Parallel Synthesis of Aldehydes and Ketone Facilitated by a New Solid-Phase Weinreb Amide

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This paper describes a novel supported Weinreb amide resin that facilitates parallel synthesis of aldehydes and ketones on a scale useful for chemical library synthesis. This new resin makes it possible to produce custom aldehydes and ketones from a wide range of carboxylic acids, including N-BOC-amino acids. A variety of commercially unavailable aldehydes are easily synthesized in parallel and obtained in high purity via a simple filtration workup, thus facilitating parallel synthesis of lead optimization libraries that typically require custom synthesis of aldehyde intermediates for development of structure–activity relationships. To demonstrate the utility of this method, we synthesized a small library based on a supported Horner–Emmons reagent. This is the first time it has been shown that aldehydes generated via a supported Weinreb amide could be used directly as reagents in chemical library synthesis employing moisture-sensitive reactions. The analogous solution reaction is not suited for parallel synthesis because of the laborious extractive workup procedure necessary and, at times, the instability of these reactive intermediates.

Introduction

The recent development of parallel and combinatorial chemical library synthesis has created a renewed interest in polymeric solid-phase reagents.1 They offer the advantage of easy separation from low molecular weight reactants or products by filtration or selective precipitation and are very suitable for automation of chemical library synthesis.

Reduction of Weinreb amides is a classical method for converting carboxylic acids into aldehydes and ketones.2 This paper describes a novel supported Weinreb amide3 that greatly facilitates parallel synthesis of aldehydes compared to classical solution methods. The advantage of using the supported reagent as opposed to the solution method becomes apparent during the workup of the reaction. The solid-phase method offers an extremely simple filtration workup in contrast to the aqueous extractive workup necessary for the solution method. The solid-phase method, although not suited for multigram quantities of a few select aldehydes, becomes the method of choice when greater than 20 aldehydes are needed on a multi-milligram scale.

Custom, commercially unavailable aldehydes and ketones were sought as building blocks for use in chemical library synthesis of acrylic acids based on a solid-phase Horner–Emmons4 reaction and in the Ugi four-component condensation.5 The purpose and focus of this work was not development of a method for the preparation of individual aldehydes that would be superior to the existing solution method. The purpose was to develop a method that would allow a simple parallel synthesis of greater than 20 aldehydes in multimilligram quantities of high enough purity to be used directly as intermediates in chemical library synthesis. The emphasis on purity of the produced aldehydes is based on the following considerations. First, it was quickly revealed that one person could not rapidly generate the required number of aldehydes by the solution method as it was classically practiced, due to the nature of the aqueous extractive workup procedure. The second consideration was that many of the desired aldehydes were unstable, and especially for this class of aldehydes it was necessary to use a method that facilitated the workup and handling of these unstable reagents.

Since the goal of this work was to develop a facile method to produce aldehydes as reagents in chemical library synthesis, it was quite important that the utility of the method be demonstrated. Therefore, a small library was executed using a supported Horner–Emmons reaction. The supported Horner–Emmons reaction is sensitive to moisture and purity of the aldehyde; thus, it was felt this reaction would be a good validation of the aldehyde synthesis.

Because this new supported version of Weinreb amides facilitates the parallel conversion of carboxylic acids to aldehydes or ketones of high enough purity to be used directly in library synthesis, this method provides a fast

1 Dedicated to the memory of George N. Salvino (6/24/29–10/27/98).
The polymeric Wang-O-hydroxylamine resin (3) has been synthesized by a straightforward procedure providing kilogram quantities of resin. N-Hydroxypthalimide was coupled to Wang resin (1) using Mitsunobu conditions. The phthalimido protecting group was removed by methylaminolysis in THF instead of the commonly used hydrazinolysis procedure, offering significant safety advantages on the kilogram scale. The Wang-O-hydroxylamine resin (3) may be directly acylated with a carboxylic acid and then cleaved using 50% TFA in DCM as a general means to generate hydroxamic acids (5). Acylation of the Wang-O-hydroxylamine resin (3) followed by N-alkylation was explored as a general route to supported Weinreb amides (Scheme 2).

