A Synthesis of Highly Substituted Aromatics through Regiocontrolled Construction of Cyclobutenones Bearing Unsaturated Substituents at the 4-Position

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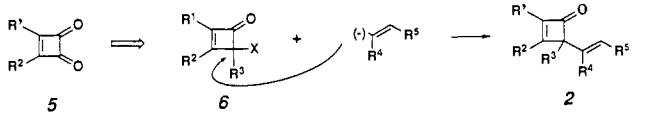
Abstract: 2,3-Substituted 4-chloro-2-cyclobutenones, prepared by regiospecific transformations of substituted cyclobutenediones, undergo palladium-catalyzed cross-coupling with vinyl- and arylstannanes and vinylzirconium reagents to form 4-R_{unsat}-2-cyclobutenones. On thermolysis (100 °C), these substrates transform into substituted phenols in high yield. A pentasubstituted aromatic and a variety of tri- and tetrasubstituted aromatic compounds were prepared in a regiospecific fashion using this chemistry.

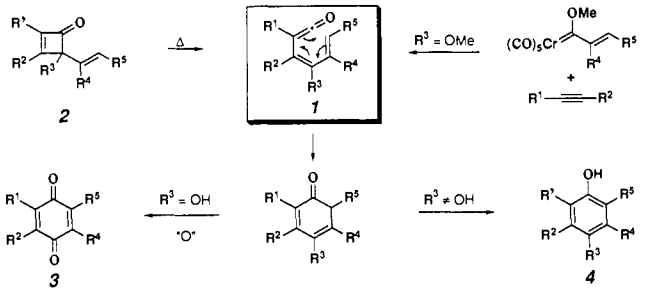
Dienyl ketenes (**1**) generated by thermolysis of cyclobutenones bearing an unsaturated substituent at the 4-position (**2**)[1-13] or via chromium carbene technology[14-16] transform into substituted phenols in a particularly general fashion (Scheme I). Crucial to the success of the cyclobutenone method is the requirement of a general and practical synthetic access to 4-R_{unsat}-2-cyclobutenones (**2**). When R^3 = OH, the requisite cyclobutenones are easily prepared by addition of organolithium nucleophiles to substituted cyclobutenediones, and the reaction products, after thermolysis and oxidation, are highly substituted quinones (**3**).[2,3,5,6] In order to generate cyclobutenones (**2**) where $R^3 \neq$ OH, which are precursors of highly substituted phenols (**4**), alternate methods of construction must be considered. Danheiser has documented an original and novel solution to the synthetic problem that relies on the [2 + 2] cycloaddition of electron-rich alkynes to vinylketene species generated either by thermolysis of cyclobutenones or via a photo-Wolff reaction of α'-diazo-α,β-unsaturated ketones.[1,7,8,17] Alternatively, regiocontrolled introduction of the unsaturated substituent onto a cyclobutenone core bearing a leaving group at the 4-position would provide a direct entry to the target structures (eq 1). General methods for the preparation of substituted



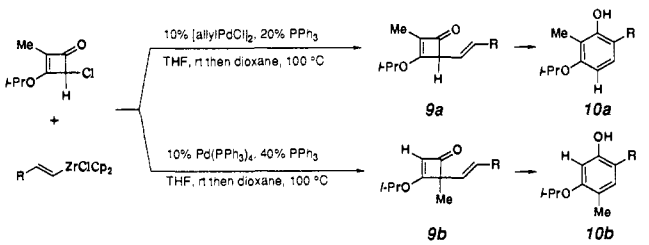
cyclobutenediones (**5**) have been described,[18-24] and simple procedures allowing the construction of 2,3-disubstituted 4-hydroxy-2-cyclobutenones (**6**, X = OH) by the regiospecific addition of nucleophiles to *either* carbonyl of **5** are in hand.[25] Conversion of **6** (X = OH) to 4-chloro-2,3-disubstituted-2-cyclobutenones can be accomplished by treatment with PPh_3/CCl_4. Documented herein is a general method for the synthesis of highly substituted phenols that commences with a palladium-catalyzed cross-coupling of 4-chloro-2-cyclobutenones (**6**, X = Cl) with R_{unsat}-organostannanes and organozirconium reagents.

For the early stages of this project, the synthetic problem was simplified by focusing on 4-chlorocyclobutenone substrates with R^3 = H (**7**), which were prepared following established procedures. Regiospecific construction of the desired substrates was achieved either directly from cyclobutenediones bearing one alkoxy or amino substituent (selective hydride reduction of the more reactive carbonyl group with 1 equiv of $LiAl(t\text{-}BuO)_3H$ followed by chlorination with PPh_3/CCl_4 in CH_3CN) or via the appropriate cyclobutenedione monoacetal (reduction of the unprotected carbonyl group with diisobutylaluminum hydride and hydrolysis to

Scheme I



Scheme II



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(25) (a) Cyclobutenediones bearing one alkoxy or amino substituent react with nucleophiles exclusively at the non-vinylogous ester or non-vinylogous amide carbonyl group. (b) When the substituents attached to the cyclobutenedione double bond do not provide differentiation of the two carbonyl groups, selective construction of 4-hydroxy-4-substituted-2-cyclobutenones is easily achieved via the appropriate cyclobutenedione monoketals.[24] Nucleophilic addition to the unprotected carbonyl group followed by gentle hydrolysis provides the 4-hydroxy-4-substituted-2-cyclobutenones.

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the corresponding 4-hydroxycyclobutenones, which were converted to the allylic chlorides on treatment with PPh_3/CCl_4). The results of treatment of 4-chlorocyclobutenones (**7**) with organostannanes under allylic chloride/organostannane palladium-catalyzed cross-coupling conditions[26,27] are shown in Table I. Alkoxy, amino, dialkyl, and alkyl aryl substitution on the cyclobutenone was surveyed by reaction with four different organostannanes. From the set of examples shown, the phenol synthesis appears to be quite general. Although the cross-coupling could occur at either of two termini of the π-alkylpalladium intermediate, the reaction products are those derived from bond formation exclusively at the less substituted end of the π-allyl intermediate, a regiochemical outcome precedented in allyl halide/organostannane cross-couplings.[26,27] Regioisomeric phenols are easily prepared by the control inherent in the construction of the 4-chloro-2-cyclobutenones. For example, the regioisomeric pair of cyclobutenones **7d** and **7c** are easily prepared via cyclobutenedione monoketal technology,[25b] and they provide a simple access to the isomeric 1,2,3-trisubstituted aromatics shown in entries 9 and 10 of Table I. The use of organostannanes bearing functional groups should allow the ready preparation of more highly derivatized phenols; one example is shown in entry 11 of Table I.

Literature precedent suggested that cross-coupling partners other than organostannanes should participate in the phenol synthesis.[28-30] To date, vinylzirconium reagents prepared in situ by the hydrozirconation of alkynes[31] have been briefly studied. Not only do vinylzirconium reagents participate in fast and efficient cross-coupling reactions with 4-chlorocyclobutenones, but an uncommon and possibly useful ligand-induced variation of cross-coupling regiochemistry was observed (Scheme II). Cross-coupling of cyclobutenone **7a** with (E)-$Cp_2Zr(Cl)CH{=}CH$-*n*-Bu in the presence of 10 mol % $[allylPdCl]_2$ and 20 mol % PPh_3 (low phosphine conditions) in THF followed by thermolysis in dioxane at 100 °C gave phenol regioisomer **10a** (R = *n*-Bu) in 66% yield. The same reactants under high phosphine conditions (10 mol % $Pd(PPh_3)_4$ and 40 mol % PPh_3) gave the regioisomeric phenol **10b** (R = *n*-Bu) in 41% yield. In each case the observed regioselectivity was ~20:1.[32] The same effect of high phosphine concentration was observed in the reaction of 4-chlorocyclobutenone **7a** with (E)-$Cp_2Zr(Cl)CH{=}CHPh$, which gave phenol **10b** (R = Ph) in 58% yield. Establishing the generality and deducing the origin of this synthetically intriguing ligand effect will require further study. A number of observations remain unexplained at the present time: (1) initial attempts to extend the (E)-$Cp_2Zr(Cl)CH{=}CHPh$ reaction to low phosphine cross-coupling conditions led to a complex mixture; (2) cyclobutenone **7b** did not participate in palladium-catalyzed cross-coupling with vinylzirconium reagents under the conditions employed; and (3) cyclobutenone **7c** reacted with (E)-$Cp_2Zr(Cl)$-$CH{=}CH$-*n*-Bu to give 2,3,6-tri-*n*-butylphenol regardless of the amount of PPh_3 used.

