JOC The Journal of Organic Chemistry

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Cycloaromatization Protocol for Synthesis of Polysubstituted Phenol Derivatives: Method Development and Mechanistic Studies

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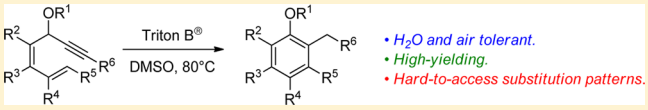
Supporting Information

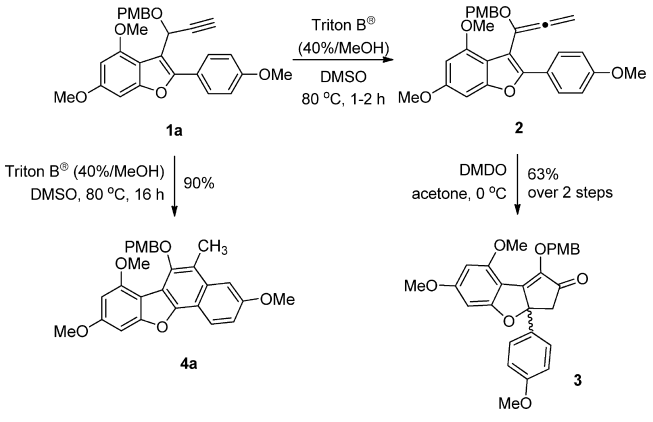
ABSTRACT: The scope of the cycloaromatization of propargylic ethers was explored using operationally simple air- and moisture-insensitive conditions. Highly substituted phenol derivatives were obtained in high yields. Mechanistic experiments indicate that the reaction occurs by an electrocyclization followed by 1,3-proton transfer.



Because of their pervasive presence in naturally occurring compounds, drugs, and materials, new protocols for the synthesis of substituted phenols are of value, especially if they can be conducted inexpensively and conveniently. Procedures that deliver the aromatic system in one step from an acyclic precursor are valuable components of the toolbox because they can allow access to substitution patterns that cannot be installed directly through conventional aromatic substitution or cross-coupling chemistry. In this note, we report an efficient method for the preparation of functionalized phenol derivatives.

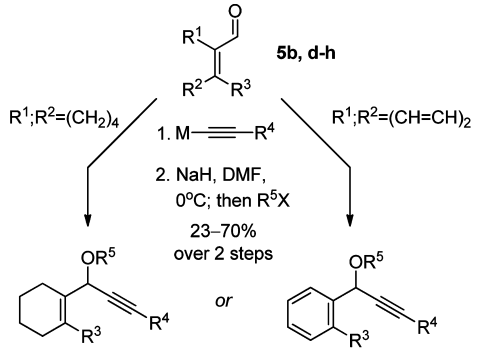
We recently reported our synthetic efforts toward the synthesis of the cytostatic natural product (±)-rocaglamide,[1] in which the key step was an oxidation-initiated Nazarov cyclization[2] of a benzofuryl allene intermediate. During these studies, we found that treatment of propargylic ether **1a** with a substoichiometric amount of Triton B in DMSO was the most effective way to isomerize **1a** to terminal allene **2** (Scheme 1). Oxidation-initiated Nazarov cyclization with dimethyldioxirane (DMDO) produced *des*-phenyl rocaglamide intermediate **3**. It was interesting to find that when **1a** was treated with Triton B in DMSO at 80 °C overnight, the product isolated was **4a** (90% yield), instead of the expected alkoxyallene **2**.

Scheme 1. Cyclization Reactions of Propargylic Ether 1a



We were impressed by the high yield and operational simplicity of the reaction, which could be run in wet solvent under air and gave **4a** in high purity after workup without chromatography. A variety of propargylic ethers were prepared to test the scope of the reaction (Scheme 2). We expected that

Scheme 2. Synthesis of Propargylic Ethers



1b: R^3 = Ph, R^4 = H, R^5 = Me
1c: R^3 = Ph, R^4 = H, R^5 = Bn
1d: R^3 = 1-naphthyl, R^4 = H, R^5 = Me
1e: R^3 = 2-thienyl, R^4 = H, R^5 = Me
1h: R^3 = vinyl, R^4 = Ph, R^5 = Me
1f: R^3 = Ph, R^4 = H, R^5 = Me
1g: R^3 = 2-propenyl, R^4 = H, R^5 = Me

substrates of type **1**, bearing an alkoxyl substituent, would facilitate the initial allene isomerization and polarize electrocyclization of the resulting dienyl allene. As such, we treated aldehydes **5a**, **5b**, and **5d–h** with an alkynylmetal to form intermediate propargylic alcohols, which were O-alkylated to give propargylic ethers **1a–h**.

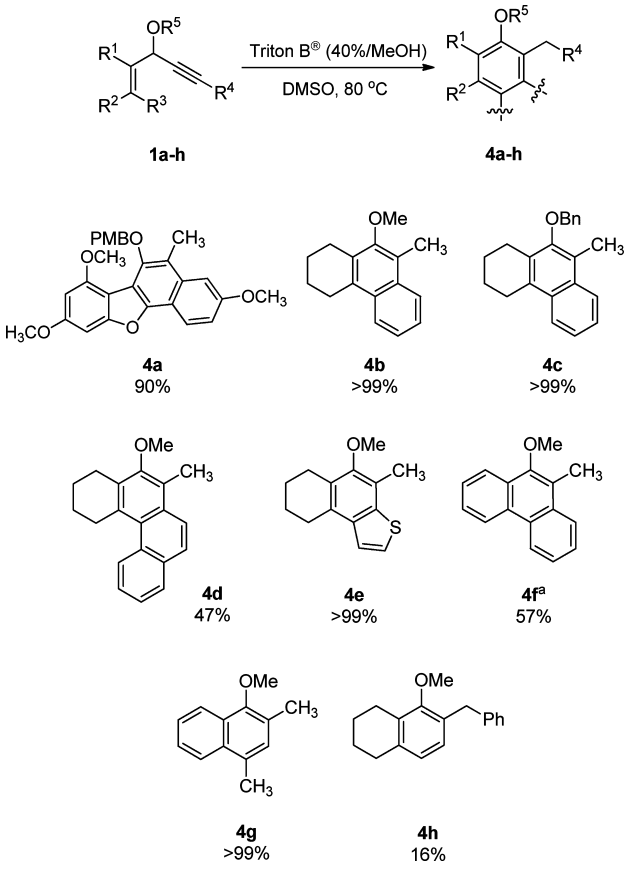
Subjection of propargylic ethers **1a–h** to the cycloaromatization conditions (Triton B, DMSO, 80 °C) provided benzenoid products **4a–h** (Scheme 3).

