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Ring-Opening Metathesis Polymerization-based Recyclable Magnetic Acylation Reagents

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An operationally simple method for the acylation of amines utilizing carbon-coated metal nanoparticles as recyclable supports is reported. Highly magnetic carbon-coated cobalt (Co/C) and iron (Fe/C) nanobeads were functionalized with a norbornene tag (Nb-tag) through a "click" reaction followed by surface activation employing Grubbs-II catalyst and subsequent grafting of acylated *N*-hydroxysuccinimide ROMPgels (ROMP = ring-opening metathesis polymerization). The high loading (up to 2.6 mmol g^{-1}) hybrid material was applied in the acylation of various primary and secondary amines. The products were isolated in high yields (86–99%) and excellent purities (all > 95% by NMR spectroscopy) after rapid magnetic decantation and simple evaporation of the solvents. The spent resins were successfully re-acylated by acid chlorides, anhydrides, and carboxylic acids and reused for up to five consecutive cycles without considerable loss of activity.

Introduction

Although polymer-supported reagents for organic synthesis have been around for a while, they remain of current interest especially in the field of combinatorial chemistry, with new methods and new supports being continuously developed.[1] The main reason for their popularity is the combination of well-established solution-phase chemistry (along with sophisticated analytical techniques) with ease of purification (mostly filtration) and the possibility for automation. Among them, a wide variety of acyl transfer resins have been developed, for example, polymer-supported *ortho*-nitrophenol,[2] *para*-(hydroxyphenyl)sulfone,[3] a range of supported mixed anhydrides,[4] and, more recently, tetrafluorophenol.[5] However, one of the most commonly utilized resins for acylation reactions is supported *N*-hydroxybenzotriazole (HOBt).[6,7] Although its reactivity in acylations can be advantageous, it is hampered by poor stability in DMF.[8]

Active esters derived from *N*-hydroxysuccinimide (NHS) are considered to be more stable and were frequently applied to the activation of amino acids, the introduction of carbamate protecting groups, and as staining, radiolabeling, or crosslinking agents in various biological systems.[9] Several polymer-supported NHS analogues are known, for example, copoly(ethylene-*N*-hydroxymaleimide),[10] and copoly(styrene-*N*-hydroxymaleimide).[11] In addition, Adamczyk and co-workers demonstrated the immobilization of NHS on commercially available Merrifield and ArgoPore-Cl resins.[12,13] We herein report acyl derivatives of a NHS high capacity ROMPgel (ROMP = ring-opening metathesis polymerization) grafted on magnetic Co/C or Fe/C nanobeads as versatile and recyclable active-ester equivalents for the acylation of various primary and secondary amines.

Results and Discussion

Polymers and oligomers derived from ring-opening metathesis polymerization (ROMP) of monomers containing the functionality of the desired reagent and a strained alkene have been developed by the group of Barrett[14,15] and by Buchmeiser.[16] More recently, Hanson and co-workers contributed to this field with the development of new oligomeric reagents[17] as well as scavengers.[18] The main advantages of these "designer" polymers (termed as ROMPgels) over conventional polystyrene-based polymers are the high mechanical stability, excellent quality, and quantitative loading because of functionalization performed usually on the monomer stage. Active esters of a NHS ROMPgel were successfully utilized by Barrett et al. for the synthesis of various amides, ureas, carbamates,[19] and oxadiazoles[20] in excellent yields and purities. Recently, Roberts[21] reported the grafting of NHS ROMPgels on Wang resins to combine the convenience of a bead format with the high loading of the ROMPgels. Despite the good site accessibility, limitations in the choice of acylating reagents occurred and perfluorinated solvents had to be employed to achieve adequate yields.

Magnetic nanoparticles as supports would even further facilitate the workup process by replacing the energy-intensive pumping to draw solvent through a filter and the tedious recovery of the polymer by an operationally simple magnetic decantation. Furthermore, the magnetic properties of the nano-

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beads also allow application under continuous-flow conditions by confining them within a magnetic field rather than in a membrane reactor.[22] Recently, Stark et al. reported the synthesis of carbon-coated cobalt (Co/C)[23] or iron (Fe/C)[24] nanoparticles on multigram scale ($>30\,g\,h^{-1}$) from inexpensive metal carboxylates by performing reducing-flame spray pyrolysis. These metal nanoparticles combine excellent thermal and chemical stabilities with high magnetization (up to 158 $emu\,g^{-1}$). The surface of the nanobeads is accessible by covalent and/or non-covalent functionalization,[25] which allows for applications such as extraction of analytes or contaminants from water,[26,27] purification of blood,[28] or as recyclable support for catalysts.[22,29,30]

ROMPgels based on magnetic Co/C nano-supports have previously been reported by our group for the immobilization of a highly active and recyclable palladium complex for Suzuki–Miyaura cross-coupling reactions.[31] Furthermore, such nanoparticles were applied for the facile purification of intermolecular[32] as well as intramolecular[33] Mitsunobu reactions utilizing norbornene-tagged (Nb-tagged) reagents and a surface-initiated sequestration protocol. It has been demonstrated that because of the explicitly high magnetic moment of the cobalt nanobeads the overall magnetization of the resulting hybrid material is significantly higher than that of polymer-coated iron oxide nanoparticles with comparable metal content, thus allowing rapid separation of the ROMPgel from reaction mixtures. The high loadings achieved using this approach make the development of other supported reagents, which can be recycled through rapid and simple magnetic decantation and subsequent regeneration of the reactive groups, desirable.

Clearly, loadings of this magnitude, limited by the diazonium functionalization step from **1** to **2**, are not very attractive for the direct immobilization of reagents because of the sheer mass of support needed for considerable amounts of reactive groups.

