JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

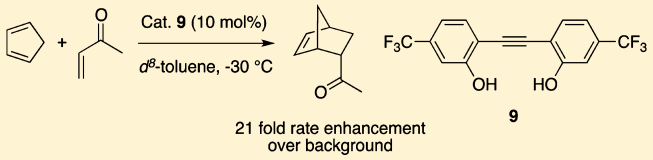
Exploring the Potential of Diarylacetylenediols as Hydrogen Bonding Catalysts

Yunus E. Türkmen and Viresh H. Rawal*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

Supporting Information

ABSTRACT: In the course of a search for new classes of hydrogen bonding catalysts, we have examined diarylacetylenediols as potential catalysts for the Diels–Alder reaction. General and efficient methods have been developed for the preparation of these diols. Their structures were systematically modified, and increased activity was observed for those possessing an electron-withdrawing group on the aryl groups. The electron-deficient diarylacetylenediol catalysts, while more active, undergo spontaneous cyclization to the corresponding benzo[*b*]furans. A mechanism is postulated to explain this facile transformation. Computational studies performed on 2-ethynylphenol help to explain the effect of the alkyne on the conformation and hydrogen bond donating ability of the adjacent OH group. Finally, the crystal structure of one of the diols is reported, and it displays an intricate network of intermolecular hydrogen bonds.



INTRODUCTION

The past decade has witnessed the mushrooming growth of metal-free catalysis. The field has gone from having representation through isolated examples to a position where it now challenges the longstanding dominance of metal-based catalysis.[1] An important and blossoming subset of this field, one that shares conceptual similarities to metal-based Lewis acid catalysis, is hydrogen bond catalysis.[2] Analogous to metal activation, hydrogen bond formation increases the electrophilicity of a reactant by lowering its LUMO energy. Moreover, the compatibility of hydrogen bond donors with many functional groups, such as amines, phosphines, pyridines, etc., makes them excellent partners in bifunctional organocatalysis.[3]

In considering different hydrogen bond donor functionalities, we were attracted to the possibility of using phenols, as such compounds had already been utilized to catalyze reactions. In a seminal 1942 paper, Wassermann noted modest rate acceleration for the Diels–Alder reaction of cyclopentadiene with benzoquinone in the presence of phenol.[4] This area remained more or less dormant until, in their pioneering studies, Hine and co-workers showed that biphenylenediols, functioning as dual hydrogen bond donors (Figure 1), catalyze the opening of phenyl glycidyl ether with diethylamine.[5] Kelly and co-workers used a soluble, nitro-substituted biphenylenediol derivative as a catalyst in Diels–Alder reactions and obtained up to ∼30 fold higher conversion over the uncatalyzed reaction with 40 mol % catalyst loading.[6] Since these early reports, the field has expanded dramatically and numerous other classes of hydrogen bond donors—such as taddols,[7] chiral thioureas,[3b−d] phosphoric acids,[2b,d] guanidines/guanidiniums,[8] peptides,[2h] and squaramides[9]—have been prepared and successfully utilized in a variety of reactions.[2] In addition to these frequently used classes, new hydrogen bond donor scaffolds have been reported in recent years and applied to catalysis.[10]

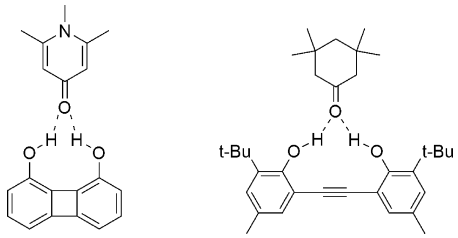


Figure 1. Hydrogen-bonded complex of biphenylenediol and a pyridone reported by Hine et al. and hydrogen-bonded complex of a diarylacetylenediol and a cyclohexanone reported by Saied et al.

The remarkable achievements in this area over the past few years have revolutionized our view of the scope of reactions that can be catalyzed by hydrogen bond donors and Brønsted acids. Development of new catalyst scaffolds has the potential to expand this scope even further, to include reactions and functional groups that remain unexplored. We are especially interested in the activation of carbonyl compounds with dual hydrogen bond donor catalysts. Such binding not only is expected to provide better activation than the single-point binding but also would result in a rigid, well-organized complex due to the reduced rotational freedom. The latter aspect is expected to be important in enantioselective catalysis. The total hydrogen bond strength of a hydrogen-bonded complex depends on several variables, such as hydrogen bond donating and accepting abilities of the components,[11] hydrogen bond distances between them, and the geometric arrangement between the donor and the acceptor groups. As a result, the

Received: May 4, 2013
Published: July 19, 2013

   dx.doi.org/10.1021/jo400926n | *J. Org. Chem.* 2013, 78, 8340–8353

spatial arrangements of the hydrogens of a dual hydrogen bond donor can, in principle, be optimized through careful investigation of different scaffolds in order to generate catalysts with enhanced activities. For instance, our development of the squaramide core as a hydrogen bonding catalyst was motivated by a desire to explore two-point hydrogen bond donors having a larger H−H bond distance than that found in thioureas, the dominant scaffold for hydrogen bond catalysis.[9a] Whereas the H−H bond distance in the thiourea core is ca. 2.13 Å, it is 2.72 Å in squaramides, roughly 25% larger.

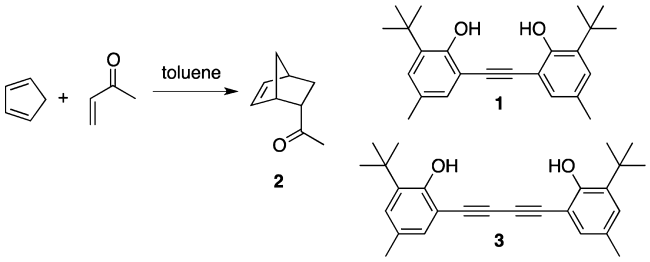
Although they are one of the first functional groups to be used for hydrogen bonding activation, phenols remain relatively unexplored as catalytic units for carbonyl activation.[12] A search for additional structural support for the interaction between phenolic diols and carbonyl groups uncovered an X-ray crystal structure reported by Saied, Simard, and Wuest of a diarylacetylenediol bound to a cyclohexanone by dual hydrogen bonds (Figure 1).[13] We recapitulated the essential features of this complex in silico using DFT calculations within the Spartan'08 molecular modeling program. We also used this approach to evalute several other diols as potential dual hydrogen bond donors.[14] An interesting aspect of the diphenylacetylenediol is that the alkyne imparts both rigidity and flexibility to the scaffold. Although the alkyne rigidly holds the two aryl rings in a linear arrangement, the distance between the two phenolic hydrogens can vary widely, between 2 and 5 Å, due to free rotation about the single bond. Despite the ease of synthesis of diarylacetylenediols and their potential to function as dual hydrogen bond donor catalysts, there are no reports in the literature on the examination of such compounds as hydrogen bonding catalysts.

RESULTS AND DISCUSSION

Initial Evaluation of Wuest's Diol. The objective of the initial studies was to determine if simple diarylacetylenediols would function as hydrogen bond donor catalysts for activating carbonyl group containing reactants, potentially through dual hydrogen bonding interactions. The study was initiated by evaluating the catalysis capability of the known diol **1**, which was prepared easily following the procedure reported by Wuest.[15] The Diels−Alder reaction of cyclopentadiene and methyl vinyl ketone (MVK) to give cycloadduct **2** was selected as the test reaction.[16] The reactions were carried out at various temperatures in toluene, and conversions were determined at regular intervals by ^{1}H NMR. The rate constants were calculated for both catalyzed and uncatalyzed reactions (Table 1). With 40 mol % of diol **1** at 20 °C, the relative rate constant ($k_{rel} = k_{obs}/k_{background}$) was found to be 2.8, indicating clear, but low, catalytic activity at room temperature (entry 1).[17] This ratio increased noticeably at lower temperatures. With 20 mol % of the catalyst, a k_{rel} value of 6.5 was obtained at 0 °C, and 9.4 at −20 °C (entries 2 and 3). The data convincingly showed that Wuest's diol functions as a catalyst for the Diels−Alder reaction.

The working hypothesis was that diol **1** functions through a two-point hydrogen bond to the carbonyl oxygen. To test this premise, we prepared the known homologous diacetylenic diol **3**,[15b] in which the two phenol rings are separated by a diyne unit. This diol was expected to have electronic properties similar to those of **1** but have a larger distance between the two OH's. Molecular mechanics calculations show the two donor oxygen atoms in **3** at their minimum distance to be 6.8 Å apart (vs 3.9 Å in **1**), a distance that is believed to be too large for a good two-point hydrogen bond. Under the standard reaction conditions, diol **3** exhibited lower catalytic activity (k_{rel} = 2.3, entry 4) than **1**. While seemingly consistent with the original hypothesis, the interpretation of these results is less than straightforward, explainable through other considerations, including a one-point activation model. Wuest and co-workers had noted through IR studies that, in solution, both phenols in **1** are internally hydrogen-bonded by O−H···π interaction to the shared alkyne.[15a] The presence of two alkynes in **3** means that, rather than sharing an alkyne, each hydroxyl would be internally hydrogen-bonded to the proximal alkyne, one alkyne per hydroxyl. As such, the hydroxyls in **3** are expected to be less available than in **1** for intermolecular hydrogen bonding activation, consistent with the observed results. These initial results motivated us to prepare and examine the activity of a wider range of structurally modified diarylacetylenediol catalysts.

Table 1. Diels−Alder Reaction of Cyclopentadiene and MVK Catalyzed by Diols 1 and 3



entry	catalyst	cat. mol %	T (°C)	k(obs)/k(back)
1	**1**	40	20	2.8
2	**1**	20	0	6.5
3	**1**	20	−20	9.4
4	**3**	20	−20	2.3

Substituted Diphenylacetylenediols. Having shown that the diarylacetylenediol backbone is effective for activating the carbonyl group, we next focused on the preparation of several additional phenols and diphenols, some designed to assess the effect of steric and electronic perturbations on catalysis activity, and others to serve as controls (Figure 2). We recognized that the *ortho*-*tert*-butyl groups in **1** and **3**, through steric compression and entropic constraints, would cause the hydroxyl groups to be more strongly hydrogen-bonded to the alkyne, thereby making the phenols less effective for intermolecular hydrogen bond activation.[15a] To tease out the effect of the *tert*-butyl group on catalyst activity, we considered the unsubstituted diol **4** available through the route used for **1**. Diol **5**, having the electron-withdrawing −CF_3 group para to the phenols, was expected to be a more effective catalyst than those discussed above. Structurally similar monophenol derivatives **6** and **7** as well as the diyne-separated diol **8** were expected to serve as controls. Diol **9**, having the −CF_3 groups meta to the phenols, would show the effect of the position of this withdrawing group on catalyst activity.

