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High-Load, Hybrid Si-ROMP Reagents

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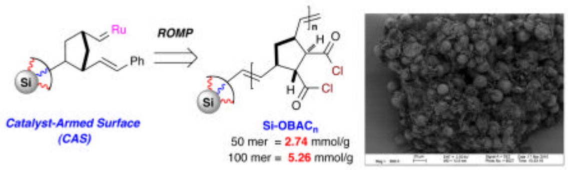
Abstract



The combination of norbornenyl-tagged (Nb-tagged) silica particles and functionalized Nb-tagged monomers for the generation of hybrid Si-ROMP reagents and scavengers is reported. Specifically Si-ROMP-derived *bis*-acid chloride, dichlorotriazine and triphenylphosphine scavenger/reagents have been grafted from the surface of silica particles utilizating surface-initiated, ring-opening metathesis polymerization (ROMP). These hybridpolymeric materials combine the physical properties of current immobilized silica reagents and represent a key advancement in load by merging the inherent tunable properties of the ROMP-derived oligomers with silica supports for application in parallel synthesis.

The development of new immobilized reagents and scavengers for application in facilitated synthetic protocols is an important facet of drug discovery. The ability to rapidly generate collections of small molecules without the need of time consuming, expensive purification protocols has inspired the development of immobilized reagents and scavengers. Since the introduction of polystyrene immobilized resins,[1] a variety of advancements have been developed for the immobilization of functionalized reagents including silica,[2] fluorous,[3] monolith,[4] and soluble polymers generated from ring-opening metathesis polymerization (ROMP).[5]

A pivotal emerging technology in drug discovery has been the development and utilization of automated parallel technologies.[6] Despite the large investment in the design and advancement of several platforms, limited advancements in the immobilized reagent cartridges for in-line diversification or purification have been made. Though current functionalized silica reagents have circumvented many of the traditional limitations associated with classical resin-bound reagents, current available reagents suffer from low load levels typically expressed in mmol/g.

Recently, surface functionalization of nanoparticles[7] has emerged as a well-established method for the preparation of polymeric hybrid materials as reported by Buchmeiser and co-workers.[8] Such hybrid nano-materials combine the physical properties of the inorganic shell

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Supporting Information Available: Experimental details and spectral characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(particle size, pore and shape) with the tunable properties of the grafted organic polymer.[9] Key reports have demonstrated the potential scope of surface-initiated ROM polymerization for the grafting of organic-polymers from inorganic nano-particles,[10] carbon nano-tubes,[11] metal surfaces,[12] and resins.[13]

Recently, ROMP-derived oligomeric and polymeric reagents/scavengers have surfaced for application in facilitated synthetic protocols. These reagents possess several inherent characteristics that address classical limitations associated with traditional immobilized reagents, i.e load, tunable properties, heterogeneous reaction kinetics etc.[5,14,15,16] Inspired by these developments, it was envisioned that by combining the inherent high-load, tunable properties of soluble ROMP-derived oligomers with an insoluble silica support, a new variety of hybrid immobilized functionalized reagents could be achieved. Unlike current methods of functionalizing the surface of silica particles, the application of surface-initiated ROM polymerization addresses the limitation of load by allowing the grafting of multiple monomer units into an oligomeric chain from each Nb-tagged site on the silica particle (Figure 1).

We initially focused on the synthesis of a Si-ROMP-derived bis-acid chloride scavenger (Si-OBAC) by starting with the corresponding Nb-tagged BAC-functionalized monomer utilized for the generation of OBAC soluble oligomers.[17] Previously, simple ROM polymerization of the corresponding Nb-tagged bis-acid chloride monomer **3** using metathesis catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; cat-**B**],[18,19] generated the desired high-load soluble scavenger possessing a theoretical load of 9.1 mmol/g. Therefore, it was envisioned that preactivation of Nb-tagged silica **2** with Grubbs catalyst would generate a catalyst-armed surface (CAS) capable of efficient polymerization off the silica surface with Nb-tagged monomer **3**, while maintaining the high-load nature of the reagent.

