A New Process for the Regiocontrolled Synthesis of Substituted Catechols and Other 1,2-Dioxygenated Aromatics: Conjugate Addition of Vinyl-, Aryl-, and Heteroarylcopper Reagents to Cyclobutenediones Followed by Thermal Rearrangement

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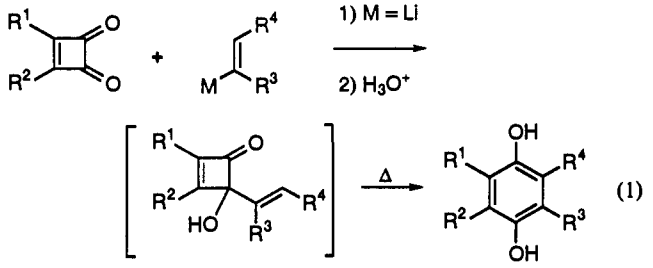
Abstract: A general method for the synthesis of substituted catechol derivatives has been developed utilizing the 1,4-addition of vinyl-, aryl-, and heteroarylcuprates to cyclobutenediones followed by thermal rearrangement. *In situ* protection with (methoxyethoxy)methyl chloride of the enolate derived from addition of the cuprate yields 2-alkoxy-4-$R^{unsat'd}$-2-cyclobutenones, which rearrange thermally to substituted catechols with differentiated hydroxy groups. Monosubstituted cyclobutenediones undergo highly regioselective 1,4-addition at the unsubstituted carbon; alternatively, regiocontrol can be exerted by addition to cyclobutenedione monoacetals. Differentially disubstituted cyclobutenedione monoacetals undergo regiospecific 1,4-addition to the unprotected enone moiety. Protection of the intermediate enolate and mild hydrolysis of the acetal yield 3,4-disubstituted 2-alkoxy-4-$R^{unsat'd}$-2-cyclobutenones regiospecifically. Thermolysis of these products delivers substituted catechol monoethers regiospecifically.

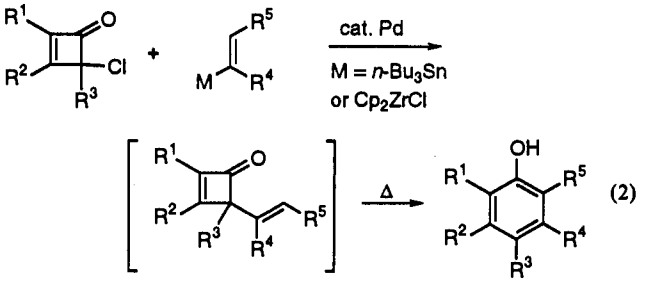
Introduction

4-Vinyl-(or aryl or heteroaryl)-2-cyclobutenones, prepared by the addition of carbon nucleophiles to cyclobutenediones (eq 1)[1-8] or by the palladium catalyzed cross-coupling of organotin or organozirconium reagents with 4-chloro-2-cyclobutenones (eq 2),[9,10] on thermolysis give diversely substituted aromatic compounds in excellent yields. The former process directly forms 1,4-hydroquinones which are easily oxidized to the corresponding quinones, while the latter process provides access to highly substituted phenols.



(1)

By virtue of the easy preparation of 4-chloro-3-alkoxy-2-cyclobutenones (eq 2, R^2 = *O*-alkyl), the 1,3-dioxygenated aromatic substitution pattern of resorcinols is easily prepared using the palladium catalyzed cross-coupling and thermolysis route.[9-11] However, the 1,2-dioxygenated aromatic substitution



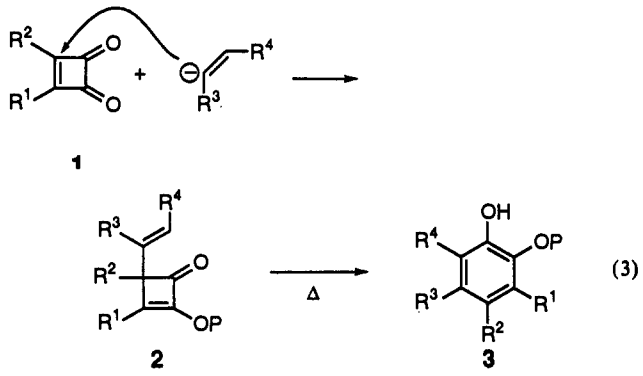
(2)

pattern of catechols is not easily established in this way. One solution to the important problem of 1,2-dioxygenated aromatic ring synthesis[12-15] evolves from the conjugate addition of unsaturated carbon nucleophiles directly to cyclobutenediones **1** (eq 3). Trapping of the enolate formed on conjugate addition would lead to 4-$R^{unsat'd}$-2-oxygenated-2-cyclobutenones **2**, which upon thermolysis would convert selectively to monoprotected catechols **3**. Newly developed and general methods for the preparation of substituted cyclobutenediones and cyclobutenedione monoacetals[16-25] make this strategy potentially general and efficient. Herein is documented the successful realization of this plan using

(1) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.
(2) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065.
(3) Selwood, D. L.; Jandu, K. S. *Heterocycles* **1988**, *27*, 1191.
(4) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996.
(5) Liebeskind, L. S.; Zhang, J. *J. Org. Chem.* **1991**, *56*, 6379.
(6) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326.
(7) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.
(8) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896.
(9) Edwards, J. P.; Krysan, D.; Liebeskind, L. S. *J. Org. Chem.*, in press.
(10) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412.
(11) Liebeskind, L. S.; Wang, J. *J. Org. Chem.*, in press.
(12) Tius, M. A.; Thurkauf, A. *J. Org. Chem.* **1983**, *48*, 3839.
(13) Tius, M. A.; Cullingham, J. M.; Ali, S. *J. Chem. Soc., Chem. Commun.* **1989**, 867.
(14) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
(15) Merlic, C. A.; Xu, D. Q. *J. Am. Chem. Soc.* **1991**, *113*, 7418.
(16) Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, in press.
(17) Sidduri, A.; Budries, N.; Laine, R. M.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 7515.
(18) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.
(19) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
(20) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.
(21) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350.
(22) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.
(23) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477.
(24) Liebeskind, L. S.; Baysdon, S. L. *Tetrahedron Lett.* **1984**, 1747.
(25) Ohno, M.; Yamamoto, Y.; Shirasaki, Y.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 263.

0002-7863/93/1515-6101$04.00/0

a variety of cyclobutenediones and cyclobutenedione monoacetals which lead in a regiocontrolled fashion to substituted catechols and other 1,2-dioxygenated aromatics. This work is mechanistically related to Danheiser's diazoketone-based aromatic annulation strategy which can also be used to construct substituted catechols.[14,26]



(3)

Results and Discussion

To assay the feasibility of the projected chemistry and to simplify regiochemical issues, symmetrically substituted cyclobutenediones were first employed. The results of this study are listed in Table I. Cyclobutenediones **1a** and **1b** were treated with preformed higher order vinyl-, aryl-, and heteroarylcuprates in THF at −78 °C for 20 min to 1.5 h. The higher order cuprates were generated from 2 equiv of an organolithium reagent and CuCN, or from 1 equiv of an organolithium reagent and 1 equiv of (2-thienyl)CuCNLi, or by transmetalation of tri-*n*-butylvinyltin with $Me_2CuCNLi_2$.[27-30] Other lower order cuprates and copper catalyzed Grignard reagents were investigated, but all gave lower isolated yields of the 1,4-addition products and/or more impurities. The reaction mixtures were quenched with either acetic anhydride or (2-methoxyethoxy)methyl chloride (MEMCl) in order to trap the intermediate enolate. While the unprotected 2-hydroxycyclobutenone products can be isolated, *in situ* protection of the enolates resulted in higher isolated yields. In only one case was any product of 1,2-addition of a cuprate reagent noted (Table I, entry 7: 34% 1,2- and 48% 1,4-addition). This apparently was a result of the steric bulk of the reagent, $(1\text{-naphthyl})_2CuCNLi_2$; addition of $(1\text{-naphthyl})_2CuCNLi_2$ to a less hindered enone gave only the 1,4-addition product (see **2k**, Table II, entry 3).

Thermolysis of the 2-oxygenated-4-$R^{unsat'd}$-2-cyclobutenone intermediates **2** for 20 h under argon either at 100 °C in dioxane or more generally at 140 °C in xylenes gave good yields of substituted catechols **3**. Thermolysis of the 2-acetoxy-2-cyclobutenones yielded a mixture of regioisomers due to migration of the acetate protecting group between the adjacent hydroxy groups. To give a single product in these cases, the product mixture was either fully acetylated (**3a**) or deprotected to the corresponding catechol (**3d**). Upon thermolysis in base-washed glassware, the MEM protected 2-alkoxy-2-cyclobutenones rearranged to catechol monoethers without migration of the protecting group.

