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Silica-Supported Oligomeric Benzyl Phosphate (Si-OBP) and Triazole Phosphate (Si-OTP) Alkylating Reagents

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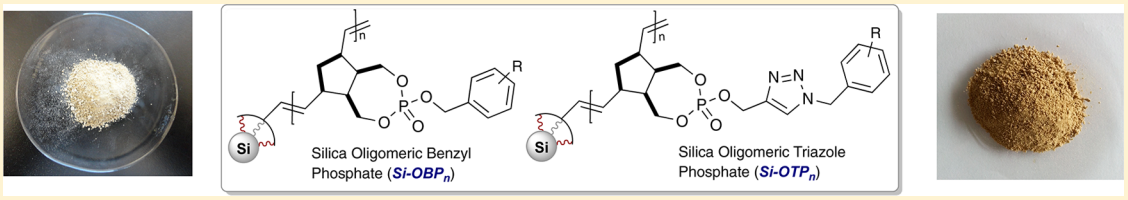
Supporting Information



ABSTRACT: The syntheses of silica-supported oligomeric benzyl phosphates (Si-OBP$_n$) and triazole phosphates (Si-OTP$_n$) using ring-opening metathesis polymerization (ROMP) for use as efficient alkylating reagents is reported. Ease of synthesis and grafting onto the surface of norbornenyl-tagged (Nb-tagged) silica particles has been demonstrated for benzyl phosphate and triazole phosphate monomers. It is shown that these silica polymer hybrid reagents, Si-OBP$_n$ and Si-OTP$_n$, can be used to carry out alkylation reactions with an array of different nucleophiles to afford the corresponding benzylated and (triazolyl)methylated products in good yield and high purity.

INTRODUCTION

The need to rapidly synthesize a wide variety of small molecules in the desired quantities with high purities and yields is an important challenge facing drug discovery and developmental chemistry.[1] To help address this need, immobilized reagents and scavengers have been developed to provide ease of synthesis and to eliminate time-consuming chromatographic separation protocols. These reagents have found frequent use in the arena of facilitated synthesis and high-throughput chemistry,[2,3] as well as in the scale-up of advanced pharmaceutical intermediates.[4] Given the large range of chemistries and conditions in which they need to be employed as reagents, scavengers, or catalysts, the field has seen a number of new innovations regarding immobilized polystyrene resins,[5] silicas,[6] soluble polyethylene glycol (PEG) polymers,[7] and monolith[8] and fluorous-tagged compounds[9] to remove impurities or excess reagents from reaction mixtures. Some of the more recent developments reported include silica-supported isocyanide ligands for scavenging ruthenium,[10] mesocellular silica-supported boronic acids as direct amidation catalysts,[11] silica-supported rhodium catalysts,[12] *N*-heterocyclic carbenes,[13] palladium and copper(I) catalysts,[14] phosphines,[15] and prolinol as well as TADDOLs.[16] However, for all of their advantages immobilized reagents are often limited by several factors, including (i) low load levels, (ii) heterogeneous reaction kinetics and nonsurface diffusion-controlled processes, (iii) immobilized reagent swelling, and (iv) poor solvent tolerance. While some of these issues have been addressed through the development of technologies such as microgels, Janda-gels, and microporous resins,[3] there is still a need for additional materials that can deliver the performance of solution-phase reagents with the ease of removal (via filtration, precipitation, extraction, etc.) afforded by their immobilization.

We have previously examined a variety of soluble, high-load, oligomeric reagents and scavengers derived through the use of ring-opening methathesis polymerization (ROMP) of functionalized norbornene and 7-oxanorbornene monomers.[17] These materials, known as ROMPgels, build on the pioneering efforts of Barrett,[18] Buchmeiser,[19] Bolm,[20] and others,[21] and they have effectively been used to mediate a number of chemical reactions. However, while these ROMPgel materials have the advantage of behaving equivalently to traditional homogeneous reagents and catalysts, they are generally removed from solution via precipitation, which can limit their use in pharmaceutical applications.

As a result, inspired by the seminal work of Buchmeister and co-workers,[22] efforts were focused on the synthesis and study of a number of hybrid materials that graft several of the ROMPgel materials onto the surface of silica particles.[23] Through this grafting process, the resulting immobilized ROMP reagents can be removed from solution by simple filtration, thus eliminating the precipitation step. In this fashion, silica-supported ROMPgel acid chloride, dichlorotriazine, and triphenylphosphine reagents were generated with properties nearly identical

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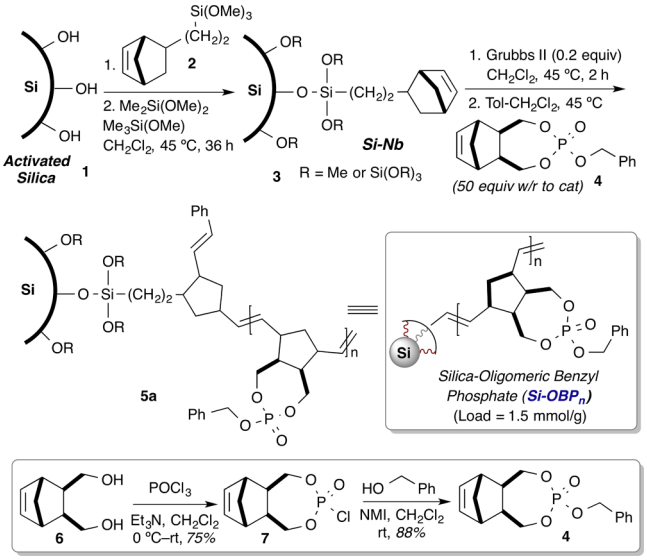
to those of the equivalent soluble ROMPgel oligomeric reagents.[23]

We herein describe our efforts to expand the family oligomeric materials that have been grafted onto silica to include ROMP-derived oligomeric benzyl phosphate (OBP_n) and triazole phosphate (OTP_n), which we previously reported as soluble alkylating reagents that were used in facilitated library generation.[24] Benzylation and triazolation are useful diversification reactions in medicinal chemistry, high-throughput chemistry, and diversity-oriented synthesis (DOS).[25] The benzylation of amines and alcohols also serves as one of the most utilized protecting group strategies in organic synthesis due to its easy incorporation and removal.[26] While these uses have spurred development of a number of alternative approaches to benzylation[27] and triazolation, we believe the generation of the analogous silica-oligomeric benzyl phosphate (Si-OBP_n) and triazole phosphate (Si-OTP_n) reagents could find efficient, safe, and cost-effective applications in chemical synthesis and library production. Key advantages of these reagents, include (i) their stability at room temperature (ii) safety in handling when compared to commercially available benzyl bromides or iodides, and (iii) ease of purification via simple filtration through Celite.

