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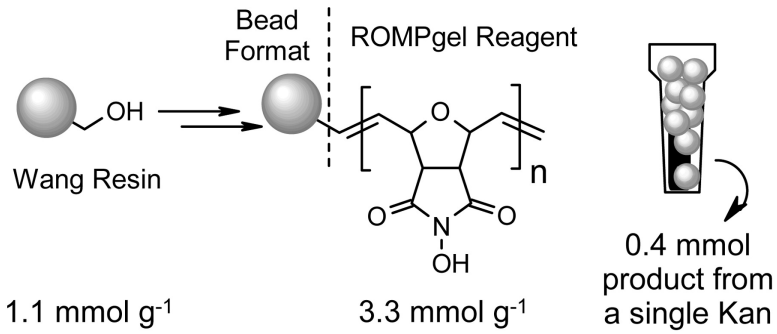

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ROMPgel Beads in IRORI Format: Acylations Revisited

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Functionalized "designer" polymers derived from ring-opening metathesis polymerization (ROMPgels) are attractive for their high loading, high purity, and ease of synthesis. Their physical state may vary from liquid to gel to granular solid, making a general method of handling these polymers difficult. By incorporating a suitable norbornene-substituted linker on standard Wang beads, ROMPgels can be easily grafted onto the resin, adding the convenience of a bead format while still maintaining the high loading and excellent site accessibility. This advantage is demonstrated by the use of an *N*-hydroxysuccinimide ROMPgel (3.3 mmol g^{-1}, a 3-fold increase from the parent linker resin) in IRORI Kan format. Conditions for the acylation of these IRORI-formatted ROMPgels are reported, along with the scope and limitations of the choice of acylating reagents. Yields are greatly improved by the use of perfluorinated solvents as a nonparticipating cosolvent in the acylation process. A simple titration method for the quantification of the acylated ROMPgels is also reported. Spent Kans are regenerated after each use without apparent loss of activity or purity after several cycles. Due to the high loading and reduced swelling of the ROMPgel resin, up to 0.39 mmol acyl group has successfully been recovered from a single IRORI miniKan, demonstrating the high capacity of the resin and applicability to both lead discovery and optimization programs.

Introduction

Acylating polymers as solid-supported reagents remain very much of current interest as new polymers, new methods and new results continue to be published. A look at the recent literature reveals a wide variety of functional groups used toward a common aim:[1] Salvino and co-workers reported the use of a tetrafluorophenol resin for both acylation and sulfonylation reactions with excellent purities.[2] The *ortho*-nitrophenol resin has also been investigated for the same use.[3] The kinetics of acylation of the Marshall linker resin have recently been reported.[4] The group of Sodeoka has shown that polystyrene-supported *N*-hydroxysuccinimide can be used for the general preparation of carbamates via conversion to the chloroformate.[5] Nájera and co-workers have extensively used a co-poly(styrene-*N*-hydroxymaleimide) resin for both the coupling and protection of amino acids.[6] Other linkers include a pyrazole-based linker,[7] a dimedone-based linker,[8] and a mixed anhydride used for the determination of enantiomeric excess of amines.[9] Possibly the most commonly utilized resin, *N*-hydroxybenzotriazole, has recently had its scope and limitations published by Gooding and co-workers.[10] Even the less reactive benzotriazole resin is finding utility in acylation, as exemplified by the synthesis of unsymmetrical ureas[11] or for the formylation of amines.[12] Although many of these resins are commercially available, the cost remains high, and the loadings remain moderate. The loadings, combined with the high swelling of the polystyrene resin, limit the maximum yield that can be obtained when using the resins in conjunction with IRORI Kan technology.[13]

The groups of Barrett,[14] Buchmeiser,[15] and, more recently, Hansen[16] have pioneered the use of "designer" polymers (here the term ROMPgel will be used), synthesized by ring-opening metathesis polymerization (ROMP) of an appropriately functionalized monomer. The *N*-hydroxysuccinimide-functionalized ROMPgel has shown great versatility for the synthesis of amides, carbamates, and ureas;[17] in the synthesis of oxadiazoles;[18] and for the facile determination of enantiomeric excess of amines through the supported Mosher's ester.[19] Reactions can be carried out equally well in large or small scale, with workup a single filtration to remove the granular ROMPgel.

For the present study, a resin was required for the parallel synthesis of sets of compounds (typically 400 members) that would display a combination of the high loading, good reaction kinetics, and ease of synthesis of ROMPgel with the convenience of use of IRORI Kan technology.

Results and Discussion

Synthesis of the Polymer. Barrett and co-workers reported the use of ROMPspheres, ROM-polymers grafted onto a polystyrene-bound Grubbs' catalyst,[20] and demonstrated the utility of these new polymers as solid supports.[21] An observation during the synthesis of this type of polymer graft was that "back-biting" reactions (cross-metathesis between the nascent ROMP chain and the excess of vinyl groups on the solid support) released active ruthenium metathesis catalyst into solution, where it caused competitive and undesired ROM-polymerization. Buchmeiser and co-workers

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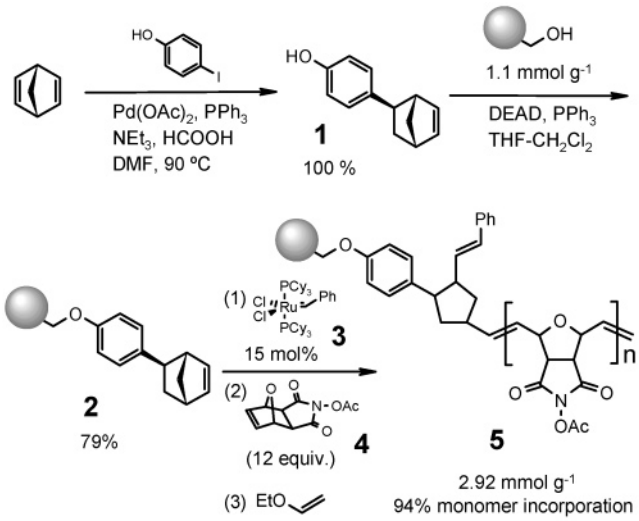
Scheme 1. Synthesis of *N*-Acetoxysuccinimide ROMPgel Beads **5**



have demonstrated the utility of norbornene units as linkers, both for polystyrene beads and silica, either by capturing living ROMP chains onto the solid support or by initiating ROM on the solid support and then growing polymer chains from there.[22]

The latter strategy was chosen as the method of synthesis. Hence, linker **1** was synthesized quantitatively in multigram quantities from 4-iodophenol via hydroarylation of norbornadiene. Mitsunobu reaction of linker **1** with Wang resin (100−200 mesh, 1.1 mmol g^{-1}) gave linker resin **2** in 79% yield, on the basis of the initial loading of the Wang. The norbornene unit of the linker was subjected to ring-opening metathesis with Grubbs' catalyst **3**. The resin was washed well to remove excess unreacted catalyst in solution. The resin was then treated with a large excess of monomer **4** for 2 days. Finally, metathesis was terminated using ethyl vinyl ether, and the resin was washed well and dried. By the increase in mass of resin **5**, it was calculated that 94% of the monomer had been incorporated, and the loading was 2.92 mmol g^{-1} (Scheme 1).

The resin produced consisted mostly of free-flowing beads, although some larger granules of polymer (1−4 mm) were also formed (Figure 1). The granules were simply separated by sieving. The swelling of the *N*-acetoxy-ROMPgel resin **5** was measured in a few common organic solvents (Table 1). In all cases, the swollen resin was more dense than the solvent. The swelling was always less than that of the parent linker resin **2**.

