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PAPER

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Horeau amplification in the sequential acylative kinetic resolution of (±)-1,2-diols and (±)-1,3-diols in flow†

Arianna Brandolese,[a,b] Mark D. Greenhalgh,[a,c] Titouan Desrues,[d] Xueyang Liu,[d] Shen Qu,[a] Cyril Bressy (ID) *[d] and Andrew D. Smith (ID) *[a]

The sequential acylative kinetic resolution (KR) of C_2-symmetric (±)-1,2-*syn* and (±)-1,3-*anti*-diols using a packed bed microreactor loaded with the polystyrene-supported isothiourea, HyperBTM, is demonstrated in flow. The sequential KRs of C_2-symmetric (±)-1,2-*syn* and (±)-1,3-*anti*-diols exploits Horeau amplification, with each composed of two successive KR processes, with each substrate class significantly differing in the relative rate constants for each KR process. Optimisation of the continuous flow set-up for both C_2-symmetric (±)-1,2-*syn* and (±)-1,3-*anti*-diol substrate classes allowed isolation of reaction products in both high enantiopurity and yield. In addition to the successful KR of C_2-symmetric (±)-1,2-*syn* and (±)-1,3-*anti*-diols, the application of this process to the more conceptually-complex scenario involving the sequential KR of C_1-symmetric (±)-1,3-*anti*-diols was demonstrated, which involves eight independent rate constants.

Introduction

The Horeau principle (often referred to as Horeau amplification) is a powerful strategy that can be used within a synthetic process to generate material of high enantiopurity. These terms can be applied to synthetic reaction processes in which material of high enantiopurity is delivered either (i) from starting material of lower enantiopurity through conversion into diastereomeric products, subsequent separation and recovery; or (ii) through carrying out successive enantioselective transformations on polyfunctional starting materials.[1] Initially demonstrated synthetically and formalised in a landmark manuscript by Horeau in 1973,[2] the basic principles of this phenomena were expanded upon mathematically by Rautenstrauch and Kagan.[3] Over the following decades the power of this process has been extended to a range of catalytic enantioselective sequences with an elegant review from Harned demonstrating the power of this process in a range of synthetic sequences.[4]

[a]EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife, KY16 9ST, UK. E-mail: ads10@st-andrews.ac.uk
[b]Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via L. Borsari, 46, 44121 Ferrara, Italy
[c]Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK
[d]Aix Marseille Univ, CNRS, Centrale Marseille, iSm2 Marseille, France. E-mail: cyril.bressy@univ-amu.fr
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A representative example of this powerful amplification process is the acylative double catalytic kinetic resolution (DoCKR) of C_2-symmetric (±)-1,2-*syn* and (±)-1,3-*anti*-diols (Fig. 1).[5–8] Due to the bis-alcohol functionality within the substrates, two KR processes can be in operation and are represented by the rate constants k_1 and k_2 for the first KR, and k_3 and k_4 for the second KR. If $k_1 > k_2$ and $k_3 > k_4$, the enantiomer of monoester preferentially generated in the 1st KR is also preferentially acylated in the 2nd KR (so called additive Horeau amplification). In principle, this allows the generation of both the diester (from two successive KRs) and diol in high enantiopurity and with opposite absolute configuration (shown in the blue and red boxes in Fig. 1). The enantiopurity and absolute
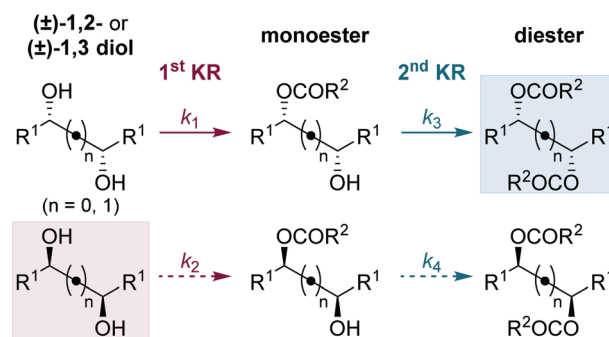

Fig. 1 Horeau amplification in the sequential double acylative KR of C_2-symmetric (±)-diols, where $k_1 > k_2$ and $k_3 > k_4$.

configuration of the monoester product will be highly dependent upon reaction conversion, with its configuration matching that of the diester at low conversion, and the diol at high conversion. By necessity, there will be an inflection point between these two extremes where the monoester is racemic. In addition, the product distribution and hence relative yields of diester, diol and monoester obtained in such a sequential KR process will be dependent upon the relative magnitude of the combined rate constants for the 1st KR process relative to the 2nd KR process. If both KR processes are reasonably selective, then this can be simplified as the relationship between the largest rate constant for each KR step (*i.e.* in the example in Fig. 1, k_1 *vs.* k_3).

