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C=O•••Isothiouronium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolution of Tertiary Heterocyclic Alcohols

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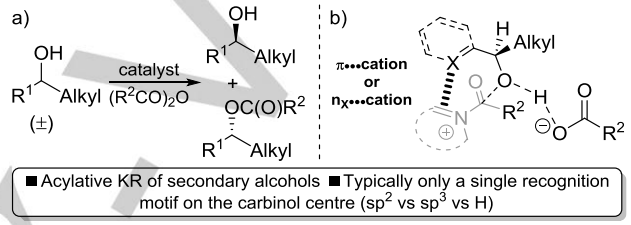
Abstract: A combination of experimental and computational studies have identified a C=O•••isothiouronium interaction as key to efficient enantiodiscrimination in the kinetic resolution of tertiary heterocyclic alcohols bearing up to three potential recognition motifs at the stereogenic tertiary carbinol center. This discrimination was exploited in the isothiourea-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 either isobutyric or acetic anhydride as the acylating agent under mild conditions.

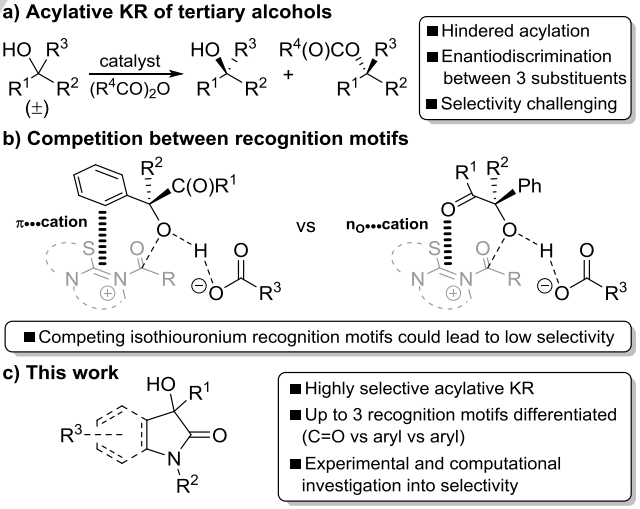
The catalytic kinetic resolution (KR) of racemates offers an effective approach to the separation of enantiomers,[1] with an enormous range of processes and catalysts developed for applications in academia and industry.[2] Among the most popular methods is the acylative KR of alcohols,[3] as this approach 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).[1,3] 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 sp^2-hybridized substituent (e.g. aryl, carbonyl), which acts as a cation recognition motif,[4] and one non-stabilizing sp^3-hybridized alkyl substituent (Scheme 1b).

Lewis basic isothiourea catalysts, first developed for acyl transfer reactions by Birman[5] and Okamoto,[6] have emerged as exceptional catalysts for the acylative KR of secondary alcohols[7] and KR or desymmetrization of diols,[8] amongst other applications.[9] 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 isothiouronium intermediate. Established recognition motifs in isothiourea-catalyzed KR include aryl,[5,7a-c,h,i] heteroaryl,[7e] alkenyl,[7a,h] alkynyl,[7a,h] C=O,[7d,f] and P=O[7g] 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.[10] 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 (*s* < 2).[7c]



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

In this context, this work investigates such cases through the isothiourea-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).



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 KRs of tertiary alcohols have been reported to date, using either a bespoke pentapeptide catalyst or

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through oxidative NHC catalysis.[11] 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,[12] 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).[13,14] The use of less sterically-hindered anhydrides provided lower *s* values, whilst alternative isothiourea catalysts, tetramisole **4** and benzotetramisole **5**, were ineffective in terms of both conversion and selectivity (*s* < 2).[13] Industrially-preferable solvents [EtOAc, *i*-PrOAc, $(MeO)_2CO$, PhMe] also provided synthetically-useful levels of selectivity (*s* = 34–41),[13,15] 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).[1c,13,16,17]