Of specific note is thermolysis of the conjugate addition product of the 2-pyridyl-derived cuprate (Table I, entry 8). Although the intermediate 2-alkoxy-3,4-di-*n*-butyl-4-(2-pyridyl)-2-cyclobutenone (**2h**) could cyclize to either a substituted quinoline or a substituted quinolizinone, only formation of the quinolizinone **3h** was observed. Further studies of this novel entry to pyridone-based molecules is under study and will be published separately. Taken together, these initial reactions suggest that a tandem conjugate addition-thermolysis protocol will be of use in the construction of a variety of 1,2-dioxygenated aromatics from cyclobutenediones and unsaturated organocopper reagents. To extend the utility of the method, two procedures for regiocontrolled introduction of the unsaturated groups to unsymmetrically substituted cyclobutenediones were explored.

Highly regioselective 1,4-addition of cuprates to the monosubstituted cyclobutenediones, 3-phenyl-3-cyclobutene-1,2-dione (**1c**) and 3-*n*-butyl-3-cyclobutene-1,2-dione (**1d**), was observed (Table II). Under the same conditions developed for the symmetrical cyclobutenediones, the unsaturated cuprate substituents were delivered selectively to the unsubstituted carbon of the monosubstituted cyclobutenedione and the corresponding intermediate enolates were trapped with MEMCl. The resulting 2-alkoxy-2-cyclobutenones were rearranged at 140 °C for 20 h to give catechols in good yields. In one case (Table II, entry 1), addition of a grain of K_2CO_3 to the cyclobutenone solution before thermolysis was necessary to inhibit acid catalyzed migration of the MEM group.

A more general and regiospecific entry to diversely substituted catechols is available from the 1,4-addition of organocopper reagents to unsymmetrically substituted cyclobutenedione monoacetals which can be prepared regiospecifically by known methodology (Table III).[12] This tactic was successful, although the cyclobutenedione monoacetals were less reactive toward nucleophilic attack by cuprates than the unprotected cyclobutenediones. This necessitated warming of the reaction mixture from −78 °C to 0 °C (for 30–60 min) after the addition of the cuprate. The enolate intermediate was protected *in situ* with MEMCl, and after workup the ketal was removed by hydrolysis with 10% aqueous HCl/THF. The 2-alkoxy-2-cyclobutenones were isolated in good yields after purification by flash silica chromatography. Thermal rearrangement under the same conditions described above (xylenes, 140 °C, 20 h) provided the corresponding catechol monoethers in excellent yields. This method provides a regiocontrolled approach to highly substituted catechol monoether regioisomers such as **3l** and **3m** and should prove to be of general utility. Note that in some cases the use of cyclobutenedione monoacetals might provide a superior entry to certain catechol systems (compare **2i**, entry 1 in Table II and entry 3 in Table III).

Conclusions

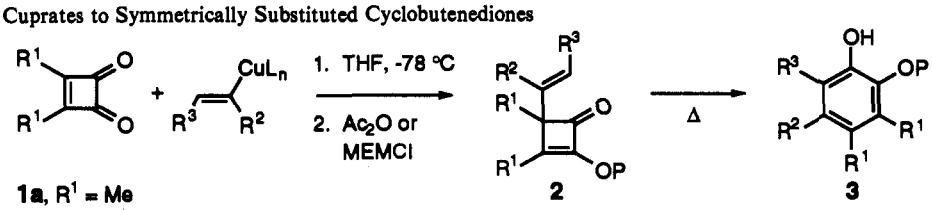
A general synthesis of substituted catechol derivatives has been developed utilizing the 1,4-addition of vinyl-, aryl-, and heteroarylcuprates to cyclobutenediones followed by thermolysis. *In situ* protection with MEMCl of the enolate derived from addition of the cuprate yields 2-alkoxy-4-$R^{unsat'd}$-2-cyclobutenones, which rearrange thermally to substituted catechols with differentiated hydroxy groups. Monosubstituted cyclobutenediones undergo highly regioselective 1,4-addition at the unsubstituted carbon; alternatively, regiocontrol can be exerted by addition to cyclobutenedione monoacetals. Differentially disubstituted cyclobutenedione monoacetals undergo regiospecific 1,4-addition to the unprotected enone moiety. Protection of the intermediate enolate and mild hydrolysis of the acetal yield 3,4-disubstituted 2-alkoxy-4-$R^{unsat'd}$-2-cyclobutenones regiospecifically. Thermolysis of these products delivers substituted catechol monoethers regiospecifically.

Experimental Section

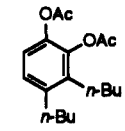
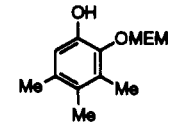
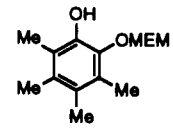
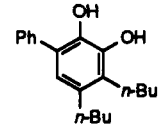
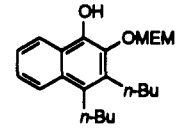
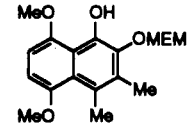
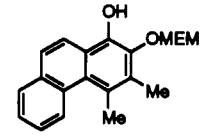
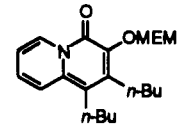
Materials and Methods. All reactions were performed under an atmosphere of dry argon in base-washed, flame-dried glassware unless otherwise indicated. Thermolyses were performed under an argon atmosphere in dry argon-sparged solvents. Solvents were dried by distillation under nitrogen from sodium-benzophenone ketyl (THF, Et_2O, *m*-xylene). Dioxane was obtained from Aldrich in Sure-Seal® containers

(26) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.
(27) Lipshutz, B. H. *Synth. Lett.* **1990**, 119.
(28) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959.
(29) Lipshutz, B.; Koerner, M.; Parker, D. *Tetrahedron Lett.* **1987**, *28*, 945.
(30) Behling, J.; Babiak, K.; Ng, J.; Campbell, A.; Moretti, R.; Koerner, M.; Lipshutz, B. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

Table I. Addition of Cuprates to Symmetrically Substituted Cyclobutenediones



1a, R^1 = Me
1b, R^1 = *n*-Bu

Entry	Dione	Cuprate	P	Cmpd	Yld	Catechol	Cmpd	Yld
1	1b	(vinyl)Cu(Me)CNLi$_2$	Ac	2a	63		3a	83[1] 95[2]
2	1a	(1-propen-2-yl)Cu(2-thienyl)CNLi$_2$	MEM	2b	65		3b	95
3	1a	(2-buten-2-yl)Cu(2-thienyl)CNLi$_2$	MEM	2c	74		3c	64
4	1b	(β-styryl)$_2$CuCNLi$_2$	Ac	2d	63		3d	75[1] 83[3]
5	1b	Ph$_2$CuCNLi$_2$	MEM	2e	71		3e	83
6	1a	(2-(1,4-dimethoxyphenyl))$_2$CuCNLi$_2$	MEM	2f	51		3f	82
7	1a	(1-naphthyl)$_2$CuCNLi$_2$	MEM	2g	48[4]		3g	64
8	1b	(2-pyridyl)$_2$CuCNLi$_2$	MEM	2h	31		3h	79

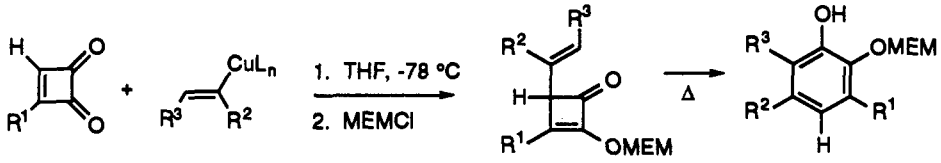
[1] Yield of mixture of catechol monoacetate isomers caused by acetate migration during thermolysis. [2] Yield of catechol diacetate. [3] Yield of free catechol by hydrolytic removal of the acetate protecting group. [4] A 34% yield of a 1,2-addition product (unprotected) was also isolated.

and used as received. CuCN was obtained from Fluka and dried in a round-bottomed flask under vacuum by flaming the flask. Lithium chloride was treated similarly. (2-Thienyl)CuCNLi was obtained from Aldrich in Sure-Seal* containers (0.25 M in THF). (2-Methoxyethoxy)methyl chloride (MEMCl) was obtained from Lancaster.

