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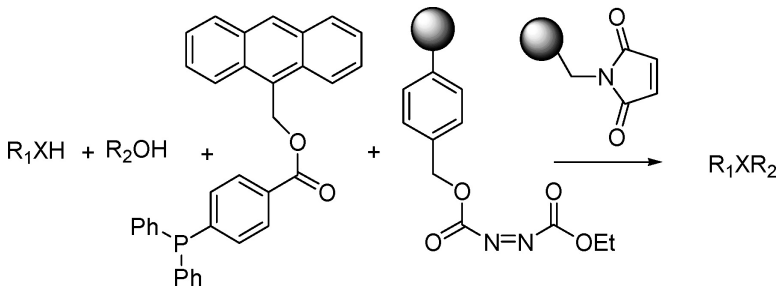

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The Development of a Chromatography-Free Mitsunobu Reaction: Synthesis and Applications of an Anthracene-Tagged Phosphine Reagent

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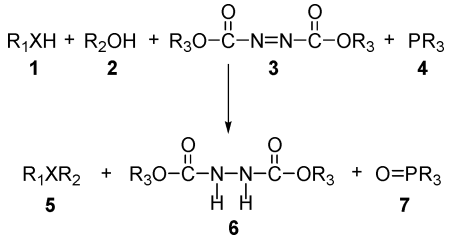
A general method for a polymer-assisted solution-phase (PASP) Mitsunobu reaction using a combination of anthracene-tagged phosphine and polymer-supported azodicarboxylate is reported. The anthracene-tagged phosphine allows for the removal of phosphine/phosphine oxide by sequestration through a chemoselective Diels−Alder reaction with a maleimide resin. The polymer-bound azodicarboxylate facilitates the removal of excess alcohol, reagent, and byproducts by simple filtration. The final pure products are obtained after a simple filtration and concentration.

Introduction

Polymer-assisted solution-phase (PASP) synthesis has become widely used in pharmaceutical, agricultural, and material science. Although solid-phase organic chemistry was initially the preferred methodology for library synthesis, more recently PASP approaches have gained considerable popularity. One of the important features of solution-phase chemistry is the ability to employ conditions from a wealth of previously known organic reactions. Additionally, solution-phase chemistry allows one to monitor the progress of reactions by traditional methods, effectively shortening validation times. PASP methodology[1] involves a number of purification techniques, including sequestration of reactants and byproducts by appropriately functionalized resins, sequestration enabling reagents (SERs)[2] to convert nonsequesterable species into chemically tagged species capable of being sequestered, and chemically tagged reagents[3] for sequestration by functionalized resins. The assortment of commercially available functionalized resins/SERs/reagents allows the practitioner to exploit the aforementioned PASP methods in various combinations for single and multistep parallel solution-phase library synthesis.

One of the chemical transformations that has received attention in PASP-based approaches is the Mitsunobu reaction.[4] The Mitsunobu reaction involves activation of alcohols **2** for attack by a range of nucleophiles **1** to form condensation products **5** using a combination of phosphines **4** and azodicarboxylates **3** (Scheme 1). The major problems associated with the broad application of this reaction in parallel synthesis are the removal of the excess starting materials, excess reagent and byproducts, specifically phosphine oxide

Scheme 1. Mitsunobu Reaction



7, hydrazine from reduced azodicarboxylate **6**, and unconsumed acidic substrate **1** or nonvolatile alcohols **2**. A number of techniques have been developed to overcome these problems. Considerable attention has been put into using polymer-attached or fluorous-tagged phosphines to facilitate the removal of phosphine oxide via filtration or precipitation.[5] While the problem of the phosphine has been largely overcome, it is often the removal of hydrazine that has been more problematic. Polymer-supported azodicarboxylate has been reported,[6] but its application in the Mitsunobu reaction with a polymer-bound phosphine is obviously limited by incompatibility due to phase separation.

Recently, a number of new methodologies involving the use of "chemically tagged" reagents were developed to enable their chemoselective removal from reaction mixtures. For example, di-*tert*-butyl-tagged azodicarboxylate greatly facilitated the removal of the hydrazine byproduct using an acidic workup for the decomposition to volatile byproducts followed by a water extraction, but compounds with basic functionality are not compatible with this method.[7] Use of masked carboxy-tagged phosphine−azo reagent pairs, purified by postreaction unmasking with an acid and subsequent sequestration with a polymer-bound basic resin, has limitations for products containing acidic groups.[8] A fluorous azodicarboxylate reagent combined with a fluorous phos-

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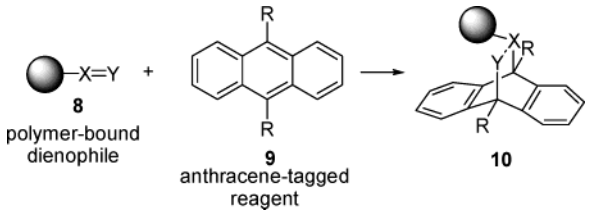
Scheme 2. Diels −Alder Cycloaddition for Anthracene Tag Removal



phine gave interesting results for library synthesis, but was limited by precipitation of highly hydrophobic substrates on a fluorous column.[9] An elegant approach termed "impurity annihilation" employed norbornene as a tag to enable selective derivatization by polymerization of all contaminants, which are then removed by simple filtration. However, it was also mentioned in the report that some compounds potentially coordinating with the metal used for polymerization are not compatible with this methodology.[10]

As part of our interest to develop new methodology for polymer-assisted solution-phase synthesis and purification of final products, we have embarked on a study of Diels−Alder cycloaddition−removable tags (CRTs), specifically anthracene-tagged reagents.[11,12] A major advantage of the cycloaddition−removable anthracene tag is the highly orthogonal and chemoselective reactivity of the Diels−Alder reaction for the removal of the tagged molecule, allowing the presence of numerous functional groups (Scheme 2). Additionally, the intense fluorescence of the anthracene permits easy monitoring of reaction progress with thin-layer chromatography.

To further evaluate polymer-supported dienophiles in addition to the polymer-supported maleimide employed in our first study,[11] the use of triazolinedione (TAD) on polystyrene was explored.[13] A polymer-bound TAD **32** was desired because of its expected highly reactive nature in the Diels−Alder cycloaddition. After unsuccessful attempts,[14] two versions of a polymer-bound maleimide were investigated. A commercial source of 4-maleimidobutyramidomethyl polystyrene **11b**,[15] containing a six-atom linker between the polymer matrix and maleimide, was compared against *N*-benzylmaleimide resin **11** in a kinetic reactivity study for the sequestration of anthracene-tagged compound **12** (Scheme 3). Second-order rate constants were determined, and no significant difference in reactivity between the two resins was observed.[16] Thus, the longer linker of resin **11b** did not appear to provide much advantage; coupled with the high

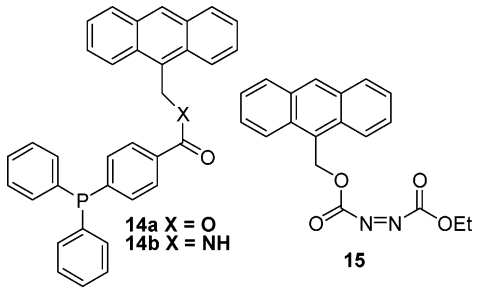


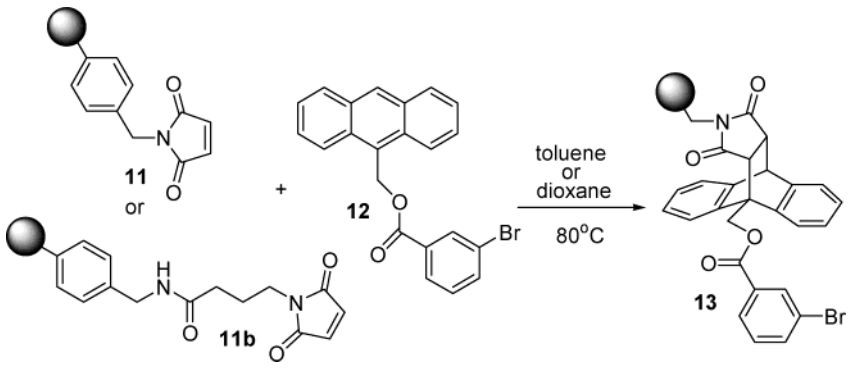
Figure 1. Anthracene-tagged phosphine and azodicarboxylate reagent pairs.

cost and low loading, it was decided to proceed with the polymer-bound *N*-benzylmaleimide **11**. Maleimide resin **11** was prepared using a slight modification of our previously reported procedure, and a loading of ∼1.6 mmol/g could be consistently obtained.[11,17] Typical conditions for cycloaddition reactions of polymer-bound maleimide with anthracene-tagged compounds require heating (∼80 °C) an excess of the resin **11** with the anthracene-tagged compound in a high-boiling solvent, such as toluene or dioxane (Scheme 3).

