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# Capture-ROMP-release: application to the synthesis of amines and alkyl hydrazines☆

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**Abstract**—Application of a capture-ROMP-release strategy for the chromatography-free purification of Mitsunobu reaction products is described. Norbornenyl-tagged reagents are utilized for standard solution phase Mitsunobu chemistry. Post-reaction phase-switching is accomplished via in situ ring-opening metathesis polymerization (ROMP) followed by precipitation of the polymer with methanol. Release of the product from the polymer affords amines and alkyl hydrazine derivatives with good yields and purities.

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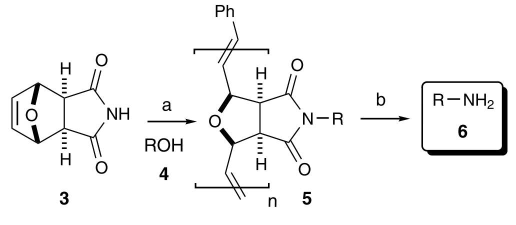
The search for efficient technologies for the preparation of large chemical libraries is currently an active area of investigation in the area of combinatorial chemistry.[1] Strategies that integrate synthesis with purification have been particularly successful.[2] Various methodologies have been explored to facilitate impurity removal/product purification, including solid polymer supports[3] and reagents;[4] scavenging resins;[5] chemical tags;[6] and organic soluble supports, reagents and scavenging agents.[7–10] In the area of chemical tagging, in situ polymerization via ring-opening metathesis polymerization (ROMP) is emerging as an attractive technology.[8,11] The salient features involve the use of organic-soluble, monomeric, norbornenyl-tagged reagents that enjoy all the features of solution phase reactions (facile reaction kinetics, ease of monitoring), and the added advantage of solid phase resins (filterability). In this strategy, the tags can be utilized in an initial capturing event (Mitsunobu reaction), followed by post-reaction in situ ROM polymerization resulting in high-load polymers that can be filtered from the reaction and isolated as free-flowing powders. Subsequent treatment with an appropriate reagent releases the captured species as a new chemical entity. This strategy allows phase switching to be utilized for purification purposes. Norbornenyl- and oxanorbornenyl-tagged reaction monomers are the reagents of choice due to their robust performance in ROM polymerization procedures, as well as their ease of preparation.



**Scheme 1.** *Reagents and conditions*: (a) i. ROH (**4**), $PPh_3$, DIAD, $CH_2Cl_2$, reflux; ii. 1 mol% **2**, $CH_2Cl_2$, reflux; iii. $EtOCH{=}CH_2$; iv. MeOH then filter; (b) $NH_2NH_2$, THF, reflux.

In the area of impurity elimination, the Mitsunobu reaction[12] has previously been the target of several groups. A variety of methods have been developed to facilitate the separation of the Mitsunobu by-products ($Ph_3PO$ and $DEADH_2$) from the desired product.[6d,13]

We have recently reported the use of a capture-ROMP-release strategy for chromatography-free purification of Mitsunobu reactions.[14] This approach incorporates an inexpensive and readily obtainable *N*-hydroxysuccinimide derivative as a norbornenyl-tagged acid in the Mitsunobu reaction. The method was inspired by the previous work of Barrett and co-workers who have taken a novel approach to the removal of Mitsunobu

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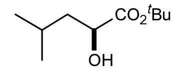
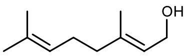
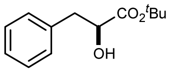
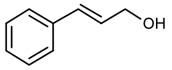
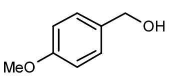
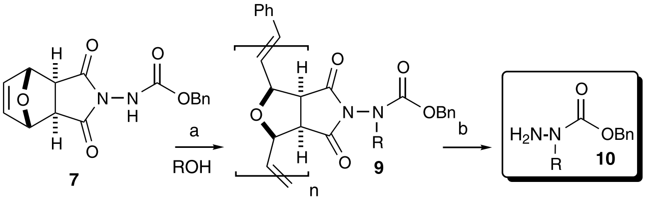
by-products with the development of an impurity annihilation reagent[15] and ROMPgel technology[8,16] utilizing the Grubbs benzylidene catalyst [$(PCy_3)_2(Cl)_2Ru$=CHPh, **1**].[17] In continuation of our interest in this area, we now describe the capture ROMP-release strategy for the synthesis of alkyl amines and hydrazine derivatives.[18]