Alkenes (**4g** and **4h**), benzene rings (**4a–c** and **4f**), and heteroaromatic rings (**4a** and **4e**) were all viable π-components

Received: June 21, 2012
Published: August 14, 2012

dx.doi.org/10.1021/jo3010952 | J. Org. Chem. 2012, 77, 7730–7736

Scheme 3. Cycloaromatization of Propargylic Ethers

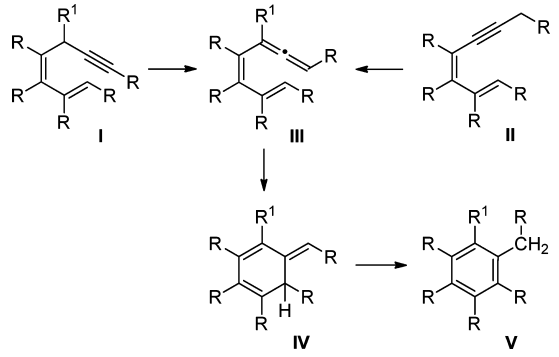


[a]Temperature of 95 °C required; 80 °C produced only allene intermediate.

in the cycloaromatization. In multiple cases (**4b**, **4c**, **4e**, and **4g**), the crude products were obtained pure and in quantitative yields. However, naphthalene-containing propargylic ether **1d** cyclized less efficiently, yielding phenanthrene product **4d** in 47% yield. Cyclization of propargylic ether **1f**, in which both non-allene π-components are benzene rings, proceeded in a modest 57% yield and required heating (95 °C) to achieve complete conversion to **4f**. Cyclization of propargylic ether **1h** (R_4 = Ph) produced a low yield of **4h** (16%). In this reaction, we observed incomplete conversion of the propargylic ether to the allenol ether, sluggish cyclization, and decomposition. Another substrate with a terminal alkyne substituent (R4 = *n*-Bu) gave a similar result: incomplete alkyne-allene isomerization and inefficient electrocyclization, resulting in a low yield.

Cycloaromatizations of both propargyl dienes of type **I**[3] and conjugated propargyl dienes of type **II**[4] have been reported. With respect to the specific case of dienyl propargylic ethers (**I**; R^1 = OR), the only examples we found involved highly reactive π-systems bearing multiple heteroatoms.[3] These cycloaromatization reactions have been postulated to begin with base-catalyzed or -promoted isomerization of **I** or **II** to dienyl allene **III**,[5] which undergoes electrocyclization to form methylenecyclohexadiene intermediate **IV**,[6,7] which finally isomerizes to aromatic system **V** (Scheme 4). In many of the reported examples, the three-step sequence converting **I**/**II** to **V** occurs in situ, without isolation or even observation of intermediates **III** and **IV**. Support for the proposed mechanism in Scheme 4 is limited to data from individual experiments across different

Scheme 4. Isomerization−Electrocyclization−Isomerization of Propargyl Dienes



intermediate π-systems,[4a,b,d,e,5b,c] with no coherent study of the entire reaction sequence. This prompted us to conduct a systematic examination of the three-step cycloaromatization sequence that converts propargyl dienes **I** into phenol derivatives **V** (R^1 = OR).

In one cycloaromatization experiment of **1h** using identical conditions as shown in Scheme 3, we isolated a methylenecyclohexadiene intermediate of type **IV** instead of the expected product **4h**. This supports electrocyclization of a dienyl allene of type **III**, which must then undergo subsequent isomerization to form the aromatic product **V**.

Two isomerization mechanisms are possible: [1,7]-hydride shift or proton transfer. In most reports of related cycloaromatizations, a mechanism for isomerization is not proposed. However, Burton[4a] and Zhou[4d] have shown through deuterium-labeling experiments that proton transfer from the solvent is at least partially responsible for isomerization. We were interested in extending these studies in the context of our system.

Experiments with base provide insight into the isomerization mechanism: when allene **2** is heated in DMSO at 80 °C in the absence of Triton B, we observed a mixture of starting allene **2**, cycloaromatized product **4a**, and some decomposition. A proton transfer mechanism is consistent with the experimental observation that base improves isomerization efficiency and suggests that a [1,7]-hydride shift is not the primary mechanistic pathway.

To examine whether the isomerization is intramolecular ([1,3]-proton transfer) or intermolecular (involving solvent), we subjected deuterium-labeled substrate **1i** to the reaction conditions (Scheme 5). We observed a mixture of 35% α-toluyl-nondeuterated product (**4i**) and 65% -deuterated (**4i′**) product, indicating that some proton transfer from the solvent must occur.[8]

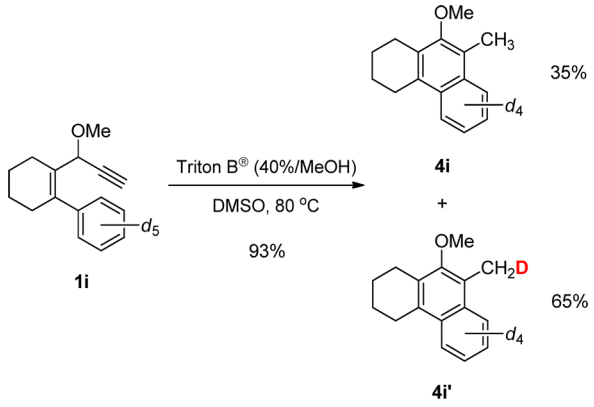
To determine whether deuterium incorporation in the product is the result of intra- or intermolecular deuterium transfer between molecules of type **IV**, we performed a deuterium-labeling crossover experiment (Scheme 6).

We subjected a 1:1 mixture of **1c**/**1i** to the reaction conditions and did not observe crossover product **4c′**, which is consistent with a [1,3]-intramolecular proton transfer mechanism.[9] The ratio of **4i** to **4i′** was the same as that obtained in the original labeling experiment (Scheme 5).

