

ROMP-Spheres: A Novel High-Loading Polymer Support Using Cross Metathesis between Vinyl Polystyrene and Norbornene Derivatives

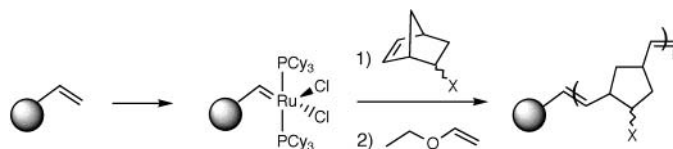
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ABSTRACT



The preparation of a polymer-supported ruthenium alkylidene metathesis catalyst is described. This immobilized catalyst has been used to initiate a ring-opening metathesis polymerization of norbornene derivatives onto a polymer support to prepare novel high-loading resins for use in combinatorial chemistry.

Combinatorial chemistry has received much attention of late as a powerful tool for the discovery of new biologically active molecules for use as pharmaceuticals and agrochemicals.¹ Associated with this is the explosion of work carried out to develop solid-phase methodologies and syntheses for the production of libraries of compounds to test in high throughput screens.² However, there remains the problem that compound loadings on resin can be low, and so quite large amounts of resin are required to obtain only a few milligrams of compound after cleavage. In addition, for single

bead screening,³ a higher loading bead would seem advantageous. High loading resins also have clear benefits in solution-phase chemistry for polymer-supported reagents.⁴

Olefin metathesis has received considerable interest of late,⁵ with the recent development of the well-defined catalysts of Schrock⁶ and Grubbs,⁷ and in particular the application to solid-phase chemistry is receiving attention.^{8–10}

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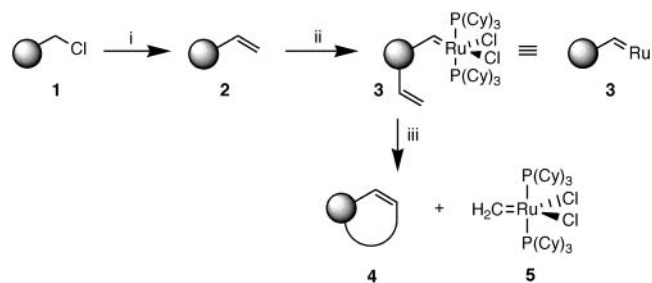
Our interest in this area is in the use of ring-opening metathesis polymerization (ROMP) for the generation of high-loading polymer supports. With ROMP, the polymer consists solely of repeating monomer units, and as such provides a method for obtaining polymers in which the loading approaches quantitative. We have described the use of such polymers for the preparation of combinatorial libraries by oxidative disassembly of the polymer backbone¹¹ and as polymer supported reagents for use in solution phase chemistry.¹²

We now describe a method for combining the high loading capacity of ROM-polymers with the versatility of conventional solid-phase synthesis on resins. In our strategy, we use a cross metathesis between an immobilized alkene and a strained ring system (such as a norbornene derivative) as a means of loading functionality onto the resin. Cross metatheses between an immobilized norbornene derivative and alkenes¹³ or norbornene derivatives¹⁴ have been described. In neither case was any polymerization observed between the immobilized norbornene units.

We use the metathesis between Grubbs catalyst¹⁵ and a terminal alkene,¹⁶ in our case vinyl polystyrene, to immobilize the ruthenium catalyst on the resin. Such immobilization of Grubbs catalyst was suggested by van Maarseveen¹⁰ during their cyclization–cleavage strategy, which in that case resulted in the need to use an alternative alkene and 100 mol % catalyst to maintain the catalytic cycle.

