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Acylative Kinetic Resolution of Alcohols Using a Recyclable Polymer-Supported Isothiourea Catalyst in Batch and Flow

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ABSTRACT: A polystyrene-supported isothiourea catalyst, based on the homogeneous catalyst HyperBTM, has been prepared and used for the acylative kinetic resolution of secondary alcohols. A wide range of alcohols, including benzylic, allylic and propargylic alcohols, cycloalkanol derivatives and a 1,2-diol, has been resolved using either propionic or isobutyric anhydride with good to excellent selectivity factors obtained (28 examples, *s* up to 600). The catalyst can be recovered and reused by a simple filtration and washing sequence, with no special precautions needed. The recyclability of the catalyst was demonstrated (15 cycles) with no significant loss in either activity or selectivity. The recyclable catalyst was also used for the sequential resolution of 10 different alcohols using different anhydrides with no cross-contamination between cycles. Finally, successful application in a continuous flow process demonstrated the first example of an immobilized Lewis base catalyst used for the kinetic resolution of alcohols in flow.

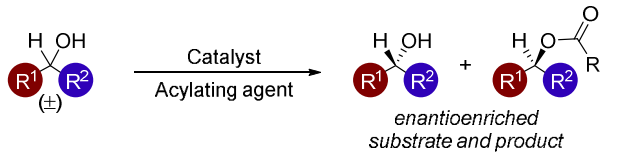
KEYWORDS: *kinetic resolution, isothioureas, Lewis base catalysis, polymer-supported catalysts, catalyst recyclability, acyl transfer reactions, enantioselective catalysis, continuous flow*

INTRODUCTION

Catalytic kinetic resolution (KR) processes allow the separation of a racemate into its two enantiomeric forms through the selective reaction of one enantiomer promoted by a chiral catalyst.[1] The efficiency of a KR is commonly characterized by its selectivity factor (*s*), defined as the rate constant for the fast reacting enantiomer divided by the rate constant for the slow reacting enantiomer ($s = k_{fast}/k_{slow}$).[2] KRs with an *s* of greater than 10 are generally considered to be synthetically useful. The preparation of enantioenriched compounds is of general interest in both academia and industry and as such a tremendous number of KR processes have been devised. Of these methods, the catalytic acylative KR of alcohols is a powerful method to prepare highly enantioenriched alcohols (Scheme 1).[3] Chiral Lewis base catalysis is most commonly applied for this transformation, with a range of excellent catalysts reported for the KR of many classes of secondary alcohols. A current limitation of this method is that the Lewis base catalyst is rarely recovered from the reaction. This is particularly problematic for methods that require high catalyst loadings (> 5 mol%) or use expensive catalysts.

A common strategy to facilitate catalyst recovery is through immobilization on an insoluble solid support.[4] The mild reaction conditions commonly required for organocatalysis makes the use of polymer resins an attractive option due to good chemical stability and efficient swelling in organic solvents. Although many solid-supported organocatalysts have been reported, there are very few examples of application in the acylative KR of alcohols (Scheme 2a).[5] Janda, Anson and Ishihara have used polymer-supported Lewis base catalysts **1**-**3** for the KR of secondary alcohols.[6–8] Although good selectivity factors were obtained for cycloalkanols and *N*-protected

Scheme 1. Catalytic Acylative KR of Secondary Alcohols

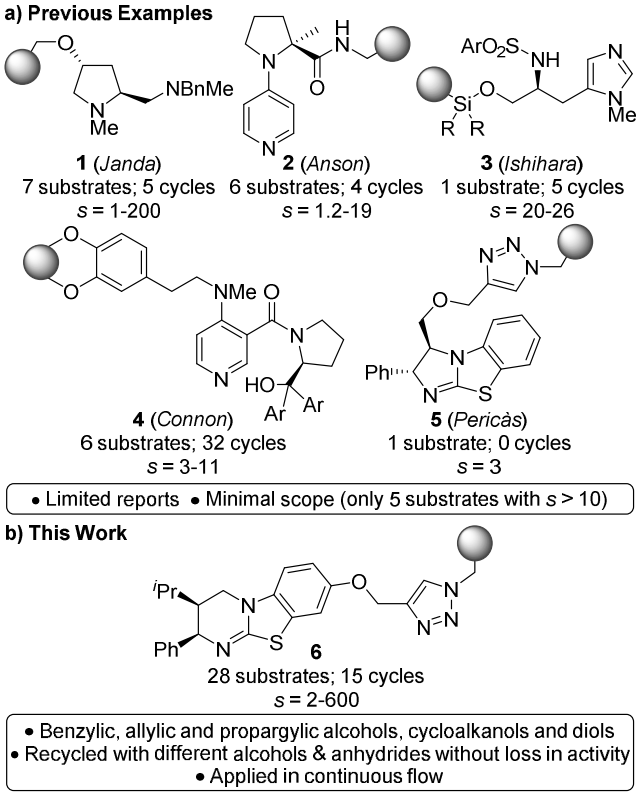


• Enantiodiscrimination requires catalyst recognition and differentiation between R^1 and R^2 (steric or electronic bias)