Determination of Loading of ROMPgel Resin 5. By the increase in mass of resin **5**, the loading was calculated as 2.92 mmol g^{-1}. Combustion analysis correlated very well with this figure, detecting 4.14% N, corresponding to a loading of 2.95 mmol g^{-1}. By a third gravimetric method, the acetate groups were cleaved from a known amount of resin with an excess of 2-methoxypropylamine, a volatile amine. Filtration and evaporation of all volatiles gave the product *N*-(2-methoxypropyl)acetamide **6**. From the yield of the amide obtained, the resin loading was calculated as 2.87 mmol g^{-1}, again in very good agreement with previous results (Scheme 2). A loading of 2.9 mmol g^{-1} signified that

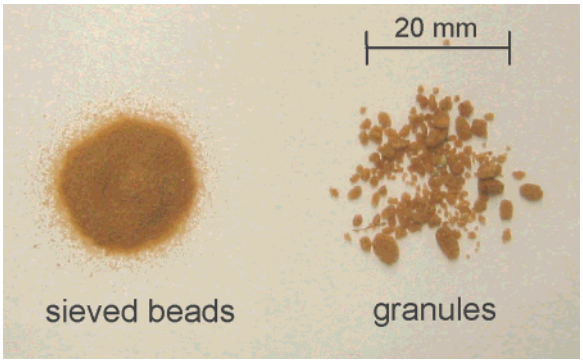


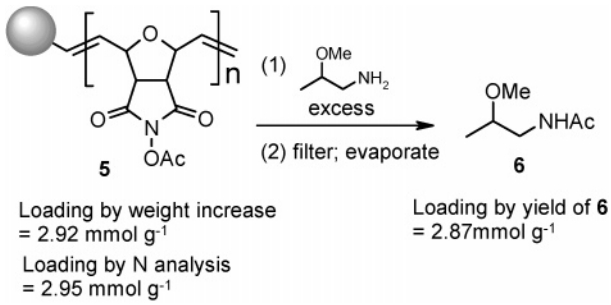
Figure 1. ROMPgel beads and granular form.

Table 1. Swelling Properties of *N*-Acetoxy ROMPgel Resin **5** Compared to Linker Resin **2**[a]

solvent	vol occupied (mL) ROMPgel resin 5	vol occupied (mL) linker resin 2
dry resin	1.0	1.0
toluene	1.8	4.6
THF	2.5	4.4
DMF	2.3	3.5
DCM	3.2	5.2

[a] The weight of 1 mL dry resin **5** was 0.78 g. The weight of 1 mL dry resin **2** was 0.68 g.

Scheme 2. Comparison of Methods for the Determination of Loading of Resin **5**

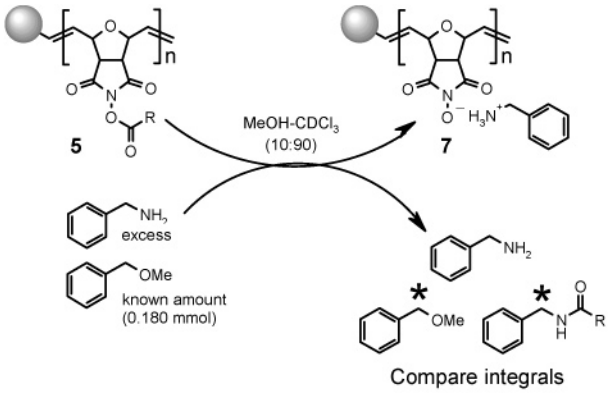


the polymer **5** consisted of 65% ROMPgel chains and 35% polystyrene by weight. During the synthesis of resin **5**, 65% of the Grubbs' catalyst **3** used was recovered from the resin washes; therefore, from the ratio of catalyst used to monomer incorporated, the average ROMP chain length was calculated as 225 monomer units per chain.

A more rapid assay was developed on the basis of ^{1}H NMR. Hence, a known weight of resin was treated directly in an NMR tube with an excess of benzylamine in (10:90) MeOH−$CDCl_3$. Direct measurement between the amount of amide produced and the amount of amine left was not an accurate method, since the liberated N−OH resin captured amine from the solution.[23] Therefore, a known amount of benzyl methyl ether was added as an inert internal standard. After 2 h, the spectrum was acquired, and the integration of the benzylic CH_2 doublet of the product amide was compared with that of the benzylic CH_2 singlet of the internal standard. The loading of ROMPgel resin **5** determined by this method was 2.85 mmol g^{-1}, in very good agreement with the value determined by previous methods (Scheme 3).

The titration worked equally well for loose resin either in a vial or in an NMR tube, as it did for resin inside an IRORI Kan. The titer was also measured in a time-course experiment

Scheme 3. Determination of Loading by ^{1}H NMR[24]



Loading of **5** by NMR analysis = 2.85 mmol g^{-1}

for equal mass samples of both the sieved beads of resin and the granules retained by sieving (Figure 1). Not only did the granules have kinetics similar to that of the sieved beads, but also their loading was slightly higher. Since the interbead spaces were presumably filled with a matrix of ROMPgel chains, it followed that the granules had a slightly higher content of ROMPgel relative to the polystyrene and, hence, a higher loading. This also demonstrated that despite the inability of the granules to physically swell in organic solvent, the site accessibility of the ROMPgel resin was essentially quantitative (Figure 2). In general, 2−3 h was sufficient time to cleave 95% of the attached acyl groups.

Reacylation of the ROMPgel. The synthesis of ROMPgel resin **5** yielded a high-loading polymer in which all of the acyl groups were acetyl. For parallel synthesis, diverse acyl groups would be needed, ideally without the need for a different resin preparation each time. Hence, a sample of resin **5** was treated with excess benzylamine to quantitatively remove the acetyl groups. The resin was washed well with 15% AcOH in DCM (dichloromethane) (to remove benzylamine salts from the resin **7**); then with DCM (to wash out any acetic acid); and finally, with ether before drying in vacuo. The *N*-hydroxysuccinimide resin **8** thus produced had a calculated loading of 3.3 mmol g^{-1}, a 3-fold increase from the original Wang resin (Scheme 4).

Initial reacylation experiments were carried out using 2-furoic acid as a model. The sometimes poor kinetics or site accessibility of reactions on solid-phase often prompts the use of large excesses of reagents in solution, the majority of which are then discarded. Acylation conditions were sought in which no more than 3 equiv of carboxylic acid would be needed for complete acylation of the resin. In a screening experiment, loose ROMPgel resin **8** was treated with varying excesses of furoic acid in the presence of dicyclohexylcarbodiimide (DIC) and *N*,*N*-(dimethylamino)-pyridine (DMAP) (Scheme 5).

For efficient reacylation, a large excess of acid (5−10 equiv) was needed. At low acid concentrations (<2 equiv) the resin was barely acylated, if at all. There was either a limiting concentration or number of equivalents of acid which were required under these conditions.

Perfluorinated Solvents and IRORI Kans. The use of perfluorinated solvents to improve the yields of reactions

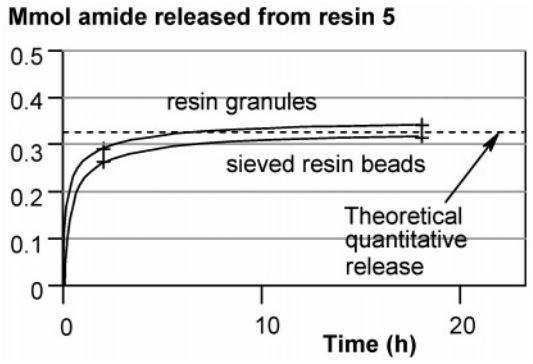
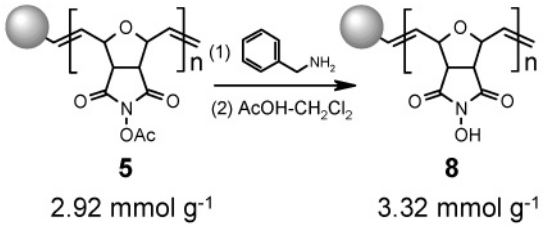
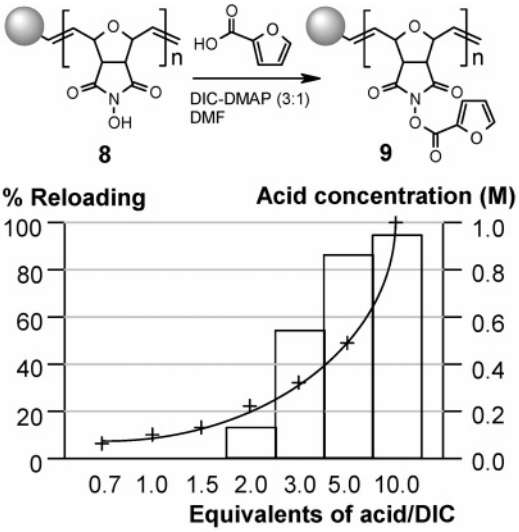


Figure 2. Loading differences between ROMPgel sieved resin beads and granules; 111 mg of resin **5** was used for each experiment. The dashed line at 0.325 mmol is the expected titration value for 100% yield of amide, based on a resin loading of 2.92 mmol g^{-1}.