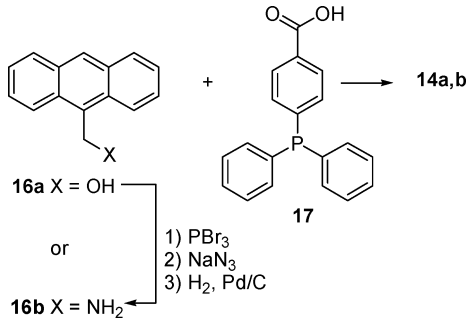
Our initial approach for the Mitsunobu reaction was to develop a homogeneous system with both anthracene-tagged triarylphosphine and azodicarboxylate components (Figure 1) allowing for the sequestration of both reagents and reagent byproducts via Diels−Alder cycloaddition with maleimide resin **11**. The synthesis of anthracene-tagged phosphine **14** is shown in Scheme 4. Esterification of the commercially available starting materials, alcohol **16a** with phosphine **17** under nitrogen, afforded the ester product **14a** in high yield (85%). On the basis of ^{31}P NMR, the anthracene-tagged product **14a** can be made in large scale (15 g) and stored at low temperature for several months without detectable oxidation. Additionally, the amide **14b** could also be prepared by reacting phosphine **17** with 9-aminomethylanthracene **16b** using typical coupling conditions. In most cases, anthracene-tagged phosphines **14a** and **14b** are exchangeable as a substitute of triphenylphosphine, but **14b** requires alternative synthesis.

The synthesis of anthracene-tagged azodicarboxylate **15** proved to be problematic (Scheme 5). The first attempt involved reaction of alcohol **16a** with triphosgene to afford the chloroformate **18**. After several failed attempts to isolate the anthracenyl formate **18**, it was realized that the formate **18** readily degrades to give 9-chloromethylanthracene **19**, as was observed by others.[18] An alternative approach

Scheme 3. Diels−Alder Cycloaddition of Polymer-Bound Maleimide with Anthracene-Tagged 12



Scheme 4. Synthesis of Anthracene-Tagged Phosphine 14

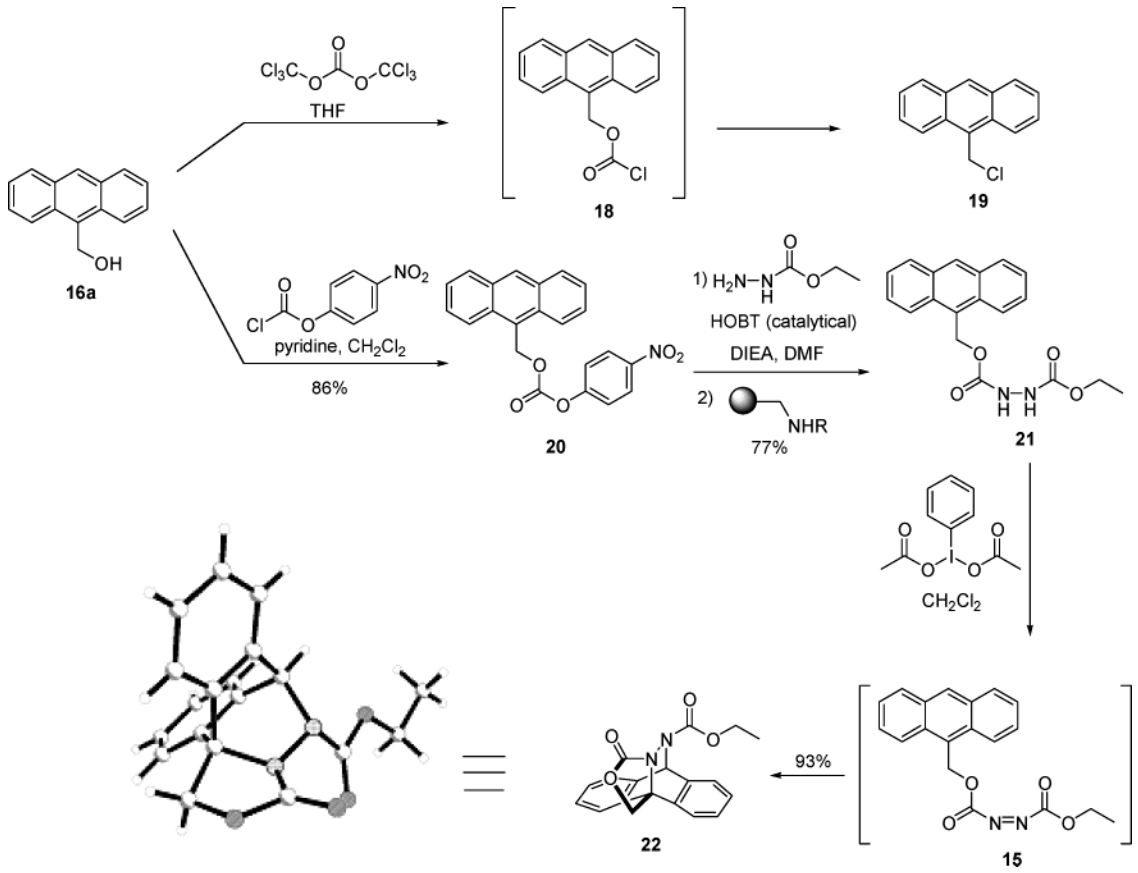


involved the reaction of 4-nitrophenyl chloroformate with 9-anthracenemethanol **16a** in the presence of pyridine to afford the desired 4-nitrophenylanthracenyl formate **20**. Several attempts to react the formate **20** with ethyl carbazate were tried, including heating to 88 °C in dioxane with DMAP, but afforded no product. 4-Nitrophenyl formate has been shown to react with primary amines instantly to form carbamates.[18] Although ethyl carbazate is less nucleophilic than primary amines, the extreme lack of reactivity between the 4-nitrophenyl formate **20** and ethyl carbazate in the presence of DMAP at high temperature was surprising. Eventually, it was found that addition of *N*-hydroxybenzotriazole (HOBt) as a catalytic additive, in combination with stoichiometric amounts of diisopropylethylamine, promoted the transformation at room temperature.[19] Treatment of the reaction mixture with polyamine resin[20] to remove both HOBt and the byproduct 4-nitrophenol followed by a silica gel chromatography afforded the desired intermediate **21** in high yield.