Synthesis of Phenols 4−9. Cross-coupling chemistry enabled the synthesis of nearly all of the compounds selected for use as catalysts in the present study. The known parent diol **4**[18] was prepared by a slightly modified route. Diol **5** was prepared through the sequence summarized in Scheme 1. Lithiation of the MOM-protected phenol derivative **10**[19] with *n*-BuLi, followed by treatment with iodine, afforded aryl iodide **11** in 98% yield. Sonogashira coupling of **11** with excess

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

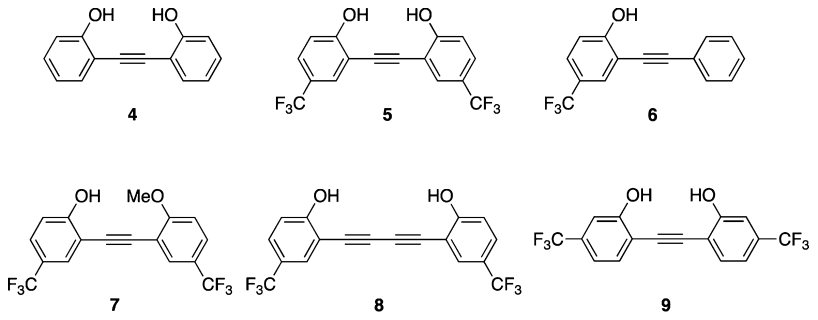
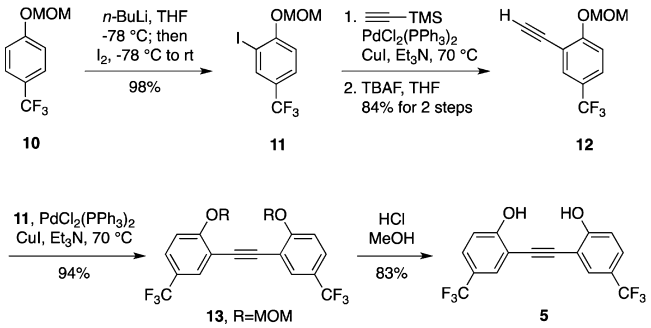


Figure 2. Substrates considered for evaluation as hydrogen bond donors.

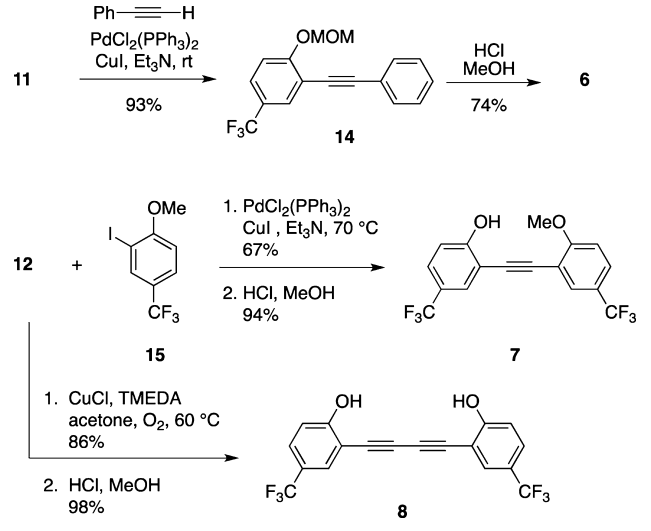
Scheme 1. Synthesis of Diol 5



ethynyltrimethylsilane and the subsequent deprotection of the TMS group with TBAF gave **12** in 84% yield over two steps. A further Sonogashira coupling of **11** with alkyne **12** provided MOM-protected acetylene-diol **13** in 94% yield. Finally, removal of the MOM groups using HCl in methanol gave diol **5** in 83% yield.

The mono-ols **6** and **7** and the diyne-separated diol **8**, all designed for use as controls, were prepared as shown in Scheme 2. Sonogashira coupling of **11** with phenylacetylene (93%) and deprotection of the MOM group afforded **6** (74%). Similarly, monomethyl protected diol **7** was obtained by the cross-coupling of **12** with **15** (67%), followed by selective deprotection of the MOM group (94%). Finally, oxidative coupling of **12** (86%) and subsequent deprotection under

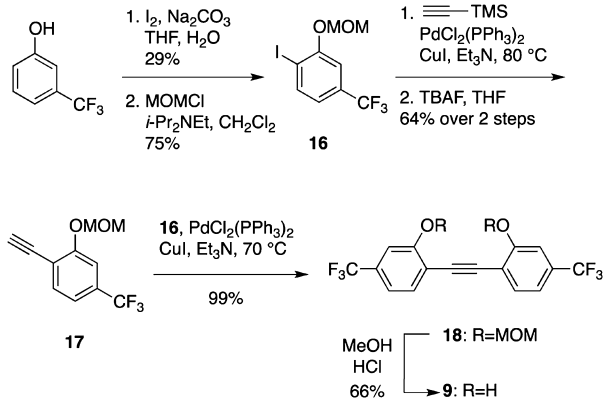
Scheme 2. Synthesis of 6, 7, and 8



acidic conditions afforded diyne linked diol **8** in high yield (98%).

The preparation of diol **9**, which is isomeric with diol **5**, was accomplished as shown in Scheme 3. Commercially available 3-

Scheme 3. Synthesis of Diol 9

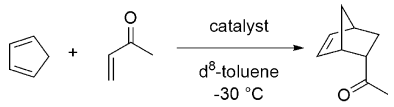


(trifluoromethyl)phenol was iodinated under basic conditions to afford the 6-iodinated phenol in 29% unoptimized yield. Protection of the phenol with a MOM group afforded aryl iodide **16** (75%),[20] which, upon Sonogashira coupling with ethynyltrimethylsilane and TMS-deprotection, afforded **17** in 64% yield over two steps. A second Sonogashira coupling of **17** and **16** gave protected diol **18** almost quantitatively (99%). Finally, deprotection of the MOM groups in acidic methanol gave diol **9** in 66% yield.

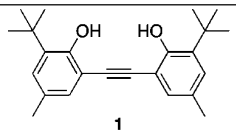
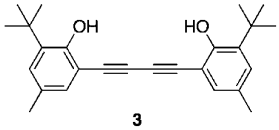
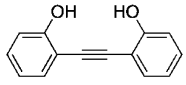
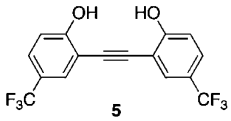
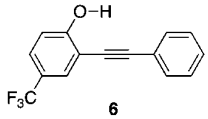
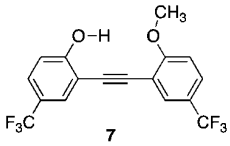
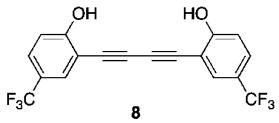
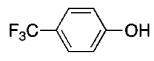
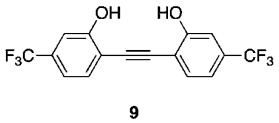
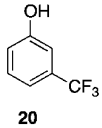
Activity of New Phenolic Catalysts. The relative activity of Wuest's diols, the newly synthesized diols, and the control compounds as hydrogen bond donor catalysts was investigated, and the results are summarized in Table 2. The kinetics studies were carried out under pseudo-first-order conditions at −30 °C using 10 mol % of diol catalysts and 20 mol % of monophenols, and conversions were determined by ^{1}H NMR. Under the new kinetics protocol, the relative rate constant for Wuest's diol **1** was found to be 3.5 (entry 1), whereas that for the diyne-separated diol was 1.3 (entry 2).[21] The parent diphenylacetylene diol **4** was found to catalyze the DA reaction with higher efficiency than the *ortho-tert*-butyl-substituted diol, **1** (entry 3). This result is consistent with the expectation that the *tert*-butyl groups enforce a stronger O−H···π interaction, thereby making the phenols less effective hydrogen bond donors. In addition, the *tert*-butyl groups prevent the "OH-out" conformation (OH away from the alkyne), whereas, in the absence of *tert*-butyl groups, such a conformation is possible, and the catalyst may function in this form. Finally, compared to the unsubstituted

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

Table 2. Diels–Alder Reaction of Cyclopentadiene and MVK at −30 °C[a,b,c]



2

Entry	Catalyst	Cat mol %	k_{rel}[b] (k_{obs}/k_{back})	$\Delta\delta$ in ^{13}C NMR (ppm)[c]
1	 **1**	10	3.5	0.14
2	 **3**	10	1.3	0.09
3	 **4**	10	9.6	1.49
4	 **5**	10	16.7	2.55
5	 **6**	20	5.0	0.72
6	 **7**	20	2.7	0.23
7	 **8**	10	10.0	2.22
8	 **19**	20	7.7	2.17
9	 **9**	10	21.8	2.68
10	 **20**	20	10.3	2.09

[a]The catalytic reactions were carried out using cyclopentadiene (1.0 M), MVK (0.1 M), and the catalyst (10 or 20 mol %) in d^8-toluene at −30 °C. [b]$k_{rel} = k_{obs}/k_{background}$ is the average of at least two runs. [c]$\Delta\delta$ represents the chemical shift change of the carbonyl carbon of MVK (0.06 M) upon addition of 100 mol % of diol or 200 mol % of phenol, in d^8-toluene.

diol, **4**, the electron-donating effect of the two alkyl groups on each aryl ring in **1** is expected to decrease the acidity of the phenols. For example, the pK_a of 4-Me phenol is 18.9, whereas that of the unsubstituted phenol is 18.0 in DMSO.[22] Entries 4–

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340–8353

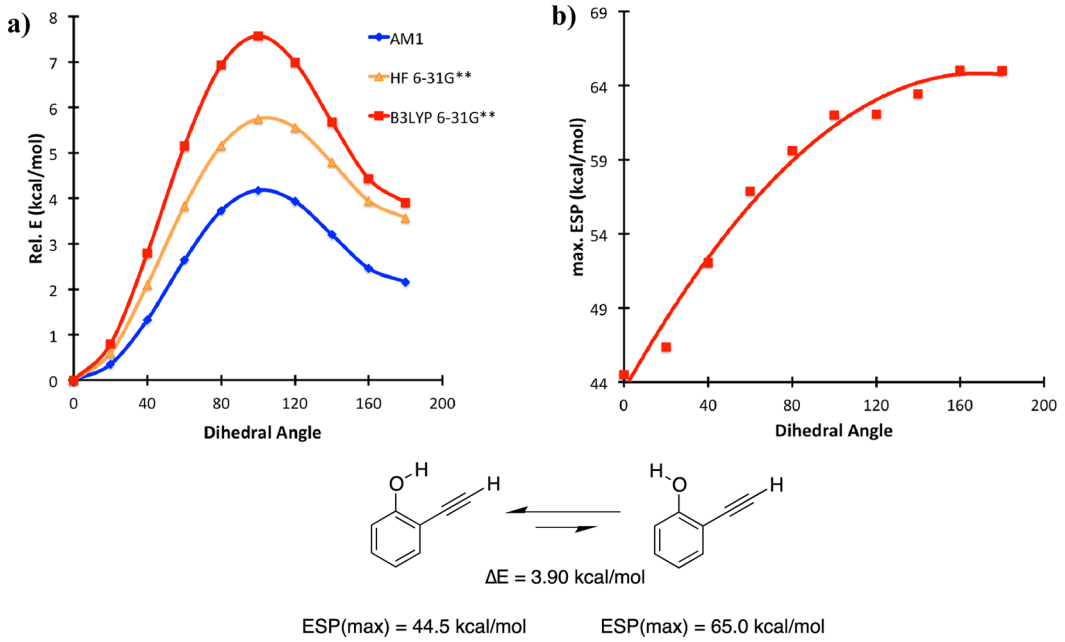


Figure 3. Dependence of (a) relative energy and (b) maximum electrostatic potential on the dihedral angle for 2-ethynylphenol.