Scheme 4. Preparation of *N*-Hydroxysuccinimide Resin **8**



Scheme 5. Reacylation of ROMPgel 8 with 2-Furoic Acid[a]



[a] Equivalents of 2-furoic acid and DIC are approximate (see Experimental Section). A similar volume of DMF was used for all experiments. Bars represent the percentage reloading of the *N*-hydroxysuccinimide-OH, measured by titration. The crosses show the effective concentration of 2-furoic acid in the DMF solution.

carried out on solid phase was first reported by the group of Morphy.[25] The fluorous nature of the bulk of the solvent seems to concentrate the small volumes of organic solvent into the resin matrix. Morphy elegantly demonstrated this phenomenon, even by using the minimum solvent necessary to completely swell the resin and still obtaining excellent yields of product. Hence, repeating the loading experiment of Scheme 5 with 3 equiv of 2-furoic acid (1.4 M in DMF, *N*,*N*-dimethylformamide) and DIC (3 equiv) and adding perfluorohexane to mostly fill the SPE cartridge, the percentage reloading increased to 66%.

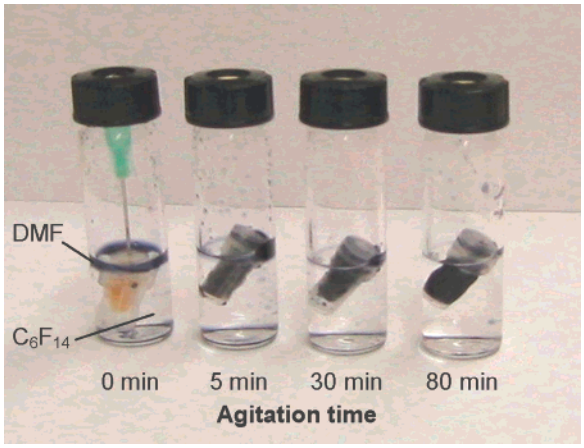


Figure 3. Absorption of DMF into Wang resin. Sufficient DMF was added to completely swell the resin within the Kans. The colorless phase is perfluorohexane. The dark traces observed on the vial walls are beads of resin that have escaped from the Kan.

Table 2. Conditions for Acylation of ROMPgel **8**[a]

run	DMAP	resin	perfluorohexane	yield, %
1	no	loose	no	35
2	yes	loose	no	55
3	no	loose	yes	66
4	yes	in Kans	yes	96[b]

[a] Experiments were run with 2-furoic acid (3 equiv) and DIC (3 equiv) in DMF. DMAP (1 equiv) was added where indicated. Concentration of acid in DMF when perfluorohexane added, 1.4 M. Runs 1−3 were were perfomed on loose resin **8** in SPE cartridges. Run 4 was performed with resin **8** loaded into IRORI miniKans. [b] Average of six results.

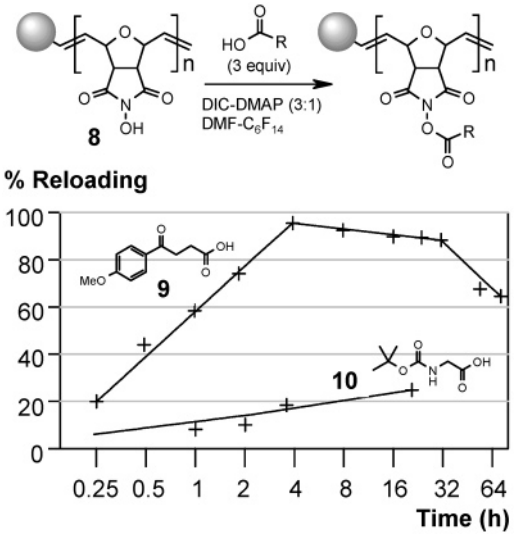
It was not obvious that the use of perfluorinated solvents could be applied to resin reactions in IRORI Kans due to the physical confinement of the resin behind a polypropylene mesh. To demonstrate the principle, standard Wang resin was loaded into IRORI microKans and agitated with a mixture of DMF (colored with ink) and perfluorohexane. Within a few minutes, the solvent was mostly absorbed into the resin matrix, completely swelling the resin within 80 min (Figure 3).

Six IRORI miniKans were loaded with known amounts of ROMPgel resin **8**. The Kans were treated together with 2-furoic acid (3 equiv, at a concentration of 1.4 M in DMF) and DIC (3 equiv), DMAP (1 equiv), and sufficient perfluorohexane to mostly fill the reaction vessel. After 24 h of agitation, the Kans were washed together, dried, and titrated individually. All six Kans gave very similar loading results between 90 and 100%, that is, all of the Kans were essentially acylated equally well under the conditions of little organic solvent. A summary of acylation results with 3 equiv of furoic acid and DIC is shown in Table 2.

With conditions seemingly optimized, a different acid coupling was attempted. Hence, ROMPgel resin **8** was loaded into IRORI Kans and treated with *N*-Boc-4-nitrophenylalanine (3 equiv), DIC (3 equiv), and DMAP (1 equiv), with an acid concentration of >1.0 M in DMF and mostly filling the remaining space with perfluorohexane. The yield was 0%.

There Is No Such Thing as an R Group! In an effort to both optimize and at the same time generalize reaction conditions, it is obvious that many acids simply will not react in the same way. Two different acids were treated under the optimized conditions outlined above. 4-(4-Methoxyphenyl)-4-oxobutanoic acid **9** reached 96% acylation after only 4 h (Scheme 6, **9**). After 2 d, the titer was still around 90%, but started to decrease on the third day. The other acid, *N*-(*tert*-butyloxycarbonyl)glycine (Boc-Gly) **10**, acylated the resin at a much slower rate, reaching only 25% acylation after 24 h (Scheme 6, **10**).

Scheme 6. Acylation of ROMPgel Resin **8** with Two Different Acids[a]



[a] Percentage reloadings were determined by titration.

The DIC/DMAP coupling conditions were generally appropriate for acids of a "moderate" reactivity, that is, neither exceptionally sluggish nor very reactive acids. For slow-reacting acids, either longer reaction times or double couplings could be used to increase the yield of acylation. Some acids were too reactive in that the activated esters formed were unstable under the reaction conditions and were hydrolyzed either by direct attack at the carbonyl or, for acids bearing α-hydrogens, probably by base-induced elimination of the ketene. In these cases, double coupling gave no improvement in the yield of acylation, since the acylation/cleavage rates were always comparable. Lower yields were generally noticeable, for example, with phenylacetic acids or with phenoxyacetic acids.