ROMP using Nb-tagged reagents is an effective method to increase the loading and to control the properties of the polymer shell around the nanobeads by varying the amount of catalyst and monomer used. Thus, the acetylated NHS monomer **4** was synthesized from furan and maleic anhydride in three steps following literature procedures.[21,35,36] Applying conditions reported by Roberts[21] for ROMP of **4** at room temperature on modified Wang beads pre-activated with Grubbs-I catalyst[37] led to no noticeable formation of ROMPgel on the Nb-tagged Co/C nanobeads **3** (Table 1, entry 1), which was confirmed by elemental analysis. A control experiment at 60 °C re-

Table 1. Screening of reaction conditions for the synthesis of **5** by ROM polymerization on the magnetic beads.[a]

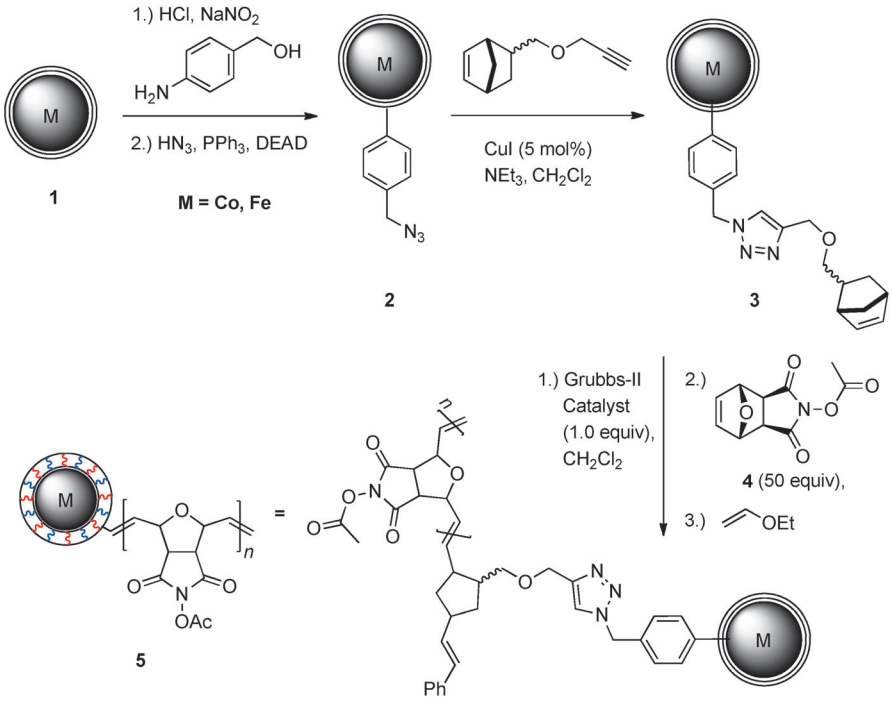
Entry	Particles	Catalyst	T [°C]	Reaction time [h]	Loading (N)[b] [$mmol\,g^{-1}$]
1	Co/C-Nb (**3**)	Grubbs-I	25	24	no gel[c]
2	Co/C-Nb (**3**)	Grubbs-I	60	10	no gel[c]
3	Co/C-Nb (**3**)	Grubbs-II	60	1	2.37
4	Fe/C-Nb (**3**)	Grubbs-II	60	1	1.96
5	Co/C-N_3 (**2**)	Grubbs-II	60	1	no gel[c]

[a] 50 Equiv. of monomer and 1.0 equiv. of catalyst with respect to the norbornene units attached on the nanobeads. [b] Determined by nitrogen microanalysis. [c] Oligomers in solution.

Synthesis of magnetic ROMPgels for acylation reactions

To render the magnetic Co/C or Fe/C nanoparticles **1** accessible to the grafting of ROMPgels, a covalent surface-functionalization strategy introducing norbornene groups was utilized. At first, well-established diazonium chemistry followed by hydroxyl azide exchange to **2** via a Mitsunobu reaction with hydrazoic acid as nucleophile was carried out (Scheme 1).[22,29] Subsequently, norbornene moieties were introduced through a copper(I)-catalyzed alkyne/azide cycloaddition (click reaction),[34] giving rise to **3**, which is a suitable precursor for subsequent ROMP with Nb-tagged catalysts or reagents.

Loadings of 0.10–0.15 mmol norbornene groups per gram nanoparticle were determined by elemental microanalysis for **3**.



Scheme 1. Synthesis of the magnetic ROMPgel. DEAD = diethyl azodicarboxylate.

vealed, that Grubbs-I catalyst is not suitable to conduct surface-initiated ROMP on the magnetic nanobeads. However, oligomers could be precipitated from the solution by addition of MeOH. Grubbs-I catalyst was also not active in the surface-initiated sequestration of Nb-tagged Mitsunobu reagents.[32,33]

In contrast, Grubbs-II catalyst[38] allowed the grafting of the desired ROMPgels on the nanobeads: To initiate ROMP on the surface of the nanobeads, Nb-tagged Co/C nanobeads **3** were dispersed in degassed CH_2Cl_2 in a sealed vessel under nitrogen atmosphere using a tempered (60 °C) ultrasonic bath. A solution of Grubbs-II catalyst (1.0 equiv. with respect to the loading with norbornene groups of **3**) was injected to generate an active ruthenium carbene species on the surface of the nanobeads by ring-opening metathesis with the immobilized norbornene moieties. A NHS ROMPgel was grafted onto the nanobeads by subsequent addition of a solution containing monomer **4** (50 equiv.). Immediately, a voluminous black gel was formed, which, after quenching with ethyl vinyl ether (EVE), contracted. The lump was dried well under vacuum and crushed for further use. Based on the gain in mass of magnetic resin **5**, more than 95% of monomer **4** was incorporated into the hybrid material. Combustion analysis revealed 4.21% nitrogen, corresponding to a loading of 2.37 mmol g^{-1} (Table 1, entry 3), thus increasing the loading from the initially azide-tagged nanobeads **2** by a factor of more than 20. Images taken by transmission electron microscopy (TEM) confirmed the encapsulation of the Co/C-particles in a polymer matrix, separating the previously densely packed nanoparticle clusters, a characteristic owed to the highly magnetic remanence of the metal nanobeads.[39]