Despite the potential to harness additive Horeau amplification in these processes, the majority of examples of catalytic acylative KR of diols are selective for formation of the monoester product,[5,6] and hence do not benefit from amplification of product enantiopurity imparted by the 2nd KR process. To date, only work from our research groups has demonstrated this concept, through the use of isothiourea catalysis in the sequential KR of (±)-1,3-*anti* and (±)-1,2-*syn* diols (Scheme 1).[7,8] The sequential KR of (±)-1,3-*anti*-diol **2a** was achieved using (2*R*,3*S*)-HyperBTM **1** as catalyst (1 mol%) and propionic anhydride as acylating agent (1.05 equiv.), to give (*R*,*R*)-diol **2a** (41% yield, >99 : 1 er), (*R*,*R*)-monoester **3a** (7% yield, 66 : 34 er) and (*S*,*S*)-diester **4a** (41% yield, 98 : 2 er). This process was shown to exhibit Horeau amplification, where both KR steps displayed the same sense of enantiodiscrimination.[7] Based on the product distribution, it can be estimated that the relative rates of each KR process are close to parity (*i.e.* $k_1 \approx k_3$). The sequential KR of (±)-1,2-*syn*-diol **5a** was also shown to satisfy
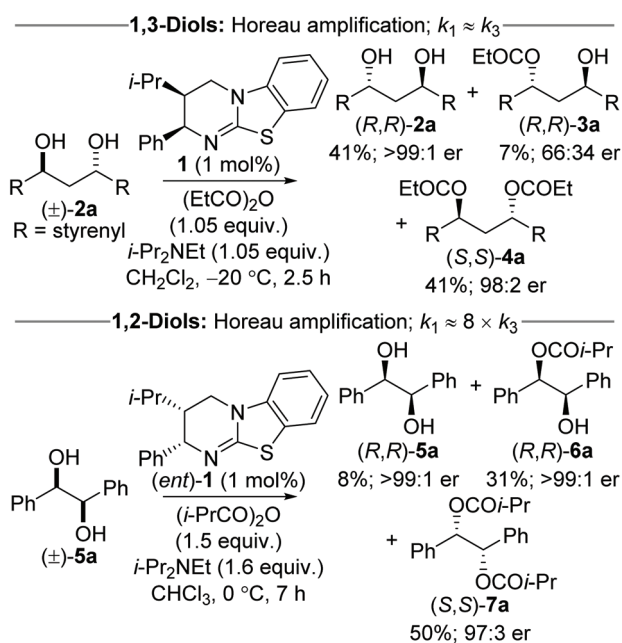
the conditions of Horeau amplification; however the relative rates of the two KR steps were significantly different, with the 1st KR being ~8 times that of the 2nd KR.[8] The significantly smaller rate constant for the second acylation can presumably be attributed to the increased steric hindrance associated with the α-ester substituent introduced following the first acylation event. This scenario makes it impossible to isolate diol and diester in both high yield and enantiopurity, and necessitates the sequential KR being driven to higher conversion to access highly enantiomerically enriched material. As such, treatment of (±)-1,2-*syn*-diol **5a** with (2*S*,3*R*)-HyperBTM (*ent*)-**1** (1 mol%) and isobutyric anhydride (1.5 equiv.) in CHCl₃ gave (*R*,*R*)-diol **5a** (8% yield, >99 : 1 er), (*R*,*R*)-monoester **6a** (31% yield, >99 : 1 er) and (*S*,*S*)-diester **7a** (50% yield, 97 : 3 er).[8] In this case, the diol and monoester can be combined to give the (*R*,*R*)-enantiomer in 39% yield and >99 : 1 er. These two sequential KR processes, although related, demonstrate the complexity of these systems, and how modulation of reaction conversion can be used to maximise both the yield and enantiopurity of the various reaction products.