An analytical method was needed to monitor the N-alkylation reaction on the solid phase. It was desired to use a method that monitored the N-alkylation directly. A convenient method is to incorporate a bromine or chlorine atom in the molecule used as the electrophile in the alkylation reaction and then monitor the progress of the alkylation using elemental analysis. Thus, 4-bromo- and 4-chlorobenzyl bromides were used to aid in monitoring the progress of the solid-phase N-alkylation reaction by elemental analysis of the resin. In addition, acid cleavage of the N-benzylhydroxamic acid from the solid support followed by classical solution analytical methods (1H NMR, LC/MS) was also used to optimize the N-alkylation reaction. It was found that the N-alkylation reaction worked well using a slight excess of DBU in anhydrous toluene followed by the alkylation reagent. Other conditions such as CsCO₃/DMF or DIEA/THF did not give complete alkylation or were not as clean. Several reducing agents, organometallic reagents, and workup procedures as well as a wide variety of carboxylic acids were studied to explore the scope of this solid-phase reagent.

The focus of this method was the facile preparation of aldehydes and ketones with an emphasis on the purity of the crude products released from the resin. Clearly, for this method to have utility a structurally diverse set of carboxylic acids must be converted to aldehydes with a purity enabling them to work well in further chemical reactions without the need for purification. The most important optimization criterion was the purity of aldehydes and ketones released from the resin. It was deemed of great importance to validate any method that was developed by subjecting the crude aldehydes produced to the supported Horner–Emmons synthesis protocol.

The reduction conditions employed were to suspend the N-alkylated resin in THF at 0 °C and treat it with LAH for 30 min to generate the chelated complex. Workup and product release was accomplished by treatment with aqueous potassium hydrogensulfate followed by saturated Rochelle salt. The reaction mixture was filtered through a short plug of silica gel with a bed of anhydrous sodium sulfate on the top to dry the reaction mixture. The resulting aldehydes were thus generated in acceptable yields of 30–50% and in excellent purity. Typically, 3–4 g of resin would generate 250–300 mg of aldehyde. Using simple glass-jacketed reaction vessels fitted with glass frits for filtration, one chemist could easily generate 20 aldehydes in a morning and use them immediately in a chemical reaction that afternoon.

The use of the N-benzylated-N-acylated resin produced the purest aldehydes or ketones. This may be due to increased stability of the resulting aluminum complex of the alkylation using elemental analysis. Thus, 4-bromo- and 4-chlorobenzyl bromides were shown to produce a significant amount of the undesired alcohol as a side product.

### Results and Discussion

This supported Weinreb amide synthesis was initially envisioned on the basis of a simple modification of a polymeric hydroxylamine resin that was developed in our laboratory for the conversion of carboxylic acids to hydroxamic acids, exemplified in Scheme 1.

Supporting information for this work included: (a) Prasad, V. V. K.; Warne, P. A.; Lieberman, S. J. Steroid Biochem. 1983, 18, 257.
(e) Gregor, P. R.; Prasad, V. V. K.; Lieberman, S. J. Steroid Biochem. 1983, 18, 257.
surrounded by the large lipophilic aromatic group. 4-Bromobenzyl or 4-chlorobenzyl was used only as an analytical handle to aid in monitoring the progress of the N-alkylation reaction of 4 by elemental analysis (the bromobenzyl, chlorobenzyl and benzyl moieties were essentially equivalent for aldehyde processing). The structure and isolated yields of a diverse set of aldehydes obtained by reductive cleavage are listed in Table 1.

Analysis of Table 1 reveals an interesting observation. Carboxylic acids containing secondary or tertiary nucleophilic nitrogen atoms tended to give lower yields or no desired aldehyde product (% yield lower than 30%; i.e., see 7a, d, e, l, m). These trends, although not outstandingly obvious, raised a concern about the method for the potential to alkylate the carboxylic acid substrate if it contained a nucleophilic amine. Furthermore, during the optimization of the aldehydes derived from HN-BOC amino acids this method failed. The failure was attributed to competing N-alkylation of the NH-BOC moiety suggested by examination of the MS and the 1H NMR spectrum of the aldehydes attempted using this general reaction sequence in Scheme 3.

The synthesis of aldehydes derived from N-BOC amino acids was highly desired. Therefore, to avoid the problem of undesired N-alkylation and to broaden the scope of the reaction a second route (Scheme 4) was developed in which the alkylation of the Wang-O-hydroxylamine resin (3) precedes acylation. Several methods were envisioned to accomplish this goal such as direct alkylation, reductive alkylation of the oxime, or N-alkylation of a carbamate derivative. Direct alkylation of the resin resulted in either poor conversion to monoalkylated resin or in dialkylation. Reductive alkylation of the oxime was problematic. Different reducing agents (such as NaBH(OAc)3, NaCNBH3, NaBH4, or LiBHEt3) produce varying ratios of no reduction, partial reduction to the desired hydroxylamine, and over-reduction to the amine resulting in cleavage from the resin. Fortunately N-alkylation of the Alloc derivative of the hydroxylamine resin (11) successfully generated the desired monoalkylated resin (13) after Alloc removal (Scheme 4). Note that the 4-bromobenzyl moiety could no longer be used as an analytical handle because the bromine interfered in the Pd-catalyzed Alloc deprotection step.