All thin-layer chromatography was performed using Merck Kieselgel 60 F_{254} plates with visualization by UV and phosphomolybdic acid stain. Purification by flash silica gel column chromatography was performed using 32–63 μm silica gel. ^{1}H NMR spectra were recorded on a GE QE300 spectrometer at 300 MHz or on a GE NT360 spectrometer at 360 MHz and were referenced to the $CHCl_3$ resonance (7.26 ppm). ^{13}C NMR spectra were recorded on a GE QE300 spectrometer at 75 MHz and were referenced to the $CHCl_3$ resonance (77.0 ppm) or benzene-d_6 resonance (128.0 ppm). IR spectra were recorded in solution using KCl cells on a Nicolet 510 IR spectrometer or on a Perkin-Elmer 1420 ratio recording spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. HRMS (EI) were performed on a VG 70-S by the Emory Department of Chemistry Mass Spectrometry Lab.

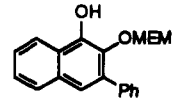
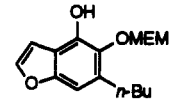
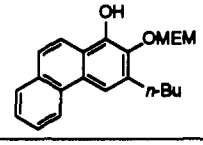
Addition of Cuprates to Symmetrically Substituted Cyclobutenediones. 2-Acetoxy-3,4-di-*n*-butyl-4-vinyl-2-cyclobutenone (2a). (Vinyl)Cu(Me)CNLi$_2$ was formed by transmetalation of tri-*n*-butylvinyltin with Me$_2$CuCNLi$_2$.[30] A suspension of CuCN (0.132 g, 1.47 mmol, 1.4 equiv) in dry THF (2 mL) under argon was cooled to 0 °C and MeLi (1.4 M in

Table II. Addition of Cuprates to Monosubstituted Cyclobutenediones



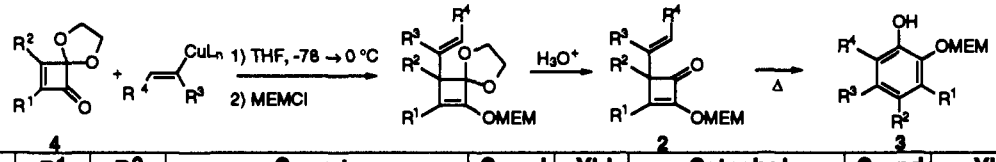
1c, R^1 = Ph
1d, R^1 = *n*-Bu

2 **3**

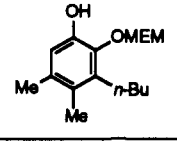
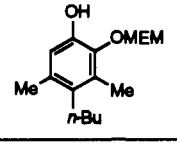
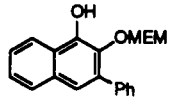
Entry	Dione	Cuprate	Cmpd	Yld	Catechol	Cmpd	Yld
1	1c	$Ph_2CuCNLi_2$	2i	65		3i	69
2	1d	$(2\text{-furyl})_2CuCNLi_2$	2j[1]	36		3j	82
3	1d	$(1\text{-naphthyl})_2CuCNLi_2$	2k	62		3k	77

[1] A trace amount of product from the 1,4-addition to the substituted enone was also isolated.

Table III. Addition of Cuprates to Cyclobutenedione Monoacetals



4 **2** **3**

Entry	R^1	R^2	Cuprate	Cmpd	Yld	Catechol	Cmpd	Yld
1	*n*-Bu	Me	(1-propen-2-yl)Cu(2-thienyl)$CNLi_2$	2l	70		3l	86
2	Me	*n*-Bu	(1-propen-2-yl)Cu(2-thienyl)$CNLi_2$	2m	62		3m	94
3	Ph	H	$Ph_2CuCNLi_2$	2i	72		3i	69[1]

[1] This yield was determined in Table 2, entry 1.

Et_2O, 2.1 mL, 2.9 mmol, 2.9 equiv) was added dropwise. The reaction mixture was warmed to room temperature and tri-*n*-butylvinyltin (Aldrich, 0.560 g, 1.77 mmol, 1.7 equiv) in dry THF (2 mL) was added. After stirring at room temperature for 1.75 h, the reaction mixture was cooled to −78 °C, and a solution of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione (**1b**)[10] (0.200 g, 1.03 mmol, 1.0 equiv) in dry THF (3 mL) was added. After stirring at −78 °C for 20 min, a mixture of pyridine (0.230 g, 2.91 mmol, 2.9 equiv) and acetic anhydride (0.300 g, 2.94 mmol, 2.9 equiv) in dry THF (2 mL) was added, and the reaction mixture was warmed to room temperature, quenched with saturated aqueous NH_4Cl, extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to an oil. The oil was dissolved in acetonitrile (10 mL), the acetonitrile was washed with hexanes (3 × 5 mL) and concentrated, and the product was purified by flash silica gel chromatography (10% EtOAc/hexanes, R_f 0.34) to yield 0.170 g (63%) of **2a** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (dd, J = 10.7, 17.6 Hz, 1H), 5.23 (d, J = 17.6 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 2.41 (t, J = 7.5 Hz, 2H), 2.18 (s, 3H), 1.82–1.53 (m, 4H), 1.43–1.22 (m, 6H), 0.91 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 169.5, 166.3, 140.0, 137.4, 116.9, 65.3, 31.0, 28.1, 27.2, 26.7, 23.0, 22.8, 20.1, 13.7, 13.5; IR ($CHCl_3$) 2962, 2935, 2877, 1773, 1650, 1468, 1372, 1194 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.52; H, 9.31.

3,4-Dimethyl-4-(1-propen-2-yl)-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2b). A solution of 2-bromopropene (Aldrich, 0.340 mL, 3.83 mmol, 1.7 equiv) in dry THF (4.5 mL) under argon was cooled to −78 °C and

(31) Smutny, E. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1955**, *77*, 3420.

t-BuLi (1.7 M in pentane, 4.5 mL, 7.7 mmol, 3.3 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 40 min, (2-thienyl)CuCNLi (0.25 M in THF, 15.1 mL, 3.8 mmol, 1.7 equiv) was added slowly, and after stirring at –78 °C for 1 h, a solution of 3,4-dimethyl-3-cyclobutene-1,2-dione (**1a**)[22] (0.250 g, 2.27 mmol, 1.0 equiv) in THF (3 mL) was added via cannula. After stirring at –78 °C for 30 min, MEMCl (1.1 mL, 9.6 mmol, 4.2 equiv) was added, and after 10 min, the mixture was quenched at –78 °C with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to a brown oil that was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.24) to yield 0.356 g (65%) of **2b** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, J = 14.4 Hz, 1H), 5.17 (d, J = 14.4 Hz, 1H), 4.89 (br s, 1H), 4.79 (br s, 1H), 3.74 and 3.49 (AA'BB', 4H), 3.31 (s, 3H), 1.95 (s, 3H), 1.67 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 154.8, 145.1, 143.8, 112.2, 93.2, 70.8, 67.6, 62.7, 58.3, 19.9, 16.8, 9.6; IR (CH_2Cl_2) 2963, 2934, 2876, 1757, 1647, 1451, 1377, 1336, 1174, 1107, 1009, 987 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.94; H, 8.42.

3,4-Dimethyl-4-(2-buten-2-yl)-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2c). A solution of 2-bromo-2-butene (Aldrich, mixture of *cis* and *trans* isomers (85:15), 0.31 mL, 3.1 mmol, 1.7 equiv) in dry THF (3.6 mL) under argon was cooled to –78 °C and *t*-BuLi (1.7 M in pentane, 3.6 mL, 6.1 mmol, 3.3 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 40 min, (2-thienyl)CuCNLi (0.25 M in THF, 12.1 mL, 3.0 mmol, 1.7 equiv) was added slowly, and after an additional 1 h at –78 °C, a solution of 3,4-dimethyl-3-cyclobutene-1,2-dione (**1a**)[22] (0.200 g, 1.82 mmol, 1.0 equiv) in THF (2 mL) was added via cannula. The reaction mixture was stirred at –78 °C for 50 min, MEMCl (0.86 mL, 7.5 mmol, 4.2 equiv) was added, and the mixture was stirred for 10 min, then quenched at –78 °C with saturated aqueous $NaHCO_3$, extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a brown oil. The oil was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.24) to yield 0.332 g (74%) of **2c** as a yellow oil. Only one isomer was evident by ^1H NMR: ^1H NMR (300 MHz, $CDCl_3$) δ 5.35–5.20 (m, 1H), 5.21 (d, J = 21.9 Hz, 1H), 5.19 (d, J = 21.9 Hz, 1H), 3.75 and 3.51 (AA'BB', 4H), 3.32 (s, 3H), 2.05 (s, 3H), 1.70 (d, J = 7.3 Hz, 3H), 1.64 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.3, 154.2, 145.6, 122.1, 93.2, 70.9, 67.6, 61.6, 58.3, 22.3, 18.5, 14.6, 13.0, 10.9; IR (CH_2Cl_2) 2968, 2925, 2888, 1764, 1650, 1452, 1377, 1322, 1111, 1051, 963 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1519.