In conclusion, a general synthesis of substituted phenols has been developed that relies on the ready synthesis of 4-chloro-2,3-disubstituted-2-cyclobutenones and their palladium-catalyzed cross-coupling with vinyl- and arylstannanes and vinylzirconium reagents. The construction of a wide range of highly substituted aromatics should be feasible through the appropriate choice of reaction partners.

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Experimental Section

General Methods and Materials. All reactions were performed under an atmosphere of extra dry nitrogen in oven-dried glassware unless otherwise indicated. Reaction mixtures containing palladium catalysts were degassed by nitrogen sparge for 10–20 min prior to addition of the palladium complex. Solvents were distilled under nitrogen from either sodium–benzophenone ketyl (THF, Et_2O) or CaH_2 (CH_2Cl_2, CH_3CN) prior to use. Chlorotrimethylsilane was distilled from quinoline prior to use. Dioxane was obtained from Aldrich in Sure-Seal containers and used as received.

All thin-layer chromatography was performed using Merck Kieselgel 60 F_{254} plates with visualization by UV unless otherwise indicated. ^1H and ^{13}C NMR spectra were recorded on a GE QE300 spectrometer at 300 MHz and 74.8 MHz, respectively, and were referenced to $CHCl_3$ resonances (7.26 and 77.0 ppm). IR spectra were recorded on a Perkin-Elmer 1420 ratio recording spectrometer or on a Nicolet 510 IR spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

Catalysts and Ligands. Palladium complexes were obtained from commercial sources and used as received: $Pd(dba)_2$ (Aldrich), $Pd(benzonitrile)_2Cl_2$ (Fluka), $[PdCl(allyl)]_2$ (Alfa). Triphenylphosphine (Alfa) was recrystallized from ethanol. Tris(2-furyl)phosphine was prepared according to the literature method.[34]

Tin Reagents. Vinyltributyltin and ethoxytributyltin were obtained from Aldrich and used as received. Phenyltrimethyltin was prepared according to a literature procedure.[35] 4-Ethoxy-4-(tri-*n*-butylstannyl)-3-buten-2-one was prepared by the unpublished procedure, shown below, developed by Dr. Guy B. Stone of our laboratories.

4-Chloro-2-cyclobutenones. 2-Methyl-3-isopropoxy-4-chloro-2-cyclobutenone (7a). 3-Isopropoxy-4-methyl-3-cyclobutene-1,2-dione (3.03 g, 19.6 mmol, 1.0 equiv), prepared according to the published procedure,[22] was dissolved in dry THF (60 mL) under N_2 in a two-necked, 200-mL round-bottomed flask equipped with a N_2 inlet tube, septum, and magnetic stirring bar. The solution was cooled to −40 °C and treated dropwise with $LiAl(t\text{-}BuO)_3H$ (21.6 mL, 1.0 M in THF, 1.1 equiv) via syringe. After 1 h, TLC analysis indicated that the starting material had been consumed (50% Et_2O/hexanes, starting material R_f = 0.34). The reaction was quenched by slow addition of 6 N HCl in THF (20 mL) at −42 °C. The mixture froze and was allowed to warm to room temperature. The resulting solution was partitioned between water (50 mL) and Et_2O (100 mL). The organic layer was washed with saturated aqueous NaCl (30 mL), and the combined aqueous layers were backwashed witlt Et_2O (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow oil. The crude oil was purified by flash silica gel chromatography (50% EtOAc/hexanes, R_f = 0.19) and dried in vacuo to give 1.96 g (64%) of 2-methyl-3-isopropoxy-4-hydroxy-2-cyclobutenone as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (bs, 1 H), 5.02 (s, 1 H), 4.84 (quintet, J = 6.2 Hz, 1 H), 1.47 (s, 3 H), 1.28 (overlapping d, J = 6.2, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.0, 182.0, 122.0, 84.7, 81.2, 22.8, 22.3, 5.9; IR (CH_2Cl_2) 3573, 3320, 3060, 2986, 2927, 1752, 1615, 1389, 1320 cm^{-1}. Anal. Calcd for $C_8H_{12}O_3$: C, 61.53; H, 7.74. Found: C, 61.44; H, 7.73.

An acetonitrile solution (60 mL) of 2-methyl-3-isopropoxy-4-hydroxy-2-cyclobutenone (1.84 g, 11.8 mmol, 1.0 equiv) and triphenylphosphine (4.65 g, 17.7 mmol, 1.5 equiv) was treated with CCl_4 (5.7 mL, 58.7 mmol, 5.0 equiv). The reaction flask was kept in a water bath to moderate the mild exotherm that resulted. After 30 min, TLC indicated that the starting material had been consumed (Et_2O, starting material R_f = 0.33, vanillin). The reaction was quenched with 30% H_2O_2 (1.5 mL) to convert excess PPh_3 to triphenylphosphine oxide. The solvent was removed on a rotary evaporator to give an off-white solid that was triturated with portions of 30% EtOAc/hexanes (5 × 15 mL) to dissolve the desired product, leaving solid triphenylphosphine oxide behind. The triturant was concentrated to give a yellow oil that was purified by flash silica gel chromatography (30% EtOAc/hexanes, R_f = 0.33) and dried in vacuo to give 1.64 g (80%) of **7a** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 1 H), 4.83 (hept, J = 6.2 Hz, 1 H), 1.60 (s, 3 H), 1.35 (overlapping d, J = 6.1 Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 181.2, 174.9, 122.2, 77.7, 65.9, 22.5, 22.3, 6.9; IR (CH_2Cl_2) 3060, 2988, 2938, 1773, 1620, 1466, 1454, 1404 cm^{-1}. Anal. Calcd for $C_8H_{11}O_2Cl$: C, 55.03; H, 6.35. Found: C, 55.14; H, 6.31.

2-Methyl-3-(*N*,*N*-dibenzylamino)-4-chloro-2-cyclobutenone (7b). A solution of 4-isopropoxy-3-methyl-3-cyclobutene-1,2-dione (5.0 g, 32 mmol, 1.0 equiv) in methanol (50 mL) was treated dropwise with dibenzylamine (6.4 g, 32 mmol, 1.0 equiv). After 4 h, TLC indicated the

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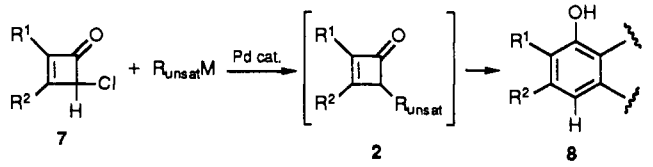
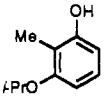
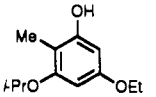
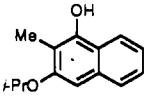
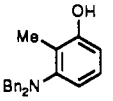
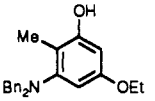
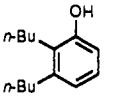
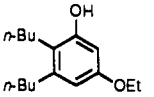
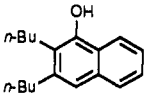
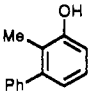
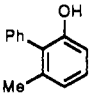
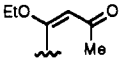
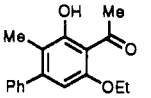
Table I. Phenol Synthesis by Cross-Coupling with 4-Chlorocyclobutenones



7 2 8

entry	compd	R^1	R^2	R_{unsat}	M	phenol	yield (%)
1[a]	**7a**	Me	O*i*-Pr	ethenyl	*n*-Bu_3Sn	 **8a**	67
2[b]	**7a**	Me	O*i*-Pr	1-ethoxyethenyl	*n*-Bu_3Sn	 **8b**	55
3[b]	**7a**	Me	O*i*-Pr	phenyl	Me_3Sn	 **8c**	53
4[b]	**7b**	Me	NBn_2	ethenyl	*n*-Bu_3Sn	 **8d**	62
5[b]	**7b**	Me	NBn_2	1-ethoxyethenyl	*n*-Bu_3Sn	 **8e**	74
6[b]	**7c**	*n*-Bu	*n*-Bu	ethenyl	*n*-Bu_3Sn	 **8f**	74
7[b]	**7c**	*n*-Bu	*n*-Bu	1-ethoxyethenyl	*n*-Bu_3Sn	 **8g**	54
8[b]	**7c**	*n*-Bu	*n*-Bu	phenyl	Me_3Sn	 **8h**	77
9[b]	**7d**	Me	Ph	ethenyl	*n*-Bu_3Sn	 **8i**	75
10[b]	**7e**	Ph	Me	ethenyl	*n*-Bu_3Sn	 **8j**	75
11[b]	**7d**	Me	Ph		*n*-Bu_3Sn	 **8k**	50

