Isothiourea-Catalysed Sequential Kinetic Resolution of Acyclic (±)-1,2-Diols

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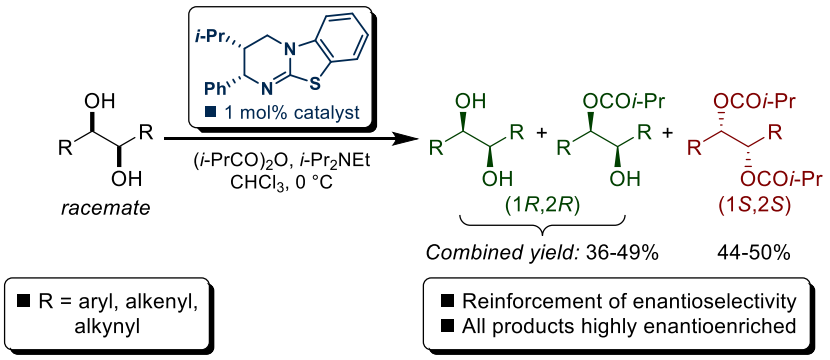

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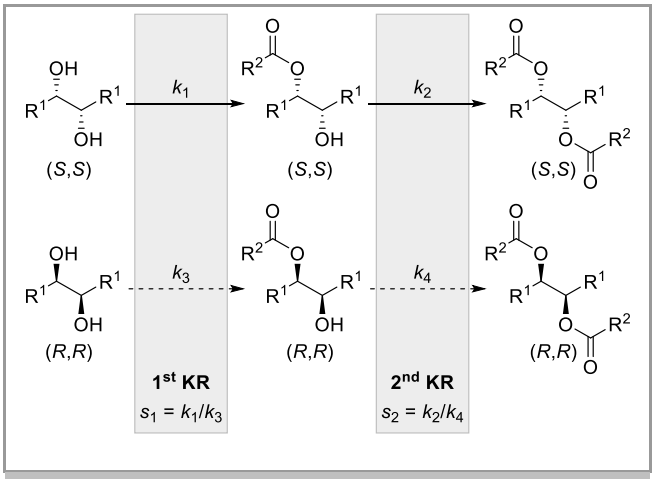
Abstract The isothiourea-catalysed acylative kinetic resolution of a range of acyclic (±)-1,2-diols is reported using 1 mol% of catalyst under operationally-simple conditions. Significantly, the bifunctional nature of (±)-1,2-diols was exploited in a sequential double kinetic resolution, in which both kinetic resolutions operate synergistically to provide access to highly enantioenriched products. The principles that underpin this process are discussed, and selectivity factors for the individual kinetic resolution steps are reported in a model system.

Key words Kinetic Resolution; Isothiourea; (±)-1,2-Diols; Enantioselective Acylation

Chiral 1,2-diols are important intermediates in organic synthesis; are present in a range of bioactive compounds; and have found application as chiral auxiliaries, ligands and organocatalysts.[1] The most common approaches to access chiral 1,2-diols include enantioselective Sharpless dihydroxylation of alkenes,[1a,2] pinacol coupling of aldehydes,[1a,3] reduction of ketones[1a,4] and hydrolysis of epoxides.[1a,5] Although incredibly powerful, these methods are generally reliant on the use of toxic or expensive transition metals as stoichiometric reagents or catalysts. The organocatalytic kinetic resolution (KR) of (±)-1,2-diols therefore represents a potentially-attractive alternative.[6] KR processes provide access to enantioenriched compounds with unrivalled control of enantiopurity through simply modulating the reaction conversion.[7] In addition, products from enantioselective synthetic methods are often only obtained as a scalemic mixture, and therefore a suitable KR can also be applied as a subsequent complementary process to improve product enantiopurity.

The acylative KR of C_2-symmetric (±)-1,2-diols embodies an interesting class of KRs, where, by virtue of the bis-functionality of the substrate, two sequential KR processes can operate (Scheme 1).[8] Where both KRs display the same sense of enantiodiscrimination (e.g. $k_1 > k_3$ and $k_2 > k_4$), the enantiomer of monoester preferentially formed from the first KR is rapidly consumed in the second KR. This process is related to the principles of Horeau amplification,[9] and leads to the final diester product being obtained in highly enantioenriched form. By exploiting this effect, highly enantioenriched compounds can be obtained even if each individual KR step displays only moderate selectivity.

