Green Chemistry

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View Article Online
DOI: 10.1039/C8GC02020E

Journal Name

ARTICLE

Evaluating polymer-supported isothiourea catalysis in industrially-preferable solvents for the acylative kinetic resolution of secondary and tertiary heterocyclic alcohols in batch and flow†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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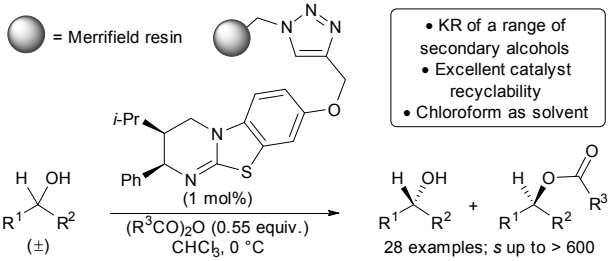
Polymer-supported Lewis base catalysts, based on the homogeneous isothioureas HyperBTM and BTM, have been synthesised and applied for the acylative kinetic resolution of secondary and tertiary heterocyclic alcohols. In batch, the use of industrially-preferable solvents was investigated, with dimethyl carbonate proving to be most generally-applicable. Significantly, the HyperBTM-derived immobilised catalysts were readily recycled, with no loss in either activity or selectivity. In addition to the kinetic resolution of secondary benzylic, propargylic, allylic and cycloalkanol derivatives, a range of 22 tertiary heterocyclic alcohols, based on privileged 3-hydroxyoxindole and 3-hydroxypyrrolidinone substructures, were resolved with up to excellent selectivity (*s* = 7–190). Finally, the immobilised isothiourea catalysts were applied in a packed bed reactor to demonstrate the first example of the kinetic resolution of tertiary heterocyclic alcohols in a continuous flow process. High selectivities were obtained for the resolution of 3-hydroxyoxindole derivatives in ethyl acetate (*s* up to 70); and for 3-hydroxypyrrolidinones derivatives in toluene (*s* up to 42).

Introduction

Enantioselective organocatalysis has become a diverse and vibrant research area over recent decades, with many highly efficient and selective methods having been developed.[1] In the context of sustainability and potential industrial applicability, one common criticism of the area is the use of relatively high loadings of the organocatalyst, which is typically neither reisolated nor recycled following a given reaction. One potential general solution is the immobilisation of the organocatalyst onto a heterogeneous polymer support.[2] In principle, recovery of the catalyst can be achieved following the reaction by a simple filtration; alternatively the polymer-supported catalyst can be incorporated into a continuous flow set-up, improving the ease of catalyst recycling even further.[3] To compensate the additional time and energy costs associated with catalyst synthesis, the immobilised catalyst must be obtained via a straightforward and high yielding route, and be sufficiently stable to allow recycling multiple times without any loss in activity or selectivity.

In this area, we recently reported the synthesis of a Merrifield resin-derived polymer-supported chiral isothiourea based upon a homogeneous Lewis basic catalyst, HyperBTM, and applied this immobilised catalyst for the kinetic resolution (KR) of secondary alcohols (Scheme 1).[4–8] A range of alcohols, including benzylic, allylic and propargylic alcohols, as well as cycloalkanol derivatives and a 1,2-diol, were resolved with up to excellent selectivity factors [where selectivity factor (*s*) is defined as the rate constant for the fast reacting enantiomer divided by the rate constant for the slow reacting enantiomer ($s = k_{fast}/k_{slow}$)].[9] Significantly, this immobilised catalyst could be recycled at least 15 times with no appreciable loss in either activity or selectivity. The broad scope and excellent catalyst recyclability in comparison to previously reported KRs using immobilised catalysts indicated substantial potential of this catalyst for future applications.[4,5]

Prior work: Polymer-supported HyperBTM-catalysed KR of 2° alcohols



Scheme 1 Previous work on the KR of secondary alcohols using a Merrifield resin-supported isothiourea catalyst.

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† Electronic Supplementary Information (ESI) available: experimental procedures, product characterisation data (mpt, NMR, IR, HRMS, $[\alpha]_D$, HPLC,), traces (NMR, HPLC). See DOI: 10.1039/x0xx00000x.

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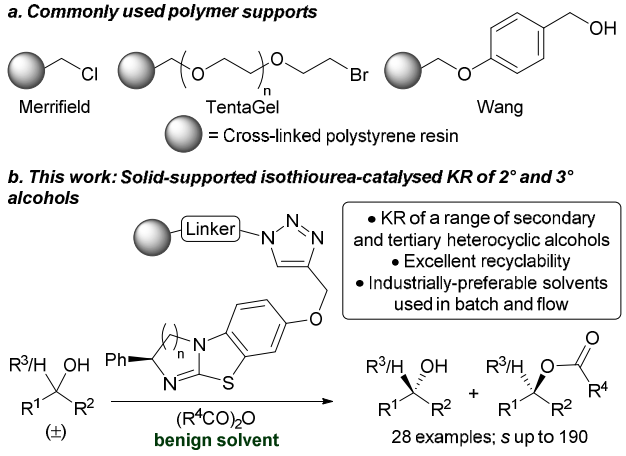
Although demonstrating proof-of-concept in this area, one potential obstacle for industrial application of this method was the reliance upon using chloroform as the reaction solvent. As the solvent typically constitutes the majority of the mass in any synthetic transformation, the nature of the solvent has a substantial impact on the sustainability of the process. These considerations are of particular importance in the chemical industry. Over the last 15 years, considerable effort has been made to identify the suitability of different solvents, taking into account environmental impact, health and safety, cost and life-cycle management considerations. This has resulted in a range of reports from pharmaceutical companies that have broadly categorised solvents into a number of groupings, that for simplicity and the purpose of this manuscript we have classified as "best to avoid", "usable" and "preferred".[10]

In order to enhance the potential industrial-applicability of our polymer-supported isothiourea catalyst, we recognised that solvent compatibility with industrially-preferable solvents was of paramount importance. A variety of differentially-functionalised polymer supports are commercially-available due to their application in solid phase peptide synthesis (Scheme 2a),[11] where modulation of the polymer functionality is known to have a substantial effect on the stability and swelling properties of the polymer in different solvents. The synthesis of isothiourea catalysts immobilised on different polymer supports was therefore envisioned to allow assessment of solvent compatibility and sustainability. In addition, the change in chemical environment around the Lewis basic isothiourea in each immobilised catalyst could be expected to lead to changes in both activity and selectivity. Herein, we report the synthesis of a range of polymer-supported isothiourea catalysts and demonstrate their application and recyclability for the KR of secondary and tertiary alcohols in both batch and continuous flow, with a particular focus on the compatibility of industrially-preferable solvents (Scheme 2b).

