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High-load, soluble oligomeric benzenesulfonyl azide: application to facile diazo-transfer reactions

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Abstract—The development of a high-load, soluble oligomeric sulfonyl azide using ROM polymerization is reported. The utility in diazo transfer reactions with active methylene compounds is demonstrated using an efficient protocol, with most reactions showing completion in 30 min. The sulfonamide byproduct, being insoluble in the reaction solvent, can be completely removed by simple filtration through a silica gel SPE cartridge.

1. Introduction

The growing demand for facilitated synthesis protocols to aid in drug discovery has directed efforts aimed at integrating the sciences of organic synthesis and purification. Towards this goal, the production of designer polymers with tunable properties has become a powerful technological advancement in the arena of facilitated synthesis. In this context, an array of polymer-bound reagents and scavengers[1] has appeared, effectively streamlining synthetic methods to simple mix, filter and evaporate protocols. The hallmark of these methods is that they avoid the use of insoluble polymers during the actual synthesis, yet retain the virtues of both solution-phase and solid-phase approaches. Despite advances in this area, limitations in reaction homogeneity (nonlinear reaction kinetics), low resin-load capacities, and means of distributing reagents, continue to warrant the development of new polymers for library production.

In order to address these limitations, novel soluble polymers have surfaced as a means of utilizing solution-phase reaction kinetics with all the advantages of their solid phase counterparts.[2] In the course of these developments, ring-opening metathesis (ROM) polymerization,[3,4] has emerged as a powerful means of generating high-load, immobilized reagents with tunable properties that circumvent many of the problems associated with conventional immobilized reagents. There are several salient features that make ROM polymers ideal supports for reagents. First, ROM polymerization is a very versatile technique in that the properties of the generated polymers can be readily modified by the addition of comonomers or cross-linking agents as well as by changing which catalyst is employed. Second, because noncrosslinked oligomers are often soluble in organic solvents, slow reaction kinetics can be avoided. Third, the ROM polymers are often insoluble in methanol and do not pass through silica gel columns, thereby minimizing purification. Lastly, because ROM polymerization is highly functional group tolerant, active polymeric reagents can often be formed directly from the corresponding monomer, minimizing the need for functionalizing the polymer itself. Furthermore because each polymerized monomer contains an active functional group, this technique has potential to generate very highly loaded polymers. In addition, ease of monomer production should not be overlooked, as most monomers are accessible through Diels–Alder or reductive Heck chemistry. To this end, we now report the development and utility of a high-load, soluble oligomeric sulfonyl azide using ROM polymerization.

Diazo compounds are important intermediates in organic synthesis.[5] Of particular interest is the rich chemistry associated with their transition metal-catalyzed reactions.[6]

Keywords: Sulfonyl azide; Ring-opening metathesis polymerization (ROMP); Diazo transfer; High-load polymer; Soluble polymer; Supported reagents.
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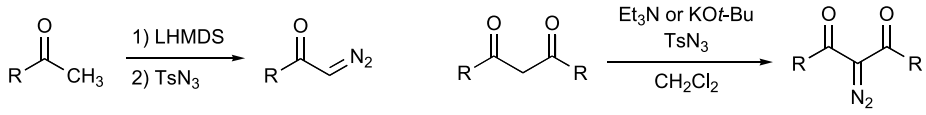


Scheme 1.

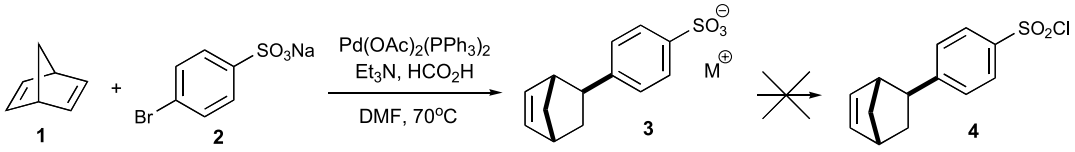
While many methods exist for synthesizing these compounds,[7] one of the most popular is through the reaction of an enolate or active methylene compound with a sulfonyl azide, typically tosyl azide (Scheme 1). While these methods have proven to be very reliable, at times they can be problematic due to stoichiometric amounts of *p*-toluenesulfonamide that are produced.

