

# Synthesis of High-Load, Hybrid Silica-Immobilized Heterocyclic Benzyl Phosphate (Si–OHBP) and Triazolyl Phosphate (Si–OHTP) Alkylating Reagents

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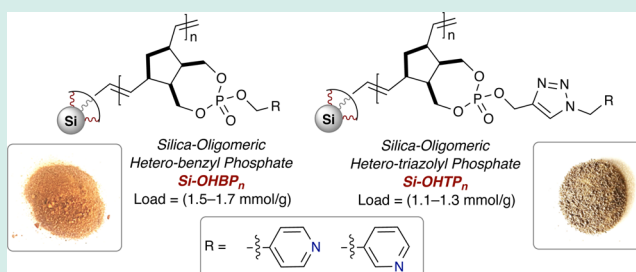
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**S** Supporting Information

**ABSTRACT:** The development of new ROMP-derived silica-immobilized heterocyclic phosphate reagents and their application in purification-free protocols is reported. Grafting of norbornenyl norbornenyl-functionalized (Nb-tagged) silica particles with functionalized Nb-tagged heterocyclic phosphate monomers efficiently yield high-load, hybrid silica-immobilized oligomeric heterobenzyl phosphates (Si–OHBP) and heterotriazolyl phosphates (Si–OHTP) as efficient alkylation agents. Applications of these reagents for the diversification of N-, O-, and S-nucleophilic species, for efficient heterobenzylation and hetero(triazolyl)methylation have been validated.

**KEYWORDS:** silica-immobilized reagents, ROMP reagents, alkylating agents, heterobenzylation, hetero(triazolyl)methylation



Heterocycles are prevalent in small molecule drugs and natural compounds<sup>1</sup> and often they are used to manipulate structural and electronic properties of small molecules that are key to regulating molecular lipophilicity, polarity, and hydrogen bonding capacity.<sup>2</sup> Despite these attributes, introduction of N-heterocyclic functionality into core structures can be problematic in subsequent purification stages due to increased polarity and basicity in combinatorial synthesis. Immobilized reagents offer many advantages that can potentially circumvent these issues. Compared to traditional solution-phase synthesis, solid-phase techniques<sup>3</sup> have shown advantages in simplifying the purification process, especially in flow-through chemistry and automated synthesis.<sup>4</sup> As part of our program aimed at the development of immobilized reagents to facilitate synthetic pathways, we herein report the development of hybrid silica-immobilized oligomeric heterobenzyl phosphates (Si–OHBP<sub>n</sub>) and heterotriazolyl phosphate (Si–OHTP<sub>n</sub>) as efficient alkylating reagents. We envision that, these high load ring-opening metathesis polymerization (ROMP)-derived reagents are highly applicable in purification-free protocols to install heterocycles, namely pyridines and pyridine-substituted triazoles in N-, O-, and S-nucleophilic species, in the synthesis of complex molecules. In addition to these benefits, the titled Si–OHBP<sub>n</sub> and Si–OHTP<sub>n</sub> reagents are bench stable, environmental friendly, and have ease of purification via simple filtration through Celite. Furthermore, the low cost, commercial availability of the starting pyridine methanol derivatives, as compared to their corresponding

bromomethylpyridines, is another advantage that inspired us to produce the titled silica-supported phosphate analogs.

When compared to their polymeric counterparts, silica-supported reagents and scavengers have shown a number of advantages, including (i) elimination of the precipitation step and (ii) elimination of polymeric swelling. These features have inspired the recent development of a number of silica-supported reagents/catalysts, include an isocyanide reagent<sup>5</sup> developed by Diver and co-workers for the removal of ruthenium, a chiral dirhodium(II) catalyst<sup>6</sup> developed by Davies and co-workers for enantioselective carbenoid reactions, an iron BPMEN-inspired catalysts<sup>7</sup> for C–H bond functionalization and hybrid sulfonic acid catalysts<sup>8</sup> demonstrated by Jones and co-workers, a tungsten oxo alkylidene<sup>9</sup> as a highly active metathesis catalyst developed by Copéret–Schrock and co-workers, and a peracid<sup>10</sup> developed by González-Núñez and co-workers for the epoxidation of olefins.

