

Free Radical Reactions on Soluble Supports from Ring-Opening Metathesis

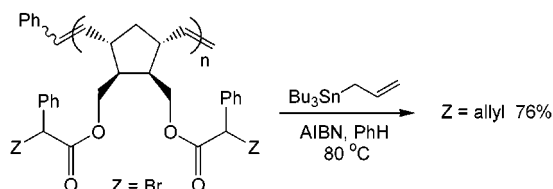
Eric J. Enholm* and Maria E. Gallagher

Department of Chemistry, University of Florida, Gainesville, Florida 32611

enholm@chem.ufl.edu

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ABSTRACT



Free radical reactions were performed on soluble ring-opening metathesis (ROM) polymers. These polymers have high substrate loading, short reaction times, and the benefit of a facile purification. All reactions on these supports were obtained in good yields as white crystalline-like materials readily separated from tin byproducts.

Recent interest in soluble organic supports has demonstrated that these polymers can be applied to a variety of standard synthetic transformations and offer significant advantages over popular classic hard resin supports.¹ Unlike standard solid-phase organic synthesis, huge excesses and/or concentrated reagents are not necessary because soluble support offers the faster reaction kinetics of a single solution phase. These supports, soluble in chloroform, THF, ether, hexanes, and CH_2Cl_2 , can also be conveniently monitored by standard ^1H NMR spectroscopy without cleavage from the polymer backbone.

Since most soluble supports are not readily available commercially, we have prepared them by custom synthesis for each particular application as “designer supports”. We now report a soluble designer support compatible with free radical transformations made from ring-opening metathesis polymerizations. Prior to our work, soluble organic supports were not applied to radical reactions.²

Each monomer unit contains one or two reaction sites integrated into the backbone so that the designer polymer essentially has 100–200% loading capacity. Standard solid-

phase resins cannot achieve this level of loading mainly because the substrate is incompletely covalently attached to the polymer. With this methodology, the substrate is completely incorporated into each monomer and then subsequently polymerized.

We decided to use norbornyl monomers in these studies for three reasons.³ First, they polymerize readily by ring-opening metathesis with Grubbs well-defined ruthenium catalysts.⁴ The small amount of strain inherent with norbornenes assists and accelerates the metathesis.⁵ Second, a wide variety of norbornenes are commercially available or

(2) For recent examples of radical reactions on solid-phase resins, see: (a) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535. (b) Caddick, S.; Hamza, D.; Wadman, S. N. *Tetrahedron Lett.* **1999**, *40*, 7285. (c) Zhu, X.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 157. (d) Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997**, 8929–8932.

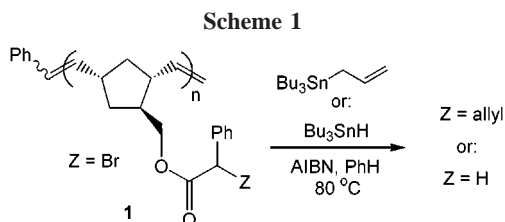
(3) For examples of ROMP supports in synthesis, see: (a) Ball, C. P.; Barrett, A. G. M.; Poutout, L. F.; Smith, M. L.; Thorn, Z. E. *Chem. Commun.* **1998**, 2453–2454. (b) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **1999**, *1*, 579–582. (c) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 261–264. (d) Arnauld, T.; Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 2663–2666.

(4) (a) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459–3469. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *1*, 953–956. Chang, S.; Jones, L.; Wang, C. M.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 3460–3465.

(5) Makovetsky, K. L.; Finkelshtein, E. S.; Ostrovskaya, I. Y.; Portnykh, E. B.; Gorbacheva, L. I.; Goldberg, A. L.; Ushakov, N. V.; Yampolsky, Y. P. *J. Mol. Catal.* **1992**, *76*, 107–121.

