Formation of *meta*-substituted phenols by transition metal-free aromatization: use of 2-bromo-cyclohex-2-en-1-ones

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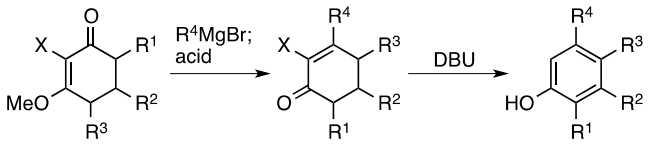


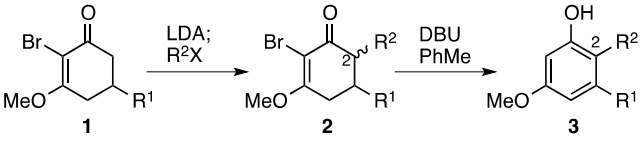
X = Br, Cl; R^1 = H, allyl, benzylic, F; R^2 = Me, Ph, thiophen-3-yl; R^3 = H, F; R^4 = Me, cyclopropyl, vinyl, allyl, benzylic, acetylenic, aryl, naphthyl, heteroaryl

ABSTRACT: Addition of Grignard- or other organometallic reagents to 3-halocyclohex-2-en-1-ones bearing an alkyl or aryl group at C-5, followed by mild acid treatment and exposure to DBU at room temperature, generates *meta*-substituted phenols in which the newly introduced *meta* substituent originates from the Grignard reagent. The range of effective organometallic reagents includes alkyl, allyl, alkynyl, aryl and heteroaryl compounds including those with fluorine substituents. The initial halocyclohexenone can be deprotonated at C-6 and reacted with carbon, fluorine or sulfur electrophiles before the Grignard addition so as to generate highly substituted phenols.

INTRODUCTION

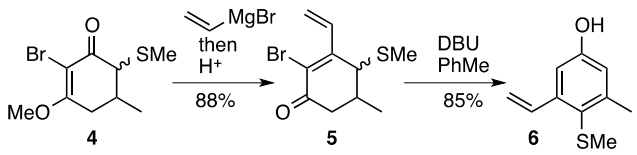
Two publications[1,2] from this laboratory have described the aromatization of bromoenones **1** into phenols. The bromoenones were initially[1] converted into their kinetic enolates and alkylated (Scheme 1, **1**→**2**, R^2 = alkyl group) with reactive halides such as allylic and propargylic halides, methyl iodide and an α-halo ester but it was later found[2] that the enolates react smoothly with a much wider range of electrophiles so as to introduce at C-2 various substituents (R^2 = SR, SAr,

Scheme 1. Aromatization of bromoenones



SePh, N_3, F, OH, OTHP, CH(OH)R, CH(OH)Ar, and CH($NHSO_2Ar$). Treatment with DBU at room temperature then effected efficient aromatization (**2**→**3**) by deconjugation of the double bond and 1,4-elimination of HBr. Among the many examples described was a single case[2] (Scheme 2) in which the particular bromoenone **4**, bearing a SMe group, was treated with vinylmagnesium bromide to afford **5**. On reaction with DBU it gave **6**,

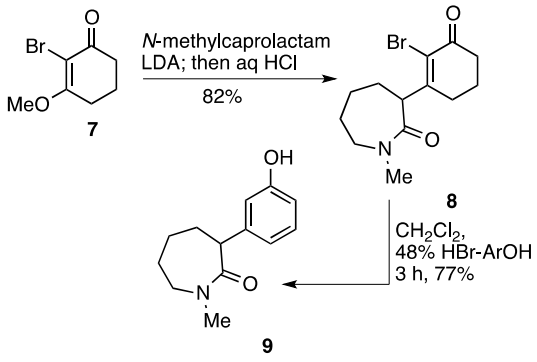
Scheme 2. Reaction of a bromoenone with a Grignard reagent



in which the substituent that had been introduced by Grignard addition is *meta* to the phenolic hydroxyl. The formation of *meta*-substituted phenols by classical methods of electrophilic substitution is not straightforward, but in the last few years various methods based on transition metal catalysis have been invented.[3] We have now explored the generality of the process represented by the conversion **4→6** and report here our results.

While the organometallic addition and acid treatment sequence applied to *non*-halogenated 3-alkoxycyclohex-2-en-1-ones is part of the classical Stork-Danheiser experiment,[4] we are aware of only a few cases[5] in which the starting cyclohexenone carried a halogen at C-2 and of these, only the work of Sheppard and White[5a,c] (Scheme 3) constitutes a realistic analogy to the method we have studied because their intermediate bromoenones (e.g. **8**, Scheme 3) were aromatized by treatment with 48% HBr/AcOH. However, the synthetic possibilities offered by aromatization of 2-bromocyclohex-2-en-1-ones do not seem to have been fully appreciated, and it may be that the strongly acidic conditions reported for aromatization are deemed unattractive. Reaction sequences in which a 2-halocyclohex-2-en-1-one is alkylated at C-6, treated with an organometallic and then aromatized must be very rare, if they have been reported at all, as we can locate no examples besides those studied in this laboratory.

Scheme 3. Prior analogy for the present Stork-Danheiser/aromatization sequence



RESULTS AND DISCUSSION

Some of the examples we have examined are listed in Table 1. Each of the starting materials was prepared by adding an excess of the appropriate organometallic reagent—usually a Grignard reagent but, in the case of entries 4 and 5, an organocerium reagent—to 2-bromo-3-methoxy-5-methylcyclohex-2-en-1-one (**10**). This particular substrate was used for all the reactions

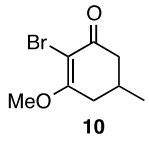
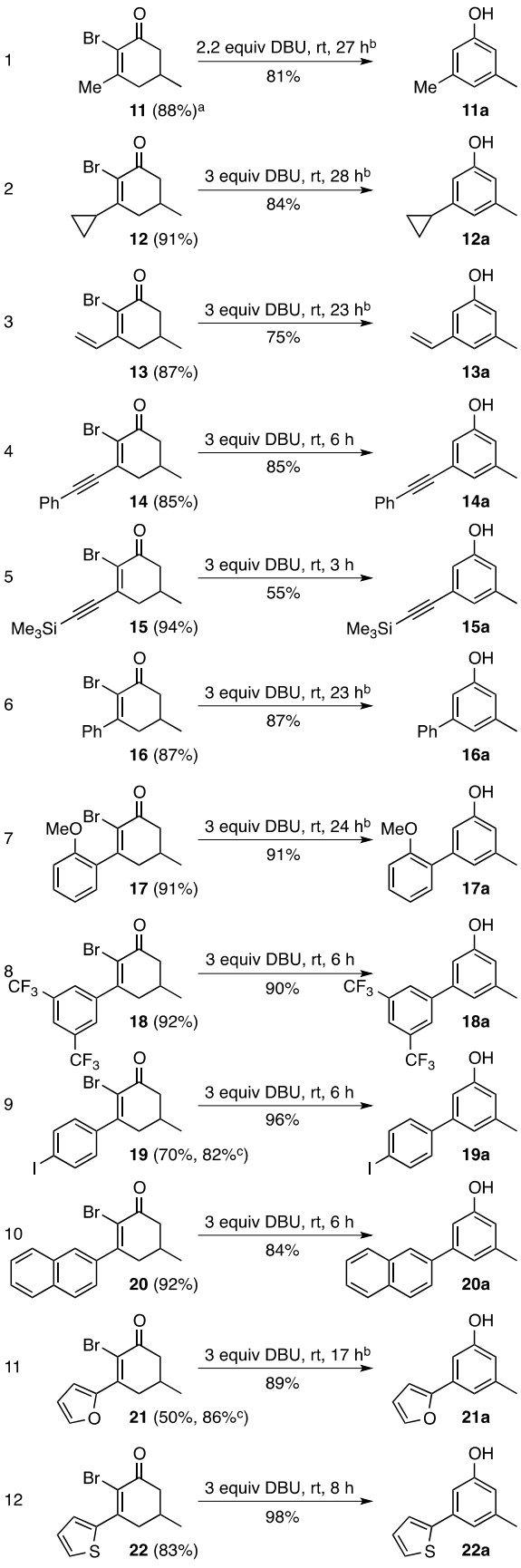


Table 1. Yields for organometallic addition-acid hydrolysis and aromatization


1
2.2 equiv DBU, rt, 27 h[b]
81%
11 (88%)[a]
11a
2
3 equiv DBU, rt, 28 h[b]
84%
12 (91%)
12a
3
3 equiv DBU, rt, 23 h[b]
75%
13 (87%)
13a
4
3 equiv DBU, rt, 6 h
85%
14 (85%)
14a
5
3 equiv DBU, rt, 3 h
55%
15 (94%)
15a
6
3 equiv DBU, rt, 23 h[b]
87%
16 (87%)
16a
7
3 equiv DBU, rt, 24 h[b]
91%
17 (91%)
17a
8
3 equiv DBU, rt, 6 h
90%
18 (92%)
18a
9
3 equiv DBU, rt, 6 h
96%
19 (70%, 82%[c])
19a
10
3 equiv DBU, rt, 6 h
84%
20 (92%)
20a
11
3 equiv DBU, rt, 17 h[b]
89%
21 (50%, 86%[c])
21a
12
3 equiv DBU, rt, 8 h
98%
22 (83%)
22a

[a]Yield for organometallic addition to **10** and acid-induced hydrolysis. [b]Reaction monitored (TLC) for at least 5 h and then left overnight. [c]Yield corrected for recovered **10**.

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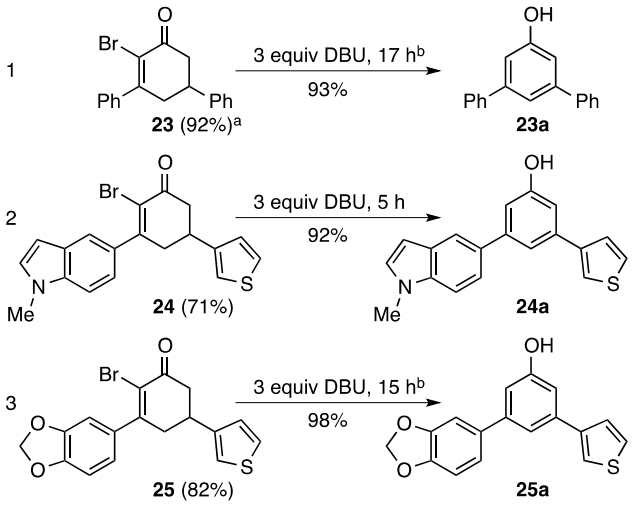
summarized in Table 1, but the method is not at all limited to this compound, and different starting bromoenones having other substituents in place of the C-5 methyl of **10** are discussed below. After addition of the organometallic the reaction mixture was diluted with 2 N hydrochloric acid, and in most cases this procedure effected hydrolysis to the desired enones **11**–**22**. In the case of entries 9 and 11 a slightly modified procedure was used: flash chromatography silica gel was added to the mixture after organometallic addition, followed by a few drops of 2 N hydrochloric acid. Under these conditions unreacted **10** was not hydrolyzed and so the yield of **19** and **21** could be corrected for the extent of conversion. Treatment of the enones shown in Table 1 with 3 equiv of DBU in THF at room temperature served to generate the expected *meta*-substituted phenols, generally in good yield (55–98%, average 84.5%). In some cases the reaction was over within 6 h, but where the process was slower (TLC monitoring) the mixtures were left overnight. With compound **16** as a test case, the use of 2.2 equiv DBU gave a slightly lower yield (80%) after the same reaction time.

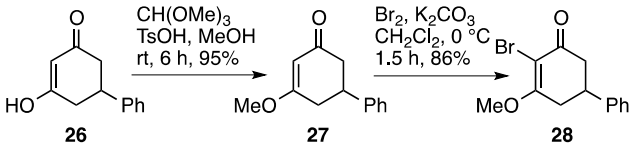
We also examined two compounds (Table 2) where the C-5 substituent in the starting bromoenone was not a methyl group. The required bromoenones for the Grignard reaction were readily accessible from commercial starting materials by the short sequences summarized in Schemes 4 and 5.

Table 2. Aromatization of 5-aryl-substituted enones

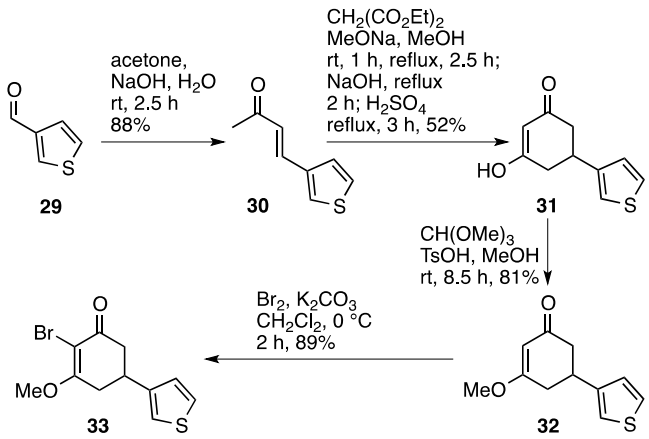


[a]Yield for Grignard addition and acid-induced hydrolysis. [b]Reaction monitored (TLC) for at least 5 h and then left overnight.