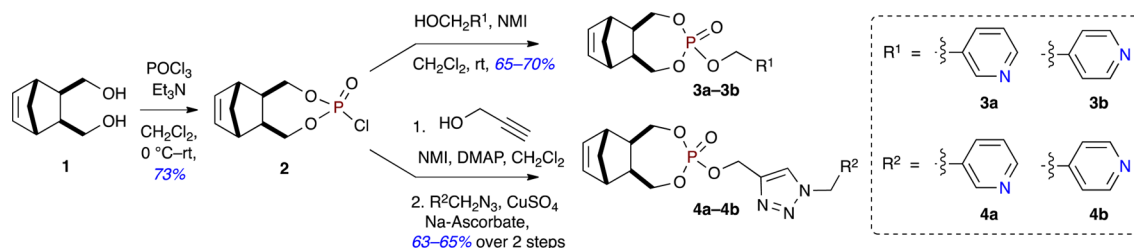
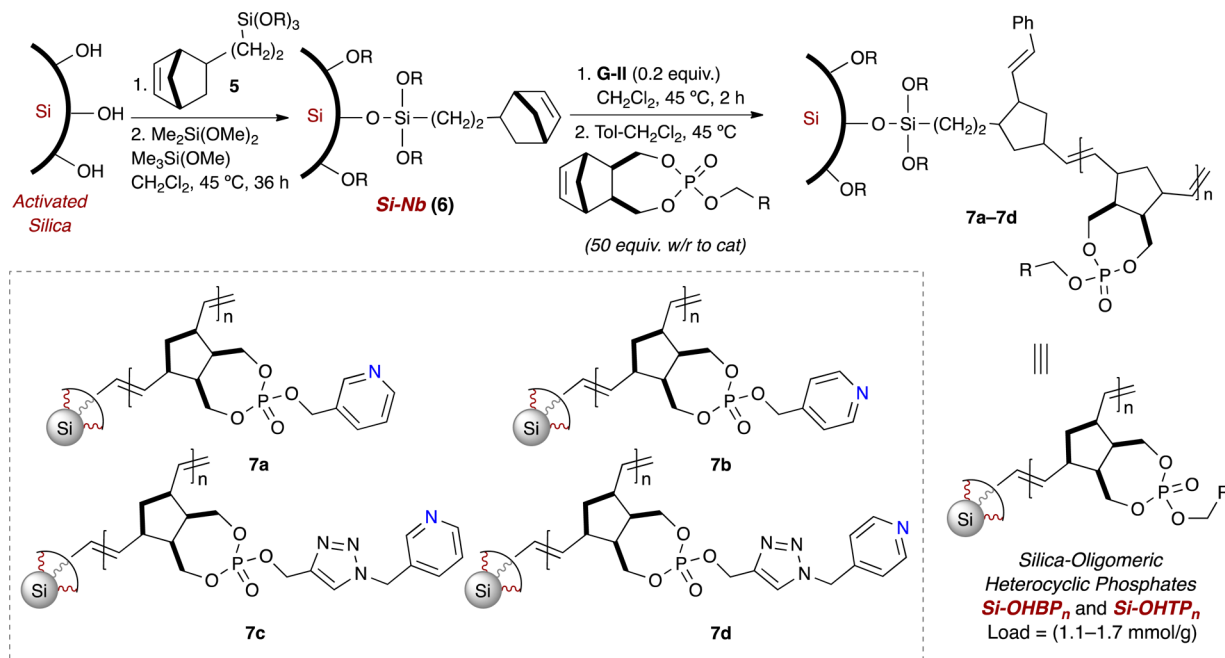
A critical part in developing successful silica-supported reagents and scavengers is to find a suitable technology to install functional groups on the surface of silica. There have been, a number of grafting methods reported for immobilized compounds, such as immobilized polystyrene resins,<sup>11</sup> silicas,<sup>12</sup> soluble polyethylene glycol (PEG) polymers,<sup>13</sup> monolith,<sup>14</sup> and fluorine-tagged compounds.<sup>15</sup> In particular, using ring-opening metathesis polymerization (ROMP) to attach functional groups