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The N-benzylhydroxylamine resin (13) was acylated with N-BOC phenylalanine, treated with LAH, and then worked up as previously described. The C-terminal

### Table 1. Aldehydes Obtained by Reductive Cleavage

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R1</th>
<th>% Yield</th>
<th>Purity</th>
<th>Cmpd</th>
<th>R1</th>
<th>% Yield</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td></td>
<td>49</td>
<td>85*</td>
<td>7i</td>
<td></td>
<td>31</td>
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<td></td>
<td>30</td>
<td>93*</td>
<td>7n</td>
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<td>-</td>
</tr>
<tr>
<td>7g</td>
<td></td>
<td>18</td>
<td>86*</td>
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<td></td>
<td>26</td>
<td>94*</td>
<td>7p</td>
<td></td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

* Purity estimated by HPLC (A% at UV220). ^ Purity estimated by 1H NMR.
aldehyde was generated in excellent purity in yields comparable to those obtained by Martinez. Table 2 lists a set of aldehydes obtained via reductive cleavage utilizing this method.

To validate the utility of this method as a means to synthesize aldehydes in parallel for use as reagents in library production, crude aldehydes were used directly in a supported Horner–Emmons reaction. The supported Horner–Emmons reaction was a good test reaction to determine the quality of these aldehydes due to the nature of the reaction. Thus, 4-bromo-3-methyl benzaldehyde, 3,4-dimethyl cinnamaldehyde, and N-phenylanthranilic aldehyde were generated (Scheme 2) and were used crude in the supported Horner–Emmons reaction (Table 3).

The aldehydes reacted well in the supported Horner–Emmons synthesis and after TFA cleavage from the resin produced substituted acrylic acids in excellent purity. This confirmed the high degree of purity of these aldehydes and served to validate our process, demonstrating its usefulness for library production. These aldehydes were also successfully used in combinatorial libraries based on the Ugi 4-component condensation (data not shown). On the basis of these results, resin 13 has been shown to be a useful and general means to produce aldehydes in a parallel fashion for use in a variety of chemical libraries (Scheme 5).

Ketones may also be formed by reaction of the supported Weinreb amides with Grignard reagents. A cursory examination using ethyl Grignard suggested the potential of this conversion (Table 4). Future work in our laboratory will concentrate on broadening the scope of this process with a focus on library production.

Conclusion

The N-benzyl derivative of resin 3, resin 13 is a new tool useful in the synthesis of aldehydes or ketones for use in chemical libraries. The supported Weinreb amide facilitates parallel synthesis of aldehydes for milligram scale production. The scope of the reaction has been demonstrated to be quite wide, no alcohol side product is observed, and the purity of the resulting aldehyde or ketone is such that it may be used directly as a building block in combinatorial or parallel synthesis of chemical libraries.

Experimental Section

General Methods. The reactions were carried out on a Burrell wrist action shaker Model 75. Solvents used were EM Science of OmniSolv distilled grade unless specified otherwise. The following abbreviations were used: DCM = dichloromethane, DMF = dimethylformamide, THF = tetrahydrofuran, Et₂O = diethyl ether, DMSO = dimethyl sulfoxide, DIEA = N,N-diisopropylethylamine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA = trifluoroacetic acid, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, LAH = lithium aluminum hydride, LiHMDS = lithium hexamethyldisilazane. ¹H NMR spectra were recorded on a 300 MHz ARX Bruker spectrometer in CDCl₃ unless otherwise stated. Mass spectra were recorded on a Finnigan 4500 EI and Sciex API 313 spectrometers.

