

Organocatalysis

Isothiourea-Catalyzed Acylative Kinetic Resolution of Tertiary α -Hydroxy EstersShen Qu⁺, Samuel M. Smith⁺, Víctor Laina-Martín, Rifahath M. Neyyappadath, Mark D. Greenhalgh, and Andrew D. Smith*

Abstract: A highly enantioselective isothiourea-catalyzed acylative kinetic resolution (KR) of acyclic tertiary alcohols has been developed. Selectivity factors of up to 200 were achieved for the KR of tertiary alcohols bearing an adjacent ester substituent, with both reaction conversion and enantioselectivity found to be sensitive to the steric and electronic environment at the stereogenic tertiary carbinol centre. For more sterically congested alcohols, the use of a recently-developed isoselenourea catalyst was optimal, with equivalent enantioselectivity but higher conversion achieved in comparison to the isothiourea HyperBTM. Diastereomeric acylation transition state models are proposed to rationalize the origins of enantiodiscrimination in this process. This KR procedure was also translated to a continuous-flow process using a polymer-supported variant of the catalyst.

Introduction

Tertiary alcohols and their derivatives are present within many natural products and bioactive molecules, however, their synthesis in enantiopure form remains a significant challenge.^[1] Towards this goal, the most commonly investigated method is the enantioselective addition of carbon-centred nucleophiles to ketones.^[1a–c] Challenging facial differentiation and the potential for unwanted side reactions currently impacts the scope and effectiveness of these methods. The catalytic kinetic resolution (KR)^[2,3] of tertiary alcohols therefore represents a potentially attractive option. KR is equally applicable to racemic and scalemic substrates, thus allowing KR to be used as either alternative or complementary processes. In contrast to the catalytic KR of secondary alcohols,^[4] there are currently very few efficient methods for the KR of tertiary alcohols. The challenges associated with the KR of tertiary alcohols are two-fold:

1) tertiary alcohols are sterically hindered, thus reducing their nucleophilicity; and 2) the catalyst is required to differentiate between three non-hydrogen substituents at the stereogenic carbinol centre.

To date, only nine methods have been reported for the non-enzymatic catalytic KR of tertiary alcohols in which an enantioenriched chiral product is obtained (Figure 1).^[5,6] Chiral phosphoric acid catalysis has been exploited by the List^[5a,b] and Yang^[5c,d] groups in intra- and intermolecular approaches for the KR of tertiary alcohols, amino alcohols, and diols; whilst the KR of tertiary propargylic alcohols has been reported by the Oestreich^[5e] and Ma^[5f] using Cu and co-operative Pd/phosphoric acid catalysis, respectively. The acylative KR of alcohols is a particularly attractive option as simple separation of products, coupled with facile ester hydrolysis, provides straightforward access to both enantiomers of the alcohol. The Lewis base catalyzed acylative KR of heterocyclic tertiary alcohols has been achieved by Zhao and co-workers^[5g] and our group^[5h] using oxidative NHC catalysis^[7] and isothiourea catalysis, respectively. To date, the only example of the catalytic acylative KR of acyclic alcohols was reported by Miller and co-workers using a pentapeptide catalyst.^[5i,j] Relatively high catalyst loading (10 mol %) and

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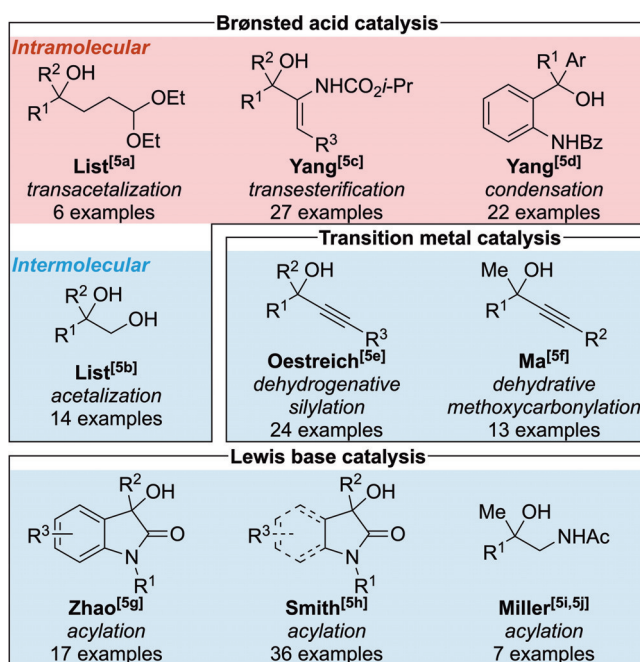


Figure 1. Approaches reported for the catalytic KR of tertiary alcohols.

excess anhydride (50 equiv) was required for the KR of seven amino alcohol substrates, thus demonstrating the remaining challenge associated with the acylative KR of this important class of tertiary alcohol.

Lewis basic isothiourea catalysts^[8] have been applied for the acylative KR of a wide range of alcohols, including primary alcohols,^[9] secondary alcohols,^[10] and diols.^[11] We recently reported an isothiourea-catalyzed KR of tertiary heterocyclic alcohols,^[5b] in which coordinated experimental and computational studies were used to identify the origins of enantiodiscrimination (Figure 2a). Interrogation of the acylation transition state structure for the fast-reacting enantiomer of the alcohol revealed three key interactions: 1) an O...S interaction,^[12] which holds the acyl group of the acylated catalyst *syn*-coplanar to the isothiuronium core; 2) chelation of the carboxylate counterion through non-classical C-H...O hydrogen bonding,^[13] and 3) a C=O...isothiuronium interaction, which is primarily electrostatic in nature. The transition state structure for the slow-reacting enantiomer lacked the C=O...isothiuronium interaction, and therefore it was hypothesized this interaction was critical for effective enantiodiscrimination.