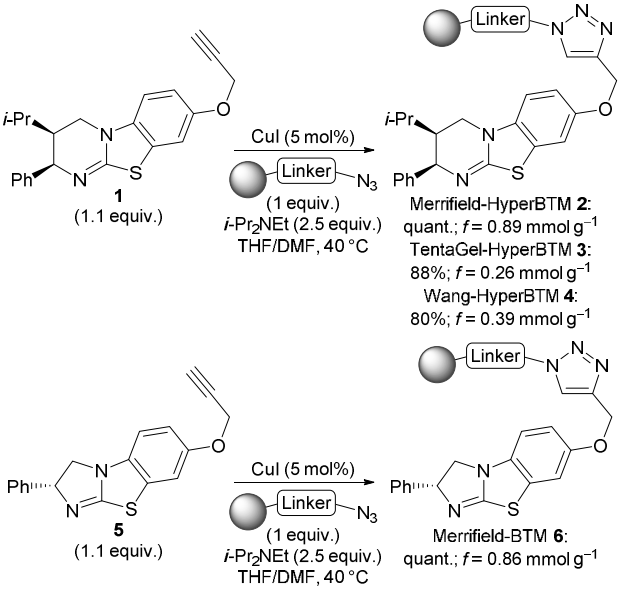


Scheme 2 a) Commercially-available polymer supports used in this study; **b)** KR of secondary and tertiary alcohols using a range of supported isothiourea catalysts in batch and flow using industrially-preferable solvents.

Results and discussion

Synthesis of polymer-supported isothiourea catalysts

The synthesis of immobilised HyperBTM derivatives **2–4** was achieved through a Cu-catalysed azide-alkyne cycloaddition between alkyne-substituted HyperBTM derivative **1** and azide-functionalised Merrifield, TentaGel and Wang resins (Scheme 3).[12] Elemental analysis of each immobilised catalyst allowed calculation of polymer functionalisation based on nitrogen content,[13,14] with these values used to determine catalyst loading in all subsequent KRs.[15] A Merrifield resin-supported derivative of the isothiourea BTM **6** was also synthesised by a similar procedure starting from alkyne-substituted BTM derivative **5**. In all cases the isothiourea-functionalised polystyrene resins were obtained in high yield.



Scheme 3 Preparation of solid-supported HyperBTM and BTM catalysts.

KR of secondary alcohols: solvent compatibility

Investigations began by comparing the activity and selectivity of HyperBTM-derived immobilised catalysts **2–4** for the KR of (±)-1-(naphthalen-2-yl)ethan-1-ol **7** using isobutyric anhydride in a range of solvents (Table 1).[14,16] All KRs were conducted at room temperature to aid practically and to enable future application. The KRs were first performed in chloroform to provide a direct comparison with the previously-reported methodology.[4] All immobilised isothioureas catalysed the KR of alcohol **7** with excellent selectivity (*s* = 45–80, entries 1–3). The use of industrially-preferable solvents was next investigated.[10,17] Excellent selectivities were obtained with all catalysts in toluene (*s* = 60–70), with Merrifield and TentaGel-derived catalysts **2** and **3** providing optimal conversion (entries 4–5), whilst lower conversion was obtained using Wang derivative **4** (entry 6). A more significant solvent effect was observed when using *tert*-amyl alcohol, with high conversion and selectivity only obtained with TentaGel-derived catalyst **3** (entries 7–9).

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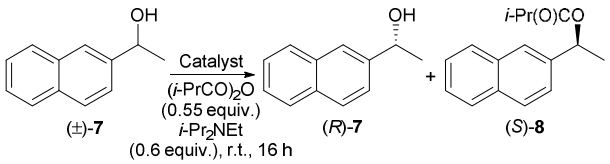
Table 1 KR of (±)-**7** using supported catalysts **2**–**4** and **6**: Effect of solvent



Entry	Catalyst	Solvent	c (%)	7 er[a]	8 er[b]	*s*	
1[c]	**2**	$CHCl_3$	50	95:5	96:4	80	AVOID
2	**3**	$CHCl_3$	40	81:19	96:4	45	
3	**4**	$CHCl_3$	32	72:28	97:3	50	
4[c]	**2**	PhMe	52	98:2	95:5	70	USABLE
5	**3**	PhMe	52	97:3	94:6	60	
6	**4**	PhMe	32	72:28	98:2	70	
7	**2**	*t*-AmOH	17	59:41	93:7	16	
8	**3**	*t*-AmOH	49	89:11	94:6	43	
9	**4**	*t*-AmOH	3	51:49	87:13	7	
10	**2**	*i*-PrOAc	52	97:3	93:7	49	PREFERRED
11	**3**	*i*-PrOAc	47	89:11	94:6	39	
12	**4**	*i*-PrOAc	44	81:19	90:10	16	
13	**2**	$(MeO)_2CO$	50	94:6	94:6	45	
14	**3**	$(MeO)_2CO$	46	89:11	96:4	60	
15	**4**	$(MeO)_2CO$	45	88:12	96:4	49	
16	**6**	$(MeO)_2CO$	27	33:67	4:96	38	

