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Ring-Opening Metathesis Phase-Trafficking (ROMpt) Synthesis: Multistep Synthesis on Soluble ROM Supports

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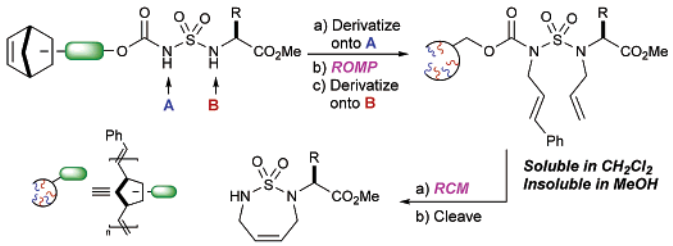
ABSTRACT



The use of ring-opening metathesis (ROM) oligomers as soluble supports for a multistep reaction sequence is described. A Mitsunobu reaction followed by an in situ ROMP-mediated phase-trafficking purification is utilized to generate soluble ROM oligomers that are isolated via precipitation with methanol. Once formed, the ROM oligomers serve as soluble supports for further solution-phase reactions, including a ring-closing metathesis. After each step, the support-bound products are isolated by precipitation with a suitable solvent.

The development of new technologies to eliminate or lessen the need for chromatographic separation of mixtures is of continued interest in the field of synthetic organic chemistry[1] and combinatorial chemistry.[2] Over the past 40 years, the use of resin-bound supports and reagents has dominated the literature with great success. Although very powerful, limitations with regard to reaction kinetics and load capacity have led to the emergence of alternative approaches. Among these, organic soluble polymer supports and reagents[3] are attractive substitutes because they allow multistep syntheses to proceed in the solution phase but still offer the convenience of easy product isolation. This is achieved by precipitation and filtration of the support-bound product. However, these systems have traditionally suffered from decreased load capacity. To address this issue, new polymeric systems have emerged. Among these, dendritic[4] and ring-opening metathesis (ROM)-derived polymers[5] have recently been employed. We now report the first use of high-load ROM

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(1) Reviews: (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195. (b) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125−150.

(2) (a) *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997. (b) Bunin, B. A. *The Combinatorial Index*; Academic Press: New York, 1998. (c) *Combinatorial Chemistry: A Practical Approach*; Fenniri, H., Ed.; Oxford University Press: New York, 2000; The Practical Approach Series 233.

(3) Review: (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546−554. (c) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325−3344. (d) ROM polymers as soluble catalysts: Bolm, C.; Dinter, C. L.; Seger, A.; Höcker, H.; Brozio, J. *J. Org. Chem.* **1999**, *64*, 5730−5731.

(4) (a) Review: Haag, R. *Chem. Eur. J.* **2001**, *7*, 327−335. (b) Haag, R.; Sunder, A.; Hebel, A.; Roller, S. *J. Comb. Chem.* **2002**, *4*, 112−119.

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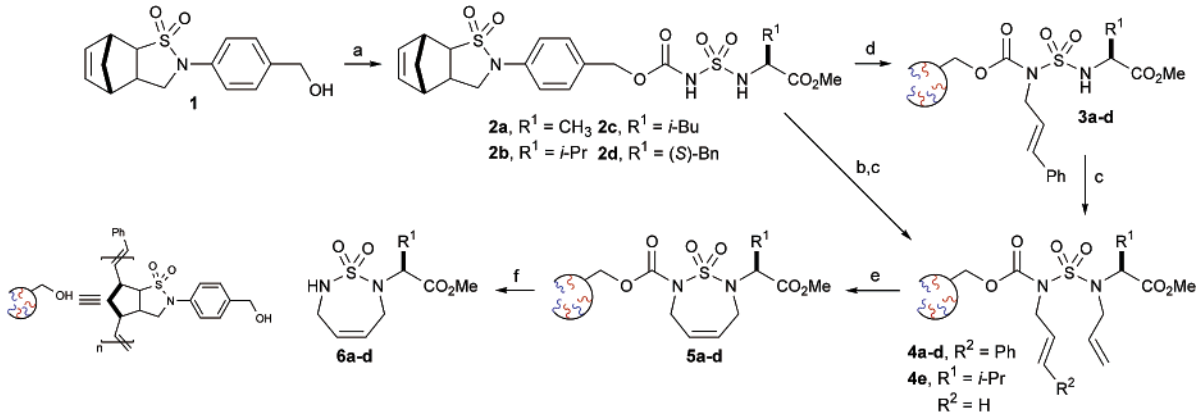
Scheme 1[a]



