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Reduction of Solid-Supported Olefins and Alkynes

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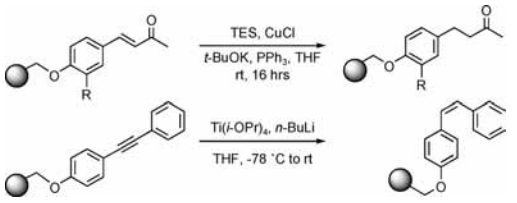

The reduction of carbon−carbon multiple bonds in alkynes and olefins supported on a polystyrene resin has been investigated. Homogeneous catalysis by titanocene reagents is effective for the stereoselective preparation of *cis*-olefins from diarylacetylenes, while the use of copper(I) hydride reagents is effective for the reduction of α,β-unsaturated ketones.

Since Merrifield's seminal report in 1963 on the synthesis of a tetrapeptide anchored to a cross-linked polystyrene resin,[1] solid-phase organic synthesis (SPOS) has evolved into an invaluable tool for the combinatorial synthesis of organic molecule libraries[2] using a vast and ever increasing array of techniques.[3] Recent reviews on solid-phase methods for C−C bond formation,[4] polymer-supported catalysts,[5] Pd-catalyzed reactions,[6] and "click" reactions[7] illustrate the breadth of the field. Surprisingly, however, few methods have been reported for the solid-phase reduction of C−C multiple bonds, due in large part to the kinetic and entropic limitations of solid-on-solid interactions between solid-supported substrates and heterogeneous catalysts commonly used in hydrogenation reactions.[8] These limitations have been circumvented, though rarely, using noncross-linked, soluble resins. Lindlar's catalyst, for example, was successfully employed by Janda to reduce internal alkynes in the solid-phase synthesis of prostanoids on noncross-linked polystyrene.[9] Homogenous catalysts, such as Wilkinson's[10] and $Pd(OAc)_2$,[6] have also seen rare applications. Lacombe, also noting the lack of SPOS hydrogenation methods, first demonstrated the use of diimide for the reduction of olefin and alkyne moieties in substrates anchored to Wang resin.[11] A modification of this method was recently reported by Buszek in which diimide was generated from 2-nitrobenzenesulfonohydrazide with an excess of Et_3N in DCM at rt for 24 h. These relatively mild conditions were able to reduce a wide range of C−C multiple bonds in various steric and electronic environments, including those anchored to labile polystyrene diethyl silyl ethers.[12]

Due to the limited methods available for the solid-phase reduction of C−C multiple bonds, we sought to evaluate whether olefins and alkynes anchored to Merrifield resin could be reduced utilizing a Cu(I) hydride and a $Ti(Bu)_2(O\text{-}i\text{-}Pr)_2$ reagent, respectively. If successful, these methods would significantly expand the current set of techniques available for reduction of C−C multiple bonds. In light of our quest, we required expeditious access to simple solid-supported olefins for method development. Zingerone (**1a**) and rheosmin (**1b**) were attractive candidates, since both precursors possessed the requisite olefin and contained a phenolic linker that would enable facile attachment and removal to Merrifield resin.[13] Each substrate could be prepared from simple starting materials—vanillin (**2a**) and *p*-hydroxybenzaldehyde (**2b**)—through a Claisen−Schimdt condensation with acetone. Additionally, the pharmacological properties of zingerone (**1a**)[14] and rheosmin (**1b**)[15] made them interesting targets.

Immobilization of **2a** and **2b** onto Merrifield resin (**10**) employed an adaptation of Katritsky's method,[13] using K_2CO_3 and *t*-BuOH in DMF, which resulted in efficient conversion to solid-supported vanillin (**3a**) and *p*-hydroxybenzaldehyde (**3b**)[16] (Scheme 1). The extent of conversion was quantified by Volhard titration.[17] Generally, more than 80% of the active Cl was displaced after 96 h at rt, although, slightly higher loadings could be obtained after only 48 h at 70 °C.