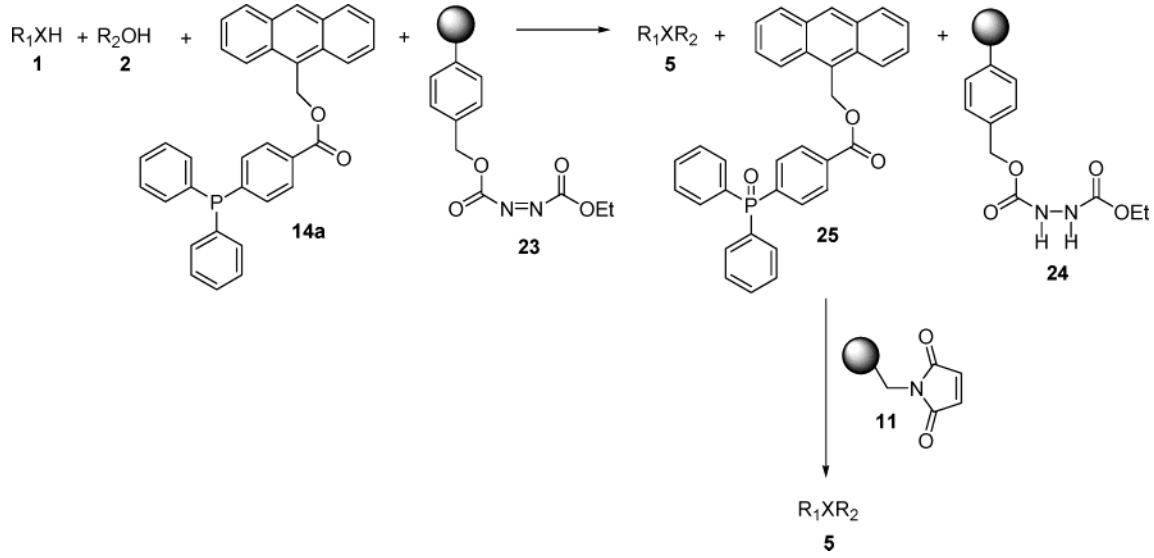
With the intermediate **21** in hand, the final step to prepare the anthracene-tagged azodicarboxylate **15** was attempted. The intermediate **21** was treated with iodobenzene diacetate in CH_2Cl_2 at room temperature to afford a product with the correct molecular weight observed by LC/MS ($M + 1 = 337$) but the proton NMR was inconsistent with the expected product **15**. Further characterization by X-ray crystallography revealed that the compound was an intramolecular Diels−Alder product between the anthracene tag and the azo functionality, namely compound **22**. There are some interesting structural features worthy of mentioning. The compound has several ring systems, including a spiro-oxazolidinone. The crystal structure showed the molecule as a caved structure with hydrophobic and hydrophilic groups separately occupying two sides. Despite the long history of azodienophiles,[21] the intramolecular Diels−Alder application of this group of compounds is rare.[22] In some reported cases, high temperature (80 °C) was required to effect Diels−Alder cycloadditions. Other experiments were conducted to further investigate this reaction, including mixing compound **21** with DEAD at room temperature and elevated temperatures for prolonged periods of time, but no intermolecular Diels−Alder reaction was observed.

As a result of the inability to prepare an anthracene-tagged azodicarboxylate, an alternative approach was developed using a combination of anthracene-tagged phosphine and polymer-bound azodicarboxylate **23** (Scheme 6). Polystyrene-attached azodicarboxylate **23** has been commercially avail-

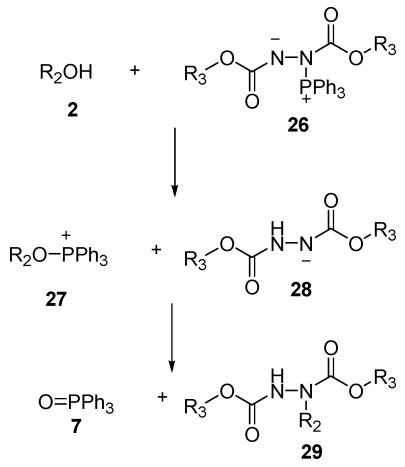
Scheme 5. Synthesis of Anthracene-Tagged Azodicarboxylate



Scheme 6. Mitsunobu Reaction Using Anthracene-Tagged Phosphine and Polymer-Bound Azodicarboxylate



Scheme 7. A Mitsunobu Side Reaction: the Nucleophilic Substitution of Azodicarboxylate



able for some time,[23] but there have been few reports concerning its application in Mitsunobu reactions, likely because of the dominant usage of polymer-bound triphenylphosphine. Nevertheless, there are several advantages the polymer-supported azodicarboxylate may offer. One obvious advantage is that the byproduct hydrazine and the excess azodicarboxylate can be removed by simple filtration. A less obvious advantage is the removal of the excess starting materials, particularly the alcohol, by polymer-supported azodicarboxylate. In the absence of an acidic reactant or when a substrate is not acidic enough, a competing reaction occurs involving the substitution of one nitrogen of the azodicarboxylate for the alcohol (Scheme 7).[24] This side reaction was originally noticed by Mitsunobu with benzyl and allyl alcohols.[25] Other reports showed that the side reaction was not limited to only benzyl or allyl alcohols, but was a more general observation for most primary and secondary alcohols.[26]

During solution-phase Mitsunobu model studies, similar chemistry was observed. When 1 equiv of the acidic substrate was used with 1.5 equiv of the alcohol, the desired Mitsunobu product plus alcohol-substituted hydrazine was obtained, on the basis of NMR and LC/MS without any free alcohol.

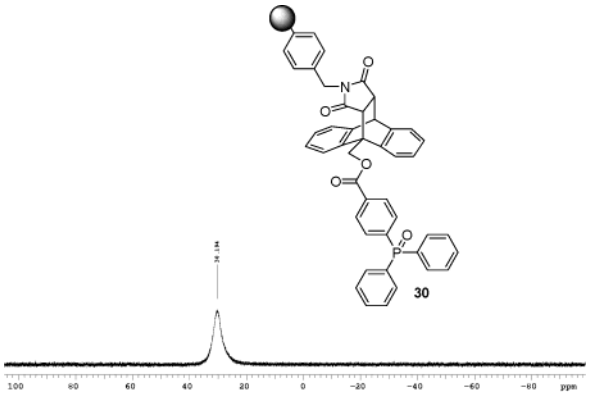


Figure 2. Phosphorus NMR spectra of polymer-bound Diels–Alder adduct **30**.

Considering the synthesis of combinatorial libraries, alcohol diversity reagents are generally commercially available and, therefore, used in excess to drive the reaction to completion. Therefore, it was reasoned that using polymer-supported azodicarboxylate **23** as a sequestration agent for excess alcohols through the Mitsunobu side reaction should simplify product purification.

Initially, the same reaction condition from the solution-phase model studies was applied on the polymer-supported reaction. After completion of reaction, the polymer-bound azodicarboxylate **23** and its byproducts were filtered, and the filtrate was concentrated. Proton NMR of the filtrate surprisingly showed a trace of remaining alcohol in addition to the desired Mitsunobu product. Apparently, the sequestration of excess alcohol by polymer-supported azodicarboxylate **23** was not as efficient as when the reaction was run in solution-phase. However, when the amount of alcohol was reduced to 1.2 equiv, the result showed complete sequestration of the excess alcohol.

To demonstrate the application of this methodology, a parallel array of reactions involving a variety of acidic substrates and alcohols (Figure 3) was designed. The acidic nucleophiles were chosen to exemplify the typical substrates used in Mitsunobu reactions, and the alcohols selected include primary and secondary alcohols. The reaction was

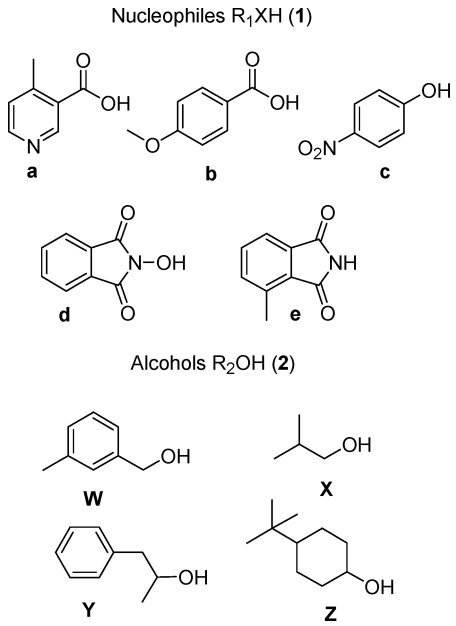


Figure 3. Nucleophiles and alcohols for Mitsunobu reaction.

