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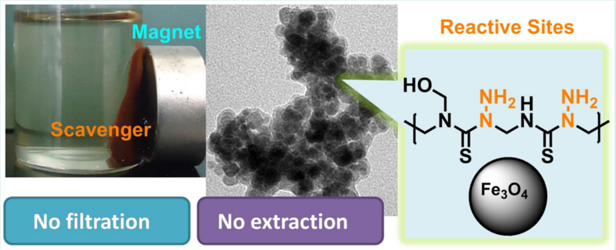
Magnetically Retrievable Nanocomposite Based on Thiosemicarbazide−Formaldehyde Resin as a Versatile Nucleophilic Scavenger

Maomin Zhen, Danfeng Zhang, Zeyu Zhang, and Yanqing Peng*

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China

Ⓢ *Supporting Information*

ABSTRACT: A magnetically retrievable nanocomposite was prepared by in situ polycondensation and entrapment of iron oxide nanoparticles. This material was found to be efficient in trapping excess electrophilic reagents such as carbonyl compounds, acid chlorides and isothiocyanates. Advantages of the new scavenger include facile preparation, high loading capacity, low cost, satisfactory swelling properties in polar solvents, and convenient magnetic recovery.



KEYWORDS: *purification, scavenger, nanocomposite, polycondensation, magnetic separation*

Combinatorial synthetic techniques are widely applied in pharmaceutical and agrochemical research for the synthesis and identification of new leads by screening and optimization of drug candidates.[1] Among the routine strategies of combinatorial chemistry, solution-phase synthesis offers many advantages over solid-phase ones, such as homogeneous reaction conditions and easier analysis and manipulation.[2] To aid in the rapid purification or isolation of desired compounds from homogeneous reaction mixtures, scavenger resins of varying types have been employed to remove impurities, byproducts, or desired products.[3] While a number of scavenger resins are available commercially, there is considerable scope for improvement. For example, the use of functionalized ionic liquids as novel scavengers has been reported by our group[4] and others.[5]

Most commercially available polymeric scavengers are based on cross-linked polystyrene gel-type resins sized on the micrometer scale. As is well-known, when the size of a heterogeneous reagent is decreased to the sub-micrometer or nanometer scale, the reagent can be dispersed in reaction media to form quasi-homogeneous systems with improved mass transfer characteristics. However, the isolation of such nanoreagents is also a problem because of their small dimensions. A convenient solution to this problem is magnetic separation, which has been applied most often to nanosized heterogeneous catalysts[6] but not commonly to scavengers. Recent examples include magnetic aminomethylated polystyrene resin as a scavenger of sulfonyl chlorides,[7] and magnetically recyclable reagents and scavengers based on Co/C or Fe/C nanoparticles from Reiser and co-workers.[8]

Thiosemicarbazide−formaldehyde resin has previously been reported as a polymeric ligand (polychelate); showed antibacterial activities after forming complexes with transition metal cations such as Cu(II).[9] However, no effort has been made to use this material in synthetic chemistry. We reasoned that such a polymer could be used as a scavenger due to the reactivity of the hydrazino groups on thiosemicarbazide with a range of reagents. Herein a new and convenient method for the synthesis of a magnetic nanocomposite based on thiosemicarbazide−formaldehyde resin (denoted as TFR) was reported, and its use as a hydrazide-type nucleophilic scavenger for solution−phase parallel synthesis. The distinctive advantages of this novel scavenger include (1) facile preparation procedure, polycondensation between thiosemicarbazide and formaldehyde is a very simple operation, needing no special apparatus or manipulation; (2) high loading, hydrazino groups are brought into the material as part of each monomer rather than by post-synthetic functionalization; (3) low cost, the two monomers are inexpensive and readily available (thiosemicarbazide = USD \$130/500 g, from Sigma-Aldrich); (4) satisfactory swelling in polar solvents; (5) regenerable after scavenging; and (6) readily recovered by laboratory magnets, making filtration and extraction manipulations unnecessary. For these reasons, this new resin is well suited for application in both small-scale laboratory synthesis and scaled-up processes.