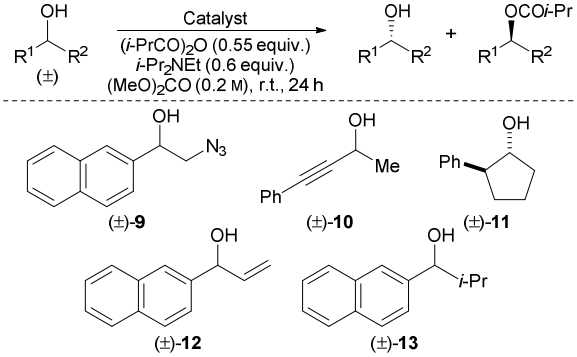
'Avoid', 'Usable' and 'Preferred' indicate the industrial applicability of the solvent.[10] Conditions: (±)-**7** (0.2 mmol), **2** or **6** (5 mol%), or **3** or **4** (3 mol%), (*i*-PrCO)$_2$O (0.55 equiv.), *i*-Pr$_2$NEt (0.6 equiv.), solvent (0.2 M), r.t., 16 h. Conversion (c) and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using er of **7** and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). [a] *R*:*S*. [b] *S*:*R*. [c] Data taken from ref. 4.

This solvent effect is consistent with the expected swelling of each polymer support in *tert*-amyl alcohol, with the polyethylene glycol linker present in TentaGel providing enhanced swelling in polar protic solvents. The use of acetate solvents was also tolerated, with good conversions obtained in isopropyl acetate using each catalyst (entries 10–12). The selectivity obtained using each catalyst was more variable however; with Merrifield-derived catalyst **2** providing an *s* value of 49 (entry 10), but Wang-derived catalyst **4** providing an *s* value of only 16 (entry 12). More consistent data were obtained when using dimethyl carbonate, with 45–50% conversion and *s* = 45–60 obtained for all three catalysts (entries 13–15). The use of immobilised BTM catalyst **6** also proved reasonably effective, with good selectivity (*s* = 38) and moderate conversion obtained (27%). Although less effective than immobilised HyperBTM derivatives **2**–**4**, the activity of this BTM derivative is promising when compared to a previously-reported polymer-supported variant of BTM, which was shown to be ineffective for KRs (*s* = 3 for the KR of 1-phenylethanol in $CDCl_3$).[8a] Based on these results, the use of dimethyl carbonate was further investigated for the KR of a range of secondary alcohols using each immobilised catalyst.

Catalyst recycling

The recyclability and robustness of each polymer-supported isothiourea catalyst was investigated through the sequential KR of five different secondary alcohols in dimethyl carbonate (Table 2). In each case, the catalyst was recovered by filtration and washed sequentially with CH_2Cl_2/MeOH (1:1), MeOH, THF and CH_2Cl_2 before drying under high vacuum for 2 h. The secondary alcohols were selected from the scope previously reported in chloroform,[4] with these five alcohols chosen to probe catalyst versatility for the KR of benzylic, allylic, propargylic and cycloalkanols.[16] Differences in catalyst activity and selectivity for the KR of each substrate, in addition to changes in activity following catalyst recycling, were assessed. First, the KR of 1,2-azidoalcohol **9** was performed with all four catalysts (Table 2). Each of the HyperBTM derivatives **2**–**4** gave similar conversions and selectivities (c = 46–52%; *s* = 22–29); however BTM derivative **6** provided only low conversion and selectivity (c = 16%; *s* = 3). Each catalyst was then recovered and applied for the KR of propargylic alcohol **10**. All of the HyperBTM-derived catalysts **2**–**4** provided optimal conversion, however more variation in selectivity was observed, with Wang-derived catalyst **4** providing the highest selectivity (*s* = 15). In contrast, BTM derivative **6** was completely inactive. Next, the KR of *trans*-phenylcyclopentanol **11** with each HyperBTM-derived catalyst **2**–**4** provided similar conversions and selectivities (c = 48–53%; *s* = 27–29), whilst BTM-derived

Table 2 Recycling supported catalysts **2**–**4** and **6** for the sequential KR of five secondary alcohols (±)-**9**–**13**



Catalyst	Cycle	Substrate	c (%)	Alc. er[a]	Est. er[b]	*s*
	1	**9**	52	6:94	10:90	25
	2	**10**	55	89:11	81:19	10
2	3	**11**	53	95:5[c]	90:10[d]	27
	4	**12**	48	85:15	87:13	14
	5	**13**	52	> 99:1	96:4	140
	1	**9**	46	13:87	9:91	22
	2	**10**	52	81:19	79:21	7
3	3	**11**	48	90:10[c]	92:8[d]	29
	4	**12**	47	85:15	90:10	18
	5	**13**	43	87:13	99:1	170
	1	**9**	50	10:90	8:92	29
	2	**10**	51	88:12	87:13	15
4	3	**11**	49	91:9[c]	92:8[d]	29
	4	**12**	47	85:15	89:11	16
	5	**13**	44	88:12	> 99:1	190
	1	**9**	16	54:46	70:30	3
6	2	**10**	0	-	-	-
	3	**11**	0	-	-	-

Conditions: **9**–**13** (0.2–0.4mmol), **2** or **6** (5 mol%), or **3** or **4** (3 mol%), (*i*-PrCO)$_2$O (0.55 equiv.), *i*-Pr$_2$NEt (0.6 equiv.), (MeO)$_2$CO (0.2 M), r.t., 24 h. Conversion (c) and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). [a] *R*:*S*. [b] *S*:*R*. [c] 1*R*,2*S*:1*S*,2*R*. [d] 1*S*,2*R*:1*R*,2*S*.

