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Capture-ROMP–Release: Application for the Synthesis of *O*-Alkylhydroxylamines

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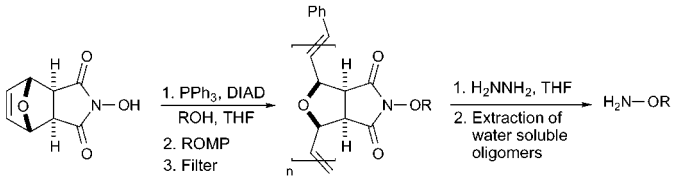
ABSTRACT



A new capture-ROMP–release method for chromatography-free purification of *N*-hydroxysuccinimde Mitsunobu reactions is described. The Mitsunobu reaction captures a variety of alcohols onto a norbornenyl *N*-hydroxysuccinimide monomer. Subjection of the resulting crude reaction mixture to ROM-polymerization generates a polymer that can be precipitated with methanol and filtered from the Mitsunobu byproducts. Treatment of the polymer with hydrazine releases the substrate from the water-soluble polymer, producing a variety of *O*-alkylhydroxylamines with good purity.

The development of new technologies to aid in the production of large target libraries is of continued interest for the field of combinatorial chemistry.[1] To facilitate impurity removal/product purification, several strategies can be employed, including solid polymer supports[2] and reagents,[3] scavenging resins,[4] chemical tags,[5] and organic soluble supports.[6] One recently developed purification strategy is capture−release.[7] This approach utilizes a functionalized resin to selectively capture the product from a solution-phase reaction via covalent or ionic interactions. The resin-bound product is then filtered away from the reaction impurities; subsequent cleavage releases the product from the resin.[7b] We now report a new post-capture polymerization method for chromatography-free purification of Mitsunobu reactions that we have termed capture-ring-opening metathesis polymerization−release (capture-ROMP−release). This strategy incorporates a cheap, easily obtainable *N*-hydroxysuccinimide analogue as a norbornenyl-tagged acid in the Mitsunobu reaction. This method was inspired by the previous work of Barrett and co-workers who have taken a novel approach to impurity removal with the development of an impurity annihilation reagent[8] and ROMPgel technology[9,10] utilizing

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(3) Review: Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217−1239.

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(7) Review: (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Chem. Eur. J.* **2000**, *6*, 4445−4450. Covalent resin capture: (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583. (c) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331−6332. (d) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076−7077. (e) Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W. *J. Comb. Chem.* **2000**, *2*, 597−599. (f) Pirrung, M. C.; Tumey, L. N. *J. Comb. Chem.* **2000**, *2*, 675−680. Ionic resin capture: (g) Liu, Y.-S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471−3473. (h) Lobrégat, V.; Alcaraz, G.; Bienaymé, H.; Vaultier, M. *Chem. Commun.* **2001**, 817−818.

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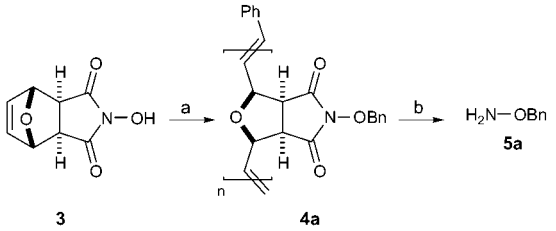
Scheme 1[a]



[a] Reagents and conditions: (a) i. BnOH, PPh_3, DIAD, THF, rt; ii. 5 mol % of **2**, CH_2Cl_2, reflux; iii. $EtOCH{=}CH_2$; iv. MeOH then filter; (b) NH_2NH_2, THF, rt, 72% from BnOH.