RESULTS AND DISCUSSION

Initial efforts centered on the synthesis of the silica-grafted oligomeric benzyl phosphate reagent, as outlined in Scheme 1,

Scheme 1. Synthesis of Silica-Supported Oligomeric Benzyl Phosphate (Si-OBP_n)



using a modification of the procedure reported by Buchmeiser.[28] The activated silica **1** (60 Å, 20 μm) was tagged with commercially available norbornene silyl reagent [$(MeO)_3Si-(CH_2)_2-Nb$ (**2**)] followed by capping with trimethoxymethylsilane and dimethoxydimethylsilane to afford the norbornene-functionalized silica (Si–Nb) **3** (Scheme 1). It was observed that the use of $(MeO)_3Si-(CH_2)_2-Nb$ (**2**) dramatically increased the norbornene load of Si–Nb (**3**), compared to 5-(bicycloheptenyl)-triethoxysilane [$Nb-Si(OEt)_3$], which was previously used for silica tagging.[23] By this optimized method, we prepared norbornene-functionalized silica **3** (Si–Nb) on gram scale with a 0.4 mmol/g loading (determined by a modified bromine titration method).[29] With this Si-tagged nanoparticle (**3**) in hand, a metathesis catalyst-armed surface-initiated polymerization was established using the C848 [Grubbs second generation catalyst, **G-II**][30] (20 mol %, based on Si–Nb load) in CH_2Cl_2 and toluene as solvents, followed by addition of the Nb-tagged benzyl phosphate monomer **4** to rapidly generate the desired hybrid material **5a**, silica oligomeric benzyl phosphate (Si-OBP_n). The benzyl phosphate monomer **4** was itself easily synthesized in good yield and purity according to previously reported methods.[24a] Norbornene *exo*-diol **6** was reacted with $POCl_3$ and Et_3N in the presence of catalytic DMAP to generate the Nb-tagged monochlorophosphate compound **7** in moderate yields as a white solid (Scheme 1). This material was then reacted with benzyl alcohol in NMI, and CH_2Cl_2 at room temperature to yield **4**. The scale-up synthesis of the monomeric reagent, as well as Si-OBP_n, have been carried out on gram scale as stable, free-flowing powders. The SEM images of Si-OBP_n and Si-OTP_n silica hybrid materials demonstrate the grafting of the corresponding monomer on the silica surface and inherent morphology of hybrid materials (Figure 1).

The utilization of silica oligomeric benzyl phosphate **5a** (Si-OBP_n) for benzylation with various *N*-, *O*-, *S*- nucleophiles, including anilines, amines, phenols, thiols, and sulfonamides (Table 1), was next examined. The reactions were carried out in a sealed pressure tube with different nucleophiles (1 equiv), Si-OBP_n (1.5 equiv), Cs_2CO_3 (3.0 equiv), and NaI (0.2 equiv) in THF at 80 °C (oil bath temperature) to yield the products after simple filtration via Celite-SPE to remove the Si-phosphate byproduct. The corresponding benzylated analogs (**8a–8h**) were isolated in excellent purities (>90%, determined by LC-MS) and yields. We have screened wide varieties of nucleophiles for benzylation. Initially, a variety of amines and phenols (Table 1, entries 1–4) were utilized and then extended to thiophenols and sulfonamides (Table 1, entries 5–8) to yield (>90%) the benzylated products.

With these results in hand, an expanded set of Si-OBP_n derivatives were next examined (Figure 2). These high load reagents (**5b–5d**) were synthesized in an analogous fashion to

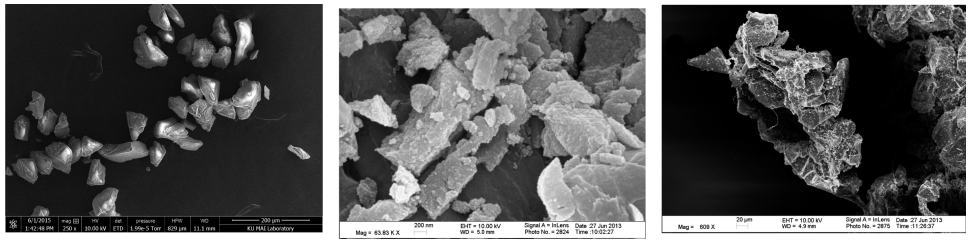


Figure 1. SEM images of Si–Nb (left), Si-OBP_n (middle), and Si-OTP_n (right).

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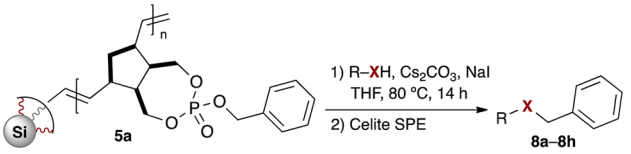
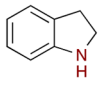
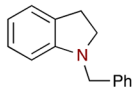
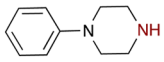
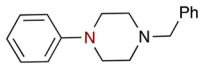
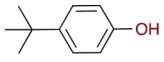
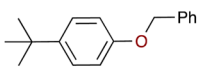
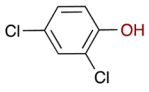
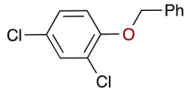
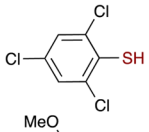
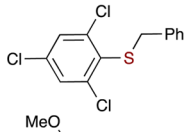
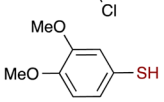
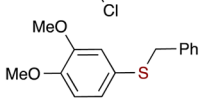
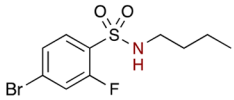
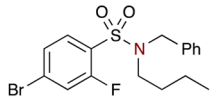
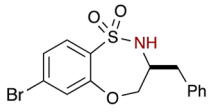
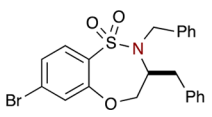
Table 1. Benzylation of *N*-, *O*-, and *S*-Nucleophiles Utilizing Si-OBP$_n$