1,2-aminoalcohols, the resolution of benzylic alcohols was inefficient ($s \leq 2$) and application to other substrate classes was not reported. In all cases the catalysts were recycled up to 5 times, with either none or only minimal catalyst deactivation observed. In an alternative approach, Connon prepared chiral DMAP derivative **4** on the surface of magnetic Fe_3O_4 nanoparticles (Scheme 2a).[9] The catalyst was recycled an impressive 32 times, and used for the resolution of 6 alcohols. Unfortunately the substrate scope was limited to cycloalkanols, and the selectivity factors obtained were generally low (s = 3–11).[10] Additionally, there are currently no examples in which immobilized Lewis base catalysts have been applied for the kinetic resolution of alcohols in a continuous flow process.[11,12]

To address these current limitations, this manuscript reports the development of a recyclable polymer-supported Lewis base catalyst capable of resolving a diverse range of secondary alcohols in both batch and flow. Considering the additional time and cost required to prepare polymer-supported catalysts, we considered catalyst recycling of more than 10 cycles necessary to show acceptable recyclability. In addition, the ideal catalyst would be capable of sequentially resolving different alcohols using different acylating agents without loss in activity or cross-contamination of products.

Scheme 2. Solid-Supported Lewis Base Catalysts used for KR of Alcohols



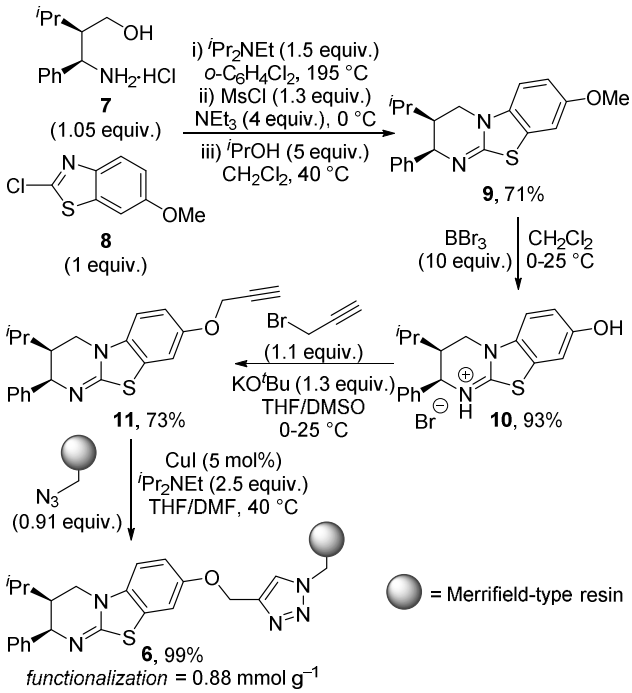
Isothioureas have been successfully applied as Lewis base catalysts for a range of enantioselective processes,[13] building upon Birman's initial application as enantioselective acylation catalysts.[14] They have proven useful in the KR of a wide range of secondary alcohols including benzylic, allylic and propargylic alcohols, cycloalkanols and α-hydroxy alkanoates.[14–16] Recently Pericàs reported the synthesis of the first polymer-supported isothiourea **5**, and applied it as a catalyst for formal [4+2], [2+2] and [8+2] cycloaddition reactions (Scheme 2a).[17] A range of heterocyclic products were obtained in good yields and with excellent diastereo- and enantiocontrol, with the catalyst used in both batch and continuous flow processes. It was noted however that the catalyst was inefficient for the KR of (±)-1-phenylethanol, with only a low conversion and minimal selectivity obtained after an extended reaction time.[17a] This is in contrast to the homogenous variant of this catalyst, benzotetramisole (BTM), which has been successfully applied for this transformation.[14]

An alternative isothiourea catalyst, HyperBTM,[18] developed in our laboratory has also been applied for the KR of benzylic, allylic and propargylic alcohols.[16] Herein we describe the synthesis of a polystyrene-supported variant of the isothiourea catalyst HyperBTM **6**, and demonstrate its application as a catalyst for the KR of a range of secondary alcohols (Scheme 2b). The durability of the catalyst is demonstrated in recycling studies using either the same alcohol and anhydride or different alcohols and anhydrides, and through application in a continuous flow procedure.

RESULTS AND DISCUSSION

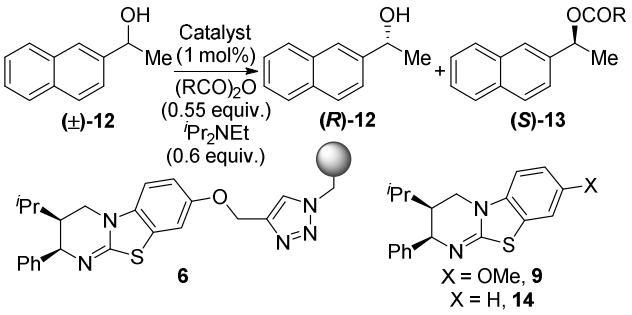
Synthesis of Polystyrene-Supported HyperBTM. The synthesis of a polystyrene-supported variant of HyperBTM **6**, began with the coupling of the HCl salt of (*R*)-2-((*R*)-amino(phenyl)methyl)-3-methylbutan-1-ol **7**[19] with 2-chloro-6-methoxybenzo[*d*]thiazole **8** followed by *in situ* cyclization to give 8-MeO-HyperBTM **9** in 71% yield (Scheme 3). Demethylation, followed by propargylation gave alkyne-substituted HyperBTM derivative **11** (68% over 2 steps), which could be attached to a Merrifield resin-derived azidomethyl polystyrene support by a Cu-catalyzed azide-alkyne cycloaddition reaction.[20] The nitrogen content of polymer **6**, determined by elemental analysis, was used to calculate the functionalization of **6** (0.88 mmol g^{-1}),[21,22] with this value used to determine catalyst loading in all subsequent KRs.