A selection of different coupling agents was examined to see if acylation yields could be improved for some acids (Figure 4). In general, coupling agents that proceeded through formation of the acyl chloride or bromide (e.g., PyBrOP, **17** or the Vilsmeyer reagent, **19**), or acid chlorides themselves, were observed to give poor yields. In contrast, the uronium salts HATU **12** and *O*-benzotriazole-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU **13**) and the imidazolinium salt CIP (**11**) generally gave improved yields as compared to DIC. HBTU was selected as a general coupling agent, since the cost per millimole of reagent is comparatively small compared to both HATU and CIP.[26] Additionally, isocyanates could also be successfully incorporated onto ROMPgel resin **8**, giving supported carbamates, and by subsequent reaction with amines, ureas. Isothiocyanates

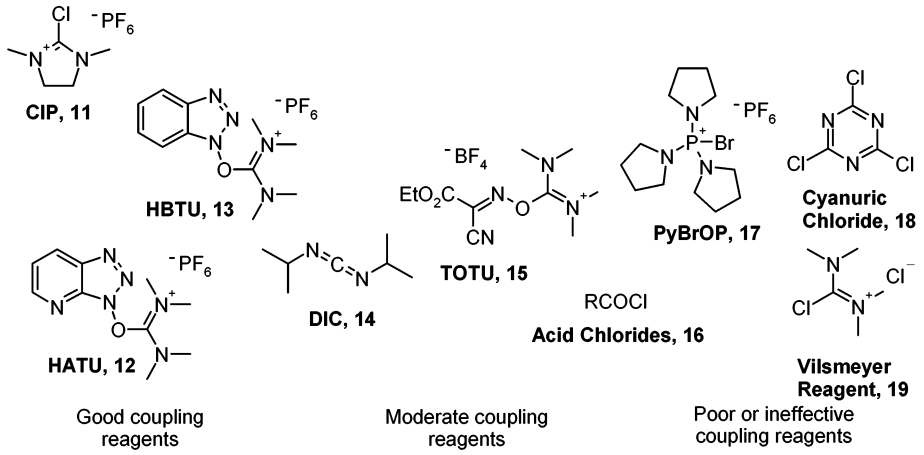


Figure 4. Various coupling agents for the acylation of ROMPgel resin **8**.

however, failed to react in a similar manner. To date, over 150 different acids, isocyanates and isothiocyanates have been tested as acylating reagents for ROMPgel resin **8**. A selection of yields of acylation is shown in Table 3. Yields of acylation were determined by the benzylamine titration method described above.

Despite the often moderate yield of reacylation, the functionalized resins could still be used for parallel synthesis of compounds due to their high initial loading. ROMPgel resin **5** was loaded into IRORI miniKans, the weight distribution between 70 and 120 mg resin per Kan corresponding to 0.2−0.3 mmol per Kan. Once tagged, sealed, washed with benzylamine to remove the acetate groups, and reacylated, even a 50% yield in the reacylation still signified 0.10−0.15 mmol per Kan. Typically, reactions were run using 0.08 mmol of amine nucleophile to ensure that the activated ester was always used in excess.

Comparison of ROMPgel Resin 8 with Other Acylating Polymers. ROMPgel resin **8** was compared with several commercially available resins for density, swelling capacity, loading efficiency, release kinetics, and absolute loading capacity. The resins selected were polystyrene *N*-hydroxybenzotriazole (PS−HOBt),[27] tetrafluorophenol resin (PS-TFP),[28] 4-hydroxythiophenol resin (Marshall)[29] and 4-nitrobenzophenone oxime resin (Kaiser)[30] (Figure 5). Equal weights of the resins were acylated with furoic acid (5 equiv, 0.3 M in DMF), DIC (5 equiv), and DMAP (1.6 equiv) on the basis of the loadings quoted by the suppliers. Once washed and dried, the acylated resins were loaded into NMR tubes and titrated as normal, following the development of the product amide (Scheme 7).

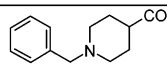
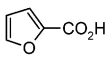
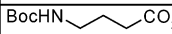
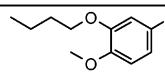
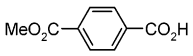
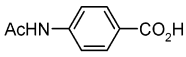
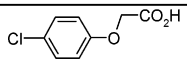
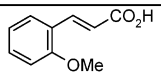
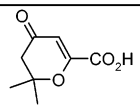
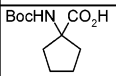
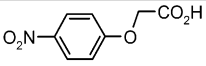
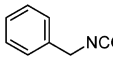
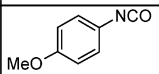
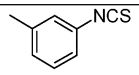
Surprisingly, the PS−HOBt failed to acylate under the reaction conditions used. Only DMAP was detected in the NMR titration, displaced from its salt with the resin by benzylamine. For the other resins, the kinetics of release of the acyl group followed a clear order: PS-TFP > ROMPgel > Kaiser > Marshall (Scheme 7). In terms of the efficiency of acylation of the resins, 83% of the hydroxy groups of ROMPgel **8** were loaded. For the other three commercial resins, the amount of acyl group incorporated was >100% based on the manufacturers' quoted loadings (Table 4). Acylation and cleavage may therefore be a valid method for accurate determination of resin functionalization. Finally, in terms of the absolute amount of amide released for a fixed weight of resin, the order was ROMPgel > PS-TFP = Marshall > Kaiser (Scheme 6 and Table 4).

Maximum Capacity of a Single IRORI MiniKan. A comparison of resins was performed in IRORI miniKans to evaluate the absolute capacity of amide that could be released per Kan. ROMPgel **8** was compared against PS-TFP resin in Kans loaded with incremental weights of resin. In one experiment, Kans loaded with 25−125 mg of each resin were acylated all together with furoic acid/DIC/DMAP using the perfluorinated solvent method. In a separate experiment, Kans loaded with 150−200 mg of resin were acylated together under similar conditions. The release of amide per Kan was determined by titration after 2.5 and 18 h (Figure 6).

In miniKans loaded with up to 125 mg of resin, both ROMPgel **8** and PS-TFP showed essentially linear release of amide. For ROMPgel **8**, ∼75% of the OH groups available were acylated, whereas PS-TFP was essentially loaded quantitatively. Additionally, the release of amide was >95% complete after 2.5 h for both resins. Only in the more fully filled Kans did physical effects start to affect both the loading and release of the acyl group. Both resins showed slower release kinetics in that only ∼80% of the total acyl groups were released after 2.5 h. PS-TFP seemed to hit a maximum limit of ∼0.24 mmol per Kan. The cutoff point for resin filling may be around 125−150 mg per miniKan for this resin. For ROMPgel **8**, the amount of amide released weight for weight of resin seemed to be roughly linear up to ∼175 mg resin per Kan. Only in the Kan loaded with ∼200 mg resin was the loading efficiency clearly affected. The absolute loadings and cutoff points may be susceptible to physical variables, such as rate and type of agitation, air bubbles within the Kans, etc.; however, the experiment demonstrated in one case that 0.39 mmol of amide (78 mg) product was synthesized from a single IRORI miniKan using ROMPgel **8**.

Longevity of Acylated ROMPgel Resin. The shelf-stability of the acylated resins was not indefinite. In the case of acetate-loaded ROMPgel **5**, ∼25% loss of acid was observed after 8 months of storage. Other activated esters were less stable, and showed complete hydrolysis after only 2 weeks.

Table 3. Yields of Acylation of ROMPgel Resin **8**[a]

Run	Reagent	Conditions	Acylation Yield
1		A*	93%
2		B*	84%
3		A*	83%
4		A*	82%
5		A*	81%
6		A*	77%
7		A*	71%
8		A*	55%
9		A*	47%
10		A	25%
11		A	9%
12		B*	0%
13		C	82%
14		C	57%
15		C	0%

[a] Conditions: (A) Acid (3 equiv), HBTU (3 equiv), NEt_3 (6 equiv), THF−R_F solvent. (B) Acid (3 equiv), DIC (3 equiv), DMAP (1 equiv), DMF−R_F solvent. (C) Iso(thio)cyanate (3 equiv), $CHCl_3$−R_F solvent. All reactions were run for 2 d. Concentration of acylating agent in organic solvent >1.2 M. R_F solvent refers to either perfluorohexane or perfluorodecalin. * Denotes the reactions were run on >20 IRORI Kans at the same time. Yields were determined by the benzylamine titration method.