[a] Reagents and conditions: (a) (i) $ClSO_2NCO$, CH_2Cl_2, 0 °C; (ii) amino ester, Et_3N, CH_2Cl_2, 82−96%. (b) 5 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux. (c) Allyl bromide, K_2CO_3, NaI, DMF, 50 °C. (d) (i) Cinnamyl alcohol, PPh_3, DIAD, THF, rt; (ii) 5 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux; (iii) $EtOCH{=}CH_2$; (iv) MeOH and then filter. (e) 10 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 50 °C. (f) 1:1 TFA/CH_2Cl_2, 49−53% over four steps.

oligomers as soluble supports for a multistep synthesis to produce a series of unsymmetric sulfamide peptidomimetics.

The utility of ROM supports in combinatorial chemistry was first reported by Barrett and co-workers through the development of ROMPgel reagents[6] and an "impurity annihilation" reagent.[7] Recently, Enholm has used ROM oligomers as soluble supports for single-step free radical reactions.[5] We have since reported the use of capture−ROMP−release[8] and ROMP scavenging[9] as alternative ROMP-based techniques that exploit organic-soluble polymers.

We have recently reported the synthesis and ROM polymerization of various amino acid-derived sulfonamide monomers.[10] During the course of this work, we envisioned that norbornenyl-functionalized substrates could provide a manifold for accomplishing (1) functional group protection via a norbornenyl-tagged Wang-like protecting group (NWPG); (2) phase-trafficking purification; (3) mid-stage morphing of synthesis onto soluble supports; and (4) Wang-sensitive TFA release of final products. This 4-fold utilization of norbornenyl-tagged chemistry is termed ring-opening metathesis phase-trafficking[11] (ROMpt). After each step, the ROM oligomer is isolated from reaction impurities, simply by precipitation with a suitable agent, i.e., one that reaction impurities are soluble in. Once isolated, the oligomers can be redissolved in typical reaction solvents to allow further functionalization. This paper describes our initial results of this 4-fold ROMpt strategy.

We initially chose to apply monomer **1**[12,13] (Scheme 1) to our reported synthesis of cyclic sulfamide peptidomimetics.[14] NWPG **1** was reacted with chlorosulfonyl isocyanate followed by coupling with valine methyl ester. The NWPG-protected sulfamoyl carbamate **2b** was then polymerized with 5 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$. Unfortunately, the resulting oligomer (20-mer of **2**) was not soluble in CH_2Cl_2. However, it was sufficiently soluble in DMF to allow for subsequent bis-allylation resulting in the production of **4e**, which was isolated by precipitation with water in order to remove the DMF and inorganic salts. The CH_2Cl_2-soluble oligomer **4e** was then treated with 10 mol % Grubbs benzylidene catalyst to produce **5b**. Cyclic sulfamide **6b** was then cleaved from the support with 1:1 TFA/CH_2Cl_2. While we were pleased with the success of this ROM-supported RCM sequence, we felt that the narrow solubility profile of the oligomer produced from **2b** warranted a change in strategy. We felt that employing a Mitsunobu reaction and a subsequent ROMP-mediated phase-trafficking purification would allow the Mitsunobu products to be formed and isolated on the ROM-polymer phase, thus avoiding the generation of an oligomer containing two hydrogen bond donors. Additionally, in order to carry out such a protocol, it would be necessary to utilize a phenyl-protected olefin, which we have previously shown to be compatible with ROM polymerization protocols.[8]

To this end (Scheme 1), sulfamoyl carbamates **2** were reacted with cinnamyl alcohol under Mitsunobu conditions. The norbornenyl-tagged products were then induced to undergo phase-trafficking purification by in situ polymeri-

(5) (a) Enholm, E. J.; Gallagher, M. E. *Org. Lett.* **2001**, *3*, 3397−3399. (b) Enholm, E. J.; Cottone, J. S. *Org. Lett.* **2001**, *3*, 3959−3962.