Scheme 4. Preparation of 28, the precursor to 23



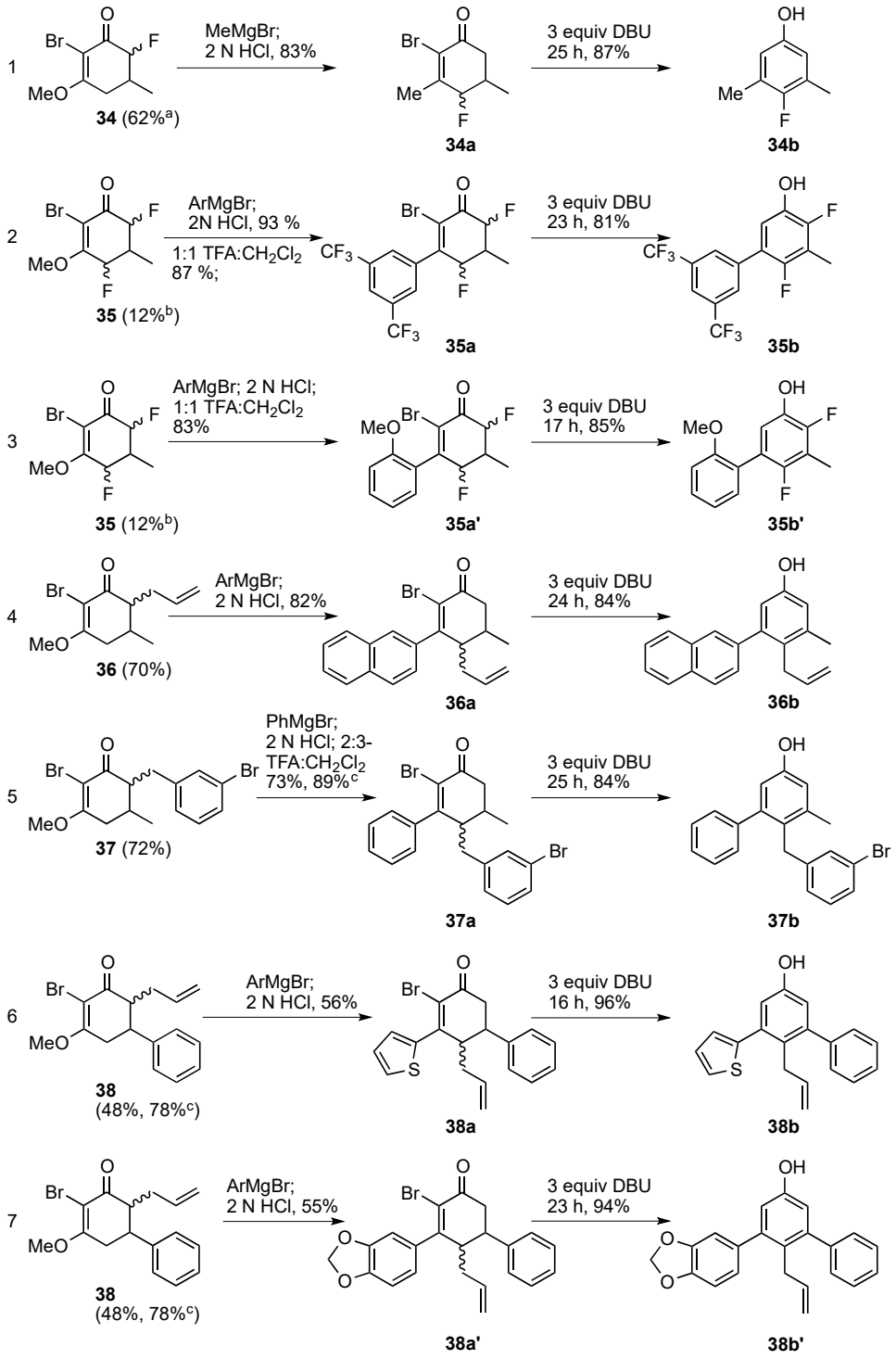
Scheme 5. Preparation of 33, the precursor to 24 and 25



In all three cases (Table 2, **23**, **24** and **25**) the reaction with DBU proceeded smoothly giving the expected aromatized materials in high yield (93%, 92% and 98%, respectively) under our standard conditions. Compound **25a** is an intermediate[6] in the synthesis of RO5101576, a leukotriene B4 receptor inhibitor which has been made *inter alia* by transition metal-based coupling procedures.[7] Our approach is transition metal-free.

We have also studied examples in which the starting bromoenone was first kinetically deprotonated at C-6 and treated with an electrophile (Table 3).

Table 3. Yields for Grignard addition and aromatization for highly-substituted cyclohexenones



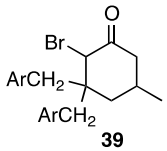
[a]Yield for reaction of 5-substituted 2-bromo-3-methoxycyclohex-2-en-1-one with electrophile. [b]Byproduct from the preparation of **34**. [c]Yield corrected for recovered starting material.

We used the electrophiles allyl bromide, *meta*-bromobenzyl bromide and *N*-fluorobenzenesulfonimide to prepare compounds **34**–**38**. In our first example, which was reported in an earlier publication,[2] we had used $MeSSO_2Tol$ to introduce an SMe group at C-6. Treatment of the C-6 substituted compounds **34**–**38** with Grignard reagents, followed by exposure to acid, afforded the expected cyclohexenones **34a**, **35a**, **35a'**, **36a**–**38a**, **38a'** in yields of 55–89%. Once again, the action of DBU at room temperature effected aromatization in high yield.

Limitations

In addition to the examples shown in Tables 1–3 we have found several cases where the organometallic addition or the acid hydrolysis step did not work.

The bulky Grignard reagents *i*-PrMgCl, cyclohexylmagnesiun bromide, *t*-BuMgBr and mesitylmagnesium bromide gave little, if any, of the addition product with 2-bromo-3-methoxy-5-methylcyclohex-1-en-2-one (**10**). With benzylmagnesium chloride or *p*-methoxybenzyl-magnesium chloride the outcome of the addition reaction was unusual[8] as in both experiments a geminally disubstituted cyclohexanone **39** was formed (38% with 2 equiv BnMgCl, 56% with 1.5 equiv of $4\text{-}MeOC_6H_4CH_2MgCl$); with the benzylmagnesium reagent this was the case even with only 1 equiv of the reagent (we did not examine the use of 1 equiv of *p*-methoxybenzylmagnesium chloride).



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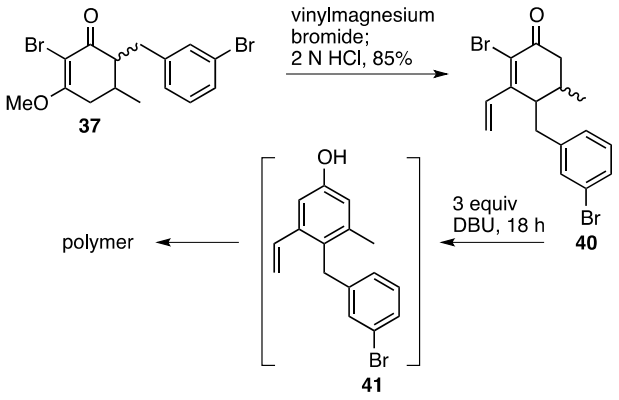
We suspect that an initial 1,2-addition to the carbonyl group is followed by rapid in situ conversion to a cyclohexenone that then undergoes (a rare) 1,4-addition.[9] However, we cannot yet, exclude the possibility of a 1,4-addition/elimination followed by a second 1,4-addition. A few examples have been reported[10] in which a benzylic Grignard reagent adds normally to 3-alkoxycyclohex-2-ene-1-ones and so the anomalous behavior of our cyclohexenone must be due to the presence of the halogen substituent. We did not examine the influence, if any, of the nature of the alkoxy group.

Although the reaction of vinylmagnesium bromide with **37** proceeded normally to give, after acid treatment, the ketones **40** (Scheme 6), aromatization with DBU appeared to generate a polymer of the desired vinylic phenol in high yield (>90%), this conclusion being based on the MALDI mass spectrum and the ^{1}H NMR spectrum of the final product.

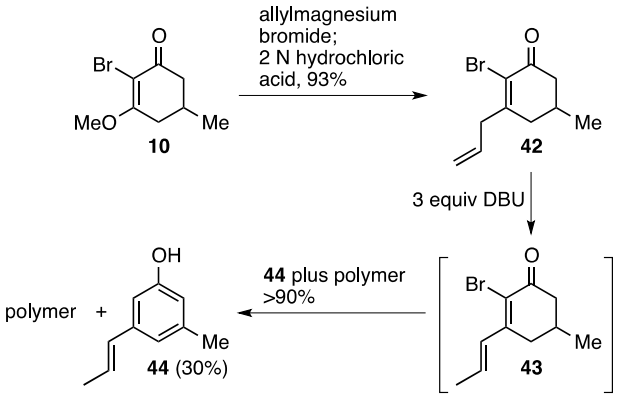
Scheme 6. Polymer formation from vinyl enone 40



Reaction of allylmagnesium bromide with **10**, followed by mild acid treatment (Scheme 7, **10**→**42**) proceeded normally, but DBU caused double bond migration faster than

aromatization, ultimately leading to **44**. Consequently, it was possible to isolate some of the intermediate **43** and establish the *trans* geometry of the double bond based on a ^{3}J value of 15.5 Hz for the olefinic hydrogens. The ^{1}H NMR spectrum gave absolutely no indication of the presence of any *cis* isomer. Likewise, the final aromatic product **44** (30% yield) was exclusively

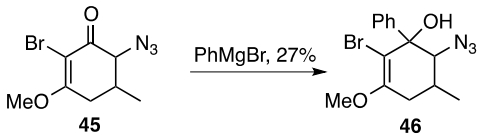
Scheme 7. Isomerization and aromatization of allyl bromoenone 42



trans. The MALDI mass spectrum of the crude product, before isolation of **44**, indicated that also in this experiment some polymerization occurred.

The last sequence that was problematic involved reaction of azide **45** with phenylmagnesium bromide (Scheme 8). The intermediate alcohols **46** could be isolated, although only in poor yield (27%), but exposure of the compounds to 2 *N* HCl in THF or to silica gel in THF produced a complex mixture.

Scheme 8. Reaction of azide 45 with PhMgBr



Comments on the initial organometallic addition and acid hydrolysis

We generally used 1.5 or more equiv of the organometallic reagent, initially at 0 °C and then at room temperature for periods of several h and, in a few cases, for more than 12 h. The reactions were monitored by TLC and, where necessary, additional aliquots of titrated Grignard reagent were added at intervals. Both the allyl and methyl Grignard reagents reacted rapidly (<2 h, 0 °C) and a large excess was not required.

With **10** and trimethylsilylacetylene as a test combination we observed little, if any, reaction when we used the derived acetylenic lithium salt, and a poor yield (ca 34%) with the magnesium salt. Because of the possibility that such unsatisfactory performance was due to premature enolization we tried the less basic cerium salt, which proved to be a very effective reagent. Accordingly, only the cerium salt of phenyl acetylene was examined.

The outcome of the overall process, of course, depends not only on the Grignard addition step but also on the acid-induced hydrolysis. This step was generally over within 0.5–2 h with 2 *N* hydrochloric acid in THF, except in a few cases where the reaction was very slow and in these we examined the use of CF_3CO_2H in CH_2Cl_2. When fluorine substitution was present either in the Grignard reagent or in the starting bromoenone, we were obliged to use 2 *N* hydrochloric acid for a prolonged time or CF_3CO_2H in CH_2Cl_2.

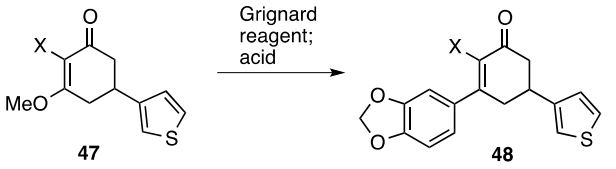
The tertiary alcohol precursor to **35a'** suffered only partial hydrolysis in 2 *N* hydrochloric acid during 2 h, but was completely hydrolyzed within 1 h with CF_3CO_2H in CH_2Cl_2 (83%). The corresponding precursor to **35a** was unchanged during 1 h by 2 *N* HCl in THF but was

hydrolyzed with CF_3CO_2H in CH_2Cl_2 during 45 h (TLC monitoring, 83%). The immediate precursor to **18** was hydrolyzed by 2 *N* HCl in THF when the mixture was left overnight; little, if any reaction being observe during the first 3 h. These slow acid hydrolyses reveal that strongly-electron-withdrawing groups exert an appreciable influence on the rate.

The tertiary alcohol precursor to benzyl-substituted compound **37a** was only partially hydrolyzed by 2 N HCl in THF during 30 min, but hydrolysis was extensive within 28 h with CF_3CO_2H in CH_2Cl_2 (73% or 89% corrected for recovered starting material).

In order to avoid the requirement for an excess of Grignard reagent we carried out several experiments with **47** to optimize the Grignard addition (see Table 4). A change of solvent to Et_2O instead of THF did not offer any improvement; neither did the presence of LiCl in THF.[11] If the initial substrate concentration was 0.21 M then use of just 1.25 equiv of the Grignard reagent was sufficient, provided the reaction time was extended to 2 days. When the concentration of the **47** (X = Br) was 0.105 M, use of 2.5 equiv of the Grignard reagent served to complete the reaction in under 6 h.

Table 4. Effect of solvent and concentration on the Grignard addition to bromo- and chlorocyclohexenones



X	47 concn.	Solvent	Equiv. ArMgBr & conditions	Yield
Br	0.105 M	THF	1.5 equiv, 0 °C, 2.5 h; 1 equiv, 0 °C to rt over 3 h	82%
Br	0.21M	THF	1.25 equiv. 0 °C, 4 h; rt, 43 h[a]	76%
Br	0.21M	Et_2O[b]	1.25 equiv. 0 °C, 4 h; rt, 48 h[a]	47% (70%[c])
Br	0.21M	THF + LiCl	1.25 equiv. 0 °C, 4 h; rt, 65 h[a]	56% (69%[c])
Cl	0.105 M	THF	1.5 equiv. 0 °C, 2 h	89%

[a]Monitored by TLC every 2 h during daytime. [b]Starting material not completely soluble in Et_2O. [c]Corrected for recovered starting material.

Because of the slowness of the Grignard addition we wondered if chloroenones would react faster as steric factors should be less severe in the case of chlorine. Indeed, with **47** (X = Cl) as a test case, the Grignard addition (Table 4, last entry) was noticeably faster and the DBU-mediated aromatization was proceeded just as smoothly and efficiently (94% yield) as with the bromides.

Comparison with other methods

The present route to *meta*-substituted aromatics is complementary to existing approaches because 3-alkyl- or 3-arylcyclohex-2-en-1-ones, which can be made in a number of ways,[12] including by Stork-Danheiser reaction,[4] can themselves be aromatized using conditions that are very different from the present method. Common reagents and conditions that have been employed are Pd-C at high temperature;[13] DDQ in refluxing dioxane;[14] $CuBr_2$-LiBr in MeCN;[15] $Hg(OAc)_2$, in hot AcOH;[16] stoichiometric[17] or catalytic[3b,18] Pd(II) at or above room temperature;

phenylselenation/oxidation,[19] and bromination-elimination.[20] The many reported examples of these methods—usually applied to simple substrates—cover a very wide range of yields even for closely related substances.

CONCLUSIONS

While phenols are firmly established as an important compound class,[21] the preparation of *meta*-substituted phenols (or synthetically equivalent boronic acid derivatives) has been the subject of a number of contemporary publications,[3] partly in response to the chemical challenge of bypassing the normal *ortho*/*para* directing effect of the phenolic hydroxyl group and partly because a number of *meta*-substituted phenolic structures are used in the preparation of pharmaceutically useful compounds.[6] Our route to *meta*-substituted phenols, including those bearing two aryl substituents, is general; it works under mild conditions and the yields are usually very good. No transition metals are required. All but one of our experiments have been done with bromides, but we suspect that use of the corresponding chlorides can be advantageous, as indicated by the reaction of **47** (X = Cl).

Our method should be especially useful in those cases where conventional reagents for aromatization are inappropriate, either because of the requirement for unacceptably high temperatures or because of the presence of subunits sensitive to traditional reagents. The method tolerates the presence of double and triple bonds in the substrate as well as furan, thiophene and indole units. The example of Table 1, entry 9 with an aryl iodide is a case where Pd-mediated aromatization methods would probably be inappropriate. Fluorinated compounds are readily accessible by our method. The starting bromoenones used for reaction with the organometallics are themselves accessible by straightforward classical means, and another advantage is that the

brominated intermediates for the aromatization step are generally crystalline solids. Each of the substituents in the final aromatic product is installed in a completely regiochemically controlled manner and each can have a wide range of values. The formation of compound **25a** illustrates an application to pharmaceutical chemistry, an area where exclusion of transition metals can be important.

