Conversion of Cycloalk-2-en-1-ones into 2-Methylcycloalkane-1,3-diones and Formation of *meta*-Substituted Phenols

by

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Abstract

The first chapter of this thesis describes the studies towards conversion of cycloalk-2-enones into 2-methylcyclo-alkane-1,3-diones. The key step is a Tamao–Fleming oxidation where a silyl group serves as a masked hydroxy group. Examination of various Tamao-Fleming procedures are discussed. In particular, mechanistic insight into the use of the Me_3SiMe_2Si unit is revealed.

The second chapter describes studies aimed at the synthesis of *meta*-substituted phenols via transition metal-free aromatization. Based on the previous work from this laboratory, a general route to 3,5-disubstituted and polysubstituted phenols has been developed. Each of the substituents in the final aromatic product is installed in a completely region-controlled manner and each can have a wide range of values. A demonstration of this method in the synthesis of pharmaceutically important intermediates is described as well. Further application of this methodology towards the total synthesis of Fulvestrant (a breast cancer drug) is currently under investigation.

To My Teachers, Friends and Family

Acknowledgement

I would like to express my appreciation to Prof. Derrick L. J. Clive for his superb guidance during the course of my MSc program. I learned a lot of organic chemistry both experimental and theoretical.

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List of Abbreviations

Ac	acetyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
t-BuXPhos	2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
m-CPBA	*meta*-chloroperoxybenzoic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
EI	electron ionization
ESI	electrospray ionization
FTIR	fourier transform infrared spectroscopy
H-BPin	pinacolborane
HRMS	high-resolution mass spectrometry
IBX	2-iodoxybenzoic acid
LDA	lithium diisopropylamide

mp	melting point
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
rt	room temperature
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
μW	microwave

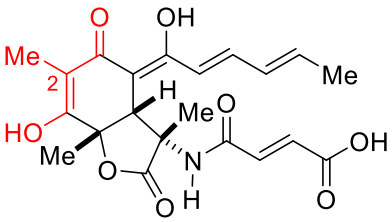
Chapter 1

Conversion of Cycloalk-2-enones into 2-Methylcyclo-alkane-1,3-diones—Assessment of Various Tamao-Fleming Procedures and Mechanistic Insight into the Use of the Me_3SiMe_2Si Unit

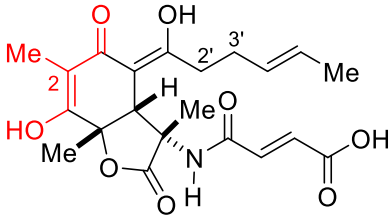
1 INTRODUCTION

1.1 General

In connection with studies towards the total synthesis of sobicillactone A (**1.1**) (an anti-leukemia and anti-HIV compound) and sorbicillactone B (**1.2**) (Scheme 1), a precursor of a cyclohexane-1,3-dione unit is needed so-constituted that regioselective alkylation at the eventual C(2) position is possible *before* the generation of the 1,3-dione system, which it was intended to liberate at a late stage in the synthetic route.[1]



Sorbicillactone A (1.1)

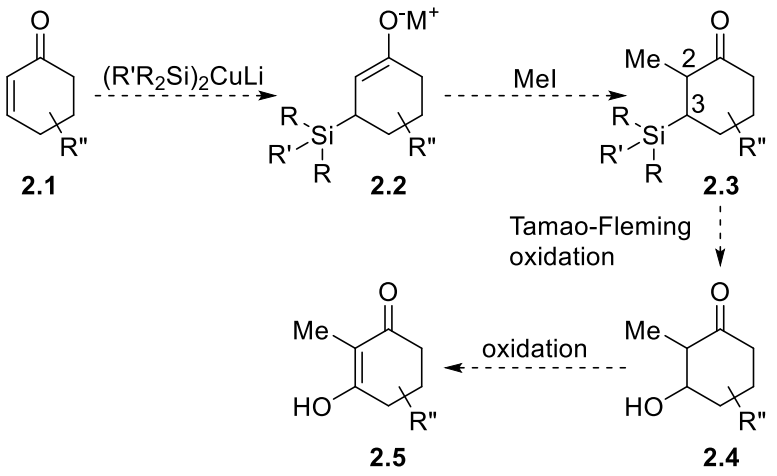


Sorbicillactone B (1.2)

Scheme 1.

Our plan (Scheme 2) was to effect this transformation by conjugate addition of a silicon unit (**2.1**→**2.2**), followed by trapping of the intermediate enolate with MeI (**2.2**→**2.3**). The C(3)—Si bond would then be converted into a C—OH bond by Tamao-Fleming oxidation, and further oxidation of the resulting hydroxyl was expected to give the desired 1,3-dione (**2.3**→**2.5**). In this way a cyclohex-2-en-1-one (or its parent cyclohexanone) subunit would serve as a masked 2-methylcyclohexane-1,3-dione that could be liberated at a late stage

of a synthesis when its reactivity would no longer interfere with other transformations.

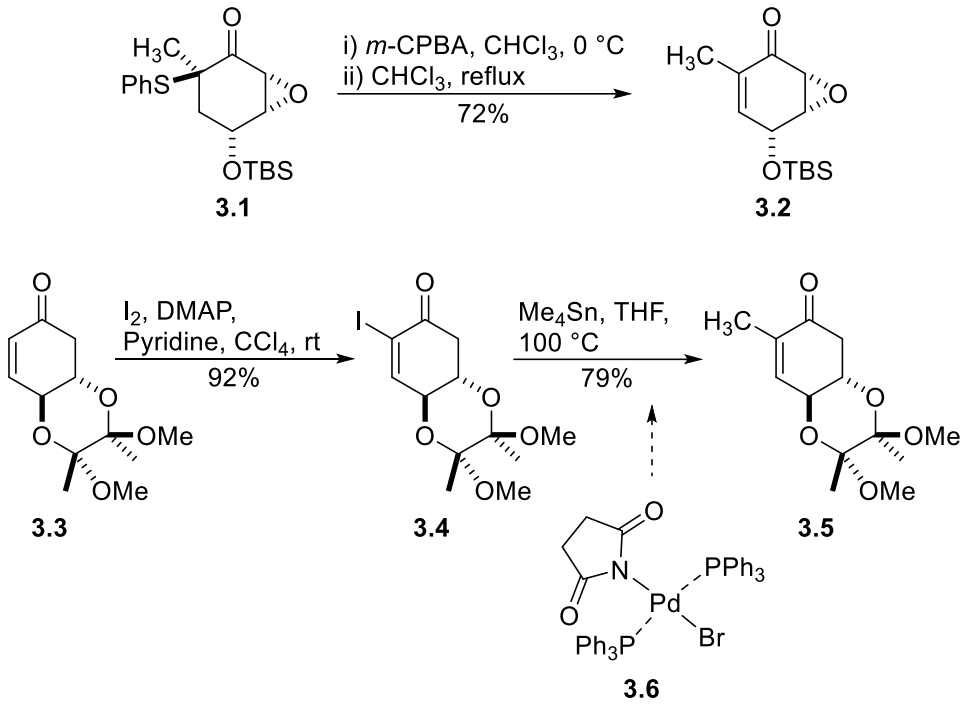


Scheme 2.

Although conjugate additions of the type we contemplated, together with in situ trapping of the resulting enolate by electrophiles, are known[2] and there are many examples in which a silicon-carbon bond is replaced by a carbon-oxygen bond,[3] the particular combination of steps presented here has not been reported before and it satisfies the requirements of our synthetic plan by allowing a potential 1,3-dione system to be carried through a variety of synthetic operations in a conveniently masked form. Simple though this scheme appears, it proved to require considerable experimentation and could not be reduced to practice without incorporating protection-deprotection steps. Our results established that the procedure we eventually developed is general.

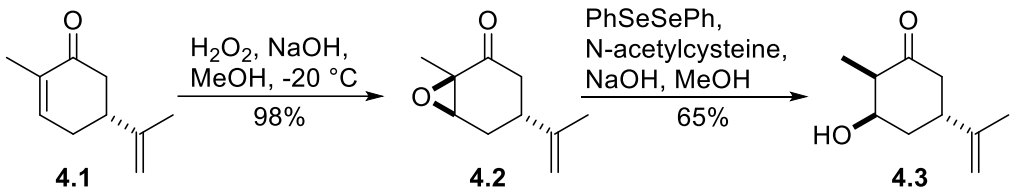
1.2 Literature approaches

The method described above to compounds of type **2.4** and **2.5** is more direct than one based on literature approaches shown below. A 2-methylcyclohex-2-en-1-one substructure can be formed by oxidation of **3.1** to the sulfoxide followed by subsequent pyrolysis,[4] or by iodination of **3.3** on the α position of an enone, followed by Stille coupling (Scheme 3).[5]



Scheme 3.

After installing the 2-methylcyclohex-2-en-1-one substructure, epoxidation and subsequent reductive ring opening afforded the β hydroxy ketone unit (Scheme 4).[6]



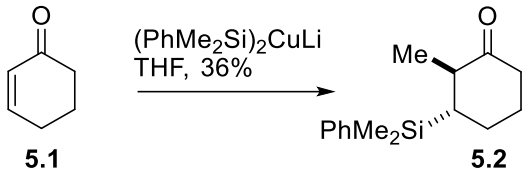
Scheme 4.

2. RESULTS AND DISCUSSION

2.1 Examination of different monosilicon units

2.1.1 Use of the $PhMe_2Si$ group

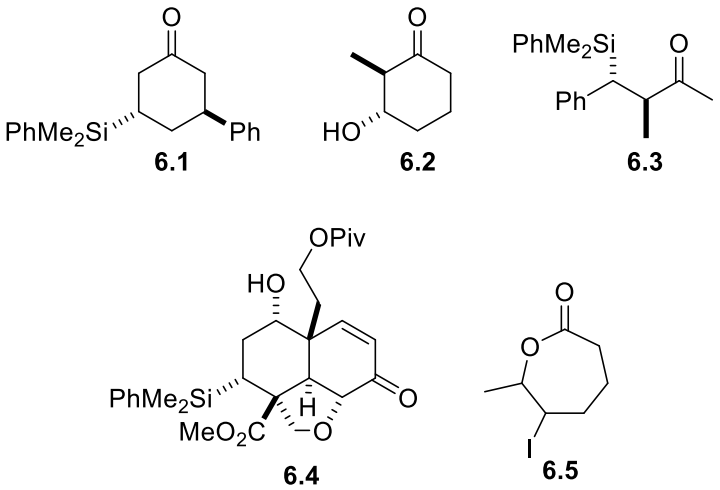
We first added the $PhMe_2Si$ group, a very popular silicon unit in Tamao-Fleming oxidation, to cyclohex-2-en-1-one and trapped the intermediate enolate with MeI (Scheme 5, **5.1**→**5.2**), as reported in the literature,[2c] and we then applied several of the standard methods for Tamao-Fleming oxidation that had been used successfully with compounds containing a ketone group.



Scheme 5.

Treatment of **5.2** with $HBF_4.OEt_2$ and then with *m*-CPBA, conditions that had been used with **6.1**,[7] failed to give **6.2**. Likewise, treatment with $Hg(OAc)_2/AcOH/CF_3CO_2H$, followed by AcOOH/AcOH, a reagent combination that worked for **6.3**,[7] was unsuccessful. A simple variation—use of $Hg(OCOCF_3)_2$ in $AcOH\text{-}CF_3CO_2H$, followed by addition of AcOOH, which gave an 85% yield in the case of **6.4**, which contains a cyclohexenone substructure[8]—again afforded PhOH as the only product we isolated. When we used ICl in Et_2O[9] on **5.2**, followed by *m*-CPBA, we obtained **6.5** in 12% yield,

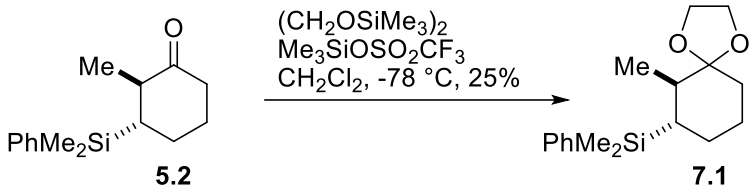
but not the desired hydroxy ketone **6.2**; in this last reaction, substitution of AcOOH for *m*-CPBA resulted in a complex mixture.



Scheme 6.

Ketone **5.2** appeared to be inert to $BF_3 \cdot AcOH$[7,10,11] at room temperature, apart from slow epimerization at C(2).

As attempts to carry out the Tamao-Fleming oxidation on ketone **5.2** were unsuccessful, we accepted that protection of the carbonyl was necessary. Formation of the ethylene ketal (**5.2**→**7.1**) was achieved, but only in 25% yield; use of camphorsulfonic acid (CSA), ethylene glycol and $MeC(OMe)_3$ resulted in loss of the Ph group from the silicon unit. A brief attempt to improve the yield by use of catalytic *p*-TsNHOH[12,13] was unsuccessful, leading only to recovery of starting ketone **5.2**.

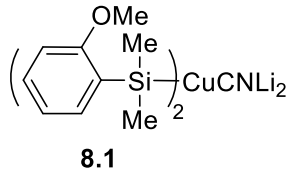


Scheme 7.

A sample of **7.1** was treated with Br_2 in AcOH and then with AcOOH/AcOH,[7] but no identifiable material was isolated.

2.1.2 Use of the (2-methoxyphenyl)dimethylsilyl group

Corey's report on the (2-methoxylphenyl)dimethylsilyl group[14] seemed to offer advantages over the parent phenyldimethylsilyl group as the methoxy substituent promotes the desilylation step and thus facilitates the Tamao-Fleming sequence. However, the generation of the cuprate **8.1** is technically difficult and we were unsuccessful in the single attempt that we made.

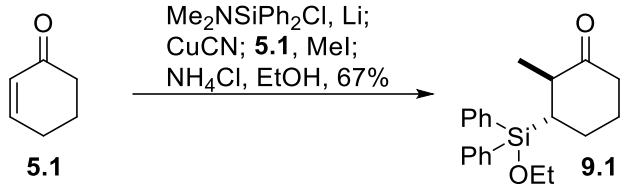


Scheme 8.

2.1.3 Use of the $Ph_2(EtO)Si$ group

At this point, we decided to examine other silicon groups in the hope that at least one of the steps of the Tamao-Fleming oxidation would be facilitated.

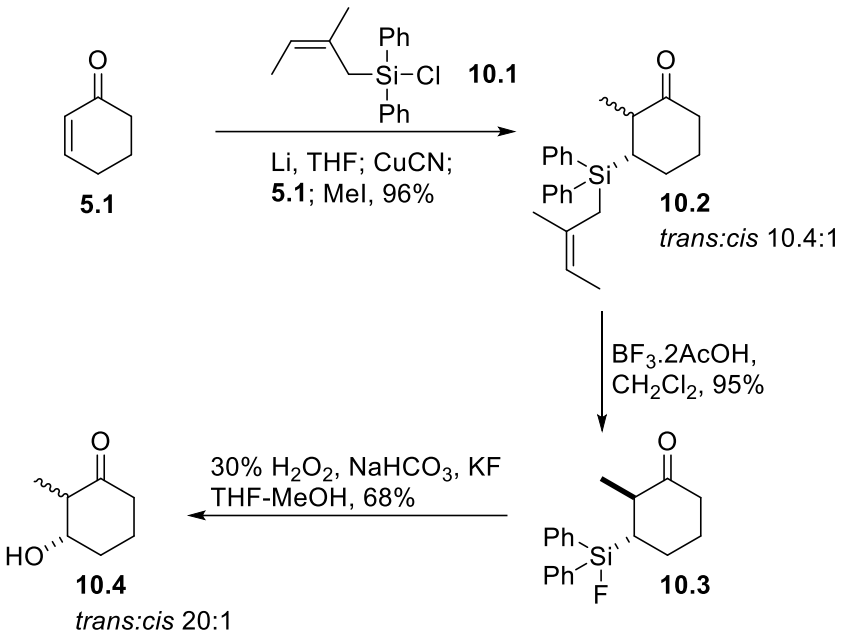
Cyclohex-2-en-1-one was therefore converted into **9.1** (67% yield) by conjugate addition and alkylation.[15] However, treatment of **9.1** with *m*-CPBA and KHF_2[16] gave only PhOH.



Scheme 9.

