JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

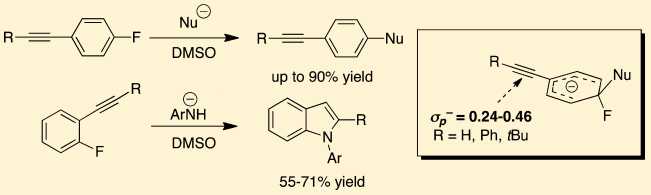
An Alternative Role for Acetylenes: Activation of Fluorobenzenes toward Nucleophilic Aromatic Substitution

Nicholas P. Bizier, Jay Wm. Wackerly, Eric D. Braunstein, Mengfei Zhang, Stephen T. Nodder, Stephen M. Carlin, and Jeffrey L. Katz*

Department of Chemistry, Colby College, 5754 Mayflower Hill Drive, Waterville, Maine 04901, United States

Supporting Information

ABSTRACT: Acetylenes are increasingly versatile functional groups for a range of complexity-building organic transformations and for the construction of desirable molecular architectures. Herein we disclose a previously underappreciated aspect of arylacetylene reactivity by utilizing alkynes as electron-withdrawing groups (EWG) for promoting nucleophilic aromatic substitution (S_NAr) reactions. Reaction rates for the substitution of 4-(fluoroethynyl)benzenes by *p*-cresol were determined by ^1H NMR spectroscopy, and these rate data were used to determine substituent (Hammett) constants for terminal and substituted ethynyl groups. The synthetic scope of acetylene-activated S_NAr reactions is broad; fluoroarenes bearing one or two ethynyl groups undergo high-yielding substitution with a variety of oxygen and arylamine nucleophiles.



INTRODUCTION

Acetylenes have emerged as increasingly important and powerful functional groups in synthetic design and small molecule and materials applications.[1] The prevalence of acetylenes in modern research efforts is evident from the number of recent comprehensive treatises on the subject of their use.[2] Access to complex acetylene-containing systems has been enabled by recent synthetic advances, most notably the palladium-catalyzed cross coupling of terminal alkynes and aryl halides as described by Sonogashira, Tohda, and Hagihara in 1975.[3] The generality and efficiency of this Sonogashira coupling method, and more modern variants,[4] for the synthesis of arylacetylenes has spawned the rapid development of chemical, materials, and biological applications. Along with methods for their synthesis, the accessibility of acetylenic precursors has facilitated a parallel resurgence in reaction development using alkynyl groups.[5−7]

The considerable research efforts devoted to the synthesis and applications of acetylenes mask that a fundamental aspect of acetylene chemistry remains underexplored. While both experiment and theory predict that sp-hybridized carbon atoms are significantly more electronegative than higher-valence carbon bonding motifs,[8] questions remain regarding the electronic nature of the acetylene moiety. An electron-withdrawing polarization for acetylenes was reported nearly a century ago by Baker, Cooper, and Ingold after analyzing the product mixtures from nitration reactions of phenylpropiolic acids and esters.[9] The substituent constants for the ethynyl and phenylethynyl groups were first measured by Brown[10] and by Kochi and Hammond,[11] with continued refinement by Charton,[12] Landgrebe,[13] Taft,[14] and others[15] for those and related acetylenic groups. The electronic complexity of the ethynyl group was discussed by Landgrebe, who measured and analyzed the inductive and resonance contributions to the Hammett constants through a comparison of σ_m, σ_m^+, σ_p, and σ_p^+ values. These experiments confirmed that the ethynyl group is overall electron-withdrawing, but Landgrebe also reported that the group manifested an opposing electron-donating resonance contribution in the stabilization of positive charge ($\sigma_p^+ - \sigma_m^+ = -0.16$).[13]

The electronic complexity of acetylenes is also evident from more modern spectroscopic, computational, and experimental investigations.[16] For example, a recent computational study by Frontera and Deya[17] focused on the ability of the ethynyl group to perturb the ion−π interactions of an appended arene. As expected, electron-withdrawing ethynyl substitution was found to enhance anion−π interactions on pendant benzenes. However, the authors also discovered that cation−π binding was strengthened for certain cations and attributed this enhanced binding to the ethynyl group's ability to increase arene polarizability.

Our research group has a longstanding interest in the use of nucleophilic aromatic substitution (S_NAr) reactions for the formation of heteracalixarene macrocycles.[18] In surveying the literature, we were struck by the lack of definitive studies on the activating effect of ethynyl groups on nucleophilic halobenzene substitution. Further, while electron-withdrawing character has long been attributed to alkynes (vide supra), the compatibility of ethynyl groups with S_NAr reactions remained uncertain, as there are very few reported examples of halobenzene S_NAr reactions with solely ethynyl activating groups.[19]

Several σ_p^- values for ethynyl groups, expected to be most predictive of their effect on S_NAr reaction rates, have been

Received: March 29, 2013
Published: May 21, 2013

   dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

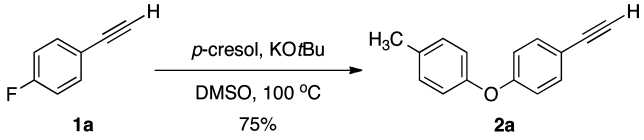
previously reported. Eaborn measured the substituent constant for the ethynyl group at σ_p^- = 0.53 via the alkaline solvolysis of benzylstannanes and silanes.[20] Exner[21] and Litvinenko[22] independently determined the value for the phenylethynyl group at σ_p^- = 0.39 and 0.30, respectively. However, we questioned the utility of these values for predicting the effect of ethynyl groups on S_NAr reaction rates; it is unintuitive that a phenylethynyl group is significantly weaker in electron-withdrawing capacity than an ethynyl group, and the reactions used to measure the substituent constants did not involve intermediates that resemble the Meisenheimer complex of an S_NAr process.

With the goal of more completely describing the electronic behavior of such an important functional group, we investigated the electron-withdrawing polarization of ethynyl groups in the context of S_NAr reactions. We now report that ethynyl groups are sufficiently electron-withdrawing to activate fluorobenzenes for nucleophilic substitution by oxygen and arylamine nucleophiles. Below we detail our quantitative rate measurements and describe the scope of "acetylene-activated" S_NAr reactions with respect to both nucleophile and electrophile.

RESULTS AND DISCUSSION

To the best of our knowledge, nucleophilic fluorine displacement of (4-fluorophenyl)acetylene (**1a**) has never been reported, which suggests either that the ethynyl functional group is unable to sufficiently stabilize the intermediate Meisenheimer complex or that anionic alkyne addition is chemoselectively favored over aromatic substitution. However, under conditions well established to promote S_NAr reactions, we found that (4-fluorophenyl)acetylene (**1a**) underwent substitution by *p*-cresol (KO*t*Bu, DMSO, 100 °C, 12 h; Scheme 1) to afford diaryl ether **2a** in a remarkable 75%

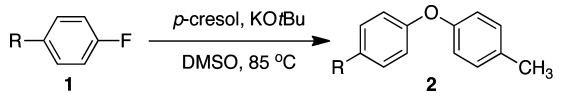
Scheme 1. Substitution of (4-Fluorophenyl)acetylene (1a) by *p*-Cresol



isolated yield. Furthermore, only traces of products resulting from addition of the phenoxide nucleophile to the terminal ethynyl group were observed.

Measurement of substituent constants for ethynyl groups required the establishment of a linear free energy relationship (LFER). Reaction rates were first measured using functional groups with known σ_p^- values[23−25] in the 4-position of fluorobenzene (**1e−g**). The LFER was generated by plotting the obtained rates versus the reported substituent constants for the 4-position functional groups in **1e−g** (see the Supporting Information). Upon establishing the LFER, the reaction rates measured for acetylenes **1a−c** allowed calculation of σ_p^- values for the ethynyl, phenylethynyl, and *tert*-butylethynyl groups (Table 1). Our measured substituent constants for the ethynyl and phenylethynyl groups (σ_p^- = 0.42 and 0.46, respectively) vary in order and magnitude from the previously published σ_p^- values, with the phenylethynyl group promoting a faster substitution rate relative to ethynyl.[20−22] The σ_p^- value for the *tert*-butylethynyl group (σ_p^- = 0.24) had not previously been determined. The ethynyl and phenylethynyl groups in

Table 1. Kinetics of 4-Fluorobenzenes 1 Reacted with *p*-Cresol



entry	electrophile	product	rate (k)[a]	σ_p^-
1	**1a** (R = C≡CH)	**2a**	28.8	0.53,[20] 0.42[b]
2	**1b** (R = C≡CPh)	**2b**	55.9	0.30,[22] 0.46[b]
3	**1c** (R = C≡C-*t*Bu)	**2e**	3.18	0.24[b]
4	**1d** (R = C≡C-*n*Bu)	**2d**		
5	**1e** (R = COMe)	**2e**	7150	0.84[23]
6	**1f** (R = CF_3)	**2f**	636	0.65[24]
7	**1g** (R = Br)	**2g**	3.70	0.25[25]

[a]In units of 10^6 L mol^{-1} s^{-1}. [b]This work.

1a,b (Table 1, entries 1 and 2) exhibit remarkably strong electron-withdrawing capacities for all-carbon functional groups, with the measured substitution rate for phenylethynyl-substituted **1b** only about 11 times slower than that for the *p*-CF_3-substituted system **1f**.

The inductive and resonance contributions to the electron-withdrawing polarization of the ethynyl and phenylethynyl groups were also investigated by reacting 3-(fluoroethynyl)-benzene and 1-fluoro-3-(phenylethynyl)benzene[26] with *p*-cresol. Using 3-(fluoroethynyl)benzene (*p*-cresol, KO*t*Bu, DMSO, 100 °C, 18 h), preferential alkyne addition was observed. For 1-fluoro-3-(phenylethynyl)benzene (*p*-cresol, KO*t*Bu, DMSO, 100 °C, 18 h), only recovered starting material was obtained. Reaction of *p*-cresol and 1-fluoro-3-(phenylethynyl)benzene under forcing conditions (KO*t*Bu, DMSO, 130 °C, 48 h) and analysis of the reaction mixture by GC/MS revealed a mixture of unreacted starting material, alkyne addition products (mixture of olefin isomers), and the aromatic substitution product. These data indicate that the inductive electron-withdrawing effect of the ethynyl and phenylethynyl groups alone is insufficient to promote selective aromatic substitution and establishes that an electron-withdrawing resonance effect is critical for reactivity in S_NAr reactions.

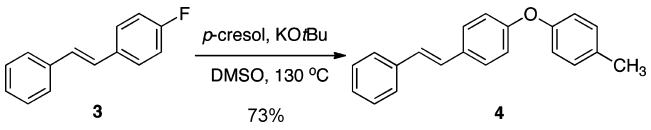
A large reduction in reaction rate is observed when moving from the ethynyl-substituted fluorobenzene **1a** to the *tert*-butylethynyl-substituted system **1c** (Table 1, entry 3). This is likely a reflection of increased electron density of the internal carbon of the *tert*-butyl group, adding electron density to the alkyne,[16,17] and a manifestation of hyperconjugative donation into the alkyne by the *tert*-butyl substituent. Only traces of substitution products were observed for the reaction of *p*-cresol with the *n*-butylethynyl-substituted fluorobenzene **1d** (entry 4), preventing the calculation of a substituent constant for this functional group. This reaction instead furnished a complex mixture of products, which included products derived from alkyne addition of *p*-cresol or *tert*-butoxide, as well as higher molecular weight oligomeric species. We speculate that the divergent reactivity observed for **1d** (as compared to isomeric **1c**) results from both the reduced steric suppression of alkyne addition relative to **1c** and the sensitivity of the propargylic protons under the anionic reaction conditions.