Table 1. Parallel Synthesis Results[a]

	Mitsunobu product **5**, yield,[b] purity[c] alcohols (**2**)			
nucleophiles (**1**)	W	X	Y	Z
a	**5aW**, 91, 89	**5aX**, 81, 95	**5aY**, 85, 89	**5aZ**, 77, 95
b	**5bW**, 85, 88	**5bX**, 80, 83	**5bY**, 81, 89	**5bZ**, 81, 80
c	**5cW**, 80, 95	**5cX**, 86, 95	**5cY**, 93, 95	**5cZ**, 73, 95
d	**5dW**, 82, 95	**5dX**, 86, 95	**5dY**, 84, 95	**5dZ**, 93, 89
e	**5eW**, 82, 91	**5eX**, 89, 94	**5eY**, 89, 90	**5eZ**, 63, 90

[a] All experiments were conducted using **23** (0.6 mmol), **14a** (0.6 mmol), the alcohol **2** (0.36 mmol), and the nucleophile **1** (0.3 mmol). [b] Yields are based on mass recovery. [c] Purity refers to the purity of the Mitsunobu product as judged by ^{1}H NMR. Purities determined by LC/MS (ELSD) were >95% unless otherwise indicated.

conducted such that 2 equiv of polymer-bound azodicarboxylate **23** was added to a THF solution containing 1 equiv of nucleophilic substrate **1**, 2 equiv of the anthracene-tagged phosphine **14a**, and 1.2 equiv of alcohol **2** at 0 °C under nitrogen (Scheme 6). Upon completion of the reaction, a filtration to remove the excess of the polymer-bound azodicarboxylate **23** and the resulting byproduct **24** followed by evaporation afforded a product mixture containing the desired product **5** and anthracene-tagged phosphine oxide **25**. The product mixture was dissolved in dioxane and incubated with 4 equiv of polymer-bound maleimide **11**. The mixture was heated to 80 °C to effect complete sequestration of the phosphine oxide **25**. A phosphorus NMR of the filtered resin **30** in *d*-chloroform shows one peak at ~30 ppm (Figure 2), corresponding to the sequestered anthracene-tagged triphenylphosphine oxide. Simple filtration and rinsing with THF yielded a filtrate whereupon evaporation of the solvent left highly purified products **5**. Table 1 summarizes the results obtained. The Mitsunobu product yields ranged from 63 to 93% on the basis of mass recovery with reversed-phase LC purities >95% and NMR purities ranging from 80 to 95%.

In conclusion, we have developed a general method for the Mitsunobu reaction using the combination of polymer-supported azodicarboxylate and anthracene-tagged phosphine. A polymer-supported azodicarboxylate greatly facilitated removal of reaction byproducts as well as excess alcohol through simple filtration. The anthracene-tagged phosphine allows for the removal of the phosphine/phosphine oxide by sequestration through a Diels−Alder reaction using a polymer-bound maleimide dienophile. The tagged phosphine may easily be prepared in large quantities and behaves similarly to triphenylphosphine in initial experiments. Chemoselective removal of the anthracene-tagged phosphine through Diels−Alder cyclization is highly orthogonal and allows for the tolerance of a broad range of functional groups. This methodology is limited only by final products that would react with the polymer-bound dienophile. We are currently investigating the use of the anthracene-tagged phosphines and other reagents for additional chemical transformations and catalyst systems, which will be the topic of future publications.

Experimental Section

General Information. ^{1}H NMR spectra were recorded on a 300-MHz spectrometer at ambient temperature unless otherwise stated. ^{13}C NMR spectra were recorded on a 75.4-MHz spectrometer at ambient temperature. ^{31}P NMR spectra were recorded on a 121.1-MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to TMS. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), and coupling constants. All ^{13}C and ^{31}P NMR spectra were recorded with complete proton decoupling. Unfunctionalized polystyrene resin was obtained from Eastman Fine Chemical. Sample purities were determined by HPLC analysis (Hewlett-Packard series 1100) equipped with a mass spec detector using a C18 3.5-μm, 30 × 2.1-mm column, eluting with a gradient system of 5:95−95:5 acetonitrile/water with a buffer consisting of 0.1% TFA over 4.5 min at 1 mL/min and detected by ELSD. Thin-layer chromatography was performed on 0.25-mm silica gel 1B-F plates (J. D. Baker). Flash chromatography was performed using 230−400 mesh silica gel (Aldrich). Preparative HPLC was performed on Waters LC 2000. The XPERTEK filtration cartridge (15 and 70 mL) was obtained from P. J. Cobert Associates. All reagents and solvents were used as supplied by Sigma-Aldrich, Fluka, and Lancaster.

Synthesis of Maleimide Resin (11) and Determination of the Loading. To a 500-mL round-bottom flask were added unfunctionalized polystyrene resin (2% cross-linking) (13 g) and *N*-chloromethylmaleimide[14(b)] (4.16 g, 28.6 mmol, 1 equiv) followed by 100 mL of CH_2Cl_2 under nitrogen. The mixture was stirred with a stir bar for 10 min. $FeCl_3$ (1.31 g, 8.06 mmol, 0.28 equiv) was added in one portion and followed by 100 mL of CH_2Cl_2. The reaction was stirred at room temperature for 3 days. Using a vacuum suction tube, the resin was washed with CH_2Cl_2 (2 × 250 mL), 1:1 THF/1 M HCl (4 × 250 mL), THF (4 × 250 mL), and CH_2Cl_2 (1 × 250 mL). The extensive washing was necessary to ensure the removal of trace $FeCl_3$. The light yellow resin was dried in a vacuum overnight to afford the maleimide resin **11**.

To determine the synthetically accessible loading of **11**, maleimide resin (100 mg) was mixed with excess of

anthracene compound **12** (78 mg, 0.2 mmol) in toluene (2 mL). The mixture was heated at 80 °C (outside temperature) for 1 day. The resin was filtered and washed with CH_2Cl_2. The filtrate was collected and dried in a vacuum. The recovered anthracene compound **12** was weighed (12 mg; therefore, 66 mg of it reacted with maleimide resin), and the loading was determined on the basis of the weights of the consumed anthracene compound **12** and the resin used (1.69 mmol/g).

Sequestration Efficiency with Anthracene-Tagged Compounds. Anthracene compound **12** (39 mg, 0.1 mmol, 1 equiv) was mixed with excess maleimide resin **11** (120 mg, 1.69 mmol/g loading, 0.20 mmol, 2 equiv) in toluene (1 mL). The reaction was heated at 80 °C with stirring for 1 day. After filtration and washing several times, the combined filtrate was concentrated and dried in a vacuum. ^{1}H NMR of the residue showed no detectable anthracene compound **12** present.

