Polymer-Supported Alkyl Azodicarboxylates for Mitsunobu Reactions

Lee D. Arnold, Hanaa I. Assil, and John C. Vederas*

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received September 9, 1988*

Abstract: Reaction of hydroxymethyl polystyrene **1** (1% cross-linked) with phosgene followed by methyl carbazate gives methyl hydrazodicarboxylate polystyrene resin **2**, which upon oxidation (e.g., *N*-bromosuccinimide/pyridine or chlorine/water) affords methyl azodicarboxylate polystyrene resin **3**. This substitute for soluble dialkyl azodicarboxylates functions well as an easily separable (insoluble) and nonexplosive reagent in Mitsunobu reactions. In the cases examined, yields of hydroxyl replacement by oxygen, nitrogen, and carbon nucleophiles are comparable, product purification is facilitated, and the polymeric reagent can be reoxidized and reused at least five times without loss of activity.

The Mitsunobu reaction, which involves activation of an alcohol by the adduct of triphenylphosphine and a dilakyl azodicarboxylate, is an extremely versatile means of nucleophilic replacement of hydroxyl groups (Figure 1).[1] This reaction, whose mechanism has been extensively studied,[2] generally requires that the nucleophile be present as its conjugate acid, HX, with $pK_A \leq 11$.[3] Since this process usually proceeds under mild conditions with complete inversion of configuration by C, N, O, and halogen nucleophiles,[1] it is a popular synthetic method,[4] especially for alteration of alcohol stereochemistry. Major limitations on its large-scale use are associated with the azodicarboxylate reagent.[5] These include the expense of dialkyl azodicarboxylates, the tendency of some of them to explode,[6] and difficulties in separation of any unconsumed reagent and its reduced form from desired products. Our interest in Mitsunobu cyclization of N-protected serines to α-amino-β-propiolactone derivatives for use in amino acid syntheses[7] led us to search for means to overcome these problems. The present work describes the preparation and use of an immobilized (polystyrene supported)[8] alkyl azodicarboxylate reagent that is safe, easily separated, and can be recycled repeatedly with negligible loss of activity.

Table I. Active Sites on Polystyrene Resins **1**, **2**, and **3**

	resin					
	1		**2**		**3**	
	mequiv/g[a]	mol %[a]	mequiv/g[b]	mol %[b]	mequiv/g[c]	mol %[c]
a	1.0	11.0	0.75	8.7	0.61	7.3
b	4.2	50.0	2.4	43.0	2.1	38.0
c	0.55	5.8	0.40	4.5	0.27	3.0

[a] Values given for commercial material. [b] Hydrazodicarboxylate sites based on N elemental analysis. [c] Accessible azodicarboxylate sites based on reaction with Ph_3P and H_2O.

Results and Discussion

Preparation and Analysis of Polystyrene-Supported Methyl Azodicarboxylate. An ideal polymeric support matrix for the Mitsunobu reaction should be available in insoluble bead form for easy separation, mechanically stable to physical manipulations, inert to reaction conditions, hydrophobic, and capable of swelling in organic solvents to facilitate reactions.[8] In addition, an initial absence of nitrogen aids measurement of loading by elemental combustion analysis. These considerations suggest that commercially available 1% cross-linked hydroxymethyl polystyrene resin **1** is a suitable starting material.

Resins with intermediate (**a** series), heavy (**b** series), and light (**c** series) degrees of "loading" of functional groups have been prepared. The resin **1a** (1 mequiv/g, ~10 mol % loading) was swollen in dichloromethane, converted to the corresponding chloroformate with phosgene and pyridine, and subsequently treated with methyl carbazate (hydrazinocarboxylate) and triethylamine to produce the methyl hydrazodicarboxylate resin **2a** (Figure 2). Incorporation of this functionality was evident from the very strong carbonyl band in the IR spectrum (1790–1680 cm^{-1}, Fluorolube mull). Elemental analysis was consistent with derivatization of 88% of the available hydroxymethyl groups (i.e., 0.75 mequiv/g, 9 mol %). A resin more heavily loaded with hydroxymethyl groups, **1b** (4.2 mequiv/g, ~50 mol % loading), could be generated from commercially available chloromethylated polystyrene (Merrifield peptide resin[9]) by a simple two-step literature procedure.[10] Both **1b** and the more lightly loaded resin

(1) (a) Mitsunobu, O. *Synthesis* **1981**, 1-28. (b) Castro, B. R. *Organic Reactions*; Wiley: New York, 1983; Vol. 29, pp 1-162.

(2) (a) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557-563. (b) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876-6877. (c) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843-1845. (d) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235-4238. (e) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487-6491.