Utilizing a protocol reported by Buchmeiser and coworkers in 2000,[8] activated spherical silica **1** (70Å, 20 μm particle size) was tagged with 5-(bicycloheptenyl)-triethoxy silane, followed by capping with trimethoxymethylsilane and dimethoxydimethylsilane to yield the desired Nb-tagged silica (Si-Nb) **2** (Scheme 1). With this tagged nanoparticle in hand, the surface was armed with metathesis catalyst cat-**B** (0.6–0.8 equivalents), followed by addition of the Nb-tagged BAC monomer **3** to rapidly generate the desired hybrid material, Si-OBAC$_{50}$ **4**.[20,21] A number of key parameters were critical, including reaction concentration, and pre-arming of the silica surface with 0.8 equivalents of cat-**B** before the addition of the Nb-tagged monomeric species. This was important to insure that all the metathesis catalyst was attached from the Nb-tagged silica surface and potentially preventing polymerization of the Nb-tagged monomer **3** by any free catalyst in solution.[20]

After optimization of the reaction conditions, Si-OBAC$_{50}$ **4** possessing a theoretical load of 2.74 mmol/g, was readily accessed as a free flowing solid on gram scale.[22,23] Utilizing the inherent tunable characteristics of ROMP-derived oligomers, the theoretical load of this hybrid material was further increased by extending the oligomeric chain length to 100 monomeric units (100-mer), yielding Si-OBAC$_{100}$ **5** possessing a theoretical load of 5.26 mmol/g (Scheme 1). This key advancement exploits the inherent properties of Si-ROMP hybrid materials, whereby simply increasing the ratio of monomer **3** to silica **2** (ie 50:1 to 100:1) increases the polymer chain length and hence gives rise to increased theoretical loads. Furthermore, Si-ROMP scavengers **4** and **5** are highly favorable in comparison to commercially available Si-immobilized scavengers of nucleophiles with loads ranging from 0.7–1.2 mmol/g.[24] Taken collectively, this represents a significant cost savings and environmental impact to the field.

Utilizing scanning electron microscopy (SEM), detailed images of the hybrid materials surface morphology were obtained. Notably, the comparison between Si-OBAC$_{50}$ **4** and the longer chained Si-OBAC$_{100}$ **5** is visually noticed by the SEM images (Figure 2).

With Si-OBAC$_{50}$ **4** in hand, the hybrid material was evaluated for the scavenging of nucleophilic species. A variety of alcohols were benzoylated to yield the corresponding esters **6a–h**, whereby excess alcohol (0.5 equivalents) was scavenged efficiently with Si-OBAC$_{50}$ **4** (Scheme 2).[25] Utilizing 1.0 equivalent of Si-OBAC$_{50}$ **4**, the desired esters **6 a–h** were isolated in high crude purity and conversion after simple filtration thru a Celite® SPE, demonstrating the efficient ability of **4** to work as a facile scavenger without the need for conventional silica chromatography. Identical results were observed when utilizing the high-load, hybrid Si-OBAC$_{100}$ **5**, demonstrating comparable scavenging efficiency to the previously reported oligomeric OBAC derivative.[17]