Scheme 3. Synthesis of Polystyrene-Supported HyperBTM 6



Reaction Optimization. Initial studies focused on the KR of a model secondary alcohol, (±)-1-(naphthalen-2-yl)ethan-1-ol **12**, using polystyrene-supported HyperBTM **6** (1 mol%) as catalyst (Table 1). Using propionic anhydride as acyl donor (0.55 equiv.) in chloroform at room temperature resulted in an efficient KR of (±)-**12**, giving 51% conversion within 4 h and a selectivity factor of 44 (entry 1).[23,24] Increasing the steric bulk of the anhydride, from propionic to isobutyric, gave an improved selectivity factor of 80 (entry 2). As the choice of solvent is known to have a significant effect on the swelling properties of polymer supports,[4c] a range of solvents were tested for applicability in the developed KR process (entries 2-7). With the exception of acetonitrile (entry 3) all other solvents provided ideal conversion of ~50%, with chloroform and toluene giving the highest selectivity factors (80 and 70 respectively, entries 2 and 7). Notably, industrially-preferable solvents such as EtOAc also gave good conversion and selectivity (s = 42),[25] however chloroform and toluene were chosen for further optimization. Lowering the reaction temperature to 0 °C further improved selectivity (entries 8–9), with chloroform out-performing toluene in terms of both reaction conversion and selectivity factor (conversion = 47%, s = 100). To provide a direct comparison with homogenous isothiourea catalysts, the KR of (±)-**12** using 8-OMe-HyperBTM **9** and HyperBTM **14** was performed under analogous reaction

Table 1. KR of (±)-12 using Polystyrene-Supported HyperBTM 6: Optimization[a]



Entry	Cat.	R	Solvent	T (°C)	Conv. (%)	12 er[b]	13 er[c]	*s*
1	**6**	Et	$CHCl_3$	r.t.	51	95:5	94:6	44
2	**6**	^{i}Pr	$CHCl_3$	r.t.	50	95:5	96:4	80
3	**6**	^{i}Pr	MeCN	r.t.	36	73:27	92:8	18
4	**6**	^{i}Pr	CH_2Cl_2	r.t.	50	93:7	93:7	38
5	**6**	^{i}Pr	THF	r.t.	50	94:6	95:5	50
6	**6**	^{i}Pr	EtOAc	r.t.	50	93:7	94:6	42
7	**6**	^{i}Pr	PhMe	r.t.	52	98:2	95:5	70
8	**6**	^{i}Pr	PhMe	0	41	83:17	98:2	80
9	**6**	^{i}Pr	$CHCl_3$	0	47	92:8	98:2	100
10	**9**	^{i}Pr	$CHCl_3$	0	52	>99:1	95:5	100
11	**14**	^{i}Pr	$CHCl_3$	0	52	>99:1	95:5	110

[a] Reaction conditions: alcohol (0.2 mmol), Catalyst **6**, **9** or **14** (1 mol%), ^{i}Pr$_2$NEt (0.6 equiv.), anhydride (0.55 equiv.), solvent (0.2 M), 4-7 h. Conversion and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using er of **12** and reaction conversion (see ref. 2), and rounded according to estimated associated errors (see ref. 24). [b] *R*:*S*. [c] *S*:*R*.

conditions (entries 10-11). Both homogenous catalysts gave slightly higher conversion (52%), but essentially equal selectivity (*s* = 100–110), suggesting that the 8-alkoxy substituent and polystyrene support of **6** do not have detrimental effects on catalyst selectivity.

Catalyst Recyclability. Encouraged by the excellent activity and selectivity obtained using polystyrene-supported HyperBTM **6**, the recyclability and robustness of the catalyst was investigated. The catalyst could be recovered by filtration, followed by washing sequentially with $CHCl_3$, MeOH and THF and finally drying under high vacuum for 2 h. Using the KR of **(±)-12** in chloroform at 0 °C for 7 h as standard, the catalyst was recovered and reused in 15 consecutive KRs (Figure 1). Reaction conversion remained very consistent over all 15 cycles (47 ± 3%) indicating the activity of the catalyst remained unaltered, and corresponding to a combined turnover number (TON) of over 700. The selectivity factor was more variable (90 ± 12), however there was no overall loss in selectivity, with the selectivity factor for the 15th cycle essentially equal to that obtained for the 1st cycle. The variability observed in *s* most likely result from a combination of inconsistencies in experimental set-up and catalyst regeneration following each cycle, and the inherent error present when calculating selectivity factors for highly selective KRs.[1,2,24]

Substrate Scope and Limitations. The limited range of secondary alcohols previously resolved using polymer-supported Lewis base catalysts inspired us to probe the scope of the current method. In particular, different classes of structurally-diverse secondary alcohols were targeted. The KR of secondary benzylic alcohols is considered a 'benchmark' reaction for Lewis base catalyzed acylative KR, however previous