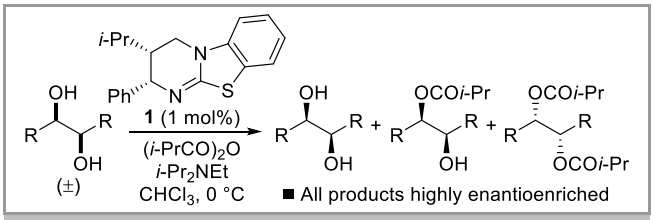


Scheme 1 Sequential kinetic resolution (KR) of C_2-symmetric (±)-1,2-diols

To date, there have been four approaches reported for the organocatalytic acylative KR of C_2-symmetric (±)-1,2-diols.[10] In each of these examples only minimal formation of the diester product was observed, and therefore these methods could be simply considered as a single KR process (i.e. $k_1 > k_3 >> k_2 \approx k_4$). The efficiency of these KRs was therefore reported by only calculating the selectivity factor (s)[11] of the 1st KR process. Fujimoto reported the first of these processes using a bifunctional phosphinite-derived cinchona alkaloid catalyst.[10a]

The KR of a small selection of cyclic and acyclic diols was achieved with up to excellent selectivity (6 substrates, *s* = 11 to > 200). Schreiner has since published a series of seminal studies on the KR of cyclic (±)-1,2-diols using oligopeptide catalysts (7 substrates, *s* = 4 to > 50);[10b–g] whilst Takasu and Yamada have demonstrated the successful use of NHC redox catalysis for the KR of cyclic (±)-1,2-diols (5 substrates, *s* = 18 to > 200).[10h,i] Arguably the most general method for the KR of (±)-1,2-diols was reported recently by Suga.[10j,k] In this work, a bifunctional chiral DMAP derivative was applied for the KR of a broad range of cyclic and acyclic (±)-1,2-diols with up to excellent selectivity (22 substrates, *s* = 2 to 180). The selective mono-acylation reported in these literature examples, although impressive, negates the opportunity to use a sequential KR process to enhance the enantiopurity of the products in both antipodal series.

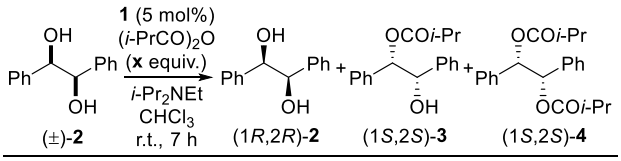
Lewis basic isothioureas have emerged as versatile catalysts for the acylative KR of primary,[12] secondary[13] and tertiary alcohols[14] and the acylative desymmetrisation of *meso*-diols,[15] amongst other applications.[16] Recently, isothiourea catalysis has also been applied for the acylative KR of (±)-1,3-diols[17] and axially-chiral biaryl diols.[18] Herein we report the development of the catalytic acylative KR of C_2-symmetric acyclic (±)-1,2-diols using HyperBTM **1**, in which a synergistic sequential KR process is exploited to enable the highly efficient separation of the 1,2-diol enantiomers (Scheme 2).



Scheme 2 This work: Isothiourea-catalysed KR of C_2-symmetric acyclic (±)-1,2-diols

Initial studies focussed on the KR of (±)-1,2-diphenylethane-1,2-diol **2**[19] using isobutyric anhydride as the acyl donor unit and HyperBTM **1** as the isothiourea catalyst (Table 1).[20] Using 0.55 equivalents of isobutyric anhydride allowed isolation of diol (1*R*,2*R*)-**2** and monoester (1*S*,2*S*)-**3** in good enantiopurity, along with a small quantity of essentially enantiopure diester (1*S*,2*S*)-**4** (Table 1, entry 1). This result indicated that both KR processes were in operation, and therefore we attempted to exploit this sequential KR by driving the reaction to higher conversion through increasing the equivalents of isobutyric anhydride. Using 1 equivalent of isobutyric anhydride provided both diol (1*R*,2*R*)-**2** and diester (1*S*,2*S*)-**4** in very high enantiopurity (99:1 er), although the major reaction component (40%) was monoester (1*S*,2*S*)-**3**, which was isolated with low enantiopurity (65:35 er) (entry 2). Increasing the equivalents of isobutyric anhydride to 1.5 provided 51% conversion to diester (1*S*,2*S*)-**4** (97:3 er), with the isolated diol **2** and monoester **3** both enriched in the (1*R*,2*R*) enantiomer (both > 98:2 er) (entry 3). These results demonstrate the elegance of using a sequential KR process for the highly-efficient separation of enantiomers.