Amines and hydrazine derivatives have a wide variety of biological activities besides their obvious applications in organic synthesis. The method we employ utilizes a post-capture polymerization event that effectively removes Mitsunobu by-products without the use of chromatography. For the synthesis of amines we have performed Mitsunobu reaction between *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (**3**) and a variety of alcohols **4a–e** (Scheme 1).[19] These intermediates were phase-switched by subjecting the crude reaction mixture to ROMP conditions using 0.5–1.0 mol% of $(ImesH_2)(PCy_3)$-$(Cl)_2Ru$=CHPh (**2**)[20,21] catalyst at 0.2 M concentration. Once the monomer was consumed in the reaction (as monitored by GC and TLC), the reaction mixture was quenched with excess ethyl vinyl ether to generate a differentially soluble polymer that is soluble in organic solvents such as THF, $CH_2Cl_2$, $CHCl_3$ and insoluble in MeOH. The differential solubility behavior of the polymer was exploited by precipitating it from methanol. Excess Mitsunobu reagents and by-products were next removed by filtration and washing the polymer 2–3 times with methanol to yield **5** as a free-flowing powder in good to excellent yields (Table 1).

A second phase switching operation was carried out to release the corresponding amine **6** from the alkylsuccinate functionalized polymer **5** using hydrazine. Biphasic extraction ($Et_2O/H_2O$) of the reaction mixture resulted in the removal of spent polymer and excess hydrazine yielding the desired amines in good purity (Table 1). Mosher ester analysis was used to determine the ee of amine **6c** and was found to be 92% ee. No traces of $Ph_3PO$ or $DIADH_2$ were observed by GC or $^1H$ NMR analysis. No polymeric residue was observed by $^1H$ NMR of the crude, isolated amines.[22] In addition, an ICP-MS measurement following the protocol reported by Georg and co-workers[22] was used to determine the ruthenium level that was found to be 0.043 µg per 5 mg of sample. This level is well below the acceptable ranges that have been reported for ruthenium removal in RCM processes.[22,23]

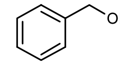
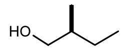
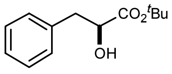
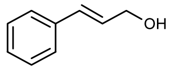
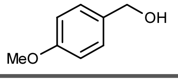
**Table 1.** Capture-ROMP-release to amines

| *entry* | *ROH 4* | *oligomer **5*** *(% yield)* | ***6*** *(% yield)* |
|---|---|---|---|
| **4a** |  | 91 | 99 |
| **4b** |  | 61 | 68 |
| **4c** |  | 98 | 92 |
| **4d** |  | 89 | 83 |
| **4e** |  | 99 | 72 |



**Scheme 2.** *Reagents and conditions*: (a) i. ROH, $PPh_3$, DIAD, $CH_2Cl_2$, reflux; ii. 1 mol% **2**, $CH_2Cl_2$, reflux; iii. EtOCH=$CH_2$; iv. MeOH then filter; (b) $NH_2NH_2$, THF, reflux.

**Table 2.** Capture-ROMP-release to alkylhydrazines

| *entry* | *alcohol* | *oligomer **9*** *(% yield)* | ***10*** *(% yield)* |
|---|---|---|---|
| **8a** |  | 61 | 82 |
| **8b** |  | 40* | 76 |
| **4c** |  | 69 | 78 |
| **4d** |  | 65 | 80 |
| **4e** |  | 87 | 71 |

