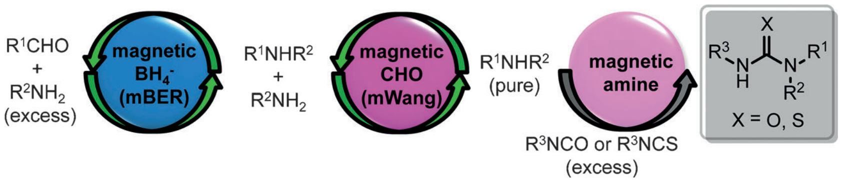

Do it magnetically! A small library of trisubstituted ureas and thioureas was synthesized in high yields and purities by a multistep sequence exclusively applying magnetic reagents and scavengers. No purification steps were necessary apart from magnetic decantation, and the resins were recycled if possible. The novel resins were conveniently and efficiently prepared starting from polymer-coated magnetic Co/C or Fe/C nanobeads by microwave protocols.

Synthetic Methods

*Q. M. Kainz, M. Zeltner, M. Rossier, W. J. Stark, O. Reiser** .... ▮▮▮▮–▮▮▮▮

Synthesis of Trisubstituted Ureas by a Multistep Sequence Utilizing Recyclable Magnetic Reagents and Scavengers

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Synthesis of Trisubstituted Ureas by a Multistep Sequence Utilizing Recyclable Magnetic Reagents and Scavengers

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Abstract: Unprecedented magnetic borohydride exchange (mBER), magnetic Wang aldehyde (mWang) and magnetic amine resins were prepared from highly magnetic polymer-coated cobalt or iron nanoparticles. Microwave irradiation was used to obtain excellent degrees of functionalization (>95 %) and loadings (up to 3.0 mmol$\,g^{-1}$) in short reaction times of 15 min or less. A small library of ureas and thioureas was synthesized by the exclusive application of these magnetic resins. As a first step, a reductive amination of aromatic and aliphatic aldehydes was carried out with mBER. The excess of primary amine needed to complete the reaction was subsequently scavenged selectively by mWang. Simple magnetic decantation from the resins resulted in secondary amines in good to excellent yields and purities. The used magnetic resins were efficiently regenerated and reused for the next run. In a second step, the secondary amines were converted to trisubstituted (thio)ureas in excellent yields and purities by stirring with an excess of iso(thio)cyanate, which was scavenged by addition of the magnetic amine resin after completion of the reaction. The whole reaction sequence is carried out without any purification apart from magnetic decantation; moreover, conventional magnetic stirring can be used as opposed to the vortexing required for polystyrene resins.

Keywords: amination · magnetic reagents · microwave chemistry · nanoparticles · synthetic methods

Introduction

Initiated by the pioneering work of Merrifield[1] five decades ago, polymer resins as insoluble supports have been of considerable and steadily growing interest in the field of organic synthesis. Solid-phase organic synthesis (SPOS)[2] revolutionized the synthesis of polypeptides and polynucleotides by the adaptation of established solution-phase reactions to the solid phase. Driven by the demand of the pharmaceutical industry for high-speed parallel synthesis, an alternative solution-phase technique utilizing reagents,[3,4] catalysts[5] and scavengers[6] supported on functional polymers evolved recently. In contrast to SPOS, this complementary approach is considerably simpler, since it dispenses with the need for linker chemistry and spares two additional steps for attaching the starting material to the resin and cleaving the product from the solid support.[7]Additional advantages are the facile monitoring of reaction progress by standard analytical techniques like TLC and potential reuse of the catalysts and regeneration of the reagents supported on the polymer resins.[4] Workup consists of simple filtration and evaporation of the solvents, leads generally to very clean products in high yield and avoids complex and expensive purification steps that also might generate additional waste.

While a lot of effort was put into the diversification of reagents, catalysts and scavengers, the resins themselves are still dominated largely by simple cross-linked polystyrene. To bring the supports to the next level, we envisaged introducing highly magnetic cores into the polystyrene beads to enable even quicker and more convenient separation of the supports from reaction mixtures by rapid magnetic decantation. This would avoid clogging of filters, facilitate recovery and subsequent recycling of the resins and allow for continuous-flow applications using magnetic fields rather than membranes to contain the supports.[8] Recently, Stark et al. developed the large-scale synthesis (>30 g$\,h^{-1}$) of carbon-coated cobalt (Co/C)[9] and iron (Fe/C)[10] nanobeads by reducing flame-spray pyrolysis of inexpensive metal carboxylates. The raw materials cost for manufacturing carbon-coated nanoparticles by this route can be estimated as less than 100 USD$\,kg^{-1}$.[11] These nanoparticles have excellent thermal and chemical stability due to the graphene-like shell, and the core of pure metal leads to an exceptionally high saturation magnetization of up to 158 emu$\,g^{-1}$, which is five times higher than for common iron oxide (e.g., magnetite) beads.[12] Effective covalent and/or non-covalent functionalization of the surface[13] led to applications in the extraction of organic compounds and metals from aqueous solutions up to the ton-per-hour scale,[14] in the purification of

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blood[15] and as recyclable supports for catalysts.[16,8] To increase the loading with functional groups by at least one order of magnitude, polymer shells were introduced by surface-initiated ring-opening metathesis polymerization (ROMP)[17] or radical polymerization on the nanoparticle surface.[18,19] ROMP-based scavengers for Mitsunobu reactions as well as recyclable acylation reagents were already established.[20]