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Scheme 1. Synthesis of Hetero-benzyl and Hetero-triazole Phosphate Monomers

Scheme 2. Synthesis of Silica-Supported Oligomeric Hetero-benzyl (Si-OHBP<sub>n</sub>) and Hetero-triazole (Si-OHTP<sub>n</sub>) Phosphates

on Nb-tagged silica core, have been proven to be an efficient method to bring high-loading functionality on cost-effective and environmentally benign silica particles.<sup>16</sup> A number of ROMP-derived Si-supported reagents have been developed, including oligomeric bis-acid chloride Si-OBAC<sub>50</sub> as scavenger,<sup>17</sup> dichlorotriazine Si-ODCT<sub>50</sub> as a coupling reagent,<sup>17a</sup> and triphenylphosphine Si-OTPP<sub>50</sub>.<sup>17a</sup> Recently, our group has reported silica-immobilized benzyl phosphate Si-OBP<sub>n</sub> and triazole phosphate Si-OTP<sub>n</sub> as efficient alkylating reagents.<sup>18</sup> Taken collectively, these examples have showcased the synthesis of high-load, ROMP-derived silica-immobilized reagents and their utilization in a variety of organic reactions.

The route to the titled phosphates began with reduction of *exo*-norbornenyl carbic anhydride (readily derived from commercially available *endo*-norbornenyl carbic anhydride)<sup>19</sup> to the corresponding diol using LiAlH<sub>4</sub>, followed by phosphorylation of the norbornenyl (Nb) *exo*-diol **1** using freshly distilled POCl<sub>3</sub> and Et<sub>3</sub>N, to afford the Nb-phosphorochloridate **2** as a white solid in 73% yield (Scheme 1). This reagent was conveniently stored up to several months as a solid over argon in a desiccator for use in preparing various phosphate monomer analogs. Addition of **2** into a solution containing heterobenzyl alcohol, NMI, and CH<sub>2</sub>Cl<sub>2</sub> at room temperature cleanly afforded heterobenzyl phosphates **3a–3b** in good yields (65–70%). Similarly, phosphorylation of Nb-tagged phosphorochloridate **2** with propargyl alcohol, followed by a “click”-capture event of an azidomethylpyridine, afforded

the corresponding heterobenzyl triazole phosphate monomers **4a–4b** in good yields (63–65% over two steps).

Utilizing a similar protocol reported in our previous work,<sup>17a</sup> we tagged activated silica (60 Å, 20 μm particle size) with (MeO)<sub>3</sub>Si-(CH<sub>2</sub>)<sub>2</sub>-(Nb) **5**, and the unreacted hydroxyl groups were capped with trimethoxymethylsilane and dimethoxydimethylsilane (Scheme 2). Using this method, we obtained Nb-tagged silica particles (Si-Nb) **6** in gram-scale quantities with 0.3–0.4 mmol/g loading (determined using a bromine titration method).<sup>20</sup> It should be noted that we observed an increased norbornene loading of Si-Nb when (MeO)<sub>3</sub>Si-(CH<sub>2</sub>)<sub>2</sub>-(Nb) [(2-(bicyclo[2.2.1]hept-5-en-2-yl)ethyl)trimethoxysilane] was utilized, as compared to using bicyclo[2.2.1]hept-5-en-2-yltriethoxysilane.