2.1.4 Use of an allylic silane group

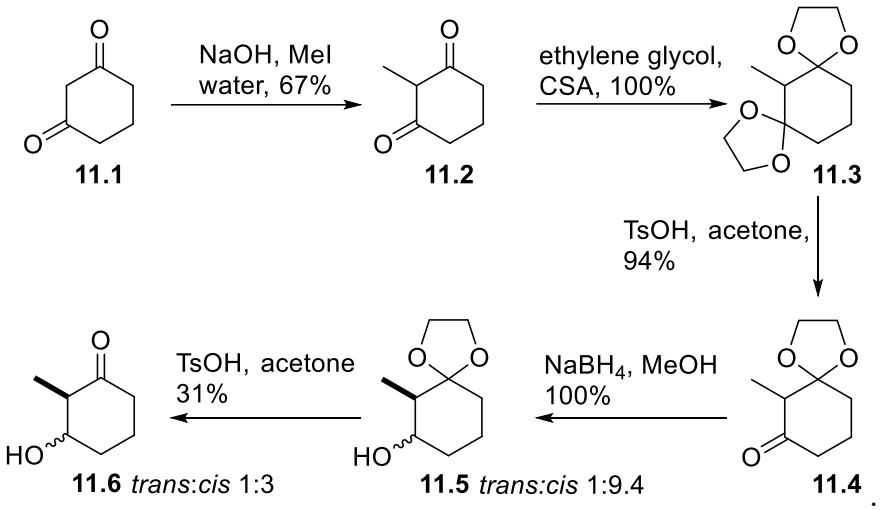
Use of Fleming's allylic silane was also examined.[17a] We prepared the allylic silane **10.2** (Scheme 10) in 98% yield. The required cuprate reagent is easy[17b] to make from chlorosilane **10.1**. Treatment of **10.2** with $BF_3 \cdot 2AcOH$ gave **10.3** in ca 95% yield, which appeared to be a single *trans* isomer. The compound partially decomposes on silica gel, but the crude material is satisfactory for the next step. Treatment of **10.2** with $HBF_4.OEt_2$ in CH_2Cl_2 gave the same product **10.3** in 62% yield as a 3.4:1 *trans*:*cis* mixture of isomers. When the fluorosilane **10.3** was exposed to the action of 30% H_2O_2 in the presence of $NaHCO_3$ and KF in THF-MeOH for 3 days at room temperature we obtained the desired hydroxy ketones **10.4** in 68% yield as a 20:1 *trans*:*cis* mixture of stereoisomers; a four-day period gave 64% yield.



Scheme 10.

2.2 Oxidation of β-hydroxy ketone to 1,3-diketone

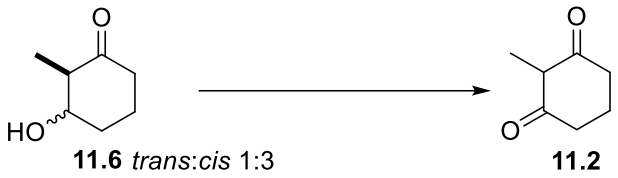
We now sought to oxidize the β-hydroxy ketones **10.4** to the 1,3-diketone **11.2**, and for these experiments it was convenient to make a sample of the β-hydroxy ketone **11.6** (as a mixture of *cis* and *trans* isomers) by the method[18,19] summarized in Scheme 11.



Scheme 11.

We examined the following conditions[20] for direct conversion of **11.6** into **11.2** (Table 1): TPAP/NMO/4Å sieves[21] in CH_2Cl_2-MeCN, IBX in DMSO,[22] the Dess-Martin reagent,[23] PCC,[24] PDC,[25] the Jones reagent,[26] CrO_3-Et_2O-CH_2Cl_2,[27] $K_2Cr_2O_7$-Bu_4NHSO_4,[28] the Corey-Kim oxidation,[29] and the Bobbitt reagent.[30] We usually obtained complex mixtures or a small amount of the desired β-diketone **11.2**, but a common observation was the early appearance (tlc monitoring) of the desired product and its subsequent disappearance, while much starting hydroxy ketone remained. If experiments with the Jones reagent were worked up well before all the starting hydroxy ketone had reacted it was possible to isolate the β-diketone **11.2** in 54% yield. Similarly, premature workup of oxidations with $K_2Cr_2O_7$–Bu_4NHSO_4 gave a 24% yield of the β-diketone.

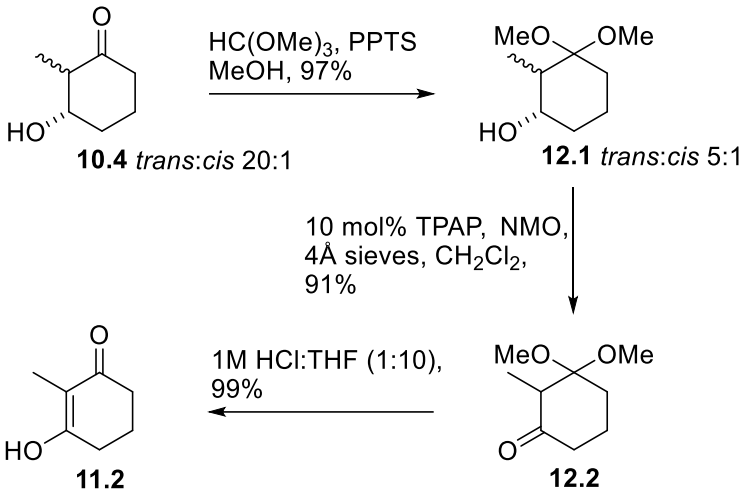
Table 1.



11.6 *trans*:*cis* 1:3 **11.2**

Oxidation Method	Observations
TPAP Oxidation IBX DMP PCC PDC CrO_3-Et_2O-CH_2Cl_2	DP appeared then disappeared after prolonging the reaction time while much SM still remains
Jones Oxidation	38% (54% for recovered SM)
$K_2Cr_2O_7$-Bu_4NHSO_4	15% (24% for recovered SM)
Corey-Kim Oxidation	Complex Mixture
Bobbitt Reagent	No Reaction

In the light of the above findings, the β-hydroxy ketone (obtained by the route of Scheme 10) was converted into the dimethoxy ketal **12.1** using $HC(OMe)_3$ and PPTS (Scheme 12). When TsOH was used as the catalyst the main pathway was dehydration, but with PPTS at room temperature only ketalization occurred and the yield was high (97%). TPAP oxidation to **12.2** was also efficient and the desired 2-methylcyclohexane-1,3-dione **11.2** was then liberated almost quantitatively by hydrolysis with 1M hydrochloric acid[31] in THF.

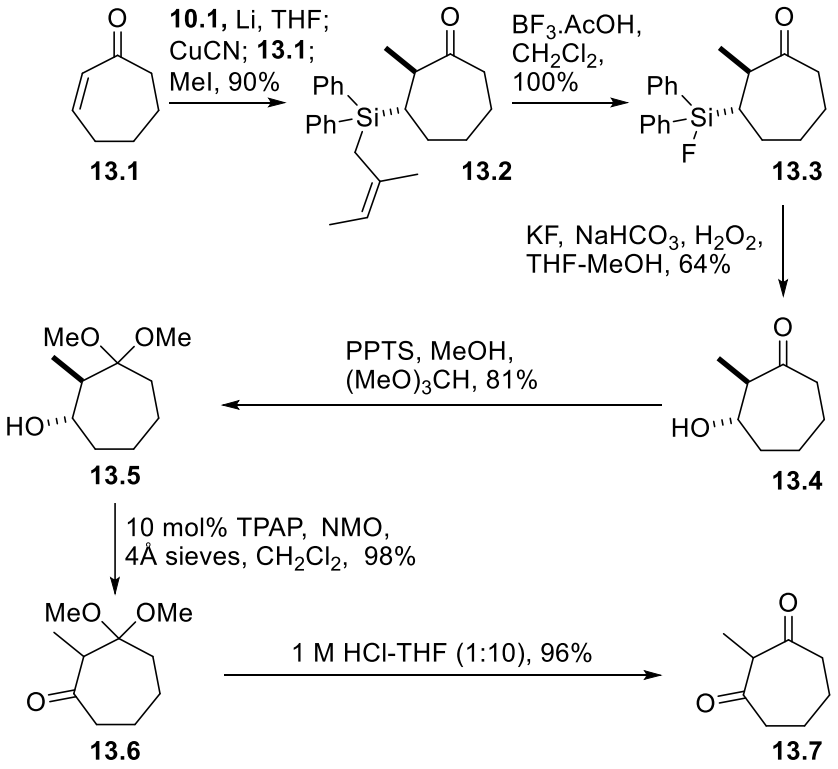


Scheme 12.

2.3 Use of the allylic silane group on cycloheptenone and cyclopentenone

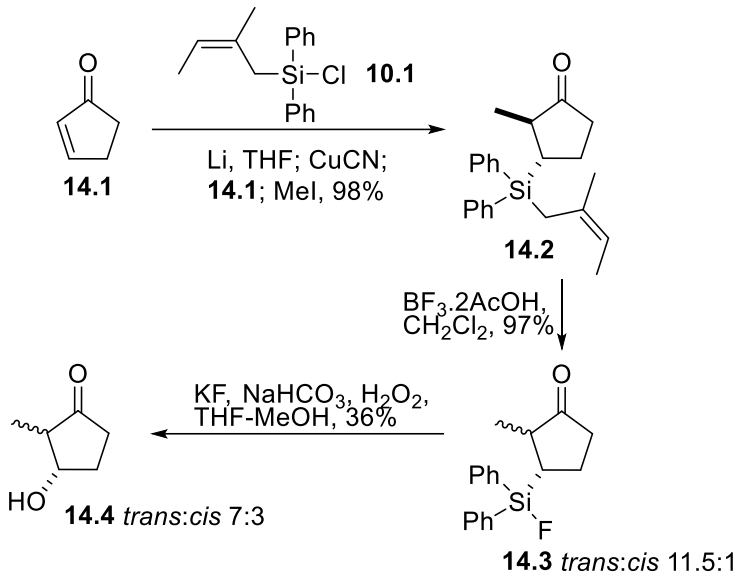
The sequences of Schemes 10 and 12 defined a route to accomplish our aim of converting a cyclohex-2-en-1-one into a 2-methylcyclohexane-1,3-dione, and we next applied it to cyclohept-2-en-1-one, a ketone that was best made by Saegusa oxidation[32] from cycloheptanone.[33]

Conjugate addition of the Fleming allylic silyl cuprate derived from **10.1** gave **13.2** (90% yield); no *cis* isomer was isolated. Replacement of the allylic unit by fluorine was quantitative and the second stage of the Tamao-Fleming oxidation (**13.3**→**13.4**) afforded the keto alcohol in 64% yield. Again, direct oxidation with TPAP generated some of the desired 1,3-diketone but this disappeared while much starting material remained. Accordingly, **13.4** was ketalized (**13.4**→**13.5**) and then TPAP oxidation worked well (**13.5**→**13.6**, 98%). Finally, acid hydrolysis gave **13.7**[34] (96%) which, according to its ^{1}H NMR spectrum ($CDCl_3$), was in the diketo form and not enolized.



Scheme 13.

We also applied the method of Scheme 13 to cyclopent-2-en-1-one. Formation of the conjugate addition product **14.2** was very efficient (98%), as was replacement of the allylic unit by fluorine (**14.2**→**14.3**, 97%). However, the yield in the oxidation step of the Tamao-Fleming process **14.3**→**14.5** under normal conditions used successfully for **10.3** (68%) and **13.3** (64%) was too low (36%) to be useful.



Scheme 14.

A few more experiments were carried out in the hope of improving the yield (Table 2.). Prolonging the reaction time from 1.5 days to 3 days did not offer a better yield. Using the anhydrous form of H_2O_2 as H_2O_2-urea[35] instead of 30% aqueous solution afforded no advantage. Unfortunately, the yield was too low to warrant studies on further conversion to a 1,3-dione.

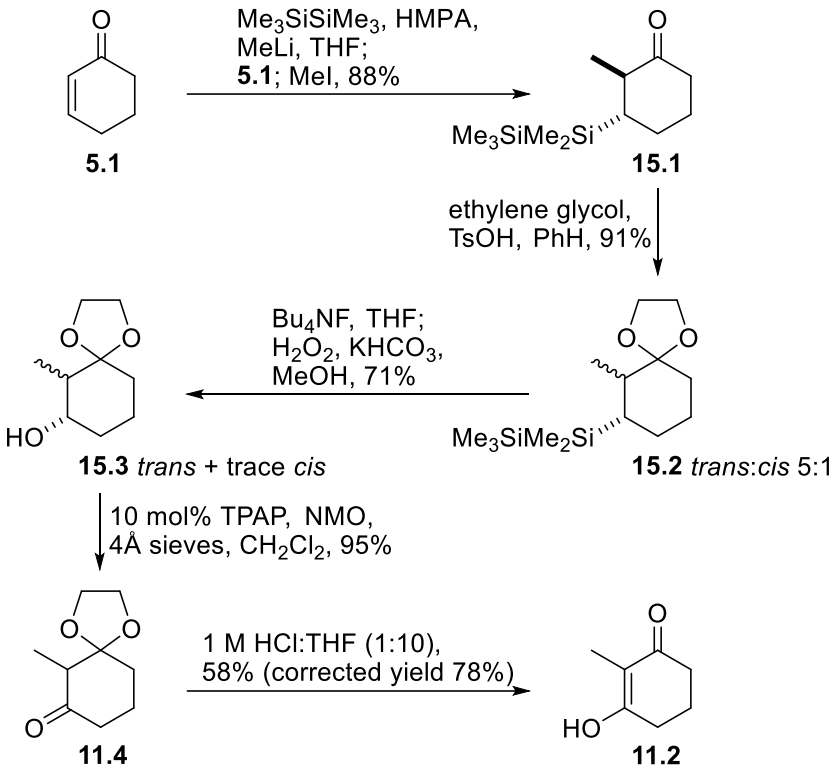
Table 2.

Conditions	Yields
KF, $NaHCO_3$, 30% H_2O_2, THF-MeOH, **1.5 d**	**36%**
KF, $NaHCO_3$, 30% H_2O_2, THF-MeOH, **3 d**	18%
KHF_2, H_2O_2-Urea THF-MeOH, **2.5 d**	4%
KHF_2, H_2O_2-Urea THF-MeOH, **5 d**	30%

2.4 Examination of the pentamethyldisilyl group

During the course of our experimental work it became desirable to impose the additional requirement that the intermediate silane be of such a nature that a number of further reactions could be carried out before replacing the silicon unit by an oxygen. Both a phenyl and an allyl group on silicon rendered the compounds rather sensitive to acidic conditions; however, the $Me_3SiSiMe_2$– unit seemed ideal for conferring greater stability. This group has been used on only a few occasions[16,36,37] and so its merits have not yet been firmly established, but we applied it to the case of cyclohex-2-en-1-one for comparison with our earlier route, and then to cyclopent-2-en-1-one and cyclohept-2-en-1-one.

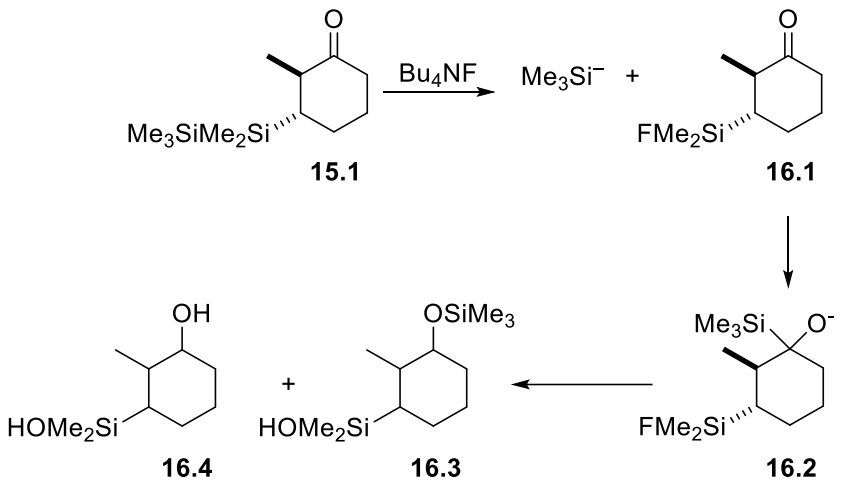
An additional advantage of the Me_3SiMe_2Si group is that formation of a cuprate is unnecessary, as the second silicon modifies the properties of the anion $Me_3SiMe_2Si^-$ in a way that causes it to add 1,4 to cycloalk-2-en-1-ones.