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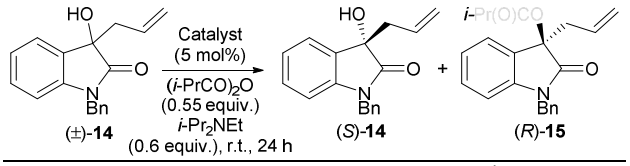
catalyst **6** again proved to be completely inactive. Based on these results, the use of BTM-derived catalyst **6** in these recycling experiments was discontinued. The KR of the next substrate, aryl-alkenyl-substituted carbinol **12**,[7l] was achieved using all HyperBTM derivatives **2**–**4**, with similar conversions and selectivities obtained once more (c = 47–48%; *s* = 14–18). Finally, the KR of benzylic alcohol **13** using each HyperBTM-derived catalyst **2**–**4** was achieved with good conversions and exceptional selectivities (*s* = 140–190). It should be noted that the *s* values obtained in these experiments using dimethyl carbonate are lower than those previously-reported for the same substrates in chloroform.[4] Nonetheless, these experiments demonstrate the feasibility of using an industrially-prefererable solvent to obtain synthetically-useful levels of selectivity. It is noteworthy that all of the immobilised HyperBTM derivatives **2**–**4** are readily recycled and are considerably more robust than BTM analogue **6**. Decomposition of the homogeneous isothiourea catalyst BTM has been reported in the presence of anhydrides and alcohols,[7i] with the operation of a similar deactivation pathway for the immobilised analogue consistent with the results of these recycling experiments.

KR of tertiary alcohols: reaction optimisation and scope

To expand the scope and impact of this method, the polymer-supported catalysts **2**–**4** and **6** were investigated for the KR of tertiary heterocyclic alcohols in industrially-preferable solvents in both batch and continuous flow. The acylative KR of tertiary alcohols is a significant challenge due to the sterically-hindered nature of the substrates, and the requirement for the catalyst to differentiate between three substituents at the stereogenic carbinol centre. As such, only three methods have been previously reported,[7m,18] including a recent example from ourselves using the homogeneous version of HyperBTM.[7m] The KR of a range of tertiary heterocyclic alcohols was reported, however chloroform was used as the optimal solvent and the ability to recover or recycle the catalyst was not demonstrated, thus limiting industrial applicability.

Optimisation studies began with the KR of 3-allyl-3-hydroxyoxindole derivative **14** using Merrifield resin-supported HyperBTM **2** and isobutyric anhydride in batch (Table 3).[16,19] Initially, the use of chloroform, which proved most effective in the homogeneous system,[7m] was investigated. After 24 h at room temperature only 22% conversion was observed, however encouragingly high selectivity was obtained (*s* = 60) (Table 3, entry 1). To provide context, the KR of alcohol **14** in chloroform at room temperature using homogeneous HyperBTM (1 mol%) provided a conversion of 53% and an *s* value of 90.[7m] This indicates the polymer-supported variant of the catalyst displays reduced activity, but still provides similarly high enantiodiscrimination. The use of more industrially-preferable solvents was investigated next.[10,17] Using either toluene or ethyl acetate resulted in significantly improved conversion, albeit with lower selectivity (entries 2–3). The KR of **14** in ethyl acetate was also investigated using TentaGel and Wang resin-supported HyperBTM **3** and **4**, with similar conversions and selectivities obtained in each case (entries 4–5). Finally, the KR of **14** was examined in dimethyl carbonate with all three immobilised HyperBTM catalysts **2**–**4** (entries 6–8). TentaGel-supported catalyst **3** gave the highest selectivity (*s* = 29; entry 7), however significantly better conversion was obtained using Merrifield resin-supported HyperBTM **2** (entry 6). As conversions of > 50% are desirable in KRs to allow isolation of substrate in highly enantioenriched form, further optimisation using Merrifield resin-supported HyperBTM **2** in dimethyl carbonate was targeted. Although similar conversions and selectivites were obtained using both ethyl acetate and dimethyl carbonate, the use of dimethyl carbonate was considered preferrable due to its reduced flammability, increased stability and lower environmental impact.[10b,d,e] The reaction conversion in dimethyl carbonate was improved to 53% by increasing the equivalents of anhydride, to provide the optimised conditions for this KR using Merrifield resin-supported HyperBTM **2** (entry 9). Consistent with our work using the homogeneous analogues of these isothiourea catalysts, the use of Merrifield resin-supported BTM derivative **6** led to very low conversion and selectivity (entry 10).[7m]

Table 3 Reaction optimisation for the KR of 3-allyl-3-hydroxyoxindole derivative (±)-**14**



Entry	Catalyst	Solvent	c (%)	14 er[a]	15 er[b]	*s*	
1	**2**	$CHCl_3$	22	64:36	98:2	60	
2	**2**	PhMe	46	85:15	91:9	21	USABLE
3	**2**	EtOAc	47	87:13	91:9	22	USABLE
4	**3**	EtOAc	42	88:12	78:22	13	USABLE
5	**4**	EtOAc	47	86:14	90:10	20	USABLE
6	**2**	$(MeO)_2CO$	48	88:12	90:10	21	PREFERRED
7	**3**	$(MeO)_2CO$	38	77:23	94:6	29	PREFERRED
8	**4**	$(MeO)_2CO$	36	74:26	92:8	19	PREFERRED
9[c]	**2**	$(MeO)_2CO$	53	93:7	88:12	20	PREFERRED
10	**6**	$(MeO)_2CO$	1	50:50	66:34	2	PREFERRED

'Usable' and 'Preferred' indicate the industrial applicability of the solvent.[10] Conditions: **14** (0.1 mmol), **2**, **3**, **4** or **6** (5 mol%), (*i*-PrCO)$_2$O (0.55 equiv.), *i*-Pr$_2$NEt (0.6 equiv.), solvent (0.2 M), r.t., 24 h. Conversion (c) and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). [a] *S*:*R*. [b] *R*:*S*. [c] 0.7 equiv. of (*i*-PrCO)$_2$O used.