Vinyl polystyrene¹⁷ **2** (~0.8 mmol g⁻¹) was treated with Grubbs catalyst **6** (8 mol %, CH₂Cl₂, 1–2 h) to give a brown resin and an almost colorless solution. Filtration of the resin under an inert atmosphere, washing, and drying yielded the supported ruthenium alkylidene **3** (Scheme 1). *Once dried,*

Scheme 1. Immobilization of Grubbs Catalyst on Resin^a



^a Reagents: (i) Me₃S⁺I⁻, *n*BuLi, THF; (ii) PhCH= Ru(PCy₃)₂Cl₂ **6** (8 mol %), CH₂Cl₂, 1–2 h; (iii) CH₂Cl₂, 5 h.

resin **3** was stable under normal atmospheric conditions for several months with no loss of catalytic activity. In the presence of solvent however (such as dichloromethane) the

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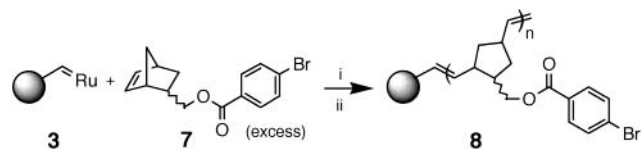
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catalyst was found to degrade over a period of about 5 h, and if then isolated by filtration, the resin was found to be inactive. This is possibly due to the ring-closing metathesis between the ruthenium alkylidene and free vinyl groups present on the resin (“biting back”), releasing the unstable ruthenium methylidene **5** into solution.¹⁸

The supported catalyst **3** was treated with varying amounts of 5-norbornen-2-ylmethyl 4-bromobenzoate **7** in dichloromethane and shaken for between 2 and 24 h, before terminating the polymerization with ethyl vinyl ether¹⁹ (Scheme 2). The resins so produced were filtered and washed

Scheme 2. Cross Metathesis^a



^a Reagents: (i) CH₂Cl₂; (ii) EtOCH=CH₂.

thoroughly to remove any remaining monomer **7** and small amounts of ROM-polymer produced in solution. Incorporation of the monomer was confirmed by infrared analysis (carbonyl stretch at 1716–1724 cm⁻¹).

We believe that the ROM-polymer in solution arises from the “biting back” of the growing polymer chain onto the residual vinyl groups on the resin. Any liberated ruthenium methylidene **5** in solution could then undergo ROMP with the remaining monomer **7**, and/or decompose. The resin beads **8**, obtained as in Scheme 2, were visibly larger than vinyl polystyrene beads **2** and granular in consistency (Figure 1). We call these beads ROMP-Spheres.

Loadings of the ROMP-Spheres produced were calculated from the increase in weight of the resin. We investigated the effect of differing ratios of monomer **7** relative to catalyst

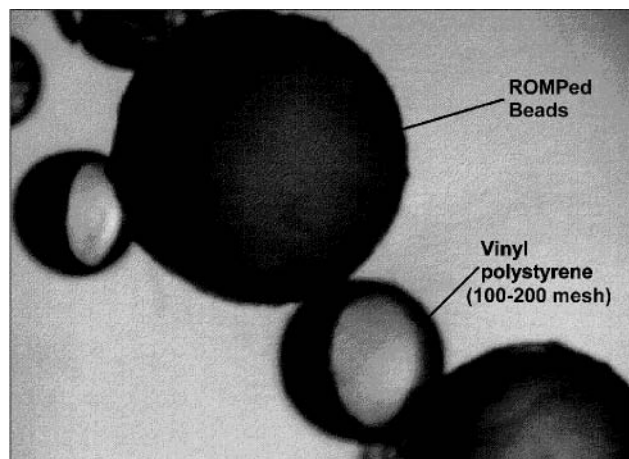


Figure 1.

Table 1. Polymer Loading of ROMP-Spheres **8**

run	ratio 7:3 ^a	equivs ^b	% incorp ^c	loading ^d
1	4:1	200	83	2.52
2	8:1	412	82	2.82
3	12:1	612	66	2.89
4	20:1	1050	69	3.04
5	100:1	5150	12	3.03

^a Weight ratio of monomer **7**:resin bound catalyst **3**. ^b Molar equivalents of monomer **7** to the calculated ruthenium loading of catalyst **3**. ^c Percentage of applied monomer **7** incorporated onto resin (calculated by weight increase). ^d ROMP-Sphere **8** loading (mmol g⁻¹).