Scheme 15.

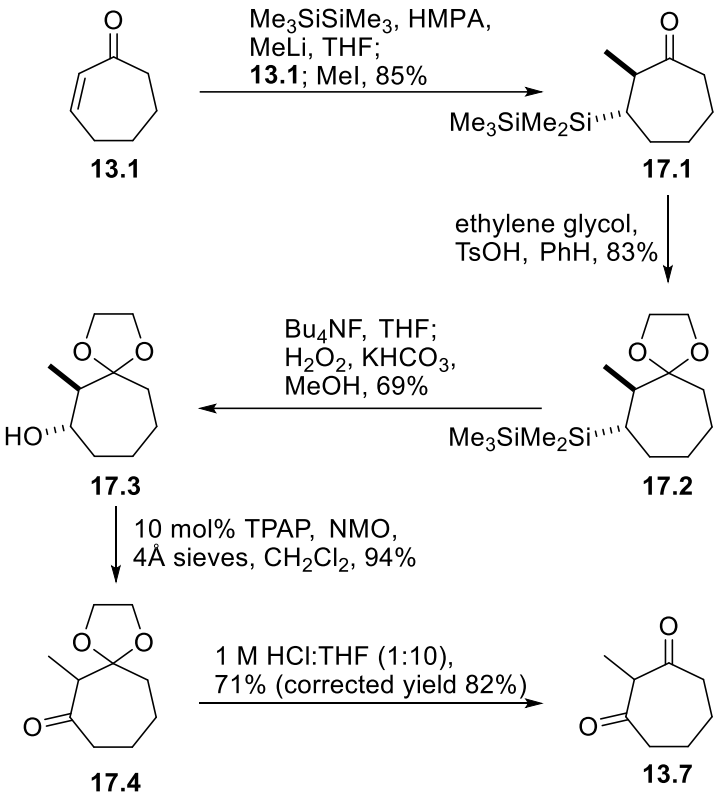
We generated Me_3SiMe_2SiLi in the manner reported in the literature,[37] although we found it better to prolong to 30 min the initial period after addition of MeLi. We also found that the subsequent dilution with THF should be done slowly[36d] (over ca 30 min). Unlike the situation with $PhMe_2Si$ (cf. Scheme 7, **5.1**→**7.1**) ketalization (**15.1**→**15.2**) was easily achieved in the presence of TsOH. The Tamao-Fleming steps provided the hydroxy ketal **15.3** (71%), and oxidation (95%) took the route as far as **11.4**. The final acid hydrolysis (58%, 78% for recovered starting material) was best stopped before completion, at least when using HCl-THF, which was the only reagent we examined.

The above sequence was not the first we tried with the pentamethyldisilane reagent. Initially, we did not protect the ketone and we found that in the Tamao-Fleming step three byproducts were formed that revealed details of the mechanism and established the need for ketone protection. While we did not deduce the structure of one of these byproducts the other two were clearly **16.3** and **16.4** (of undetermined stereochemistry), and we interpret their formation as resulting from attack of the Me_3Si^- anion[38] on the ketone carbonyl (**16.1**→**16.2**), followed by Brook rearrangement to **16.3**. On the basis of this proposal we obviously had to protect the ketone carbonyl before the Tamao-Fleming sequence. We did examine the possibility of using acetone as a sacrificial trap for Me_3Si^-, but this modification did not alter the outcome.



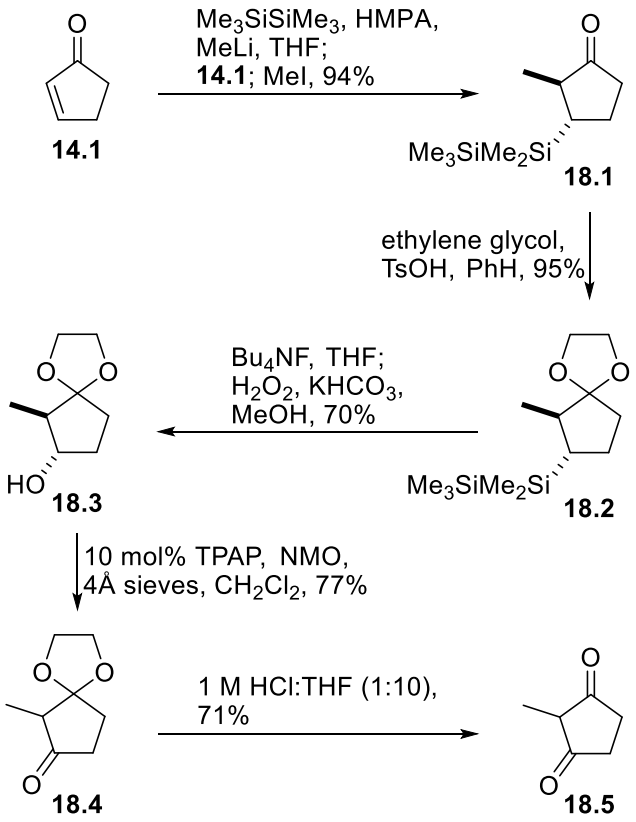
Scheme 16.

We next applied the procedure of Scheme 15 to the case of cyclohept-2-en-1-one and found that each of the steps proceeded without incident (Scheme 17).



Scheme 17.

Finally, in view of the difficulties we had met with cyclopent-2-en-1-one (see Scheme 14), we applied the pentamethyldisilane approach to this ketone; again all the steps worked smoothly (Scheme 18).


Me3SiSiMe3, HMPA,
MeLi, THF;
14.1; MeI, 94%
14.1
Me3SiMe2Si
18.1
ethylene glycol,
TsOH, PhH, 95%
Bu4NF, THF;
H2O2, KHCO3,
MeOH, 70%
HO
18.3
Me3SiMe2Si
18.2
10 mol% TPAP, NMO,
4Å sieves, CH2Cl2, 77%
1 M HCl:THF (1:10),
71%
18.4
18.5

Scheme 18.

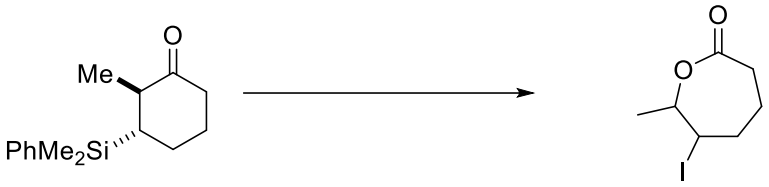
3 CONCLUSION

Conjugate addition of Me_3SiMe_2SiLi to cycloalk-2-en-1-ones, ketalization, Tamao-Fleming oxidation (Bu_4NF, then H_2O_2, $KHCO_3$), TPAP oxidation and acid hydrolysis generates 2-methyl cycloalkane-1,3-diones. This route is general for 5, 6, and 7-membered rings. Ketalization is needed in order to prevent addition of Me_3Si^- to the carbonyl. The pentamethyldisilanyl group has advantages over other silicon units that are used in Tamao-Fleming procedures, as the presence of the silicon units $PhMe_2Si$ (e.g. as in **5.2**) and $(C_5H_9)Ph_2Si$ (e.g. as in **10.2**) generally render the compounds sensitive to acids and impose restrictions on the types of transformations that can be carried out. The Me_3SiMe_2Si unit, however, does not suffer from this disadvantage, and deserves to be more widely used, especially where other structural features of the substrate are immune to attack by Me_3Si^-.

4 EXPERIMENTAL

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. Gradient flash chromatography was done by stepwise small increases in the content of the more polar solvent.

6-Iodo-7-methyloxepan-2-one (6.5).

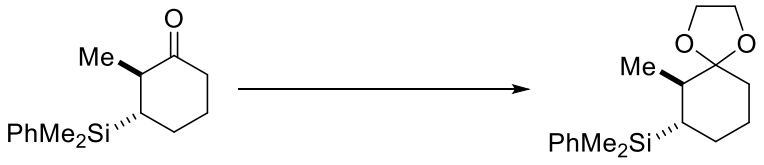


5.2 **6.5**

ICl (0.43 mL, 0.43 mmol) was added to a stirred solution of **5.2** (50 mg, 0.21 mmol) in Et_2O (1.0 mL) (Ar atmosphere). After 3 h, the reaction mixture

was cooled to 0 °C and *m*-CPBA (149 mg, 0.82 mmol, purified from wet commercial material) was added, followed by a solution of Et_3N (34 μL, 0.25 mmol) in Et_2O (1 mL). The ice bath was left in place, but not recharged, and stirring was continued overnight. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (ca 5 mL) and saturated aqueous $NaHCO_3$ (ca 5 mL) and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine, 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 **6.5** (6 mg, 12%) as an oil: FTIR ($CDCl_3$, cast) 2958, 1736, 1443, 1239, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.62–1.72 (m, 1 H), 1.82–1.93 (m, 1 H), 1.96 (d, *J* = 7.0 Hz, 3 H), 1.93–2.01 (m, 1 H), 2.22–2.29 (m, 1 H), 2.42–2.51 (m, 1 H), 2.57–2.66 (m, 1 H), 3.93–4.01 (m, 1 H), 4.22–4.30 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2 (t), 23.9 (q), 27.1 (t), 29.2 (d), 29.4 (t), 84.3 (d), 170.4 (s); exact mass (ESI) *m*/*z* calcd for $C_7H_{11}INaO_2$ $(M + Na)^+$ 276.9696, found 276.9692. Additional small signals in the ^{13}C NMR spectrum suggested the presence of a second stereoisomer.

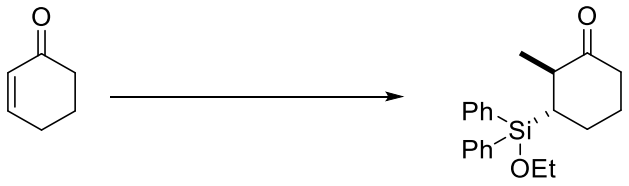
Dimethyl[*trans*-6-methyl-1,4-dioxaspiro[4,5]decan-7-yl]phenylsilane (7.1).



5.2 **7.1**

$(Me_3SiOCH_2)_2$ (340 mg, 1.65 mmol) in CH_2Cl_2 (2 mL) and $CF_3SO_2OSiMe_3$ (8.0 μL, 0.045 mmol) were added sequentially to a stirred and cooled (–78 °C) solution of **5.2** in CH_2Cl_2 (3 mL) (Ar atmosphere). Stirring was continued for 4 h and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (ca 15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 3% EtOAc-hexanes, gave **7.1** (33 mg, 25%) as an oil: FTIR ($CDCl_3$, cast) 3068, 2975, 2879, 1878 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.28 (s, 3 H), 0.31 (s, 3 H), 0.81 (d, J = 6.5 Hz, 3 H), 1.05–1.18 (m, 2 H), 1.31 (td, J = 13.5, 4.0 Hz, 1 H), 1.43–1.53 (m, 1 H), 1.56–1.63 (m, 1 H), 1.63–1.72 (m, 2 H), 1.75–1.82 (m, 1 H), 3.84–4.00 (m, 4 H), 7.30–7.36 (m, 3 H), 7.46–7.52 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –3.0 (q), –2.9 (q), 14.3 (q), 25.5 (t), 27.7 (t), 29.6 (d), 35.3 (t), 41.7 (d), 65.0 (t), 65.1 (t), 110.8 (s), 127.6 (d), 128.6 (d), 133.8 (d), 139.7 (s); exact mass (EI) calcd for $C_{17}H_{26}O_2Si$ $(M)^+$ 290.1702, found 290.1705.

***Trans*-3-(Ethoxydiphenylsilyl)-2-methylcyclohexan-1-one (9.1).**



5.1 **9.1**

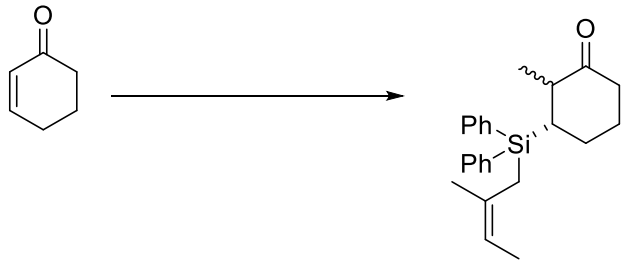
A solution of the dimethylaminodiphenylsilyl cuprate reagent was prepared as follows: Lithium wire (113 mg, 16.4 mmol) was cut into strips (ca 1 cm long), washed with dry hexane, blotted and weighed. The strips were quickly cut into small pieces (1-2 mm) and transferred to a round-bottomed flask containing Me_2NPh_2SiCl (2.16 mL, 8 mmol) in THF (16 mL) (Ar atmosphere). The mixture was stirred vigorously for 5 min and then at 0 °C for 4 h to generate a dark green solution.

Dry CuCN (kept for 12 h under oil pump vacuum, 358 mg, 4.0 mmol) was added to another flask containing THF (4 mL) and HMPA (6 mL) and the mixture was stirred and cooled (0 °C) (Ar atmosphere). The silyllithium solution was taken up into a syringe and added dropwise over ca 5 min to the stirred CuCN mixture. After the addition, stirring was continued at 0 °C for 0.5 h and then at –78 °C for 4.5 h to generate the cuprate reagent.

Cyclohex-2-en-1-one (0.43 mL, 4 mmol) in THF (5.0 mL) was added dropwise to the cooled (–78 °C) cuprate solution and stirring was continued for 1.5 h. MeI (2.5 mL, 40 mmol) was added and stirring at –78 °C was continued overnight (large silvered Dewar filled with dry ice/acetone). The mixture was then quenched with a slurry of saturated aqueous NH_4Cl (2.14 g, 40 mmol) in absolute ethanol (10 mL) and stirred at room temperature for 24 h. The mixture was then diluted with Et_2O (150 mL), washed with water (100 mL), and the organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using a 5–20% EtOAc–hexanes gradient, gave the *trans* isomer **9.1** (906 mg, 67%) as a thick oil: FTIR ($CDCl_3$,

cast) 3069, 2972, 1709, 1445 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.5 Hz, 3 H), 1.13 (t, *J* = 7 Hz, 3 H), 1.52–1.68 (m, 2 H), 1.68–1.80 (m, 1 H), 1.99 (br d, *J* = 16 Hz, 1 H), 2.06–2.15 (m, 1 H), 2.15–2.30 (m, 2 H), 2.38 (br d, *J* = 13.5 Hz, 1 H), 3.60–3.70 (m, 2 H), 7.38–7.50 (m, 6 H), 7.60–7.69 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2 (q), 18.2 (q), 26.6 (t), 30.0 (t), 33.3 (d), 42.0 (t), 45.7 (d), 59.4 (t), 127.9 (d), 128.0 (d), 130.03 (d), 130.06 (d), 133.3 (s), 133.5 (s), 135.1 (d), 135.2 (d), 214.3 (s); exact mass (ESI) *m*/*z* calcd for $C_{21}H_{26}NaO_2Si$ $(M + Na)^+$ 338.1702, found 338.1707.

***Trans*-2-Methyl-3-{[(2*Z*)-2-methylbut-2-en-1-yl]diphenylsilyl}cyclohexan-1-one (10.2).**



5.1 **10.2**

A solution of the allyl silyl cuprate reagent was prepared as follows: Lithium wire (65.5 mg, 9.5 mmol) was cut into strips (ca 1 cm), washed with dry hexane, blotted and weighed. The strips were quickly cut into pieces (1–2 mm) and transferred into a cooled (0 °C) round-bottomed flask containing chloro[(2*Z*)-2-methylbut-2-en-1-yl]diphenylsilane (**10.1**)[17] (717.5 mg, 2.5 mmol)

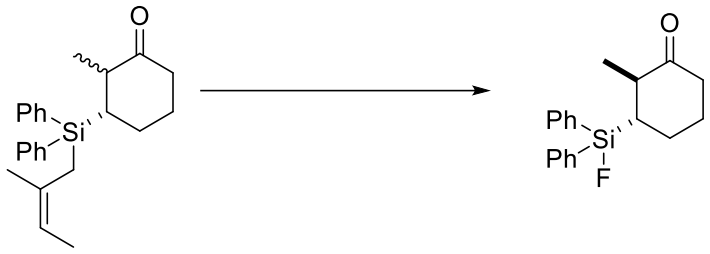
in THF (5 mL) (Ar atmosphere). The reaction mixture was stirred overnight to produce a deep dark green solution.