Alternatively, ROMPgels supported on Fe/C nanoparticles were successfully synthesized, giving rise to high loading magnetic resins consisting of biologically well acceptable components (Table 1, entry 4). The morphology and performance of the Fe/C ROMPgel was identical with the Co/C analogue, whereas variations in the overall loading arose from slightly different loadings of norbornene moieties from batch to batch. To demonstrate that the ROMPgel was actually covalently bound to the magnetic support and not just encapsulating the nanobeads, a control experiment employing the azide-functionalized nanobeads **2** instead of the Nb-tagged variant **3** was performed. In this case no nanoparticle-supported ROMPgel **5** could be formed and nanoparticles **2** were recovered from the solution, while oligomers remained in solution upon precipitation with MeOH.

The swelling properties of both resins were in line with literature reports for ROMPgels.[15,21] The resins exhibited a distinct volume increase in THF, CH_2Cl_2, and $CHCl_3$, whereas solvents such as MeOH and Et_2O did not induce such an effect. In DMF, however, the formation of a gummy like mass was observed. Spectroscopic data of the various beads was obtained by infrared spectroscopy using the attenuated total reflectance sampling technique (IR-ATR). The azide-functionalized nanoparticles **2** show a characteristic massive peak at 2100 cm^{-1}, which vanished after the click reaction yielded the Nb-tagged beads **3** (Figure 1). After ROMP, the characteristic carbonyl stretches of monomer **4** were present in the spectrum of the magnetic

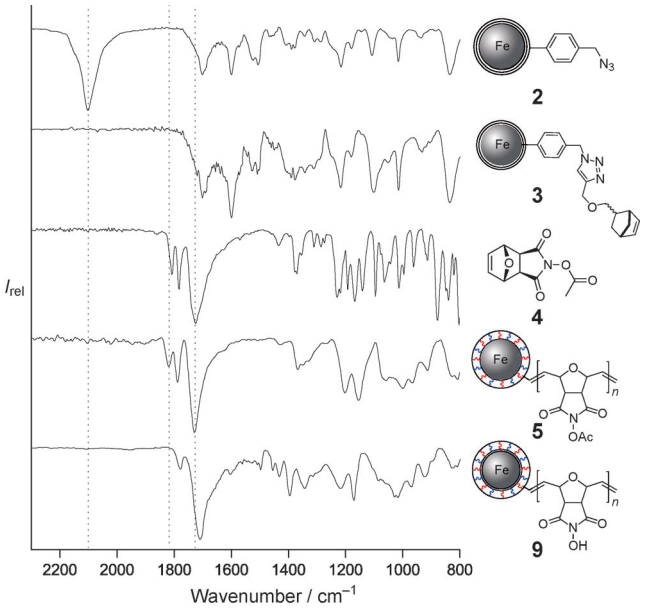


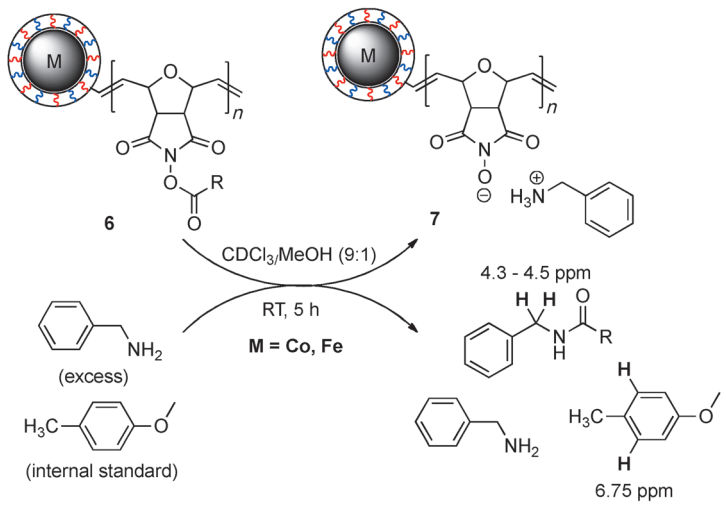
Figure 1. IR-ATR spectra of functionalized nanobeads **2** and **3**, the monomer **4**, and the corresponding magnetic ROMPgels **5** and **9**.

ROMPgel **5** (1822, 1788, and 1731 cm^{-1}). A peak broadening, typical for magnetic nanobeads functionalized with organic molecules, was apparent at lower wavenumbers. For resin **9** bearing hydroxyl groups, the peak at 1822 cm^{-1} disappeared completely indicating successful cleavage of the acetyl group in **5**.

To optimize the loading of magnetic ROMPgel **5**, a series of experiments was performed by varying the amount of monomer **4** from 50 to 100 equivalents while keeping the amount of nanobeads **3** and Grubbs-II catalyst constant (Table 2). The particle yields and loadings increased up to 80 equivalents of monomer **4**; however, when using 100 equivalents of **4**, a decrease in loading and yield was observed. Moreover, the gel lump showed to be of inhomogeneous composition with darker (more nanobeads) and lighter areas (more polymer) caused by irregular polymerization, which was also confirmed by inconsistent data obtained from multiple elemental analysis. Hence, 80 equivalents of monomer **4** seemed to be optimal with respect to the amount of ROMPgel produced, loading, and sufficient homogeneity.