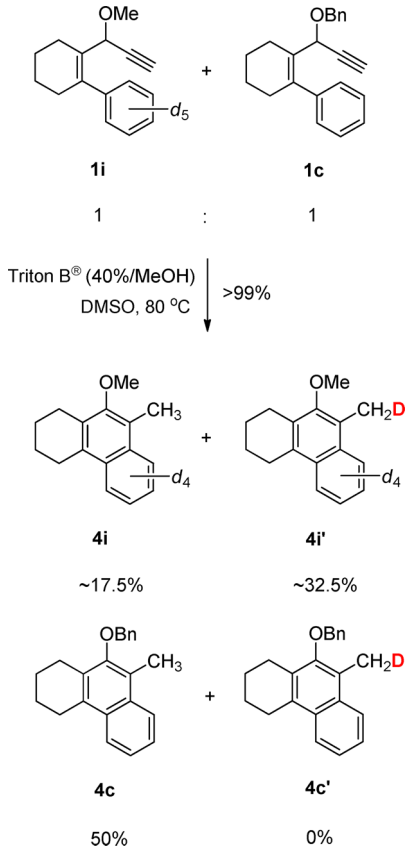
If the basic conditions employed in the cycloisomerization of deuterated substrate **1i** were altered, different product ratios were observed. When sodium methoxide powder in DMSO was used rather than Triton B (40% in methanol) in DMSO, nearly

dx.doi.org/10.1021/jo3010952 | J. Org. Chem. 2012, 77, 7730−7736

Scheme 5. Deuterium-Labeling Experiment

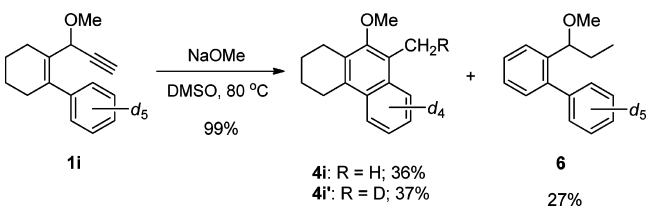


Scheme 6. Double-Labeling Crossover Experiment



a 1:1 mixture of cycloaromatization products **4i** and **4i′** (73% combined yield) was obtained, along with 27% of unexpected biaryl product **6** (Scheme 7). Finally, when **1i** was treated with sodium methoxide in neat methanol,[10] no reaction was observed.

Scheme 7. Competing Isomerization



If the electrocyclization rate is unchanged, isolation of the uncyclized product suggests that the isomerization following electrocyclization is less favorable under these reaction conditions. Furthermore, the 1:1 ratio of **4i**/**4i′** indicates a decrease in intramolecular proton transfer relative to that observed using Triton B (~2:1 ratio; see Scheme 5). One possible explanation is that, at low methanol concentrations, the methanol−carbanion complex in the intramolecular 1,3-proton transfer mechanism proposed by Cram is less likely to form.[9] This would result in a decrease in the rate of intramolecular 1,3-proton transfer relative to intermolecular proton transfer and may allow the simple isomerization pathway that produces **6** to become competitive. The heightened basicity of the medium may also favor the conversion of **1i** to **6**.[11]

It seems plausible that biaryl product **6** may be formed from intermediate allene of type **III** (Scheme 4) through a series of base-catalyzed double-bond transpositions. Since reducing the alcohol content in the alcohol/DMSO solvent systems is known to dramatically increase the rates of alkoxide-catalyzed isomerizations and other reactions that involve deprotonation,[11] it is not surprising that this alternate pathway competes with cycloaromatization under these conditions.

In conclusion, we have demonstrated a simple method for the base-catalyzed cycloaromatization of propargylic ethers and provided mechanistic evidence that the reaction proceeds through the electrocyclization of an allenyl diene followed by a combination of intra- and intermolecular proton transfer. The reaction is not air- and moisture-sensitive, tolerates a range of alkenyl and aromatic π-components, and proceeds in good to excellent yields, making it an appealing option for the synthesis of phenol derivatives.

EXPERIMENTAL SECTION

General Experimental Methods. Reactions were carried out in oven- or flame-dried glassware under argon with magnetic stirring unless otherwise specified. Dry solvents were obtained from a solvent purification system or distilled over calcium hydride prior to use. Reagents were used as received unless otherwise specified. *n*-Butyl lithium was titrated periodically with diphenylacetic acid. Thin layer chromatography was visualized with *p*-anisaldehyde/heat, potassium permanganate/heat, vanillin/heat, or a UV lamp. ^{1}H NMR and ^{13}C NMR spectroscopy were performed at ambient temperature. 2-Bromocyclohex-1-enecarbaldehyde,[12] phenylboronic acid-d_5,[13] and 4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-carbaldehyde (**5a**)[1b] were prepared according to literature procedures.

General Procedure for the Synthesis of Aldehydes 5b and 5d−i. To an argon-sparged solution of the corresponding bromide (400 mg, 2.13 mmol), boronic acid derivative (519 mg, 4.26 mmol), and cesium carbonate (2.08 g, 6.39 mmol) in dry THF (21 mL) was added tetrakis(triphenylphosphine)palladium(0) (492 mg, 0.426 mmol). After an additional 2 min sparging, the mixture was stirred at 60 °C for 16 h at which time it was diluted with water (100 mL) and extracted with dichloromethane (3 × 150 mL). The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was flash chromatographed on silica gel to afford the product aldehyde.

*3,4,5,6-Tetrahydro-[1,1′-biphenyl]-2-carbaldehyde (**5b**).* Compound **5b** was obtained from 2-bromocyclohex-1-enecarbaldehyde and phenylboronic acid following the general procedure. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded aldehyde **5b** (360 mg, 92%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.50−7.36 (m, 3H), 7.33−7.25 (m, 2H), 2.61−2.58 (m, 2H), 2.43−2.39 (m, 2H), 1.94−1.67 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 159.3, 139.4, 135.7, 128.6, 128.2, 128.1, 33.9, 22.4, 22.3, 21.4 (lit.[14] ^{1}H NMR, ^{13}C NMR).

dx.doi.org/10.1021/jo3010952 | J. Org. Chem. 2012, 77, 7730−7736

*2-(Naphthalen-1-yl)cyclohex-1-enecarbaldehyde (**5d**).* Compound **5d** was obtained from 2-bromocyclohex-1-enecarbaldehyde and 1-naphthylboronic acid following the general procedure. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded aldehyde **5d** (845 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.90−7.79 (m, 2H), 7.76−7.65 (m, 1H), 7.57−7.38 (m, 3H), 7.38−7.28 (m, 1H), 2.64−2.55 (m, 1H), 2.46−2.36 (m, 2H), 1.89−1.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 158.6, 137.5, 137.1, 133.5, 131.4, 128.5, 128.2, 126.7, 126.2, 125.8, 125.1, 125.1, 34.7, 30.9, 22.5, 22.0, 21.7; HRMS (ESI+, TOF) m/z calcd for $C_{17}H_{17}O$ [M + H] 237.1279, found 237.1269.

