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A Self-Immolative Spacer That Enables Tunable Controlled Release of Phenols under Neutral Conditions

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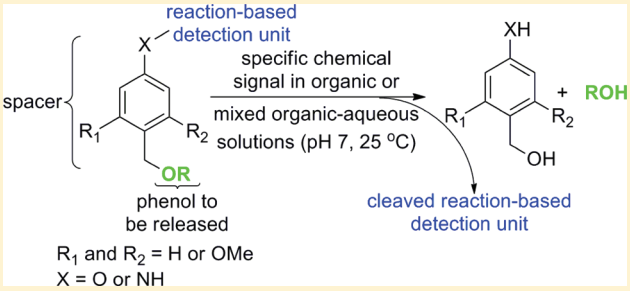
Supporting Information

ABSTRACT: A current challenge in the area of responsive materials is the design of reagents and polymers that provide controlled release of phenols in environments that are less polar than water. In these contexts, a molecular strategy that enables release of nearly any phenol with predictable and tunable rates and without complication from background hydrolysis would substantially increase the precision with which materials can be designed to respond to a particular signal. This Article addresses this problem at the fundamental level by describing the design, synthesis, and physical-organic characterization of two small molecule self-immolative spacers that are capable of releasing phenols in organic and mixed organic–aqueous solutions. The rate of release from these small molecule model systems is predictable and tunable, such that nearly any type of phenol, regardless of pK_a value, can be released in neutral solutions without complications from nonspecific background release due to hydrolysis. Furthermore, the release properties of the spacers can be predicted from bond length and conformation data (obtained from crystal structures). On the basis of these results, it should now be possible to incorporate these design elements into materials to enable precise response properties in environments that are not 100% aqueous.



INTRODUCTION

Effective molecular strategies are needed for releasing phenols in response to specific stimuli in organic and mixed organic–aqueous solutions without complication from background hydrolysis and with precise control over the rate of release. Solutions to this problem will be useful in diverse areas, including responsive dendrimers,[1−7] molecular sensors,[8] and smart nano- and micrometer-scale capsules[9−11] that operate in coatings, self-healing materials, and other environments that are substantially less polar than water. Often in these types of responsive materials, a phenol is attached to a portion of a polymer or small molecule or integrated into the polymer to form the backbone of the material. When these types of materials are exposed to a specific stimulus, the phenol is released in a disassembly process that translates detection of the stimulus into a specific response of the material.

Phenols (and alcohols) frequently are attached to polymers and small molecules of this type through a spacer group[12−16] that enables effective translation of reaction with the stimulus to release of the phenol; the functionality used to attach the phenol to the spacer can be a carbonate,[17] ester,[18] acetal,[19] ether,[20−23] hemiaminal ether,[24] carbamate,[11,16,25−27] or related functionalities.[28,29] In these contexts, however, we[19] and others[20] have observed substantial background release of phenols from the spacer groups due to hydrolysis (even in neutral, mixed organic–aqueous solutions) when the phenols are connected to the spacer as an ester, carbonate, or acetal. Furthermore, the hydrolysis reaction is particularly problematic when the phenol is acidic. We also have recognized the need for highly tunable spacer groups that enable predictable rates of release of any phenol in response to a specific stimulus; predictable rates of release would enhance the number of applications to which these types of disassembling materials can be applied, and a tunable spacer would enable release of any type of phenol, rather than being limited to acidic phenols. Solutions to both of these issues (i.e., background hydrolysis and tunable spacers) will improve the precision with which responsive materials/reagents perform their designed function.[30]

In an effort to address these challenges, we now describe the design, synthesis, and physical-organic characterization of two spacers (Figure 1) that are capable of releasing phenols without complications from nonspecific background release reactions and with tunable rates of release. These spacers function in a variety of solvents (organic to mixed organic–aqueous) and are capable of releasing nearly all types of phenols. In this Article, we characterize the response properties of these spacers in model systems with the objective that the results of these studies can be used in future efforts to guide the rational design of stimuli-responsive materials.[30]

Design of the Spacers. In our designs (Figure 1), one end of the spacer is connected to a reaction-based detection unit (e.g., a substrate for an enzyme; this unit is referred to as a

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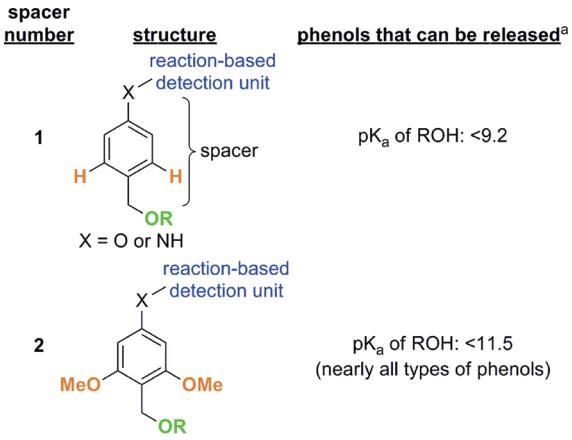


Figure 1. Two spacers described in this Article for releasing phenols in response to specific stimuli in organic and mixed organic–aqueous solutions. The phenol is connected to the spacer through an ether bond to minimize background release caused by nonspecific hydrolysis, and the methyl ethers are included in entry 2 to increase the rate of release of the phenol (i.e., they provide the ability to tune the release rate).

trigger in some literature[13]), and the other end is attached to the phenol through a hydrolytically stable ether bond.[31] The presence of the specific chemical signal cleaves the bond between the reaction-based detection unit and the spacer, thus revealing an aniline or phenol that initiates release of the pendant phenol via a presumed azaquinone methide or quinone methide intermediate, respectively (see the Abstract image for the general disassembly reaction that occurs).

Only a handful of previous studies[20−23] have linked phenols to spacers (similar to those shown in Figure 1) via ether bonds and have demonstrated that phenols with pK_a values of <9.8 can be released under neutral conditions. These studies were conducted in aqueous solutions in which the high polarity of the solvent accelerates the rate of the release reaction (vide infra), presumably by stabilizing dipoles that are formed in the transition state. When the same type of release reaction is performed in organic or even mixed organic–aqueous solutions, the release rate is substantially slowed (vide infra).

An alternative strategy (than shown in Figure 1) for controlling the release rate of phenols that are linked to spacers as ethers is to change reaction conditions to favor the rate of release. This approach works particularly well when basic reaction conditions are employed and when the spacer proceeds through quinone methide.[1−6] Because basic reaction conditions are not always feasible in the context of stimuli-responsive materials, we sought a more general strategy that involved modifying the spacer, rather than adjusting the conditions for the release reaction.

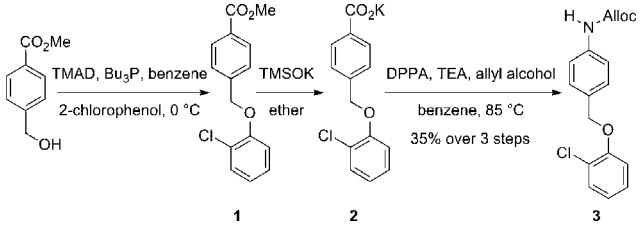
In order to release phenols from stimuli-responsive materials/reagents in organic and mixed organic–aqueous solutions, the ideal spacer would be (i) stable over days or even months in aqueous or mixed organic–aqueous solutions without background release; (ii) capable of releasing the pendant alcohol only when exposed to a specific signal; (iii) designed to enable predictable and tunable rates of release so that the reagent can be modified to release any phenol at any desired rate; (iv) capable of releasing phenols under neutral conditions (i.e., pH 7.0 and 25 °C), in polar organic or mixed organic–aqueous solutions; and (v) accessible via a short, efficient, and modular synthesis, thus facilitating variation of both the reaction-based detection unit and the pendant phenol.

Figure 1 illustrates two related spacers that were designed with these criteria in mind. These spacers rapidly release phenols with pK_a values <9.2 (spacer 1) and <11.5 (i.e., nearly all types of phenols) (spacer 2). Although similar to spacer 1, spacer 2 possesses two methyl ethers at strategic positions on the central benzene ring. We hypothesized that the addition of methyl ethers ortho to the benzylic ether would increase the energy of the HOMO of the aromatic ring, thus increasing the strength of the HOMO–LUMO interaction between π and σ^*_{C-O}. This orbital interaction would raise the ground state energy of the controlled release reagent and thus increase the rate of the release reaction. Moreover, stronger orbital interactions between π and σ^*_{C-O} would, in theory, lengthen the benzylic C–O bond and shorten the $C_{benzene}$–$C_{benzylic}$ bond. Hence, we reasoned that the addition of methyl ethers on the spacer would weaken the ether bond and enable rapid rates of release for any type of phenol.[32−34] Our efforts to develop these designs and test this hypothesis are described below.

RESULTS AND DISCUSSION

Preparation and Analysis of a Spacer for the Controlled Release of Acidic Phenols (pK_a Values <9.2). To evaluate the effectiveness of spacer 1, we employed an allyloxycarbonyl (Alloc) group as a model reaction-based detection unit, which would detect Pd(0) as the model chemical signal. Five derivatives were prepared via an efficient three-step synthesis (see Scheme 1 for the synthesis of reagent

Scheme 1. Synthetic Route to Reagent 3 (a Derivative of Spacer 1 in Figure 1), Which Contains 2-Chlorophenol Attached to the Spacer



3) to ascertain a range of phenols that can be released from this first-generation spacer.

The rate of release of phenol from each spacer was measured as follows: (i) The controlled-release reagent was exposed to 8.9 mol % $Pd(PPh_3)_4$, excess Bu_3SnH, and excess AcOH in THF for 3 min (Figure 2a). Quantitative deprotection of the Alloc group occurred, but no alcohol was released in this nonpolar solvent. (ii) A 10-μL aliquot of this reaction mixture then was diluted with 1 mL of 1:1 CH_3CN/water (pH 7.1). (iii) The release of the pendant alcohol was monitored over time by repetitive injections (20 min intervals) into an HPLC connected to a mass spectrometer (LC–MS) (Figure 2b).

The half-life for the release of phenol from this spacer is exponentially dependent on the pK_a of the alcohol (Figure 3). In other words, to achieve a reasonable rate of release (which we are defining to be $t_{1/2} \leq 3$ h), only alcohols with pK_a values less than 9.2 can be used under the specific release conditions. Given this pK_a constraint, spacer 1 is useful only for the controlled release of relatively acidic phenols under these

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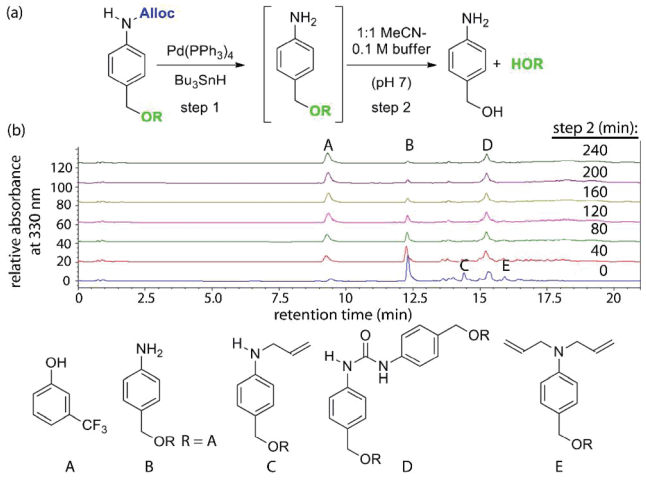

Figure 2. Method for measuring the release of phenols from the self-immolative spacers shown in Figure 1. (a) Reaction conditions used for measuring the rate of release of each alcohol in response to Pd(0). (b) Example of a stacked LC–MS plot over the course of the release reaction (step 2). This example is for compound **7**, where R = 3-trifluoromethylphenyl. The rate of release of the alcohol was measured over time by following the disappearance of the aniline intermediate B at 330 nm.

reaction conditions. It is noteworthy that in the absence of Pd(0) (the model analyte) even derivative **3** (which contains the most acidic phenol, pK_a = 8.51[35]) shows no signs of background release when stored in 1:1 MeCN/buffered water (pH 7) at 25 °C (i.e., the conditions of step 2 in Figure 2a) for