Determination of the loading and stability tests

Although determination of the loading through nitrogen elemental analysis is possible, for higher sample throughput a ^1H NMR assay was developed. An assay for the NMR titration of ROMPgels as described by Roberts[21] was adjusted to fit the needs of this project. Briefly, acylated ROMPgel **6** was treated with an excess of benzylamine in a mixture of deuterated chloroform and nondeuterated methanol (9:1). An internal standard was added as accurate determination of the benzylamine remaining in solution is not possible because the liberated *N*-hydroxyl resin **7** can capture amines from the solution (Scheme 2).[40,41] We found the internal standard used by Rob-



Scheme 2. Determination of the loading by using an NMR assay (50 mg test reactions).

erts, benzyl methyl ether, not to be ideal because of an overlap with the product in some cases. Therefore, we used 4-methylanisole instead. Owing to its magnetic properties, resin **7** had to be removed from the solution by magnetic decantation before acquiring the ^{1}H NMR spectrum. To determine the loading, the benzylic CH_2 doublet of the resulting amide was compared with that of the phenylic CH groups of the standard.[38] Loadings determined by this method closely matched the values obtained by elemental analysis (Table 2).

To examine the long-time stability of the acetylated resin **5**, one batch was stored five months in the fridge and was then analyzed again by elemental microanalysis and ^{1}H NMR assay (Table 3). NMR analysis revealed a decrease in loading of less than one percent, whereas the data obtained from elemental analysis indicated a slightly higher degree of decomposition (4–7%).

Table 2. Tuning of the hybrid material by variation of the amount of monomer.[a]

Entry	Monomer [equiv.]	Yield [mg]	Loading [mmol g^{-1}] calculated	observed (N)[b]	observed (NMR assay)
1	50	147	2.31	2.16	2.24
2	60	163	2.50	2.23	2.32
3	80	201	2.79	2.46	2.60
4	100	196	2.99	2.09[c]	2.36

[a] For each reaction 70 mg of Co/C nanobeads and 1.0 equiv. of Grubbs-II catalyst were used. [b] Determined by nitrogen analysis. [c] Inhomogeneous.

Table 3. Stability test of ROMPgel **5** by comparing the loading.

Entry	Storage time [month]	Loading [mmol g^{-1}] C[a]	N[b]	NMR
1	0	2.30	2.34	2.28
2	5	2.15	2.24	2.26

[a] Determined by carbon analysis. [b] Determined by nitrogen analysis.

Acylation of various amines using magnetic ROMPgels

After detailed investigation of the synthesis, loading, and stability of magnetic ROMPgels, the acylation of amines and the recycling of the ROMPgel were examined (Scheme 3). In the first step, benzylamine as an initial test substrate was stirred with a slight excess of the acetylated Fe/C ROMPgel **5**. After completion of the acylation, ROMPgel was fully recovered by using a magnet and benzylamide **8a** was isolated by simple decantation and evaporation of the solvents (Figure 2).

Pure chloroform alone was not the ideal solvent with respect to yield (82%) and product purity, but addition of 10 vol% methanol gave rise to the benzylamide in high yield (93%) and purity (>95% by NMR). The solvent mixture was removed by simple

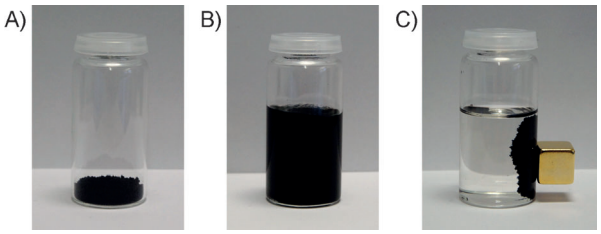
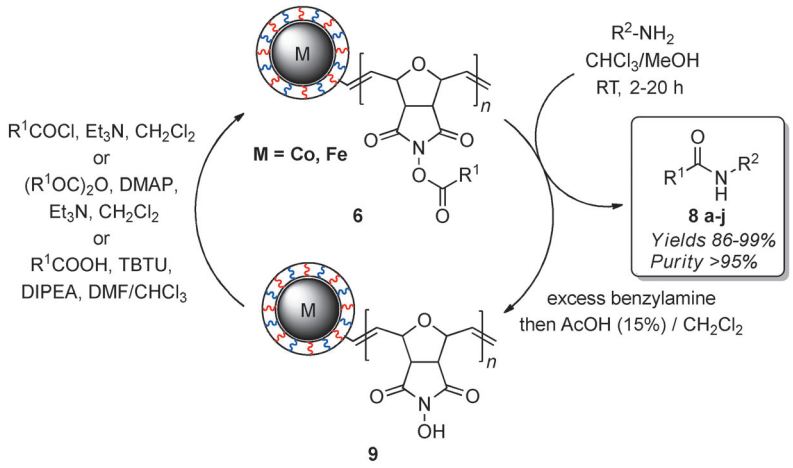


Figure 2. Pictures of Fe/C ROMPgel **5**: pristine (A), dispersed in $CHCl_3$/MeOH (9:1) by a magnetic stirrer (B), and after recovery by an external magnet (C).

distillation and reused for the next run. Also other, more sustainable, solvents were tested. The yields are slightly lower using EtOAc (89%) or THF (83%) while the product purity remained excellent. However, the solvent range applicable for this reaction is limited as sufficient swelling of the resin has to be ensured during the reaction.