(6) Review: Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301−3324.

(7) Barrett, A. G. M.; Roberts, R. S.; Schröder, J. *Org. Lett.* **2000**, *2*, 2999−3001.

(8) Harned, A. M.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1007−1010.

(9) Moore, J. D.; Harned, A. M.; Henle, J.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1847−1849.

(10) Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett.* **2002**, *43*, 917−921.

(11) For a review on phase-trafficking, see: Flynn, D. L. *Med. Res. Rev.* **1999**, *19*, 408−431.

(12) Monomer (±)-**1** was prepared as an ~8:1 mixture of endo/exo diastereomers that were carried through as a mixture for ease of use.

(13) Monomer (±)-**1** is prepared on a multigram scale in five steps from styrene sulfonyl chloride. The only chromatography required in this synthesis is the removal of dicyclopentadiene from the Diels−Alder adduct and the removal of any aluminum salts from **1**. In both cases, the careful collection of fractions is not necessary. For more details, see Supporting Information.

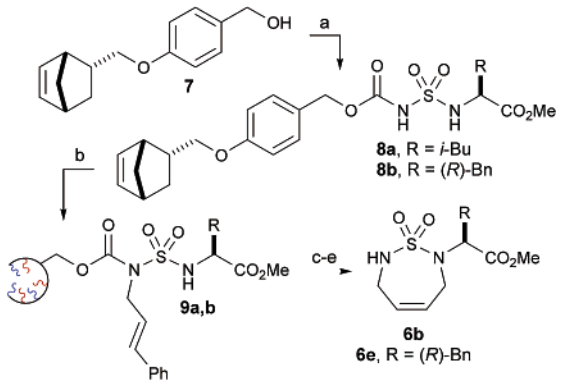
(14) Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781−9790.

zation mediated by the second generation Grubbs catalyst.[8] The crude reaction mixtures were poured into methanol to precipitate oligomers **3** away from the Mitsunobu byproducts, thus avoiding the tedious separation process often associated with the Mitsunobu reaction. Oligomers **3** were then utilized as organic-soluble polymer supports in subsequent steps. Allylation gave rise to diene intermediates **4**, which were subjected to RCM conditions to give cyclic sulfamides **5**. Intermediates **4** and **5** were easily purified and isolated by pouring the crude reaction mixtures into water or methanol, respectively.

Wang-like tethered RCM intermediates **5** were then treated with 1:1 TFA/CH_2Cl_2 to mediate release of the final products from the soluble support. The spent oligomers were precipitated with MeOH and filtered away from cleaved products **6a**−**d**. The crude isolated products were then passed through a short plug of silica, eluting with 1:1 hexane/EtOAc. All final products **6a**−**d** were isolated in >90% purity as judged by ^{1}H NMR[15] and 49−53% overall yield over four steps.

Similarly, we were able to start with alcohol **7**[16] (Scheme 2), producing **6b**,**e** in >90% purity as judged by ^{1}H NMR[15]

Scheme 2[a]



[a] Reagents and conditions: (a) (i) $ClSO_2NCO$, CH_2Cl_2, 0 °C; (ii) amino ester, Et_3N, CH_2Cl_2, 60−87%. (b) (i) Cinnamyl alcohol, PPh_3, DIAD, THF, rt; (ii) 5 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux; (iii) $EtOCH{=}CH_2$; (iv) MeOH and then filter. (c) Allyl bromide, K_2CO_3, NaI, DMF, 50 °C. (d) 10 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 50 °C. (e) 1:1 TFA/CH_2Cl_2, 45−55% over four steps.

and 55 and 45% overall yields, respectively. The facile production of **7** (two steps from commercially available material) may lead to more widespread use compared to **1**. However, we have found that both **1** and **7** can be readily prepared on a large scale.