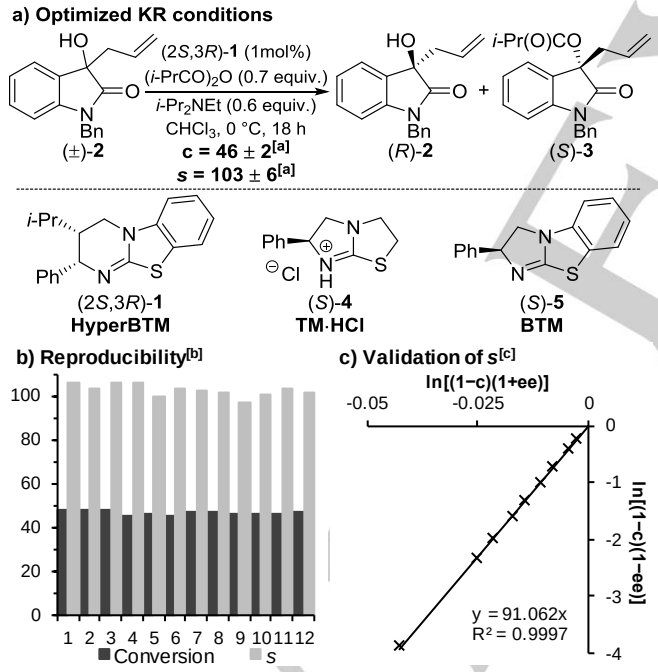
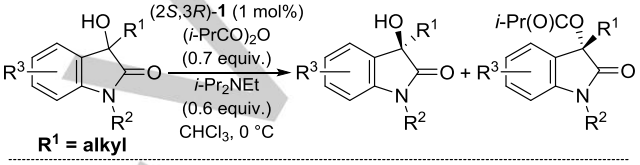
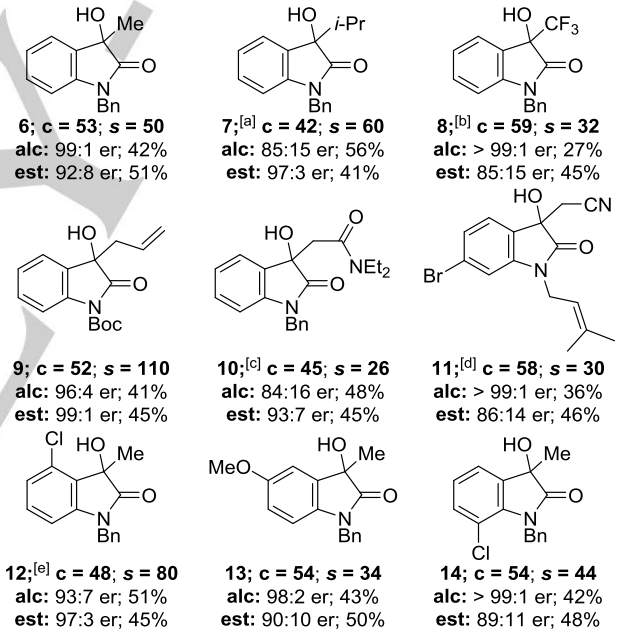


Figure 1. KR of 3-hydroxyoxindole (±)-**2**. Conversion (**c**) determined by chiral HPLC analysis. *s* calculated using equations given in ref. 1a. [a] Mean of 12 repeat reactions (see part b); errors given as 2 standard deviations of mean. [b] 12 repeat KRs of (±)-**2** at 0 °C. [c] Linear regression analysis of the KR of (±)-**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* = 32–110), 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*-Pr_2NEt 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).[13] 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: 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. 1a, and rounded as detailed in ref. 17. See SI for reaction concentration and time. [a] 2 mol% (2*S*,3*R*)-**1**. [b] −40 °C. [c] 5 mol% (2*S*,3*R*)-**1**. [d] 0.6 equiv. (*i*-$PrCO)_2O$, 0.5 equiv. *i*-$PrCO_2H$, no *i*-Pr_2NEt used. [e] 10 mol% (2*S*,3*R*)-**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, 2-naphthyl and aryl groups bearing both electron-withdrawing and -donating at the 3-position gave excellent selectivity (*s* = 60–200).[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