Thiosemicarbazide−formaldehyde resin (TFR) was previously synthesized via polycondensation between thiosemicarbazide and formaldehyde at 40 °C for 24 h using DMF as a solvent.[9] Because both thiosemicarbazide and formaldehyde are water-soluble reagents, we performed this condensation reaction in water containing 10 mol % acetic acid and were

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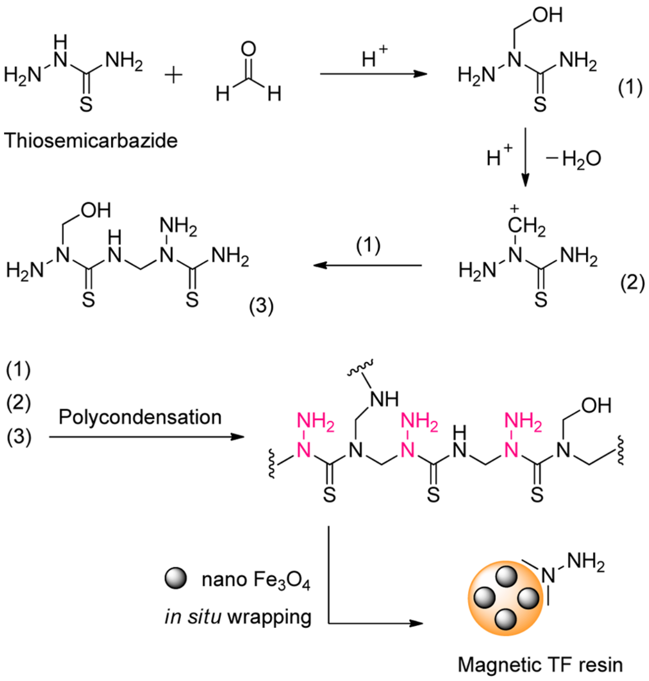
delighted to find that it proceeded smoothly at 40 °C, affording desired product in 82% yield after drying. While TFR has been reported to be insoluble in water, methanol, ethanol and nonpolar solvents but soluble in THF, DMF and DMSO at room temperature, our material was insoluble in common organic solvents including THF and DMF. We assume this is due to more extensive cross-linking, perhaps occurring at the sites of hydroxymethyl groups under the influence of acidic catalyst as shown in Scheme 1.

Scheme 1. Synthesis of Magnetic TFR Nanocomposites and Proposed Crosslinking Mechanism



Solvent-induced swelling is usually essential to the use of a polymer scavenger in purification operations, since this promotes diffusion of reagents or impurities through the material. The swelling property of TFR was measured by a standard method[10] and reported in percentage terms in Figure 1. Substantial swelling was observed in polar solvents such as alcohols, water, and DMF, with relatively poor swelling in water and low-polarity solvents. Since many reactions in drug synthesis are carried out in polar solvents, but many polystyrene-based scavengers are poorly swelled in these solvents, the TFR material is a beneficial supplement to the toolbox of combinatorial synthetic chemistry.

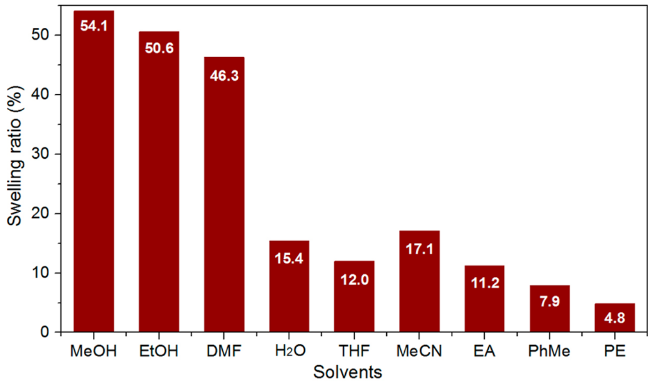


Figure 1. Swelling behavior of TFR prepared in this work.

To allow for efficient manipulation in parallel purifications, a magnetic TFR nanocomposite was prepared by the direct incorporation of Fe_3O_4 particles into the resin matrix in a one-pot process (Scheme 1). To a stirred suspension of Fe_3O_4 nanoparticles in aqueous solution of thiosemicarbazide containing 10 mol % acetic acid was added dropwise 37% formaldehyde under continuous stirring. After 24 h, the resulting solid products were separated magnetically and washed several times with distilled water, DMF and ethanol to remove impurities. It was presumed that the formation of this nanocomposite included not only physical entrapment but also chemical anchoring. TFR is an efficient polymeric chelate to transition metal cations; therefore the polymer might anchor onto the magnetite through coordination interactions between the chelating groups in polymer chain and the nanoparticle surface.