In contrast to our previous work on the KR of heterocyclic alcohols,^[5b] the additional conformational flexibility of acyclic substrates (Figure 2b) presents additional challenges to overcome: 1) increased steric hindrance at the carbinol centre attenuating the rate of acylation; and 2) the potential for the other carbinol substituents to act as competitive recognition motifs, thus resulting in reduced enantiodiscrimination. We report herein the development of the acylative KR of acyclic tertiary alcohols using isothiourea catalysis. Key to this transformation is the incorporation of a suitable carbonyl donor adjacent to the tertiary stereogenic carbinol centre to act as a recognition motif for the acylated catalyst.

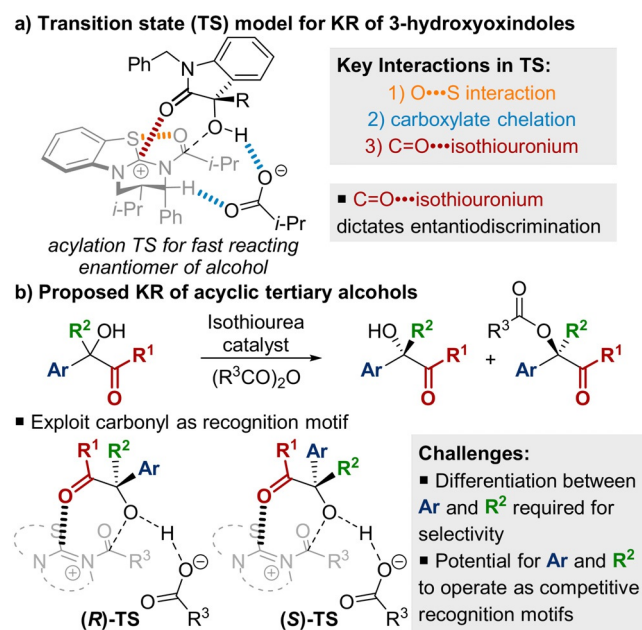


Figure 2. Proposed transition-state models.

Results and Discussion

Initial studies probed the feasibility of the acylative KR of acyclic α -hydroxy carbonyl derivatives, using the isothiourea HyperBTM (**1**) as catalyst (Table 1). The attempted KR of tertiary amide **2** led to no conversion (entry 1), however the use of different secondary amide derivatives provided some promise.^[14] Following optimization the KR of secondary amide **3** was achieved with good conversion but moderate selectivity ($s=7$),^[15] which could not be improved upon further (entry 2). Next, the KR of α -hydroxy ketones and esters was investigated (entries 3 and 4). Whilst low selectivity was obtained for both substrates ($s=3$), the KR of α -hydroxy ester **5** was achieved using lower catalyst loading and with fewer equivalents of anhydride, thus indicating greater potential for further optimization through variation of solvent, temperature, base, and anhydride (see the Supporting Information for full details). Improved selectivity was obtained when the reaction was conducted in Et₂O ($s=15$, entry 5), with additional optimization to $s=60$ achieved by using isobutyric anhydride as the acylating agent (entry 6). Finally, in the absence of an auxiliary base (NEt₃), good conversion and excellent selectivity was maintained (entry 7). Under these optimized conditions, variation of the ester group was investigated, with the highest selectivity obtained using benzyl ester **8** ($c=50\%$, $s=130$, entry 10).^[16] The scalability of the method was demonstrated, with comparable conversion and selectivity obtained when conducting the KR on a gram scale ($c=50\%$, $s=120$, entry 11).

We recently reported the isoselenourea HyperSe (**9**) as a highly efficient catalyst for a range of processes, including the KR of heterocyclic tertiary alcohols at catalyst loadings as low as 500 ppm.^[17] Applying this catalyst to the current KR

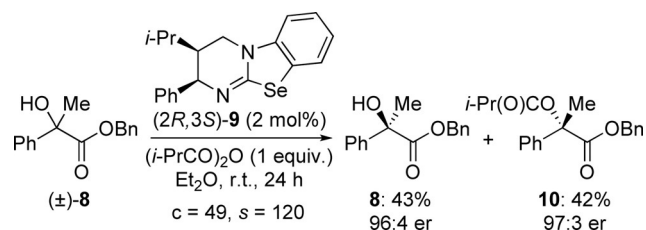
Table 1: Carbonyl group screening.

| Entry | R ¹ | R ² (x) | Base (equiv) | Solvent | c | s |
|--------------------|-------------------------------|---------------------------|----------------------|---------------------------------|----|-----|
| 1 ^[a,b] | NMe ₂ (2) | Me (5) | TMP (10) | CHCl ₃ | 0 | – |
| 2 ^[a] | NHPh (3) | <i>i</i> -Pr (5) | TMP (2) | CH ₂ Cl ₂ | 59 | 7 |
| 3 ^[a,c] | Ph (4) | Me (3) | NEt ₃ (5) | CH ₂ Cl ₂ | 36 | 3 |
| 4 | OMe (5) | Me (1) | NEt ₃ (1) | CH ₂ Cl ₂ | 44 | 3 |
| 5 | OMe (5) | Me (1) | NEt ₃ (1) | Et ₂ O | 43 | 15 |
| 6 | OMe (5) | <i>i</i> -Pr (2) | NEt ₃ (3) | Et ₂ O | 47 | 60 |
| 7 | OMe (5) | <i>i</i> -Pr (2) | none | Et ₂ O | 41 | 70 |
| 8 | OEt (6) | <i>i</i> -Pr (2) | none | Et ₂ O | 32 | 60 |
| 9 | O <i>t</i> -Bu (7) | <i>i</i> -Pr (2) | none | Et ₂ O | 15 | 7 |
| 10 | OBn (8) | <i>i</i> -Pr (2) | none | Et ₂ O | 50 | 130 |
| 11 ^[d] | OBn (8) | <i>i</i> -Pr (2) | none | Et ₂ O | 50 | 120 |

Conversion (c) and selectivity factor (s) calculated using the enantiomeric ratios of recovered alcohol and ester (see Ref. [3a]). *s* values rounded according to estimated errors (see Ref. [3b]). Reactions performed on 0.16–0.32 mmol scale, see SI for full details.