Encouraged by the promising results using Merrifield resin-supported HyperBTM **2** in dimethyl carbonate at room temperature, the scope of the KR was investigated (Table 4).[16] The introduction of a sterically-hindered *i*-Pr group or an electron- withdrawing CF_3 group at C(3) were both tolerated, with **17** and **18** resolved with good selectivity (*s* = 13–21). The incorporation of an aromatic group at C(3) was also successful, with phenyl-substituted alcohols **19**–**21** resolved with optimal conversion and excellent selectivity (*s* = 60–70) allowing recovery of the alcohol in highly enantioenriched form in each case. Aromatic substituents at C(3) bearing both electron-donating and -withdrawing groups were tolerated, as was the introduction of heteroaromatic substituents, with alcohols **22**–

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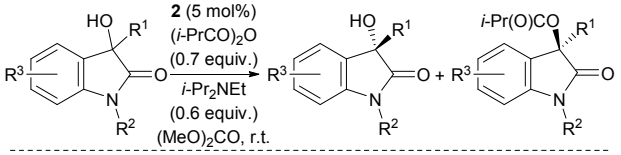
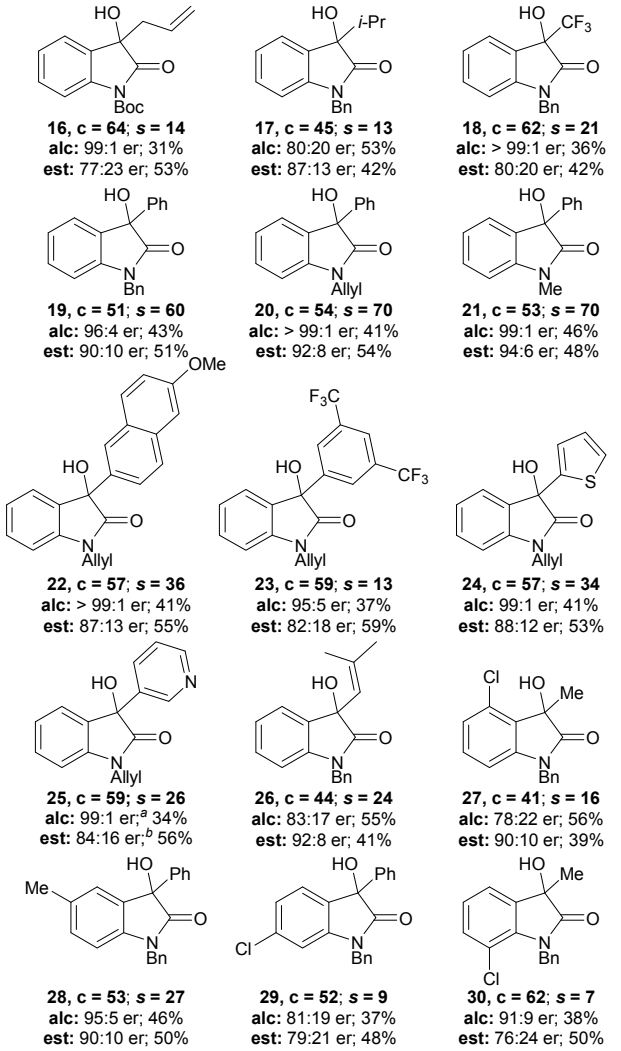
25 all resolved with good selectivity (*s* = 13–36). The method was equally applicable for the KR of 3-alkenyl-substituted alcohol **26** (*s* = 24). It is noteworthy that these examples demonstrate the immobilised isothiourea catalyst can differentiate between three sp^2-hybridised substituents at the tertiary carbinol centre (two π-systems and a carbonyl).[20] Finally, substitution of the benzenoid ring was generally tolerated, with 4-chloro- and 5-methyl-substituted oxindole derivatives **27** and **28** resolved with good selectivity (*s* = 16–27); however 6- and 7-chloro-substituted derivatives **29** and **30**

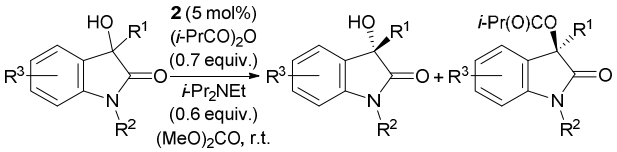
Table 4 Substrate Scope for the KR of 3-substituted-3-hydroxyoxindole derivatives

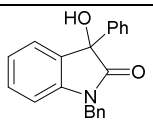
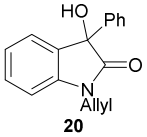
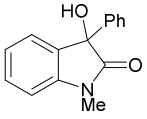
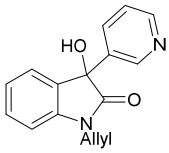
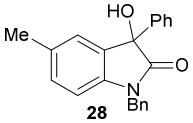
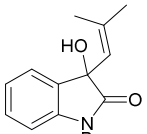




Conditions: alcohol (0.1 mmol), **2** (5 mol%), $(i\text{-PrCO})_2O$ (0.7 equiv.), $i\text{-Pr}_2NEt$ (0.6 equiv.), $(MeO)_2CO$ (0.2 M), 24–48 h. Conversion (c) and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). Alcohol er given as *S*:*R*, ester er given *R*:*S*. [a] *R*:*S*. [b] *S*:*R*.