The surface morphology of magnetic TFR was observed by scanning electron microscopy (SEM) as shown in Figure 2A. It shows that the resin particles present regular surface morphology of aggregates. Microstructural features of the magnetic TFR were characterized by transmission electron microscopy (TEM, Figure 2B). In this representative image, the dark points are magnetite nanoparticles (average size around 25 nm) and the light gray domain is the polymeric matrix of TFR (Figure 2B). The sample shows a typical nanostructure of an inorganic−organic hybrid nanocomposite.

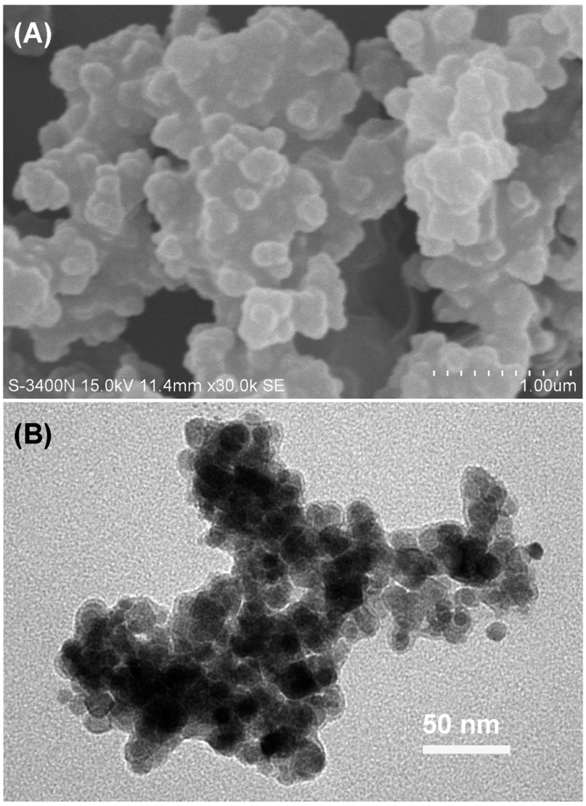


Figure 2. SEM and TEM images of magnetic TFR.

Thermogravimetric analysis (TGA) of magnetic TFR under air atmosphere showed the main weight loss in the range of 215−345 °C, indicating thermal decomposition of TFR in that range (Figure 3). Weight loss below 150 °C is assigned to the removal of physically adsorbed water. Magnetite was found to represent approximately 63% of the mass of the material.

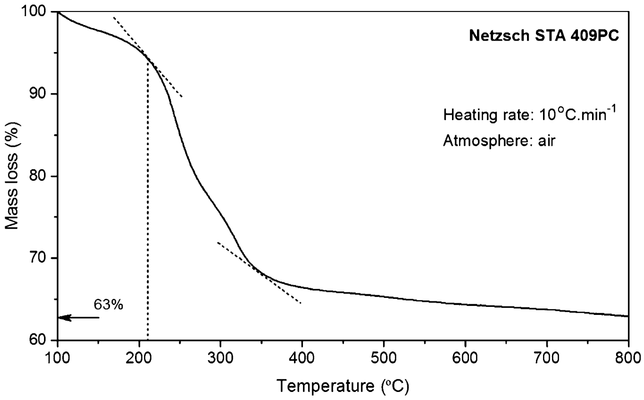


Figure 3. Thermogravimetric analysis curve of magnetic TFR.

The use of magnetic TFR as scavenger was first demonstrated in the sequestration of aldehydes using 2-hydroxy-5-phenylazo salicylaldehyde as a chromogenic reagent (Figure 4). An orange solution of this reagent was decolorized with magnetic TFR in approximately 8 h in methanol. In contrast, unsatisfactory results were obtained in toluene and THF and intermediate scavenging rate was observed in acetonitrile, reflecting the swelling properties of the resin. Because no other semicarbazide-type scavenger has been reported in the literatures, we compared this performance to a known polymer-supported benzylhydrazine resin,[11] which required 24 h and a small amount of catalyst to remove the same amount of aldehyde as sequestered by magnetic TFR within 8 h in refluxing MeOH without any catalyst.