Several researchers have attempted to solve these problems by developing alternatives to *p*-toluenesulfonyl azide[8] or to generate the reagent in situ.[9] However, all of these approaches have been designed with an eye towards 'large scale' synthesis and still require purification of the diazo compound away from the sulfonamide byproduct. Surprisingly there have only been a few scattered reports on the use of polymeric sulfonyl azides,[10,11] a potentially useful strategy for parallel synthesis that would limit purification to a simple filtration step. These examples have focused on the use of insoluble polystyrene-based polymers. To the best of our knowledge, there are no examples of using soluble, high-load polymers to eliminate impurities from diazo transfer reactions. We felt that one way to facilitate the purification of these compounds would be through construction of a polymeric sulfonyl azide. Ideally, such a polymeric reagent would possess the following attributes: (1) high-load capacity, (2) broad solubility profile, allowing for delivery of the reagent via cannula, (3) facile removal from the reaction products, and (4) convenient availability via construction from cheap, readily available materials, thereby allowing for use in large-scale reactions. It was our belief that a ROM polymer-based sulfonyl azide would satisfy all of these requirements. We describe herein our development of such a reagent and its utility in diazo transfer reaction with active methylene compounds.

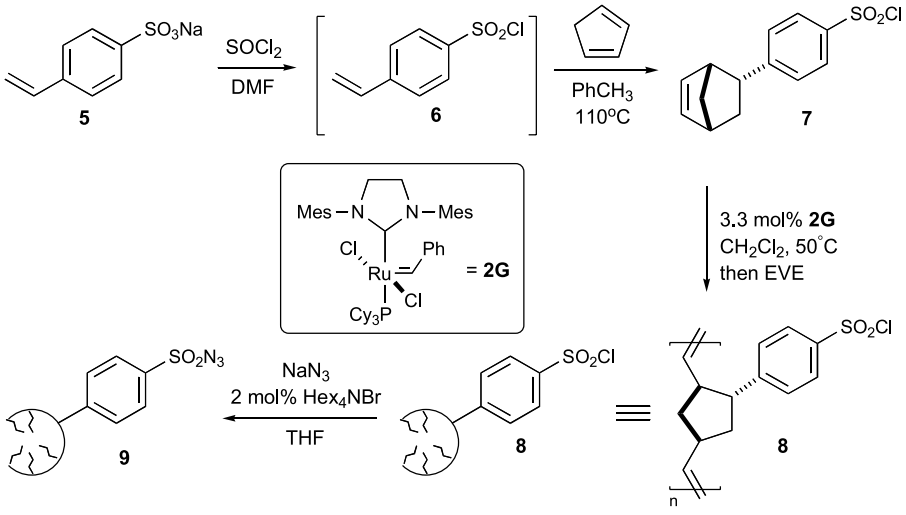
2. Results and discussion

Our initial approach to an oligomeric sulfonyl azide began with a reductive Heck reaction[12] between norbornadiene (**1**) and sodium *p*-bromobenzenesulfonate (**2**),[13] followed by chlorination of the resulting sulfonate **3** (Scheme 2). While the reductive Heck reaction proceeded smoothly, problems were encountered in attempting to convert sulfonate **3** into sulfonyl chloride **4**. Various standard reaction conditions were attempted, but all resulted in general decomposition of sulfonate **3**. We attribute this to adverse reactions occurring with the norbornene ring system.

In order to circumvent this problem, we decided to employ a Diels–Alder reaction to construct the requisite norbornenyl-tagged sulfonyl chloride. To this end, commercially available sodium 4-styrenesulfonate (**5**) was treated with $SOCl_2$ to form sulfonyl chloride **6** (Scheme 3).[14] Initial attempts at reacting purified sulfonyl chloride **6** with cyclopentadiene were unsuccessful as this compound



Scheme 2.



Scheme 3.

spontaneously polymerizes when concentrated and purified.[14] However, we found that when **6** was utilized directly after its formation, it smoothly reacted with cyclopentadiene to form Diels–Alder adduct **7**. By using this method, we could produce **7** on a multi-gram scale with an 8:1 *exo*/*endo* mixture as determined by ^{1}H NMR of the isolated material.