Dry CuCN (kept for 12 h under oil pump vacuum, 112 mg, 1.25 mmol) was added to another flask containing THF (1 mL) and the mixture was stirred and cooled (0 °C) (Ar atmosphere). The silyllithium solution was taken up into a syringe and added dropwise over ca 5 min to the stirred CuCN mixture. After the addition, stirring was continued at 0 °C for 2 h to generate the cuprate reagent.

The solution of the cuprate reagent was cooled to –78 °C, and cyclohex-2-en-1-one (0.10 mL, 1.0 mmol) was added dropwise (Ar atmosphere). Stirring was continued for 1.5 h at –78 °C. MeI (0.62 mL, 10 mmol) was then added, the cold bath was left in place, but not recharged, and stirring was continued overnight, by which time the mixture had reached room temperature. The mixture was then quenched with saturated aqueous NH_4Cl (ca 15 mL) and stirring was continued for 15 min. The mixture was then extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.3 × 18 cm), using 10% EtOAc–hexanes, gave the *trans* isomer **10.2** (355 mg, 98%) as an oil: FTIR ($CDCl_3$, cast) 3069, 2933, 1709, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, J = 7 Hz, 3 H), 1.08 (d, J = 6.5 Hz, 3 H), 1.47 (s, 3 H), 1.70–1.60 (m, 2 H), 1.82–1.70 (m, 1 H), 2.12 (d, J = 4 Hz, 2 H), 2.25–2,00 (m, 4 H), 2.39 (br d, J = 13 Hz, 1 H), 4.94 (q, J = 6.5 Hz, 1 H), 7.45–7.32 (m, 6 H), 7.62–7.54 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5 (q), 15.7 (q), 19.4 (t),

26.5 (q), 27.5 (t), 30.1 (t), 33.0 (d), 41.9 (t), 46.7 (d), 118.6 (d), 127.6 (d), 127.8 (d), 129.44 (d), 129.47 (d), 132.0 (s), 133.9 (s), 134.3 (s), 135.50 (d), 135.52 (d), 214.1 (s); exact mass (ESI) calcd for $C_{24}H_{30}NaOSi$ $(M + Na)^+$ 385.1958, found 385.1961.

***Trans*-3-(Fluorodiphenylsilyl)-2-methylcyclohexan-1-one (10.3).**



10.2 **10.3**

$BF_3 \cdot 2AcOH$ (0.51 mL, 1.98 mmol) was added to a stirred and cooled (0 °C) solution of **10.2** (240 mg, 0.66 mmol) in CH_2Cl_2 (12 mL) (Ar atmosphere). Stirring was continued for 30 min, and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (ca 20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the *trans* isomer **10.3** (196 mg, 95%) as an oil: FTIR ($CDCl_3$, cast) 3071, 2935, 1709, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, J = 6.5 Hz, 3 H), 1.62–1.82 (m, 3 H), 1.88–1.89 (m, 1 H), 2.10–2.20 (m, 1 H), 2.24–2.34 (m, 1 H), 2.37–2.48 (m, 2 H), 7.34–7.54 (m, 6 H), 7.60–7.74 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.99 (q), 15.01 (q), 26.41 (t), 26.43 (t), 29.9 (t), 33.8 (d), 33.9 (d), 41.9 (t), 45.2 (d), 128.3 (d), 130.85 (d), 130.88 (d), 131.9 (s), 132.0 (s),

132.2 (s), 132.3 (s), 134.3 (d), 134.36 (d), 134.39 (d), 134.4 (d), 213.0 (s); exact mass (EI) calcd for $C_{19}H_{21}OFSi$ $(M)^+$ 312.1346, found 312.1344.

3-Hydroxy-2-methylcyclohexan-1-one (10.4)[39] from (10.3).

10.3 **10.4**

KF (53 mg, 0.90 mmol), $NaHCO_3$ (214 mg, 2.55 mmol) and H_2O_2 (30 wt% in water, 0.25 mL, 2.40 mmol) were added sequentially to a stirred solution of **10.3** (94 mg, 0.30 mmol) in THF (2 mL) and MeOH (2 mL) (Ar atmosphere). Stirring was continued for 72 h. Without aqueous workup, silica gel (ca 1 g) was added to the reaction mixture and 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 (1.3 × 15 cm) made up with hexanes. Flash chromatography, using a 10–30% acetone-hexanes gradient, gave **10.4** (26 mg, 68%) as an oil which was a 20:1 mixture of *trans* and *cis* isomers. The material had: FTIR ($CDCl_3$, cast) 3428, 2937, 2873, 1708, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (signals of major isomer only) δ 1.17 (d, J = 6.5 Hz, 3 H), 1.48–1.60 (m, 1 H), 1.69–1.80 (m, 2 H), 1.96–2.06 (m, 1 H), 2.21–2.12 (m, 1 H), 2.23–2.33 (m, 1 H), 2.34–2.46 (m, 2 H), 3.44–3.54 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (signals of major isomer only) δ 10.8 (q), 20.8 (t), 33.8 (t), 40.4

(t), 53.9 (d), 75.9 (d), 210.4 (s); exact mass (EI) calcd for $C_7H_{12}O_2$ $(M)^+$ 128.0837, found 128.0837.

3-Hydroxy-2-methylclohex-2-en-1-one (11.2).[19]

11.1 **11.2**

3-Hydroxyclohex-2-en-1-one (13.4 g, 120 mmol) was added slowly to a solution of NaOH (4.80 g, 120 mmol) in water (24 mL) in a Morton flask at room temperature. MeI (14.9 ml, 240 mmol) was added slowly to the reaction mixture which was then stirred vigorously for 15 min, after which the stirred mixture was heated at 65 °C. After 2 days, the reaction mixture was cooled and filtered. The solids were washed with petroleum ether (2 × 30 mL) and cold water (30 mL), and dried under oil pump vacuum to give **11.2** (10.2 g, 67%) as a solid: mp 202–204 °C (lit.[19] 198-200 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 (s, 3 H), 1.80 (quintet, J = 6.5 Hz, 2 H), 2.28 (br s, 4 H), 10.3 (br s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 7.2, 20.5, 30.2 (br s), 109.5.

6-Methyl-1,4,8,11-tetraoxadispiro[4.1.4^7.3^5]tetradecane (11.3).[40]

11.2 **11.3**

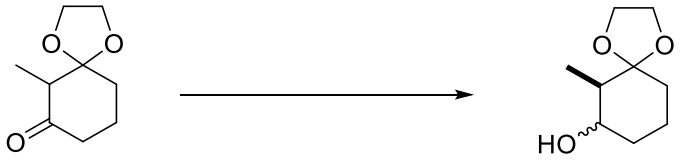
Ethylene glycol (23.0 mL, 407 mmol) and TsOH (280 mg, 1.63 mmol) were added sequentially to a solution of 3-hydroxy-2-methylclohex-2-en-1-one (10.2 g, 81.4 mmol) in C_6H_6 (250 mL). The reaction mixture was refluxed for 1 day using a Dean-Stark apparatus and then cooled to room temperature. The solvent was evaporated and the residue was dissolved in Et_2O (100 mL) and washed with water (2 × 50 mL). The organic extract was dried ($MgSO_4$) and evaporated to give **11.3** (17.4 g, 100%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.5 Hz, 3 H), 1.32–1.42 (m, 2 H), 1.53–1.65 (m, 2 H), 1.80 (dt, *J* = 13.5, 4.0 Hz, 2 H), 2.09 (q, *J* = 6.5 Hz, 1 H), 3.84–3.90 (m, 2 H), 3.90–3.98 (m, 4 H), 4.01–4.09 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.3 (q), 19.4 (t), 34.2 (t), 46.9 (d), 64.5 (t), 65.6 (t), 110.8 (s).

6-Methyl-1,4-dioxaspiro[4,5]decan-7-one (11.4).[40]

11.3 **11.4**

TsOH (149 mg, 0.86 mmol) was added to a stirred solution of **11.3** (17.4 g, 81.4 mmol) in acetone (150 mL). After 2 h, the mixture was evaporated and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give **11.4** (13.2 g, 94%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.5 Hz, 3 H), 1.67–1.92 (m, 3 H), 1.94–2.02 (m, 1 H), 2.22–2.32 (m, 1 H), 2.39–2.48 (m, 1 H), 2.73 (q, *J* = 6.5 Hz, 1 H), 3.88–4.03 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.5 (q), 20.0 (t), 34.0 (t), 39.9 (t), 54.5 (d), 65.3 (t), 65.6 (t), 111.9 (s), 209.3 (s).

6-Methyl-1,4-dioxaspiro[4,6]undecan-7-ol (11.5).[18,41]



11.4 **11.5**

$NaBH_4$ (7.35 g, 194 mmol) was added in portions over 10 min to a stirred and cooled (0 °C) solution of **11.4** (13.2 g, 77.7 mmol) in MeOH (150 mL). The reaction was monitored closely by TLC. After 1 h, all of the **11.4** and been consumed and the reaction mixture was quenched by slow addition of hydrochloric acid (6 M) until H_2 evolution stopped. The mixture was then washed with water (100 mL) and extracted with CH_2Cl_2 (5 × 150 mL). The

organic extracts were evaporated to give **11.5** (13.4 g, 100%) as an oil which was a 9.4:1 mixture of *cis* and *trans* isomers. Small samples of the individual isomers were separated. The major (*cis* isomer, less polar) isomer had: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, *J* = 7.0 Hz, 3 H), 1.32–1.47 (m, 2 H), 1.50–1.60 (m, 1 H), 1.70–1.84 (m, 3 H), 1.91 (qd, *J* = 7.0, 3.0 Hz, 1 H), 2.89 (d, *J* = 9.5 Hz, 1 H), 3.82–4.02 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.3 (q), 18.3 (t), 32.4 (t), 34.4 (t), 42.5 (d), 64.4 (t), 65.5 (t), 72.2 (d), 111.0 (s).

The minor (*trans*, more polar) isomer had: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.5 Hz, 3 H), 1.34–1.45 (m, 2 H), 1.45–1.55 (m, 1 H), 1.66–1.88 (m, 4 H), 2.32 (br s, 1 H), 3.57 (qd, *J* = 7.5, 4.0 Hz, 1 H), 3.88–4.00 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1 (q), 19.2 (t), 31.9 (t), 32.8 (t), 45.8 (d), 64.6 (t), 64.8 (t), 73.6 (d), 110.9 (s).

3-Hydroxy-2-methylcyclohexan-1-one (11.6) from (11.5).[18,39]

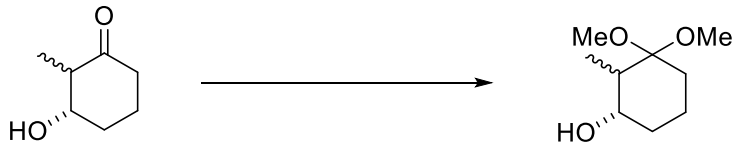
11.5 **11.6**

TsOH (136 mg, 0.77 mmol) was added to a stirred solution of **11.5** (13.4 g, 77.7 mmol) in acetone (150 mL) and stirring was continued for 28 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL), and CH_2Cl_2 (150 mL) was added. The mixture was washed with $NaHCO_3$ (150 mL)

and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 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–hexanes gradient, gave **11.6** (3.05 g, 31%) as an oil which was a 3:1 mixture of *cis* and *trans* isomers. The *cis* isomer had: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J = 7.0 Hz, 3 H), 1.53 (d, J = 3.5 Hz, 1 H), 1.85–1.95 (m, 2 H), 1.97–2.05 (m, 1 H), 2.07–2.18 (m, 1 H), 2.26–2.35 (m, 1 H), 2.39–2.46 (m, 1 H), 2.59 (qdd, J = 7.5, 3.5, 1.0 Hz, 1 H), 4.27 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (q), 21.4 (t), 32.1 (t), 41.3 (t), 50.0 (d), 74.6 (d), 211.5 (s).

The *trans* isomer had: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3 H), 1.48–1.60 (m, 1 H), 1.69–1.80 (m, 2 H), 1.96–2.06 (m, 1 H), 2.21–2.12 (m, 1 H), 2.23–2.33 (m, 1 H), 2.34–2.46 (m, 2 H), 3.44–3.54 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8 (q), 20.8 (t), 33.8 (t), 40.4 (t), 53.9 (d), 75.9 (d), 210.4 (s).

3,3-Dimethoxy-2-methylcyclohexan-1-ol (12.1).



10.4 **12.1**

Pyridinium *p*-toluenesulfonate (287 mg, 1.14 mmol) and $CH(OMe)_3$ (0.84 mL, 7.6 mmol) were added sequentially to a stirred solution of **10.4** (97

mg, 0.76 mmol) in MeOH (4.5 mL) (Ar atmosphere). After 40 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (ca 10 mL) and stirring was continued for 5 min. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to afford **12.1** (128 mg, 97%) as an oil which was a 5:1 mixture of *trans* and *cis* isomers. A small sample of the *trans* isomer was separated; it had: FTIR ($CDCl_3$, cast) 3421, 2951, 2829, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, J = 7.0 Hz, 3 H), 1.28–1.39 (m, 1 H), 1.39–1.52 (m, 2 H), 1.52–1.65 (m, 3 H), 1.65–1.72 (m, 1 H), 2.22 (dq, J = 10.5, 6.0 Hz, 1 H), 3.16 (s, 3 H), 3.18 (s, 3 H), 3.94 (ddd, J = 10.5, 9.5, 4.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8 (q), 18.9 (t), 26.3 (t), 28.8 (t), 40.4 (d), 47.2 (q), 47.7 (q), 70.3 (d), 103.3 (s); exact mass (EI) calcd for $C_9H_{18}O_3$ $(M)^+$ 174.1256, found 174.1257.

3,3-Dimethoxy-2-methylcyclohexan-1-one (12.2).

12.1 **12.2**

N-Methylmorpholine *N*-oxide (129 mg, 1.11 mmol), powdered 4Å molecular sieves (369 mg) and Pr_4NRuO_4 (26 mg, 0.074 mmol) were added sequentially to a stirred solution of **12.1** (128 mg, 0.74 mmol) in CH_2Cl_2 (1.5 mL) (Ar atmosphere). After 40 min, the reaction mixture was filtered through a short pad of silica gel and the filtrate was evaporated to give **12.2** (115 mg, 91%)

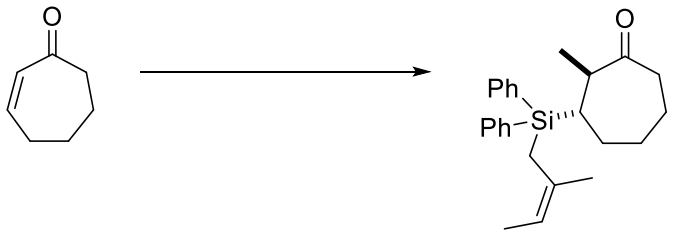
as an oil: FTIR ($CDCl_3$, cast) 2957, 2832, 1716, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7.5 Hz, 3 H), 1.56–1.67 (m, 1 H), 1.76–1.86 (m, 2 H), 1.93–2.01 (m, 1 H), 2.18–2.26 (m, 1 H), 2.46 (ddd, *J* = 15, 13, 7.0 Hz, 1 H), 2.75 (qt, *J* = 7.5, 1.5 Hz, 1 H), 3.16 (s, 3 H), 3.17 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4 (q), 19.2 (t), 26.0 (t), 36.1 (t), 47.5 (q), 47.8 (q), 51.8 (d), 103.6 (s), 211.9 (s); exact mass (EI) calcd for $C_9H_{16}O_3$ $(M)^+$ 172.1099, found 172.1096.

3-Hydroxy-2-methylcyclohex-2-en-1-one (11.2)[19] from (12.2).

12.2 **11.2**

A solution of **12.2** (115 mg, 0.67 mmol) in a 1:10 mixture (3.5 mL) of hydrochloric acid (1 M) and THF was stirred for 3.5 h. Evaporation of the solvent gave **11.2** (84 mg, 99%) as a solid: ^1H NMR (500 MHz, DMSO-d_6) δ 1.53 (s, 3 H), 1.80 (quintet, *J* = 6.5 Hz, 2 H), 2.28 (br s, 4 H), 10.3 (br s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 7.2, 20.5, 30.2 (br s), 109.5.

