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Molecularly Imprinted Polymers for (Thio)urea Organocatalyst Recovery and Recycling

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Cite This: *ACS Appl. Polym. Mater.* 2022, 4, 7770−7777

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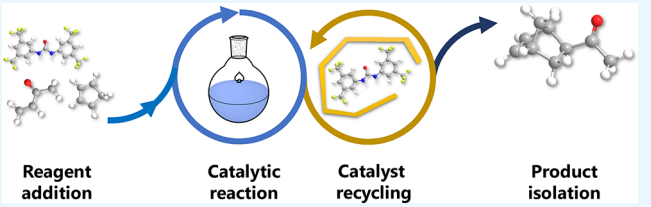
ABSTRACT: The strong binding affinity of carboxylate-based ion pair monomers toward ureas and thioureas (>10^5 L mol^{-1} in DMSO-d_6) has been utilized to prepare organocatalyst-selective molecularly imprinted polymers for the first time. These polymers exhibited exceptionally strong binding for the organocatalyst targets and were applied in the reversible capture of Schreiner's urea and thiourea from reaction mixtures. Recycling and reuse of these precious homogeneous catalysts is achieved using rapid and straightforward solid-phase extraction protocols. Catalyst recoveries of up to 98% from Diels−Alder and Baylis−Hillman reactions are demonstrated, while the polymers themselves are stable for at least 100 extraction cycles without loss of performance.



KEYWORDS: *organocatalysis, catalyst recycling, molecular recognition, molecular imprinting, polymers, solid-phase extraction*

INTRODUCTION

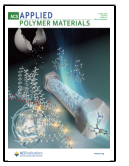
Organocatalysts are a class of chemical reaction catalysts that consist of non-metal elements and are used in a wide variety of chemical reactions, such as Diels−Alder, Michael, Mannich, and aldol reactions.[1−5] As is the case for all types of catalysts, their sustainability and the economic viability of their use are greatly improved if a catalyst can be reused for several reactions. This is particularly true for many organocatalysts, as relatively high catalyst loadings are often required. To address this, various strategies have been employed: derivatives of catalysts have been prepared that enable them to be tethered to solid supports,[6] such as polymers,[7,8] silica,[9] and MOFs.[10] However, immobilization can pose problems as, for example, the tethered catalyst often demonstrates inferior performance in terms of reaction times or product selectivity. This approach can also increase the complexity and cost, hindering the application in large-scale industrial settings, which has been highlighted for immobilized transition metal complexes.[11] Alternative approaches to covalent immobilization include the use of multiphasic systems, such as ionic liquids,[12] ionic polymers,[13] and switchable solvent systems.[14] Possibly, the simplest approach is to filter the catalyst from the homogeneous solution, as has been previously reported. Nanofiltration is indeed a promising concept that has been used to separate homogeneous organocatalysts from reaction products.[15] In the case of organocatalysis, some catalysts are not greatly different in size from the products; therefore, derivatization of the catalyst may still be required.[16,17]

Here, we present the use of molecularly imprinted polymers (MIPs) as selective sorbents for organocatalyst recovery and recycling. MIPs are a class of porous solid materials that have memory for specific molecules or groups of molecules due to the formation of selective binding sites within the polymer matrix during their synthesis, by templated polymerization.[18] MIPs have been used for the selective binding of target molecules in a wide range of applications but have not been widely exploited for the separation of organocatalysts. Tang and co-workers reported photo-switchable MIP systems, which used UV light to induce a trans to cis isomerization in azobenzene functionalized polymers.[19,20] Initially, this photo-isomerization was used to control the capture and release of an L-proline catalyst from the polymer. Later, a proline derivative was built into the polymer structure, and the azobenzene motif was used to controllably block the catalyst site and hinder the reaction. In the present study, we present the development of efficient and robust MIPs that can separate organocatalysts via a simple filtration process.