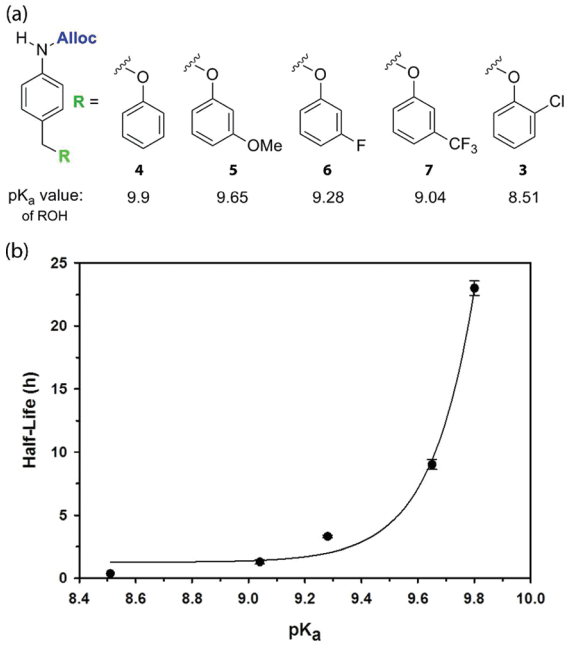

Figure 3. Controlled release of ether-linked phenols from spacer 1 in Figure 1. (a) Structures used to create the graph in (b). The pK_a values were obtained from reference 35. The reaction conditions used for measuring the rate of release of each alcohol in response to Pd(0) are shown in Figure 2a. The rate of release was quantified using LC–MS as shown in Figure 2b. (b) Correlation between release half-life and the pK_a value of the pendant phenol. All kinetics experiments were performed in triplicate; most error bars are the size of the data points or smaller.

38 days. On the basis of these results, we conclude that spacer 1 will be useful in situations in which it is desirable to release acidic phenols without complications from background release due to hydrolysis.

Effect of Solvent Polarity on the Rate of Release from Spacer 1. As indicated in the Introduction, qualitative observations suggest that the polarity of the environment in which the release reaction occurs can have a substantial effect on the rate of the release reaction. Responsive materials (such as responsive capsules) that operate in purely aqueous solutions have substantially lower polarity environments within the shell wall of the capsule and at the surface of the capsule (where the release reaction occurs) as compared to the bulk solvent.[36,37] The consequence of the low polarity of these local environments on slowing the rate of the release reaction likely is substantial, thus leading to slow responses in the stimuli-responsive material.[38,30]

To determine the consequence of polarity on the rate of release of the spacers described herein, we performed a quantitative release experiment using compound **7** as a model system. The experiment involved repeating the release reaction shown in Figure 2a, with the exception that the solvent composition (and, hence, the solvent polarity) was varied in step 2 of the reaction. Figure 4 shows that, as predicted, there is

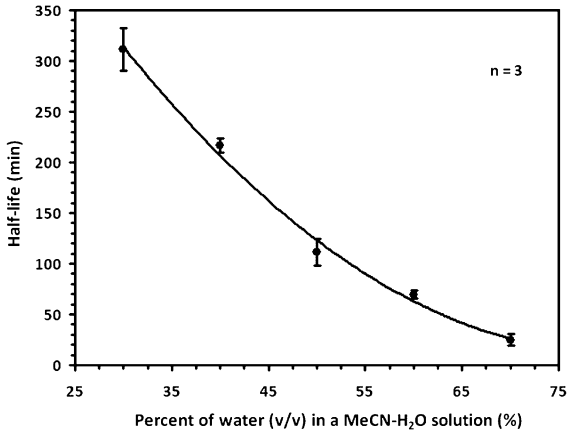

Figure 4. Effect of solvent polarity on the half-life for the release of 3-trifluoromethylphenol (pK_a = 9.04[35]) from compound **7** using the release experiment outlined in Figure 2a. The solvent polarity was varied in step 2 of the reaction in Figure 2a. The release reactions were performed in triplicate; the average values and standard deviations from the average are shown in the graph.

a direct relationship between solvent polarity and rate of release, i.e., as the polarity increases, the rate of release increases proportionally. The rapid rate of release in 70% H_2O/MeCN is further corroborated by the recent release studies reported by Cohen et al. in 100% water.[20] This graph makes clear that to enable rapid release of **7** in a nonpolar environment (such as in the shell of a capsule), further structural changes must be made to the linker to enhance the rate of release. The following sections describe spacer 2 that provides a solution to this issue.

Preparation and Analysis of a Spacer for the Controlled Release of All Phenols. As shown in Figure 3b, phenols with pK_a values >9.2 are released slowly from spacer 1. In order to facilitate release of these less acidic phenols, our second spacer design (spacer 2, Figure 1) includes two methyl ether substituents positioned ortho to the benzylic position where the phenol is attached. According to our

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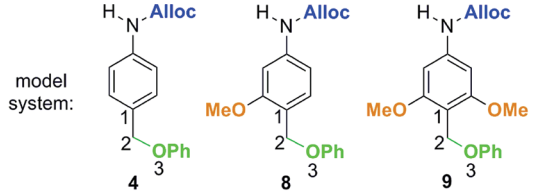
hypothesis, the addition of these methyl ethers would increase the interaction between π and σ^*_{C-O}, thus lengthening the benzylic C−O bond and enhancing the rate of release of a pendant phenol. Experimental data for spacers containing zero, one, and two methyl ethers, as well as calculations (NWChem program package[39] using B3LYP and the 6-311G* basis sets), further support this hypothesis by way of predicted and experimental bond lengths for the three model reagents (and spacers) shown in Figure 5.



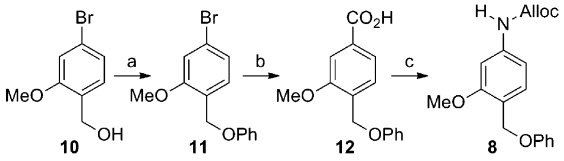
	4	8	9
$t_{1/2}$ for release of phenol (h)[a]:	23 ± 0.6	0.59 ± 0.06	<0.017[b]
bond length C_1-C_2 (Å):	1.502 (1.504)	1.500 (1.497)	1.498 (1.485)
bond length C_2-O_3 (Å):	1.435 (1.418)	1.437 (1.423)	1.441 (1.445)

[a] Rates of release were measured after exposure to Pd(0) using the conditions shown in Figure 2a.
[b] Phenol was released completely within minutes of diluting the Alloc-deprotected material in 1:1 MeCN-water (pH 7). This time-frame was faster than the time-frame for complete HPLC analysis.

Figure 5. Effect of methyl ethers (orange) on the rate of release of phenol (green). The $t_{1/2}$ values were obtained using the experimental conditions outlined in Figure 2a. Bond lengths were obtained both from theoretical calculations and from X-ray analysis of crystals (the experimental values are in parentheses).

To test the theoretical prediction, derivatives **4**, **8**, and **9** (syntheses of **8** and **9** are shown in Schemes 2 and 3) were

Scheme 2. Synthetic Route to Reagent 8[a]

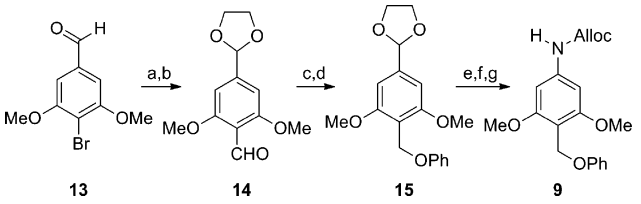


[a]Reagents and conditions: (a) DIAD, PPh_3, phenol, 0 °C (49%); (b) *n*-BuLi, CO_2, −78 °C; (c) DPPA, Et_3N, allyl alcohol, 85 °C (84% over 2 steps).

subjected to the same experimental conditions shown in Figure 2a. The half-life data for these reagents reveals a clear and striking trend (Figure 5): addition of one methyl ether to the linker (compound **8**) increases the rate of release of phenol 39-fold relative to that of **4**, and addition of a second methyl ether (compound **9**) increases the rate 35-fold relative to that of **8**. In other words, reagent **9** releases phenol >10^3 times faster than reagent **4**. Of equal importance is the observation that none of these compounds exhibited background release over a period of 1 month when exposed only to the conditions in step 2 (Figure 2a) (i.e., when not exposed to Pd(0) in step 1).

X-ray crystallographic data for compounds **4**, **8**, and **9** support the theoretical calculations by revealing that each methyl ether results in an increase in the C_2−O_3 bond length

Scheme 3. Synthetic Route to Reagent 9[a]



[a]Reagents and conditions: (a) PPTS, ethylene glycol, benzene, 105 °C; (b) *n*-BuLi, DMF, THF, −78 °C (80% over 2 steps); (c) $NaBH_4$, CH_2Cl_2/MeOH; (d) TMAD, Bu_3P, phenol, benzene, 0 °C (76% over 2 steps); (e) TsOH, THF; (f) $NaClO_2$, NaH_2PO_4, acetone/water; (g) DPPA, TEA, allyl alcohol, benzene, 85 °C (62% over 3 steps).

(Figure 5), as well as a corresponding decrease in the C_1−C_2 bond length. (The experimental bond lengths are shown in parentheses below the theoretical values in Figure 5.)

On the basis of the results in Figure 5, we hypothesized that even the least acidic phenols would likely release effectively from spacer 2, and therefore, this spacer could serve as a general spacer for the release of all types of phenols. Using the general synthetic route shown in Scheme 3, we prepared derivatives **9**−**19** (Figure 6) and tested them using the Pd(0)-detection and LC−MS analysis procedure described in Figure 2a. The results of these experiments reveal that phenols with pK_a values up to ∼11.5 (i.e., the least acidic types of phenols) can be released at reasonable rates ($t_{1/2} \leq 3$ h) (Figure 6b). In

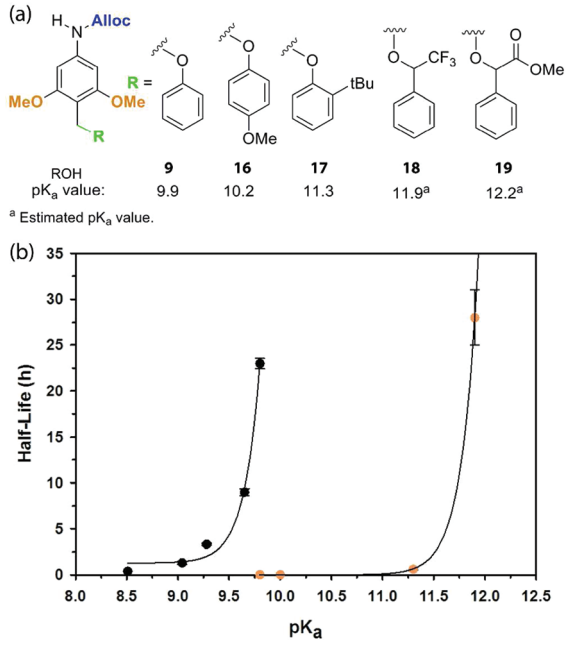


Figure 6. Controlled release of phenols using a spacer that contains two methyl ethers ortho to the benzylic ether (i.e., entry 2 in Figure 1). (a) Structure and pK_a value for the phenol. (b) Correlation between the pK_a value for phenol and the half-life for the release reaction (orange data points). The experimental procedure for studying the release reaction is shown in Figure 2a. The black data points correspond to the data from Figure 3b and are included to compare the effects of two methyl ethers on release rate with the spacer that lacks methyl ethers. Experimental and estimated pK_a values were obtained from the following sources: **16**,[35] **17**,[35] **18**,[40] and **19**.[40] All kinetics experiments were performed in triplicate; most error bars are smaller than the data points.