9-Anthrylmethyl-4-(diphenylphosphino)benzoate (14a). To a 500-mL round-bottom flask were added 9-anthracenemethanol **16a** (6.00 g, 28.81 mmol, 1 equiv), 4-(diphenylphosphino)benzoic acid **17** (8.82 g, 28.81 mmol, 1 equiv) and 4,4-(dimethylamino)pyridine (1.40 g, 11.52 mmol, 0.4 equiv), followed by CH_2Cl_2 (100 mL). The suspension was stirred for 5 min, then 1,3-dicyclohexylcarbodiimide (5.94 g, 28.82 mmol, 1 equiv) was added as a solid, followed by more CH_2Cl_2 (80 mL). After stirring under nitrogen overnight, the mixture was filtered through a tightly packed Celite plug, followed by washing with CH_2Cl_2. Most of the white powder 1,3-dicyclohexylurea was removed by the filtration. The brownish filtrate was concentrated to a small volume and purified with preparative HPLC (EtOAc/hexane = 10/90) to afford anthracene-tagged phosphine **14a** as a light yellow foam (12.19 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ 8.56 (1H, s), 8.51 (2H, d, J = 8.7 Hz), 8.09 (2H, d, J = 8.1 Hz), 8.03 (2H, d, J = 6.9 Hz), 7.67−7.62 (2H, m), 7.56 (2H, t, J = 7.3 Hz), 7.40−7.32 (12H, m), 6.46 (2H, s); ^{13}C NMR ($CDCl_3$) δ 166.8, 144.5 (d, J_{CP} = 14.3 Hz), 136.4 (d, J_{CP} = 10.6 Hz), 134.2 (d, J_{CP} = 20.0 Hz), 133.4 (d, J_{CP} = 18.7 Hz), 131.6 (d, J_{CP} = 18.2 Hz), 130.2, 129.8 (d, J_{CP} = 6.4 Hz), 129.6, 129.5, 129.4, 129.0 (d, J_{CP} = 7.2 Hz), 127.0, 126.5, 125.4, 124.3, 59.7; ^{31}P NMR ($CDCl_3$) δ −3.9 ppm; HRMS m/z calcd for $C_{34}H_{26}PO_2$ (M + H) 497.1665, found 497.1633.

***N*-(9-Anthrylmethyl)-4-(diphenylphosphino)benzamide (14b).** To a 500-mL round-bottom flask was added 4-(diphenylphosphino)benzoic acid **17** (4.20 g, 13.80 mmol, 1.1 equiv), EDC (2.65 g, 13.80 mmol, 1.1 equiv), and HOBt (1.86 g, 13.80 mmol, 1.1 equiv), followed by addition of CH_2Cl_2 (140 mL). The mixture was stirred under nitrogen for 5 min prior to the addition of 9-aminomethylanthracene **16b** (2.6 g, 12.54 mmol, 1 equiv) in DMF (28 mL). The afforded orange solution was stirred under nitrogen overnight. Polystyrene-diethylenetriamine[18] (26.20 g, 2.63 mmol/g loading, 68.90 mmol, 5 equiv to HOBt) was added to the solution followed by CH_2Cl_2 (100 mL). The mixture was stirred for 2 h, followed by filtration and washing with CH_2Cl_2. Final concentration of the filtrate and flash chromatography (EtOAc/hexane = 10/90, then EtOA/hexane = 50/50) gave **14b** as a light yellow solid (4.30 g, 69% yield). ^{1}H NMR ($CDCl_3$) δ 8.53 (1H, s), 8.38 (2H, d, J = 9.0 Hz), 8.09 (2H, d, J = 8.1 Hz), 7.69−7.51 (6H, m), 7.36−7.26 (12H, m), 6.30 (1H, b), 5.66 (2H, d, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 142.4 (d, J_{CP} = 13.7 Hz), 136.5 (d, J_{CP} = 10.4 Hz), 134.1 (d, J_{CP} = 19.8 Hz), 133.8 (d, J_{CP} = 19.0 Hz), 131.8, 130.7, 129.6, 129.5, 129.3, 128.9 (d, J_{CP} = 7.2 Hz), 128.6, 128.4, 127.2 (d, J_{CP} = 6.6 Hz), 127.1, 125.5, 124.0, 37.0; ^{31}P NMR ($CDCl_3$) δ −4.4 ppm; LC/MS: m/z = 496 (M + 1) at T_R = 4.25 min.

9-Anthrylmethyl 4-Nitrophenyl Carbonate (20). To a stirred solution of *p*-nitrophenylchloroformate (1.06 g, 5.28 mmol, 1.1 equiv) was added pyridine (0.42 g, 5.28 mmol, 1.1 equiv). The formed white slurry was cooled to 0 °C, and 9-anthracenemethanol **16a** (1 g, 4. 80 mmol, 1 equiv) was added as a solid in several portions to maintain a temperature of 0 °C. After complete addition, the yellow mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and subsequently washed with 0.5 N HCl (10 mL), water (4 × 20 mL), and brine (20 mL); dried with Na_2SO_4; and concentrated under reduced pressure. The yellow residue was purified by column chromatography (EtOAc/hexane = 15/85) to yield **20** as light yellow needles (1.57 g, 86% yield). ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, s), 8.46 (2H, d, J = 9.0 Hz), 8.31−8.28 (2H, m), 8.11 (2H, d, J = 8.4 Hz), 7.70−7.64 (2H, m), 7.60−7.55 (2H, m), 7.42−7.40 (2H, m), 6.44 (2H, s); ^{13}C NMR ($CDCl_3$) δ 155.8, 153.0, 131.6, 131.5, 130.4, 129.5, 127.4, 125.54, 125.50, 124.6, 123.9, 122.0, 63.9 ppm; LC/MS: m/z = 191 (fragmentation) at T_R = 3.7 min.

9-Anthrylmethyl Ethyl Hydrazine-1,2-dicarboxylate (21). A mixture of 9-anthrylmethyl *p*-nitrophenyl carbonate **20** (100 mg, 0.268 mmol, 1 equiv), ethyl carbazate (31 mg, 0.295 mmol, 1.1 equiv), and HOBt (7.2 mg, 0.054 mmol, 0.2 equiv) in DMF (2 mL) was treated with diisopropylethylamine (34.6 mg, 0.268 mmol, 1 equiv). The afforded solution turned orange immediately and was stirred overnight. The solution was diluted with CH_2Cl_2 (10 mL), and polystyrene-diethylenetriamine[18] (700 mg, 2.62 mmol/g, 1.84 mmol) was added to the solution. The mixture was stirred overnight, filtered, and washed with CH_2Cl_2. LC/MS confirmed the removal of most HOBt and *p*-nitrophenol. The yellow filtrate was concentrated, and the residue was purified by column chromatography (EtOAc/hexane = 20/80, 50 mL; EtOAc/hexane = 30/70, 100 mL; EtOAc/hexane, 40/60, 100 mL) to yield **21** as a light yellow solid (70 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (1H, s), 8.34 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.4 Hz), 7.58−7.53 (2H, m), 7.49−7.45 (2H, m), 6.48 (1H, b), 6.41 (1H, b), 6.20 (2H, s), 4.18 (2H, b), 1.26−1.22 (3H, m); ^{13}C NMR ($CDCl_3$) δ 157.0, 156.9, 131.6, 131.3, 129.7, 129.3, 127.0, 125.9, 125.4, 124.2, 62.6, 60.7, 14.6 ppm; LC/MS: m/z = 191 (fragmentation) at T_R = 2.75 min; HRMS m/z calcd for $C_{19}H_{22}N_3O_4$ (M + NH_4) 356.1605, found 356.1603.

Ethyl 13-Oxo-10*H*-10,9,9-(diazane[1,2,2]triylmethanooxymethano)anthracene-11-carboxylate (22). Iodobenzene diacetate (80 mg, 0.248 mmol, 1.2 equiv) was added to a solution of hydrazine **21** (70 mg, 0.207 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at 0 °C. Additional CH_2Cl_2 (1 mL) was

added, and the yellow solution was stirred at room temperature overnight. The solution was concentrated, and the residue was purified by column chromatography (hexane, 100 mL; EtOAc/hexane = 10/90, 50 mL; EtOAc/hexane = 20/80, 50 mL; EtOAc/hexane, 30/70, 50 mL; EtOAc/hexane = 40/60, 50 mL) to yield **22** as white solid (65 mg, 93% yield). LC/MS: $m/z = 337$ (M + 1) at $T_R = 2.41$ min was observed. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.39 (2H, m), 7.22−7.19 (6H, m), 6.27 (1H, s), 5.17 (2H, b), 4.10 (2H, q, $J = 7.2$ Hz), 1.15 (3H, t, $J = 7.2$ Hz).