***Trans*-2-Methyl-3-{[(2*Z*)-2-methylbut-2-en-1-yl]diphenylsilyl}cyclo-heptan-1-one (13.2).**



13.1 **13.2**

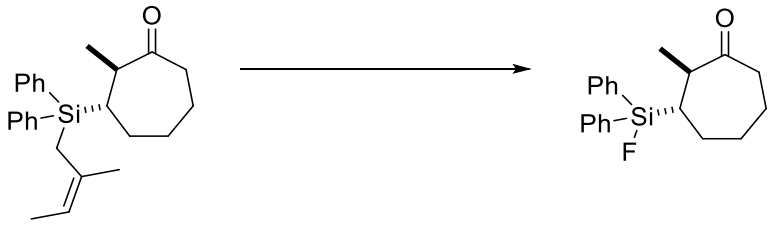
A solution of the allyl silyl cuprate reagent was prepared as follows: Lithium wire (196.6 mg, 28.5 mmol) was cut into strips (ca 1 cm), washed with dry hexane, blotted and weighed. The strips were quickly cut into pieces (1-2 mm) and transferred to a cooled (0 °C) round-bottomed flask containing allyl silane **10.1** (2.15 g, 7.5 mmol) in THF (5 mL) (Ar atmosphere). The mixture was stirred overnight to produce a dark green solution.

Dry CuCN (kept for 12 h under oil pump vacuum, 336 mg, 3.75 mmol) was added to another flask containing THF (1 mL) and the mixture was stirred and cooled (0 °C) (Ar atmosphere). The silyl lithium solution was taken up into a syringe and added dropwise over ca 5 min to the stirred CuCN mixture. After the addition, stirring was continued at 0 °C for 2 h to generate the cuprate reagent.

The solution of the cuprate reagent was cooled to –78 °C, and cyclohept-2-en-1-one (347.4 mg, 3.0 mmol) was added dropwise (Ar atmosphere). Stirring was continued for 1.5 h at –78 °C, MeI (1.89 mL, 30 mmol) was then added and stirring at –78 °C was continued overnight (large silvered Dewar filled with dry ice/acetone). The mixture was then quenched with saturated aqueous NH_4Cl (ca

25 mL) and stirring was continued for 15 min. The mixture was extracted with Et_2O (3 × 75 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using a 5–10% EtOAc–hexanes gradient, gave **13.2** (1.02 g, 90%) as an oil which was the *trans*-isomer: FTIR ($CDCl_3$, cast) 3069, 2929, 2857, 1701, 1445 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.00–1.12 (m, 1 H), 1.19 (d, J = 6.5 Hz, 3 H), 1.26–1.34 (m, 1 H), 1.36–1.46 (m, 2 H), 1.52 (s, 3 H), 1.84–2.00 (m, 2 H), 2.06–2.20 (m, 3 H), 2.22–2.30 (m, 1 H), 2.60 (dq, J = 10.5, 7.0 Hz, 1 H), 2.75 (td, J = 10.5, 3.0 Hz, 1 H), 5.01 (q, J = 6.5 Hz, 1 H), 7.30–7.42 (m, 6 H), 7.50–7.60 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7 (q), 18.7 (t), 19.2 (q), 26.2 (t), 26.6 (q), 28.5 (d), 30.0 (t), 32.1 (t), 39.2 (t), 49.9 (d), 118.6 (d), 127.7 (d), 127.8 (d), 129.4 (d), 129.5 (d), 132.3 (s), 134.7 (s), 134.8 (s), 135.4 (d), 135.5 (d), 216.7 (s); exact mass (ESI) calcd for $C_{25}H_{32}NaOSi$ $(M + Na)^+$ 399.2115, found 399.2119.

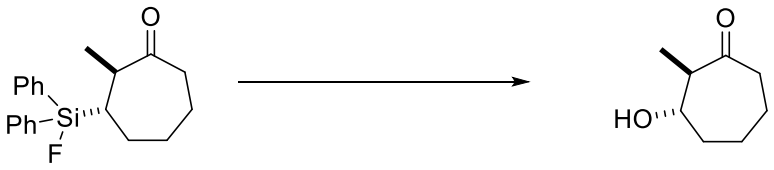
***Trans*-3-(Fluorodiphenylsilyl)-2-methylcycloheptan-1-one (13.3).**



13.2 **13.3**

$BF_3 \cdot 2AcOH$ (0.13 mL, 0.91 mmol) was added to a stirred and cooled (0 °C) solution of **13.2** (114 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) (Ar atmosphere). After 10 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (ca 10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford **13.3** (99 mg, 100%) as an oil which was the *trans*-isomer: FTIR ($CDCl_3$, cast) 3072, 2927, 1702, 1122 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (dd, J = 7.0, 1.0 Hz, 3 H), 1.04–1.20 (m, 1 H), 1.30–1.52 (m, 3 H), 1.84–1.98 (m, 2 H), 2.03 (dd, J = 15, 5.5 Hz, 1 H), 2.28–2.38 (m, 1 H), 2.67 (dq, J = 11.0, 7.0 Hz, 1 H), 2.75 (td, J = 12.0, 2.5 Hz, 1 H), 7.38–7.46 (m, 4 H), 7.46–7.52 (m, 2 H), 7.60–7.66 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.57 (q), 18.59 (q), 26.0 (t), 28.11 (t), 28.13 (t), 29.0 (d), 29.1 (d), 31.6 (t), 39.4 (t), 48.6 (d), 128.25 (d), 128.27 (d), 1130.87 (d), 130.90 (d), 131.4 (s), 131.5 (s), 132.4 (s), 132.5 (s), 134.43 (d), 134.44 (d), 134.47 (d), 216.2 (s); exact mass (ESI) calcd for $C_{20}H_{23}FNaOSi$ $(M)^+$ 349.1394, found 349.1401.

***Trans*-3-Hydroxy-2-methylcycloheptan-1-one (13.4).**[42]



13.3 **13.4**

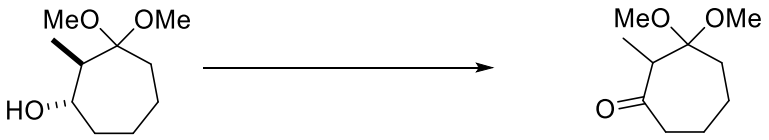
KF (51 mg, 0.87 mmol), $NaHCO_3$ (208 mg, 2.48 mmol) and H_2O_2 (30 wt% in water, 0.24 mL, 2.32 mmol) were added sequentially to a stirred solution of **13.3** (95 mg, 0.29 mmol) in a mixture of THF (2 mL) and MeOH (2 mL) (Ar atmosphere). Stirring was continued for 31 h. The reaction was quenched with solid $Na_2S_2O_3$ (2.30 g, 14.6 mmol) and stirring was continued for a further 15 min. Without aqueous workup, silica gel (ca 2 g) was added to the reaction mixture and the solvent was evaporated in vacuo at room temperature (rotary evaporator, water pump). The residue was added to the top of a column of flash chromatography silica gel (1.8 × 18 cm) made up with hexanes. Flash chromatography, using a 10–15% acetone-hexanes gradient, gave **13.4** (26.5 mg, 64%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 3431, 2934, 2863, 1695, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J = 7.0 Hz, 3 H), 1.42–1.54 (m, 1 H), 1.56 (d, J = 5.0 Hz, 1 H), 1.68–1.97 (m, 5 H), 2.42–2.55 (m, 2 H), 2.66–2.744 (m, 1 H), 3.57–3.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6 (q), 24.2 (t), 24.7 (t), 37.2 (t), 42.6 (t), 54.3 (d), 73.7 (d), 214.2 (s); exact mass (EI) calcd for $C_8H_{14}O_2$ $(M)^+$ 142.0994, found 142.0995.

***Trans*-3,3-Dimethoxy-2-methylcycloheptan-1-ol (13.5).**

13.4 **13.5**

Pyridinium *p*-toluenesulfonate (155 mg, 0.62 mmol) and $CH(OMe)_3$ (1.8 mL, 16.4 mmol) was added sequentially to a stirred solution of **13.4** (58 mg, 0.41 mmol) in MeOH (6 mL) (Ar atmosphere). After 16 h, the reaction mixture was quenched with Et_3N (0.17 mL, 1.23 mmol) and stirring was continued for 15 min. The solution was applied directly to the top of a column (1.3 × 18 cm) of flash chromatography silica gel made up with 3% Et_3N in hexanes. Flash chromatography, using 10% acetone-hexanes, gave **13.5** (63 mg, 81%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 3526, 2942, 2832, 1461, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, J = 7.5 Hz, 3 H), 1.40–1.66 (m, 3 H), 1.70–1.90 (m, 5 H), 2.38–2.46 (m, 1 H), 3.16 (s, 3 H), 3.26 (s, 3 H), 3.69–3.74 (m, 1 H), 3.76 (d, J = 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 19.5 (t), 21.1 (t), 28.7 (t), 30.7 (t), 42.2 (d), 47.7 (q), 48.3 (q), 72.6 (d), 106.7 (s); exact mass (ESI) calcd for $C_{10}H_{20}NaO_3$ $(M + Na)^+$ 211.1305, found 211.1305.

3,3-Dimethoxy-2-methylcycloheptan-1-one (13.6).

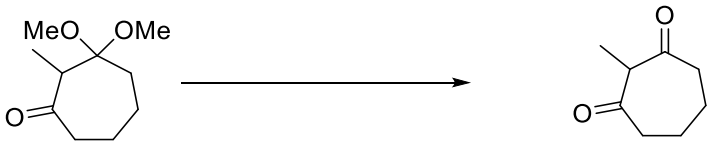


13.5 **13.6**

N-Methylmorpholine *N*-oxide (66 mg, 0.57 mmol), powdered 4Å molecular sieves (113 mg) and Pr_4NRuO_4 (8.0 mg, 0.023 mmol) were added sequentially to a stirred solution of **13.5** (43 mg, 0.23 mmol) in CH_2Cl_2 (2 mL)

(Ar atmosphere). After 40 min, the solution was applied directly onto a column of flash chromatography silica gel (1.3 × 8 cm) made up with hexanes. Flash chromatography, using 10% acetone-hexanes, gave **13.6** (41 mg, 98%) as an oil: FTIR ($CDCl_3$, cast) 2947, 2831, 1694, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, *J* = 8.0 Hz, 3 H), 1.48–1.56 (m, 1 H), 1.67–1.89 (m, 4 H), 1.98–2.06 (m, 1 H), 2.54–2.64 (m, 2 H), 2.92–3.01 (m, 1 H), 3.14 (s, 3 H), 3.20 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1 (q), 23.0 (t), 24.0 (t), 32.0 (t), 43.4 (t), 47.7 (q), 48.1 (q), 53.8 (d), 101.9 (s), 212.7 (s); exact mass (ESI) calcd for $C_{10}H_{18}NaO_3$ $(M + Na)^+$ 209.1148, found 209.1146.

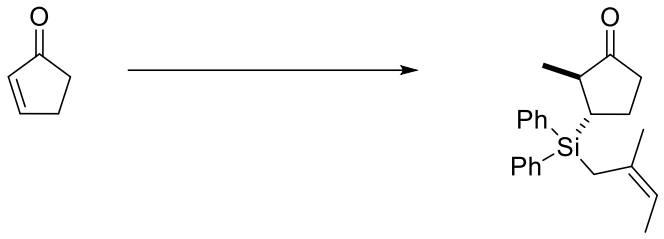
2-Methylcycloheptan-1,3-dione (13.7).[34]



13.6 **13.7**

A 1:10 mixture (0.2 mL) of hydrochloric acid (1 M) and THF was added to a stirred solution of **13.6** (41.5 mg, 0.22 mmol) in THF (2 mL). After 30 min, the solvent was evaporated to afford **13.7** (30 mg, 96%) as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, *J* = 7.0 Hz, 3 H), 1.84–1.94 (m, 2 H), 2.00–2.10 (m, 2 H), 2.46–2.55 (m, 2 H), 2.55–2.64 (m, 2 H), 3.73 (q, *J* = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2 (q), 25.8 (t), 43.4 (t), 60.9 (d), 208.0 (s).

***Trans*-2-Methyl-3-{[(2*Z*)-2-methylbut-2-en-1-yl]diphenylsilyl}cyclopentan-1-one (14.2).**



14.1 **14.2**

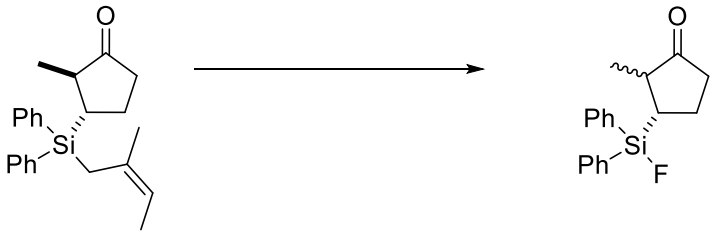
A solution of the allyl silyl cuprate reagent was prepared as follows: Lithium wire (196.6 mg, 28.5 mmol) was cut into strips (ca 1 cm), washed with dry hexane, blotted and weighed. The strips were quickly cut into small pieces (1-2 mm) and transferred into a cooled (0 °C) round-bottomed flask containing the allyl silane **10.1** (2.15 g, 7.5 mmol) in THF (15 mL) (Ar atmosphere). The mixture was stirred overnight to produce a dark green solution.

Dry CuCN (kept for 12 h under oil pump vacuum, 336 mg, 3.75 mmol) was added to another flask containing THF (5 mL) and the mixture was stirred and cooled (0 °C) (Ar atmosphere). The silyl lithium solution was taken up into a syringe and added dropwise over ca 5 min to the stirred CuCN mixture. After the addition, stirring was continued at 0 °C for 3 h to generate the cuprate reagent.

The solution of the cuprate reagent was cooled to –78 °C, and cyclopent-2-en-1-one (383.5 mg, 3.38 mmol) was added dropwise (Ar atmosphere). Stirring was continued for 4 h at –78 °C, MeI (1.89 mL, 30 mmol) was then

added and stirring at –78 °C was continued overnight (large silvered Dewar filled with dry ice/acetone). The mixture was then quenched with saturated aqueous NH_4Cl (ca 20 mL) and and stirring was continued for 15 min. The mixture was filtered through a short pad of Celite, and then extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using a 3–10% EtOAc–hexanes gradient, gave **14.2** (1.15 g, 98%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 3069, 2965, 1737, 1427 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, J = 7.0 Hz, 3 H), 1.15 (d, J = 6.5 Hz, 3 H), 1.53 (s, 3 H), 1.59–1.74 (m, 2 H), 1.78–1.86 (m, 1 H), 2.04–2.28 (m, 5 H), 4.99 (q, J = 6.5 Hz, 1 H), 7.32–7.47 (m, 6 H), 7.54–7.62 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6 (q), 15.3 (q), 18.2 (t), 23.0 (t), 26.5 (q), 29.8 (d), 37.6 (t), 46.2 (d), 118.4 (d), 127.7 (d), 127.9 (d), 129.65 (d), 129.71 (d), 131.8 (s), 133.3 (s), 133.7 (s), 135.6 (d), 222.0 (s); exact mass (ESI) calcd for $C_{23}H_{28}NaOSi$ $(M + Na)^+$ 371.1802, found 371.1801.

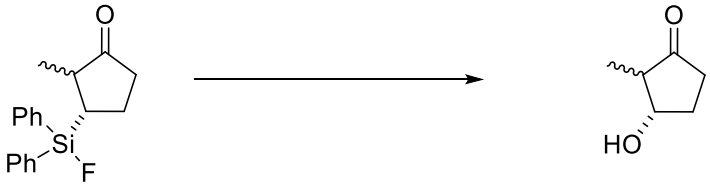
3-(Fluorodiphenylsilyl)-2-methylcyclopentan-1-one (14.3).