TMP = 2,2,6,6-tetramethylpiperidine. [a] 10 mol % catalyst used. [b] Reaction at 50°C. [c] Reaction at 40°C. [d] 1.02 g (4 mmol) scale.

procedure allowed reduction in both catalyst loading and equivalents of anhydride, whilst maintaining comparable conversion and selectivity (Scheme 1). Despite this improved activity, the reaction scope was initially investigated using the commercially available isothiourea, HyperBTM,^[18] with the isoselenourea HyperSe (**9**) reserved for the KR of particularly challenging substrates.

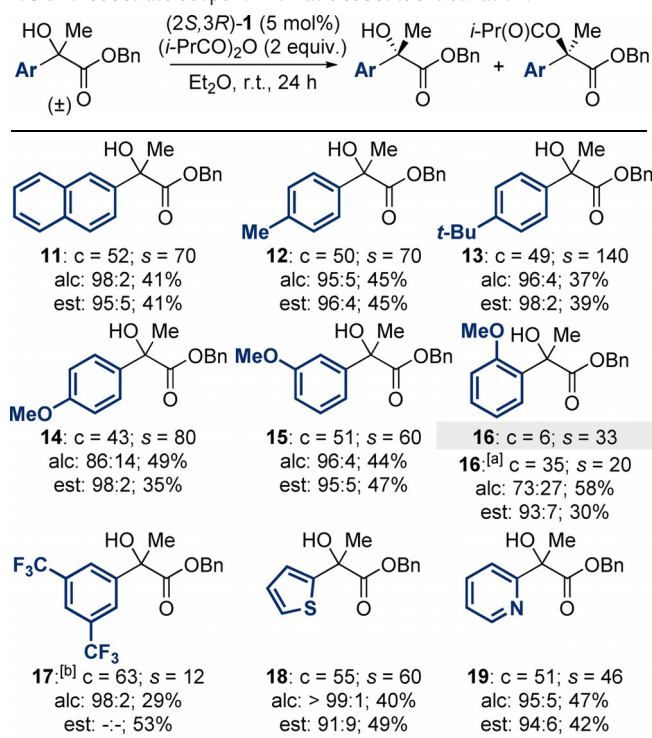


Scheme 1. KR of (\pm)-**8** using isoselenourea catalyst HyperSe (**9**).

The scope and limitations of the newly developed KR process was first evaluated through the incorporation of electronically and sterically differentiated aryl substituents at the carbinol centre (Table 2). The KR of substrates **11**–**15**, which bear electron-neutral and electron-donating aromatic substituents (naphthyl, tolyl, anisoyl), was achieved with good conversion and high selectivity ($s=60$ – 140). The incorporation of a sterically demanding *ortho*-anisoyl substituent, however, resulted in only 6% conversion. This is consistent with our previous work on the KR of heterocyclic tertiary alcohols,^[5b] where sterically encumbered substrates were less efficiently acylated. By applying the newly developed isoselenourea catalyst HyperSe (**9**) for the KR of **16**, significantly improved conversion ($c=35\%$) and good selectivity ($s=20$) was obtained. The KR of **17**, which bears an electron-withdrawing aromatic substituent, was achieved with high conversion when using HyperBTM (**1**), but reduced selectivity obtained ($s=12$). Substrates bearing heterocycles were also well tolerated, with 2-thienyl- and 2-pyridyl-substituted tertiary alcohols **18** and **19** resolved with good conversion and excellent selectivity ($s=46$ – 60).

Next, the effect of varying the alkyl substituent at the carbinol centre was evaluated (Table 3). Replacing the methyl group with more sterically-demanding substituents led to significantly lower conversion when using HyperBTM and (*i*-PrCO)₂O. For example, the KR of homoallylic alcohol **20** under the standard KR conditions provided only 4% conversion. By replacing (*i*-PrCO)₂O with (MeCO)₂O, good conversion and reasonable selectivity was obtained ($c=42\%$, $s=9$). The introduction of an ethyl or *n*-butyl substituent at the carbinol centre also resulted in very low conversion (<2%), however a combination of the isoselenourea HyperSe (**9**; 2 mol%) and (EtCO)₂O allowed the KR of **21** and **22** with good conversion and selectivity ($c=56$ – 57% , $s=9$ – 10). The KR of trifluoromethyl-substituted tertiary alcohol **23** also benefitted from the use of HyperSe (**9**) to increase reaction conversion from 26% to 48%. The catalytic system was further challenged through the introduction of an additional π -system at the carbinol centre to provide substrates with three potential recognition motifs. The KR of allylic