One approach to improve the sustainability of organocatalytic transformations is the immobilisation of the organocatalyst on a heterogeneous polymer support.[9,10] In order to off-set the additional time and expense associated with synthesis, the supported catalyst must be readily recovered and recycled multiple times without loss in activity. The use of a packed bed reactor and application in a continuous flow set-up is a particularly-attractive technological solution that significantly simplifies catalyst recovery.[9e–h] The use of polymer-supported isothioureas as recyclable enantioselective catalysts was first demonstrated by Pericàs in formal cycloaddition processes.[11] Further collaborative work between Pericàs and Smith has established the use of polymer-supported isothioureas for the KR of secondary alcohols, tertiary alcohols and BINOL derivatives in batch and flow.[12] Building on these precedents, this manuscript investigates the possibility of performing the sequential KR of C_2-symmetric (±)-1,2-*syn*- and (±)-1,3-*anti*-diols, as well as C_1-symmetric (±)-1,3-*anti*-diols, in flow[13] using a polymer-supported variant of HyperBTM.

Scheme 1 Acylative DoCKR of (±)-1,3- and (±)-1,2-diols using isothiourea catalysis.
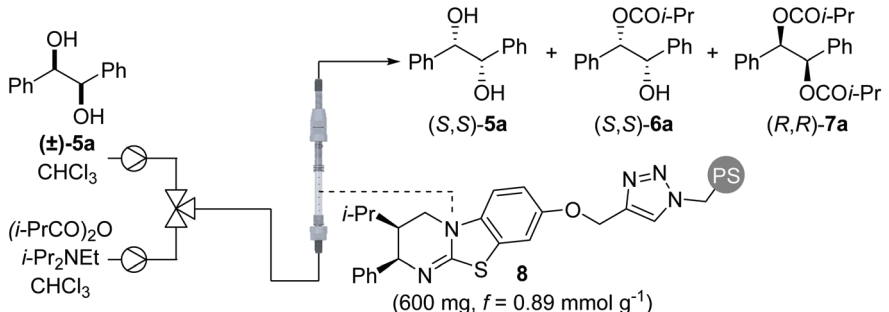
Results and discussion

Sequential KR of C_2-symmetric (±)-1,2-*syn*-diols in flow

Using a packed bed microreactor loaded with polystyrene-supported (2*R*,3*S*)-HyperBTM **8**,[12a] initial studies focused on the KR of (±)-1,2-diphenylethane-1,2-diol **5a** using isobutyric anhydride as the acylating agent and i-Pr₂NEt as the base (Table 1). Unlike simple KRs where the selectivity factor (*s*) can be easily calculated using substrate or product enantiopurity and reaction conversion,[14] interrogation of the selectivity of a sequential KR is complicated by the operation of two enantioselective processes.[15] As such, reaction optimisation was assessed by targeting the isolation of all reaction components in high enantiopurity. Initially replicating the optimal conditions used in our previously-reported homogenous system,[8] the use of 1.5

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Table 1 Optimisation study for the sequential kinetic resolution of (±)-**5a** in flow[a]

Entry	(±)-**5a** [M]	(i-PrCO)$_2$O [M]	i-Pr$_2$Net [M]	Product ratio (**5a** : **6a** : **7a**)[b]	**5a** er (S,S) : (R,R)[c]	**6a** er (S,S) : (R,R)[c]	**7a** er (R,R) : (S,S)[c]
1	0.2	0.3	0.32	17 : 39 : 44	99 : 1	85 : 15	95 : 5
2	0.1	0.15	0.16	10 : 44 : 46	>99 : 1	75 : 25	94 : 6
3	0.2	0.4	0.44	1 : 40 : 59	—	>99 : 1	75 : 25
4	0.2	0.35	0.35	7 : 41 : 52	99 : 1	97 : 3	90 : 10
5[d,e]	**0.2**	**0.35**	**0.35**	7 : 40 : 53	>99 : 1 (3%)[f]	98 : 2 (35%)[f]	94 : 6 (48%)[f]

[a] Conditions: (±)-**5a** (0.5 mmol), r.t., flow rate 0.1 mL min^{-1}. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product mixture. [c] Determined by CSP-HPLC analysis. [d] Diol and anhydride in one syringe, i-Pr$_2$NEt in the other. [e] 2.0 mmol scale. [f] Isolated yield.