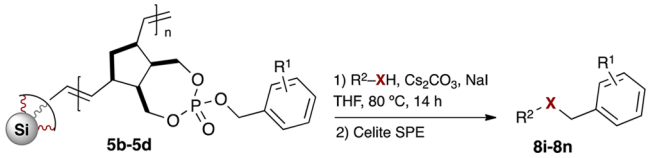


Entry	Nucleophile	Pdt		Yield (%)
1			**8a**	97
2			**8b**	95
3			**8c**	97
4			**8d**	98
5			**8e**	98
6			**8f**	98
7			**8g**	99
8			**8h**	97`

the Si-OBP$_n$ reagent in Scheme 1 and were also obtained on gram scales as free-flowing powders. Utilization of these reagents in substitution reactions with *O*- and *S*-nucleophiles were next carried out to afford benzylated products (**8i–8n**) in good yields (>90%) and excellent purity after Celite-SPE filtration (Table 2). Diversification of the Si-OBP$_n$ reagents via substituting electron-withdrawing groups, as well as electron-donating groups, on the aryl moiety were next examined, and in all cases, analogous results to Table 1 were obtained (see Table 2).

Attention was next placed on the gram-scale generation of silica oligomeric triazole phosphate hybrid reagents (Si-OTP$_n$). Triazoles and their derivatives have demonstrated a wide variety of biological activity, with many reports focusing on antifungal activity.[31] We previously reported soluble oligomeric triazole phosphates to construct a wide array of triazole-

Table 2. Benzylation of *N*-, *O*-, and *S*-Nucleophiles Utilizing Various Si-OBP$_n$ Analogs



entry	Si-OBP$_n$	nucleophile	Pdt	yield (%)
1	**5b**	2,4-Cl-PhOH	**8i**	98
2	**5b**	2,4,6-Cl-PhSH	**8j**	94
3	**5c**	2,4-Cl-PhOH	**8k**	96
4	**5c**	2,4,6-Cl-PhSH	**8l**	95
5	**5d**	2,4-Cl-PhOH	**8m**	98
6	**5d**	2,4,6-Cl-PhSH	**8n**	94

containing compounds. Silica-immobilized oligomeric triazole phosphate **10a** (Si-OTP$_n$) was synthesized via grafting of the Nb-tagged benzyl triazole phosphate monomer **9** onto the surface of norbornene-functionalized silica (Si–Nb) **3** through the same protocol discussed for the synthesis of Si-OBP$_n$ in Scheme 1. The product, **10a** (Si-OTP$_n$), was isolated as a free-flowing solid in high-load (1.15 mmol/g) (Scheme 2). The triazole phosphate monomer **9** was synthesized in good yield and purity according to previously reported methods.[24] Phosphorylation of propargyl alcohol with Nb-tagged phosphonyl chloride **7**, followed by a "Click"-capture event of the corresponding azide, yields the desired monomer **9** in an efficient fashion (Scheme 2). The triazole phosphate monomer and silica oligomeric triazole phosphate reagents (Si-OTP$_n$) have been synthesized on gram scale as stable, free-flowing solids.

With Si-OTP$_n$ **10a** in hand, the hybrid material was evaluated for (triazolyl)methylation on various nucleophiles including amines, phenols, thiophenols, and sulfonamides in good yields and high purity with chromatography-free purification. The reaction was carried out in a pressure tube with different nucleophiles (1 equiv), Si-OTP$_n$ (1.5 equiv), Cs_2CO_3 (3.0 equiv), and NaI (0.2 equiv) in DMF at 90 °C for overnight. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite to give the corresponding (triazolyl)-methylated products. Optimal results were achieved in DMF compared to THF. A variety of *N*-, *O*-, *S*-nucleophiles were utilized for nucleophilic substitution reactions with the Si-OTP$_n$ triazolating reagent giving the (triazolyl)methylated products (**11a–11g**) in excellent yield and high purity (>85%, determined by LC-MS) (Table 3). In all cases, similar results (Table 3) were obtained as compared to Si-OBP$_n$ in THF in Table 1.

Building on these results, the project was expanded to the synthesis of additional variants of Si-OTP$_n$ hybrid reagents (**10b–10d**, Figure 3) on gram scales as free-flowing powders in an analogous fashion to the Si-OTP$_n$ reagent in Scheme 2.

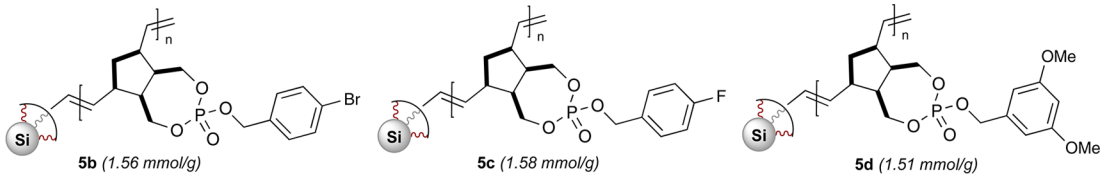


Figure 2. Various silica-supported oligomeric benzyl phosphate (Si-OBP$_n$) analogs.