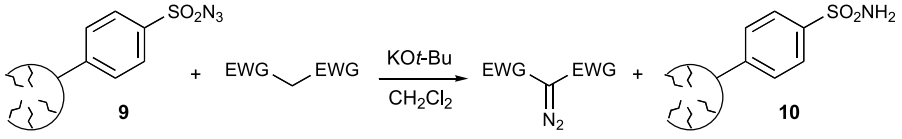
The diastereomeric mixture was not separated, and was found to polymerize readily with 1.6 (60-mer), 2.0 (50-mer), and 3.3 mol% (30-mer) using the second generation Grubbs catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; cat-**2G**].[15] Subsequent quenching with ethyl vinyl ether (EVE), and precipitation from heptane, yielded the oligomeric sulfonyl chloride (OSC) **8**[16,17] as a free-flowing, light grey solid.[18] This oligomer was found to have a diverse solubility profile, as it was soluble in CH_2Cl_2, THF, and DMF while remaining insoluble in benzene, heptane, ether, acetone, and acetonitrile. Interestingly, the solubility in $CHCl_3$ could be altered simply by altering the length of the polymer formed (i.e., by changing the amount of catalyst). Oligomers produced with 3.3 mol% cat-**2G** were completely soluble in $CHCl_3$, while those produced with 1.6 and 2.0 mol% cat-**2G** were insoluble.

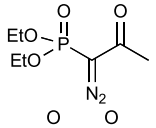
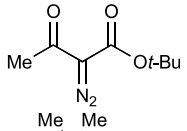
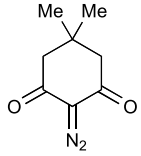
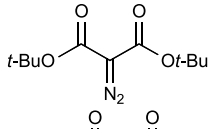
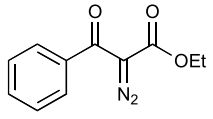
Initial attempts at forming sulfonyl azide **9** centered on reacting **8** with NaN_3 in DMF. While this method did form the desired sulfonyl azide, we observed inconsistent results when subsequent diazo transfer reactions were attempted. This may be due to reaction between DMF and polymer **8**; forming a Wilsmeyer–Haack-type product. However, it was subsequently found that reacting **8** with NaN_3 in THF, in the presence of 2 mol% Hex_4NCl,[19] cleanly produced the desired sulfonyl azide **9**. This oligomeric sulfonyl azide ($^{2G}OSA_{30}$)[20] has a theoretical yield of 3.6 mmol/g, and was found to be soluble in CH_2Cl_2, $CHCl_3$ (partially), THF, and DMF, but insoluble in heptane, methanol, acetonitrile, benzene, ethyl acetate, and Et_2O. We found that while OSA could be produced on >1 g scale, it underwent slow, nonviolent decomposition even if kept in the refrigerator. Best results were obtained if the polymer was used within 1–2 weeks of preparation. We believe this instability is due to the trace Ru impurities in oligomer **8**.[18] Several alternative purification methods were attempted to further purify oligomer **8** but were abandoned due to cost (large scale size exclusion chromatography) or decomposition during extended periods in solution (dialysis in THF or CH_2Cl_2 over several days).

Despite the absence of long-term stability, oligomer **9** was found to efficiently participate in diazo transfer reactions with various active methylene substrates (Table 1). Most reactions were found to be complete within 30 min as judged by TLC. We were pleased to find that product **11** (entry 1) could be produced in high yield and purity,[21] even on 200 mg scale. This diazo phosphonate has proven to be a useful alternative to the Seyferth–Gilbert reagent in the conversion of aldehydes to terminal alkynes.[22,23]

In practice, **9** was added as a solid to a CH_2Cl_2 solution of the substrate and KO^{t}Bu. Because the diazo transfer in this

Table 1.



Entry	Product	Time (min)	Yield[a] (%)	Purity[b] (%)
1		120	97[c]	>95[d]
2		30	88	>95
3		30	75	>95
4		30	74	>95[e]
5		30	90	>90

[a] All reactions performed on 0.2–0.26 mmol scale, with addition of 1.5 equiv **9** as a solid, unless otherwise noted.
[b] Purity by ^{1}H NMR of crude isolated products.
[c] Performed on 1 mmol scale.
[d] Contained 5% diethyl diazomethylphosphonate.
[e] Contained 7% starting material.