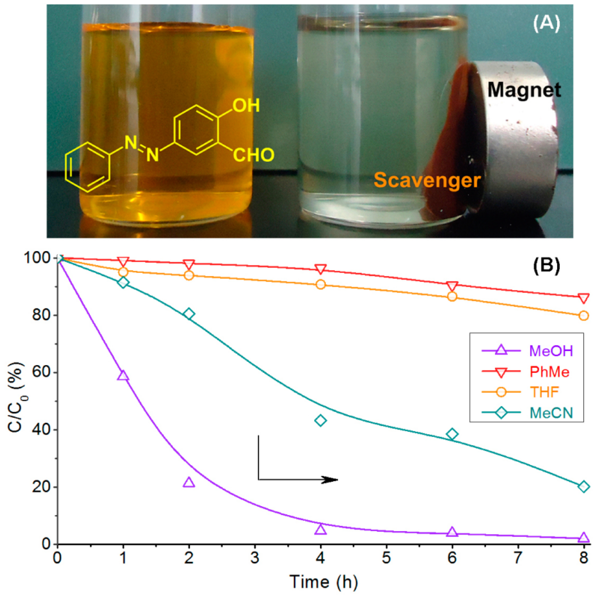


Figure 4. Sequestration of 2-hydroxy-5-phenylazo salicylaldehyde (1 mmol in 15 mL solvents) by magnetic TFR (4.00 g) at 65 °C in different stirred solvents.

The loading capacity of accessible hydrazino groups in magnetic TFR was determined by saturation with excess benzaldehyde in methanol, revealing there to be approximately 0.82 mmol of available hydrazines per gram of resin. Benzaldehyde and acetophenone were taken up with similar time-course profiles by magnetic TFR (molar ratio of hydrazino:carbonyl groups = 3:1), with scavenging of the ketone occurring somewhat more slowly as expected.

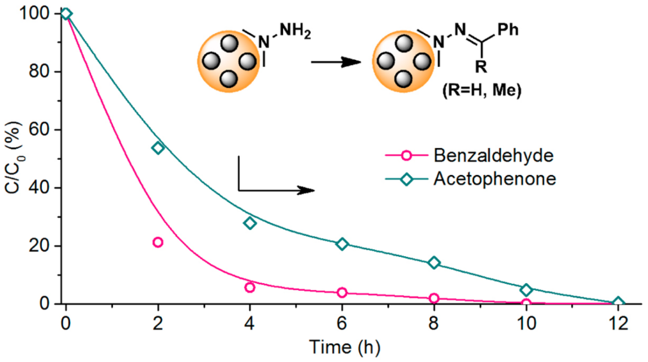


Figure 5. Kinetic profiles in the capture of representative aldehyde and ketone.

Regeneration[12] of magnetic TFR was thought to be feasible because thiosemicarbazides make less stable hydrazones than do hydrazines. The trapping of 4-cyanobenzaldehyde by magnetic TFR was followed by FTIR spectroscopy, monitoring the characteristic CN absorption band around 2240 cm^{-1} (Figure 6A, B). The resin was then treated with 80% hydrazine monohydrate (5 equiv) in refluxed methanol for 8 h. Quantitative removal of the aldehyde was shown by the complete disappearance of the CN band (Figure 6C), and the resulting resin was indistinguishable from freshly prepared material in subsequent scavenging tests.