(3) In certain cases reactions will proceed even if HX has a higher pK_A: Townsend, C. A.; Nguyen, L. *Tetrahedron Lett.* **1982**, *23*, 4859-4862. In other examples the nucleophile can be attached to another electrophile or "nucleophile carrier". For instance, methyl iodide will react with an alcohol in the presence of Ph_3P and diethyl azodicarboxylate (DEAD) to give an alkyl iodide.[1] However attack by an external nucleophile can be difficult; addition of sodium benzoate (a good nucleophile) to a mixture of alcohol, Ph_3P, DEAD, and trifluoroacetic acid causes rapid decomposition of the intermediate alkoxyphosphonium salt to give exclusively the trifluoroacetate ester and no significant amount of benzoate ester.[2d]

(4) For a few recent examples see: (a) Smith, A. B., III; Hale, K. J.; Rivero, R. A. *Tetrahedron Lett.* **1986**, *27*, 5813-5816. (b) Hayashida, M.; Sakairi, N.; Kuzuhara, H. *Carbohydr. Res.* **1986**, *154*, 115-126. (c) Jenkins, I. D.; Goren, M. B. *Chem. Phys. Lipids* **1986**, *41*, 225-235. (d) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961-5968. (e) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978-4984. (f) Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med. Chem.* **1987**, *80*, 1837-1842. (g) Kori, M.; Itoh, K.; Sugihara, H. *Chem. Pharm. Bull.* **1987**, *35*, 2319-2326. (h) Hanessian, S.; Sahoo, S. P.; Botta, M. *Tetrahedron Lett.* **1987**, *28*, 1143-1146. (i) Jarosz, S.; Glodek, J.; Zamojski, A. *Carbohydr. Res.* **1987**, *163*, 289-296. (j) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190-192. (k) Weinges, K.; Haremsa, S.; Maurer, W. *Carbohydr. Res.* **1987**, *164*, 453-458. (l) Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218-1219. (m) Pautard, A. M.; Evans, S. A., Jr. *J. Org. Chem.* **1988**, *53*, 2300-2303.

(5) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49-56.

(6) Kauer, J. C. In *Organic Syntheses*, Collect. IV; Rabjohn, N., Ed.; Wiley: New York, 1963; pp 411-415.

(7) (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105-7109. (b) Ramer, S. E.; Moore, R. N.; Vederas, J. C. *Can. J. Chem.* **1986**, *64*, 706-713. (c) Arnold, L. D.; Drover, J. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649-4659. (d) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237-2241.

(8) For recent reviews of polymer-supported reagents see: (a) Hodge, P. *Annu. Rep. Prog. Chem., Sect. B* **1987**, *83*, 283-302. (b) Frêchet, J. M. J.; Darling, G. D.; Itsuno, S.; Lu, P.-Z.; Vivas de Meftahi, M.; Rolls, W. A., Jr. *Pure Appl. Chem.* **1988**, *60*, 353-364. (c) Guyot, A. *Pure Appl. Chem.* **1988**, *60*, 365-376.

(9) (a) Birr, C. *Aspects of the Merrifield Peptide Synthesis*; Springer-Verlag: Berlin, 1978. (b) Bodanszky, M. *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; pp 159-173.

(10) The chloromethyl polystyrene resin was transformed to the acetoxymethyl form with potassium acetate; this was then cleaved to the hydroxymethyl polystyrene with lithium aluminum hydride or, preferably, with hydrazine. See: Wang, S. S. *J. Org. Chem.* **1975**, *40*, 1235-1239.

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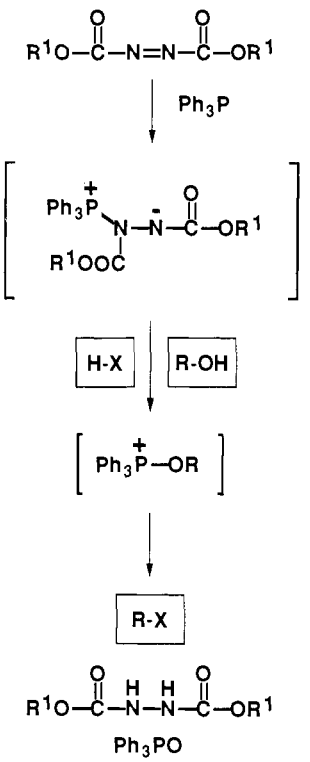

Figure 1. The Mitsunobu reaction.