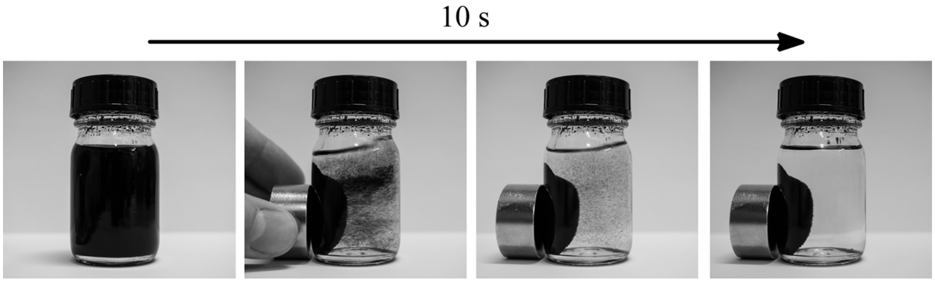
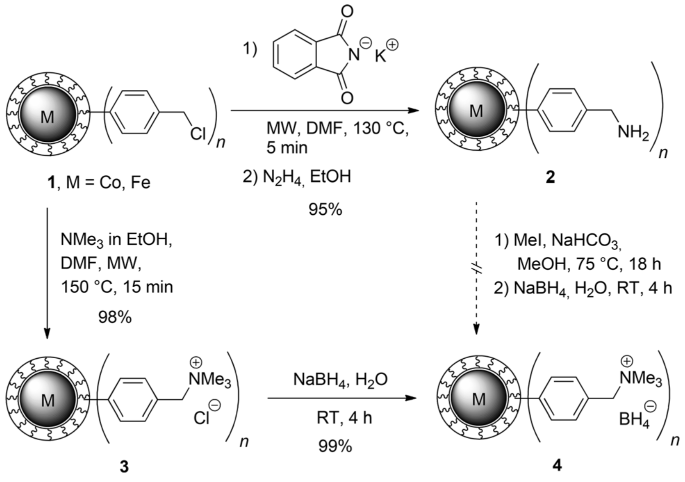


Figure 1. Magnetic recovery of polystyrene-coated nanobeads **1** from a CH_2Cl_2 solution. The golden-coloured cylinder is a neodymium-based magnet.

Building on the results of Kaldor et al.[21] and Guinó et al.,[22] we herein report the—to the best of our knowledge—first multistep synthesis achieved by exclusively combining magnetic reagents and scavengers. A small library of secondary amines was prepared by reductive amination followed by conversion to trisubstituted ureas or thioureas. All magnetic resins were functionalized by quick and efficient microwave protocols and recycled for several runs whenever possible.

Results and Discussion

Synthesis of magnetic borohydride resin (mBER): To synthesize a magnetic variant of the borohydride exchange resin (BER)[23] carbon-coated cobalt or iron nanoparticles with an additional polystyrene shell (**1**) were used as basis (Scheme 1). They were easily prepared on multigram scale in three steps starting from pristine Co/C or Fe/C nanobeads.[19] High loadings of 3.0–3.5 mmol benzyl chloride moieties per gram of magnetic resin were obtained for **1**, as determined by chlorine microanalysis. The swelling of the resin is analogous to that of conventional polystyrene beads, and the exceptionally high magnetic moment of the metal core leads to an overall saturation magnetization ($>33\ \mathrm{emu\,g^{-1}}$)[19] that allows rapid separation of the hybrid material from reaction mixtures (Figure 1). Neither irreversible aggregation of the nanobeads nor limited recovery was observed under the conditions used in this work. Besides magnetic separation, the nanoparticles can be agitated by internal or external magnetic stirring, and this is a distinct advantage over polystyrene resins, which require agitation by vortexing.



Scheme 1. Microwave-assisted synthesis of magnetic borohydride exchange resin **4** (mBER).

Preparation of mBER (**4**) via resin-bound benzylamine **2** was envisioned by quaternization with methyl iodine and counterion exchange with an aqueous solution of sodium borohydride (Scheme 1). Thus, a protocol for the Gabriel synthesis described by Rotello et al.[24] was modified to use a focussed microwave oven to quickly and efficiently heat the metal nanoparticles, which are highly susceptible to microwave irradiation,[25] and this allowed the reaction time for the functionalization to be shortened to 5 min. After cleavage with hydrazine the amino-modified beads **2** were obtained with a loading of $3\ \mathrm{mmol\,g^{-1}}$ (95 % of benzyl chloride substituted), as determined by elemental microanalysis. The reaction was conveniently monitored by using attenuated total reflectance IR spectroscopy (ATR-IR).[26] The functionalized nanobeads **2** can be applied as scavengers for electrophiles (see below). However, the planned quaternization with methyl iodide en route to **4** was not exhaustive according to elemental analysis and it was impossible to monitor the reaction progress conclusively by ATR-IR.