4-O-(Methylhydroxylamine)phenoxymethylpoly(styrene-1%-divinylbenzene) resin (100–200 Mesh) (3). A 1-L jacketed reactor with a bottom valve and overhead stirrer (Ace catalog no. 8090) was charged with Wang resin (18.35 g; 20 mmol) and anhydrous THF (450 mL). This mixture was...
Table 3. Solid-Phase Horner–Emmons Reactions with Crude Aldehydes

<table>
<thead>
<tr>
<th>Compd</th>
<th>R1</th>
<th>R2</th>
<th>% Yield</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>H</td>
<td></td>
<td>81</td>
<td>99%</td>
</tr>
<tr>
<td>17b</td>
<td>Et</td>
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<tr>
<td>17c</td>
<td>H</td>
<td>Cl</td>
<td>72</td>
<td>91%</td>
</tr>
<tr>
<td>17d</td>
<td>Et</td>
<td></td>
<td>68</td>
<td>92%</td>
</tr>
<tr>
<td>17e</td>
<td>H</td>
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<td>82</td>
<td>89%</td>
</tr>
<tr>
<td>17f</td>
<td>Et</td>
<td></td>
<td>31</td>
<td>96%</td>
</tr>
</tbody>
</table>

a Purity estimated by HPLC (% at UV220).

Table 4. Ketones Obtained by Reaction with Grignard Reagents

<table>
<thead>
<tr>
<th>Compd</th>
<th>R1</th>
<th>R2</th>
<th>% Yield</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td></td>
<td>Et</td>
<td>68</td>
<td>97%</td>
</tr>
<tr>
<td>18b</td>
<td></td>
<td>Et</td>
<td>23</td>
<td>78%</td>
</tr>
</tbody>
</table>

a Purity was estimated by GC analysis and 1H NMR.

the temperature at <5 °C. When the addition was complete, the stirred mixture was allowed to warm slowly to room temperature and stirred overnight. As much of the reaction liquors as possible was removed by aspiration through the dip tube as above. The resin was washed by charging DMF (200 mL), stirring the mixture for 3–5 min, and then removing by aspiration as much of the wash solution as possible. Similarly, the resin was washed sequentially with DMF (200 mL), methanol (2 × 200 mL), THF (2 × 200 mL), and methanol (200 mL). A portion of the resin was removed for analysis: IR 1734 cm⁻¹ (C=O).

To the resin remaining in the reactor was added THF (400 mL) and a 40% aqueous solution of methylamine (200 mL; 2.31 mol). This reaction mixture was stirred gently at 40 °C for 2 h and then cooled to room temperature (the mixture may be held overnight at this temperature). As much of the reaction liquor as possible was removed by aspiration, and the resin was washed with the solvent array as above. Following the final methanol wash, additional methanol was used to flush the resin out of the bottom of the reactor and isolate it by filtration. The filtered resin was dried at 40 °C under vacuum. Yield 18–18.5 g resin: amine load 1.02 mequiv/g (based on potentiometric titration of a THF suspension with p-toluenesulfonic acid); IR (microscopy) 3316 cm⁻¹ (w, –NH₂). Anal. found C, 87.07; H, 7.77; N, 1.58, which corresponds to 1.13 nitrogen atoms/g resin.

Preparation of 4-Nitrophenylethanohydroxamic Acid.

A 200 mg sample of the dried resin (ca. 0.2 mmol) was charged to a 5- or 10-mL resin reactor (a polypropylene syringe barrel fitted with a polypropylene frit). The resin was swelled for about 15 min in dry DMF (4 mL), and then EDCI (118 mg; 0.6 mmol) was added. To this mixture was then added 4-nitrophenylacetic acid (155 mg, 0.6 mmol). The reactor was capped, and the mixture was agitated slowly overnight (a rocker bed apparatus was used). The reaction liquors were removed by vacuum filtration, and the resin was washed with several small (2–3 mL) portions of the following solvents: DMF (four to five portions), 50% aqueous DMF (three to four portions), THF (three to four portions), and MeOH (two to three portions). The resin was dried for 4 h under vacuum at 40 °C. To this dried resin was added DCM (2 mL) followed by TFA (2 mL containing 20 μL of water). The mixture was allowed to react for about 1 h, and the reaction liquors were drained into a tared collector. The resin was washed with DCM (2 × 1 mL) followed by toluene (2 × 1 mL). The combined filtrates were concentrated to about 2 mL at 30 °C, additional toluene (2 mL) was added, and the resulting solution was concentrated to dryness under vacuum at 30 °C. The residue was weighed and analyzed for weight % purity (HPLC, using the carboxylic acid as a response factor standard). Typical results for 4-nitrophenylhydroxamic acid: 29–30 mg solids at 60–70 wt % purity, 90–97 A% purity (261 nm); [H NMR (CD₃OD) δ 8.13 (d, 2H), 7.25 (d, 2H), 4.85 (bs, OH, NH), 3.55 (s, 2H); ¹³C NMR δ 169.4, 144.3, 131.3, 124.6, 40.2. This reflects a chemical yield of 50–55% assuming resin loading at 1 mequiv/g.