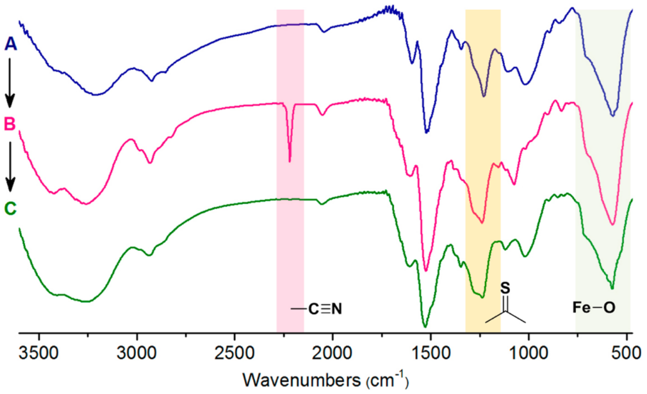
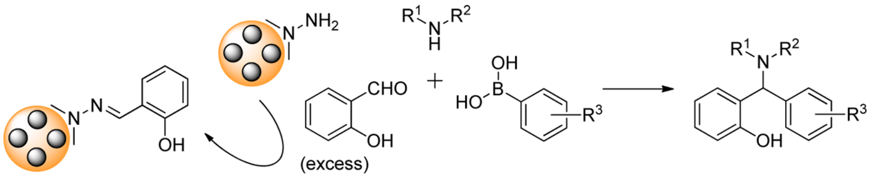


Figure 6. FTIR spectra of (A) fresh, (B) used, and (C) regenerated scavengers.

The use of magnetic TFR in the context of chemical synthesis was illustrated with the three-component Petasis borono−Mannich reaction involving a boronic acid, an amine, and an aldehyde.[13] Eight variations of the reaction were performed; in each case, a 1.5-fold excess of salicylaldehyde was used to ensure the consumption of the other substrates. Upon completion of the reaction (as monitored by TLC), magnetic TFR (3 equiv with respect to excess reagent) was added to react with the excess salicylaldehyde, after which the resin was magnetically separated and the resulting solution evaporated. All of the reactions in this exercise were conducted on a scale of

Table 1. Petasis Reaction among Salicylaldehyde, Secondary Amines,and Arylboronic Acids Using Magnetic TFR as Scavenger[c]



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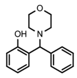
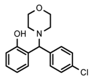
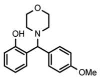
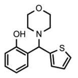
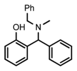
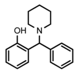
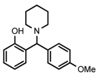
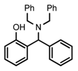
	Time:15h [a]Yield:88% [b]Purity:96%		Time:17h Yield:84% Purity:97%		Time:13h Yield:89% Purity:96%		Time:16h Yield:88% Purity:96%
	Time:18h Yield:84% Purity:94%		Time:13h Yield:86% Purity:95%		Time:16h Yield:88% Purity:95%		Time:20h Yield:87% Purity:95%

[a]Isolated yields. [b]Purity was determined by HPLC. [c]Reagents and conditions: amine (2 mmol), arylboronic acids (2 mmol), salicylaldehyde (3 mmol), magnetic TFR (3.65 g, 3 mmol), MeOH (5 mL), reflux.

2 mmol of substrates using 5 mL of solvent, and the results obtained are summarized in Table 1. Yields were generally in the 84−89% range, and the final products were found to be free of aldehyde and essentially pure even in cases in which yields were not so high. All of the products have been previously reported and characterized by ^{1}H and ^{13}C NMR.

We also performed scavenging experiments using magnetic TFR to sequester other representative electrophiles such as benzoyl chloride and phenyl isothiocyanate from solution (1 mmol in 5 mL acetonitrile, respectively) monitored by GC (Figure 7). At ambient temperature, when using three equivalent of scavenger resin (hydrazino groups relative to the excess electrophilic reagent), 99% of benzoyl chloride and 92% of phenyl isothiocyanate was sequestrated within 3 h. After 5 h, the isothiocyanate was no longer detectable in the mixture. Magnetic TFR should also be a suitable scavenger for other electrophiles such as sulfonyl halides and isocyanates. It should be noted that, while the resin could be regenerated after reaction with aldehydes and ketones, regeneration after loading with acid chlorides or isocyanates gave unsatisfactory results.

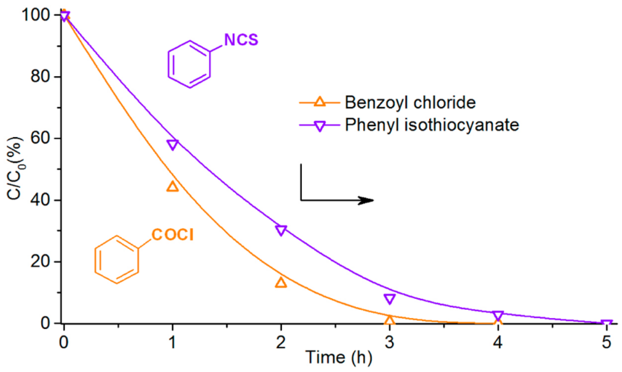


Figure 7. Removal of acid chloride and isothiocyanate by magnetic TFR.