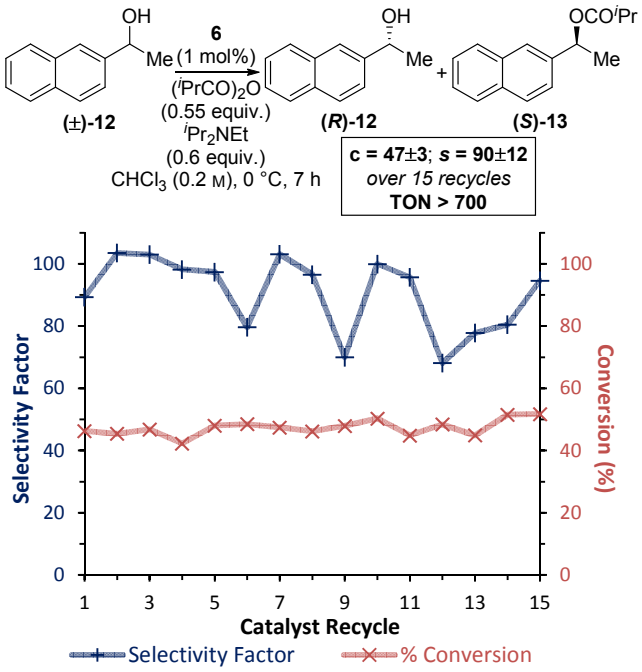
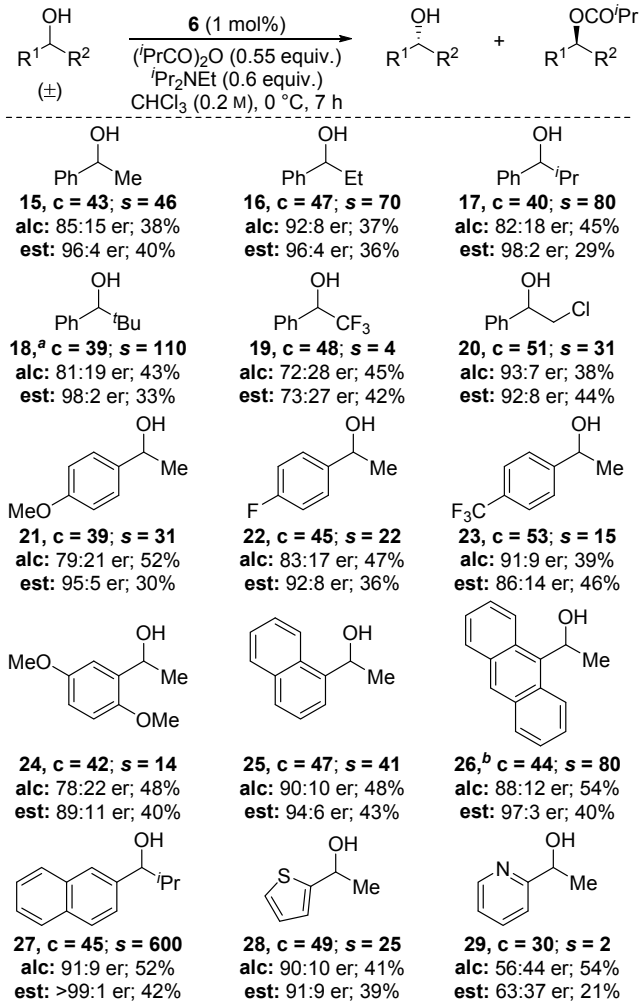


Figure 1. Recycling of **6** for the KR of **(±)-12**

polymer-supported variants have proved ineffective for this substrate class (highest reported *s* = 3). The KR of benzylic alcohols bearing various substituents at the α-position and on the aromatic ring was therefore investigated (Table 2). Applying the previously optimized conditions, the KR of (±)-1-phenylethanol **15** was achieved with good conversion and selectivity (*s* = 46). Increasing the steric bulk of the α-alkyl substituent (**15**→**18**) resulted in improved selectivity, although increased catalyst loading (5 mol%) and reaction time (30 h) were required for good conversion with *t*-Bu-substituted benzylic alcohol **18**. Although α-trifluoromethyl benzyl alcohol **19** was resolved with only low selectivity, the α-chloromethyl-substituted analogue **20** was resolved with a good *s* of 31. The introduction of both electron-donating (OMe, **21**) and withdrawing substituents (F, CF_3, **22** and **23**) on the aromatic ring was tolerated, however lower selectivity factors were obtained for substrates **22** and **23** bearing electron-withdrawing groups. This is in keeping with previous reports of isothiourea-catalyzed KR of alcohols and is consistent with a π-cation interaction between the benzylic alcohol and the acyl isothiouronium playing a significant role in substrate recognition.[15g] *ortho*-Substitution on the aromatic ring was also tolerated, with substrates **24**–**26** resolved with good selectivity (*s* = 14–80), although the KR of sterically-hindered **26** did require resolution at room temperature to obtain good conversion. An exceptionally high selectivity factor of 600 was obtained for the resolution of 2-naphthyl derivative **27**. The KR of heteroaromatic alcohols was also briefly studied. 2-Thienyl alcohol **28** was resolved with good selectivity (*s* = 25), however 2-pyridyl analogue **29** was resolved with very poor selectivity (*s* = 2), highlighting a current limitation.