*Using 3 mol% catalyst **2**

Similarly, the synthesis of hydrazine derivatives can be achieved using a variety of alcohols **8a–b** and **4c–e** as outlined in Scheme 2. Thus, alcohols **8a–b** and **4c–e** were captured on *exo*-*N*-benzyloxycarbonylamino-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (**7**) via the Mitsunobu reaction (Scheme 2). After completion of the reaction, the reaction mixture was evaporated to dryness. Following a similar ROMP protocol as described above, a differentially soluble polymer was obtained. The reaction mixture was poured into methanol to precipitate the polymer **9a–e** in moderate to good yields (Table 2). The hydrazine derivatives were cleaved from the polymer by refluxing **9** in THF in the presence of anhydrous hydrazine for 5 h. Finally, the polymeric by-product was removed by biphasic extraction ($Et_2O/H_2O$) to afford hydrazine derivatives **10a–e** in good yields and purities (Table 2). Again, Mosher ester analysis was used to establish the stereochemical integrity of hydrazine derivative **10c** which was found to be 96% ee.

It is important to note that the conditions of the ROM polymerization event ultimately affect the properties of the resulting polymers. The concentration of the reaction mixture during the ROM polymerization was critical, with concentration between 0.1–0.2 M being sufficient. If the reaction mixture was too concentrated, gel formation was observed in some cases, and traces of Mitsunobu by-product were observed in the final products, presumably due to inclusion during the polymerization process. Also, the length of the polymer plays an important role. Generally, we found that a better yield of polymer was obtained when using 0.5 mol% of catalyst (Gaussian distribution of ∼200-*mers*) when compared to 1.0–3.0 mol% (Gaussian distribution of ∼100- to 33-*mers*), presumably because of the ease of filtration of the large particle size in the former cases. When catalyst loads of less than 0.5 mol% (Gaussian distribution of >200-*mers*) were used, the resulting polymer was insoluble in most common organic solvents and difficult to characterize by conventional methods ($^1$H NMR). Interestingly, even when the polymer was not soluble in THF, hydrazinolysis could be achieved.

It is noteworthy that ROMP could be carried out in presence of olefin containing substrates **4b** and **4d** without any observed cross-metathesis occurring between the substrate and polymer backbone. Furthermore, when the norbornenyl system (carbon bridgehead) was used instead of oxynorbornenyl-tagged monomer, traces of polymer were found in the final product. Further research is underway in our laboratory to extend synthetic utility of this work and also explore various properties of the polymer with ultimate goal of synthesizing designer polymers with tunable properties.

In conclusion, we have developed a capture-ROMP-release strategy for the synthesis of amines and hydrazine derivatives eliminating the need for chromatographic purification. This method is high yielding and generates oligomers with tunable properties. The combined use of Grubbs catalyst-mediated ROM polymerization and norbornenyl-tagging of reactants offers a powerful and general platform for solution-phase chemical library synthesis. Noteworthy features of this methodology include in situ polymerization after solution-phase reactions, high-load levels of the resulting oligomers, phase switching operations, and high tolerance to a wide variety of organic functional groups.

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19. **Capture-ROMP-release experimental**: To the alcohol (0.100 g) solution in $CH_2Cl_2$ (0.5 M) at 0°C, oxo-bicyclic imide (1.10 equiv.) and triphenylphosphine or tributylphosphine (1.0 equiv.) were added followed by dropwise addition of diisopropyl azodicarboxylate (1.10 equiv.). The mixture was allowed to warm to room temperature and heated in an oil bath at 40°C for 4 h. The reaction was concentrated under reduced pressure, dissolved in $CH_2Cl_2$ (0.2 M, degassed with argon for 15 min) in a sealed tube, and the second generation Grubbs catalyst was added (0.5 mol%). The reaction was allowed to stir at 40°C for 4 h, cooled to room temperature, quenched with ethyl vinyl ether, and stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, precipitated from methanol, filtered through a fritted glass funnel, and dried under high vacuum to yield polymer as a white solid. The polymer was dissolved in anhydrous THF (0.5 M) in a pressure tube, and hydrazine (5.0 equiv.) was added to the solution at room temperature. The reaction mixture was allowed to stir at 65°C in an oil bath for 5 h, filtered through a pad of Celite®, and extracted with water and ether. The ether solution was dried over $Na_2SO_4$ and concentrated to yield pure product.
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