[a] Conditions: 5 mol % $Pd(dba)_2$ and 10 mol % tris(2-furyl)phosphine (TFP)[33] in dioxane at 60 °C for 5 h. [b] Conditions: 5 mol % $Pd(PhCN)_2Cl_2$ and 10 mol % TFP in dioxane at 100 °C, 4–18 h.

total consumption of starting material. The reaction mixture was partitioned between water (50 mL) and Et_2O (75 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined Et_2O layers were washed with water and brine. After concentration, the crude product was purified by flash silica gel chromatography (50% EtOAc/hexanes, R_f = 0.35) to give 7.0 g (74%) of 3-methyl-4-(*N*,*N*-dibenzylamino)-3-cyclobutene-1,2-dione as a brown solid: mp 88–90 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.14 (m, 10 H), 4.85 (s, 2 H), 4.47 (s, 2 H), 2.19 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.8, 191.7, 167.1, 134.4, 129.2, 128.9, 128.6, 128.4, 128.3, 128.2, 127.1, 126.9, 52.3, 52.1,

10.6; IR (CH_2Cl_2) 3035, 3010, 2945, 1786, 1736, 1601, 1445 cm^{-1}. Anal. Calcd for $C_{19}H_{17}O_2N$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.41; H, 5.94; N, 4.80.

A solution of 3-methyl-4-(*N*,*N*-dibenzylamino)-3-cyclobutene-1,2-dione (2.1 g, 7.2 mmol, 1.0 equiv) was prepared in dry THF (50 mL) under N_2. $LiAl(t\text{-}BuO)_3H$ (7.3 mL, 1.0 M in THF, 7.3 mmol, 1.0 equiv) was added dropwise at room temperature and cooled as needed with an ice bath. The solution was stirred at room temperature for 14 h, at which time TLC indicated total consumption of the starting material (50% EtOAc/hexanes, starting material $R_f = 0.35$). The reaction mixture was poured into 1 N HCl (100 mL), stirred until all solids had dissolved, and extracted with Et_2O (3 × 30 mL). The combined organic fractions were washed with 1 N HCl (20 mL) and water (20 mL), dried (Na_2SO_4), and concentrated. The crude product was recrystallized from CH_2Cl_2/hexane to give 1.8 g (85%) of 2-methyl-3-(*N*,*N*-dibenzylamino)-4-hydroxy-2-cyclobutenone as an off-white solid: mp 117–118 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 10 H), 6.22 (bs, 1 H), 5.30 (s, 1 H), 4.64–4.52 (m, 2 H), 4.45 (s, 2 H), 1.67 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 189.2, 171.5, 135.4, 129.0, 128.7, 128.4, 128.0, 127.1, 113.0, 80.4, 53.5, 51.5, 7.3; IR (CH_2Cl_2) 3300, 3058, 2979, 1742, 1594, 1578, 1497, 1113 cm^{-1}. Anal. Calcd for $C_{19}H_{19}O_2N$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.68; H, 6.58; N, 4.77.

The 4-chlorocyclobutenone **7b** was prepared as described for **7a**. A slurry of 2-methyl-3-(*N*,*N*-dibenzylamino)-4-hydroxy-2-cyclobutenone (1.7 g, 5.8 mmol, 1.0 equiv) and triphenylphosphine (2.0 g, 7.3 mmol, 1.25 equiv) was treated with carbon tetrachloride (2.7 g, 1.7 mmol, 2.9 equiv). Workup and purification by flash silica gel chromatography (50% CH_2Cl_2/EtOAc, $R_f = 0.7$) gave 0.80 g (44%) of **7b** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.17 (m, 10 H), 5.28 (s, 1 H), 4.63–4.40 (m, 4 H), 1.73 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 179.9, 166.3, 135.4, 135.4, 128.7, 128.6, 128.4, 127.8, 127.5, 115.7, 66.6, 53.6, 51.4, 7.8; IR (CH_2Cl_2) 3056, 1762, 1603, 1586, 1441, 1497, 1364, 1211, 1110, 1030 cm^{-1}. Anal. Calcd for $C_{19}H_{18}ClON$: C, 73.29; H, 5.83; N, 4.50. Found: C, 73.24; H, 5.85; N, 4.55.

2,3-Di-*n*-butyl-4-chloro-2-cyclobutenone (7c). 3,4-Di-*n*-butyl-3-cyclobutene-1,2-dione was prepared via a one-pot modification of the published procedure.[22] A solution of diisopropyl squarate (20.0 g, 101 mmol, 1.0 equiv) in dry THF (200 mL) was prepared under N_2 in a three-necked, 500-mL round-bottomed flask equipped with an addition funnel, N_2 inlet tube, septum, and magnetic stirring bar. The solution was cooled to −78 °C, and *n*-BuLi (42.0 mL, 2.5 M in hexanes, 105 mmol, 1.0 equiv) was added dropwise. The resulting solution was stirred for 1 h and then treated with chlorotrimethylsilane (12.0 g, 110 mmol, 1.1 equiv). The solution was allowed to warm to room temperature over a 1-h period before being recooled to −78 °C. A second aliquot of *n*-BuLi (60.0 mL, 2.5 M in hexanes, 150 mmol, 1.5 equiv) was added, and the solution was stirred for 1 h before being quenched with saturated NH_4Cl (aq). The mixture was warmed to room temperature and extracted with Et_2O. The Et_2O layers were washed with water and concentrated to give a yellow oil. The crude oil was immediately dissolved in CH_2Cl_2 (500 mL) and treated with concentrated HCl (40 drops). The solution was stirred for 3 h, during which time it darkened to a red color. The solution was then poured into saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with water, and concentrated to give a red oil. The crude oil was purified by flash silica gel chromatography (15% EtOAc/hexanes, $R_f = 0.3$, vanillin) to give 14.5 g (74%) of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (t, $J = 7.5$ Hz, 4 H), 1.65 (overlapping t, $J = 7.8$ Hz, 4 H), 1.39 (sextet, $J = 7.5$ Hz, 4 H), 0.97 (t, $J = 7.2$ Hz, 6 H); IR (CH_2Cl_2) 3100, 2990, 2910, 1810, 1612, 1483 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1211.

A THF solution of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione (14.5 g, 74.6 mmol, 1.0 equiv) was treated with $LiAl(t\text{-}BuO)_3H$ (75 mL, 1.0 M in hexanes, 75 mmol, 1.0 equiv). The reaction was quenched with excess chlorotrimethylsilane, stirred for 1 h, and subjected to workup. Purification by flash silica gel chromatography (20% EtOAc/hexanes) gave 12.0 g (82%) of 2,3-di-*n*-butyl-4-hydroxy-2-cyclobutenone as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.02 (s, 1 H), 4.33 (bs, 1 H), 2.51 (t, $J = 7.6$ Hz, 2 H), 2.07–1.96 (m, 2 H), 1.63–1.15 (m, 8 H), 0.89–0.79 (overlapping t, $J = 7.3$ Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.5, 180.1, 151.4, 83.7, 28.8, 28.0, 27.0, 22.8, 22.7, 22.4, 13.6, 13.5, 13.4; IR (CH_2Cl_2) 3577, 3392, 3060, 2962, 2935, 2875, 1756, 1627, 1468, 1381 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1462.

