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# Sonogashira Reactions with Propyne: Facile Synthesis of 4-Hydroxy-2-methylbenzofurans from Iodoresorcinols

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**Abstract:**

**The Sonogashira reaction of terminal alkynes and ortho-halophenols with subsequent cyclization is a well-precedented method for the synthesis of substituted benzofurans. Here we describe the extension of this method to the coupling of 2-iodoresorcinols and terminal alkynes, including propyne, to give 4-hydroxy-2-substituted benzofurans. In particular, we describe the screening, method development, and scaleup of the reaction with propyne using standard hydrogenation equipment.**

## Introduction

For a recent project, we had need to prepare kilogram quantities of the 4-hydroxy-2-methylbenzofuran-6-carboxylic acid ester **1** (Figure 1) to support drug discovery efforts. Initially, our medicinal chemistry colleagues employed the existing three step literature synthesis of **1-Et** (the related ethyl ester) to generate material (Scheme 1).[1] Stobbe condensation of 5-methylfurfural with diethyl succinate provides acid **2**, which is cyclized under Friedel−Crafts conditions to give protected benzofuran **3**. Deprotection of **3** provides the target benzofuran. This procedure was sufficiently robust to enable delivery of lots of up to 100 g of final product, but variable and modest yields of the Stobbe reaction (40−60%) and complicated workup and isolation[2] led us to investigate other routes. The patent literature[3] offers an alternative synthesis of benzofuran **1** that differs only in the synthesis of ester acid **2**, which is obtained in two steps by reaction of 5-methylfurfural with phosphorane **4** followed by tert-butyl ester deprotection. This process offers no practical improvement over the medicinal chemistry synthesis due to an increase in number of steps, the need to synthesize **4**, and poor atom economy from triphenylphosphine-derived residues. Other reported syntheses of 4-hydroxybenzofurans rely upon arene oxidation; examples include the aromatization of tetrahydrobenzofuranones[4] and phenol generation via Baeyer−Villiger oxidation of a 4-carboethoxybenzofuran.[5]

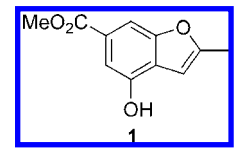


***Figure 1.*** **4-Hydroxy-6-methoxycarbonyl-2-methylbenzofuran.**

Among general approaches to benzofurans, we were initially most interested in well-documented furan annulation methods involving oxidative cyclization of allylphenols.[6] However, we quickly determined that synthesis of the requisite allylresorcinol **5** via several different methods[7] (Scheme 2) was not amenable to scaleup. Suzuki coupling of the resorcinol bromide and allylpinacol boronate proved to be low yielding, a direct alkylation approach was ineffective and required protection of the phenols, and Claisen rearrangement has previously been established to proceed with the undesired regioselectivity.[7c] These results prompted us to reconsider our synthetic strategy and evaluate a Sonogashira-based process to access **1**.

The coupling of terminal alkynes with aryl halides in the presence of catalytic transition metal salts (Sonogashira reaction and variants) has proven to be a powerful method for the construction of carbon−carbon bonds. The scope and application of the Sonogashira reaction has been the subject of several recent reviews[8] and its versatility has been demonstrated in numerous large-scale applications.[9] The use of Sonogashira reactions in the synthesis of benzofurans and their precursors has been demonstrated,[10] but there are few examples of Sonogashira reactions with resorcinol derivatives, and these employ fully protected substrates and do not form benzofurans

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(1) Simoni, D.; Romagnoli, R.; Baruchello, R.; Rondanin, R.; Rizzi, M.; Pavani, M. G.; Alloatti, D.; Giannini, G.; Marcellini, M.; Riccioni, T.; Castorina, M.; Guglielmi, M. B.; Bucci, F.; Carminati, P.; Pisano, C. *J. Med. Chem.* **2006**, *49*, 3143–3152.

(2) Complications were caused by the need to purge unreacted and polymerized succinate residues.

(3) McKerrecher, D.; Rayner, J. W. WO Patent 046139 A1, 2004.

(4) (a) Yamaguchi, S.; Yamamoto, K.; Ueda, T.; Morikawa, T.; Kawase, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 4066–8. (b) Mphahlele, M. J.; Moekwa, T. B. *Org. Biomol. Chem.* **2005**, *3*, 2469–2475.

(5) Sun, L.; Takaki, K.; Chen, J.; Iben, L.; Knipe, J. O.; Pajor, L.; Mahle, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5157–5160.

(6) For example, see: (a) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, M.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481–485. (b) Yadav, A. K.; Singh, B. K.; Singh, N.; Tripathi, R. P. *Tetrahedron Lett.* **2007**, *48*, 6628–6632.

(7) For representative Suzuki reactions of allylboronic acids and boronate esters, see: (a) Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877. (b) Fürstner, A.; Seidel, G. *Synlett* **1998**, 161. Claisen rearrangement: (c) Occielli, E.; DePaoli, A; Nathansohn, G. *Gazz. Chim. Ital.* **1981**, *111*, 383.

(8) Recent reviews: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922. (b) Pleino, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954–6956. (c) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871. (d) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605–1644. (e) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46–49.