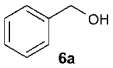
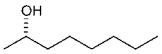
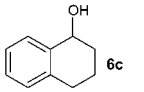
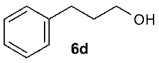
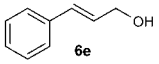
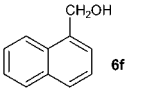
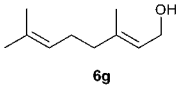
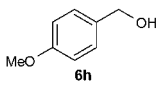
the Grubbs benzylidene catalyst [$(PCy_3)_2(Cl)_2Ru{=}CHPh$, **1**].[11]

In the course of developing a facile route to *O*-alkylhydroxylamines,[12,13] we encountered difficulty removing Mitsunobu byproducts. Our previous experience with the generation of soluble, ROMP-derived sulfonamide oligomers[14] led us to believe that oligomers derived via ROMP may have utility as capture−release agents due to their tunable properties and unique solubility profiles. This hypothesis has led to the development of the capture-ROMP−release strategy that we now report.

The method we employ (Scheme 1) utilizes a post-capture polymerization/filtration event that effectively removes Mitsunobu byproducts without the use of chromatography. The Mitsunobu reaction is first utilized to capture a variety of alcohols onto *exo*-*N*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (**3**).[15] Subjection of the crude reaction mixture to ROM-polymerization conditions using 5 mol % of $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (**2**)[16,17] generates a differentially soluble polymer **4** that was isolated by precipitation from methanol. Filtration away from the Mitsunobu byproducts gave **4** as a free-flowing powder in good to excellent yield (Table 1). Hydrazinolysis (anhydrous NH_2-NH_2/THF, rt), followed by biphasic extraction (Et_2O/H_2O), resulted in the release of the target *O*-alkylhydroxylamine **5** in good purity (Table 1). No traces of PPh_3O or $DIADH_2$ were observed by GC or ^1H NMR analysis. In addition, no polymeric byproducts were observed by ^1H NMR of the crude, isolated *O*-alkylhydroxylamines.[18] The major contaminant in all cases was residual hydrazine (5−12% by GC, Table 1) which could be azeotropically removed with toluene under reduced pressure.

In the area of impurity elimination, the Mitsunobu reaction[20] has previously been the target of several groups. A variety of methods[21] have been developed to facilitate the separation of the Mitsunobu byproducts (Ph_3PO and $DEADH_2$) from the desired reaction product. Our approach incorporates

Table 1. Formation of *O*-Alkylhydroxylamines **5a**−**d**[a]

alcohol	yield of **4** (%)	yield of **5**[b] (%)	purity[c] (%)	Residual N_2H_4[c] (%)
 **6a**	95	72	84	6
 **6b**	83[d] 97[d,e]	59 89[e]	69 73[e]	12 n/a
 **6c**	99 93[e]	95 77[e]	91 67[e]	6 n/a
 **6d**	>99	97[12c]	82	5
 **6e**	99	79[19]	84	8
 **6f**	>99	96	63	9
 **6g**	63[d]	61	73	7
 **6h**	>99	58[19]	79	9

[a] Reactions performed as outlined in Scheme 1. [b] Based on original amount of alcohol. [c] Determined by GC before azeotropic removal of hydrazine. [d] Polymerization conducted with 2 mol % of **2**. [e] Cleavage with$MeNH_2$/MeOH.

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(15) Narita, M.; Teramoto, T.; Okawara, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1084−1089.

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(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(18) See ^1H NMR spectra of crude **5a**−**h** in the Supporting Information.

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a cheap, easily obtainable *N*-hydroxysuccinimide analogue **3** as a norbornenyl-tagged acid that effectively undergoes Mitsunobu reaction with a variety of alcohols (Scheme 1, Table 1).

Our investigation of the Mitsunobu reaction was initiated with norbornenyl *N*-hydroxysuccinimide monomer **3** serving as the acidic reagent.[22] Compound **3** was initially reacted with benzyl alcohol under typical Mitsunobu conditions (Scheme 1). Once the reaction was complete, the crude reaction mixture was evaporated to dryness and enough CH_2Cl_2 was added to bring the products to ROMP concentration (0.1 M). Polymerization was then initiated by the addition of 5 mol % of **2** followed by heating to reflux for 45 min.[23] Once consumption of monomer was complete, the polymerization was quenched by the addition of excess ethyl vinyl ether. The reaction mixture was then poured into MeOH to precipitate oligomer **4a**, which could be filtered and collected. The polymer was characterized by ^{1}H NMR.