Vinyl groups have been previously measured as significantly weaker electron-withdrawing groups than their ethynyl counterparts. To quantify this comparative activation in the context of nucleophilic aromatic substitution, we subjected *trans*-4-

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

fluorostilbene (**3**) to substitution by *p*-cresol.[27] As expected on the basis of the published substituent constant of the *trans*-β-styryl group (σ_p^- = 0.13[10]), nucleophilic substitution of **3** proceeded much more slowly than for the analogous phenylethynyl system **1b**, but extended reaction times did lead to high-yielding aryl ether formation (Scheme 2). We

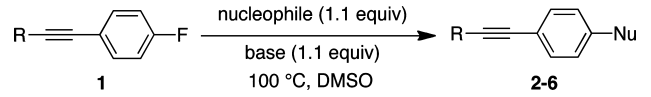
Scheme 2. Reaction of *trans*-4-Fluorostilbene (3)



measured a substituent constant for the *trans*-β-styryl group of σ_p^- = 0.24 under our reaction conditions, which is significantly lower than that of the phenylethynyl group but nearly identical with that of the more weakly activating *tert*-butylethynyl group (see Table 1).

Having quantified the electron-withdrawing capacity of the alkynes in **1a−c** and established the viability of acetylene-activated S_NAr reactions, we next sought to examine the synthetic scope. DMSO solvent was optimal; analogous reactions conducted using DMF or NMP proceeded to lower conversion and produced inferior yields of aromatic substitution products even at extended reaction times. Potassium *tert*-butoxide was found to be the optimal base with respect to operational simplicity and yield, but substitution of **1a**,**b** was also observed using *p*-cresol with NaH base. On a preparative scale, phenylethynyl-activated electrophile **1b** underwent efficient substitution by *p*-cresol, producing aryl ether **2b** in 88% yield (Table 2, entry 2). Although it was significantly less activated toward substitution, *tert*-butylethynyl fluorobenzene **1c** also underwent high-yielding aryl ether formation with *p*-cresol at 130 °C over 72 h, furnishing product **2c** in 86% yield

Table 2. Nucleophile Scope for S_NAr Reactions of (4-Fluorophenyl)acetylenes 1



entry	electrophile	nucleophile	base	product (yield, %)
1	**1a** (R = H)	*p*-cresol	KO*t*Bu	**2a** (75)
2	**1b** (R = Ph)	*p*-cresol	KO*t*Bu	**2b** (88)
3	**1c** (R = *t*Bu)	*p*-cresol	KO*t*Bu	**2c** (86)[a]
4	**1d** (R = *n*Bu)	*p*-cresol	KO*t*Bu	**2d** (<5)[b]
5	**1b** (R = H)	*o*-cresol	KO*t*Bu	**2h** (63)
6	**1b** (R = Ph)	*o*-cresol	KO*t*Bu	**2i** (80)
7	**1b** (R = Ph)	ethanol	NaH	**5a** (90)
8	**1b** (R = Ph)	isopropyl alcohol	NaH	**5b** (76)
9	**1b** (R = Ph)	KOtBu	none	**5c** (38)
10	**1b** (R = Ph)	allyl alcohol	NaH	**5d** (80)
11	**1a** (R = H)	benzyl alcohol	NaH	**5e** (54)
12	**1b** (R = Ph)	benzyl alcohol	NaH	**5f** (76)
13	**1b** (R = Ph)	*p*-toluidine	KO*t*Bu	**6a** (84)
14	**1b** (R = Ph)	*o*-toluidine	KO*t*Bu	**6b** (70)
15	**1b** (R = Ph)	4-CH_3PhSH	KO*t*Bu	**2j** (<5)[c]
16	**1b** (R = Ph)	ethanethiol	KO*t*Bu	**2k** (<5)[c]

[a]Conducted at 130 °C. [b]A complex mixture of products resulted from alkyne addition and isomerization. [c]Alkyne addition was the predominant reaction pathway.

(entry 3). Increased steric bulk on the phenoxy nucleophile was also accommodated. *o*-Cresol was successfully condensed with **1a**,**b**, giving 63% and 80% yields of diaryl ethers **2h**,**i**, respectively (entries 5 and 6).

Substitution reactions of alternative nucleophiles with phenylethynyl-substituted fluorobenzene **1b** were next evaluated. Sodium ethoxide induced efficient fluorine substitution of **1b**, furnishing the corresponding aryl ethyl ether **5a** in 90% yield (ethanol, NaH, DMSO, 100 °C, 18 h, entry 7). NaH was found to be the optimal base for alkoxide nucleophiles, but DMSO remained the optimal solvent. Use of DMF or NMP required longer reaction times and resulted in reduced yields of substitution products. Increased steric bulk on the alkoxide nucleophile was also accommodated. The product yield remained high for the reaction of sodium isopropoxide with **1b**, affording substitution product **5b** in 76% yield (entry 8). Substitution became very sluggish, however, using potassium *tert*-butoxide as the nucleophile, furnishing only a 38% yield of aryl ether product **5c** (entry 9). Sodium allyloxide was also an effective nucleophile when it was condensed with **1b**, furnishing the corresponding allyl aryl ether **5d** in 80% yield (entry 10). Electrophiles **1a**,**b** were each reacted with sodium benzyloxide,[28] resulting in 54% (**5e**) and 76% yields (**5f**) of the corresponding aryl ethers (entries 11 and 12). It should be noted that alkyne addition of benzyloxide to **1a** was the major side product leading to the diminished yield of **5e** and that use of DMF or NMP as solvent did not significantly alter the observed ratio of aromatic substitution to alkyne addition.

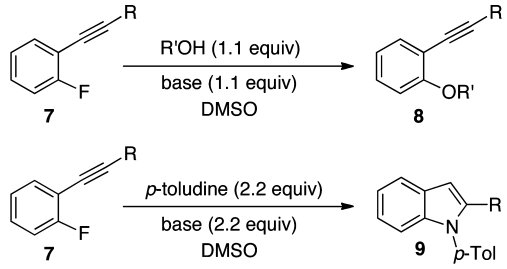
Arylamines were also found to be viable nucleophiles for the substitution of **1b**. Condensation of **1b** with *p*-toluidine furnished a high yield of the corresponding diaryl amine substitution product **6a** (84%, entry 13), as did reaction of **1b** with the more sterically encumbered *o*-toluidine (**6b**, 70%, entry 14). However, attempts to substitute electrophile **1b** using aliphatic amines have not yet provided synthetically useful yields of substitution products.

Chemoselectivity shifted almost completely for sulfur-based nucleophiles, which were found to strongly favor alkyne addition.[29] The reaction between alkyne **1b** and 4-methylbenzenethiol (KO*t*Bu, DMSO, 4 h, 85 °C, entry 15) produced only trace amounts of substitution product. The same propensity for alkyne addition was also observed using ethanethiol (KO*t*Bu, DMSO, 18 h, 80 °C, entry 16). Alternative bases and solvents were screened for each thiol nucleophile but did not alter ratios of alkyne addition versus substitution.

The reaction scope was investigated beyond simple (4-fluorophenyl)acetylenes **1a−c**, leading to further insights into the factors that influence fluorine substitution versus alkyne addition. When (2-fluorophenyl)acetylene **7a** (R = H; see Table 3) was subjected to reaction with *p*-cresol (KO*t*Bu, DMSO, 100 °C), only 5% of diaryl ether **8a** was obtained. The balance of the reaction mixture consisted of products resulting from addition of *p*-cresol across the alkyne (mixture of olefin isomers) and higher molecular weight materials. A similar product mixture strongly favoring alkyne addition was also obtained for the reaction of **7a** with sodium benzyloxide. When the more sterically shielded 1-fluoro-2-(phenylethynyl)benzene **7b** was subjected to reaction with *p*-cresol (KO*t*Bu, DMSO, 100 °C), fluorine substitution again became the dominant reaction pathway. Using *p*-cresol or ethanol nucleophiles produced the corresponding aryl ether products **8b**,**c** in only slightly lower yields as compared to reactions with the 4-fluoro

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

Table 3. Reactions of 2-Fluorophenylacetylenes 7



entry	electrophile	nucleophile	base	product (yield, %)
1	**7b** (R = Ph)	*p*-cresol	KO*t*Bu	**8b** (74)[a]
2	**7b** (R = Ph)	ethanol	NaH	**8c** (86)[a]
3	**7b** (R = Ph)	*p*-toluidine	KO*t*Bu	**9a** (71)[a]
4	**7c** (R = *t*Bu)	*p*-cresol	KO*t*Bu	**8d** (67)[b]
5	**7c** (R = *t*Bu)	ethanol	NaH	**8e** (56)[b]
6	**7c** (R = *t*Bu)	*p*-toluidine	KO*t*Bu	**9b** (55)[b]

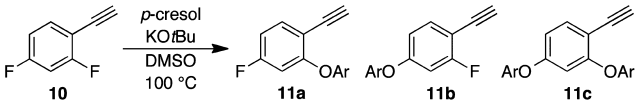
[a]Conditions: 100 °C, 18 h. [b]Conditions: 150 °C, 72 h.

analogue **1b** (74% and 86% yields, respectively; Table 3, entries 1 and 2). When *p*-toluidine was examined as a nucleophile in the reaction with **1b**, not only was substitution at the fluorine atom observed but also the substrate underwent subsequent 5-*endo*-dig anionic cyclization to produce 2-arylindole **9a** (entry 3).[30]

Under more vigorous reaction conditions (72 h, 150 °C), 1-fluoro-2-(*tert*-butylethynyl)benzene (**7c**) also underwent preferential aromatic substitution. *p*-Cresol and ethanol reacted with **7c** to produce the corresponding ethers **8d** (67% yield, entry 4) and **8e** (56% yield, entry 5). Furthermore, use of *p*-toluidine once again led to the corresponding 2-*tert*-butylindole (**9b**, 55% yield, entry 6) via tandem substitution−cyclization.

Although **7b,c** proved viable electrophiles for preferential aromatic substitution, we remained concerned that the alkyne addition observed with (2-fluorophenyl)acetylene **7a** (vide supra) indicated that unsubstituted ethynyl groups were incompatible with *o*-fluorine atoms for S_NAr activation. We subsequently subjected (2,4-difluorophenyl)acetylene (**10**) to reactions with *p*-cresol in varying stoichiometric ratios (Scheme 3). In dramatic contrast to **7a**, difluorophenylacetylene **10**

Scheme 3. Substitution of 2,4-Difluorophenylacetylene (10)

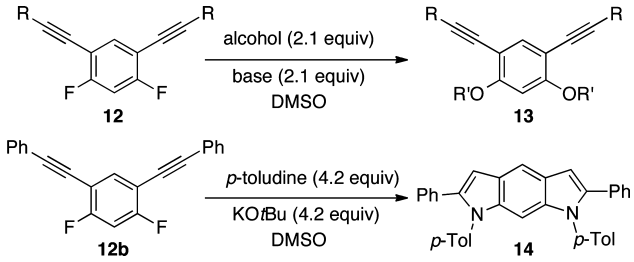


entry	equiv *p*-cresol	Time	product ratio (yield) 11a:	11b:	11c
1	1.0 equiv	6 h	2.9	5.3	1
2	2.0 equiv	6 h	trace	1	7.2
3	2.1 equiv	15 h	trace	trace	>95 (91%)

underwent preferential and high-yielding aromatic substitution. Using 1 equiv of nucleophile led to modest selectivity for substitution of the *p*- over the *o*-fluorine atom (3:5 *ortho*:*para*, **11a**:**11b**, entry 1), while use of 2.1 equiv of *p*-cresol at longer reaction times formed the disubstitution product **11c** in 91% isolated yield. The divergent outcomes observed with electrophiles **7a** and **10** suggest that multiple electronic factors play a role in chemoselectivity for these processes. First, the weakly electron-withdrawing *m*-fluoro[31] or *m*-phenoxy[32] substituents present on substrate **10** and subsequent substitution products increase aromatic substitution rates as compared to those for **7a**. Second, the presence of a weakly electron-donating *p*-fluoro[31] or *p*-phenoxy[32] substituent, present on **10** but not **7a**, is expected to increase the electron density of the alkynyl moiety in **10** and reduce the rate of alkyne addition relative to **7a**.[33]

Following the successful substitution of both fluorine atoms from **10**, we turned to evaluating electrophiles bearing multiple acetylene groups. As shown in Table 4, addition of a second