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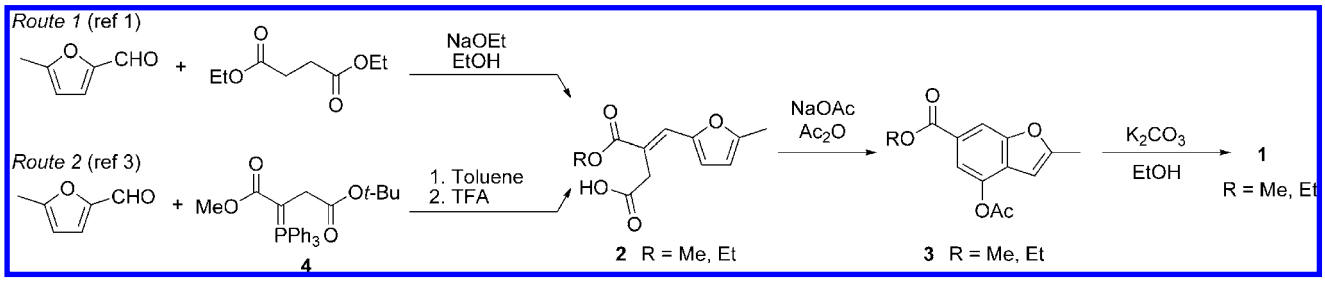
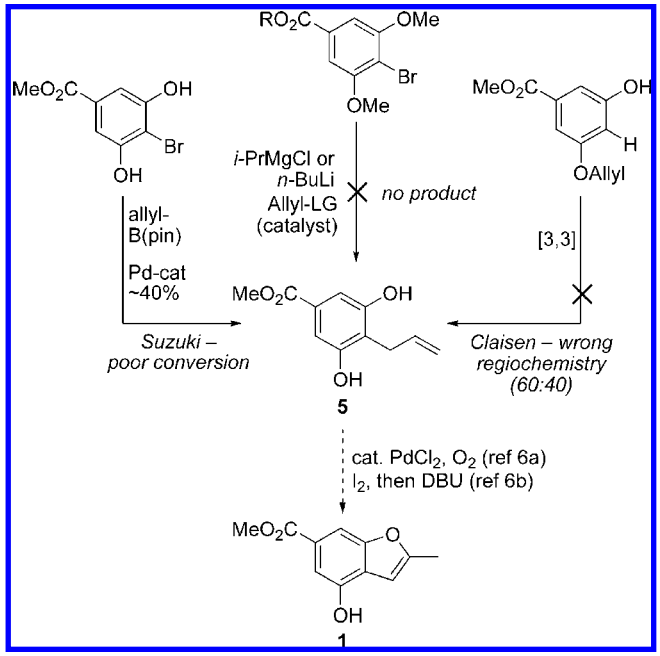
***Scheme 1.*** **Previous syntheses of benzofuran 1 Me and Et esters**

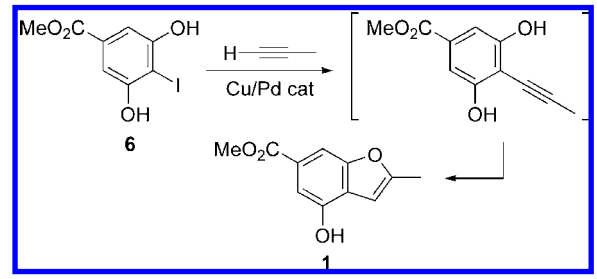



***Scheme 2.*** **Attempted synthesis of 1 from allylresorcinols**




as terminal products.[11] A Sonogashira approach to 4-hydroxy-2-methylbenzofuran **1** would offer the advantage of brevity as the synthesis would be a single step from readily available,

***Scheme 3.*** **Synthesis of a 4-hydroxy-2-methylbenzofuran via a sonogashira reaction**




symmetric 2-haloresorcinol-5-carboxylic esters and propyne gas (Scheme 3).[12] Only a single example of benzofuran synthesis using propyne has been published,[13] which is surprising given the prevalence of 2-methylbenzofurans in the medicinal chemistry literature.[14] In this paper, we describe the development and scaleup of a Sonogashira reaction with propyne to synthesize a 4-hydroxy-2-methylbenzofuran using hydrogenation screening equipment typically found in process development laboratories.

## Results and Discussion

When we started this work there were no reports in the literature describing Sonogashira reactions between alkynes and unprotected 2-halo-1,3-resorcinols. Therefore, our initial experiments were designed to evaluate this reactivity. We initially prepared several esters of 2-bromo- and 2-iodoresorcinols[15] and evaluated these in the Sonogashira reaction with methyl propargyl ether and propargyl alcohol as test substrates (Scheme 4). Under standard reaction conditions,[16] we obtained benzofuran products in good yields in reactions with iodoresorcinols; the bromoresorcinols were recovered unchanged.

The first reactions with propyne were conducted as single experiments in sealed glass pressure vessels. Excess propyne (3−5 equiv) was measured by condensing the gas in a precooled (−78 °C) graduated cylinder and using a cannula to transfer

(9) (a) Houpis, I. N.; Shilds, D.; Nettekoven, U.; Schnyder, A.; Bappert, E.; Weerts, K.; Canters, M.; Vermuelen, W. *Org. Process Res. Dev.* **2009**, *13*, 598–606. (b) Li, H.; Xia, Z.; Chen, S.; Koya, K.; Ono, M.; Sun, L. *Org. Process Res. Dev.* **2007**, *11*, 246–250. (c) Dorow, R. L.; Herrinton, P. M.; Hohler, R. A.; Maloney, M. T.; Mauragis, M. A.; McGhee, W. E.; Moeslein, J. A.; Strohbach, J. W.; Veley, M. F. *Org. Process Res. Dev.* **2006**, *10*, 493–499. (d) Ripin, D. H. B.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M., III; Vetelino, M. G.; Wei, L. *Org. Process Res. Dev.* **2005**, *9*, 440–450.

(10) (a) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans 1* **1997**, 2815–2820. (b) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441–1444. (c) Bang, H. B.; Han, S. Y.; Choi, D. H.; Yang, D. M.; Hwang, J. W.; Lee, H. S.; Jun, J.-G. *Synth. Commun.* **2009**, *39*, 506–515. (d) Grigg, R.; Sridharan, V.; Sykes, D. A. *Tetrahedron* **2008**, *64*, 8952–8962. (e) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem. Lett.* **2005**, *13*, 4796–4805.

(11) (a) Gericke, K. M.; Chai, D. I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002–6014. (b) Hennrich, G.; Omenat, A.; Asselberghs, I.; Foerier, S.; Clays, K.; Verbiest, T.; Serrano, J. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4203–4206. (c) Hauss, F.; Liu, J.; Michelucci, A.; Coowar, D.; Morga, E.; Heuschling, P.; Luu, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4218–4222.

(12) When investigating a Sonogashira approach to **1**, our initial concerns centered on the cost and handling of propyne. While somewhat costly on research scale, propyne (which is isolated in pure form by distillation of MAPP gas) is readily available on scale from several suppliers at low cost (less than $150/kg or $6/mol). MAPP gas is composed of propyne, allene, propane, and propene.