Therefore, an alternative synthetic route was developed. Direct conversion of benzyl chloride moieties to quaternary ammonium cations has been reported for the synthesis of water-soluble calix[*n*]arene[27] or porphyrins[28] by using trimethylamine gas or, more conveniently, aqueous or ethanolic solutions of trimethylamine with the addition of co-solvents. The latter method was applied to benzyl chloride functionalized nanobeads **1** by using a 33 % ethanolic solution of trimethylamine and DMF as co-solvent ensuring efficient swelling of the polystyrene shell to prepare nanobeads loaded with quaternary ammonium cations (**3**, Scheme 1). Stirring for two days at room temperature as indicated in the literature[27,28] led to a good degree of substitution (91 %), as concluded from nitrogen elemental analysis (Table 1, entry 1). Again, microwave irradiation was used to

Table 1. Functionalization of polymer-coated nanobeads **1** with quaternary ammonium ions under microwave heating.

Entry	Particles	DMF co-solvent	T [°C]	t	DoF [%][a]
1	Fe/C	yes	25[b]	2 days	91
2	Fe/C	yes	140	30 min	95
3	Co/C	yes	150	10 min	90
4	Co/C	no	150	10 min	93
5[c]	Co/C	no	150	15 min	97
6[c]	Fe/C	no	150	15 min	98

[a] Degree of functionalization, determined by nitrogen elemental analysis. [b] No microwave irradiation applied. [c] Scale: 1 g.

shorten reaction times (Table 1, entries 2–6). The higher pressures of up to 15 bar due to gaseous trimethylamine and temperatures above the boiling point of ethanol were tolerated by the microwave oven and the glassware alike. A control experiment without the co-solvent DMF led to an even higher degree of functionalization (93 %, Table 1, entry 4) compared to the experiment with added DMF (90 %, Table 1, entry 3). Under optimized conditions (150 °C, 15 min, no DMF) the benzyl chloride moieties were substituted almost quantitatively regardless of whether polystyrene-coated Co/C or Fe/C nanoparticles were used (Table 1, entries 5 and 6).

The progress of the functionalization was again conveniently monitored by ATR-IR (Figure 2). The characteristic benzyl chloride peak at 1263 cm^{-1} vanished completely upon nucleophilic substitution by the amine, and after stirring with an aqueous solution of sodium borohydride for 4 h characteristic peaks for the borohydride counterion (2203 and 1070 cm^{-1}) appeared. Elemental microanalysis revealed that 99 % of the chlorine was substituted by this ion exchange, and the reducing capacity of the novel mBER resin **4** was determined by a ^{1}H NMR assay with an excess of 4-nitrobenzaldehyde as substrate and 4-methoxyanisole as internal standard.[26] The obtained loadings (up to 3.3 mmol g^{-1}) are on par with or in some cases slightly higher than those reported in the literature[23] and those of commercially available Amberlite IRA-400 and Amberlyst A-26 resins functionalized with borohydride ions (2.5–3.3 mmol g^{-1}). While TEM images of pristine Co/C or Fe/C nanoparticles and polymer-coated nanoparticles **1** clearly differ due to the additional polymer shell around the nanobeads, no substantial changes are apparent when **1** is compared to functionalized mBER resin **4**. This demonstrates the stability of the carbon-coated nanobeads during microwave functionalization at elevated temperature.[26]

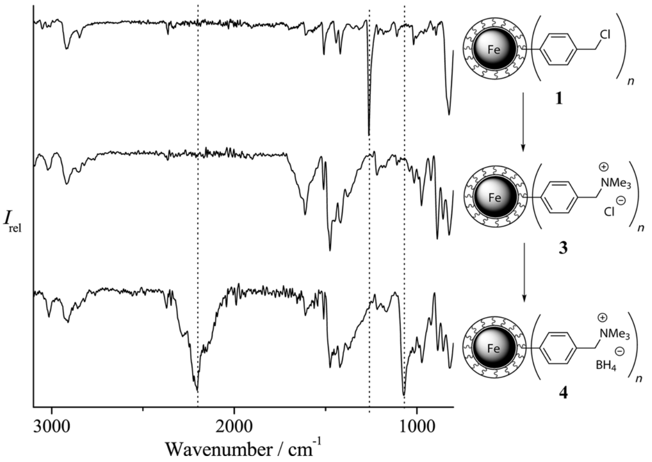
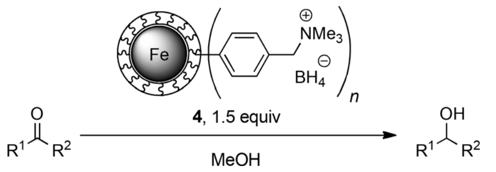
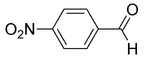
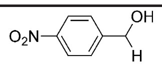
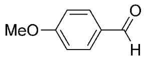
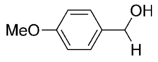
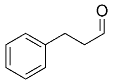
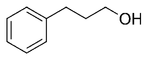
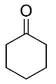
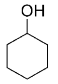
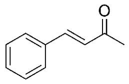
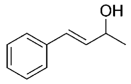


Figure 2. IR-ATR spectra of polymer-coated Fe/C nanobeads bearing chloro moieties (**1**, top), after conversion to quaternary ammonium ions (**3**, middle) and subsequent exchange of the chlorine counterion with borohydride (**4**, bottom).

Table 2. Reduction of aldehydes, ketones and α,β-unsaturated substrates with Fe/C–mBER (**4**) in methanol.



Entry	Substrate	Product (**5a–e**)	t [h]	Yield [%][a]
1			2	88
2			3	89
3			2	88
4			3	98
5			3	99

[a] Yields of isolated compounds. Purity >95 % in all cases, as determined by NMR spectroscopy.