Table 4. Reaction of Diethynyldifluorobenzenes 12



entry	electrophile	nucleophile	base	temp, °C	product (yield, %)
1	**12a** (R = H)	*p*-cresol	KO*t*Bu	60	**13a** (93)
2	**12b** (R = Ph)	*p*-cresol	KO*t*Bu	60	**13b** (89)
3	**12c** (R = *t*Bu)	*p*-cresol	KO*t*Bu	80	**13c** (87)
4	**12d** (R = *n*Bu)	*p*-cresol	KO*t*Bu	60	**13d** (45)
5	**12b** (R = Ph)	ethanol	NaH	60	**13e** (82)
6	**12b** (R = Ph)	*p*-toluidine	KO*t*Bu	100	**14** (38)

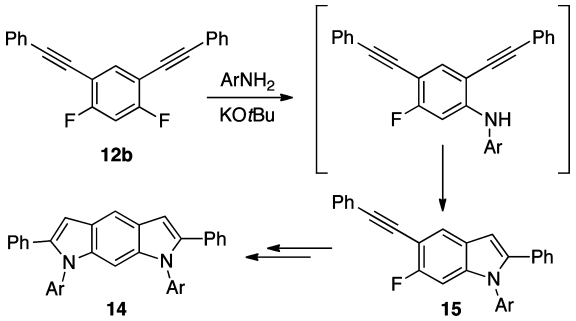
ethynyl group to the fluorobenzene lowers the required reaction temperatures and increases yields of substitution products. Diethynyl- and diphenylethynyl-substituted electrophiles **12a,b** undergo high-yielding substitution of both fluorine atoms by *p*-cresol, furnishing the aryl ether products in 93% (**13a**) and 89% yields (**13b**), respectively (Table 4, entries 1 and 2). The di-*tert*-butylethynyl-substituted electrophile **12c** reacts smoothly but more slowly with *p*-cresol than **12a,b**, furnishing the disubstitution product **13c** in 87% yield (entry 3). Furthermore, unlike *n*-butylethynyl-substituted substrate **1d**, di-*n*-butylethynyl-substituted compound **12d** does furnish appreciable amounts of substitution product **13d** on reaction with *p*-cresol (45% yield, entry 4). Sodium ethoxide was also found to cleanly displace both fluorine atoms on **12b** (82%, entry 5). Use of *p*-toluidine as a nucleophile (entry 6) leads to a double substitution−anionic cyclization cascade, producing benzodipyrrole **14** in 38% yield in which six new σ bonds are formed. Benzodipyrrole **14** is only sparingly soluble in lower-polarity organic solvents, and the lower isolated yield in part reflects the difficulty of purification of this compound. Analysis of this reaction at reduced temperature reveals the order of bond-forming events (Scheme 4). Following the initial fluorine displacement, the reaction proceeds first to exclusively form intermediate indole **15**, which displays reduced aromatic electrophilicity relative to **12b**. Slow substitution of the second fluorine atom, followed by rapid anionic cyclization, then leads to benzodipyrrole **14**.

■ CONCLUSION

For the first time, the electron-withdrawing capabilities of ethynyl, phenylethynyl, and *tert*-butylethynyl groups have been

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

Scheme 4. Bond-Formation Sequence Yielding Benzodipyrrole 14



quantified, and substituent constants determined, in the context of S_NAr reactions. Furthermore, we have explored the scope of these acetylene-activated S_NAr reactions and shown that high-yielding substitution of (4-fluoroethynyl)benzenes **1a–c**, (2-fluoroethynyl)benzenes **7**, and (difluoroethynyl)benzenes **12** can be achieved with a variety of oxygen and arylamine nucleophiles. Arylamine nucleophiles were found to react with (2-fluoroethynyl)benzenes **7** and (difluoroethynyl)benzenes **12** via tandem substitution–cyclization to furnish 2-substituted *N*-aryl indoles **9** and benzodipyrroles **14**, respectively.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Triethylamine and (trimethylsilyl)-acetylene were distilled onto activated 3 Å molecular sieves under an atmosphere of Ar. *p*-Toluidine was purified via sublimation prior to use. Synthesized compounds **1b**,[34] **1d**,[35] **3**,[36] **7b**,[37] **9a**,[38] and **12a**[39] have been previously reported, and in each case our obtained characterization data match the literature values. Analytical thin-layer chromatography was performed with 0.25 mm silica gel 60-F TLC plates. Flash column chromatography was carried out with silica gel (230–400 mesh). NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts are expressed in parts per million (δ) using residual solvent peaks as internal standards. All potentially ambiguous signals were further characterized and assigned on the basis of COSY, HMQC, HMBC, and/or NOESY spectroscopy. Mass spectra were obtained using an accurate mass TOF spectrometer with a DART interface.

Kinetics and Linear Free Energy Relationship. Following the precedent established by Miller[40] and Bevan,[41] S_NAr reaction rates were measured for a series of fluorobenzenes (**1a–g**). The reactions were carried out in DMSO with an excess of the nucleophile *p*-cresol. Substitution was observed to occur with reasonable rates at 85 °C, and this temperature was used for all rate measurements, which were quantified by ^{1}H NMR. Anionic alkyne addition side reactions were minimal for **1a–c** and did not interfere with the rate measurements.

General Procedure for Rate Measurements. A dry reaction tube was charged with *p*-cresol (1.6 mmol) and KO*t*Bu (1.6 mmol). After the atmosphere was purged with Ar, dry DMSO (2.7 mL) containing 280 mM 1,3-dimethyl-2-imidazolidone as an internal standard was added. The solution was heated to 85 °C in an oil bath, and once the temperature had stabilized, the electrophile **1** (1.0 mmol) was added to initiate the reaction. Reactions were run on time scales ranging from 30 min to 200 h. Between 8 and 10 aliquots (0.07 mL each) were taken for each reaction. For analysis, each aliquot was removed via syringe, quenched with 1 M HCl (1.5 mL), and extracted into $CDCl_3$ (1 mL). Aliquots were analyzed by ^{1}H NMR with the concentrations of unreacted nucleophile and electrophile calculated by integration in comparison to the internal standard. Nonlinear least-squares curve fitting was used to obtain the second-order rate constants at 85 °C. Reactions were run in duplicate or triplicate, and the averages of these data were used.

1-Fluoro-4-(phenylethynyl)benzene (1b). In a sealed tube were added $PdCl_2(PPh_3)_2$ (94.9 mg, 0.135 mmol) and CuI (188 mg, 0.986 mmol). The mixture was purged with Ar for 5 min, and then degassed 4-fluoro-1-iodobenzene (1.00 mL, 8.75 mmol), degassed phenylacetylene (0.980 mL, 8.92 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 2 h and then was diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown powder. Purification by silica gel flash chromatography (hexanes) gave 1.54 g (7.84 mmol, 90%) of **1b** as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.54 (m, 2H), 7.53–7.51 (m, 2H), 7.40–7.37 (m, 1H), 7.36–7.35 (m, 2H), 7.05 (dd, J = 8.8, 8.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5 (d, J = 249.4 Hz), 133.5 (d, J = 8.4 Hz), 131.5, 128.4, 128.3, 123.1, 119.4 (d, J = 3.3 Hz), 115.6 (d, J = 22.3 Hz), 89.0, 88.3. TLC: R_f = 0.38 (hexanes). IR (KBr pellet): 3268 (m), 2922 (w), 2111 (w), 1881 (w), 1654 (w), 1508 (s), 1594 (s), 1486 (s), 1442 (m), 1388 (m), 1217 (s) cm^{-1}. HRMS (DART):: calcd for $[C_{14}H_9F]^+$ 196.0688, found 196.0688.

1-Fluoro-4-(*tert*-butylethynyl)benzene (1c). In a sealed tube were added $PdCl_2(PPh_3)_2$ (261 mg, 0.372 mmol) and CuI (150 mg, 0.785 mmol). The mixture was purged with Ar for 5 min, and then degassed 4-fluoro-1-iodobenzene (2.00 mL, 17.3 mmol), degassed *tert*-butylacetylene (4.25 mL, 34.5 mmol), and triethylamine (24.0 mL) were added in that order. The mixture was stirred at room temperature for 2 h then was diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel plug (hexanes) gave 2.80 g (15.9 mmol, 92%) of **1c** as a clear, colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, J = 8.9, 5.4 Hz, 2H), 6.96 (dd, J = 8.8, 8.8 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.0 (d, J = 248.0 Hz), 133.3 (d, J = 8.2 Hz), 120.1 (d, J = 3.4 Hz), 115.3 (d, J = 21.8 Hz), 98.1 (d, J = 1.6 Hz), 77.9, 31.0, 27.9. TLC: R_f = 0.60 (hexanes). IR (thin film): 2970 (s), 2901 (s), 2195 (w), 1890 (w), 1602 (m), 1507 (s), 1475 (m), 1292 (m), 1231 (s), 1155 (m) cm^{-1}. HRMS (DART): calcd for $[C_{12}H_{14}FH]^+$ 177.1074, found 177.1076.

1-Fluoro-4-(*n*-butylethynyl)benzene (1d). In a sealed tube were added $PdCl_2(PPh_3)_2$ (85.2 mg, 0.121 mmol) and CuI (47.8 mg 0.251 mmol). The mixture was purged with Ar for 5 min, and then degassed 4-fluoro-1-iodobenzene (1.00 mL, 8.75 mmol), degassed *n*-butylacetylene (1.03 mL, 8.93 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 2 h and then was diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes) gave 1.33 g (7.52 mmol, 86%) of **1d** as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (dd, 2H, J = 8.9, 5.5 Hz), 6.97 (dd, J = 8.8, 8.8 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 1.85–1.84 (m, 2H), 1.53–1.45 (m, 2H), 0.95 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.0 (d, J = 248.4 Hz), 133.3 (d, J = 8.4 Hz), 120.1 (d, J = 3.7 Hz), 115.3 (d, J = 21.9 Hz), 90.0 (d, J = 1.4 Hz), 79.5, 30.8, 22.0, 19.0, 13.6. TLC: R_f = 0.46 (hexanes). IR (thin film): 2962 (s), 2934 (s), 2203 (m), 1712 (m), 1673 (m), 1601 (m), 1507 (s), 1234 (s), 1155 (s) cm^{-1}. HRMS (DART): calcd for $[C_{12}H_{13}F]^+$ 176.1001, found 176.1026.

1-Ethynyl-4-(*p*-tolyloxy)benzene (2a). In a reaction flask under Ar, **1a** (125 mg, 1.04 mmol), *p*-cresol (127 mg, 1.17 mmol), and DMSO (3 mL) were added. The reaction was started with the addition of KO*t*Bu (129 mg, 1.15 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 12 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987–5998

over Na_2SO_4. The solvent was carefully removed in vacuo to give a brown oil (the product is somewhat volatile). Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/5) gave 163 mg (0.782 mmol, 75%) of **2a** as a clear, colorless, viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 3.02 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 153.7, 133.7, 133.7, 130.4, 119.7, 117.7, 116.1, 83.3, 76.3, 20.7. TLC: R_f = 0.26 (CH_2Cl_2/hexanes, 1/10). IR (CH_2Cl_2) 3287 (m), 3038 (w), 2923 (w), 2108 (w), 1895 (w), 1773 (w), 1598 (m), 1508 (m), 1493 (s), 1413 (w), 1380 (w), 1279 (m), 1235 (s), 1208 (m), 1166 (m), 1103 (m), 1043 (w), 1016 (m) cm^{-1}. HRMS (DART): calcd for $[C_{15}H_{12}OH]^+$ 209.0961, found 209.0966.

1-(Phenylethynyl)-4-(*p*-tolyloxy)benzene (2b). In a reaction flask under Ar, **1b** (194 mg, 0.988 mmol), *p*-cresol (118 mg, 1.09 mmol), and DMSO (3 mL) were added. The reaction was started with the addition of KO*t*Bu (120 mg, 1.08 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/4) gave 247 mg (0.867 mmol, 88%) of **2b** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55−7.53 (m, 2H), 7.48 (d, J = 8.9 Hz, 2H), 7.36−7.33 (m, 3H), 7.17 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1, 153.9, 133.6, 133.1, 131.5, 130.4, 128.3, 128.1, 123.4, 119.6, 117.9, 117.4, 89.0, 88.6, 20.7. TLC: R_f = 0.60 (CH_2Cl_2/hexanes, 1/9). IR (KBr pellet): 3284 (m), 2925 (s), 2107 (w), 1729 (s), 1573 (s), 1495 (s), 1370 (s), 1279 (m), 1215 (s), 1149 (s) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{16}O]^+$ 284.1201, found 284.1221.