14.2 **14.3**

$BF_3 \cdot 2AcOH$ (0.96 mL, 6.78 mmol) was added to a stirred and cooled (0 °C) solution of **14.2** (0.79 g, 2.26 mmol) in CH_2Cl_2 (15 mL) (Ar atmosphere). After 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (ca 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford **14.3** (657 mg, 97%) as an oil which was an 11.5:1 mixture of *trans* and *cis* isomers. The material had: FTIR ($CDCl_3$, cast) 3071, 2966, 1739, 1122 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (signals of major isomer only) δ 1.07 (d, J = 7.0 Hz, 3 H), 1.66–1.90 (m, 2 H), 2.02–2.22 (m, 3 H), 2.32 (dd, J = 16.5, 9.0 Hz, 1 H), 7.36–7.55 (m, 6 H), 7.63–7.74 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) (signals of major isomer only) δ 14.80 (q), 14.81 (q), 22.0 (t), 22.1 (t), 30.6 (d), 30.7 (d), 37.61 (t), 37.62 (t), 45.0 (d), 128.28 (d), 128.32 (d), 131.01 (d), 131.02 (d), 131.03 (d), 131.04 (d), 131.4 (s), 131.5 (s), 131.7 (s), 131.9 (s), 134.30 (s), 134.32 (d), 134.4 (d), 134.5 (d), 220.94 (s), 220.95 (s); exact mass (ESI) calcd for $C_{18}H_{19}FNaOSi$ $(M + Na)^+$ 321.1081, found 321.1079.

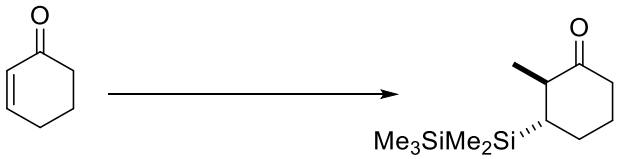
3-Hydroxy-2-methylcyclopentan-1-one (14.4).[18]



14.3 **14.4**

KF (191 mg, 3.30 mmol), $NaHCO_3$ (785 g, 9.35 mmol) and H_2O_2 (30 wt% in water, 0.90 mL, 8.80 mmol) were added sequentially to a stirred solution of **14.3** (328 mg, 1.10 mmol) in THF (5 mL) and MeOH (5 mL) (Ar atmosphere), and stirring was continued for 39 h. Without aqueous workup, silica gel (ca 2 g) was added to the reaction mixture and the solvent was evaporated in vacuo at room temperature (rotary evaporator, water pump). The residue was added to the top of a column of flash chromatography silica gel (1.8 × 18 cm) made up with hexanes. Flash chromatography, using a 10–15% acetone-hexanes gradient, gave **14.4** (44.8 mg, 36%) as an oil which was a 7:3 mixture of *trans* and *cis* isomers. The material had: FTIR ($CDCl_3$, cast) 3440, 2969, 2877, 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J = 7.0 Hz, 0.9 H), 1.14 (d, J = 7.0 Hz, 2.1 H), 1.46 (d, J = 7.5 Hz, 0.3 H), 1.80 (d, J = 7.5 Hz, 0.7 H), 1.81–1.90 (m, 0.7 H), 2.00–2.45 (m, 3.6 H), 2.51 (qdd, J = 9.5, 3.5, 1.5 Hz, 0.7 H), 3.96–4.04 (m, 0.7 H), 4.50 (br s, 0.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8 (q), 11.8 (q), 29.8 (t), 30.0 (t), 33.9 (t), 36.1 (t), 50.0 (d), 52.5 (d), 72.7 (d), 76.6 (d), 217.5 (s), 218.7 (s); exact mass (EI) calcd for $C_6H_{10}O_2$ $(M)^+$ 114.0681, found 114.0680.

Trans-2-Methyl-3-(pentamethyldisilan-1-yl)cyclohexan-1-one (15.1).



5.1 **15.1**

MeLi (1.6 M in Et_2O, 1.88 mL, 3.0 mmol) was added slowly to a stirred and cooled (0 °C) solution of $Me_3SiSiMe_3$ (1.25 mL, 6.0 mmol) in HMPA (4.0 mL) (Ar atmosphere). After 30 min, the reaction mixture was diluted in a dropwise manner with THF (12.0 mL) over 30 min and the solution was then cooled to –78 °C. Cyclohex-2-en-1-one (0.16 mL, 1.5 mmol) was added dropwise over 30 min, and stirring was continued for 1 h. MeI (1.02 mL, 15.0 mmol) in THF (3 mL) was then added slowly to the reaction mixture, the cold bath was left in place, but not recharged, and stirring was continued for 5 h during which time the mixture reached room temperature. The mixture was quenched with saturated aqueous NH_4Cl (ca 3 ml) and stirring was continued for 5 min. The mixture was then washed with water (20 mL) and extracted with Et_2O (3 × 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% EtOAc–hexanes gradient, gave **15.1** (321 mg, 88%) as an oil which was the *trans*-isomer: FTIR ($CDCl_3$, cast) 2948, 2894, 1711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06–0.18 (m, 15 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.00–1.08 (m, 1 H), 1.57 (qd, J = 12.5, 4.0 Hz, 1 H), 1.73 (qt, J = 12.5, 4.0 Hz, 1 H), 1.82–1.90 (m, 1 H), 2.12–2.20 (m, 1 H), 2.27–2.39 (m, 2 H), 2.39–2.46 (dm, J = 13.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –3.8 (q), –3.6 (q), –1.3 (q), 15.2 (q), 28.3 (t), 30.5 (t), 35.1 (d), 41.9 (t), 47.3 (d), 214.3 (s); exact mass (EI) calcd for $C_{11}H_{23}OSi_2$ $(M - CH_3)^+$ 227.1288, found 127.1285.

1,1,1,2,2-Pentamethyl-2-[*trans*-6-methyl-1,4-dioxaspiro[4,5]decan-7-yl]disilane (15.2).

15.1 **15.2**

Ethylene glycol (0.46 mL, 8.16 mmol) and TsOH (7.0 mg, 0.04 mmol) were added sequentially to a solution of **15.1** (99 mg, 0.41 mmol) in C_6H_6 (4 mL). The solution was refluxed for 4.5 h, using a Dean-Stark apparatus. The solution was cooled, quenched with saturated aqueous $NaHCO_3$ (ca 20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford **15.2** (107 mg, 91%) as an oil which was a 5:1 mixture of *trans* and *cis* isomers. The material had: FTIR ($CDCl_3$, cast) 2943, 2882, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (signals of major isomer only) δ 0.01–0.18 (m, 15 H), 0.87–0.94 (m, 3 H), 0.94–1.01 (m, 1 H), 1.07–1.20 (m, 1 H), 1.33 (td, J = 13.5, 4.0 Hz, 1 H), 1.44–1.55 (m, 1 H), 1.64–1.76 (m, 3 H), 1.81 (br d, J = 13 Hz, 1 H), 3.87–4.03 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) (signals of major isomer only) δ –3.6 (q), –3.4 (q), –1.2 (q), 14.36 (q), 25.7 (t), 28.6 (t), 30.1 (d), 35.4 (t), 42.5 (d), 64.9 (t), 65.1 (t), 110.8 (s); exact mass (EI) calcd for $C_{13}H_{27}O_2Si_2$ $(M - CH_3)^+$ 271.1550, found 271.1550.

6-Methyl-1,4-dioxaspiro[4,5]decan-7-ol (15.3).[41]

15.2 **15.3**

Bu_4NF (1.0 M in THF, 1.80 mL, 1.80 mmol) was added slowly to a stirred solution of **15.2** (85.8 mg, 0.30 mmol) in THF (5.0 mL) (Ar atmosphere) and stirring was continued for 15 min. MeOH (5.0 mL), H_2O_2 (30 wt% in water, 0.73 mL, 7.18 mmol) and $KHCO_3$ (119.7 mg, 1.20 mmol) were added sequentially and stirring was continued for 23 h. Without aqueous workup, silica gel (ca 2 g) was added to the reaction mixture and 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 × 18 cm) made up with hexanes. Flash chromatography, using a 3–10% acetone–hexanes gradient, gave **15.3** (37 mg, 71%) as an oil which was the *trans* isomer containing a trace of the *cis* isomer: FTIR ($CDCl_3$, cast) 3415, 2940, 2883, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 7.0 Hz, 3 H), 1.34–1.45 (m, 2 H), 1.45–1.56 (m, 1 H), 1.67–1.81 (m, 3 H), 1.81–1.88 (m, 1 H), 2.33 (br s, 1 H), 3.53–3.61 (m, 1 H), 3.88–4.00 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1 (q), 19.2 (t), 31.9 (t), 32.8 (t), 45.8 (d), 64.6 (t), 64.8 (t), 73.6 (d), 111.0 (s); exact mass (EI) calcd for $C_9H_{16}O_3$ $(M)^+$ 172.1099, found 172.1100.

6-Methyl-1,4-dioxaspiro[4,5]decan-7-one (11.4).[40]

15.3 **11.4**

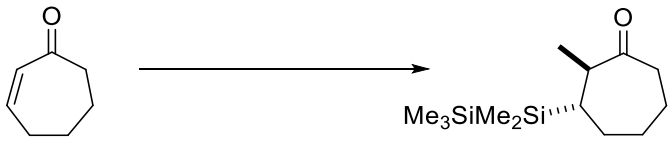
N-Methylmorpholine *N*-oxide (96.7 mg, 0.83 mmol), powdered 4Å molecular sieves (275 mg) and Pr_4NRuO_4 (19.3 mg, 0.055 mmol) were added sequentially to a stirred solution of **15.3** (94.8 mg, 0.55 mmol) in CH_2Cl_2 (8 mL) (Ar atmosphere). After 20 min, the solution was applied directly to a column of flash chromatography silica gel (1.3 × 8 cm) made up with hexanes. Flash chromatography, using 10% acetone-hexanes, gave **11.4** (89.3 mg, 95%) as an oil: FTIR ($CDCl_3$, cast) 2948, 2884, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 6.5 Hz, 3 H), 1.68–1.91 (m, 3 H), 1.99–2.02 (m, 1 H), 2.22–2.32 (m, 1 H), 2.40–2.48 (m, 1 H), 2.73 (q, J = 7.0 Hz, 1 H), 3.88–4.03 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.5 (q), 20.0 (t), 34.0 (t), 39.9 (t), 54.4 (d), 65.3 (t), 65.6 (t), 111.9 (s), 209.3 (s); exact mass (EI) calcd for $C_9H_{14}O_3$ $(M)^+$ 170.0943, found 170.0941.

3-Hydroxy-2-methylcyclohex-2-en-1-one (11.2)[19] from (11.4).

11.4 **11.2**

A 1:10 mixture (0.3 mL) of hydrochloric acid (1 M) and THF was added to a stirred solution of **11.4** (51 mg, 0.30 mmol) in THF (3 mL) and stirring was continued for 10 h. Without aqueous workup, silica gel (ca 1 g) was added to the reaction mixture and the solvent was evaporated in vacuo at room temperature (rotary evaporator, water pump). The residue was added to the top of a column of flash chromatography silica gel (1.5 × 15 cm) made up with hexanes. Flash chromatography, using a 10–20% acetone-hexanes gradient, gave **11.2** [22.2 mg, 58%, 78% corrected for recovered **11.4** (12.9 mg)]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 (s, 3 H), 1.80 (quintet, J = 6.5 Hz, 2 H), 2.28 (br s, 4 H), 10.3 (br s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 7.2, 20.5, 30.2 (br s), 109.5.

***Trans*-2-Methyl-3-(pentamethyldisilan-1-yl)cycloheptan-1-one (17.1).**



13.1 **17.1**

MeLi (1.6 M in Et_2O, 4.45 mL, 7.12 mmol) was added slowly to a stirred and cooled (0 °C) solution of $Me_3SiSiMe_3$ (2.97 mL, 14.2 mmol) in dry HMPA (9.5 mL) (Ar atmosphere). After 40 min, the reaction mixture was diluted over 40 min in a dropwise manner with THF (12.0 mL) and the solution was cooled to –78 °C. Cyclohept-2-en-1-one (392 mg, 3.56 mmol) was added slowly and stirring was continued for 30 min. MeI (2.24 mL, 35.6 mmol) in THF (7 mL) was added slowly and, after 20 min, the cooling bath was replaced with an ice bath and stirring was continued for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (ca 5 ml) and stirring was continued for 5 min. The mixture was diluted with water (40 mL) and extracted with Et_2O (3 × 50 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 1–5% EtOAc–hexanes gradient, gave **17.1** (779 mg, 85%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 2948, 2852, 1703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02–0.16 (m, 15 H), 0.69 (t, J = 10 Hz, 1 H), 0.96–1.07 (m, 1 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.23–1.35 (m, 1 H), 1.44 (qt, J = 13, 3.0 Hz, 1 H), 1.76–1.98 (m, 3 H), 2.22–2.32 (m, 1 H), 2.46 (dq, J = 10.5, 7.0 Hz, 1 H), 2.69 (td, J = 12, 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.5 (q), –3.2 (q), –1.4 (q), 19.1 (q), 26.1 (t), 29.6 (d), 30.1 (t), 32.1 (t), 39.2 (t), 50.2 (d), 216.9 (s); exact mass (EI) calcd for $C_{12}H_{25}OSi_2$ $(M - CH_3)^+$ 241.1444, found 241.1444.

1,1,1,2,2-Pentamethyl-2-[*trans*-6-methyl-1,4-dioxaspiro[4,6]undecan-7-yl]disilane (17.2).

17.1 **17.2**

Ethylene glycol (0.70 mL, 12.3 mmol) and TsOH (10.6 mg, 0.062 mmol) were added sequentially to a solution of **17.1** (158 mg, 0.616 mmol) in C_6H_6 (6 mL) and the mixture was refluxed for 23 h, using a Dean-Stark apparatus. The solution was cooled, quenched with saturated aqueous $NaHCO_3$ (ca 10 mL) and water (20 mL), and extracted with Et_2O (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 1–5% EtOAc–hexanes gradient, gave **17.2** (154 mg, 83%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 2945, 2683, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ –0.10–0.20 (m, 15 H), 0.52–0.64 (m, 1 H), 1.01 (d, J = 7.0 Hz, 3 H), 1.08–1.20 (m, 1 H), 1.42–1.58 (m, 2 H), 1.58–1.68 (m, 3 H), 1.80–1.92 (m, 3 H), 3.80–3.95 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.5 (q), –3.9 (q), –1.3 (q), 20.6 (q), 23.6 (t), 28.9 (t), 31.8 (d), 32.6 (t), 33.3 (t), 42.4 (d), 63.5 (t), 64.4 (t), 114.4 (s); exact mass (EI) calcd for $C_{14}H_{29}O_2Si_2$ $(M - CH_3)^+$ 285.1706, found 285.1699.

***Trans*-6-Methyl-1,4-dioxaspiro[4,6]undecan-7-ol (17.3).**

17.2 **17.3**

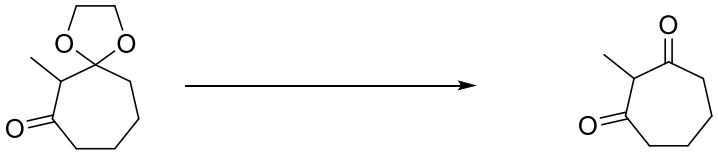
Bu_4NF (1.0 M in THF, 2.56 mL, 2.56 mmol) was slowly added to a stirred solution of **17.2** (133 mg, 0.44 mmol) in THF (4.0 mL) (Ar atmosphere) and stirring was continued for 30 min. MeOH (4.0 mL), H_2O_2 (30 wt% in water, 1.08 mL, 10.6 mmol) and $KHCO_3$ (176 mg, 1.76 mmol) were added sequentially and stirring was continued for 23 h. The reaction mixture was evaporated. Et_2O (ca 10 mL) and silica gel (ca 2 g) were added and 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 (1.5 × 15 cm) made up with hexanes. Flash chromatography, using a 10–15% acetone–hexanes gradient, gave **17.3** (56.8 mg, 69%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 3434, 2933, 2692, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 7.0 Hz, 3 H), 1.44–1.57 (m, 2 H), 1.61–1.74 (m, 2 H), 1.74–1.94 (m, 4 H), 2.04–2.14 (m, 1 H), 3.03 (d, J = 7.0 Hz, 1 H), 3.64 (d, J = 6.0 Hz, 1 H), 3.84–4.04 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (q), 20.8 (t), 22.0 (t), 33.3 (t), 33.4 (t), 47.6 (d), 64.1 (t), 64.6 (t), 76.8 (d), 113.8 (s); exact mass (EI) calcd for $C_{10}H_{18}O_3$ $(M)^+$ 186.1256, found 186.1257.

6-Methyl-1,4-dioxaspiro[4,6]undecan-7-one (17.4).