The substrate scope was extended to allylic and propargylic alcohols, with π-cation interactions between the substrate and catalyst again expected to enable enantiodiscrimination (Table 3). Cinnamyl alcohol derivative **30** underwent effective KR (*s* = 17).[23] The resolution of a potentially-challenging aryl-alkenyl alcohol **31**, where the catalyst would be required to

Table 2. KR of Benzylic Alcohols

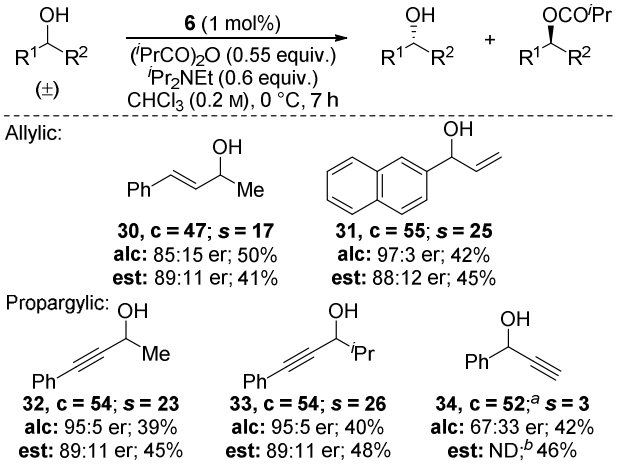


Conversion and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 2) , and rounded according to estimated associated errors (see ref. 24). Alcohol er given as *R*:*S*, ester er given *S*:*R*. [a] 5 mol% **6**, r.t., 30 h. [b] r.t.

differentiate between two π-systems, was also attempted.[16b] An efficient KR was still achieved (*s* = 25), with the enantiodiscrimination obtained consistent with the naphthalene unit acting as the dominant recognition motif in this case.[23,16b] Propargylic alcohols **32** and **33** were also resolved with good selectivity (*s* = 23–26).[23] The resolution of an aryl-alkynyl alcohol **34** was also attempted to again probe catalyst differentiation between two π-systems. In this example very low selectivity was obtained (*s* = 3), consistent with the respective π-cation interactions between the phenyl and acetylene units and an acyl-isothiouronium intermediate being comparable in magnitude.[23]

The KR of cycloalkanols was next studied (Table 4). Previous isothiourea-catalyzed methods have demonstrated the need for an adjacent substituent (generally aryl) which can interact with the catalyst to provide effective enantiodiscrimination.[15b,c] With this pre-requisite in mind, the resolutions of *trans*- and *cis*-phenylcyclohexanol **35** and **37** were first studied. Consistent with the work of Birman,[15b] propionic anhydride gave improved conversion and selectivity factors relative to isobutyric anhydride.[22] Both diastereoisomers underwent effective KR, with *trans*-phenylcyclohexanol **35** giving the higher selectivity factor (*s* = 50).[26] Indole-substituted

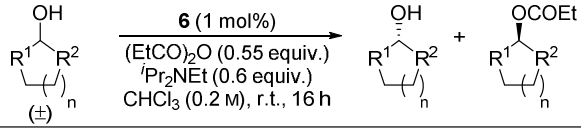
Table 3. KR of Allylic and Propargylic Alcohols



Conversion and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 2). Alcohol er given as *R*:*S*, ester er given *S*:*R*. [a] Conversion determined by ^{1}H NMR spectroscopy. [b] er could not be determined by chiral HPLC or GC.

cyclohexanol **39** was also efficiently resolved (*s* = 50), whilst reducing the ring size to *trans*-phenylcyclopentanol **41** was also well tolerated (*s* = 70). Interestingly, for the resolution of *trans*-phenylcyclopentanol **41**, isobutyric anhydride proved the optimal acyl donor, with propionic anhydride providing significantly lower selectivity (*s* = 36).[22] An acyclic analogue,

Table 4. KR of Cycloalkanol derivatives



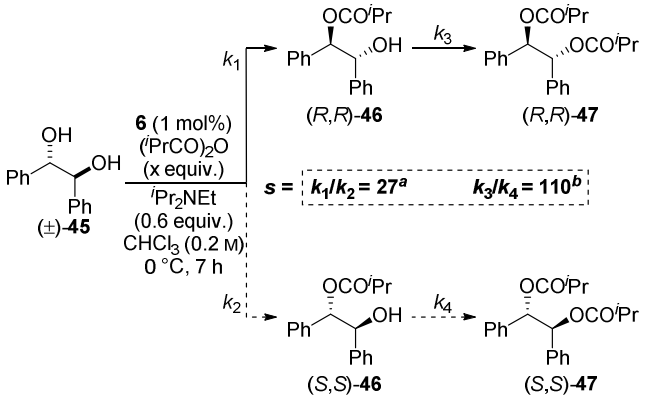
substrate	conv	alcohol	ester	s
(±)-**35**	54	(1*R*,2*S*)-**35** 99:1 er; 42%	(1*S*,2*R*)-**36** 91:9 er; 50%	50
(±)-**37**	50	(1*R*,2*R*)-**37** 84:16 er; 38%	(1*S*,2*S*)-**38** 84:16 er; 46%	11
(±)-**39**	46	(1*R*,2*S*)-**39** 89:11 er; 48%	(1*S*,2*R*)-**40** 96:4 er; 39%	50
(±)-**41**[a,b]	51	(1*R*,2*S*)-**41** 98:2 er; 45%	(1*S*,2*R*)-**42** 95:5 er; 43%	70
(±)-**43**[b]	47	(*R*)-**43** 77:23 er; 45%	(*S*)-**44** 80:20 er; 38%	7

Conversion and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 2), and rounded according to estimated associated errors (see ref. 24). [a] (^{i}PrCO)$_2$O (0.55 equiv.) used in place of (EtCO)$_2$O. [b] 7 h

homobenzylic alcohol **43**, was resolved with low selectivity (*s* = 7), suggesting that the conformational rigidity of the cycloalkanol derivatives may be beneficial for effective recognition by the catalyst.[15g]