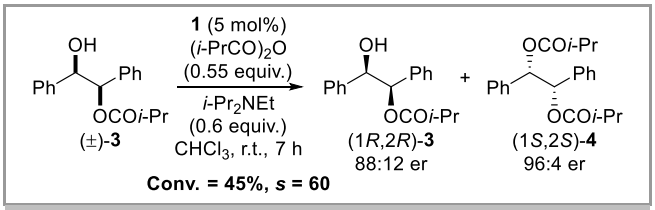
Table 1 Reaction optimisation I: Variation of anhydride equivalents



Entry	x	Ratio[a]	**2** er[b] (1*R*,2*R*):(1*S*,2*S*)	**3** er[b] (1*S*,2*S*):(1*R*,2*R*)	**4** er[b] (1*S*,2*S*):(1*R*,2*R*)
1	0.55	54:41:5	83:17	88:12	> 99:1
2	1.0	36:40:24	99:1	65:35	99:1
3	1.5	13:36:51	> 99:1	2:98	97:3

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product;
[b] Determined by HPLC analysis using a chiral support.

To provide further insight into this process, *s* values for the individual KR steps were calculated. An *s* value for the KR of (±)-1,2-diphenylethane-1,2-diol **2** was evaluated based on the data obtained using 0.55 equivalents of isobutyric anhydride (Table 1, entry 1). Using the enantiomeric purity of the recovered diol, and the reaction conversion determined by ^{1}H NMR spectroscopy, an *s* value of 16 was calculated for this 1st KR step.[21] The *s* value of the 2nd KR process was simply determined by performing the KR of (±)-monoester **3** (Scheme 3). This KR provided an *s* value of 60, demonstrating that the 2nd KR is significantly more selective than the 1st KR. Both KR steps displayed selectivity for acylation of the (1*S*,2*S*) enantiomer of substrates **2** and **3**, confirming the synergistic nature of the overall sequential KR process. These results directly contrast the work of Suga on the KR of (±)-1,2-diols, where selectivity was solely attributable to a highly selective 1st KR, with essentially no operation of, or selectivity associated with, the 2nd KR.[10j]



Scheme 3 KR of racemic monoester (±)-**3**

These *s* values were then applied in the SeKiRe software, developed by Faber,[8g] to simulate the variation in enantioenrichment of the diol, monoester and diester over the course of the reaction (Figure 1).[22] Plotting conversion to diester **4** on the x-axis provides insight into how varying the reaction conversion, through modulation of the equivalents of anhydride used, affects the enantioenrichment of each reaction component. It also provides a useful visual guide to show how the level of enantioenrichment, and the absolute configuration, of the monoester **3** is particularly sensitive to reaction conversion. For example, using this simulation the change in the configuration of the isolated monoester **3** from the (1*S*,2*S*)-enantiomer (Table 1, entries 1 and 2), to the (1*R*,2*R*)-enantiomer (Table 1, entry 3), can be understood. The complex kinetic scenario of this sequential KR clearly highlights the challenge associated with direct comparison between reactions run under different conditions and to different conversions.

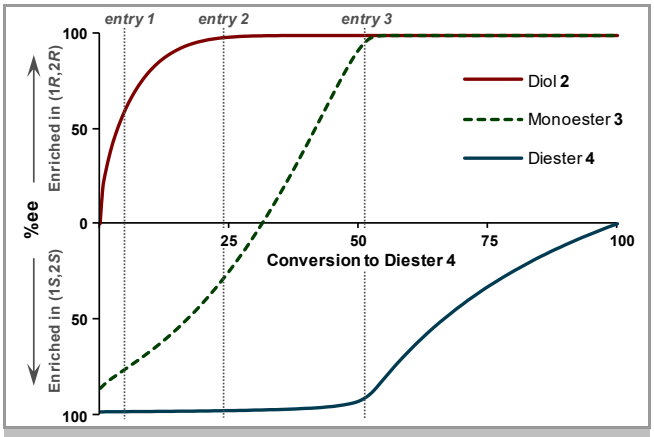
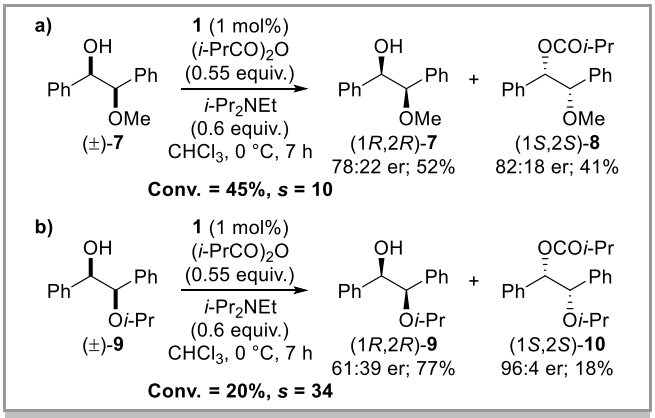