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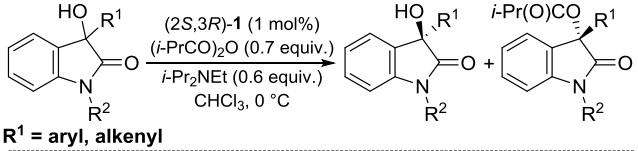
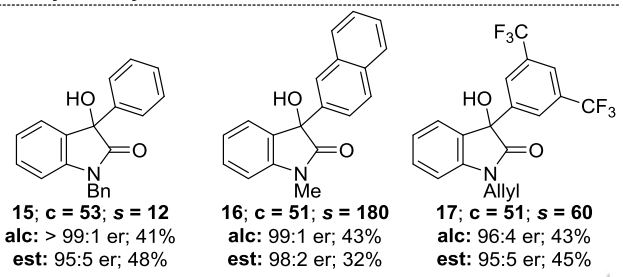
racemate (52:48 er). This phenomenon is attributed to racemization of the ester by reversible ionization promoted by the presence of the electron-donating NMe_2 group. Various heteroaromatic substituents were successfully incorporated including furyl, benzoxazolyl and Brønsted and Lewis basic 2- and 3-pyridyl groups (**20**–**23**, *s* = 15–70). The method was equally applicable for the KR of 3-alkenyl-substituted 3-hydroxyoxidinole derivatives **24**–**26**, in which the catalyst was again capable of differentiating between three potential recognition motifs at the carbinol stereocenter. Excellent *s* values were obtained in each case (*s* = 50–80), however incorporation of an alkyne substituent at the tertiary alcohol center (sp^2 vs sp^2 vs sp) resulted in very low selectivity (*s* = 2).[13]

Table 2: 3-Aryl- and alkenyl-3-hydroxyoxindole derivatives (sp^2 vs sp^2 vs sp^2)



R^1 = aryl, alkenyl



15; **c = 53**; ***s* = 12**
alc: > 99:1 er; 41%
est: 95:5 er; 48%

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

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

18;[a] **c = 49**; ***s* = 20**
alc: 97:3 er; 50%
est: 98:2 er; 48%

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

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

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

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

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

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

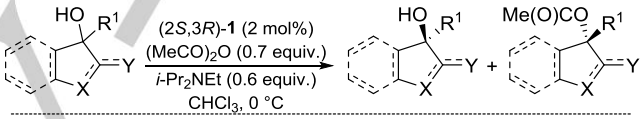
25; **c = 40**; ***s* = 80**
alc: 83:17 er; 60%
est: 98:2 er; 33%

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

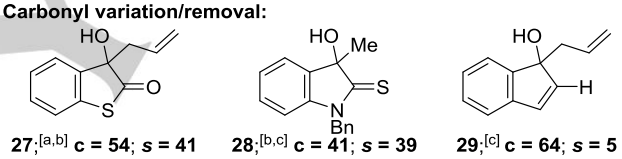
Conversion (**c**) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 1a, and rounded as detailed in ref. 17. See SI for reaction concentration and time. [a] 2 mol% (2*S*,3*R*)-**1**. [b] 10 mol% (2*S*,3*R*)-**1**. Conversion determined by ^{1}H NMR spectroscopy. [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* = 110), 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* = 60–200). 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* value of 25 was obtained.