In some cases the product solution was filtered over cotton to remove traces of finely dispersed resin or degraded polymer. An NMR comparison of the product before and after filtration showed slightly better line separation in the spectrum acquired after filtration.[39] To quantify the effectiveness of the magnetic decantation, we performed an additional experiment, for which we determined the weight of the product before and after filtration. Only 1 wt% was lost during filtration, which is in line with the marginal weight gain of the filter. The material collected by the filter corresponded to less than 0.3 wt% of the initial resin, which underlines the effectiveness of the magnetic decantation.[39]

Keeping in mind our goal to develop a protocol that will allow the use of different types of acyl transfer reagents, the spent resin was stirred with an excess of benzylamine to cleave the remaining acetyl groups. As free N–OH resins are capable of capturing amine from the solution,[40,41] a washing step with acetic acid (15 vol%) in CH_2Cl_2 followed by THF was conducted to regenerate **9**.



Scheme 3. Acylation of amines using magnetic ROMPgels and subsequent recycling of the resin.

To investigate the recycling and reloading potential of the magnetic ROMPgel, a series of reactions was performed. Co/C ROMPgel **5** with an initial loading of 1.52 mmol g^{-1} was used to synthesize *N*-benzylacetamide (**8a**) in 91% yield and excellent purity by stirring for 5 h (Table 4). Remaining acyl groups were cleaved and the resin washed with acid as described above. Effective re-acylation (91%, 1.39 mmol g^{-1}) of the resin was achieved by stirring with acetyl chloride (3 equiv.) in the presence of an excess of triethylamine. The high product yields (91–99%) and the ability for reloading (82–98%) were maintained for five consecutive cycles (Table 4). Despite the numerous washing steps, 76% of the initial amount of nanobeads was recovered after five runs, but with a slightly lower loading of 1.41 mmol g^{-1}. Images acquired by using a TEM revealed no substantial differences between freshly prepared and reisolated (after five cycles) ROMPgel **5**.[39]

Table 4. Consecutive synthesis of *N*-benzylacetamide (**8a**) and subsequent regeneration of the magnetic Co/C acylation reagent.

Entry	Run	Yield (isolated) [%]	Purity[a] [%]	Loading after recycling[a] [mmol g^{-1}]	Regeneration of initial loading[b] [%]
1	1	91	>95	1.39	91
2	2	98	>95	1.49	98
3	3	99	>95	1.24	82
4	4	98	>95	1.32	87
5	5	91	>95	1.41	93

[a] Determined by NMR. [b] Initial loading: 1.52 mmol g^{-1}.

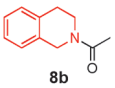
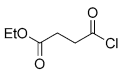
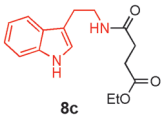
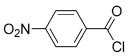
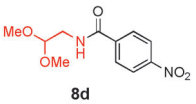
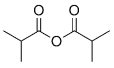
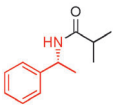
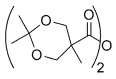
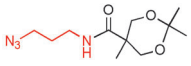
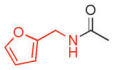
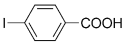
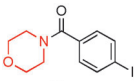
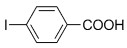
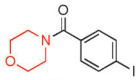
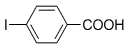
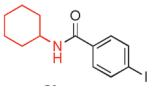
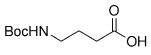
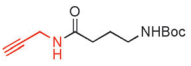
Having successfully demonstrated the reacyclation of magnetic NHS resin **9** using the same acid chloride for five consecutive cycles, we next examined whether it is possible to arm the resin with various acid chlorides, anhydrides, or carboxylic acids (Scheme 3). Especially, the potential emergence of product mixtures within the amides **8** after consecutive reacylation of resin **9** with different acylating agents was of particular interest, as such cross-contamination would clearly restrict the versatility and reusability of the resin.

Different acid chlorides readily reacylated the Fe/C ROMPgel **9** following the procedure described above. Three equivalents of acid chloride were sufficient to reach high loadings (> 2 mmol g^{-1}), and the subsequent acylation of different primary as well as secondary amines yielded the corresponding amides (**8b–d**) in high purities and yields with no detectable cross-contamination (Table 5). Likewise, anhydrides were able to reload the free N–OH resin **9** on addition of 4-(dimethylamino)pyridine (DMAP) as a nucleophilic catalyst with slightly decreased efficiency when compared to acid chlorides (Table 5, entries 4 and 5). Notably, no racemization occurred using an enantiomeric pure amine as substrate, demonstrating that the magnetic ROMPgels are very mild acylating agents applicable to sensitive compounds.

However, in some cases acid chlorides or anhydrides are neither readily available nor easily synthesized and their high reactivity might cause stability problems, for example, racemization.[42] Therefore, acylation of the magnetic Fe/C ROMPgel **9** by coupling with aryl and alkyl carboxylic acids was investigated (Table 5, entries 7–10). Initially, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC; free-base form) was applied as coupling reagent in a mixture of DMF and CH_2Cl_2 (1:1) leading to a moderate loading (0.74 mmol g^{-1}), which corresponded to 47% functionalization with acyl groups taking into account the distinct mass increase; subsequently, the corresponding amide 8 h was formed in high yields and purities. Other coupling reagent and base combinations, such as 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate/ethyldiisopropylamine (TBTU/DIPEA) or diisopropylcarbodiimide/DMAP (DIC/DMAP), showed slightly improved loadings when using the same acid, with the best result (0.89 mmol g^{-1}, 56% functionalization) achieved by the most reactive reagent (TBTU; Table 5, entry 8). In all cases three equivalents of acid and three equivalents of coupling reagent were used. The high purities of the product amides underline the successful removal of the spent coupling reagents from the resin in the washing steps, which is sometimes not trivial when using extraction to purify the reaction mixture. Moreover, entries 7 and 8 (Table 5) demonstrate the reproducibility of the acylation when using the same amine.