The KR of a 1,2-diol, (±)-1,2-diphenylethane-1,2-diol **45**, was next investigated (Table 5). Under standard conditions a mixture of diol **(*S*,*S*)-45**,[27] monoester **(*R*,*R*)-46** and diester **(*R*,*R*)-47** was obtained (entry 1). The selectivity factor for the KR of diol **(±)-45** was determined to be 27,[28] however, diester **(*R*,*R*)-47** was obtained in highly enantioenriched form (99:1), indicating an amplification in enantiopurity through operation of a second KR of monoester **46**. A control KR using racemic monoester **(±)-46** revealed this second KR proceeds with very high selectivity (conversion = 47%, *s* = 110) and the same sense of enantiodiscrimination,[22] consistent with the observed amplification in enantiopurity of diester **(*R*,*R*)-47**. This effect was exploited for the KR of diol **(±)-45** by using 1.5 equiv. of anhydride to increase reaction conversion and allow the isolation of highly enantioenriched diol **(*S*,*S*)-45** and diester **(*R*,*R*)-47** (both > 99:1 er) (entry 2). A similar effect was recently reported in the isothiourea-catalysed KR of 1,3-diols,[29a] however, to the best of our knowledge, this is the first example of an isothiourea-catalyzed KR of a 1,2-diol.[29,30]

Table 5. KR of a 1,2-Diol

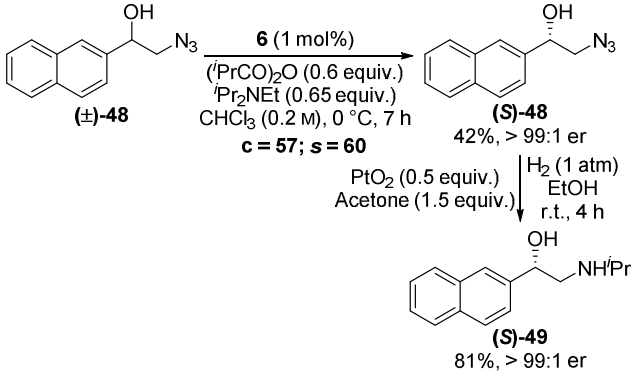


Entry	(^{i}PrCO)$_2$O equiv.	**45** (*R*,*R*:*S*,*S*) (yield, %)	**46** (*R*,*R*:*S*,*S*) (yield, %)	**47** (*R*,*R*:*S*,*S*) (yield, %)
1	0.55	16:84 er (54%)	89:11 er (34%)	> 99:1 er (7%)
2	1.5	< 1:99 er (20%)	18:82 er (27%)	> 99:1 er (43%)

Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 2), and rounded according to estimated associated errors (see ref. 24). [a] *s* calculated based on er of recovered diol from entry 1, and reaction conversion determined by ^{1}H NMR spectroscopic analysis of the crude reaction products. [b] *s* calculated by performing isolated KR of (±)-**46**.

The developed method was next applied to the enantioselective synthesis of the (*S*)-enantiomer of β-blocker pronethalol **(*S*)-49** (Scheme 4).[31] The KR of 1,2-azidoalcohol **48** was achieved with an excellent *s* of 60, allowing recovery of **(*S*)-48** in 42% yield and > 99:1 er. Subsequent reduction of the azide and *in situ* reductive amination of acetone provided (*S*)-pronethalol in 81% yield. The excellent selectivity factor obtained for the KR of 1,2-azidoalcohol **48** indicates this method could be successfully applied more generally to the synthesis of enantiopure 1,2-aminoalcohols.

Scheme 4. KR of 1,2-Azidoalcohol 48 and Synthesis of (*S*)-Pronethalol (*S*)-49



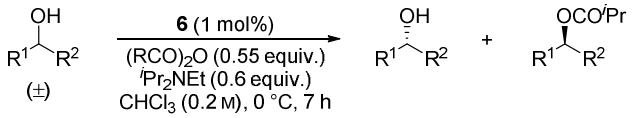
Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 2), and rounded according to estimated associated errors (see ref. 24).

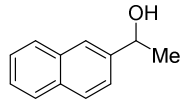
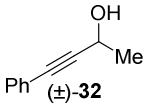
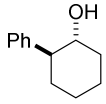
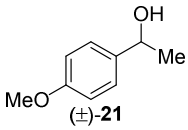
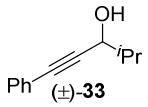
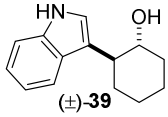
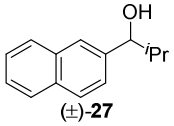
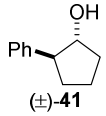
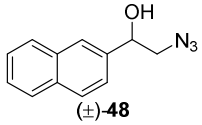
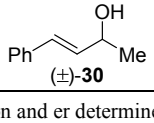
Having demonstrated the KR of a range of classes of secondary alcohols, the recyclability of polystyrene-supported HyperBTM **6** was finally tested for the sequential KR of 10 different alcohols (Table 6). Significantly either propionic or isobutyric anhydride could be used without any cross-contamination between cycles. Generally, slightly lower conversions and selectivity factors were obtained compared to the results obtained using fresh catalyst (data shown italicized in square brackets), however there was no overall drop in activity over the course of the cycling, with the final cycle (entry 10) providing a similar conversion and identical selectivity factor to that obtained using fresh catalyst.