Figure 1 Simulation of evolution of %ee of diol **2**, monoester **3** and diester **4** over the course of the sequential KR at room temperature (entry numbers refer to Table 1)

Further reaction optimisation was targeted through variation of the isothiourea catalyst, reaction solvent and temperature (Table 2). As demonstrated above, the calculation of *s* values for both KR processes is a relatively labor intensive process. It was therefore considered to be impractical to calculate these values for each set of conditions during reaction optimisation. It has previously been proposed that the overall selectivity of a sequential KR can be represented by using the conversion to, and enantiomeric purity of, the final product to calculate the *s* value that would be required in a hypothetical single step KR to give the product with the observed enantiopurity.[8d,e,f,23] Whilst this approach may allow more straightforward comparison between experiments, we found this value to be dependent on reaction conversion and therefore did not consider it as a meaningful metric in this case.[24]

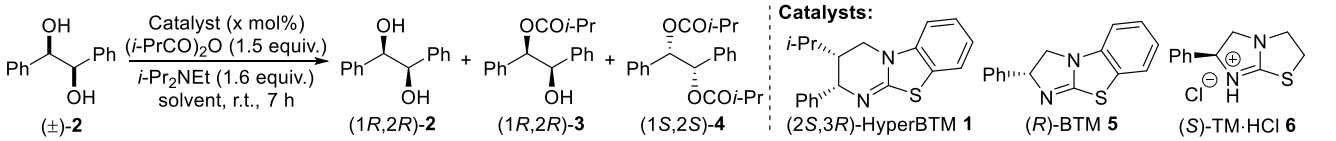
Reaction optimisation was therefore assessed by aiming for ~50% conversion to diester, and comparing the enantiopurity of the diester. Using this approach, alternative isothiourea catalysts, BTM **5** and tetramisole **6**, gave useful product selectivities but were considered to be less selective than HyperBTM **1** (Table 2, entries 2–3). Studying the KR using HyperBTM **1** in a range of solvents demonstrated that THF provided low selectivity and conversion (entry 4); whilst PhMe, EtOAc, MeCN and DMSO provided good conversion and high enantiopurity of the diester (entries 5–8), however the original results using $CHCl_3$ as solvent were still considered to be optimal. Further studies showed that by performing the KR in $CHCl_3$ at 0 °C, and using 1 mol% HyperBTM **1**, provided 51% conversion to diester and gave all three products in highly enantioenriched form (entry 9). Overall this process allowed isolation of (1*S*,2*S*)-diester **4** in 50% yield and 97:3 er and the (1*R*,2*R*)-enantiomer of both the diol **2** and monoester **3** in a combined 39% yield and > 99:1 er. Under the optimised conditions at 0 °C, the individual *s* values for each KR step were also measured.[22] Performing the KR of (±)-1,2-diphenylethane-1,2-diol **2** using 0.55 equivalents of anhydride, to limit reaction conversion, allowed calculation of the *s* value for the 1st KR as 36. The KR of (±)-monoester **3** was used to calculate an *s* value of 80 for the 2nd KR. The fact that both of these *s* values were higher than those calculated previously at room temperature confirmed the advantage of performing this synergistic sequential KR process at 0 °C.

At this point we were intrigued to investigate further (i) the influence of the diol motif on the selectivity of the KR and (ii) the origin of the higher selectivity obtained in the 2nd KR process. It has been demonstrated previously for the KR of simple benzylic alcohols that substrates bearing larger α-substituents are generally resolved with higher *s* values.[13] To provide some insight towards answering both questions outlined above, the KRs of sterically-differentiated mono-alkylated derivatives of 1,2-diphenylethane-1,2-diol, (±)-**7** and (±)-**9**, were performed (Scheme 4). The KR of (±)-**7**, bearing the small methyl substituent, was achieved with an *s* value of 10; whilst the KR of (±)-**9**, bearing the larger isopropyl substituent, was achieved with an *s* value of 34. These experiments