Although the loadings obtained with carboxylic acids cannot compete with the excellent loadings obtained using acid chlorides, they are comparable with other acyl transfer resins.[7,12,13] Reasons might be the reduced reactivity of activated esters compared to acid chlorides and the steric demand of the coupling reagents. The loadings might be significantly improved when using more equivalents of acid and coupling reagent or double couplings.[21] However, one has to decide for

Table 5. Reloading of ROMPgel **9** by acid chlorides, anhydrides, and acids and subsequent synthesis of amides (**8b–j**) recycling the resin after each run.

Entry	Cycle	Acylating agent	Additives for coupling	Loading[a] [mmol g^{-1}]	Product amide[b]	Yield [%]
1	1		Et_3N	2.26	 **8b**	96
2	2		Et_3N	2.27	 **8c**	94
3	3		Et_3N	2.18	 **8d**	86
4	4		DMAP, Et_3N	1.80	 **8e**	91
5	5		DMAP, Et_3N	1.36	 **8f**	95
6	1		Et_3N	2.14	 **8g**	95
7	2		EDC	0.74	 **8h**	90
8	3		TBTU, DIPEA	0.89	 **8h**	88
9	4		DIC, DMAP	0.80	 **8i**	87
10	5		TBTU, DIPEA	0.67	 **8j**	97

[a] Determined by NMR assay. [b] Purity >95% in all cases based on NMR. [b] Product 8b–j. [c] Acylation on monomer stage.

each application, if slightly increased loadings compensate for the need for higher amounts of high molecular weight coupling reagents and potentially laborious acids.

Conclusions

We have demonstrated the successful synthesis of acylated magnetic ROMPgels starting from readily synthesized carbon coated iron or cobalt nanoparticles. Whereas Grubbs-I catalyst failed to initiate the polymerization on the nanoparticle surface, Grubbs-II catalyst efficiently catalyzed the formation of magnetic ROMPgels, which were rapidly recovered from reaction mixtures by magnetic decantation. Further experiments revealed an optimal amount of 80 equivalents of monomer, leading to a high loading (up to 2.6 mmol g^{-1}) hybrid material that was stable for more than five months. Furthermore, IR spectra, TEM pictures, and an NMR-assay were applied to thoroughly characterize the ROMPgels.

Synthesis of various amides in excellent yields and purities followed by subsequent regeneration of the magnetic acyl transfer resin was achieved for at least five consecutive cycles. The resin was efficiently recovered by magnetic decantation after each step, dispensing the need of tedious and energy-intensive filtration or even chromatography. No cross-contamination was detected when using different acylation reagents or amines, suggesting the magnetic resins to be reliable and readily recyclable acyl transfer reagents. Although acid chlorides and anhydrides readily reacylated the resin, couplings with carboxylic acids only generated moderate loadings regardless of the coupling reagent or reaction conditions. Further studies, which are currently conducted in our laboratories, include the improvement of these loadings, the use of more sophisticated substrates, and the use of ROMPgels as support for fluorescent labels. Also, the upscaling to multi-gram experiments is planned, for which the advantages of the magnetic resins should even be more apparent.

Experimental Section

Materials and methods

The carbon-coated cobalt nanomagnets (Co/C, 20.5 $m^2 g^{-1}$, mean particle size ≈25 nm) were purchased from Turbobeads Llc, Switzerland. Prior to use, they were washed five times for 24 h in a concentrated HCl (Merck, puriss.)/deionized water (Millipore) mixture (1:1). Acid residuals were removed by washing with Millipore water (5×), and the particles were dried at 50 °C in a vacuum oven.[27] Azide- (**2**)[22,29] and norbornene- (**3**)[31] functionalized nanobeads were synthesized according to literature procedures. Acetylated monomer **4** was prepared in three steps following literature-known syntheses.[21,35,36] All other commercially available compounds were used as received. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded by using a Bruker AC300 spectrometer with $CHCl_3$ (7.26 ppm) as a standard. Magnetic nanobeads were dispersed using an ultrasound bath (Sonorex RK 255 H-R, Bandelin) and recovered with the aid of a neodymium-based magnet (side length 12 mm). They were characterized by using a IR-ATR spectrometer equipped with a Specac Golden Gate Diamond Single Reflection ATR-System and elemental microanalysis (LECO CHN-900).

Synthesis of magnetic ROMPgel (5)

In a typical experiment, Nb-tagged, carbon-coated iron nanoparticles (400 mg, 0.12 mmol g^{-1}) were dispersed in dry CH_2Cl_2 (5 mL) by sonication for 15 min in a sealed reaction vessel under nitrogen atmosphere. A solution of Grubbs-II catalyst (40.8 mg, 48 μmol, 1.0 equiv. with respect to the loading with Nb) in dry CH_2Cl_2 (3 mL) was injected and the dispersion subjected to sonication for 30 min with the ultrasonic bath tempered to 60 °C. Next, a solution of the acetylated *N*-hydroxysuccinimide monomer **4** (672 mg, 2.88 mmol, 60 equiv.) in dry CH_2Cl_2 (10 mL) was added and the sonication continued for 1 h at 60 °C. The pressure in the reaction vessel was released from time to time to allow formation of ROMPgel **5** after a few minutes. The magnetic gel was separated by an external magnet and washed with CH_2Cl_2 (3×5 mL). To quench the reaction, a CH_2Cl_2/EVE (1:1; 5 mL) mixture was added followed by sonication at ambient temperature for 20 min. The gel lump was washed with CH_2Cl_2 (3×5 mL), dried under vacuum, and crushed to yield NHS-functionalized magnetic ROMPgel.
Incorporation of monomer: >95%; IR: $\tilde{\nu}$ = 1822, 1788, 1731, 1368, 1200, 1154, 1059, 1002, 967, 914, 809, 729 cm^{-1}; elemental microanalysis: 35.77% C; 2.58% H, 3.84% N.