2-Acetoxy-3,4-di-*n*-butyl-4-(β-styryl)-2-cyclobutenone (2d). A solution of β-bromostyrene (Aldrich, predominantly *trans*, 0.28 mL, 2.2 mmol, 2.9 equiv) in dry THF (2.5 mL) under argon was cooled to –78 °C and *t*-BuLi (1.6 M in pentane, 2.8 mL, 4.5 mmol, 5.7 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, and a solution of CuCN (0.099 g, 1.1 mmol, 1.4 equiv) and LiCl (0.094 g, 2.2 mmol, 2.0 equiv) dissolved in dry THF (2 mL) and precooled to –78 °C was added via cannula. The reaction mixture was stirred at –78 °C for 1.5 h, and then a solution of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione (**1b**)[10] (0.150 g, 0.77 mmol, 1.0 equiv) in THF (1.5 mL) was added via cannula. After stirring at –78 °C for 45 min, the reaction mixture was treated with acetic anhydride (0.21 mL, 2.2 mmol, 2.9 equiv), stirred for an additional 15 min, quenched at –78 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl, extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a green oil. The oil was purified by flash silica gel chromatography (10% EtOAc/hexanes) to yield 0.167 g (63%) of **2d** as a yellow oil. The product was predominantly the *trans* isomer, with 10% of the *cis* isomer evident by ^1H NMR and showing unique shifts at δ 6.70 (d, J = 10.0 Hz, 1H), 5.58 (d, J = 10.0 Hz, 1H), and at 2.72 (t, J = 7.7 Hz, 2H). The major isomer showed the following: ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5H), 6.56 (d, J = 16.3 Hz, 1H), 6.21 (d, J = 16.3 Hz, 1H), 2.48 (t, J = 7.7 Hz, 2H), 2.20 (s, 3H), 1.95–1.59 (m, 6H), 1.44–1.33 (m, 4H), 1.00–0.87 (m, 6H); IR (CH_2Cl_2) 3068, 3029, 2962, 2935, 2875, 1779, 1650, 1600, 1497, 1468, 1372, 1194 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{28}O_3$ 340.20383, found 340.20385.

3,4-Di-*n*-butyl-4-phenyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2e). A solution of bromobenzene (Aldrich, 0.155 mL, 1.47 mmol, 2.9 equiv) in dry THF (4 mL) under argon was cooled to –78 °C and *t*-BuLi (1.4 M in pentane, 2.1 mL, 2.9 mmol, 5.7 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 45 min, and then a solution of CuCN (0.066 g, 0.74 mmol, 1.4 equiv) and LiCl (0.062 g, 1.5 mmol, 2.9 equiv) dissolved in dry THF (3 mL) and precooled to –78 °C was added via cannula. Stirring was continued at –78 °C for 30 min, and then a solution of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione (**1b**)[10] (0.100 g, 0.52 mmol, 1.0 equiv) in THF (2 mL) was added via cannula. The reaction was stirred at –78 °C for 1.5 h, MEMCl (0.21 mL, 1.8 mmol, 3.6 equiv) was added, and after stirring for 10 min, the mixture was quenched at –78 °C with saturated aq $NaHCO_3$, extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil. The oil was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.36) to yield 0.132 g (71%) of **2e** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.32 (m, 3H), 7.29–7.23 (m, 2H), 5.36 (s, 2H), 3.84 and 3.58 (AA'BB', 4H), 3.39 (s, 3H), 2.52–2.40 (m, 2H), 2.18–2.05 (m, 1H), 2.00–1.88 (m, 1H), 1.72–1.58 (m, 2H), 1.43–1.24 (m, 6H), 0.94 and 0.93 (overlapping t, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 158.5, 146.9, 141.1, 128.4 (2 coincident C), 126.8, 126.2 (2 coincident C), 94.1, 71.5, 68.3, 65.6, 59.0, 32.8, 28.6, 27.9, 26.9, 23.2, 23.0, 14.0, 13.7; IR (CH_2Cl_2) 2961, 2933, 2874, 1758, 1644, 1497, 1466, 1456, 1339, 1202, 1173, 1110, 985 cm^{-1}; HRMS (LSIMS, 2-NBA+Li) calcd for $C_{22}H_{32}O_4$+Li 367.24606, found 367.24606. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.99.

4-(2-(1,4-Dimethoxyphenyl))-3,4-dimethyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2f). A solution of 1-bromo-2,5-dimethoxybenzene (Aldrich, 0.585 mL, 3.89 mmol, 2.9 equiv) in dry THF (10 mL) under argon was cooled to –78 °C and *t*-BuLi (1.5 M in pentane, 5.2 mL, 7.8 mmol, 5.7 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, and then a solution of CuCN (0.174 g, 1.94 mmol, 1.4 equiv) and LiCl (0.165 g, 3.89 mmol, 2.9 equiv) in dry THF (3 mL) under argon was added via cannula. The reaction was stirred at –78 °C for 1.25 h, and then a solution of 3,4-dimethyl-3-cyclobutene-1,2-dione (**1a**)[22] (0.15 g, 1.4 mmol, 1.0 equiv) in THF (2 mL) was added via cannula. After stirring at –78 °C for 40 min, MEMCl (0.55 mL, 4.8 mmol, 3.6 equiv) was added and, after 5 min at –78 °C, the reaction mixture was allowed to warm to room temperature. After 25 min at room temperature, the reaction mixture was quenched with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl, and then it was extracted with EtOAc (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to a gold oil that was purified by flash silica gel chromatography (30% EtOAc/hexanes, R_f 0.21) to yield 0.233 g (51%) of **2f** as a yellow oil: ^1H NMR (360 MHz, $CDCl_3$) δ 6.98 (d, J = 2.9 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 6.74 (dd, J = 9.0, 2.9 Hz, 1H), 5.29 (d, J = 17.5 Hz, 1H), 5.28 (d, J = 17.5 Hz, 1H), 3.82 and 3.55 (AA'BB', 4H), 3.77 (s, 3H), 3.75 (s, 3H), 3.37 (s, 3H), 2.09 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 156.7, 153.6, 151.7, 145.7, 131.1, 114.1, 112.4, 112.3, 94.0, 71.5, 68.3, 61.2, 59.0, 55.7 (2 resolved C), 19.7, 11.3; IR (CH_2Cl_2) 3064, 2935, 2836, 1760, 1651, 1610, 1586, 1499, 1466, 1229, 1111, 1052, 1027 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.01; H, 7.26.

3,4-Dimethyl-4-(1-naphthyl)-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2g). A solution of 1-bromonaphthalene (Aldrich, 0.84 mL, 6.0 mmol, 3.3 equiv) in dry THF (15 mL) under argon was cooled to –78 °C and *t*-BuLi (1.5 M in pentane, 8.1 mL, 12 mmol, 6.7 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 2.3 h, and then a solution of CuCN (0.271 g, 3.03 mmol, 1.7 equiv) and LiCl (0.257 g, 6.06 mol, 3.3 equiv) in dry THF (5 mL) under argon was added to the reaction mixture via cannula. The mixture was stirred at –78 °C for 1.3 h, then a solution of 3,4-dimethyl-3-cyclobutene-1,2-dione (**1a**)[22] (0.200 g, 1.82 mmol, 1.0 equiv) in THF (2 mL) was added via cannula, and, after stirring at –78 °C for 1 h, MEMCl (0.86 mL, 7.53 mmol, 4.2 equiv) was added. The mixture was stirred for 30 min and then quenched at –78 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oily solid consisting of two major products. The mixture was purified by flash silica gel chromatography (30% EtOAc/hexanes, R_f 0.28) to yield 0.207 g (48%) of **1g** as a yellow oil: ^1H NMR (360 MHz, $CDCl_3$) δ 8.57 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.74 (t, J = 4.7 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.38 (coincident d, J = 4.7 Hz, 2H), 5.33 (d, J = 11.7 Hz, 1H), 5.31 (d, J = 11.7 Hz, 1H), 3.81 and 3.54 (AA'BB', 4H), 3.35 (s, 3H), 2.44 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 154.4, 146.6, 140.2, 134.5, 131.3, 128.6, 127.9, 127.2, 125.6, 125.5, 125.2, 123.2, 94.1, 71.5, 68.5, 64.6, 59.0, 21.7, 12.1; IR (CH_2Cl_2) 2929, 2893, 2822, 1759, 1655, 1595, 1510, 1453, 1379, 1325, 1175, 1111, 1053, 961 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.59; H, 6.81.