Table 3: Tertiary alcohol structure-selectivity relationships



Carbonyl variation/removal:

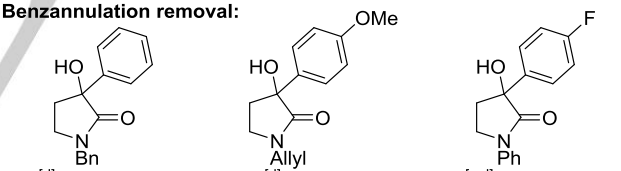


27;[a,b] **c = 54**; ***s* = 41**
alc: 97:3 er; 33%
est: 92:8 er; 41%

28;[b,c] **c = 41**; ***s* = 39**
alc: 81:19 er; 50%
est: 95:5 er; 30%

29;[c] **c = 64**; ***s* = 5**
alc: 86:14 er; 30%
est: 70:30 er; 51%

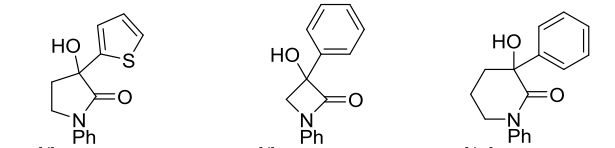
Benzannulation removal:



30;[d] **c = 45**; ***s* = 110**
alc: 90:10 er; 48%
est: 98:2 er; 41%

31;[d] **c = 38**; ***s* = 60**
alc: 79:21 er; 59%
est: 97:3 er; 32%

32;[c,d] **c = 49**; ***s* = 100**
alc: 95:5 er; 43%
est: 97:3 er; 41%



33;[d] **c = 52**; ***s* = 20**
alc: > 99:1 er; 43%
est: 97:3 er; 39%

34;[d] **c = 61**; ***s* = 10**
alc: 95:5 er; 32%
est: 78:22 er; 54%

35;[d,e] **c = 48**; ***s* = 25**
alc: 89:11 er; 44%
est: 92:8 er; 44%

Conversion (**c**) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 1a, and rounded as detailed in ref. 17. See SI for reaction concentration and time. [a] 1 mol% (2*S*,3*R*)-**1**. [b] (*i*-PrCO)$_2$O. [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

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2.[13] Significantly, the conformation of the acylation TSs of the (*S*)- and (*R*)-enantiomers are independent of the alcohol substrate, allowing a general model to 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 *s* value of 50 ($\Delta\Delta G^{\ddagger}$ = 2.1 kcal/mol). The increased value of $\Delta\Delta G^{\ddagger}$ calculated for the KR of **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 overestimated.[25]

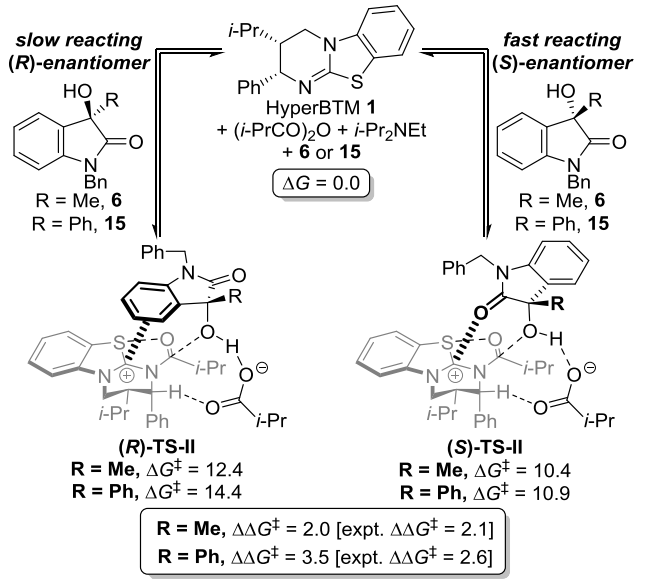


Figure 2. Computed TSs for the acylation of (*R*)- and (*S*)-**6** and **15**. Energies given in kcal/mol.