1-(*tert*-Butylethynyl)-4-(*p*-tolyloxy)benzene (2c). In a reaction flask under Ar, **1c** (174 mg, 0.985 mmol), *p*-cresol (117 mg, 1.08 mmol), and DMSO (3 mL) were added. The reaction was started with the addition of KO*t*Bu (120 mg, 1.07 mmol). The reaction mixture was stirred in an oil bath at 130 °C for 26 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was carefully removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/10) gave 225 mg (0.850 mmol, 86%) of **2c** as a clear, colorless, viscous liquid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.32 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 2.30 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.0, 153.3, 133.3, 132.9, 130.5, 119.4, 117.6, 117.4, 97.6, 78.3, 30.8, 27.5, 20.3. TLC: R_f = 0.33 (thin film/hexanes, 1/10). IR (CH_2Cl_2): 3039 (w), 2968 (m), 2900 (w), 2925 (w), 2867 (w), 2400 (w), 1888 (w), 1600 (m), 1496 (s), 1456 (w), 1411 (w), 1362 (w), 1273 (m), 1235 (s), 1208 (m), 1166 (m), 1102 (m), 1041 (w), 1016 (m) cm^{-1}. HRMS (DART): calcd for $[C_{19}H_{20}O]^+$ 264.1514, found 264.1519.

1-Ethynyl-4-(*o*-tolyloxy)benzene (2h). In a reaction flask under Ar, **1a** (63.0 mg, 0.525 mmol), *o*-cresol (62.3 mg, 0.577 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (64.7 mg, 0.577 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was carefully removed in vacuo to give a brown oil (the product is somewhat volatile). Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 87.3 mg (0.330 mmol, 63%) of **2h** as a clear, colorless, viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48−7.39 (m, 1H), 7.32−7.23 (m, 1H), 7.12 (td, J = 7.5, 1.5 Hz, 1H), 6.95 (dd, J = 8.0, 1.5 Hz, 1H), 6.88−6.76 (m, 2H), 3.20 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 153.5, 133.7, 131.6, 130.3, 127.3, 124.7, 120.5, 116.7, 115.7, 83.4, 76.2, 16.1. TLC: R_f = 0.33 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 3287 (m), 3033 (w), 2107 (w), 1601 (m), 1583 (m), 1499 (s), 1487 (s), 1234 (s), 1180 (s), 1110 (m) cm^{-1}. HRMS (DART): calcd for $[C_{15}H_{12}OH]^+$ 209.0960, found 209.0961.

1-(Phenylethynyl)-4-(*o*-tolyloxy)benzene (2i). In a reaction flask under Ar, **1b** (49.1 mg, 0.250 mmol), *o*-cresol (29.7 mg, 0.275 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (30.8 mg, 0.257 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 56.8 mg (0.200 mmol, 80% yield) of **2i** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55−7.51 (m, 2H), 7.50−7.46 (m, 2H), 7.39−7.32 (m, 3H), 7.31−7.26 (m, 1H), 7.24−7.19 (m, 1H), 7.13 (td, J = 7.5, 1.3 Hz, 1H), 6.98 (dd, J = 8.0, 1.3 Hz, 1H), 6.90−6.85 (m, 2H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2, 153.7, 133.2, 131.6, 131.5, 130.3, 128.3, 128.1, 127.3, 124.6, 123.5, 120.4, 117.0, 116.9, 89.1, 88.5, 16.1. TLC: R_f = 0.50 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 3056 (w), 2923 (w), 2852 (w), 2216 (w), 1893 (w), 1595 (m), 1583 (m), 1505 (s), 1488 (s), 1237 (s) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{16}O]^+$ 284.1201, found 284.1220.

(*E*)-1-Fluoro-4-styrylbenzene (3). In a sealed tube were added $PdCl_2(PPh_3)_2$ (70.3 mg, 0.0100 mmol) and $CsCO_3$ (1.70 g, 5.23 mmol). The mixture was purged with Ar for 5 min, and then *trans*-vinylboronic acid (746 mg, 5.07 mmol), DMF/H_2O (8 mL/2 mL, respectively), and 4-fluoro-1-iodobenzene (0.576 mL, 5.07 mmol) were added in that order. The mixture was heated to 100 °C for 10 min, then tetrabutylammonium bromide (322 mg, 0.999 mmol) was added, and the mixture was heated for 2 h at 100 °C, followed by 18 h at 65 °C. After this time period the reaction mixture was diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown powder. Purification by silica gel flash chromatography (hexanes) gave 0.463 g (2.34 mmol, 45%) of **3** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47−7.45 (m, 4H), 7.38 (dd, J = 8.4, 6.9 Hz, 2H), 7.31−7.26 (m, 1H), 7.12−7.01 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5 (d, J = 251 Hz), 133.5, 133.4, 128.4, 128.4, 128.3, 123.1, 119.4, 119.4, 115.6 (d, J = 25 Hz). TLC: R_f = 0.28 (hexanes). IR (KBr pellet): 3022 (w), 1893 (m), 1831 (m), 1593 (s), 1508 (s), 1448 (s), 1236 (s), 1158 (s), 1097 (s) cm^{-1}. HRMS (DART): calcd for $[C_{14}H_{11}F]^+$ 198.0845, found 198.0847.

(*E*)-1-Methyl-4-(4-styrylphenoxy)benzene (4). In a reaction flask under Ar, **6** (196 mg, 1.00 mmol), *p*-cresol (116 mg, 1.07 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.09 mmol). The reaction mixture was stirred in an oil bath at 120 °C for 72 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/5) gave 208 mg (0.727 mmol, 73% yield) of **4** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.1 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.26 (tt, J = 7.3, 1.2 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 19.3 Hz, 2H) 6.99−6.98 (m, 2H), 6.97 (d, J = 13.9 Hz, 1H), 6.96 (d, J = 13.8 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.5, 154.5, 137.4, 133.1, 132.2, 130.3, 128.7, 128.0, 127.8, 127.6, 127.4, 126.4, 119.2, 118.5, 20.7. TLC: R_f = 0.33 (EtOAc/hexanes, 1/20). IR (KBr pellet): 3058 (w), 3025 (m), 2341 (w), 1950 (w), 1888 (m), 1601 (s), 1593 (s), 1507 (s), 1448 (s), 1284 (s), 1260 (s), 1169 (s), 1104 (m) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{18}O]^+$ 286.1357, found 286.1370.

1-Ethoxy-4-(phenylethynyl)benzene (5a). In a reaction flask under Ar, 60% NaH in mineral oil (60.0 mg, 1.50 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

hexanes was removed. DMSO (1.0 mL) and ethanol (0.116 mL, 1.99 mmol) were added and stirred for 1 h at 50 °C (until the solution became homogeneous). **1b** (197 mg, 1.01 mmol) dissolved in DMSO (2.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 50 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 2/3) gave 200 mg (0.901 mmol, 90%) of **5a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.0, 1.6 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H), 7.37−7.30 (m, 3H), 6.87 (d, J = 8.9 Hz, 2H), 4.05 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0, 133.0, 131.4, 128.3, 127.9, 123.6, 115.2, 114.5, 89.4, 88.0, 63.5, 14.8. TLC: R_f = 0.60 (CH_2Cl_2/hexanes, 2/3). IR (ATR): 3048 (w), 3028 (w), 2916 (m), 2402 (w), 2219 (w), 1890 (w), 1781 (w), 1602 (m), 1589 (s), 1500 (s), 1400 (m), 1252 (s) cm^{-1}. HRMS (DART): calcd for $[C_{16}H_{14}O]^+$ 222.1045, found 222.1045.

1-Isopropoxy-4-(phenylethynyl)benzene (5b). In a reaction flask under Ar, 60% NaH in mineral oil (23.2 mg, 0.581 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed. DMSO (1.0 mL) and isopropyl alcohol (0.045 mL, 0.58 1 mmol) were added and stirred for 1 h at 50 °C (until the solution became homogeneous). **1b** (103 mg, 0.525 mmol) dissolved in DMSO (1.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 94.1 mg (0.399 mmol, 76%) of **5b** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57−7.41 (m, 4H), 7.40−7.24 (m, 3H), 6.92−6.82 (m, 2H), 4.59 (sep, J = 6.0 Hz, 1H), 1.36 (d, J = 6.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 133.1, 131.4, 128.3, 127.9, 123.7, 115.7, 115.0, 89.5, 87.9, 69.9, 22.0. TLC: R_f = 0.25 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 3033 (m), 2926 (m), 2219 (w), 1972 (w), 1900 (w), 1678 (w), 1595 (s), 1508 (s), S1454 (m), 1378 (m), 1281 (m), 1241 (s), 1175 (m) cm^{-1}. HRMS (DART): calcd for $[C_{17}H_{16}OH]^+$ 237.1274, found 237.1277.

1-*tert*-Butoxy-4-(phenylethynyl)benzene (5c). In a reaction flask was added **1b** (50.1 mg, 0.256 mmol), DMSO (1.0 mL), and KO*t*Bu (30.8 mg, 0.275 mmol), and the mixture was then stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 23.8 mg (0.095 mmol, 38%) of **5c** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55−7.49 (m, 2H), 7.48−7.42 (m, 2H), 7.37−7.31 (m, 2H), 7.27 (d, J = 1.4 Hz, 1H), 7.01−6.95 (m, 2H), 1.38 (d, J = 1.2 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7, 132.4, 131.5, 128.3, 128.0, 123.8, 123.4, 117.9, 89.2, 88.7, 79.1, 28.9. TLC: R_f = 0.14 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 2974 (m), 2927 (w), 2213 (w), 1908 (w), 1726 (w), 1593 (m), 1499 (s), 1441 (m), 1364 (s), 1234 (s), 1154 (s), 1096 (m) cm^{-1}. HRMS (DART): calcd for $[C_{18}\ H_{18}OH]^+$ 251.1430, found 251.1435.

1-(Allyloxy)-4-(phenylethynyl)benzene (5d). In a reaction flask under Ar, 60% NaH in mineral oil (18 mg, 0.43 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed. DMSO (1.0 mL) and allyl alcohol (0.032 mL, 0.47 mmol) were added, and the mixture was stirred for 1 h at 50 °C (until the solution became homogeneous). **1b** (84.4 mg, 0.471 mmol) dissolved in DMSO (1.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 80.2 mg (0.342 mmol, 80%) of **5d** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.51 (m, 2H), 7.48 (dt, J = 9.0, 3.0 Hz, 2H), 7.37−7.32 (m, 3H), 6.91 (dt, J = 9.0, 2.0 Hz, 2H), 6.07 (ddt, J = 17.0, 10.5, 5.0 Hz, 1H), 5.44 (dq, J = 17.0, 1.5 Hz, 1H), 5.32 (dq, J = 10.5, 1.5 Hz, 1H), 4.57 (dt, J = 5.0, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 133.0, 132.9, 131.4, 128.3, 127.9, 123.6, 117.9, 115.5, 114.8, 89.3, 88.1, 68.8. TLC: R_f = 0.18 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 3034 (s), 2917 (w), 2859 (w), 2217 (w), 1954 (w), 1669 (m), 1592 (m), 1505 (s), 1281 (m), 1231 (s) cm^{-1}. HRMS (DART): calcd for $[C_{17}H_{14}OH]^+$ 235.1117, found 235.1117.