RESULTS AND DISCUSSION

In order to develop such MIPs, we chose Schreiner's thiourea and urea catalysts (STU and SU in Figure 1) as the templates. These catalysts have been used in a wide range of chemical reactions but can also demonstrate a proof of concept for the separation of urea type catalysts, which are an important class of organocatalysts.[21] In terms of designing polymers that would have a high affinity for these hydrogen bond donor

Received: July 29, 2022
Accepted: September 16, 2022
Published: September 28, 2022



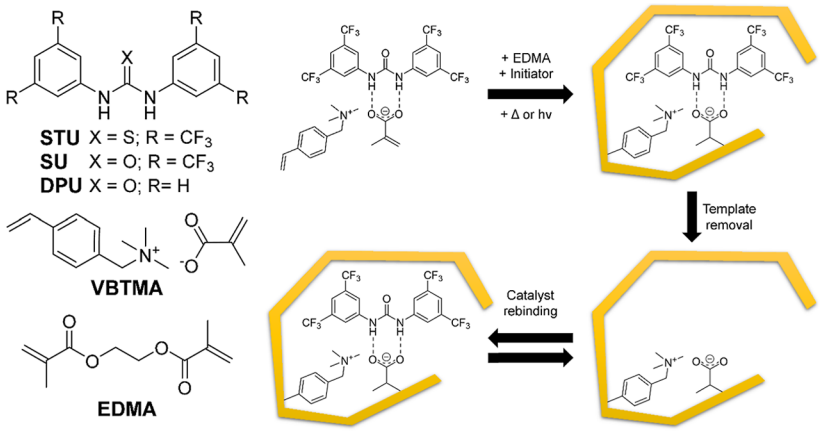


Figure 1. Structure of *N,N′*−bis[3,5−bis(trifluoromethyl)phenyl]−thiourea (Schreiner's thiourea—STU), *N,N′*-bis[3,5−bis(trifluoromethyl)-phenyl]−urea (Schreiner's urea—SU), DPU, ion pair monomer VBTMA, and overview of polymer synthesis.

catalysts, we decided to explore the use of ion pair monomers (Figure 1).

Previous work in our laboratory exploring MIPs for the recognition of sulfonylurea-based drugs indicated that ion pair monomers such as 4-(vinylbenzyl)-trimethylammonium methacrylate (VBTMA) had advantages over using simple monomers such as methacrylic acid.[22,23] Ion pairs offer the possibility of a higher number and strength of interactions with the target molecules, and it was previously shown that the resultant polymers do not need to be regenerated due to the occurrence of ion exchange. A number of such polymers were synthesized for this study, and their composition is summarized in Table 1.

Table 1. Composition of Imprinted and NIPs Used in This Study[a]

polymer ID	template	ratio FM/T/CL	initiation
MIP1	STU	1:1:20	Δ (ABDV)
NIP1		1:1:20	Δ (ABDV)
MIP2	SU	1:1:20	Δ (ABDV)
NIP2		1:1:20	Δ (ABDV)
MIP3	SU	1:1:20	UV (IRG184)
NIP3		1:1:20	UV (IRG184)
MIP4	STU	4:4:20	Δ (ABDV)
MIP5	SU	4:4:20	UV (IRG184)
MIP6	DPU	4:4:20	UV (IRG184)

[a]In all cases, VBTMA was used as functional monomer, EDMA as a cross-linker, and acetonitrile as a porogen. The free-radical initiator was 2,2′-azobis-(2,4-dimethylvaleronitrile) (ABDV) or 1-hydroxycyclohexyl phenyl ketone (IRG-184).

The binding strength between the functional monomers and the template plays a key role in determining the quality of the binding cavities obtained within the final MIP. Therefore, before polymerization, monomer-template complexation was studied by ^{1}H nuclear magnetic resonance (NMR) titrations to ascertain the strength and type of interactions between the (thio)ureas and the functional monomers. This data and further discussion are shown in the Supporting Information, Figures S1 and S2. When examining VBTMA, it was found that STU had the strongest interactions followed by SU and then diphenyl urea (DPU), which follows the trend for the p*K*a values in DMSO-d_6 (8.5, 13.8, and 18.7, respectively). Job plots confirmed that all three catalysts formed 1:1 complexes with the ion pair monomer. It was also found that increasing the alkyl chain length of the quaternary ammonium salt (from 1 to 4 carbons) and the use of 4-vinylbenzoic rather than methacrylic acid as the counterion do not improve the complexation of the templates with the monomers (data not shown). Therefore, VBTMA was used as the functional monomer as it is the simplest and least expensive to prepare.