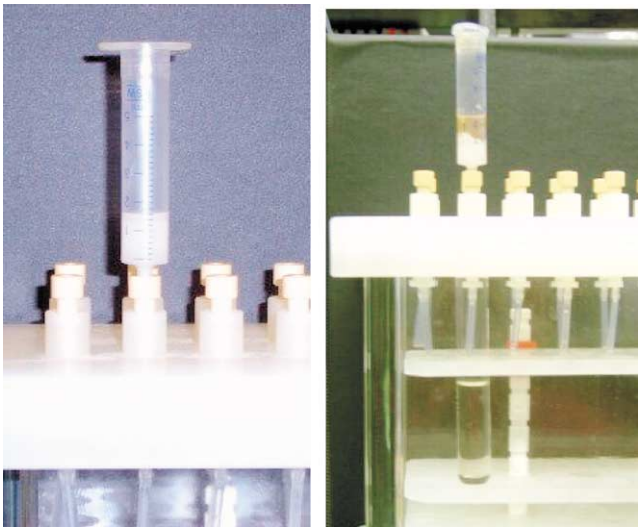
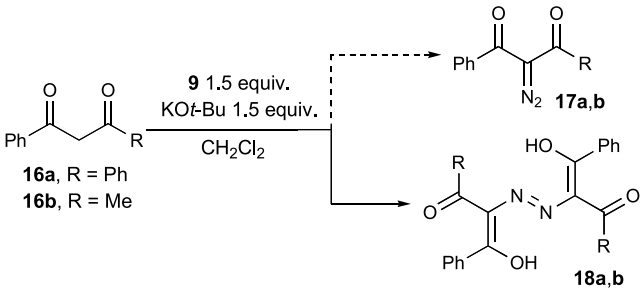


Figure 1. Silica gel SPE cartridge affixed to SPE manifold before filtering reaction (left), and after filtration (right).

system is so efficient, the polymeric sulfonyl azide is rapidly converted into polymeric primary sulfonamide **10**, which is not soluble in CH_2Cl_2. Due to this insolubility issue, the sulfonamide byproduct could be completely removed from the reaction products simply by filtering through a silica gel solid-phase extraction (SPE) cartridge and washing with EtOAc. As can be seen in Figure 1, the SPE cartridge retains all precipitated polymer, while the isolated filtrate is completely clear. Using this simple workup, all diazo products were isolated in high yield and excellent purity as judged by GC and ^{1}H NMR, which indicated an absence of any polymeric material (Fig. 2).

Interestingly, with dibenzoylmethane (**16a**) and 1-benzoylacetone (**16b**), the reaction took a different course (Scheme 4). In these cases, an 'azo coupling' reaction took place to generate azo compounds **18a**,**b**. This type of reaction has been reported by Regitz and Stadler by utilizing 0.5 equiv of TsN_3.[24] Various attempts were made to circumvent these spurious results (changing order of addition, changing base to Et_3N), but to no avail. It is interesting to note that this was not observed in the case of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (Table 1, entry 5). Perhaps there is a steric effect involved with the enolates derived from **16a**,**b** that is not felt with the flat enolate generated from dimedone.



Scheme 4.

3. Conclusion

In conclusion, we have constructed a high-load, oligomeric sulfonyl azide and demonstrated its utility in diazo transfer reactions with active methylene compounds. This system is extremely efficient with most reactions showing completion in 30 min. The sulfonamide byproduct, being insoluble in the reaction solvent, can be completely removed by a simple filtration through a silica gel SPE cartridge. Application of this reagent in the synthesis of synthetically relevant diazo compounds, as well as in other reaction types are being investigated and will be reported in due course.