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Scheme 2. Synthesis of Silica-Supported Oligomeric Triazole Phosphate (Si-OTP$_n$)

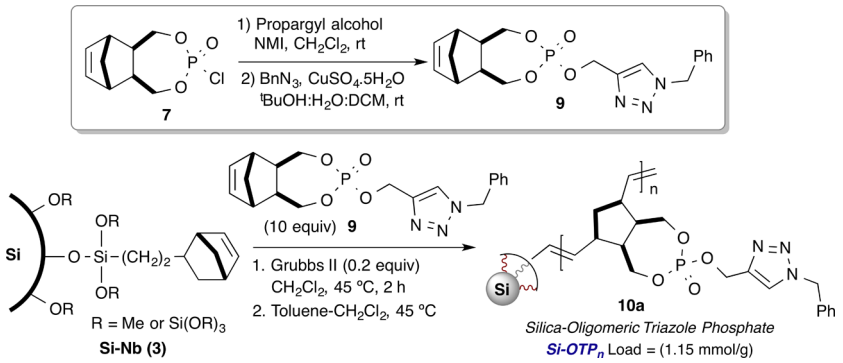
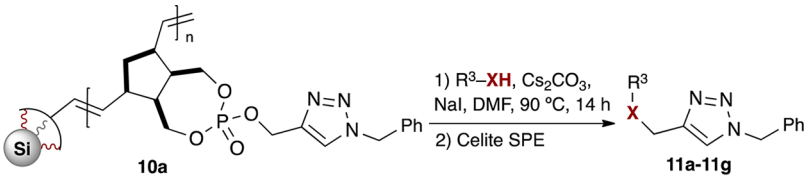
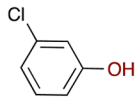
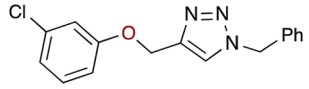
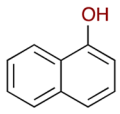
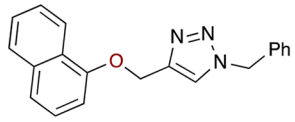
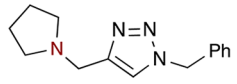
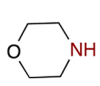
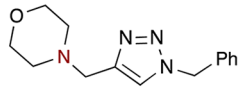
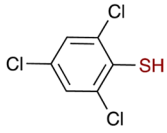
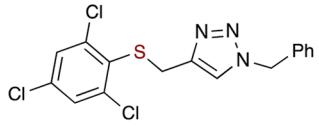
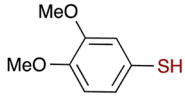
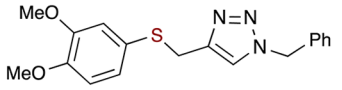
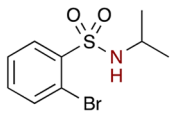
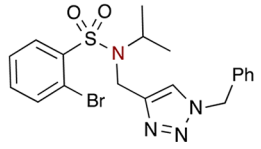


Table 3. Triazolation Utilizing Si-OTP$_n$ with *O*-, *N*-, and *S*-Nucleophiles



Entry	Nucleophile	Pdt		yield (%)
1			**11a**	91
2			**11b**	90
3			**11c**	84
4			**11d**	83
5			**11e**	92
6			**11f**	94
7			**11g**	89

These Si-OTP$_n$ hybrid reagents were utilized for (triazolyl)-methylation of *O*- and *S*-nucleophiles. In all cases, (triazolyl)-methylated products (**11h**–**11m**) were isolated in excellent yield and high purity after passing through a Celite SPE (Table 4).

In conclusion, the combination of Nb-tagged silica particles and functionalized Nb-tagged monomers efficiently yields high-load, hybrid Si-ROMP benzylating and (triazolyl)methylating reagents. A metathesis catalyst-armed surface (CAS)-initiated polymerization was key to functionalization of units off the silica particle surface. With this technology, we developed Si-immobilized oligomeric benzyl phosphate (Si-OBP$_n$) as a benzylating reagent and triazole phosphate (Si-OTP$_n$) as a (triazolyl)methylating reagent on gram scale as stable, free-

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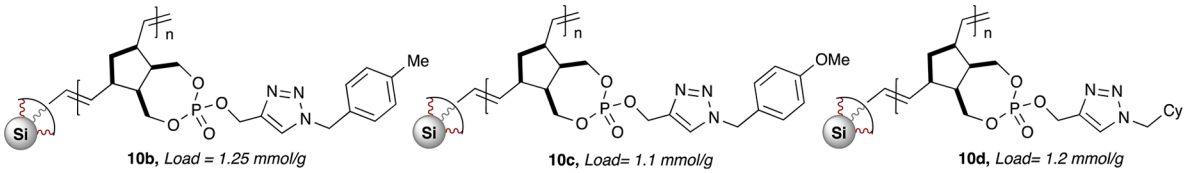
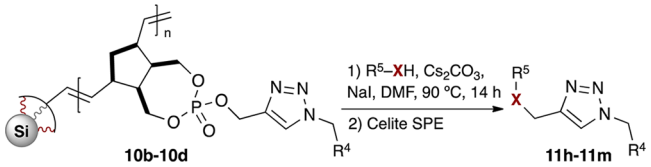


Figure 3. Various silica-supported oligomeric triazole phosphate (Si-OTP$_n$) analogs.

Table 4. Triazolation of *N*-, *O*-, and *S*-Nucleophiles Utilizing Various Si-OTP$_n$ Analogs



entry	Si-OTP$_n$	nucleophile (R^5–XH)	Pdt	yield (%)
1	**10b**, R^4 = 4-MePh	4-Br-PhOH	**11h**	85
2	**10b**, R^4 = 4-MePh	2,4,6-Cl-PhSH	**11i**	87
3	**10c**, R^4 = 4-OMePh	4-Br-PhOH	**11j**	89
4	**10c**, R^4 = 4-OMePh	2,4,6-Cl-PhSH	**11k**	86
5	**10d**, R^4 = cyclohexyl	4-Br-PhOH	**11l**	86
6	**10d**, R^4 = cyclohexyl	2,4,6-Cl-PhSH	**11m**	88

flowing powders in all cases, utilizing ROMP of Nb-tagged phosphate monomers. SEM imaging was utilized to demonstrate the successful grafting of the corresponding oligomer and the inherent morphology of the hybrid materials. Utilization of these reagents for representative small molecule synthesis, under purification free protocols, was demonstrated to afford corresponding products in excellent yield and with high purity. Since benzylation is a key transformation in many synthetic processes, we are currently working on expanding the scope of nucleophiles (i.e., alcohols, *bis*-nucleophilic, etc.), as well as the scale on which these transformations can be carried out.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere. Stirring was achieved with oven-dried magnetic stir bars. Et_2O and CH_2Cl_2 were purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518−1520). $CHCl_3$ was passed through basic alumina and dried over molecular sieves. Et_3N was purified by passage through basic alumina or distilled over CaH_2 and stored over KOH. For Celite-SPE, 6 mL empty cartridges were used. All the solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using silica gel (300−400 mesh) with the indicated solvents. Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 or 500 MHz (^{1}H NMR) and 100 or 125 MHz (^{13}C NMR) spectrometers using $CDCl_3$ as the solvent and TMS as the internal standard. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and number of protons. High-resolution mass spectra were obtained using a high-resolution ESI-TOF mass spectrometer.