Regeneration of ROMPgel Resin 8. The ROMPgel system was designed to be fully recyclable once sealed inside an IRORI Kan. The titrations had demonstrated that it was possible to quantitatively remove all of the attached acyl groups; hence, repetitive acylation, use, and regeneration should be possible. To test the principle, ROMPgel Kans in their fifth cycle of use were acylated with 2-methylbenzoic acid (HBTU/NEt_3) in 58% yield. One of the Kans was treated with benzylamine (0.9 equiv), and the reaction mixture was analyzed directly by HPLC. After 3 h, HPLC showed only desired product in 98.1% pure (detection by UV at 210 nm)

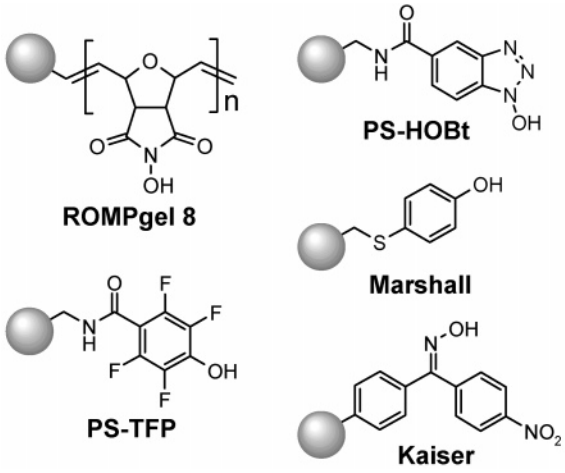
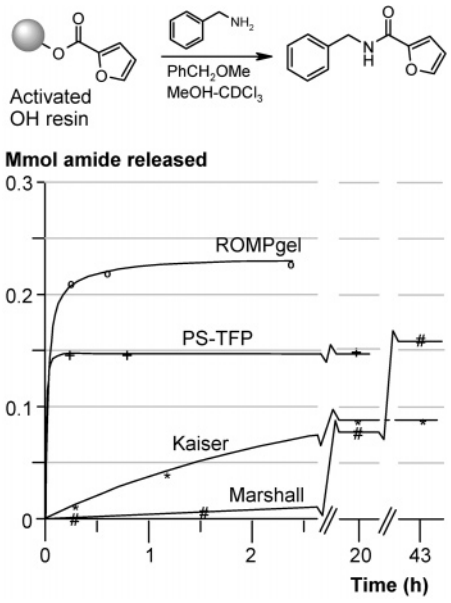


Figure 5. Activated ester resins used in comparative test.

Scheme 7. Comparative Reaction Kinetics for the Release of Activated Ester



form. The mixture was reanalyzed after 20 h, again detecting the desired product in 95.3% purity (Scheme 8).

Therefore, it seems that the resin can be reused several times with no apparent loss of activity or purity. One possible drawback to their reuse was the gradual loss of resin from the IRORI Kans. In every batch acylation, a Kan was included which contained an accurately weighed amount of resin (normally 0.175 mmol). After reaction and washing, this Kan was identified through its radio tag and titrated directly to measure the percentage acylation for the batch. Loss of resin from these Kans meant that the measured loading values were lower than in reality. Hence, these Kans were refilled with a fresh sample of ROMPgel to the correct weight every three uses. Summarized conditions for the continual reuse of ROMPgel is shown in Scheme 9.

Conclusions

The technologies of polystyrene beads, ROMPgel, and IRORI were successfully combined to provide a reusable acylation system suitable for parallel synthesis. Neither the high loading nor the excellent site accessibility of the

Table 4. Comparative Resin Data

	ROMPgel 8	PS−HOBt	PS-TFP	Marshall	Kaiser
loading[a] (mmol g^{-1})	3.32	0.62	1.34	1.58	0.5
bead size range (μm)	>75−150	75−150	150−300	150−300	35−75
wt (g) of 1 mL dry resin	0.76	0.58	0.68	0.74	0.58
swelling vol (mL) in DMF of 1 mL dry resin	2.3	4.6	5.4	5.6	5.2
mmol/mL volume (swollen resin)	1.10	0.08	0.17	0.21	0.06
total amide released (mmol)	0.215	0.001	0.157	0.158	0.083
percentage acylation of resin OH groups[a]	83	2	128	109	189
amide purity[b] (%)	99	DMAP	99	95	92

[a] All reactions were run on 100 mg dry resin in SPE cartridges. * Manufacturers values of loading. [b] Purity determined by HPLC of the NMR solutions at the end of the run, subtracting peaks due to the benzylamine and benzyl methyl ether.

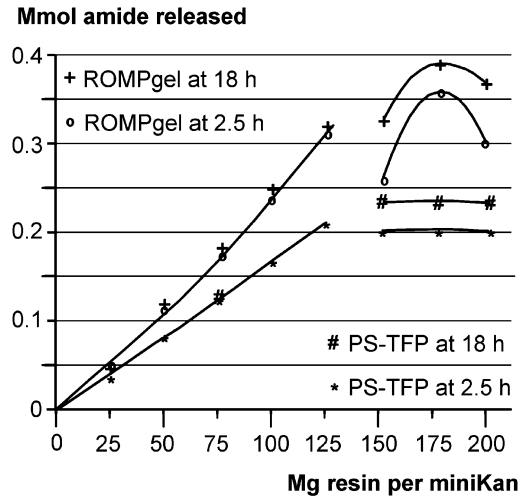
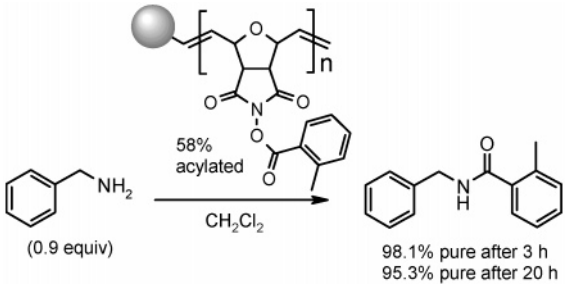
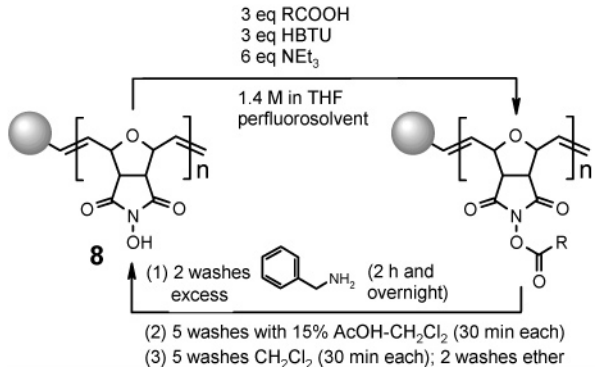


Figure 6. Release of amide per single IRORI miniKan.

Scheme 8. Purity of Product after **5** Cycles of Purities Measured by UV at 210 nm



Scheme 9. Preparation and Reuse of ROMPgel 8 in IRORI Kans



ROMPgel resin was compromised by incorporation into a bead, while the convenience of a Kan format was added. Additionally, the use of perfluorinated solvents to improve yields of solid-phase reactions in IRORI Kans was demonstrated. The kinetics of both loading and releasing acyl groups from the *N*-hydroxysuccinimide function was competitive with other commercially available resins. Additionally, the high loading allowed 30−50% more product to be obtained weight-for-weight with these other resins. There were some limitations in the range of acids that could be attached to the resin; however, titration allowed accurate quantification of the loading before use, and the high capacity of each Kan still allowed production of milligram quantities of product, even for poorly loaded resins. Further applications of polystyrene-grafted ROMPgels will be reported in due course.

Experimental Section

Solvents and reagents were used as received from general suppliers. The standard solvent abbreviations of DCM (dichloromethane), DMF (*N*,*N*-dimethylformamide), and THF (tetrahydrofuran) are used. HBTU refers to *O*-benzotriazole-*N*,*N*,*N*′*N*′-tetramethyluronium hexafluorophosphate **13**. DIC refers to diisopropylcarbodiimide **14**. DMAP refers to 4-(*N*,*N*-dimethylamino)pyridine. Wang resin was obtained from Senn chemicals. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were recorded on a Varian Gemini 2000 spectrometer. ^{13}C NMR (100 MHz) spectra were recorded on a Varian Mercury spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane, with the solvent resonance as internal standard ($CDCl_3$: δ 7.25). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), and integration. Column chromatography was performed on SDS 60 A (40−63 μm) silica gel. Gas chromatograms were recorded with a Hewlett-Packard 5890 series II instrument. Mass spectra were recorded on a Hewlett-Packard 5971 series mass selective detector. HPLC/MS were obtained on a Waters Alliance HT 2795 instrument using a Waters symmetry 2.1 × 100 mm C18 3.5-μm column (linear gradient of 100% water containing 0.1% formic acid and adjusted to pH 3 with ammonia to 100% acetonitrile containing 0.1% formic acid and adjusted to pH 3 with ammonia over 10 min and holding for 2 min). Peak areas (UV) were integrated at 210 nm. Mass detection was performed using a Micromass ZMD. Microanalysis was performed on a Fisons EA 1108 instrument, taking the average of three results. Infrared spectra were recorded on a FT-IR Mattson Genesis II.