In summary, we show here the synthesis and use of a magnetically retrievable nanocomposite based on thiosemicarbazide−formaldehyde resin as nucleophilic scavenger for the purification of solution-phase combinatorial libraries. Magnetic TFR was found to be very efficient in trapping excess reagents such as carbonyl compounds, acid chloride and isothiocyanate, and was illustrated with the Petasis reaction as a model. There advantages of this new scavenger including facile preparation, high loading capacity, low cost, and satisfactory swelling properties in polar solvents.

■ EXPERIMENTAL PROCEDURES

Preparation of Magnetic TFR. To a stirred mechanically suspension of Fe_3O_4 (50.00 g) in deionized water (500 mL) was added thiosemicarbazide (27.30 g, 0.3 mol) and acetic acid (1.80 g, 30 mmol). After the thiosemicarbazide was dissolved completely, 37% aqueous solution of formaldehyde (72.98 g, 0.9 mol) was added dropwise under continuous stirring. The mixture was then stirred at 40 °C for 24 h, while the black precipitates were collected by a magnet, washed repeatedly with deionized water (150 mL × 2) and ethanol (150 mL × 2), successively, and dried in vacuo to give magnetic TFR (82.76 g).

Regeneration of Used Magnetic TFR with Hydrazine. The label compound 4-cyano benzaldehyde (0.13 g, 1 mmol) was captured onto magnetic TFR (3.65g, 3 equiv of hydrazino groups to aldehyde) by refluxing in MeOH (5 mL) for 10 h, followed by washing with ethanol (5 mL × 4). To regenerate the used scavenger, the resin thus obtained was treated with 80% hydrazine hydrate (0.31 g, 5 mmol) in refluxed methanol (5 mL) for 8 h. The resin was collected with magnet and washed with ethanol until no species could be detected in the washing. After dried in vacuo, the resin was characterized by FTIR spectroscopy.

General Procedure for Scavenging Experiments: Petasis Reaction. Various secondary amines (2 mmol) and arylboronic acids (2 mmol) in methanol (5 mL) were intentionally treated with an excess of salicylaldehyde (0.37 g, 3 mmol, 1.5 equiv). The mixture was stirred under refluxing for 13−20 h (Table 1) until the arylboronic acids were consumed completely as monitored by TLC, after which magnetic TFR (3.65 g, 3 mmol, at a molar ratio of hydrazino groups: excess reagent 3:1) was added. The resulting suspension was stirred for further 12 h. The scavenger was isolated using a magnet and washed with methanol (5 mL × 2). The solvent in combined filtrates was evaporated off under reduced pressure, and the solid residue was washed with 1 mL of 30% aqueous EtOH to remove possible impurities. After dried under vacuum, all of the products were checked by HPLC and ^{1}H NMR and were essentially pure.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00090.

Detailed experimental procedures and analytical and spectroscopic data for all compounds described (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +86-21-64252603. E-mail: yqpeng@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Thompson, L. A.; Ellman, J. A. Synthesis and application of small molecule libraries. *Chem. Rev.* **1996**, *96*, 555−600. (b) Hall, D. G.; Manku, S.; Wang, F. Solution- and Solid-Phase Strategies for the Design, Synthesis, and Screening of Libraries Based on Natural Product Templates: A Comprehensive Survey. *J. Comb. Chem.* **2001**, *3*, 125−150. (c) Kodadek, T. The rise, fall and reinvention of combinatorial chemistry. *Chem. Commun.* **2011**, *47*, 9757−9763.

(2) (a) An, H.; Cook, P. D. Methodologies for Generating Solution-Phase Combinatorial Libraries. *Chem. Rev.* **2000**, *100*, 3311−3340. (b) Baldino, C. M. Perspective Articles on the Utility and Application of Solution-Phase Combinatorial Chemistry. *J. Comb. Chem.* **2000**, *2*, 89−103.