7 illustrate the effect of electron-withdrawing groups on the aryl units. As expected, the electron-withdrawing CF_3 groups in **5** increased the activity of the diol catalyst, giving a k_{rel} value of 16.7 (entry 4). To the extent that diol **5** promotes the cycloaddition through two-point hydrogen bond activation, the analogous monophenolic compounds **6** and **7** were expected to serve as controls, as they would form a one-point hydrogen bond. Phenols **6** and **7** were utilized at 20 mol % loading (to have equal Brønsted acid concentration) and found to be less effective as catalysts than **5**, giving k_{rel} values of 5.0 and 2.7, respectively (entries 5−6). The differences in the catalytic activities of **6** and **7** can be understood by considering their stable conformations, wherein the phenolic hydroxyls are expected to be stabilized through hydrogen bonding interactions, as drawn in entries 5 and 6. Although too far for a good hydrogen bond, the methoxy group oxygen in **7** can provide weak electrostatic stabilization to the phenol. Also, resonance contribution by the methoxy group will render the alkyne more electron-rich, strengthening the hydrogen bond to the phenolic hydroxyl. Interestingly, the alkyne-expanded diol **8**, while less active than **5**, was more effective as a catalyst than the alkynyl control compounds, monophenols **6** and **7**, and even 4-trifluoromethylphenol (**19**, entries 5−8). Catalyst **9** with CF_3 groups at the meta position to OH showed a further increase in catalyst activity (k_{rel} = 21.8, entry 9), whereas 3-trifluoromethyl phenol (**20**) gave a k_{rel} value of 10.3 (20 mol %, entry 10). Overall, the kinetics data provide clear evidence that phenolic hydrogen bond donors catalyze the Diels−Alder reaction between cyclopentadiene and methyl vinyl ketone. Diarylacetylene diols designed to provide two-point hydrogen bonding were more effective at accelerating the cycloaddition reaction compared to the monophenols, but only moderately so.

Correlation of Catalyst Activity with NMR Chemical Shifts. We have sought to correlate the activities of the different catalysts with the strength of their interaction with the dienophile. On the far right column of Table 2 are presented the chemical shift changes upon complexation of the different catalysts with MVK. In each case, a 1:1 mixture of the diol, 0.06 M,[23] and MVK was prepared in d^8-toluene, and their ^{13}C NMR spectra were recorded. The chemical shift differences of the MVK carbonyl carbon in these solutions with that in the blank MVK solution were determined. While diols **1** and **3** induced very small changes (0.14 and 0.09 ppm, respectively; entries 1 and 2), the catalytically active diols **5** and **9** gave $\Delta\delta$ values of 2.55 and 2.68 ppm, respectively (entries 4 and 9). For comparison purposes, monophenol derivatives were also investigated, but with a 2:1 phenol/MVK ratio (0.12 M phenol concentration). As expected, the monophenols gave smaller $\Delta\delta$ values than their diol analogues, indicative of poorer binding (entries 5, 6, 8, and 10). When these values are compared with the observed k_{rel} values, they clearly show a close relation between the chemical shift changes upon complexation and the activity of the catalyst.

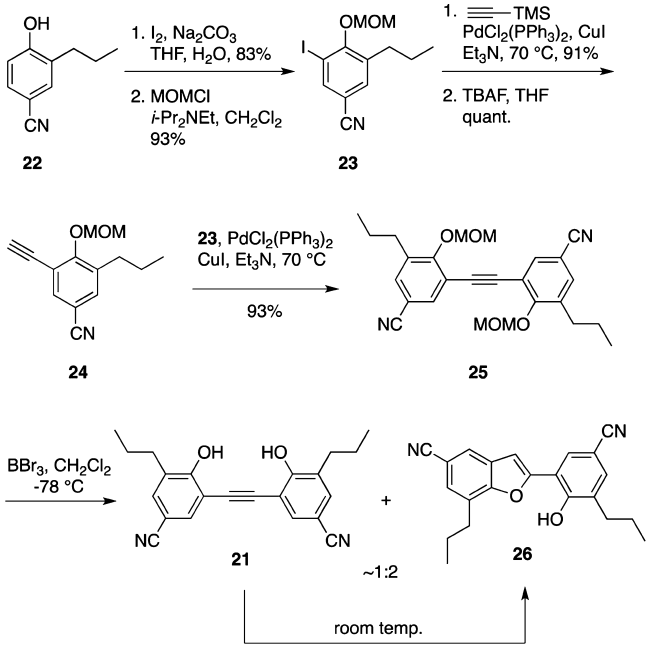
Computational Studies. We next investigated computationally the effect of the alkyne moiety on the conformation and hydrogen bond donating ability of the −OH group in 2-alkynyl phenols. While the steric effect of the alkynyl group is expected to be small, it can influence the properties of the nearby phenol through hydrogen bonding interactions.[24] Indeed, on the basis of IR stretches, Wuest and co-workers had proposed that, in the absence of a hydrogen bond acceptor, the two OH's of **1** make intramolecular hydrogen bonds to the triple bond.[15a] To determine whether such an interaction is playing a role in the hydrogen bonding capability of the phenols, we carried out calculations on 2-ethynylphenol using Spartan'08. Single-point energies were calculated at AM1, HF 6-31G**, and DFT B3LYP 6-31G** levels of theory at each 20° increment in the H1−O1−C1−C2 dihedral angle between 0 and 180° (Figure 3). The energy difference between the 0° and 180° conformations was found to be 2.16 kcal/mol by AM1, whereas HF 6-31G** and DFT B3LYP 6-31G** gave 3.57 and 3.90 kcal/mol, respectively (Figure 3a). The last value is in excellent agreement with the report of Mulder and co-workers,[24d] who had determined the $\Delta H_{intra\text{-}HB}$ of 2-ethynylphenol to be −3.8 kcal/mol by DFT calculations. In

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

addition to the energy profile, molecular electrostatic potential (ESP) surfaces were calculated for each conformation. These potentials have been used in the literature as measures of hydrogen bond donating or accepting abilities of different functional groups.[25] According to DFT calculations, the electrostatic potential of the OH hydrogen decreases from +65.0 to +44.5 kcal/mol (ΔESP = 20.5 kcal/mol) when the dihedral angle changes from 180° to 0° (Figure 3b). The same calculation was also carried out using AM1 and HF 6-31G**, and the ESP differences between two conformers were found to be 10.4 and 21.8 kcal/mol, respectively.[26] When considered together, these two results indicate that the orientation of the OH hydrogen toward the alkyne is favored energetically by 3.90 kcal/mol, and this orientation is expected to diminish the hydrogen bond donating ability of the hydroxyl group. It should be noted that such a conformational preference might be a result of an attractive interaction between the alkyne and the OH group or a repulsive interaction between the oxygen lone pairs and the alkyne π-bond(s), or a combination of both of these effects.

Synthesis and Chemistry of Diol 21. The significant increase in catalyst activity by the introduction of $-CF_3$ groups (diols **5** and **9**) prompted us to prepare diol catalysts with even stronger electron-withdrawing groups. Among the common groups considered, the cyano unit was expected to provide the required electron-withdrawing ability without adding steric factors. In particular, we decided to prepare diol **21**, with CN groups at the para positions. In their work on biphenylene diols, Kelly and co-workers had found the nitro-substituted derivatives to be poorly soluble and had prepared a diol with propyl groups ortho to the hydroxyls.[6] We decided to follow a similar strategy in the case of the cyano-substituted diarylacetylenediol (Scheme 4). Phenol **22** was prepared in three steps from the commercially available 4-cyanophenol, following a reported procedure.[27] Iodination of **22** under basic conditions (83%), followed by MOM protection, afforded cleanly the aryl iodide **23** (93%). The Sonogashira coupling of **23** with ethynyltrimethylsilane (91%) and its subsequent desilylation with TBAF gave quantitatively acetylene **24**. The protected diol **25** was obtained in 93% yield by a second Sonogashira coupling. The final deprotection step, however, proved to be problematic. Treatment of **25** with HCl in methanol at room temperature resulted in complete formation of the benzo[*b*]furan derivative **26**.[28,29] The use of BBr_3 in CH_2Cl_2 at room temperature did not provide an improvement. However, when **25** was treated with BBr_3 at −78 °C for 45 min and quenched with half-saturated $NaHCO_3$ solution, a mixture of **21** and **26**, in a 1:2 ratio, was obtained (determined by ^1H NMR). After the solvent was evaporated and the sample was kept at room temperature for 3 h, TLC showed that it had completely converted to **26**, the structure of which was further confirmed by HRMS, and ^1H and ^{13}C NMR. This observation suggests that diol **21** spontaneously converts to benzo[*b*]furan **26** at room temperature. A plausible mechanism for the benzo[*b*]furan formation is shown in Scheme 5.

Scheme 4. Studies on the Synthesis of Diol 21



Proposed Mechanism for the Benzo[*b*]furan Formation. 2-Alkynylphenol derivatives have been shown to be useful substrates for the synthesis of benzo[*b*]furans by the use of transition metals,[18,30] various electrophiles,[31] Brønsted acids,[32] and bases.[33] In addition, diarylacetylenediols have been observed, by us and others, to undergo a facile transformation to the corresponding benzo[*b*]furans under acidic and basic conditions.[18,28,34] In our hands, this conversion was more common with diols having electron-withdrawing groups, wherein some substrates cyclized spontaneously to the benzo[*b*]furans. For instance, diols **5**[35] and **9** undergo a slow, but clear, transformation to the corresponding benzo[*b*]furans, even when stored in the refrigerator (~0 °C). Additionally, as described in the previous section, we were unable to prepare diol **21**, due to its fast conversion to **26**.[36]