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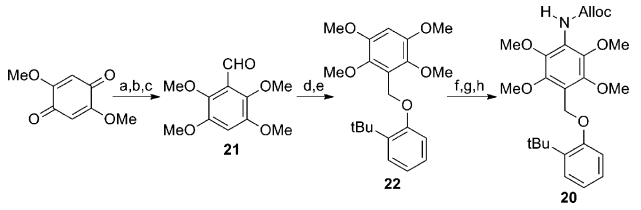
other words, the presence of two methyl ethers on the spacer molecule enables the release of pendant phenols that are 23-fold less acidic (2.3 pK_a units higher) than is possible when the methyl ethers are absent. This spacer now allows nearly any phenol to be released in mixed organic–aqueous solutions.

Attempt To Prepare a Spacer for the Rapid Controlled Release of Alcohols (Other than Phenols) with pK_a Values >11.5. The results shown in Figures 5 and 6 suggest that additional methyl ether substituents might further enhance the rate of release of a pendant phenol in low polarity environments and might even enable the release of other types of alcohols that are connected to the spacer through an ether bond (the synthesis of an example derivative is shown in Scheme 4). In contrast to this prediction, we found that

Scheme 4. Synthetic Route to Reagent 20 (a Tetramethyl Ether Spacer)[a]



[a]Reagents and conditions: (a) $Na_2S_2O_4$) MeOH/water; (b) MeI, K_2CO_3, DMF; (c) *n*-BuLi, DMF, THF, −78 °C; (d) $NaBH_4$, CH_2Cl_2/MeOH; (e)TMAD, Bu_3P, 2-*tert*-butylphenol, benzene, 0 °C (20% over 5 steps); (f) *n*-BuLi, DMF, THF, −78 °C; (g) $NaClO_2$, Na_2HPO_4, acetone/water; (h) DPPA, TEA, allyl alcohol, benzene, 85 °C (54% over 3 steps).

additional methyl ethers on the spacer introduce unfavorable nonbonding interactions between adjacent methyl ethers, thus positioning the oxygen lone-pairs out of alignment with π^* on the aromatic ring (Figure 7a). Hence, the methyl ethers no

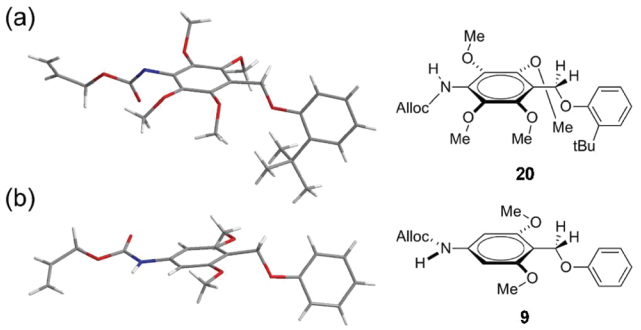
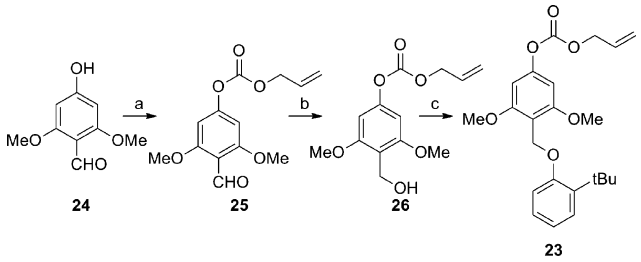


Figure 7. X-ray crystal structures of spacers that contain four methyl ethers (a) and two methyl ethers (b). The oxygen lone pairs on the methyl ethers in panel b are aligned for interactions with $\pi^*_{aromatic}$, whereas in panel a they are not.

longer significantly donate electron density through lone-pair–$\pi^*_{aromatic}$ interactions. The consequence of this conformation is apparent not only by comparison of X-ray crystallographic data (Figure 7) but also by rates of release of 2-*tert*-butylphenol: using the conditions shown in Figure 2a, the half-life for release of 2-*tert*-butylphenol from reagent **20** (Figure 7a) is 110 ± 5 h, whereas the corresponding one- (**58**) and two-methyl (**9**) ether derivatives released 2-*tert*-butylphenol with half-lives of 9.2 ± 0.5 h (12× faster) and 0.62 ± 0.07 h (177× faster), respectively.

Comparison of Azaquinone Methide and Quinone Methide Spacers. The spacers discussed up to this point all have released phenols through a presumed azaquinone methide intermediate, but the release should be possible via quinone methide as well. To determine the effectiveness of release via quinone methide, we prepared reagent **23** (Scheme 5). Reagent

Scheme 5. Synthetic Route to 23, Which Releases 2-*tert*-Butylphenol through Quinone Methide[a]



[a]Reagents and conditions: (a) allyl chloroformate, pyridine, CH_2Cl_2 (84%); (b) $NaBH_4$, MeOH–CH_2Cl_2; (c) TMAD, Bu_3P, 2-*tert*-butylphenol, benzene (40% over 2 steps).

23 is analogous to reagent **17**, with the exception that **23** releases 2-*tert*-butylphenol via a quinone methide intermediate, whereas **17** proceeds through a presumed azaquinone methide intermediate. The rate of release of 2-*tert*-butylphenol from **23** was measured using the same experimental conditions described in Figure 2a.

The half-life for release of 2-*tert*-butylphenol from **23** is 158 ± 14 min, while the half-life for release of the same phenol from **17** is 37 ± 4 min. This result indicates that, in mixed organic–aqueous solutions at pH 7, a phenol spacer (Figure 1) is ∼4.3× slower to release phenols than an aniline spacer, which is consistent with the general sentiment in the literature.[14] As the pH of the solution is raised, however, this difference in release rate is likely to diminish as the phenol intermediate (i.e., the precursor to quinone methide) becomes deprotonated.[1]

■ CONCLUSION

In conclusion, we have developed a general set of self-immolative spacers for the controlled release of phenols (with pK_a values ≤11.5) in neutral, mixed organic–aqueous solutions without background release due to nonspecific hydrolysis. The syntheses of these spacers are modular and should enable ready access to reagents that contain different reaction-based detection units and that release various types of phenols. The choice of which spacer to use depends on the type of phenol being released, but in general, as the number of methyl ethers on the spacer increases (i) the rate of release of a given phenol increases and (ii) a broader range of phenols can be released, including relatively nonacidic phenols. However, synthetic accessibility may be a consideration as well when choosing a spacer: the spacer with no methyl ethers is prepared in approximately half the number of synthetic steps as the spacer with two methyl ethers. Overall, the appropriate choice of spacer depends on the pK_a value of the phenol, the desired rate of release, and synthetic accessibility. Taken together, the results of this study now provide a framework for guiding the rational design of responsive materials/reagents that release phenols in environments that are less polar than water.

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EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed in flame-dried glassware under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (25−40 mmHg) at ambient temperature. All reagents were purchased commercially and were used as received. Acetonitrile (MeCN), dichloromethane, *N*,*N*-dimethylformamide, benzene, triethylamine, and tetrahydrofuran were purified by the method of Pangborn et al.[41] Flash-column chromatography was performed as described by Still et al.,[42] employing silica gel (60-Å pore size, 32−63 μm, standard grade). Thin-layer chromatography was carried out on silica gel TLC (20 m × 20 cm w/h, F-254, 250 μm). Deionized water was purified using a Millipore purification system. Kinetics experiments were carried out in 2-mL HPLC vials.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using an NMR spectrometer at 25 °C. Proton chemical shifts are expressed in parts per million (ppm) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.24 ppm).[43] Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), integration, and coupling constant (*J*) in hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a 75 MHz NMR spectrometer at 25 °C. Carbon chemical shifts are expressed in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0). Kinetics and rate of release studies were performed using an HPLC with a UV detector and a 150 mm × 2.1 mm betasil phenyl-hexyl column. The column was equilibrated in 9:1 H_2O/MeCN at 1 mL/min flow rate. After injection of the sample, a solvent gradient was established by ramping to 1:9 H_2O/MeCN over 15 min. Low resolution and high resolution mass spectra were acquired using mobile phases containing 5 mM ammonium formate.

Synthesis Procedures.

*4-Phenoxymethyl-bromobenzene (**27**).* Phenol (0.56 g, 6.0 mmol, 3.0 equiv) and tetrabutylammonium iodide (73 mg, 0.20 mol, 0.1 equiv) were dissolved in tetrahydrofuran (10 mL), and the reaction mixture was cooled to 0 °C. Sodium hydride (99%, 0.14 g, 7.0 mmol, 3.5 equiv) was added to the reaction solution, and the suspension was stirred for 15 min at 0 °C. 4-Bromobenzyl bromide (0.50 g, 2.0 mmol, 1 equiv) was added, and the suspension was stirred at 23 °C for 16 h. Ethyl acetate (30 mL) was added to the reaction mixture, followed by dropwise addition of 1 M aqueous sodium hydroxide solution (1 mL). The layers were separated, and the organic layer was washed with 1 M aqueous sodium hydroxide solution (3 × 30 mL), followed by saturated aqueous sodium chloride solution (1 × 30 mL). The organic layer was dried over sodium sulfate, the solid sodium sulfate was removed by filtration, and the dried solution was concentrated by rotary evaporation. 4-Phenoxymethyl-bromobenzene (**27**, colorless oil) was used without further purification.

*4-Phenoxymethylbenzoic Acid (**28**).* Compound **27** (0.53 g, 2.0 mmol, 1 equiv) was dissolved in tetrahydrofuran (10 mL), and the solution was cooled to −78 °C. *n*-Butyllithium (1.6 mL, 2.4 M in hexanes, 2.0 equiv) was added dropwise to the −78 °C solution, and the resulting mixture was stirred for 5 min. Dry carbon dioxide was bubbled through an 18-gauge metal needle into the reaction mixture for 15 min, and then the reaction mixture was allowed to warm to 23 °C. Aqueous sodium hydroxide solution (1 N, 1 mL) was added to the reaction mixture, followed by ethyl acetate (20 mL). The layers were separated, and the organic layer was extracted with 1 M aqueous sodium hydroxide (2 × 20 mL). The combined aqueous layers were acidified to pH 2 by addition of concentrated hydrochloric acid. The acidic aqueous solution was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over sodium sulfate, and the solid sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to afford compound **28** as a white solid, which was used without further purification.

*(4-Phenoxymethylphenyl)carbamic Acid Allyl Ester (**4**).* Compound **28** (0.37 g, 1.6 mmol, 1 equiv) was dissolved in benzene (6.5 mL). Triethylamine (0.30 mL, 2.1 mmol, 1.3 equiv) and diphenylphosphoryl azide (0.46 mL, 2.1 mmol, 1.3 equiv) were added to the reaction mixture. The solution was heated to 80 °C for 2 h, and then allyl alcohol (0.33 mL, 4.9 mmol, 3.0 equiv) was added to the hot solution. The solution was heated to 90 °C for 3 h, was allowed to cool to 23 °C, and was concentrated by rotary evaporation. The residue was purified by silica gel flash column chromatography (20% ethyl acetate in hexanes, increasing to 40% ethyl acetate in hexanes) to afford (**4**) as a white solid (0.33 mg, 1.2 mmol, 56% over three steps): mp 92−95 °C; IR (cm^{-1}) 3295, 1695, 1537; ^{1}H NMR δ 7.51−7.32 (m, 7H), 7.07−7.02 (m, 3H), 6.08−5.97 (m, 1H), 5.47 (dd, 1H, *J* = 18, 1.2 Hz), 5.41 (dd, 1H, *J* = 10.5, 0.9 Hz), 5.06 (s, 2H), 4.76 (d, 2H, *J* = 5.4 Hz); ^{13}C NMR δ 159.2, 153.9, 138.2, 132.9, 132.5, 130.0, 128.9, 121.4, 119.4, 118.7, 115.4, 70.0, 66.4; MS (TOF MS AP +, *m*/*z*) 306.2 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{17}H_{21}N_2O_3$ (M + NH_4^+) 301.1552, found 301.1548.