The 4-chloro-2-cyclobutenone **7c** was prepared as described for **7a**. An acetonitrile slurry of 2,3-di-*n*-butyl-4-hydroxy-2-cyclobutenone (12.0 g, 61.1 mmol, 1.0 equiv) and triphenylphosphine (24.1 g, 92.0 mmol, 1.5 equiv) was treated with carbon tetrachloride (28.3 g, 184 mmol, 3.0 equiv). Workup and purification by flash silica gel chromatography (10% EtOAc/hexanes) gave 3.0 g (62%) of **7c** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (s, 1 H), 2.57 (m, 2 H), 2.18 (m, 2 H), 1.76–1.23 (m, 8 H), 0.93 (overlapping t, $J = 9.0$ Hz, 6 H); IR (CH_2Cl_2) 3060, 2961, 2936, 2875, 1771, 1628, 1468, 1381, 1344 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{19}OCl$ 214.1124, found 214.1122.

2-Methyl-3-phenyl-4-chloro-2-cyclobutenone (7d). 3-Isopropoxy-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal (4.50 g, 17.3 mmol, 1.0 equiv), prepared according to the published procedure,[24] was dissolved in dry THF (13.5 mL) under argon and cooled to −78 °C. MeLi (12.5 mL, 1.4 M in hexanes, 17.5 mmol, 1.0 equiv) was added dropwise. After the reaction was stirred at −78 °C for 1 h, TLC showed total consumption of the starting material (50% Et_2O/hexanes, starting material $R_f = 0.20$). The reaction was quenched with water (10 mL) at −78 °C. The mixture was warmed to room temperature and extracted with Et_2O (3 × 50 mL). The combined Et_2O layers were dried ($MgSO_4$), concentrated to an oil, and dried in vacuo to give 4.29 g (90%) of 4-hydroxy-2-isopropoxy-4-methyl-3-phenyl-2-cyclobutenone ethylene acetal as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.61 (m, 2 H), 7.41–7.16 (m, 3 H), 4.54 (hept, $J = 6.0$ Hz, 1 H), 4.04–4.01 (m, 4 H), 2.59 (s, 1 H), 1.53 (s, 3 H), 1.33 (d, $J = 6.0$ Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 193.6, 174.2, 153.4, 129.3, 128.3, 128.2, 119.8, 65.9, 10.9; IR (CH_2Cl_2) 3563, 2980, 2940, 2880, 1673, 1378, 1348, 1335, 1280, 1155, 1127, 1100, 1023 cm^{-1}.

A THF solution (10 mL) of 4-hydroxy-2-isopropoxy-4-methyl-3-phenyl-2-cyclobutenone ethylene acetal (4.17 g, 15.1 mmol, 1.0 equiv) was stirred with 10% aqueous HCl (10 mL) at room temperature. After 5 min, TLC indicated total consumption of the starting material (30% EtOAc/hexanes, starting material $R_f = 0.3$). The reaction mixture was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting crude oil was purified by flash silica gel chromatography (30% EtOAc/hexanes, $R_f = 0.39$) to give 2.53 g (78%) of 3-methyl-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.69 (m, 2 H), 7.41–7.32 (m, 3 H), 4.18–4.09 (m, 4 H), 2.37 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.1, 174.6, 154.0, 129.8, 128.8, 128.7, 127.8, 120.4, 66.4, 11.4; IR (CH_2Cl_2) 3060, 2980, 2900, 1766, 1635, 1286, 1097, 1020, 953 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.00; H, 5.61.

3-Methyl-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal (2.48 g, 11.5 mmol, 1.0 equiv) was dissolved in dry Et_2O and cooled to 0 °C. DIBAL (13.8 mL, 1.0 M in toluene, 13.8 mmol, 1.2 equiv) was added dropwise. After the reaction was stirred for 30 min at 0 °C, TLC indicated no starting material remained (30% EtOAc/hexanes, starting material $R_f = 0.39$). The reaction was quenched with 30% aqueous potassium sodium tartrate (150 mL) and extracted with EtOAc (4 × 50 mL). The EtOAc layers were combined, dried ($MgSO_4$), and concentrated to an oil. The crude oil was purified by flash silica gel chromatography (30% EtOAc/hexanes with 10% triethylamine, $R_f = 0.34$) and dried in vacuo to give 1.49 g (60%) of 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone ethylene acetal as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2 H), 7.39–7.29 (m, 3 H), 4.89 (d, $J = 10$ Hz, 1 H), 4.05 (s, 4 H), 2.39 (d, $J = 10$ Hz, 1 H), 1.93 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.5, 136.7, 131.9, 127.9, 127.9, 126.9, 108.8, 78.2, 64.8, 64.3, 9.0; IR (CH_2Cl_2) 3560, 3058, 2980, 2905, 1491, 1447, 1388, 1343, 1296, 1137, 1035 cm^{-1}.

2-Hydroxy-4-methyl-3-phenyl-3-cyclobutenone ethylene acetal (1.45 g, 6.64 mmol, 1.0 equiv) was dissolved in THF (30 mL) and stirred with 10% aqueous HCl (15 mL) at room temperature. After 30 min, TLC (50% Et_2O/hexanes) showed no remaining starting material. The reaction was diluted with water (30 mL) and extracted with Et_2O (4 × 100 mL). The Et_2O layers were combined, dried ($MgSO_4$), and concentrated to an oil. The crude product was recrystallized from Et_2O/hexanes and dried in vacuo to give 0.97 g (84%) of 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone as a white solid: mp 115–117 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.72 (m, 2 H), 7.48–7.45 (m, 3 H), 5.51 (d, $J = 1$ Hz, 1 H), 3.93 (s, 1 H), 2.01 (d, $J = 1$ Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 184.4, 165.8, 145.3, 132.0, 129.6, 129.6, 129.2, 67.2, 9.7; IR (CH_2Cl_2) 3590, 3400, 3060, 2930, 1751, 1615, 1569, 1446, 1375, 1343, 1143, 1020, 970 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.95; H, 5.79.

The 4-chloro-2-cyclobutenone **7d** was prepared as described for **7a**. A slurry of 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone (0.15 g, 0.86 mmol, 1.0 equiv) and triphenylphosphine (0.34 g, 1.3 mmol, 1.5 equiv) in acetonitrile was treated with carbon tetrachloride (2.0 mL, 19 mmol, 22 equiv). Workup and purification by flash silica gel chromatography (acetonitrile) gave a white solid. The solid was further purified by preparative TLC (Merck SiO_2, 50% Et_2O/hexanes, $R_f = 0.53$). The product was washed from the SiO_2 with acetone, concentrated, and dried in vacuo to give 0.14 g (82%) of **7d** as a white solid: mp 80–81 °C; ^1H NMR (300 Mhz, $CDCl_3$) δ 7.81–7.65 (m, 2 H), 7.56–7.51 (m, 3 H), 5.61 (d, $J = 1$ Hz, 1 H), 2.08 (d, $J = 1$ Hz, 3 H); ^{13}C NMR (300 MHz,

$CDCl_3$) δ 184.4, 165.8, 145.3, 132.0, 129.6, 129.6, 129.2, 67.2, 9.7; IR (CH_2Cl_2) 3070, 2980, 1767, 1616, 1569, 1445, 1378, 1349, 1214, 1013, 817 cm^{-1}. Anal. Calcd for $C_{11}H_9OCl$: C, 68.58; H, 4.71. Found: C, 68.24; H, 4.63.

2-Phenyl-3-methyl-4-chloro-2-cyclobutenone (7e). 3-Isopropoxy-4-methyl-3-cyclobutene-1,2-dione 2-ethylene acetal (3.1 g, 16 mmol, 1.0 equiv) was dissolved in dry THF under N_2 and cooled to −78 °C. PhLi (9.8 mL, 1.8 M in hexanes, 18 mmol, 1.1 equiv) was added dropwise. After 1 h at −78 °C, TLC (30% EtOAc/hexanes) showed total consumption of the starting material. The reaction was quenched with saturated NH_4Cl (aq) at −78 °C. The mixture was warmed to room temperature, extracted with Et_2O, dried (Na_2SO_4), and concentrated to give a yellow oil. The crude oil was dissolved in THF (50 mL) and stirred with 10% aqueous HCl (50 mL) at room temperature. After TLC showed consumption of the starting material, the reaction mixture was poured into saturated $NaHCO_3$ (aq) and extracted with Et_2O. The Et_2O layers were concentrated, and the resulting yellow oil was purified by flash silica gel chromatography (40% EtOAc/hexanes) to give 2.1 g (62%) of 4-methyl-3-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal as a yellow solid: mp 78–79 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.45 (m, 5 H), 4.23 (s, 4 H), 2.09 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 233.5, 195.9, 171.6, 153.1, 130.8, 129.0, 128.4, 128.1, 128.0, 126.5, 119.9, 65.7, 8.8; IR (CH_2Cl_2) 3060, 2980, 2900, 1760, 1620, 1378, 1342 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.11; H, 5.55.