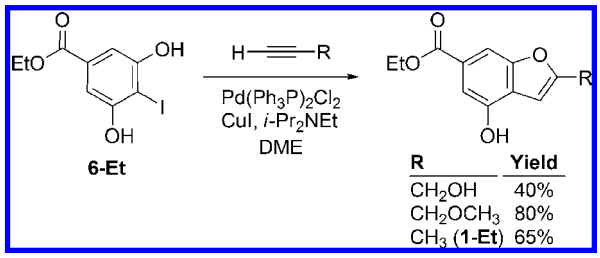
(13) (a) Hong, Y.; Kania, R. S. U.S. Patent 0137395 A1, 2005. One use of propyne in the synthesis of indoles via a Sonogashira-cyclization reaction has been reported: (b) Xu, L.; Lewis, I. R.; Davidsen, S. K.; Summers, J. B. *Tetrahedron Lett.* **1998**, *39*, 5159–5162.

(14) A SciFinder search revealed over 2000 unique 2-methylbenzofuran-containing compounds prepared over the past 30 years and one compound (trioxysalen) in clinical use.

(15) Bromoresorcinol derivatives were prepared by esterification (ROH, $H_2SO_4$) of commercial 4-bromo-3,5-dihydroxybenzoic acid (Sigma-Aldrich). Iodoresorcinols were prepared by iodination of commercial methyl 3,5-dihydroxybenzoic acid with $I_2$. See the experimental section for details.

(16) 5% $Pd(Ph_3P)_2Cl_2$ and 5% CuI with *i*-$Pr_2NEt$ as base in DME was chosen as a reference starting point for reaction exploration based on literature precedent.

***Scheme 4.*** **Initial synthesis of 4-hydroxy-2-alkylbenzofurans**




the liquid to a cooled reaction vessel, which was then sealed and heated. While labor intensive and not readily scalable, these first experiments demonstrated that the reaction worked well with propyne. The reaction proceeded at elevated temperature (60 °C), reaching completion in less than four hours, and at ambient temperature, reaching completion within 72 h. Yields in these reactions were similar although the reaction at lower temperature provided a higher purity product. On the basis of these proof-of-concept experiments, we decided to initiate a more extensive screen of reaction conditions. Since downstream ester hydrolysis rendered identity of the ester unimportant, we chose the 4-iodoresorcinol methyl ester (**6**) as the substrate for additional optimization due to the ease of its synthesis and crystallization.

**Reaction Screening.** Sonogashira reactions with propyne have been reported using subsurface gaseous delivery at ambient pressure[17] (bubbling propyne through the reaction mixture), liquid delivery[18] (condensing propyne at cryogenic temperatures and transferring it as a liquid) or in situ propyne formation.[19] From a process development perspective, we elected to pursue a different approach and employ hydrogenation screening equipment to evaluate this chemistry. The use of pressure reactors has several advantages, including convenient gas metering and delivery on systems designed for low-volume parallel screens (Biotage Endeavor) and lab scale preparative runs (Biotage Atlantis and Parr reactors). A further advantage is that the effects of propyne pressure and reaction temperature can be explored while avoiding the handling challenges and reproducibility problems associated with sparging and cryo-loading techniques.

The first reaction parameters examined were solvent and base. Bis(triphenylphosphine)palladium(II) dichloride and copper iodide were used in all reactions, as they are competent catalysts, readily available, and relatively inexpensive. As the total iodoresorcinol loading was 200 mg for each of these reactions, catalyst loading was not evaluated on this scale but held at 5 mol % for both Pd and Cu. The reactions with varied solvent and bases were carried out for 24 h at 25 °C and 5 psig propyne. Under these conditions, it was expected that the proof-of-concept conditions should show partial conversion, providing an opportunity to find faster and/or cleaner conditions for benzofuran formation. Solvents were chosen with a range of polarities and to substitute for DME. A series of secondary and tertiary amines were chosen to cover a range of steric bulk, basicity, and nucleophilicity. A representative selection of the bases and solvents screened can be found in Figure 2. Each reaction was analyzed based on the relative amount of starting iodide, desiodide, product, and related impurities[20] as measured by HPLC. The reaction run with dimethylacetamide (DMAc) and diisopropylamine (*i*-$Pr_2NH$) provided the highest yield and purity.

Given the high conversion and purity of the DMAc/*i*-$Pr_2NH$ conditions, further small scale screening was carried out to determine the most appropriate temperature and pressure of propyne for this reaction. The proof-of-concept experiments illustrated that temperatures above 50 °C increased byproduct formation. For this reason, the temperature range in the screen was kept between ambient and 45 °C. Pressure was varied between 1 and 15 psig.[21] The best product distribution was observed at 35 °C and 10 psig (Figure 3).

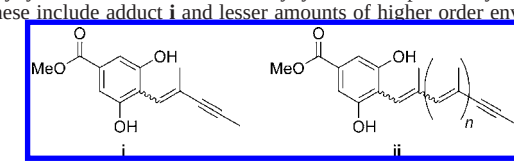
**Propyne Solubility Calculations.** On the basis of the results from these screening experiments, we sought further insight into the relative solubility of propyne as a contributing factor in reaction outcome. Accurate prediction of the vapor−liquid equilibrium (VLE) of nonideal solutions (and therefore solubility) requires composition-dependent correlation for activity coefficients (gammas) for each component of a mixture. To estimate activity coefficients for propyne and each organic solvent of interest in binary mixtures,[22] we employed COSMOtherm[23] quantum chemical calculations of chemical potential based on screening charge density of components.[24] Pure component vapor pressure data and mixture activity coefficients were paired in Aspen Plus[25] to calculate propyne solubility in each solvent of interest as a function of pressure and temperature. The calculated equilibrium weight percent concentration of propyne in each of seven solvents from 15 to

(17) (a) Fürstner, A.; Mamane, V.; Seidel, G.; Laurich, D. *Org. Synth.* **2006**, *83*, 103–110. (b) Ritchey, R. N.; Yu, H. *Org. Process Res. Dev.* **2009**, *13*, 315–320.

(18) (a) Kim, J. T.; Butt, J.; Gevorgyan, V. *J. Org. Chem.* **2004**, *69*, 5638–5645. (b) Nelson, M. L.; Ismail, M. Y.; McIntyre, L.; Bhatia, B.; Viski, P.; Rennie, G.; Andorsky, D.; Messersmith, D.; Stapleton, K.; Dumornay, J.; Sheahan, P.; Verma, A. K.; Warchol, T.; Levy, S. B. *J. Org. Chem.* **2003**, *68*, 5838–5851.