*Methyl 4-((3-Methoxyphenoxy)methyl)benzoate (**29**).* Tributylphosphine (0.30 mL, 1.2 mmol, 1.2 equiv) was added to a solution of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) (0.21 g, 1.2 mmol, 1.2 equiv) in benzene (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 15 min. 4-(Hydroxymethyl) benzoate (0.17 g, 1.0 mmol, 1 equiv) and 3-methoxyphenol (0.13 mL, 1.2 mmol, 1.2 equiv) were added as a solution in benzene (5 mL). The resulting reaction mixture was stirred at 23 °C for 1 h. The product mixture was diluted with ethyl acetate (20 mL), and the solution was washed with saturated aqueous sodium chloride solution (2 × 20 mL). The organic layer was dried over sodium sulfate, the sodium sulfate was removed by filtration, and the solvent was removed by rotary evaporation. The resulting oil was filtered through a plug of silica gel (5% ethyl acetate in hexanes, increasing to 20% ethyl acetate in hexanes) to provide compound **29**, which was used without further purification.

*Potassium 4-((3-Methoxyphenoxy)methyl)benzoate (**30**).* Compound **29** (0.18 g, 0.65 mmol, 1 equiv) and potassium trimethylsilanolate (91 mg, 0.71 mmol, 1.1 equiv) were dissolved in diethyl ether (12 mL), and the resulting solution was stirred at 23 °C for 16 h. The reaction mixture was filtered, and the white solid was washed with a 3:1 mixture of ether−hexanes (3 × 20 mL). The white solid (**30**) was dried under reduced pressure and was used without further purification.

*Allyl 4-((3-Methoxyphenoxy)methyl)phenylcarbamate (**5**).* Triethylamine (44 μL, 0.32 mmol, 1.2 equiv) and diphenylphosphoryl azide (70 μL, 0.32 mmol, 1.2 equiv) were added to a solution of compound **30** (78 mg, 0.26 mmol, 1 equiv) in benzene (1.5 mL) at 23 °C. The reaction mixture was heated to 80 °C. After 2 h of stirring at 80 °C, allyl alcohol (90 μL, 1.3 mmol, 5.0 equiv) was added. The solution was heated to 90 °C, held at 90 °C for 3 h, and allowed to cool to 23 °C. The solvent was removed by rotary evaporation, and the residue was dissolved in ethyl acetate (8 mL) and sequentially washed with water (10 mL) and a saturated sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate, and the solid sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (10% ethyl acetate in hexanes, increasing to 30% ethyl acetate in hexanes) to afford compound **5** as a white solid (0.11 g, 0.35 mmol, 35% over 3 steps). IR (cm^{-1}) 3322, 1711, 1599; ^{1}H NMR δ 7.40−7.34 (m, 4H), 7.07 (td, 3H, *J* = 7.6, 1.1 Hz), 6.68 (s, 1H), 6.56−6.49 (m, 4H), 6.00−5.90 (m, 1H), 5.38 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.27 (dd, 1H, *J* = 10.4, 1.3 Hz), 4.97 (s, 2H), 4.66 (d, 2H, *J* = 5.7 Hz); ^{13}C NMR δ 160.8, 159.9, 137.5, 132.3, 132.0, 129.9, 128.5 (2 carbons), 118.7, 118.3, 106.9, 106.6, 101.3, 69.6, 65.9, 55.2; MS (TOF MS AP+, *m*/*z*) 336.1 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{18}H_{23}N_2O_4$ (M + NH_4^+) 331.1646, found 331.1658.

*Methyl 4-((3-Fluorophenoxy)methyl)benzoate (**31**).* Compound **31** (white solid) was prepared using the same conditions as those described for compound **29** with the exception that 3-fluorophenol was used instead of 3-methoxyphenol. The quantities of reagents used were *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (0.21 g, 1.2 mmol, 1.2 equiv), tributylphosphine (0.30 mL, 1.2 mmol, 1.2 equiv) 4-(hydroxymethyl)benzoate (0.17 g, 1.0 mmol, 1 equiv), and 3-fluorophenol (0.11 mL, 1.2 mmol, 1.2 equiv).

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*Potassium 4-((3-Fluorophenoxy)methyl)benzoate (**32**).* Compound **32** (white solid) was prepared using the same conditions as those described for compound **30**. The quantities of reagents used were **31** (0.18 g, 0.62 mmol, 1 equiv) and potassium trimethylsilanolate (87 mg, 0.68 mmol, 1.1 equiv).

*Allyl 4-((3-Fluorophenoxy)methyl)phenylcarbamate (**6**).* Compound **6** (white solid, 2% over three steps) was prepared using the same conditions as those described for compound **4**. The quantities of reagents used were **32** (77 mg, 0.27 mmol, 1 equiv), diphenylphosphoryl azide (70 μL, 0.32 mmol, 1.2 equiv), triethylamine (45 μL, 0.32 mmol, 1.2 equiv) and allyl alcohol (92 μL, 1.4 mmol, 5.0 equiv). IR (cm^{-1}) 3328, 1703, 1590; ^1H NMR δ 7.40−7.33 (m, 4H), 7.24−7.16 (m, 1H), 6.73−6.71 (m, 1H), 6.68−6.62 (m, 3H), 5.99−5.90 (m, 1H), 5.37 (dd, 1H, *J* = 17.3, 1.5 Hz), 5.27 (dd, 1H, *J* = 10.4, 1.2 Hz), 4.97 (s, 2H), 4.66 (d, 2H, *J* = 5.7 Hz); ^{13}C NMR δ 137.7, 132.3, 131.5, 130.2, 130.1, 128.5, 118.3, 110.6, 110.5, 107.8, 107.6 102.7, 102.4, 69.8, 65.9; MS (TOF MS AP+, *m*/*z*) 302.1 (M + H^+). HRMS (TOF MS AP+) calcd for $C_{17}H_{20}N_2O_3F$ (M + NH_4^+) 319.1458, found 319.1441.

*Methyl 4-((3-(Trifluoromethyl)phenoxy)methyl)benzoate (**33**).* Compound **33** (white solid) was prepared using the same conditions as those described for compound **29** with the exception that 3-trifluoromethylphenol was used instead of 3-methoxyphenol. The quantities of reagents used were *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (0.21 g, 1.2 mmol, 1.2 equiv), tributylphosphine (0.30 mL, 1.2 mmol, 1.2 equiv) methyl 4-(hydroxymethyl)benzoate (0.17 g, 1.0 mmol, 1 equiv), and 3-trifluoromethylphenol (0.15 mL, 1.2 mmol, 1.2 equiv).

*Potassium 4-((3-(Trifluoromethyl)phenoxy)methyl)benzoate (**34**).* Compound **34** (white solid) was prepared using the same conditions as those described for compound **30**. The quantities of reagents used were **33** (0.16 g, 0.58 mmol, 1 equiv) and potassium trimethylsilanolate (90 mg, 0.71 mmol, 1.1 equiv).

*Allyl (4-((3-(Trifluoromethyl)phenoxy)methyl)phenyl)carbamate (**7**).* Compound **7** (pale yellow solid, 29% over three steps) was prepared using the same conditions as those described for compound **4**. The quantities of reagents used were **34** (0.13 g, 0.44 mmol, 1 equiv), diphenylphosphoryl azide (0.11 mL, 0.53 mmol, 1.2 equiv), triethylamine (75 μL, 0.53 mmol, 1.2 equiv) and allyl alcohol (0.15 mL, 2.2 mmol, 5.0 equiv). IR (cm^{-1}) 3323, 1712, 1600; ^1H NMR δ 7.42−7.34 (m, 5H), 7.21−7.19 (m, 2H), 7.11 (d, 1H, J = 9.4), 6.69 (s, 1H), 6.01−5.90 (m, 1H), 5.38 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.27 (dd, 1H, *J* = 10.4, 1.3 Hz), 5.02 (s, 2H), 4.67 (d, 2H, *J* = 5.7 Hz); ^{13}C NMR δ 158.8, 137.8, 132.3, 132.0 131.2, 129.9, 128.6, 118.7, 118.3, 118.2, 117.6, 117.5, 111.7, 111.6, 69.9, 65.9; MS (TOF MS AP+, *m*/*z*) 352.0 (M + H^+). HRMS (TOF MS AP+) calcd for $C_{18}H_{20}N_2O_3F_3$ (M + NH_4^+) 369.1432, found 369.1426.

*Methyl 4-((2-Chlorophenoxy)methyl)benzoate (**1**).* Compound **1** (white solid) was prepared using the same conditions as those described for compound **29** with the exception that 2-chlorophenol was used instead of 3-trifluoromethylphenol. The quantities of reagents used were *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (0.21 g, 1.2 mmol, 1.2 equiv), tributylphosphine (0.30 mL, 1.2 mmol, 1.2 equiv) methyl 4-(hydroxymethyl)benzoate (0.17 g, 1.0 mmol, 1 equiv), and 2-chlorophenol (0.12 mL, 1.2 mmol, 1.2 equiv).

*Potassium 4-((2-Chlorophenoxy)methyl)benzoate (**2**).* Compound **2** (white solid) was prepared using the same conditions as those described for compound **30**. The quantities of reagents used were **1** (0.16 g, 0.58 mmol, 1 equiv) and potassium trimethylsilanolate (0.11 g, 0.87 mmol, 1.5 equiv).

*Allyl (4-((2-Chlorophenoxy)methyl)phenyl)carbamate (**3**).* Compound **3** (white solid, 35% over three steps) was prepared using the same conditions as those described for compound **4**. The quantities of reagents used were **2** (0.15 g, 0.51 mmol, 1 equiv), diphenylphosphoryl azide (0.13 mL, 0.60 mmol, 1.2 equiv), triethylamine (85 μL, 0.60 mmol, 1.2 equiv) and allyl alcohol (0.17 mL, 23.6 mmol, 5.0 equiv). IR (cm^{-1}) 3322, 1704, 1596; ^1H NMR δ 7.38−7.34 (m, 5H), 7.18 (t, 1H, *J* = 8.3), 6.94−6.86 (m, 2H), 6.69 (s, 1H), 6.00−5.90 (m, 1H), 5.37 (d, 1H, *J* = 17.9 Hz), 5.26 (d, 1H, *J* = 10.4 Hz), 5.08 (s, 2H), 4.66 (d, 2H, *J* = 5.7 Hz); ^{13}C NMR δ 154.2, 137.6, 132.4, 131.6, 130.4, 128.2 (2 carbons), 127.7, 123.3, 121.7, 118.8, 118.4, 114.3, 70.5, 65.9; MS (TOF MS AP+, *m*/*z*) 318.2 (M + H^+). HRMS (TOF MS AP+) calcd for $C_{17}H_{20}N_2O_3Cl$ (M + NH_4^+) 335.1162, found 335.1153.

*3-Methoxy-4-phenoxymethyl-bromobenzene (**11**).* Diisopropyl azodicarboxylate (0.30 mL, 1.0 mmol, 1.5 equiv) was dissolved in benzene (5 mL), and the reaction mixture was cooled to 0 °C. Triphenylphosphine (0.39 g, 1.5 mmol, 1.5 equiv) was added to the reaction mixture, and the solution was stirred at 0 °C for 10 min. 4-Bromo-2-methoxybenzyl alcohol (**10**) (0.22 g, 1.0 mmol, 1 equiv) and phenol (0.14 g, 1.5 mmol, 1.5 equiv) were then added as a solution in benzene (5 mL), and the reaction mixture was stirred at 23 °C for 2 h. The solvent was removed by rotary evaporation, and the resulting oil was purified by silica gel flash column chromatography (30% ethyl acetate in hexanes, increasing to 60% ethyl acetate in hexanes) to afford compound **11** as an oil (0.14 g, 0.49 mmol, 49%). IR (cm^{-1}) 2931, 1590, 1495; ^1H NMR δ 7.33−7.26 (m, 3H), 7.11 (d, 1H, *J* = 8.0 Hz), 6.98−6.93 (m, 3H), 5.04 (s, 2H,), 3.84 (s, 3H); ^{13}C NMR δ 158.6, 157.2, 129.5, 129.4, 124.6, 123.5, 122.0, 120.9, 114.7, 113.8, 64.4, 55.6.