4-Methyl-3-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal (2.1 g, 9.7 mmol, 1.0 equiv) was dissolved in dry Et_2O (30 mL) under N_2 and cooled to 0 °C. The solution was treated with DIBAL (11.7 mL, 1.0 M, 1.17 mmol, 1.2 equiv). After 40 min, TLC showed the consumption of starting material, and the reaction mixture was poured into HCl/THF and stirred for 45 min. The mixture was extracted with EtOAc, washed with water and saturated NaCl (aq), dried (Na_2SO_4), and concentrated to give 1.35 g of 4-hydroxy-3-methyl-2-phenyl-2-cyclobutenone as a crude yellow oil (purity estimated at ~90% by ^1H NMR). The crude product was used directly without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.60 (m, 2 H), 7.39–7.20 (m, 3 H), 5.18 (s, 1 H), 2.47 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 191.7, 173.6, 146.4, 129.2, 128.7, 128.6, 128.4, 127.6, 127.4, 85.7, 13.9; IR (CH_2Cl_2) 3577, 3056, 2988, 2307, 1760, 1495, 1422 cm^{-1}.

The 4-chloro-2-cyclobutenone **7e** was prepared as described for **7a**. A slurry of 4-hydroxy-3-methyl-2-phenyl-2-cyclobutenone (1.1 g, 6.3 mmol, 1.0 equiv) and triphenylphosphine (2.8 g, 11 mmol, 1.7 equiv) in acetonitrile was treated with carbon tetrachloride (5.5 mL, 5.7 mmol, 9.0 equiv). Workup and purification by flash silica gel chromatography (20% EtOAc/hexanes, R_f = 0.57) gave 0.95 g (78%) of **7e** as a yellow oil: ^1H NMR (300 Mhz, $CDCl_3$) δ 7.71–7.68 (m, 2 H), 7.42–7.32 (m, 3 H), 5.32 (s, 1 H), 2.48 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 182.4, 168.0, 146.8, 133.6, 129.9, 129.0, 128.8, 128.6, 127.4, 71.1, 13.5; IR (CH_2Cl_2) 3064, 2981, 1806, 1773, 1634, 1599, 1495 cm^{-1}; HRMS (EI) cacld for $C_{11}H_9OCl$ 192.0342, found 192.0341.

General Procedure for the Cross-Coupling/Rearrangement of 4-Chlorocyclobutenones to Phenols. 2,3-Di-*n*-butylphenol (8f). A dioxane solution (3 mL) of 4-chloro-2-cyclobutenone **7c** (0.35 g, 1.6 mmol, 1.0 equiv) and vinyltributyltin (0.51 g, 1.6 mmol, 1.0 equiv) was prepared in a 25-mL Schlenk tube and degassed by N_2 sparge for 10 min. The solution was treated with a solid mixture of Pd(benzonitrile)$_2Cl_2$ (26 mg, 0.04 equiv) and tris(2-furyl)phosphine (TFP) (37 mg, 0.1 equiv). The mixture was stirred for 10 min at room temperature until all solids had dissolved and then was heated to 100 °C. After 3 h, GLC showed consumption of the starting material, and the mixture was heated for an additional 2 h to insure complete rearrangement to the phenol. The black solution was then partitioned between Et_2O (25 mL) and water (15 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated to give a reddish oil. The crude oil was dissolved in acetonitrile (25 mL) and extracted with hexane (3 × 30 mL) to remove residual tin. The combined hexane washes were backwashed once with acetonitrile (20 mL), and the combined acetonitrile layers were concentrated to give a reddish oil that was purified by flash silica gel chromatography (30% EtOAc/hexanes) to give 0.25 g (74%) of **8f** as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (t, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 6.62 (d, J = 8.1 Hz, 1 H), 5.02 (s, 1 H), 2.68 (m, 4 H), 1.61–1.29 (m, 8 H), 0.92 (t, J = 6.0 Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.7, 142.5, 127.2, 126.2, 121.8, 112.8, 33.8, 32.7, 32.2, 25.8, 23.2, 22.9, 14.0; IR (CH_2Cl_2) 3590, 2961, 2932, 2875, 1750, 1584, 1464 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O$ 206.167, found 206.1676.

3-Isopropoxy-2-methylphenol (8a). Prepared as described for **8f**. A dioxane solution of **7a** (0.15 g, 0.86 mmol, 1.0 equiv) and vinyltributyltin (0.27 g, 0.85 mmol, 1.0 equiv) with Pd(dba)$_2$ (25 mg, 0.05 equiv) and TFP (20 mg, 0.1 equiv) was heated to 60 °C for 5 h. Workup and purification by flash silica gel chromatography (20% Et_2O/hexanes, R_f = 0.4) gave 0.095 g (67%) of **8a** as a yellow oil. [Use of Pd(dba)$_2$ often results in contamination of the final product with traces of dba. Later experiments used Pd(benzonitrile)$_2Cl_2$ to avoid this.] **8a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (t, J = 8.1 Hz, 1 H), 6.51 (d, J = 8.1 Hz, 1 H), 6.43 (d, J = 8.1 Hz, 1 H), 5.21 (s, 1 H), 4.51 (quintet, J = 6.0 Hz, 1 H), 2.14 (s, 3 H), 1.35 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.1, 154.7, 126.3, 113.9, 107.9, 106.6, 71.0, 22.3, 8.4; IR (CH_2Cl_2) 3600, 2920, 2850, 1615, 1590, 1464, 1450 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.54.

5-Ethoxy-3-isopropoxy-2-methylphenol (8b). Prepared as described for **8f**. A dioxane solution of **7a** (0.5 g, 2.9 mmol, 1.0 equiv) and (1-ethoxyvinyl)tributyltin (1.3 g, 3.6 mmol, 1.2 equiv) with Pd(benzonitrile)$_2Cl_2$ (55 mg, 0.05 equiv) and TFP (74 mg, 0.1 equiv) was heated to 100 °C for 6 h. Workup and purification by flash silica gel chromatography (20% EtOAc/hexanes, R_f = 0.3) gave 0.33 g (55%) of **8b** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 1 H), 6.00 (s, 1 H), 5.57 (s, 1 H), 4.42 (quintet, J = 6.0 Hz, 1 H), 3.89 (qt, J = 7.0 Hz, 2 H), 2.03 (s, 3 H), 1.38–1.26 (m, 9 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.7, 157.3, 154.9, 106.0, 94.6, 94.1, 70.9, 70.7, 63.4, 22.1, 14.65, 7.8; IR (CH_2Cl_2) 3590, 2983, 1622, 1591, 1508, 1435, 1385 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.70, H, 8.69.

3-Isopropoxy-2-methylnaphthol (8c). Prepared as described for **8f**. A dioxane solution of **7a** (0.50 g, 2.9 mmol, 1.0 equiv) and phenyltrimethyltin (0.84 g, 3.5 mmol, 1.2 equiv) with Pd(benzonitrile)$_2Cl_2$ (55 mg, 0.05 equiv) and TFP (74 mg, 0.1 equiv) was heated to 100 °C for 6 h. Workup and purification by flash silica gel chromatography (10% EtOAc/hexanes, R_f = 0.3) gave 0.33 g (53%) of **8c** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.31 (t, J = 7.8 Hz, 1 H), 6.79 (s, 1 H), 5.21 (s, 1 H), 4.69 (quintet, J = 6.0 Hz, 1 H), 2.27 (s, 3 H), 1.41 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 154.8, 149.3, 132.9, 126.2, 125.8, 122.6, 120.7, 119.7, 110.2, 100.3, 70.0, 22.0, 21.9, 8.6; IR (CH_2Cl_2) 3589, 3056, 2988, 2364, 2308, 1422 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.50.