Single-Crystal Structure Determination of 22. $C_{19}H_{16}N_2O_4$; Space group: $P2_1/n$; cell parameters: $a = 7.6579$ Å, $b = 9.0882$ Å, $c = 22.5020$ Å, $\beta = 90.690°$; molecular weight = 336.34; $Z = 4$; calculated density = 1.43 g/cm^3. A clear, chunky crystal was selected and mounted on a glass fiber. The data were collected on a Bruker SMART 6K CCD X-ray area detector with window diameter of 13.5 cm. It was controlled by an NT-based PC computer with SMART-NT version 5.0 software (Bruker, 1998), at low temperature (−120 °C), with graphite-monochromatized Cu$K\alpha$ radiation [λ(Cu$K\alpha$) = 1.5405 Å]. All reflections were measured in six image groups, with 606 frames in each group; the exposure time was 5 s/frame. Three groups of images were collected at $2\theta = -40°$, and the other three groups were at $2\theta = -80°$. The sample/detector distance was 5.073 cm. The data reduction program, SAINT-NT version 5.0 (Bruker, 1998), determined the Laue group was 2/m, and a total of 2160 unique reflections were integrated for structure solution and refinements. The structure was solved by direct methods, using SHELXS version 5.0 (Bruker, 1995). The trial solution obtained 25 non-hydrogen atoms in the asymmetrical unit. Least squares refinement included all non-hydrogen atomic coordinates and anisotropic thermal parameters. With one molecule in the asymmetrical unit, the final refinement cycle, with all 2160 reflections, $R = 0.0422$, $S = 1.071$, $R_w = 0.1262$; with 1944 reflections having intensities $>4\sigma$, $R = 0.0391$.

Loading Determination of Commercially Available Azodicarboxylate on Polystyrene. Two commercially available samples were tested. One was from Fluka (diethyl azodicarboxylate on polystyrene; Lot no., 12359/1 62502; reported loading, 0.6 mmol/g; light yellow chunk); the other was from Novabiochem (ethoxycarbonylazocarboxymethyl polystyrene, Lot no. A27447; reported loading, 1.30 mmol/g; deep yellow separate beads).

Into separate vials was added the polymer-supported azodicarboxylate **23** either from Fluka (200 mg, theoretically 0.12 mmol, 1 equiv) or from Novabiochem (200 mg, theoretically 0.26 mmol, 1 equiv) followed by the corresponding amount of triphenylphosphine (31.5 mg, 0.12 mmol, 1 equiv for Fluka sample; 68.2 mg, 0.26 mmol, 1 equiv for Novabiochem sample) and THF (2 mL/each) as solvent. The mixtures were stirred at room temperature for 30 min, and no obvious color fading was observed. After addition of water (500 μL/each), immediate color fading was observed for both reactions. The mixtures were stirred for another 30 min, then filtered and washed with THF. The yellow filtrates were concentrated and dried in a vacuum to give a yellow solid. ^{1}H NMR (CD_3OD) analysis of the ratio of remaining triphenylphosphine (δ 7.3) to triphenylphosphine oxide (δ 7.5) indicated the level of active azodicarboxylate units. Examination of the sample from Fluka in this manner showed 0.33 mmol/g of usable azodicarboxylate units, corresponding to 55% of the 0.6 mmol/g possible. Similar examination of the sample from Novabiochem gave 1.19 mmol/g available units, corresponding to 92% of the 1.3 mmol/g possible.

General Mitsunobu Reaction Procedure Using Anthracene-Tagged Phosphine and Polymer-Bound Azodicarboxylate. The nucleophilic substrate R_1XH **1** (0.3 mmol, 1 equiv) was weighed into a vial followed by addition of the anthracene-tagged phosphine **14a** (298 mg, 0.6 mmol, 2 equiv) and alcohol R_2OH **2** (0.36 mmol, 1.2 equiv). THF (4.5 mL) was added as solvent to dissolve the mixture. The solution was cooled to 0 °C, and polystyrene-supported azodicarboxylate from Novabiochem (500 mg, 1.19 mmol/g loading, 0.6 mmol, 2 equiv) was added. The reaction was maintained at 0 °C for ∼1 h and then gradually warmed to room temperature with stirring. After stirring overnight, the reaction was filtered and washed with THF. The combined filtrate was concentrated and dried in a vacuum. ^{1}H NMR taken at this point generally showed the desired product and the phosphine oxide, which was further confirmed by ^{31}P NMR as a single peak at 29 ppm. The product mixture was dissolved in dioxane (8 mL) and then transferred into a vial containing maleimide resin **11** (800 mg, loading 1.5−1.7 mmol/g, ∼2 equiv to phosphine oxide). The vial was tightly capped, and the mixture was heated at 80 °C with stirring. After 1 day, the reaction was cooled to room temperature, filtered through Celite, and washed with THF to give a colorless or very light pale yellow filtrate. The filtrate was concentrated and dried in a vacuum to afford the desired product.

3-Methylbenzyl 4-Methylnicotinate (5aW). ^{1}H NMR ($CDCl_3$) δ 9.18 (1H, d, $J = 1.8$ Hz), 8.23 (1H, dd, $J = 2.4$, 8.1 Hz), 7.31−7.18 (5H, m), 5.37 (2H, s), 2.65 (3H, s), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$) δ 165.5, 163.4, 150.7, 138.6, 137.8, 135.8, 129.4, 129.2, 128.8, 125.6, 123.2, 67.2, 24.9, 21.6 ppm; LC/MS: $m/z = 242$ (M + 1), $T_R = 2.06$ min; HRMS m/z calcd for $C_{15}H_{16}NO_2$ (M + H) 242.1176, found 242.1164.

Isobutyl 4-Methylnicotinate (5aX). ^{1}H NMR ($CDCl_3$) δ 9.14 (1H, d, $J = 2.1$ Hz), 8.22 (1H, dd, $J = 2.1$, 8.1 Hz), 7.27 (1H, d, $J = 8.1$ Hz), 4.14 (2H, d, $J = 6.6$ Hz), 2.66 (3H, s) 2.15−2.04 (1H, m), 1.04 (6H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 165.6, 163.1, 150.4, 137.8, 124.0, 123.3, 71.5, 28.1, 24.8, 19.4 ppm; LC/MS: $m/z = 194$ (M + 1), $T_R = 1.54$ min; HRMS m/z calcd for $C_{11}H_{16}NO_2$ (M + H) 194.1176, found 194.1214.

1-Methyl-2-phenylethyl 4-methylnicotinate (5aY). ^{1}H NMR ($CDCl_3$) δ 9.10 (1H, d, $J = 1.8$ Hz), 8.16 (1H, dd, $J = 2.1$, 8.1 Hz), 7.31−7.23 (6H, m), 3.09 (1H, dd, $J = 6.7$, 13.5 Hz), 2.94 (1H, dd, $J = 6.3$, 13.5 Hz), 2.64 (3H, s), 1.39 (3H, d, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 165.1, 163.1, 150.6, 137.6, 137.5, 129.7, 128.7, 126.8, 124.1, 123.2, 72.8, 42.5, 24.9, 19.8 ppm; LC/MS: $m/z = 256$ (M + 1), $T_R = 2.11$ min; HRMS m/z calcd for $C_{16}H_{18}NO_2$ (M + H) 256.1332, found 256.1335.

4-*tert*-Butylcyclohexyl 4-Methylnicotinate (5aZ). NMRs are reported as the mixture of cis and trans isomers, ratio 1:4. ^{1}H NMR ($CDCl_3$) δ 9.14 (1H, d, J = 2.1 Hz, major) and 9.10 (1H, d, J = 1.8 Hz, minor), 8.21−8.16 (1H, m, mixture of major and minor), 7.27−7.22 (1H, m, mixture of major and minor), 5.31−5.30 (1H, m, major) and 4.96−4.85 (1H, m, minor), 2.64 (3H, s, major) and 2.63 (3H, s, minor), 2.19−1.07 (9H, m, mixture of major and minor), 0.90 (9H, s, major) and 0.89 (9H, s, minor); ^{13}C NMR ($CDCl_3$) δ 165.0, 163.1, 150.6, 137.6 (minor) and 137.5 (major), 124.5, 123.2 (major) and 123.0 (minor), 74.9 (minor) and 70.7 (major), 47.7 (major) and 47.4 (minor), 32.8 (major) and 32.6 (minor), 32.4 (minor) and 30.9 (major), 27.8 (minor) and 27.7 (major), 25.0 (major) and 24.9 (minor), 25.7 (minor) and 22.0 (major) ppm; LC/MS: m/z = 276 (M + 1), T_R = 2.89 min; HRMS m/z calcd for $C_{17}H_{26}NO_2$ (M + H) 276.1958, found 276.1931.