*3-Methoxy-4-phenoxylmethylbenzoic Acid (**12**).* *n*-Butyllithium (0.39 mL from 2.5 M in hexanes, 0.98 mmol, 2.0 equiv) was added dropwise to a solution of compound **11** (0.14 g, 0.49 mmol, 1 equiv) in tetrahydrofuran (5 mL) at −78 °C. The reaction solution was stirred for 5 min at −78 °C. Dry carbon dioxide was bubbled into the reaction mixture for 15 min, and then the solution was allowed to warm to 23 °C. Aqueous sodium hydroxide (1 M, 0.5 mL) was added dropwise to the solution, and the resulting mixture was diluted with ethyl acetate (15 mL). The organic phase was separated from the aqueous layer and was washed with 1 M aqueous sodium hydroxide (2 × 20 mL). The aqueous layers were combined and acidified to pH 2 by addition of concentrated aqueous hydrochloric acid. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to afford compound **12** as a white solid, which was used without further purification.

*(3-Methoxy-4-phenoxylmethylphenyl)carbamic Acid Allyl Ester (**8**).* Triethylamine (66 μL, 0.47 mmol, 1.2 equiv) and diphenylphosphoryl azide (0.10 mL, 0.47 mmol, 1.2 equiv) were added to a solution of compound **12** (0.10 g, 0.40 mmol, 1 equiv) in benzene (2 mL) at 23 °C. The solution was heated to 80 °C. After 2 h of stirring at 80 °C, allyl alcohol (0.80 mL, 1.2 mol, 3.0 equiv) was added to the reaction mixture, and the solution was heated to 90 °C. After 3 h of stirring at 90 °C, the solution was allowed to cool to 23 °C, and the solvent was removed by rotary evaporation. The residue was purified by silica gel flash column chromatography (20% ethyl acetate in hexanes, increasing to 40% ethyl acetate in hexanes) to afford **8** as a waxy white solid (0.10 g, 0.33 mmol, 84% over two steps): mp 86−89 °C; IR (cm^{-1}) 3318, 1707, 1601; ^1H NMR δ 7.41−7.26 (m, 5H), 7.04−6.96 (m, 3H), 6.88 (s, 1H), 6.18−5.8 (m, 1H), 5.47 (dd, 1H, *J* = 9.0, 3.0 Hz), 5.44 (dd, 1H, *J* = 18, 1.5 Hz), 5.33 (dd, 1H, *J* = 10.5, 1.2 Hz), 5.09 (s, 2H), 4.72 (d, 2H, *J* = 6.0 Hz), 3.88 (s, 3H); ^{13}C NMR δ 159.4, 158.0, 153.5, 139.3, 132.8, 130.2, 129.84, 129.7, 121.2, 120.8, 118.7, 115.3, 102.5, 66.3, 65.2, 55.9; MS (TOF MS AP+, *m*/*z*) 313.2 (M^+). HRMS (TOF MS AP+) calcd for $C_{18}H_{20}NO_4$ (M + H)$^+$ 314.1397, found 314.1392.

*2-(4-Bromo-3,5-dimethoxyphenyl)-[1,3]dioxolane (**35**).* 4-Bromo-3,5-dimethoxybenzaldehyde (**13**) (2.5 g, 10 mmol, 1 equiv), pyridinium *p*-toluenesulfonate (0.50 g, 2.0 mmol, 0.2 equiv), and ethylene glycol (2.2 mL, 40 mmol, 4.0 equiv) were dissolved in benzene (50 mL). A Dean−Stark apparatus was affixed to the reaction flask, and the solution was heated to 105 °C. After 5 h of stirring at 105 °C, the product solution was cooled to 23 °C. Benzene was removed by rotary evaporation, and the residue was dissolved in ethyl acetate (50 mL). The resulting solution was washed sequentially with saturated aqueous sodium bicarbonate solution (1 × 50 mL) and saturated aqueous sodium chloride solution (1 × 50 mL). The organic layer was dried over sodium sulfate. The sodium sulfate was removed by filtration, and the solution was concentrated by rotary evaporation to yield compound **35** as a white solid, which was used without further purification.

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*4[1,3]Dioxolan-2-yl-2,6-dimethoxybenzaldehyde (**14**).* *n*-Butyllithium (8.0 mL, 2.5 M in hexanes, 20 mmol, 2.0 equiv) was added dropwise to a −78 °C solution of compound **35** (2.9 g, 10 mmol, 1 equiv) in tetrahydrofuran (50 mL). The mixture was allowed to stir for 5 min at −78 °C, and then *N*,*N*-dimethylformamide (3.9 mL, 50 mmol, 5.0 equiv) was added. The reaction solution was stirred for 30 min at −78 °C and then was allowed to warm to 23 °C. After 1 h of stirring at 23 °C, the solution was slowly diluted with water (dropwise addition) (5 mL), followed by ethyl acetate (100 mL) and then saturated aqueous sodium bicarbonate solution (1 × 150 mL). The layers were separated, and the organic layer was washed with saturated aqueous sodium chloride (1 × 150 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (40% ethyl acetate in hexanes, increasing to 80% ethyl acetate in hexanes), yielding compound **14** (1.9 g, 8.0 mmol, 80% over two steps) as a pale yellow solid: mp 74−76 °C; IR (cm^{-1}) 3506, 2942, 2884, 1676, 1613, 1566; ^1H NMR δ 10.43 (s, 1H), 6.66 (s, 2H), 5.73 (s, 1H), 4.07−4.00 (m, 4H), 3.86 (s, 6H); ^{13}C NMR δ 189.0, 162.1, 146.0, 114.3, 102.6, 101.6, 65.2, 56.0; MS (TOF MS AP+, *m*/*z*) 261.2 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{12}H_{15}O_5$ (M + $H)^+$ 239.0919, found 239.0914.

*(4[1,3]Dioxolan-2-yl-2,6-dimethoxyphenyl)methanol (**36**).* Sodium borohydride (0.30 g, 8.0 mmol, 1.0 equiv) was added to a solution of compound **14** (1.9 g, 8.0 mmol, 1 equiv) in a mixture of dichloromethane (20 mL) and methanol (20 mL) at 23 °C. The reaction mixture was stirred for 5 min at 23 °C and then was slowly diluted (dropwise addition) with saturated aqueous ammonium chloride solution (5 mL). Dichloromethane (50 mL) and saturated aqueous ammonium chloride solution (80 mL) were added, and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1 × 80 mL) and was dried over sodium sulfate. The sodium sulfate was removed by filtration, and the solvent was removed by rotary evaporation to provide compound **36** as a pale yellow solid, which was used without further purification.

*2-(3,5-Dimethoxy-4-phenoxymethylphenyl)-[1,3]dioxolane (**15**).* Tributylphosphine (0.16 mL, 0.65 mmol, 1.3 equiv) was added to a solution of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) (0.11 g, 0.65 mmol, 1.3 equiv) in benzene (2.5 mL) at 0 °C, and the mixture was immersed in a 0 °C bath and stirred for 15 min. To this mixture was added a solution of compound **36** (0.12 g, 0.50 mmol, 1 equiv) and phenol (61 mg, 0.65 mmol, 1.3 equiv) in benzene (2.5 mL). The resulting reaction mixture was allowed to warm to 23 °C and then was stirred at 23 °C for 1 h. The mixture was diluted with ethyl acetate (10 mL), and the solution was washed with saturated aqueous sodium chloride (2 × 15 mL). The organic layer was dried over sodium sulfate, the sodium sulfate was removed by filtration, and the solvent was removed by rotary evaporation. The resulting oil was purified by silica gel flash column chromatography (30% ethyl acetate in hexanes, increasing to 60% ethyl acetate in hexanes) to afford compound **15** as a white solid (0.12 g, 0.38 mmol, 76% over two steps). IR (cm^{-1}) 2942, 2884, 1595; ^1H NMR δ 7.30 (t, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 6.93 (t, 1H, *J* = 7.6 Hz), 6.73 (s, 2H), 5.82 (s, 1H), 5.12 (s, 2H), 4.13−4.01 (m, 4H), 3.84 (s, 6H); ^{13}C NMR δ 160.0, 159.8, 140.9, 129.7, 120.8, 115.5, 113.9, 103.9, 102.3, 65.6, 59.5, 56.4; MS (TOF MS AP+, *m*/*z*) 317.2 (MH^+). HRMS (TOF MS AP+) calcd for $C_{18}H_{21}O_5$ (M + $H)^+$ 317.1389, found 317.1377.

*3,5-Dimethoxy-4-phenoxymethylbenzaldehyde (**37**).* Compound **15** (0.12 g, 0.38 mmol, 1 equiv) was dissolved in tetrahydrofuran (3 mL). *p*-Toluenesulfonic acid monohydrate (7.0 mg, 38 μmol, 0.1 equiv) was added to the reaction mixture as a solution in water (0.5 mL). The resulting solution was stirred at 23 °C for 14 h. Triethylamine (16 μL, 0.11 mmol, 0.3 equiv) was added to the reaction mixture, and the solvent was removed by rotary evaporation. The residue was dissolved in ethyl acetate (10 mL), and the organic solution was washed with saturated aqueous ammonium chloride solution (1 × 10 mL) followed by saturated aqueous sodium chloride (1 × 10 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to afford compound **37**, which was used without further purification.

*3,5-Dimethoxy-4-phenoxymethylbenzoic Acid (**38**).* Compound **37** (0.10 g, 0.37 mol, 1 equiv) and 2-methyl-2-butene (0.24 mL, 2.2 mmol, 6.0 equiv) were dissolved in acetone (3 mL). A solution of sodium dihydrogen phosphate monohydrate (0.31 g, 2.3 mmol, 6.0 equiv) and sodium chlorite (0.20 g, 2.3 mmol, 6.0 equiv) in water (3 mL) was added to the reaction mixture. The suspension was stirred vigorously for 30 min at 23 °C. Acetone was removed by rotary evaporation, and the aqueous solution was diluted with ethyl acetate (13 mL). The layers were separated, and the organic layer was washed sequentially with 1 M hydrochloric acid (1 × 10 mL), saturated aqueous sodium chloride (2 × 10 mL), saturated aqueous sodium thiosulfate (1 × 10 mL), and saturated aqueous sodium chloride (1 × 10 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to afford compound (**38**) as a white solid, which was used without further purification.

*(3,5-Dimethoxy-4-phenoxymethylphenyl)carbamic Acid Allyl Ester (**9**).* Triethylamine (0.10 mL, 0.77 mmol, 1.2 equiv) and diphenylphosphoryl azide (0.17 mL, 0.77 mmol, 1.2 equiv) were added to a solution of compound **38** (0.19 g, 0.64 mmol, 1 equiv) in benzene (3 mL) at 23 °C. The reaction mixture was heated to 80 °C. After 2 h of stirring at 80 °C, allyl alcohol (0.13 mL, 1.9 mmol, 3.0 equiv) was added. The solution was heated to 90 °C, was held at 90 °C for 3 h, and then was allowed to cool to 23 °C. The solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (10% ethyl acetate in hexanes, increasing to 30% ethyl acetate in hexanes) to afford compound **9** as a pale yellow solid (0.17 g, 0.49 mmol, 62% over 3 steps): mp 91−94 °C; IR (cm^{-1}) 3318, 2942, 1731, 1607; ^1H NMR δ 7.37−7.25 (m, 2H), 7.08−6.95 (m, 4H), 6.72 (s, 2H), 5.97 (m, 1H), 5.41 (d, 1H, *J* = 16.8 Hz), 5.30 (d, 1H, *J* = 10.4 Hz), 5.10 (s, 2H), 4.69 (d, 2H, *J* = 4.8 Hz), 3.78 (s, 6H); ^{13}C NMR δ 159.7, 159.4, 153.0, 140.1, 132.3, 129.2, 120.3, 118.0, 114.9, 107.8, 94.6, 65.7, 59.0, 55.7; MS (TOF MS AP+, *m*/*z*) 366.2 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{19}H_{21}NO_5Na$ (M + Na^+) 366.1317, found 366.1332.