^{1}H NMR assay for the determination of the loading

A stock solution was prepared by introducing benzyl amine (1.64 mL, 15 mmol), *p*-methylanisole (378 μL, 3 mmol), and methanol (2.5 mL, nondeuterated) into a 25 mL volumetric flask and filling up with $CDCl_3$. To the Co/C-ROMPgel or Fe/C-ROMPgel **6** (50 mg) in a capped vial, stock solution (1.00 mL) was added and the ROMPgel suspended by magnetic agitation utilizing the intrinsic magnetic properties of the material. After agitation for 5 h at RT, the magnetic beads were separated by using an external magnet and the solution was filtered over cotton. NMR spectra were acquired, and the integration of the benzylic CH_2 doublet of the product (typically 4.3–4.5 ppm) was compared with that of the phenylic CH groups of the standard (typically 6.75 ppm).

General procedure for the acylation of amines using magnetic ROMPgels

An excess (1.3 equiv. acyl groups) of magnetic ROMPgel **7** was stirred with amine (1.0 equiv) in 5 mL of a $CHCl_3$/MeOH (9:1) mixture at RT for 2–16 h (TLC monitoring). The nanoparticles were recovered by using a magnet, the solution decanted, and the nanobeads washed three times with a $CHCl_3$/MeOH (9:1; 5 mL) mixture. The combined solutions were filtered over cotton, the solvents were distilled for reuse in the next cycle, and the crude product was dried under high vacuum.
The recovered particles were subsequently stirred in a solution of CH_2Cl_2/MeOH/benzylamine (8:1:1; ≈1 mL per 100 mg resin) overnight. After decantation of the solution, the particles were washed with 15% AcOH/CH_2Cl_2 (3x), THF (3x), and Et_2O (1x). 1 mL of solvent per 100 mg resin was used in each washing step, and the particles were suspended by stirring for 15 min. The particles were dried under vacuum for 5 h.
***N*-Benzylacetamide (8a):** According to the general procedure Fe/C ROMPgel **5** (508 mg, 0.71 mmol, 1.39 mmol g^{-1}) loaded with acetyl groups was used to acetylate benzylamine (59 μL, 543 μmol) while stirring for 5 h. Crude *N*-benzylacetamide **8a** (79.9 mg, 536 μmol, 99%) was obtained as a pale brown solid and the resin recycled for the next run.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 5H), 6.11 (bs, 1H), 4.39 (d, *J* = 5.6 Hz, 2H), 1.98 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 138.3, 128.8, 127.9, 127.6, 43.8, 23.3 ppm; MS (ESI-MS): *m/z* (%) = 150.1 (50) [M^+–H], calc. 149.1.
1-[3,4-Dihydroisoquinolin-2(1*H*)-yl]ethanone (8b): ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.24–7.04 (m, 9H, r_{maj} + r_{min}), 4.73 (s, 3H, r_{maj}), 4.61 (s, 2H, r_{min}), 3.82 (t, *J* = 6.0 Hz, 2H, r_{min}), 3.67 (t, *J* = 5.9 Hz, 3H, r_{maj}), 2.90 (t, *J* = 5.9 Hz, 3H, r_{maj}), 2.85 (t, *J* = 5.9 Hz, 2H, r_{min}), 2.18 (s, 3H, r_{min}), 2.17 ppm (s, 4H, r_{maj}); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ = 169.5, 169.4, 135.1, 134.1, 133.6, 132.6, 129.0, 128.3, 126.9, 126.7, 126.6(4), 126.5(6), 126.4, 126.1, 48.1, 44.1, 44.0, 39.5, 29.5, 28.6, 22.0, 21.7 ppm; MS (ESI-MS): *m/z* (%) = 351.0 (100) [$2M^+$–H], calc. 51.2.
4-{[2-(1*H*-Indol-3-yl)ethyl]amino}-4-oxobutanoate (8c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 1.6 Hz, 1H), 5.73 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 12.8 Hz, 6.5, 2H), 2.96 (t, *J* = 6.7 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.40 (t, *J* = 6.8 Hz, 2H), 1.23 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 171.5, 136.5, 127.5, 122.2(8), 122.2(6), 119.6, 118.8, 113.0, 111.4, 60.8, 39.9, 31.2, 29.7, 25.4, 14.3 ppm; MS (ESI-MS): *m/z* (%) = 288.9 (50) [M^+–H], calc. 288.2.
***N*-(2,2-Dimethoxyethyl)-4-nitrobenzamide (8d):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32–7.26 (m, 2H), 7.96–7.91 (m, 2H), 6.44 (bs, 1H), 4.50 (t, *J* = 5.0 Hz, 1H), 3.63 (t, *J* = 5.4 Hz, 2H), 3.44 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 149.8, 140.0, 128.3, 124.0, 102.6, 54.9, 41.8 ppm; MS (ESI-MS): *m/z* (%) = 255.1 (100) [M^+–H], calc. 255.1.
(*R*)-*N*-(1-Phenylethyl)isobutyramide (8e): $[\alpha]_D = +118^\circ$ (1.0 g per 100 mL in $CHCl_3$, 21 °C); *ee* >99%, determined by HPLC analysis using a Chiralpak AS-H column eluting with a 95:5 heptane/2-propanol mixture; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5H), 5.65 (bs, 1H), 5.23–5.04 (m, 1H), 2.43–2.24 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.15 ppm (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 143.5, 128.8, 127.4, 126.3, 48.5, 35.8, 21.8, 19.7 ppm; MS (ESI-MS): *m/z* (%) = 192.2 (100) [M^+–H], calc. 192.1.
***N*-(3-Azidopropyl)-2,2,5-trimethyl-1,3-dioxane-5-carboxamide (8f):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (bs, 1H), 3.90 (d, *J* = 12.4 Hz, 2H), 3.77 (d, *J* = 12.4 Hz, 2H), 3.46–3.35 (m, 4H), 1.84 (p, *J* = 6.7 Hz, 2H), 1.48 (s, 3H), 1.43 (s, 3H), 1.00 ppm (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$): $\delta = 175.3$, 98.7, 68.4, 67.3, 49.3, 40.3, 37.0, 29.2, 28.9, 18.3, 17.9 ppm; IR (ATR): $\tilde{\nu} = 3375$, 2989, 2937, 2872, 2095, 1650, 1537, 1454, 1375, 1265, 1201, 1082, 828, 637 cm^{-1}; MS (ESI-MS): *m/z* (%) = 257.1605 (100) [M^+–H], calc. 257.1608.