1c (0.55 mequiv/g, 6 mol % loading) were readily converted to **2b** and **2c**, respectively, by reactions analogous to those used to synthesize **2a**. Attempts to replace phosgene in these procedures with phenyl chloroformate were partially successful, but resins prepared in this way could not be reliably recycled (see below). Oxidation of the white methyl hydrazodicarboxylate resins **2a**, **2b**, and **2c** by *N*-bromosuccinimide and pyridine in dichloromethane afforded the corresponding yellow-orange methyl azodicarboxylates **3a**, **3b**, and **3c** (≥94% conversion). Such oxidations were also readily done with chlorine and water, and less effectively (not optimized) with dinitrogen tetraoxide.[6,11]

The extent of reaction was estimated by elemental analysis and by comparison of relative intensities of the N–H absorption bands at 3360 cm^{-1}. In order to determine the concentration of accessible (i.e., synthetically usable) azodicarboxylate functionalities on the resin, the polystyrene derivatives **3** were treated with a known amount of excess triphenylphosphine in THF, and the resulting adduct was quenched with excess water. ^1H NMR analysis of the ratio of remaining triphenylphosphine (δ 7.3) to triphenylphosphine oxide (δ 7.5) indicated the level of active azodicarboxylate units.[12] Examination of **3a** in this manner showed 0.61 (±0.03) mequiv/g of usable azodicarboxylate units corresponding to 82% of the 0.75 mequiv/g possible. Application of the same procedure to **3b** and **3c** gave analogous results (Table I). Repeated analyses demonstrated that the resins **3** are stable for many weeks at room temperature if protected from light and stored dry. Exposure of resins **3** to severe mechanical shock, grinding, or heat (400 °C) showed that these materials have no tendency to explode or ignite.

Mitsunobu Reactions and Recycling of Polystyrene-Supported Methyl Azodicarboxylate. The immobilized methyl azodicarboxylate reagents **3** function well in Mitsunobu reactions (Figure 3) and give yields comparable to those with soluble dialkyl azodicarboxylates. More importantly, the use of these resins greatly aids isolation of products. For example, purification of (*S*)-*N*-(*tert*-butoxycarbonyl)-α-amino-β-propiolactone (**4**) obtained by cyclization of (*S*)-*N*-(*tert*-butoxycarbonyl)-L-serine using dimethyl azodicarboxylate and triphenylphosphine requires careful chromatography.[7a] However, if resin **3a** is used in this reaction, simple precipitation of triphenylphosphine oxide from the filtered reaction mixture with ether, followed by filtration and direct recrystallization of the filtrate, gives the pure β-lactone **4** (a useful precursor for amino acid synthesis[7]) in 51% yield. Similarly, facile removal of unreacted **3** and product **2** by filtration substantially enhances product purification for the other conversions shown in Figure 3. In the cases examined, the polystyrene-supported azodicarboxylates **3** appear to be fully capable of replacing soluble analogues in the Mitsunobu procedure. Resin **3** is compatible with most common solvents; tetrahydrofuran was chosen for these reactions because of increased swelling of the resin (and presumably better access to reactive sites) in this solvent. Related elimination reactions with triphenylphosphine[1] also function reasonably well (e.g., formation of **11**). Presumably other types of reactions of dialkyl azodicarboxylates[13] are also possible with **3** and may provide new approaches for attachment of molecules to a solid support.

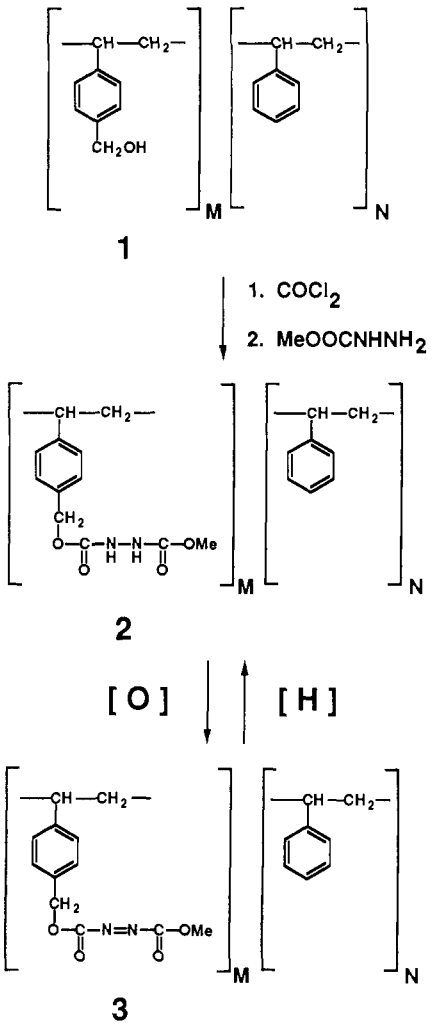

Figure 2. Synthesis of methyl azodicarboxylate polystyrene resin **3**. During Mitsunobu reactions, **3** is reduced to methyl hydrazodicarboxylate polystyrene resin **2**. Maximum mole percent loading for **1** is $M/(M + N) \times 100$.