2-Methyl-3-(*N*,*N*-dibenzylamino)phenol (8d). Prepared as described for **8f**. A dioxane solution of **7b** (0.10 g, 0.32 mmol, 1.0 equiv) and vinyltributyltin (0.11 g, 0.35 mmol, 1.1 equiv) with Pd(benzonitrile)$_2Cl_2$ (6 mg, 0.05 equiv) and TFP (8 mg, 0.1 equiv) was heated to 100 °C for 4 h. Workup and purification by flash silica gel chromatography (50% EtOAc/hexanes) gave 0.060 g (62%) of **8d** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.23 (m, 10 H), 6.94 (t, J = 8.0 Hz, 1 H), 6.59 (d, J = 8.0 Hz, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 4.08 (s, 4 H), 2.37 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 154.5, 151.2, 147.4, 138.3, 132.1, 129.0, 128.6, 128.0, 126.8, 125.8, 120.9, 119.4, 115.0, 110.7, 110.6, 110.3, 56.8, 10.7; IR (CH_2Cl_2) 3588, 3056, 2988, 2364, 2308, 1584, 1495, 1422 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{21}ON$ 303.1623, found 303.1625.

3-(*N*,*N*-Dibenzylamino)-5-ethoxy-2-methylphenol (8e). Prepared as described for **8f**. A dioxane solution of **7b** (0.10 g, 0.32 mmol, 1.0 equiv) and (1-ethoxyvinyl)tributyltin (0.11 g, 0.31 mmol, 1.0 equiv) with Pd(benzonitrile)$_2Cl_2$ (6 mg, 0.05 equiv) and TFP (8 mg, 0.1 equiv) was heated to 100 °C for 12 h. Workup and purification by flash silica gel chromatography (30% EtOAc/hexanes, R_f = 0.34) gave 0.082 g (74%) of **8e** as a brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.21 (m, 10 H), 6.16 (d, J = 2.2 Hz, 1 H), 6.13 (d, J = 2.2 Hz, 1 H), 4.03 (s, 4 H), 3.86 (quintet, J = 7.0 Hz, 2 H), 2.27 (s, 3 H), 1.31 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.3, 155.0, 151.8, 138.3, 138.3, 128.5, 128.0, 126.8, 111.2, 102.1, 101.64, 97.2, 63.2, 56.7, 56.4, 14.8, 14.6, 10.2; IR (CH_2Cl_2) 3589, 3056, 2987, 1615, 1584, 1495, 1478, 1453, 1383 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{25}O_2N$ 347.1885, found 347.1892. Anal. Calcd for $C_{23}H_{25}O_2N$: C, 79.51; H, 7.24; N, 4.03. Found: C, 79.37; H, 7.29, N, 4.05.

2,3-Di-*n*-butyl-5-ethoxyphenol (8g). Prepared as described for **8f**. A dioxane solution of **7c** (0.30 g, 1.4 mmol, 1.0 equiv) and (1-ethoxyvinyl)tributyltin (0.51 g, 1.4 mmol, 1.0 equiv) with Pd(benzonitrile)$_2Cl_2$ (24 mg, 0.04 equiv) and TFP (33 mg, 0.1 equiv) was heated to 110 °C for 4 h. Workup and purification by flash silica gel chromatography (10% EtOAc/hexanes) gave 0.19 g (54%) of **8g** as a dark yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 2.2 Hz, 1 H), 6.20 (d, J = 2.2 Hz, 1 H), 4.75 (s, 1 H), 3.96 (quintet, J = 5.4 Hz, 2 H), 2.59 (m, 4 H), 1.60–1.20 (m, 11 H), 0.96 (t, J = 5.4 Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.6, 154.5, 143.1, 119.2, 107.9, 99.6, 63.3, 33.6, 32.9, 32.5, 25.3, 23.1, 22.8, 14.9, 14.0; IR (CH_2Cl_2) 3590, 2961, 2932, 1750, 1615, 1586, 1501, 1466, 1339 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1926.

2,3-Di-*n*-butylnaphthol (8h). Prepared as described for **8f**. A dioxane solution of **7c** (0.35 g, 1.63 mmol, 1.0 equiv) and phenyltrimethyltin (0.39 g, 1.62 mmol, 1.0 equiv) with Pd(benzonitrile)$_2Cl_2$ (26 mg, 0.04 equiv) and TFP (37 mg, 0.1 equiv) was heated to 110 °C for 5 h. Workup and purification by flash silica gel chromatography (10% EtOAC/hexanes)

gave 0.32 g (77%) of **8h** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d of d, J = 3.3 Hz, 1 H), 7.70 (d of d, J = 3.0 Hz, 1 H), 7.42 (d, J = 3.6 Hz, 1 H), 7.39 (d, J = 3.0 Hz, 1 H), 7.28 (s, 1 H), 5.22 (s, 1 H), 2.76 (quintet, J = 7.7 Hz, 4 H), 1.72–1.25 (m, 8 H), 1.00 (t, J = 7.7 Hz, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.4, 140.0, 132.8, 127.2, 125.4, 124.5, 123.0, 121.5, 120.7, 119.9, 33.5, 33.3, 26.0, 23.2, 22.9, 14.1, 14.0, 13.9; IR (CH_2Cl_2) 3687, 3602, 2961, 2932, 2875, 1800, 1649, 1603, 1460, 1381 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{24}O$ 256.1827, found 256.1827. Anal. Calcd for $C_{18}H_{24}O \cdot H_2O$: C, 78.79; H, 9.55. Found: C, 78.69; H, 9.32.

3-Hydroxy-2-methylbiphenyl (8i). Prepared as described for **8f**. A dioxane solution of **7d** (0.04 g, 0.21 mmol, 1.0 equiv) and vinyltributyltin (0.08 g, 0.25 mmol, 1.2 equiv) with Pd(benzonitrile)$_2$Cl$_2$ (8 mg, 0.01 equiv) and TFP (11 mg, 0.2 equiv) was heated to 100 °C for 6 h. Workup and purification by flash silica gel chromatography (10% EtOAc/hexanes, R_f = 0.3) gave 0.029 g (75%) of **8i** as a yellow solid: mp 50–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.31 (m, 5 H), 7.13 (t, J = 8.0 Hz, 1 H), 6.87 (d, J = 7.0 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 5.00 (s, 1 H), 2.17 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.4, 143.1, 141.0, 128.7, 127.4, 126.2, 121.9, 121.0, 113.2, 12.4; IR (CH_2Cl_2) 3595, 3410, 3050, 2930, 1584, 1468, 1439, 1309, 1204, 1180 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{12}O$ 184.0885, found 184.0888.

2-Hydroxy-6-methylbiphenyl (8j). Prepared as described for **8f**. A dioxane solution of **7e** (0.25 g, 1.30 mmol, 1.0 equiv) and vinyltributyltin (0.50 g, 1.58 mmol, 1.2 equiv) with Pd(benzonitrile)$_2$Cl$_2$ (24 mg, 0.05 equiv) and TFP (33 mg, 0.1 equiv) was heated to 100 °C for 6 h. Workup and purification by flash silica gel chromatography (30% EtOAc/hexanes) gave 0.18 g (75%) of **8j** as a white solid: mp 51–53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.43 (m, 5 H), 7.31 (d, J = 7.4 Hz, 2 H), 7.19 (t, J = 7.8 Hz, 1 H), 6.87 (d, J = 7.9 Hz, 1 H), 4.79 (s, 1 H), 2.09 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.7, 137.0, 135.2, 130.1, 129.3, 128.4, 128.0, 128.0, 121.9, 112.6, 20.3; IR (CH_2Cl_2) 3546, 3054, 2984, 1615, 1582, 1466, 1443 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.56. Found: C, 84.71; H, 6.61.

6′-Ethoxy-2′-hydroxy-3′-methyl-4′-phenylacetophenone (8k). 4-Ethoxy-4-(tri-*n*-butylstannyl)-3-buten-2-one was prepared as follows: 3-ethoxy-2-cyclobutenone (4.05 g, 36.1 mmol, 1 equiv) and *n*-Bu$_3$SnSiMe$_3$ (13.1 g, 36.1 mmol, 1 equiv) were dissolved in 190 mL of dry THF and cooled to −22 °C while stirring under N_2. Bu_4NCN (0.24 g, 0.89 mmol, 0.025 equiv) dissolved in 2 mL of dry THF was added dropwise over 2 min. The mixture was stirred for 1 h (TLC showed no 3-ethoxycyclobutenone present) and then warmed to room temperature over 2 h. Removal of the solvent by rotary evaporation and vacuum pump left a dark orange oil. Purification by flash chromatography (1 L of hexanes then 6% EtOAc in hexanes) gave a yellow band (R_f = 0.56 in 10% EtOAc in hexanes). Removal of the solvent gave 11.87 g (82%) of 4-ethoxy-4-(tri-*n*-butylstannyl)-3-buten-2-one as a bright yellow oil: IR (CH_2Cl_2, cm^{-1}) 2970, 2950, 1660, 1520, 1480, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1 H), 3.82 (quintet, J = 7.0 Hz, 2 H), 2.13 (s, 3 H), 1.48 (m, 6 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.27 (m, 6 H), 0.95 (m, 6 H), 0.85 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 197.0, 195.7, 109.8, 64.6, 29.4, 28.4, 26.6, 13.5, 13.0, 10.6. Anal. Calcd for $C_{18}H_{36}O_2Sn$: C, 53.62; H, 9.00; Found: C, 53.52; H, 9.03.