General Procedure for Silica Oligomeric Benzyl Phosphate (Si-OBP$_n$) and Triazole Phosphate (Si-OTP$_n$). Si−Nb (load ∼0.4 mmol/g, 1 equiv) was heated with C848 (**G-II**, 0.2 equiv) at 45 °C in dichloromethane for 2 h under argon. The OBP or OTP monomer was added (50 equiv w/r to cat. **G-II**) in CH_2Cl_2 and toluene to the reaction mixture and heated at 45 °C for overnight. The reaction mixture was cooled to room temperature and EVE was added, with stirring for an additional 1 h at room temperature. The reaction mixture was filtered and washed with a mixture of toluene/CH_2Cl_2 (1:1) and dried via high *vacuo* pump.

Procedure A: General Procedure for Different Nucleophilic Substitution with Si-OBP$_n$. In a sealed pressure tube was added Si-OBP$_n$ **5a** (1.5 equiv), followed by addition of sodium iodide (0.2 equiv), Cs_2CO_3 (3.0 equiv), and solvent THF (0.2 M). The mixture was stirred rapidly, and then nucleophiles were added. The reaction was sealed under argon and heated to 80 °C with stirring for 12 h. After such time, the reaction was cooled to rt and the crude mixture was filtered via a Celite-packed SPE and rinsed several times with a mixture of hexanes/EtOAc (1:2). The resulting eluent was concentrated *in vacuo* to yield the benzylated products in good to excellent yields and purities.

Procedure B: General Procedure for Different Nucleophilic Substitution with Si-OTP$_n$. In a pressure tube was added Si-OTP$_n$ **10a** (1.5 equiv), followed by addition of NaI (0.2 equiv), Cs_2CO_3 (3.0 equiv), and solvent DMF (0.2 M). The nucleophile was added, and the resulting mixture was stirred rapidly. The reaction was sealed under argon and heated to 90 °C w/stirring for (12−14 h), after which time DMF was removed in *vacuo*. The crude mixture was filtered via Celite-SPE and rinsed with EtOAc. The resulting eluent was then concentrated *in vacuo* to yield the products in good to excellent yields and purities.

1-(Benzyloxy)-4-(*tert*-butyl)benzene (8c). Utilizing general procedure A, **8c** (18.5 mg, 0.077 mmol, 97%) was isolated as a white solid. MP: 65 °C; FTIR (neat): 3056, 3024, 2960, 2866, 1610, 1512, 1456, 1242, 1182, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.43 (m, 2H), 7.42−7.38 (m, 2H), 7.36−7.30 (m, 3H), 6.92−6.96 (m, 2H), 5.06 (s, 2H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.6, 143.7, 137.3, 128.5 (2C), 127.9, 127.5 (2C), 126.2 (2C), 114.2 (2C), 70.0, 34.1, 31.4 (3C); GC-MS (EI$^+$) calculated for $C_{17}H_{20}O$ 240.15; found 240.1 (M$^+$ 7), 91.0 (100).[32a]

1-(Benzyloxy)-2,4-dichlorobenzene (8d). Utilizing general procedure A, **8d** (30 mg, 0.119 mmol, 98%) was isolated as a thick liquid. FTIR (neat): 3031, 2931, 2835, 1597, 1481, 1452, 1382, 1290, 1249, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.44 (m, 2H), 7.43−7.38 (m, 3H), 7.37−7.33 (m, 1H), 7.18 (dd, J = 2.6, 8.7 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.0, 136.1, 130.1, 128.7 (2C), 128.1, 127.5, 127.1 (2C), 126.0, 124.1, 114.8, 71.2; GC-MS (EI$^+$) $C_{13}H_{10}Cl_2O$ calculated 252.01; found 251.9 (M$^+$ 4), 91.0 (100).[32b]

Benzyl(2,4,6-trichlorophenyl)sulfane (8e). Utilizing general procedure A, **8e** (21 mg, 0.07 mmol, 98%) was isolated as a yellow solid. MP: 112 °C; FTIR (neat): 3087, 2935, 2850, 1583, 1454, 1321, 1116, 1054 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.37−7.33 (m, 4H), 7.32−7.39 (m, 2H), 4.15 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.3, 135.3, 132.0, 131.3, 130.6, 130.0, 129.5, 128.9 (2C), 128.8 (2C), 127.8, 37.6; GC-MS (EI$^+$) $C_{13}H_9Cl_3S$ calculated 301.95; found 301.9 (32), 169 (7), 91.0 (100).

Benzyl(3,4-dimethoxyphenyl)sulfane (8f). Utilizing general procedure A, **8f** (22 mg, 0.085 mmol, 98%) was isolated as a thick liquid. FTIR (neat): 2933, 2833, 1595, 1504, 1251, 1228, 1135, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.19 (m, 5H), 6.95 (dd, J = 8.3, 2.2 Hz, 1H), 6.0−6.74 (m, 2H), 4.02 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.7 (2C), 138.2, 129.0 (2C), 128.4 (2C), 127.0, 126.2, 125.3, 115.9, 111.3, 55.9, 55.8, 41.2;

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GC-MS (EI$^+$) $C_{15}H_{16}O_2S$ calculated 260.09; found 260.0 (32), 169 (30), 91.0 (100).

***N*-Benzyl-4-bromo-*N*-butyl-2-fluorobenzenesulfonamide (8g).** Utilizing general procedure A, **8g** (24 mg, 0.060 mmol, 99%) was isolated as a thick liquid. FTIR (neat): 3089, 3025, 2958, 2931, 1589, 1472, 1456, 1396, 1344, 1161, 1135 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (t, J = 7.70 Hz, 1H), 7.43−7.38 (m, 2H), 7.34−7.28 (m, 5H), 4.47 (s, 2H), 3.19 (t, J = 7.60 Hz, 2H), 1.35−1.29 (m, 2H), 1.16−1.11 (m, 2H), 0.76 (t, J = 7.45 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.44 ($^1J_{C-F}$ = 259 Hz), 136.1, 131.8, 128.6 (2C), 128.2 (2C), 128.0, 127.8 (3C), 120.7 (^2J = 25.0 Hz), 51.4, 47.3, 29.7, 19.7, 13.5. GC-MS (EI$^+$) $C_{17}H_{19}BrFNO_2S$ calculated 399.3; found 399.0 (M$^+$ 3), 401.2 (M+2 2), 355.8 (60), 357.8 (60), 91 (100).