*2-(Thiophen-3-yl)cyclohex-1-enecarbaldehyde (**5e**).* Compound **5e** was obtained from 2-bromocyclohex-1-enecarbaldehyde and 3-thienylboronic acid following the general procedure. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded aldehyde **5e** (575 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.37 (dd, J = 5.0, 3.0 Hz, 1H), 7.20 (dd, J = 3.0, 1.2 Hz, 1H), 7.07 (dd, J = 5.0, 1.2 Hz, 1H), 2.62−2.49 (m, 2H), 2.42−2.28 (m, 2H), 1.86−1.64 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 153.5, 139.7, 136.5, 128.0, 126.0, 125.1, 33.3, 22.6, 22.5, 21.4; HRMS (EI+, sector instrument) m/z calcd for $C_{11}H_{12}OS$ [M] 192.0609, found 192.0616.

*[1,1′-Biphenyl]-2-carbaldehyde (**5f**).* Compound **5f** was obtained from 2-bromobenzaldehyde and phenylboronic acid following the general procedure. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded aldehyde **5f** (1.36 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.65 (dt, J = 7.8, 1.3 Hz, 1H), 7.56−7.33 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 145.9, 137.7, 133.7, 133.5, 130.8, 130.1, 128.4, 128.1, 127.8, 127.5 (lit.[15] ^{1}H NMR, ^{13}C NMR).

*2-(Prop-1-en-2-yl)benzaldehyde (**5g**).* Compound **5g** was obtained from 2-bromobenzaldehyde and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane following the general procedure, using potassium phosphate as the base. Silica gel purification eluting with 99:1−96:4 hexanes/EtOAc afforded aldehyde **5g** (657 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.00−7.89 (m, 1H), 7.64−7.52 (m, 1H), 7.50−7.32 (m, 4H), 5.48 (s, 1H), 4.96 (s, 1H), 2.22 (s, 3H) (lit.[16] ^{1}H NMR).

*2-Vinylcyclohex-1-enecarbaldehyde (**5h**).* Compound **5h** was obtained from 2-bromocyclohex-1-enecarbaldehyde and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane following the general procedure, using potassium phosphate as the base. Silica gel purification eluting with 99:1−8:2 hexanes/EtOAc afforded aldehyde **5h** (30 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.29 (dd, J = 17.2, 11.1 Hz, 1H), 5.51 (d, J = 17.2 Hz, 1H), 5.40 (d, J = 11.1 Hz, 1H), 2.40 (t, J = 6.1 Hz, 2H), 2.28 (t, J = 6.1 Hz, 2H), 1.71−1.53 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 151.9, 135.6, 131.7, 119.1, 27.0, 22.8, 21.7, 21.4; HRMS (EI+, sector instrument) m/z calcd for $C_9H_{12}O$ [M] 136.0888, found 136.0880.

*3,4,5,6-Tetrahydro-[1,1′-biphenyl]-2-carbaldehyde-d_5 (**5i**).* Compound **5i** was obtained from 2-bromocyclohex-1-enecarbaldehyde and phenylboronic acid-d_5 following the general procedure. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded aldehyde **5i** (184 mg, 61%).

General Procedure for the Synthesis of Propargylic Ethers 1a−i. To a solution of aldehyde (250 mg, 0.8 mmol) in tetrahydrofuran (8 mL) was added ethynylmagnesium bromide[17] (0.5 M in tetrahydrofuran, 1.8 mL, 0.88 mmol) at −78 °C. After addition, the cooling bath was removed and the reaction solution was stirred at room temperature for 16 h. The solution was quenched with saturated aqueous ammonium chloride (50 mL) and partially concentrated in vacuo to remove tetrahydrofuran. Distilled water (150 mL) was added, then the mixture was extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel to afford the product propargylic alcohol.

To a solution of propargylic alcohol (218 mg, 0.64 mmol) in dry *N*,*N*-dimethylformamide (5.4 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 31 mg, 0.77 mmol) in one portion. The deep red suspension was stirred for 45 min, after which an alkyl halide (0.10 mL, 0.77 mmol) was added slowly. The mixture was stirred to room temperature over 16 h, then diluted with saturated aqueous ammonium chloride (70 mL) and a 5% w/w aqueous solution of lithium chloride (80 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 × 150 mL), and the combined organics were washed with a 5% w/w aqueous solution of lithium chloride (4 × 50 mL) and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow residue was purified by flash chromatography on silica gel (95:5−7:3 hexanes/ethyl acetate) to afford the product propargylic ether.

*4,6-Dimethoxy-3-(1-((4-methoxybenzyl)oxy)prop-2-yn-1-yl)-2-(4-methoxyphenyl)benzofuran (**1a**).* Compound **1a** was obtained from compound **5a** following the general procedure, using *para*-methoxybenzyl chloride as the alkylating agent. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded propargylic ether **1a** (125 mg, 36% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.9 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 1.9 Hz, 1H), 6.30 (d, J = 1.9 Hz, 1H), 6.02 (d, J = 2.4 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.37 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 159.2, 158.9, 155.4, 154.3, 152.5, 130.1, 129.7, 128.3, 123.1, 113.6, 113.5, 111.9, 111.7, 94.6, 87.9, 81.5, 73.6, 69.8, 61.6, 55.8, 55.4, 55.3; HRMS (ESI+, TOF) m/z calcd for $C_{28}H_{26}O_6Na$ [M + Na^+] 481.1627, found 481.1631.

*6-(1-Methoxyprop-2-yn-1-yl)-2,3,4,5-tetrahydro-1,1′-biphenyl (**1b**).* Compound **1b** was obtained from compound **5b** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded propargylic ether **1b** (184 mg, 52% over 2 steps) along with recovered propargylic alcohol (48 mg, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 7.28−7.22 (m, 1H), 7.19−7.14 (m, 2H), 4.46 (d, J = 2.1 Hz, 1H), 3.19 (s, 3H), 2.45 (d, J = 2.1 Hz, 1H), 2.42−2.18 (m, 4H), 1.78−1.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 138.5, 130. 5, 128.2, 128.1, 126.9, 82.1, 73.7, 71.2, 55.8, 32.5, 23.3, 23.0, 22.5; HRMS (ESI+, TOF) m/z calcd for $C_{16}H_{19}O$ [M + H^+] 227.1436, found 227.1436.

*6-(1-(Benzyloxy)prop-2-yn-1-yl)-2,3,4,5-tetrahydro-1,1′-biphenyl (**1c**).* Compound **1c** was obtained from compound **5b** following the general procedure, using benzyl bromide as the alkylating agent. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded propargylic ether **1c** (240 mg, 73% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 8H), 7.18−7.08 (m, 2H), 4.69 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.33 (d, J = 11.6 Hz, 1H), 2.48 (d, J = 2.2 Hz, 1H), 2.46−2.19 (m, 4H), 1.84−1.68 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 138.4, 137.9, 130.7, 128.5, 128.3, 128.3, 128.1, 127.6, 126.9, 82.4, 74.0, 70.0, 69.0, 32.6, 23.6, 23.1, 22.6; HRMS (ESI+, TOF) m/z calcd for $C_{22}H_{22}ONa$ [M + Na^+] 325.1568, found 325.1568.