equivalents of isobutyric anhydride allowed isolation of diester (R,R)-**7a** and recovered diol (S,S)-**5a** with high enantioenrichment, however monoester (R,R)-**6a** was obtained with only moderate enantioenrichment (Table 1, entry 1). Encouraged by this initial result, increasing the enantioenrichment of monoester (1R,2R)-**6a** was targeted by increasing reaction conversion and aiming for ∼50% conversion to diester. Increasing the concentration of reagents was hampered by the low solubility of diol **5a** in CHCl$_3$ above 0.2 M, whilst decreasing the concentration of all the three reagents provided both the monoester **6a** and diester **7a** in lower enantiopurity (entry 2). Subsequent studies focused on increasing the equivalents of anhydride and base.[16] Using 2 equivalents of anhydride gave almost full consumption of diol **5a** and 59% conversion to the diester **7a** (entry 3). This high conversion had a negative impact on the enantiopurity of diester **7a**, demonstrating the need for a subtle balance to obtain all three products in high enantiopurity. Using 1.75 equivalents of anhydride provided the ideal compromise, with all three products obtained in high enantiopurity (entry 4). Finally, the method for delivering the reagents was varied, with the combination of diol and anhydride in a single syringe proving more optimal that the initial set-up, in which the anhydride and base were delivered from the same syringe. Increasing the scale of this process to 2 mmol allowed isolation of diester (R,R)-**7a** in 48% yield and 94 : 6 er, along with the (S,S)-enantiomer of both diol **5a** and monoester **6a** in >99 : 1 er and 98 : 2 er, respectively, and a combined yield of 38% (entry 5).
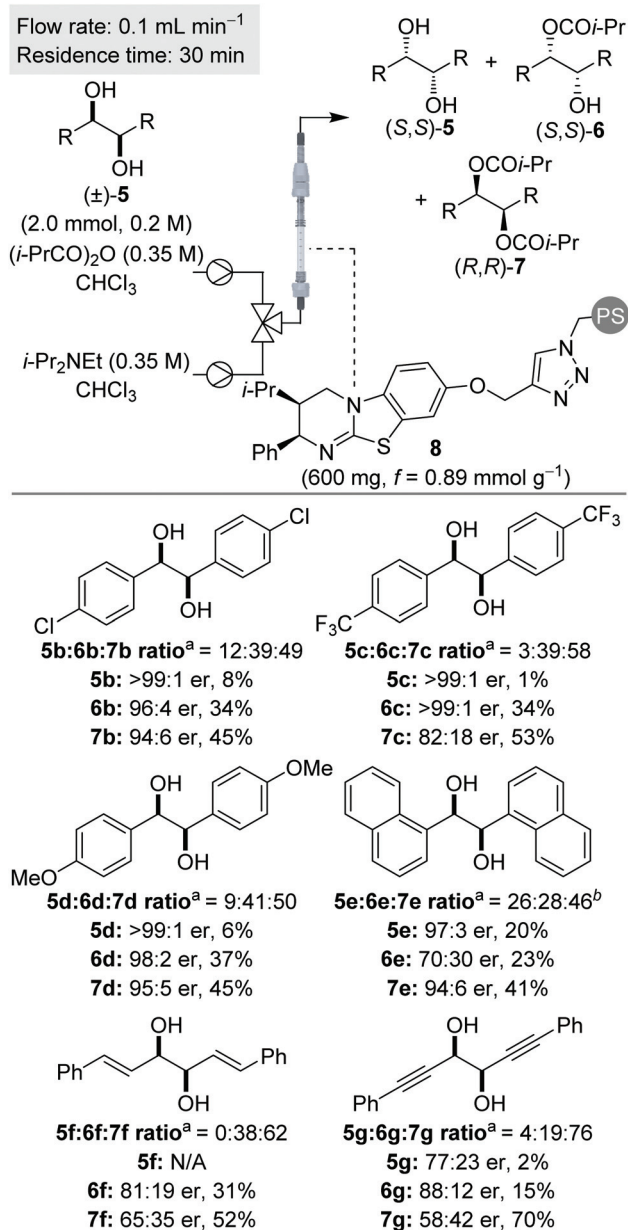
Using the conditions optimised for diol **5a**, the generality of this sequential KR process in flow was investigated using a selection of electronically- and sterically-differentiated (±)-1,2-diols (Scheme 2). (±)-1,2-Diarylethane-1,2-diol derivatives **5b**–**5d** were all resolved with excellent selectivity with results comparable with those obtained with the homogeneous catalyst.[8]