The general polymer synthesis approach is illustrated in Figure 1. Briefly, to a solution of the template and monomer, ethyleneglycol dimethacrylate (EDMA) as the cross-linking agent and a free-radical initiator are added, and the polymerization is initiated either thermally or using UV irradiation. Corresponding non-imprinted polymers (NIPs) were also prepared omitting the template during the synthesis. In this study, polymers were made using a functional monomer/template/cross-linker (FM/T/CL) ratio of 1:1:20 and 4:4:20. In the case of the 4:4:20 polymers, the corresponding NIPs could not be prepared due to the limited solubility of the functional monomers in acetonitrile in the absence of a template. Following the polymerization, MIP and NIP monoliths were coarsely ground, and the template and unreacted monomers were removed by Soxhlet extraction with 10% formic acid in methanol. The extracts were analyzed by high-performance liquid chromatography (HPLC) and NMR as it was hoped that the template catalysts could be recovered using the MIP they had been used to create. This was found not to be feasible when STU was used as the template, as significant catalyst decomposition was detected. The decomposition was confirmed to be happening during the polymerization stage rather than the washing stage by dissolving STU in acetonitrile in the presence of a radical initiator and analyzing this mixture directly. The same signals observed in the extraction solution were found in this acetonitrile solution by HPLC and ^{19}F NMR. These findings are consistent with previous studies exploring the reactivity of similar (thio)urea molecules in polymerization reactions[24,25] and act as free radical scavengers.[26] We also found that the degradation of STU had a significant influence on the quality of the corresponding imprinted polymers; however, urea templates were stable in the presence of free radicals. SU was thus successfully recovered in pure form from the washing solution using the MIP it had been used to synthesize.

In order to compare the performance of the MIPs and NIPs synthesized and their ability to recapture the templates,

https://doi.org/10.1021/acsapm.2c01308
ACS Appl. Polym. Mater. 2022, 4, 7770−7777

equilibrium rebinding experiments were carried out for each of the prepared polymers. These experiments are carried out by allowing a standard amount of polymer to equilibrate with various concentrations of the target catalyst and then measuring the amount of free catalyst left in solution by HPLC. Although STU exhibited the strongest interactions with the VBTMA monomer, the effect of STU breakdown during polymerization can be seen in Figures 2 and 3. Thus, it

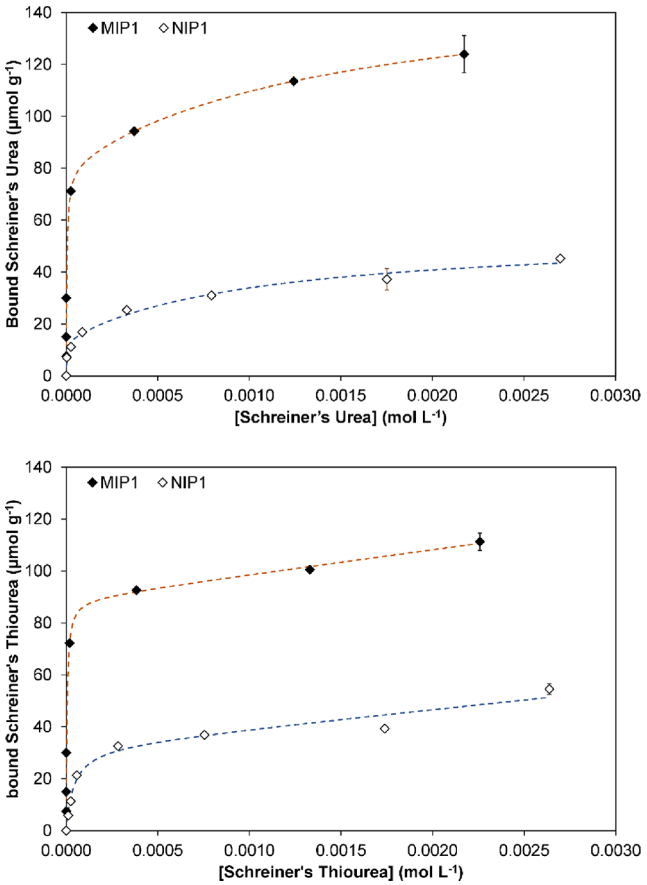


Figure 2. Urea (top) and thiourea (bottom) catalyst equilibrium rebinding isotherms for MIPs prepared with an FM/T/CL ratio of 1:1:20 and STU as the template.