3,4-Dimethoxycinnamic Aldehyde (7a). A glass-jacketed reaction vessel fitted with a porous glass frit via vacuum aspiration. Fresh THF (450 mL) was added, followed by triphenylphosphine (15.74 g; 60 mmol) and N-hydroxysuccinimide (16.31 g; 100 mmol). The resulting mixture was stirred and cooled to 0 °C. Diisopropylazodicarboxylate (11.8 mL; 60 mmol) is added slowly so as to maintain the temperature at <5 °C. When the addition was complete, the stirred mixture was allowed to warm slowly to room temperature and stirred overnight. As much of the reaction liquors as possible was removed by aspiration through the dip tube as above. The resin was washed by charging DMF (200 mL), stirring the mixture for 3–5 min, and then removing by aspiration as much of the wash solution as possible. Similarly, the resin was washed sequentially with DMF (200 mL), methanol (2 × 200 mL), THF (2 × 200 mL), and methanol (200 mL). A portion of the resin was removed for analysis: IR 1734 cm⁻¹ (C=O).
dry resin was swollen in anhydrous THF (12 mL) under nitrogen, shaken for 10 min, and cooled to 0 °C for 30 min. Then LAH (1 M in THF; 0.5 mL, 0.5 mmol) was added, and the reaction vessel was shaken at 0 °C for 30 min. Then saturated KHSO4 (0.5 mL) and K, Na tartrate (0.3 mL) solutions were added, and the reaction mixture was gently agitated for 20 min while being warmed to room temperature. Excess water was removed by addition of anhydrous Na2SO4. The mixture was filtered under low nitrogen pressure and washed with DCM (3 × 8 mL). The filtrate was further dried with Na2SO4 (ca. 500 mg) and filtered through a short (1 in.) bed of silica gel 60 for column chromatography (particle size 0.040–0.063 mm). The column was rinsed afterward with DCM (1 × 10 mL). Concentration in vacuo afforded 94 mg (49% yield) of

The following examples were synthesized following the above procedure:

**4-Phenylbutyraldehyde (7b):** 40 mg (27% yield); pH NMR δ 9.75 (s, 1H), 7.05–7.30 (m, 5H), 2.58–2.68 (m, 2H), 2.41–2.50 (t, 2H), 1.91–2.02 (m, 2H); MS (EI) m/z = 149 [M + H]+ LC area (UV 220) = 90%.

**3-Acetamidobenzaldehyde (7c):** 30 mg (18% yield); pH NMR δ 9.98 (s, 1H), 7.97 (s, 1H), 7.86 (d, 1H), 7.62 (d, 1H), 7.48 (t, 1H), 2.21 (s, 3H); MS (EI) m/z = 164 [M + H]+ LC area (UV 220) = 95%.

**2-Benzylaldehyde (7d):** 76 mg (36% yield); pH NMR δ 10.18 (1H), 7.83 (1H), 7.14–7.52 (m, 8H), 3.30 (t, 2H), 2.87 (t, 2H); MS (EI) m/z = 211 [M + H]+ LC area (UV 220) = 86%.

**4-(n-Propylphenyl)benzaldehyde (7e):** 98 mg (44% yield); pH NMR δ 10.02 (s, 1H), 7.92 (d, 2H), 7.72 (d, 2H), 7.53 (d, 2H), 2.65 (t, 2H), 1.68 (dt, 2H), 0.95 (t, 3H); MS (EI) m/z = 225 [M + H]+ LC area (UV 220) = 97%.

**4-Bromo-3-methylbenzaldehyde (7f):** 60 mg (30% yield); pH NMR δ 9.94 (s, 1H), 7.70 (d, 2H), 7.52 (d, 2H), 2.45 (s, 3H); MS (EI) m/z = 196/200 [M + H]+ LC area (UV 220) = 93%.

**4-Methoxy-2-formylquinoline (7g):** 27 mg (14% yield); pH NMR δ 10.17 (1H), 8.27 (d, 1H), 8.18 (d, 1H), 7.78 (t, 1H), 7.62 (t, 1H), 7.38 (1H), 4.12 (3H); MS (EI) m/z = 188 [M + H]+ LC area (UV 220) = 86%.

**3-Formylquinoline (7h):** 41 mg (26% yield); pH NMR δ 10.26 (s, 1H), 9.38 (s, 1H), 8.64 (s, 1H), 8.20 (s, 1H), 7.98 (t, 1H), 7.89 (t, 1H), 7.65 (t, 1H); MS (EI) m/z = 158 [M + H]+ LC area (UV 220) = 94%.

