bears a partial positive charge (Figure S5).^[14] The high selectivity of this resolution is then a result of effective discrimination between the three carbinol center substituents by their ability to stabilize the partial carbocation character within the heavily preorganized acylated HyperBTM (Figure S8-S10).^[14] In **(S)-TS-II**, the substrate carbonyl is in close proximity to the isothiouonium carbon. NBO analyses show no bonding character between the isothiouonium carbon and the carbonyl oxygen (bond order of 0.01) which, in addition to partial charge calculations, suggests the C=O \cdots isothiouonium interaction is primarily electrostatic in nature.^[14] In contrast, the critical stabilizing interaction in the disfavored **(R)-TS-II** is a $\pi\cdots$ isothiouonium interaction involving the substrate benzenoid. This model is in agreement with the experimental findings (Table 3). Alternative TSs for the acylation of **15** in which the 3-phenyl substituent acts as the recognition motif were significantly higher in energy [(R): $\Delta G^\ddagger = 17.8$

kcal/mol; (S): $\Delta G^\ddagger = 22.8$ kcal/mol] consistent with this group not being instrumental for enantiodiscrimination.^[14]

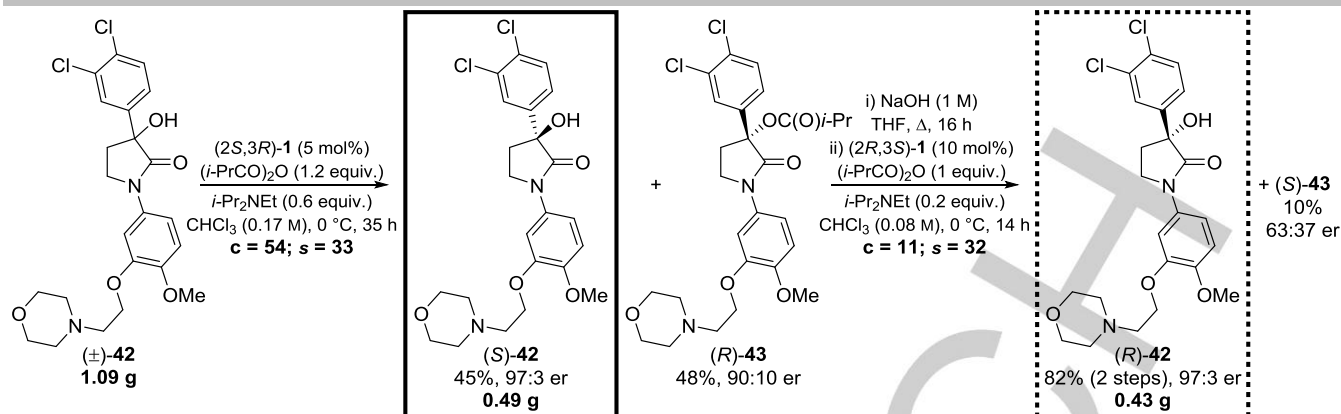
The significance of the C=O \cdots isothiouonium interaction for enantiodiscrimination indicated that modulation of the Lewis basicity of the amide oxygen should affect the relative energies of the diastereomeric acylation TSs. To investigate this hypothesis, a series of 3-phenyl-3-hydroxyoxindole derivatives **36–41** were prepared with electronically-differentiated substituents at the 5-position, where the C=O stretching frequency of each substrate was used as a proxy for the Lewis basicity of the amide oxygen (Table 4).^[28] The KR of this series of substrates followed the expected trend, with the highest selectivity obtained for the resolution of the electron-rich 5-NMe₂-substituted derivative **36** (*s* = 138) and the lowest selectivity for the electron-withdrawn 5-NO₂-substituted derivative **41** (*s* = 11). This trend in selectivity is consistent with the ability of the amide of the fast reacting enantiomer to engage in a TS-stabilizing C=O \cdots isothiouonium interaction.