Building on these results, the project was expanded to the synthesis of additional Si-ROMP hybrid reagents and scavengers. In this regard, investigations focused on the synthesis of the corresponding Si-hybrid materials Si-ODCT$_{50}$ **7** and Si-OTPP$_{50}$ **9**, synthesized via the grafting of the corresponding Nb-tagged dichlorotriazine,[14b] and Nb-tagged triphenylphosphine (Figure 3).[14e] Utilizing the same protocol reported for the synthesis of Si-OBAC$_{50}$ **4** (Scheme 1), Si-ODCT$_{50}$ **7** (theoretical load = 2.79 mmol/g) and Si-OTPP$_{50}$ **9** (theoretical load = 1.4 mmol/g) were successfully isolated as free-flowing powders. The theoretical load of both reagents was further increased by extending the oligomeric length to 100 monomer units, yielding the corresponding materials Si-ODCT$_{100}$ **8** (3.7 mmol/g)[26] and Si-OTPP$_{100}$ **10** (2.3 mmol/g),[27] respectively.[24] Both reagents are highly favorable in comparison to commercially available immobilized silica reagents,.[24] Utilizing SEM, detailed images of **7** and **9** were obtained demonstrating once again the morphology of the hybrid materials obtained via surface-initiated ROMP off the spherical silica particles (Figure 4).

We have previously reported the versatile utilization of oligomeric dichlorotriazine (ODCT) as an efficient coupling reagent, scavenger and activator in parallel synthesis.[14b] In this regard, Si-ODCT$_{50}$ was investigated as a coupling reagent for the synthesis of amides **11a–h** from simple acids and amines under mild conditions (Scheme 3).

The desired amides **11 a–h** were efficiently coupled together utilizing Si-ODCT$_{50}$ **7** in high conversion and crude purity without the need for standard chromatography. It is key to note that Si-ODCT$_{50}$ **7** demonstrated the same efficiency in comparison to the soluble oligomeric version ODCT for the formation of amides.[28]

In conclusion, the combination of Nb-tagged silica particles and functionalized Nb-tagged monomers efficiently yields high-load, hybrid Si-ROMP reagents. A catalyst-armed surface (CAS)-initiated polymerization was key to functionalization of units off the silica particle surface. Utilizing this technology, a high load Si-ROMP derived bis-acid chloride (Si-OBAC) scavenger was successfully synthesized and utilized in batch. Additionally, high-load, Si-ROMP-derived dichlorotriazine (Si-ODCT) and triphenylphosphine (Si-OTP) were readily prepared. SEM imaging was utilized to demonstrate the successful grafting of the corresponding oligomer and the inherent morphology of the hybrid materials. Current efforts are focusing on the application and utilization of high load Si-ROMP reagents in parallel synthesis and continuous flow-through protocols for in-line purification and diversification of small molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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19. A variety of metathesis catalyst were investigated, including $[(PCy_3)_2(Cl)_2Ru{=}CHPh$; cat-**A**], $[(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; cat-**B**], and the Hoveyda-Grubbs 2nd-generation catalyst. In all cases studied, cat-**B** was ideal in both thermal stability and initiation rate.

20. Si-OBAC$_{50}$ denotes the inorganic surface [Si], followed by the ROMP-derived oligomer grafted [OBAC], followed by the theoretical number of Nb monomer units grafted.

21. We have previously found that there is a good correlation between the mol % of Grubbs catalyst added and the Gaussian distribution of oligomers formed, which is the case with several other oligomers formed [see ref 5d]. We have made these reagents several times with good reproducibility and consistency. MALDITOF and/or GPC data are normally attained on all oligomers; however, both methods have failed to give good results for previously published reactive oligomers.

22. Control reaction was run with activated silica, 50 eq. of OBAC monomer in CH_2Cl_2 (0.8 M) for 30 mins. After such time, the resulting crude mixture did not gel as observed for Si-OBAC hybrid materials and was instead isolated via precipitation in Et_2O.

23. OBAC load stated as mmol/g of acid chloride (ROCl) and further details are reported in ref 17. For load calculation see supplementary information S4.

24. www.biotage.com, www.silicycle.com and www.fluorous.com (June 2010).

25. In comparison to their soluble variants (OBAC, ref 17 and ODCT ref 14b) under identical conditions no difference in reaction stoichiometry and kinetics was observed. Currently there is no commercially available silica immobilized *bis*-acid chloride variant for direct comparison, however, Si-ROMP reagents reported within this manuscript produced similar conversions/yields under identical conditions to their soluble variants (OBAC and ODCT).