We hypothesize that three critical interactions govern enantiodiscrimination:

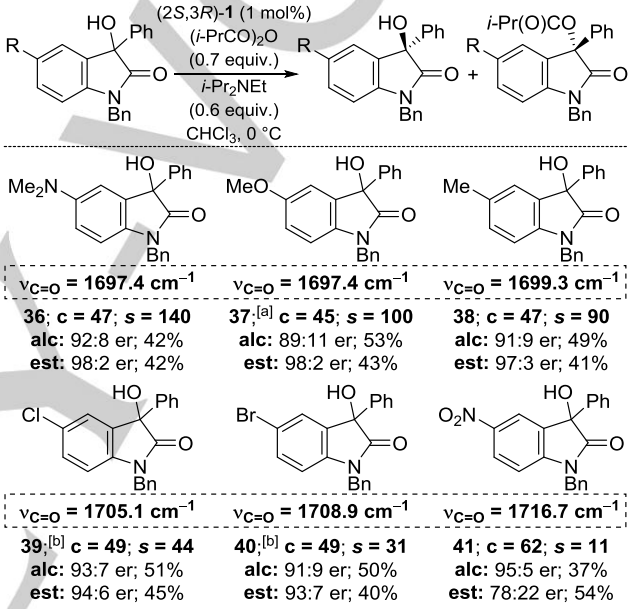
i) S•••O Interaction: The most stable conformation of acylated HyperBTM exhibits *syn*-coplanarity of the 1,5-O and S atoms. This arrangement is favored by 6.5 kcal/mol over the *anti* conformation (Figure S4).[13,26] With the acyl group held rigid a single prochiral face is exposed, with the opposite 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) Isothiouronium interaction: The diastereomeric TSs for the acylation of both enantiomers of the alcohol share the S•••O interaction and the two-point isobutyrate binding. NBO analyses show that the isothiouronium carbon bears a partial positive charge (Figure S5).[13] 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).[13] In **(*S*)-TS-II**, the substrate carbonyl is in close proximity to the isothiouronium carbon. NBO analyses show no bonding character between the isothiouronium carbon and the carbonyl oxygen (bond order of 0.01) which, in addition to partial charge calculations, suggests the C=O•••isothiouronium interaction is primarily electrostatic in nature.[14] In contrast, the critical stabilizing interaction in the disfavored **(*R*)-TS-II** is a π•••isothiouronium 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.[13]

The significance of the C=O•••isothiouronium 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, with the C=O stretching frequency of each substrate used as a proxy for the Lewis basicity of the amide oxygen (Table 4).[28] The KR of this series followed the expected trend, with the highest selectivity obtained for the resolution of the 5-NMe_2-substituted derivative **36** (*s* = 140) and the lowest selectivity obtained for the 5-NO_2-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•••isothiouronium interaction.

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



Conversion (**c**) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 1a, and rounded as detailed in ref. 17. See SI for reaction concentration and time. [a] 5 mol% (2*S*,3*R*)-**1**. [b] 2 mol% (2*S*,3*R*)-**1**.

Finally, the developed method was applied in the enantioselective synthesis of 5-HT2C 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 (±)-**42** was synthesized in five steps from commercially-available reagents in an overall 64% yield.[13] Gram-scale KR using 5 mol% (2*S*,3*R*)-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 (2*R*,3*S*)-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 (±)-**42**, demonstrating the powerful nature of the developed KR methodology.