17.3 **17.4**

N-Methylmorpholine *N*-oxide (44.4 mg, 0.38 mmol), powdered 4Å molecular sieves (127 mg) and Pr_4NRuO_4 (8.9 mg, 0.025 mmol) were added sequentially to a stirred solution of **17.3** (47.2 mg, 0.253 mmol) in CH_2Cl_2 (5 mL) (Ar atmosphere). After 25 min, the solution was applied directly to the top of a column of flash chromatography silica gel (1.3 × 8 cm) made up with hexanes. Flash chromatography, using 10% acetone-hexanes, gave **17.4** (44 mg, 94%) as an oil: FTIR ($CDCl_3$, cast) 2980, 2886, 1703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7.0 Hz, 3 H), 1.60–1.86 (m, 5 H), 1.92–2.02 (m, 1 H), 2.48–2.64 (m, 2 H), 2.96 (q, *J* = 7.0 Hz, 1 H), 3.86–4.02 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (q), 23.9 (t), 24.0 (t), 37.6 (t), 43.1 (t), 55.6 (d), 64.7 (t), 65.1 (t), 109.4 (s), 212.4 (s); exact mass (EI) calcd for $C_{10}H_{16}O_3$ $(M)^+$ 184.1099, found 184.1099.

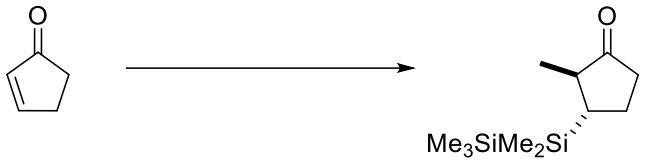
2-Methylcycloheptan-1,3-dione (13.7).[34]



17.4 **13.7**

A 1:10 mixture (1.0 mL) of hydrochloric acid (1 M) and THF was added to a stirred solution of **17.4** (40.7 mg, 0.22 mmol) in THF (3 mL). The mixture was refluxed for 17 h and then cooled to room temperature. Silica gel (ca 1 g) was added to the mixture and the solvent was evaporated in vacuo at room temperature (rotary evaporator, water pump). The residue was added to the top of a column of flash chromatography silica gel (1.5 × 10 cm) made up with hexanes. Flash chromatography, using a 5–10% acetone-hexanes gradient, gave **13.7** [22 mg, 71% or 82% corrected for recovered **17.4** (5.4 mg)] as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, J = 7.0 Hz, 3 H), 1.84–1.94 (m, 2 H), 2.00–2.10 (m, 2 H), 2.46–2.55 (m, 2 H), 2.55–2.64 (m, 2 H), 3.73 (q, J = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2 (q), 25.8 (t), 43.4 (t), 60.9 (d), 208.0 (s).

***Trans*-2-Methyl-3-(pentamethyldisilan-1-yl)cyclopentan-1-one (18.1).**

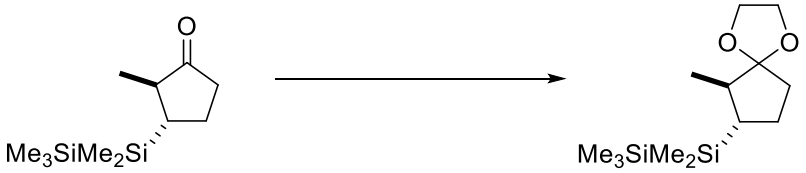


14.1 **18.1**

MeLi (1.6 M in Et_2O, 1.88 mL, 3.0 mmol) was added slowly to a stirred and cooled (0 °C) solution of $Me_3SiSiMe_3$ (1.25 mL, 6.0 mmol) in dry HMPA (4.0 mL) (Ar atmosphere). After 30 min, the reaction mixture was diluted over 40 min in a dropwise manner with THF (12.0 mL) and the orange solution was then cooled to –78 °C. Cyclopent-2-en-1-one (0.15 mL, 1.5 mmol) was added

dropwise over ca 5 min and stirring was continued for 1 h. MeI (1.02 mL, 15.0 mmol) in THF (3 mL) was added slowly, the cold bath was left in place, but not recharged, and stirring was continued for 3 h during which time the mixture reached room temperature. The mixture was quenched with saturated aqueous NH_4Cl (ca 3 ml) and stirring was continued for 5 min. The mixture was then washed with water (30 mL) and extracted with Et_2O (3 × 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 10% EtOAc–hexanes, gave **18.1** (322 mg, 94%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 2952, 2894, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06–0.14 (m, 15 H), 1.00–1.10 (m, 1 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.54–1.66 (m, 1 H), 1.91 (sextet, J = 6.5 Hz, 1 H), 1.99–2.08 (m, 1 H), 2.08–2.18 (m, 1 H), 2.33 (dd, J = 19, 8.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.5 (q), –4.9 (q), –1.5 (q), 15.1 (q), 23.9 (t), 31.6 (d), 38.2 (t), 46.7 (d), 222.6 (s); exact mass (EI) calcd for $C_{11}H_{24}OSi_2$ $(M)^+$ 228.1366, found 228.1365.

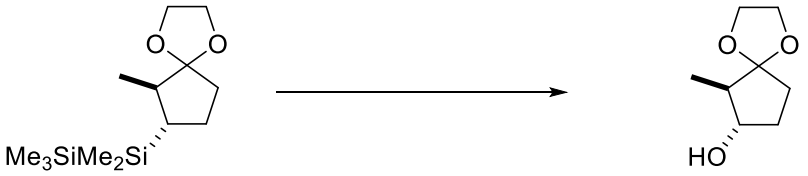
1,1,1,2,2-Pentamethyl-2-[*trans*-6-methyl-1,4-dioxaspiro[4,4]nonan-7-yl]disilane (18.2).



18.1 **18.2**

Ethylene glycol (1.24 mL, 22.1 mmol) and TsOH (19 mg, 0.11 mmol) were added sequentially to a solution of **18.1** (253 mg, 1.11 mmol) in C_6H_6 (10 mL). The solution was refluxed for 6 h, using a Dean-Stark apparatus. The solution was cooled, quenched with saturated aqueous $NaHCO_3$ (ca 20 mL) and water (ca 10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford **18.2** (285 mg, 95%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 2951, 2879, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02–0.12 (m, 15 H), 0.86–1.00 (m, 1 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 1.40–1.51 (m, 1 H), 1.68–1.81 (m, 3 H), 1.84–1.92 (m, 1 H), 3.82–3.98 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.7 (q), –4.8 (q), –1.5 (q), 14.5 (q), 24.4 (t), 30.4 (d), 36.2 (t), 43.5 (d), 64.6 (t), 64.8 (t), 119.2 (s); exact mass (EI) calcd for $C_{12}H_{25}O_2Si_2$ $(M - CH_3)^+$ 257.1393, found 257.1393.

***Trans*-6-Methyl-1,4-dioxaspiro[4.4]nonan-7-ol (18.3).**[41]

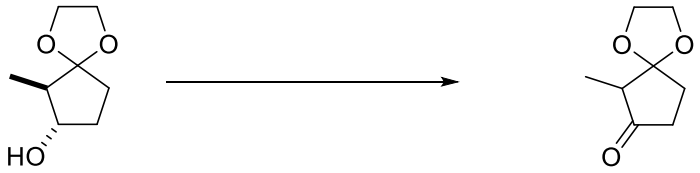


18.2 **18.3**

Bu_4NF (1.0 M in THF, 1.10 mL, 1.10 mmol) was slowly added to a stirred solution of **18.2** (50.1 mg, 0.184 mmol) in THF (4.0 mL) (Ar atmosphere). After 20 min MeOH (4.0 mL), H_2O_2 (30 wt% in water, 0.45 mL, 4.42 mmol) and $KHCO_3$ (74 mg, 0.74 mmol) were added sequentially and

stirring was continued for 20 h. Without aqueous workup, silica gel (ca 1 g) was added to the reaction mixture and 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 (1.3 × 15 cm) made up with hexanes. Flash chromatography, using a 10–20% acetone–hexanes gradient, gave **18.3** (20.6 mg, 70%) as an oil which was the *trans* isomer: FTIR ($CDCl_3$, cast) 3425, 2968, 1457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, J = 7.0 Hz, 3 H), 1.56–1.66 (m, 1 H), 1.81 (ddd, J = 13.5, 10.0, 7.0 Hz, 1 H), 1.88–2.00 (m, 2 H), 2.02–2.15 (m, 2 H), 3.81 (br s, 1 H), 3.85–3.96 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5 (q), 30.9 (t), 31.1 (t), 49.0 (d), 64.4 (t), 64.8 (t), 77.5 (d), 116.8 (s); exact mass (EI) calcd for $C_8H_{14}O_3$ $(M)^+$ 158.0943, found 158.0943.

6-Methyl-1,4-dioxaspiro[4.4]nonan-7-one (18.4).[43]



18.3 **18.4**

N-Methylmorpholine *N*-oxide (67.6 mg, 0.58 mmol), powdered 4Å molecular sieves (193 mg) and Pr_4NRuO_4 (TPAP, 13.5 mg, 0.0385 mmol) were added sequentially to a stirred solution of **18.3** (60.9 mg, 0.385 mmol) in CH_2Cl_2 (6 mL) (Ar atmosphere). After 30 min, the solution was applied directly to the top of a column of flash chromatography silica gel (1.5 × 6 cm) made up with

hexanes. Flash chromatography, using 15% acetone-hexanes, gave **18.4** (46.5 mg, 77%) as an oil: FTIR ($CDCl_3$, cast) 2979, 2886, 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 7.0 Hz, 3 H), 2.04 (dt, J = 13.5, 10.5 Hz, 1 H), 2.12–2.20 (m, 1 H), 2.30–2.40 (m, 1 H), 2.42–2.51 (m, 2 H), 3.97–4.07 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.2 (q), 32.1 (t), 36.6 (t), 51.6 (d), 65.2 (t), 65.4 (t), 114.4 (s), 215.5 (s); exact mass (EI) calcd for $C_8H_{12}O_3$ $(M)^+$ 156.0786, found 156.0787.

3-Hydroxy-2-methylcyclopent-2-en-1-one (18.5).[44]

18.4 **18.5**

A 1:10 mixture (1.0 mL) of hydrochloric acid (1 M) and THF was added to a stirred solution of **18.4** (40.5 mg, 0.26 mmol) in THF (5 mL) and stirring was continued for 2.5 h. Without aqueous workup, silica gel (ca 1 g) was added to the reaction mixture and the solvent was evaporated in vacuo at room temperature (rotary evaporator, water pump). The residue was added to the top of a column of flash chromatography silica gel (1.3 × 10 cm) made up with hexanes. Flash chromatography, using a 30–50% acetone-hexanes gradient, gave **18.5** (20.6 mg, 71%) as a solid: mp 208–210 °C (lit.[38] 214–216 °C); ^1H

NMR (500 MHz, DMSO-d_6) δ 1.46 (s, 3 H), 2.33 (s, 4 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 5.8, 30.0, 111.5.

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Chapter 2

Formation of *meta*-Substituted Phenols by Transition Metal-free Aromatization

1 INTRODUCTION

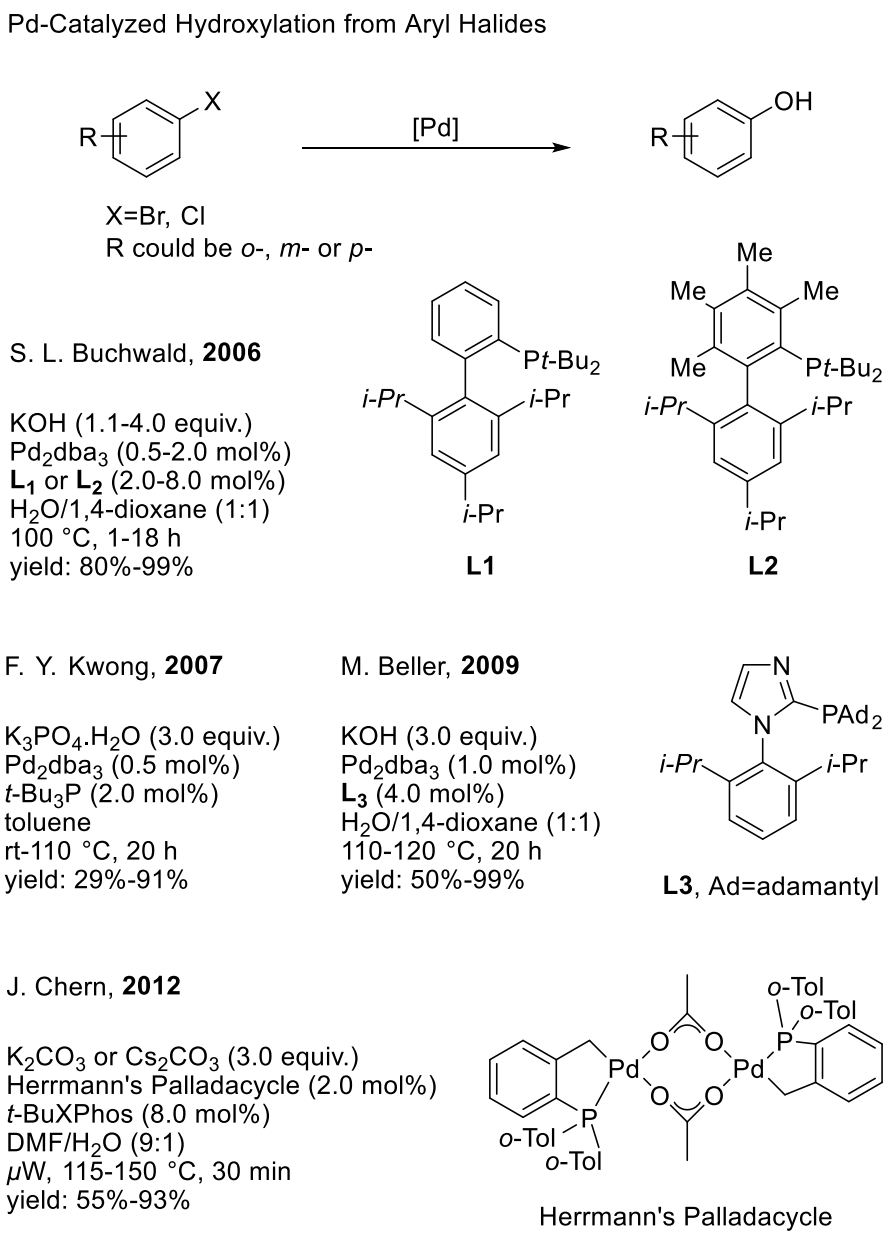
1.1 General

Phenols are firmly established as an important compound class.[1] In particular, the preparation of *meta*-substituted phenols has been the interest of chemists, partly in response to the chemical challenge of bypassing the classic *ortho*/*para* directing effect of the phenolic hydroxy group and partly because phenolic structures are important building blocks of useful pharmaceuticals and polymers.[1,2] Herein, a number of recent methods of making *meta*-substituted phenols are described.

1.2 Formation of *meta*-substituted phenols via transition metal catalysis

1.2.1 Pd-Catalyzed hydroxylation of aryl halides

Palladium has been used in the direct hydroxylation of aryl halides (Scheme 1). The groups of Buchwald (2006)[3] and Kwong (2007)[4] have independently disclosed an unprecedented direct transformation of aryl halides into the corresponding substituted phenols, including *meta*-substituted phenols using Pd-catalyzed C–O bond formation. Later on in 2009, Beller's group[5] developed a new practical imidazole-based phosphine ligand that is readily accessible and scalable for this Pd-catalyzed hydroxylation. In another study by Chern's group (2012),[6] an efficient protocol utilizing microwave irradiation successfully shortened the reaction time from the previously 1–20 h to 30 min.

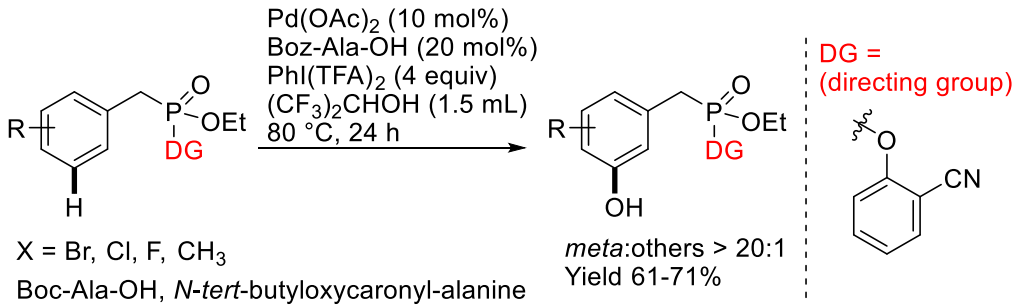


Scheme 1.