Table 5 Recycling of polymer-supported HyperBTM **2**



Cycle	Substrate	c (%)[a]	Alcohol er;[b] yield	Ester er;[c] yield	*s* [a]
1	 **19**	56 [*56*]	> 99:1; 43%	90:10; 51%	60 [*60*]
2	 **20**	54 [*54*]	> 99:1; 46%	92:8; 49%	80 [*70*]
3	**19**	54 [*56*]	> 99:1; 43%	92:8; 51%	70 [*60*]
4	 **21**	52 [*53*]	99:1; 47%	95:5; 50%	90 [*70*]
5	**19**	53 [*56*]	99:1; 45%	94:6; 48%	70 [*60*]
6	 **25**	60 [59]	>99:1;[c] 39%	84:16;[b] 57%	44 [*26*]
7	**19**	54 [*56*]	> 99:1; 45%	93:7; 50%	70 [*80*]
8	 **28**	55 [*53*]	99:1; 44%	89:11; 52%	37 [*27*]
9	**19**	54 [*56*]	> 99:1; 45%	92:8; 53%	80 [*60*]
10	 **26**	49 [*44*]	89:11; 48%	92:8; 48%	26 [*24*]

Conditions: alcohol (0.25–0.4 mmol), **2** (5 mol%), $(i\text{-PrCO})_2O$ (0.7 equiv.), $i\text{-Pr}_2NEt$ (0.6 equiv.), $(MeO)_2CO$ (0.2 M), 18–48 h. Conversion (c) and er determined by chiral HPLC analysis. Selectivity factors (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). [a] Conversion (c) and *s* data for resolutions using fresh catalyst shown in italics in brackets. [b] *S*:*R*. [c] *R*:*S*.

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provided relatively low selectivity (*s* = 7–9). Overall, substrates bearing a variety of N-substituents were successfully applied, including *N*-*tert*-butoxycarbonyl (Boc), *N*-benzyl, *N*-allyl and *N*-methyl-substituted 3-hydroxyoxindole derivatives. Although slightly lower than those previously reported using homogeneous HyperBTM in chloroform,[7m] synthetically-useful levels of selectivity were obtained in the majority of cases.

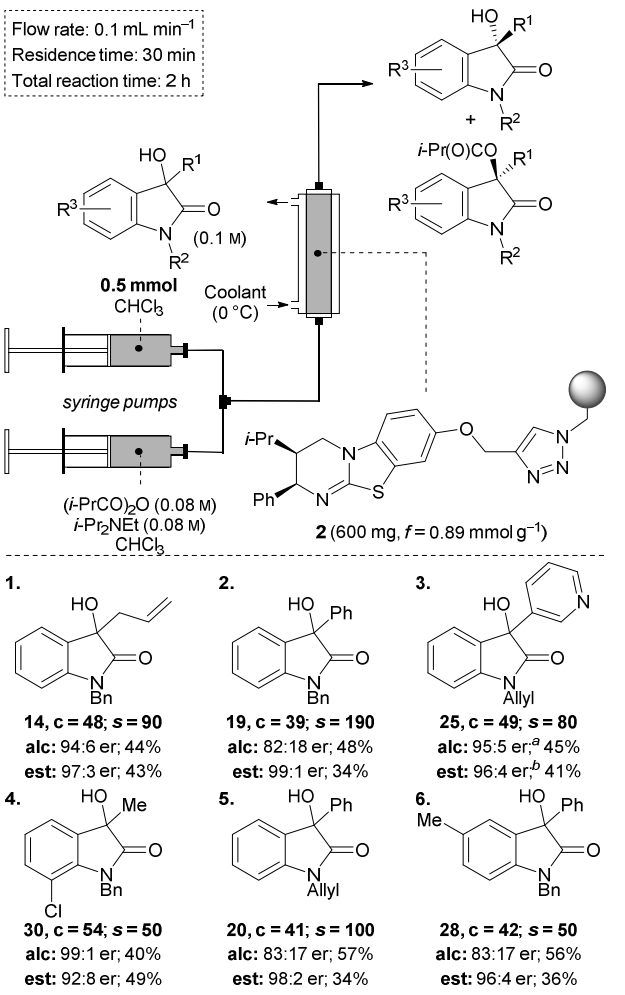
Catalyst recycling

The robustness and reusability of Merrifield resin-supported HyperBTM catalyst **2** was further probed through a recycling experiment in which the catalyst was recovered and reused ten times (Table 5). In this experiment, six different tertiary alcohol substrates were applied, with the KR of *N*-benzyl-3-phenyl-substituted hydroxyoxindole **19** performed on alternate cycles. This approach was adopted to: (i) investigate if the same sample of catalyst could be used to resolve different substrates without cross-contamination, and (ii) provide insight into whether there is any loss in activity or selectivity of the catalyst upon recycling. All six substrates were resolved with very comparable conversion and selectivity to when fresh catalyst was used (this data is provided italicized and in square brackets in table 5 for clarity). The KR of **19** was also remarkably consistent, with conversions of 53–56% and *s* values of 60–80 obtained for the five cycles. These experiments indicate excellent stability of Merrifield resin-supported HyperBTM catalyst **2** over the course of this recycling protocol. Significantly, no cross-contamination between KRs was observed in any case, demonstrating excellent potential for further applications.

Application in continuous flow

Based on the excellent recyclability of Merrifield resin-supported HyperBTM catalyst **2** for the KR of tertiary alcohols, application in a continuous flow set-up was investigated. To the best of our knowledge the KR of tertiary alcohols in continuous flow has not been reported previously. We therefore initially investigated the feasibility of the process under the conditions used previously for the KR of secondary alcohols in continuous flow using chloroform as solvent.[4] The immobilised catalyst **2** (600 mg, 0.53 mmol) was swollen in a medium pressure borosilicate glass column in chloroform to create a packed bed reactor, and solutions of racemic tertiary alcohol (0.1 M) and a mixture of anhydride (0.08 M) and base (0.08 M) were passed through using a syringe pump. Based on optimisation studies using hydroxyoxindole derviative **14**,[14] a reaction temperature of 0 °C and an elution rate of 0.1 mL min^{-1}, to provide a residence time of 30 min, was chosen and applied in each case. The packed bed reactor was used for the sequential KR of six different 3-substituted-3-hydroxyoxindole derivatives **14**, **19**, **25**, **30**, **20** and **28** using isobutyric anhydride (Table 6, entries 1–6). Good conversions and exceptional selectivities were obtained in each case (*s* = 50–190). Each KR was carried out on a 0.5 mmol scale, with the packed bed reactor flushed with a solution of 10% methanol in chloroform, followed by pure chloroform between KRs to regenerate the catalyst and avoid any cross-contamination.