*1-(2-(1-Methoxyprop-2-yn-1-yl)cyclohex-1-en-1-yl)naphthalene (**1d**).* Compound **1d** was obtained from compound **5d** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 98:2−92:8 hexanes/EtOAc afforded propargylic ether **1d** (532 mg, 56% over 2 steps) as a 1:1 mixture of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.81 (m, 4H), 7.78 (d, J = 8.3 Hz, 2H), 7.53−7.38 (m, 6H), 7.25 (d, J = 8.3 Hz, 2H), 4.19 (s, 2H), 3.16 (s, 3H), 3.00 (s, 3H), 2.63−2.19 (m, 10H), 1.99−1.75 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 139.9, 137.0, 136.5, 133.8, 133.7, 132.6, 132.1, 131.3, 130.9, 128.3, 128.3, 127.2, 126.1, 126.0, 125.9, 125.8, 125.7, 125.6, 125.4, 125.0, 82.2, 81.7, 73.7, 73.3, 71.6, 71.2, 56.2, 55.83, 32.9, 32.7, 23.2, 23.1, 23.1, 23.0, 22.7; HRMS (ESI+, TOF) m/z calcd for $C_{20}H_{21}O$ [M + H^+] 277.1592, found 277.1589.

*3-(2-(1-Methoxyprop-2-yn-1-yl)cyclohex-1-en-1-yl)thiophene (**1e**).* Compound **1e** was obtained from compound **5e** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 98:2−92:8 hexanes/EtOAc afforded propargylic ether **1e** (191 mg, 70% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 4.9, 2.9 Hz, 1H), 7.09 (d, J = 2.9 Hz, 1H), 6.99 (d, J = 4.9 Hz, 1H), 4.67 (d, J = 2.0 Hz, 1H), 3.25 (s, 3H), 2.48 (d, J =

dx.doi.org/10.1021/jo3010952 | J. Org. Chem. 2012, 77, 7730−7736

2.0 Hz, 1H), 2.42−2.16 (m, 4H), 1.81−1.62 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 133.1, 131.5, 127.9, 125.1, 122.0, 82.0, 74.0, 71.3, 55.8, 32.1, 23.7, 22.9, 22.3; HRMS (ESI+, TOF) m/z calcd for $C_{14}H_{16}OSNa$ [M + Na^+] 255.0820, found 255.0822.

*2-(1-Methoxyprop-2-yn-1-yl)-1,1′-biphenyl (**1f**).* Compound **1f** was obtained from compound **5f** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 99:1−97:3 hexanes/EtOAc afforded propargylic ether **1f** (180 mg, 23% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.6, 1.4 Hz, 1H), 7.50−7.35 (m, 7H), 7.30 (dd, J = 7.6, 1.4 Hz, 1H), 4.98 (d, J = 2.1 Hz, 1H), 3.36 (s, 3H), 2.62 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 140.3, 136.0, 130.1, 129.4, 128.5, 128.2, 128.1, 128.0, 127.4, 82.2, 75.5, 70.0, 56.2; HRMS (ESI+, TOF) m/z calcd for $C_{16}H_{14}ONa$ [M + Na^+] 245.0942, found 245.0932.

*1-(1-Methoxyprop-2-yn-1-yl)-2-(prop-1-en-2-yl)benzene (**1g**).* Compound **1g** was obtained from compound **5g** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 99:1−97:3 hexanes/EtOAc afforded propargylic ether **1g** (309 mg, 37% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.2, 1.8 Hz, 1H), 7.47−7.28 (m, 2H), 7.20 (dd, J = 7.2, 1.8 Hz, 1H), 5.34−5.25 (m, 2H), 4.99 (s, 1H), 3.46 (s, 3H), 2.63 (d, J = 2.1, 1H), 2.15−2.08 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 143.2, 135.2, 128.4, 127.8, 127.5, 116.0, 82.4, 75.3, 69.9, 56.2, 25.4; HRMS (EI+, sector instrument) m/z calcd for $C_{13}H_{14}O$ [M − H^+] 185.09665, found 185.09758.

*1-(1-Methoxyprop-2-yn-1-yl)-2-(prop-1-en-2-yl)benzene (**1h**).* Compound **1h** was obtained from compound **5h** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 99:1−8:1 hexanes/EtOAc afforded propargylic ether **1h** (225 mg, 36% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 2H), 7.33−7.27 (s, 3H), 6.88 (dd, J = 17.3, 10.9 Hz, 1H), 5.28 (d, J = 17.3 Hz, 1H), 5.11 (d, J = 10.9 Hz, 1H), 3.44 (s, 3H), 2.51−2.19 (m, 4H), 1.73−1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6, 133.4, 132.9, 131.8, 128.3, 128.2, 122.8, 113.6, 87.0, 86.0, 70.0, 56.0, 25.7, 25.3, 22.5, 22.4; HRMS (ESI+, TOF) m/z calcd for $C_{18}H_{20}O$ [M^+] 252.1509, found 252.1506.

*1-(1-Methoxyprop-2-yn-1-yl)-2-(prop-1-en-2-yl)benzene-d_5 (**1i**).* Compound **1i** was obtained from compound **5i** following the general procedure, using iodomethane as the alkylating agent. Silica gel purification eluting with 99:1−8:1 hexanes/EtOAc afforded propargylic ether **1i** (123 mg, 56% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (d, J = 2.1 Hz, 1H), 3.20 (s, 3H), 2.46 (d, J = 2.2 Hz, 1H), 2.44−2.19 (m, 4H), 1.81−1.68 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 138.5, 130.5, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 82.1, 73.8, 71.2, 55.8, 32.5, 23.3, 23.1, 22.5; HRMS (ESI+, TOF) m/z calcd for $C_{16}H_{14}D_5O$ [M + H^+] 232.1750, found 232.1754.

General Cycloaromatization Procedure. To a solution of propargylic ether (44 mg, 0.13 mmol) in DMSO (0.31 mL) was added a 40% w/w solution of benzyltrimethylammonium hydroxide in methanol (Triton B, 0.03 mL, 0.06125 mmol) in one portion. Upon addition of the base, the reaction turned a deep red color. The mixture was stirred at 80 °C over 16 h, then diluted with saturated aqueous ammonium chloride (40 mL) and water (20 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organics were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide the benzenoid product which was either pure in crude form or purified by flash chromatography on silica gel.