A dioxane solution of **7d** (0.20 g, 1.04 mmol, 1.0 equiv) and 4-ethoxy-4-(tri-*n*-butylstannyl)-3-buten-2-one (0.42 g, 1.04 mmol, 1.0 equiv) with Pd(benzonitrile)$_2$Cl$_2$ (17 mg, 0.04 equiv) and TFP (23 mg, 0.1 equiv) was heated to 100 °C for 18 h. Workup and purification by two successive flash silica gel chromatographies (20% EtOAc/hexanes) gave 0.27 g (50%) of **8k** as a yellow solid: mp 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5 H), 6.27 (s, 1 H), 4.09 (quintet, J = 6.9 Hz, 2 H), 2.73 (s, 3 H), 2.07 (s, 3 H), 1.48 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.1, 163.2, 158.1, 149.3, 147.4, 141.3, 128.7, 128.2, 127.5, 116.6, 110.9, 109.7, 103.2, 64.3, 33.8, 14.8, 12.4; IR (CH_2Cl_2) 3056, 2986, 1616, 1562, 1385, 1298, 1142 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.54; H, 6.71. Found: C, 75.59; H, 6.73.

Typical Experimental Procedure for the Cross-Coupling/Rearrangement of 4-Chlorocyclobutenones and Vinylzirconium Reagents to Phenols. 2-Phenyl-5-isopropoxy-4-methylphenol (10b, R = Ph). A 25-mL Schlenk flask equipped with a magnetic stirring bar was charged with dry THF (3 mL) and was degassed by a N_2 sparge for 10 min. Cp_2ZrClH (0.30 g, 1.2 mmol, 2.0 equiv) was added, and the suspension was treated with phenylacetylene (0.12 g, 1.1 mmol, 2.0 equiv). After 15 min, disappearance of the solids and formation of a dark red solution indicated that the hydrozirconization was complete. The solution was treated with $Pd(PPh_3)_4$ (60 mg, 0.1 equiv) and triphenylphosphine (66 mg, 0.4 equiv) followed by the addition of the 4-chlorocyclobutenone **7a** (0.1 g, 0.57 mmol, 1.0 equiv). The solution was stirred 14 h, quenched with MeOH (~2 mL), and stirred for 10 min before being stripped of the volatiles in vacuo. The residue was extracted into 30% EtOAc/hexanes and chromatographed (30% EtOAc/hexanes, R_f = 0.85) to give 0.081 g (58%) of **10b** (R = Ph) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.42 (m, 3 H), 7.38–7.32 (m, 2 H), 7.01 (s, 1 H), 6.54 (s, 1 H), 5.34 (bs, 1 H), 4.51 (quintet, J = 6.0 Hz, 1 H), 2.17 (s, 3 H), 1.36 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.6, 151.1, 137.4, 131.6, 129.1, 129.0, 128.7, 128.5, 128.4, 127.2, 119.8, 119.5, 100.9, 70.3, 22.2, 15.5; IR (CH_2Cl_2) 3556, 3056, 2986, 1624, 1487, 1422, 1314 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1310.

2-*n*-Butyl-5-isopropoxy-4-methylphenol (10b, R = *n*-Bu). Prepared as described for **10b** (R = Ph). Hydrozirconization of 1-hexyne (0.09 g, 1.1 mmol, 2.0 equiv) with Cp_2ZrClH (0.30 g, 1.2 mmol, 2.0 equiv) was followed by the addition of $Pd(PPh_3)_4$ (66 mg, 0.1 equiv), triphenylphosphine (66 mg, 0.4 equiv), and the 4-chlorocyclobutenone **7a** (0.10 g, 0.57 mmol, 1.0 equiv). The solution was stirred for 3 h, at which time GLC analysis showed consumption of the starting material. The reaction was quenched with MeOH and concentrated. The residue was treated with Et_2O (20 mL), and the resulting suspension was filtered through a 2-in. pad of silica gel with Et_2O as eluent. The solution was concentrated to give a red-brown oil, which contained a mixture of the cyclobutenone coupling product and the rearranged phenol. The crude oil was dissolved in dioxane (3 mL), transferred to a sealable Teflon-capped tube, and degassed. The tube was sealed and heated to 100 °C for 4 h. After cooling, the solution was diluted with Et_2O (15 mL), washed with water (3 × 15 mL), dried (Na_2SO_4), and concentrated to give a dark yellow oil. Flash silica gel chromatography (15% EtOAc/hexane, R_f = 0.3, PMA) gave 0.052 g (41%) **10b** (R = *n*-Bu) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1 H), 6.34 (s, 1 H), 4.90 (s, 1 H), 4.37 (quintet, J = 6.0 Hz, 1 H), 2.50 (t, J = 7.5 Hz, 2 H), 2.11 (s, 3 H), 1.61–1.51 (m, 2 H), 1.43–1.33 (m, 2 H), 1.29 (d, J = 6.0 Hz, 6 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 154.7, 151.7, 131.7, 119.8, 119.7, 101.9, 70.7, 67.0, 32.4, 28.9, 22.6, 22.2, 15.5, 13.9; IR (CH_2Cl_2) 3592, 2961, 2932, 2861, 1773, 1620, 1593, 1512, 1466, 1383 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1615.

2-*n*-Butyl-5-isopropoxy-6-methylphenol (10a, R = *n*-Bu). Prepared as described for **10b** (R = Ph). Hydrozirconization of 1-hexyne (0.09 g, 1.1 mmol, 1.9 equiv) with Cp_2ZrHCl (0.30 g, 1.2 mmol, 2.0 equiv) was followed by the addition of $[allylPdCl]_2$ (21 mg, 0.1 equiv), triphenylphosphine (31 mg, 0.2 equiv), and the 4-chlorocyclobutenone **7a** (0.10 g, 0.57 mmol, 1.0 equiv). The solution was stirred for 1.5 h, at which time GLC analysis showed consumption of the starting material. Workup gave crude product which was dissolved in dioxane and heated to 100 °C for 4 h. Workup and purification by flasht silica gel chromatography (10% EtOAc/hexanes, R_f = 0.26, PMA) gave 0.068 g (66%) of **10a** (R = *n*-Bu) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8.3 Hz, 1 H), 6.43 (d, J = 8.4 Hz, 1 H), 4.65 (s, 1 H), 4.44 (quintet, J = 6.0 Hz, 1 H), 2.53 (t, J = 7.5 Hz, 2 H), 2.12 (s, 3 H), 1.62–1.52 (m, 2 H), 1.44–1.34 (m, 2 H), 1.31 (d, J = 6.1 Hz, 6 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 154.9, 152.3, 126.5, 120.3, 113.0, 106.6, 70.7, 32.1, 29.5, 22.6, 22.3, 13.9, 8.5; IR (CH_2Cl_2) 3600, 2981, 2932, 2875, 1616, 1589, 1466 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_2$ 222.1619, found 222.1620.