was found that MIP2, despite being templated with the SU, had a higher capacity for the STU compared with the STU imprinted MIP1. UV initiated free radical polymerization was also found to give polymers with superior capacity than their thermally initiated counterparts as shown in Figure 3. At higher temperatures, such as those required for thermal initiation, the non-covalent interactions between the VBTMA monomer and the template are disrupted, and the template and monomer spend more time un-complexed in the polymerization mixture, resulting in fewer specific binding sites in the corresponding imprinted polymer. Nevertheless, as evidenced from the isotherms shown in Figure 3, templated polymers performed much better than the corresponding NIPs. Indeed, the binding capacities for SU were 124.4 μmol g^{-1} on MIP2 and 192.9 μmol g^{-1} on MIP3, versus 68.7 μmol g^{-1} and 69.8 μmol g^{-1} on NIP2 and NIP3, respectively. The corresponding capacities for STU were 138.5 and 171.6 μmol g^{-1} on MIP2 and MIP3 and 64.5 and 76.8 μmol g^{-1} on the corresponding control polymers. These values suggest that although SU is a better

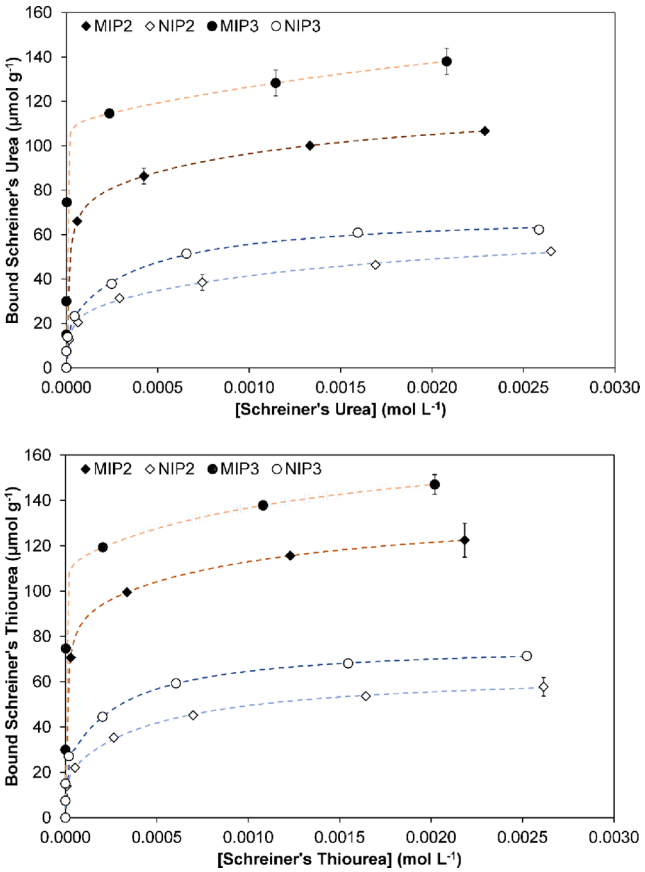


Figure 3. Influence of initiation method on the performance of the polymer rebinding of urea (top) and thiourea (bottom) catalysts, for polymers prepared with an FM/T/CL ratio of 1:1:20.

template in terms of stability during polymerization, the resulting polymers exhibit comparable binding properties for both SU and STU, which is a valuable feature when it comes to applying these materials in organocatalyst recovery. It is noteworthy that due to the exceptionally strong binding demonstrated at the low end of the concentration range, whereby the imprinted polymers removed nearly 100% of the catalyst, we were not able to accurately determine binding affinity constants for these materials; however, these are estimated to be in the range of 10^5 to 10^6 mol L^{-1} using a Langmuir or Bi-Langmuir model.

In an effort to introduce a higher population of binding sites within the MIPs and thus increase their binding capacities, the ratio of monomer/template/cross-linker was increased 4-fold from 1:1:20 to 4:4:20. In theory, these MIPs should have 4 times the number of binding sites and 4 times the capacity of the previously made polymers. Indeed, it was found that the capacity scales almost linearly and the MIPs are capable of binding much greater amounts of catalyst, well above 500 μmol g^{-1} in the case of SU binding on MIP5. It is noteworthy that the theoretical maximum capacity of the 1:1:20 polymers is ~220 μmol g^{-1} and that of the 4:4:20 polymers is ~500 μmol g^{-1}. Thus, the prepared polymers contained 50−90% of the theoretically available active binding sites, suggesting that a high proportion of the complexes between functional monomer and template was converted to active binding sites. Figure 4 shows the equilibrium rebinding isotherms obtained with these MIPs for the recapture of SU and STU. The benefit of using the polymerization stable urea templates and UV