(1) Merrifield, R. B. *J. Am. Chem. Soc.* **2002**, *85*, 2149–2154.
(2) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600.
(3) Dorwald; F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2002.
(4) (a) Lorsbach, B. A.; Kurth, M. *J. Chem. Rev.* **1999**, *99*, 1549–1582. (b) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137–202.
(5) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.
(6) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885.
(7) (a) Loaiza, P. R.; Lober, S.; Hubner, H.; Gmeiner, P. *J. Comb. Chem.* **2006**, *8*, 252–261. (b) Bouillon, C.; Meyer, A.; Vidal, S.; Jochum, A.; Chevolot, Y.; Cloarec, J.-P.; Praly, J.-P.; Vasseur, J.-J.; Morvan, F. *J. Org. Chem.* **2006**, *71*, 4700–4702. (c) Turner, R. A.; Oliver, A. G.; Lokey, R. S. *Org. Lett.* **2007**, *9*, 5011–5014.
(8) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley Interscience: New York, 2001.
(9) (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724–8725. (b) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943–3946. (c) Lopez-Pelegrin, J. A.; Janda, K. D. *Chem.—Eur. J.* **2000**, *6*, 1917–1922.
(10) Whelan, A. N.; Elaridi, J.; Harte, M.; Smith, S. V.; Jackson, W. R.; Robinson, A. J. *Tetrahedron Lett.* **2004**, *45*, 9545–9547.
(11) Lacombe, P.; Castagner, B.; Gareau, Y.; Ruel, R. *Tetrahedron Lett.* **1998**, *39*, 6785–6786.
(12) Buszek, K. R.; Brown, N. *J. Org. Chem.* **2007**, *72*, 3125–3128.
(13) Katritzky, A. R.; Toader, D.; Watson, K.; Kiely, J. S. *Tetrahedron Lett.* **1997**, *38*, 7849.
(14) Nurtjahja-Tjendraputra, E.; Ammit, A. J.; Roufogalis, B. D.; Tran, V. H.; Duke, C. C. *Thrombosis Res.* **2003**, *111*, 259.
(15) Morikawa, T.; Tao, J.; Ueda, K.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull.* **2003**, *51*, 62.
(16) Cernerud, M.; Reina, J. A.; Tegenfeldt, J.; Moberg, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2863.
(17) Lu, G.; Mojsov, S.; Tam, J, P.; Merrifield, R. B. *J. Org. Chem.* **1981**, *46*, 3433.

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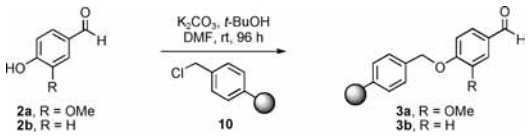
SCHEME 1. Immobilization of 2a and 2b onto Merrifield Resin



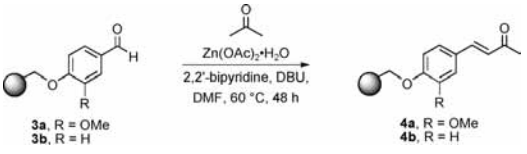
The conversion from **2** to **3** was confirmed by the presence of an IR carbonyl band at 1690 cm^{-1} and a Fermi C−H doublet for the aldehyde at 2721 and 2730 cm^{-1}. The IR spectra of **3a** and **3b** were obtained as solid suspensions in compressed KBr. Due to interference from the polystyrene backbone, only strong vibrations of the immobilized molecule were observed. Colorimetric analysis of the resin with Schiff's reagent (fuchsin and sulfurous acid) resulted in a violet-colored resin, which also confirmed the presence of an aldehyde.[18]

The Claisen−Schmidt crossed-aldol reaction of **3a** and **3b** did not provide the desired α,β-unsaturated ketones when acidic (boric acid) or basic (LiOH) conditions were employed. However, Sensfuss' adaptation[19] of Irie and Watanabe's[20] original solution-phase protocol did provide resins **4a** and **4b**, which contained IR bands characteristic of α,β-unsaturated ketones (Scheme 2). Although it was evident by IR that the aldehyde moieties were completely consumed, the conversion to the desired enones appeared to be low.[21] This is not entirely surprising since acid-catalyzed aldol condensations with acetone are known to produce dimers and trimers, which can then participate as undesirable nucleophiles.[22] In an effort to quantify the efficacy of these transformations, attempts were made to cleave the enones from resins **4a** and **4b** (20% TFA, DCM); however, only polymeric material was recovered in each instance.