Application in Continuous Flow. The exceptional recyclability and versatility of polystyrene-supported catalyst **6** prompted application in a continuous flow set-up. Polystyrene-supported catalyst **6** (600 mg, 0.54 mmol) was swollen in $CHCl_3$ in a size-adjustable, medium pressure borosilicate glass column to create a packed bed reactor. A cooling jacket was attached to maintain a constant reaction temperature and solutions of racemic alcohol (0.4 M) and a mixture of anhydride (0.24 M) and base (0.26 M) in $CHCl_3$ were passed through the vertical packed bed reactor using a syringe pump. Improved selectivity factors were obtained at 0 °C relative to room temperature; and a combined flow rate of 0.1 mL min^{-1}, providing a residence time of 30 min, was found to be optimal to achieve > 50% conversion (Scheme 5). The KR of 1-phenylethanol (±)-**15** using isobutyric anhydride was highly reproducible, with 54–56% conversion and *s* of 27–30 obtained in five consecutive 4 mmol scale reactions.[22] The robustness of the same packed bed reactor was exemplified by the KR of 28.8 mmol of 1-phenylethanol (±)-**15** over a 24 h period in a continuous flow process (Scheme 5). A conversion of 55% and *s* of 28 were obtained, with (*R*)-1-phenylethanol **(*R*)-15** recovered in 40% yield (11.5 mmol) and 97:3 er.

To further demonstrate the applicability of the continuous flow process, the same packed bed reactor that had been used for optimization studies and the resolution of 1-phenylethanol was then used for sequential KRs using 9 different alcohol/anhydride combinations (Table 7). Each KR was carried out on a 4 mmol scale, with the packed bed reactor simply flushed with $CHCl_3$ or $CHCl_3$/MeOH (9:1) between reactions.[32] A selection of benzylic, allylic, propargylic and cycloalkanol derivatives were resolved with optimal conversion (49–63%) and good to excellent selectivity factors (*s* =

Table 6. Recycling of Polystyrene-Supported HyperBTM 6 for the KR 10 Different Substrates

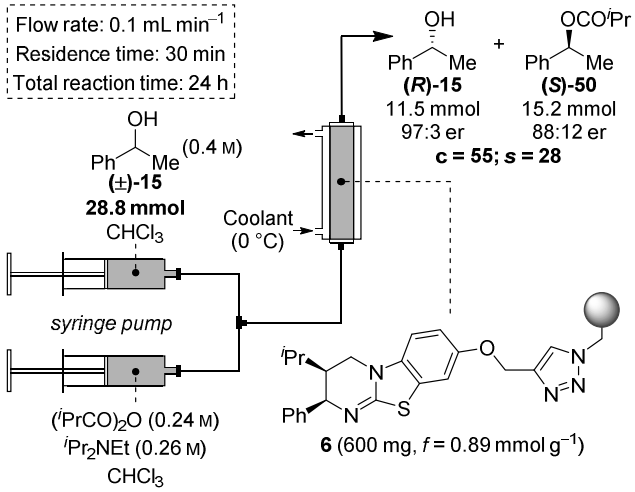


Cycle	Substrate	R	Conv. (%)[a]	alc. er (yield, %)	Est. er (yield, %)	s[a]
1	 (±)-**12**	^{i}Pr	50 [*47*]	96:4 (47)	97:3 (48)	90 [*100*]
2	 (±)-**32**	^{i}Pr	55 [*54*]	93:7 (39)	85:15 (49)	16 [*23*]
3[b]	 (±)-**35**	Et	54 [*54*]	98:2 (41)	91:9 (44)	37 [*50*]
4	 (±)-**21**	^{i}Pr	34 [*39*]	73:27 (65)	95:5 (33)	28 [*31*]
5	 (±)-**33**	^{i}Pr	52 [*54*]	91:9 (37)	88:12 (45)	18 [*26*]
6[b]	 (±)-**39**	Et	50 [*46*]	93:7 (50)	93:7 (45)	36 [*50*]
7	 (±)-**27**	^{i}Pr	38 [*45*]	81:19 (54)	99:1 (35)	200 [*600*]
8	 (±)-**41**	^{i}Pr	45 [*51*]	88:12 (50)	96:4 (39)	60 [*70*]
9	 (±)-**48**	^{i}Pr	50 [*57*]	95:5 (45)	95:5 (46)	60 [*60*]
10	 (±)-**30**	^{i}Pr	40 [*47*]	77:23 (56)	91:9 (37)	18 [*17*]

Conversion and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 2), and rounded according to estimated associated errors (see ref. 24). [a] Conversion and *s* data for resolutions using fresh catalyst (from Tables 1-4) shown in italics in square brackets. [b] r.t., 16 h.

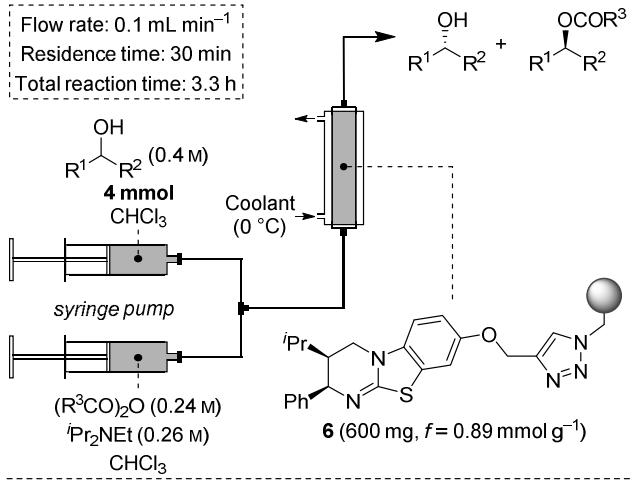
11–200), allowing isolation of the enantioenriched alcohol in 92:8–99:1 er in each case. Significantly, the use of different alcohols and anhydrides with the same packed bed reactor gave spectroscopically-pure products in each case with no evidence of cross-contamination or catalyst deactivation observed. Remarkably, all the flow experiments described in this paper, including optimization and repeat reactions, were performed with the same sample of polystyrene-supported catalyst **6**, resulting in a total operation time in excess of 100 h.