EXPERIMENTAL SECTION

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time of flight analyzer and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer. Unless otherwise stated, Grignard reagents were commercial reagents. Gradient flash chromatography was done by stepwise small increases in the content of the more polar solvent.

2-Bromo-3,5-dimethylcyclohex-2-en-1-one (11). MeMgBr (3.0 M in Et_2O, 0.10 mL, 0.30 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **10**[1] (52 mg, 0.24 mmol) in THF (1.5 mL) (Ar atmosphere). Stirring at 0 °C was continued for 2.5 h. The reaction mixture was quenched with hydrochloric acid (2 N, 5 mL) and stirred for 15 min. More hydrochloric acid (2 N, 10 mL) was added and the reaction mixture was extracted with

EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using a 10–20% EtOAc–hexanes gradient, gave **11** (43.2 mg, 88%) as a solid: mp 48–50 °C; FTIR ($CDCl_3$, cast) 2957, 1682, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J = 5.6 Hz, 3 H), 2.16 (s, 3 H), 2.16–2.31 (m, 3 H), 2.45–2.59 (m, 1 H), 2.60–2.74 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 25.8 (q), 29.2 (d), 42.3 (t), 45.6 (t), 122.6 (s), 159.3 (s), 191.2 (s); exact mass (EI) *m*/*z* calcd for $C_8H_{11}{}^{81}BrO$ $(M)^+$ 203.9973, found 203.9974.

3,5-Dimethylphenol (11a).[6] DBU (0.13 mL, 0.83 mmol) was added to a stirred solution of **11** (77 mg, 0.38 mmol) in THF (2.0 mL) and stirring was continued for 27 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 20 mL) and stirring was continued for 20 min. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 8 cm), using a 5–10% EtOAc–hexanes gradient, gave **11a** (37.5 mg, 81%) as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 6 H), 4.52 (s, 1 H), 6.46 (s, 2 H), 6.58 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3 (q), 113.0 (d), 122.6 (d), 139.5 (s), 155.4 (s).

2-Bromo-3-cyclopropyl-5-methylcyclohex-2-en-1-one (12). Cyclopropylmagnesium bromide (1.0 M in 2-methyltetrahydrofuran, 1.0 mL, 1.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **10** (108.6 mg, 0.50 mmol) in THF (4.0 mL) (Ar atmosphere). The cold bath was left in place, but not recharged, and stirring was continued for 2.5 h during which the mixture reached room temperature. More cyclopropylmagnesium bromide (1.0 M in 2-methyltetrahydrofuran, 2.0 mL, 2.0 mmol) was added and stirring was continued for 21 h. The reaction mixture was quenched with hydrochloric acid (2 N, 5 mL) and stirred for 20 min. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25

mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using a 5–10% acetone–hexanes gradient, gave **12** (104 mg, 91%) as a white solid: mp 94–95 °C; FTIR ($CDCl_3$, cast) 3320, 2951, 1670 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 0.80–0.92 (m, 2 H), 0.96–1.12 (m, 2 H), 1.04 (d, *J* = 6.5 Hz, 3 H), 1.74 (dd, *J* = 17.5, 10.5 Hz, 1 H), 1.88–1.96 (m, 1 H), 2.05–2.17 (m, 1 H), 2.17–2.26 (m, 1 H), 2.37–2.47 (m, 1 H), 2.64–2.73 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 7.3 (t), 8.1 (t), 19.4 (q), 20.7 (d), 29.0 (d), 34.5 (t), 46.0 (t), 122.6 (s), 163.0 (s), 190.5 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{13}{}^{81}BrO$ $(M)^+$ 230.0129, found 230.0129.

3-Cyclopropyl-5-methylphenol (12a). DBU (89 μL, 0.58 mmol) was added to a stirred solution of **12** (44.4 mg, 0.19 mmol) in THF (1.5 mL) and stirring was continued for 28 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 5 mL) and stirring was continued for 15 min. More hydrochloric acid (5%$^w/_v$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% EtOAc–hexanes, gave **12a** (24.1 mg, 84%) as an oil: FTIR ($CDCl_3$, cast) 3331, 3007, 2920, 1595 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 0.63–0.70 (m, 2 H), 0.89–0.95 (m, 2 H), 1.76–1.85 (m, 1 H), 2.26 (s, 3 H), 4.50 (s, 1 H), 6.33 (s, 1 H), 6.43 (s, 1 H), 6.49 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.1 (t), 15.2 (d), 21.5 (q), 109.4 (d), 113.1 (d), 119.3 (d), 139.5 (s), 145.9 (s), 155.5 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{12}O$ $(M)^+$ 148.0888, found 148.0889.

2-Bromo-3-ethenyl-5-methylcyclohex-2-en-1-one (13). Vinylmagnesium bromide (1.0 M in THF, 1.51 mL, 1.51 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **10** (221 mg, 1.01 mmol) in THF (6.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 2.5 h. The reaction mixture was quenched with hydrochloric acid (2 N, 10 mL)

and stirred for 30 min. More hydrochloric acid (2 N, 10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using 10% EtOAc–hexanes, gave **13** (189 mg, 87%) as a solid: mp 45–46 °C; FTIR ($CDCl_3$, cast) 3343, 3096, 2957, 1679 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.12 (d, J = 5.7 Hz, 3 H), 2.15–2.34 (m, 3 H), 2.68–2.83 (m, 2 H), 5.64 (d, J = 10.9 Hz, 1 H), 5.82 (d, J = 17.5 Hz, 1 H), 7.16 (dd, J = 17.5, 10.9 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 (q), 28.9 (d), 35.6 (t), 46.1 (t), 123.7 (t), 124.6 (s), 137.0 (d), 152.3 (s), 191.9 (s); exact mass (EI) m/z calcd for $C_9H_{11}{}^{81}BrO$ $(M)^+$ 215.9973, found 215.9970.

3-Ethenyl-5-methylphenol (13a). DBU (0.15 mL, 0.99 mmol) was added to a stirred solution of **13** (71 mg, 0.33 mmol) in THF (2.0 mL) and stirring was continued for 23 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 10 mL) and stirring was continued for 30 min. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% EtOAc–hexanes, gave **13a** (33 mg, 75%) as an oil: FTIR ($CDCl_3$, cast) 3355, 3030, 2922, 1591, 1305 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 4.55 (br s, 1 H), 5.22 (d, J = 10.8 Hz, 1 H), 5.70 (d, J = 17.6 Hz, 1 H), 6.56 (s, 1 H), 6.62 (dd, J = 17.6, 10.8 Hz, 1 H), 6.70 (s, 1 H), 6.80 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3 (q), 109.9 (d), 114.1 (t), 115.6 (d), 120.1 (d), 136.6 (d), 139.1 (s), 139.9 (s), 155.6 (s); exact mass (EI) m/z calcd for $C_9H_{10}O$ $(M)^+$ 134.0732, found 134.0729.

2-Bromo-5-methyl-3-(2-phenylethynyl)cyclohex-2-en-1-one (14). *n*-BuLi (2.50 M in hexanes, 1.27 mL, 3.17 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of phenylacetylene (0.39 mL, 3.49 mmol) in THF (4.0 mL) and stirring was continued for 30 min

(Ar atmosphere). The dry ice/acetone bath was replaced by an ice bath, and stirring was continued for 40 min. The ice bath was removed and the solution was stirred for a further 40 min. The resulting (2-phenylethynyl)lithium solution was taken up into a syringe and added dropwise to a stirred and cooled (−78 °C) suspension of anhydrous $CeCl_3$ (782 mg, 3.17 mmol) in THF (5.0 mL) which had been prepared by suspending $CeCl_3$ in THF and stirring the mixture overnight at room temperature (Ar atmosphere).[22] Stirring at −78 °C was continued for 1 h. A solution of **10** (139 mg, 0.64 mmol) in THF (3.0 mL) was added dropwise to the solution of dichloro(2-phenylethynyl)cerium at –78 °C and stirring was continued for 4 h. The reaction mixture was quenched with hydrochloric acid (2 N, 25 mL), and EtOAc (30 mL) was added. Stirring was continued for 15 min and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using a 5–10% EtOAc–hexanes gradient, gave **14** (156 mg, 85%) as a solid: mp 76–78 °C; FTIR ($CDCl_3$, cast) 3338, 2957, 1679, 1258 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.12 (d, J = 5.8 Hz, 3 H), 2.27–2.45 (m, 3 H), 2.69–2.82 (m, 2 H), 7.34–7.46 (m, 3 H), 7.53–7.59 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 29.9 (d), 41.0 (t), 45.8 (t), 88.8 (s), 106.2 (s), 121.9 (s), 127.4 (s), 128.6 (d), 130.0 (d), 132.1 (d), 142.0 (s), 190.8 (s); exact mass (EI) m/z calcd for $C_{15}H_{13}{}^{81}BrO$ $(M)^+$ 290.0129, found 290.0131.

3-Methyl-5-(2-phenylethynyl)phenol (14a). DBU (91 μL, 0.60 mmol) was added to a stirred solution of **14** (57.4 mg, 0.20 mmol) in THF (1.2 mL) and stirring was continued for 6 h. The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 5 mL) (Ar atmosphere). EtOAc (5 mL) was added and stirring was continued for 20 min. More hydrochloric acid (2 N, 10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over

silica gel (1.5 × 10 cm), using 10% EtOAc–hexanes, gave **14a** (35 mg, 85%) as an oil: FTIR ($CDCl_3$, cast) 3375, 3055, 2921, 1588, 1028 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 4.63 (s, 1 H), 6.65 (s, 1 H), 6.81 (s, 1 H), 6.96 (s, 1 H), 7.34 (qd, J = 4.9, 1.8 Hz, 3 H), 7.47–7.54 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2 (q), 89.07 (s), 89.12 (s), 115.3 (d), 116.6 (d), 123.2 (s), 124.2 (s), 125.2 (d), 128.27 (d), 128.34 (d), 131.6 (d), 139.9 (s), 155.2 (s);exact mass (EI) m/z calcd for $C_{15}H_{12}O$ $(M)^+$ 208.0888, found 208.0887.

2-Bromo-5-methyl-3-[2-(trimethylsilyl)ethynyl]cyclohex-2-en-1-one (15). *n*-BuLi (2.50 M in hexanes, 1.22 mL, 3.04 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of trimethylsilylacetylene (0.47 mL, 3.34 mmol) in THF (4.0 mL) and stirring was continued for 30 min (Ar atmosphere). The dry ice/acetone bath was replaced by an ice bath, and stirring was continued for 30 min. The resulting (2-lithioethynyl)trimethylsilane solution was taken up into a syringe and added dropwise to a stirred and cooled (−78 °C) fine suspension of anhydrous $CeCl_3$ (748 mg, 3.04 mmol) in THF (5.0 mL) which had been prepared by suspending $CeCl_3$ in THF and stirring the mixture overnight at room temperature (Ar atmosphere).[22] Stirring at −78 °C was continued for 2 h. A solution of **10** (133 mg, 0.61 mmol) in THF (3.0 mL) was added dropwise to the resulting solution of [2-(dichlorocerio)ethynyl]trimethylsilane at –78 °C. The cold bath was left in place, but not recharged, and stirring was continued for 4 h during which the mixture reached 0 °C. The reaction mixture was quenched with hydrochloric acid (2 N, 25 mL), and EtOAc (20 mL) was added. Stirring was continued for 15 min and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using a 3–5% EtOAc–hexanes gradient, gave **15** (163 mg, 94%) as a thick oil: FTIR ($CDCl_3$, cast) 3352, 2959, 2143, 1685,

1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.26 (s, 9 H), 1.08 (d, J = 5.6 Hz, 3 H), 2.21–2.33 (m, 3 H), 2.60–2.76 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –0.5 (q), 20.5 (q), 29.8 (d), 41.0 (t), 45.8 (t), 102.9 (s), 113.7 (s), 128.1 (s), 141.6 (s), 190.9 (s); exact mass (EI) m/z calcd for $C_{12}H_{17}{}^{81}BrOSi$ $(M)^+$ 286.0212, found 286.0218.

3-Methyl-5-[2-(trimethylsilyl)ethynyl]phenol (15a). DBU (0.12 mL, 0.76 mmol) was added to a stirred solution of **15** (72 mg, 0.25 mmol) in THF (1.5 mL) and stirring was continued for 3 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 5 cm), using 20% EtOAc–hexanes, gave **15a** (29 mg, 55%) as an oil: FTIR ($CDCl_3$, cast) 3408, 2959, 2156, 1588, 1250 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 0.24 (s, 9 H), 2.27 (s, 3 H), 4.61 (br s, 1 H), 6.62 (s, 1 H), 6.73 (s, 1 H), 6.89 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –0.0 (q), 21.1 (q), 93.8 (s), 104.8 (s), 115.6 (d), 116.8 (d), 124.0 (s), 125.5(s), 139.8 (s), 155.1 (s); exact mass (EI) m/z calcd for $C_{12}H_{16}OSi$ $(M)^+$ 204.0971, found 204.0971.

2-Bromo-5-methyl-3-phenylcyclohex-2-en-1-one (16). PhMgBr (1.7 M in THF, 0.22 mL, 0.37 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **10** (54 mg, 0.25 mmol) in THF (1.5 mL) (Ar atmosphere). Stirring at 0 °C was continued for 50 min. The ice bath was removed and stirring was continued for 50 min. The reaction mixture was quenched with hydrochloric acid (2 N, 5 mL) and stirred for 15 min. More hydrochloric acid (2 N, 15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using a 5–10% EtOAc–hexanes gradient, gave **16** (56.9 mg, 87%) as a solid: mp 75–78 °C; FTIR ($CDCl_3$, cast) 3057, 2975, 1678 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 1.14 (d, *J* = 6.0 Hz, 3 H), 2.33–2.47 (m, 2 H), 2.48–2.57 (m, 1 H), 2.74–2.86 (m, 2 H), 7.29–7.38 (m, 2 H), 7.35–7.47 (m, 3 H);^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 29.7 (d), 43.2 (t), 45.7 (t), 122.3 (s), 126.8 (d), 128.4 (d), 128.8 (d), 140.8 (s), 159.8 (s), 191.8 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{13}{}^{81}BrO$ $(M)^+$ 266.0129, found 266.0129.