To demonstrate the versatility, efficiency and recyclability of the magnetic borohydride resin, a series of different substrates was reduced by stirring with 1.5 equiv of mBER **4** in methanol for 2-3 h (Table 2). Aromatic as well as aliphatic aldehydes were readily reduced to the corresponding alcohols in high yields and purities (Table 2, entries 1–3), and also ketones are amenable for reduction by **4** (Table 2, entries 4 and 5). Notably, when using an α,β-unsaturated ketone the carbonyl group was reduced selectively leaving the double bond untouched (Table 2, entry 5). The activity and selectivity of **4** is consistent with literature reports on polystyrene-based borohydride resins.[23] However, in contrast to these conventional beads, the spent mBER can be collected by a magnet within seconds (Figure 1). To obtain the pure product in solution the supernatant was conveniently decanted and the particles were washed by re-suspending in methanol. Usually, more than 99.7 wt % of the nanoparticles was recovered after drying under vacuum. To prevent line broadening in the NMR spectrum due to trace amounts of magnetic material, in some cases additional filtration of the product solution was nevertheless necessary.[26] The spent resin was washed with aqueous sodium hydroxide followed by aqueous sodium chloride to regenerate the chlorine form **3** of the resin, while stirring with a borohydride solution finally restored the mBER **4**. An NMR assay of the recycled resin **4** revealed loadings (2.5–3.3 mmol g^{-1}) that were comparable to that of pristine mBER **4** and thus indicated efficient recharging. The recycled resin **4** was applied for the next run without apparent cross contamination.

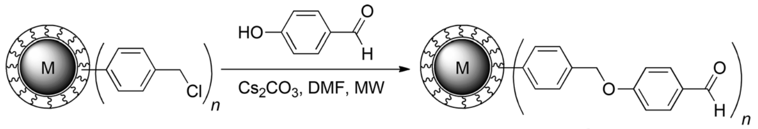
Preparation of a magnetic Wang aldehyde resin (mWang): With mBER resin **4** in hand, a magnetic scavenger for reductive amination was synthesized next. While several polymer-based scavengers for amines are known in the literature,[29] the Wang aldehyde resin is one of the most frequently used. It has been successfully employed for sequestration of primary amines in the presence of secondary amines,[21,22,30] in the synthesis of 2,3-dihydro-4-pyridones[31] and, more recently, in the synthesis of α,α-disubstituted amino acid derivatives.[32] This resin is also commercially available nowadays on the multigram scale.

For the preparation of the magnetic variant **6** of the Wang aldehyde resin (mWang) a modified microwave synthesis[32] was used to efficiently functionalize nanobeads **1** (Table 3). A control experiment under thermal conditions with 4-hydroxybenzaldehyde as nucleophile and Cs_2CO_3 as a base only resulted in a moderate conversion of 73% after stirring at 80 °C for 3 d (Table 3, entry 1). Microwave irradiation and increasing the temperature to 130 °C drastically speeded up the transformation, which reached 89% Cl displacement after only 5 min regardless of whether cobalt or iron nanoparticles were used (Table 3, entries 2 and 3). By increasing the temperature to 140 °C and the reaction time to 15 min, almost quantitative functionalization was achieved for a batch of 1 g. This demonstrates the effectiveness of this microwave transformation (Table 3, entry 4). Considering the gain in molecular mass during this functionalization, the loadings determined by chlorine elemental analysis (2.5–2.7 mmol g^{-1}) are excellent and on par with those of commercially available Wang aldehyde resins (up to 3.0 mmol g^{-1}), despite the metal core of the hybrid material. TEM analysis revealed no noticeable differences between polystyrene-coated nanoparticles **1**, the mBER variant **4** and the mWang resin **6**.[26]

To test the scope and effective loading of the new magnetic scavenger an excess of various benzylic and aliphatic primary amines was heated to reflux with **6** overnight (Table 4). Resin-supported imines **7** were generated in high loadings (1.9–2.2 mmol g^{-1}) corresponding to yields of 89–99%, as determined by nitrogen elemental analysis. These results are considerably better than those for conventional Wang aldehyde polystyrene resin, for which yields of 59–82% are obtained for a comparable series of amines.[22] Subsequently, the spent mWang resin **6** was regenerated by stirring **7** with aqueous HCl in THF/H_2O overnight followed by several washing cycles with water, methanol and acetone. The loadings of residual imine after hydrolysis were at the detection limit of elemental microanalysis (0.01–0.05 mmol g^{-1}), which indicates quantitative cleavage.

To demonstrate the recyclability of the mWang **6**, the cycle of immobilization and hydrolysis was repeated thrice (Table 4, entries 5–7). While the loading with imine increased from 94 to 99% in the second cycle, the loadings

Table 3. Introduction of aldehyde functionalities onto magnetic nanoparticles by nucleophilic substitution under microwave heating.