Table 4: Effect of 5-substituent on C=O stretching frequency and KR selectivity

Substrate	$\nu_{C=O}$ (cm ⁻¹)	c	s	alc	est
36 ; 47 ; 38	1697.4	47	138	92:8 er; 42%	98:2 er; 42%
37 ^[a]	1697.4	45	100	89:11 er; 53%	98:2 er; 43%
38	1699.3	47	87	91:9 er; 49%	97:3 er; 41%
39 ^[b]	1705.1	49	44	93:7 er; 51%	94:6 er; 45%
40 ^[b]	1708.9	49	31	91:9 er; 50%	93:7 er; 40%
41	1716.7	62	11	95:5 er; 37%	78:22 er; 54%

Conversion (c) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 2. See SI for reaction concentration and time. [a] 5 mol% (2S,3R)-**1**. [b] 2 mol% (2S,3R)-**1**.

Finally, the developed method was applied in the enantioselective synthesis of 5-HT_{2C} antagonist **42** (Scheme 3).^[22a] By taking advantage of the non-destructive nature of acylative KR, and the readily availability of both enantiomers of HyperBTM **1**, both enantiomers of the target compound were accessed. Racemic bioactive target (\pm)-**42** was synthesized in five steps from commercially-available reagents in an overall 64% yield.^[14] Gram-scale KR using 5 mol% (2S,3R)-HyperBTM **1** gave (S)-**42** in 45% yield and with excellent enantioenrichment (97:3 er). The recovered (R)-isobutyrate ester (R)-**43** (48% yield, 90:10 er) underwent facile hydrolysis with NaOH, and the enantiopurity of the resulting (R)-alcohol (R)-**42** (90:10 er) was enhanced by performing a second KR. Enantiomeric (2R,3S)-HyperBTM **1** was used to selectively acylate the remaining (S)-enantiomer, requiring only 11% conversion to obtain highly enantiomerically-enriched (R)-**42** (97:3 er). Overall, both (S)- and (R)-**42** were isolated in highly enantioenriched form in a combined 84% yield from (\pm)-**42**, demonstrating the powerful nature of the developed KR methodology.



Scheme 3. Application in the synthesis of both enantiomers of 5-HT_{2C} antagonist **42**. Conversion (c) and er determined by chiral HPLC analysis. s calculated using equations given in ref. 2.

In conclusion, a C=O \cdots isothiuronium interaction has been identified as the key recognition motif that leads to efficient enantiodiscrimination in the KR of a number of heterocyclic tertiary alcohols. By exploiting this interaction, a combination of isothiurea catalyst HyperBTM **1** (generally 1 mol%) and isobutyric anhydride allows the KR of a range of heterocyclic tertiary alcohols with excellent selectivity (38 examples, s up to > 200). Significantly, the substrate scope includes tertiary alcohol substrates which contain up to three recognition motifs at the stereogenic tertiary carbinol center. The interactions identified as a requirement for selectivity in this KR process should be readily applicable to other enantioselective transformations, and work is currently underway to exploit these in alternative catalytic processes.^[29]

Acknowledgements

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Keywords: Kinetic resolution • Lewis bases • Organocatalysis • Tertiary alcohols • Acylation

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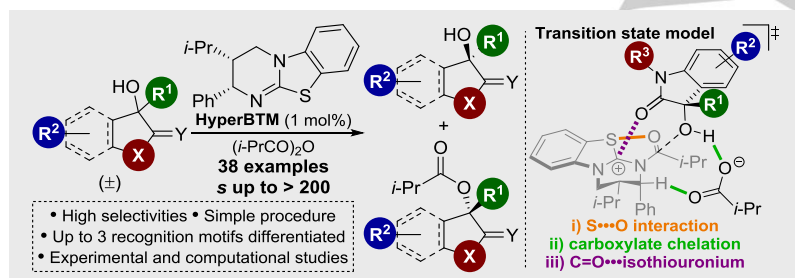
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Experimental and computational studies have identified a C=O...isothiouronium interaction as key to efficient enantiodiscrimination in the kinetic resolution (KR) of tertiary heterocyclic alcohols bearing up to three recognition motifs at the stereogenic tertiary carbinol center. The KR of a range of tertiary heterocyclic alcohols was achieved using low loadings of an isothiouronium catalyst and isobutyric anhydride, with excellent selectivity factors obtained (38 examples, s up to > 200).