(19) (a) Abraham, E.; Suffert, J. *Synlett* **2002**, 328. (b) Rudyanto, M.; Tomizawa, Y.; Morita, H.; Honda, T. *Org. Lett.* **2008**, *10*, 1921–1922.

(20) Primary resorcinol-based impurities are enyne products derived from alkynylation of the intermediate alkynylresorcinol prior to cyclization. These include adduct **i** and lesser amounts of higher order enynes **ii**.




(21) When running on the Endeavor system, 100 g tanks of propyne were attached to the secondary gas port. Each reaction was purged with $N_2$ and then placed under a propyne blanket. No propyne purges were carried out.

(22) Temperature-dependent activity coefficient data are frequently obtained from binary VLE measurements. Measurement of VLE data in the laboratory can be time consuming; therefore, computational methods accounting for functional group contributions or molecular interaction potential are used to estimate composition and temperature dependent activities of components in a mixture of interest.

(23) *COSMOthermX, version C21_0108*, software for technical computation; COSMOlogic GmbH & Co. KG: Leverkusen, Germany, 2008.

(24) The non-random two-liquid (NRTL) solution model was chosen as a descriptor for mixture activity coefficients. COSMOtherm data was regressed into NRTL binary interaction parameters for each solvent pairing with propyne, which were then transferred into an Aspen Plus databank. Reference for NRTL: Seader, J. D.; Henley, E. J. *Separation Process Principles*; Wiley: New York, 2006; pp 55−56.

(25) *Aspen Plus*, version 7.1 software for technical computation; Aspen Technology: Burlington, MA, 2008.

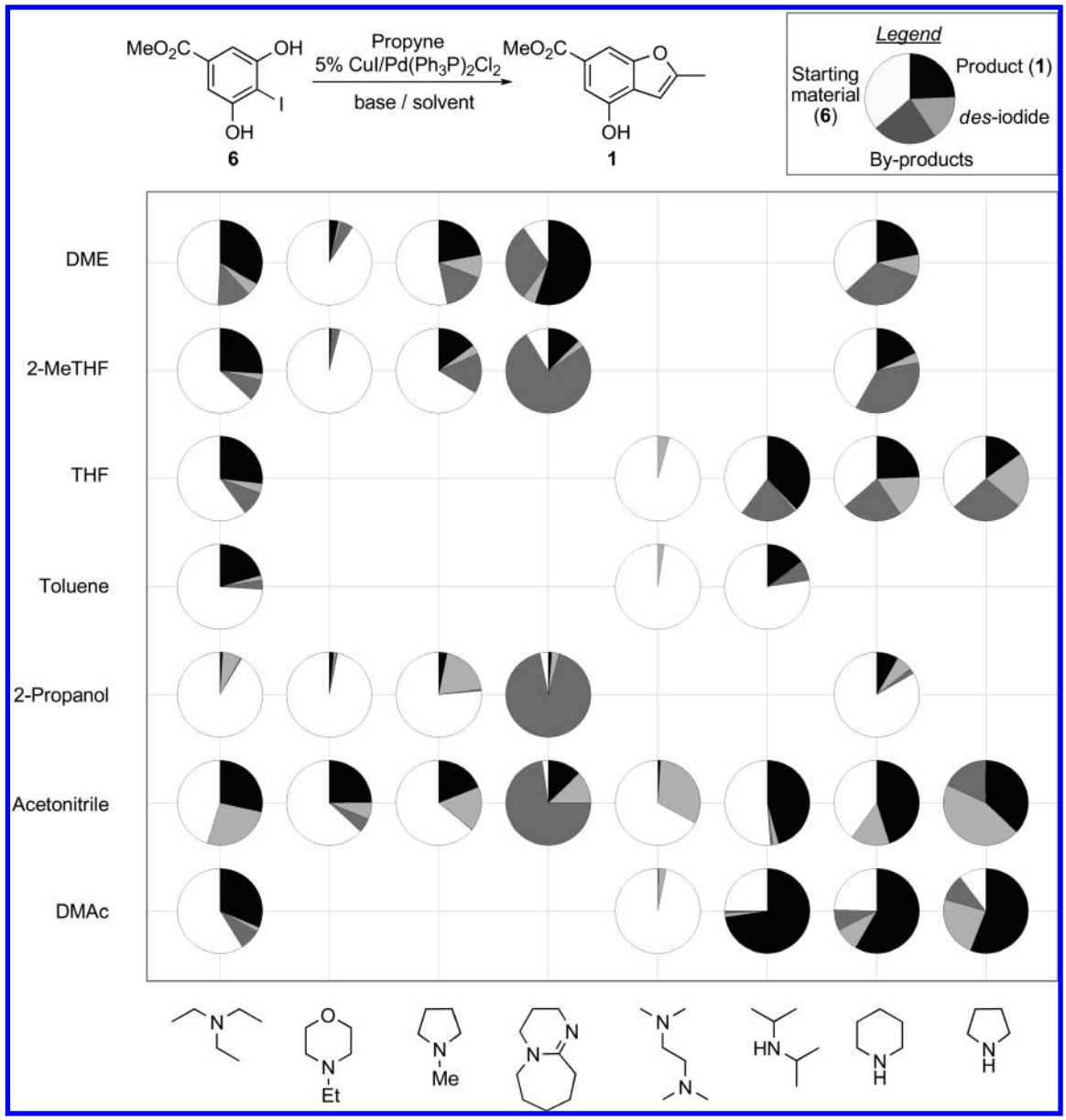



***Figure 2.*** **Product distribution as a function of solvent and base. All reactions run with 200 mg of iodoresorcinol 6, 3 equiv base, 10 mL/g solvent, and 5 mol % of both catalysts at 25 °C under 5 psig propyne for 24 h.**

50 °C at 10 psig is shown in Figure 4.[26] Although calculated solubility is higher than measured solubility for our system (vide infra), the modeled data is consistent with the measured product distribution in screening reactions (Figure 2), with the highest calculated concentrations of propyne correlating to the highest yielding reactions.