We were pleased to find that the post-capture polymerization of the Mitsunobu product proceeded smoothly without the need for prior purification. We initially felt that the Ph_3PO byproduct may hinder the metathesis event by deactivating the catalyst. Recently, Georg and co-workers have shown that Ph_3PO is one reagent that can be used to remove ruthenium byproducts from ring-closing metathesis reactions.[24] For this reason we chose to use catalyst **2** which has been shown to be much more active than **1** in various polymerization reactions.[25] It is also noteworthy to mention that a slight excess of diisopropyl azodicarboxylate (DIAD) relative to triphenylphosphine (PPh_3) was used to ensure that no free PPh_3 would be present during the polymerization, a factor that could also possibly hinder polymerization.[26] In practice, it was found that the polymerization was indeed more efficient with catalyst **2**.[27]

To verify the necessity and higher efficiency of catalyst **2** versus catalyst **1**, we ran comparison experiments. Indeed, it was found that not only is the polymerization more efficient when **2** is employed but the properties of the resulting oligomers are also affected by the choice of catalyst. When the monomer derived from **6b** was polymerized with 5 mol % of **1**, the resulting oligomer precipitated as a fine suspension when the reaction mixture was poured into methanol, yielding **4b** in only 59%. This decrease in yield was attributed to a higher solubility in MeOH. With the same

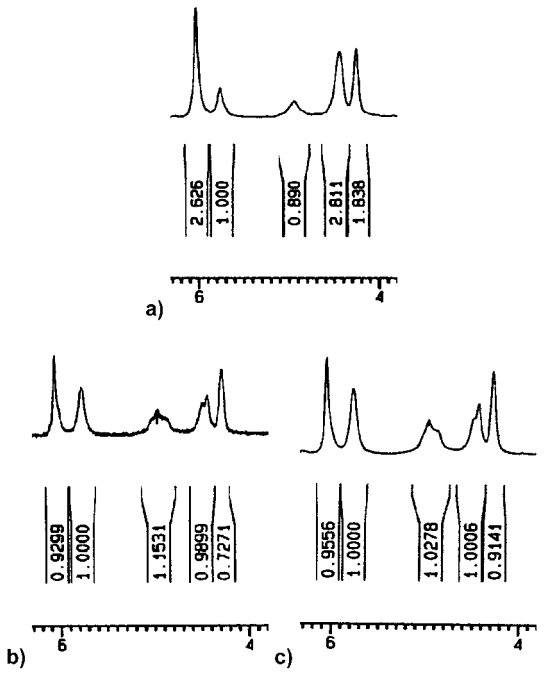

Figure 1. ^{1}H NMR analysis of oligomer **4b** in $CDCl_3$. Olefin backbone protons at 6.1 (trans) and 5.8 (cis) ppm. (a) Oligomer generated with 5 mol % of **1**. (b) Oligomer generated with 5 mol % of **2**. (c) Oligomer generated with 2 mol % of **2**.

loading of catalyst **2**, the resulting precipitated oligomer could be filtered to produce **4b** in 89% yield. One plausible explanation for this difference in solubility could be a change in the cis/trans ratio of the polymer backbone (Figure 1).[28] However, when 2 mol % of **2** was employed to produce longer oligomers, the filtration became much easier due to a larger particle size. This same phenomenon was also observed for the geraniol-derived polymer **4g**. Clearly, the physical properties of the alcohol unit also play some role in defining the properties of the resulting oligomers.