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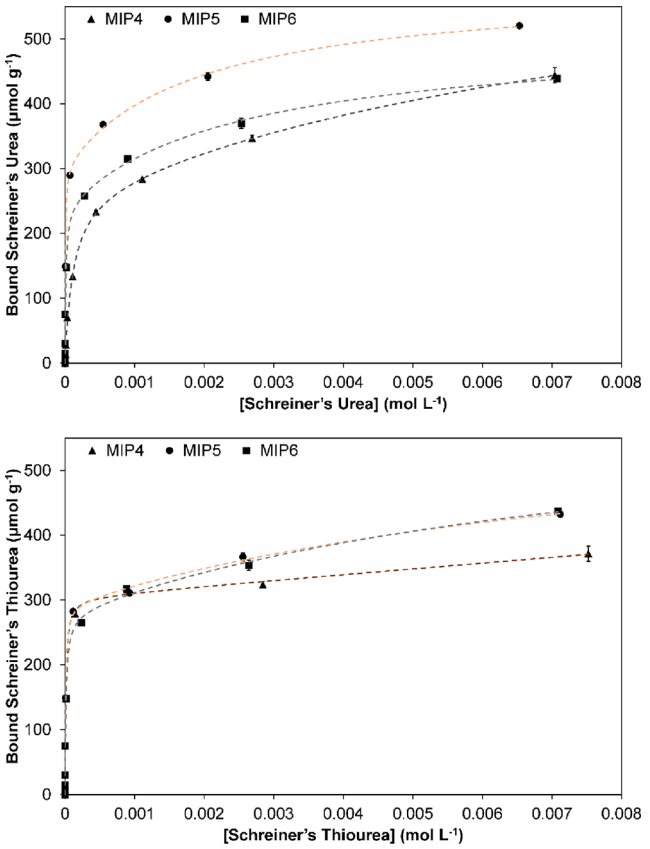

Figure 4. Urea (top) and thiourea (bottom) catalyst equilibrium rebinding isotherms for MIPs prepared with an FM/T/CL ratio of 4:4:20.

initiation can again be seen with both MIP5 and MIP6 outperforming MIP4. There was, however, no discernible difference in uptake of SU when comparing the SU templated MIP5 with the DPU templated MIP6. No further attempts were made to increase the binding capacity of the polymers, as the solubility limit of the monomer and templates in the used porogen was reached. MIP5 was therefore selected to be used in catalyst recycling experiments.

SU and STU were then used as organocatalysts in a number of chemical reactions, whereby a reaction−recovery−recycle workflow was developed. The recovery procedure was based on a simple solid-phase extraction (SPE) protocol: the crude reaction mixtures were poured into the cartridge, and the contents were percolated through the polymer bed using mild vacuum. The catalyst bound on the selective sites within imprinted polymer as the rest of the reaction mixture components passed through. Finally, once all contaminants had been satisfactorily removed from the cartridge, the catalyst was eluted in its pure form using a polar solvent, usually a MeOH/formic acid mixture. The elution solvent was finally evaporated, and the catalyst was directly reused in further reactions.

We initially studied the Diels−Alder reaction between cyclopentadiene and methyl vinyl ketone using 1 mol % STU as the catalyst (Figure 5). Reaction progress was monitored by GC, and reaction profiles of both the catalyzed and uncatalyzed reactions were obtained in order to establish the yield versus time for both reactions to reach completion (Figure S4 in Supporting Information). When carrying out catalyst recycling studies in a batch operation, it is important that reactions are not run to completion or given too long a reaction time as this can mask catalyst deactivation and loss.[27] This is particularly important in the case of reactions where the reaction can still proceed in the absence of catalysts as is often the case with organocatalytic processes. It was thus decided to examine the recycling of the catalyst when the Diels−Alder reaction had been run for 2 h. An SPE protocol that allowed the catalyst to be recovered in pure form was developed (Table S3 in Supporting Information). Each fraction of the SPE procedure was evaporated to dryness and re-dissolved in acetonitrile prior to analysis for catalyst content. The vast