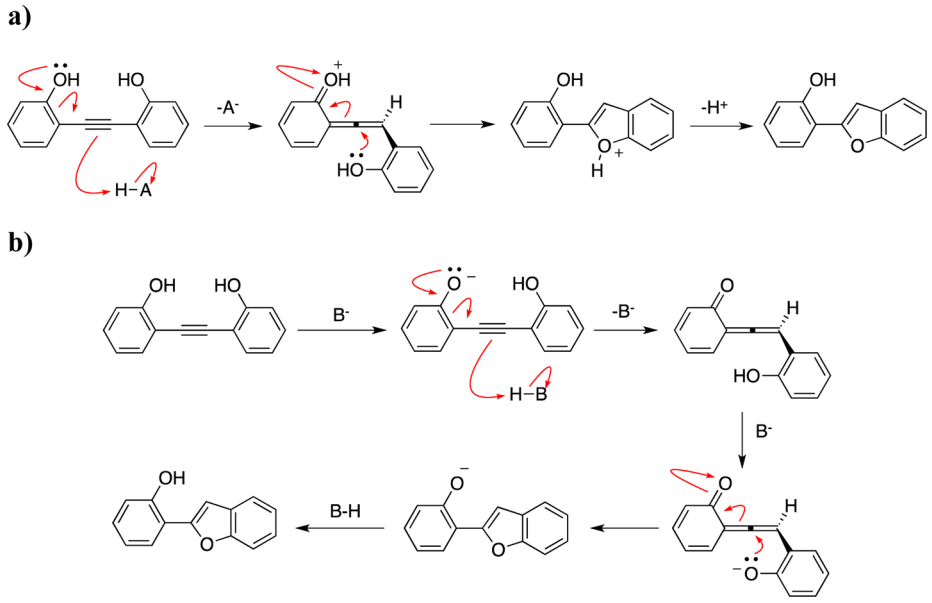
A plausible mechanism to rationalize the facile transformation of diarylacetylenediols to the benzo[*b*]furans under acidic and basic conditions is presented in Scheme 5. The *ortho*-hydroxyl is expected to increase the basicity of the alkyne so that, under acidic conditions, it can be protonated to form a protonated allenone-type species. In this intermediate, the planes of the two six-membered rings are perpendicular to each other and the phenol −OH lies in proximity to the π^* of the allenone moiety. The high electrophilicity of the protonated allenone, coupled with the rearomatization driving force, would lead to a fast 5-*exo*-*dig*-cyclization to give the protonated benzo[*b*]furan, which would regenerate the acid catalyst upon deprotonation. It should be noted that the acidic diols with strong electron-withdrawing groups would act as acid catalysts by themselves and would not require an external acid, which would explain the spontaneous decomposition of some of the diols studied.[37]

A similar mechanism can be written for the base-catalyzed benzo[*b*]furan formation (Scheme 5b). This time, the initially formed phenolate, upon deprotonation, would increase the electron density of the alkyne, reducing its barrier to protonation, whether inter- or intramolecularly, to give an allenone. Nucleophilic addition of the second phenol or phenolate would result in cyclization and give the benzo[*b*]furan phenolate, the protonation of which would regenerate the base catalyst.

Crystal Structure of Diol 5. A search of the literature showed that, surprisingly, the crystal structure of a diarylacetylenediol has not been reported, except for the cocrystal shown in Figure 1. To get some insight on the structural

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

Scheme 5. Proposed Mechanism for the Formation of Benzo[*b*]furan under (a) Acidic and (b) Basic Conditions



parameters and conformation of a free diarylacetylenediol, good quality crystals of diol **5** were obtained, and its X-ray crystal structure was determined. As shown in Figure 4, both hydroxyl

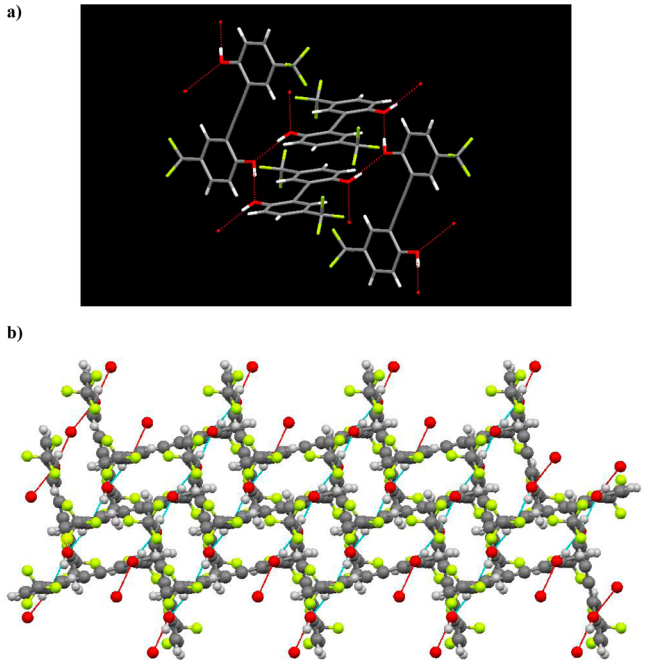


Figure 4. Different views of the crystal structure of diol **5**: (a) hydrogen-bonded network showing the $R_4^4(22)$ motif; (b) side view of the hydrogen-bonded network.

groups in the molecule lie in the same plane, but on opposite sides of the alkyne, with the hydrogens of the OH groups facing away from the triple bond. All the hydrogens and oxygens of the hydroxyl groups participate in hydrogen bonding in an efficient way to form a 3D hydrogen-bonded network. From the pattern analysis, its graph set was determined as $R_4^4(22)$.[38] Because of the symmetry in the molecular network, all the hydrogen bonds are equivalent with an O···O distance of 2.76 Å and an O–H···O angle of 167.9°. There is also a weak C–H···F–C short contact[39] with H···F and C···F distances of 2.58 and 3.43 Å, respectively, and a C–H···F angle of 148.3°.

CONCLUSIONS

In this study, we demonstrated the first use of diarylacetylenediols as hydrogen bond donor catalysts. General and efficient methods were developed for the preparation of various diarylacetylenediols. Of the different diols examined, diols **5** and **9** were found to be among the better catalysts for the Diels–Alder reaction of cyclopentadiene and MVK, resulting in up to a 21-fold rate enhancement over the background reaction. It is likely that such diols can be used for the promotion of other reactions involving carbonyl group activation. The diols studied showed higher catalytic activities than their monophenol counterparts in control experiments. However, the differences were small, indicating that the contribution from dual hydrogen bond activation may be limited with this scaffold. While the activity of the diols was found to increase with the introduction of electron-withdrawing groups, the observed tendency to undergo spontaneous cyclization to the corresponding benzo[*b*]furans may limit the range of modifications that can be carried out on these catalysts. A mechanism involving an allenone-type intermediate is proposed to rationalize the formation of the benzo[*b*]furan products. We have also shown through computational studies that 2-ethynylphenol prefers the internally hydrogen-bonded conformation by 3.90 kcal/mol, and this conformation reduces the electrostatic potential on OH hydrogen by 20.5 kcal/mol. Finally, the crystal structure of diol **5** was obtained and found to possess an intricate network of intermolecular hydrogen bonds.

EXPERIMENTAL SECTION

General Information. All air-sensitive reactions were performed using oven-dried glassware under a N_2 or Ar atmosphere. Reactions were monitored by TLC on silica gel 60 Å F254 plates visualized by UV and $KMnO_4$ staining solution. Flash column chromatography was performed on 32–63 μm Flash silica gel. NMR spectra were measured at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra and calibrated from residual solvent signals (chloroform at 7.26 ppm, toluene at 6.98 ppm, acetone at 2.05 ppm, acetonitrile at 1.94 ppm,

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340–8353

and methanol at 3.31 ppm for ^{1}H spectra; chloroform at 77.0 ppm, toluene at 20.4 ppm, acetone at 206.68 ppm, and acetonitrile at 118.69 ppm for ^{13}C spectra). Infrared spectra were measured on NaCl plates. Melting points are uncorrected. High-resolution mass spectra (ESI) were obtained using an ion trap mass analyzer.

Dichloromethane (CH_2Cl_2), toluene, benzene, and tetrahydrofuran (THF) were purified by passage over activated alumina using a solvent purification system. Cyclopentadiene was obtained by cracking dicyclopentadiene at 170 °C and distillation under nitrogen before every use. Methyl vinyl ketone was distilled under nitrogen and stored at −10 °C. Triethylamine (HPLC grade) was stored over KOH pellets. CuI and $PdCl_2[P(C_6H_5)_3]_2$ were stored in a desiccator. ***Caution!*** *The reactions in sealable pressure tubes were carried out in a well-ventilated fume hood behind a blast shield.*

Diols **1**[15a] and **3**[15b] were prepared according to the reported procedures.

2-Iodo-1-(methoxymethoxy)-4-(trifluoromethyl)benzene (11). To a solution of **10**[19] (1.70 g, 8.22 mmol) in 40 mL of anhydrous THF at −78 °C was added slowly *n*-BuLi (1.6 M solution in hexanes, 6.2 mL, 9.9 mmol), and the resulting solution was stirred at −78 °C for 30 min. In a separate round-bottom flask, I_2 (3.13 g, 12.3 mmol) was dissolved in 10 mL of anhydrous THF under argon and added dropwise to the reaction mixture via syringe. The resulting reddish brown mixture was allowed to warm to room temperature and stirred under nitrogen for 22 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and stirred until the color turned light yellow. The aqueous phase was extracted twice with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **11** (2.68 g, 98%) as a yellow oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 2.0 Hz, 1H), 7.54 (dd, J = 8.5, 1.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 5.29 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 136.5 (q, J_{C-F} = 3.8 Hz), 126.8 (q, J_{C-F} = 3.8 Hz), 125.4 (q, J_{C-F} = 32.8 Hz), 123.1 (q, J_{C-F} = 270.4 Hz), 113.9, 94.7, 86.5, 56.5; IR (film) 2960, 2911, 2830, 1604, 1496, 1396, 1324, 1297, 1124, 1081, 1036, 982, 821, 667 cm^{-1}; HRMS (ESI) Calcd for $C_9H_8F_3IO_2Na$ $(M + Na)^+$, 354.9413; found, 354.9415.

2-Ethynyl-1-(methoxymethoxy)-4-(trifluoromethyl)benzene (12). Compound **11** (365 mg, 1.10 mmol) was dissolved in 3.0 mL of Et_3N in a sealable tube fitted with a septum, at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (46 mg, 0.066 mmol), CuI (21 mg, 0.11 mmol), and ethynyltrimethylsilane (457 μL, 3.30 mmol) were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 70 °C, and stirred at this temperature for 18 h. After cooling down to room temperature, the reaction mixture was quenched with a 1:1 brine−H_2O mixture and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford a brown oil. This crude oil was dissolved in 10 mL of anhydrous THF under nitrogen and cooled to 0 °C. TBAF (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added slowly, and the reaction mixture was stirred for 30 min. The mixture was then quenched with 10 mL of H_2O and diluted with 40 mL of Et_2O. The two phases were partitioned in a separatory funnel, and the organic phase was washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford a brown oil. Purification by flash column chromatography (EtOAc/hexanes 1:19) gave **12** (212 mg, 84% over 2 steps) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 8.5, 2.0 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 5.31 (s, 2H), 3.52 (s, 3H), 3.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 131.3 (q, J_{C-F} = 3.8 Hz), 127.1 (q, J_{C-F} = 3.8 Hz), 124.0 (q, J_{C-F} = 33.8 Hz), 123.7 (q, J_{C-F} = 270.0 Hz), 114.5, 112.9, 94.7, 82.4, 78.5, 56.4; IR (film) 3304, 2962, 2913, 2832, 2113, 1614, 1503, 1421, 1336, 1274, 1252, 1131, 1086, 985, 827 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{10}F_3O_2$ $(M + H)^+$, 231.0627; found, 231.0630.