Scheme 4 KRs of model monoalkylated compounds (±)-**7** and (±)-**9**

Table 2 Reaction optimisation II: Variation of catalyst, solvent and temperature



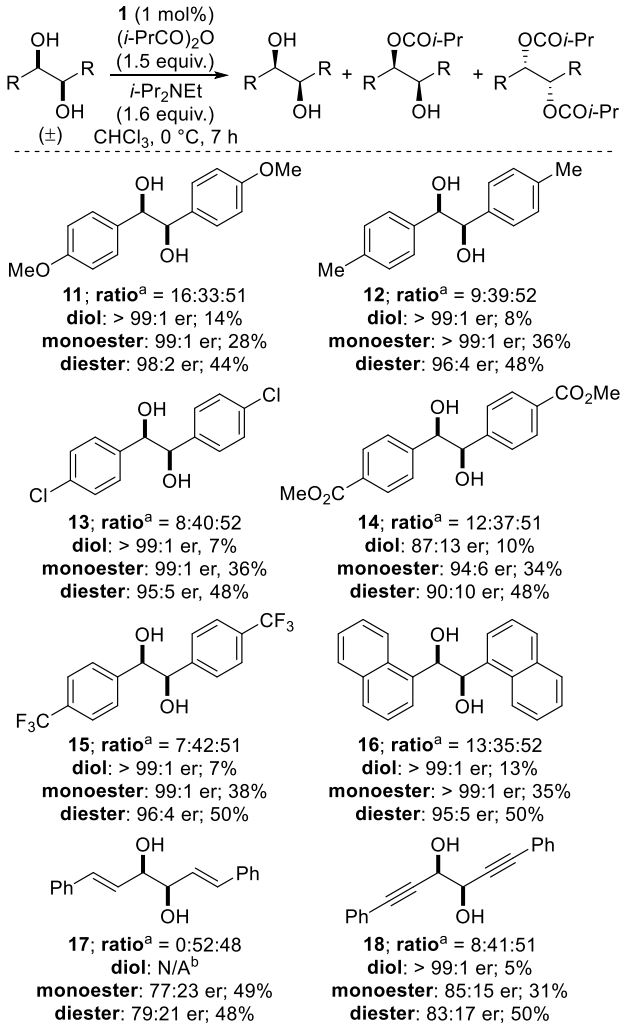
Entry	Catalyst (mol%)	Solvent	Product Ratio (**2**:**3**:**4**)[a]	**2** er (1*R*,2*R*):(1*S*,2*S*)[b]	**3** er (1*R*,2*R*):(1*S*,2*S*)[b]	**4** er (1*S*,2*S*):(1*R*,2*R*)[b]
1	**1** (5)	$CHCl_3$	13:36:51	> 99:1	98:2	97:3
2	**5** (5)	$CHCl_3$	7:40:53	> 99:1	99:1	94:6
3	**6** (5)	$CHCl_3$	18:42:40	1:99	30:70	6:94
4	**1** (5)	THF	49:36:15	94:6	10: 90	93:7
5	**1** (5)	PhMe	12:34:54	> 99:1	> 99:1	92:8
6	**1** (5)	EtOAc	10:36:54	> 99:1	> 99:1	91:9
7	**1** (5)	MeCN	14:33:53	> 99:1	> 99:1	93:7
8	**1** (5)	DMSO	28:20:52	> 99:1	99:1	96:4
9[c]	**1** (1)	$CHCl_3$	13:36:51	> 99:1 (8%)[d]	> 99:1 (31%)[d]	97:3 (50%)[d]

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product; [b] Determined by HPLC analysis using a chiral support; [c] Reaction temperature 0 °C; [d] Isolated yield.

highlight a beneficial effect of increasing the size of the α-substituent, however both *s* values were lower than those obtained for the KR of diol (±)-**2** and monoester (±)-**3**. This suggests that the additional hydrogen bond donor and/or acceptor abilities of the diol and monoester may also have an influential role in enhancing the selectivities observed in this sequential KR.