28. For comparison to reported uses of silica-immobilized dichlorotriazine see: Kowalski JA, Leonard SF, Lee GE Jr. J Comb Chem. 2006; 8:774–779. [PubMed: 16961413]

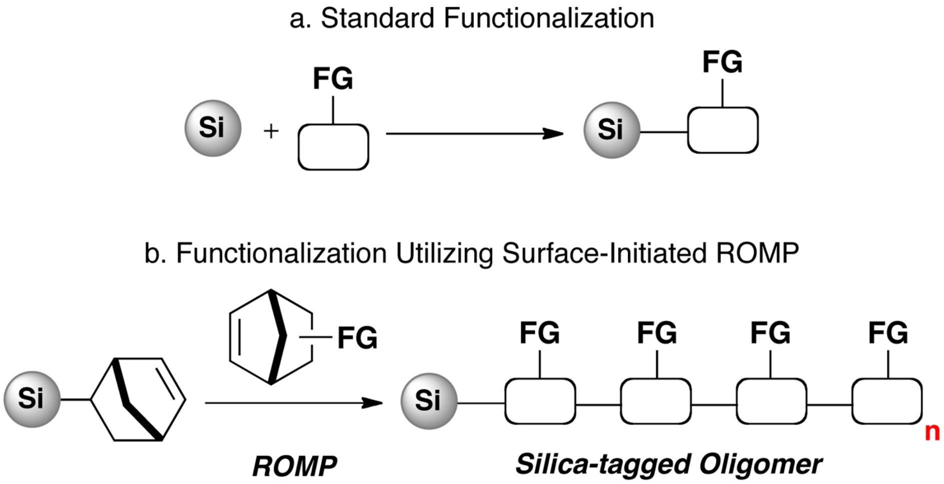


Figure 1.

a). Standard functionalization of silica reagents. b). Functionalization of Nb-tagged silica particles utilizing surface-initiated ROM polymerization.

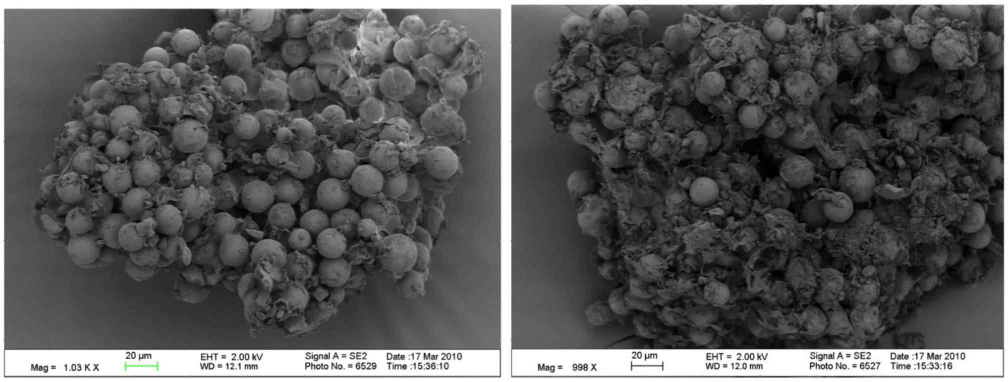


Figure 2.

SEM images of Si-OBAC$_{50}$ **4** 50-mer (left) and Si-OBAC$_{100}$ 100-mer **5** (right).