1-(Benzyloxy)-4-ethynylbenzene (5e). In a reaction flask under Ar, 60% NaH in mineral oil (43 mg, 0.11 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed. DMSO (2.0 mL) and benzyl alcohol (0.117 mL, 0.110 mmol) were added, and the mixture was stirred for 1 h at 50 °C (until the solution became homogeneous). **1a** (116 mg, 0.966 mmol) dissolved in DMSO (1.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (ether:-hexanes, 1/9) gave 111 mg (0.534 mmol, 54%) of **5e** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47−7.36 (m, 6H), 7.35 (dt, J = 7.3, 1.5 Hz, 1H), 6.94 (dt, J = 8.5, 3.0 Hz, 2H), 5.09 (s, 2H), 3.02 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.1, 136.5, 133.6, 128.6, 128.1, 127.5, 114.7, 114.5, 83.6, 75.9, 70.0. TLC: R_f = 0.11 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 3271 (m), 2104 (w), 1897 (w), 1653 (m), 1637 (m), 1599 (m), 1540 (s), 1466 (m), 1455 (m), 1384 (m), 1224 (s), 1171 (m) cm^{-1}. HRMS (DART): calcd for $[C_{15}H_{12}OH]^+$ 209.0961, found 209.0967.

1-(Benzyloxy)-4-(phenylethynyl)benzene (5f). In a reaction flask under Ar, 60% NaH in mineral oil (8.1 mg, 0.18 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed. DMSO (1.0 mL) and benzyl alcohol (0.021 mL, 0.20 mmol) were added, and the mixture was stirred for 30 min at 50 °C (until the solution became homogeneous). **1b** (35.3 mg, 0.198 mmol) dissolved in DMSO (1.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 38.4 mg (0.135 mmol, 76%) of **5f** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47−7.21 (m, 11 H), 7.18 (s, 1H), 6.91−6.85 (m, 2H), 5.01 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.8, 136.6, 133.1, 131.5, 128.6, 128.3, 128.1, 127.9, 127.5, 123.6, 115.0, 114.9, 89.3, 88.1, 70.0. TLC: R_f = 0.06 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 3033 (w), 2921 (w), 2853 (w), 2220 (w), 1899 (w), 1596 (m), 1508 (m), 1454 (m), 1377 (m), 1280 (m), 1238 (m) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{16}OH]^+$ 285.1274, found 285.1274.

4-Methyl-*N*-(4-(phenylethynyl)phenyl)aniline (6a). In a reaction flask under Ar, **1b** (197 mg, 1.00 mmol), *p*-toluidine (214 mg, 1.99 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (231 mg, 2.06 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

chromatography (hexanes → EtOAc/hexanes, 1/10) gave 237 mg (0.838 mmol, 84%) of **6a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, J = 8.1, 1.5 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.36−7.30 (m, 3H), 7.14 (dd, J = 8.6, 0.6 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.75 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.3, 139.0, 132.9, 132.0, 131.4, 129.9, 128.3, 127.7, 123.8, 120.1, 115.5, 113.9, 90.0, 87.8, 20.7. TLC: R_f = 0.38 (EtOAc/hexanes, 1/9). IR (KBr pellet): 3413 (s), 3052 (w), 2916 (w), 2214 (m), 1891 (w), 1609 (s), 1594 (s), 1524 (s), 1324 (s), 1177 (m) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{17}N]^+$ 283.1361, found 283.1368.

2-Methyl-*N*-(4-(phenylethynyl)phenyl)aniline (6b). In a reaction flask under Ar, **1b** (49.3 mg, 0.251 mmol), *o*-toluidine (60.3 mg, 0.553 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (61.9 mg, 0.552 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → EtOAc/hexanes, 1/10) gave 50.0 mg (0.175 mmol, 70%) of **6b** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54−7.52 (m, 2H), 7.45−7.39 (m, 2H), 7.38−7.15 (m, 6H), 7.03 (tt, J = 7.4, 1.2 Hz, 1H), 6.91−6.82 (m, 2H), 5.52 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.6, 139.9, 132.9, 131.4, 131.1, 129.9, 128.2, 127.7, 126.8, 123.8, 123.3, 120.9, 115.8, 113.9, 90.0, 87.8, 17.9. TLC: R_f = 0.29 (EtOAc/hexanes, 1/9). IR (ATR): 3393.7 (w), 3029.6 (w), 2924.5 (w), 2210.9 (m), 1610 (m), 1593 (m), 1513 (s), 1412 (m), 1319 (m), 1295 (m), 1181 (m) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{17}N]^+$ 283.1361, found 283.1368.

1-Fluoro-2-(phenylethynyl)benzene (7b). In a sealed tube were added $PdCl_2(PPh_3)_2$ (125 mg, 0.178 mmol) and CuI (188 mg 0.986 mmol). The mixture was purged with Ar for 5 min, and then degassed 2-fluoro-1-iodobenzene (1.00 mL, 8.75 mmol), degassed phenylacetylene (0.980 mL, 8.92 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 2 h and then was diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown powder. Purification by silica gel flash chromatography (hexanes) gave 1.54 g (7.84 mmol, 90%) of **7b** as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62−7.55 (m, 2H), 7.42−7.38 (m, 3H), 7.37−7.32 (m, 1H), 7.17−7.12 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.6 (d, J = 250.1 Hz), 133.4, 131.6, 129.9 (d, J = 7.7 Hz), 128.5, 128.3, 123.9 (d, J = 2.6 Hz), 122.9, 115.4 (d, J = 20.8 Hz), 111.9 (d, J = 15.3 Hz), 94.4, 82.7. TLC: R_f = 0.6 (hexanes). IR (ATR): 3060 (w), 2214 (w), 1949 (w), 1875 (w), 1670 (w), 1595 (m), 1570 (m), 1497 (s), 1450 (s), 1441 (s), 1262 (s), 1218 (s), 1158 (m), 1096 (m) cm^{-1}. HRMS (DART): calcd for $[C_{14}H_9FH]^+$ 197.0761, found 197.0765.

1-Fluoro-2-(*tert*-butylethynyl)benzene (7c). In a sealed tube were added $PdCl_2(PPh_3)_2$ (261 mg, 0.372 mmol) and CuI (149 mg 0.785 mmol). The mixture was purged with Ar for 5 min, and then degassed 4-fluoroiodobenzene (2.00 mL, 17.3 mmol), degassed *tert*-butylacetylene (4.25 mL, 34.5 mmol), and triethylamine (24 mL) were added in that order. The mixture was stirred at room temperature for 2 h and then was diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel plug (hexanes) gave 2.80 g (15.9 mmol, 83%) of **7c** as a clear, colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (dt, J = 8.0, 2.0 Hz, 1H), 7.27−7.22 (m, 1H), 7.08−7.04 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.7 (d, J = 248.8 Hz), 133.5, 129.0, 123.7, 115.3, 112.5, 103.9, 72.4, 30.9, 28.2. TLC: R_f = 0.55 (hexanes). IR (thin film): 2967 (s), 2854 (s), 2244 (m), 1719 (w), 1578 (m), 1572 (m), 1493 (s), 1475 (s), 1453 (s), 1363 (s), 1302 (s), 1263 (s), 1103 (s) cm^{-1}. HRMS (DART): calcd for $[C_{12}H_{13}FH]^+$ 177.1074, found 177.1064.

1-Ethynyl-2-(*p*-tolyloxy)benzene (8a). In a reaction flask under Ar, **7a** (130 mg, 1.08 mmol), *p*-cresol (130 mg, 1.20 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (134 mg, 1.19 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 16 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was carefully removed in vacuo to give a brown oil (the product is somewhat volatile). Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/5) gave 14.3 mg (0.0687 mmol, 5.0%) of **8a** as a light yellow, viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (dd, J = 7.7, 1.7 Hz, 1H), 7.27−7.25 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.04 (dt, J = 7.5, 1.1 Hz, 1H), 6.94 (d, J = 8.5 Hz, 2H), 6.83 (dd, J = 8.3, 0.9 Hz, 1H), 3.25 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0, 154.4, 134.2, 133.2, 130.2, 130.1, 122.7, 119.1, 117.8, 113.8, 81.5, 79.5, 20.7. TLC: R_f = 0.17 (CH_2Cl_2/hexanes, 1/10). IR (thin film): 3296 (m), 2920 (s), 2850 (s), 2107 (w), 1719 (m), 1599 (m), 1495 (m), 1462 (m), 1377 (m), 1208 (m), 1165 (w) cm^{-1}. HRMS (DART): calcd for $[C_{15}H_{12}OH]^+$ 209.0961, found 209.0976.

1-(Phenylethynyl)-2-(*p*-tolyloxy)benzene (8b). In a reaction flask under Ar, **7b** (64.9 mg, 0.331 mmol), *p*-cresol (39.0 mg, 0.361 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (40.7 mg, 0.363 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (230 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 69.3 mg (0.244 mmol, 74%) of **8b** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 10 Hz, 1H), 7.43 (dd, J = 6.6, 2.9 Hz, 2H), 7.35−7.26 (m, 4H), 7.18 (d, J = 10 Hz, 2H), 7.12 (t, J = 10 Hz, 1H), 6.99−6.96 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.9, 155.1, 133.6, 132.7, 131.7, 130.2, 130.1, 129.6, 128.2, 123.3, 123.2, 118.9, 118.5, 115.6, 94.2, 85.3, 20.7. TLC: R_f = 0.31 (CH_2Cl_2/hexanes, 1/9). IR (thin film): 3062 (m), 2923 (m), 2855 (w), 2222 (w), 1950 (w), 1596 (m), 1572 (m), 1505 (s), 1482 (s), 1445 (s), 1223 (s). HRMS (DART): calcd for $[C_{21}H_{16}OH]^+$ 285.1274, found 285.1288.

1-Ethoxy-2-(phenylethynyl)benzene (8c). In a reaction flask under Ar, 60% NaH in mineral oil (18.5 mg, 0.460 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed. DMSO (1.0 mL) and ethanol (0.116 mL, 0.460 mmol) were added, and the mixture was stirred for 1 h at 50 °C (until the solution became homogeneous). **7b** (82.0 mg, 0.418 mmol) dissolved in DMSO (2.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 88 mg (35.9 mmol, 86%) of **8c** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dt, J = 8.0, 1.5 Hz, 2H), 7.51 (dt, J = 8.0, 1.5 Hz, 1H), 7.41−7.24 (m, 4H), 6.98−6.87 (m, 2H), 4.15 (q, J = 7.0, 2H), 1.51 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.5, 133.4, 131.6, 129.6, 128.2, 128.0, 123.8, 120.4, 112.9, 112.2, 93.4, 85.9, 64.4, 14.8. TLC: R_f = 0.42 (CH_2Cl_2/hexanes, 1/9). IR (thin film): 3062 (w), 2222 (w), 1950 (w), 1596 (m), 1571 (m), 1497 (s), 1482 (s), 1451 (m), 1443 (m), 1262 (m), 1220 (s), 1097 (m) cm^{-1}. HRMS (DART): calcd for $[C_{16}H_{14}OH]^+$ 223.1117, found 223.1118.

1-(*tert*-Butylethynyl)-2-(*p*-tolyloxy)benzene (8d). In a reaction flask under Ar, **7c** (127 mg, 0.722 mmol), *p*-cresol (85.8 mg, 0.794 mmol), and DMSO (2.0 mL) were added. The reaction was started with the addition of KO*t*Bu (88.9 mg, 0.794 mmol). The reaction

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

mixture was stirred in an oil bath at 150 °C for 72 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 30 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 1/9) gave 128 mg (0.484 mmol, 67%) of **8d** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 7.5 Hz, 1H), 7.27−7.22 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.7, 140.9, 138.5, 137.5, 130.5, 129.6, 126.8, 121.1, 119.7, 119.6, 110.3, 99.0, 33.3, 31.0, 21.3. TLC: R_f = 0.18 (CH_2Cl_2/hexanes, 1/9). IR (thin film): 2968 (s), 2925 (s), 2242 (w), 1612 (m), 1599 (m), 1574 (m), 1505 (s), 1487 (s), 1446 (s), 1362 (m), 1263 (s), 1236 (s), 1206 (s) cm^{-1}. HRMS (DART): calcd for $[C_{19}H_{20}OH]^+$ 265.1587, found 265.1573.