With **4a** in hand we next investigated the cleavage of the polymer from the substrate. The oligomer was treated with excess $MeNH_2$ in MeOH or anhydrous hydrazine in THF at room temperature. In the case of $MeNH_2$, the slightly pink polymer quickly turned white and the solution turned green, possibly due to complexation of $MeNH_2$ with catalyst impurities. Surprisingly, the oligomer suspension became a clear solution within 5 min but then precipitated again upon prolonged reaction. The reaction was allowed to stir at ambient temperature for 1 h at which time the reaction was filtered through a plug of Celite to remove the insoluble polymer and washed with MeOH. GC and ^{1}H NMR analysis of the MeOH wash indicated that *O*-benzylhydroxylamine (**5a**) was present in good purity. Alternatively, treatment of a THF solution of the oligomer with excess anhydrous hydrazine for 1.5 h, followed by extraction of the water-

(21) Polymer-bound triphenylphosphine: (a) Amos, R. A.; Emblidge, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598−3600. (b) Tunoori, A. R.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, *39*, 8751−8754. Acid extractable Diphenyl-2-pyridylphosphine and di-*tert*-butyl azodicarboxylate (DBAD). (c) Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999**, *40*, 4497−4500. (d) Bis(5-norbornenyl-2-methyl) azodicarboxylate (DNAD), see ref 8.

(22) Barrett has previously shown that **3** can be used to construct a ROMPgel acylating agent, see ref 9c.

(23) When the polymerization was performed at ambient temperature, a reaction time of 3 h was required for complete consumption of monomer.

(24) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

(25) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903−2906.

(26) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.

(27) When **1** was employed, the polymerization required refluxing for multiple hours, while **2** only required 45 min at reflux.

(28) ^{1}H NMR assignments were made according to the reported shifts of poly(7-oxabicyclo[2.2.1]hept-2-ene) derivatives. See: Benedicto, A. D.; Novak, B. M.; Grubbs, R. H. *Macromolecules* **1992**, *25*, 5893−5900.

soluble polymer, also produced **5a** (Table 1), thus avoiding chromatography. This strategy was then applied to other alcohols (**6b**−**f**), producing *O*-alkylhydroxylamines **5b**−**5f** in high yield and good purity. In all cases residual hydrazine was the major impurity observed by GC (Table 1). Simple azeotropic removal with toluene under reduced pressure was sufficient to eliminate this contaminant. We were pleased to find that this approach was applicable to the olefin-containing substrates, cinnamyl alcohol (**6e**) and geraniol (**6g**). Interestingly, while the Mitsunobu capture event proceeded smoothly,[29] the monomer derived from menthol failed to polymerize to an appreciable extent.

In conclusion, we have developed a novel capture-ROMP−release strategy to eliminate the chromatographic separation of Mitsunobu byproducts. This approach should be amenable to other reactions as well as the purification of combinatorial libraries. Several advantages are apparent; most importantly, the post-capture polymerization event gives one the ability to monitor reaction progress via conventional methods. Furthermore, the method is high yielding and generates oligomers with tunable properties. We are currently working to expand this approach and will report the further utility of this method in due course.

(29) For an example of Mitsunobu reactions with menthol and other hindered alcohols, see: Sammakia, T.; Jacobs, J. S. *Tetrahedron Lett.* **1999**, *40*, 2685−2688.

Acknowledgment. This investigation was generously supported by funds provided by the National Science Foundation (NSF Career 9984926) and a NIH Dynamic Aspects in Chemical Biology Training Grant for A.M.H. The authors thank Dr. David Vander Velde for NMR assistance as well as Dr. Todd Williams and Larry Seib for HRMS analysis. The authors also thank Dr. Daniel L. Flynn for many helpful discussions.

Supporting Information Available: Detailed experimental procedure and characterization and ^{1}H NMR spectra of oligomers **4a**−**h** and compounds **5a**−**h**. This material is available free of charge via the Internet at http://acs.pubs.org.

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