Synthesis of Linker 1. 4-Iodophenol (18.8 g, 85 mmol) and bicyclo[2.2.1]hepta-2,5-diene (46 mL, 425 mmol, 5

equiv) were dissolved in DMF (120 mL) under nitrogen. Triphenylphosphine (2.0 g, 7.6 mmol, 9 mol %) was added, and the mixture was stirred to dissolve the solid. Palladium (II) acetate (850 mg, 3.8 mmol, 4.5 mol %) was added (the suspension turning a dark yellow-green color), followed by 40 mL of triethylamine, then 7.8 mL of 98% formic acid. The mixture was stirred at room temperature for 30 min, then heated to 90 °C and stirred overnight. The dark mixture was diluted with 300 mL of ether and washed successively with water, 1% aqueous HCl, saturated Na_2CO_3, and brine. The organics were dried over anhydrous Na_2SO_4 and evaporated to give 27 g of a dark oil. Flash chromatography [SiO_2, 100% hexane, then ethyl acetate−hexane (10:90)] gave 15.7 g (100%) of the desired *exo*-phenol as a pale yellow solid. The phenol probably contained a small amount (<5%) of the endo isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, J = 6 Hz, 1H), 1.5−1.7 (m, 3H), 2.64 (m, 1H), 2.84 (2, 1H), 2.95 (s, 1H), 4.80 (s, 1H), 6.16 (m, 1H), 6.23 (m, 1H), 6.76 (d, J = 6 Hz, 2H), 7.15 (d, J = 6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.6, 42.1, 42.8, 45.6, 48.3, 115.1, 128.6, 137.2, 138.2, 153.1. MS [EI] *m*/*z* 186, 120, 91, 77, 66.

Synthesis of Linker Resin 2. A 27.3-g portion of Wang resin (100−200 mesh, 1.1 mmol g^{-1}, 30 mmol) was loaded into a three-necked 1000-mL flask fitted with a mechanical stirrer and a dropping funnel. THF-DCM (400 mL, 50:50) was added, and the resin was allowed to swell for 10 min. Phenol **1** (16.8 g, 90 mmol, 3 equiv) dissolved in a little THF was added to the resin. Nitrogen was then bubbled through the slurry, with stirring, for 10 min. Diethyl azodicarboxylate (14.2 mL, 90 mmol, 3 equiv) was added, coloring the solution yellow. Finally, triphenylphosphine (23.6 g, 90 mmol, 3 equiv) was dissolved in 200 mL of THF/DCM (50:50) and added to the slurry over 5 min with stirring, the yellow color fading from solution. After stirring for 3 h, a precipitate had formed, so 100 mL THF was added, and the slurry was stirred overnight. The mixture was then further diluted with 150 mL of a mixture of water/MeOH/THF (20:10:70). The resin was collected by filtration and washed successively with water/THF (10:90, 3), THF (3×), DCM (3×), and ether (2×). The solid was dried at 50 °C in vacuo to give 31.3 g of tan resin **2** (loading 0.76 mmol g^{-1}, 79% yield). IR 2980, 1603, 1509, 1492, 1452, 1222, 1174, 1028, 1015, 821, 756, 696.

Synthesis of Monomer 4. *exo*-*N*-Hydroxy-7-oxabicyclo-[2.2.1]hept-5-ene-2,3-dicarboxamide (40.4 g, 223 mmol) was dissolved in 46 mL of triethylamine (335 mmol, 1.5 equiv) and 500 mL of DCM, and the solution was cooled to 5 °C. A solution of acetyl chloride (20.6 mL, 290 mmol, 1.3 equiv) dissolved in 200 mL of DCM was added dropwise with stirring. The mixture was stirred for 3 h, the solution darkening and a precipitate forming. The precipitate was collected by filtration and washed with DCM until white. The combined filtrates were washed sequentially with water, twice with saturated Na_2CO_3, and brine. The organics were dried over anhydrous Na_2SO_4 and evaporated to give 47.0 g of monomer **4** (95%) as a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H,), 2.90 (s, 2H), 5.35 (s, 2H), 6.54 (2, 2H).

Synthesis of ROMPgel Resin 5. Linker resin **2** (22.5 g, 17 mmol) was loaded into a 500-mL three-necked flask fitted with a mechanical stirrer, a nitrogen inlet, and a bubbler. DCM (180 mL) was added, and the slurry was stirred for 5 min under nitrogen. Grubbs' catalyst **3** (2.0 g, 2.4 mmol, 14 mol %) was partially dissolved in 20 mL DCM and added to the resin slurry. Remaining undissolved catalyst **3** was washed through with an additional 10 mL of DCM. The purple slurry was stirred for 100 min, then poured into a filtration plate (no. 2) fitted with a mechanical stirred and blanketed from above with nitrogen. The resin was filtered and washed 5 times with 200 mL DCM, each wash carried out in the filter plate with stirring for 5 min. The red-purple resin was then reloaded into the original 500-mL flask and suspended in 50 mL of DCM. Monomer **4** (44.5 g, 200 mmol) was dissolved in 200 mL of DCM and was added to the resin slurry. The mixture was stirred for 2 days. The resin was then filtered as before and was washed four times with 200 mL of DCM until the washings were almost colorless. The resin was then stirred with 100 mL of ethyl vinyl ether dissolved in 200 mL of chloroform for 30 min. The resin was filtered, and the ethyl vinyl ether procedure was repeated. Finally, the resin was drained and washed successively with DMF (2×), DCM (2×), ether, DCM (3×), and ether (2×). The resin was dried first in a stream of air and then at 50 °C in vacuo. Total yield 64.2 g (94% monomer incorporation, loading 2.92 mmol g^{-1}) of a tan, mostly free-flowing resin containing some larger granules. The granules could be separated by sieving the resin through a nylon stocking. Microanalysis 4.137% N corresponds to a loading of 2.95 mmol g^{-1}. Infrared (Golden gate) 1820, 1789, 1734, 1602, 1510, 1493, 1371, 1206, 1160, 1072, 1009, 968, 698 cm^{-1}. The washings containing Grubbs's catalyst were evaporated to leave a dark purple solid. The residue was suspended in 20 mL of acetone, precipitating a lilac solid. This was collected by filtration and was washed 3 times with acetone until the washings were a very pale purple. The solid was dried in vacuo to give 1.32 g (66% recovery) of the Grubbs' catalyst **3**.

Titration by Weight of Amide 6. ROMPgel resin **5** (130 mg) was suspended in 1 mL of chloroform in a vial and 130 mg (1.46 mmol, excess) of 2-methoxypropylamine was added. The vial was capped and agitated overnight. The resin was filtered and washed with DCM (2 × 10 min). The combined filtrates were evaporated to give 48.9 mg (0.373 mmol) of *N*-(2-methoxypropyl)acetamide **6**. Hence, loading of resin by this method was 2.87 mmol g^{-1}. ^{1}H NMR ($CDCl_3$) 1.20 (d, J = 7 Hz, C*H*$_3$CH), 1.98 (s, 3H, CH_3CO), 3.38 (m, 5H, C*H*$_2$NH and CH_3O), 4.18 (m, 1H, C*H*OCH_3), 5.9 (br s, 1H, NH).

General Procedure for Titration of ROMPgel 5. A stock solution was prepared from benzyl methyl ether (2.220 g, 18.00 mmol), benzylamine (6.5 mL, 60 mmol), and MeOH (nondeuterated, 10 mL), made up to 100 mL with $CDCl_3$ in a volumetric flask. For loose resin, a known weight of resin (typically 100 mg) was suspended in 1.00 mL of the titration solution in an NMR tube. The tube was capped and agitated by gentle rotation for the appropriate time (typically 2−4 h). The NMR spectrum was acquired directly. For resin in

IRORI Kans, a Kan (initially loaded with 0.175 mmol of OH functionality) was loaded into a screw-cap vial and suspended in 0.7 mL of $CDCl_3$ and 1.00 mL of the titration mixture (0.180 mmol benzyl methyl ether, excess benzylamine). The vial was capped and agitated for the appropriate time (typically 2−4 h). The NMR spectrum was acquired directly from the solution. Loadings of acyl group were determined by comparison of the integration of the methylene singlet peak of benzyl methyl ether (typically 4.35 ppm) with that of the methylene doublet peak of the benzylamide (typically 4.3−4.5 ppm).