Table 6 Continuous flow KR of 3-substituted-3-hydroxyoxindole derivatives in chloroform using the same packed bed reactor



Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). Alcohol er given as *S*:*R*, ester er given *R*:*S*. [a] *R*:*S*. [b] *S*:*R*.

Next, the use of industrially-preferable solvents for the KR of 3-substituted-3-hydroxyoxindole derivatives was investigated. Optimisation studies using Merrifield-supported HyperBTM **2** and hydroxyoxindole derviative **14** found that low selectivities were obtained using dimethyl carbonate (*s* = 9), and that toluene was unsuitable due to the low solubility of **14**.[14] The use of ethyl acetate was relatively successful however, with a moderate *s* and good conversion obtained at 0 °C, albeit when using an increased concentration of anhydride (0.2 M). The swelling of Merrifield-supported HyperBTM **2** was inefficient in ethyl acetate and therefore the use of TentaGel-supported HyperBTM **3** was also investigated, however only low conversion and selectivity were obtained (c = 10%; *s* = 9).[14] The scope of the KR of 3-substituted-3-hydroxyoxindole derivatives using Merrifield-supported HyperBTM **2** in ethyl acetate was therefore investigated in more detail (Table 7). The same packed bed reactor that had been used in the previous studies

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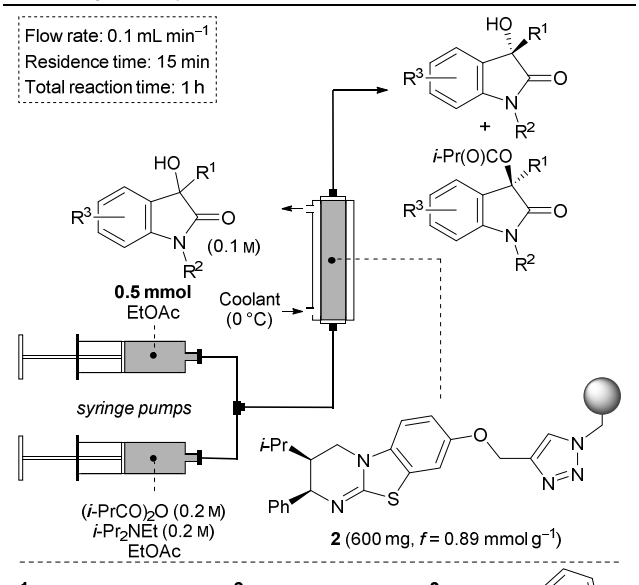
was used for the sequential KR of six different 3-substituted-3-hydroxyoxindole derivatives **14**, **19**, **25**, **28**, **22** and **30**. The diminished swelling of the polymer support in ethyl acetate resulted in a shorter residence time of 15 min. The resolution of 3-allyl-substituted derivative **14** proceeded with high conversion and good selectivity (*s* = 14; entry 1) to provide the recovered alcohol with high enantioenrichment (98:2 er). The resolution of 3-aryl-substituted 3-hydroxyindolin-2-one derivatives **19**, **25**, **28** and **22** proceeded with optimal conversions and high selectivities in each case (*s* = 29–70; entries 2–5). In contrast, the KR of 3-methyl-substituted analogue **30** only provided an *s* value of 8, albeit still allowing for the isolation of recovered alcohol (*S*)-**30** with excellent enantiopurity (> 99:1 er) at 76% conversion (entry 6).

Table 7 Continuous flow KR of 3-substituted-3-hydroxyoxindole derivatives in ethyl acetate using the same packed bed reactor



1. **14, c = 63**; ***s* = 14**
alc: 98:2 er; 33%
est: 78:22 er; 60%

2. **19, c = 50**; ***s* = 70**
alc: 95:5 er; 43%
est: 95:5 er; 48%

3. **25, c = 55**; ***s* = 32**
alc: 98:2 er;[a] 43%
est: 89:11 er;[b] 54%

4. **28, c = 42**; ***s* = 31**
alc: 82:18 er; 54%
est: 94:6 er; 41%

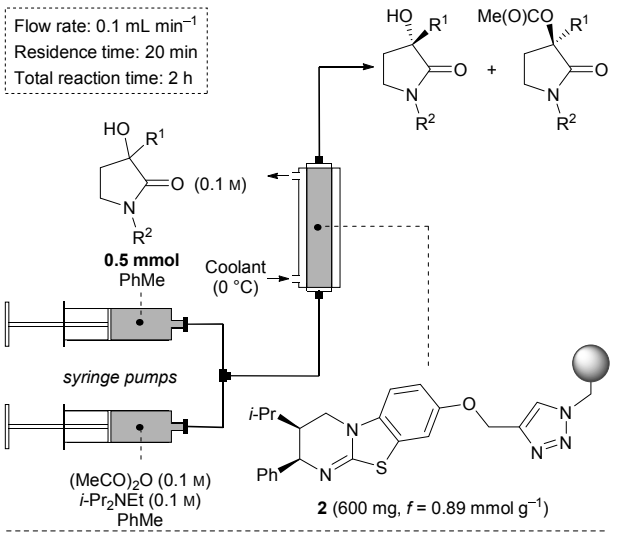
5.[c] **22, c = 52**; ***s* = 29**
alc: 95:5 er; 47%
est: 91:9 er; 51%

6.[c,d] **30, c = 76**; ***s* = 8**
alc: > 99:1 er; 24%
est: 66:34 er; 73%

Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). Alcohol er given as *S*:*R*, ester er given *R*:*S*. [a] *R*:*S*. [b] *S*:*R*. [c] 0.25 mmol scale. [d] **30** (0.07 M), (*i*-PrCO)$_2$O, *i*-PrNEt$_2$ (0.14 M).