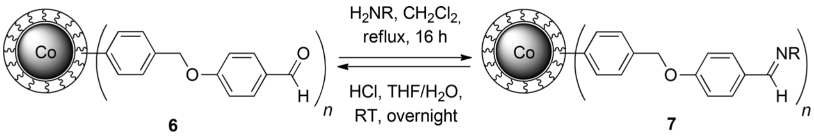
1, M = Fe, Co

6

Entry	Particles	T [°C]	Microwaves	t	DoF [%][a]
1	Fe/C	80	no	3 days	73
2	Fe/C	130	yes	5 min	89
3	Co/C	130	yes	5 min	89
4[b]	Co/C	140	yes	15 min	98

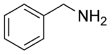
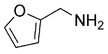
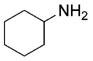
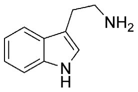
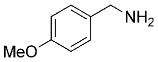
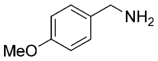
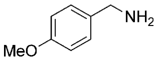
[a] Degree of functionalization, determined by chlorine elemental analysis. [b] Scale: 1 g.

Table 4. Reversible scavenging of primary amines by mWang resin **6**.



6

7

Entry	Run	Amine	Loading[a] [mmol g^{-1}]	Yield [%]	Loading after hydrolysis[a] [mmol g^{-1}]
1	1		1.91	88	0.01
2	1		1.97	89	0.03
3	1		1.94	88	0.01
4	1		2.00	98	0.05
5	1		2.06	94	0.02
6	2		2.19	99	0.03
7	3		2.19	99	0.04

[a] Loading determined by nitrogen elemental analysis.

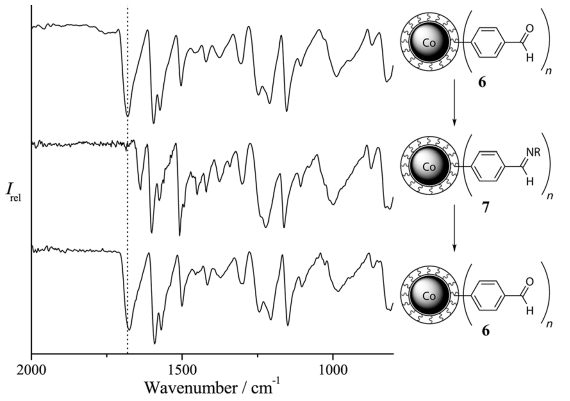
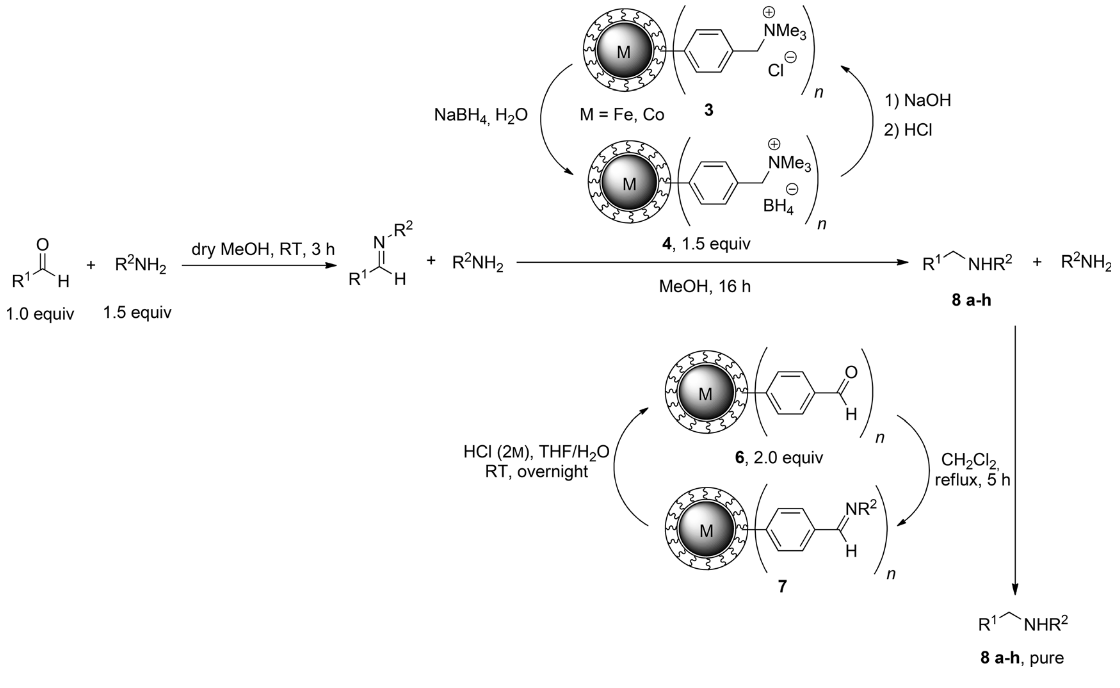


Figure 3. IR-ATR spectra of mWang resin **6** (top), after immobilization of benzylamine (middle) and subsequent hydrolysis with aqueous HCl (bottom). The spectra of **6** before and after one cycle coincide perfectly, indicating complete regeneration of the aldehyde scavenger.

after hydrolysis remained at a negligibly low level. Additional qualitative analysis of the functionalization and cleavage was provided by ATR-IR analysis (Figure 3). In the spectrum of mWang resin **6**, a dominant broad peak at 1676 cm^{-1} can be assigned to the carbonyl group of the immobilized aldehyde. After conversion to the resin-bound imine **7**, the aldehyde peak completely vanished and a new peak appeared at 1636 cm^{-1} corresponding to resin-bound imine groups. After the aldehyde groups were restored by hydrolysis of the imine, the obtained spectrum (Figure 3, bottom) perfectly matched that of as-prepared mWang resin **6** (Figure 3, top), underlining the good recyclability of the resin.