**Scaleup of Reaction and Propyne Delivery.** Once conditions had been identified on small scale, we scaled up to multigram runs. It became apparent immediately, through variable reaction outcomes, that the development of a robust method for propyne purging and pressurization was essential to maximize propyne content in the reaction vessel. Consequently, it was necessary to determine the number of propyne purges needed to saturate the reaction mixture. Propyne was charged to ~400 mL of DMAc in a 600 mL Parr reactor.[27] The reactor was weighed after each propyne purge cycle and the solution was found to be ~13% by weight propyne at 30 °C at ambient pressure (0 psig) after 4 cycles. Degassing is audible (and visible on the pressure gauge) when the solution is saturated with propyne. Given this result, the finalized purging protocol was as follows: each reaction mixture was purged three times with nitrogen without stirring at 50 psig (to remove $O_2$ from the headspace), three times with nitrogen with stirring at 50 psig (to remove $O_2$ from solution), and then four times with propyne with stirring at 10 psig. Each propyne pressurization takes a significant amount of time as the propyne largely dissolves into the DMAc solution. The dissolution of propyne is exothermic and the reactor temperature was controlled to maintain an internal temperature between 25 and 35 °C. Because

(26) Complete descriptions and data on solubility calculations can be found in the supporting information.

(27) The 600 mL Parr reactor used for these experiments has a dip tube for subsurface gas delivery.

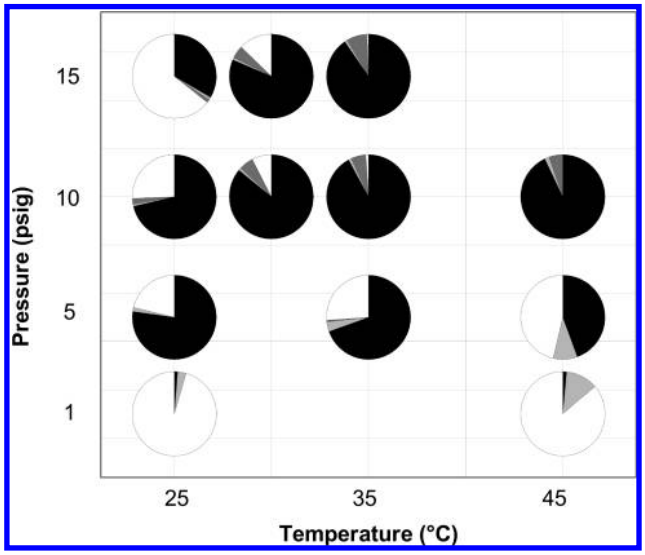



***Figure 3.*** **Product distribution as a function of temperature and pressure. All reactions run with 200 mg of 6, 3 equiv diisopropylamine, 10 mL/g DMAc, and 5 mol % of both catalysts for 24 h. Legend: black, 1; white, 6; light grey, des-iodide; dark grey, byproduct.**

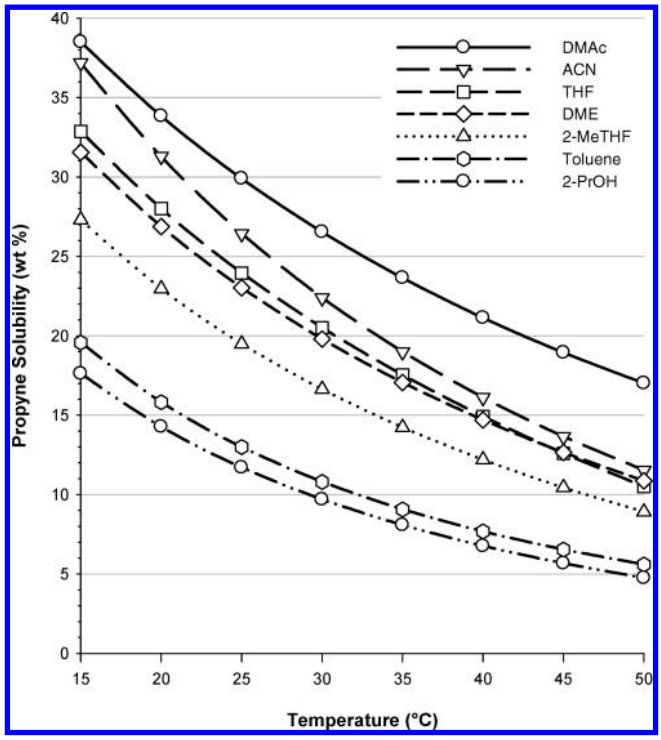



***Figure 4.*** **Calculated propyne solubility in organic solvents at 10 psig (weight percent propyne vs temperature).**

of the low pressure of the propyne source tank (60 psig at 20 °C), certain accommodations need to be made. In reactors without automatic valve closures, the tank should be closed off after purging so that the reaction mixture does not flow back into the propyne regulator and tank as the pressure drops. The low delivery pressure and high solubility of propyne in many organic solvents make the traditional uptake data provided by hydrogenation equipment and linear flow rates for delivery less valuable. We found on kilogram scale that the easiest way to measure propyne usage was to position the tank on a balance to monitor the change in mass over time.[28]

With the propyne purge protocol, it was possible to conduct further small scale reactions (5−10 g) to examine the effect of concentration and catalyst loading. The amount of solvent was found to be crucial to high conversion, presumably since lowering the amount of DMAc also decreases the amount of propyne that can be dissolved for the reaction. As a result, we continued to run the reaction with 10 volumes of DMAc. The catalyst loading could be reduced to 3 mol % of both the Pd and Cu catalysts when sufficiently pure **6** was used. However, our bulk lot contained small amounts of iodine and necessitated the use of 5 mol % catalyst to ensure adequate reaction performance. Under these conditions, we observed typical conversions of greater than 90% with formation of minimal des-iodide byproduct on scales ranging from 5 g to 1.67 kg.

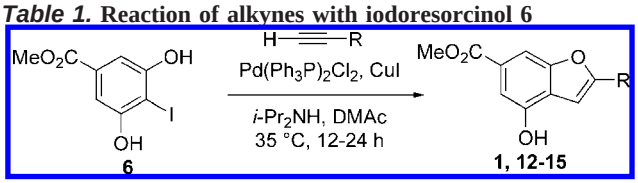
**Workup Development.** During initial development, standard aqueous workups were employed, requiring high volumes and numerous washes to fully extract benzofuran **1** from the aqueous mixtures. The crude product, isolated as a brown-black semisolid of modest purity, was chromatographed on silica gel and treated with thiol-modified silica gel to reduce Pd below 300 ppm.[29] While serviceable for small-scale experiments, this workup and isolation procedure was not suitable for larger-scale work. Several factors complicated efforts to develop an efficient isolation for **1**, most notably the presence of propyne gas[30] and related polymers and oligomers, excess diisopropylamine, as well as metal salts and aggregates.