In the case of coincidence of these peaks, the entire titration mixture was spiked with a known amount (typically 20 mg) of benzyl phenyl ether. Comparison of the integration of the methylene singlet of benzyl phenyl ether (5.06 ppm) with the combined peak of (benzylamide + benzyl methyl ether) allowed calculation of the loading.

General Procedure for Synthesis or Regeneration of ROMPgel 8. ROMPgel **5** (either loose resin or in IRORI miniKan format) was suspended in a solution of benzylamine/MeOH/DCM (10:10:80, ∼1 M in benzylamine, ∼1 mL/100 mg of loose resin or 1 mL/IRORI Kan). The mixture was agitated for 2 h before the solution was drained. The resin was resuspended in the same amount of benzylamine solution and left agitating overnight. The solution was again drained, and the resin was washed five times with 15% AcOH/DCM, then five times (30 min agitation per wash). Finally the resin was suspended in ether and agitated briefly, and the solution drained, then resuspended in ether, agitated, and drained again. The resin was then dried at 40 °C in vacuo (typically 50 mmHg) for 2 h. In the first synthesis of ROMPgel **8**, the loading was derived by calculation: difference of molecular weights between *N*-acetoxy monomer **4** and its *N*-hydroxy precursor = (223−181) = 42. Therefore, 1 g of *N*-acetoxy-ROMPgel **5** (2.92 mmol g^{-1}) loses (2.92 × 42) = 122 mg of weight. *N*-hydroxy-ROMPgel **8** therefore contains 2.92 mmol OH in (1−0.122) = 0.878 g. Loading = 3.32 mmol g^{-1}.

Acylation of ROMPgel Resin 8 with Furoic Acid, DIC and DMAP (0.7−3.0 equiv). ROMPgel resin **5** (60−65 mg, 0.175−0.190 mmol) was loaded into 4-mL SPE cartridges. The resins were each suspended in 3 mL of benzylamine solution [1.0 M in MeOH/THF/$CHCl_3$ (10:45:45)] and agitated for 45 min. The solutions were drained, and the benzylamine treatment was repeated. The resins were then washed for 1 h with 3 mL of AcOH/MeOH/$CHCl_3$ (10:10:80). The solution was drained, the resins were rinsed through with DCM, and the acetic acid wash was repeated. Finally, the resins were washed with DCM (5×) and ether (3×) before being dried in vacuo. Each resin was suspended in the solutions of 2-furoic acid (1.0 M in DMF, see table). Solutions of DMAP (0.2 M in DMF) and DIC (1.0 M in DMF) were added to the resins, and the required quantity of DMF was added. The SPE cartridges were capped, loaded horizontally onto an orbital shaker, and agitated for 16 h. The resins were drained and washed with DMF (5 × 10 min), DCM (3 × 10 min), and ether (2 × 2 min). The resins were dried in vacuo at 60 °C and titrated as outlined above.

	resin **5**		acid sol'n,	DMAP sol'n,	DIC sol'n,	DMF added,	acid	
run	mg	mmol	mL	mL	mL	mL	equiv	concn
1	63	0.185	0.12	0.12	0.12	1.2	0.7	0.075
2	65	0.190	0.17	0.23	0.17	0.9	0.9	0.115
3	63	0.185	0.23	0.35	0.23	0.6	1.3	0.165
4	65	0.190	0.35	0.35	0.35	0.5	1.9	0.225
5	64	0.187	0.52	0.52	0.52	0	2.8	0.335

Acylation of ROMPgel Resin 8 with Furoic Acid, DIC, and DMAP (5−10 equiv). Freshly regenerated ROMPgel resin **8** (65 mg, 0.215 mmol) was loaded into 4-mL SPE cartridges. The resins were each suspended in DMF (see table). Furoic acid was added, followed by the DMAP, and the mixtures were shaken briefly to dissolve the solids. Finally, DIC was added neat. The SPE cartridges were capped, loaded horizontally onto an orbital shaker, and agitated for 18 h. The resins were drained and washed with DMF (5 × 10 min), DCM (3 × 10 min), and ether (2 × 2 min). The resins were dried in vacuo at 60 °C and titrated as outlined above.

	resin **8**		acid,	DMAP,	DIC,	DMF added,	acid	
run	mg	mmol	mg	mg	mL	mL	equiv	concn
1	65	0.215	124	26	0.17	1.9	5.0	5.0
2	63	0.210	237	40	0.33	1.6	10.0	10.0

Acylation of ROMPgel Resin 8 with Furoic Acid and DIC Using Perfluorohexane. Freshly regenerated ROMPgel resin **8** (∼60 mg, 0.20 mmol) was loaded into 4-mL SPE cartridges. The resins were each suspended in a solution of furoic acid (3 equiv) dissolved in DMF (see table). DIC (0.1 mL, 0.63 mmol) was added neat. Finally, the appropriate amount of perfluorohexane was added. The SPE cartridges were capped, loaded vertically onto an orbital shaker, and agitated for 18 h. The resins were drained and washed with DMF (5 × 10 min), DCM (3 × 10 min), and ether (2 × 2 min). The resins were dried in vacuo at 60 °C and titrated as outlined above.

	resin **8**		furoic acid,	DMF added,	R_F hexane	acid concn,
run	mg	mmol	mg	mL	added, mL	mmol/mL
1	58.3	0.194	64.7	1.5		0.36
2	58.8	0.196	65.8	0.9	0.6	0.59
3	56.5	0.188	63.0	0.3	1.2	1.4

Titration Results

	amide released by titration,	resin **5** used for titration,	acyl group released from resin,	OH resin in titration sample		resin
run	mmol	mg	mg	mg	mmol	reloading
1	0.046	55.4	4.3	51.1	0.170	27%
2	0.074	57.3	7.0	50.3	0.167	44%
3	0.106	58.3	10.0	48.3	0.160	66%

Comparative Resin Loading Test. A 100-mg portion of each of the following resins, ROMPgel **8** (3.32 mmol g^{-1}, 0.33 mmol), PS−HOBt (0.62 mmol g^{-1}, 0.062 mmol), PS-TFP (1.34 mmol g^{-1}, 0.13 mmol), Marshall (1.58 mmol g^{-1}, 0.16 mmol), and Kaiser (0.5 mmol g^{-1}, 0.05 mmol), was loaded into 7-mL screw-cap vials. A solution was prepared

Table 5.

	ROMPgel 8	PS−HOBt	PS-TFP	Marshall	Kaiser
loading[a] (mmol g^{-1})	3.32	0.62	1.34	1.58	0.5
acid/DMAP soln added (mL)	5.53	1.03	2.23	2.63	0.83
DIC added (mL)	0.260	0.048	0.105	0.123	0.039
total amide released (mmol)	0.215	0.001	0.157	0.158	0.083
wt of resin used in titration (mg)	98.7	103.3	106.5	106.5	95.8
wt of furoate in resin sample (mg)	20.2	0.1	14.8	14.8	7.8
wt of OH resin in sample (mg)	78.5	103.2	92.7	91.7	88.0
% reloading	83	2	128	109	189
resin loading at least			1.71	1.72	0.94

[a] Based on manufacturer's specifications.