3-Methyl-5-phenylphenol (16a).[6] DBU (78 μL, 0.51 mmol) was added to a stirred solution of **16** (45 mg, 0.17 mmol) in PhMe (1.0 mL) and stirring was continued for 23 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (2 N, 15 mL) and stirring was continued for 20 min. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% EtOAc–hexanes, gave **16a** (27.5 mg, 87%) as an oil: ^{1}H NMR (498 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 4.71 (s, 1 H), 6.65 (s, 1 H), 6.87 (s, 1 H), 6.99 (s, 1 H), 7.28–7.39 (m, 1 H), 7.37–7.46 (m, 2 H), 7.53–7.59 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (q), 111.2 (d), 114.9 (d), 120.7 (d), 127.1 (d), 127.4 (d), 128.7 (d), 140.1 (s), 140.9 (s), 142.9 (s), 155.8 (s).

2-Bromo-3-(2-methoxyphenyl)-5-methylcyclohex-2-en-1-one (17). Preparation of the aryl Grignard reagent: 2-Bromoanisole (1.90 mL, 15.0 mmol) was added dropwise over <5 min to a stirred solution of Mg (401 mg, 16.5 mmol) in THF (40 mL) (Ar atmosphere). After the addition, a condenser with a drying tube was connected to the round bottomed flask. The reaction mixture was stirred for 3 h, and the resulting Grignard reagent was titrated according to the literature procedure[23] before use.

2-Methoxyphenylmagnesium bromide (0.30 M in THF, 1.61 mL, 0.48 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **10** (97 mg, 0.44 mmol) in THF (3.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 30 min. The ice bath was removed

and stirring was continued for 1 h. More 2-methoxy-phenylmagnesium bromide (0.73 mL, 0.22 mmol) was added slowly to the reaction mixture and stirring was continued for 30 min. The mixture was quenched with hydrochloric acid (2 N, 10 mL), stirred for 20 min, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 8 cm), using 10% EtOAc–hexanes, gave **17** (119 mg, 91%) as a solid: mp 102–104 °C; FTIR ($CDCl_3$, cast) 3350, 3070, 2957, 1685, 1252 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.12 (d, J = 6.0 Hz, 3 H), 2.06–3.07 (m, 5 H), 3.83 (s, 3 H), 6.93–7.04 (m, 2 H), 7.05–7.12 (m, 1 H), 7.31–7.39 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 29.8 (q), 42.0 (t), 45.9 (t), 55.7 (d), 111.3 (d), 120.6 (d), 123.3 (s), 128.0 (d), 130.0 (d), 130.2 (s), 155.0 (s), 159.7 (s), 191.9 (s); exact mass (EI) m/z calcd for $C_{14}H_{15}{}^{81}BrO_2$ $(M)^+$ 296.0235, found 296.0237.

3-(2-Methoxyphenyl)-5-methylphenol (17a).[13] DBU (92 μL, 0.60 mmol) was added to a stirred solution of **17** (59 mg, 0.20 mmol) in THF (1.0 mL) and stirring was continued for 24 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 10 mL), and EtOAc (10 mL) was added. Stirring was continued for 30 min and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% EtOAc–hexanes, gave **17a** (39.2 mg, 91%) as an oil: FTIR ($CDCl_3$, cast) 3407, 3030, 2924, 1596, 1242 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 3.81 (s, 3 H), 4.61 (br s, 1 H), 6.64 (s, 1 H), 6.83 (s, 1 H), 6.90 (s, 1 H), 6.94–7.04 (m, 2 H), 7.27–7.35 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (q), 55.6 (q), 111.2 (d), 113.7 (d), 114.8 (d), 120.8 (d), 123.0 (d), 128.7 (d), 130.4 (s), 130.8 (d), 139.3 (s), 139.9 (s), 155.0 (s), 156.4 (s); exact mass (ESI) m/z calcd for $C_{14}H_{13}O_2$ $(M–H)^-$ 213.0921, found 213.0922.

3-[3,5-Bis(trifluoromethyl)phenyl]-2-bromo-5-methylcyclohex-2-en-1-one (18). Preparation of the aryl Grignard reagent:[24] 1,3-Bis(trifluoromethyl)-5-bromo-benzene (1.74 mL, 10.0 mmol) in THF (4.0 mL) was added dropwise over 1 h to a stirred and heated (gentle reflux) mixture of Mg (510 mg, 21.0 mmol) and THF (10 mL) (Ar atmosphere). Stirring was continued at reflux for 1 h and the resulting Grignard reagent was titrated according to the literature procedure[23] before use.

[3,5-Bis(trifluoromethyl)phenyl]magnesium bromide solution (0.58 M in THF, 2.69 mL, 1.56 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **10** (115 mg, 0.52 mmol) in THF (4.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 20 min, the ice bath was removed and stirring was continued for 2 h. The reaction mixture was quenched with hydrochloric acid (2 N, 5 mL) and stirring was continued overnight. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using 10% EtOAc–hexanes, gave **18** (193 mg, 92%) as a white solid: mp 86–88 °C; FTIR ($CDCl_3$, cast) 3088, 2963, 1692 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3 H), 2.42 (dd, J = 15.5, 12.5 Hz, 1 H), 2.44–2.53 (m, 1 H), 2.57 (dd, J = 17.5, 9.5 Hz, 1 H), 2.77 (dd, J = 18.0, 2.5 Hz, 1 H), 2.84 (d, J = 14.5 Hz, 1 H), 7.79 (s, 2 H), 7.90 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 29.8 (d), 42.5 (t), 45.5 (t), 122.6 (d),123.0 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 124.3 (s),127.5 (d), 132.1 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 142.5 (s), 155.7 (s), 190.9 (s); exact mass (EI) m/z calcd for $C_{15}H_{11}{}^{81}BrF_6O$ $(M)^+$ 401.9877, found 401.9879.

3-[3,5-Bis(trifluoromethyl)phenyl]-5-methylphenol (18a). DBU (65 μL, 0.42 mmol) was added to a stirred solution of **18** (57 mg, 0.14 mmol) in THF (1.5 mL) and stirring was continued for 6 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid

(5%$^{w}/_{v}$, 3 mL). CH_2Cl_2 (3 mL) was added and stirring was continued for 10 min. More hydrochloric acid (5%$^{w}/_{v}$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% EtOAc–hexanes, gave **18a** (40.8 mg, 90%) as a white solid: mp 88–89 °C; FTIR ($CDCl_3$, cast) 3317, 2961, 1618 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 4.78 (s, 1 H), 6.74 (s, 1 H), 6.88 (s, 1 H), 6.99 (s, 1 H), 7.84 (s, 1 H), 7.98 (s, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4 (q), 111.4 (d), 116.5 (d), 120.7 (d), 121.0 (d), 123.4 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 127.2 (d), 132.0 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 139.7 (s), 140.9 (s), 143.0 (s), 156.1 (s); exact mass (EI) *m*/*z* calcd for $C_{15}H_{10}F_6O$ $(M)^+$ 320.0636, found 320.0634.

2-Bromo-3-(4-iodophenyl)-5-methylcyclohex-2-en-1-one (19). *i*-PrMgCl (2.0 M in Et_2O, 0.78 mL, 1.56 mmol) was added dropwise to a stirred and cooled (−30 °C) solution of *p*-diiodobenzene (513 mg, 1.56 mmol) in THF (6.0 mL) and stirring was continued for 6 h (Ar atmosphere). The resulting Grignard reagent[25] was taken up into a syringe and added dropwise to a stirred and cooled (0 °C) solution of **10** (56.8 mg, 0.26 mmol) in THF (2.5 mL) (Ar atmosphere). After 30 min, the ice bath was removed and stirring was continued for 16 h. Silica gel (ca 800 mg) and several drops of hydrochloric acid (2 N) were added to the reaction mixture and stirring was continued for 30 min. The mixture was diluted with water (40 mL) and filtered. The filtrate was extracted with EtOAc (2 × 40 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using a 5–10% acetone–hexanes gradient, gave **19** [71 mg, 70%, 82% corrected for recovered **10** (8.5 mg)] as a solid: mp 145–146 °C; FTIR ($CDCl_3$, cast) 2956, 1684 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.0 Hz, 3 H), 2.32–2.53 (m, 3 H), 2.69–2.84 (m, 2 H), 7.08 (d, *J* = 8.5 Hz,

2 H), 7.77 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 29.7(d), 42.5 (t), 45.7 (t), 94.8 (s), 122.7 (s), 128.7 (d), 137.6 (d), 140.2 (s), 158.4 (s), 191.5 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{12}{}^{81}BrIO$ $(M)^+$ 391.9096, found 391.9098.

3-(4-Iodophenyl)-5-methylphenol (19a). DBU (38 μL, 0.25 mmol) was added to a stirred solution of **19** (32.4 mg, 0.083 mmol) in THF (1.0 mL) and stirring was continued for 6 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 5 mL). CH_2Cl_2 (5 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^{w}/_{v}$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% acetone–hexanes, gave **19a** (24.7 mg, 96%) as a white solid: mp 142–143 °C; FTIR ($CDCl_3$, cast) 3338, 3053, 2923, 1616 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 4.69 (s, 1 H), 6.66 (s, 1 H), 6.82 (s, 1 H), 6.94 (s, 1 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.74 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (q), 93.1 (s), 111.0 (d), 115.4 (d), 120.4 (d), 129.0 (d), 137.8 (d), 140.35 (s), 140.40 (s), 141.6 (s), 155.9 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{11}OI$ $(M)^+$ 309.9855, found 309.9854.

2-Bromo-5-methyl-3-(naphthalen-2-yl)cyclohex-2-en-1-one (20). Preparation of the Grignard reagent: 2-Bromonaphthalene (3.11 g, 15.0 mmol) was added to a stirred solution of Mg (365 mg, 15.0 mmol) in THF (30 mL) (Ar atmosphere). After the addition, a condenser with a drying tube was connected to the round bottomed flask. The reaction mixture was stirred at room temperature for 30 min and refluxed at 70 °C for 2 h. The resulting Grignard reagent[26] was titrated according to the literature procedure[23] before use.

2-Naphthylmagnesium bromide (0.36 M in THF, 2.50 mL, 0.90 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **10** (131 mg, 0.60 mmol) in THF

(4.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 1 h. The ice bath was removed and more 2-naphthylmagnesium bromide (1.67 mL, 0.60 mmol) was added dropwise over five min to the reaction mixture. Stirring was continued for 1 h. The reaction mixture was quenched with hydrochloric acid (2 N, 6 mL). EtOAc (6 mL) was added and stirring was continued for 5 min. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using a 5–10% acetone–hexanes gradient, gave **20** (173.4 mg, 92%) as a solid: mp 114–116 °C; FTIR ($CDCl_3$, cast) 3348, 3056, 2956, 1684 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.2 Hz, 3 H), 2.38–2.55 (m, 2 H), 2.62 (dd, *J* = 18.0, 9.5 Hz, 1 H), 2.84 (d, *J* = 14.3 Hz, 1 H), 2.86–2.95 (m, 1 H), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.49–7.58 (m, 2 H), 7.81 (s, 1 H), 7.84–7.93 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.7 (q), 29.9 (d), 43.3 (t), 45.7 (t), 122.6 (s), 124.7 (d), 126.4 (d), 126.7 (d), 127.0 (d), 127.8 (d), 128.1 (d), 128.3 (d), 132.8 (s), 133.2 (s), 138.2 (s), 159.7 (s), 191.8 (s); exact mass (EI) *m*/*z* calcd for $C_{17}H_{15}{}^{81}BrO$ $(M)^+$ 316.0286, found 316.0287.

3-Methyl-5-(naphthalen-2-yl)phenol (20a). DBU (0.11 mL, 0.70 mmol) was added to a stirred solution of **20** (74 mg, 0.24 mmol) in THF (1.5 mL) and stirring was continued for 6 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 5 mL), and EtOAc (5 mL) was added. Stirring was continued for 30 min. More hydrochloric acid (5%$^w/_v$, 15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% acetone–hexanes, gave **20a** (56 mg, 84%) as an oil: FTIR ($CDCl_3$, cast) 3359, 3054, 2920, 1593 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 4.75 (s, 1 H), 6.69 (s, 1 H), 7.00 (s, 1 H), 7.13 (s, 1 H), 7.45–7.57 (m, 2 H), 7.71 (dd, *J* = 8.5, 1.9 Hz, 1

H), 7.80–7.93 (m, 3 H), 8.02 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (q), 111.5 (d), 115.0 (d), 121.0 (d), 125.5 (d), 125.8 (d), 125.9 (d), 126.3 (d), 127.6 (d), 128.2 (d), 128.3 (d), 132.7 (s), 133.6 (s), 138.2 (s), 140.2 (s), 142.7 (s), 155.9 (s); exact mass (EI) *m*/*z* calcd for $C_{17}H_{14}O$ $(M)^+$ 234.1045, found 234.1042.

2-Bromo-3-(furan-2-yl)-5-methylcyclohex-2-en-1-one (21). *n*-BuLi (2.46 M in hexanes, 0.73 mL, 1.79 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of furan (0.13 mL, 1.79 mmol) in THF (3.0 mL) (Ar atmosphere). The cold bath was left in place, but not recharged, and stirring was continued for 2 h during which the mixture reached 0 °C. This furan-2-yllithium solution was added dropwise to a stirred and cooled (0 °C) solution of $MgBr_2.OEt_2$ (461 mg, 1.79 mmol) in THF (1.8 mL) (Ar atmosphere).[27] The cold bath was removed and stirring was continued for 1 h.

The Grignard solution was taken up into a syringe and added dropwise to a stirred and cooled (0 °C) solution of **10** (260 mg, 1.19 mmol) in THF (6.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 20 min. The ice bath was removed and stirring was continued for 19 h. Without aqueous workup, silica gel (ca 2 g) and hydrochloric acid (2 N, several drops) were added to the reaction mixture, and stirring was continued until all the intermediate rearranged to the final product (monitored by TLC, silica, 30% EtOAc-hexane). The solvent was evaporated in vacuo at room temperature (rotary evaporator, water pump). The residue was added to the top a column of flash chromatography silica gel (1.8 × 15 cm) made up with hexanes. Flash chromatography, using a 10–30% EtOAc-hexanes gradient and later 30% acetone-hexanes, gave **21** [150 mg, 50%, 86% corrected for recovered **10** (110 mg)] as a solid: mp 65–66 °C; FTIR ($CDCl_3$, cast) 3115, 2956, 1675, 1267 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 5.9 Hz, 3 H), 2.24–2.41 (m, 2 H), 2.45–2.57 (m, 1 H), 2.71–2.85 (m, 1 H), 3.19–3.30 (m, 1 H), 6.61 (dd, *J*

= 3.7, 1.8 Hz, 1 H), 7.63 (d, *J* = 1.7 Hz, 1 H), 7.75 (d, *J* = 3.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 (q), 29.1 (d), 37.6 (t), 45.8 (t), 112.6 (d), 118.1 (d), 118.1 (s), 144.8 (d), 145.1 (s), 150.9 (s), 191.5 (s); exact mass (EI) *m*/*z* calcd for $C_{11}H_{11}{}^{81}BrO_2$ $(M)^+$ 255.9922, found 255.9919.