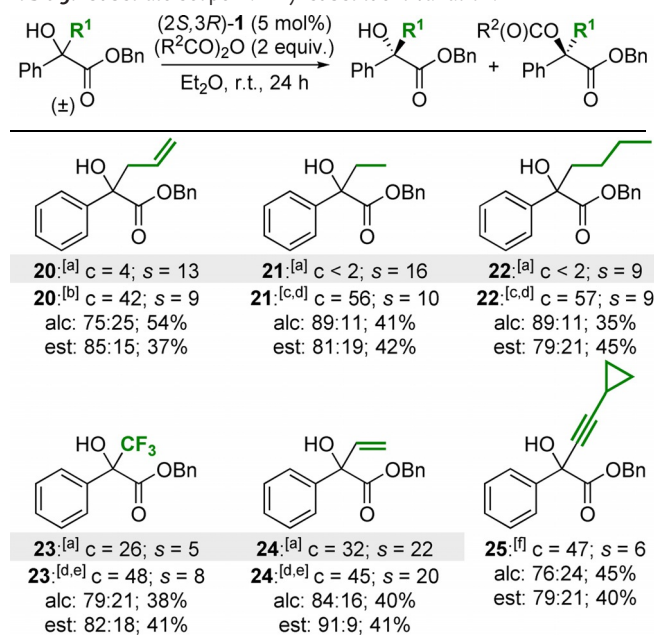
Table 2: Substrate scope I: Aromatic-substituent variation.



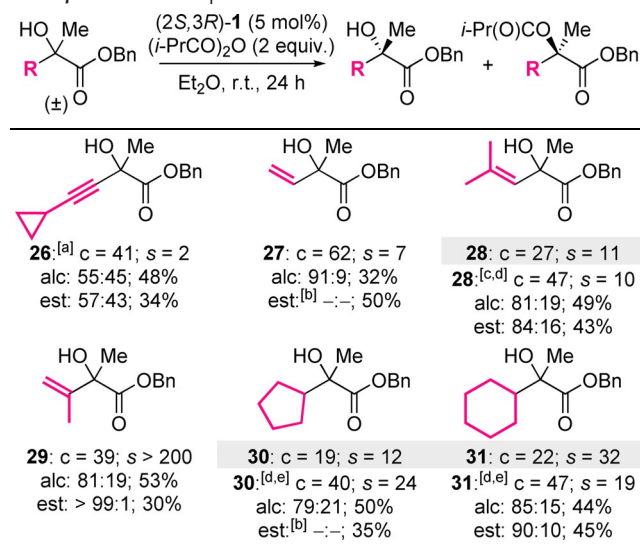
Conversion (c) and selectivity factor (s) calculated using the enantiomeric ratios of recovered alcohol and ester (see Ref. [3a]). s values rounded according to estimated errors (see Ref. [3b]). Reactions performed on 0.16–0.64 mmol scale; see the Supporting Information for full details. alc = alcohol, est = ester. [a] (2*R*,3*S*)-HyperSe (**9**; 5 mol%) used; the alcohol and ester were obtained in the opposite enantiomeric series to that shown in the Scheme due to the (2*R*,3*S*) configuration of **9**. [b] (*i*-PrCO)₂O (1 equiv) used; separation of the ester enantiomers was not possible by HPLC, conversion based on ¹H NMR spectroscopic analysis of crude reaction product mixture.

tertiary alcohol **24** was achieved with good selectivity ($s=20$), with the use of the isoselenourea HyperSe (**9**) as catalyst again proving beneficial for increasing conversion. Finally, the KR of propargylic alcohol **25** was achieved with slightly reduced selectivity ($s=6$). Consistent with the lower steric hindrance of this substituent, good conversion was obtained when using HyperBTM (**1**).

Based on the lower selectivity values obtained for the KR of substrates bearing longer alkyl chains (Table 3), it was hypothesized that catalyst discrimination between the aryl and alkyl substituents may predominantly originate from steric differences.^[19] To investigate this hypothesis, the aryl substituent was replaced with a series of sterically-differentiated groups (Table 4). As expected, the KR of alcohols **26** and **27**, which bear small alkynyl or vinyl substituents at the carbinol centre, was achieved with relatively low selectivity ($s=2$ – 7).^[20] Increasing the steric hindrance of the vinyl substituent through the introduction of two β -methyl groups resulted in a small improvement in selectivity ($s=10$); however the introduction of an α -methyl group had a significant effect, with alcohol **29** resolved with excellent selectivity ($s > 200$). Based on these results, the KR of substrates bearing two sterically differentiated alkyl substituents at the carbinol

Table 3: Substrate scope II: Alkyl-substituent variation.

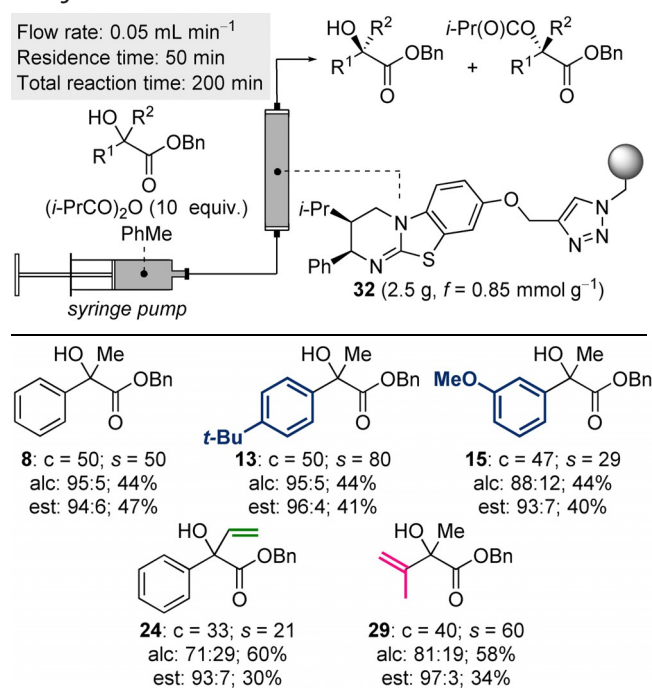
Conversion (c) and selectivity factor (s) calculated using the enantiomeric ratios of recovered alcohol and ester (see Ref. [3a]). Reactions performed on 0.2–0.32 mmol scale; see the Supporting Information for full details. [a] (*i*-PrCO)₂O used. [b] (MeCO)₂O used; [c] (2*R*,3*S*)-HyperSe (**9**; 2 mol%), (EtCO)₂O, and NEt₃ (2 equiv) used. [d] The alcohol and ester were obtained in the opposite enantiomeric series to that shown in the Scheme due to the (2*R*,3*S*) configuration of **9**; [e] (2*R*,3*S*)-**9** (2 mol%) and (*i*-PrCO)₂O used. [f] (*i*-PrCO)₂O (0.55 equiv) used.