Table 6. ROMPgel **8** Results

	Mg in Kan							
	25	50	75	100	125	150	175	193
total resin OH content (mmol)	0.083	0.166	0.249	0.332	0.415	0.498	0.581	0.641
amide released at 2.5 h (mmol)	0.050	0.113	0.173	0.240	0.311	0.255	0.357	0.302
% acylation of OH resin	60	68	69	72	75	51	61	47
amide released at 18 h (mmol)	0.047	0.117	0.182	0.250	0.317	0.326	0.388	0.364
% acylation of OH resin	57	70	73	75	76	65	67	57

in DMF (20 mL) of furoic acid (0.67 g, 6 mmol, 0.3 M) and DMAP (0.24 g, 2 mmol, 0.1 M). The appropriate amount of solution (5 equiv acid, see below) was added to each resin, and the resins were allowed to swell for 5 min. DIC (5 equiv, see below) was added neat to each resin. The vials were capped and agitated horizontally for 18 h. The resins were transferred to SPE cartridges and washed successively with DMF (5 × 10 min), DCM (2 × 10 min), and ether (2 × 2 min). The resins were dried in a stream of air for 10 min. Known weights of each resin were loaded into NMR tubes and titrated using the general procedure. Spectra were acquired at intervals. After the final spectrum was acquired, the solutions were analyzed by HPLC for the purity of the benzyl furylcarboxamide (see Table 5)

Acylation of ROMPgel Resin 8 and PS-TFP with Furoic Acid, DIC and DMAP (25−125 mg per Kan). Radio-tagged IRORI miniKans were loaded with 25, 50, 75, 100, and 125 mg of ROMPgel resin **8** (3.32 mmol g^{-1}, total weight 375 mg, 1.25 mmol). IRORI miniKans were also loaded with 25, 50, 75, 100, and 125 mg of tetrafluorophenol resin PS-TFP (1.71 mmol g^{-1}, loading modified in light of previous experiment, total weight 375 mg, 0.64 mmol). Furoic acid (0.63 g, 5.64 mmol) and DMAP (0.23 g, 1.88 mmol) were dissolved in DMF (5 mL) in a 50-mL screw-cap bottle. All Kans were added, followed by perfluorodecalin (30 mL). Finally, DIC (0.88 mL, 5.64 mmol) was added neat, and the bottle was capped and agitated for 18 h. The resins were drained and washed with DMF (5 × 15 min), DCM (2 × 15 min), and ether (2 × 2 min). The resins were dried in a stream of nitrogen for 15 min. The Kans were titrated according to the general procedure. After the spectrum at 2.5 h, the solutions used for the NMR experiments were returned to the vials where the titration was being performed, thereby maintaining the reagent concentrations (See Table 6).

Acylation of ROMPgel Resin 8 and PS-TFP with Furoic Acid, DIC and DMAP (150−200 mg per Kan). Radio-tagged IRORI miniKans were loaded with 150, 175, and 193 mg of ROMPgel resin **8** (3.32 mmol g^{-1}, total weight 518 mg, 1.72 mmol). IRORI miniKans were also loaded with 150, 175, and 200 mg of tetrafluorophenol resin PS-TFP (1.71 mmol g^{-1}, total weight 525 mg, 0.90 mmol). Furoic acid (0.89 g, 7.9 mmol) and DMAP (0.32 g, 2.6 mmol) were dissolved in DMF (7 mL) in a 50-mL screw-cap bottle. All Kans were added, followed by perfluorodecalin (30 mL). Finally, DIC (1.24 mL, 7.9 mmol) was added neat, and the bottle was capped and agitated for 18 h. The resins were drained and washed with DMF (5 × 15 min), DCM (2 × 15 min), and ether (2 × 2 min). The resins were dried in a stream of nitrogen for 15 min. The Kans were titrated according to the general procedure. After the spectrum at 2.5 h, the solutions used for the NMR experiments were returned to the vials where the titration was being performed, thereby maintaining the reagent concentrations.

PS-TFP Results

	mg in Kan							
	25	50	75	100	125	150	175	200
total resin OH content (mmol)	0.043	0.086	0.128	0.171	0.214	0.257	0.299	0.342
amide released at 2.5 h (mmol)	0.038	0.080	0.123	0.167	0.210	0.200	0.199	0.197
acylation of OH resin, %	89	94	96	98	98	78	66	58
amide released at 18 h (mmol)			0.125			0.238	0.233	0.235
acylation of OH resin, %			97			93	78	69

Preparation of ROMPgel Resin 8 in IRORI MiniKans. ROMPgel resin **5** (∼50 g) was sieved to remove larger granules and leave a free-flowing resin. Four hundred IRORI miniKans were first loaded with a radio frequency tag. The loose resin was loaded into the miniKans using a Bohdan resin-dispensing plate (75 mg calibration). Weighing the resin

content of several Kans at random showed a bell-curve weight distribution in which 85% of the Kans were loaded with between 70 and 120 mg (0.20−0.35 mmol per Kan). Additionally, 40 miniKans were loaded by hand with resin **5**, adding 60 ± 1 mg (0.175 mmol) to each Kan. These Kans were always used for titrations in batch acylations. The Kans were sealed, and their radio-tags were encoded. All 440 Kans were then treated with benzylamine as described above to give the IRORI-formatted resin **8**.

General Method of Acylation of ROMPgel 8 with Carboxylic Acids and DIC. The carboxylic acid (16.5 mmol), DMAP (0.61 g, 6.5 mmol), and DMF (7 mL) were loaded into a 100-mL screw-cap Schott bottle and stirred manually to either dissolve the solids or form a homogeneous paste. Twenty IRORI miniKans containing ROMPgel resin **8** (0.20−0.35 mmol range) and 2 hand-weighed Kans (0.175 mmol each) were added to the bottle. The bottle was filled to three-quarters full with either perfluorohexane or perfluorodecalin. Finally, DIC (2.6 mL, 16.5 mmol) was added, and the bottle was capped and agitated by rotation for 2 d. The solution was drained, and the Kans were washed successively with DMF (5 × 30 min), DCM (5 × 30 min), and ether (2 × 5 min) before drying in vacuo at 40 °C. One of the Kans loaded with 0.175 mmol of resin was identified by its radio-tag, removed, and titrated as described above. The second titration Kan served as a spare in case either a repeat titration or repeat acylation was necessary.

General Method of Acylation of ROMPgel 8 with Carboxylic Acids and HBTU. The carboxylic acid (16.5 mmol) and triethylamine (4.6 mL, 33 mmol) were mixed together in a 100-mL screw-cap Schott bottle and stirred manually to form a homogeneous paste. THF (12 mL) was added to either dissolve or loosen the paste. Twenty IRORI miniKans containing ROMPgel resin **8** (0.20−0.35 mmol range) and 2 hand-weighed Kans (0.175 mmol each) were added to the bottle. The bottle was filled to three-quarters full with either perfluorohexane or perfluorodecalin. Finally, HBTU (6.25 g, 16.5 mmol) was added, and the bottle was capped and agitated by rotation for 2 d. The solution was drained, and the Kans were washed successively with THF (3 × 30 min), DMF (3 × 30 min), DCM (3 × 30 min), and ether (2 × 5 min) before drying in vacuo at 40 °C. One of the Kans loaded with 0.175 mmol resin was identified by its radio-tag, removed, and titrated as described above. The second titration Kan served as a spare in case either a repeat titration or repeat acylation was necessary.

General Method of Acylation of ROMPgel 8 with Acid Chlorides. A 5-mL screw-cap vial was loaded with an IRORI miniKan containing ROMPgel resin **8** (0.175 mmol). The vial was filled to three-quarters full with perfluorohexane. Pyridine (90 μL, 1.1 mmol) was added, followed by the acid chloride (0.52 mmol) dissolved in $CHCl_3$ (0.4 mL). The vial was capped and agitated for 24 h. The solution was drained, and the Kan was washed successively with DMF (5 × 10 min), DCM (3 × 10 min), and ether (2 × 5 min) before drying in vacuo at 40 °C. The Kans were titrated as described above.

General Method of Acylation of ROMPgel 8 with Isocyanates. The isocyanate acid (16.5 mmol) was dissolved in toluene (12 mL) in a 100-mL screw-cap Schott bottle. Twenty IRORI miniKans containing ROMPgel resin **8** (0.20−0.35 mmol range) and 2 hand-weighed Kans (0.175 mmol each) were added to the bottle. The bottle was filled to three-quarters full with either perfluorohexane or perfluorodecalin. The bottle was capped and agitated by rotation for 2 d. The solution was drained, and the Kans were washed successively with THF (3 × 30 min), DMF (3 × 30 min), DCM (3 × 30 min), and ether (2 × 5 min) before drying in vacuo at 40 °C. One of the Kans loaded with 0.175 mmol resin was identified by its radio frequency tag, removed, and titrated as described above. The second titration Kan served as a spare in case either a repeat titration or repeat acylation was necessary.

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