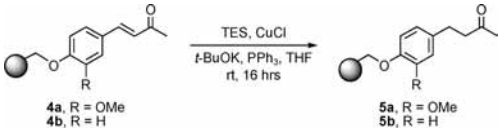
Despite our inability to improve the crossed-aldol reaction, we moved forward with our investigation. We first attempted reduction with diimide by using Lacombe's protocol.[11] Heating resins **4a** and **4b** with *p*-toluenesulfonyl hydrazide in DMF for 24 h, however, provided resins that lacked IR carbonyl bands. Therefore, each substrate was cleaved from the resin (20% TFA in DCM). ^{1}H NMR analysis of each crude material indicated the presence of a hydrazone as part of a complex mixture. Similarly, experiments using $NaBH_4$ and $NiCl_2$ to give hydrogen-saturated nickel boride were investigated.[23−25] These also produced a complex mixture of products after cleavage.

Next, we turned our attention to Cu(I) hydride complexes, which have garnered significant interest from synthetic

SCHEME 2. Claisen−Schmidt Synthesis of 4a and 4b



SCHEME 3. Solid-Phase Cu(I) Hydride Reduction of 4



chemists due to their thermal stability and chemoselective properties.[26] The most well-known is undoubtedly Stryker's reagent,[27] including catalytic variants.[28] These complexes form homogeneous solutions in organic solvents making them ideal candidates for the reduction of olefins attached to solid supports.

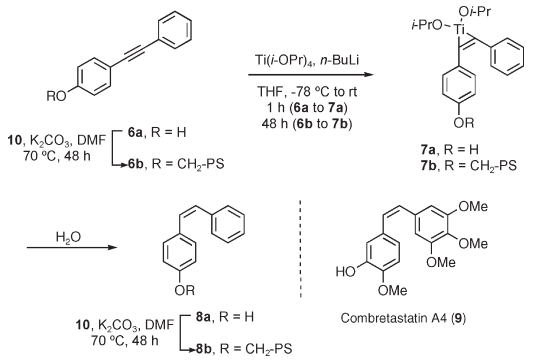
Cu(I) hydride was prepared under a blanket of nitrogen by adding Cu(I)Cl to a solution of PPh_3 and *t*-BuOK in THF. The resulting dark-red solution was then transferred by cannula to a THF solution of **4a** or **4b** and triethylsilane (TES).[29] After mixing for 16 h at rt, the resin was washed and dried under vacuum. IR analysis of the resins indicated a shift in the carbonyl stretching frequency from 1655 to 1720 cm^{-1} (**4a** → **5a**) and 1657 to 1715 cm^{-1} (**4b** → **5b**), indicative of the formation of nonconjugated ketones (Scheme 3). The conversion appeared to be near quantitative since there was little change in the intensity of the newly formed carbonyl IR bands when compared to the polystyrene internal standard.[21]

Finally, the substrates were cleaved from the resin by acidolysis (20% TFA in DCM),[30] which provided zingerone (**1a**) and rheosmin (**1b**) in greater than 90% purity as indicated by ^{1}H NMR. The overall yields of **1a** and **1b** were 7.3% and 10%, respectively, based upon the initial loading of the respective aldehyde onto Merrifield resin (**10**).