3-Methylbenzyl 4-Methoxybenzoate (5bW). ^{1}H NMR ($CDCl_3$) δ 8.10−8.06 (2H, m), 7.33−7.19 (4H, m), 6.98−6.95 (2H, m), 5.36 (2H, s), 3.90 (3H, s), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 166.5, 163.7, 138.5, 136.5, 132.0, 129.2, 129.1, 128.8, 125.5, 122.9, 113.9, 66.7, 55.7, 21.7 ppm; LC/MS: m/z = 279 (M + 23), T_R = 3.36 min; HRMS m/z calcd for $C_{16}H_{16}O_3$ (M^+) 256.1093, found 256.1089.

Isobutyl 4-Methoxybenzoate (5bX). ^{1}H NMR ($CDCl_3$) δ 8.06−8.03 (2H, m), 6.97−6.94 (2H, m), 4.11 (2H, d, J = 6.6 Hz), 3.89 (3H, s), 2.18−2.04 (1H, m), 1.05 (6H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 163.5, 131.8, 123.2, 113.8, 71.0, 55.7, 28.2, 19.5 ppm; LC/MS: m/z = 153 (fragmentation), T_R = 3.14; HRMS m/z calcd for $C_{12}H_{16}O_3$ (M^+) 208.1116, found 208.1132.

1-Methyl-2-phenylethyl 4-Methoxybenzoate (5bY). ^{1}H NMR ($CDCl_3$) δ 8.04−8.01 (2H, m), 7.37−7.23 (5H, m), 6.97−6.94 (2H, m), 5.45−5.34 (1H, m), 3.90 (3H, s), 3.12 (1H, dd, J = 6.3, 13.5 Hz), 2.94 (1H, dd, J = 6.6, 13.5 Hz), 1.38 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 166.01, 163.5, 137.9, 131.8, 129.8, 128.6, 126.7, 123.4, 113.8, 72.0, 55.7, 42.6, 19.8 ppm; LC/MS: m/z = 293 (M + 23), T_R = 3.42 min; HRMS m/z calcd for $C_{17}H_{18}O_3$ (M^+) 270.1248, found 270.1244.

4-*tert*-Butylcyclohexyl 4-Methoxybenzoate (5bZ). NMRs are reported as the mixture of cis and trans isomers, ratio 1:2. ^{1}H NMR ($CDCl_3$) δ 8.06−8.03 (2H, m), 6.98−6.95 (2H, m), 5.28−5.27 (1H, m, major) and 4.94−4.83 (1H, m, minor), 3.89 (3H, s, major) and 3.88 (3H, s, minor), 2.20−1.06 (9H, m), 0.93 (9H, s, major) and 0.91 (9H, s, minor); ^{13}C NMR ($CDCl_3$) δ 166.2 (minor) and 165.9 (major), 163.4, 131.8 (minor) and 131.7 (major), 123.9 (major) and 123.7 (minor), 113.8 (major) and 113.7 (minor), 74.2 (minor) and 69.8 (major), 55.7, 47.8 (major) and 47.4 (minor), 32.8 (major) and 32.6 (minor), 32.5 (minor) and 31.0 (major), 27.9 (minor) and 27.7 (major), 25.8 (minor) and 22.1 (major) ppm; LC/MS: m/z = 313 (M + 23), T_R = 4.19 and 4.31 min (2 isomers); HRMS m/z calcd for $C_{18}H_{26}O_3$ (M^+) 290.1879, found 290.1878.

3-Methylbenzyl 4-Nitrophenyl Ether (5cW). ^{1}H NMR ($CDCl_3$) δ 8.26−8.22 (2H, m), 7.37−7.21 (4H, m), 7.09−7.06 (2H, m), 5.17 (2H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 164.0, 138.9, 135.7, 129.6, 129.0, 128.5, 126.2, 124.9, 115.1, 71.0, 21.7 ppm; LC/MS: m/z = 244 (M + 1), T_R = 3.36 min; HRMS m/z calcd for $C_{14}H_{13}NO_3$ (M^+) 243.0889, found 243.0885.

Isobutyl 4-Nitrophenyl Ether (5cX). ^{1}H NMR ($CDCl_3$) δ 8.23−8.20 (2H, m), 6.99−6.96 (2H, m), 3.84 (2H, d, J = 6.6 Hz), 2.22−2.09 (1H, m), 1.08 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 164.6, 126.1, 114.7, 75.4, 28.4, 19.4 ppm; LC/MS: m/z = 196 (M + 1), T_R = 3.22 min; HRMS m/z calcd for $C_{10}H_{13}NO_3$ (M^+) 195.0892, found 195.0888.

1-Methyl-2-phenylethyl 4-Nitrophenyl Ether (5cY). ^{1}H NMR ($CDCl_3$) δ 8.22−8.19 (2H, m), 7.38−7.25 (5H, m), 6.97−6.94 (2H, m), 4.80−4.70 (1H, m), 3.15 (1H, dd, J = 6.4, 13.5 Hz), 2.94 (1H, dd, J = 6.1, 13.5 Hz), 1.41 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 163.4, 137.6, 129.7, 128.8, 127.0, 126.2, 115.6, 75.9, 42.8, 19.6 ppm; LC/MS: m/z = 258 (M + 1), T_R = 3.46 min; HRMS m/z calcd for $C_{15}H_{15}NO_3$ (M^+) 257.1044, found 257.1039.

4-*tert*-Butylcyclohexyl 4-Nitrophenyl Ether (5cZ). NMRs are reported as the mixture of cis and trans isomers, ratio 1:3. ^{1}H NMR ($CDCl_3$) δ 8.23−8.20 (2H, m), 7.00−6.96 (2H, m), 4.70−4.68 (1H, m, major) and 4.32−4.22 (1H, m, minor), 2.25−1.07 (9H, m), 0.92 (9H, s, minor) and 0.91 (9H, s, major); ^{13}C NMR ($CDCl_3$) δ 163.4, 126.2, 115.7 (major) and 115.5 (minor), 72.8, 47.8 (major) and 47.4 (minor), 32.8 (major) and 32.6 (minor), 32.3 (minor) and 30.4 (major), 27.9 (minor) and 27.7 (major), 25.7 (minor) and 21.6 (major) ppm; LC/MS: m/z = 278 (M + 1), T_R = 4.27 min; HRMS m/z calcd for $C_{16}H_{23}NO_3$ (M^+) 277.1684, found 277.1687.

2-[(3-Methylbenzyl)oxy]-1*H*-isoindole-1,3(2*H*)-dione (5dW). ^{1}H NMR ($CDCl_3$) δ 7.86−7.82 (2H, m), 7.79−7.75 (2H, m), 7.40−7.20 (4H, m), 5.21 (2H, s), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$) δ 173.8, 138.5, 134.7, 133.8, 130.8, 130.4, 129.2, 128.7, 127.2, 123.7, 80.2, 21.6 ppm; LC/MS: m/z = 290 (M + 23), T_R = 2.91 min; HRMS m/z calcd for $C_{16}H_{14}NO_3$ (M + H) 268.0968, found 268.0962.