***N*-(Furan-2-ylmethyl)acetamide (8g):** ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J = 1.1$ Hz, 1H), 6.32 (dd, $J = 3.0$ Hz, 1.9, 1H), 6.22 (d, $J = 3.0$ Hz, 1H), 5.87 (bs, 1H), 4.42 (d, $J = 5.4$ Hz, 2H), 2.00 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 151.3, 142.3, 110.6, 107.6, 36.7, 23.6 ppm; MS (ESI-MS): *m/z* (%) = 157.1 (100) [M^+–NH_4], calc. 157.1.

(4-Iodophenyl)(morpholino)methanone (8h): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 3.94–3.31 ppm (m, $J = 72.7$ Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.6$, 137.9, 134.8, 129.0, 96.3, 67.0 ppm; MS (ESI-MS): *m/z* (%) = 317.0 (30) [M^+–H], calc. 317.0.

***N*-Cyclohexyl-4-iodobenzamide (8i):** m.p. 171–173 °C; IR (ATR): $\tilde{\nu} = 3296$, 2934, 2853, 1715, 1623, 1585, 1537, 1477, 1445, 1330, 1151, 1006, 890, 837, 713, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.3$ Hz, 2H), 5.88 (bs, 1H), 4.03–3.88 (m, 1H), 2.08–1.96 (m, 2H), 1.82–1.52 (m, 4H), 1.53–1.33 (m, 2H), 1.32–1.18 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.9$, 137.8, 134.6, 128.6, 98.2, 49.0, 33.3, 25.7, 25.0 ppm; MS (ESI-MS): *m/z* (%) = 330.0351 (100) [M^+–H], calc. 330.0349.

***tert*-Butyl (4-oxo-4-(prop-2-yn-1-ylamino)butyl)carbamate (8j):** ^1H NMR (300 MHz, $CDCl_3$): 6.45 (bs, 1H), 4.73 (bs, 1H), 4.05 (dd, $J = 4.8$ Hz, 2.4, 2H), 3.17 (t, $J = 6.4$ Hz, 2H), 2.34–2.15 (m, 3H), 1.90–1.73 (m, 2H), 1.44 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.5$, 156.7, 79.8, 79.6, 39.7, 33.5, 29.3, 28.5, 26.6 ppm; MS (ESI-MS): *m/z* (%) = 241.1 (100) [M^+–H], calc. 241.2.

General method for the reacylation of magnetic ROMPgels using acid chlorides or anhydrides

Magnetic ROMPgel resin bearing free *N*-hydroxyl groups (**9**) was dispersed in CH_2Cl_2 by stirring for 15 min. After cooling to 0 °C, Et_3N (4.0 equiv.) and acid chloride or anhydride (3.0 equiv., dropwise/in portions) were added. In the case of anhydrides, 0.1 equiv. of DMAP were added as catalyst. The slurry was stirred for 30 min at 0 °C, and the stirring continued for 16 h at RT. Thereafter, the magnetic ROMPgel was collected by using a magnet, and the solution decanted. The particles were subsequently washed with THF (3×5 mL), CH_2Cl_2 (3×5 mL), and Et_2O (1×5 mL). After drying under high vacuum, the loading was determined by an NMR assay.

General method for the reacylation of magnetic ROMPgels using acids

Resin **9** was predispersed in a DMF/CH_2Cl_2 mixture (1:1) and cooled to 0 °C. Acid (3.0 equiv.), TBTU (3.0 equiv.), and DIPEA (3.0 equiv.) were stirred together in 3 mL DMF/CH_2Cl_2 at 0 °C for 15 min before dropwise addition to the resin. The resulting slurry was stirred for 1 h at 0 °C and overnight at RT before the ROMPgel was recovered by using a magnet. The particles were subsequently washed with THF (3×5 mL), CH_2Cl_2 (3×5 mL), and Et_2O (1×5 mL). After drying under high vacuum, the loading was again determined by using an NMR assay.

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Keywords: acylation · metathesis · magnetic nanobeads · polymerization · supported catalyst

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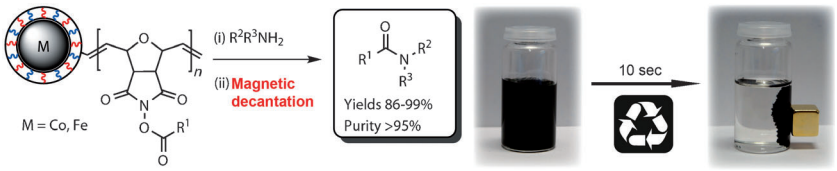
Ring-Opening Metathesis Polymerization-based Recyclable Magnetic Acylation Reagents



Do it magnetic: Amines are acylated utilizing *N*-hydroxysuccinimide ROMP-gels (ROMP = ring-opening metathesis polymerization) grafted onto highly magnetic nanobeads. The products are isolated by operationally simple magnetic decantation in excellent yields and purities, and the ROMPgel is recycled more than five times without loss of activity.