With these Nb-tagged silica particles in hand, surface-initiated polymerization of Nb-tagged phosphate monomers **3a–3b** and **4a–4b** onto the silica surface was achieved using the Grubbs second-generation catalyst (G-II), followed by washing with CH<sub>2</sub>Cl<sub>2</sub>, to furnish the desired silica-tagged heterocyclic phosphates as free-flowing solids possessing experiment loads of 1.1–1.7 mmol/g (Scheme 2).<sup>17</sup> Gram-scale syntheses were next carried out for both Si-ROMP heterobenzylating (Si-OHBP<sub>n</sub>) and hetero(triazolyl)-methylating (Si-OHTP<sub>n</sub>) reagents, **7a–7b** and **7c–7d**, respectively. The SEM images of Si-OHBP<sub>n</sub> and Si-OHTP<sub>n</sub> are shown in Figure 1 and depict grafting of the corresponding

monomer onto the silica surface and the inherent morphology of the new hybrid Si-ROMP materials.

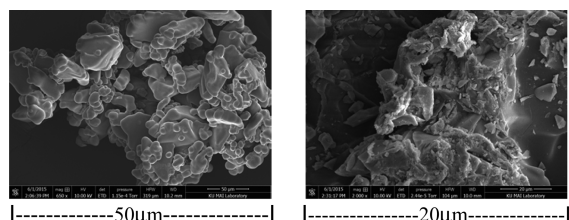


Figure 1. SEM images of Si-OHBP<sub>n</sub> (left) and Si-OHTP<sub>n</sub> (right).

With the hybrid Si-ROMP materials in hand, efforts were focused on utilization of Si-OHBP<sub>n</sub> **7a–7b** as heterobenzylating reagents. After investigating various reagent stoichiometry an optimized condition was established by using nucleophiles (1 equiv), Si-OHBP<sub>n</sub> (1.5 equiv), Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv), and NaI (0.2 equiv) in 0.1 M THF at 80 °C (oil bath temperature) in a sealed pressure tube. With these optimized conditions, the heterobenzylation of a variety of N-, O-, and S- nucleophiles was achieved using two silica oligomeric heterobenzyl phosphates (Si-OHBP<sub>n</sub>, **7a–7b**) (Table 1). Various phenols and thiophenols, as well as more complex sulfonamides were successfully alkylated to afford the corresponding heterobenzylated products **8a–8i** (Table 1). In all cases, simple filtration through a Celite SPE allowed the products to be isolated in

good to excellent yields (70–99%) and desired crude purity (>90%, calculated by UV area percent from HPLC analysis).