*3,7,9-Trimethoxy-6-((4-methoxybenzyl)oxy)-5-methylnaphtho-[1,2-b]benzofuran (**4a**).* Compound **4a** was obtained from compound **1a** following the general procedure (36 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 1.9 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.94 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 1.9 Hz, 1H), 6.43 (d, J = 1.9 Hz, 1H), 5.02 (s, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 3.69 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 159.1, 157.8, 157.8, 154.9, 151.2, 148.8, 133.1, 130.5, 128.9, 122.6, 119.6, 116.7, 114.1, 113.7, 112.5, 107.3, 104.2, 94.5, 88.5, 76.1, 55.8, 55.7, 55.3, 11.7; HRMS (ESI+, TOF) m/z calcd for $C_{28}H_{27}O_6$ [M + H^+] 459.1808, found 459.1810.

*10-Methoxy-9-methyl-1,2,3,4-tetrahydrophenanthrene (**4b**).* Compound **4b** was obtained from compound **1b** following the general procedure (45 mg, >99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.91 (m, 2H), 7.53−7.38 (m, 2H), 3.77 (s, 3H), 3.11 (t, J = 6.2 Hz, 2H), 2.89 (t, J = 6.2 Hz, 2H), 2.59 (s, 3H), 2.00−1.82 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.36, 132.27, 131.54, 130.35, 129.93, 124.95, 124.46, 124.26, 123.14, 121.77, 60.48, 25.91, 24.54, 23.03, 22.66, 11.34; HRMS (ESI+, TOF) m/z calcd for $C_{16}H_{19}O$ [M + H^+] 227.1436, found 227.1432.

*10-(Benzyloxy)-9-methyl-1,2,3,4-tetrahydrophenanthrene (**4c**).* Compound **4c** was obtained from compound **1c** following the general procedure (30 mg, >99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.92 (m, 2H), 7.59−7.30 (m, 7H), 4.86 (s, 2H), 3.18−3.06 (m, 2H), 3.02−2.86 (m, 2H), 2.63 (s, 3H), 2.01−1.79 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 137.7, 132.3, 131.6, 130.5, 130.1, 128.6, 128.0, 127.8, 125.0, 124.6, 124.4, 123.2, 122.2, 74.7, 26.0, 24.9, 23.0, 22.7, 11.7; HRMS (ESI+, TOF) m/z calcd for $C_{22}H_{23}O$ [M + H^+] 303.1749, found 303.1746.

*5-Methoxy-6-methyl-1,2,3,4-tetrahydrobenzo[c]phenanthrene (**4d**).* Compound **4d** was obtained from compound **1d** following the general procedure. Silica gel purification eluting with 99:1−98:2 hexanes/EtOAc afforded compound **4d** (20 mg, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73−8.68 (m, 1H), 7.93−7.78 (m, 2H), 7.71 (d, J = 9.0 Hz, 1H), 7.56−7.51 (m, 2H), 3.81 (s, 3H), 3.53 (t, J = 5.9 Hz, 2H), 3.06 (t, J = 6.8 Hz, 2H), 2.67 (s, 3H), 2.03−1.94 (m, 2H), 1.80−1.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 135.1, 133.0, 131.4, 130.9, 130.8, 128.4, 128.2, 127.9, 126.3, 125.2, 124.6, 123.1, 122.9, 60.4, 34.0, 24.6, 24.1, 22.4, 12.1; HRMS (ESI+, TOF) m/z calcd for $C_{20}H_{21}O$ [M + H^+] 277.1592, found 277.1589.

*5-Methoxy-4-methyl-6,7,8,9-tetrahydronaphtho[2,1-b]thiophene (**4e**).* Compound **4e** was obtained from compound **1e** following the general procedure (30 mg, >99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.30 (m, 2H), 3.78 (s, 1H), 3.07−2.95 (m, 2H), 2.92−2.79 (m, 2H), 2.50 (s, 3H), 1.97−1.80 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 138.6, 134.9, 130.2, 127.6, 124.6, 121.9, 120.8, 60.4, 27.1, 23.9, 22.9, 22.8, 14.1; HRMS (EI+, sector instrument) m/z calcd for $C_{14}H_{16}OS$ [M^+] 232.09219, found 232.09274.

*9-Methoxy-10-methylphenanthrene (**4f**).* Compound **4f** was obtained from compound **1f** following the general procedure. Silica gel purification eluting with 99:1−9:1 hexanes/EtOAc afforded compound **6f** (16 mg, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70−8.64 (m, 2H), 8.21−8.16 (m, 1H), 8.06−8.02 (m, 1H), 7.66−7.58 (m, 4H), 3.94 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 132.9, 130.8, 128.2, 127.8, 126.8, 126.7, 126.2, 125.3, 124.6, 122.8, 122.8, 122.6, 121.9, 61.4, 11.8; HRMS (ESI+, TOF) m/z calcd for $C_{16}H_{15}O$ [M^+] 223.1123, found 223.1120.

*1-Methoxy-2,4-dimethylnaphthalene (**4g**).* Compound **4g** was obtained from compound **1g** following the general procedure (31 mg, >99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.59−7.43 (m, 2H), 7.16 (s, 1H), 3.91 (s, 3H), 2.63 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 132.4, 129.9, 129.8, 128.1, 125.5, 125.4, 125.0, 124.4, 122.2, 61.2, 57.8, 18.9, 15.7; HRMS (EI+, sector instrument) m/z calcd for $C_{13}H_{14}O$ [M^+] 186.10447, found 186.10508.

*6-Benzyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (**4h**).* Compound **4h** was obtained from compound **1h** following the general procedure. Purification was performed using preparative thin layer chromatography eluting with 97:3 hexanes/EtOAc three times to afford compound **4h** (5 mg, 16%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.13 (m, 5H), 6.85 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 3.98 (s, 2H), 3.64 (s, 3H), 2.80−2.64 (m, 4H), 1.81−1.68 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 141.4, 137.1, 130.7, 130.6, 128.9, 128.3, 127.7, 125.8, 124.9, 60.1, 35.6, 29.3, 23.7, 22.9, 22.9; HRMS (EI+, sector instrument) m/z calcd for $C_{18}H_{20}O$ [M^+] 252.15142, found 252.15107.