In conclusion, a C=O•••isothiouronium 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

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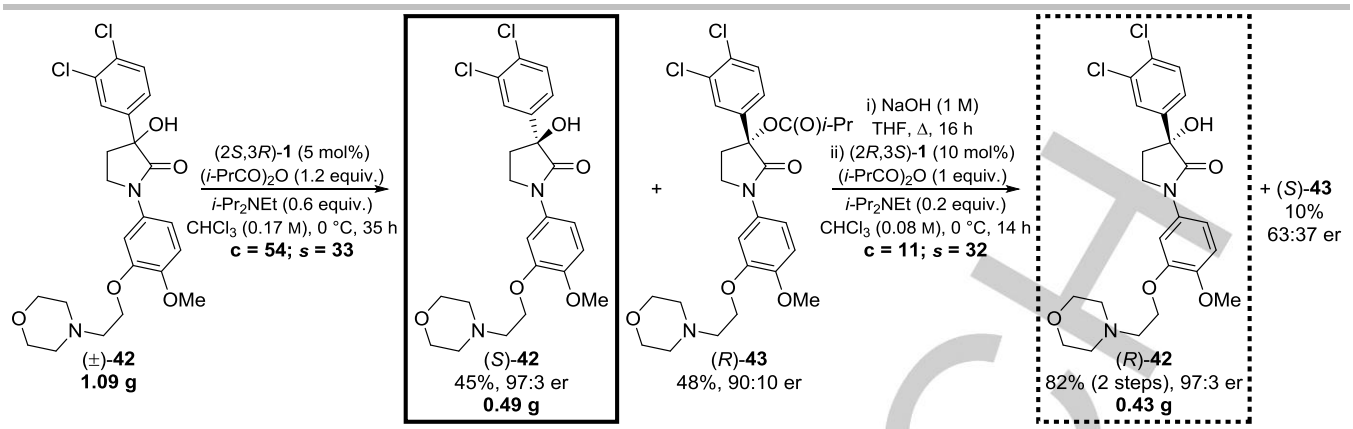

Scheme 3. Application in the synthesis of both enantiomers of 5-HT2C antagonist **42.** Conversion (**c**) and er determined by chiral HPLC analysis. *s* calculated using equations given in ref. 1a.

isothiourea catalyst HyperBTM **1** (generally 1 mol%) and either isobutyric or acetic 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]

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

[1] a) H. B. Kagan, J. C. Fiaud, in *Topics in Stereochemistry*, *Vol. 18* (Eds.: E. L. Eliel, S. H. Wilen), John Wiley & Sons, **1988**, pp. 249–330; b) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5; c) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974; *Angew. Chem.* **2005**, *117*, 4040.

[2] a) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337; b) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451.

[3] a) C. E. Müller, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 6012; *Angew. Chem.* **2011**, *123*, 6136; b) J. I. Murray, Z. Heckenast, A. C. Spivey, in *Lewis Base Catalysis in Organic Synthesis*, *Vol. 2*, (Eds.: E. Vedejs, S. E. Denmark), Wiley-VCH, Weinheim, **2016**, pp. 459–526.

[4] For a review on cation-π interactions in organocatalysis see: S. Yamada, J. S. Fossey, *Org. Biomol. Chem.* **2011**, *9*, 7275.

[5] V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351.

[6] M. Kobayashi, S. Okamoto, *Tetrahedron Lett.* **2006**, *47*, 4347.

[7] a) X. Li, H. Jiang, E. W. Uffman, L. Guo, Y. Zhang, X. Yang, V. B. Birman, *J. Org. Chem.* **2012**, *77*, 1722; b) Q. Hu, H. Zhou, X. Geng, P. Chen, *Tetrahedron* **2009**, *65*, 2232; c) P. Chen, Y. Zhang, H. Zhou, Q. Xu, *Acta Chim. Sinica* **2010**, *68*, 1431; d) I. Shiina, K. Nakata, K. Ono, M. Sugimoto, A. Sekiguchi, *Chem. Eur. J.* **2010**, *16*, 167; e) I. Shiina, K. Ono, K. Nakata, *Chem. Lett.* **2011**, *40*, 147; f) K. Nakata, K. Gotoh, K. Ono, K. Futami, I. Shiina, *Org. Lett.* **2013**, *15*, 1170; g) I. Shiina, K. Ono, T. Nakahara, *Chem. Commun.* **2013**, *49*, 10700; h) D. Belmessieri, C. Joannesse, P. A. Woods, C. MacGregor, C. Jones, C. D. Campbell, C. P. Johnson, N. Duguet, C. Concellón, R. A. Bragg, A. D. Smith, *Org. Biomol. Chem.* **2011**, *9*, 559; i) S. F. Musolino, O. S. Ojo, N. J. Westwood, J. E. Taylor, A. D. Smith, *Chem. Eur. J.* **2016**, *22*, 18916.