3-(Furan-2-yl)-5-methylphenol (21a).[6] DBU (0.10 mL, 0.66 mmol) was added to a stirred solution of **21** (56 mg, 0.22 mmol) in THF (1.5 mL) and stirring was continued for 17 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 5 mL), and EtOAc (5 mL) was added. Stirring was continued for 10 min. More hydrochloric acid (5%$^{w}/_{v}$, 10 mL) was added and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.3 × 8 cm), using 10% EtOAc–hexanes, gave **21a** (34 mg, 89%) as an oil: FTIR ($CDCl_3$, cast) 3372, 3115, 2952, 1604, 1154 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 4.66 (s, 1 H), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1 H), 6.57 (ddd, *J* = 2.3, 1.5, 0.7 Hz, 1 H), 6.61 (dd, *J* = 3.3, 0.8 Hz, 1 H), 6.96 (t, *J* = 1.9 Hz, 1 H), 7.09 (d, *J* = 1.5 Hz, 1 H), 7.45 (dd, *J* = 1.8, 0.8 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4 (q), 105.3 (d), 107.9 (d), 111.6 (d), 115.2 (d), 117.3 (d), 132.2 (s), 140.2 (s), 142.0 (d), 153.7 (s), 155.7 (s); exact mass (EI) *m*/*z* calcd for $C_{11}H_{10}O_2$ $(M)^+$ 174.0681, found 174.0680.

2-Bromo-5-methyl-3-(thiophen-2-yl)cyclohex-2-en-1-yl (22). Preparation of the aryl Grignard reagent: 2-Bromothiophene (1.48 mL, 15.0 mmol) in THF (4.0 mL) was added dropwise over 20 min to a stirred mixture of Mg (547 mg, 22.5 mmol) and THF (12 mL) and stirring was continued for 2 h (Ar atmosphere). The resulting Grignard reagent[28] was titrated according to the literature procedure[23] before use.

Thiophen-2-ylmagnesium bromide (0.82 M in THF, 0.81 mL, 0.66 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **10** (97 mg, 0.44 mmol) in THF

(3.0 mL) (Ar atmosphere). The cold bath was left in place, but not recharged, and stirring was continued for 3 h during which the mixture reached room temperature. More Grignard reagent (0.82 M in THF, 0.81 mL, 0.66 mmol) was added to the reaction mixture and after 5 h, another aliquot of the Grignard reagent (0.82 M in THF, 1.62 mL, 1.33 mmol) was added and stirring was continued for 12 h. The reaction mixture was quenched with hydrochloric acid (2 N, 5 mL) and stirring was continued for 2.5 h. More hydrochloric acid (2 N, 30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using a 5–10% EtOAc–hexanes gradient, gave **22** (99 mg, 83%) as a solid: mp 106–107 °C; FTIR ($CDCl_3$, cast) 3325, 3092, 2953, 1674 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3 H), 2.30–2.44 (m, 2 H), 2.62–2.70 (m, 1 H), 2.76–2.85 (m, 1 H), 3.07–3.16 (m, 1 H), 7.17 (dd, J = 5.0, 4.0 Hz, 1 H), 7.61 (dd, J = 5.0, 1.0 Hz, 1 H), 7.78 (dd, J = 4.0, 1.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 (q), 29.3 (d), 42.0 (t), 45.5 (t), 120.5 (s), 127.1 (d), 130.6 (d), 131.5 (d), 141.1 (s), 148.9 (s), 191.5 (s); exact mass (EI) m/z calcd for $C_{11}H_{11}{}^{81}BrOS$ $(M)^+$ 271.9694, found 271.9696.

3-Methyl-5-(thiophen-2-yl)phenol (22a).[6] DBU (64 μL, 0.42 mmol) was added to a stirred solution of **22** (37.5 mg, 0.14 mmol) in THF (1.5 mL) and stirring was continued for 8 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 5 mL). CH_2Cl_2 (5 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^w/_v$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 8 cm), using 5% acetone–hexanes, gave **22a** (25.8 mg, 98%) as an oil: FTIR ($CDCl_3$, cast) 3353, 3105, 2920, 1593 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.34 (s, 3

H), 4.66 (s, 1 H), 6.59 (s, 1 H), 6.90 (s, 1 H), 7.02 (s, 1 H), 7.06 (dd, *J* = 5.0, 3.5 Hz, 1 H), 7.25–7.32 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4 (q), 110.0 (d), 115.2 (d), 119.6 (d), 123.2 (d), 124.8 (d), 127.9 (d), 135.7 (s), 140.3 (s), 144.1 (s), 155.8 (s); exact mass (EI) *m*/*z* calcd for $C_{11}H_{10}OS$ $(M)^+$ 190.0452, found 190.0453.

2-Bromo-3,5-diphenylcyclohex-2-en-1-one (23). PhMgBr (1.7 M in THF, 0. 23 mL, 0. 38 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **28** (72 mg, 0.26 mmol) in THF (3.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 45 min. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirred for 2 h. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5% EtOAc–hexanes, gave **23** (76.8 mg, 92%) as an oil: FTIR ($CDCl_3$, cast) 3087, 2952, 1684 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 2.92 (dd, *J* = 16.5, 13.5 Hz, 1 H), 2.99–3.09 (m, 3 H), 3.52–3.62 (m, 1 H), 7.24–7.31 (m, 3 H), 7.33–7.46 (m, 7 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.3 (d), 42.7 (t), 44.3 (t), 122.5 (s), 126.6 (d), 127.0 (d), 127.4 (d), 128.4 (d), 129.0 (d), 140.5 (s), 141.9 (s), 159.4 (s), 191.1 (s); exact mass (EI) *m*/*z* calcd for $C_{18}H_{15}{}^{79}BrO$ $(M)^+$ 328.0286, found 328.0285.

3,5-Diphenylphenol (23a).[29] DBU (0.10 mL, 0.66 mmol) was added to a stirred solution of **23** (72.3 mg, 0.22 mmol) in THF (2.0 mL) and stirring was continued for 17 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 5 mL). CH_2Cl_2 (5 mL) was added and stirring was continued for 30 min. More hydrochloric acid (5%$^{w}/_{v}$, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 5% EtOAc–hexanes, gave **23a** (50.6 mg, 93%) as a solid: mp 92–93 °C

(lit.[29] 92–93 °C); FTIR ($CDCl_3$, cast) 3374, 3059, 1594 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 4.86 (s, 1 H), 7.05 (d, *J* = 1.5 Hz, 2 H), 7.34–7.42 (m, 3 H), 7.42–7.49 (m, 4 H), 7.60–7.66 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.1 (d), 119.0 (d), 127.2 (d), 127.6 (d), 128.8 (d), 140.8 (s), 143.5 (s), 156.1 (s); exact mass (EI) *m*/*z* calcd for $C_{18}H_{14}O$ $(M)^+$ 246.1045, found 246.1047.

2-Bromo-3-(1-methyl-1*H*-indol-5-yl)-5-(thiophen-3-yl)cyclohex-2-en-1-one (24). Preparation of the aryl Grignard reagent: 5-Bromo-1-methylindole (1.33 g, 6.33 mmol) was added over 30 min to a stirred suspension of Mg (185 mg, 7.59 mmol) in THF (4 mL) (Ar atmosphere).[29] After the addition, a condenser with a drying tube was connected to the round bottomed flask. The reaction mixture was stirred overnight, and the resulting Grignard reagent was titrated according to the literature procedure[23] before use.

(1-Methyl-indol-5-yl)magnesium bromide (0.73 M in THF, 0.77 mL, 0.56 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **33** (54 mg, 0.19 mmol) in THF (1.8 mL) (Ar atmosphere). Stirring was continued for 1 h. The cold bath was removed and stirring was continued for 5 days. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL). THF (3 mL) was added and stirring was continued for 20 min. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% EtOAc–hexane, gave **24** (51.5 mg, 71%) as a thick oil: FTIR ($CDCl_3$, cast) 3419, 3101, 2921, 1676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.88 (dd, *J* = 16.0, 12.5 Hz, 1 H), 3.05 (dd, *J* = 18.0, 10.5 Hz, 1 H), 3.09–3.16 (m, 1 H), 3.19–3.27 (m, 1 H), 3.63–3.72 (m, 1 H), 3.82 (s, 3 H), 6.54 (d, *J* = 3.0 Hz, 1 H), 7.05 (d, *J* = 5.0 Hz, 1 H), 7.08 (s, 1 H), 7.11 (d, *J* = 3.0 Hz, 1 H), 7.28 (d, *J* = 1.5 Hz, 1 H), 7.33 (dd, *J* = 4.5, 3.0 Hz, 1 H), 7.37 (d, *J* = 8.5 Hz, 1 H), 7.68 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.0 (q), 35.6 (d), 42.8 (t), 44.4 (t),

101.8 (d), 109.1 (d), 120.19 (d), 120.23 (d), 121.1 (d), 122.0 (s), 126.2 (d), 126.5 (d), 128.0 (s), 130.0 (d), 131.6 (s), 136.8 (s), 143.3 (s), 160.8 (s), 191.2 (s); exact mass (EI) *m*/*z* calcd for $C_{19}H_{16}{}^{79}BrNOS$ $(M)^+$ 385.0136, found 385.0138.

3-(1-Methyl-1*H*-indol-5-yl)-5-(thiophen-3-yl)phenol (24a). DBU (53 μL, 0.35 mmol) was added to a stirred solution of **24** (45 mg, 0.12 mmol) in THF (1.0 mL) and stirring was continued for 5 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 3 mL). CH_2Cl_2 (3 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^{w}/_{v}$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% EtOAc-hexanes, gave **24a** (32.8 mg, 92%) as an yellow oil: FTIR ($CDCl_3$, cast) 3380, 3101, 2937, 1609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3 H), 4.82 (s, 1 H), 6.55 (d, *J* = 3.0 Hz, 1 H), 7.02 (d, *J* = 1.5 Hz, 1 H), 7.05 (d, *J* = 1.5 Hz, 1 H), 7.10 (d, *J* = 3.0 Hz, 1 H), 7.36–7.41 (m, 2 H), 7.43 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.45–7.54 (m, 3 H), 7.87 (d, *J* = 1.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.0 (q), 101.4 (d), 109.5 (d), 111.4 (d), 113.2 (d), 118.6 (d), 119.5 (d), 120.7 (d), 121.3 (d), 126.1 (d), 126.5 (d), 128.9 (s), 129.6 (d), 132.3 (s), 136.5 (s), 137.7 (s), 142.2 (s), 144.9 (s), 156.1 (s); exact mass (EI) *m*/*z* calcd for $C_{19}H_{15}ONS$ $(M)^+$ 305.0874, found 305.0876.

3-(2*H*-1,3-Benzodioxol-5-yl)-2-bromo-5-(thiophen-3-yl)cyclohex-2-en-1-one (25). The Grignard reagent was prepared as described before. [(3,4-Methylenedioxy)-phenyl]magnesium bromide (0.66 M in THF, 0.36 mL, 0.24 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **33** (45 mg, 0.16 mmol) in THF (1.5 mL) (Ar atmosphere). After 2.5 h more Grignard reagent (0.66 M in THF, 0.24 mL, 0.16 mmol) was added. The cold bath was left in place, but not recharged, and stirring was continued for 3 h

during which the mixture reached room temperature. The reaction mixture was quenched with hydrochloric acid (2 N, 1.5 mL) and stirring was continued for 30 min. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5% EtOAc–hexane, gave **25** (48.4 mg, 82%) as a beige sold: mp 139–140 °C; FTIR ($CDCl_3$, cast) 3104, 2955, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.85 (dd, *J* = 16.5, 12.5 Hz, 1 H), 2.94 (dd, *J* = 18.0, 10.0 Hz, 1 H), 3.01–3.14 (m, 2 H), 3.57–3.68 (m, 1 H), 6.02 (s, 2 H), 6.83–6.91 (m, 3 H), 7.02 (d, *J* = 4.5 Hz, 1 H), 7.06 (s, 1 H), 7.34 (dd, *J* = 5.0, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.5 (d), 42.3 (t), 44.2 (t), 101.5 (t), 108.0 (d), 108.3 (d), 120.3 (d), 121.4 (d), 122.5 (s), 126.1 (d), 126.6 (d), 134.0 (s), 143.0 (s), 147.6 (s), 148.2 (s), 158.6 (s), 190.9 (s); exact mass (EI) *m*/*z* calcd for $C_{17}H_{13}{}^{81}BrO_3S$ $(M)^+$ 377.9748, found 377.9749.

3-(2*H*-1,3-Benzodioxol-5-yl)-4-(prop-2-en-1-yl)-5-(thiophen-3-yl)phenol (25a).[30] DBU (48 μL, 0.32 mmol) was added to a stirred solution of **25** (40 mg, 0.11 mmol) in THF (1.0 mL) and stirring was continued for 15 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 3 mL). CH_2Cl_2 (3 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^{w}/_{v}$, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using a 5–10% EtOAc–hexanes gradient, gave **25a** (30.7 mg, 98%) as an oil: FTIR ($CDCl_3$, cast) 3407, 3105, 2952, 1595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 1 H), 6.01 (s, 2 H), 6.89–6.93 (m, 2 H), 7.02 (s, 1 H), 7.05–7.11 (m, 2 H), 7.32 (s, 1 H), 7.39 (s, 1 H), 7.40 (s, 1 H), 7.48 (t, *J* = 2.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.2 (t), 107.7 (d), 108.6 (d), 112.0 (d), 112.7 (d), 118.1 (d), 120.7 (d),

120.8 (d), 126.3 (d), 126.4 (d), 135.1 (s), 137.8 (s), 141.9 (s), 143.2 (s), 147.4 (s), 148.1 (s), 156.1 (s); exact mass (EI) *m*/*z* calcd for $C_{17}H_{12}O_3S$ $(M)^+$ 296.0507, found 296.0507.

2-Bromo-3-methoxy-5-phenylcyclohex-2-en-1-one (28).[31] TsOH.H_2O (86 mg, 0.50 mmol) and $CH(OMe)_3$ (2.21 mL, 20.0 mmol) were added sequentially to a solution of **26** (1.96 g, 10.4 mmol) in MeOH (20 mL) (Ar atmosphere). Stirring was continued for 6 h and the solvent was then evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude residue (**27**) (2.00 g, 9.9 mmol) was dissolved in CH_2Cl_2 (80 mL) and K_2CO_3 (9.17 g, 66.3 mmol) was added. The mixture was stirred and cooled (0 °C), and Br_2 (0.51 mL, 9.9 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 1.5 h (Ar atmosphere). After the addition, the reaction mixture was quenched with water (80 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using a 0.5–1% acetone-CH_2Cl_2 gradient, gave **28** (2.39 g, 82% over two steps) as a beige solid: mp 162–163 °C (lit.[31] 163–164 °C); FTIR ($CDCl_3$, cast) 3032, 2949, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.72–2.83 (m, 2 H), 2.88 (dd, *J* = 16.5, 3.5 Hz, 1 H), 3.04 (dd, *J* = 17.0, 3.5 Hz, 1 H), 3.37–3.48 (m, 1 H), 3.97 (s, 3 H), 7.24–7.36 (m, 3 H), 7.36–7.44 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.7 (t), 38.9 (q), 43.4 (t), 56.6 (d), 102.8 (s), 126.7 (d), 127.6 (d), 129.1 (d), 141.6 (s), 171.9 (s), 190.1 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{13}{}^{81}BrO_2$ $(M)^+$ 282.0078, found 282.0078.