(11) (a) Rabjohn, N. In *Organic Syntheses*, Collective III; Horning, E. C., Ed.; Wiley: New York, 1955; pp 375–377. (b) Warrener, R.; Russell, R.; Tan, R. *Aust. J. Chem.* **1981**, *34*, 855–870.

(12) For accurate determinations prolonged exposure of the Ph_3P/Ph_3PO mixture to air should be avoided.

(13) For examples of amination reactions using soluble dialkyl azodicarboxylates see: (a) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6398. (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397. (c) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395. (d) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923–1926. (e) Fitzsimmons, B. J.; Leblanc, Y.; Rokach, J. *J. Am. Chem. Soc.* **1987**, *109*, 285–286. (f) Demers, J. P.; Klaubert, D. *Tetrahedron Lett.* **1987**, *28*, 4933–4934. (g) Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.* **1988**, *53*, 2131–2132.

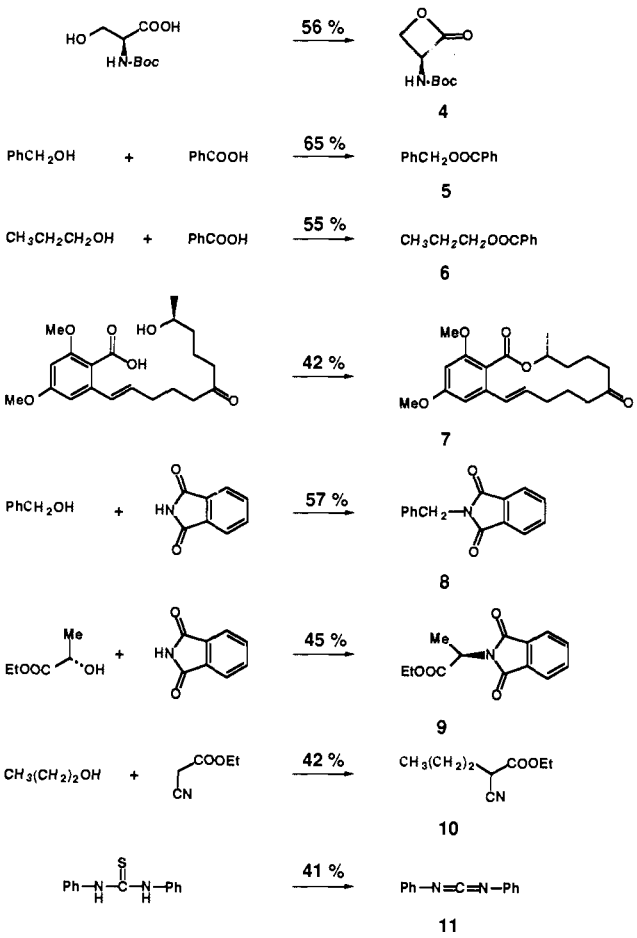

Figure 3. Unoptimized yields of reactions using 1.0–1.7 equiv of **3** and triphenylphosphine, except for preparation of **10** where 3.4 equiv was used. Analogous reactions using soluble dialkyl azodicarboxylates gave the following yields: **4**, 81%;[7a] **5**, 82%; **6**, 56%; **7**, 8%; **8**, 75%;[18] **9**, 58%;[18] **10**, 51%;[21] **11**, 79%.[22] Boc = *tert*-butoxycarbonyl.

After removal from the reaction mixtures, the reduced resin can be reoxidized to the azodicarboxylate form **3** and used again. The activity of both heavily and lightly loaded resins showed no decrease (±0.03 mequiv/g) over five redox cycles with *N*-bromosuccinimide/pyridine as oxidant. Chlorine in water was also an effective oxidant for repeated recycling of this polymeric reagent. The activity of **3** was conveniently determined after each cycle by treating a portion of the resin with triphenylphosphine and water followed by ^{1}H NMR analysis as described above. The cost of recycling recovered methyl hydrazodicarboxylate **2** by oxidation with *N*-bromosuccinimide/pyridine is less than $^1/_{10}$ of that of purchasing dialkyl azodicarboxylates (e.g., dimethyl or diethyl azodicarboxylate). In addition, the lack of explosion hazard and the ease of product purification make the use of polymer-supported alkyl azodicarboxylate attractive. Investigations with *other solid supports (e.g., silica gel, glass) are in progress.*

Experimental Section

General methods and instrumentation have been described previously.[7d,14] Solid-state ^{13}C NMR spectra were acquired by Dr. Nancy Cyr (Alberta Research Council) at 50.3 MHz on a Bruker CXP-200 spectrometer using magic-angle spinning and cross-polarization techniques. Samples of polystyrene resins were packed in a sapphire rotor equipped with KelF end caps and spun at 4 kHz. The contact time (CP time) was 2.0 ms with a 10-s recycle delay. Typically 500–2000 scans were accumulated.