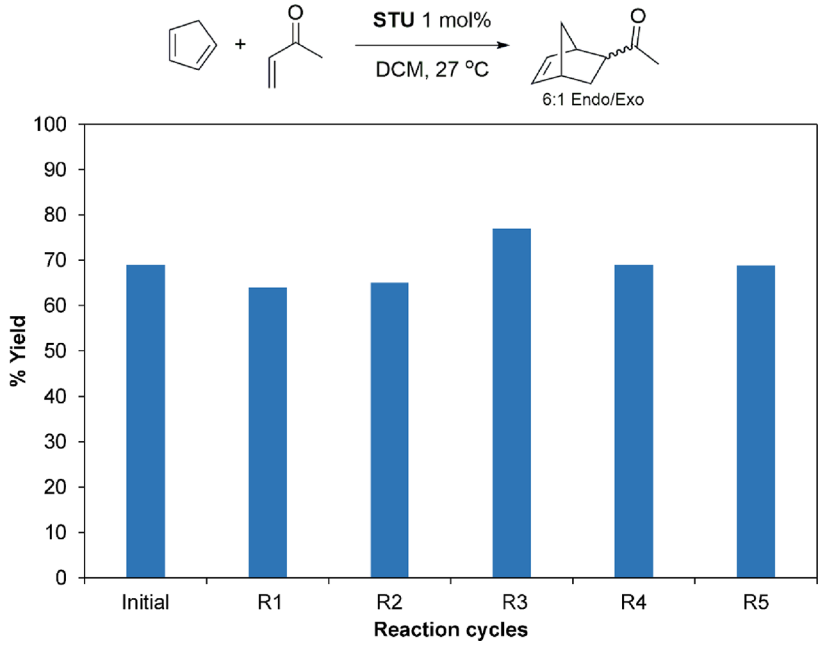

Figure 5. Diels−Alder reaction conditions (top) and reaction yield after 2 h over five reaction cycles (bottom).

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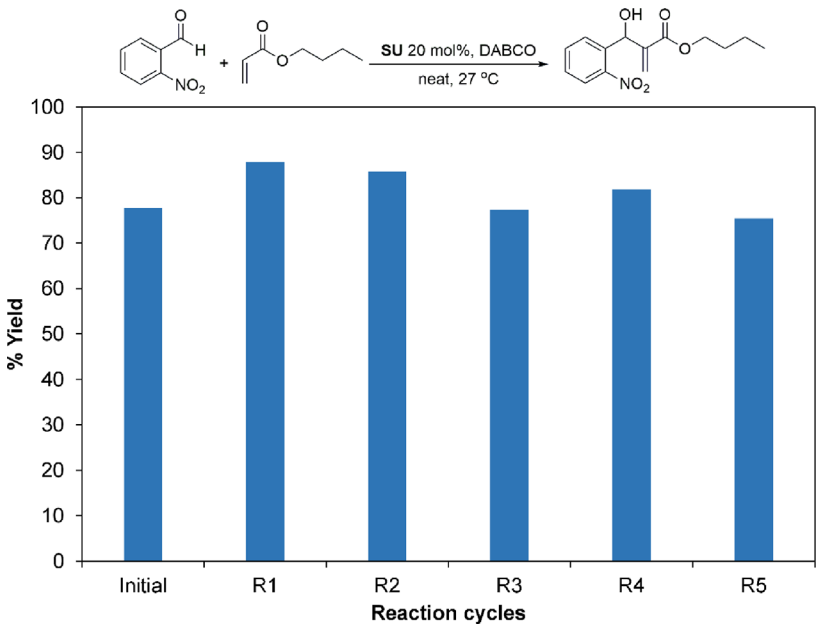

Figure 6. Baylis–Hillman reaction conditions (top) and reaction yield after 3 h over five reaction cycles.

majority of reaction product was found in the load fraction with traces in the wash fraction and was not retained by the polymer, while the catalyst was recovered in the final elution step and was not detected in any of the other fractions. After five recycles and repeats of the reaction, 90% of the catalyst was finally recovered, which corresponds to an average catalyst recovery of 98% after each cycle, while the reaction yield was consistent throughout, suggesting that the catalyst was as effective after five cycles as after the first cycle. Indeed, the catalyst recovered after five reaction cycles was analyzed by HPLC, ^{1}H, and ^{19}F NMR, and all collected data matched those of the fresh catalyst (Figures S5 and S6 in Supporting Information).