3-Hydroxy-5-(thiophen-3-yl)cyclohex-2-en-1-one (31).[32] Na (389 mg, 16.9 mmol) was dissolved in stirred absolute MeOH (6.0 mL) with occasional ice bath cooling (Ar atmosphere). The solution was cooled to 0 °C and $CH_2(CO_2Et)_2$ (2.67 mL, 17.4 mmol) was added slowly. (*E*)-

4-(Thiophen-3-yl)but-3-en-2-one (**30**)[33] (2.55 g, 16.7 mmol) was added in four equal portions over 10 min and stirring was continued for 15 min after the last addition. The ice bath was removed and stirring was continued for 1 h. More MeOH (6.0 mL) was added, the mixture was heated to reflux (oil bath at 90 °C) for 2.5 h and then cooled to room temperature. NaOH (2.0 M, 9.2 mL) was added slowly and the reaction mixture was refluxed (oil bath at 110 °C) for 2 h. The mixture was cooled to 0 °C and H_2SO_4 (2.5 M, 14.7 mL) was added slowly with stirring. The mixture was refluxed (oil bath at 110 °C) for 3 h and then cooled in ice. The precipitated crystals were filtered off, washed with EtOAc–Et_2O (1:4) and dried under oil pump vacuum to give **31** (1.69 g, 52%) as a pale yellow solid: mp 176–178 °C, FTIR (solid) 3101, 2948, 1594 cm^{-1}; ^1H NMR (498 MHz, DMSO-d_6) δ 2.28–2.72 (m, 4 H), 3.31–3.44 (m, 1 H), 5.23 (s, 1 H), 7.14 (d, *J* = 4.0 Hz, 1 H), 7.27 (d, *J* = 2.5 Hz, 1 H), 7.48 (dd, *J* = 5.0, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.2 (d), 103.6 (d), 120.2 (d), 126.2 (d), 127.1 (d), 144.7 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{10}O_2S$ $(M)^+$ 194.0402, found 194.0399.

3-Methoxy-5-(thiophen-3-yl)cyclohex-2-en-1-one (32). TsOH.H_2O (39 mg, 0.22 mmol) and $CH(OMe)_3$ (0.99 mL, 8.96 mmol) were added sequentially to a stirred solution of **31** (871 mg, 4.48 mmol) in MeOH (9.0 mL) and stirring was continued for 8.5 h (Ar atmosphere). The solvent was evaporated. and the residue was dissolved in CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using a 5–10% acetone–hexane gradient, gave **32** (756 mg, 81%) as an oil: FTIR ($CDCl_3$, cast) 3097, 2941, 1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.52 (dd, *J* = 16.5, 12.0 Hz, 1 H), 2.63 (dd, *J* = 17.0, 10.5 Hz, 1 H), 2.68–2.78 (m, 2 H), 3.40–3.51 (m, 1 H), 3.72 (s, 3 H), 5.44 (s, 1 H), 7.00 (d, *J* = 5.0 Hz, 1 H), 7.03 (s,

1 H), 7.31 (dd, J = 5.0, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.7 (q), 36.1 (t), 43.8 (t), 55.9 (d), 102.3 (d), 112.0 (d), 126.26 (d), 126.33 (d), 143.8 (s), 177.4 (s), 198.4 (s); exact mass (EI) m/z calcd for $C_{11}H_{12}O_2S$ $(M)^+$ 208.0558, found 208.0553.

2-Bromo-3-methoxy-5-(thiophen-3-yl)cyclohex-2-en-1-one (33). K_2CO_3 (1.72 g, 6.7 mmol) was added to a stirred and cooled (0 °C) solution of **32** (388 mg, 1.86 mmol) in CH_2Cl_2 (12 mL) and Br_2 (96 μL, 1.86 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 110 min (Ar atmosphere). After the addition, the reaction mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.1 × 18 cm), using 1% acetone–CH_2Cl_2, gave **33** (472 mg, 89%) as a solid: mp 148–150 °C; FTIR ($CDCl_3$, cast) 3098, 2951, 1658 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65–2.80 (m, 2 H), 2.94 (dd, J = 16.0, 3.0 Hz, 1 H), 3.08 (dd, J = 17.0, 4.0 Hz, 1 H), 3.47–3.58 (m, 1 H), 3.97 (s, 3 H), 7.02 (d, J = 5.0 Hz, 1 H), 7.08 (s, 1 H), 7.35 (dd, J = 5.0, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.17 (q), 34.21 (t), 43.4 (t), 56.6 (d), 103.0 (s), 120.6 (d), 126.0 (d), 126.8 (d), 142.6 (s), 171.6 (s), 189.9 (s); exact mass (EI) m/z calcd for $C_{11}H_{11}{}^{81}BrO_2S$ $(M)^+$ 287.9643, found 287.9636.

2-Bromo-4-fluoro-3,5-dimethylcyclohex-2-en-1-one (34a). MeMgBr (3.0 M in Et_2O, 91 μL, 0.27 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **34**[2] (43.1 mg, 0.18 mmol, a 6:4 mixture of isomers) in THF (2.0 mL) (Ar atmosphere). Stirring was continued for 45 min. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirred for 20 min. More hydrochloric acid (2 N, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 5% EtOAc–hexanes, gave **34a** (33.3 mg, 83%) as an oil which was a 7:3 mixture of isomers: FTIR ($CDCl_3$, cast) 2966, 1964

cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.16 (d, J = 7.5 Hz, 0.9 H), 1.20 (d, J = 6.5 Hz, 2.1 H), 2.14–2.32 (m, 3.7 H), 2.32–2.50 (m, 1 H), 2.54–2.70 (m, 0.6 H), 2.81 (dt, J = 16.5, 4.5 Hz, 0.7 H), 4.82 (dd, $^2J_{H\text{-}F}$ = 48.0, J = 9.0 Hz, 0.7 H), 4.96 (dd, $^2J_{H\text{-}F}$ = 48.0, J = 3.5 Hz, 0.3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.3 (q), 20.5 (q), 20.6 (q), 35.5 (d), 35.7 (d), 42.1 (t), 42.2 (t), 94.7 (d, $^1J_{C\text{-}F}$ = 178.9 Hz), 125.4 (s), 125.5 (s), 156.7 (s), 156.8 (s), 189.0 (s); exact mass (EI) *m*/*z* calcd for $C_8H_{10}{}^{81}BrFO$ $(M)^+$ 221.9879, found 221.9881.

4-Fluoro-3,5-dimethylphenol (34b).[34] DBU (46 μL, 0.30 mmol) was added to a stirred solution of **34a** (22.3 mg, 0.10 mmol, a 7:3 mixture of two isomers) in THF (1.0 mL) and stirring was continued for 25 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 3 mL). CH_2Cl_2 (5 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^w/_v$, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 8 cm), using 5% acetone–hexanes, gave **34b** (12.3 mg, 87%) as a white solid: mp 85–87 °C; FTIR ($CDCl_3$, cast) 3256, 2960, 1601, 1481 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.20 (d, J = 2.0 Hz, 6 H), 4.34 (s, 1 H), 6.46 (d, J = 5.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.7 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 114.9 (d, $^3J_{C\text{-}F}$ = 4.6 Hz), 125.3 (d, $^2J_{C\text{-}F}$ = 19.8 Hz), 150.5 (d, $^4J_{C\text{-}F}$ = 2.6 Hz), 154.5 (d, $^1J_{C\text{-}F}$ = 234.4 Hz); exact mass (EI) *m*/*z* calcd for C_8H_9FO $(M)^+$ 140.0637, found 140.0636.

1-[3,5-Bis(trifluoromethyl)phenyl]-2-bromo-4,6-difluoro-3-methoxy-5-methylcyclo-hex-2-en-1-one (precursor to 35a). The aryl Grignard reagent was prepared according to the procedure described before. [3,5-Bis(trifluoromethyl)phenyl]magnesium bromide (0.58 M in THF, 0.84 mL, 0.49 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **35** (41.3 mg, 0.16 mmol, a 1:1 mixture of two isomers) in THF (1.5 mL) (Ar

atmosphere). Stirring at 0 °C was continued for 4 h. The reaction mixture was quenched with hydrochloric acid (2 N, 20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 5% EtOAc–hexanes, gave 1-[3,5-bis(trifluoromethyl)phenyl]-2-bromo-4,6-difluoro-3-methoxy-5-methylcyclohex-2-en-1-ol, the precursor to **35a**, (75 mg, 93%) as an oil which was a 6:4 mixture of isomers. The major isomer (lower polarity) had: FTIR ($CDCl_3$, cast) 3570, 3095, 2948, 1647 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.29 (d, J = 6.5 Hz, 3 H), 2.03–2.25 (m, 1 H), 3.23 (d, J = 5.0 Hz, 1 H), 3.96 (d, J = 0.5 Hz, 3 H), 4.57 (dd, $^2J_{H\text{-}F}$ = 49.0, J = 6.5 Hz, 1 H), 5.11 (dd, $^2J_{H\text{-}F}$ = 50.0, J = 8.0 Hz, 1 H), 7.90 (s, 1 H), 7.98 (s, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0 (q), 35.5 (q), 35.6 (q), 35.8 (q), 57.91 (d), 57.94 (d), 87.8 (d), 89.2 (d), 96.2 (d), 96.3 (d), 97.67 (d), 97.74 (d), 108.4 (s), 108.5 (s), 123.0 (d), 123.1 (q, $^1J_{C\text{-}F}$ = 271.4 Hz), 127.7 (d), 132.3 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 142.3 (s), 151.7 (s), 151.9 (s); exact mass (EI) *m*/*z* calcd for $C_{16}H_{13}{}^{81}BrF_8O_2$ $(M)^+$ 469.9951, found 469.9959.

3-[3,5-Bis(trifluoromethyl)phenyl]-2-bromo-4,6-difluoro-5-methylcyclohex-2-en-1-one (35a). 1-[3,5-Bis(trifluoromethyl)phenyl]-2-bromo-4,6-difluoro-3-methoxy-5-methylcyclohex-2-en-1-ol, the precursor to **35a**, (69 mg, 0.15 mmol, a 6:4 mixture of two isomers) was dissolved in a mixture of CH_2Cl_2 (1.0 mL) and CF_3CO_2H (1.0 mL) (Ar atmosphere). Stirring was continued for 45 h and the mixture was diluted with hydrochloric acid (2 N, 15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5% EtOAc–hexanes, gave **35a** (56 mg, 87%) as an oil which was a 1:1 mixture of isomers. The material had: FTIR ($CDCl_3$, cast) 3092, 2917, 1724 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.29 (d, J = 8.5 Hz, 1.5 H), 1.45 (d, J = 8.5 Hz, 1.5 H), 2.63–2.85 (m, 0.5 H), 2.96–3.14 (m, 0.5 H), 5.17–

5.24 (m, 0.5 H), 5.21 (dd, $^{2}J_{H\text{-}F}$ = 59.5, J = 15.0 Hz, 0.5 H), 5.29–5.36 (m, 0.5 H), 5.44 (dd, $^{2}J_{H\text{-}F}$ = 59.5, J = 5.0 Hz, 0.5 H), 7.84 (s, 1 H), 7.89 (s, 1 H), 7.98 (s, 1 H); the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum was too complicated to be informative; exact mass (EI) *m*/*z* calcd for $C_{15}H_9{}^{81}BrF_8O$ $(M)^+$ 437.9688, found 437.9685.

5-[3,5-Bis(trifluoromethyl)phenyl]-2,4-difluoro-3-methylphenol (35b). DBU (46 μL, 0.30 mmol) was added to a stirred solution of **35a** (44 mg, 0.10 mmol, a 1:1 mixture of two isomers) in THF (1.0 mL) and stirring was continued for 23 h (Ar atmosphere). The mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 3 mL). CH_2Cl_2 (3 mL) was added and stirring was continued for 20 min. More hydrochloric acid (5%$^{w}/_{v}$, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 12 cm), using 5% EtOAc–hexanes, gave **35b** (28.8 mg, 81%) as a solid: mp 68–70 °C; FTIR ($CDCl_3$, cast) 3597, 3432, 3088, 2926, 1626, 1280 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 2.28–2.31 (m, 3 H), 4.98 (s, 1 H), 6.93 (dd, J = 9.0, 7.5 Hz, 1 H), 7.87 (s, 1 H), 7.94 (s, 2 H); the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum was too complicated to be informative; exact mass (EI) *m*/*z* calcd for $C_{15}H_8F_8O$ $(M)^+$ 356.0447, found 356.0444.

2-Bromo-4,6-difluoro-3-(2-methoxyphenyl)-5-methylcyclohex-2-en-1-one (35a'). The aryl Grignard reagent was prepared according to the procedure described before. (2-Methoxyphenyl)magnesium bromide (0.30 M in THF, 1.78 mL, 0.53 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **35**[2] (54.3 mg, 0.21 mmol, a 1:1 mixture of two isomers) in THF (3.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 2.5 h. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirring was continued for 2 h. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with

CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude material was dissolved in a mixture of CH_2Cl_2 (1.0 mL) and CF_3CO_2H (1.0 mL) and stirring was continued for 1 h (Ar atmosphere). The mixture was diluted with hydrochloric acid (2 N, 20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 12 cm), using 5% EtOAc–hexanes, gave **35a'** (58.2 mg, 83%) as a solid which was a 10:3 mixture of isomers. The major isomer had: mp 148–150 °C; FTIR ($CDCl_3$, cast) 3074, 2942, 1717 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.41 (d, J = 8.0 Hz, 3 H), 2.60–2.81 (m, 1 H), 3.84 (s, 3 H), 5.06–5.88 (m, 2 H), 6.98 (d, J = 10.5 Hz, 1 H), 7.02–7.10 (m, 1 H), 7.20 (d, J = 8.5 Hz, 1 H), 7.38–7.48 (m, 1 H); the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum was too complicated to be informative; exact mass (EI) m/z calcd for $C_{14}H_{13}{}^{81}BrF_2O_2$ $(M)^+$ 332.0046, found 332.0038.