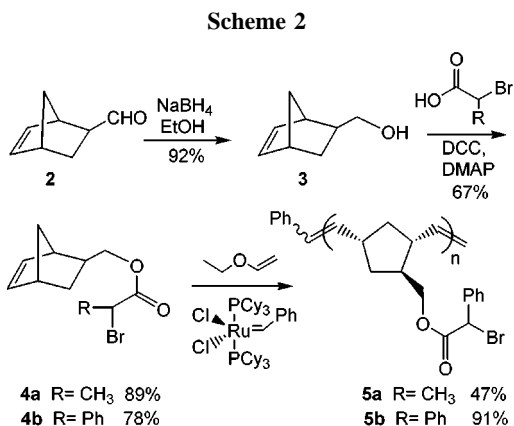
(1) (a) Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917–1924. (b) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329–6332. (c) Gravert, D. J.; Janda, K. D. *Curr. Opin. Chem. Biol.* **1997**, *1*, 107–113. (d) Enholm, E. J.; Gallagher, M. E.; Lombardi, J. S.; Moran, K. M.; Schulte, J. P. *Org. Lett.* **1999**, *1*, 689–691. (e) Enholm, E. J.; Schulte, J. P. *Org. Lett.* **1999**, *1*, 1277–1279.

readily prepared by Diels–Alder reactions. Third, they are easily substituted with halides and other radical precursors. The supports we use contain alkenes, but these are “protected” from radical reactions by the bulk of the polymer backbone as these yields readily demonstrate. The overall radical reaction process is illustrated in Scheme 1. In this



reaction, our designer ROMP support **1** tethers a bromoester on a cyclopentane ring that forms part of the backbone of the polymer. Replacement of the halogen by one of two free radical processes allows for the introduction of an allyl unit in a carbon–carbon bond-forming process or a hydrogen atom in a reductive reaction. In this reaction, a tributyltin moiety bears the transferred group that replaces the bromide in a free radical chain process.⁶ By saponification, recovery of the polymer backbone and isolation of a new carboxylic acid should also be possible, demonstrating both the feasibility of cleavage of the substrate and the possible reusability of the support.

Construction of the soluble support is shown in Scheme 2. Norbornene-1-carboxaldehyde (**2**) was reduced to 2-nor-

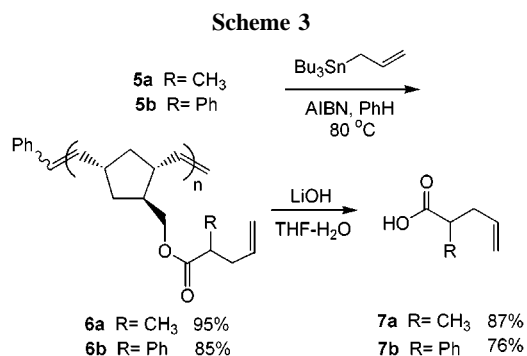


bornenemethanol (**3**). Esterification of 2-bromopropionic acid or 2-bromo-2-phenylacetic acid with DCC gave compounds **4a** and **4b**, respectively, which were then polymerized with Grubbs catalyst to prepare **5a** and **5b**. The polymerization of each norbornene was halted in 25 s by capping the

(6) For reviews of radical reactions, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: New York, 1992.

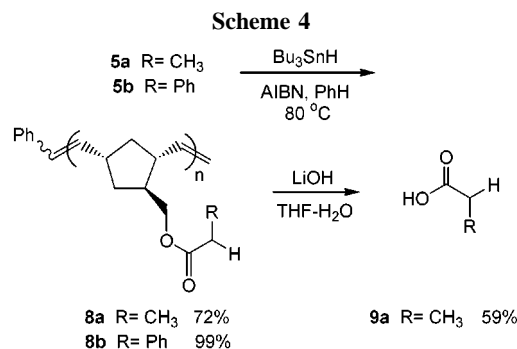
polymer with excess ethyl vinyl ether.⁷ The reaction mixture was then slowly poured into methanol with brisk agitation, producing a polymer filtered as a white solid precipitate. A longer reaction time resulted in the formation of an undesirable insoluble gel. Termination of the polymerization early in the reaction limits the molecular weights of the polymers, thereby allowing for complete solubility in organic solvents. Monitoring the polymerization reactions was conveniently done through the use of ¹H NMR spectroscopy.