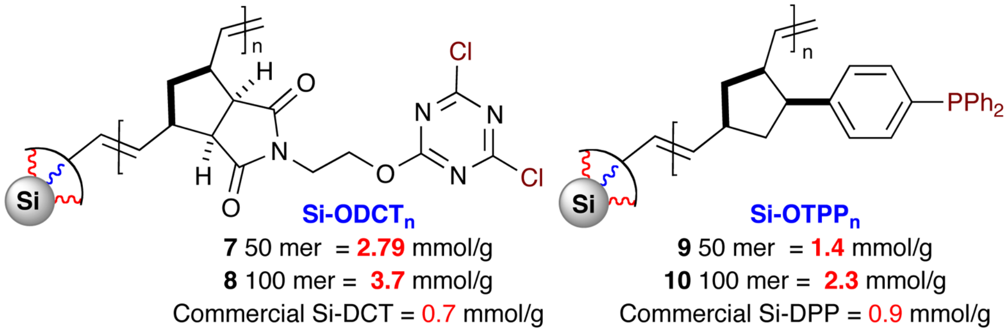


Figure 3.

Synthesis of silica-grafted oligomeric dichlorotriazine **7** and **8** (Si-ODCT$_{50}$) and triphenylphosphine **9** and **10** (Si-OTTP$_{50}$).

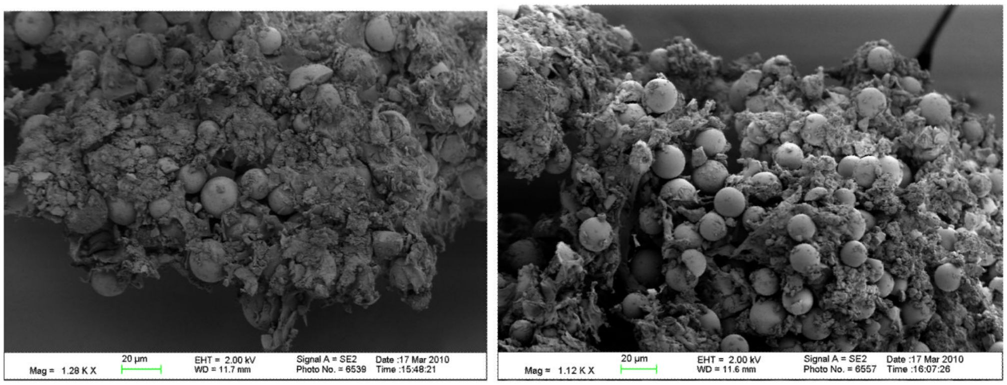
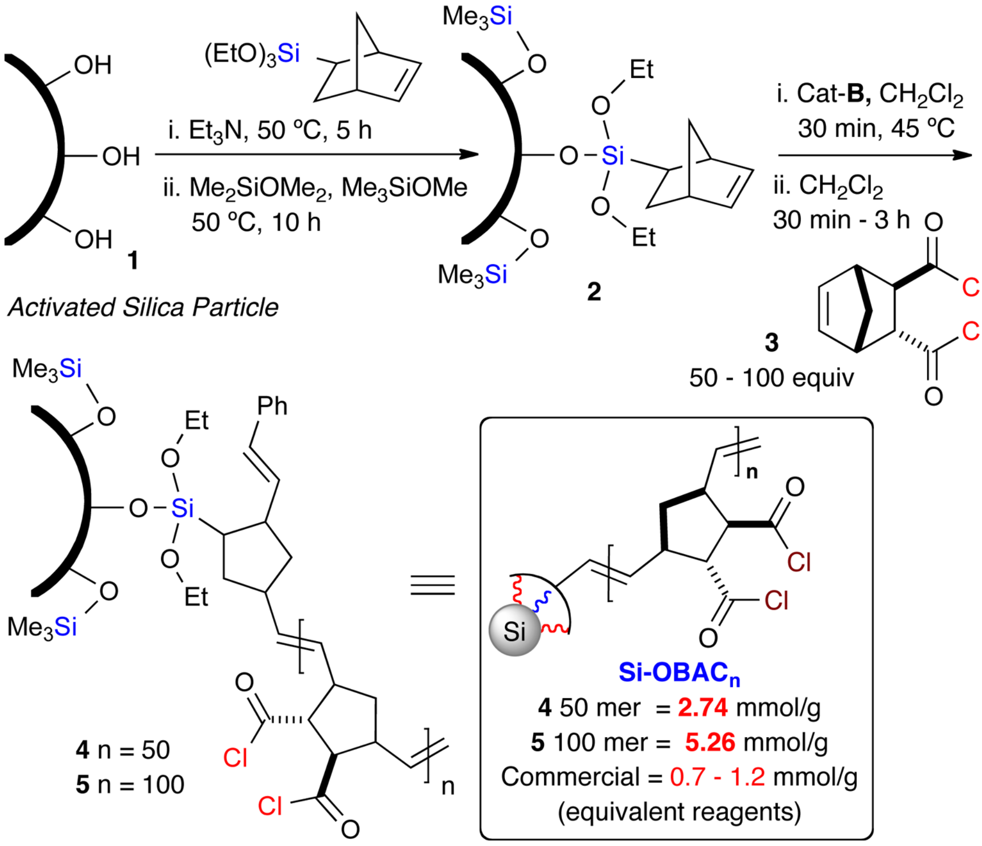