It was then decided to apply the catalyst recovery protocol to a more challenging reaction, namely, the Baylis–Hillman reaction of 2-nitrobenzaldehyde with butyl acrylate using DABCO and SU as the catalyst (Figure 6). Plots of the catalyzed versus uncatalyzed reaction were constructed (Figure S8 in Supporting Information) and a marked difference between the two reactions was observed when using a loading of 20 mol % SU, the amount employed in a previous study by Maher and Connon.[28]

When developing the SPE procedure, it was found that the SU catalyst was breaking down during the reaction, possibly due to the presence of the base. It is worth noting than in the study that first described this method, the authors recovered the SU catalyst from the reaction mixtures by column chromatography. The recovery varied depending on the reaction, but the average yield of catalyst recovered was 86%, which is in good agreement with Maher and Connon, who recovered this catalyst via column chromatography.[28] In our studies, analysis of the catalyst breakdown by HPLC revealed consistent catalyst decomposition of approximately 20% per reaction cycle. In contrast to the Diels–Alder reaction, it was found that multiple wash steps were required to fully remove undesired adsorbates from the MIP cartridge. The presumed breakdown products of the catalyst necessitated the use of a polar acetonitrile/H_2O second wash step to be removed, indicating that they were relatively strongly bound to the MIP. ^{19}F NMR analysis of this second wash fraction confirmed that these were indeed catalyst breakdown products, as evidenced by the plethora of peaks in the corresponding spectrum (Figure S10 in Supporting Information). Despite using a polar wash mixture, the MIP was able to capture the intact SU catalyst more strongly than the breakdown products, and no catalyst was recovered during this step. The HPLC traces of the post-reaction mixture and the catalyst obtained after the SPE procedure are shown in Figure 7.

A reaction time of 3 h was chosen for the recycling reactions. As previously stated, approximately 20% of the urea catalyst breaks down with each run, but this decrease in catalyst loading with each subsequent run was not reflected in the yield of product obtained, which remained relatively stable over the course of the five reaction cycles (Figure 6). Taking into account that 20% of the catalyst decomposes, the amount of catalyst recovered after each run was measured (Figure S12 in Supporting Information). As it can be seen, the MIP delivers recoveries ranging between 83 and 100%, with an average recovery of 90%. The catalyst obtained after five recycles was analyzed by ^{1}H and ^{19}F NMR and matched that of the fresh catalyst (Figures S9 and S11 in Supporting Information).

Losing 20 mol % catalyst with each reaction due to catalyst decomposition means that the catalyst loading for R5 was ~6.5 mol %. Control reactions using fresh catalyst at a loading of 10 mol % were found to give an identical yield to that of 20 mol % (Figure S13). When a catalyst loading of 5 mol % was used, an yield of 70% was obtained after 3 h. This unexpected finding may be explained by the propensity of the (thio)urea catalysts to self-aggregate in solution, particularly the ureas due to the high hydrogen bond accepting ability of the oxygen atom.[29] The degree of aggregation depends on the solvent, substrates used, and temperature. This self-association results in the lower solubility of ureas compared with thioureas in non-polar solvents. Given the high catalyst concentrations used in this reaction ([Schreiner urea] = 0.14 M) and the fact that the reaction is carried out neatly in the relatively non-polar butyl acrylate, self-association of the catalyst is likely. If extensive aggregation of the catalyst occurs, the N–H bonds are no

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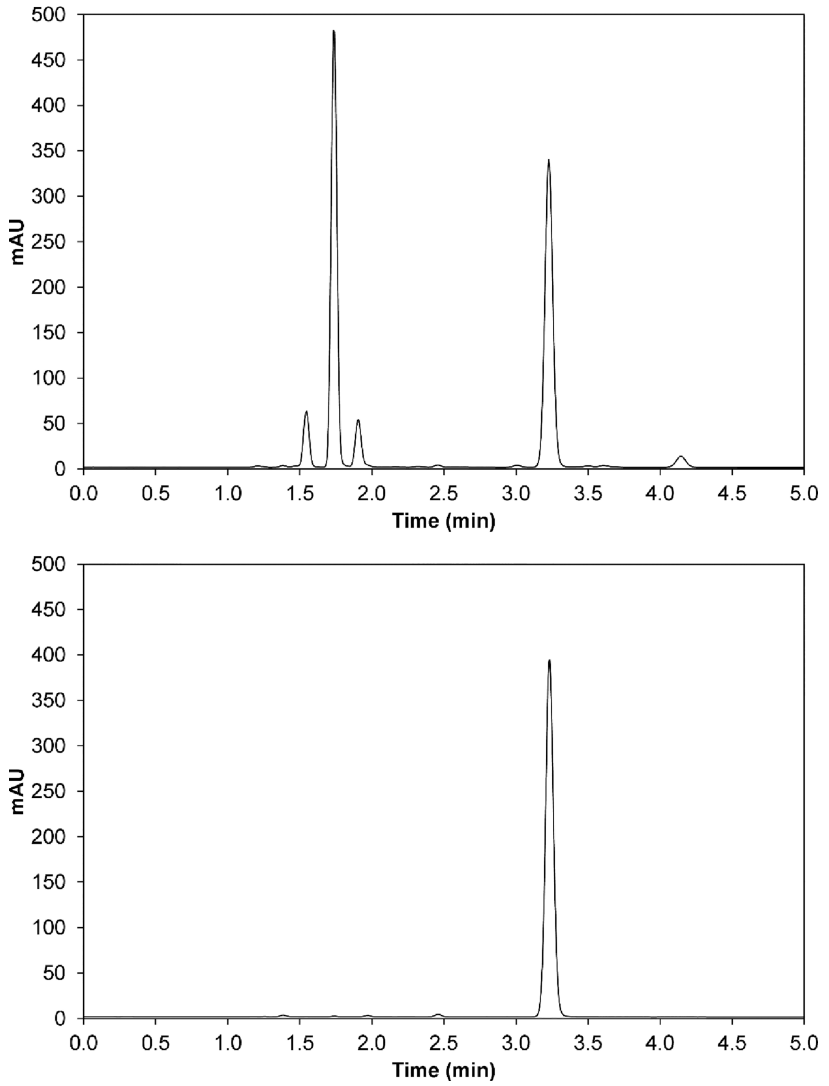