Both α -bromo ROM polymers **5a** and **5b** were treated with allyltributyltin under free radical conditions at reflux to afford the corresponding allylated products **6a** and **6b** on designer support (Scheme 3). Cleavage of the allylated esters and



recovery of the support was completed through lithium hydroxide saponification, affording acids **7a** and **7b** in 87% and 76% yields, respectively.

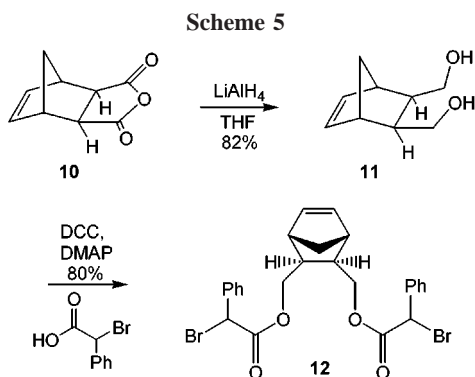
Reductive reactions by hydrogen atom transfer are shown in Scheme 4. Thus, supported bromoesters **5a** and **5b** were



also reduced with tributyltin hydride under free radical conditions, giving dehalogenated esters **8a** and **8b**, respectively. Ester **8a** was saponified and acidified to propionic acid (**9a**), which was identical to an authentic sample.

Scheme 5 shows our efforts to increase the number of reactive sites for each monomer unit. Two functional groups per unit would double the loading capacity of this polymer

(7) Gordon, E. J.; Gestwicki, J. E. Strong, L. E.; Kiessling, L. L. *Chem. Biol.* **2000**, 7, 9–16.

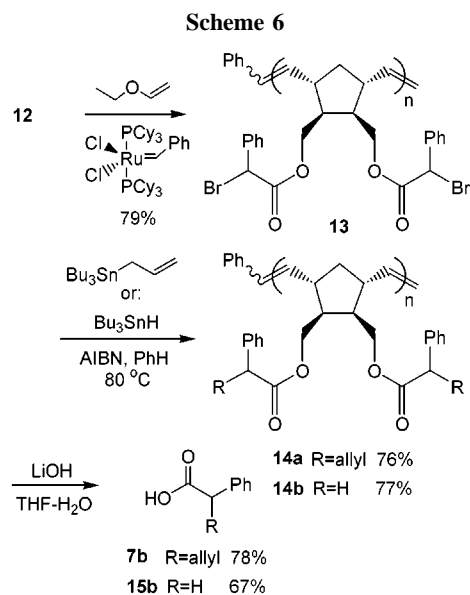


support. Norbornene-2,3-dicarboxylic anhydride (**10**) was reduced with lithium aluminum hydride to afford 5,6-bishydroxymethylnorborn-2-ene (**11**). Coupling with 2-bromo-2-phenylacetic acid gave the norbornene diester **12** in good yield.

Scheme 6 shows the polymerization of **12** using Grubbs catalyst followed by capping with ethyl vinyl ether to produce polymer **13** in 79% yield, setting the stage for subsequent radical reactions on both appendages. In net effect, this polymer is highly efficient, giving more than double the output of most standard solid-phase resins per monomer unit.

Upon treatment with allyltributyltin, under standard free radical conditions, both bromides were replaced with new carbon-carbon bonds, introducing two allyl units in **14a** in a 76% isolated yield as a white crystalline-like powder from cold methanol. A similar treatment of **14** with tributyltin hydride replaced the bromides with hydrogen atoms and constructed **14b** in 77% yield. Recovery of the polymers and the acids **7b** and **15b** was easily achieved with LiOH in saponification reactions in good yields.

In summary, radical reactions on soluble polymers derived from ring-opening metathesis provide high substrate loading and facile purification and offer the ease of 100% solution-



phase chemistry. The reaction rates on these designer supports are essentially the same as those for traditional solution-phase radical reactions, and tin pollution is virtually eliminated. To the best of our knowledge, this is the first example of a free radical reaction performed on a soluble polymer derived from a ring-opening metathesis polymerization. Efforts are currently directed to applying this support to other free radical processes.

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Supporting Information Available: Spectral information for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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