(*S*)-2,3-Dibenzyl-7-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4,5]-oxathiazepine 1,1-Dioxide (8h). Utilizing general procedure A, **8h** (30 mg, 0.066 mmol, 97%) was isolated as a white solid. MP: 170 °C; FTIR (neat): 3026, 2921, 2852, 1595, 1552, 1325, 1153, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 1H), 7.33−7.28 (m, 4H), 7.25−7.19 (m, 5H), 7.17 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 7.5 Hz, 2H), 4.85 (t, J = 12.0 Hz, 1H), 4.40 (d, J = 14.3 Hz, 1H), 4.26 (dd, J = 4.5, 13.42 Hz, 1H), 4.09 (d, J = 14.6 Hz, 1H), 3.85 (m, 1H), 2.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1, 137.4, 135.2, 129.8, 130.8, 129.0 (2), 128.7 (2), 128.6 (2), 128.1 (2), 127.1 (2), 126.7, 126.4, 124.4, 73.7, 62.4, 55.2, 37.9. HRMS calculated for $C_{22}H_{20}BrNO_3SNa$ (M+Na)$^+$ 480.0245; found 480.0258 (TOF MS).

1-((4-Bromobenzyl)oxy)-2,4-dichlorobenzene (8i). Utilizing general procedure A, **8i** (29 mg, 0.088 mmol, 98%) was isolated as a yellow solid. MP: 87 °C; FTIR (neat) 3070, 2923, 2866, 1585, 1571, 1480, 1456, 1290, 1262, 1103 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.54 (m, J = 8.4 Hz, 2H), 7.40 (d, J = 2.7 Hz, 1H), 7.32−7.34 (m, 2H), 7.15−7.18 (dd, J = 8.6, 2.4 Hz, 1H), 6.85 (d, J = 8.8, 1H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.7, 135.0, 131.8 (2C), 130.1, 128.7 (2C), 127.5, 126.3, 124.1, 122.1, 114.7, 70.3. GC-MS (EI$^+$) $C_{13}H_9BrCl_2O$ calculated 329.92; found 331.9 (M+2, 2), 169 (100), 90 (25).[32b]

(4-Bromobenzyl)(2,4,6-trichlorophenyl)sulfane (8j). Utilizing general procedure A, **8j** (25 mg, 0.066 mmol, 94%) was isolated as a white solid. MP: 54 °C; FTIR (neat) 2923, 1590, 1487, 1452, 1433, 1323, 1116, 1058, 1012 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.47 (m, 3H), 7.27 (s, 1H), 7.20−7.22 (m, 2H), 4.08 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.6, 134.5, 132.4, 131.9 (2C), 131.4, 130.7, 130.5 (2C), 130.4, 129.9, 121.7, 37.1. GC-MS (EI$^+$) $C_{13}H_8Cl_3BrS$ calculated 379.86; found 379.8 (M$^+$ 5), 381.8 (M+2, 7), 169 (100), 90 (25).

2,4-Dichloro-1-((4-fluorobenzyl)oxy)benzene (8k). Utilizing general procedure A, **8k** (24 mg, 0.088 mmol, 96%) is isolated as a thick liquid. FTIR (neat) 2931, 1604, 1510, 1483, 1379, 1226, 1060, 823, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41−7.45 (m, 2H), 7.40 (d, J = 2.5 Hz, 1H), 7.15−7.18 (dd, J = 8.6, 2.5 Hz, 1H), 7.07−7.11 (m, 2H), 6.88 (d, J = 7.5, 1H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5 ($^1J_{C-F}$ = 246.5 Hz) 152.8, 131.8, 130.1, 129.1 (^3J = 8.4 Hz, 2), 127.5, 126.6, 124.2, 115.6 (^2J = 21.6 Hz, 2) 114.9, 70.5. GC-MS (EI$^+$) $C_{13}H_9Cl_2FO$ calculated 270.00; found 269.9 (M$^+$, 2), 109 (100).

4-Fluorobenzyl)(2,4,6-trichlorophenyl)sulfane (8l). Utilizing general procedure A, **8l** (21 mg, 0.065 mmol, 95%) was isolated as a thick liquid. FTIR (neat) 2933, 1600, 1505, 1433, 1323, 1228, 1116, 1058, 837 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.31−7.34 (m, 2H), 7.29 (s, 1H), 7.01−7.05 (m, 2H), 4.13 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.3, ($^1J_{C-F}$ = 247.5 Hz) 135.8, 132.3, 131.3, 131.1 ($^4J_{C-F}$ = 3.6 Hz), 130.7, 130.5 (^3J = 8.5 Hz, 2) 130.4, 129.9, 115.7 (^2J = 22.3 Hz, 2), 36.9. GC-MS (EI$^+$). $C_{13}H_8Cl_3FS$ calculated 319.94; found 319.9 (M$^+$, 5), 109 (100).

2,4-Dichloro-1-((3,5-dimethoxybenzyl)oxy)benzene (8m). Utilizing general procedure A, **8m** (28 mg, 0.089 mmol, 98%) was isolated as a yellow solid. MP: 55 °C; FTIR (neat): 2935, 2825, 1598, 1483, 1456, 1292, 1157, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 2.5 Hz, 1H), 7.14−7.16 (dd, J = 8.7, 2.4 Hz, 1H), 6.88−6.85 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 2.2 Hz, 2H), 6.42 (t, J = 2.5 Hz, 1H), 5.09 (s, 1H), 3.80 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.0 (2C), 152.9, 138.5, 130.0, 127.5, 126.1, 124.0, 114.8, 104.7 (2C), 99.8, 70.9, 55.3 (2C). GC-MS (EI$^+$). $C_{15}H_{13}Cl_3O_2S$, calculated 312.03; found 312.0 (M$^+$, 3), 151.1 (100).