1-Ethoxy-2-(*tert*-butylethynyl)benzene (8e). In a reaction flask under Ar, 60% NaH in mineral oil (19.0 mg, 0.475 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed. DMSO (1.0 mL) and ethanol (0.028 mL, 0.475 mmol) were added, and the mixture was stirred for 1 h at 50 °C (until the solution became homogeneous). **7c** (76.0 mg, 0.432 mmol) dissolved in DMSO (2.0 mL) was added to start the reaction, and the mixture was then stirred in an oil bath at 150 °C for 72 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (CH_2Cl_2/hexanes, 2/3) gave 47.7 mg (0.236 mmol, 56%) of **8e** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (dd, J = 7.5, 2.0 Hz, 1H), 7.16−7.08 (m, 1H), 6.82−6.72 (m, 2H), 3.99 (q, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 9H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.5, 133.1, 128.7, 120.4, 113.8, 112.4, 102.7, 64.3, 31.1, 28.2, 14.8. TLC: R_f = 0.11 (CH_2Cl_2/hexanes, 1/9). IR (ATR): 2968 (m), 2240 (w), 1596 (m), 1575 (m), 1492 (s), 1474 (s), 1361 (m), 1292 (m), 1275 (s), 1260 (s), 1243 (s) cm^{-1}. HRMS (DART): calcd for $[C_{14}H_{18}O]^+$ 203.1430, found 203.1437.

2-Phenyl-1-(*p*-tolyl)-1*H*-indole (9a). In a reaction flask under Ar, **7b** (105 mg, 0.534 mmol), *p*-toluidine (239 mg, 1.07 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (245 mg, 1.68 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → EtOAc/hexanes, 1/10) gave 108 mg (0.379 mmol, 71%) of **9a** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78−7.59 (m, 1H), 7.39−7.04 (m, 12H), 6.81 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.8, 139.1, 137.0, 135.9, 132.7, 129.9, 128.9, 128.2, 128.1, 127.8, 127.2, 122.2, 120.5, 110.7, 103.4, 21.2. TLC: R_f = 0.80 (EtOAc/hexanes, 2/8). IR (ATR): 3030 (w), 2922 (w), 1698 (w), 1675 (w), 1600 (m), 1512 (s), 1455 (s), 1351 (m), 1208 (m), 1109 (m), 1020 (m) cm^{-1}. HRMS (DART): calcd for $[C_{21}H_{17}N]^+$ 283.1361, found 283.1362.

2-*tert*-Butyl-1-(*p*-tolyl)-1*H*-indole (9b). In a reaction flask under Ar, **7c** (196 mg, 1.11 mmol), *p*-toluidine (237 mg, 2.51 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (281 mg, 2.51 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → EtOAc/hexanes, 1/10) gave 162 mg (0.611 mmol, 55%) of **9b** as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 10 Hz, 1H), 7.36−7.27 (m, 4H), 7.16 (t, J = 10 Hz, 1H), 6.76 (d, J = 10 Hz, 1H), 6.55 (s, 1H), 2.55 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.7, 140.9, 138.5, 137.6, 130.5, 129.7, 121.1, 119.8, 119.7, 99.2, 31.1, 30.9, 21.3. TLC: R_f = 0.40 (CH_2Cl_2/hexanes, 2/98). IR (ATR): 3028 (w), 2987 (w), 2967 (w), 1914 (w), 1523 (m), 1509 (s), 1455 (s), 1377 (m), 1358 (s), 1309 (m), 1253 (m), 1214 (m), 1107 (m) cm^{-1}. HRMS (DART): calcd for $[C_{19}H_{21}NH]^+$ 264.1747, found 264.1754.

1-Ethynyl-2-fluoro-4-(*p*-tolyloxy)benzene (11a). In a reaction flask were added **10** (272 mg, 1.97 mmol) and *p*-cresol (212 mg, 1.96 mmol). The flask was then purged with Ar for 5 min. To this flask was added 0.40 M KO*t*Bu in DMSO (5.0 mL), and the reaction mixture was then heated to 100 °C. After 6 h the reaction was quenched with 1 M HCl. The mixture was then extracted with CH_2Cl_2 (3 × 80 mL). Then the combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. Most of the CH_2Cl_2 in a small sample of the organic solution was removed in vacuo; the residual brown liquid was dissolved in $CDCl_3$, and a ^{1}H NMR spectrum was obtained to determine the ratios of the species present. The NMR sample was recombined with the organic solution, and the solvents were removed in vacuo. Purification by silica gel flash chromatography (EtOAc/hexanes, 2/98) gave 129 mg (0.568 mmol, 29%) of **11a** as a clear, yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (t, J = 8.3 Hz, 1H), 7.21−7.18 (m, 2H), 7.00−6.95 (m, 2H), 6.70 (ddd, J = 8.6, 2.4, 0.7 Hz, 1H), 6.66 (dd, J = 10.7, 2.4 Hz, 1H), 3.24 (d, J = 0.6 Hz, 1H), 2.36 (s, 3H). ^{19}F NMR (470 MHz, $CFCl_3$): δ −107.87 (dd, J = 10.6, 8.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.1 (d, J = 252.8 Hz), 160.2 (d, J = 10.4 Hz), 152.9, 134.6 (d, J = 3.0 Hz), 134.5, 130.5, 120.0, 113.1 (d, J = 3.2 Hz), 105.0 (d, J = 24.6 Hz), 104.3 (d, J = 16.1 Hz), 81.3 (d, J = 3.2 Hz), 76.9, 20.8. TLC: R_f = 0.17 (EtOAc/hexanes, 2:98). IR (thin film): 3299 (s), 3032 (m), 2924 (s), 2854 (s), 2113 (m), 1903 (w), 1736 (w), 1620 (s), 1604 (s), 1571 (s), 1495 (s), 1418 (s), 1275 (s), 1214 (s), 1167 (s), 1098 (s) cm^{-1}. HRMS (DART): calcd for $[C_{15}H_{12}FOH]^+$ 227.0867, found 227.0868.

1-Ethynyl-4-fluoro-2-(*p*-tolyloxy)benzene (11b). Compound **11b** was never isolated as a pure sample, but it could be isolated as the major product of a mixture (contaminated with **11a** and **11c**). This was obtained by silica gel flash chromatography (run twice, EtOAc/hexanes, 2/98; CH_2Cl_2/hexanes, 1/9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (dd, J = 8.6, 6.4 Hz, 1H), 7.27−7.20 (m, 2H), 6.97−6.94 (m, 2H), 6.73 (ddd, J = 8.6, 7.9, 2.5 Hz, 1H), 6.48 (dd, J = 10.2, 2.5 Hz, 1H), 3.24 (d, J = 0.6 Hz, 1H), 2.36 (s, 3H). ^{19}F NMR (470 MHz, $CFCl_3$): δ −107.52 (ddd, J = 9.9, 7.3, 7.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.3 (d, J = 250.8 Hz), 160.8 (d, J = 10.2 Hz), 153.3, 135.2 (d, J = 10.0 Hz), 134.3, 130.4, 119.4, 109.6 (d, J = 22.3 Hz), 109.2 (d, J = 3.5 Hz), 104.7 (d, J = 25.9 Hz), 81.2 (d, J = 1.8 Hz), 78.7 (d, J = 1.2 Hz), 20.8. TLC: R_f = 0.10 (EtOAc/hexanes, 2/98). IR (thin film): 3284 (s), 3070 (w), 2924 (w), 2109 (m), 1903 (w), 1736 (w), 1626 (s), 1611 (s), 1573 (s), 1509 (s), 1496 (s), 1281 (s), 1219 (s), 1095 (s) cm^{-1}. HRMS (DART): calcd for $[C_{15}H_{12}FOH]^+$ 227.0867, found 227.0872.

1-Ethynyl-2,4-bis(*p*-tolyloxy)benzene (11c). *Nonpreparative, 6 h Reaction Time.* In a reaction flask were added **10** (148 mg, 1.07 mmol) and *p*-cresol (242 mg, 2.09 mmol). The flask was then purged with Ar for 5 min. Dry, degassed DMSO (5.0 mL) was then added to the flask. KO*t*Bu (245 mg, 2.19 mmol) was then added to the reaction flask, which was heated in an oil bath at 100 °C. After 6 h the reaction was quenched with an aqueous 1 M HCl solution. The mixture was then extracted with CH_2Cl_2 (3 × 80 mL). Then the combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. Most of the CH_2Cl_2 in a small sample of the organic solution was removed in vacuo; the residual brown liquid was dissolved in $CDCl_3$,and a ^{1}H NMR spectrum was obtained to determine the ratios of the species present.

15 h Reaction Time. In a reaction flask were added **10** (270 mg, 1.96 mmol) and *p*-cresol (460 mg, 4.25 mmol). The flask was then purged with Ar for 5 min. Dry, degassed DMSO (8.0 mL) was then added to the flask. KO*t*Bu (468 mg, 4.17 mmol) was then added to the reaction flask, which was heated in an oil bath at 100 °C. After 15 h the reaction was quenched with an aqueous 1 M HCl solution. The mixture was then extracted with CH_2Cl_2 (3 × 80 mL). Then the

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by silica gel flash chromatography (run twice, EtOAc/hexanes, 2/98) gave 558 mg (1.78 mmol, 91%) of **11c** as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.5 Hz, 1H), 7.15−7.12 (m, 2H), 6.93−6.91 (m, 2H), 6.89−6.88 (m, 2H), 6.56 (dd, J = 8.5, 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 3.19 (s, 1H), 2.32 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.3, 159.6, 153.9, 153.4, 135.0, 133.8, 133.5, 130.4, 130.3, 119.5, 119.2, 111.8, 107.8, 107.8, 80.6, 79.3, 20.7. TLC: R_f = 0.03 (EtOAc/hexanes, 2/98). IR (thin film): 3286 (s), 3031 (m), 2922 (m), 2108 (m), 1889 (w), 1599 (s), 1504 (s), 1418 (s), 1275 (s), 1206 (s), 1100 (s) cm^{-1}. HRMS (DART): calcd for $[C_{22}H_{19}O_2H]^+$ 315.1380, found 315.1358.

1,5-Diethynyl-2,4-difluorobenzene (12a). In a reaction tube were added 1,3-dibromo-4,6-difluorobenzene[42] (523 mg, 1.92 mmol), $PdCl_2(PPh_3)_2$ (31.2 mg, 0.0445 mmol), and CuI (17.8 mg 0.049 mmol). The mixture was purged with Ar for 5 min, and then degassed trimethylsilylacetylene (1.36 mL, 15.1 mmol) and triethylamine (6 mL) were added in that order. The reaction tube was sealed and heated to 80 °C for 29 h. The reaction was quenched by loading the contents onto a silica plug and eluting with EtOAc. The solvent was removed in vacuo, then 1 M TBAF in THF (2 mL, contains 5% H_2O) was added, and the mixture was stirred for 10 min. Purification by silica gel flash chromatography (hexanes) gave 178.0 mg (1.10 mmol, 57%) of **12a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (t, J = 7.7 Hz, 1H), 6.88 (t, J = 8.9 Hz, 1H), 3.28 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.3 (dd, J = 259.4, 12.1 Hz), 138.7 (t, J = 2.8 Hz), 107.6 (dd, J = 14.4, 6.5 Hz), 104.7 (t, J = 25.5 Hz), 82.9 (t, J = 2.6 Hz), 75.0. TLC: R_f = 0.40 (hexanes). IR (KBr pellet): 3299 (m), 3286 (m), 2120 (w), 1802 (w), 1618 (s), 1586 (s), 1493 (s), 1409 (s), 1299 (m), 1156 (s), 1081 (s) cm^{-1}. HRMS (DART): calcd for $[C_{10}H_4F_2H]^+$ 163.0354, found 163.0356.