Table 4: Substrate scope III: Further structural variation.

Conversion (c) and selectivity factor (s) calculated using the enantiomeric ratios of recovered alcohol and ester (see Ref. [3a]). s values rounded according to estimated errors (see Ref. [3b]). Reactions performed on 0.13–0.32 mmol scale; see the Supporting Information for full details. [a] (*i*-PrCO)₂O (0.55 equiv) used. [b] Separation of enantiomers not possible by HPLC analysis, conversion based on ¹H NMR spectroscopic analysis of crude reaction product mixture. [c] (2*R*,3*S*)-HyperSe (**9**; 2 mol%) used. [d] Alcohol and ester obtained in the opposite enantiomeric series to that shown in the scheme. [e] (2*R*,3*S*)-**9** (5 mol%) used.

centre was investigated. The introduction of a cyclopentyl or cyclohexyl group at this position resulted in only moderate conversion under the standard KR conditions ($c \approx 20\%$); however the use of HyperSe (**9**) enabled the KR of **30** and **31** with good conversion and selectivity ($c = 40$ – 47% , $s = 19$ – 24). The importance of steric differentiation between the carbinol substituents was further supported by the attempted KR of an electronically differentiated di-aryl-substituted alcohol, which resulted in essentially no selectivity.^[14]

A common perceived drawback of organocatalysis is the use of relatively high loadings of the catalyst, which is typically discarded following a given reaction. One potentially general solution is immobilization of the organocatalyst on a heterogeneous support, provided that the catalyst maintains activity and displays high stability.^[21,22] We recently addressed this issue through the development of a polymer-supported isothiourea catalyst (**32**), which could be applied for the KR of alcohols in batch and flow with no reduction in either activity or selectivity observed upon recycling.^[23] Application of this continuous-flow technology to the KR of acyclic tertiary alcohols was therefore targeted (Table 5). Since Merrifield-resin-supported catalyst **32** does not swell in Et₂O, process optimization focused on the application of alternative solvents.^[14] The use of toluene proved to be optimal, with excellent conversion and selectivity obtained for the KR of **8** ($c = 50\%$, $s = 50$). A further four structurally diverse substrates were applied under the optimal conditions. Variation of the aryl substituent was well tolerated, with **13** and **15** resolved with good conversion and good to excellent

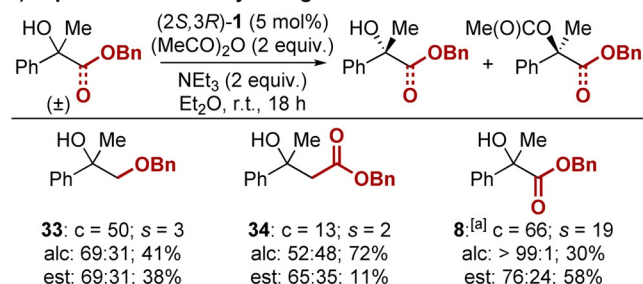
Table 5: KR in continuous flow.

Conversion (c) and selectivity factor (s) calculated using the enantiomeric ratios of recovered alcohol and ester (see Ref. [3a]). s values rounded according to estimated errors (see Ref. [3b]). Reactions performed on 0.2–0.22 mmol scale; see the Supporting Information for full details.

selectivity ($c \approx 50\%$, $s = 29\text{--}80$). The KR of allylic alcohols **24** and **29** was also successful. Although slightly lower conversion was observed under the standard continuous-flow conditions, good to excellent selectivity was obtained in each case ($s = 21\text{--}60$). To the best of our knowledge, this work represents the first example of the KR of acyclic tertiary alcohols in a continuous-flow process.

Finally, the importance of the carbonyl recognition motif was investigated to provide insight into the origins of enantiodiscrimination in this KR process (Figure 2). Attempted KR of benzyl ether **33** or homologated benzyl ester **34** resulted in essentially no conversion under the standard KR conditions. The resolution of these substrates could be achieved by switching to $(\text{MeCO})_2\text{O}$ as the acyl donor, however low selectivity was obtained ($s < 3$) (Figure 3a). In contrast, the KR of ester **8** under analogous conditions was achieved with $s = 19$. This demonstrates that the presence and proximity of the ester functionality is essential to promote acylation and allow effective enantiodiscrimination. The absolute configuration of the recovered alcohol within each substrate class [aryl/alkyl (**5,20**); alkenyl/alkyl (**29**); alkyl/alkyl (**31**)] was determined by comparison of specific rotations to reported values.^[14] Based on these data and previous computational studies,^[5h,10h,q] we propose that the ester functionality operates as a recognition motif within the acylation transition states of this KR by engaging in a stabilizing $\text{C}=\text{O}\cdots\text{isothiuronium}$ interaction with the acylated catalyst (Figure 3b). The preferential acylation of the fast-reacting enantiomer for each substrate class can then be rationalized through minimization of unfavourable steric contacts between the substrate and the acyl group of the acylated catalyst. This model helps explain why substrates bearing alkyl substituents larger than methyl at the carbinol centre were challenging to resolve and required the use of less sterically hindered anhydrides as the acyl donor.^[24]