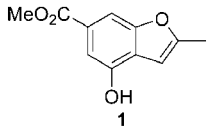
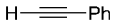
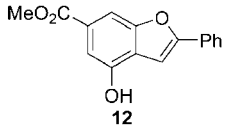
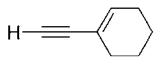
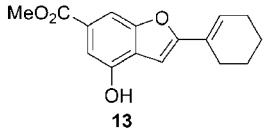
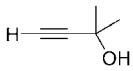
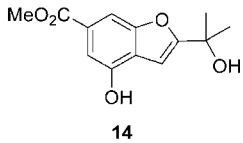
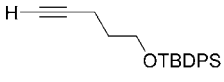
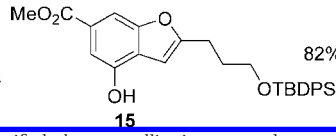
To remove the high concentrations of *i*-$Pr_2NH$ and any related salts, aqueous ammonium chloride[31] was introduced as the initial diluent following the reaction. Fortuitously, the addition of water and aqueous $NH_4Cl$ expedited the degassing of the remaining propyne in the reaction mixture.[32] The removal of the residual propyne decreased the overall volume significantly and caused precipitation of dark-colored low-density materials, presumably propyne polymers and oligomers.

To remove these polymeric materials and lower molecular weight oligomers, the aqueous solution was treated with two nonpolar washes (1% ethyl acetate in heptane).[33] These washes were performed at slightly elevated temperatures (40−50 °C) to encourage dissolution of the nonpolar materials and prevent crystallization of crude product from the aqueous phase.[34] A thick, dark rag layer of nonpolar polymeric material formed as the phases separated and was discarded with the heptane. Any residual polymer adhering to the tank walls or impeller following the wash was removed with warm acetone. The

(28) The mass flow device installed in our kilo facility pressure reactor is calibrated for hydrogen delivery and provided incorrect information during propyne charging operations.
(29) Palladium levels dropped somewhat with silica gel chromatography (3% after aqueous work up to 0.5−1.0% after chromatography).
(30) On the basis of our dissolution studies, we anticipated that propyne concentrations could be as high as 13 wt%.
(31) Water and saturated ammonium chloride were introduced in a 1:1 volume ratio. On scale, water was added first followed by the ammonium chloride solution.
(32) As a result of the rapid degassing, when running on larger scale, the water and ammonium chloride solution should be added slowly with a $N_2$ purge. Both the degassing and the heat increase related to the dissolution of DMAc in water were roughly dose controlled.
(33) This solvent system was chosen to maximize extraction of propyne related impurities and to minimize loss of benzofuran **1** from the aqueous phase.
(34) If the aqueous solution is stored at or below 20 °C, the product will crystallize and hold on to a large amount of dark nonpolar impurities.

***Table 1.*** **Reaction of alkynes with iodoresorcinol 6**




| Entry | Alkyne | Product | Yield (%)[a] |
|---|---|---|---|
| 1[b] |  7 |  1 | 68%[c] |
| 2 |  8 |  12 | 72% |
| 3 |  9 |  13 | 86% |
| 4 |  10 |  14 | 93% |
| 5 |  11 |  15 | 82% |

[a] Isolated yields. Products purified by crystallization or column chromatography. [b] Reactions with propyne conducted in hydrogenation equipment, not standard glassware. [c] Isolated yield on a 5 kg batch of **6**. Yields ranged from 64 to 75% on smaller batches.

extracted oligomers and precipitated polymers retained both Pd and Cu, eliminating the need for further remediation.

Although benzofuran **1** could be crystallized directly from the aqueous solution with cooling, the yields were comparatively low (42%). As a result, the product was extracted into ethyl acetate. Following a solvent displacement to methanol, **1** was crystallized by slow addition of water. This scavenger-free sequence was conducted successfully on 400 g scale (62% yield, 49 ppm Pd) and three times on 1.67 kg scale (68% combined yield) as described in the experimental section.

**Evaluation of Scope.** We briefly evaluated the scope of the Sonogashira reaction between iodoresorcinol **6** and various alkynes (Table 1). This reaction appears to be general for this substrate, providing the desired benzofuran products in good yield after isolation and purification.

## Conclusions

In conclusion, we have demonstrated an extension of the Sonogashira-cyclization strategy for the synthesis of benzofurans from terminal alkynes and 2-iodoresorcinols in an efficient two-step synthesis of 4-hydroxy-2-methylbenzofuran **1** from 4-iodoresorcinol **6** and propyne gas. In doing so, we developed a method for screening reactions with propyne using existing hydrogenation screening equipment. A combination of experimental and computational results allowed us to develop an initial understanding of key solubility properties of propyne in common organic solvents and identified *N*,*N*-dimethylacetamide as a particularly good solvent for reactions with propyne. We developed a workup process that efficiently purged the metal-rich propyne-derived polymers and oligomers, obviating the need for chromatography and scavenging agents to meet purity targets. This work supported the successful scaleup of a Sonogashira reaction with propyne on kilo scale.

## Experimental Section

**General Experimental.** Research samples of propyne were purchased from Sigma-Aldrich and Advanced Gas Technologies, Inc. at 98% purity and used as received. Other reagents and solvents were obtained from reputable suppliers and used without further purification. $^{1}$H NMR were obtained at 400 MHz and $^{13}$C NMR spectra were acquired at 100 MHz in DMSO-$d_6$ unless otherwise noted. HPLC data were collected on an Agilent 1100 Series with a diode array detector, using an Agilent Zorbax SB-CN column (4.6 × 150 mm) with a 10 min method (10:90 $CH_3CN$:0.2% $HClO_4$/water, 2 min isocratic, 6 min ramp to 90:10 $CH_3CN$:aqueous, then 2 min isocratic at 90:10) at 30 °C and 2 mL/min flow rate. Propyne, like all liquefied petroleum gases, is extremely flammable and forms explosive mixtures in air. All users should thoroughly familiarize themselves with available safety literature and validate their experimental setup and environmental controls before initiating any experiments.