Also isolated was 0.092 g (34%) of a 1,2-addition product (not protected as a MEM ether) as a yellow solid: (30% EtOAc/hexanes, R_f 0.18) ^1H NMR (360 MHz, $CDCl_3$) δ 8.73 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.63–7.37 (m, 4H), 2.98 (br s, 1H), 2.40 (s, 3H), 1.82 (s, 3H).

3,4-Di-*n*-butyl-4-(2-pyridyl)-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2h). A solution of 2-bromopyridine (Aldrich, 0.280 mL, 2.94 mmol, 2.9 equiv) in dry THF (7 mL) under argon was cooled to –78 °C and *t*-BuLi (1.5 M in pentane, 3.0 mL, 4.5 mmol, 4.3 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, and then a solution of CuCN (0.132 g, 1.47 mmol, 1.4 equiv) and LiCl (0.125 g, 2.95 mmol, 2.9 equiv) in dry THF (3 mL) under argon was added via cannula. The mixture was stirred at –78 °C for 1 h, and then a solution of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione (**1b**)[10] (0.200 g, 1.03 mmol, 1.0 equiv) in THF (3 mL) was added via cannula and after stirring at –78 °C for 30 min, MEMCl (0.42 mL, 3.7 mmol, 3.6 equiv) was added. The reaction mixture was stirred for 10 min and then quenched at –78 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a dark green oil. The product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.22) to yield 0.116 g (31%) of **2h** as a dark blue oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.54 (d, J = 4.0 Hz, 1H), 7.61 (d of apparent t, J = 7.8, 1.6 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 4.0, 7.2 Hz, 1H), 5.34 (d, J = 5.9 Hz, 1H), 5.32 (d, J = 5.9 Hz, 1H), 3.82 and 3.57 (AA′BB′, 4H), 3.37 (s, 3H), 2.62–2.44 (m, 2H), 2.23–2.11 (m, 1H), 2.04–1.93 (m, 1H), 1.67–1.56 (m, 2H), 1.43–1.23 (m, 6H), 0.90 (2 overlapping t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 160.8, 159.1, 149.1, 147.0, 136.2, 121.7, 121.1, 94.1, 71.5, 68.3, 67.9, 59.0, 32.0, 28.4, 27.8, 27.1, 23.1, 23.0, 14.0, 13.7; IR (CH_2Cl_2) 2962, 2934, 2875, 1758, 1644, 1588, 1467, 1340, 1172, 1110, 1025, 991 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{31}O_4N$ 361.22529, found 361.22531. Anal. Calcd for $C_{21}H_{31}O_4N$: C, 69.78; H, 8.64. Found: C, 69.87; H, 8.59.

1,2-Diacetoxy-3,4-di-*n*-butylbenzene (3a). A solution of **2a** (0.137 g, 0.52 mmol) in dry 1,4-dioxane (3 mL) was sparged with argon and heated to 100 °C with stirring for 24 h. The dioxane was removed under vacuum to give a dark yellow oil that was purified by flash silica gel chromatography (10% EtOAc/hexanes, R_f 0.10) to yield 0.113 g (83%) of the catechol as a yellow oil. ^{1}H NMR indicated a 50:50 mixture of regioisomers due to acetate migration between the ortho hydroxy groups of the catechol, and the sample was fully acetylated to simplify the spectra before full characterization. A sample of the monoacetylated catechol (0.110 g, 0.42 mmol, 1.0 equiv) was dissolved in dry Et_2O (1 mL) under argon. Triethylamine (0.12 mL, 0.87 mmol, 2.0 equiv) and acetic anhydride (0.08 mL, 0.85 mmol, 2.0 equiv) were added, and the reaction mixture was stirred at room temperature for 4.5 h and then quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with Et_2O (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated to yield 0.121 g (95%) of **3a** as a yellow solid: mp 26–28 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 2.59 (t, J = 7.8 Hz, 2H), 2.51 (t, J = 7.7 Hz, 2H), 2.29 (s, 3H), 2.23 (s, 3H), 1.59–1.53 (m, 2H), 1.46–1.36 (m, 6H), 0.94 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (2 resolved C), 140.4, 140.1, 139.6, 134.4, 126.8, 120.1, 33.3, 32.1, 32.0, 26.6, 22.9, 22.6, 20.6, 20.2, 13.8, 13.7; IR (CH_2Cl_2) 2962, 2933, 2875, 2863, 1770, 1484, 1466, 1433, 1371, 1217, 1178, 1155, 1113, 1027, 888 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.35; H, 8.52.

3,4,5-Trimethyl-2-(1,3,6-trioxaheptyl)phenol (3b). A solution of **2b** (0.346 g, 1.44 mmol) in dry *m*-xylene (4 mL) was sparged with argon and heated to 140 °C with stirring for 19 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (30% EtOAc/hexanes, R_f 0.31) to give 0.330 g (95%) of **3b** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.65 (s, 1H), 5.03 (s, 2H), 3.94 and 3.63 (AA′BB′, 4H), 3.43 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 141.9, 132.6, 128.7, 126.0, 114.7, 99.0, 71.0, 69.2, 58.3, 19.8, 14.6, 12.7; IR (CH_2Cl_2) 3359, 2935, 2898, 1594, 1484, 1403, 1370, 1345, 1308, 1189, 1109, 1059 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.93; H, 8.40.

3,4,5,6-Tetramethyl-2-(1,3,6-trioxaheptyl)phenol (3c). A solution of **2c** (0.260 g, 1.06 mmol) in dry dioxane (5 mL) was sparged with argon and heated to 100 °C with stirring for 20 h. The dioxane was removed under vacuum, but ^{1}H NMR of the crude product showed **2c** was still present. The crude product was dissolved in dry dioxane (5 mL), sparged with argon, heated to 100 °C for 18 h, the dioxane was removed under vacuum, and the product was purified by flash silica gel chromatography (25% EtOAc/hexanes, R_f 0.37) to yield 0.168 g (64%) of **3c** as a white solid: mp 33–34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H, concentration dependent OH), 5.04 (s, 2H), 3.94 and 3.64 (AA′BB′, 4H), 3.43 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 141.5, 131.4, 125.4, 125.3, 120.5, 99.1, 71.1, 69.4, 58.4, 15.5, 15.2, 12.7, 11.8; IR (CH_2Cl_2) 3381, 2933, 1586, 1465, 1400, 1306, 1175, 1111, 1081, 1048, 1013, 957; HRMS (EI) calcd for $C_{14}H_{22}O_4$ 254.15181, found 254.15181.

3,4-Di-*n*-butyl-6-phenylpyrocatechol (3d). A solution of **2d** (0.116 g, 0.341 mmol) in dry *m*-xylene (2 mL) was sparged with argon and heated to 140 °C with stirring for 20 h. The xylene was remove under vacuum, and the product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.34) to yield 0.087 g (75%) of the catechol monoacetate as a clear oil. ^{1}H NMR indicated a 70:30 mixture of regioisomers due to acetate migration between the ortho hydroxy groups of the catechol, and the acetate protecting group was removed to simplify the spectra before full characterization. A sample of the monoacetate protected catechol (0.072 g, 0.211 mmol) was stirred with methanol (2 mL), water (1 mL) and saturated aqueous $NaHCO_3$ (1 mL) producing a white suspension. After 5 min at room temperature, the reaction mixture was extracted with EtOAc (3 × 5 mL), washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to a red-brown oil. The product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.34) to yield 0.052 g (83%) of **3d** as a yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.52–7.36 (m, 5H), 6.66 (s, 1H), 5.51 (s, 1H), 5.15 (s, 1H), 2.70 (t, J = 7.9 Hz, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.62–1.53 (m, 4H), 1.52–1.39 (m, 4H), 1.00 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 137.5, 137.4, 133.9, 129.3, 129.2, 129.0, 128.9, 127.6, 127.2, 125.3, 121.2, 34.0, 32.3, 32.2, 26.2, 23.4, 22.9, 14.1, 14.0; IR (CH_2Cl_2) 3547, 2960, 2930, 2873, 2861, 1602, 1506, 1483, 1460, 1432, 1301, 1277, 1212 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{26}O_2$ 298.19328, found 298.19328.