2-Isobutoxy-1*H*-isoindole-1,3(2*H*)-dione (5dX). ^{1}H NMR ($CDCl_3$) δ 7.87−7.82 (2H, m), 7.80−7.75 (2H, m), 4.00 (2H, d, J = 6.9 Hz), 2.20−2.07 (1H, m), 1.08 (6H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 163.8, 134.6, 129.3, 123.7, 85.0, 27.8, 19.2 ppm; LC/MS: m/z = 220 (M + 1), T_R = 2.65 min; HRMS m/z calcd for $C_{12}H_{14}NO_3$ (M + H) 220.0968, found 220.0962.

2-(1-Methyl-2-phenylethoxy)-1*H*-isoindole-1,3(2*H*)-dione (5dY). ^{1}H NMR ($CDCl_3$) δ 7.87−7.82 (2H, m), 7.80−7.75 (2H, m), 7.34−7.20 (5H, m), 4.76−4.66 (1H, m), 3.27 (1H, dd, J = 5.7, 13.8 Hz), 2.92 (1H, dd, J = 7.8, 13.8 Hz), 1.36 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 164.5, 137.4, 134.7, 129.6, 129.2, 128.7, 126.8, 123.7, 84.9, 41.6, 18.6 ppm; LC/MS: m/z = 304 (M + 23), T_R = 3.02 min; HRMS m/z calcd for $C_{17}H_{16}NO_3$ (M + H) 282.1125, found 282.1138.

2-[(4-*tert*-Butylcyclohexyl)oxy]-1*H*-isoindole-1,3(2*H*)-dione (5dZ). NMRs are reported as the mixture of cis and trans isomers, ratio 1:1.8. ^{1}H NMR ($CDCl_3$) δ 7.87−7.81 (2H, m), 7.78−7.74 (2H, m), 4.50−4.46 (1H, m, major) and 4.22−4.12 (1H, m, minor), 2.23−1.02 (9H, m), 0.92 (9H, s, major) and 0.86 (9H, s, minor); ^{13}C NMR ($CDCl_3$) δ 164.6 (minor) and 164.5 (major), 134.6 (minor) and 134.5 (major), 129.4 (major) and 129.2 (minor), 123.7 (minor) and 123.6 (major), 86.8 (minor) and 82.6 (major), 47.9 (major) and

47.3 (minor), 32.9 (major) and 32.5 (minor), 31.4 (minor) and 30.0 (major), 27.8 (minor) and 27.7 (major), 25.5 (minor) and 21.5 (major) ppm; LC/MS: $m/z = 324$ (M + 23), $T_R =$ 3.78 min; HRMS m/z calcd for $C_{18}H_{24}NO_3$ (M + H) 302.1751, found 302.1754.

4-Methyl-2-(3-methylbenzyl)-1*H*-isoindole-1,3(2*H*)-dione (5eW). ^{1}H NMR ($CDCl_3$) δ 7.75 (1H, d, $J = 7.8$ Hz), 7.67 (1H, s), 7.52 (1H, d, $J = 7.8$ Hz), 7.27−7.20 (3H, m), 7.12−7.09 (1H, m), 4.83 (2H, s), 2.53 (3H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.5, 168.4, 145.5, 138.6, 136.7, 134.7, 132.8, 129.8, 129.5, 128.8, 125.9, 124.1, 123.5, 41.8, 22.2, 21.6 ppm; LC/MS: $m/z = 266$ (M + 1), $T_R = 3.19$ min; HRMS m/z calcd for $C_{17}H_{16}NO_2$ (M + H) 266.1176, found 266.1140.

2-Isobutyl-4-methyl-1*H*-isoindole-1,3(2*H*)-dione (5eX). ^{1}H NMR ($CDCl_3$) δ 7.73 (1H, d, $J = 7.5$ Hz), 7.65 (1H, s), 7.51 (1H, d, $J = 7.5$ Hz), 3.50 (2H, d, $J = 7.5$ Hz), 2.52 (3H, s), 2.20−2.06 (1H, m), 0.95 (6H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.1, 169.0, 145.3, 134.6, 132.7, 129.7, 124.0, 123.3, 45.5, 28.1, 22.2, 20.3 ppm; LC/MS: $m/z =$ 218 (M + 1), $T_R = 2.92$ min; HRMS m/z calcd for $C_{13}H_{16}NO_2$ (M + H) 218.1176, found 218.1164.

4-Methyl-2-(1-methyl-2-phenylethyl)-1*H*-isoindole-1,3-(2*H*)-dione (5eY). ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, d, $J = 7.8$ Hz), 7.58 (1H, s), 7.47 (1H, d, $J = 7.8$ Hz), 7.30−7.15 (5H, m), 4.70−4.62 (1H, m), 3.35 (1H, dd, $J = 9.1$, 13.5 Hz), 3.13 (1H, dd, $J = 6.7$, 13.5 Hz), 2.50 (3H, s), 1.55 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.7, 145.2, 138.8, 134.5, 132.5, 129.7, 129.2, 128.6, 126.7, 123.8, 123.2, 48.8, 40.2, 22.2, 18.6 ppm; LC/MS: $m/z = 280$ (M + 1), $T_R =$ 3.30 min; HRMS m/z calcd for $C_{18}H_{18}NO_2$ (M + H) 280.1332, found 280.1319.

2-(4-*tert*-Butylcyclohexyl)-4-methyl-1*H*-isoindole-1,3-(2*H*)-dione (5eZ). NMRs are reported as the mixture of cis and trans isomers, ratio 1:3. ^{1}H NMR ($CDCl_3$) δ 7.71 (1H, d, $J = 7.8$ Hz), 7.63 (1H, s), 7.50 (1H, d, $J = 7.5$ Hz), 4.42−4.33 (1H, m, major) and 4.16−4.03 (1H, m, minor), 2.52 (3H, s), 2.30−1.15 (9H, m), 0.95 (9H, s, major) and 0.91 (9H, s, minor); ^{13}C NMR ($CDCl_3$) δ 169.3, 169.2, 145.2, 134.5 (major) and 134.4 (minor), 129.8, 123.8 (minor) and 123.1 (major), 123.1 (minor) and 123.0 (major), 51.2 (minor) and 47.9 (major), 47.0 (minor) and 44.0 (major), 33.3 (major) and 32.6 (minor), 28.3 (major) and 27.8 (minor), 28.0 (major) and 27.7 (minor), 27.0 (minor) and 23.6 (major), 22.2 (major) and 21.6 (minor) ppm; LC/MS: $m/z = 300$ (M + 1), $T_R =$ 4.21 min; HRMS m/z calcd for $C_{19}H_{26}NO_2$ (M + H) 300.1958, found 300.1987.

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Supporting Information Available. Characterization data for all compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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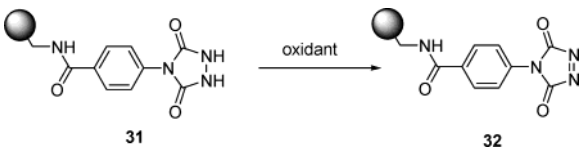
(14) The urazole **31** was successfully synthesized on polystyrene, and the loading was confirmed by elemental analysis to be 1.44 mmol/g. The oxidation of the polymer-supported urazole afforded a red resin, which is characteristic of the formation of TAD **32**. Various oxidants and reaction conditions were tested, but none gave synthetically accessible loading of **32** higher than 0.4 mmol/g.



31 **32**

(15) (4-Maleimidobutyramidomethyl)polystyrene **11b** was purchased from Fluka.

(16) The second-order kinetic rate constant for polymer-supported maleimide **11** was determined to be 10.8 M^{-1} h^{-1}; see ref

10 of Supporting Information for details. The second-order kinetic rate constant for **11b** was determined to be 17.7 M^{-1} h^{-1}, which is slightly higher than **11**, presumably as a result of better accessibility of resin **11b**. But because of the low loading, the time for >99% scavenging by resin **11b** would be 24 h, instead of 13 h by resin **11**, when the same condition was used (1 equiv anthracene-tagged compound **12**, 1.2 equiv maleimide resin, and 10 mL solvent per gram of resin).

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