Having successfully demonstrated the solid-phase reduction of alkenes **4a** and **4b**, we turned our attention to the stereoselective solid-phase reduction of a diaryl acetylene to provide a *cis*-stilbene. This method would provide a facile route to a growing number of stilbenoid natural products, including the combretastatins,[31] such as **9** and their analogues,[32] which have demonstrated potent cytotoxicity against

(18) Gaggini, F.; Porcheddu, A.; Reginato, G.; Rodriquez, M.; Taddei, M. *J. Comb. Chem.* **2004**, *6*, 805–810.
(19) Sensfuss, U. *Tetrahedron Lett.* **2003**, *44*, 2371.
(20) Irie, K.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1366.
(21) The intensities of the newly formed carbonyl IR bands were compared to an internal standard (polystyrene backbone at 1448 cm^{-1}). For similar analyses, see: Canto, L. B.; Pessan, L. A. *Polym. Test.* **2002**, *21*, 35–38.
(22) Lippert, S.; Baumann, W.; Thomke, K. *J. Mol. Catal.* **1991**, *69*, 199.
(23) Brown, C. A.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 1003.
(24) Strohmeier, W.; Steigerwald, H. *Z. Naturforsch. B* **1977**, *32b*, 111.
(25) Dhawan, D.; Grover, S. K. *Synth. Commun.* **1992**, *22*, 2405.
(26) Lipshutz, B. H. Copper(I) Mediated 1,2 and 1,4-Reduction. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: New York, 2002; pp 167−184.
(27) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677.
(28) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627.
(29) Polymethylhydrosiloxane (PHMS) was equally effective. For a comparison of silane hydride sources, see: (a) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779–2788. (b) Chiu, P.; Li, Z.; Fung, K. C. M. *Tetrahedron Lett.* **2003**, *44*, 455–457.
(30) (a) Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7607–7608. (b) Katritzky, A. R.; Rogovoy, B. V.; Vvedensky, V.; Kovalenko, K.; Forood, B. *J. Comb. Chem.* **2002**, *4*, 290–294.
(31) Pettit, G. R.; Cragg, G. M.; Singh, S. B. *J. Nat. Prod.* **1987**, *50*, 386.
(32) Siles, R.; Ackley, J. F.; Hadimani, M. B.; Hall, J. J.; Mugabe, B. E.; Guddneppanavar, R.; Monk, K. A.; Chapuis, J.-C.; Pettit, G. R.; Chaplin, D. J.; Edvardsen, K.; Trawick, M. L.; Garner, C. M.; Pinney, K. G. *J. Nat. Prod.* **2008**, *71*, 313–320.

SCHEME 4. Solid- and Solution-Phase Ti Reduction



human cancer cell lines through their inhibition of tubulin assembly (Scheme 4).[33,34]

In 2003, Eisch[35] and Tsuji[36] independently reported that thermally stable (25 °C) Ti−alkyne complexes such as **7a** were formed upon the addition of $Bu_2Ti(O\text{-}i\text{-}Pr)_2$, which is generated by the alkylation of $Ti(O\text{-}i\text{-}Pr)_4$ with *n*-BuLi. Most significantly, when treated with water, these complexes were converted to the corresponding *cis*-stilbenes in high yield and with complete stereoselectivity. Since there have been few reports of stereoselective reduction of alkynes on cross-linked resins,[37] we sought to apply this solution-phase method to the reduction of resin-bound 4-(phenylethynyl)-phenol (**6b**) as a model for the future solid-phase synthesis of the combretestatins.

4-(Phenylethynyl)phenol (**6a**) was prepared through Sonogashira coupling of 4-iodophenol with phenylacetylene.[38] This substrate was then anchored to Merrifield resin (**10**) to provide resin-bound 4-(phenylethynyl)phenol (**6b**). The alkyne stretch of **6b** was clearly visible at 2216 cm^{-1} in the Raman spectrum, which confirmed successful immobilization. Additionally, Volhard titration indicated that 77% of the active Cl was displaced. Reduction of **6b** was accomplished by shaking the resin in a solution of $Bu_2Ti(O\text{-}i\text{-}Pr)_2$ at rt for 48 h followed by protonation of the Ti−alkyne complex **7b** with water to provide the resin-bound *cis*-4-styrylphenol (**8b**). Incomplete reduction, indicated by a partial decrease in the intensity of the signal at 2216 cm^{-1} with respect to the polystyrene internal standard,[21] was observed when less than 10 equiv of $Bu_2Ti(O\text{-}i\text{-}Pr)_2$ was used; however, no signals associated with an alkyne stretch were identified in the Raman spectrum when greater than 10 equiv of $Bu_2Ti(O\text{i}\text{-}Pr)_2$ was employed.