The sequential KR of p-methoxy-substituted diol **5d** provided products with higher enantioenrichment than substrates **5b** and **5c** bearing electron-withdrawing p-chloro or p-trifluoromethyl substituents. These results are consistent with the KR of simple benzylic alcohols using isothiourea catalysts, where the presence of an electron-rich aromatic substituent provides enhanced stabilisation of the acylation transition state through π–cation interactions.[17] The method was also extended to naphthyl-substituted diol **5e**, however low solubility of **5e** in CHCl$_3$ required the use of a different solvent system (1 : 1 THF : CHCl$_3$). Under these conditions, diol **5e** and diester **7e** were recovered with high enantioenrichment (97 : 3 er and 94 : 6 er, respectively); while monoester **6e** was obtained with only moderate enantioenrichment (70 : 30 er). This can be attributed to slightly lower conversion being observed, presumably reflecting the reduced swelling of the catalyst resin in 1 : 1 THF : CHCl$_3$ and consequently leading to a lower residence time. Finally, the KR of (±)-1,2-diols **5f** and **5g** bearing alternative π-donor systems (alkene and alkyne) was also performed. Only moderate selectivity, coupled with higher conversions were obtained in both cases, consistent with the sequential KR of these substrates using the homogenous catalyst.[8] These results are also consistent with the observation that the isothiourea-catalysed KR of simple allylic and propargylic alcohols is generally less selective than the KR of benzylic alcohols.[17]

Sequential KR of C_2-symmetric (±)-1,3-*anti*-diols in flow

Considering the positive outcome of the sequential KR of 1,2-diols in continuous flow, we sought to extend this process to (±)-*anti*-1,3-diols. In our previous work on the sequential KR of 1,3-diols using a homogenous isothiourea catalyst, the KRs were performed at −20 °C in CH$_2$Cl$_2$,[7] however low substrate solubility under these conditions prohibited use of these con-

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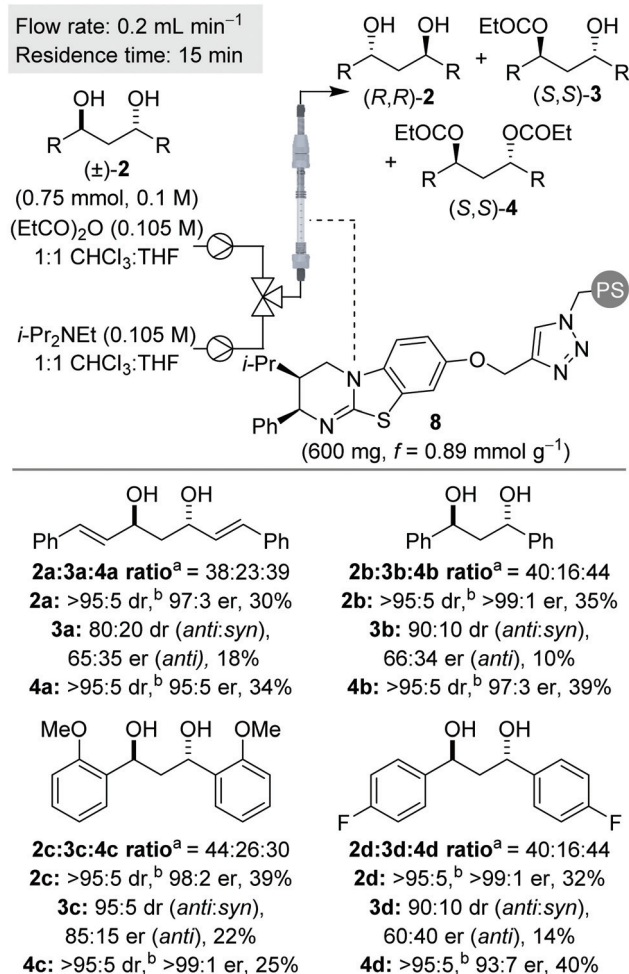This journal is © The Royal Society of Chemistry 2021

Scheme 2 Reaction scope for C_2-symmetric (±)-*syn*-1,2-diols. [a] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Solvent 1 : 1 THF : CHCl$_3$.

and a higher flow rate, relative to the KR of 1,2-diols, found to be optimal.[16]

Using the optimised conditions, the sequential KR of (±)-*anti*-1,3-diols was explored (Scheme 3). In all cases, the (±)-*anti*-1,3-diols substrates were synthesised in >95 : 5 dr, with only trace amounts of the *syn*-diastereomer present. In keeping with the KR of these substrates using the homogenous catalyst,[7] the diol and diester products were obtained in consistently good yield and enantioenrichment, whilst the monoester was isolated as a minor component with low enantioenrichment in each case. Also in keeping with the previous work,[7] the monoester was generally isolated as a mixture of *anti*- and *syn*-diastereomers, whilst both diol and diester were obtained as essentially single diastereomers. This phenomenon results in the sequential KR enhancing the diastereopurity of the products, in addition to the anticipated separation of enantiomers, and can presumably be attributed to a small rate constant for the 2nd acylation for the *syn*-diastereomer.