Hydroxymethyl polystyrene resin **1a** or **1c** (1.0 or 0.55 mequiv/g, 1% cross-linked with divinylbenzene) were obtained from Bachem Inc. (Torrance, CA). Chloromethylated polystyrene resin (Bio-Beads S-X1, 3.0 mequiv/g, 1% cross-link, 200–400 mesh) was purchased from Bio-Rad Laboratories (Richmond, CA). All resin reactions and manipulations, including drying in vacuo, were done in a jacketed glass reaction vessel equipped with a 25–50-μm glass frit at the base for filtration and an overhead stirrer. The apparatus was pretreated with a 10% hexane solution of Surfasil siliconizing agent (Pierce Chemical Co., Rockford, IL) and oven-dried for 4 h at 140 °C to minimize resin adhesion to the glass. A slight positive pressure of argon was applied through the glass frit during reactions to maintain solvents in the reactor vessel. For filtration, the argon was replaced by a vacuum. Stirring of reaction mixtures containing resin was limited to 50–140 rpm to avoid mechanical destruction of resin particles.

Hydroxymethyl Polystyrene Resin 1b. The procedure of Wang[10] was employed to convert chloromethylated polystyrene (Bio-Beads, S-X1, 30.0 g, 117 mequiv) with potassium acetate (17.3 g, 176 mmol) in dimethylacetamide (700 mL) to acetoxymethyl polystyrene. The resin was filtered and washed successively with H_2O/dimethylformamide (1/1, 2 × 500 mL), dioxane (3 × 250 mL), methanol (2 × 300 mL), and ether (2 × 300 mL). The material was dried at 50 °C in vacuo to give 32.2 g of acetoxylmethyl polystyrene: IR (Fluorolube mull) 2924, 1736, 1601 cm^{-1} (A_{1736}/A_{2924} = 1.26, A_{1736}/A_{1601} = 2.72); solid-state ^{13}C NMR (50.3 MHz) δ 171 (CH_3COO), 147 (C-1 of Ar), 137 (C-4 of Ar), 127 (Ar's), 67 (CH_2OAc), 52–35 [$CH(Ar)CH_2$], 22 (CH_3COO). Anal. Calcd (av unit formula $C_{9.503}H_{10.004}O_{1.002}$, av formula weight 140.25/unit): C, 81.38; H, 7.19. Found: C, 81.05; H, 7.09.

The acetoxymethyl polystyrene resin (31.2 g, 111 mequiv) was suspended in dimethylformamide (450 mL), and anhydrous hydrazine (100 g, 3.13 mol) was added. The mixture was stirred at 20 °C for 24 h, filtered, and washed successively with acetonitrile (2 × 400 mL), methanol (400 mL), and ether (2 × 400 mL). The material was dried in vacuo at 35 °C to give 26.4 g of hydroxymethyl resin **1b**: IR (Fluorolube mull) 3360, 2920, 1601 cm^{-1}; solid-state ^{13}C NMR (50.3 MHz) δ 147 (C-1 or Ar), 137 (C-4 of Ar), 127 (Ar's), 65 (CH_2OH), 52–35 [$CH(Ar)CH_2$]. Anal. Calcd (av unit formula $C_{8.501}H_{9.002}O_{0.501}$, av formula weight 119.19/unit): C, 85.66; H, 7.61. Found: C, 85.72; H, 7.73.

Methyl Hydrazodicarboxylate Polystyrene Resins 2. All operations were conducted in an efficient hood because of the toxicity of phosgene. In a typical procedure, resin **1b** (3.23 g, 4.20 mequiv/g) was suspended in dry THF or CH_2Cl_2 (100 mL), and phosgene (5.2 mL, 7.5 g, 76 mmol) was added through a gas inlet tube. Pyridine (1.0 mL, 12.6 mmol) was then added dropwise, and the mixture was stirred for 2 h at 20 °C. The resin was filtered and washed with dry dichloromethane (5 × 75 mL). All filtrates were treated with aqueous ammonia in the hood to destroy the toxic phosgene. The resin was resuspended in dichloromethane (100 mL), methyl carbazate (3.40 g, 37.8 mmol) was added, triethylamine (1.7 mL, 12.6 mmol) was added dropwise, and the mixture was stirred at 20 °C for 2 h. The resin was filtered and washed successively with methanol/water (1/1, 2 × 50 mL), methanol (50 mL), dichloromethane (2 × 50 mL), and ether (3 × 100 mL). The material was dried in vacuo at 20 °C to give white methyl hydrazodicarboxylate polystyrene resin **2b**: IR (Fluorolube mull) 3300, 1700 cm^{-1}. Anal. Calcd (av unit formula $C_{10.004}H_{11.006}N_{1.002}O_{2.004}$, av formula weight 177.35/unit based on maximum theoretical 50.1 mol % loading, 2.83 mequiv/g): C, 67.75; H, 6.26; N, 7.91. Found: C, 68.48; H, 6.50; N, 6.72.