**2-(Methylthio)nicotinic aldehyde (7i):** 48 mg (31% yield); pH NMR δ 10.21 (1H), 8.60 (d, 1H), 7.98 (d, 1H), 7.15 (dd, 1H), 2.60 (s, 3H); MS (EI) m/z = 196/200 [M + H]+ LC area (UV 220) = 93%.

**N-Phenylationic aldehyde (7j):** 92 mg (47% yield); pH NMR δ 9.88 (s, 1H), 7.52–7.58 (d, 1H), 7.11–7.38 (m, 7H), 6.81 (t, 1H); MS (EI) m/z = 198 [M + H]+ LC area (UV 220) = 89%.

**2-Phenyl-4-formylquinoline (7k):** 62 mg (27% yield); pH NMR δ 10.58 (s, 1H), 9.00 (d, 1H), 8.19–8.30 (m, 4H), 7.82 (t, 1H), 7.70 (t, 1H), 7.47–7.59 (m, 3H); MS (EI) m/z = 234 [M + H]+ LC area (UV 220) = 90%.

**Benzo[1]thiophene-2-aldehyde (7l):** 76 mg (46% yield); pH NMR δ 10.12 (s, 1H), 8.03 (s, 1H), 7.93 (m, 2H), 7.47 (m, 2H), MS (EI) m/z = 162 [M + H]+ LC area (UV 220) = 87%.

**3-(3,4-Methylenedioxy)propionaldehyde (7m):** 97 mg (54% yield); pHNMR δ 9.80 (s, 1H), 7.60–7.74 (m, 3H), 5.92 (s, 2H), 2.88 (t, 2H), 2.74 (t, 2H); MS (EI) m/z = 179 [M + H]+ LC area (UV 220) = 95%.

**N-(tert-Butyloxycarbonyl)-l-alanalinal (7q):** N-benzyl-4-O-(methylhydroxylamine)phenoxymethylcopoly(styrene-1%-divinylbenzene)resin (3) (2 g; 2 mmol) was swollen in DCM (15 mL) for 10 min, then DIEA (0.383 mL; 2.2 mmol) was added, and the reaction mixture was shaken for 1 h at room temperature. Then allyl chloroformate (0.234 mL; 2.2 mmol) was added, and the reaction mixture was shaken overnight at room temperature. The resin was filtered, washed with DCM (3 × 15 mL), THF (3 × 15 mL), and DCM (3 × 15 mL), and dried in vacuo. Dried resin (11) was swollen in anhydrous toluene (18 mL), and then DBU (1.5 mL; 10 mmol) was added and shaken for 1 h at room temperature. Finally benzyl bromide (1.19 mL; 10 mmol) was added, and the reaction mixture was shaken for 3 days at room temperature. The reaction vessel was drained and the resin was washed with DCM (3 × 15 mL), DMF (3 × 15 mL), THF (3 × 15 mL), and DCM (3 × 15 mL), and dried overnight in vacuo. To the resin were added THF (6 mL), DMSO (6 mL), 0.5 N HCl (2.5 mL), tetrakis(triphenylphosphine)palladium(0) (347 mg; 0.5 mol%), and morpholine (4.3 mL), and the reaction mixture was shaken overnight at room temperature. The resin was then drained, washed with DMF (3 × 15 mL), THF (3 × 15 mL), DCM (3 × 15 mL), 0.5% aqueous HCl in DCM (3 × 15 mL), 0.5% sodium diethylthiocarbamate in DCM (3 × 15 mL), DMF (3 × 15 mL), THF (3 × 15 mL), and DCM (3 × 15 mL), and then dried in vacuo. A resin sample (13) (100 mg; 0.1 mmol) was cleaved with 50% TFA in DCM (2 mL) for 1 h at room temperature, washed 2× with 1 mL of the cleavage mixture, evaporated, and dried in vacuo to give N-benzylhydroxylamine (10 mg: 0.081 mmol; 81%); pH NMR (CD3OD) δ 7.44 (m, 4H), 4.36 (s, 2H); MS (EI) m/z = 124 [M + H]+.

**4-O-(Benzyl diethylphosphonate)cophenoxy-methylcopoly(styrene-1%-divinylbenzene)resin (16a).** Wang resin (Advanced Chem Tech; 40 g; 1.09 mmol/g loading;
4.0-(Benzyldiethylphosphonopropionate)phenoxy-methylcopoly(styrene-1%-divinylbenzene)resin (16b). 16b was prepared in a method similar to that of 16a following the above procedure from diethyl-2-phosphonopropionic acid: IR C=O 1733 cm\(^{-1}\).