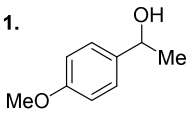
Scheme 5. KR of 1-Phenylethanol in Continuous Flow

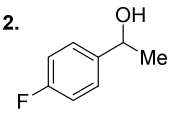


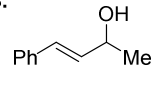
Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 2).

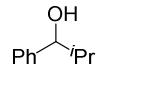
Table 7. Continuous Flow KR of Different Alcohols using the Same Packed Bed Reactor

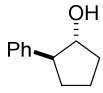


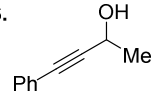
1. 
21,[a] c = 55; *s* = 27
alc: 97:3 er; 37%
est: 89:11 er; 52%

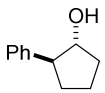
2. 
22,[a] c = 58; *s* = 14
alc: 95:5 er; 35%
est: 82:18 er; 51%

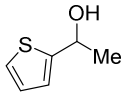
3. 
30,[a] c = 55; *s* = 15
alc: 92:8 er; 42%
est: 85:15 er; 51%

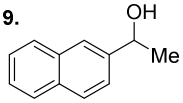
4. 
17,[a] c = 49; *s* = 200
alc: 96:4 er; 46%
est: 98:2 er; 43%

5. 
41,[a] c = 58; *s* = 25
alc: 99:1 er; 39%
est: 85:15 er; 54%

6. 
32,[a] c = 63; *s* = 11
alc: 96:4 er; 26%
est: 77:23 er; 51%

7. 
41,[b] c = 61; *s* = 16
alc: 98:2 er; 35%
est: 81:19 er; 55%

8. 
28,[a] c = 57; *s* = 21
alc: 97:3 er; 36%
est: 86:14 er; 48%

9. 
12,[a] c = 52; *s* = 26
alc: 94:6 er; 46%
est: 90:10 er; 49%

Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 2), and rounded according to estimated associated errors (see ref. 24). [a] (^{i}PrCO)$_2$O used. [b] (EtCO)$_2$O used.

CONCLUSION

The synthesis of polystyrene-supported isothiourea catalyst **6** was achieved in four steps from (*R*)-2-((*R*)-amino(phenyl)methyl)-3-methylbutan-1-ol in 48% overall yield. The KR of a range of secondary alcohols was demonstrated using **6** as catalyst (1 mol%), with the substrate scope including benzylic, allylic and propargylic alcohols, cycloalkanol derivatives and a 1,2-diol (28 examples). The majority of examples were resolved with good to excellent selectivity factors (*s* up to > 600), showing this process has a broad substrate scope, well beyond that of other solid-supported Lewis base catalysts reported to date. The recyclability of the catalyst was demonstrated for the resolution of a single alcohol (15 cycles), and for the sequential resolution of 10 different alcohols using different anhydrides, with no significant loss in activity or selectivity and with no cross-contamination observed. Based on the high catalyst activity and recyclability, a continuous flow process was developed which was applied for the efficient KR of 9 different alcohols and also utilized on a 28.8 mmol scale. Current work is focused on using this new catalyst for other isothiourea-catalyzed reactions through application in batch and continuous flow processes.[33]

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Experimental procedures; characterization data for novel compounds; ^{1}H and ^{13}C NMR spectra and HPLC traces.

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All authors have given approval to the final version of the manuscript.

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(22) See the Supporting Information for full details

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(24) The analytical error associated with the calculation of *s* has been estimated for each KR and is detailed in full in the Supporting Information. Based on this estimation of error the following rules have been applied: i) for $s < 50$, *s* is given to closest integer; ii) for $s = 50–120$, *s* is given to closest 10; iii) for $s > 150$, *s* is given to closest 100.

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(27) The absolute configuration of recovered alcohol was assigned as (*S*,*S*) through comparison of its specific rotation with literature, see Supporting information for details.

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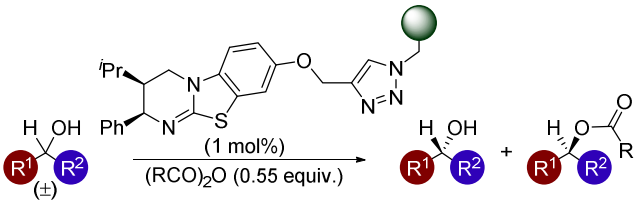
(32) When using different alcohol substrates, $CHCl_3$ was pumped at 0.1 mL min^{-1} for 45 min. When using different anhydrides, $CHCl_3$/MeOH (9:1) was pumped at 0.1 mL min^{-1} for 45 min.

(33) The research data underpinning this publication can be found at DOI: http://dx.doi.org/10.17630/5c945e1a-44ac-4c1a-8cb1-a154bcefa4c6.



• 28 examples; • 5 substrate classes (benzylic, allylic, propargylic, cycloalkanol, 1,2-diol); • *s* factors up to > 600;
• Excellent catalyst recyclability; • Applied in continuous flow