1,5-Bis(phenylethynyl)-2,4-difluorobenzene (12b). In a reaction tube were added 1,3-dibromo-4,6-difluorobenzene (1.41 g, 5.18 mmol), $PdCl_2(PPh_3)_2$ (216 mg, 0.308 mmol), and CuI (113 mg 0.595 mmol). The mixture was purged with Ar for 5 min, and then degassed phenylacetylene (2.80 mL, 25.5 mmol), DMF (6 mL), and triethylamine (6 mL) were added. The mixture was stirred under Ar for 1 h at room temperature, and then the reaction tube was sealed and heated to 80 °C for 40 h. The reaction was quenched by dilution with EtOAc and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic layers were flashed through a plug of silica gel with EtOAc (400 mL). The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes) gave 1.43 g (4.54 mmol, 88%) of **12b** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (t, J = 7.8 Hz, 1H), 7.57−7.53 (m, 4H), 7.38−7.36 (m, 6H), 6.93 (t, J = 9.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.3 (dd, J = 257.9, 11.9 Hz), 137.3 (t, J = 2.7 Hz), 131.7, 128.8, 128.4, 122.5, 108.8 (dd, J = 14.5, 6.4 Hz), 104.6 (t, J = 25.6 Hz), 94.6 (t, J = 2.6 Hz), 80.9. TLC: R_f = 0.20 (hexanes). IR (KBr pellet): 3059 (m), 2230 (w), 1681 (w), 1594 (m), 1581 (m), 1506 (s), 1406 (s), 1233 (s), 1144 (s) cm^{-1}. HRMS (DART): calcd for $[C_{22}H_{12}F_2H]^+$ 314.0907, found 314.0922.

1,5-Bis(*tert*-butylethynyl)-2,4-difluorobenzene (12c). In a reaction tube were added 1,3-dibromo-4,6-difluorobenzene (1.85 g, 6.80 mmol), $PdCl_2(PPh_3)_2$ (246 mg, 0.351 mmol), and CuI (133 mg 0.701 mmol). The mixture was purged with Ar for 5 min, and then degassed *tert*-butylacetylene (4.30 mL, 34.6 mmol), DMF (6 mL), and triethylamine (6 mL) were added. The mixture was stirred under Ar for 1 h at room temperature, and then the reaction tube was sealed and heated to 80 °C for 40 h. The reaction was quenched by dilution with EtOAc and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic layers were flashed through a plug of silica gel with EtOAc (400 mL). The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes) gave 1.79 g (6.52 mmol, 96%) of **12c** as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (t, J = 8.0 Hz, 1H), 6.77 (t, J = 9.1 Hz, 1H), 1.31 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.7 (dd, J = 255.2, 11.7 Hz), 137.6 (t, J = 2.8 Hz), 108.9 (dd, J = 14.7, 6.2 Hz), 104.0 (t, J = 25.8 Hz), 103.8 (t, J = 2.5 Hz), 70.9, 30.8, 28.1. TLC: R_f = 0.48 (hexanes). IR (thin film): 2970 (s), 2929 (m), 2869 (s), 2900 (s), 2231 (m), 1609 (m), 1587 (m), 1587 (s), 1504 (s), 1475 (s), 1404 (s), 1363 (s), 1246 (s), 1118 (s) cm^{-1}. HRMS (DART): calcd for $[C_{18}H_{20}F_2H]^+$ 275.1606, found 275.1625.

1,5-Bis(*n*-butylethynyl)-2,4-difluorobenzene (12d). In a sealed reaction vial were added 1,3-dibromo-4,6-difluorobenzene (1.19 g, 4.37 mmol), $PdCl_2(PPh_3)_2$ (165 mg, 0.235 mmol), and CuI (90.7 mg 0.476 mmol). The mixture was purged with Ar for 5 min, and then degassed 1-hexyne (2.50 mL, 21.6 mmol), DMF (6 mL), and triethylamine (6 mL) were added. The mixture was stirred under Ar for 1 h at room temperature, sealed, then heated to 80 °C for 40 h. The reaction was quenched by dilution with EtOAc and aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic layers were flashed through a plug of silica gel with EtOAc (400 mL). The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes) gave 1.03 g (3.74 mmol, 86%) of **12d** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (t, J = 7.9 Hz, 1H), 6.79 (t, J = 9.1 Hz, 1H), 2.42 (t, J = 7.0 Hz, 4H), 1.63−1.57 (m, 4H), 1.53−1.44 (m, 4H), 0.95 (t, J = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9 (dd, J = 255.1, 11.8 Hz), 137.5 (t, J = 2.9 Hz), 109.0 (dd, J = 14.7, 6.2 Hz), 104.1 (t, J = 25.8 Hz), 95.9 (t, J = 2.6 Hz), 72.3, 30.6, 21.9, 19.2, 13.6. TLC: R_f = 0.57 (hexanes). IR (thin film): 3064 (w), 2960 (s), 2934 (s), 2874 (s), 2238 (m), 2208 (m), 1712 (s), 1679 (m), 1589 (m), 1504 (s), 1407 (s), 1221 (m) cm^{-1}. HRMS (DART): calcd for $[C_{22}H_{13}F_2H]^+$ 275.1606, found 275.1616.

1,5-Diethynyl-2,4-bis(*p*-tolyloxy)benzene (13a). In a reaction flask under Ar, **12a** (163 mg, 1.01 mmol), *p*-cresol (236 mg, 2.19 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (240 mg, 2.13 mmol). The reaction mixture was stirred in an oil bath at 60 °C for 6 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/4) gave 318 mg (0.940 mmol, 93%) of **13a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.08 (d, J = 8.1 Hz, 4H), 6.84 (d, J = 8.5 Hz, 4H), 6.30 (s, 1H), 3.19 (s, 2H), 2.29 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.1, 153.6, 139.5, 133.6, 130.2, 118.8, 108.8, 107.6, 81.3, 78.1, 20.7. TLC: R_f = 0.11 (CH_2Cl_2/hexanes, 1/9). IR (KBr pellet): 3280 (s), 2923 (m), 2107 (m), 1889 (m), 1597 (s), 1561 (s), 1504 (s), 1535 (s), 1387 (s), 1294 (s), 1207 (s), 1082 (s) cm^{-1}. HRMS (DART): calcd for $[C_{24}H_{19}O_2H]^+$ 339.1380, found 339.1389.

1,5-Bis(phenylethynyl)-2,4-bis(*p*-tolyloxy)benzene (13b). In a reaction flask under Ar, **12b** (314 mg, 0.999 mmol), *p*-cresol (230 mg, 2.13 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (237 mg, 2.11 mmol). The reaction mixture was stirred in an oil bath at 60 °C for 6 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/4) gave 235 mg (0.887 mmol, 89%) of **13b** as a white, sticky solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.39−7.37 (m, 4H), 7.32−7.29 (m, 6H), 7.12 (d, J = 8.1 Hz, 4H), 6.91 (d, J = 8.6 Hz, 4H), 6.51 (s, 1H), 2.31 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 154.2, 138.1, 133.1, 131.5, 131.5, 130.2, 128.2, 123.2, 118.4, 110.6, 109.3, 93.9, 84.1, 20.7. TLC: R_f = 0.21 (CH_2Cl_2/hexanes, 1/10). IR (KBr pellet): 3075 (w), 3028 (w), 2208 (m), 1897 (w), 1590 (s), 1496 (s), 1392 (s), 1236 (s), 1192 (s), 1071 (s) cm^{-1}. HRMS (DART): calcd for $[C_{36}H_{27}O_2H]^+$ 491.2006, found 491.2006.

1,5-Bis(*tert*-butylethynyl)-2,4-bis(*p*-tolyloxy)benzene (13c). In a reaction flask under Ar, **12c** (280 mg, 1.02 mmol), *p*-cresol (238 mg, 2.20 mmol), and DMSO (3.0 mL) were added. The reaction

dx.doi.org/10.1021/jo400668v | J. Org. Chem. 2013, 78, 5987−5998

was started with the addition of KO*t*Bu (241 mg, 2.15 mmol). The reaction mixture was stirred in an oil bath at 80 °C for 20 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/4) gave 399 mg (0.887 mmol, 87%) of **13c** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.07 (d, J = 8.1 Hz, 4H), 6.81 (d, J = 8.6 Hz, 4H), 6.53 (s, 1H), 2.29 (s, 6H), 1.14 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.2, 154.9, 138.1, 132.3, 129.9, 117.6, 112.0, 111.1, 103.4, 73.6, 30.7, 28.0, 20.6. TLC: R_f = 0.08 (CH_2Cl_2/hexanes, 1/10). IR (KBr pellet): 2971 (s), 2867 (s), 2222 (m), 1982 (w), 1595 (s), 1506 (s), 1390 (s), 1327 (s), 1261 (s), 1109 (s) cm^{-1}. HRMS (DART): calcd for $[C_{32}H_{35}O_2H]^+$ 451.2632, found 451.2649.

1,3-Bis(*n*-butylethynyl)-4,6-bis(*p*-tolyloxy)benzene (13d). In a reaction flask under Ar, **12d** (267 mg, 0.975 mmol), *p*-cresol (224 mg, 2.08 mmol), and DMSO (3.0 mL) were added. The reaction was started with the addition of KO*t*Bu (231 mg, 2.05 mmol). The reaction mixture was stirred in an oil bath at 60 °C for 6 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → CH_2Cl_2/hexanes, 1/4) gave 159 mg (0.440 mmol, 45%) of **13d** as a clear, viscous, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.06 (d, J = 8.3 Hz, 4H), 6.81 (d, J = 8.6 Hz, 4H), 6.42 (s, 1H), 2.32 (t, J = 7.0 Hz, 4H), 2.29 (s, 6H), 1.49−1.42 (m, 4H), 1.40−1.35 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 154.6, 138.2, 132.6, 130.0, 118.0, 111.6, 109.9, 94.9, 75.1, 30.6, 21.8, 20.6, 19.3, 13.6. TLC: R_f = 0.10 (CH_2Cl_2/hexanes, 1/10). IR (thin film): 3031 (m), 2957 (s), 2930 (s), 2233 (m), 1881 (w), 1735 (m), 1598 (s), 1505 (s), 1487 (s), 1392 (s), 1308 (s), 1216 (s), 1168 (s), 1132 (s) cm^{-1}. HRMS (DART): calcd for $[C_{32}H_{34}O_2H]^+$ 451.2632, found 451.2653.

1,5-Diethoxy-2,4-bis(phenylethynyl)benzene (13e). In a reaction flask under Ar, 60% NaH in mineral oil (20.1 mg, 0.521 mmol) was added followed by hexanes (2.0 mL), and the mixture was stirred at room temperature for 20 min. The dispersion was allowed to settle, and the hexanes was removed via syringe. DMSO (1.0 mL) and EtOH (0.030 mL, 0.521 mmol) were added, and the mixture was stirred at room temperature for 30 min. Concurrently, **12b** (74 mg, 0.24 mol) was dissolved in DMSO (1.0 mL). At the end of the 30 min time period, the DMSO solution of **12b** was added, and the contents of the flask were sealed and heated for 18 h at 60 °C. At the end of 18 h, the reaction was quenched by the addition of 1 M HCl and CH_2Cl_2. The reaction mixture was further diluted with CH_2Cl_2 to a volume of 20 mL, and the aqueous layer was separated and discarded. The organic phase was washed with H_2O (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to give a brown solid. Purification by silica gel flash chromatography (EtOAc/hexanes, 2/8) gave 70.5 mg (0.197 mmol, 82%) of **13e** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.55−7.52 (m, 4H), 7.37−7.31 (m, 6H), 6.46 (s, 1H), 4.17 (q, J = 7.0 Hz, 4H), 1.53 (t, J = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.9, 137.6, 131.4, 128.2, 127.8, 123.9, 105.4, 97.5, 92.4, 85.1, 64.7, 14.7. TLC: R_f = 0.60 (EtOAc/hexanes, 2/8). IR (KBr pellet): 2979 (w), 2884 (w), 2214 (w), 1611 (m), 1592 (m), 1517 (m), 1421 (m), 1338 (s), 1257 (s), 1095 (m), 1044 (m) cm^{-1}. HRMS (DART): calcd for $[C_{26}H_{22}O_2]^+$ 366.1620, found 366.1630.