(3) (a) Ferritto, R.; Seneci, P. High throughput purification methods in combinatorial solution phase synthesis. *Drugs Future* **1998**, *23*, 643−654. (b) Parlow, J. J.; Devraj, R. V.; South, M. S. Solution−phase chemical library synthesis using polymer-assisted purification techniques. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336. (c) Eames, J.; Watkinson, M. Polymeric Scavenger Reagents in Organic Synthesis. *Eur. J. Org. Chem.* **2001**, *2001*, 1213−1224. (d) Seeberger, P. H. Scavengers in full flow. *Nat. Chem.* **2009**, *1*, 258−260.

(4) (a) Song, G.; Cai, Y.; Peng, Y. Amino−Functionalized Ionic Liquid as a Nucleophilic Scavenger in Solution Phase Combinatorial Synthesis. *J. Comb. Chem.* **2005**, *7*, 561−566. (b) Cai, Y.; Zhang, Y.; Peng, Y.; Lu, F.; Huang, X.; Song, G. Carboxyl−Functional Ionic Liquids as Scavengers: Case Studies on Benzyl Chloride, Amines, and Methanesulfonyl Chloride. *J. Comb. Chem.* **2006**, *8*, 636−638.

(5) (a) Lei, M.; Tao, X.-L.; Wang, Y.-G. A practical, water-soluble, ionic scavenger for the solution-phase syntheses of amides. *Helv. Chim. Acta* **2006**, *89*, 532−536. (b) Soutullo, M. D.; Odom, C. I.; Salter, E. A.; Stenson, A. C.; Sykora, R. E.; Wierzbicki, A.; Davis, J. H., Jr. Ultra-Easy Access to NH_2−Functionalized TSILs, Their Potential as Highly Volume-Efficient Electrophile Scavengers, and Insights into the Electronics of Girard's Reagent T, A Venerable Chemical Work Horse. *J. Comb. Chem.* **2007**, *9*, 571−573. (c) Muthayala, M. K.; Kumar, A. Ionic Liquid-Supported Aldehyde: A Highly Efficient Scavenger for Primary Amines. *ACS Comb. Sci.* **2012**, *14*, 5−9.

(6) Shylesh, S.; Schünemann, V.; Thiel, W. R. Magnetically Separable Nanocatalysts: Bridges between Homogeneous and Heterogeneous Catalysis. *Angew. Chem., Int. Ed.* **2010**, *49*, 3428−3459.

(7) Rana, S.; White, P.; Bradley, M. Synthesis magnetic beads for solid phase synthesis and reaction scavenging. *Tetrahedron Lett.* **1999**, *40*, 8137−8140.

(8) Kainz, Q. M.; Zeltner, M.; Rossier, M.; Stark, W. J.; Reiser, O. Synthesis of Trisubstituted Ureas by a Multistep Sequence Utilizing Recyclable Magnetic Reagents and Scavengers. *Chem. - Eur. J.* **2013**, *19*, 10038−10045.

(9) Parveen, S.; Ahamad, T.; Nishat, N. New anti-bacterial polychelates: synthesis, characterization, and anti-bacterial activities of thiosemicarbazide−formaldehyde resin and its polymer−metal complexes. *Appl. Organomet. Chem.* **2008**, *22*, 70−77.

(10) Kim, S. J.; Park, S. J.; Kim, S. I. Swelling behavior of interpenetrating polymer network hydrogels composed of poly(vinyl alcohol) and chitosan. *React. Funct. Polym.* **2003**, *55*, 53−59.

(11) Zhu, M.; Ruijter, E.; Wessjohann, L. A. New Scavenger Resin for the Reversible Linking and Monoprotection of Functionalized Aromatic Aldehydes. *Org. Lett.* **2004**, *6*, 3921−3924.

(12) Guinó, M.; Brulé, E.; de Miguel, Y. R. Recycling and Reuse of a Polymer-Supported Scavenger for Amine Sequestration. *J. Comb. Chem.* **2003**, *5*, 161−165.

(13) (a) Petasis, N. A.; Akritopoulou, I. The boronic acid mannich reaction: A new method for the synthesis of geometrically pure allylamines. *Tetrahedron Lett.* **1993**, *34*, 583−586. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. Boronic Acids and Esters in the Petasis−Borono Mannich Multicomponent Reaction. *Chem. Rev.* **2010**, *110*, 6169−6193.