Since cleavage of the substrate from the resin (TFA, CH_2Cl_2, 24 h) would likely result in addition to the alkene, we anchored an authentic sample of **8a** onto Merrifield resin (**10**) and compared the Raman spectrum of this sample to the Raman spectrum of **8b** obtained through solid-phase reduction. Thus, 4-(phenylethynyl)phenol (**6a**) was reduced in solution with 2 equiv of $Bu_2Ti(O\text{-}i\text{-}Pr)_2$. The reduction took place, as observed by TLC, only after the reaction had warmed to 20 °C, at which point it was complete in less than 15 min. Aqueous workup followed by flash-column chromatography provided **8a** in 77% yield as a single geometrical isomer. The ^1H NMR spectra of **8a** matched previously reported spectral data and indicated that the reduction was completely stereoselective.[39] Immobilization of **8a** onto Merrifield resin (**10**) then provided an authentic sample of resin-bound *cis*-4-styrylphenol (**8b**), the Raman spectra of which was identical to that obtained from solid-phase reduction of **6b**. Additionally, a Raman spectrum of Merrifield resin (**10**) was subtracted from the Raman spectrum of each resin-bound substrate in an attempt to deconvolute the overlapping bands in the region of 1640−1570 cm^{-1}, which are associated with the aromatic bands of **10**, **6b**, and **8b** as well as the alkene band in **8b**. Three overlapping signals at 1611, 1602, and 1583 cm^{-1} are observed in this region for **10** alone. When the Raman spectrum of **10** was subtracted from the Raman spectrum of **6b**, only a single sharp signal was observed in the region of interest at 1595 cm^{-1}, whereas the resin obtained from the solid-phase reduction, as well as the authentic sample of resin-bound *cis*-4-styrylphenol (**8b**), gave identical subtraction spectra with two signals at 1635 and 1596 cm^{-1}. The additional signal at 1635 cm^{-1} is consistent with that expected for the newly formed alkene moiety in resin-bound *cis*-4-styrylphenol (**8b**).

In summary, we have demonstrated that olefins and alkynes can be reduced on solid supports by Cu(I) hydride and a $Ti(Bu)_2(O\text{-}i\text{-}Pr)_2$ reagent, respectively. We are currently investigating the use of resin linkers that will allow facile cleavage of *cis*-stilbenes and are working toward applying these general methods toward the synthesis of natural products such as the combretestatins.

Experimental Section

General Procedure for Immobilizing Phenols onto Merrifield Resin. Resin-Bound 4-Hydroxybenzaldehyde (3b). A 250 mL Erlenmeyer flask was sequentially charged with Merrifield resin (**10**) (4.0 g, 8.4 mmol), DMF (40 mL), and *t*-BuOH (8 mL). After the resin was allowed to swell for 5 min, **2b** (3.10 g, 25 mmol) and powdered K_2CO_3 (3.5 g, 25 mmol) were added. The flask was sealed with a septum, purged with N_2, and placed on an orbital shaker (150 rpm) for 4 days at rt. The suspended resin was decanted from the remaining solid K_2CO_3, collected by vacuum filtration, washed sequentially with 2 × 40 mL of DMF, aqueous acetic acid (3.0 M), THF, H_2O, THF, hexanes, CH_2Cl_2 and hexanes, and then dried under vacuum (1.0 mmHg) at rt for 24 h to yield **3b** as an off white solid (4.4 g): Volhard titration (75 mg resin) 0.2 mmol of active Cl/g resin remaining, 90% displaced; IR (KBr) ν_{max} 3058, 3024, 2921, 2850, 2730, 1693, 1599, 1493, 1449, 1256, 1157, 829, 756.