Simple Deuterium-Labeling Experiment of 1i. To a solution of propargylic ether **1i** (30 mg, 0.13 mmol) in DMSO (0.30 mL) was added a 40% w/w solution of benzyltrimethylammonium hydroxide in methanol (Triton B, 0.03 mL, 0.06 mmol) in one portion. Upon addition of the base, the reaction turned a deep red color. The mixture

dx.doi.org/10.1021/jo3010952 | J. Org. Chem. 2012, 77, 7730−7736

was stirred at 80 °C over 16 h then diluted with saturated aqueous ammonium chloride (40 mL) and water (20 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organics were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide a 4:6 mixture of pure **4i**/**4i′**, the ratio of which was determined by quantitative ^{13}C NMR (28 mg, 93%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.13 (t, J = 5.9 Hz, 1H), 2.93 (t, J = 5.9 Hz, 1H), 2.62 (**4i**, s, ∼0.81H), 2.60 (**4i′**, t, J = 1.9 Hz, ∼1.56H), 2.01−1.84 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 154.3, 132.2, 131.5, 130.3, 129.9, 124.6, 124.4, 124.2, 124.1, 124.0, 123.9, 123.8, 123.7, 123.6, 122.9, 122.7, 122.5, 121.7, 121.7, 60.5, 25.9, 24.5, 23.0, 22.7, 11.3 (**4i**, s, 0.35C), 11.1 (**4i′**, t, J = 18.9 Hz, 0.65C); HRMS (EI+, sector instrument) m/z calcd for $C_{16}H_{14}D_4O$ [M^+] 230.16088, found 230.16119 (**4i**, 36.2% base); $C_{16}H_{13}D_5O$ [M^+] 231.16716, found 231.16812 (**4i′**, 61.5% base).

Deuterium-Labeling Crossover Experiment of 1c and 1i. To a solution of propargylic ether **1c** (39 mg, 0.13 mmol) and propargylic ether **1i** (30 mg, 0.13 mmol) in DMSO (0.6 mL) was added a 40% w/w solution of benzyltrimethylammonium hydroxide in methanol (Triton B, 0.06 mL, 0.13 mmol) in one portion. Upon addition of the base, the reaction turned a deep red color. The mixture was stirred at 80 °C over 16 h, then diluted with saturated aqueous ammonium chloride (60 mL) and water (30 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 × 70 mL), and the combined organics were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide a ∼5:2:3 mixture of **4c**/**4i**/**4i′**. The ratio of **4i**/**4i′** was determined by quantitative ^{13}C NMR (69 mg, >99%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.92 (**4c**, m, 2H), 7.59−7.30 (**4c**, m, 7H), 4.86 (**4c**, s, 2H), 3.77 (**4i** + **4i′**, s, 3H), 3.18−3.07 (**4c** + **4i** + **4i′**, m, 4H), 2.99−2.86 (**4c** + **4i** + **4i′**, m, 4H), 2.63 (**4c**, s, 3H), 2.61−2.54 (**4i** + **4i′**, m, 3H), 2.00−1.80 (**4c** + **4i** + **4i′**, m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4 (**4i**/**4i′**), 153.1 (**4c**), 137.7 (**4c**), 132.3 (**4c**), 132.2 (**4i**/**4i′**), 131.6 (**4c**), 131.5 (**4i**/**4i′**), 130.49 (**4c**), 130.3 (**4i**/**4i′**), 130.1 (**4c**), 129.9 (**4i**/**4i′**), 128.6 (**4c**), 128.0 (**4c**), 127.8 (**4c**), 125.0 (**4c**), 124.5 (**4i**/**4i′**), 124.3 (**4i**/**4i′**), 123.2 (**4c**), 122.2 (**4c**), 121.7 (**4i**/**4i′**), 74.7 (**4c**), 60.5 (**4i**/**4i′**), 26.0 (**4c**), 25.9 (**4i**/**4i′**), 24.9 (**4c**), 24.5 (**4i**/**4i′**), 23.0 (**4i**/**4i′**), 23.0 (**4c**), 22.7 (**4c**), 22.7 (**4i**/**4i′**), 11.7 (**4c**), 11.3 (**4i**, s, 0.35C), 11.1 (**4i′**, t, J = 18.9 Hz, 0.65C).

Deuterium-Labeling Experiment of 1i Using Sodium Methoxide without Added Methanol. To a solution of propargylic ether **1i** (50 mg, 0.22 mmol) in DMSO (0.54 mL) was added sodium methoxide powder (6.0 mg, 0.11 mmol) in one portion. The mixture was stirred at 80 °C over 16 h then diluted with saturated aqueous ammonium chloride (40 mL) and water (20 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organics were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide a 36:37:27 mixture of **4i**/**4i′**/**6** (50 mg, 99%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (7, dd, J = 7.8 Hz, 1.3 Hz, 0.37H), 7.43 (7, t, J = 7.1 Hz, 0.8 Hz, 0.37H), 7.33 (7, td, J = 7.6, 1.3 Hz, 0.37H), 7.22 (7, dd, J = 7.6, 0.8 Hz, 0.37H), 4.22 (7, dd, J = 7.6, 5.4 Hz, 0.37H), 3.80 (**4i** + **4i′**, s, 3H), 3.17 (7, s, 1H), 3.13 (**4i** + **4i′**, t, J = 5.9 Hz, 1H), 2.93 (**4i** + **4i′**, t, J = 5.9 Hz, 1H), 2.62 (**4i**, s, ∼1.25H), 2.60 (**4i′**, t, J = 1.9 Hz, ∼1.33H), 2.01−1.84 (**4i** + **4i′**, m, 4H), 1.80−1.60 (7, m, 1.13H), 0.82 (7, t, J = 7.4 Hz, 1.11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4 (**4i**/**4i′**), 154.3 (**4i**/**4i′**), 142.0 (7), 141.0 (7), 139.9 (7), 132.2 (**4i**/**4i′**), 131.5 (**4i**/**4i′**), 130.3 (**4i**/**4i′**), 129.9 (**4i**/**4i′**), 129.6 (7), 129.2 (7), 128.9 (7), 128.7 (7), 127.8 (7), 127.5 (7), 127.3 (7), 126.8 (7), 126.0 (7), 124.6 (**4i**/**4i′**), 124.4 (**4i**/**4i′**), 124.2 (**4i**/**4i′**), 124.1 (**4i**/**4i′**), 124.0 (**4i**/**4i′**), 123.9 (**4i**/**4i′**), 123.8 (**4i**/**4i′**), 123.7 (**4i**/**4i′**), 123.6 (**4i**/**4i′**), 122.9 (**4i**/**4i′**), 122.7 (**4i**/**4i′**), 122.5 (**4i**/**4i′**), 121.7 (**4i**/**4i′**), 121.7 (**4i**/**4i′**), 80.7 (7), 60.5 (**4i**/**4i′**), 56.4 (7), 30.9 (7), 25.9 (**4i**/**4i′**), 24.5 (**4i**/**4i′**), 23.0 (**4i**/**4i′**), 22.7 (**4i**/**4i′**), 11.3 (**4i**, s, 0.49C), 11.1 (**4i′**, t, J = 18.9 Hz, 0.51C), 10.4 (7).