(3,5-Dimethoxybenzyl)(2,4,6-trichlorophenyl)sulfane (8n). Utilizing general procedure A, **8n** (20 mg, 0.055 mmol, 94%) was isolated as a white solid. MP: 84 °C; FTIR (neat): 2956, 2931, 2830, 1610, 1596, 1454, 1431, 1323, 1205, 1157, 1158 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.30 (s, 1H), 6.51 (d, J = 2.25 Hz, 2H), 6.38 (t, J = 2.3, Hz 1H), 4.08 (s, 2H), 3.79 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.1 (2C), 137.5, 136.3, 131.9, 131.3, 130.6, 130.0, 129.4, 106.9 (2C), 99.8, 55.4 (2C), 37.8. GC-MS (EI$^+$). $C_{15}H_{13}Cl_3O_2S$, calculated 361.97 found 361.9 (M$^+$, 3), 151.1 (100).

1-Benzyl-4-((3-chlorophenoxy)methyl)-1*H*-1,2,3-triazole (11a). Utilizing general procedure B, 1-benzyl-4-((3-chlorophenoxy)-methyl)-1*H*-1,2,3-triazole **11a** (50 mg, 0.167 mmol, 91%) was isolated as a white solid. MP: 96 °C; FTIR (neat): 2960, 2358, 1610, 1511, 1463, 1250, 1184, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.43−7.35 (m, 3H), 7.29 (dd, J = 4.8, 2.8 Hz, 2H), 7.20 (t, J = 8.1 Hz, 1H), 6.98−6.93 (m, 2H), 6.89−6.84 (m, 1H), 5.55 (s, 2H), 5.17 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.9, 144.1, 134.9, 134.4, 130.3, 129.2 (2C), 128.9, 128.2 (2C), 122.7, 121.5, 115.4, 113.1, 62.2, 54.3. HRMS calculated for $C_{16}H_{15}ClN_3O$ (M+H)$^+$ 300.0904; found 300.0906 (TOF MS ES+).

1-Benzyl-4-((naphthalen-1-yloxy)methyl)-1*H*-1,2,3-triazole (11b). Utilizing general procedure B, **11b** (53 mg, 0.168 mmol, 90%) was isolated as a light brown solid. MP: 94 °C; FTIR (neat): 3409, 2918, 1583, 1458, 1390, 1267, 1238, 1155, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 7.54−7.44 (m, 3H), 7.43−7.36 (m, 4H), 7.34−7.25 (m, 2H), 6.98 (d, J = 7.6 Hz, 1H), 5.57 (s, 2H), 5.41 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.9, 144.8, 134.5, 129.2 (2C), 128.8, 128.1 (2C), 127.5, 126.5, 125.8, 125.6, 125.3, 122.6, 122.0, 120.9, 105.4, 62.5, 54.3. HRMS calculated for $C_{20}H_{18}N_3O$ (M+H)$^+$ 316.1450; found 316.1427 (TOF MS ES+).

1-Benzyl-4-(pyrrolidin-1-ylmethyl)-1*H*-1,2,3-triazole (11c). Utilizing general procedure B, **11c** (48 mg, 0.198 mmol, 84%) was isolated as a light brown thick liquid. FTIR (neat): 3307, 2923, 1581, 1448, 1420, 1396, 1238, 1215, 1121, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.41−7.33 (m, 3H), 7.30−7.26 (m, 2H), 5.52 (s, 2H), 3.87 (s, 2H), 2.74−2.67 (m, 4H), 1.89−1.81 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.6, 134.6, 129.1 (2C), 128.7, 128.1 (2C), 122.9, 54.2, 53.9 (2C), 50.5, 23.4 (2C). HRMS calculated for $C_{14}H_{19}N_4$ (M+H)$^+$ 243.1610; found 243.1631 (TOF MS ES+).

1-Benzyl-4-(((2,4,6-trichlorophenyl)thio)methyl)-1*H*-1,2,3-triazole (11e). Utilizing general procedure B, **11e** (63 mg, 0.164 mmol, 92%) was isolated as a white solid. MP: 137 °C; FTIR (neat): 3369, 2923, 1699, 1456, 1433, 1363, 1242, 1116, 1049, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.41−7.34 (m, 5H), 7.24−7.20 (m, 2H), 5.52 (s, 2H), 4.25 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.8, 135.1, 134.4, 132.3, 131.5, 130.7, 130.6, 130.0, 129.2 (2C), 128.9, 128.0 (2C), 122.1, 54.3, 27.8. HRMS calculated for $C_{16}H_{13}Cl_3N_3S$ (M+H)$^+$ 383.9896; found 383.9912 (TOF MS ES+).

1-Benzyl-4-(((3,4-dimethoxyphenyl)thio)methyl)-1*H*-1,2,3-triazole (11f). Utilizing general procedure B, **11f** (53 mg, 0.155 mmol, 94%) was isolated as a white solid. MP: 101 °C; FTIR (neat): 2952, 1581, 1502, 1438, 1253, 1228, 1135, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.32 (m, 3H), 7.20 (dd, J = 6.7, 2.7 Hz, 2H), 7.17 (s, 1H), 6.89 (dt, J = 5.1, 2.1 Hz, 2H), 6.72 (d, J = 8.2 Hz, 1H), 5.47 (s, 2H), 4.14 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.0, 148.7, 145.5, 134.6, 129.1 (2C), 128.7, 127.9 (2C), 125.7, 124.8, 121.9, 115.2, 111.4, 55.9, 55.9, 54.1, 30.8. HRMS calculated for $C_{18}H_{19}N_3O_2S$ (M+Na)$^+$ 364.1096; found 364.1063 (TOF MS ES+).

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-isopropylbenzenesulfonamide (11g).** Utilizing general procedure B, **11g** (47 mg, 0.104 mmol, 89%) was isolated as a colorless thick liquid. FTIR (neat): 3134, 2923, 2846, 1703, 1604, 1487, 1456, 1411, 1328, 1220, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, J = 7.8, 1.8 Hz, 1H), 7.70, (dd, J = 7.7, 1.4 Hz, 1H), 7.65 (s, 1H), 7.48−7.32 (m, 5H), 7.27−7.20 (m, 2H), 5.52 (d, J = 5.1 Hz, 2H), 4.71 (s,

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2H), 4.03−3.82 (m, 1H), 1.09 (d, J = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.1, 139.3, 135.6, 134.7, 133.5, 132.5, 129.1 (2C), 128.7, 127.9 (2C), 127.5, 123.6, 120.3, 54.2, 49.9, 38.6, 21.1 (2C). HRMS calculated for $C_{19}H_{21}BrN_4NaO_2S$ $(M+H)^+$ 471.0466; found 471.0478 (TOF MS ES+).