[8] a) V. B. Birman, H. Jiang, X. Li, *Org. Lett.* **2007**, *9*, 3237; b) J. Merad, P. Borkar, T. B. Yenda, C. Roux, J.-M. Pons, J.-L. Parrain, O. Chuzel, C. Bressy, *Org. Lett.* **2015**, *17*, 2118; c) J. Merad, P. Borkar, F. Caijo, J.-M. Pons, J.-L. Parrain, O. Chuzel, C. Bressy, *Angew. Chem. Int. Ed.* **2017**, *56*, 16052; *Angew. Chem.* **2017**, *129*, 16268.

[9] J. Merad, J.-M. Pons, O. Chuzel, C. Bressy, *Eur. J. Org. Chem.* **2016**, *2016*, 5589.

[10] For the KR of aryl-alkenyl substituted secondary alcohols, see ref. 7i.

[11] a) E. R. Jarvo, C. A. Evans, G. T. Copeland, S. J. Miller, *J. Org. Chem.* **2001**, *66*, 5522; b) M. C. Angione, S. J. Miller, *Tetrahedron* **2006**, *62*, 5254; c) S. Lu, S. B. Poh, W.-Y. Siau, Y. Zhao, *Angew. Chem. Int. Ed.* **2013**, *52*, 1731; *Angew. Chem.* **2013**, *125*, 1775.

[12] For a review on the bioactivity of 3-substituted-3-hydroxyoxindole derivatives see: S. Peddidhotla, *Curr. Bioact. Compd.* **2009**, *5*, 20.

[13] See Supporting Information for details.

[14] The absolute configuration of recovered **2** was assigned as (*R*) by comparison of its specific rotation with the literature, see SI.

[15] R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854.

[16] D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 545.

[17] The analytical error associated with s has been estimated for each KR and is detailed in full in the SI. Based on these estimations of error the following rules have been applied: i) for $s < 50$, *s* is given to the closest integer; ii) for $s = > 50$, *s* is given to the closest 10.

[18] a) A. Singh, G. P. Roth, *Org. Lett.* **2011**, *13*, 2118; b) A. Singh, G. P. Roth, *Tetrahedron Lett.* **2012**, *53*, 4889.

[19] The absolute configuration of recovered **15** was assigned as (*R*) by X-ray crystallographic analysis (CCDC 1570446).

[20] Under analogous conditions [$(MeCO)_2O$, $CHCl_3$, 0 °C], α-hydroxy-γ-lactam **30** and benzannulated analogue **15** were resolved with comparable selectivity and with the same sense of enantiodiscrimination, see SI.

[21] The absolute configuration of recovered **30** was assigned as (*S*) by X-ray crystallographic analysis (CCDC 1570447).

[22] a) F. Damiani, D. Hamprecht, A. A. Jaxa-Chamiec, F. Micheli, A. Pasquarello, G. Tedesco (Glaxo Group Ltd.), WO 03/089409 A1, **2003**; b) K.-K. Ho, W. Quan, J. Zhou (Eli Lilly and Company), WO 2017/005069 A1, **2017**; c) N. Ishida, D. Nečas, Y. Masuda, M. Murakami, *Angew. Chem. Int. Ed.* **2015**, *54*, 7418; *Angew. Chem.* **2015**, *127*, 7526; d) W. J. Brouillette, G. L. Grunewald, *J. Med. Chem.* **1984**, *27*, 202.