1,2-Bis[2-(methoxymethoxy)-5-(trifluoromethyl)phenyl]-ethyne (13). Compound **11** (143 mg, 0.43 mmol) was dissolved in 1.0 mL of Et_3N in a sealable tube fitted with a septum, at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol), CuI (8 mg, 0.043 mmol), and a solution of alkyne **12** (109 mg, 0.47 mmol) in 1.0 mL of Et_3N were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 70 °C, and stirred at this temperature for 18 h. After cooling down to room temperature, the reaction mixture was quenched with a 1:1 brine−H_2O mixture and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography (15% to 20% EtOAc in hexanes) gave **13** (175 mg, 94%) as a white solid. mp 100−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 2.0 Hz, 2H), 7.54 (dd, J = 8.5, 2.0 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 5.34 (s, 4H), 3.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 130.7 (q, J_{C-F} = 3.8 Hz), 126.9 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 33.8 Hz), 123.8 (q, J_{C-F} = 270.0 Hz), 114.8, 114.0, 94.8, 89.4, 56.4; IR (film) 2966, 2913, 2834, 1615, 1511, 1441, 1349, 1312, 1271, 1246, 1205, 1129, 1086, 992, 828 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{16}F_6NaO_4$ $(M + Na)^+$, 457.0845; found, 457.0844.

2,2′-(Ethyne-1,2-diyl)bis[4-(trifluoromethyl)phenol] (5). Compound **13** (121 mg, 0.28 mmol) was dissolved in 3 mL of MeOH and 2 mL of CH_2Cl_2, and the resulting clear solution was treated with 0.3 mL of concentrated HCl. The reaction mixture was stirred at room temperature, under air for 22 h. It was then quenched with water, and the aqueous phase was extracted once with CH_2Cl_2 and twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellowish white solid. Purification by flash column chromatography (2% MeOH in $CHCl_3$) gave **5** (80 mg, 83%) as a white solid. mp 172−174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 1.5 Hz, 2H), 7.56 (dd, J = 8.5, 2.0 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.29 (br s, 2H); ^{13}C NMR (125 MHz, acetone-d^6) δ 161.9, 130.8 (q, J_{C-F} = 3.8 Hz), 128.3 (q, J_{C-F} = 3.8 Hz), 123.2 (q, J_{C-F} = 267.5 Hz), 122.5 (q, J_{C-F} = 32.5 Hz), 117.3, 111.7, 90.5; IR (film) 3341 (br), 1444, 1394, 1342, 1273, 1123, 1072, 900 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_7F_6O_2$ $(M - H)^-$, 345.0356; found, 345.0360.

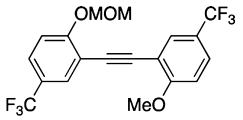
1-(Methoxymethoxy)-2-(phenylethynyl)-4-(trifluoromethyl)-benzene (14). Compound **11** (217 mg, 0.65 mmol) was dissolved in 3.0 mL of Et_3N in a round-bottom flask under nitrogen. $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), CuI (12 mg, 0.065 mmol), and phenylacetylene (108 μL, 0.98 mmol) were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The reaction mixture was stirred at room temperature for 22 h and then quenched with H_2O. The aqueous layer was extracted three times with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography (5% EtOAc in hexanes) gave **14** (185 mg, 93%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 2.5 Hz, 1H), 7.57−7.55 (m, 2H), 7.51 (dd, J = 8.5, 2.0 Hz, 1H), 7.37−7.35 (m, 3H), 7.22 (d, J = 9.0 Hz, 1H), 5.32 (s, 2H), 3.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 131.7, 130.6 (q, J_{C-F} = 3.8 Hz), 128.6, 128.5, 126.5 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 32.5 Hz), 123.9 (q, J_{C-F} = 270.0 Hz), 123.0, 114.7, 114.3, 94.8, 94.5, 84.2, 56.4; IR (film) 2960, 2830, 2221, 1612, 1598, 1505, 1338, 1270, 1243, 1150, 1115, 1085, 984, 904, 825, 757 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{14}F_3O_2$ $(M + H)^+$, 307.0940; found, 307.0942.

2-(Phenylethynyl)-4-(trifluoromethyl)phenol (6). To a solution of **14** (39 mg, 0.13 mmol) in 2 mL of MeOH was added 0.1 mL of concentrated HCl. The reaction mixture was stirred at room temperature, under air for 5.5 h, and quenched with water, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography (EtOAc/hexanes 1:9) gave **6** (25 mg, 74%) as a white solid. mp 61−62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 2.0 Hz, 1H), 7.55−7.53 (m, 2H), 7.50 (dd, J = 8.5, 1.5 Hz, 1H), 7.40−7.37 (m, 3H), 7.06 (d, J = 9.0 Hz, 1H), 6.13 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 131.7, 129.3, 129.1 (q, J_{C-F} = 3.8 Hz), 128.6, 127.4 (q, J_{C-F} = 3.8 Hz), 123.9 (q, J_{C-F} = 270.0 Hz), 123.0 (q, J_{C-F} = 32.5 Hz), 121.7, 115.2, 110.2, 97.5, 81.5; IR (film) 3317 (br), 2962,

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

2219, 1722, 1616, 1597, 1491, 1431, 1340, 1271, 1116, 905, 829, 757 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_8F_3O$ $(M - H)^-$, 261.0533; found, 261.0535.

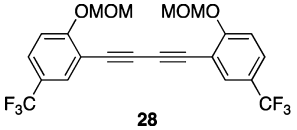
2-Iodo-1-methoxy-4-(trifluoromethyl)benzene (15). To a solution of *p*-(trifluoromethyl)anisole[40] (500 mg, 2.84 mmol) in 15 mL of anhydrous THF was added slowly *n*-BuLi (2.5 M solution in hexanes, 1.4 mL, 3.4 mmol) at −78 °C. The resulting solution was stirred at 0 °C for 45 min and cooled back to −78 °C, and a solution of I_2 in 6.0 mL of anhydrous THF was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred under nitrogen overnight. It was then quenched with saturated $Na_2S_2O_3$ solution and stirred until the color turned light yellow. The aqueous phase was extracted three times with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (2% EtOAc in hexanes) gave **15** (403 mg, 47%) as a colorless oil.[41] ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 8.5, 1.5 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 136.6 (q, J_{C-F} = 3.8 Hz), 127.0 (q, J_{C-F} = 3.8 Hz), 124.5 (q, J_{C-F} = 33.8 Hz), 123.3 (q, J_{C-F} = 270.0 Hz), 110.2, 85.6, 56.6; IR (film) 3014, 2971, 2947, 2845, 1605, 1499, 1463, 1399, 1323, 1270, 1121, 1081, 1044, 896, 816, 666 cm^{-1}; HRMS (APPI) Calcd for $C_8H_6F_3IO$ $(M)^+$, 301.9410; found, 301.9407.



27

1-Methoxy-2-((2-(methoxymethoxy)-5-(trifluoromethyl)-phenyl)ethynyl)-4-(trifluoromethyl)benzene (27). Compound **15** (191 mg, 0.63 mmol) was dissolved in 1.5 mL of Et_3N in a sealable tube fitted with a septum, at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol), CuI (8 mg, 0.042 mmol), and a solution of alkyne **12** (97 mg, 0.42 mmol) in 1.5 mL of Et_3N were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 70 °C, and stirred at this temperature for 16 h. After cooling down to room temperature, the reaction mixture was quenched with a 1:1 brine−H_2O mixture and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown oil. Flash column chromatography (10% to 20% EtOAc in hexanes), followed by recrystallization from heptane, gave **27** (114 mg, 67%) as white crystals. mp 88−89 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 8.5, 2.0 Hz, 1H), 7.54 (dd, J = 8.5, 2.0 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 5.35 (s, 2H), 3.97 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 160.0, 130.8−130.6 (m, 2C), 127.1 (q, J_{C-F} = 3.8 Hz), 126.8 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 33.8 Hz), 122.9 (q, J_{C-F} = 33.8 Hz), 114.8, 114.0, 112.9, 110.6, 94.9, 89.42, 89.37, 56.5, 56.2; IR (film) 2958, 1613, 1509, 1340, 1331, 1267, 1121, 981, 820 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{14}F_6NaO_3$ $(M + Na)^+$, 427.0739; found, 427.0736.

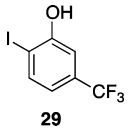
2-((2-Methoxy-5-(trifluoromethyl)phenyl)ethynyl)-4-(trifluoromethyl)phenol (7). To a solution of **27** (80 mg, 0.20 mmol) in 2 mL of MeOH and 2 mL of CH_2Cl_2 was added 0.3 mL of concentrated HCl. The reaction mixture was stirred at room temperature, under air for 20 h. It was then quenched with water, and the aqueous phase was extracted once with CH_2Cl_2 and twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexanes 1:4) gave **7** (67 mg, 94%) as a white solid. mp 85−86 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 2.0 Hz, 1H), 7.66 (s, 1H), 7.61 (dd, J = 8.5, 2.0 Hz, 1H), 7.52 (dd, J = 8.5, 2.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 7.07 (s, 1H), 7.02 (d, J = 9.0 Hz, 1H), 4.03 (s, 3H); ^1H NMR (500 MHz, CD_3OD)[42] δ 7.80 (d, J = 2.0 Hz, 1H), 7.66−7.64 (m, 2H), 7.50 (dd, J = 8.5, 2.0 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 159.8, 128.8 (q, J_{C-F} = 3.8 Hz), 127.7 (q, J_{C-F} = 3.8 Hz), 127.6−127.4 (m, 2C), 123.5 (q, J_{C-F} = 33.8 Hz), 122.8 (q, J_{C-F} = 33.8 Hz), 115.0, 112.0, 110.4, 109.8, 93.0, 86.6, 56.4; IR (film) 3416 (br), 1612, 1504, 1456, 1330, 1267, 1118, 1023, 930, 818 cm^{-1}; HRMS (APPI) Calcd for $C_{17}H_{10}F_6O_2$ $(M)^+$, 360.0580; found, 360.0574.



28

1,4-Bis(2-(methoxymethoxy)-5-(trifluoromethyl)phenyl)-buta-1,3-diyne (28). The following procedure was adapted from the work of Wuest and co-workers.[15b] To a suspension of CuCl (116 mg, 1.17 mmol) in 2.0 mL of anhydrous acetone was added TMEDA (65 μL, 0.43 mmol), and the resulting mixture was stirred at room temperature, under nitrogen for 1 h. In a separate flask, alkyne **12** (100 mg, 0.43 mmol) was dissolved in 4.0 mL of anhydrous acetone under an atmosphere of oxygen. The CuCl suspension was filtered, and the filtrate was added onto the alkyne solution. The resulting mixture was heated to 60 °C and stirred under oxygen for 45 min. The reaction mixture was then cooled to room temperature and quenched with H_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexanes 1:9 to 1:4) gave **28** (86 mg, 86%) as a white solid. mp 104−105 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 1.5 Hz, 2H), 7.55 (dd, J = 9.0, 1.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 5.32 (s, 4H), 3.54 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 131.5 (q, J_{C-F} = 3.8 Hz), 127.6 (q, J_{C-F} = 2.5 Hz), 124.1 (q, J_{C-F} = 33.8 Hz), 123.6 (q, J_{C-F} = 270.0 Hz), 114.6, 112.6, 94.7, 78.5, 77.5, 56.5; IR (film) 3009, 2977, 1611, 1503, 1320, 1272, 1251, 1158, 1132, 1080, 923, 887 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{16}F_6NaO_4$ $(M + Na)^+$, 481.0845; found, 481.0842.

