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LETTERS

A Polymer-Supported Silyl Triflate and Subsequent Functionalization: Synthesis and Solid-Phase Diels-Alder Reactions of Silyloxydienes

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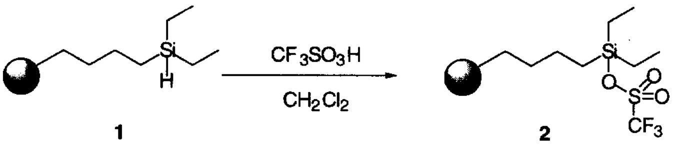
Abstract: The synthesis of a polymer-supported silyl triflate and subsequent functionalization with enolizable α,β-unsaturated aldehydes and ketones to form silyloxydienes is reported herein. This novel route is ideal for the generation of substrates for solid-phase Diels-Alder reactions. The silyl triflate and diene synthesis, subsequent [4 + 2] cycloadditions, and electrophilic cleavage are described. © 1999 Elsevier Science Ltd. All rights reserved.

Over the past several years the variety and sheer numbers of chemical reactions adapted for solid-phase chemistry in support of combinatorial library synthesis has increased rapidly.[1] In spite of the explosion of new polymer supported small molecule synthesis, the development of polymer-supported carbon-carbon bond forming reactions currently lags. The Diels-Alder reaction, the most widely used carbon-carbon bond forming reaction for the construction of six-membered rings,[2] has only been adapted for solid-phase synthesis to a limited extent.[3] We now report a general solution for the immobilization of reactive silyloxydienes and subsequent solid-phase Diels-Alder reactions.



(1)

Initial attempts at derivitizing a polymer supported silyl chloride,[4] prepared from PS-DES resin (polystyrene diethylsilane, Argonaut Technologies) with either zinc or lithium enolates of *trans*-4-methoxy-3-buten-2-one, to form a polymer supported version of Danishefsky's diene,[5] failed. Since the formation of silyloxydienes from silyltriflates does not require reactive, pre-formed enolates, conditions were developed for the activation of PS-DES resin as a silyl triflate.[6] Upon treatment with a solution of trifluoromethanesulfonic acid in methylene chloride under an inert atmosphere, PS-DES resin is quantitatively converted to the polymer-supported silyl triflate. Combined ^{29}Si and ^{19}F NMR spectra were used to verify the formation of the silyl triflate. A single resonance at 44.2 ppm (C_6D_6) in the gel-phase MAS ^{29}Si NMR spectrum and a single resonance at -79.1 ppm (C_6D_6, CCl_3F internal standard at 0.0 ppm) in the gel-phase ^{19}F NMR[7] spectrum confirm the presence of the silyl triflate and the completeness of the reaction.

The activated PS-DES triflate resin was converted to a polymer supported version of Danishefsky's diene upon treatment with a solution of *trans*-4-methoxy-3-buten-2-one and diisopropylethylamine in methylene chloride. Gel-phase ^{29}Si and ^{13}C NMR spectra confirm the formation of the diene and the completeness of the reaction. A single resonance at 19.4 ppm in the ^{29}Si NMR spectrum is consistent with the formation of a silyloxy diene and the absence of a peak at 44.2 ppm indicates consumption of the silyltriflate. Figure 1 is a ^{13}C NMR spectrum of the polymer-supported diene. Resonances at 155, 151, 104, 91, and 56 ppm are consistent with the solution phase ^{13}C NMR spectrum of the commercially available diene (*trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene).