Scheme 3 Reaction scope for C_2-symmetric (±)-*anti*-1,3-diols. [a] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] dr given is *anti* : *syn* ratio of diastereomers. er shown corresponds to *anti* diastereomer.

ditions in flow. Low diol solubility was also observed when using CHCl$_3$, however using 1 : 1 THF : CHCl$_3$ at room temperature provided good solubility. To test the suitability of this solvent system for KR selectivity, control experiments were conducted using the homogenous catalyst, HyperBTM **1**, in both CH$_2$Cl$_2$ and 1 : 1 THF : CHCl$_3$ for the KR of 1,3-diol **2a** at room temperature.[16] Comparable conversion and product enantioenrichment was obtained and therefore process optimisation in flow was conducted using this mixed solvent system. A brief optimisation was conducted using 1,3-diol **2a**, with the use of fewer equivalents of anhydride, lower reagent concentration

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Paper

Initially, the sequential KR process was applied to C_2-symmetric 1,3-diols **2a–d**, bearing a π-system adjacent to the reactive carbinol centres (Scheme 3). Allylic diol **2a** was resolved with both diol and diester obtained with excellent enantioenrichment. This result provides some contrast to the KR of 1,2-diols, where the resolution of allylic and propargylic diols was significantly less selective. The KR of benzylic 1,3-diol **2b** was achieved with even higher selectivities, again consistent with the usual observation that benzylic alcohols are resolved more selectively than allylic alcohols.[17] Variation of the electronic nature of the aromatic substituents was next probed, with the introduction of either electron-donating or electron-withdrawing substituents (**2c** and **2d**) providing diol and diester products with excellent enantioenrichment.

Sequential KR of C_1-symmetric (±)-*anti*-1,3-diols in flow

Next, we were intrigued to investigate the KR of C_1-symmetric (±)-*anti*-1,3-diols in flow. For the KR of these substrates, the kinetic scenario is further complicated by the intermediacy of four isomeric monoesters: two sets of enantiomers arising from acylation of either hydroxyl group (Scheme 4). Overall this leads to a sequential KR composed of 8 independent rate constants, where both the formation and consumption of each isomeric monoester is controlled by the chiral isothiourea catalyst.

To probe this scenario, two C_1-symmetric (±)-*anti*-1,3-diols, **2e** and **2f**, were applied in the sequential KR process with excellent selectivity. Diols **2e** and **2f**, and their corresponding diesters, **4e** and **4f**, were recovered in good yield and with high enantioenrichment. The corresponding monoesters **3e′** and **3e″** and **3f′** and **3f″** were all isolated with low er and with lower dr than the starting *anti*-1,3-diols. Of particular note, the two constitutional isomers of monoester obtained from each reaction (for example **e′** and **e″**) were determined to have opposite configuration: whilst monoester **e′/f′** was enriched in the same enantiomeric series as the (*R*,*R*)-diol, the monoester **e″/f″** was

enriched in the same enantiomeric series as the (*S*,*S*)-diester. At low conversion both constitutional isomers of monoester would be enriched in the (*S*,*S*)-enantiomer, whilst at high conversion both constitutional isomers of monoester would be enriched in the (*R*,*R*)-enantiomer. The intriguing results displayed in Scheme 5 can therefore be explained as a product of the 8 independent rate constants outlined above and the reaction conversion, which is controlled by the concentration of reagents, catalyst bed loading and flow-rate. Overall these results conveniently highlight the kinetic complexity of this system, and embody many of the principles popularised by Horeau.