Resin-bound 4-hydroxy-3-methoxybenzaldehyde (3a): Volhard titration (75 mg resin) 0.3 mmol of active Cl/g resin remaining, 85% displaced; IR (KBr) ν_{max} 3058, 3025, 2921, 2851, 2721, 1687, 1591, 1508, 1451, 1268, 1130, 1025, 758.

Resin-Bound (3*E*)-4-(4-Hydroxyphenyl)but-3-en-2-one (4b). A 125 mL Erlenmeyer flask was sequentially charged with **3b** (4.0 g, 8.4 mmol), DMF (68 mL), and acetone (4.1 mL, 55.0

(33) (a) Pettit, G. R.; Rhodes, M. R. *Anti-Cancer Drug Des.* **1998**, *13*, 183–191. (b) Pettit, G. R.; Lippert, J. W. III. *Anti-Cancer Drug Des.* **2000**, *15*, 203.

(34) (a) Hamel, E.; Lin, C. M. *Biochem. Pharmacol.* **1983**, *32*, 3864–3867. (b) Pettit, G. R.; Singh, S. B. *Can. J. Chem.* **1987**, *65*, 2390–2396.

(35) Eisch, J. J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24–26.

(36) Obora, Y.; Moriya, H.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2003**, 2820–2821.

(37) (a) A notable exception is the hydroboration of a resin-bound acetylene with bis(1,2-dimethylpropyl)borane, which gave the corresponding alkene with Z/E > 9:1: Fyles, T. M.; Leznoff, C. C.; Weatherston, J. *J. Org. Chem.* **1977**, *55*, 4135–4143.

(38) Mohamed, A.; Mohamed, S.; Mori, A. *Tetrahedron* **2004**, *60*, 9977.

(39) (a) ^1H NMR (acetone-d_6) gave δ_H values of 6.53 and 6.47 for the vinylic protons with J = 12 Hz. (b) For ^1H NMR ($CDCl_3$) analysis, see: Tarzia, G.; Duranti, A.; Tontini, A.; Piersanti, G.; Mor, M.; Rivara, S.; Plazi, P.; Park, C.; Kathuria, S.; Piomelli, D. *J. Med. Chem.* **2003**, *46*, 2352–2360.

mmol). The mixture was allowed to swell for 5 min. In a separate flask, $Zn(OAc)_2 \cdot 2H_2O$ (2.39 g, 10.9 mmol) was dissolved in DMF (5 mL) followed by addition of 2,2′-bipyridine (1.7 g, 10.9 mmol). The resulting solution of zinc(II) bipyridine complex was mixed until it became cloudy white, at which point it was transferred to the flask containing the resin and DMF. DBU (1.2 mL, 10.9 mmol) was then added, after which the flask was sealed with a septum, purged with N_2, and then placed on an orbital shaker and mixed (150 rpm) at 70 °C for 48 h. After being cooled to rt, the resin was collected by vacuum filtration, sequentially washed with 2 × 20 mL of DMF, H_2O, THF, hexanes, THF, and hexanes, and then dried under vacuum (1.0 mmHg) at rt for 24 h to yield **4b** (3.65 g) as a yellow solid: IR (KBr) ν_{max} 3057, 3023, 2915, 2851, 1657, 1596, 1504, 1446, 1165, 754.

Resin-bound (3*E*)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one (4a): IR (KBr) ν_{max} 3057, 3023, 2916, 2851, 1655, 1597, 1495, 1448, 1252, 1167, 1022, 970, 818, 751, 692.

Resin-Bound 4-(4-Hydroxyphenyl)butan-2-one (5b). A 50 mL Erlenmeyer flask was charged with resin **4b** (0.5 g, 1.05 mmol), THF (8.0 mL), and triethylsilane (0.24 mL, 1.5 mmol), after which it was sealed with a septum, purged with N_2, and allowed to swell for 5 min. Separately, solid *t*-BuOK (22.0 mg, 0.2 mmol) was added to a solution of PPh_3 (52.0 mg, 0.2 mmol) dissolved in THF (2.0 mL) followed by addition of CuCl (20.0 mg, 0.2 mmol). The contents were mixed at rt for 10 min and then transferred by cannula to the solution containing the resin. The flask was then placed in an orbital shaker and mixed (100−150 rpm) at rt for 16 h. The resin was collected by vacuum filtration, sequentially washed with 2 × 10 mL of THF, H_2O, THF, and hexanes, and then dried under vacuum (1.0 mmHg) at rt for 24 h to yield **5b** (0.47 g) as a gray/green solid: IR (KBr) ν_{max} 3057, 3025, 2921, 2851, 1715, 1645, 1600, 1508, 1450, 1422, 1371, 1306, 1231, 1171 cm^{-1}.