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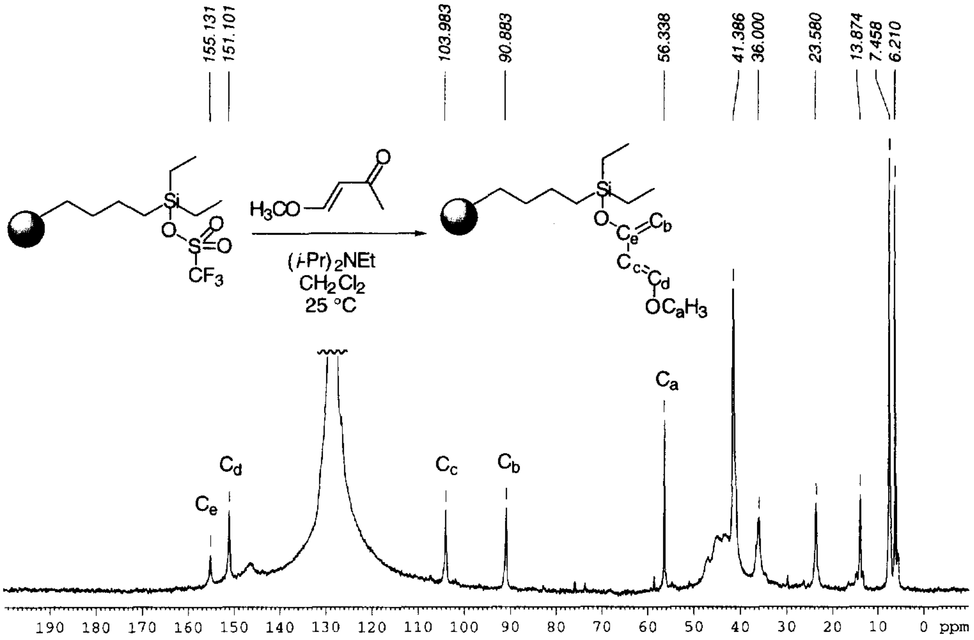
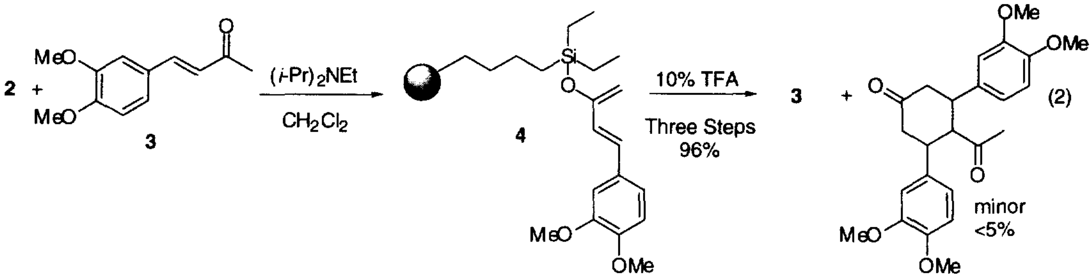


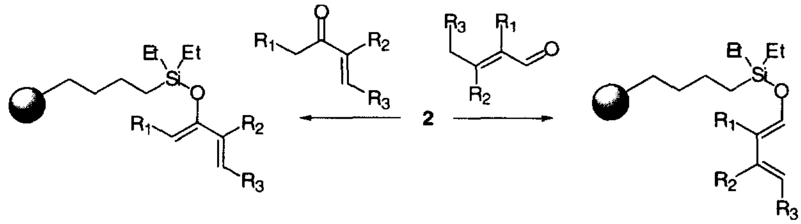
Figure 1. Gel-phase ^{13}C NMR spectrum (125 MHz, C_6D_6) of a polymer supported version of Danishefsky's diene.

The efficiency with which the silyl triflate resin could be used to immobilize silyloxydienes was tested in the following control experiment. The silyl triflate resin was treated with a solution of the non-volatile α,β-unsaturated ketone **3** and diisopropylethylamine in methylene chloride to form the polymer supported silyloxydiene **4**.[8] After careful washing to remove any excess enone, the silyloxy diene was electrophilically cleaved from the resin with a solution of trifluoroacetic acid in methylene chloride to afford ketone **3** with a 96% mass recovery. It should be noted, however, that in this and other cases a small amount of the silyloxydiene and its enone precursor undergo a [4 + 2] cycloaddition (^{1}H NMR purity was greater than 95% in this case).



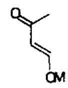
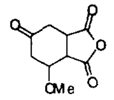
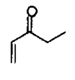
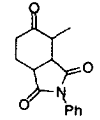
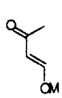
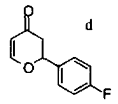
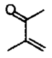
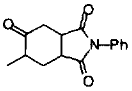
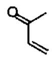
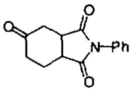
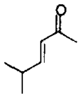
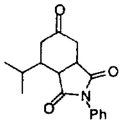
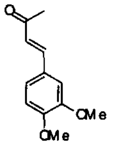
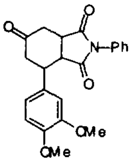
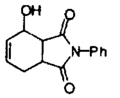
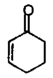
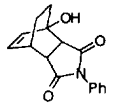
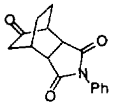
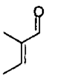
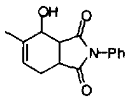
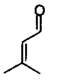
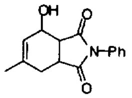
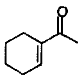
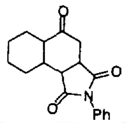
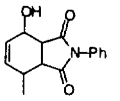
(2)

To demonstrate the generality of this procedure, a variety of α,β-unsaturated ketones and aldehydes were immobilized on PS-DES resin. Aldehydes were immobilized as derivatives of 1-silyloxy-1,3-butadienes and ketones were immobilized as derivatives of 2-silyloxy-1,3-butadienes.[9] These reactive dienes were then trapped with dienophiles via [4 + 2] cycloadditions,[10] and the products were electrophilically cleaved with a solution of trifluoroacetic acid. The results from these reactions are listed in Table 1.