**Methyl 4-iodo-3,5-dihydroxybenzoate (6).**[35] Methyl 3,5-dihydroxybenzoate (4.00 kg, 97 wt/wt % pure, 23.1 mol), sodium bicarbonate (5.82 kg, 69.2 mol, 3 equiv), water (40 L), and THF (12 L) were charged to an inerted 200 L glass-lined reactor, and the contents were cooled to 5 °C. Iodine (11.7 kg, 46.2 mol, 2 equiv) was dissolved in THF (28 L) and added over 30 min while maintaining the internal temperature between 2−8 °C. After stirring 1 h, MTBE (20 L) was added in one portion, followed by a solution of sodium sulfite (3.22 kg, 25.4 mol, 2 equiv) in water (12 L) over 30 min (gas evolution) keeping the internal temperature between 2−10 °C. The resulting biphasic mixture was warmed to ambient temperature and the lower aqueous phase was withdrawn. The light yellow product-rich organic phase was concentrated at atmospheric pressure to 20 L and then displaced into methanol via constant-volume azeotropic distillation, stopping when GC headspace analysis indicated <2% THF. The dark red solution was cooled to 45 °C and adjusted to 28 L with methanol. Water (28 L) was then added over 15 min, during which time the product crystallized as off-white to orange needles. The slurry was cooled to ambient temperature, granulated for 2 h, and the product was isolated by filtration, washed with 12 L of 1:1 methanol:water, and dried in the vacuum oven. A total of 5.68 kg (84%) of the title product was isolated as cinnamon-colored needles. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 10.50 (s, 2H), 6.93 (s, 2H), 3.79 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 166.0, 158.2, 130.5, 105.8, 81.8, 52.2. HRMS-ESI *m*/*z*: [M−H]$^-$ calcd

(35) Procedure reference: Denieul, M.-P.; Laursen, B.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 6052–6060. The procedure was modified to accommodate solvent restrictions in our scaleup facilities and to improve robustness.

for $C_8H_6O_4{}^{127}I$, 292.93054; found, 292.93128. HPLC: rt 5.30 min (product), 4.03 min (starting material).

**General Procedure for Screening Sonogashira Reactions between Propyne and Methyl 4-Iodo-3,5-dihydroxybenzoate (6).** Each glass Endeavor tube[36] was charged with iodoresorcinol **6** (200 mg, 0.68 mmol), bis(triphenylphosphine)palladium dichloride (24 mg, 0.034 mmol, 0.05 equiv), copper iodide (7 mg, 0.03 mmol, 0.05 equiv), solvent (10 mL/g), and amine base (3 equiv). The tubes were placed into an Endeavor system and sealed. The reactions were then purged with $N_2$ twice with stirring (250 rpm). The reactors were then warmed to the appropriate temperature, stirred at 1000 rpm, and pressurized with propyne to the target pressure. After 24 h, the reactions were purged with $N_2$ and removed for analysis.

**4-Hydroxy-6-methoxycarbonyl-2-methylbenzofuran (1).** A 30 L hastelloy pressure reactor was charged with methyl 3,5-dihydroxy-4-iodobenzoate (1.66 kg, 5.64 mol, 1 equiv), copper(I) iodide (0.050 kg, 0.05 equiv), bis(triphenylphosphine)-palladium dichloride (0.20 kg, 0.05 equiv), *N*,*N*-dimethylacetamide (16.6 L, 10 volumes), and diisopropylethylamine (1.71 kg, 3 equiv). The reactor was sealed and purged three times with nitrogen (25 psig) with stirring. The reactor was then purged four times with propyne with agitation. Dissolution of propyne was exothermic; during this process the internal temperature was controlled between 25−35 °C. Purges were continued until the internal pressure reached 6 psig (first purge), 8 psig (second purge), and 10 psig (third and fourth purge), at which time the reactor was vented. After four purges, the solution was saturated (as demonstrated by continuous degassing of the solution while the vent valve was open), so propyne was added to adjust the internal pressure to 10 psig, the reaction was heated to 38 °C and maintained under a 10 psig propyne atmosphere for 20 h. Approximately 1.1−1.2 kg of propyne was used for the purges and reaction pressurization. The dark, homogeneous reaction mixture was cooled to 15 °C, sparged with nitrogen for 15 min, and transferred to another reactor where it was placed under vacuum for 30 min. The reaction was repeated two more times on identical scale and the crude reaction mixtures were combined.

For workup, the crude reaction mixture was split in three equal portions and each portion was processed identically as described below. The crude reaction mixture was transferred to a 75 L reactor, heated to 40 °C, and water (16.4 L, 10 volumes) was added over 30 min, maintaining the internal temperature between 40−50 °C. Saturated aqueous ammonium chloride (16.4 L, 10 volumes) was then added, during which time dark semisolid polymer precipitated from the reaction mixture. While maintaining the internal temperature between 40−50 °C, the product-rich aqueous phase was washed twice with 8.2 L (5 volumes each wash) of 100:1 heptane:ethyl acetate to remove the insoluble polymer from the aqueous phase. Between washes the reactor was rinsed with acetone to remove any polymer that remained in the tank after the organic phase was drained. The aqueous phase was returned to the cleaned reactor, cooled to ambient temperature, and extracted three times with ethyl acetate (8.2 L, 5 volumes each time).

All ethyl acetate extracts from the three workups were combined and concentrated at atmospheric pressure to 10 L final volume. Methanol (25 L) was added and the remainder of the ethyl acetate was displaced by constant-volume azeotropic distillation until GC headspace analysis indicated <2% ethyl acetate was present. The solution was then concentrated to 10 L and cooled to 30 °C. Water (12 L) was added slowly to crystallize the product. The slurry was cooled to 15 °C, granulated for 8 h, isolated by filtration, and washed with water (28 L). After drying (vacuum, 50 °C) a total of 2.36 kg (11.5 mol, 68%) of the title product was obtained as an off-white solid. $^1$H NMR (400 MHz, DMSO) $\delta$: 10.19 (s, 1H), 7.52 (dd, $J$ = 1.0, 1.1 Hz, 1H), 7.21 (d, $J$ = 1.1 Hz, 1H), 6.66 (dd, $J$ = 0.9, 1.0 Hz, 1H), 3.83 (s, 3H), 2.44 (d, $J$ = 1.0 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$: 166.5, 156.9, 155.0, 150.1, 125.4, 122.5, 108.3, 103.4, 100.7, 52.1, 13.9. HRMS-ESI *m*/*z*: $[M-H]^-$ calcd for $C_{11}H_{10}O_4$, 205.0495; found, 205.0507. HPLC: rt 6.04 min (product), 5.30 min (starting material).