5-(3,4-Dimethoxyphenyl)penta-2,4-dienoic Acid (17a). Resin 16a (100 mg; 0.063 mmol) was swollen in dry THF (1.5 mL) for 15 min at room temperature and then cooled under nitrogen to 0 °C for 15 min. LiHMDS (1 M in hexane; 0.16 mL; 0.16 mmol) was added and the reaction mixture brought to ambient temperature for 3 days. The reaction mixture was vigorously agitated for 18 h and then quenched by the addition of 2 M HCl (aqueous) (approximately pH 3 is obtained). The mixture was agitated for 30 min. Sodium sulfate was added, and the mixture was filtered through a plug of silica gel, washed thoroughly with DCM, and concentrated to give of 6-phenyl-hexan-3-one (13 mg; 0.0748 mmol; 68%): GC MS (EI) area \(\text{UV}_{220}\) 92%.

1-(4-Bromo-3-methylbenzylidene)propan-1-one (18b). Dry 4-O-(methylhydroxylamine)phenoxymethylcopoly(styrene-1%-divinylbenzene)resin (3 mg; 0.015 mmol) was added to DMF (3 mL) for 10 min and then treated with 4-bromo-3-methylbenzaldehyde (1.93 g; 9 mmol) and EDCI (1.725 g; 9.2 mmol) was added, and the reaction mixture was vigorously agitated for 1 h and then quenched by the addition of 2 M HCl (aqueous) (approximately pH 3 is obtained). The mixture was agitated for 30 min. Sodium sulfate was added, and the mixture was filtered through a plug of silica gel, washed thoroughly with DCM, and concentrated to give of 6-phenyl-hexan-3-one (13 mg; 0.0748 mmol; 68%): GC MS (EI) area \(\text{UV}_{220}\) 92%.

Cleavage from Resin To Confirm Loading. N-(4-Bromo-3-methylbenzoyl)-4-(methylhydroxylamine)phenoxymethylcopoly(styrene-1%-divinylbenzene)resin (100 mg; 0.075 mmol) was suspended in 50% TFA/CH\(_2\)Cl\(_2\) for 2 h. The resin was filtered and washed three times with DCM and then concentrated to give N-hydroxy-4-bromo-3-methylbenzamide (17.2 mg; 0.075 mmol): LC MS m/z 268/270 [M + H]\(^+\) area = 78%; \(^1\)H NMR \(\delta 2.42, 1H, 7.4\) (dd, 1H, 7.8, 1H, 7.58 (dd, 1B = 7.89, 1H, 2.1 mmol) was suspended in toluene (27 mL), and the mixture was agitated for 10 min. The resin was filtered and washed with 2 M HCl (aqueous) (0.015 mmol) was added, and the mixture was agitated for 2 h on a wrist shaker. 4-Chlorobenzyl bromide (6.47 g; 31.5 mmol) was added, and the reaction mixture was vigorously agitated for 3 days. The resin was filtered, washed with DMF (3 x 30 mL), 20% aqueous DMF (3 x 30 mL), THF (3 x 50 mL), and Et\(_2\)O (3 x 50 mL), and dried under vacuum at 40 °C to give N-4-phenoxybutyl-1-oyl-4-(methylhydroxylationenephoxy-methylcopoly(styrene-1%-divinylbenzene)resin (2.2 g): IR C=O 1670 cm\(^{-1}\). Anal. Calcd: C, 10.5. Found: C, 10.7.

N-4-Phenylbutyl-1-oyl-4-O-(methylhydroxylationenephoxy-methylcopoly(styrene-1%-divinylbenzene)resin (1.46 g; 1.095 mmol) was suspended in toluene (26 mL) for 10 min. DBU (0.83 mL; 5.5 mmol) was added, and the mixture was agitated for 2 h on a wrist shaker. 4-Bromobenzyl bromide (4.1 g; 16.425 mmol) was added, and the reaction mixture was vigorously agitated for 4 days. The resin was filtered, washed with DMF (3 x 50 mL), 20% aqueous DMF (3 x 50 mL), DMF (3 x 50 mL), THF (3 x 50 mL), and Et\(_2\)O (3 x 50 mL), and dried under vacuum at 40 °C to give N-4-bromobenzyl-N-4-phenylbutyl-1-ylcarbonyl-4-O-(methylhydroxylationenephoxy-methylcopoly(styrene-1%-divinylbenzene)resin (1.4 g): IR C=O 1668 cm\(^{-1}\). Anal. Calcd: Br, 5.3; N, 0.9. Found: Br, 5.4; N, 0.85.