2,2′-(Buta-1,3-diyne-1,4-diyl)bis(4-(trifluoromethyl)phenol) (8). Compound **28** (44 mg, 0.095 mmol) was dissolved in 2 mL of MeOH and 1 mL of CH_2Cl_2, and the resulting clear solution was treated with 0.2 mL of concentrated HCl. The reaction mixture was stirred at room temperature, under air for 24 h, at which time additional concentrated HCl solution (0.1 mL) was added. At the end of 31 h, it was quenched with water and the aqueous phase was extracted once with CH_2Cl_2 and twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexanes 1:2) gave **8** (35 mg, 98%) as a white solid. mp 139−141 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 1.0 Hz, 2H), 7.56 (dd, J = 8.5, 2.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 6.08 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 130.4 (q, J_{C-F} = 3.8 Hz), 128.8 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 270.0 Hz), 123.5 (q, J_{C-F} = 33.8 Hz), 115.9, 108.3, 80.3, 76.7; IR (film) 3321 (br), 1614, 1501, 1333, 1280, 1162, 1126, 1075, 902 cm^{-1}; HRMS (APPI) Calcd for $C_{18}H_8F_6O_2$ $(M)^+$, 370.0423; found, 370.0420.



29

2-Iodo-5-(trifluoromethyl)phenol (29). To a solution of 3-(trifluoromethyl)phenol (**20**) (1.22 g, 7.55 mmol) in 8 mL of THF were added H_2O (8 mL), $Na_2CO_3·H_2O$ (1.12 g, 9.0 mmol), and I_2 (2.3 g, 9.06 mmol) sequentially. The resulting brown mixture was stirred for 2 days at room temperature, covered with an aluminum foil. The mixture was then quenched with a 1:1 mixture of saturated $Na_2S_2O_3$ and NH_4Cl solutions, and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a light yellow oil. Purification by flash column chromatography (EtOAc/hexanes 1:7)

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

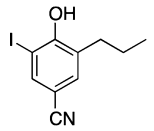
gave **29** (640 mg, 29%) as a white solid. mp 48−49 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.5, 0.5 Hz, 1H), 7.23 (d, J = 1.5 Hz, 1H), 6.94 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H), 5.48 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 138.9, 132.8 (q, J_{C-F} = 33.8 Hz), 123.4 (q, J_{C-F} = 271.3 Hz), 118.8 (q, J_{C-F} = 3.8 Hz), 112.0 (q, J_{C-F} = 3.8 Hz), 89.8; IR (film) 3483 (br), 1436, 1418, 1333, 1277, 1172, 1128, 1074, 913 cm^{-1}; HRMS (ESI) Calcd for $C_7H_3F_3IO$ $(M - H)^-$, 286.9186; found, 286.9190.

1-Iodo-2-(methoxymethoxy)-4-(trifluoromethyl)benzene (16). To a solution of **29** (458 mg, 1.59 mmol) in 10 mL of anhydrous CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (554 μL, 3.18 mmol) and MOMCl (181 μL, 2.38 mmol) sequentially at room temperature, under nitrogen. The resulting clear solution was stirred for 17 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic extracts were dried over over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. Purification by flash column chromatography (3% EtOAc in hexanes) gave **16** (398 mg, 75%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.5 Hz, 1H), 7.29 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 5.28 (s, 2H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 140.0, 132.0 (q, J_{C-F} = 32.5 Hz), 123.6 (q, J_{C-F} = 270.0 Hz), 120.0 (q, J_{C-F} = 3.8 Hz), 111.2 (q, J_{C-F} = 3.8 Hz), 95.1, 91.5, 56.6; IR (film) 2960, 2913, 2834, 1596, 1581, 1481, 1427, 1388, 1328, 1159, 1132, 1082, 987, 923, 880, 818, 740 cm^{-1}; HRMS (ESI) Calcd for $C_9H_8F_3IO_2Na$ $(M + Na)^+$, 354.9413; found, 354.9413.

1-Ethynyl-2-(methoxymethoxy)-4-(trifluoromethyl)benzene (17). Compound **16** (222 mg, 0.67 mmol) was dissolved in 2.5 mL of Et_3N in a sealable tube fitted with a septum, at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (28 mg, 0.040 mmol), CuI (13 mg, 0.067 mmol), and ethynyltrimethylsilane (278 μL, 2.0 mmol) were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 80 °C, and stirred at this temperature for 20 h. After cooling down to room temperature, the reaction mixture was quenched with a 1:1 brine−H_2O mixture and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford a brown oil. This crude oil was dissolved in 5 mL of anhydrous THF under nitrogen and cooled to 0 °C. TBAF (1.0 M solution in THF, 1.34 mL, 1.34 mmol) was added slowly, and the reaction mixture was stirred for 30 min. The mixture was then quenched with H_2O and diluted with Et_2O. The two phases were partitioned in a separatory funnel, and the organic phase was washed once with brine, dried over $MgSO_4$, filtered, and concentrated to afford a brown oil. Purification by flash column chromatography (4% EtOAc in hexanes) gave **17** (99 mg, 64% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.30 (s, 2H), 3.53 (s, 3H), 3.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 134.4, 131.8 (q, J_{C-F} = 32.5 Hz), 123.5 (q, J_{C-F} = 271.3 Hz), 118.4 (q, J_{C-F} = 3.8 Hz), 116.2, 111.8 (q, J_{C-F} = 3.8 Hz), 95.0, 83.2, 78.7, 56.4; IR (film) 3296, 2963, 2916, 2832, 2113, 1614, 1575, 1505, 1431, 1393, 1328, 1238, 1158, 1121, 1085, 990, 830, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{10}F_3O_2$ $(M + H)^+$, 231.0627; found, 231.0626.

1,2-Bis[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-ethyne (18). Compound **16** (138 mg, 0.42 mmol) was dissolved in 1.0 mL of Et_3N in a sealable tube fitted with a septum at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol), CuI (5.5 mg, 0.029 mmol), and a solution of alkyne **17** (67 mg, 0.29 mmol) in 1.0 mL of Et_3N were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 70 °C, and stirred at this temperature for 21 h. After cooling down to room temperature, the reaction mixture was quenched with a 1:1 brine−H_2O mixture and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown solid. Purification by flash column chromatography (5−10% EtOAc in hexanes) gave **18** (125 mg, 99%) as a white solid. mp 88−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.40 (s, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.33 (s, 4H), 3.56 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 133.8, 131.7 (q, J_{C-F} = 32.5 Hz), 123.6 (q, J_{C-F} = 271.3 Hz), 118.5 (q, J_{C-F} = 3.8 Hz), 117.3, 112.2 (q, J_{C-F} = 3.8 Hz), 95.2, 90.4, 56.5; IR (film) 3080, 2965, 2916, 2832, 1614, 1574, 1519, 1431, 1328, 1229, 1160, 1125, 1080, 981, 912, 825, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{16}F_6NaO_4$ $(M + Na)^+$, 457.0845; Found, 457.0844.

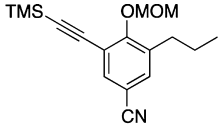
6,6′-(Ethyne-1,2-diyl)bis[3-(trifluoromethyl)phenol] (9). Compound **18** (75 mg, 0.17 mmol) was dissolved in 2 mL of MeOH and 1 mL of CH_2Cl_2, and the resulting clear solution was treated with 0.2 mL of concentrated HCl. The reaction mixture was stirred at room temperature, under air for 8.5 h. It was then quenched with water, and the aqueous phase was extracted once with CH_2Cl_2 and twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a white solid. Purification by flash column chromatography (1% MeOH in $CHCl_3$) gave **9** (39 mg, 66%) as a white solid. mp 131 °C (decomp.); ^{1}H NMR (500 MHz, CD_3CN) δ 7.83 (br s, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.21−7.19 (m, 4H); ^{13}C NMR (125 MHz, CD_3CN) δ 159.2, 134.4, 132.8 (q, J_{C-F} = 32.5 Hz), 125.2 (q, J_{C-F} = 270.0 Hz), 118.0 (q, J_{C-F} = 3.8 Hz), 115.0, 113.5 (q, J_{C-F} = 3.8 Hz), 92.1; IR (film) 3356, 1446, 1424, 1326, 1279, 1169, 1114, 1068, 926, 747 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_7F_6O_2$ $(M - H)^-$, 345.0356; found, 345.0363.



30

4-Hydroxy-3-iodo-5-propylbenzonitrile (30). Iodination of **22**[27] (581 mg, 3.60 mmol) was performed following the same procedure used for the iodination of **20**. Purification by flash column chromatography (EtOAc/hexanes 1:9 to 1:4) gave 4-hydroxy-3-iodo-5-propylbenzonitrile (**30**) (855 mg, 83%) as a white solid. mp 83−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 5.79 (s, 1H), 2.65 (t, J = 7.5 Hz, 2H), 1.63 (sext, 7.5 Hz, 2H), 0.96 (t, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 139.5, 134.3, 130.4, 117.6, 105.7, 86.0, 32.8, 22.2, 13.8; IR (film) 3346 (br), 2959, 2929, 2872, 2231, 1592, 1453, 1316, 1281, 1244, 1210, 1152, 1109, 734 cm^{-1}; HRMS (ESI) Calcd for $C_{10}H_9INO$ $(M - H)^-$, 285.9734; found, 285.9733.

3-Iodo-4-(methoxymethoxy)-5-propylbenzonitrile (23). To a solution of **30** (821 mg, 2.86 mmol) in 10 mL of anhydrous CH_2Cl_2 was added *N*,*N*-diisopropylethylamine (996 μL, 5.72 mmol), and the reaction mixture was cooled to 0 °C. MOMCl (326 μL, 4.29 mmol) was added slowly, the ice bath was removed, and the resulting clear solution was stirred at room temperature overnight. It was then quenched with saturated $NaHCO_3$ solution, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. Purification by flash column chromatography (EtOAc/hexanes 1:19 to 1:9) gave **23** (883 mg, 93%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 1.5 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 5.10 (s, 2H), 3.66 (s, 3H), 2.70 (t, J = 8.0 Hz, 2H), 1.63 (sext, 7.5 Hz, 2H), 0.98 (t, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 140.6, 138.7, 134.1, 117.1, 109.9, 100.5, 92.8, 57.9, 32.7, 23.1, 13.9; IR (film) 2960, 2932, 2872, 2231, 1546, 1453, 1435, 1398, 1261, 1232, 1160, 1127, 1079, 930 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{15}INO_2$ $(M + H)^+$, 332.0142; found, 332.0145.