Finally, to provide further insight into these processes, and contrast the sequential KR of (±)-*syn*-1,2- and (±)-*anti*-1,3-diols, selectivity values (s)[14] for the individual KR steps were calculated for each process (Scheme 6). The s value for the first KR step was evaluated in each case by using the conversion and er of the recovered diol. This calculation assumes the diol only
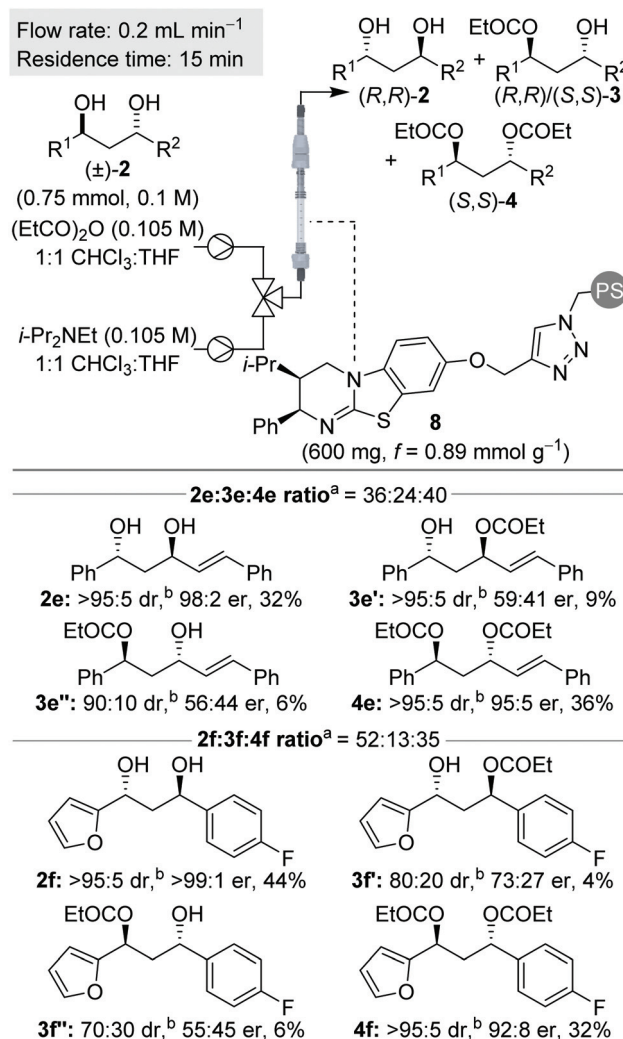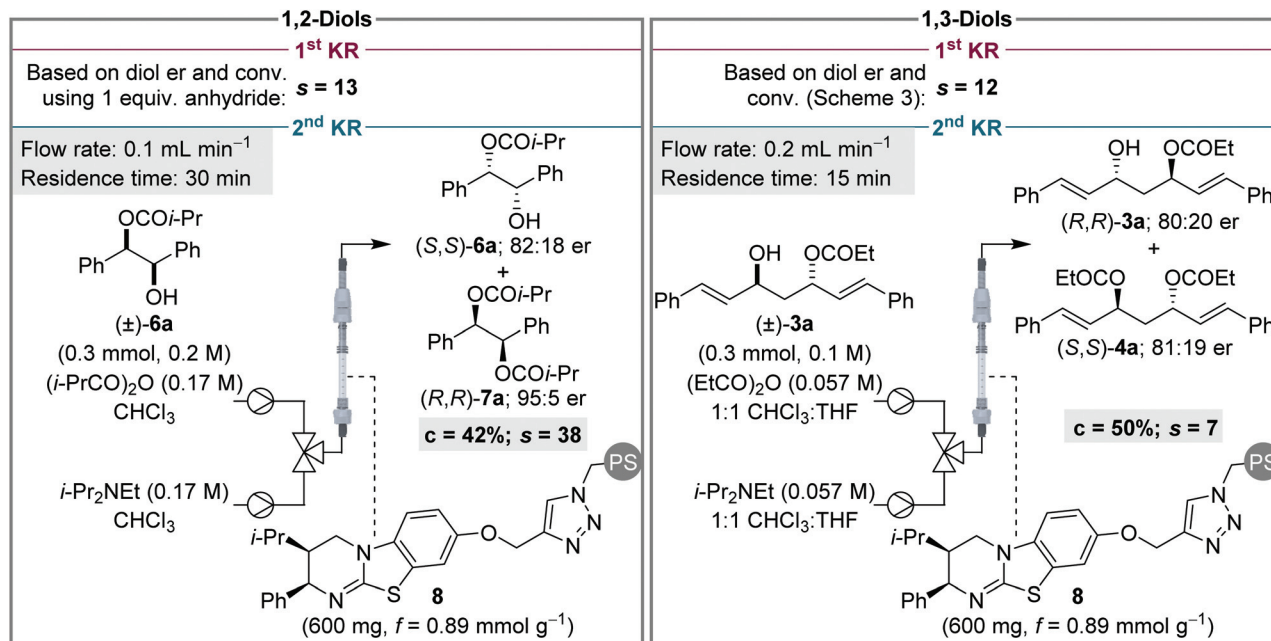
Scheme 5 Reaction scope for C_1-symmetric (±)-*anti*-1,3-diols. [a] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] dr given is *anti* : *syn* ratio of diastereomers. er shown corresponds to *anti* diastereomer.
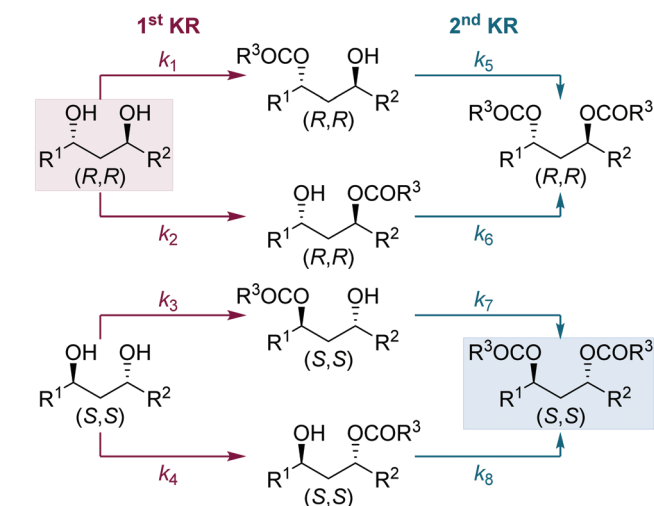
Scheme 4 Double organocatalytic kinetic resolution of C_1-symmetric (±)-*anti*-1,3-diols.