Methyl Azodicarboxylate Polystyrene Resin 3 by Oxidation of 2 with *N*-Bromosuccinimide. In a typical example, resin **2b** (3.06 g, 8.6 mequiv) in dichloromethane (90 mL) was treated with pyridine (0.70 mL, 8.7 mmol). The mixture was protected from light, and *N*-bromosuccinimide (1.70 g, 9.6 mmol) was added in small portions over 10 min with stirring. The mixture was stirred for 1 h at 20 °C, filtered, and washed successively with acetonitrile (5 × 50 mL) and ether (2 × 500 mL). The yellow-orange resin **3b** was dried at 30 °C in vacuo: IR (Fluorolube mull) 3060, 3020, 2920, 2845, 1780, 1600 cm^{-1}. Anal. Calcd (av unit formula $C_{10.004}H_{10.004}N_{1.002}O_{2.004}$, av formula weight 176.34/unit based on maximum theoretical 50.1 mol % loading, 2.84 mequiv/g): C, 68.14; H, 5.72; N, 7.96. Found: C, 69.11; H, 6.01; N, 6.76.

Methyl Azodicarboxylate Polystyrene Resin 3 by Oxidation of 2 with Chlorine/Water. In a typical example, resin **2c** (2.02 g, 0.81 mequiv) in THF/H_2O (1/1 v/v, 40 mL) was cooled to 4 °C, protected from light, and treated with chlorine gas (ca. 1.1 equiv). The mixture was stirred at 5–10 °C for 6 h and then filtered. The resin was washed with water (2 × 200 mL), 10% sodium bicarbonate (2 × 200 mL), water (2 × 200 mL), acetone (200 mL), and ether (2 × 200 mL). It was then dried at 40 °C in vacuo to give **3c**: IR (Fluorolube mull) 3060, 3020, 2920, 2845, 1780, 1600 cm^{-1}. Anal. Calcd (av unit formula $C_{8.232}H_{8.232}N_{0.116}O_{0.232}$, av formula weight 112.15/unit based on maximum theoretical 5.8 mol % loading): C, 87.88; H, 7.38; N, 1.44. Found: C, 86.41; H, 7.44; N, 1.11.

Determination of Available Reactive Sites on Methyl Azodicarboxylate Polystyrene Resins 3. In a typical procedure, resin **3c** (0.111 g, ~0.043

(14) Noguchi, H.; Harrison, P. H.; Arai, K.; Nakashima, T. T.; Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *10*, 2938–2945.

mequiv based on N analysis) was suspended in THF (10 mL), and a solution of excess triphenylphosphine (60.5 mg, 0.231 mmol) in THF (5 mL) was added at 25 °C. The mixture was stirred 30 min and quenched with excess water (ca. 1 mL). The resin was filtered and washed with THF and methanol. The combined filtrate and washings were concentrated to dryness in vacuo and redissolved in CD_3OD. Integration of the peaks at δ 7.5 (Ph_3PO) and δ 7.3 (Ph_3P) in the ^1H NMR spectrum provided the proportion of triphenylphosphine that was converted (after correction for any residual Ph_3PO in the Ph_3P starting material).[12]

(*S*)-*N*-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (4). Methyl azodicarboxylate polystyrene resin **3a** (6.55 g, 4.0 mequiv) was swollen briefly (15 min) in dry THF (100 mL). The stirred suspension was cooled to −45 °C and *N*-(*tert*-butoxycarbonyl)-L-serine (473 mg, 2.30 mmol) was added. To this was added dropwise a solution of triphenylphosphine (1.06 g, 4.0 mmol) in dry THF (5 mL) over 10 min. The mixture was stirred 30 min at −45 °C, allowed to warm to 0 °C over 1 h, and then stirred an additional 2 h. Water (36 μL) was added, the mixture was filtered, and the resin was washed with THF (2 × 100 mL) and acetonitrile (100 mL). The combined filtrate and washings were concentrated in vacuo at 35 °C. Flash chromatography (35% EtOAc/hexane) of the residue yielded 243 mg (56%) of pure **4** that possessed physical and spectral properties identical with those previously described.[7a]

Alternatively, **4** could be secured in 51% yield without chromatography as follows. The residue obtained above after concentration in vacuo was treated with boiling anhydrous ether (60 mL) and cooled to 4 °C (16 h). Precipitated triphenylphosphine oxide (1.08 g, ~95%) was removed by filtration. The filtrate was concentrated in vacuo and recrystallized by addition of hexane (~60 mL) to a solution of the residue in chloroform (3 mL) and carbon tetrachloride (7 mL) until persistent cloudiness was obtained at 45 °C. The mixture was filtered at 25 °C, and the filtrate was cooled to −20 °C (48 h). Pure crystalline β-lactone **4** (220 mg, 51%) was collected by filtration.