2,4-Difluoro-5-(2-methoxyphenyl)-3-methylphenol (35b'). DBU (67 μL, 0.44 mmol) was added to a stirred solution of **35a'** (48.2 mg, 0.15 mmol, a 10:3 mixture of two isomers) in THF (1.5 mL) and stirring was continued for 17 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 5 mL). CH_2Cl_2 (5 mL) was added and stirring was continued for 30 min. More hydrochloric acid (5%$^w/_v$, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5% EtOAc–hexanes, gave **35b'** (30.9 mg, 85%) as a solid: mp 99–100 °C; FTIR ($CDCl_3$, cast) 3413, 3064, 2935, 1484 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 3.81 (s, 3 H), 4.84 (s, 1 H), 6.83 (dd, J = 9.5, 7.0 Hz, 1 H), 6.95–7.05 (m, 2 H), 7.22 (d, J = 7.0 Hz, 1 H), 7.32–7.40 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 7.7 (q), 55.7 (q), 111.1 (d), 113.2 (s), 113.3 (s), 113.5 (s), 115.7 (d), 120.5 (d), 121.4 (s), 121.6 (s), 124.5 (s), 129.4 (d), 131.3 (d), 138.9 (s), 139.0 (s), 148.7 (dd,

$^{1}J_{C\text{-}F}$ = 235.6, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 151.8 (dd, $^{1}J_{C\text{-}F}$ = 239.5, $^{3}J_{C\text{-}F}$ = 7.0 Hz) 156.9 (s); exact mass (EI) *m*/*z* calcd for $C_{14}H_{12}F_2O_2$ $(M)^+$ 250.0805, found 250.0813.

2-Bromo-5-methyl-3-(naphthalen-2-yl)-4-(prop-2-en-1-yl)cyclohex-2-en-1-one (36a). The aryl Grignard reagent was prepared according to the procedure described before. 2-Naphthylmagnesium bromide solution (0.64 M in THF, 0.80 mL, 0.51 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **36**[1] (43.3 mg, 0.17 mmol, a 6:1 mixture of two isomers) in THF (2.0 mL) (Ar atmosphere). The cold bath was left in place, but not recharged, and stirring was continued for 2.5 h during which the mixture reached room temperature. Stirring was continued for 16 h. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirred for 1.5 h. More hydrochloric acid (2 N, 20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 5% EtOAc–hexanes, gave **36a** (48.7 mg, 82%) as an oil which was a 11:1 mixture of two isomers. The major isomer had: FTIR ($CDCl_3$, cast) 3056, 2956, 1686 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 1.29 (d, *J* = 7.0 Hz, 3 H), 2.22–2.33 (m, 1 H), 2.34–2.42 (m, 1 H), 2.42–2.50 (m, 1 H), 2.55 (dd, *J* = 17.0, 3.5 Hz, 1 H), 2.71–2.80 (m, 1 H), 2.96 (dd, *J* = 17.0, 5.0 Hz, 1 H), 4.97–5.08 (m, 2 H), 5.57–5.69 (m, 1 H), 7.38 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.51–7.58 (m, 2 H), 7.73 (s, 1 H), 7.84–7.94 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.9 (q), 29.8 (d), 36.0 (t), 40.5 (t), 50.9 (d), 117.8 (s), 122.6 (s), 125.2 (d), 126.6 (d), 126.7 (d), 126.9 (d), 127.9 (d), 128.1 (d), 128.3 (d), 132.8 (s), 133.1 (s), 135.2. (d), 137.8 (s), 161.5 (s), 190.8(s); exact mass (EI) *m*/*z* calcd for $C_{20}H_{19}{}^{81}BrO$ $(M)^+$ 356.0599, found 356.0604.

3-Methyl-5-(naphthalen-2-yl)-4-(prop-2-en-1-yl)phenol (36b). DBU (53 μL, 0.35 mmol) was added to a stirred solution of **36a** (41.2 mg, 0.12 mmol, a 11:1 mixture of two

isomers) in THF (1.0 mL) and stirring was continued for 24 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 4 mL). CH_2Cl_2 (4 mL) was added and stirring was continued for 10 min. More hydrochloric acid (5%$^{w}/_{v}$, 20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5% EtOAc–hexanes, gave **36b** (26.6 mg, 84%) as an oil: FTIR ($CDCl_3$, cast) 3351, 3075, 2974, 1592 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.25 (d, *J* = 5.5 Hz, 2 H), 4.58 (s, 1 H), 4.80 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.01 (dd, *J* = 10.0, 1.5 Hz, 1 H), 5.80–5.93 (m, 1 H), 6.67 (d, *J* = 2.5 Hz, 1 H), 6.73 (d, *J* = 2.5 Hz, 1 H), 7.44 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.47–7.54 (m, 2 H), 7.76 (s, 1 H), 7.80–7.92 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.0 (q), 33.8 (t), 114.8 (d), 115.0 (s), 116.5 (d), 125.8 (d), 126.1 (d), 127.3 (d), 127.5 (d), 127.6 (d), 127.7 (d), 127.8 (s), 128.0 (d), 132.4 (s), 133.1 (s), 137.2 (d), 139.3 (s), 139.6 (s), 144.0 (s), 153.1 (s); exact mass (EI) *m*/*z* calcd for $C_{20}H_{18}O$ $(M)^+$ 274.1358, found 274.1365.

2-Bromo-4-[(3-bromophenyl)methyl]-5-methyl-3-phenylcyclohex-2-en-1-one (37a). PhMgBr (1.7 M in THF, 0.37 mL, 0.63 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **37**[1] (81.5 mg, 0.21 mmol, a 5:1 mixture of two isomers) in THF (3.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 3 h. The ice bath was removed and, after 2 h, more Grignard reagent (1.7 M in THF, 0.19 mL, 0.32 mmol) was added and stirring was continued for 1 h. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirring was continued for 30 min. More hydrochloric acid (2 N, 20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using a 5–10% EtOAc–hexanes gradient, gave **37** (13.7 mg) and a mixture of the

intermediates as well as **37a**. The intermediates and **37a** were dissolved in a mixture of CH_2Cl_2 (1.5 mL) and CF_3CO_2H (1.0 mL) and stirring was continued for 28 h (Ar atmosphere). The reaction mixture was diluted with hydrochloric acid (2 N, 20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 18 cm), using 20% acetone–hexanes, gave **37a** [66.8 mg, 73%, 89% corrected for recovered **37** (13.7 mg)] as an oil which was a 4:1 mixture of isomers. The major isomer had: mp 106–107 °C; FTIR ($CDCl_3$, cast) 3057, 2958, 1685 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.17 (d, *J* = 7.0 Hz, 3 H), 2.15–2.26 (m, 1 H), 2.54 (dd, *J* = 17.0, 1.5 Hz, 1 H), 2.68 (dd, *J* = 14.0, 11.0 Hz, 1 H), 2.79–2.86 (m, 1 H), 2.90 (dd, *J* = 14.0, 3.5 Hz, 1 H), 2.98 (dd, *J* = 17.0, 5.0 Hz, 1 H), 6.94 (d, *J* = 7.5 Hz, 1 H), 7.08–7.17 (m, 2 H), 7.28–7.36 (m, 3 H), 7.39–7.51 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.8 (q), 29.0 (d), 37.2 (t), 39.7 (t), 53.0 (d), 122.4 (s), 122.8 (s), 127.3 (d), 127.4 (d), 128.5 (d), 129.0 (d), 129.9 (d), 130.2 (d), 131.5 (d), 140.2 (s), 141.2 (s), 160.8 (s), 190.4(s); exact mass (EI) *m*/*z* calcd for $C_{20}H_{18}{}^{79}Br_2O$ $(M)^+$ 431.9724, found 431.9726.

4-[(3-Bromophenyl)methyl]-3-methyl-5-phenylphenol (37b). DBU (55 μL, 0.36 mmol) was added to a stirred solution of **37a** (52 mg, 0.12 mmol, a 4:1 mixture of two isomers) in THF (1.0 mL) and stirring was continued for 25 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 5 mL) and CH_2Cl_2 (5 mL), and stirring was continued for 10 min. More hydrochloric acid (5%$^w/_v$, 15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 5% EtOAc–hexanes, gave **37b** (35.6 mg, 84%) as an oil: FTIR ($CDCl_3$, cast) 3359, 3058, 2925, 1592 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.16 (s, 3 H), 3.87 (s, 2 H), 4.62 (s, 1 H), 6.64 (d, *J* =

2.5 Hz, 1 H), 6.73 (d, *J* = 2.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 7.02–7.10 (m, 2 H), 7.13–7.20 (m, 2 H), 7.23–7.34 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5 (q), 34.9 (t), 114.8 (d), 116.7 (d), 122.5 (s), 126.5 (d), 127.0 (d), 127.3 (s), 128.0 (d), 128.7 (d), 128.8 (d), 129.8 (d), 130.9 (d), 139.5 (s), 141.7 (s), 143.9 (s), 144.7 (s), 153.5 (s); exact mass (EI) *m*/*z* calcd for $C_{20}H_{17}{}^{81}BrO$ $(M)^+$ 352.0463, found 352.0469.

2-Bromo-3-methoxy-5-phenyl-6-(prop-2-en-1-yl)cyclohex-2-en-1-one (38). *n*-BuLi (2.5 M in hexanes, 0.38 mL, 0.93 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.14 mL, 1.01 mmol) in THF (3.0 mL) (Ar atmosphere). Stirring at –78 °C was continued for 1 h and a solution of **28** (237 mg, 0.84 mmol) in THF (3.0 mL) was added dropwise over <1 min. A rinse of THF (1.0 mL) was used to transfer residual **28** to the reaction mixture. Stirring was continued and the cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 6.5 h. The mixture was then recooled to –78 °C, and a solution of allyl bromide (0.26 mL, 2.87 mmol) in THF (2.0 mL) was added dropwise over <1 min. The cold bath was left in place, but not recharged, and stirring was continued overnight, during which the mixture reached 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.3 × 15 cm), using a 5–10% EtOAc–hexanes gradient, gave **38** [129 mg, 48%, 70% corrected for recovered **28** (76 mg)] as a solid: mp 184–185 °C; FTIR ($CDCl_3$, cast) 3073, 2946, 1651 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 1.99–2.09 (m, 1 H), 2.64–2.72 (m, 1 H), 2.77 (dd, *J* = 17.5, 10.5 Hz, 1 H), 2.83 (dt, *J* = 10.5, 4.5 Hz, 1 H), 2.98 (dd, *J* = 17.5, 5.0 Hz, 1 H), 3.25 (td, *J* = 10.5, 5.0 Hz, 1 H), 3.90 (s, 3 H), 4.80 (d, *J* = 17.5 Hz, 1 H), 4.96 (d, *J* = 10.5 Hz, 1 H), 5.61–5.73 (m, 1 H), 7.20–7.26 (m, 2 H), 7.28–7.34 (m, 1 H), 7.34–7.41 (m, 2 H);^{13}C NMR (126 MHz, $CDCl_3$) δ 31.9 (t), 35.0 (t),

42.4 (q), 49.9 (d), 56.3 (d), 103.0 (t), 117.7 (s), 127.5 (d), 127.6 (d), 129.0 (d), 134.6 (d), 141.2 (s), 170.4 (s), 191.0 (s); exact mass (EI) *m*/*z* calcd for $C_{16}H_{17}{}^{81}BrO_2$ $(M)^+$ 322.0392, found 322.0389.

2-Bromo-5-phenyl-4-(prop-2-en-1-yl)-3-(thiophen-2-yl)cyclohex-2-en-1-one (38a). The Grignard reagent was prepared as described before. Thiophen-2-ylmagnesium bromide (0.62 M in THF, 0.67 mL, 0.42 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **38** (44 mg, 0.14 mmol) in THF (1.5 mL) (Ar atmosphere). The cold bath was left in place, but not recharged, and stirring was continued for 4 h during which the mixture reached room temperature. The reaction mixture was cooled to 0 °C and more Grignard reagent (0.62 M in THF, 0.67 mL, 0.42 mmol) was added. The cold bath was left in place, but not recharged, and stirring was continued for 15 h during which the mixture reached room temperature. The reaction mixture was quenched with hydrochloric acid (2 N, 2 mL) and acetone (2 mL) and stirring was continued for 3 h. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using a 5–10% EtOAc–hexanes gradient, gave **38a** (24 mg) and the intermediate. The intermediate was dissolved in acetone (2 mL) and hydrochloric acid (2 N, 2 mL). Stirring was continued overnight. More hydrochloric acid (2 N, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography in a pipette column, using 5% EtOAc–hexanes, gave **38a** (4.8 mg), making the total yield 56%. The material was an oil: FTIR ($CDCl_3$, cast) 3027, 2975, 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.40–2.58 (m, 2 H), 3.04 (dd, *J* = 17.5, 3.0 Hz, 1 H), 3.15 (dd, *J* = 17.5, 6.0 Hz, 1 H), 3.37–3.45 (m, 1 H), 3.54–3.60 (m, 1 H), 5.13–5.22 (m, 2 H),

5.79–5.91 (m, 1 H), 7.11–7.24 (m, 4 H), 7.25–7.33 (m, 2 H), 7.56 (d, J = 5.0 Hz, 1 H), 7.64 (d, J = 3.5 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.9 (t), 38.6 (t), 39.6 (d), 50.2 (d), 118.4 (t), 121.8 (s), 126.9 (d), 127.2 (d), 127.4 (d), 128.8 (d), 129.8 (d), 131.3 (d), 135.0 (d), 140.6 (s), 142.7 (s), 152.0 (s), 189.9 (s); exact mass (EI) m/z calcd for $C_{19}H_{17}{}^{81}BrOS$ $(M)^+$ 374.0163, found 374.0156.

3-Phenyl-4-(prop-2-en-1-yl)-5-(thiophen-2-yl)phenol (38b). DBU (26 μL, 0.17 mmol) was added to a stirred solution of **38a** (22 mg, 0.06 mmol) in THF (0.8 mL) and stirring was continued for 16 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 3 mL). CH_2Cl_2 (3 mL) was added and stirring was continued for 30 min. More hydrochloric acid (5%$^{w}/_{v}$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 5% acetone–hexanes, gave **38b** (16.2 mg, 96%) as an oil: FTIR ($CDCl_3$, cast) 3373, 3100, 2975, 1588 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 3.31 (d, J = 5.5 Hz, 2 H), 4.56 (dd, J = 17.0, 1.5 Hz, 1 H), 4.66 (s, 1 H), 4.87 (dd, J = 10.5, 1.5 Hz, 1 H), 5.63–5.75 (m, 1 H), 6.74 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 2.5 Hz, 1 H), 7.05 (dd, J = 5.0, 3.5 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.28–7.42 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.9 (t), 115.3 (t), 117.2 (d), 117.5 (d), 125.3 (d), 126.8 (d), 126.9 (d), 127.1 (d), 127.9 (d), 128.2 (s), 129.1 (d), 136.5 (s), 138.2 (d), 141.7 (s), 142.6 (s), 145.0 (s), 152.8 (s); exact mass (EI) m/z calcd for $C_{19}H_{16}OS$ $(M)^+$ 292.0922, found 292.0917.