Finally, the generality of this sequential KR process was investigated by using a selection of electronically- and sterically-differentiated (±)-1,2-diols (Table 3).[20] (±)-1,2-Diarylethane-1,2-diol derivatives **11**–**16** bearing both electron-donating and -withdrawing substituents on the aryl units were resolved with good conversion and, with the exception of dimethyl ester-substituted derivative **14**, excellent selectivity. In general, the KR of derivatives bearing electron-donating groups provided products of higher enantiomeric purity than the KR of substrates bearing electron-withdrawing groups. These observations are consistent with selectivity trends observed for the KR of secondary benzylic alcohols, and can be rationalised by the more electron-rich aromatic substituents providing more effective stabilisation of the positively-charged acylated-catalyst intermediate in the acylation transition state.[13h] It was therefore hypothesised that this method may be extended for the KR of other (±)-1,2-diols bearing adjacent π-donor systems.[13a,b,g,h,l] The KRs of allylic and propargylic diols **17** and **18** were achieved with moderate selectivity, however these chiral diols would be challenging to synthesise through alternative enantioselective methods such as dihydroxylation. In conclusion, we have reported a synergistic sequential acylative KR of (±)-1,2-diols using Lewis base organocatalysis, which provides access to C_2-symmetric 1,2-diols in highly enantioenriched form. Optimal selectivities were obtained by using a readily prepared and commercially-available isothiourea Lewis base catalyst (HyperBTM)[25,26] and reagents (isobutyric anhydride, Hünig's base) at 0 °C, making this KR process operationally-simple to perform.[27]

Table 3 Reaction scope



[a] Ratio of diol:monoester:diester determined by ^{1}H NMR spectroscopic analysis of the crude reaction product; [b] N/A = not applicable

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

YES (this text will be updated with links prior to publication)

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(11) 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 ($s = k_{fast}/k_{slow}$) and is calculated using the reaction conversion and either the ee of the recovered substrate {$s = \ln[(1-c)(1-ee_{substrate})] / \ln[(1-c)(1+ee_{substrate})]$} or ee of the reaction product {$s = \ln[(1-c(1+ee_{product})] / \ln[(1-c(1-ee_{product})]$}. See references 7a and 7c for more details. For biocatalysed processes an analogous metric, *E* (enantiomeric ratio), is used, see reference 7b.

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(19) **(±)-1,2-Diphenylethane-1,2-diol (2)**
THF (4 equiv.) was added to a solution of $TiCl_4$ (1 equiv.) in anhydrous CH_2Cl_2 (0.5 M) under an N_2 atmosphere at r.t. and was allowed to stir for 30 seconds. Zinc powder (0.5 equiv.) was added, and after a further 30 seconds *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.5 equiv.) was added. After 30 seconds, a solution of benzaldehyde (1 equiv.) in CH_2Cl_2 (1 M) was added and the mixture allowed to stir at r.t. for 1 h. HCl (1 M) was added and the mixture extracted with EtOAc (3 times). The combined organic fractions were washed with brine, dried (Na_2SO_4), filtered and concentrated to give a residue, which was purified by Biotage flash silica column chromatography (0→40% EtOAc in hexane) to give a colourless solid, which was further purified by recrystallisation: the material was dissolved hot PhMe:hexane (1:1), allowed to cool to r.t. then cooled in a freezer overnight. The product was filtered and washed with cold hexane to give (±)-1,2-diphenylethane-1,2-diol as colourless crystals (single diastereoisomer, 72%). mp 121 °C [Lit.[25] mp 121 °C]; ^{1}H NMR (500 MHz, $CDCl_3$) δH: 2.84 (2H, s, O_H), 4.72 (2H, s, *H*COH), 7.10–7.16 (4H, m, Ar*H*), 7.21–7.27 (6H, m, Ar*H*). Spectral data in accordance with the literature.[28]

(20) **General procedure for the KR of (±)-1,2-diols**
HyperBTM **1** (x mol%), (*i*-PrCO)$_2$O (*y* equiv.) and *i*-Pr$_2$NEt (*z* equiv.) were added to a solution of the appropriate (±)-1,2-diol (1 equiv.) in the given solvent (0.2 M) and at the given temperature, and the mixture allowed to stir for 7 h. HCl (1 M) was added and the mixture extracted with EtOAc (3 times). The combined organic fractions were washed sequentially with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated to give a residue, which was purified by Biotage flash silica column chromatography (0→40% EtOAc in hexane) to give the diester, monoester and diol products, which were analysed by HPLC using a chiral support – see Supporting Information for more details.

(21) This *s* value was calculated using $s = \ln[(1-c)(1-ee_{substrate})] / \ln[(1-c)(1+ee_{substrate})]$, and assumes the reaction is irreversible and the er of the diol substrate is exclusively determined by the selectivity associated with the 1st KR process.

(22) See supporting information for more details.

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(26) Both enantiomers are available from Apollo Scientific [(2*S*,3*R*) CAS: 1203507-02-1; (2*R*,3*S*) CAS: 1699751-03-5].

(27) The research data underpinning this publication can be found at: https://doi.org/10.17630/45a265c9-c200-47ef-979d-cb3ed157e4c0.

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