**General Procedure for Example Sonogashira Reactions.** Iodoresorcinol **6** (1 equiv), bis(triphenylphosphine)palladium dichloride (3 mol %), copper(I) iodide (3 mol %), and dimethylacetamide (10 volumes) were combined and degassed with nitrogen. Alkyne (3 equiv) and diisopropylamine (3 equiv) were charged and the mixture heated to 40−50 °C and held until the reaction was complete. The crude reaction mixture was partitioned between EtOAc and half-saturated ammonium chloride solution, and the organic phase was removed, dried, and concentrated to a brown oil. Chromatography on silica gel was utilized to isolate pure benzofuran product.

**4-Hydroxy-6-methoxycarbonyl-2-phenylbenzofuran (12).** Prepared from **6** (1.017 g) and phenylacetylene (1.2 mL) at 40 °C for 23 h. Chromatography (5−25% EtOAc/hexanes) provided 671 mg **12** (72% yield) as a beige solid. An additional 236 mg of uncyclized alkyne was obtained (25% yield). $^1$H NMR (400 MHz, DMSO) $\delta$: 10.48 (s, 1H), 7.95 (m, 2H), 7.65 (dd, $J$ = 1.0, 1.0 Hz, 1H), 7.52 (m, 2H), 7.51 (m, 1H), 7.43 (m, 1H), 7.28 (d, $J$ = 1.1 Hz, 1H), 3.86 (s, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$: 166.3, 156.3, 155.1, 151.0, 129.3, 129.2, 129.1, 126.6, 124.8, 122.7, 108.5, 103.7, 99.8, 52.2. HRMS-ESI *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{12}O_4$, 269.0808; found, 269.0810. HPLC: rt 7.79 min.

**2-(Cyclohex-1-enyl)-4-hydroxy-6-(methoxycarbonyl)benzofuran (13).** Prepared from **6** (1.0 g) and 1-ethynylcyclohexene (1.2 mL) at 40 °C for 24 h. Chromatography (5−10% EtOAc/hexanes) provided 801 mg **12** (86% yield) as a beige solid. $^1$H NMR (400 MHz, DMSO) $\delta$: 10.35 (s, 1H), 7.52 (dd, $J$ = 1.1, 1.2 Hz, 1H), 7.22 (d, $J$ = 1.3 Hz, 1H), 6.81 (m, 1H), 6.56 (m, 1H), 3.83 (s, 3H), 2.34 (m, 2H), 2.23 (m, 2H), 1.71 (m, 2H), 1.62 (m, 2H). $^{13}$C NMR (100 MHz, DMSO) $\delta$: 166.4, 157.7, 154.6, 150.7, 127.0, 126.6, 126.2, 122.5, 108.4, 103.3, 98.3, 52.1, 24.9, 24.2, 21.8, 21.5. HRMS-ESI *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{16}O_4$, 273.1121; found, 273.1122. HPLC: rt 8.03 min.

**4-Hydroxy-2-(2-hydroxypropan-2-yl)-6-(methoxycarbonyl)benzofuran (14).** Prepared from **6** (1.07 g) and 2-methyl-3-butyn-2-ol (1.1 mL) at 40 °C for 24 h. Chromatography (15−30% EtOAc/hexanes) provided 850 mg **12** (93% yield) as a beige solid. $^1$H NMR (400 MHz, DMSO) $\delta$: 10.24 (s, 1H), 7.55 (dd, $J$ = 1.0, 1.2 Hz, 1H), 7.22 (d, $J$ = 1.2 Hz, 1H), 6.75

(36) An ~7 mL disposable glass tube purchased from Biotage for use on the Endeavor system.

(d, $J$ = 0.9 Hz, 1H), 5.45 (s, 1H), 3.84 (s, 3H), 1.51 (s, 6H). $^{13}$C NMR (100 MHz, DMSO) $\delta$: 166.4, 166.1, 154.9, 150.7, 125.9, 121.9, 108.3, 103.7, 97.9, 67.6, 52.1, 28.9. HRMS-ESI $m/z$: $[M + H]^+$ calcd for $C_{13}H_{14}O_5$, 251.0914; found, 251.0914. HPLC: rt 5.15 min.

**2-[3-(*tert*-Butyldiphenylsiloxy)propyl]-4-hydroxy-6-(methoxycarbonyl)benzofuran (15).** Prepared from **6** (1.01 g) and 1-(*tert*-butyldiphenylsiloxy)pentyne[37] (3.3 mL) at 40 °C for 24 h. Chromatography (3−15% EtOAc/hexanes) provided 1.382 g **12** (82% yield) as an off-white solid. $^1$H NMR (400 MHz, DMSO) $\delta$: 10.20 (s, 1H), 7.60 (m, 4H), 7.52 (dd, $J$ = 1.0, 1.1 Hz, 1H), 7.43 (m, 2H), 7.41 (m, 4H), 7.22 (d, $J$ = 1.1 Hz, 1H), 6.66 (m, 1H), 3.84 (s, 3H), 3.72 (t, $J$ = 6.1 Hz, 2H), 2.90 (t, $J$ = 7.1 Hz, 2H), 1.96 (m, 2H), 1.00 (s, 9H). $^{13}$C NMR (100 MHz, DMSO) $\delta$: 166.5, 160.2, 154.9, 150.2, 135.0, 133.1, 129.8, 127.8, 125.5, 122.2, 108.3, 103.5, 100.1, 62.4, 52.1, 29.8, 26.6, 24.2, 18.8. HRMS-ESI $m/z$: $[M + H]^+$ calcd for $C_{29}H_{32}O_5Si$, 489.2092; found, 489.2096. HPLC: rt 9.30 min.

(37) Clark, R. C.; Lee, S. Y.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 12355–12369.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## Supporting Information Available

Detailed information and discussion of the methods used to calculated propyne solubility in reaction solvents and $^1$H and $^{13}$C NMR spectra of compounds **1**, **6**, **12**, **13**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.


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