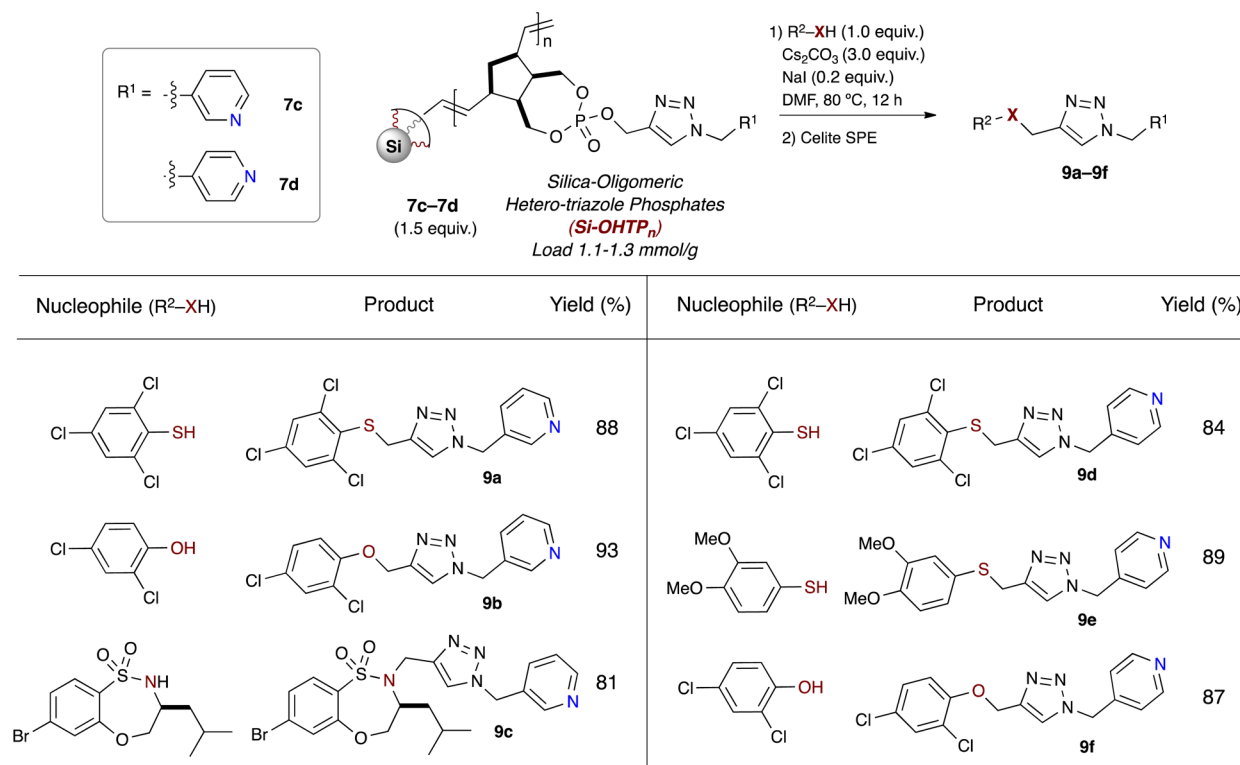
With these results in hand, silica-immobilized triazoly phosphate derivatives **7c–7d** were synthesized on gram scale having load of 1.1–1.3 mmol/g as free-flowing powders. Utilization of these reagents in nucleophilic substitution reactions with N-, O-, and S-nucleophiles afforded (triazolyl)-methylated products **9a–9f** in excellent yield (81–93%) and purities (>90%, calculated by UV area percent from HPLC analysis) using simple filtration through a Celite SPE (Table 2).

Efforts to expand the scope of these reagents in multi-component reactions (one-pot processes) toward drug-related heterocycles, and improvement in scale-up are continued for further applications in diversity-oriented synthesis. These efforts and corresponding results will be reported in due course.

Grafting of Nb-tagged silica particles with functionalized Nb-tagged heterocyclic phosphate monomers using ROM polymerization efficiently yields high-load, hybrid Si-immobilized oligomeric heterobenzyl (Si-OHBP<sub>n</sub>) and triazolyl phosphates (Si-OHTP<sub>n</sub>). Further application of these ROMP-derived oligomeric heterocyclic phosphate reagents have been demonstrated for diversification of various N-, O-, and S-nucleophilic species, for efficient heterobenzylation and (triazolyl)-methylation in purification-free protocols. Further applications of these Si-ROMP reagents in one-pot protocols and in diversification of core scaffolds for the synthesis of drug-like molecules is underway and will be reported in due time.

Table 1. Hetero-benzylation of N-, O-, and S-Nucleophiles Utilizing Si-OHBP<sub>n</sub>

Nucleophile (R <sup>2</sup> -XH)	Product	Yield (%)	Nucleophile (R <sup>2</sup> -XH)	Product	Yield (%)
		97			99
		72			84
		70			96
		97			72
		97			

Table 2. Hetero-(triazolyl)methylation of N-, O-, and S-Nucleophiles Utilizing Si-OHTP<sub>n</sub>

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00042.

Experimental details and NMR spectral data for new compounds (PDF)

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### Notes

The authors declare the following competing financial interest(s): P.R.H. is on the Scientific Advisory Board of Materia, Inc.

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