Benzyl Benzoate (5). Resin **3a** (6.55 g, 4.0 mequiv) was swollen in dry THF (100 mL) for 15 min, and benzoic acid (366 mg, 3.0 mmol) in THF (50 mL) was added. The mixture was stirred at 25 °C, and a solution of triphenylphosphine (786 mg, 3.0 mmol) and benzyl alcohol (360 μL, 3.5 mmol) in THF (5 mL) was added dropwise. The resin was stirred overnight, filtered, and washed with dichloromethane (4 × 150 mL). The combined filtrate and washings were concentrated in vacuo at 30 °C and purified by flash chromatography (3.5% EtOAc/hexane) to yield 417 mg (65%) of benzyl benzoate (**5**): IR (film) 1720, 1272 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.25–8.05 (m, 2 H), 7.65–7.25 (m, 8 H), 5.32 (s, 2 H); exact mass 212.0839 (212.0837 calcd for $C_{14}H_{12}O_2$).

Propyl Benzoate (6). The procedure used to make **5** was employed to convert benzoic acid (0.134 g, 1.10 mmol) and 1-propanol (0.180 g, 3 mmol) with resin **3c** (4.0 g, 1.1 mequiv) and triphenylphosphine (0.288 g, 1.11 mmol) to propyl benzoate (**6**) in 55% yield after flash chromatography (0.5% EtOAc/hexane): IR (film) 2970, 1721, 1276 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.30 (m, 2 H), 7.43 (m, 3 H), 4.25 (t, 2 H, 7 Hz), 1.75 (m, 2 H), 0.98 (t, 3 H, 7 Hz); exact mass 164.0836 (164.0838 calcd for $C_{10}H_{12}O_2$).

(*R*)-(−)-Zearalenone Dimethyl Diether (7). Resin **3b** (67 mg, 0.12 mequiv) was suspended in dry THF (5 mL), and a solution of triphenylphosphine (26 mg, 0.10 mmol) in THF (2 mL) was added. A solution of the lactone-opened form of (*S*)-(+)zearalenone dimethyl ether[15] (26 mg, 0.070 mmol) in THF (2 mL) was added at 20 °C, and the mixture was stirred for 48 h. The resin was filtered and washed with THF (5 mL), and the combined filtrate and washings were concentrated in vacuo. Flash chromatography (EtOAc/hexane, 3/7) of the residue gave 10 mg (42%) of (*R*)-(−)-zearalenone dimethyl ether (**7**): mp 111–112 °C [for (+) isomer lit.[16] mp 111–112 °C]; $[\alpha]^{25}_D$ −23.2° (*c* 1, MeOH) [for natural (+) isomer lit.[15] $[\alpha]_D$ +25° (*c* 1, MeOH)]; IR ($CHCl_3$ cast) 2940, 1715, 1600, 1265, 1204 cm^{-1}; ^1H NMR[17] (300 MHz, $CDCl_3$) δ 6.61 (d, 1 H, 2 Hz, 3-C*H*), 6.39 (m, 1 H, 1′-C*H*), 6.35 (m, 1 H, 5-C*H*), 6.00 (m, 1 H, 2′-C*H*), 5.30 (m, 1 H, 10′-C*H*), 3.85 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 2.71 (m, 1 H, 5′-C*H*H), 2.38 (m, 3 H, 7′-CH_2, 3′-C*H*H), 2.14 (m, 3 H, 3′-C*H*H, 5′-C*H*H, 4′-C*H*H), 1.75 (m, 5 H, 4′-C*H*H, 9′-CH_2, 8′-CH_2), 1.34 (d, 3 H, 6 Hz, 11′-CH_3); exact mass 346.1772 (346.1781 calcd for $C_{20}H_{26}O_5$).