3,4-Di-*n*-butyl-2-(1,3,6-trioxaheptyl)-1-naphthol (3e). A solution of **2e** (0.100 g, 0.277 mmol) in dry *m*-xylene (2 mL) was sparged with argon and heated to 140 °C with stirring for 20 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.34) to yield 0.083 g (83%) of **3e** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 8.6 Hz, 1H), 8.16 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.46–7.35 (m, 2H), 5.17 (s, 2H), 4.06 and 3.72 (AA′BB′, 4H), 3.49 (s, 3H), 2.98 (t, J = 7.9 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 1.66–1.45 (m, 8H), 1.01 and 1.00 (overlapping t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 140.0, 133.1, 130.2, 127.9, 125.3, 124.7, 123.9, 123.6, 122.8, 100.0, 71.5, 69.6, 59.0, 33.6, 33.1, 28.1, 27.6, 23.3 (2 coincident C), 14.0, 13.9; IR (CH_2Cl_2) 3685, 3346, 2960, 2933, 2875, 1598, 1459, 1391, 1370, 1192, 1173, 1156, 1109, 1067, 1015 cm^{-1}; HRMS (LSIMS, 2-NBA + Li) calcd for $C_{22}H_{32}O_4$ + Li 367.24606, found 367.24606.

5,8-Dimethoxy-3,4-dimethyl-2-(1,3,6-trioxaheptyl)-1-naphthol (3f). A solution of **2f** (0.199 g, 0.592 mmol) in dry *m*-xylene (2 mL) was sparged with argon and heated to 140 °C for 20 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.25) to yield 0.163 g (82%) of **3f** as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.27 (s, 2H), 3.99 (s, 3H), 3.98 and 3.60 (AA′BB′, 4H), 3.84 (s, 3H), 3.39 (s, 3H), 2.69 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 150.0, 143.2, 139.8, 131.8, 124.5, 123.9, 116.1, 104.3, 103.4, 97.6, 71.8, 69.1, 59.0, 56.5, 55.8, 18.9, 14.1; IR (CH_2Cl_2) 3354, 2943, 2842, 1619, 1576, 1507, 1466, 1453, 1391, 1370, 1308, 1212, 1057, 994 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.29; H, 7.19. Found: C, 64.09; H, 7.17.

3,4-Dimethyl-2-(1,3,6-trioxaheptyl)-1-phenanthrol (3g). A solution of **2g** (0.103 g, 0.432 mmol) in dry *m*-xylene (2 mL) was sparged with argon and heated to 140 °C for 20 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (50% Et_2O/hexanes, R_f 0.31) to yield 0.066 g (64%) of **3g** as an off-white solid: mp 81–83 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.62–8.67 (m, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.10 (s, 1H), 7.91–7.87 (m, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.56–7.53 (m, 2H), 5.18 (s, 2H), 4.03 and 3.71 (AA′BB′, 4H), 3.51 (s, 3H), 2.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 141.1, 133.7, 130.7, 130.2, 128.6, 128.2, 125.6, 125.5, 125.3, 125.1, 124.6, 122.2, 121.0, 99.8, 71.6, 70.1, 59.0, 21.8, 14.5; IR (CH_2Cl_2) 3326, 3053, 2931, 2897, 1650, 1598, 1454, 1395, 1333, 1172, 1091, 1054, 992, 937 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}O_4$ 326.15180, found 326.15181.

1,2-Di-*n*-butyl-3-(1,3,6-trioxaheptyl)quinolizin-4-one (3h). A solution of **2h** (0.111 g, 0.307 mmol) in dry *m*-xylene (1 mL) was sparged with argon and heated to 140 °C for 20 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (EtOAc, R_f 0.31) to yield 0.088 g (79%) of **3h** as a yellow/brown oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.06 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.20–7.15 (m, 1H), 6.88 (m, 1H), 5.47 (s, 2H), 3.97 and

3.58 (AA'BB', 4H), 3.37 (s, 3H), 2.83–2.71 (m, 4H), 1.60–1.40 (m, 8H), 0.99 and 0.98 (2 overlapping t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6) δ 153.2, 143.0, 136.7, 134.9, 126.9, 125.6, 121.4, 112.9, 112.0, 96.3, 71.9, 69.3, 58.4, 33.1, 32.3, 27.5, 26.8, 23.4, 22.9, 13.9, 13.8; IR (CH_2Cl_2) 2962, 2933, 2875, 1644, 1634, 1561, 1536, 1468, 1403, 1160, 1106, 1019. Anal. calcd for $C_{21}H_{31}O_4N$: C, 69.78; H, 8.64. Found: C, 69.60; H, 8.69.

Addition of Cuprates to Monosubstituted Cyclobutenediones. 3-Phenyl-3-cyclobutene-1,2-dione (1c).[31] 4-(*tert*-Butyldimethylsiloxy)-2,3-diisopropoxy-2-cyclobutenone was prepared from diisopropyl squarate by standard procedures.[22] 4-(*tert*-Butyldimethylsiloxy)-2,3-diisopropoxy-2-cyclobutenone (1.92 g, 6.11 mmol, 1.0 equiv) was dissolved in dry THF (20 mL) under argon and cooled to –78 °C. PhLi (1.8 M in cyclohexane/Et_2O 70/30, 4.4 mL, 7.9 mmol, 1.3 equiv) was added dropwise, and the reaction mixture was stirred for 10 min and then quenched at –78 °C with saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to an oil. The oil was dissolved in CH_2Cl_2 (20 mL) and treated with 15 drops of concentrated HCl, and the reaction mixture was stirred at room temperature for 5 h and then washed with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL), and the combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid that was recrystallized from hexane and then sublimed (0.2 mmHg, 105 °C, –78 °C coldfinger) to give 0.369 g (38%) of 3-phenyl-3-cyclobutene-1,2-dione (**1c**) as a yellow solid: mp 149–150 °C (lit.[31] mp 152–153 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.99–8.05 (m, 2H), 7.55–7.68 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (2 coincident C), 195.3, 178.1, 134.5, 129.4 (2 coincident C), 129.3 (2 coincident C), 127.2; IR (CH_2Cl_2) 1783, 1711, 1602, 1553, 1484, 1079 cm^{-1}.

3,4-Phenyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2i). A solution of bromobenzene (Aldrich, 0.16 mL, 1.5 mmol, 2.9 equiv) in dry THF (2 mL) under argon was cooled to –78 °C and *t*-BuLi (1.1 M in pentane, 2.8 mL, 3.1 mmol, 5.7 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, and then a solution of CuCN (0.069 g, 0.77 mmol, 1.4 equiv) and LiCl (0.065 g, 1.5 mmol, 2.9 equiv) in dry THF (3 mL) under argon and precooled to –78 °C was added to the reaction mixture via cannula. The mixture was stirred at –78 °C for 1.5 h, and then a solution of 3-phenyl-3-cyclobutene-1,2-dione (**1c**) (0.085 g, 0.54 mmol, 1.0 equiv) in THF (3 mL) was added via cannula. The reaction mixture was stirred at –78 °C for 40 min, MEMCl (0.22 mL, 1.9 mmol, 3.6 equiv) was added, stirring was continued for 10 min, and then the reaction was quenched at –78 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a gold oil that was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.18) to yield 0.113 g (65%) of **2i** as a yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.42–7.36 (m, 3H), 7.33–7.25 (m, 5H), 5.59 (s, 2H), 4.63 (s, 1H), 3.92 and 3.61 (AA'BB', 4H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0, 146.6, 145.1, 136.4, 130.6, 130.3, 129.3 (2 coincident C), 128.8 (2 coincident C), 128.7 (2 coincident C), 127.5, 127.4 (2 coincident C), 95.0, 71.5, 68.9, 59.3, 50.1; IR (CH_2Cl_2) 2928, 2896, 2823, 2753, 1630, 1494, 1449, 1352, 1109, 947 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}O_4$ 324.136156, found 324.13615.