a) Importance of carbonyl recognition motif for effective KR



b) Proposed diastereomeric transition state structures

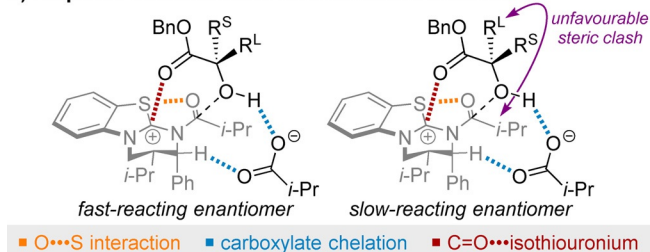


Figure 3. Experimental insights and proposed origin of enantiodiscrimination, where R^L is sterically larger than R^S . [a] $(\text{MeCO})_2\text{O}$ (1 equiv) used.

Conclusion

In conclusion, a highly enantioselective isothioureacatalyzed acylative kinetic resolution (KR) of acyclic tertiary alcohols has been developed. Through utilizing an adjacent carbonyl substituent as a recognition motif for the acylated catalyst, the KR of 25 α -hydroxy ester derivatives was achieved with selectivity factors of up to 200. Increased steric hindrance at the tertiary carbinol centre resulted in low conversion; however this issue was circumvented by performing the KR of these substrates by using the recently developed isoselenourea catalyst HyperSe (**9**). This new KR procedure was also applied in continuous flow using a polymer-supported isothioureacatalyst to resolve acyclic tertiary alcohols with good to excellent selectivity. Based on mechanistic control reaction, and previous computational studies, it is proposed that stabilization and enantiodiscrimination within the acylation transition-state structure originates through maximization of a $\text{C}=\text{O}\cdots\text{isothiuronium}$ interaction between the α -hydroxy ester substrate and acylated catalyst. Although not demonstrated in this manuscript, the known derivatization^[25] of structurally related products with conservation of *er* should allow access to further tertiary-alcohol-containing motifs using this method.^[26]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acyl transfer · enantioselectivity · kinetic resolution · organocatalysis · tertiary alcohols

- [1] a) Y.-L. Liu, X.-T. Lin, *Adv. Synth. Catal.* **2019**, *361*, 876–918; b) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969–5994; c) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873; d) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; e) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888; f) R. Kourist, P. Domínguez de María, U. T. Bornscheuer, *ChemBioChem* **2008**, *9*, 491–498; g) R. Kourist, U. T. Bornscheuer, *Appl. Microbiol. Biotechnol.* **2011**, *91*, 505–517; h) L. Chen, X.-P. Yin, C.-H. Wang, J. Zhou, *Org. Biomol. Chem.* **2014**, *12*, 6033–6048.