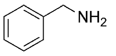
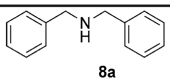
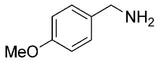
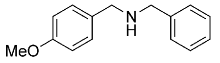
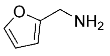
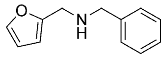
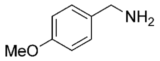
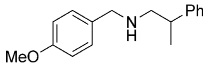
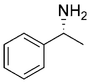
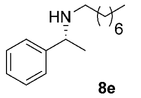
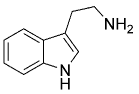
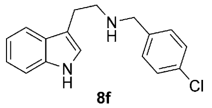
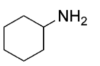
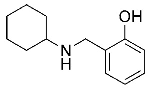
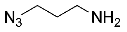
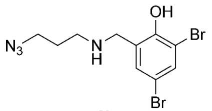
Reductive amination with mBER and mWang: The combination of these two recyclable resins was probed next in the synthesis of a small library of secondary amines by reductive amination of various aldehydes. To allow complete formation of the intermediary imines, aromatic or aliphatic aldehydes were stirred with an excess (1.5 equiv) of primary amine in dry MeOH for three hours at room temperature (Scheme 2). The imines were readily reduced to secondary amines **8a–h** by adding an excess of mBER resin **4** and continuing stirring overnight. In some literature reports on reductive amination with conventional polystyrene reagents,[22] MeOH turned out to be not effective, so a 1:1 mixture of MeOH and CH_2Cl_2 was applied instead. In our case, however, adding CH_2Cl_2 slowed down the reduction noticeably and no conversion to the secondary amines **8** was observed when pure CH_2Cl_2 was used. By using MeOH and mBER **4** we were able to decrease the excess of reducing reagent from 2.5 to 1.5 equivalents and the reaction time from 48 to 16 h. The spent resin was efficiently collected by a magnet, washed and recycled for the next run, as described above.

To obtain pure product solutions the initial excess of primary amine had to be removed from the reaction mixtures. Selective and complete sequestration was achieved by heating to reflux with mWang resin **6** in CH_2Cl_2 for 5 h (Scheme 2). After simple magnetic decantation, washing of the particles and evaporation of the solvent, the remaining secondary amines **8a–h** were obtained in good yields (49–99 %) and purities (all >95 % by NMR; Table 5). In some cases, however, filtration over cotton was necessary to remove traces of magnetic material before acquiring the NMR spectrum. The spent mWang scavenger **7** was regenerated by hydrolysis with aqueous HCl, as described above,



Scheme 2. Combination of mBER **4** and mWang resin **6** for the reductive amination of aldehydes leading to secondary amines **8a–h**.

Table 5. Small library of secondary amines **8a–h** synthesized by reductive amination of various aldehydes.

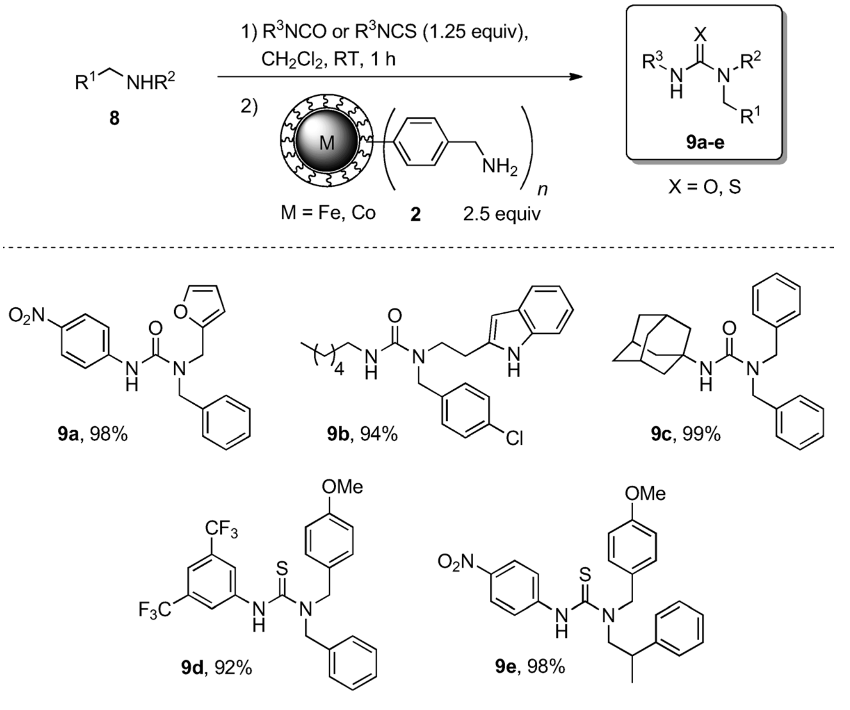
Entry	Primary amine	Product	Yield [%][a]	Purity [%][b]
1		 **8a**	97	>95
2		 **8b**	96	>95
3		 **8c**	91	>95
4		 **8d**	95	>95
5		 **8e**	80	> 95
6		 **8f**	97	>95
7[c]		 **8g**	99	>95
8[c]		 **8h**	49	>95

[a] Yields of isolated compounds. [b] Determined by NMR spectroscopy. [c] No need for scavenging due to the low boiling point of the amines.

and reused in the next run without apparent cross-contamination (Scheme 2).