Scheme 6 Assessment and comparison of s values for individual KR steps for the sequential KR of both (±)-1,2- and (±)-1,3-diols.

participates in the first step, and that its er is unaffected by the KR of the monoester. Due to the high conversion required for the sequential KR of (±)-*syn*-1,2-diols, the s value calculated for the 1st KR would be very inaccurate and therefore the sequential KR was repeated using 1 equiv. of anhydride.[16] The s value for the 2nd KR is more conveniently assessed by performing a simple KR of a racemic sample of monoester. For the sequential KR of (±)-*syn*-1,2-diols, the s values for the 1st and 2nd KR steps were calculated as 13 and 38, respectively, demonstrating the 2nd KR step is significantly more selective than the 1st KR. This trend is in keeping with the sequential KR process using the homogenous catalyst,[8,12a] albeit the magnitude of the s values in flow are slightly lower than observed in batch. For the KR of (±)-*anti*-1,3-diols, the opposite relationship between the two KR steps was observed, with the s values for the 1st and 2nd KR steps calculated as 12 and 7, respectively, demonstrating the 1st KR step is more selective. This subtle difference between the KR of 1,2- and 1,3-diols, in addition to the difference in product distribution obtained due to different overall rate constants for diol and monoester acylation, highlights how appreciation of Horeau's pioneering work and insight is essential for understanding these sequential KR processes. It is also notable that although none of the individual s values are particularly high (*e.g.* >50), the products are still obtained in highly enantioenriched form due to the operation of the additive Horeau amplification.

Conclusions

In conclusion an isothiourea-catalysed sequential kinetic resolution of (±)-1,2-*syn*-diols and (±)-1,3-*anti*-diols in continu-

ous flow has been presented. Excellent results have been obtained for both processes, allowing isolation of diol, diester, and in some cases monoester products in excellent enantiopurity and yield. It is notable that the developed procedure has been conducted at room temperature, in place of the low temperatures typically used when using the homogeneous version of the catalyst.[7,8,17] The use of room temperature makes the process operationally simple to perform, whilst the use of a continuous flow system simplifies catalyst recovery and recycling to improve the overall sustainability of the process. Moreover, the same packed bed reactor loaded with immobilised HyperBTM resin was used for all optimisation and reaction scope experiments reported in this manuscript, without loss in efficiency.[18] This equates to more than 100 h operation time using the same catalyst and demonstrates the highly recyclable nature of this immobilised organocatalyst.[19]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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