N-4-Bromobenzyl-N-4-phenylbutyl-1-oyl-4-O-(methylhydroxylationenephoxy-methylcopoly(styrene-1%-divinylbenzene)resin (0.15 g (ca. 0.75 mmol/g); 0.11 mmol) was suspended in diethyl ether (1 mL) and treated with ethylmagnesium bromide (1 M in THF) (0.34 mL, 0.34 mmol). The reaction mixture was agitated for 18 h and then quenched by the addition of 2 M HCl (aqueous) (approximately pH 3 is obtained). The mixture was agitated for 30 min. Sodium sulfate was added, and the mixture was filtered through a plug of silica gel, washed thoroughly with DCM, and concentrated to give of 6-phenyl-hexan-3-one (13 mg; 0.0748 mmol; 68%): GC MS (EI) area = 97.1%, m/z 176.2 (M\(^+\)); MS (EI-LRP) m/z 176 (M\(^\ddagger\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 1.02\) (t, 3H), 1.9 (m, 2H), 2.4 (m, 4H) 2.6 (m, 2H), 7.2–7.3 (m, 5H).

1-(4-Bromo-3-methylphenyl)acrylic Acid. Dry 4-O-(methylhydroxylamine)phenoxymethylcopoly(styrene-1%-divinylbenzene)resin (3 mg; 0.015 mmol) was added to DMF (3 mL) for 10 min and then treated with 4-bromo-3-methylbenzoic acid (1.93 g; 9 mmol) and EDCI (1.725 g; 9.2 mmol). The mixture was suspended in 50% TFA/CH\(_2\)Cl\(_2\) for 2 h. The resin was filtered and washed three times with DCM and then concentrated to give N-hydroxy-4-bromo-3-methylbenzamide (17.2 mg; 0.075 mmol): LC MS m/z 268/270 [M + H]\(^+\) area = 78%; \(^1\)H NMR \(\delta 2.42, 1H, 7.4\) (dd, 1H, 7.8, 1H, 7.58 (dd, 1B = 7.89, 1H, 2.1 mmol) was suspended in toluene (27 mL), and the mixture was agitated for 10 min. The resin was filtered and washed with 2 M HCl (aqueous) (0.015 mmol) was added, and the mixture was agitated for 2 h on a wrist shaker. 4-Chlorobenzyl bromide (6.47 g; 31.5 mmol) was added, and the reaction mixture was vigorously agitated for 3 days. The resin was filtered, washed with DMF (3 x 30 mL), 20% aqueous DMF (3 x 30 mL), THF (3 x 50 mL), and Et\(_2\)O (3 x 30 mL), and dried under vacuum at 40 °C to give N-4-chlorobenzyl-N-(4-bromo-3-methylbenzoyl)-4-O-(methylhydroxylationenephoxy-methylcopoly(styrene-1%-divinylbenzene)resin (3g): IR C=O 1664 cm\(^{-1}\). Anal. Calcd: Br, 4.2; Cl, 1.9; N, 0.8. Found: Br, 4.8; Cl, 0.5; N, 0.9.

N-4-Chlorobenzyl-N-(4-bromo-3-methylbenzoyl)-4-O-(methylhydroxylationenephoxy-methylcopoly(styrene-1%-divinylbenzene)resin (0.23 g (ca. 0.55 mmol/g); 0.115 mmol) was suspended in diethyl ether (1 mL) and treated with ethylmagnesium bromide (1 M in THF, 0.23 mL; 0.23 mmol). The reaction mixture was agitated for 18 h and then quenched by the addition of 2 M HCl (aqueous) (pH ~3 is obtained). The
mixture was agitated for 30 min. Sodium sulfate was added, and the mixture was filtered through a plug of silica gel, rinsing with DCM (2 x 20 mL). The residue was concentrated to give 1-(4-bromo-3-methylphenyl)propan-1-one (6.0 mg; 0.026 mmol; 23%): GC area = 78.7%; MS (EI) m/z 226 Br [M+ - H]; 1H NMR δ 1.22 (t, J = 7.89, 3H), 2.96 (q, J = 7.89, 2H), 7.6 (bs, 2H), 7.8 (s, 1H).

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Supporting Information Available: 1H NMR and mass spectra for compounds 7a–m, q–v and 17a–f.