2,3,6-Tri-*n*-butylphenol. Prepared as described for **10b** (R = Ph). Hydrozirconization of 1-hexyne (0.20 g, 2.4 mmol, 2.0 equiv) with Cp_2ZrHCl (0.62 g, 2.4 mmol, 2.0 equiv) was followed by the addition of $Pd(PPh_3)_4$ (0.14 g, 0.1 equiv) and the 4-chlorocyclobutenone **7c** (0.25 g, 1.2 mmol, 1.0 equiv). The solution was stirred for 6 h and subjected to workup to yield a mixture of coupled product and phenol. The mixture was dissolved in dioxane and heated to 100 °C for 4 h. Workup and purification by flash silica gel chromatography (10% EtOAc/hexanes, R_f = 0.8, PMA) gave 0.17 g (56%) of 2,3,6-tri-*n*-butylphenol as a dark yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J = 7.8 Hz, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 4.72 (s, 1 H), 2.65–2.53 (m, 6 H), 1.60–1.22 (m, 12 H), 0.99–0.87 (three overlapping triplets, 9 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 151.4, 139.5, 126.6, 126.5, 125.0, 121.0, 33.6, 32.5, 32.0, 31.8, 29.7, 25.9, 23.1, 22.7, 22.6, 22.5, 13.8; IR (CH_2Cl_2) 3606, 3050, 2961, 2932, 2863, 1802, 1711, 1576, 1466, 1379 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{30}O$ 262.2297, found 262.2296.

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Registry No. 7a, 138151-56-1; **7b**, 138151-57-2; **7c**, 138180-42-4; **7d**, 16547-35-6; **7e**, 138151-58-3; **8a**, 138151-59-4; **8b**, 138151-60-7; **8c**, 138151-61-8; **8d**, 138151-62-9; **8e**, 138151-63-0; **8f**, 138151-64-1; **8g**,

138151-65-2; **8h**, 138151-66-3; **8i**, 106912-94-1; **8j**, 14845-77-3; **8k**, 138151-67-4; **10a** (R = Bu), 138151-68-5; **10b** (R = Ph), 138151-69-6; **10b** (R = *n*-Bu), 138151-70-9; 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione, 114094-69-8; 2-methyl-3-isopropoxy-4-hydroxy-2-cyclobutenone, 138151-71-0; dibenzylamine, 103-49-1; 3-methyl-4-(*N*,*N*-dibenzylamino)-3-cyclobutene-1,2-dione, 138151-72-1; 2-methyl-3-(*N*,*N*-dibenzylamino)-4-hydroxy-2-cyclobutenone, 138151-73-2; diisopropyl squarate, 138151-74-3; 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione, 122967-65-1; 2,3-di-*n*-butyl-4-hydroxy-2-cyclobutenone, 138151-75-4; 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 128242-44-4; 4-hydroxy-2-isopropoxy-4-methyl-3-phenyl-2-cyclobutenone ethylene acetal, 138151-76-5; 3-methyl-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 138151-77-6; 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone ethylene acetal, 138151-78-7; 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone, 138151-79-8; 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 128242-41-1; 4-methyl-3-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 129034-75-9; 4-hydroxy-3-methyl-2-phenyl-2-cyclobutenone, 138151-80-1; vinyltributyltin, 7486-35-3; (1-ethoxyethenyl)tributylstannane, 97674-02-7; phenyltrimethyltin, 934-56-5; 3-ethoxy-2-cyclobutenone, 4683-54-9; 4-ethoxy-4-(tri-*n*-butylstannyl)-3-buten-2-one, 138151-81-2; phenylacetylene, 536-74-3; 1-hexyne, 693-02-7; 2,3,6-tri-*n*-butylphenol, 138151-82-3.

Treating the Camphors with Potassium in Liquid Ammonia Leads to a Double Horeau Duplication

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Abstract: When potassium dissolves in solutions of the enantiomeric camphors *R*-**1** and *S*-**1**, variously enantioenriched camphors (**1**), and racemic camphor *RS*-**1** in liquid ammonia/THF at −77 °C, potassium alcoholates of the borneols *R*-**2** and *S*-**2** and isoborneols *R*-**3** and *S*-**3** plus equivalent amounts of the potassium enolates of *R*-**1** and *S*-**1**—enantiomeric, enantioenriched, and racemic—are produced by a transfer of a β-hydrogen from some **1**-derived unit to another [a ketyl disproportionation (hydrogen atom transfer)?]; the exact mechanism is still unknown. Hydrolysis gives enantiomeric, racemic, and enantioenriched **1**-**3**. The mole fractions and enantiomeric compositions (ec's) of **2** and **3** were determined and plotted against the ec's of the substrates **1**. The extremes of the resulting three curves are defined by the enantiomers *R*-**1** and *S*-**1** leading to about 1/1 mixtures of *R*-**2** and *R*-**3** and *S*-**2** and *S*-**3**, respectively, and the turning points by *RS*-**1** leading to a 9/1 mixture of *RS*-**2** and *RS*-**3**. The ec vs ec curve is close to linear in the case of **2** and strongly nonlinear in the case of **3**: from enantioenriched substrates **1**, one obtains isoborneols **3** with ec's that are strongly amplified with respect to the ec's of the substrates. Fitting the plots into a statistical kinetic model suggests (1) that **3** is formed via one homochiral process (involving units with the same chirality) and **2** via a combination of second homochiral process with a single heterochiral one (involving units with opposite chirality), (2) that the rate-determining steps in these processes are fourth order with respect to the substrates **1** (!), and (3) that all parallel steps have similar or identical rate constants. The homochiral process that leads to **3** amounts to a double Horeau duplication. Statistical oligomerization or condensation of enantioenriched monomers to short oligomers leads to homochiral oligomers with strongly amplified ec. (+)-Camphor *R*-**1** (ec 99.6%) and (−)-camphor *S*-**1** (ec 98.3%) from the chiral pool were not quite enantiopure.

1. Introduction

Exposure to alkali metals may be the oldest known method for transforming a ketone into the corresponding alcohol(s), and the camphors may be the oldest known organic chemicals.[1] There are many ways of doing these reductions[2] and one of the simplest—exposure to sodium suspended in hot toluene followed by hydrolysis—was applied by Baubigny[3a] to (+)-camphor *R*-**1**[4] as early as the 1860s, when both the structure and the functional group were still unknown. He nevertheless has already described the phenomenon we are concerned with here,[3a] and in the 1890s, the sodium/ethanol reduction of *R*-**1** was even carried out industrially.[3b] These particular procedures are called dissolving metal reductions and were thought to involve nascent hydrogen.[3a] A number of procedural variants are still in use today, and the theory behind them is of considerable interest: while they start out with one of the simplest and most basic reactions imaginable, reaction with an electron, what happens afterward is often complicated and still far from understood.

This paper is concerned with the extraordinarily complex sequence of chemical events that takes place when the camphors **1** are exposed to the blue solution of ammoniated electrons (e^-_{am}) and potassium ions that is formed when metallic potassium dissolves in liquid ammonia, and its starting point was the resolution of a minor controversy. Three groups had studied this reaction and one had come up with results quite different from those of the other two. Much later, we realized that the reason for this was that the enantiomers and the racemate behave differently.[5d] This was conclusive proof that a bimolecular step involving two camphor-derived units intervenes, but we had already found independent, equally conclusive evidence for such a step before

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(1) Almost everything has been tried with the camphors! See: (a) *Beilstein.* (b) Simonsen, J. L. *The Terpenes*, 2nd ed.; Cambridge University Press: Cambridge, U.K., 1949; Vol. 2, pp 349-367, 373-512. For example, when Wynberg and Feringa first systematically explored enantiomeric recognition and interaction, they studied the $LiAlH_4$ reduction of the camphors (ref 6a),[22] and Hoffmann and Laszlo chose representations of *R*-**1** to illustrate what the representations mean: (c) Hoffmann, R.; Laszlo, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1-16, cf. **1-14**.

(2) Reviews: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; Chapter 3. Caine, D. *Org. React.* (*N. Y.*) **1976**, *23*, 1-258.

(3) (a) Baubigny, H. *Ann. Chim. Phys.* **1870**, [IV] *19*, 221-272. (b) Beckmann, E. *J. Prakt. Chem.* **1897**, *55*, 14-40. Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2348-2350.

(4) IUPAC rules: (1*R*,4*R*)-**1**, etc. For brevity, only the centers C(1) are specified and the locants and parentheses omitted throughout.

(5) (a) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1976**, *98*, 5035-5037. (b) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1977**, *99*, 6280-6286, 8373-8374. (c) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Burger, U. *Helv. Chim. Acta* **1981**, *64*, 2109-2137. (d) Rautenstrauch, V. *Helv. Chim. Acta* **1982**, *65*, 402-406. (e) Rautenstrauch, V. *Tetrahedron* **1988**, *44*, 1613-1618. (f) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1986**, 1558-1560.

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