- [2] a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26; b) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001; *Angew. Chem.* **2005**, *117*, 4040–4069.
- [3] a) H. B. Kagan, J. C. Fiaud in *Topics in Stereochemistry, Vol. 18* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1988**, pp. 249–330; b) M. D. Greenhalgh, J. E. Taylor, A. D. Smith, *Tetrahedron* **2018**, *74*, 5554–5560.
- [4] a) C. E. Müller, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042; *Angew. Chem.* **2011**, *123*, 6136–6167; 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; c) H. Pellissier, *Tetrahedron* **2018**, *74*, 3459–3468.
- [5] a) I. Čorić, S. Müller, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 17370–17373; b) J. H. Kim, I. Čorić, C. Palumbo, B. List, *J. Am. Chem. Soc.* **2015**, *137*, 1778–1781; c) S. Rajkumar, S. He, X. Yang, *Angew. Chem. Int. Ed.* **2019**, *58*, 10315–10319; *Angew. Chem.* **2019**, *131*, 10421–10425; d) S. Rajkumar, M. Tang, X. Yang, *Angew. Chem. Int. Ed.* **2020**, *59*, 2333–2337; *Angew. Chem.* **2020**, *132*, 2353–2357; e) J. Seliger, X. Dong, M. Oestreich, *Angew. Chem. Int. Ed.* **2019**, *58*, 1970–1974; *Angew. Chem.* **2019**, *131*, 1991–1996; f) W. Zhang, S. Ma, *Chem. Commun.* **2018**, *54*, 6064–6067; g) S. Lu, S. B. Poh, W.-Y. Siau, Y. Zhao, *Angew. Chem. Int. Ed.* **2013**, *52*, 1731–1734; *Angew. Chem.* **2013**, *125*, 1775–1778; h) M. D. Greenhalgh, S. M. Smith, D. M. Walden, J. E. Taylor, Z. Brice, E. R. T. Robinson, C. Fallan, D. B. Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H.-Y. Cheong, A. D. Smith, *Angew. Chem. Int. Ed.* **2018**, *57*, 3200–3206; *Angew. Chem.* **2018**, *130*, 3254–3260; i) E. R. Jarvo, C. A. Evans, G. T. Copeland, S. J. Miller, *J. Org. Chem.* **2001**, *66*, 5522–5527; j) M. C. Angione, S. J. Miller, *Tetrahedron* **2006**, *62*, 5254–5261.
- [6] Isolated examples of non-enzymatic catalytic KR of tertiary alcohols as a part of an alternative methodological study: a) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev, H. M. L. Davis, *J. Am. Chem. Soc.* **2012**, *134*, 15497–15504; b) J. L. Olivares-Romero, Z. Li, H. Yamamoto, *J. Am. Chem. Soc.* **2013**, *135*, 3411–3413; For examples of non-enzymatic catalytic *chiroablative* KR of tertiary alcohols, see: c) S.-Y. Tosaki, K. Hara, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 11776–11777; d) R. Shintani, K. Takatsu, T. Hayashi, *Org. Lett.* **2008**, *10*, 1191–1193.
- [7] Selected other examples of NHC-catalyzed KR of alcohols: a) Y. Suzuki, K. Yamauchi, K. Muramatsu, M. Sato, *Chem. Commun.* **2004**, 2770–2771; b) T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* **2005**, *7*, 1347–1349; c) S. Kuwano, S. Harada, B. Kang, R. Oriez, Y. Yamaoka, K. Takasu, K. Yamada, *J. Am. Chem. Soc.* **2013**, *135*, 11485–11488; d) S. Lu, S. B. Poh, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 11041–11045; *Angew. Chem.* **2014**, *126*, 11221–11225; e) B. Liu, J. Yan, R. Huang, W. Wang, Z. Jin, G. Zanoni, P. Zheng, S. Yang, Y. R. Chi, *Org. Lett.* **2018**, *20*, 3447–3450; f) J. Bie, M. Lang, J. Wang, *Org. Lett.* **2018**, *20*, 5866–5871.
- [8] J. Merad, J.-M. Pons, O. Chuzel, C. Bressy, *Eur. J. Org. Chem.* **2016**, 5589–5610.
- [9] A. S. Burns, A. J. Wagner, J. L. Fulton, K. Young, A. Zakarin, S. D. Rychnovsky, *Org. Lett.* **2017**, *19*, 2953–2956.
- [10] a) V. B. Birman, L. Guo, *Org. Lett.* **2006**, *8*, 4859–4861; b) I. Shiina, K. Nakata, *Tetrahedron Lett.* **2007**, *48*, 8314–8317; c) V. B. Birman, X. Li, *Org. Lett.* **2008**, *10*, 1115–1118; d) I. Shiina, K. Nakata, M. Sugimoto, Y. Onda, T. Ikzumi, K. Ono, *Heterocycles* **2009**, *77*, 801–810; e) Y. Zhang, V. B. Birman, *Adv. Synth. Catal.* **2009**, *351*, 2525–2529; f) Q. Hu, H. Zhou, X. Geng, P. Chen, *Tetrahedron* **2009**, *65*, 2232–2238; g) H. Zhou, Q. Hu, P. Chen, *Tetrahedron* **2010**, *66*, 6494–6499; h) I. Shiina, K. Nakata, K. Ono, M. Sugimoto, A. Sekiguchi, *Chem. Eur. J.* **2010**, *16*, 167–172; i) K. Nakata, A. Sekiguchi, I. Shiina, *Tetrahedron: Asymmetry* **2011**, *22*, 1610–1619; j) I. Shiina, K. Ono, K. Nakata, *Chem. Lett.* **2011**, *40*, 147–149; k) D. Belmessieri, C. Joannesse, P. A. Woods, C. MacGregor, C. Jones, C. D. Campbell, C. P. Johnson, N. Dugué, C. Concellón, R. A. Bragg, A. D. Smith, *Org. Biomol. Chem.* **2011**, *9*, 559–570; l) X. Li, H. Jiang, E. W. Uffman, L. Guo, Y. Zhang, X. Yang, V. B. Birman, *J. Org. Chem.* **2012**, *77*, 1722–1737; m) K. Nakata, K. Gotoh, K. Ono, K. Futami, I. Shiina, *Org. Lett.* **2013**, *15*, 1170–1173; n) I. Shiina, K. Ono, T. Nakahara, *Chem. Commun.* **2013**, *49*, 10700–10702; o) S. F. Musolino, O. S. Ojo, N. J. Westwood, J. E. Taylor, A. D. Smith, *Chem. Eur. J.* **2016**, *22*, 18916–18922; p) K. Nakata, E. Tokumaru, T. Saitoh, T. Nakahara, K. Ono, T. Murata, I. Shiina, *Heterocycles* **2017**, *95*, 277–289; q) T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules* **2018**, *23*, 2003–2021.
- [11] a) J. Merad, P. Borkar, F. Caijo, J.-M. Pons, J.-L. Parrain, O. Chuzel, C. Bressy, *Angew. Chem. Int. Ed.* **2017**, *56*, 16052–16056; *Angew. Chem.* **2017**, *129*, 16268–16272; b) S. Qu, M. D. Greenhalgh, A. D. Smith, *Chem. Eur. J.* **2019**, *25*, 2816–2823; c) S. Harrer, M. D. Greenhalgh, R. M. Neyyappadath, A. D. Smith, *Synlett* **2019**, *30*, 1555–1560.
- [12] a) B. R. Beno, K.-S. Yeung, M. D. Bartberger, L. D. Pennington, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 4383–4438; b) V. B. Birman, X. Li, Z. Han, *Org. Lett.* **2007**, *9*, 37–40; c) M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2014**, *136*, 4492–4495; d) E. R. T. Robinson, D. M. Walden, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong, A. D. Smith, *Chem. Sci.* **2016**, *7*, 6919–6927; e) 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*, 4366–4375; f) D. J. Pascoe, K. B. Ling, S. L. Cockroft, *J. Am. Chem. Soc.* **2017**, *139*, 15160–15167.
- [13] a) S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem. Eur. J.* **2005**, *11*, 4751–4757; b) V. Lutz, J. Glatthaar, C. Würtele, M. Serafin, H. Hausmann, P. R. Schreiner, *Chem. Eur. J.* **2009**, *15*, 8548–8557; c) E. Larionov, M. Mahesh, A. C. Spivey, Y. Wei, H. Zipse, *J. Am. Chem. Soc.* **2012**, *134*, 9390–9399; d) C. E. Cannizzaro, K. N. Houk, *J. Am. Chem. Soc.* **2002**, *124*, 7163–7169; e) R. C. Johnston, P. H.-Y. Cheong, *Org. Biomol. Chem.* **2013**, *11*, 5057–5064.
- [14] See the Supporting Information for more details.
- [15] Selectivity factor (*s*) is the most commonly used metric to report the efficiency of a KR; is defined as the rate constant for the fast reacting enantiomer divided by the rate constant for the slow reacting enantiomer ($s = k_{\text{fast}}/k_{\text{slow}}$) and is calculated using the reaction conversion and either the *ee* of the recovered substrate $\{s = \ln[(1-c)(1-ee_{\text{substrate}})]/\ln[(1-c)(1+ee_{\text{substrate}})]\}$ or *ee* of the reaction product $\{s = \ln[(1-c)(1+ee_{\text{product}})]/\ln[(1-c)(1-ee_{\text{product}})]\}$. See Ref. [3] for more details.
- [16] For the KR of benzyl ester **8**, extended π - π interactions between the benzyl substituent and the catalyst may provide further stabilization of the acylation transition state. See Figure 3b for proposed transition-state structures.
- [17] C. M. Young, A. Elmi, D. J. Pascoe, R. K. Morris, C. McLaughlin, A. M. Woods, A. B. Frost, A. de la Houpliere, K. B. Ling, T. K. Smith, A. M. Z. Slawin, P. H. Willoughby, S. L. Cockroft, A. D. Smith, *Angew. Chem. Int. Ed.* **2020**, *59*, 3705–3710; *Angew. Chem.* **2020**, *132*, 3734–3739.
- [18] Both enantiomers are available from Apollo Scientific: (2*S*,3*R*) CAS Reg. No. [1203507-02-1]; (2*R*,3*S*) CAS Reg. No. [1699751-03-5].
- [19] a) J. A. Hirsch in *Topics in Stereochemistry, Vol. 1* (Eds.: N. L. Allinger, E. L. Eliel), Wiley, New York, **1967**, pp. 199–217; b) M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 1552–1556; c) M. Charton, *J. Org. Chem.* **1976**, *41*, 2217–2220; d) H. Förster, F. Vögtle, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 429–441; *Angew.*