31

4-(Methoxymethoxy)-3-propyl-5-[(trimethylsilyl)ethynyl]-benzonitrile (31). Compound **23** (377 mg, 1.14 mmol) was

dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353

dissolved in 3.0 mL of Et_3N in a sealable tube fitted with a septum at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (48 mg, 0.068 mmol), CuI (22 mg, 0.11 mmol), and ethynyltrimethylsilane (473 μL, 3.42 mmol) were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 70 °C, and stirred at this temperature for 36 h. After cooling down to room temperature, the reaction mixture was quenched with a 1:1 brine−H_2O mixture and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexanes 1:19) gave **31** (312 mg, 91%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 5.33 (s, 2H), 3.59 (s, 3H), 2.65 (t, J = 8.0 Hz, 2H), 1.63 (sext, 7.5 Hz, 2H), 0.96 (t, 7.5 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 137.8, 135.7, 133.7, 118.2, 117.6, 107.4, 101.2, 99.6, 99.5, 57.7, 32.0, 23.0, 13.9, −0.4; IR (film) 2961, 2229, 2159, 1456, 1251, 1160, 1076, 943, 846, 761 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{23}NO_2SiNa$ $(M + Na)^+$, 324.1390; found, 324.1387.

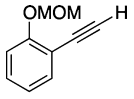
3-Ethynyl-4-(methoxymethoxy)-5-propylbenzonitrile (24). Compound **31** (304 mg, 1.01 mmol) was dissolved in 10 mL of anhydrous THF under nitrogen and cooled to 0 °C. TBAF (1.0 M solution in THF, 1.5 mL, 1.5 mmol) was added slowly, and the reaction mixture was stirred for 15 min. The mixture was then quenched with H_2O and diluted with Et_2O. The two phases were partitioned in a separatory funnel, and the organic phase was washed once with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford **24** (230 mg, quant.) as a brown oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 5.33 (s, 2H), 3.59 (s, 3H), 3.35 (s, 1H), 2.66 (t, J = 7.5 Hz, 2H), 1.64 (sext, 7.5 Hz, 2H), 0.97 (t, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 138.0, 135.9, 134.1, 118.0, 116.7, 107.6, 99.7, 83.2, 78.7, 57.7, 32.0, 23.0, 13.9; IR (film) 3289, 2962, 2934, 2873, 2230, 1593, 1456, 1437, 1398, 1232, 1198, 1160, 1076, 941 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$, 230.1176; found, 230.1177.

5,5′-(Ethyne-1,2-diyl)bis[4-(methoxymethoxy)-3-propylbenzonitrile] (25). Compound **23** (156 mg, 0.47 mmol) was dissolved in 1.0 mL of Et_3N in a sealable tube fitted with a septum at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol), CuI (9 mg, 0.047 mmol), and a solution of alkyne **24** (130 mg, 0.57 mmol) in 2.0 mL of Et_3N were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The tube was sealed by the replacement of the septum with the screw cap, heated to 70 °C, and stirred at this temperature for 19 h. After cooling down to room temperature, the reaction mixture was quenched with brine and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography (EtOAc/hexanes 1:4) gave **25** (189 mg, 93%) as a yellowish white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 2.0 Hz, 2H), 7.49 (d, J = 1.5 Hz, 2H), 5.37 (s, 4H), 3.61 (s, 6H), 2.70 (t, J = 7.5 Hz, 4H), 1.66 (sext, 7.5 Hz, 4H), 1.00 (t, 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 138.2, 135.1, 134.2, 118.0, 117.1, 107.8, 99.8, 89.9, 57.8, 32.0, 23.0, 13.9; IR (film) 2959, 2931, 2872, 2827, 2226, 1456, 1441, 1198, 1158, 1074, 937 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{32}N_3O_4$ $(M + NH_4)^+$, 450.2387; found, 450.2394.

2-(5-Cyano-2-hydroxy-3-propylphenyl)-7-propylbenzofuran-5-carbonitrile (26). To a solution of **25** (21 mg, 0.05 mmol) in 2.0 mL of anhydrous CH_2Cl_2 at −78 °C was added BBr_3 (1.0 M solution in CH_2Cl_2, 242 μL, 0.242 mmol) slowly, and the resulting solution was stirred at −78 °C for 45 min. It was then quenched with half-saturated $NaHCO_3$ solution at −78 °C and allowed to warm to room temperature, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a pale yellow solid. ^{1}H NMR of the crude product indicated a mixture of **21** and **26** in a 1:2 ratio. After the solvent was evaporated and the sample was kept at room temperature for 3 h, both TLC and ^{1}H NMR showed that it completely converted to **26**. Purification by flash column chromatography (EtOAc/hexanes 1:4) gave **26** as a white solid. mp 207−208 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 2.0 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.44 (s, 1H), 7.24 (s, 1H), 7.18 (br s, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H), 1.84 (sext, 7.5 Hz, 2H), 1.72 (sext, 7.5 Hz, 2H), 1.06−1.02 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 154.6, 153.6, 134.1, 131.6, 129.7, 128.53, 128.47, 127.6, 123.9, 119.3, 118.7, 116.5, 107.8, 105.3, 104.6, 31.7, 31.4, 22.7, 22.2, 13.9; IR (film) 3345, 2960, 2927, 2870, 2227, 1606, 1466, 1261, 1186, 1153, 1093, 1019 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{20}N_2NaO_2$ $(M + Na)^+$, 367.1417; found, 367.1414.

32

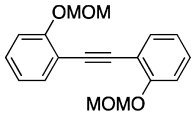
1-Iodo-2-(methoxymethoxy)benzene (32). To a solution of 2-iodophenol (2.00 g, 9.09 mmol) in 10 mL of anhydrous CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (3.2 mL, 18.2 mmol) and MOMCl (1.0 mL, 13.6 mmol) sequentially at 0 °C, under nitrogen. The ice bath was removed, and the resulting clear solution was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. Purification by flash column chromatography (EtOAc/hexanes 1:9) gave **32** (2.36 g, 98%) as a colorless oil. The analytical data are in accordance with the literature:[43] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.5, 1.5 Hz, 1H), 7.26 (dt, J = 8.5, 1.5 Hz, 1H), 7.05 (dd, J = 8.5, 1.5 Hz, 1H), 6.74 (dt, J = 7.5, 1.0 Hz, 1H), 5.22 (s, 2H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 139.4, 129.3, 123.6, 114.8, 94.8, 87.1, 56.3; IR (film) 2955, 2825, 1583, 1472, 1235, 1154, 1083, 751 cm^{-1}.



33

1-Ethynyl-2-(methoxymethoxy)benzene (33). Compound **32** (519 mg, 1.97 mmol) was dissolved in 3.0 mL of Et_3N in a round-bottom flask at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (83 mg, 0.12 mmol), CuI (38 mg, 0.2 mmol), and ethynyltrimethylsilane (0.41 mL, 2.95 mmol) were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The reaction mixture was stirred at room temperature for 22 h, then quenched with a 1:1 brine−H_2O mixture, and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown oil. To a solution of the crude product in 10 mL of anhydrous THF was added TBAF (1.0 M solution in THF, 2.96 mL, 2.96 mmol) slowly at room temperature, under nitrogen, and the reaction mixture was stirred for 45 min. The mixture was then quenched with 10 mL of H_2O and diluted with 50 mL of Et_2O. The two phases were partitioned in a separatory funnel, and the organic phase was washed once with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an oil. Purification by flash column chromatography (EtOAc/hexanes 1:19) gave **33** (240 mg, 75% over 2 steps) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.5, 1.5 Hz, 1H), 7.29 (dt, J = 7.5, 1.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.96 (dt, J = 7.5, 1.0 Hz, 1H), 5.27 (s, 2H), 3.52 (s, 3H), 3.29 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 134.1, 130.1, 121.7, 114.9, 112.4, 94.8, 81.0, 80.0, 56.2; IR (film) 3282, 2958, 2107, 1597, 1574, 1488, 1450, 1238, 1154, 991, 922, 756 cm^{-1}; HRMS (ESI) Calcd for $C_{10}H_{11}O_2$ $(M + H)^+$, 163.0754; found, 163.0754.

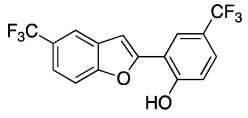
dx.doi.org/10.1021/jo400926n | J. Org. Chem. 2013, 78, 8340−8353



34

1,2-Bis(2-(methoxymethoxy)phenyl)ethyne (34). Compound **32** (206 mg, 0.78 mmol) was dissolved in 2.0 mL of Et_3N in a round-bottom flask at room temperature, under nitrogen. $PdCl_2(PPh_3)_2$ (30 mg, 0.043 mmol), CuI (14 mg, 0.074 mmol), and a solution of alkyne **33** (115 mg, 0.71 mmol) in 1.0 mL of Et_3N were added sequentially, and the system was briefly evacuated and filled with nitrogen three times after each addition. The reaction mixture was stirred at room temperature for 5 h and quenched with a 1:1 brine−H_2O mixture. The aqueous layer was extracted three times with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown solid. Purification by flash column chromatography (5−10% EtOAc in hexanes) gave **34** (197 mg, 93%) as a yellow solid. mp 49−50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.5, 1.0 Hz, 2H), 7.26 (dt, J = 7.5, 1.0 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.99 (t, J = 7.5 Hz, 2H), 5.28 (s, 4H), 3.53 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 133.4, 129.5, 121.9, 115.6, 114.3, 95.1, 89.6, 56.2; IR (film) 2955, 2825, 1497, 1482, 1274, 1232, 1151, 1078, 988 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{22}NO_4$ $(M + NH_4)^+$, 316.1543; found, 316.1548.

2,2′-(Ethyne-1,2-diyl)diphenol (4). Compound **34** (76 mg, 0.25 mmol) was dissolved in 2 mL of MeOH and 1 mL of CH_2Cl_2, and the resulting clear solution was treated with 0.3 mL of concentrated HCl. The reaction mixture was stirred at room temperature, under air for 2 h, and then quenched with water. The aqueous phase was extracted once with CH_2Cl_2 and twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a white solid with a slight brown color. Purification by flash column chromatography (EtOAc/hexanes 1:9 to 1:6) gave **4** (39 mg, 73%) as a white solid. mp 122−124 °C (decomp); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 7.5, 1.5 Hz, 2H), 7.28 (dt, J = 7.5, 1.5 Hz, 2H), 6.98 (dd, J = 8.5, 1.0 Hz, 2H), 6.93 (dt, J = 7.5, 1.0 Hz, 2H), 6.13 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 131.4, 130.8, 120.6, 114.9, 109.3, 90.4; IR (film) 3321 (br), 1584, 1484, 1452, 1365, 1235, 827 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{11}O_2$ $(M + H)^+$, 211.0754; found, 211.0758.