*2-[3,5-Dimethoxy-4-(4-methoxyphenoxymethyl)phenyl]-[1,3]-dioxolane (**39**).* Compound **39** (pale yellow oil, 64% two steps) was prepared using the same conditions as described for compound **15** with the exception that 4-methoxyphenol was used instead of phenol. The quantities of reagents used were *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (0.23 g, 1.3 mmol, 1.3 equiv), tributylphosphine (0.33 mL, 1.3 mmol, 1.3 equiv), **36** (0.25 g, 1.0 mmol, 1 equiv), and 4-methoxyphenol (0.17 g, 1.3 mmol, 1.3 equiv). IR (cm^{-1}) 2942, 1584; ^1H NMR δ 6.96 (d, 2H, *J* = 8.8 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 6.70 (s, 2H), 5.80 (s, 1H), 5.04 (s, 2H), 4.11−4.00 (m, 4H), 3.82 (s, 6H), 3.75 (s, 3H); ^{13}C NMR δ 159.8, 154.2, 154.1, 140.8, 116.8, 114.8, 114.2, 103.8, 102.4, 65.6, 60.4, 56.5, 56.5; MS (TOF MS AP+, *m*/*z*) 347.2 (MH^+). HRMS (TOF MS AP+) calcd for $C_{19}H_{23}O_6$ (M + $H)^+$ 347.1495, found 347.1496.

*3,5-Dimethoxy-4-(4-methoxyphenoxymethyl)benzaldehyde (**40**).* Compound **40** (white solid) was prepared using the same conditions as those described for compound **37**. The quantities of reagents used were **39** (0.22 g, 0.64 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (24 mg, 0.13 mmol, 0.2 equiv).

*3,5-Dimethoxy-4-(4-methoxyphenoxymethyl)benzoic Acid (**41**).* Compound **41** (white solid) was prepared using the same conditions as those described for compound **38**. The quantities of reagents used were **40** (0.19 g, 0.64 mmol, 1 equiv), $NaClO_2$ (0.46 g, 5.1 mmol, 8.0 equiv), NaH_2PO_4 monohydrate (0.70 g, 5.1 mmol, 8.0 equiv) and 2-methyl-2-butene (0.20 mL, 1.9 mmol, 3.0 equiv).

*[3,5-Dimethoxy-4-(4-methoxyphenoxymethylphenyl)]carbamic Acid Allyl Ester (**16**).* Compound **16** (pale yellow film, 32% over three steps) was prepared using the same conditions as those described for compound **9**. The quantities of reagents used were **41** (80 mg, 0.25 mmol, 1 equiv), diphenylphosphoryl azide (70 μL, 0.33 mmol, 1.3 equiv), triethylamine (45 μL, 0.33 mmol, 1.3 equiv) and allyl alcohol (51 μL, 0.75 mmol, 3.0 equiv). IR (cm^{-1}) 3325, 2938, 1732, 1609; ^1H NMR δ 6.96 (d, 2H, *J* = 9.0 Hz), 6.82−6.79 (m, 3H), 6.66 (s, 2H),

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5.95−5.89 (m, 1H), 5.37 (dd, 1H, J = 17.1, 1.2 Hz), 5.27 (dd, 1H, J = 10.5, 1.2 Hz), 4.98 (s, 2H), 4.65 (d, 2H, J = 5.7 Hz), 3.76 (s, 6H), 3.75 (s, 3H); ^{13}C NMR δ 159.7, 153.7, 152.9, 139.9, 132.3, 118.2, 116.1, 114.4, 108.2, 94.5, 65.8, 59.9, 55.8, 55.7; MS (TOF MS AP+, m/z) 396.3 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{20}H_{24}NO_6$ (M + $H)^+$ 374.1604, found 374.1598.

*2-[4-(2-tert-Butylphenoxymethyl)-3,5-dimethoxyphenyl]-[1,3]-dioxolane (**42**).* Compound **42** (waxy white solid, 83% two steps) was prepared using the same conditions as those described for compound **15** with the exception that 2-*tert*-butylphenol was used instead of phenol. The quantities of reagents used were *N,N,N′,N′*-tetramethylazodicarboxamide (0.24 g, 1.4 mmol, 1.4 equiv), tributylphosphine (0.35 mL, 1.4 mmol, 1.4 equiv), **36** (0.24 g, 1.0 mmol, 1 equiv), and 2-*tert*-butylphenol (0.21 mL, 1.4 mmol, 1.4 equiv). IR (cm^{-1}) 2954, 2872, 1595; ^{1}H NMR δ 7.26−7.23 (m, 1H), 7.18 (t, 1H, J = 7.2 Hz), 7.10 (d, 1H, J = 10.8 Hz), 6.87 (t, 1H, J = 7.2 Hz), 6.71 (s, 2H), 5.79 (s, 1H), 5.08 (s, 2H), 4.15−4.05 (m, 4H), 3.81 (s, 6H), 1.27 (s, 9H); ^{13}C NMR δ 159.3, 158.2, 139.8, 138.2, 126.8, 126.3, 119.7, 114.0, 112.2, 103.5, 101.7, 65.2, 58.6, 55.6, 34.7, 29.6; MS (TOF MS AP+, m/z) 373.3 (M + $H)^+$. HRMS (TOF MS AP+) calcd for $C_{22}H_{29}O_5$ (M + $H)^+$ 373.2015, found 373.2013.

*4-(2-tert-Butylphenoxymethyl)-3,5-dimethoxybenzaldehyde (**43**).* Compound **43** (white solid) was prepared using the same conditions as those described for compound **37**. The quantities of reagents used were **42** (0.31 g, 0.82 mmol, 1 equiv), and *p*-toluenesulfonic acid monohydrate (31 mg, 0.16 mmol, 0.2 equiv).

*4-(2-tert-Butylphenoxymethyl)-3,5-dimethoxybenzoic Acid (**44**).* Compound **44** (white solid) was prepared using the same conditions as those described for compound **38**. The quantities of reagents used were **43** (0.16 g, 0.46 mmol, 1 equiv), $NaClO_2$ (0.27 g, 2.7 mmol, 6.0 equiv), NaH_2PO_4 monohydrate (0.41 g, 2.7 mmol, 6.0 equiv) and 2-methyl-2-butene (0.17 mL, 1.6 mmol, 3.5 equiv).

*[4-(2-tert-Butylphenoxymethyl)-3,5-dimethoxyphenyl]carbamic Acid Allyl Ester (**17**).* Compound **17** (waxy pale yellow solid, 34% three steps) was prepared using the same conditions as those described for compound **9**. The quantities of reagents used were **44** (0.14 g, 0.40 mmol, 1 equiv), diphenylphosphoryl azide (0.10 mL, 0.47 mmol, 1.2 equiv), triethylamine (66 μL, 0.47 mmol, 1.2 equiv) and allyl alcohol (80 μL, 1.2 mmol, 3.0 equiv). IR (cm^{-1}) 3320, 2955, 1708, 1610; ^{1}H NMR δ 7.32−7.24 (m, 2H), 7.15 (d, 1H, J = 8.0 Hz), 6.93−6.87 (m, 2H), 6.75 (s, 2H), 6.05−5.98 (m, 1H), 5.43 (d, 1H, J = 17.2 Hz), 5.33 (d, 1H, J = 10.4 Hz), 5.10 (s, 2H), 4.73 (d, 2H, J = 5.6 Hz), 3.81 (s, 6H), 1.34 (s, 9H); ^{13}C NMR δ 159.7, 158.3, 153.1, 139.7, 138.3, 132.3, 126.8, 126.3, 119.6, 118.2, 112.4, 108.7, 94.5, 65.8, 58.6, 55.6, 34.7, 29.5; MS (TOF MS AP+, m/z) 322.2 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{23}H_{33}N_2O_5$ (M + NH_4^+) 417.2389, found 417.2399.

*2-[3,5-Dimethoxy-4-(2,2,2-trifluoro-1-phenylethoxymethyl)-phenyl]-[1,3]dioxolane (**45**).* Compound **45** (yellow oil, 70% over two steps) was prepared using the same conditions as those described for compound **15** with the exception that α-(trifluoromethyl)benzyl alcohol was used instead of phenol. The quantities of reagents used were *N,N,N′,N′*-tetramethylazodicarboxamide (51 mg, 0.30 mmol, 1.5 equiv), tributylphosphine (75 μL, 0.3 mmol, 1.5 equiv), **36** (48 mg, 0.20 mmol, 1 equiv), and α-(trifluoromethyl)benzyl alcohol (42 μL, 0.30 mmol, 1.5 equiv). IR (cm^{-1}) 2942, 2872, 1595; ^{1}H NMR δ 7.44 (s, 2H), 7.37 (s, 3H), 6.67 (s, 2H), 5.77 (s, 1H), 4.72 (t, 2H, J = 7.2 Hz), 4.64 (d, 1H, J = 10.8 Hz), 4.11−3.99 (m, 4H), 3.79 (s, 6H); ^{13}C NMR δ 159.4, 140.4, 133.6, 128.9, 128.3, 128.0, 125.3, 122.6, 113.5, 103.3, 101.6 (2 carbons), 78.4 (q), 65.1, 60.2, 55.6; MS (TOF MS AP +, m/z) 399.3 (M + $H)^+$. HRMS (TOF MS AP+) calcd for $C_{20}H_{25}NO_5F_3$(M + NH_4^+) 416.1685, found 416.1693.

*3,5-Dimethoxy-4-(2,2,2-trifluoro-1-phenylethoxymethyl)-benzaldehyde (**46**).* Compound **46** (off-white solid) was prepared using the same conditions as those described for compound **37**. The quantities of reagents used were **45** (0.29 g, 0.69 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (13 mg, 69 μmol, 0.1 equiv).

*3,5-Dimethoxy-4-(2,2,2-trifluoro-1-phenylethoxymethyl)benzoic Acid (**47**).* Compound **47** (white solid) was prepared using the same conditions as those described for compound **38**. The quantities of reagents used were **46** (0.21 g, 0.59 mmol, 1 equiv), $NaClO_2$ (0.43 g, 4.7 mmol, 8.0 equiv), NaH_2PO_4 monohydrate (0.65 g, 4.7 mmol, 8.0 equiv) and 2-methyl-2-butene (0.19 mL, 1.8 mmol, 3.0 equiv).

*[3,5-Dimethoxy-4-(2,2,2-trifluoro-1-phenylethoxymethyl)phenyl]-carbamic Acid Allyl Ester (**18**).* Compound **18** (pale yellow solid, 36% three steps) was prepared using the same conditions as those described for compound **9**. The quantities of reagents used were **47** (0.20 g, 0.54 mmol, 1 equiv), triethylamine (90 μL, 0.65 mmol, 1.2 equiv), diphenylphosphoryl azide (0.14 mL, 0.65 mmol, 1.2 equiv), and allyl alcohol (0.11 mL, 1.6 mmol, 3.0 equiv). IR (cm^{-1}) 3328, 2941, 1735, 1609; ^{1}H NMR δ 7.46−7.43 (m, 2H), 7.36−7.34 (m, 3H), 6.86 (s, 1H), 6.60 (s, 2H), 5.99−5.90 (m, 1H), 5.38 (dd, 1H, J = 17.4, 1.5 Hz), 5.27 (dd, 1H, J = 10.2, 1.2 Hz), 4.71−4.68 (m, 1H), 4.66−4.64 (m, 3H), 4.57 (d, 1H, J = 10.5 Hz), 3.71 (s, 6H); ^{13}C NMR δ 159.8, 153.0, 140.0, 133.6, 132.3, 129.0 (2 carbons), 128.4, 128.0 (2 carbons), 118.2, 107.9, 94.3, 78.5 (q), 65.8, 60.3, 55.5; MS (TOF MS AP+, m/z) 426.2 (M + $H)^+$. HRMS (TOF MS AP+) calcd for $C_{21}H_{23}NO_5F_3(M + H)^+$ 426.1528, found 426.1527.