(3)

Table 1. Results from diene synthesis, subsequent [4 + 2] cycloadditions, and electrophilic cleavage.

Entry	Diene Precursor	Diels-Alder Product	Yield (%)[a]	Purity (%)[b]	Entry	Diene Precursor	Diels-Alder Product	Yield (%)[a]	Purity (%)[b]
1			77	>90[c]	7			18	76
2			58	69	8			73	92
3			62	81	9			63[e]	98
4			99	87	10			83	98
5		 (1.4:1) 	69[f]	81[f]	11			83	95
					12			97	0[g]
6			100	90	13			31	80

(a) Yield is percent mass recovery based on resin loading after cleavage with trifluoracetic acid. (b) Purity is determined by analytical HPLC MS. Integration values are based on UV absorption at 212.5 nm. (c) Purity assessed by ^1H NMR integration. (d) This reaction is catalyzed by Eu(fod)$_3$.[11] (e) The starting material for this reaction is only 81% pure. (f) Values reflect combined yields and purity. (g) The product from this reaction undergoes post-cleavage elimination and oxidation reactions.

The examples in Table 1 were used to explore the formation and reactivities of a variety of different dienes that give rise to products with diverse structural and electronic properties. The substrates in entries 1 and 2 give rise to a version of Danishefky's diene which is used in the formation of cyclohexanones and dihydropyranones. Entry 5 demonstrates the ability to make reactive "inner-ring" dienes, and entry 6 demonstrates the ability to make "inner-outer-ring" dienes.[2] Entries 7-9 explore the effects of alkyl substituents in the formation and reactivity of 2-silyloxybutadienes, and similarly entries 11-13 explore the effects of alkyl substituents on 1-silyloxybutadienes.

In entries 7 and 13, lack of control in the formation of these silyloxydienes gives rise to mixtures of *cis-trans-* and *trans-trans*-dienes, and low yields observed for these entries reflect the decreased reactivity of *cis-trans*-dienes in the Diels-Alder reaction. In general, the formation of these dienes and the subsequent cycloaddittion reactions follow that expected for solution phase chemistry.

The above results demonstrate a novel method for the preparation of polymer-supported reactive dienes and subsequent cycloaddition reactions. Although the products of these reactions were cleaved from the resin with acid, these Diels-Alder adducts are synthetically useful compounds and provide the opportunity to perform additional on-resin reactions. For example, since the cycloaddition products arising from derivatives of 2-silyloxy-1,3-butadienes are silyl-enol-ethers, they may be useful for subsequent aldol, Michael, alkylation, or acylation reactions. Current work is underway to optimize the chemistry described in this paper and to explore the utility of silyl-ether intermediates towards subsequent carbon-carbon bond forming reactions. A similar preparation of the PS-DES triflate and its use in another application are described in the accompanying manuscript.[12]

Acknowlegments

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References and Notes

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5. (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.
6. A typical procedure for synthesizing the PS-DES triflate is as follows: Under an inert atmosphere, PS-DES resin (500 mg, 0.36 mmol based on loading of 0.72 mmol/g) was washed with three 10-mL portions of methylene chloride. To the resin was then added 5 mL of methylene chloride, and then a solution of trifluoromethanesulfonic acid (96 µL, 1.08 mmol) in 5 mL methylene chloride. After shaking five minutes, the solution was drained, and the resin was washed with three 10-mL portions of methylene chloride to afford a bright orange resin.
7. Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649.
8. A typical procedure for the derivitization of PS-DES triflate is as follows: To PS-DES triflate resin (0.358 mmol) was added 5 mL of methylene chloride and then a solution of diisopropylethylamine (0.19 mL, 1.07 mmol) and 3,4-dimethoxybenzylideneacetone (0.081g, 0.394 mmol) in 5 mL methylene chloride. After shaking 10 min., the solution was drained, and the resin was washed with three 10-mL portions of methylene chloride to afford **4** as a light tan resin.
9. When derivitizing the triflate resin with ketones such as 2-cyclohexenone, where two, competing acidic protons are present, the reaction is not regioselective, and a mixture of 1- and 2-silyloxy-1,3-butadiene derivatives are generated.
10. Conditions for performing cycloaddition reactions will vary depending on the substrates chosen. A general procedure used for preparing many of the compounds listed in Table 1 is as follows: Polymer-supported silyloxydienes were shaken under an inert atmosphere in a methylene chloride solution of *N*-phenylmaleimide (0.5 M, 10 equivalents, 25°C). After 14 h., the solution was drained, and the resin was washed with three 10-mL portions of methylene chloride to afford resin bound Diels-Alder adducts.
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