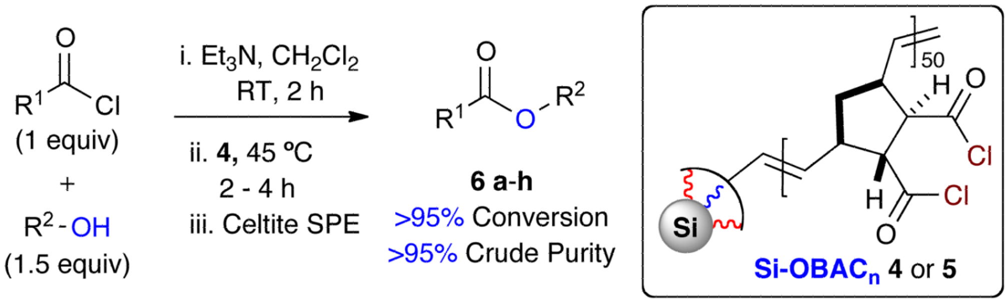
Figure 4.

SEM images of Si-ODCT$_{50}$ 50 mer **7** (left) and (b) Si-OTPP$_{50}$ 50 mer **9** (right).

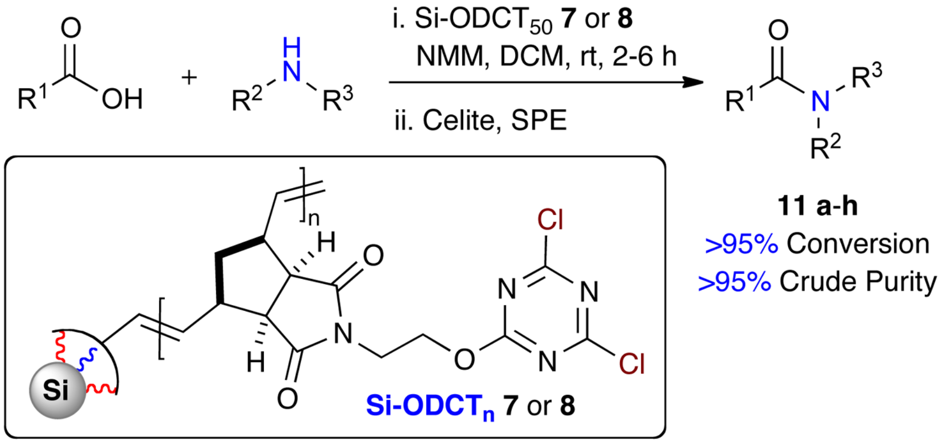


Scheme 1.

Synthesis of silica-grafted oligomeric bis-acid chloride **4** and **5** (Si-OBAC)



Scheme 2.
Benzoylation reactions utilizing Si-OBAC$_{50}$ **4** to scavenge excess alcohol.



Scheme 3.
Amide coupling reactions utilizing Si-ODCT.