The KR of a second class of tertiary alcohol, 3-substituted-3-hydroxypyrrolidin-2-ones,[7m,21] was next investigated in continuous flow using the same packed bed reactor. In line with the previously-reported KR using homogeneous HyperBTM,[7m] the use of acetic anhydride as acylating agent was required for high conversions. Good solubility of the substrates in toluene allowed effective resolution, despite the diminished swelling of the polymer support resulting in a residence time of only 20 min. The sequential KR of six 3-substituted-3-hydroxypyrrolidin-2-one derivatives **31–36** was performed, with very good conversions and selectivities obtained in each case (c = 40–53%; *s* = 18–42) (Table 8).[16] The robustness of the same packed bed reactor was further exemplified by the 7.25 mmol-scale KR of *N*-benzyl-3-hydroxy-3-phenylpyrrolidin-2-one **33** in a continuous flow process over a 24 h period (Scheme 4). Significantly, all continuous flow experiments described in this manuscript, including

Table 8 Continuous flow KR of pyrrolidin-2-one derivatives in toluene using the same packed bed reactor



1. **31, c = 40**; ***s* = 42**
alc: 80:20 er; 57%
est: 96:4 er; 33%

2. **32, c = 45**; ***s* = 29**
alc: 85:15 er; 50%
est: 93:7 er; 41%

3. **33, c = 52**; ***s* = 27**
alc: 93:7 er; 43%
est: 91:9 er; 46%

4. **34, c = 52**; ***s* = 25**
alc: 94:6 er;[a] 41%
est: 90:10 er;[b] 48%

5. **35, c = 52**; ***s* = 29**
alc: 94:6 er; 42%
est: 91:9 er; 45%

6. **36, c = 53**; ***s* = 18**
alc: 92:8 er; 40%
est: 87:13 er; 44%

Conversion and er determined by chiral HPLC analysis. Selectivity factor (*s*) calculated using alcohol er and reaction conversion (see ref. 9a), and rounded according to estimated associated errors (see ref. 9b). Alcohol er given as *R*:*S*, ester er given *S*:*R*. [a] *S*:*R*. [b] *R*:*S*.

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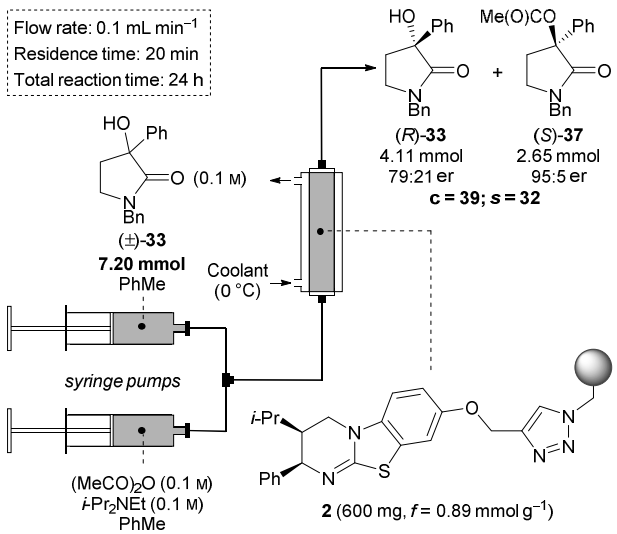
optimisation studies, were performed with the same sample of Merrifield resin-supported HyperBTM catalyst **2**, resulting in a total operation time of over 100 h.



Scheme 4 Continuous flow KR of *N*-benzyl-3-hydroxy-3-phenylpyrrolidin-2-one (±)-**33**.

Conclusions

The synthesis of polymer-supported Lewis base catalysts, based on the homogeneous isothioureas HyperBTM and BTM, was achieved, and these catalysts were applied for the acylative kinetic resolution of a range of secondary and tertiary heterocyclic alcohols. In batch, the use of industrially-preferable solvents was investigated, with dimethyl carbonate proving the most generally applicable. Notably, the HyperBTM-derived immobilised catalysts were readily recycled, with no loss in either activity or selectivity. In contrast, the polymer-supported BTM derivative showed diminished reactivity, with the catalyst being deactivated following a single experiment.[7i] In addition to the kinetic resolution of secondary benzylic, propargylic, allylic and cycloalkanol derivatives, a range of 22 tertiary heterocyclic alcohols, based on privileged 3-hydroxyoxindole and 3-hydroxypyrrolidinone substructures, were resolved with up to excellent selectivity (*s* = 7–190). The immobilised HyperBTM catalysts were applied in a packed bed reactor to demonstrate the first example of the kinetic resolution of tertiary alcohols in a continuous flow process. Although using chloroform as solvent gave the highest selectivities in flow, high selectivities were also obtained for the resolution of 3-hydroxyoxindole and 3-hydroxypyrrolidinone derivatives in the industrially-preferable solvents of ethyl acetate and toluene.[22]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Royal Society and the Science and Engineering Board of India (SERB) for the award of a Royal Society-SERB Newton International Fellowship (N.R.G.). We also thank the EPSRC Centre for Doctoral Training in Critical Resource Catalysis (CRITICAT, grant code EP/L016419/1, R.M.N.P.) for funding. Financial support from the EPSRC (EP/K000411/1) is gratefully acknowledged (R.C.). We thank the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) ERC grant agreement no. 279850 (A.D.S). A.D.S. thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University. C.R.-E. and M.A.P. acknowledge the financial support from CERCA Programme/Generalitat de Catalunya, MINECO (CTQ2015-69136-R, AEI/MINECO/FEDER, UE and Severo Ochoa Excellence Accreditation 2014–2018, SEV-2013-0319) and DEC Generalitat de Catalunya (Grant 2014SGR827).

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Highly recyclable isothiourea catalysts on various polymer supports are reported for the kinetic resolution of secondary and tertiary alcohols using industrially-preferable solvents.