3 on the ultimate loading of ROMP-Spheres **8** (Table 1). The maximum loading possible in this case (i.e. the loading obtained when preparing a ROM-polymer) is 3.26 mmol g⁻¹, however even using a large excess of the **7**, we appear to reach a maximum at about 3.03 mmol g⁻¹ (~93% of the theoretical loading).²⁰

To investigate the use of the resin for solid-phase chemistry, we looked at the swelling capacity of the beads. Using 0.5 g of the dry ROMP-Spheres **8** at ~2.8 mmol g⁻¹ (run 2) in each case, and a selection of 9 different solvents, we were able to show that the beads did in fact swell in some solvents and not in others (Figure 2), although the extent of swelling is perhaps not as extreme as would be seen by more conventional resins.²¹

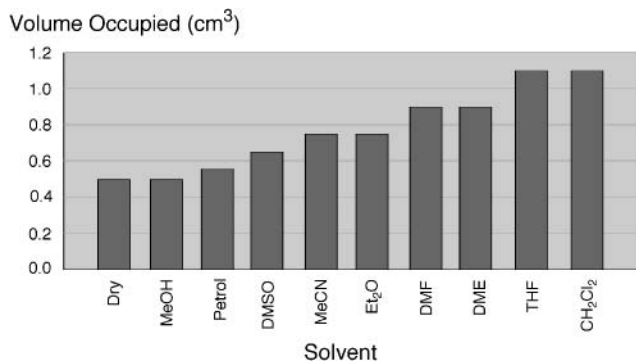


Figure 2. Swelling properties of ROMP-Spheres **8**. The approximate volume occupied by 0.5 g of resin after swelling with the appropriate solvent and allowing to equilibrate for 1 week is indicated.

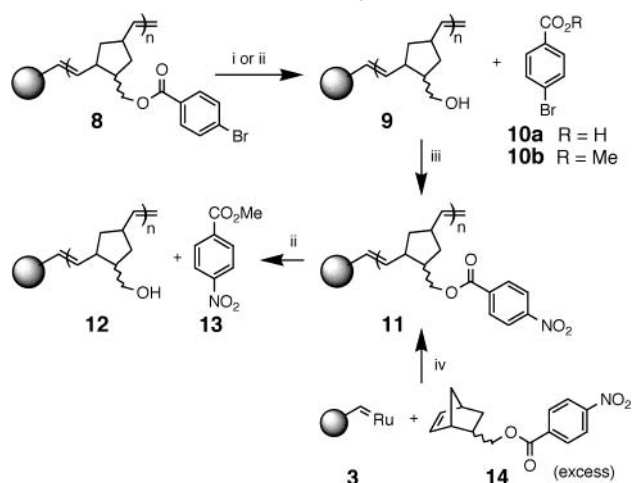
Cleavage of the ester in resin **8** via hydrolysis (LiOH, THF, MeOH, H₂O, 48 h) gave the expected 4-bromobenzoic acid **10a** (98%, confirming the calculated loading figure of 2.8 mmol g⁻¹). Alternatively transesterification (0.1–0.2 equiv of NaOMe, MeOH–THF, 48 h) gave methyl 4-bromoben-

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zoate **10b** (95%). Complete hydrolysis or transesterification was confirmed by infrared spectroscopy of the recovered beads. The hydroxy resin **9** could then be re-esterified (4-nitrobenzoyl chloride, DMAP, CH₂Cl₂, 48 h). The ROMP-Spheres **11** showed an identical infrared spectrum to those produced by the reaction of the catalyst **3** with the appropriate amount of monomer **14**. This was again cleaved from the resin (NaOMe, THF, MeOH) to give a quantitative recovery of methyl 4-nitrobenzoate **13** (Scheme 3).

Scheme 3. Cleavage of Resins^a

^a Reagents: (i) LiOH, THF–MeOH–H₂O (5:1:1); (ii) NaOMe (0.2 equiv), THF–MeOH (4:1); (iii) 4-NO₂C₆H₄COCl, DMAP, CH₂Cl₂; (iv) CH₂Cl₂, and then EtOCH=CH₂.