2,6-Diphenyl-1,7-di-*p*-tolyl-1,7-dihydropyrrolo[3,2-*f*]indole (14). In a reaction flask under Ar, **12b** (137 mg, 0.436 mmol), *p*-toluidine (207 mg, 1.91 mmol), and DMSO (2.0 mL) were added. The reaction was started with the addition of KO*t*Bu (213 mg, 1.91 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (hexanes → EtOAc/hexanes, 4/6) gave 81 mg (0.17 mmol, 38%) of **14** as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.85 (s, 6H), 7.27−7.21 (m, 14H), 7.10−7.19 (m, 4H), 6.89 (s, 1H), 2.33 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.8, 138.2, 136.6, 136.3, 133.1, 129.8, 128.7, 128.0, 127.7, 126.8, 125.1, 110.1, 103.3, 90.4, 21.1. TLC: R_f = 0.73 (EtOAc/hexanes, 3/7). IR (ATR): 3035 (w), 1604 (m), 1542 (m), 1512 (s), 1474 (m), 1438 (m), 1388 (s), 1292 (m), 1245 (m), 1212 (s), 1107 (m) cm^{-1}. HRMS (DART): calcd for $[C_{36}H_{28}N_2H]^+$ 489.2325, found 489.2337.

6-Fluoro-2-phenyl-5-(phenylethynyl)-1-(*p*-tolyl)-1*H*-indole (15). In a reaction flask under Ar, **12b** (28.0 mg, 0.0891 mmol), *p*-toluidine (9.72 mg, 0.0891 mmol), and DMSO (0.8 mL) were added. The reaction was started with the addition of KO*t*Bu (21.4 mg, 0.178 mmol). The reaction mixture was stirred in an oil bath at 100 °C for 18 h. The reaction was quenched by dilution with CH_2Cl_2 and 1 M HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by silica gel flash chromatography (run twice, hexanes → CH_2Cl_2/hexanes, 3/7) gave 10 mg (0.029 mmol, 26%) of **15** as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 6.8 Hz, 1H), 7.54−7.48 (m, 2H), 7.32−7.23 (m, 3H), 7.21−7.13 (m, 7H), 7.07−7.01 (m, 2H), 6.91 (d, J = 10.2 Hz, 1H), 6.67 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.5 (d, J = 228 Hz), 142.2 (d, J = 3.75 Hz), 139.1, 139.0, 137.7, 135.2, 132.0, 131.6, 130.7, 128.7, 128.3, 128.2, 128.0, 127.5, 127.4, 125.0, 125.0, 124.4, 123.6, 105.2 (d, J = 18.2 Hz), 103.2, 97.5 (d, J = 26.3 Hz), 92.1, 84.4, 21.2. TLC: R_f = 0.37 (CH_2Cl_2/hexanes, 3/7). IR (ATR): 3064 (w), 2921 (m), 2852 (w), 2220 (w), 1736 (w), 1620 (m), 1606 (m), 1511 (s), 1465 (s), 1457 (s), 1380 (s), 1323 (s), 1261 (s), 1177 (s), cm^{-1}. HRMS (DART): calcd for $[C_{29}H_{20}FNH]^+$ 402.1653, found 402.1682.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving details of rate measurements and calculation of substituent constants and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for J.L.K.: jlkatz@colby.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation (CHE-0640729, CHE-0552292, CHE-1062944), the Dreyfus Foundation, and Colby College.

■ REFERENCES

(1) (a) Shao, Z.; Peng, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9566−9568. (b) Majumdar, K. C.; Ray, K. *Synthesis* **2011**, *23*, 3767−3783. (c) Slavin, S.; Burns, J.; Haddleton, D. M.; Becer, C. R. *Eur. Polym, J.* **2011**, *47*, 435−446.

(2) (a) Katritzky, A. R.; Taylor, R. J. K. Alkynes. *Comprehensive Organic Functional Group Transformation II*; Elsevier: Amsterdam, 2005; Vol. *1*, pp 1083−1176. (b) Diedrich, F.; Stang, P. J.; Tykwinski, R. R. *Acetylene Chemistry*; Wiley-VCH: New York, 2005. (c) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937−2980.

(3) (a) Sonogashira, K.; Tohda, Y, Y.; Hagihra, N. *Tetrahedron Lett.* **1975**, *107*, 4467−4470. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46−49.

(4) (a) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642−13643. (b) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874−922. (c) Hutchings, J. H.; Brust, M.; Schmidbaur, H. *Chem. Soc. Rev.* **2008**, *37*, 1759−1765. (d) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643−710. (e) Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 12078−12079. (f) Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084−5121. (g) Schilz, M.; Plenio, H. *J. Org. Chem.* **2012**, *77*, 2798−2807.
(5) (a) Huisgen, R.; Szeimies, G.; Moebius, L. *Chem. Ber.* **1976**, *100*, 2492−2507. (b) Lwowski, W. In *1,3 Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. *1*, Chapter 5. (c) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613−628. (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (e) Amblard, F.; Cho, J. H.; Schinazi, R. *Chem. Rev.* **2009**, *109*, 4207−4220.
(6) (a) Pennella, F.; Banks, R. L.; Bailey, G. C. *Chem. Commun.* **1968**, 1548−1549. (b) Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, *97*, 1592−1594. (c) Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145−180. (d) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3758−3578. (e) Heppekansen, J.; Stade, R.; Goddard, R.; Furstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11045−11053.
(7) (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422−424. (b) Siemsen, P.; Livingston, R. L.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657. (c) Paixo, M. W.; Weber, M.; Bruga, A. L.; de Azeredo, J. B.; Deobald, A. M.; Sefuni, H. A. *Tetrahedron Lett.* **2008**, *49*, 2366−2370. (d) Liu, C.; Zhang, H.; Sui, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780−1824.
(8) (a) Coulson, C. A. *Valence*, 2nd ed.; Oxford University Press: Oxford, U.K., 1961; p 218. (b) Wiberg, K. B.; Bader, R. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001−1012. (c) Boyd, R. J.; Boyd, S. *J. Am. Chem. Soc.* **1992**, *114*, 1652−1655.
(9) Baker, J. W.; Cooper, K. E.; Ingold, C. K. *J. Chem. Soc.* **1928**, 426−431.
(10) Brown, H. C.; Flethcer, R. S. *J. Am. Chem. Soc.* **1949**, *71*, 1845−1854.
(11) Kochi, J. K.; Hammond, G. S. *J. Am. Chem. Soc.* **1953**, *75*, 3452−3458.
(12) (a) Charton, M. *J. Org. Chem.* **1961**, *26*, 735−738. (b) Charton, M. *J. Org. Chem.* **1965**, *30*, 552−557. (c) Charton, M. *J. Org. Chem.* **1965**, *30*, 557−560.
(13) Landgrebe, J. A.; Rynbrandt, R. H. *J. Org. Chem.* **1966**, *31*, 2583−2585.
(14) (a) Marriot, S.; Reynolds, W. F.; Taft, R. W.; Topsom, R. D. *J. Org. Chem.* **1984**, *49*, 959−965. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(15) (a) Streitwieser, A. *J. Am. Chem. Soc.* **1956**, *78*, 4935−4938. (b) Hine, J.; Bailey, W. C., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 2075−2078.
(16) (a) Rubin, M.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10243−10249. (b) Kleinpeter, E.; Schulenburg, A. *J. Org. Chem.* **2006**, *71*, 3869−3875. (c) Music, Z.; Vianello, R. *Tetrahedron* **2006**, *62*, 3402−3411.
(17) (a) Lucas, X.; Quinonero, D.; Frontera, A.; Deya, P. M. *J. Phys. Chem. A* **2009**, *113*, 10367−10375. (b) Lucas, X.; Quinonero, D.; Frontera, A.; Deya, P. M. *J. Phys. Chem. A* **2010**, *114*, 1926−1930.
(18) (a) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91−94. (b) Katz, J. L.; Geller, B. J.; Conry, R. R. *Org. Lett.* **2006**, *8*, 2755−2758. (c) Katz, J. L.; Geller, B. J.; Foster, P. D. *Chem. Commun.* **2007**, 1026−1028. (d) Wackerly, J. W.; Meyer, J. M.; Crannell, W. C.; King, S. B.; Katz, J. L. *Macromolecules* **2009**, 8181−8186. (e) Katz, J. L.; Tschaen, B. *Org. Lett.* **2010**, *19*, 4300−4303. (f) Bizier, N. P.; Vernamonti, J. P.; Katz, J. L. *Eur. J. Org. Chem.* **2012**, *12*, 2303−2307.
(19) (a) Paventi, M.; Hay, A. S. *Tetrahedron Lett.* **1993**, *34*, 999−1002. (b) Strukelj, M.; Paventi, M.; Hay, A. S. *Macromolecules* **1993**, *26*, 1777−1778. (c) Hennrich, G.; Echavarren, A. M. *Tetrahedron Lett.* **2004**, *45*, 1147−1149.
(20) Eaborn, C.; Thompson, A. R.; Walton, D. R. M. *J. Chem. Soc. B* **1969**, 859−861.
(21) Exner, O. In *Correlation Analysis in Chemistry*; Chapman, M. B., Shorter, J., Eds.; Plenum: New York, 1978; Chapter 10.
(22) Litvinenko, L. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1962**, *11*, 1653−1661.
(23) Fringuelli, F.; Serena, B.; Taticchi, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 971−975.
(24) Sheppard, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 1314.
(25) Cohen, L. A.; Jones, W. M. *J. Am. Chem. Soc.* **1963**, *85*, 3397−3402.
(26) Gholap, A. R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2005**, *70*, 4869−4872.
(27) Subjection of 4-fluorostyrene to nucleophilic substitution by *p*-cresol furnished only mixtures of oligomeric products.
(28) Benzyl alcohol was chosen for reaction with **1a** because substitution products using lower molecular weight alcohols were quite volatile and this created difficulties in obtaining consistent and accurate product yields.
(29) (a) Kohler, E. P.; Potter, H. A. *J. Am. Chem. Soc.* **1935**, *57*, 1316−1318. (b) Truce, W. E.; Simms, J. A.; Boudakkian, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 695−696. (c) Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2005**, *70*, 6468−6473.
(30) For related cyclizations, see: (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652−7662. (c) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275−5278. (d) Kabaalka, G. H.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, 8017−8028. (e) Alonso, F.; Belestkaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3160. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, 2285−2310. (g) Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311−11316.
(31) Chambers, R. D.; Seabury, M. J.; Williams, D. L. H.; Hughes, N. *J. Chem. Soc., Perkin Trans. 1* **1988**, 251−254.
(32) Taylor, P. J.; Wait, A. R. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1765−1770.
(33) Biggs, A. I.; Robinson, R. A. *J. Chem. Soc.* **1961**, 388−393.
(34) (a) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527−1530. (b) Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008**, *35*, 5946−5951.
(35) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670−12671.
(36) Brown, J.; Cooley, N.; Price, D. *J. Chem. Soc., Chem. Commun.* **1989**, *8*, 458−460.
(37) Nagassa, F.; Lindsey, E.; Haines, B. *Tetrahedron* **2009**, *65*, 4085−4091.
(38) Ackerman, L. *Org. Lett.* **2005**, *7*, 439−442.
(39) Schulze, B.; Escudero, D.; Friebe, C.; Siebert, R.; Gorls, H.; Sinn, S.; Thomas, M.; Mai, S.; Popp, J.; Dietzek, B.; Gonzalez, L.; Schubert, U. *Chem. Eur. J.* **2012**, *18*, 4010−4025.
(40) (a) Heppolette, R. L.; Miller, J. *J. Am. Chem. Soc.* **1953**, *75*, 4265−4268. (b) Miller, J. *J. Am. Chem, Soc.* **1954**, *76*, 448−450. (c) Heppolette, R. L.; Miller, J. *J. Chem. Soc.* **1955**, 2929−2931. (d) Miller, J.; Kai-Yan, W. *J. Chem. Soc.* **1963**, 3492−3495. (e) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: London, 1968.
(41) (a) Bevan, C. W. L. *J. Chem. Soc.* **1951**, 2340−2342. (b) Bevan, C. W. L. *J. Chem. Soc.* **1953**, 655−657. (c) Bevan, C. W. L.; Bye, G. C. *J. Chem. Soc.* **1954**, 3091−3094.
(42) Manka, J. T.; McKenzie, V. C.; Kaszynski, P. *J. Org. Chem.* **2004**, *69*, 1967−1971.