Figure 7. HPLC chromatograms of Baylis–Hillman reaction mixture showing 2-nitrobenzaldehyde (1.5 min), butyl acrylate (1.7 min), and SU (3.25 min) (top) and the recovered SU catalyst (bottom).

longer readily available to activate the substrates, and the effective amount of active, monomeric catalyst in solution could be much lower. Song and co-workers performed ^{19}F DOSY NMR analysis on a bifunctional thiourea catalyst at varying concentrations ranging from 100 to 0.5 mol % catalyst loading in $CDCl_3$, observing faster diffusions at lower catalyst loadings due to less catalyst aggregation.[30]

As a final validation of the superior performance of the organocatalyst selective materials presented in this study, we tested the commercially available DOWEX MAC-3, an ion exchange resin with protonated carboxylic acid functional groups, in the capture of STU. The resin was activated by washing with a tetrabutylammonium hydroxide solution to deprotonate the acid functional groups, before a solution of the thiourea catalyst was passed through. The load fraction was analyzed by HPLC and was found to contain 97% of the STU catalyst, showing that the STU catalyst was not retained by this resin.

CONCLUSIONS

In conclusion, we have demonstrated the use of multifunctional ion pair monomers as binding elements in the molecular imprinting of urea and thiourea organocatalysts. The VBTMA monomer was found to have the highest affinity for the (thio)urea catalysts studied, with association constants $>10^5$ M^{-1} in DMSO-d_6. Polymerization using ureas as templates and UV initiated free radical polymerization gave rise to the best performing polymers, while thioureas were found to be unsuitable as templates due to their decomposition during polymerization. The templated urea catalysts were also shown to be recyclable from Soxhlet extraction solutions using the MIP that they had been used to synthesize. Using the best performing imprinted polymer (MIP5), both Schreiner's urea and thiourea were captured from homogenous reaction mixtures and isolates as pure catalysts. Furthermore, MIP5 was reused over 100 times for catalyst recapture without any loss in performance. A comparison between MIP5 and the commercially available DOWEX MAC-3 resin showed that the ion exchange resin was not capable of binding these catalysts from solution. Coupled with the significantly smaller volumes of solvent required for SPE extraction compared to conventional column chromatography, the materials developed in this work are proposed as greener and more desirable sorbents for recovery of urea and thiourea organocatalysts. These materials

https://doi.org/10.1021/acsapm.2c01308
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are currently applied in the recovery of other H-bond donor organocatalysts, such as squaramides and binol derivatives, while their production in larger quantities by suspension polymerization is also being explored. The resulting narrow-dispersed spherical particles should exhibit improved flow characteristics as well as mechanical stability compared to ground particles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsapm.2c01308.

Materials and methods, experimental details, reaction conditions, kinetic plots, and analytical methods (PDF)

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Author Contributions

F.P. and M.B. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Joseph Magill Foundation and the Department for the Economy (NI) for PhD scholarships to F.P. and M.B., respectively.

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https://doi.org/10.1021/acsapm.2c01308
ACS Appl. Polym. Mater. 2022, 4, 7770−7777