4. Experimental

4.1. General methods

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon using standard gas-tight syringes, cannulas, and septa. CH_2Cl_2,

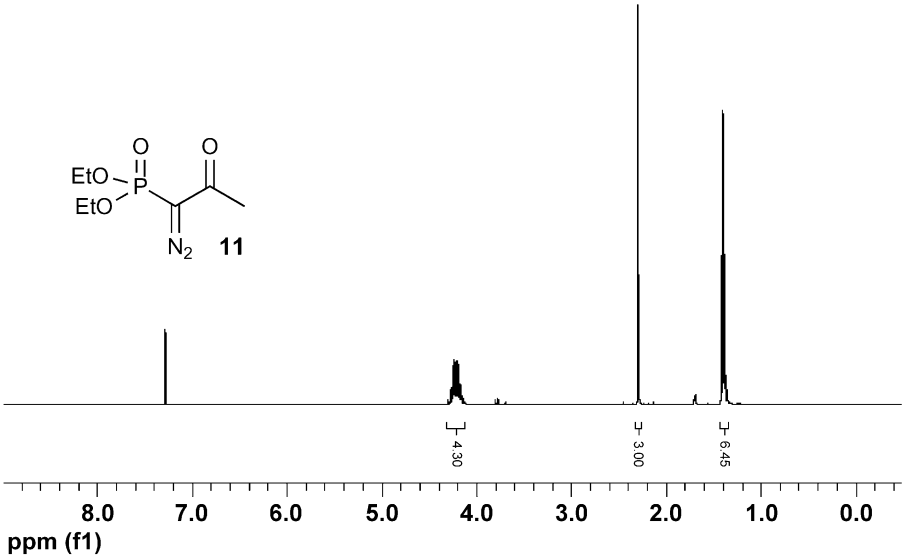


Figure 2. ^{1}H NMR spectrum of crude **11**.

THF, Et_2O, CH_3CN, and toluene were purified by passage through a Solv-Tek (www.solvtek.com) purification system employing activated Al_2O_3 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Benzene was purified by distillation over CaH_2. Et_3N was purified by passage through a column of basic alumina and stored over KOH. The second-generation Grubbs metathesis catalyst was obtained from Materia, Inc. and used without further purification. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Visualization of TLC spots was effected using $KMnO_4$ stain. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230–400 mesh). Deuterochloroform ($CDCl_3$) was purchased from Cambridge Isotope Laboratories and stored over molecular sieves (4 Å) at rt. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on either a Bruker DRX-400 MHz spectrometer operating at 400 and 100 MHz, respectively; or a Bruker Avance-500 MHz spectrometer operating at 500 and 126 MHz, respectively, and references to residual $CHCl_3$ peaks (7.26 and 77.0 ppm for ^1H and ^{13}C, respectively). High resolution mass spectrometry (HRMS) and FAB spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas using a VG Instrument ZAB double-focusing mass spectrometer. Inductively coupled plasma mass spectrometry (ICPMS) was performed using a VG PlasmaQuad II+XS inductively coupled plasma mass spectrometer and run against calibration standards (1, 5, 10, 50 and 100 ppb) which were made from commercial Ru stock solution (provided in 10% HCl) by diluting with distilled 6 N nitric acid to the same acid strength as the samples. Prior to analysis, samples were weighed (~5 mg) into screw-top glass vials and 0.3 mL 4:1 H_2SO_4/35% aq H_2O_2 was added. *Caution: this mixture is extremely corrosive*. The 35% aq H_2O_2 should be added extremely slowly with the temperature of the mixture not allowed to rise above 50–60 °C. Once dissolution was complete (1–2 days), the samples were dissolved in 3 mL of distilled 6 N HNO_3 acid, capped, and placed on a 50 °C hot plate for 1–2 days. The samples were then cooled and transferred to acid-cleaned high-density polyethylene bottles, sonicated for one hour, and diluted to a total volume of approximately 100 mL with distilled acid and distilled-deionized water to a final acid concentration of about 2%.