3-(2*H*-1,3-Benzodioxol-5-yl)-2-bromo-5-phenyl-4-(propo-2-en-1-yl)cyclohex-2-en-1-yl (38a'). Preparation of the aryl Grignard reagent: 1,2-(Methylenedioxy)-4-bromobenzene (1.23 mL, 10.0 mmol) was added dropwise over 5 min to a stirred mixture of Mg (292 mg, 12 mmol) and THF (15 mL) (Ar atmosphere).[28] After the addition, a condenser with a drying tube

was connected to the round bottomed flask and the mixture was stirred overnight. The resulting Grignard reagent was titrated according to the literature procedure[23] before use.

[(3,4-Methylenedioxy)phenyl]magnesium bromide (0.66 M in THF, 0.71 mL, 0.47 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **38** (50 mg, 0.16 mmol) in THF (1.5 mL) (Ar atmosphere). The cold bath was left in place, but not recharged, and stirring was continued for 25 h. During the first 4 h the mixture reached room temperature. More Grignard reagent (0.66 M in THF, 0.71 mL, 0.47 mmol) was added and stirring was continued for 42 h. The reaction mixture was quenched with hydrochloric acid (2 N, 5 mL) and stirring was continued for 5 h. More hydrochloric acid (2 N, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 18 cm), using a 5–10% EtOAc–hexanes gradient, gave **38a'** (35.4 mg, 55%) as an oil: FTIR ($CDCl_3$, cast) 3072, 2903, 1684 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.22–2.39 (m, 2 H), 2.99 (dd, *J* = 17.5, 6.0 Hz, 1 H), 3.04–3.14 (m, 2 H), 3.50 (dd, *J* = 10.0, 5.5 Hz, 1 H), 5.06 (d, *J* = 17.0 Hz, 1 H), 5.13 (d, *J* = 10.0 Hz, 1 H), 5.65–5.76 (m, 1 H), 6.00 (d, *J* = 3.0 Hz, 2 H), 6.59–6.65 (m, 2 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 7.19 (d, *J* = 7.5 Hz, 2 H), 7.23–7.30 (m, 1 H), 7.31–7.38 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.2 (t), 39.7 (t), 40.5 (d), 50.8 (d), 101.4 (t), 108.1 (d), 108.2 (d), 118.5 (s), 121.3 (d), 123.4 (s), 127.0 (d), 127.2 (d), 128.9 (d), 133.5 (s), 134.7 (d), 142.8 (s), 147.5 (s), 148.0 (s), 160.9 (s), 190.5 (s); exact mass (EI) *m*/*z* calcd for $C_{22}H_{19}{}^{81}BrO_3$ $(M)^+$ 412.0497, found 412.0507.

3-(2*H*-1,3-Benzodioxol-5-yl)-5-phenyl-4-(prop-2-en-1-yl)phenol (38b'). DBU (34 μL, 0.23 mmol) was added to a stirred solution of **38a'** (31 mg, 0.075 mmol) in THF (1.0 mL) and stirring was continued for 23 h (Ar atmosphere). The reaction mixture was quenched with

hydrochloric acid (5%$^{w}/_{v}$, 4 mL). CH_2Cl_2 (4 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^{w}/_{v}$, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using a 5–10% acetone–hexanes gradient, gave **38b'** (23.4 mg, 94%) as an oil: FTIR ($CDCl_3$, cast) 3418, 3079, 2975, 1502 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 3.20 (d, *J* = 5.5 Hz, 2 H), 4.47 (dd, *J* = 17.0, 1.5 Hz, 1 H), 4.61 (s, 1 H), 4.78 (dd, *J* = 10.0, 1.5 Hz, 1 H), 5.50–5.61 (m, 1 H), 5.99 (s, 2 H), 6.71 (s, 2 H), 6.78 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.82 (d, *J* = 7.5 Hz, 2 H), 7.29–7.41 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.6 (s), 101.0 (t), 107.8 (d), 109.9 (d), 115.0 (s), 116.4 (d), 116.5 (d), 122.5 (d), 127.0 (d), 127.3 (s), 127.9 (d), 129.1 (d), 135.7 (s), 137.9 (d), 141.9 (s), 144.1 (s), 144.6 (s), 146.6 (s), 147.1 (s), 152.8 (s); exact mass (EI) *m*/*z* calcd for $C_{22}H_{18}O_3$ $(M)^+$ 330.1256, found 330.1249.

2-Bromo-4-[(3-bromophenyl)methyl]-3-ethenyl-5-methylcyclohex-2-en-1-one (40). Vinylmagnesium bromide (1.0 M in THF, 0.57 mL, 0.57 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **37**[2] (73 mg, 0.19 mmol, a 5:1 mixture of two isomers) in THF (3.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 2 h. The reaction mixture was quenched with hydrochloric acid (2 N, 4 mL) and stirred for 20 min. More hydrochloric acid (2 N, 15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using a 5–10% EtOAc–hexanes gradient, gave **40** (61.5 mg, 85%) as an oil which was a 7:5 mixture of isomers. The major isomer had: mp 106–107 °C; FTIR ($CDCl_3$, cast) 3333, 3097, 2958, 1677 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 0.99 (d, *J* = 7.0 Hz, 3 H), 2.14–2.24 (m, 1 H), 2.51 (d, *J* = 17.5 Hz, 1 H), 2.68 (dd, *J* = 14.0, 11.0 Hz, 1 H), 2.90–3.05 (m, 3 H), 5.73 (d, *J* = 11.0 Hz, 1 H), 5.92 (d, *J* = 17.5 Hz,

1 H), 7.08–7.24 (m, 3 H), 7.34 (s, 1 H), 7.40 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.7 (q), 28.8 (d), 39.1 (t), 40.0 (t), 45.2 (d), 122.9 (s), 123.6 (s), 124.6 (s), 127.4 (d), 130.0 (d), 130.4 (d), 131.6 (d), 136.8 (d), 141.4 (s), 153.7 (s), 190.2 (s); exact mass (EI) m/z calcd for $C_{16}H_{16}{}^{81}Br_2O$ $(M)^+$ 385.9527, found 385.9517.

4-[(3-Bromophenyl)methyl]-3-ethenyl-5-methylphenol polymer. DBU (62 μL, 0.41 mmol) was added to a stirred solution of **40** (53 mg, 0.14 mmol, a 7:5 mixture of two isomers) in THF (1.5 mL) and stirring was continued for 18 h (Ar atmosphere). More DBU (124 μL, 0.82 mmol) was added and stirring was continued for 24 h. The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a polymer (shown in MALDI) of **41** (40.4 mg, 97% crude yield) as an oil.

2-Bromo-5-methyl-3-(prop-2-en-1-yl)cyclohex-2-en-1-one (42). Allylmagnesium bromide (1.0 M in Et_2O, 0.75 mL, 0.75 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **10** (164 mg, 0.75 mmol) in THF (4.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 30 min. The reaction mixture was quenched with hydrochloric acid (2 N, 10 mL) and stirred for 5 min. More hydrochloric acid (2 N, 15 mL) was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 10 cm), using 10% EtOAc-hexanes, gave **42** (159 mg, 93%) as an oil: FTIR ($CDCl_3$, cast) 3307, 2957, 1685 cm^{-1}; ^{1}H NMR (498 MHz, $CDCl_3$) δ 1.07 (d, J = 6.0 Hz, 3 H), 2.12–2.31 (m, 3 H), 2.48–2.60 (m, 1 H), 2.63–2.73 (m, 1 H), 3.20 (dd, J = 14.0, 7.0 Hz, 1 H), 3.29 (dd, J = 14.0, 7.0 Hz, 1 H), 5.14–5.24 (m, 2 H), 5.73–5.84 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (q), 29.4 (d), 40.2 (t), 43.3 (t),

45.7 (t), 118.4 (t), 123.0 (s), 131.6 (d), 159.8 (s), 191.4 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{13}{}^{81}BrO$ $(M)^+$ 230.0129, found 230.0127.

2-Bromo-5-methyl-3-[(1*E*)-(prop-1-en-1-yl)]cyclohex-2-en-1-one (43). DBU (0.10 mL, 0.67 mmol) in THF (0.5 mL) was added dropwise to a stirred solution of **42** (73 mg, 0.32 mmol) in THF (1.0 mL) and stirring was continued for 5 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 5 mL), and EtOAc (5 mL) was added. Stirring was continued for 15 min. More hydrochloric acid (5%$^{w}/_{v}$, 10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 10% EtOAc-hexanes, gave **43** (8.0 mg, 11%) as a white solid and **44** (12.8 mg, 27%) as a colorless oil. Compound **43** had: mp 73–74 °C; FTIR ($CDCl_3$, cast) 3308, 3052, 2949, 1662 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.11 (d, *J* = 5.5 Hz, 3 H), 1.96 (dd, *J* = 6.5, 1.0 Hz, 3 H), 2.15–2.32 (m, 3 H), 2.68–2.82 (m, 2 H), 6.34–6.44 (m, 1 H), 6.89 (d, *J* = 15.5 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.4 (q), 20.8 (q), 29.0 (d), 36.3 (t), 46.1 (t), 122.3 (s), 132.1 (d), 137.5 (d), 152.7 (s), 191.9 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{13}{}^{81}BrO$ $(M)^+$ 230.0129, found 230.0131. Compound **44** had: FTIR ($CDCl_3$, cast) 3343, 3024, 2957, 1591 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.86 (dd, *J* = 6.5, 1.5 Hz, 3 H), 2.28 (s, 3 H), 4.55 (s, 1 H), 6.20 (dq, *J* = 16.0, 6.5 Hz, 1 H), 6.30 (dd, *J* = 16.0, 1.5 Hz, 1 H), 6.50 (s, 1 H), 6.61 (s, 1 H), 6.73 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.5 (q), 21.3 (q), 109.6 (d), 114.5 (d), 119.6 (d), 126.1 (d), 130.7 (d), 139.5 (s), 139.7 (s), 155.6 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{12}O$ $(M)^+$ 148.0888, found 148.0889.

3-Methyl-5-[(1E)-prop-1-en-1-yl]phenol (44). DBU (0.22 mL, 1.47 mmol) was added to a stirred solution of **42** (112 mg, 0.49 mmol) in THF (2.50 mL) and stirring was continued for

25 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^{w}/_{v}$, 5 mL) and CH_2Cl_2 (5 mL) was added. Stirring was continued for 15 min. More hydrochloric acid (5%$^{w}/_{v}$, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The MALDI spectrum of the crude residue showed clearly a polymer of **44**. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% EtOAc-hexane, gave **44** (22.4 mg, 30%) as a colorless oil. For characterization data see above.

2-Chloro-3-methoxy-5-(thiophen-3-yl)cyclohex-2-en-1-one (47, X = Cl). NCS (120 mg, 0.88 mmol) in THF (2 mL) was added dropwise to a stirred and cooled (0 °C) solution of **32** (155 mg, 0.80 mmol) in THF (8 mL) and DMF (3 mL). Stirring was continued for 7 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 15 cm), using 0.5% acetone-CH_2Cl_2, gave **47** (X = Cl) (156 mg, 85%) as a solid: mp 134–135 °C; FTIR ($CDCl_3$, cast) 3100, 2951, 1663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 16.5, 13.0 Hz, 1 H), 2.77 (dd, *J* = 17.5, 11.0 Hz, 1 H), 2.91 (dd, *J* = 17.5, 4.0 Hz, 1 H), 3.09 (dd, *J* = 17.5, 4.0 Hz, 1 H), 3.47–3.58 (m, 1 H), 3.97 (s, 3 H), 7.02 (d, *J* = 5.0 Hz, 1 H), 7.08 (d, *J* = 3.0 Hz, 1 H), 7.36 (dd, *J* = 5.0, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.8 (t), 32.9 (q), 43.5 (t), 56.6 (d), 111.8 (s), 120.5 (d), 126.0 (d), 126.8 (d), 142.7 (s), 169.7 (s), 189.9 (s); exact mass (EI) *m*/*z* calcd for $C_{11}H_{11}{}^{35}ClO_2S$ $(M)^+$ 242.0168, found 242.0164.

3-(2*H*-1,3-Benzodioxol-5-yl)-2-chloro-5-(thiophen-3-yl)cyclohex-2-en-1-one (48, X = Cl). The Grignard reagent was prepared as described before. [(3,4-Methylenedioxy)-phenyl]magnesium bromide (0.67 M in THF, 0.47 mL, 0.32 mmol) was added dropwise over 5

min to a stirred and cooled (0 °C) solution of **47** (X = Cl) (51.3 mg, 0.21 mmol) in THF (2.0 mL) (Ar atmosphere). Stirring was continued for 2 h. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirring was continued for 30 min. More hydrochloric acid (2 N, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 5% acetone-hexane, gave **48** (X = Cl) (62.5 mg, 82%) as an beige solid: mp 124–125 °C; FTIR ($CDCl_3$, cast) 3103, 2900, 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 16.5, 12.5 Hz, 1 H), 2.98 (dd, *J* = 18.0, 10.5 Hz, 1 H), 3.02–3.13 (m, 2 H), 3.57–3.67 (m, 1 H), 6.02 (s, 2 H), 6.84–6.89 (m, 1 H), 6.90–6.95 (m, 2 H), 7.03 (d, *J* = 5.0 Hz, 1 H), 7.06 (s, 1 H), 7.34 (dd, *J* = 5.0, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.4 (d), 41.3 (t), 44.5 (t), 101.5 (t), 108.28 (d), 108.32 (d), 120.3 (d), 121.8 (d), 126.1 (d), 126.6 (d), 128.7 (s), 132.1 (s), 143.1 (s), 147.6 (s), 148.4 (s), 154.6 (s), 190.9 (s); exact mass (EI) *m*/*z* calcd for $C_{17}H_{13}{}^{35}ClO_3S$ $(M)^+$ 332.0274, found 332.0269.

3-(2*H*-1,3-Benzodioxol-5-yl)-5-(thiophen-3-yl)phenol (25a) from 48 (X = Cl).[30] DBU (86 μL, 0.56 mmol) was added to a stirred solution of **48** (X = Cl) (62.5 mg, 0.19 mmol) in THF (1.8 mL) and stirring was continued for 16 h (Ar atmosphere). The reaction mixture was quenched with hydrochloric acid (5%$^w/_v$, 3 mL). CH_2Cl_2 (3 mL) was added and stirring was continued for 15 min. More hydrochloric acid (5%$^w/_v$, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using a 5–10% EtOAc-hexanes gradient, gave **25a** (52.3 mg, 94%) as an colorless oil: FTIR ($CDCl_3$, cast) 3407, 3105, 2952, 1595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 1 H), 6.01 (s, 2 H), 6.89–6.93 (m,

2 H), 7.02 (s, 1 H), 7.05–7.11 (m, 2 H), 7.32 (s, 1 H), 7.39 (s, 1 H), 7.40 (s, 1 H), 7.48 (t, J = 2.0 Hz, 1 H).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of NMR spectra of new compounds (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

Both authors thank Natural Sciences and Engineering Research Council of Canada for financial support and Dr. W. Shao for advice.

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