Resin-bound 4-(4-hydroxy-3-methoxyphenyl)butan-2-one (5a): IR (KBr) ν_{max} 3058, 3025, 2920, 2849, 1720, 1601, 1491, 1448, 1265, 757, 699.

Rheosmin (1b). A 50 mL Erlenmeyer flask was charged with resin **5b** (0.5 g, 1.0 mmol) and CH_2Cl_2 (8.0 mL) and the resin allowed to swell for 5 min. The flask was sealed with a septum and purged with N_2, after which trifluoroacetic acid (2.0 mL) was added. The flask was then placed in an orbital shaker and mixed (150 rpm) for 24 h at rt. The resin was collected by gravity filtration and washed with CH_2Cl_2 (2 × 10 mL). The combined filtrates were treated with 10 mL of saturated aqueous $NaHCO_3$ and mixed until gas evolution ceased. The organic and aqueous phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure to provide **1b** as a yellow film (15 mg, 10% based on Volhard titration of **3b**): IR (film) ν_{max} 3372, 3021, 2947, 2923, 2862, 1691, 1610, 1512, 1443, 1366, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.01 (d, J = 8.3 Hz, 2 H), 6.77 (d, J = 8.3 Hz, 2 H), 6.60 (br s, 1 H), 2.82 (t, J = 7.0 Hz, 2 H), 2.74 (d, J = 7.0 Hz, 2 H), 2.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.5, 154.6, 132.3, 129.4, 115.6, 45.6, 30.3, 29.0.

Zingerone (1a). Resin **5a** (0.5 g, 1.0 mmol) was treated in a similar manner as above to provide **1a** as a yellow film (12 mg, 7.3%, based on Volhard titration of **3a**): IR (film) ν_{max} 3420, 3002, 2937, 2845, 1709, 1606, 1516, 1269, 1236, 1157, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, J = 8.0 Hz, 2 H), 6.69 (d, J = 2.0 Hz, 1 H), 6.69 (dd, J = 8.0, 1.9 Hz, 1 H), 5.70 (brs, 1 H), 3.86 (s, 3 H), 2.82 (t, J = 7.5 Hz, 2 H), 2.73 (t, J = 7.5 Hz, 2 H), 2.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 146.6, 143.8, 133.0, 120.9, 114.5, 111.2, 56.0, 45.6, 30.2, 29.6.

***cis*-4-Styrylphenol (8a).** A flame-dried round-bottom flask, under an atmosphere of nitrogen, was charged with THF (40 mL) and Ti(*i*-OPr)$_4$ (2.3 mL, 7.72 mmol) and then cooled to −78 °C. *n*-BuLi (6.2 mL, 2.5 M, 15.4 mmol) was added dropwise followed by a solution of 4-(phenylethynyl)phenol (**6a**) (750 mg, 3.86 mmol) in THF (10 mL). After the mixture was stirred at −78 °C for 10 min, the cold bath was removed and the reaction allowed to warm to rt over 1 h, after which the reaction was quenched with satd aqueous NH_4Cl (20 mL) and partitioned between EtOAc (50 mL) and H_2O (50 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting solid was purified by flash chromatography (Et_2O/hexanes, 1:4) to provide **8a** (581 mg, 77%) as a white solid: mp 54−56 °C; R_f 0.66 (Et_2O/hexanes, 1:3); FT-IR (diamond-ATR, uncorr) ν_{max} 3238 (br), 3072, 3045, 3009, 1604, 1586, 1509, 1435, 1402, 1192, 1169, 1104 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ_H 8.56 (br s, 1 H), 7.28−7.14 (m, 5 H), 7.09 (d, J = 8.5 Hz, 2 H), 6.70 (d, J = 8.5 Hz, 2 H), 6.53 (d, J = 12 Hz, 1 H), 6.47 (d, J = 12 Hz, 1 H); ^{13}C NMR (125 MHz, d_6-acetone) δ_C 157.7, 138.7, 131.0 (2 C), 130.9, 129.6 (2 C), 129.3, 129.1 (2 C), 128.8, 127.8 115.9 (2 C); HRMS-EI calcd for $C_{14}H_{12}O$ $[M]^+$ 196.0888, found 196.0890.