4-((4-Bromophenoxy)methyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole (11h). Utilizing general procedure B, **11h** (52 mg, 0.145 mmol, 85%) was isolated as a white solid. MP: 103 °C; FTIR (neat): 3087, 2920, 1589, 1490, 1384, 1282, 1242, 1022, 825, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.19 (m, 4H), 6.85 (d, J = 8.8 Hz, 2H), 5.49 (s, 1H), 5.14 (s, 1H), 2.36 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.3, 144.1, 138.8, 132.3 (2C), 131.3, 129.8 (2C), 128.2 (2C), 122.6, 116.6 (2C), 113.5, 62.2, 54.1, 21.2. HRMS calculated for $C_{17}H_{17}BrN_3O$ $(M+H)^+$ 358.0555; found 358.0558 (TOF MS ES+).

1-(4-Methylbenzyl)-4-(((2,4,6-trichlorophenyl)thio)methyl)-1*H*-1,2,3-triazole (11i). Utilizing general procedure B, **11i** (48 mg, 0.120 mmol, 87%) was isolated as a white solid. MP: 136 °C; FTIR (neat): 3083, 2920, 1515, 1434, 1323, 1151, 1116, 1058, 871 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.38 (s, 1H), 7.31 (s, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 5.45 (s, 2H), 4.23 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.7, 138.2, 135.1, 132.3, 131.5, 131.3, 130.7, 130.5, 130.0, 129.8 (2C), 128.0 (2C), 122.0, 54.1, 27.9, 21.2. HRMS calculated for $C_{17}H_{15}Cl_3N_3S$ $(M+H)^+$ 398.0052; found 398.0063 (TOF MS ES+).

4-((4-Bromophenoxy)methyl)-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole (11j). Utilizing general procedure B, **11j** (67 mg, 0.179 mmol, 89%) was isolated as a white solid. MP: 98 °C; FTIR (neat): 3137, 2933, 1612, 1514, 1487, 1461, 1247, 1176, 1049, 1031, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.36 (dd, J = 9.6, 2.5 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.47 (s, 2H), 5.14 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.0, 157.3, 144.1, 132.3 (2C), 129.8 (2C), 126.3, 122.4, 116.6 (2C), 114.5 (2C), 113.5, 62.2, 55.4, 53.9. HRMS calculated for $C_{17}H_{16}BrN_3NaO_2$ $(M+Na)^+$ 396.0324; found 396.0331 (TOF MS ES+).

1-(4-Methoxybenzyl)-4-(((2,4,6-trichlorophenyl)thio)methyl)-1*H*-1,2,3-triazole (11k). Utilizing general procedure B, **11k** (50 mg, 0.120 mmol, 86%) was isolated as a yellow solid. FTIR (neat): 3082, 2931, 1612, 1514, 1434, 1323, 1249, 1176, 1118, 1058 cm^{-1}; MP: 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.31 (m, 1H), 7.22 (s, 1H), 7.20−7.17 (m, 1H), 7.09 (dd, J = 8.5, 1.8 Hz, 2H), 6.82 (dd, J = 8.4, 2.1 Hz, 2H), 5.34 (s, 2H), 4.14 (s, 2 H), 3.74 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.0, 143.6, 135.2, 132.3, 131.5, 130.7, 130.5, 130.0, 129.6 (2C), 126.3, 121.9, 114.5 (2C), 55.4, 53.8, 27.9. HRMS calculated for $C_{17}H_{15}Cl_3N_3OS$ $(M+H)^+$ 414.0001; found 414.0007 (TOF MS ES+).

4-((4-Bromophenoxy)methyl)-1-(cyclohexylmethyl)-1*H*-1,2,3-triazole (11l). Utilizing general procedure B, **11l** (52 mg, 0.148 mmol, 86%) was isolated as a white solid. FTIR (neat): 2921, 2852, 1488, 1446, 1384, 1244, 1224, 1112, 1054 cm^{-1}; MP: 90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.54 (s, 1H), 7.41−7.35 (ddd, J = 10.2, 3.4, 2.2, 2H), 6.91−6.85 (ddd, J = 10.2, 3.4, 2.2, 2H), 5.19 (s, 2H), 4.18 (d, J = 7.2 Hz, 2H), 1.94−1.83 (m, 1H), 1.76−1.61 (m, 5H), 1.29−1.14 (m, 3H), 1.04−0.94 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.3, 143.5, 132.3, 123.1, 116.7, 113.5, 62.3, 56.6, 38.7, 30.5 (2C), 26.0, 25.5 (2C). HRMS calculated for $C_{16}H_{21}BrN_3O$ $(M+H)^+$ 350.0868; found 350.0870 (TOF MS ES+).

1-(Cyclohexylmethyl)-4-(((2,4,6-trichlorophenyl)thio)methyl)-1*H*-1,2,3-triazole (11m). Utilizing general procedure B, **11m** (48 mg, 0.122 mmol, 88%) was isolated as a white solid. FTIR (neat): 2925, 2852, 1450, 1427, 1215, 1153, 1116 cm^{-1}; MP: 141 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.39 (d, J = 5.3 Hz, 2H), 4.27 (s, 2H), 4.14 (d, J = 7.2 Hz, 2H), 1.89−1.79 (m, 1H), 1.76−1.61 (m, 4H), 1.58−1.50 (m, 2H), 1.28−1.09 (m, 4H), 0.95 (qd, J = 12.2, 3.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.1, 135.2, 132.3, 131.5, 130.7, 130.5, 130.0, 122.6, 56.6, 38.7, 30.4 (2C), 27.8, 26.0, 25.5 (2C). HRMS calculated for $C_{16}H_{19}Cl_3N_3S$ $(M+H)^+$ 390.0365; found 390.0377 (TOF MS ES+).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01456.

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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