35

4-(Trifluoromethyl)-2-(5-(trifluoromethyl)benzofuran-2-yl)-phenol (35). Isolated from the spontaneous conversion of diol **5** as a white solid: mp 107−108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 1.5 Hz, 1H), 7.92 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 8.5, 1.5 Hz, 1H), 7.54 (dd, J = 8.5, 1.5 Hz, 1H), 7.32 (d, J = 1.0 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 155.3, 153.8, 128.7, 127.3 (q, J_{C-F} = 3.8 Hz), 126.3 (q, J_{C-F} = 32.5 Hz), 124.8 (q, J_{C-F} = 3.8 Hz), 123.7 (q, J_{C-F} = 32.5 Hz), 122.1 (q, J_{C-F} = 3.8 Hz), 119.0 (q, J_{C-F} = 3.8 Hz), 117.6, 116.3, 111.5, 105.4; IR (film) 3514, 1598, 1502, 1449, 1332, 1276, 1250, 1222,, 1161, 1108, 1075, 891, 827, 816, 802 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_7F_6O_2$ $(M - H)^-$, 345.0356; Found, 345.0362.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of the catalytic and computational studies, X-ray crystallographic data for **5**, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vrawal@uchicago.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by National Institutes of Health (R01GM069990). We thank Dr. Ian Steele (University of Chicago) for obtaining the crystal structure of **5**.

■ REFERENCES

(1) For reviews, see: (a) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406−2447. (b) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1−26. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638−4660. (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304−308. (e) Dalko, P. I., Ed. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (f) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (g) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575−2600. (h) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8−27. (i) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

(2) Reviews: (a) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, 1−22. (b) Terada, M. *Synthesis* **2010**, 1929−1982. (c) Pihko, P. M., Ed. *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH: Weinheim, 2009. (d) Terada, M. *Chem. Commun.* **2008**, 4097−4112. (e) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516−532. (f) Connon, S. J. *Chem. Commun.* **2008**, 2499−2510. (g) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713−5743. (h) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759−5812. (i) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744−5758. (j) McGilvra, J. D.; Gondi, V. B.; Rawal, V. H. Asymmetric Proton Catalysis. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; pp 189−254. (k) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418−5427. (l) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (m) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942. (n) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296.

(3) (a) Bhadury, P. S.; Song, B. A.; Yang, S.; Hu, D. Y.; Xue, W. *Curr. Org. Synth.* **2009**, *6*, 380−399. (b) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593−601. (c) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785−795. (d) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306.

(4) (a) Wassermann, A. *J. Chem. Soc.* **1942**, 618−621. (b) Rubin, W.; Steiner, H.; Wassermann, A. *J. Chem. Soc.* **1949**, 3046−3057.

(5) (a) Hine, J.; Ahn, K.; Gallucci, J. C.; Linden, S.-M. *J. Am. Chem. Soc.* **1984**, *106*, 7980−7981. (b) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 1082−1083. (c) Hine, J.; Hahn, S.; Miles, D. E.; Ahn, K. *J. Org. Chem.* **1985**, *50*, 5092−5096. (d) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Org. Chem.* **1985**, *50*, 5096−5099. (e) Hine, J.; Hahn, S.; Miles, D. E. *J. Org. Chem.* **1986**, *51*, 577−584. (f) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2083−2086. (g) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2089−2091.

(6) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381−3384.

(7) (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846−5850. (c) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336−1337. (d) Du, H.; Zhao, D.; Ding, K. *Chem.—Eur. J.* **2004**, *10*, 5964−5970. (e) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080−1081. (f) Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 7754−7755. (g) Beemelmanns, C.; Husmann, R.; Whelligan, D. K.; Özçubukçu, S.; Bolm, C. *Eur. J.*

Org. Chem. **2012**, 3373−3376. (h) Imahori, T.; Yamaguchi, R.; Kurihara, S. *Chem.—Eur. J.* **2012**, *18*, 10802−10807.
(8) (a) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (b) Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* **2007**, *129*, 14112−14113. (c) Leow, D.; Tan, C.−H. *Chem.—Asian J.* **2009**, *4*, 488−507. (d) Terada, M. *J. Synth. Org. Chem., Jpn.* **2010**, *68*, 1159−1168.
(9) (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417. (b) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153−156. (c) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028−2031. (d) Cheon, C. H.; Yamamoto, H. *Tetrahedron Lett.* **2009**, *50*, 3555−3558. Review: (e) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330−2346.
(10) For selected examples, inter alia, see: (a) Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179−181. (b) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418−3419. (c) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054−10055. (d) Muñiz, F. M.; Montero, V. A.; de Arriba, A. L. F.; Simón, L.; Raposo, C.; Morán, J. R. *Tetrahedron Lett.* **2008**, *49*, 5050−5052. (e) Coulembier, O.; Sanders, D. P.; Nelson, A.; Hollenbeck, A. N.; Horn, H. W.; Rice, J. E.; Fujiwara, M.; Dubois, P.; Hedrick, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5170−5173. (f) Rodriguez, A. A.; Yoo, H.; Ziller, J. W.; Shea, K. J. *Tetrahedron Lett.* **2009**, *50*, 6830−6833. (g) McGarraugh, P. G.; Brenner, S. E. *Tetrahedron* **2009**, *65*, 449−455. (h) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120−123. (i) Annamalai, V. R.; Linton, E. C.; Kozlowski, M. C. *Org. Lett.* **2009**, *11*, 621−624. (j) Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. *J. Am. Chem. Soc.* **2010**, *132*, 4536−4537. (k) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307−1309. (l) Huynh, P. N. H.; Walvoord, R. R.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 15621−15623.
(11) The pK_a of a catalyst has been shown to correlate with its catalytic activity: (a) Li, G.-L.; Zhao, G. *J. Org. Chem.* **2005**, *70*, 4272−4278. (b) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748−4750. (c) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194−7201. (d) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2010**, *16*, 450−455.
(12) (a) Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *Synlett* **2003**, 1121−1124. (b) Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *Adv. Synth. Catal.* **2004**, *346*, 1117−1130. (c) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094−12095. (d) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680−3681. (e) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175−3178. (f) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190−1195.
(13) Saied, O.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1998**, *63*, 3756−3757.
(14) The complex formation between several bisphenolic compounds and formaldehyde was evaluated computationally. Please see the Supporting Information for some of the diols that were investigated.
(15) (a) Saied, O.; Simard, M.; Wuest, J. D. *Organometallics* **1996**, *15*, 2345−2349. (b) Saied, O.; Simard, M.; Wuest, J. D. *Organometallics* **1998**, *17*, 1128−1133.
(16) For use of achiral thioureas in this reaction, see: Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407−414.
(17) The reactions were performed using equimolar amounts of cyclopentadiene and MVK, and second-order rate constants were calculated for both catalyzed and uncatalyzed reactions. See the Supporting Information for details.
(18) Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339−4346.
(19) Marzi, E.; Mongin, F.; Spitaleri, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2911−2915.
(20) (a) Morice, C.; Domostoj, M.; Briner, K.; Mann, A.; Suffert, J.; Wermuth, C.-G. *Tetrahedron Lett.* **2001**, *42*, 6499−6502. (b) Selliah, R.; Dantanarayana, A.; Haggard, K.; Egan, J.; Do, E. U.; May, J. A. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 173−183.
(21) When the reactions were carried out at −40 °C, there was no background reaction detectable by ^{1}H NMR, and therefore, k_{back} could not be determined at this temperature.
(22) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424−1427.
(23) A concentration of 0.06 M was chosen to make sure that all solutions were homogeneous.
(24) (a) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: New York, 1999; pp 164−185. (b) Prey, V.; Berbalk, H. *Monatsh. Chem.* **1951**, *82*, 990−1007. (c) Visser, T.; van der Maas, J. H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1649−1652. (d) Korth, H.-G.; de Heer, M. I.; Mulder, P. *J. Phys. Chem. A* **2002**, *106*, 8779−8789.
(25) Hunter, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5310−5324.
(26) See the Supporting Information for details.
(27) Rudolph, J.; Chen, L.; Majumdar, D.; Bullock, W. H.; Burns, M.; Claus, T.; Dela Cruz, F. E.; Daly, M.; Ehrgott, F. J.; Johnson, J. S.; Livingston, J. N.; Schoenleber, R. W.; Shapiro, J.; Yang, L.; Tsutsumi, M.; Ma, X. *J. Med. Chem.* **2007**, *50*, 984−1000.
(28) Crisp, G. T.; Bubner, T. P. *Tetrahedron* **1997**, *53*, 11881−11898.
(29) A benzofuran derivative similar to **26** without the propyl groups was prepared by the direct Sonogashira coupling of the corresponding unprotected phenol: Bakunov, S. A.; Bakunova, S. M.; Wenzler, T.; Barszcz, T.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. *J. Med. Chem.* **2008**, *51*, 6927−6944.
(30) (a) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071−4078. (b) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. (c) Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594−1595. (d) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365−2368. (e) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727−4729. (f) Novák, Z.; Timári, G.; Kotschy, A. *Tetrahedron* **2003**, *59*, 7509−7513. (g) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235−2239. (h) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214−4226. (i) Russo, O.; Messaoudi, S.; Hamze, A.; Olivi, N.; Peyrat, J.-F.; Brion, J.-D.; Sicsic, S.; Berque-Bestel, I.; Alami, M. *Tetrahedron* **2007**, *63*, 10671−10683. (j) Csékei, M.; Novák, Z.; Kotschy, A. *Tetrahedron* **2008**, *64*, 8992−8996. (k) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329−1331.
(31) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432−1434. (b) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409−2412. (c) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292−10296. (d) Okitsu, T.; Nakazawa, D.; Taniguchi, R.; Wada, A. *Org. Lett.* **2008**, *10*, 4967−4970.
(32) Jacubert, M.; Hamze, A.; Provot, O.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 3588−3592.
(33) Damera, K.; Ke, B.; Wang, K.; Dai, C.; Wang, L.; Wang, B. *RSC Adv.* **2012**, *2*, 9403−9405.
(34) Wuest and co-workers also reported the complete formation of the corresponding benzo[*b*]furan derivative during their studies to prepare diol **1** from its diacetate precursor under conventional deprotection methods (ref 15a).
(35) The full characterization of the benzo[*b*]furan obtained from diol **5** is given in the Experimental Section.
(36) Arcadi and co-workers reported a similar spontaneous cyclization of 2-phenylethynyl-pyridin-3-ol upon storage (ref 31b).
(37) Whether the proton transfer is intra- or intermolecular is unclear at the moment.
(38) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120−126. (b) Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1555−1573.
(39) (a) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: New York, 1999; pp 205−215. (b) Thalladi, V. R.; Weiss, H.-C.; Bläser, D.; Boese, R.; Nangia, A.; Desiraju, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 8702−8710. (c) D'Oria, E.; Novoa, J. J. *CrystEngComm* **2008**, *10*, 423−436.

(40) Laali, K. K.; Koser, G. F.; Subramanyam, S.; Forsyth, D. A. *J. Org. Chem.* **1993**, *58*, 1385−1392.
(41) For the preparation of **15** by a different method, see: Ali, A.; Napolitano, J. M.; Deng, Q.; Lu, Z.; Sinclair, P. J.; Taylor, G. E.; Thompson, C. F.; Quraishi, N.; Smith, C. J.; Hunt, J. A.; Dowst, A. A.; Chen, Y.-H.; Li, H. PCT Int. Appl. WO2006014413, 2006.
(42) ^{1}H NMR spectrum of **7** was recorded in CD_3OD in addition to $CDCl_3$ to prove the existence of the −OH group.
(43) Okitsu, T.; Nakazawa, D.; Taniguchi, R.; Wada, A. *Org. Lett.* **2008**, *10*, 4967−4970.