Resin-Bound 4-(Phenylethynyl)phenol (6b). A reactor vial was sequentially charged with Merrifield resin (**10**) (2.00 g, 3.4 mmol), DMF (25 mL), 4-(phenylethynyl)phenol (**6a**) (1.27 g, 6.54 mmol), and K_2CO_3 (1.0 g, 7.2 mmol). The vial was purged with N_2, capped, and then placed on an orbital shaker (200 rpm) at 70 °C for 48 h. After being cooled to rt, the resin was collected by vacuum filtration, washed sequentially with 2 × 5 mL of DMF, H_2O, THF, H_2O, THF, hexanes, CH_2Cl_2, and hexanes, and then dried under vacuum (1.0 mmHg) for 24 h at rt to provide **6b** (2.6 g) as a white solid: Volhard titration (0.20 g resin) 0.37 mmol of active Cl/g resin remaining, 77% displaced; FT-IR (diamond-ATR, uncorr) ν_{max} 3081, 3056, 3026, 2918, 2851, 1594, 1509, 1493, 1451 cm^{-1}; Raman ν_{max} 3056, 3006, 2908, 2856, 2216, 1596, 1450, 1182 cm^{-1}.

Resin-Bound *cis*-4-Styrylphenol (8b): Immobilization. Volhard titration (0.20 g resin) 0.37 mmol of active Cl/g resin remaining, 77% displaced; FT-IR (diamond-ATR, uncorr) ν_{max} 3081, 3056, 3022, 2918, 2848, 1602, 1583, 1509, 1493, 1451, 1263 cm^{-1}; Raman ν_{max} 3053, 3002, 2976, 2906, 2853, 1635, 1602, 1583, 1449, 1323, 1265, 1194, 1182, 1155 cm^{-1}.

Resin-Bound *cis*-4-Styrylphenol (8b): Ti(II) Reduction. An oven-dried reactor vial was charged with resin-bound 4-(phenylethynyl)phenol (**6b**) (0.45 g, 0.55 mmol **6a**/g resin as calculated by Volhard titration), capped with a self-healing seal, and then placed under an atmosphere of N_2. Distilled THF (15 mL) was added by syringe followed by Ti(*i*-OPr)$_4$ (1.42 mL, 4.80 mmol) after which the vial was cooled to −78 °C. With stirring, *n*-BuLi (4.0 mL, 1.6 M, 6.4 mmol) was added dropwise. The mixture was allowed to warm to rt and then placed in an orbital shaker (200 rpm). After the mixture was stirred for 48 h at rt, H_2O (5 mL) was added and the mixture shaken for an additional 1 h after which the resin was collected by vacuum filtration, washed sequentially with 2 × 5 mL of DMF, H_2O, THF, H_2O, THF, hexanes, CH_2Cl_2, and hexanes, and then dried in an oven (70 °C) for 24 h to provide **8b** (0.45 g) as an off-white solid: Raman ν_{max} 3053, 3002, 2976, 2910, 2854, 1635, 1601, 1584, 1449, 1322, 1265, 1193, 1183, 1155 cm^{-1}.

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Supporting Information Available: Experimental procedures for **1a**, **3a**, **4a**, **5a**, **6a**, **8b**, and Volhard titrations. NMR data for **1a**, **b**, **6a**, and **8a**. Raman data for **8b**, **6b**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.