*(4-[1,3]Dioxolan-2-yl-2,6-dimethoxy-benzyloxy)-phenyl Acetic Acid Methyl Ester (**48**).* Compound **48** (white solid, 36%) was prepared using the same conditions as those described for compound **15** with the exception that methyl DL-mandelate was used instead of phenol. The quantities of reagents used were *N,N,N′,N′*-tetramethylazodicarboxamide (0.25 g, 1.5 mmol, 1.5 equiv), tributylphosphine (0.37 mL, 1.5 mmol, 1.5 equiv), **36** (0.24 g, 1.0 mmol, 1 equiv), and methyl DL-mandalate (0.25 g, 1.5 mmol, 1.5 equiv). IR (cm^{-1}) 2954, 2884, 1742, 1584; ^{1}H NMR δ 7.47 (m, 2H), 7.34 (m, 3H), 6.70 (s, 2H), 5.81 (s, 1H), 4.97 (s, 1H), 4.75 (s, 2H), 4.13−4.05 (m, 4H), 3.84 (s, 6H), 3.67 (s, 3H); ^{13}C NMR δ 171.7, 159.5, 140.1, 137.2, 128.2 (2 carbons), 127.4, 113.9, 103.4, 101.8, 79.2, 65.1, 59.4, 55.7, 51.9; MS (TOF MS AP+, m/z) 406.4 (M + NH_4^+). HRMS (TOF MS AP+) calcd for $C_{21}H_{28}NO_7$ (M + NH_4^+) 406.1866, found 406.1879.

*(4-Formyl-2,6-dimethoxybenzyloxy)phenyl Acetic Acid Methyl Ester (**49**).* Compound **49** (white solid) was prepared using the same conditions as those described for compound **37**. The quantities of reagents used were **48** (0.14 g, 0.36 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (14 mg, 72 μmol, 0.2 equiv).

*3,5-Dimethoxy-4-(methoxycarbonylphenyl-methoxymethyl)-benzoic Acid (**50**).* Compound **50** (white solid) was prepared using the same conditions as those described for compound **38**. The quantities of reagents used were **49** (0.12 g, 0.36 mmol, 1 equiv), $NaClO_2$ (0.20 g, 2.2 mmol, 6.0 equiv), NaH_2PO_4 monohydrate (0.30 g, 2.2 mmol, 6.0 equiv) and 2-methyl-2-butene (0.12 mL, 1.1 mmol, 3.1 equiv).

*(4-Allyloxycarbonylamino-2,6-dimethoxybenzyloxy)phenyl Acetic Acid Methyl Ester (**19**).* Compound **19** (oily pale yellow solid, 55% over three steps) was prepared using the same conditions as those described for compound **9**. The quantities of reagents used were triethylamine (50 μL, 0.36 mmol, 1.3 equiv), diphenylphosphoryl azide (77 μL, 0.36 mmol, 1.3 equiv), **50** (0.11 g, 0.28 mmol, 1 equiv), and allyl alcohol (56 μL, 0.83, 3.0 equiv). IR (cm^{-1}) 3333, 2951, 1732, 1609; ^{1}H NMR δ 7.46−7.43 (m, 2H), 7.30−7.28 (m, 3H), 6.04 (s, 1H), 6.61 (s, 2H), 5.95−5.89 (m, 1H), 5.37 (dd, 1H, J = 17.1, 1.5 Hz), 5.26 (dd, 1H, J = 11.4, 1.2 Hz), 4.96 (s, 1H), 4.64−4.62 (m, 3H), 3.71 (s, 6H), 3.65 (s, 3H); ^{13}C NMR δ 171.8, 159.7, 153.05, 140.0, 137.2, 132.3, 128.3, 128.2, 127.4, 118.1, 108.1, 94.2, 79.3, 65.7, 59.5, 55.5, 52.0; MS (TOF MS AP+, m/z) 433.4 (M + NH_4^+). HRMS (TOF MS AP+) calcd for $C_{22}H_{29}N_2O_7$ (M + NH_4^+) 433.1975, found 433.1969.

*2,5-Dimethoxybenzene-1,4-diol (**51**).* To a stirred suspension of 2,5-dimethoxy-1,4-benzoquinone (1.6 g, 9.5 mmol, 1 equiv) in methanol (60 mL) and water (120 mL) was added sodium hydrosulfite (6.6 g, 38 mmol, 4.0 equiv). The reaction mixture was stirred for 15 min at 23 °C, and then another portion of sodium hydrosulfite (3.3 g, 19 mmol, 2.0 equiv) was added to the mixture. The solution was stirred for 2 h at 23 °C. Methanol was removed by rotary evaporation, and the aqueous solution was extracted with ethyl acetate (2 × 120 mL). The combined organic layers were washed with saturated sodium chloride (1 × 120 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration.

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The solvent was removed by rotary evaporation to provide compound **51** as a white solid, which was used without further purification.

*1,2,4,5-Tetramethoxybenzene (**52**).* Anhydrous potassium carbonate (10.7 g, 76 mmol, 8.0 equiv) was added to a stirred solution of compound **51** (1.6 g, 9.5 mmol, 1 equiv) in *N*,*N*-dimethylformamide (40 mL). Iodomethane (4.7 mL, 76 mmol, 8.0 equiv) was added dropwise to the reaction mixture. The reaction mixture then was heated to 50 °C and was stirred at 50 °C for 16 h. The suspension was cooled to 23 °C, and *N*,*N*-dimethylformamide was removed by rotary evaporation. The residue was diluted with ethyl acetate (100 mL), and the organic solution was washed with water (1 × 100 mL) and then was washed with 2 M aqueous sodium hydroxide until the aqueous layer remained colorless (6 × 100 mL). The organic layer then was washed with saturated sodium chloride (1 × 100 mL). The organic layer was dried over sodium sulfate, and the solid sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to give compound **52** as a pale yellow solid, which was used without further purification.

*2,3,5,6-Tetramethoxybenzaldehyde (**21**).* *n*-Butyllithium (3.3 mL, 2.5 M in hexanes, 8.4 mmol, 2.0 equiv) was added dropwise to a −78 °C solution of compound **52** (0.83 g, 4.2 mmol, 1 equiv) in tetrahydrofuran (20 mL). The mixture was allowed to stir for 5 min at −78 °C and then was warmed to −10 °C. The reaction mixture was stirred at −10 °C for 1 h and then was cooled to −78 °C. *N*,*N*-Dimethylformamide (1.6 mL, 21 mmol, 5.0 equiv) was added to the reaction solution, and the solution was allowed to warm to 23 °C. After 1 h of stirring at 23 °C, the solution was slowly diluted (dropwise addition) with 1 M hydrochloric acid solution (2 mL). Ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (1 × 100 mL) were added, and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1 × 100 mL) and was dried over sodium sulfate. The sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the residue was filtered through a plug of silica gel (30% ethyl acetate in hexanes) to provide compound **21** (containing some residual **52**; ∼7:1 mixture of **21**:**52**), which was used without further purification.

*(2,3,5,6-Tetramethoxyphenyl)methanol (**53**).* Compound **21** (0.79 g, 3.5 mmol, 1 equiv) was dissolved in dichloromethane (10 mL) and methanol (10 mL). Sodium borohydride (0.13 mg, 3.5 mmol, 1.0 equiv) was added to the reaction mixture, and the solution was stirred for 5 min at 23 °C. Saturated aqueous ammonium chloride (5 mL) was added, and the reaction mixture was diluted with dichloromethane (50 mL). The layers were separated, and the organic layer was washed with saturated aqueous ammonium chloride (1 × 50 mL) and saturated sodium chloride (1 × 50 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to provide compound **53** as a white solid, which was used without further purification.

*3-((2-tert-Butylphenoxy)methyl)-1,2,4,5-tetramethoxybenzene (**22**).* *N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide (0.63 g, 3.7 mmol, 1.3 equiv) was dissolved in benzene (14 mL), and the reaction mixture was cooled to 0 °C. Tributylphosphine (0.92 mL, 3.7 mmol, 1.3 equiv) was added to the reaction solution, and the mixture was stirred at 0 °C for 15 min. A solution of compound **53** (0.64 g, 2.8 mmol, 1 equiv) and 2-*tert*-butylphenol (0.56 mL, 3.7 mmol, 1.3 equiv) in benzene (14 mL) was added, and the resulting solution was allowed to warm to 23 °C over 1 h. The reaction mixture was diluted with ethyl acetate (50 mL), and the diluted solution was washed with water (1 × 50 mL) and saturated aqueous sodium chloride solution (1 × 50 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the resulting oil was purified by silica gel flash column chromatography (5% ethyl acetate in hexanes, increasing to 40% ethyl acetate in hexanes) to afford compound **22** as a white solid (0.67 g, 1.9 mmol, 20% over 5 steps). IR (cm^{-1}) 2954; ^1H NMR δ 7.31−7.16 (m, 3H), 6.93 (td, 1H, J = 16.1, 1.5 Hz), 6.62 (s, 1H), 5.08 (s, 2H), 3.88 (s, 6H), 3.78 (s, 6H), 1.31 (s, 9H); ^{13}C NMR δ 158.1, 148.8, 142.1, 138.3, 127.0, 126.5, 124.6, 120.2, 112.7, 99.8, 61.7, 59.9, 56.3, 34.7, 29.9; MS (TOF MS AP+, m/z) 361.2 (M + H^+). HRMS (TOF MS AP+) calcd for $C_{21}H_{32}NO_5$ (M + NH_4^+) 378.2280, found 378.2264.

*4-((2-tert-Butylphenoxy)methyl)-2,3,5,6-tetramethoxybenzaldehyde (**54**).* *n*-Butyllithium (1.3 mL, 2.5 M in hexanes, 3.3 mmol, 1.75 equiv) was added dropwise to a −78 °C solution of compound **22** (0.67 g, 1.9 mmol, 1 equiv) in tetrahydrofuran (10 mL). The mixture was stirred for 5 min at −78 °C and then was warmed to −10 °C. The reaction mixture was stirred at −10 °C for 1 h and then was cooled to −78 °C. *N*,*N*-Dimethylformamide (0.72 mL, 9.3 mmol, 5.0 equiv) was added, and the solution was allowed to warm to 23 °C. After 1 h of stirring at 23 °C, the solution was slowly diluted (dropwise addition) with 1 M hydrochloric acid solution (1 mL). Ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate (50 mL) were added, and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride (1 × 50 mL) and was dried over sodium sulfate. Sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the residue was filtered through a plug of silica gel (20% ethyl acetate in hexanes) to provide crude compound **54** (with residual **2**, 6:1 mixture of **54**:**22**), which was used without further purification.

*4-((2-tert-Butylphenoxy)methyl)-2,3,5,6-tetramethoxybenzoic Acid (**55**).* A solution of sodium dihydrogen phosphate monohydrate (0.94 g, 5.1 mmol, 6.0 equiv) and sodium chlorite (0.62 g, 5.1 mmol, 6.0 equiv) in water (9 mL) was added to a solution of compound **54** (0.33 g, 0.85 mol, 1 equiv) and 2-methyl-2-butene (0.72 mL, 5.1 mmol, 6.0 equiv) in acetone (9.0 mL). The suspension was stirred vigorously for 30 min at 23 °C. Acetone was removed by rotary evaporation, and the aqueous reaction mixture was diluted with ethyl acetate (20 mL) and 1 M hydrochloric acid (10 mL). The layers were separated, and the organic layer was washed sequentially with saturated aqueous sodium chloride (2 × 20 mL), saturated aqueous sodium thiosulfate (1 × 20 mL), and saturated aqueous sodium chloride solution (1 × 20 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to afford compound **55** as a white solid, which was used without further purification.