To further demonstrate the amenability of the ROMP-Spheres to chemical transformations we carried out a palladium-catalyzed coupling reaction between the resin-bound bromobenzoate **8** and an aryl zincate (ArMgBr, ZnCl₂, PdCl₂(dppf) (10 mol %), THF, DME). The resultant biphenyl derivative **15** was cleaved (NaOMe, THF–MeOH). However, in this case, a stoichiometric amount of sodium methoxide at reflux was needed, as otherwise incomplete transesterification was observed (Scheme 4).

ROMP is a living polymerization and as such is ideal for the formation of block copolymers. Thus, supported catalyst **3** was sequentially treated with two different monomers (ester **7**, CH₂Cl₂, filtration of the intermediate **17** and then ester **14**, CH₂Cl₂, and termination) to give the desired block

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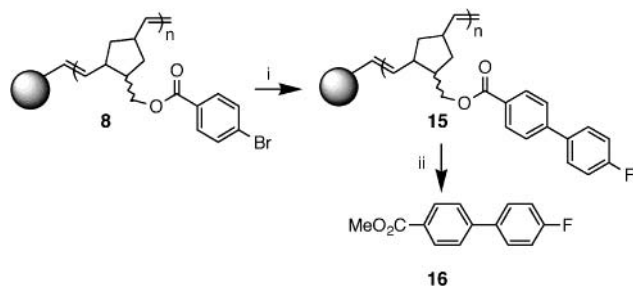
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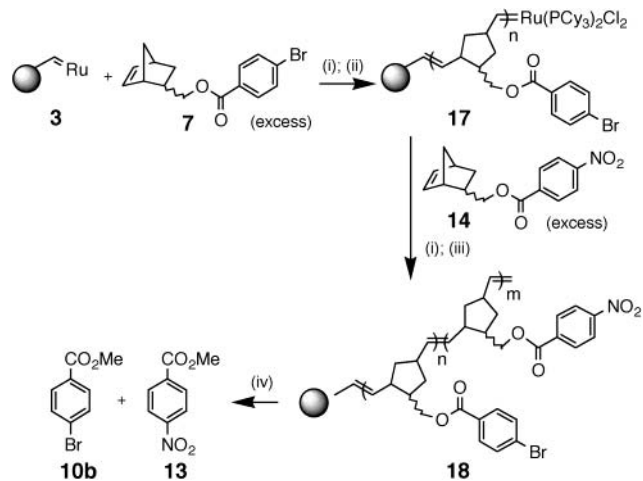
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Scheme 4. Zincate Coupling^a

^a Reagents: (i) 4-F-C₆H₄MgBr, ZnCl₂, PdCl₂(dppf) (10 mol %), THF–DME (8:1); (ii) NaOMe (1 equiv), THF–MeOH (4:1).

copolymer **18** (Scheme 5). This was cleaved as before (0.2 equiv of NaOMe, THF–MeOH). Provided that the first polymerization was stopped after only 2 h, the polymer remained “living” and equivalent amounts of the two esters **10b** and **13** were formed. However if the first polymerization reaction mixture was allowed to proceed for too long, the active carbene sites degraded and little of the second norbornene derivative was incorporated. We believe that this may again be due to the “biting back” described previously.

In conclusion, we have demonstrated the preparation of a polymer-supported Grubbs catalyst and its use to prepare high-loading polymer supports. We have carried out some preliminary investigations into the use of the resins produced in this way for combinatorial applications and to produce block copolymers. Further uses of the supported catalyst for example as a catalyst for ring-closing metathesis will be reported in due course.²² Other applications of the high loading resin beads in combinatorial chemistry including polymer supported reagents will also be reported in due course.

Scheme 5. Block Copolymer Formation^a

^a Reagents: (i) CH₂Cl₂; (ii) filter; (iii) EtOCH=CH₂; (iv) NaOMe (0.2 equiv), THF–MeOH (4:1).

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Supporting Information Available: Experimental procedures for compounds **3**, **8**, **9**, **11**, **15**, **16**, and **18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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