*2-(1-Methoxypropyl)-1,1′-biphenyl-d_5 (**6**):* ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.43 (t, J = 7.1 Hz, 0.8 Hz, 1H), 7.33 (td, J = 7.6, 1.3 Hz, 1H), 7.22 (dd, J = 7.6, 0.8 Hz, 1H), 4.22 (dd, J = 7.6, 5.4 Hz, 1H), 3.17 (s, 3H), 1.80−1.60 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 141.0, 139.9, 129.6, 129.2, 128.9, 128.7, 127.8, 127.5, 127.3, 126.8, 126.0, 80.7, 56.4, 30.9, 10.4; HRMS (EI+, sector instrument) m/z calcd for $C_{16}H_{13}D_5O$ [M^+] 231.16716, found 231.16640.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of new compounds and X-ray crystallographic views for compounds **4a** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Professor Joseph P. Dinnocenzo (University of Rochester) for helpful discussions. We are also grateful to Dr. Furong Sun (University of Illinois at Urbana—Champaign) and Dr. A. Bergmann (SUNY Buffalo) for carrying out high-resolution mass spectrometry, and Dr. W. Brennessel for solving the X-ray structures of **4a** and **6**. This work was funded by the NIH (NIGMS R01GM079364).

■ REFERENCES

(1) (a) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560−7561. (b) Malona, J. A.; Cariou, K. C.; Spencer, W. T.; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891−1908.

(2) Spencer, W. T.; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2011**, *13*, 414−417.

(3) Choshi, T.; Hibino, S. *Heterocycles* **2011**, *83*, 1205−1239 and references therein.

(4) (a) Xu, J.; Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 2555−2558. (b) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 5295−5298. (c) Wang, Y.; Burton, D. J. *Tetrahedron Lett.* **2006**, *47*, 9279−9281. (d) Zhou, H.; Xing, Y.; Yao, J.; Chen, J. *Org. Lett.* **2010**, *12*, 3674−3677. (e) Zhou, H.; Xing, Y.; Yao, J.; Lu, Y. *J. Org. Chem.* **2011**, *76*, 4582−4590.

(5) Intermediate **III** is also available through ring opening of 2-alkynylcyclobutenones: (a) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 3274−3275. Or metal-catalyzed reactions: (b) Wang, F.; Tong, X.; Cheng, J.; Zhang, Z. *Chem.—Eur. J.* **2004**, *10*, 5338-−5344. (c) Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884−7886. (d) Saifuddin, M.; Agarwal, P. K.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10122−10128.

(6) For electrocyclizations of simple dienyl-allene systems, see: (a) Brinker, U. H.; Fleischhauer, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 396−397. (b) Balme, G.; Malacria, M.; Gore, J. *Tetrahedron Lett.* **1979**, 7−10. (c) Bross, H.; Schneider, R.; Hopf, H. *Tetrahedron Lett.* **1979**, 2129−2132. (d) Bell, T. W.; Bowes, C. M.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 3299−3302. (e) Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6115−6117. (f) Miller, B.; Baghdadchi, J. *J. Org. Chem.* **1987**, *52*, 2391−2396. (g) Pasto, D. J.; Kong, W. *J. Org. Chem.* **1989**, *54*, 4028−4033. (h) Porter, N. A.; Hogenkamp, D. J.; Khouri, F. F. *J. Am. Chem. Soc.* **1990**, *112*, 2402−2407. (i) Andemichael, Y. W.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 796−798. (j) Ezcurra, J. E.; Pham, C.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 4787−4789. (k) Wang, K. K.; Zhang, Q.; Liao, J. *Tetrahedron Lett.* **1996**, *37*, 4087−4090.

(7) For electrocyclizations of ene-diallenes, see: (a) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, 3181−3184. (b) Braverman, S.; Segev, D. *J. Am. Chem. Soc.* **1974**, *96*, 1245−1247. (c) Braverman, S.; Duar, Y.; Segev, D. *Tetrahedron Lett.* **1976**, 3181−3184. (d) Braverman, S.; Duar, Y. *Tetrahedron Lett.* **1978**, 1493−1496. (e) Braverman, S.; Duar, Y. *J. Am. Chem. Soc.* **1990**, *112*,

5830−5837. (f) Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* **2001**, *57*, 3761−3767. (g) Generation of ene-diallene by cyclobutene ring opening: Ezcurra, J. E.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*, 6177−6180. (h) Taing, M.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 329−340. (i) Generation of ene-diallene by [2,3]-sigmatropic rearrangement of sulfenates: Kitagaki, S.; Ohdachi, K.; Katoh, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 95−98. (j) Hakuba, H.; Kitagaki, S.; Mukai, C. *Tetrahedron* **2007**, *63*, 12639−12645.

(8) This result is in good agreement with that of Burton's in a similar system (see ref 4a).

(9) Intramolecular proton transfer proceeding through a hydrogen-bonded conjugate acid−carbanion complex: (a) Cram, D. J.; Uyeda, R. T. *J. Am. Chem. Soc.* **1962**, *84*, 4358−4359. (b) Cram, D. J.; Willey, F.; Fischer, H. P.; Scott, D. A. *J. Am. Chem. Soc.* **1964**, *86*, 5370−5371. (c) Cram, D. J.; Willey, F.; Fischer, H. P.; Relles, H. M.; Scott, D. A. *J. Am. Chem. Soc.* **1966**, *88*, 2759−2766.

(10) Potassium *tert*-butoxide in *tert*-butyl alcohol is used by Hibino to cycloaromatize propargylic ether intermediates in the syntheses of nitrogenous heteroaromatic ring systems (see ref 3).

(11) (a) Cram, D. J.; Rickborn, B.; Kingsbury, C. A.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 3678−3687. (b) Bank, S.; Schriesheim, A.; Rowe, C. A., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3244−3245. (c) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; pp 32−46. (d) Bank, S. *J. Org. Chem.* **1972**, *37*, 114−118. (e) Exner, J. H.; Steiner, E. C. *J. Am. Chem. Soc.* **1974**, *96*, 1782−1787.

(12) Salem, B.; Delort, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 2307−2310.

(13) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006−14008.

(14) Schumacher, A.; Schrems, M. G.; Pfaltz, A. *Chem.—Eur. J.* **2011**, *17*, 13502−13509.

(15) Saifuddin, M.; Agarwal, P. K.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10122−10128.

(16) Yao, S.; Gallenkamp, D.; Woelfel, K.; Lueke, B.; Schindler, M.; Scherkenbeck, J. *Bioorg. Med. Chem.* **2011**, *19*, 4669−4678.

(17) For the synthesis of propargylic ether **1h**, lithium phenylacetylide was used as the alkynylmetal species.