- Chem.* **1977**, *89*, 443–455; e) G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.
- [20] Due to the low enantiodiscrimination observed for alcohols **26** and **27**, the absolute configuration of the products could not be unambiguously determined or inferred by analogy.
- [21] a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429; b) A. F. Trindade, P. M. P. Gois, C. A. M. Alfonso, *Chem. Rev.* **2009**, *109*, 418–514; c) T. E. Kristensen, T. Hansen, *Eur. J. Org. Chem.* **2010**, 3179–3204; d) B. Altava, M. I. Burguete, E. Garcia-Verdugo, S. V. Luis, *Chem. Soc. Rev.* **2018**, *47*, 2722–2771.
- [22] a) C. Rodríguez-Esrich, M. A. Pericàs, *Eur. J. Org. Chem.* **2015**, 1173–1188; b) C. Rodríguez-Esrich, M. A. Pericàs, *Chem. Rec.* **2019**, *19*, 1872–1890; c) T. Yu, Z. Ding, W. Nie, J. Jiao, H. Zhang, Q. Zhang, C. Xue, X. Duan, Y. M. A. Yamada, P. Li, *Chem. Eur. J.* **2020**, *26*, 5729–5747; d) C. De Risi, O. Bortolini, A. Brandolise, G. Di Carmine, D. Ragno, A. Massi, *React. Chem. Eng.* **2020**, *5*, 1017–1052.
- [23] a) R. M. Neyyappadath, R. Chisholm, M. D. Greenhalgh, C. Rodríguez-Esrich, M. A. Pericàs, G. Hähner, A. D. Smith, *ACS Catal.* **2018**, *8*, 1067–1075; b) N. R. Guha, R. M. Neyyappadath, M. D. Greenhalgh, R. Chisholm, S. M. Smith, M. L. McEvoy, C. M. Young, C. Rodríguez-Esrich, M. A. Pericàs, G. Hähner, A. D. Smith, *Green Chem.* **2018**, *20*, 4537–4546; c) J. Lai, R. M. Neyyappadath, A. D. Smith, M. A. Pericàs, *Adv. Synth. Catal.* **2020**, *362*, 1370–1377.
- [24] The low selectivity values obtained for propargylic alcohols cannot be easily rationalized by these proposed TSs, and may indicate that the alkyne substituent operates as a competitive recognition motif in these examples. See Ref. [10a] for the isothioureia-catalyzed KR of propargylic alcohols
- [25] Representative examples of hydrolysis (a,b) and reduction (c) of derivatives closely related to the parent esters **5–8** without loss of enantiopurity: a) C. Wang, L. Zong, C.-H. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 10677–10682; b) J.-M. Xiang, B.-L. Li, *Helv. Chim. Acta* **2010**, *93*, 2015–2022; c) T. Karasawa, R. Oriz, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2018**, *140*, 12290–12295.
- [26] The research data underpinning this publication can be found at DOI: <https://doi.org/10.17630/df9887af-d9c0-433b-a7c0-1dbe06a96be8>.

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