To demonstrate the broad reaction scope, benzylic (Table 5, entries 1–5) and aliphatic (Table 5, entries 6–8) primary amines were treated with aromatic (Table 5, entries 1–3, 6 and 7) or aliphatic (Table 5, entries 4 and 5) aldehydes. In only two cases was the obtained yield below 90%: When a long-chain aliphatic aldehyde was used (Table 5, entry 5), which is known to be a difficult substrate,[22] and when using an aldehyde with a strongly acidic group (Table 5, entry 8), which might result in product loss due to protonation of the resin and binding by electrostatic interactions. An aromatic alcohol that lacks electron-withdrawing groups (**8g**, Table 5, entry 7) was perfectly tolerated. Also, no racemization was observed when using enantiopure primary amines (**8e**, Entry 5). Additionally, scale-up to 1.5 mmol of aldehyde and 2.3 mmol of amine was carried out for **8a** with an equally good yield of 96%.[26]

Synthesis of trisubstituted (thio)ureas by using magnetic resins: As the third step in the sequence, secondary amines **8** were converted to trisubstituted (thio)ureas by stirring with an excess (1.25 equiv) of isocyanate or isothiocyanate in CH_2Cl_2 for 1 h (Scheme 3). To remove the excess of reagent from the products **9a–e**, a second magnetic scavenger was used. The polymer-coated magnetic nanobeads functionalized with benzylic amine (**2**), which are accessible by Gabriel synthesis (Scheme 1), readily sequestered the excess of iso(thio)cyanate upon further stirring for 2 h. By applying an external magnet to the side of the reaction vessel (Figure 1) the entire magnetic scavenger was collected within seconds and the product solution decanted. After several washing steps and evaporation of the solvents, the pure products **9a–e** were isolated in high yields (92–99%) and purities (>95% by NMR) without the need for further purification (Scheme 3). Aromatic (**9a**) and aliphatic (**9b**, **9c**) isocyanates were applicable in this transformation including strongly hindered ones (**9c**), and isothiocyanates (**9d**, **9e**) worked equally well (Scheme 3). No limitations arose from the choice of amine regardless of whether dibenzylic or monobenzylic secondary amines were used, and scales of up to 1.4 mmol amine were successfully tested.[26] In contrast to the other two magnetic resins, this scavenger cannot be recycled due to irreversible formation of resin-bound (thio)urea.



Scheme 3. Synthesis of a small library of trisubstituted (thio)ureas **9a–e** by using magnetic amine **2** as scavenger of excess reagent.

Conclusion

We have demonstrated the efficient synthesis of three novel magnetic reagents and scavengers based on Co/C or Fe/C nanoparticles, which are produced from low-cost raw materials and are commercially available on a kilogram scale. The highly loaded magnetic resins were prepared by surface-initiated polymerization followed by quantitative functionalization under microwave irradiation. The progress of the syntheses was conveniently monitored by ATR-IR spectroscopy, and TEM analysis showed no noticeable differences between the various magnetic resins. The highly magnetic core of the hybrid material allowed rapid recovery of the resin from reaction mixtures by an external magnet followed by convenient decantation of the product solution.

The magnetic borohydride exchange resin (mBER) was subsequently tested in the reduction of various aldehydes, ketones and α,β-unsaturated substrates leading to the corresponding alcohols in excellent yields and purities. The magnetic Wang aldehyde scavenger (mWang) was successfully applied in the reversible sequestration of primary amines. Next, both magnetic resins were applied consecutively in the reductive amination of aldehydes. The imines formed by stirring aldehydes with an excess of primary amines were readily reduced by mBER, and the residual primary amines selectively scavenged by the mWang resin. A small library of secondary amines was synthesized in good to excellent yields and excellent purities. Apart from magnetic decantation, no additional purification steps were needed, and the resins were recycled for eight consecutive runs with different substrates without noticeable cross-contamination. The secondary amines were converted to trisubstituted (thio)ureas. The excess of iso(thio)cyanate used was scavenged by a third magnetic resin bearing amino groups, giving excellent yields and purities of ureas and thioureas.

The successful demonstration of this multistep synthesis applying exclusively magnetic reagents and scavengers opens new possibilities for reaction automatization such as magnetic flow reactors, which are under investigation in our laboratories.

Experimental Section

Synthesis of polymer-coated nanobeads bearing amino groups (2): Polystyrene-coated iron nanobeads **1** (1.0 g, 3.0 mmol of benzyl chloride moieties) were heated with potassium phthalimide (5.6 g, 30 mmol) in dry DMF (30 mL) under a nitrogen atmosphere in a microwave reactor to 130 °C for 5 min. After the mixture had cooled to room temperature, the particles were recovered by using magnet, washed with H_2O (2×30 mL), MeOH (2×30 mL), acetone (2×30 mL) and CH_2Cl_2 (2×30 mL), and dried under vacuum. IR (ATR): $\tilde{\nu}$=2918, 2845, 1770, 1705, 1510, 1388, 1325, 1081, 934, 802, 713 cm^{-1}.