3-*n*-Butyl-4-(2-furyl)-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2j). A solution of furan (Aldrich, 0.351 mL, 4.83 mmol, 3.3 equiv) in dry THF (10 mL) under argon was cooled to –78 °C and *n*-BuLi (2.6 M in hexanes, 1.9 mL, 4.9 mmol, 3.3 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C for 1 h, and then added under argon with vigorous stirring via cannula to a suspension of CuCN (0.216 g, 2.41 mmol, 1.7 equiv) in dry THF (5 mL) that had been cooled to –42 °C. The resulting reaction mixture was stirred at –42 °C for 1.3 h, and then 3-*n*-butyl-3-cyclobutene-1,2-dione (**1d**)[22] (0.200 g, 1.45 mmol, 1.0 equiv) in THF (2 mL) was added via cannula. The reaction mixture was stirred at –42 °C for 1 h, MEMCl (0.69 mL, 6.0 mmol, 4.2 equiv) was added, and, after stirring for an additional 30 min, the mixture was quenched at –42 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to an oil that was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.26) to yield 0.153 g (36%) of **2j** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 1.5 Hz, 1H), 6.32 (dd, J = 3.2, 1.5 Hz, 1H), 6.18 (d, J = 3.2 Hz, 1H), 5.33 (d, J = 10.8 Hz, 1H), 5.31 (d, J = 10.8 Hz, 1H), 4.28 (s, 1H), 3.82 and 3.57 (AA'BB', 4H), 3.38 (s, 3H), 2.58–2.37 (m, 2H), 1.55–1.47 (m, 2H), 1.41–1.31 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 153.5, 150.9, 148.1, 142.1, 110.5, 107.5, 94.3, 71.5, 68.5, 59.0, 53.8, 28.0, 26.7, 22.7, 13.7; IR (CH_2Cl_2) 2963, 2933, 2877, 1767, 1649, 1503, 1467, 1456, 1341, 1111, 969 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.49; H, 7.60.

3-*n*-Butyl-4-naphthyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2k). A solution of 1-bromonaphthalene (Aldrich, 0.503 mL, 3.62 mmol, 3.3 equiv) in dry THF (8 mL) under argon was cooled to –78 °C and *t*-BuLi (1.5 M in pentane, 2.7 mL, 4.1 mmol, 3.7 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 2 h, and then a solution of CuCN (0.162 g, 1.81 mmol, 1.7 equiv) and LiCl (0.153 g, 3.61 mmol, 3.3 equiv) in dry THF (2 mL) was added via cannula under argon. Stirring was continued at –78 °C for 1 h, and then a solution of 3-*n*-butyl-3-cyclobutene-1,2-dione (**1d**)[22] (0.150 g, 1.09 mmol, 1.0 equiv) in THF (2 mL) was added via cannula. Stirring was continued at –78 °C for 30 min, then MEMCl (0.52 mL, 4.6 mmol, 4.2 equiv) was added, and after 15 min the mixture was quenched at –78 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3 × 40 mL), dried ($MgSO_4$), filtered, and concentrated to a blue oil that was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.20) to yield 0.240 g (62%) of **2k** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.58–7.47 (m, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 5.37 (s, 2H), 5.08 (s, 1H), 3.86 and 3.60 (AA'BB', 4H), 3.40 (s, 3H), 2.73–2.64 (m, 1H), 2.52–2.46 (m, 1H), 1.62–1.51 (m, 2H), 1.42–1.31 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 153.9, 147.8, 133.9, 133.5, 132.5, 128.6, 127.8, 126.3, 125.9, 125.3, 123.5, 123.4, 94.3, 71.6, 68.5, 59.1, 56.0, 28.3, 26.9, 22.8, 13.7; IR (CH_2Cl_2) 3065, 2962, 2933, 2876, 1763, 1647, 1466, 1457, 1341, 1174, 1109, 1027, 1007, 965 cm^{-1}; HRMS (LSIMS, 2-NBA) calcd for $C_{22}H_{26}O_4$+H 355.19094, found 355.19092. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.43; H, 7.38.

3-Phenyl-2-(1,3,6-trioxaheptyl)-1-naphthol (3i). A solution of **2i** (0.101 g, 0.311 mmol) in dry *m*-xylene (3 mL) was sparged with argon. A grain of K_2CO_3 was added (to prevent acid catalyzed migration of the protecting group), and the solution was heated with stirring to 140 °C for 18 h. The solvent was removed under vacuum to give a brown oil that was purified by flash silica gel chromatography (40% Et_2O/hexanes, R_f 0.29) to yield 0.070 g (69%) of **3i** as a yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.23–8.27 (m, 2H), 7.76–7.73 (m, 1H), 7.59 (d, J = 7.2 Hz, 2H), 7.46–7.32 (m, 6H), 4.75 (s, 2H), 3.85 and 3.63 (AA'BB', 4H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 138.7, 138.2, 134.6, 131.4, 129.4 (2 coincident C), 128.3 (2 coincident C), 127.4, 127.3, 125.8, 125.1, 124.7, 122.3, 120.2, 99.8, 71.6, 70.1, 59.0; IR (CH_2Cl_2) 3306, 2935, 2898, 1595, 1571, 1456, 1435, 1398, 1194, 1138, 1103, 1070, 1022, 935 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.91; H, 6.24.

6-*n*-Butyl-4-hydroxy-5-(1,3,6-trioxaheptyl)benzofuran (3j). A solution of **2j** (0.148 g, 0.503 mmol) in dry *m*-xylene (2 mL) was sparged with argon and heated to 140 °C for 20 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.29) to yield 0.122 g (82%) of **3j** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 6.84–6.87 (m, 2H), 5.08 (s, 2H), 4.00 and 3.68 (AA'BB', 4H), 3.47 (s, 3H), 2.63 (t, J = 7.7 Hz, 2H), 1.64–1.54 (m, 2H), 1.43–1.35 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 143.4, 142.6, 139.3, 133.0, 115.6, 104.5, 102.7, 100.2, 71.5, 69.7, 58.9, 32.8, 30.6, 22.6, 14.0; IR (CH_2Cl_2) 3317, 2959, 2934, 2898, 1601, 1448, 1401, 1368, 1226, 1185, 1139, 1101, 1060, 997, 978 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_5$ 294.14671, found 294.14672. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.25; H, 7.56.

3-*n*-Butyl-2-(1,3,6-trioxaheptyl)-1-phenanthrol (3k). A solution of **2k** (0.232 g, 0.654 mmol) in dry *m*-xylene (3 mL) was sparged with argon and heated to 140 °C for 20 h. The xylene was removed under vacuum, and the product was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.26) to yield 0.178 g (77%) of **3k** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 8.2 Hz, 1H), 8.29 (s, 1H), 8.19 (d, J = 9.1 Hz, 1H), 8.00 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.62–7.53 (m, 2H), 5.20 (s, 2H), 4.07 and 3.73 (AA'BB', 4H), 3.51 (s, 3H), 2.80 (t, J = 7.8 Hz, 2H), 1.74–1.65 (m, 2H), 1.50–1.41 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 141.6, 135.2, 132.0, 129.8, 128.5, 128.0, 126.2, 126.1, 125.2, 122.8, 121.8, 121.0, 114.1, 99.9, 71.5, 69.9, 59.0, 32.9, 31.1, 22.8, 14.1; IR (CH_2Cl_2) 3331, 2950, 2932, 2897, 2874, 1620, 1600, 1455, 1402, 1364, 1220, 1172, 1104, 1068, 1037, 999 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.30; H, 7.39.

Addition of Cuprates to Cyclobutenedione Monoacetals. 3-*n*-Butyl-4-(1-propen-2-yl)-4-methyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2l). A solution of 2-bromopropene (Aldrich, 0.453 mL, 5.10 mmol, 3.3 equiv) in dry THF (6 mL) under argon was cooled to −78 °C and *t*-BuLi (1.7 M in pentane, 6.0 mL, 10 mmol, 6.7 equiv) was added dropwise. The reaction mixture was stirred for 45 min at −78 °C, and CuCN (0.228 g, 2.55 mmol, 1.7 equiv) was added. The reaction mixture was stirred for 2 h, and then a solution of 4-*n*-butyl-3-methyl-3-cyclobutene-1,2-dione 2-ethylene acetal[21] (0.300 g, 1.53 mmol, 1.0 equiv) in THF was added via cannula. The reaction mixture was stirred at −78 °C for 30 min, warmed to 0 °C for 1 h, MEMCl (0.73 mL, 6.4 mmol, 4.2 equiv) was added, and after 5 min the reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (3 × 50 mL), concentrated to a yellow oil, dissolved in THF (10 mL) and treated with 10% aqueous HCl (10 mL). After stirring at room temperature for 6 h, the mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil that was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.34) to yield 0.302 g (70%) of **2l** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (d, J = 6.0 Hz, 1H), 5.21 (d, J = 6.0 Hz, 1H), 4.93 (s, 1H), 4.83 (s, 1H), 3.76 and 3.52 (AA′BB′, 4H), 3.32 (s, 3H), 2.41–2.26 (m, 2H), 1.69 (s, 3H), 1.63–1.52 (m, 2H), 1.42–1.30 (m, 2H), 1.32 (s, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 159.7, 145.8, 144.6, 113.0, 94.0, 71.4, 68.2, 63.1, 58.9, 28.5, 26.1, 23.0, 20.5, 18.1, 13.6; IR (CH_2Cl_2) 3058, 2964, 2935, 2877, 1756, 1648, 1451, 1422, 1380, 1339, 1175, 1109, 1009, 990 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{26}O_4$ 282.18311, found 282.18310. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.26; H, 9.29.