4.1.1. 4-(Bicyclo[2.2.1]hept-5-en-2-yl)benzene-1-sulfonyl chloride (7). A flask was charged with $SOCl_2$ (85 mL, 891 mmol) and cooled with an ice bath. Sodium 4-styrenesulfonate (26.37 g, 128 mmol) was added portion-wise with heavy stirring over 1 h. DMF (35 mL) was added slowly and the mixture warmed to RT. After 6 h the flask was placed in a refrigerator overnight. The cold mixture was then carefully poured onto ~800 mL of ice. The mixture was extracted with Et_2O, and evaporated. The residue was dissolved in toluene (60 mL), freshly cracked cyclopentadiene (~10 mL) was added, and the solution heated to reflux. Fresh cyclopentadiene was added in 10 mL increments every hour for 5 h. After the last addition the mixture was kept at reflux for 2 h. After cooling to RT, the reaction was concentrated under reduced pressure. Flash chromatography [heptane (to remove dicyclopentadiene) and then 10:1 heptane/EtOAc, all mixed fractions were resubjected to flash chromatography] afforded **7** (24.52 g, 71%) as a slightly yellow solid (8:1 *endo*/*exo* mixture). TLC (5:1 heptane/EtOAc) R_f 0.11; IR (thin film) 3059, 2968, 1589, 1375, 1175 cm^{-1}.

Major *endo* isomer: ^1H NMR (400 MHz, $CDCl_3$) 7.87 (d, 2H, $J=8.1$ Hz), 7.35 (d, 2H, $J=8.5$ Hz), 6.32 (dd, 1H, $J=5.6$, 3.1 Hz), 5.76 (dd, 1H, $J=5.6$, 2.8 Hz), 3.49 (ddd, 1H, $J=8.6$, 4.0, 4.0 Hz), 3.12 (br s, 1H), 3.02 (br s, 1H), 2.26 (ddd, 1H, $J=12.7$, 9.4, 3.8 Hz), 1.56 (br d, 1H, $J=8.3$ Hz), 1.51 (br d, 1H, $J=8.1$ Hz), 1.33 (ddd, 1H, $J=11.9$, 4.4, 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 154.0, 141.4, 138.0, 132.1, 129.2, 126.4, 50.3, 48.8, 44.0, 43.2, 33.0.

Minor *exo* isomer: ^1H NMR (400 MHz, $CDCl_3$) 7.94 (d, 2H, $J=8.0$ Hz), 7.49 (d, 2H, $J=8.5$ Hz), 6.27 (dd, 1H, $J=5.6$, 3.0 Hz), 6.22 (dd, 1H, $J=5.8$, 2.8 Hz), 3.02 (br s, 1H), 2.97 (br s, 1H), 2.81 (dd, 1H, $J=7.4$, 7.4 Hz), 2.26 (ddd, 1H, $J=12.7$, 9.4, 3.8 Hz), 1.56 (br d, 1H, $J=8.3$ Hz), 1.51 (br d, 1H, $J=8.1$ Hz), 1.33 (ddd, 1H, $J=11.9$, 4.4, 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 155.2, 141.3, 137.7, 136.8, 128.7, 126.9, 47.8, 45.7, 44.1, 42.3, 33.9.

4.1.2. Formation of oligomeric sulfonyl chloride (8). A flask was charged with **7** (8.5814 g, 31.9 mmol) and CH_2Cl_2 (100 mL) was added. The mixture was degassed with argon for 20 min. Catalyst **2G** was added (895 mg, 1.05 mmol) and the solution was heated to 50 °C. The reaction was monitored by TLC (8:1 heptane/EtOAc) and upon completion (about 30 min), the solution was cooled to rt and 20 mL ethyl vinyl ether (EVE) was added. The mixture was stirred for 1 h and then added to 3 L heptane via cannula with stirring. The precipitate was allowed to settle and the supernatant was then decanted through a fritted glass funnel. The precipitate was washed with three 500 mL portions of 10:1 heptane/$CHCl_3$ followed by heptane. Oligomer **8** (8.6396 g, 99%) was collected as a free-flowing, light grey solid: IR (thin film) 3059, 2943, 1589, 1411, 1373, 1173, 1084, 972, and 837 cm^{-1}.

4.1.3. Formation of oligomeric sulfonyl azide (9). To a mixture of **8** (1.0124 g, 3.77 mmol) and Hex_4NCl (35.9 mg, 0.0826 mmol) in THF (10 mL), was added NaN_3 (394.3 mg, 6.07 mmol). Caution: NaN_3 should not be measured out with metal utensils. The end of a glass pipette was always used to weigh the necessary amount. The heterogeneous mixture was stirred at rt for 15 h. The reaction was then added to a stirred mixture of H_2O/MeOH (70 mL/30 mL). The precipitate was filtered with a coarse glass frit and washed with H_2O, MeOH, and heptane to afford oligomer **9** (1.0745 g, 99%) as a brown solid. Caution: while we have had no problems with handling oligomer **9**, safety shields should be utilized when handling large quantities: IR (thin film) 3051, 2943, 2125, 1593, 1371, 1169, 1088 cm^{-1}.