*Allyl 4-((2-tert-Butylphenoxy)methyl)-2,3,5,6-tetramethoxyphenylcarbamate (**20**).* Triethylamine (0.12 mL, 0.85 mmol, 1.2 equiv) and diphenylphosphoryl azide (0.18 mL, 0.85 mmol, 1.2 equiv) were added to a solution of compound **55** (0.29 g, 0.71 mmol, 1 equiv) in benzene (4 mL) at 23 °C. The reaction mixture was heated to 80 °C. After 2 h of stirring at 80 °C, allyl alcohol (0.24 mL, 3.6 mmol, 5.0 equiv) was added. The solution was heated to 90 °C, was held at 90 °C for 3 h, and then was allowed to cool to 23 °C. The solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (10% ethyl acetate in hexanes, increasing to 25% ethyl acetate in hexanes) to afford compound **20** as a white solid (0.17 g, 0.36 mmol, 54% over 3 steps): mp 104−106 °C; IR (cm^{-1}) 3310, 2944, 1726; ^1H NMR δ 7.30−7.20 (m, 2H), 7.1 (d, 1H, J = 8.2 Hz), 6.93 (t, 1H, J = 7.4), 6.25 (s, 1H), 6.02−5.92 (m, 1H), 5.38 (dd, 1H, J = 17.3, 1.6 Hz), 5.33 (dd, 1H, J = 10.4, 1.4 Hz), 5.02 (s, 2H), 4.69 (dt, 2H, J = 5.5, 1.4 Hz), 3.82 (s, 12H), 1.29 (s, 9H); ^{13}C NMR δ 158.0, 154.4, 148.6, 144.4, 138.4, 132.5, 127.0, 126.6, 125.3, 122.5, 120.3, 117.9, 112.6, 66.2, 61.45, 60.7, 59.7, 34.7, 29.8; MS (TOF MS AP+, m/z) 460.2 (M + H^+). HRMS (TOF MS AP+) calcd for $C_{25}H_{34}NO_7$ (M + H^+) 460.2335, found 460.2317.

*4-Bromo-1-((2-tert-butylphenoxy)methyl)-2-methoxybenzene (**56**).* *N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide (0.27 g, 1.2 mmol, 1.2 equiv) was dissolved in benzene (10 mL), and the reaction mixture was cooled to 0 °C. Tributylphosphine (0.30 mL, 1.2 mmol, 1.2 equiv) was added to the reaction solution, and the mixture was stirred at 0 °C for 15 min. A solution of 4-bromo-2-methoxybenzyl alcohol (0.22 g, 1.0 mmol, 1 equiv) and 2-*tert*-butylphenol (0.18 mL, 1.2 mmol, 1.2 equiv) in benzene (10 mL) was added. The resulting solution was allowed to warm to 23 °C over 1 h and then was stirred at 23 °C for 16 h. The product solution was diluted with ethyl acetate (50 mL) and then was washed with water (1 × 50 mL) and saturated sodium chloride (1 × 50 mL). The organic layer was dried over sodium sulfate, and the sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the resulting oil was filtered

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through a plug of silica gel (100% hexanes, increasing to 10% ethyl acetate in hexanes) to afford compound **56** as a yellow oil, which was used without further purification.

*4-((2-tert-Butylphenoxy)methyl)-3-methoxybenzoic Acid (**57**).* Compound **56** (0.23 g, 0.64 mmol, 1 equiv) was dissolved in tetrahydrofuran (6 mL), and the solution was cooled to −78 °C. *n*-Butyllithium (0.52 mL, 2.4 M in hexanes, 2.0 equiv) was added dropwise, and the resulting mixture was stirred at −78 °C for 5 min. Dry carbon dioxide was bubbled through an 18 gauge metal needle into the reaction mixture for 15 min, and then the reaction mixture was allowed to warm to 23 °C. Aqueous sodium hydroxide solution (1 M, 1 mL) was added to the reaction mixture, followed by ethyl acetate (20 mL). The layers were separated, and the organic layer was extracted with 1 M aqueous sodium hydroxide (2 × 20 mL). The combined aqueous layers were acidified to pH 2 by addition of concentrated hydrochloric acid. The acidic aqueous solution was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over sodium sulfate, and the solid sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to afford compound **57** as a white solid that was used without further purification.

*Allyl 4-((2-tert-Butylphenoxy)methyl)-3-methoxyphenylcarbamate (**58**).* Triethylamine (90 μL, 0.65 mmol, 1.2 equiv) and diphenylphosphoryl azide (0.14 mL, 0.65 mmol, 1.2 equiv) were added to a solution of compound **57** (0.17 g, 0.54 mmol, 1 equiv) in benzene (2.5 mL) at 23 °C. The reaction mixture was heated to 80 °C. After 2 h of stirring at 80 °C, allyl alcohol (0.18 mL, 2.7 mmol, 5.0 equiv) was added. The solution was heated to 90 °C, was held at 90 °C for 3 h, and then was allowed to cool to 23 °C. The solvent was removed by rotary evaporation, and the residue was purified by silica gel flash column chromatography (5% ethyl acetate in hexanes, increasing to 20% ethyl acetate in hexanes) to afford compound **58** as a white solid (0.15 g, 0.41 mmol, 41% over 3 steps). IR (cm^{-1}) 3323, 2955, 1708; ^1H NMR δ 7.37−7.27 (m, 3H), 7.1 (td, 1H, J = 8.2, 1.7 Hz), 6.95 (dd, 1H, J = 8.2, 1.1), 6.9 (td, 1H, J = 7.5, 1.2 Hz), 6.73−6.69 (m, 2H), 6.00−5.92 (m, 1H), 5.38 (dd, 1H, J = 19.1, 1.5 Hz), 5.28 (dd, 1H, J = 10.4, 1.3 Hz), 5.06 (s, 2H), 4.67 (d, 2H, J = 5.7 Hz), 3.84 (s, 3H), 1.37 (s, 9H); ^{13}C NMR δ 157.8, 157.5, 153.2, 138.6, 138.2, 132.4, 129.1, 127.0, 126.6, 120.9, 120.3, 118.3, 112.6, 110.2, 101.4, 65.9, 65.1, 55.4, 34.9, 29.8; MS (TOF MS AP+, m/z) 392.2 (M + Na^+). HRMS (TOF MS AP+) calcd for $C_{22}H_{31}N_2O_4$ (M + NH_4^+) 387.2284, found 387.2269.

*Carbonic Acid Allyl Ester 4-Formyl-3,5-dimethoxy-phenyl Ester (**25**).* 4-Hydroxy-2,6-dimethoxybenzaldehyde (**24**) (0.18 g, 1.0 mmol, 1 equiv) was dissolved in dichloromethane (8.0 mL) and pyridine (1.6 mL, 20 mmol, 20 equiv), and the mixture was cooled to 0 °C. Allyl chloroformate (1.1 mL, 10 mmol, 10 equiv) was added dropwise, and the reaction solution was allowed to warm to 23 °C over 2 h. The reaction mixture then was diluted with dichloromethane (20 mL) and was washed sequentially with saturated aqueous ammonium chloride solution (2 × 30 mL) saturated aqueous sodium chloride solution (1 × 30 mL). The organic layer was dried over sodium sulfate, and the solid sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (20% ethyl acetate in hexanes, increasing to 60% ethyl acetate in hexanes) to yield **25** as an opaque white film (0.22 g, 0.84 mmol, 84%). IR (cm^{-1}) 2946, 1764, 1686, 1599; ^1H NMR δ 10.36 (s, 1H), 6.42 (s, 2H), 5.98−5.90 (m, 1H), 5.41 (d, 1H, J = 17.2), 5.31 (d, 2H, J = 10.4), 4.70 (d, 2H, J = 4.8), 3.82 (s, 6H); ^{13}C NMR δ 187.9, 163.0, 156.7, 152.2, 130.6, 119.8, 112.1, 97.3, 69.4, 56.2; MS (TOF MS AP+, m/z) 289.3 (14, M + Na), 267.3 (100, MH+). HRMS (TOF MS AP+) calcd for $C_{13}H_{15}O_6$ (MH+) 267.0862, found 267.0869.

*Carbonic Acid Allyl Ester 4-Hydroxymethyl-3,5-dimethoxy-phenyl Ester(**26**).* Sodium borohydride (32 mg, 0.84 mmol, 1.0 equiv) was added to a solution of compound **25** (0.22 g, 0.84 mmol, 1 equiv) in dichloromethane (4 mL) and methanol (4 mL). The reaction mixture was stirred for 5 min and then was diluted with saturated aqueous ammonium chloride (1 mL) and dichloromethane (20 mL). The layers were separated, and the organic layer was washed with saturated aqueous ammonium chloride (1 × 20 mL) and saturated aqueous sodium chloride (1 × 20 mL). The organic layer was dried over sodium sulfate, and the solid sodium sulfate was removed by filtration. The solvent was removed by rotary evaporation to yield **26** as a white solid, which was used without further purification.

*Carbonic Acid Allyl Ester 4-(2-tert-Butyl-phenoxymethyl)-3,5-dimethoxy-phenyl Ester (**23**).* Tributylphosphine (0.20 μL, 0.78 mmol, 1.4 equiv) was added to a 0 °C solution of diamide (0.13 g, 0.78 mmol, 1.4 equiv) in benzene (2.5 mL), and the resulting reaction mixture was stirred at 0 °C for 15 min. To this cold solution was added a solution of compound (**26**) (0.15 g, 0.56 mmol, 1 equiv) and 2-*tert*-butylphenol (0.12 mL, 0.78 mmol, 1.4 equiv) in benzene (2.5 mL). The resulting solution was allowed to warm to 23 °C over 1 h. The solvent was removed by rotary evaporation, and the resulting oil was purified by silica gel flash column chromatography (5% ethyl acetate in hexanes, increasing to 20% ethyl acetate in hexanes) to afford compound **23** (90 mg, 0.23 mmol, 40% over 2 steps) as a white solid: mp 69−71 °C; IR (cm^{-1}) 2955, 1763, 1607; ^1H NMR δ 7.35 (dd, 1H, J = 7.8, 1.8 Hz), 7.26 (t, 1H, J = 5.4 Hz), 7.18 (dd, 1H, J = 8.1, 0.9 Hz), 6.95 (td, 1H, J = 7.5, 1.2 Hz), 6.12−6.01 (m, 1H), 5.54 (dd, 1H, J = 17.1, 1.2 Hz), 5.43 (dd, 1H, J = 10.5, 0.9 Hz), 5.14 (s, 2H), 4.83 (d, 2H, J = 5.7 Hz), 3.85 (s, 6H), 1.37 (s, 9H); ^{13}C NMR δ 159.7, 158.2, 153.2, 152.7, 138.3, 131.0, 126.8, 126.3, 119.8, 119.6, 112.3, 111.2, 69.2, 58.5, 55.8, 34.7, 29.6; MS (TOF MS AP+, m/z) 423.3 (20, M + Na), 251.3 (100). HRMS (TOF MS AP+) calcd for $C_{23}H_{32}NO_6$ (M + NH_4) 418.2234, found 418.2230.

General Conditions for Measuring the Release Kinetics. An Alloc-protected compound (0.01 mmol) and tetrakis-(triphenylphosphine)palladium(0) (1.1 mg) were dissolved in 0.1 mL of tetrahydrofuran in a 2-mL vial. Acetic acid (1.5 μL) and tributyltin hydride (5 μL) were added to the reaction mixture, and the solution was shaken for 3 min. An aliquot (10 μL) of the solution was added to an HPLC vial and was diluted with acetonitrile (0.5 mL) and phosphate buffer (0.1 M, pH 7.1, 0.5 mL). The solution was shaken for 10 s and then was filtered through a syringe filter (PTFE, 0.22 μm). The release of the alcohol/phenol was inferred by monitoring the disappearance of the aniline intermediate by HPLC using a UV detector set at 254 nm or 330 nm. The relative quantity of the aniline intermediate that is formed after Alloc deprotection was measured over time by integration of the peak area at 254 nm or 330 nm. The HPLC spectra showed clean conversion of this aniline intermediate into the byproducts depicted in Figure 2. Identical kinetics data were obtained when the quantity of phenol was measured over time (by integration of the peak area at 254 nm or 330 nm), but for some derivatives, the released phenol was too close to the solvent front for accurate integration.

General Procedure for Crystallizing Compounds 4, 8, 9, and 20. Compounds **4**, **8**, **9**, and **20** were crystallized by vapor diffusion in benzene and pentane. Each compound (∼10 mg) was dissolved in a minimum amount of benzene. Pentane was allowed to diffuse into the benzene solution through a pin-sized hole in an aluminum foil cover over the course of 24−48 h. White, opaque needles were formed in all cases.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables giving experimental data, figures giving crystallographic data in CIF format, and figures giving ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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