4-*n*-Butyl-4-(1-propen-2-yl)-3-methyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2m). A solution of 2-bromopropene (Aldrich, 0.453 mL, 5.10 mmol, 3.3 equiv) in dry THF (6 mL) under argon was cooled to −78 °C and *t*-BuLi (1.7 M in pentane, 6.0 mL, 10 mmol, 6.7 equiv) was added dropwise. After stirring for 45 min at −78 °C, CuCN (0.228 g, 2.55 mmol, 1.7 equiv) was added, the reaction mixture was stirred for 2 h, and then 3-*n*-butyl-4-methyl-3-cyclobutene-1,2-dione 2-ethylene acetal[21] (0.300 g, 1.53 mmol, 1.0 equiv) in THF was added via cannula. After 30 min at −78 °C, the mixture was warmed to 0 °C for 1 h, MEMCl (0.73 mL, 1.7 mmol, 4.2 equiv) was added, stirring was continued for 5 min, and the reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (3 × 50 mL) and concentrated to a yellow oil that was dissolved in THF (10 mL) and treated with 10% aqueous HCl (10 mL) at room temperature for 3 h with stirring. The mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil that was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.25) to yield 0.268 g (62%) of **2m** as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (s, 2H), 4.91 (s, 1H), 4.84 (s, 1H), 3.78 and 3.54 (AA′BB′, 4H), 3.36 (s, 3H), 2.03 (s, 3H), 1.73 (s, 3H), 1.80–1.59 (m, 2H), 1.31–1.16 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 153.9, 146.4, 144.8, 112.2, 93.8, 71.4, 68.1, 67.3, 58.9, 30.3, 27.7, 23.1, 20.7, 13.9, 11.1; IR (CH_2Cl_2) 2961, 2934, 2875, 1763, 1654, 1640, 1456, 1378, 1323, 1200, 1173, 1114, 1063, 970 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.94; H, 9.23.

4-Phenyl-3-cyclobutene-1,2-dione 2-Ethylene Acetal. 3-Isopropoxy-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal (1.23 g, 4.73 mmol, 1.0 equiv), prepared by standard procedures,[21] in dry Et_2O (20 mL) under argon was treated dropwise with a solution of lithium aluminum hydride (1.0 M in THF, 3.8 mL, 15 mmol, 3.2 equiv). The reaction mixture was stirred at room temperature for 20 min, quenched by the dropwise addition of water (0.30 mL, 17 mmol, 3.5 equiv), stirred for 30 min, filtered through Celite to remove a white precipitate, dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. The oil was dissolved in CH_2Cl_2 (15 mL) and treated with trifluoroacetic acid (0.25 mL, 3.3 mmol, 0.7 equiv), and the reaction mixture was stirred at room temperature for 20 min. K_2CO_3 was added, the mixture was filtered through a plug of silica gel eluting with CH_2Cl_2 (15 mL), the eluent was concentrated, and purified by flash silica gel chromatography (30% EtOAc/hexanes, R_f 0.36) to give 0.150 g (23%) of 4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal as a yellow oil: ^1H NMR (360 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.78–7.81 (m, 2H), 7.43–7.49 (m, 3H), 4.15–4.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 161.1, 158.7, 131.1, 128.9 (2 coincident C), 128.1 (2 coincident C), 127.9, 120.5, 66.2 (2 coincident C); IR (CH_2Cl_2) 3067, 2995, 2965, 2899, 1769, 1450, 1309, 1144, 1041, 1015, 946 cm^{-1}.

3,4-Diphenyl-2-(1,3,6-trioxaheptyl)-2-cyclobutenone (2i). A solution of bromobenzene (Aldrich, 0.174 mL, 1.66 mmol, 3.3 equiv) in dry THF (2 mL) under argon was cooled to −78 °C and *t*-BuLi (1.4 M in pentane, 2.4 mL, 3.4 mmol, 6.7 equiv) was added dropwise. After stirring at −78 °C for 45 min, a solution of CuCN (0.074 g, 0.83 mmol, 1.7 equiv) and LiCl (0.070 g, 1.7 mmol, 3.3 equiv) dissolved in dry THF (2 mL) and precooled to −78 °C was added to the reaction mixture via cannula. The reaction mixture was stirred at −78 °C for 1.5 h, then a solution of 4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal (0.100 g, 0.495 mmol, 1.0 equiv) in THF (1 mL) was added via cannula, and the reaction mixture was allowed to warm from −78 °C to 0 °C. After stirring for 30 min, MEMCl (0.19 mL, 1.7 mmol, 3.3 equiv) was added, stirring was continued an additional 5 min, then the reaction was quenched at 0 °C with a 1/9 mixture of NH_4OH (30% aqueous)/saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (3 × 50 mL) and concentrated to a yellow oil, and the oil was dissolved in THF (5 mL). After addition of 10% aqueous HCl (5 mL), the mixture was stirred at room temperature for 2.5 h, then extracted with EtOAc (3 × 30 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil. The product was purified by flash silica chromatography (20% EtOAc/hexanes, R_f 0.29) to yield 0.116 g (72%) of **2i** as a yellow oil: ^1H NMR (360 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.42–7.36 (m, 3H), 7.33–7.25 (m, 5H), 5.59 (s, 2H), 4.63 (s, 1H), 3.92 and 3.61 (AA′BB′, 4H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0, 146.6, 145.1, 136.4, 130.6, 130.3, 129.3 (2 coincident C), 128.8 (2 coincident C), 128.7 (2 coincident C), 127.5, 127.4 (2 coincident C), 95.0, 71.5, 68.9, 59.3, 59.1; IR (CH_2Cl_2) 2928, 2896, 2823, 2753, 1630, 1494, 1449, 1352, 1109, 947 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}O_4$ 324.136156, found 324.13615.

3-*n*-Butyl-4,5-dimethyl-2-(1,3,6-trioxaheptyl)-1-phenol (3l). A solution of **2l** (0.236 g, 0.836 mmol) in dry *m*-xylene (3 mL) was sparged with argon and heated with stirring to 140 °C for 20 h. The xylene was removed under vacuum, and the resulting yellow oil was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.30) to yield 0.203 g (86%) of **3l** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.65 (s, 1H), 5.04 (s, 2H), 3.95 and 3.64 (AA′BB′, 4H), 3.42 (s, 3H), 2.58–2.53 (m, 2H), 2.17 (s, 3H), 2.09 (s, 3H), 1.42–1.37 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 142.6, 134.4, 133.7, 125.9, 115.7, 99.8, 71.4, 69.5, 58.9, 32.2, 27.2, 23.1, 20.4, 14.8, 13.9; IR (CH_2Cl_2) 3377, 2960, 2933, 2875, 1608, 1592, 1480, 1318, 1191, 1104, 1059, 1007, 986 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.6; H, 9.28. Found: C, 68.21; H, 9.30.

4-*n*-Butyl-3,5-dimethyl-2-(1,3,6-trioxaheptyl)-1-phenol (3m). A solution of **2m** (0.147 g, 0.521 mmol) in dry *m*-xylene (3 mL) was sparged with argon and heated with stirring to 140 °C for 20 h. The xylene was removed under vacuum and the resulting yellow oil was purified by flash silica gel chromatography (20% EtOAc/hexanes, R_f 0.26) to yield 0.139 g (94%) of **3m** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.64 (s, 1H), 5.03 (s, 2H), 3.95 and 3.64 (AA′BB′, 4H), 3.42 (s, 3H), 2.52–2.45 (m, 2H), 2.21 (s, 3H), 2.16 (s, 3H), 1.47–1.32 (m, 4H), 0.94 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 142.6, 132.8, 131.5, 129.0, 115.7, 99.4, 71.5, 69.7, 58.9, 31.7, 29.3, 23.1, 19.6, 13.9, 12.6; IR (CH_2Cl_2) 3369, 2960, 2933, 2875, 1592, 1484, 1341, 1312, 1189, 1108, 1044, 978 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.98; H, 9.27.

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