4.2. General procedure for diazo transfer reaction with OSA

An oven-dried vial was charged with the active methylene compound (1 equiv), and KO*t*-Bu (1.5 equiv) and dissolved in CH_2Cl_2 (0.2 M). Oligomer **9** (1.5–2 equiv) was added and the mixture stirred at rt and monitored by TLC. When the reaction was complete, EtOAc (1 mL) was added

and the mixture filtered through a SPE cartridge containing ~650 mg silica. The cartridge was washed with EtOAc (4×1 mL). The filtrate was evaporated under reduced pressure to afford pure diazo compound.

4.3. Characterization of diazo transfer products 11–15

4.3.1. Diethyl (1-diazo-2-oxopropyl)phosphonate (11). The general procedure above was followed starting with diethyl (2-oxopropyl)phosphonate (200 μL, 1.04 mmol), KO*t*-Bu (131.4 mg, 1.17 mmol), and **9** (433.5 mg, 1.56 mmol), to afford **11** (224.5 mg, 97%) as an orange oil: IR (thin film) 2986, 2123, 1659, 1267, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.21 (dq, 4H, J=7.0, 8.4 Hz), 2.28 (s, 3H), 1.39 (dt, 6H, J=7.1, 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 190.1 (J_{CP}=13.8 Hz), 63.4 (J_{CP}=5.6 Hz), 27.2, 16.1 (J_{CP}=6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) −12.49.

4.3.2. *t*-Butyl 2-diazo-3-oxobutanoate (12). The general procedure above was followed starting with *t*-butyl acetoacetate (45 mg, 0.284 mmol), KO*t*-Bu (51.6 mg, 0.460 mmol), and **9** (120.4 mg, 0.433 mmol) to afford **12** (46 mg, 88%) as a yellow-orange oil:[10c] IR (thin film) 2980, 2934, 2131, 1659, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 2.45 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 190.5, 160.5, 83.1, 28.2, 28.1.

4.3.3. 2-Diazo-5,5-dimethyl-1,3-cyclohexanedione (13). The general procedure above was followed starting with 5,5-dimethyl-1,3-cyclohexanedione (33.1 mg, 0.236 mmol), KO*t*-Bu (45.1 mg, 0.402 mmol), and **9** (99.3 mg, 0.357 mmol) to afford **13** (29.5 mg, 75%) as a pale yellow solid: mp 103–105 °C (lit.[25] 105–107 °C), IR (thin film) 2962, 2137, 1643, 1312, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 2.44 (s, 4H), 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 189.8, 50.5, 31.1, 28.3.

4.3.4. Di-*t*-butyl 2-diazomalonate (14). The general procedure above was followed starting with di-*t*-butyl malonate (46.3 mg, 0.214 mmol), KO*t*-Bu (38.8 mg, 0.346 mmol), and **9** (95.9 mg, 0.345 mmol) to afford **14** (38.3 mg, 74% containing 7% starting material) as a yellow-orange oil: IR (thin film) 2980, 2133, 1747, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.50 (s); ^{13}C NMR (125 MHz, $CDCl_3$) 160.3, 82.6, 28.2.

4.3.5. Ethyl 2-diazo-3-oxo-3-phenylpropanoate (15). The general procedure above was followed starting with ethyl benzoylacetate (39.7 mg, 0.207 mmol), KO*t*-Bu (43.3 mg, 0.386 mmol), and **9** (99.6 mg, 0.359 mmol) to afford **15** (40.5 mg, 90%) as a yellow-orange oil: IR (thin film) 3061, 2984, 2143, 1728, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.66–7.61 (m, 2H), 7.56–7.51 (m, 1H), 7.46–7.40 (m, 2H), 4.24 (q, 4H, J=7.1 Hz), 1.26 (t, 6H, J=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 186.9, 161.0, 137.1, 132.2, 128.3, 127.8, 61.6, 14.1.

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