It was found that the progress of the RCM could be monitored by NMR analysis. Furthermore, the Wang-type linker affords ample space to eliminate communication between the stereocenters of the backbone and the amino ester moiety, thus allowing for the acquisition of simplified NMR spectra. Analysis of the DEPT spectrum of allylated oligomer **10** (Figure 1a) revealed a single negative peak in the olefin region at 117.1 ppm corresponding to the terminal

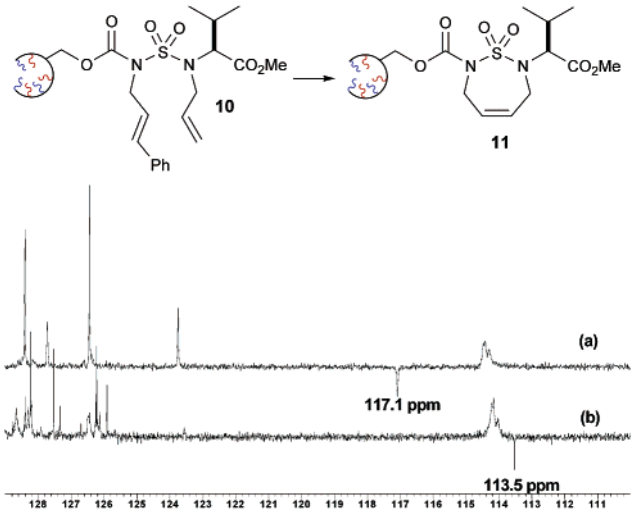


Figure 1. (a) DEPT spectrum (129−110 ppm) of **10** before RCM. (b) Crude DEPT spectrum (129−110 ppm) of **11**. Both **10** and **11** were derived from **7**.

CH_2 of the allyl group. After RCM, the spectrum of the crude reaction mixture showed that the peak at 117.1 ppm had completely disappeared, and a new peak at 113.5 ppm had appeared (Figure 1b). The peak at 113.5 ppm corresponds to the styrene that is evolved during the RCM reaction. Consequently, after precipitation and isolation of the metathesized oligomer, the peak at 113.5 ppm was not present.

In conclusion, we have shown that ROMpt provides an integrated platform for accomplishing functional group protection, phase-trafficking-induced purification of intermediates, downstream soluble-supported synthesis, and chemospecific release of final products. The load capacity of the soluble supports is high and the cleaved support is easily separated from the product by simple precipitation with MeOH. Additionally, we have demonstrated that RCM reactions can be accomplished with these ROM soluble supports under typical RCM conditions, using only 10 mol % catalyst.[17] We feel that the robust nature of these soluble Wang-type supports will be applicable to a wide range of reaction sequences. We are currently pursuing the use of these and other similar supports in ROMpt reaction sequences. These results will be reported in due course.

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(15) ^{1}H NMR spectra of crude isolated products are available in Supporting Information.

(16) For the synthesis of (±)-**7**, see Supporting Information.

(17) For comparison, there are reports of performing RCM reactions on the solid phase with as little as 10 mol % catalyst (see: (a) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, 138−144. (b) Reichwein, J. F.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 2335−2344.); however, loads of ≥30 mol % have also been reported (see: (c) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614. (d) Tang, Q.; Wareing, J. R. *Tetrahedron Lett.* **2001**, *42*, 1399−1401. (e) Schmiedeberg, N.; Kessler, H. *Org. Lett.* **2002**, *4*, 59−62. (f) Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 398−408).

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Supporting Information Available: Details of the synthesis of monomers **1** and **7** and experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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