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Title: C=O***Isothiouonium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolution of Tertiary Heterocyclic Alcohols

Authors: Mark Greenhalgh; Samuel Smith; Daniel Walden; James Taylor; Zamira Brice; Emily Robinson; Charlene Fallon; David Cordes; Alexandra Slawin; Hannah Camille Richardson; Markas Grove; Paul Cheong; Andrew David Smith

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


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 potential recognition motifs at the stereogenic tertiary carbinal 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 isotopic 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 enantioselectively-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).[4,5] 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,[4] and one non-stabilizing sp²-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 carbinol, allowing one enantiomer to react preferentially with a chiral acyl isothiouuronium intermediate. Established recognition motifs in isothiourea-catalyzed KR include aryl,[5,7a-c,h,i] heteroaryl,[7j] alkynyl,[7a,n] C=O,[7a,m] and P=O[7b] substituents. Consequently, high selectivity is only commonly observed for stereogenic carbinals 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 (ar-system and carbonyl), is ineffective (s < 2).[10]


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 carbinal 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 carbinal 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.
through oxidative NHC catalysis. In both cases high catalyst loadings (10 mol%) are required. Herein, the isothiourea-catalyzed acylative KR of tertiary 3-hydroxyxindole and 3-hydroxyoxindole-2-one derivatives, which either two or three of the carbinal 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-hydroxyxindole 2, which bears two potential recognition motifs at the tertiary carbinal 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 isobutyril anhydride in CHCl₃ at 0 °C (Figure 1a). The use of less sterically hindered anhydrides provided lower s values, whilst alternative isothiourea catalysts, tetramisole and benzotetramisole 5, were ineffective in terms of both conversion and selectivity (s < 2). Industrially-preferable solvents [EtOAc, i-ProAc, (MeO)₂CO, PhMe] also provided synthetically-useful levels of selectivity (s = 34–41) albeit lower than those obtained in CHCl₃. 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).

### a) Optimized KR conditions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conversion</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-2</td>
<td>46 ± 2%</td>
<td>92.8% er, 51%</td>
</tr>
<tr>
<td>(R)-2</td>
<td>46 ± 2%</td>
<td>92.8% er, 51%</td>
</tr>
</tbody>
</table>

### b) Reproducibility

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conversion</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-2</td>
<td>46 ± 2%</td>
<td>92.8% er, 51%</td>
</tr>
<tr>
<td>(R)-2</td>
<td>46 ± 2%</td>
<td>92.8% er, 51%</td>
</tr>
</tbody>
</table>

### c) Validation of s

\[ \ln[(1-c)(1+ee)] = 91.062x - 0.09997 \]

The developed method was next challenged in the KR of 3-aryl-substituted 3-hydroxyxindole derivatives, in which all three carbinal 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 bearing phenyl, 2-naphthyl and aryl groups bearing both electron-withdrawing and -donating at the 3-position gave excellent selectivity (s = 60–200). The resolution of 4-N,N-dimethylaminophenyl-substituted alcohol allowed the isolation of highly enantiomerically-enriched (R)-19 (97.3% er) at 49% conversion; however the isobutyric ester was obtained as a potential product.
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COMMUNICATION

The broad substrate scope of the KR process had demonstrated good selectivities for a range of (S) substrates, indicating that this reaction is unlikely to act as a dominant recognition motif in this resolution. To provide further insight into the core of the Viola’s mechanism, a selection of (S)-enantiomers of each substrate were calculated following the computational studies on the KR of (S)-enantiomer (Table 3). The lowest energy diastereomeric transition state structures were calculated using the established enantiodifferentiation in hydroxyoxindole derivatives, and the predicted selectivity was calculated using the equations given in ref. 13, and rounded as detailed in ref. 17. See SI for details.

The conversion determined by chiral HPLC analysis of isobutyric anhydride in benzoxazolone derivatives (Table 3) was calculated using the equations given in ref. 1a, and rounded as detailed in ref. 11. See SI for details.

The effect of the carbonyl group and benzannulation (Table 2) was calculated using the equations given in ref. 1a, and rounded as detailed in ref. 17. See SI for details.

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The effect of the carbonyl group and benzannulation (Table 2) was calculated using the equations given in ref. 1a, and rounded as detailed in ref. 17. See SI for details.
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).[23] The KR of this series followed the expected trend, with the highest selectivity obtained for the resolution of the 5-NMe2-substituted derivative 36 (s = 140) and the lowest selectivity obtained for the 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•••isothiouronium interaction.

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>C=O Stretching Frequency (cm⁻¹)</th>
<th>Selectivity (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>1697.4 cm⁻¹</td>
<td>114</td>
</tr>
<tr>
<td>37</td>
<td>1697.4 cm⁻¹</td>
<td>90</td>
</tr>
<tr>
<td>38</td>
<td>1699.3 cm⁻¹</td>
<td>78</td>
</tr>
<tr>
<td>39</td>
<td>1705.1 cm⁻¹</td>
<td>93</td>
</tr>
<tr>
<td>40</td>
<td>1708.9 cm⁻¹</td>
<td>96</td>
</tr>
<tr>
<td>41</td>
<td>1716.7 cm⁻¹</td>
<td>86</td>
</tr>
</tbody>
</table>

Conversion (c) and er determined by chiral HPLC analysis. Values calculated using equations given in ref. 1a, and rounded as detailed in ref. 17. 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-H2C2 antagonist 42 (Scheme 3).[23] 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% (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 enantipurity 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 enantioenriched (S)-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
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, up to >200). Significantly, the substrate scope includes tertiary alcohol substrates which contain up to three recognition motifs at the stereogenic tertiary carbonyl 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.[20]

Acknowledgements

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

[10] For the KR of aryli-alkenyl substituted secondary alcohols, see ref. 7l.
[14] The absolute configuration of recovered 2 was assigned as (R) by comparison of its specific rotation with the literature, see SI.
[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.
[19] The absolute configuration of recovered 15 was assigned as (R) by X-ray crystallographic analysis (CCDC 1570446).
[20] Under analogous conditions [[MeCO]O]2CHCl2, 0 °C], α-hydroxy-γ-lactam 30 and benzannulated analogue 15 were resolved with comparable selectivity and with the same sense of enantiomeric discrimination, see SI.
[21] The absolute configuration of recovered 30 was assigned as (S) by X-ray crystallographic analysis (CCDC 1570447).

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.


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.


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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