The phthalimide-functionalized particles were stirred in a refluxing mixture of hydrazine monohydrate (16 mL) and EtOH (64 mL) overnight. After magnetic decantation, the amine particles **2** were washed with H_2O (3×30 mL), MeOH (3×30 mL) and CH_2Cl_2 (3×30 mL), and dried under vacuum to give the product resin **2** (952 mg). IR (ATR): $\tilde{\nu}$ = 3347, 3290, 2906, 2845, 1636, 1567, 1506, 1477, 1439, 1417, 1362, 1147, 808 cm^{-1}; elemental analysis (%) found: C 47.95, H 4.65, N 5.72, Cl 0.58.

Preparation of polymer-coated nanobeads bearing quaternary ammonium ions (3): Polystyrene-coated iron nanobeads **1** (1.0 g, 3.5 mmol of benzyl chloride moieties) were introduced into a microwave vial followed by the addition of trimethylamine solution (17 mL; 4.2 M in EtOH). The slurry was stirred for 15 min at 150 °C under microwave heating. The particles were collected by using an external magnet, washed with acetone (3×5 mL) and Et_2O (2×5 mL), and dried under vacuum to give the functionalized beads **3** (1.14 g; loading: 2.9 mmol g^{-1}). IR (ATR): $\tilde{\nu}$=3371, 3021, 2919, 2852, 2769, 1612, 1511, 1475, 1418, 1218, 974, 888, 823 cm^{-1}; elemental analysis (%) found: C 53.58, H 6.19, N 4.00, Cl 5.44.

General procedure for the preparation of magnetic borohydride resin mBER (4): Polymer-coated iron nanobeads bearing quaternary ammonium ions **3** (1.09 g, 3.3 mmol) were dispersed in water (15 mL) by stirring for 10 min. Then, a solution of $NaBH_4$ (372 mg, 9.9 mmol) in H_2O (10 mL) was added dropwise and stirring was continued for 4 h. The particles were recovered by magnetic decantation, washed with H_2O (3×20 mL) and MeOH (20 mL), and dried under vacuum for at least 5 h to give borohydride-functionalized nanobeads **4** with a borohydride loading of 3.0 mmol g^{-1}. IR (ATR): $\tilde{\nu}$= 3014, 2910, 2280, 2203, 1610, 1510, 1475, 1418, 1376, 1071, 972, 885, 820 cm^{-1}; elemental analysis (%) found: C 55.77 C, H 6.58, N 4.08, Cl 0.1.

General procedure for the synthesis of magnetic Wang aldehyde mWang (6): Polystyrene-coated cobalt nanobeads **1** (500 mg, 1.75 mmol of benzyl chloride moieties) were stirred in dry DMF (8 mL) under a nitrogen atmosphere in a microwave vessel. Subsequently, 4-hydroxybenzaldehyde (427 mg, 3.5 mmol) and Cs_2CO_3 (1.71 g, 5.25 mmol) were added and the slurry was heated to 140 °C for 15 min in a focussed microwave oven. The particles were recovered by magnetic decantation and thoroughly washed with H_2O/MeOH/acetone (1/1/1, 3×5 mL), MeOH/acetone (1/1, 3×5 mL), acetone (3×5 mL), CH_2Cl_2 (3×5 mL) and Et_2O (1×5 mL). After drying under vacuum for 5 h mWang resin **6** (601 mg) with a loading of 2.5 mmol g^{-1} was obtained. IR (ATR): $\tilde{\nu}$=2919, 2845, 2726, 1683, 1596, 1506, 1422, 1379, 1249, 1212, 1155, 991, 814 cm^{-1}; elemental analysis (%) found: C 63.55; H 4.90, N 0.05; Cl 0.22.

Reductive amination of aldehydes with mBER and mWang resins: Aldehyde (0.5 mmol) and an excess of primary amine (0.75 mmol) were stirred in dry methanol (2 mL) under a nitrogen atmosphere for 3 h in a flame-dried Schlenk tube. Then, mBER resin **4** (250 mg, 0.75 mmol) was added to the reaction mixture and the stirring was continued for 16 h. The particles were recovered by magnetic decantation, washed with MeOH (3×3 mL) and the combined solutions were evaporated to dryness. Then CH_2Cl_2 (5 mL) and mWang resin **6** (200 mg, 0.5 mmol) were added and the slurry was heated to reflux at 50 °C for 5 h. The product solution was decanted with the aid of a magnet and the resin was washed with CH_2Cl_2 (3×5 mL). Evaporation of the solvent resulted in pure secondary amines **8a–h** in high yields. Before NMR analysis, some $CDCl_3$ solutions had to be filtered over cotton. Both magnetic resins were regenerated by following the general procedures described above.

General procedure for synthesis of trisubstituted ureas 9a–e: In a flame-dried Schlenk tube secondary amine **8** (0.4 mmol) and isocyanate or isothiocyanate (0.5 mmol) were dissolved in dry CH_2Cl_2 (3 mL). The mixture was stirred at room temperature under a nitrogen atmosphere for 2 h. Amine-functionalized magnetic polymer beads **2** (83 mg, 0.25 mmol) were added and stirring was continued for 2 h. The resin was collected by using an external magnet, the solution was decanted, and the beads were washed with CH_2Cl_2 (3×5 mL). Evaporation of the combined solutions yielded trisubstituted ureas **9a–e** in excellent purities.

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