N-Benzylphthalimide (8). Resin **3c** (4.0 g, 1.12 mequiv) was suspended in dry THF (150 mL) for 15 min. A solution of triphenylphosphine (0.295 g, 1.13 mmol), phthalimide (0.170 g, 1.16 mmol), and benzyl alcohol (0.119 g, 1.10 mmol) in THF was added dropwise, and the mixture was stirred at 25 °C for 23 h. The resin was filtered and washed with THF (2 × 100 mL) and with ether (2 × 100 mL). The combined filtrate and washings were concentrated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane, 1/3) to give 0.149 g (57%) of *N*-benzylphthalimide (**8**):[18] mp 109–110 °C (lit.[19] mp 114–115 °C); IR (KBr) 1773, 1702, 1612 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (m, 2 H), 7.73 (m, 2 H), 7.46 (m, 2 H), 7.33 (m, 3 H), 4.88 (s, 2 H); exact mass 237.0791 (237.0790 calcd for $C_{15}H_{11}NO_2$).

***N*,*N*-Phthaloyl-D-alanine Ethyl Ester (9).** Resin **3b** (1.78 g, 3.8 mequiv) was suspended in dry THF (130 mL). A solution of phthalimide (0.432 g, 2.94 mmol), triphenylphosphine (1.03 g, 3.93 mmol), and ethyl L-(+)-lactate (0.340 g, 2.88 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at 20 °C for 48 h. The resin was filtered and washed successively with methanol (2 × 75 mL), chloroform (2 × 75 mL), and ether (3 × 100 mL). The combined filtrate and washings were concentrated in vacuo. The residue was separated by flash chromatography (EtOAc/hexane, 1/3) and then recrystallized from ether to give **9** (0.322 g, 45%): mp 57–58 °C (lit.[18] mp 60–61 °C); $[\alpha]^{25}_D$ +18.2° (*c* 1, MeOH);[20] IR (KBr) 1736, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 2 H, Ar*H*), 7.75 (m, 2 H, Ar*H*), 4.95 (q, 1 H, 7.4 Hz, C*H*CH$_3$), 4.22 (q, 2 H, 7.0 Hz, OCH_2), 1.70 (d, 3 H, 7.4 Hz, CHCH_3), 1.22 (t, 3 H, 7 Hz, CH$_2$CH_3); exact mass 247.0846 (247.0845 calcd for $C_{13}H_{13}NO_4$). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.18; H, 5.06; N, 5.67.

Ethyl 2-Cyanopentanoate (10). Resin **2b** (0.502 g, 0.90 mequiv) was suspended in dry THF (30 mL), and a solution of triphenylphosphine (0.235 g, 0.896 mmol) in THF (5 mL) was added. The mixture was then treated dropwise with a solution of ethyl cyanoacetate (32 mg, 0.281 mmol) and *n*-propyl alcohol (16 mg, 0.27 mmol) in THF (2 mL). The mixture was stirred at 20 °C for 24 h. The resin was filtered and washed with THF (2 × 5 mL). The combined filtrate and washings were concentrated in vacuo and the resulting residue was purified by flash chromatography (EtOAc/hexane, 3/2) to give ethyl 2-cyanopentanoate (**10**) as an oil (18 mg, 42%):[21] IR ($CHCl_3$ cast) 2978, 2939, 2878, 2241, 1746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.27 (q, 2 H, 7 Hz, OCH_2), 3.56 (t, 1 H, 7 Hz, C*H*), 2.01 (m, 2 H, CH_2CH), 1.63 (m, 2 H, CH$_3$CH_2), 1.42 (t, 3 H, 7.5 Hz, CH_2CH$_2$O), 1.10 (t, 3 H, 7 Hz, CH_3CH$_2$); exact mass 155.0947 (155.0946 calcd for $C_8H_{13}NO_2$).

***N*,*N*′-Diphenylcarbodiimide (11).** Resin **3b** (0.934 g, 1.10 mequiv) was suspended in dry THF (25 mL), and a solution of *N*,*N*′-diphenylthiourea (0.225 g, 0.987 mmol) in THF (3 mL) was added dropwise. The mixture was stirred at 20 °C for 24 h. The resin was filtered and washed successively with methanol (2 × 50 mL) and chloroform (2 × 50 mL). The combined filtrates and washings were concentrated in vacuo, and the residue was extracted with petroleum ether to remove product from insoluble triphenylphosphine oxide. Concentration in vacuo of the extract gave an oil that was purified by flash chromatography (EtOAc/hexane, 3/7) to give pure *N*,*N*′-diphenylcarbodiimide (**11**) (78 mg, 41%):[22] IR ($CHCl_3$ cast) 2140, 2106, 1590, 1487 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 4 H), 7.17 (m, 6 H); exact mass 194.0845 (194.0845 calcd for $C_{13}H_{10}N_2$).

Acknowledgment. We are grateful to Dr. Nancy Cyr (Alberta Research Council) for acquisition of solid-state ^{13}C NMR spectra. These investigations were generously supported by the Natural Sciences and Engineering Research Council of Canada (Grants A0845 and CRD0040921) and by Merck Frosst Canada Inc.

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