10.1002/anie.201712456

[23] Geometries and energies were computed at the M06-2X/6-311++G(2df,p)/PCM($CHCl_3$)//M06-2X/6-31G(d)/PCM($CHCl_3$) level of theory, see: a) M. J. Frisch, et al. Gaussian 09 (Gaussian, Inc. Wallingford, Connecticut, **1973**); b) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215; c) W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257; d) P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta.* **1973**, *28*, 213; e) S. Miertuš, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117.

[24] E. Larionov, M. Mahesh, A. C. Spivey, Y. Wei, H. Zipse, *J. Am. Chem. Soc.* **2012**, *134*, 9390.

[25] Overestimation of calculated $\Delta\Delta G^{\ddagger}$ in KR processes has been previously reported, see ref. 7e, 24, 27a, b and: X. Li, P. Liu, K. N. Houk, V. L. Birman, *J. Am. Chem. Soc.* **2008**, *130*, 13836.

[26] a) B. R. Beno, K.-S. Yeung, M. D. Bartberger, L. D. Pennington, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 4383; b) V. B. Birman, X. Li, Z. Han, *Org. Lett.* **2007**, *9*, 37; c) M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2014**, *136*, 4492; d) T. H. West, D. M. Walden, J. E. Taylor, A. C. Brueckner, R. C. Johnson, P. H.-Y. Cheong, G. C. Lloyd-Jones, A. D. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 4366; e) E. R. T. Robinson, D. M. Walden, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong, A. D. Smith, *Chem. Sci.* **2016**, *7*, 6919; f) D. J. Pascoe, K. B. Ling, S. L. Cockroft, *J. Am. Chem. Soc.* **2017**, *139*, 15160.

[27] a) P. Liu, X. Yang, V. B. Birman, K. N. Houk, *Org. Lett.* **2012**, *14*, 3288; b) X. Yang, P. Liu, K. N. Houk, V. B. Birman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9638; *Angew. Chem.* **2012**, *124*, 9776; c) R. C. Johnston, P. H.-Y. Cheong, *Org. Biomol. Chem.* **2013**, *11*, 5057; d) C. E. Cannizzaro, K. N. Houk, *J. Am. Chem. Soc.* **2002**, *124*, 7163; e) V. Lutz, J. Glatthaar, C. Würtele, M. Serafin, H. Hausmann, P. R. Schreiner, *Chem. Eur. J.* **2009**, *15*, 8548; f) S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem. Eur. J.* **2005**, *11*, 4751.

[28] J. P. Idoux, R. Zarrillo, *J. Org. Chem.* **1975**, *40*, 1519.

[29] The research data underpinning this publication can be found at DOI: http://dx.doi.org/10.17630/e8b7bd1c-15d2-4ea3-9f34-02d87ad0435c

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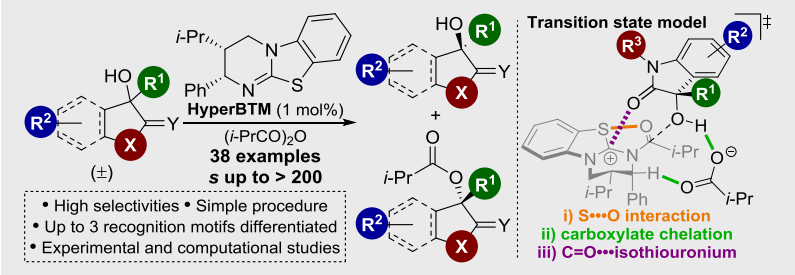

Experimental and computational studies have identified a C=O•••isothiouronium interaction as key to efficient enantiodiscrimination in the kinetic resolution (KR) of tertiary heterocyclic alcohols bearing up to three potential recognition motifs at the stereogenic tertiary carbinol center. The KR of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

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C=O•••Isothiouronium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolution of Tertiary Heterocyclic Alcohols