1.2.2 Pd-Catalyzed meta-selective C-H hydroxylation

The groups of Bera and Maiti (2016)[7] showed a template-based directing group-assisted approach to *meta*-selective hydroxylation of arenes under mild

oxidizing condition. The hydroxy group was generated by using $PhI(TFA)_2$ as the hydroxylating agent followed by *in situ* hydrolysis.

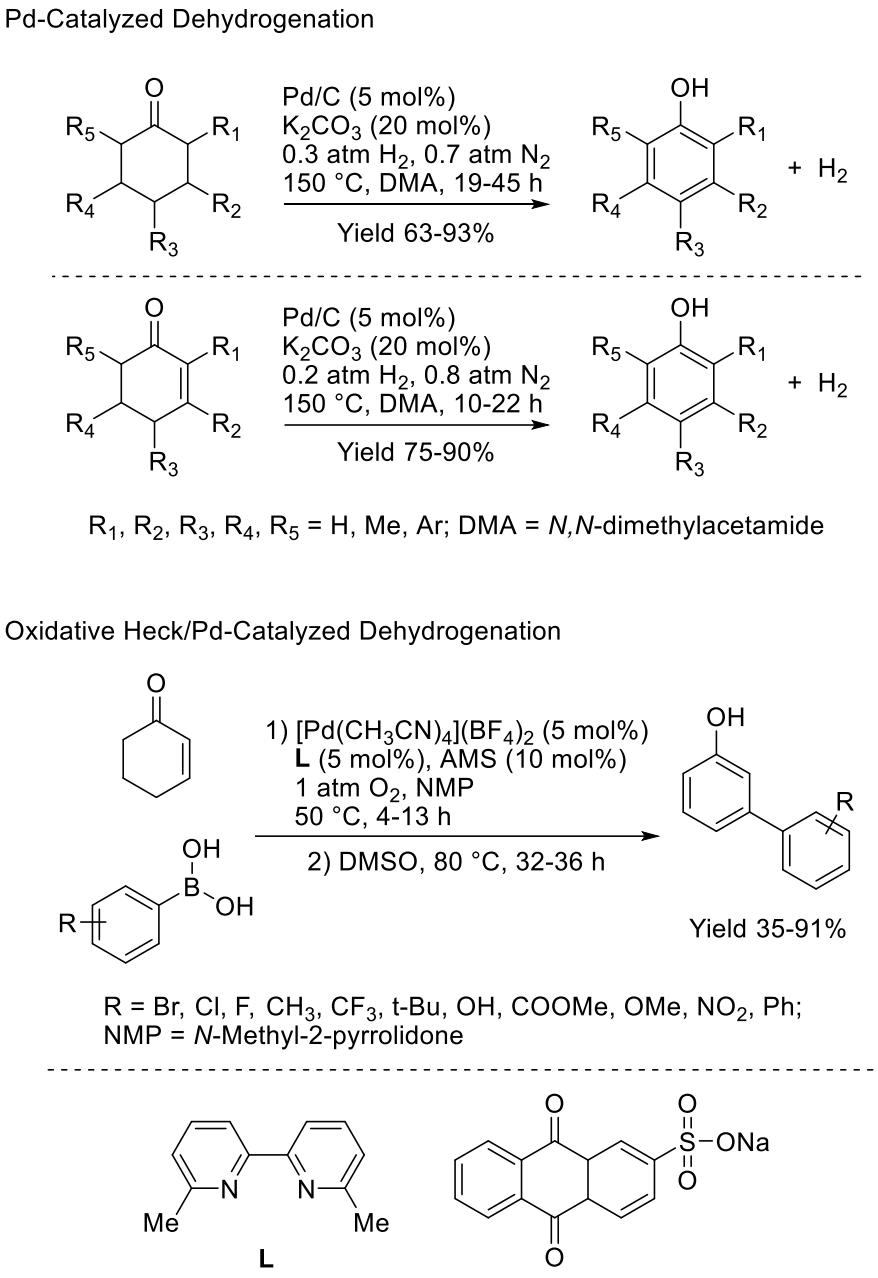


Scheme 2.

1.2.3 Pd-Catalyzed dehydrogenation

Liu's group (2015)[8] reported an oxidant-free dehydrogenation of cyclohexanones and 2-cyclohexenones to the corresponding phenols with H_2 as the only byproduct. The *meta*-substituents are pre-installed. The reaction is catalyzed by Pd/C in combination with H_2 at 150 °C.

Stahl and his co-workers (2013)[9] developed a one-pot aerobic oxidative Heck/dehydrogenation sequence to achieve coupling between a cyclohexenone and a boronic acid in a *meta*-selective fashion. The following dehydrogenation utilized the Pd catalyst in the Heck coupling to furnish the *in situ* aromatization.

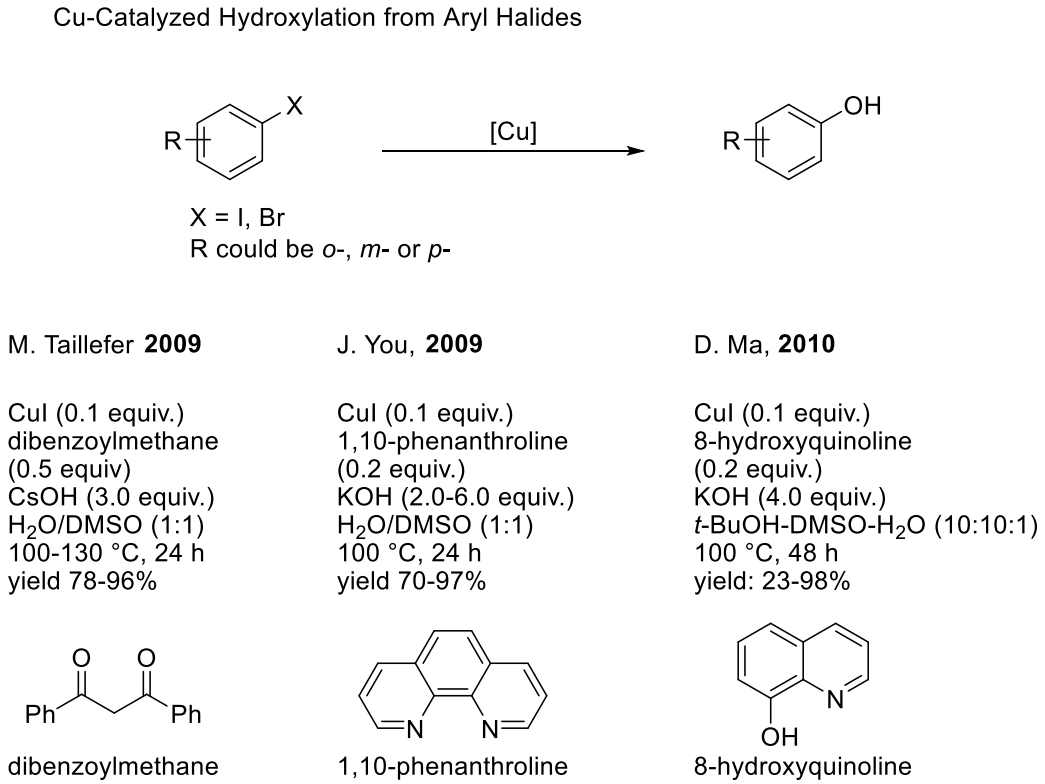


Scheme 3.

1.2.4 Cu-Catalyzed hydroxylation of aryl halides

The direct hydroxylation of aryl halides using Cu (Scheme 4) which has been developed by the groups of Taillefer (2009),[10] You (2009)[11] and Ma (2010)[12] serves as a lower cost route to *meta*-substituted phenols than one based

on Pd-catalyzed hydroxylation. An aryl iodide or bromide is required under relatively mild reaction conditions and with easily accessible ligands. Taillefer's study also demonstrated that without Cu and ligand, the yield (7-27%) for the conversion to phenols is much lower than in the normal Cu-catalyzed conditions (78-96%).

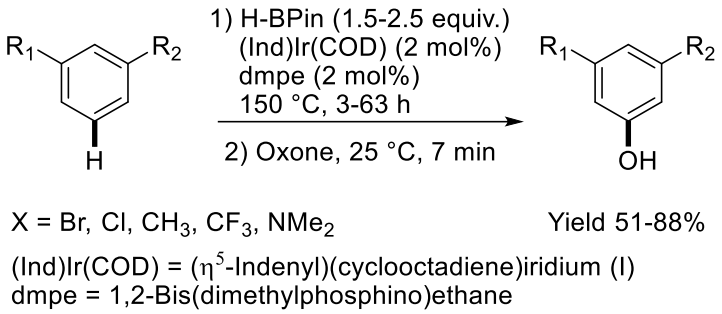


Scheme 4.

1.2.4 Ir-Catalyzed C-H activation/borylation/oxidation to meta-substituted phenols

A one-pot route to *meta*-substituted phenols bearing *ortho*/*para* directing groups has been developed by the groups of Maleczka and Smith.[13] The

protocol incorporates a sterically controlled Ir-catalyzed aromatic borylation and the *in situ* Oxone oxidation of the resulting arylboronic esters.

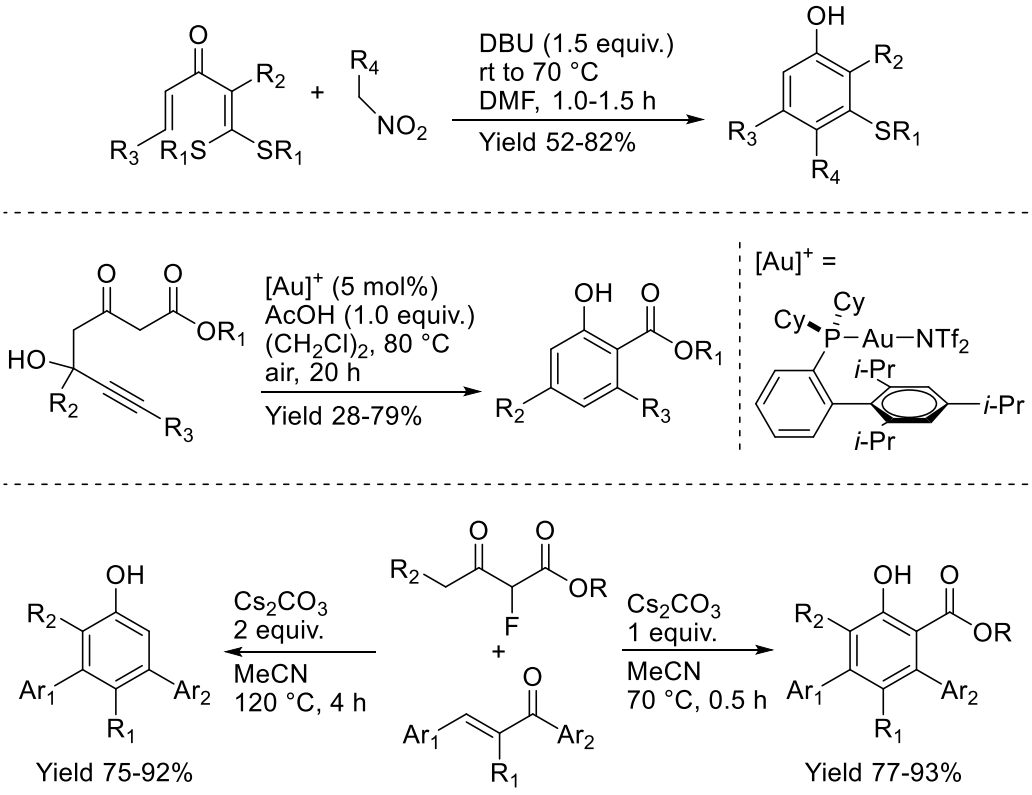


Scheme 5.

1.3 Formation of *meta*-substituted phenols via acyclic precursors

Alternative synthetic methods using acyclic precursors have been developed over the past few years. Some representative methods are listed in the Scheme 6. The groups of Dong and Liu (2005)[14] developed a [5 +1] annulation strategy for the synthesis of highly substituted phenols. Chan (2014)[15] reported a method to prepare phenolic esters via gold(I)-catalyzed benzannulation. In another study by Yi and Zhang's group (2015),[16] 3,5-disubstituted and polysubstituted phenols were synthesized through a one-pot Robinson annulation of α,β-unsaturated ketones with α-fluoro-β-ketoesters followed by *in situ* dehydrofluorination and tautomerization.

Aromatization to *meta*-Substituted Phenols via Acyclic Precursors

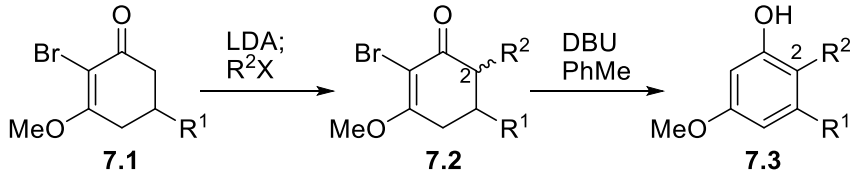


Scheme 6.

2. RESULTS AND DISCUSSION

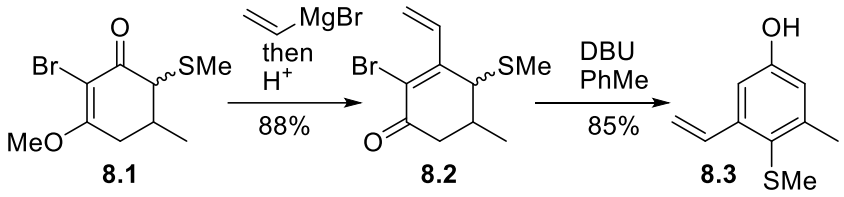
2.1 Research objectives

Previous work[16] from this laboratory has described the aromatization of bromoenones **7.1** into phenols. The bromoenones were initially[16b] converted into their kinetic enolates and alkylated (Scheme 7, **7.1**→**7.2**, 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[16c] 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, 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 (**7.2**→**7.3**).



Scheme 7.

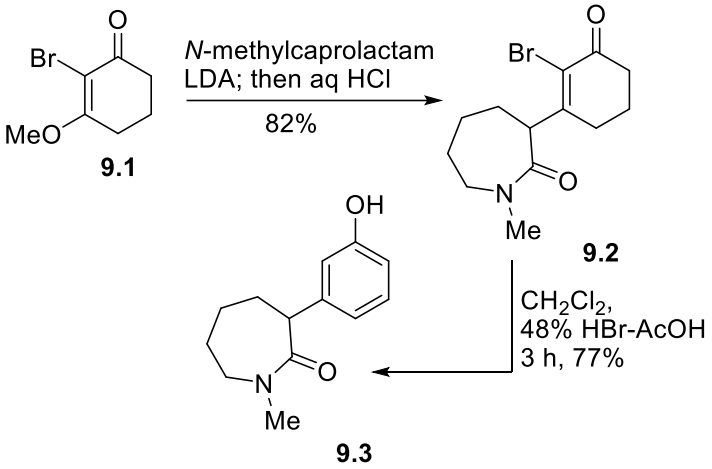
Among the many examples described was one case[16c] (Scheme 8) in which the particular bromoenone **8.1**, bearing a SMe group, was treated with vinylmagnesium bromide to afford **8.2**. On reaction with DBU it gave **8.3**, in which the substituent that had been introduced by Grignard addition is *meta* to the phenolic hydroxyl.



Scheme 8.

While the organometallic addition and acid treatment sequence applied to *non*-halogenated 3-alkoxycyclohex-2-en-1-ones is the classical Stork-Danheiser experiment,[17] we are aware of only a few cases[18] in which the starting cyclohexenone carried a halogen at C-2 and of these, only the work of Sheppard and White[18a,c] (Scheme 9) constitutes a realistic analogy to the method we have studied because their intermediate bromoenones (e.g. **9.2**, Scheme 9) 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 the one reported from this laboratory.

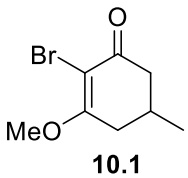


Scheme 9.

We have now explored the generality of the process represented by the conversion **8.1**→**8.3** (Scheme 8.) and report here our results.

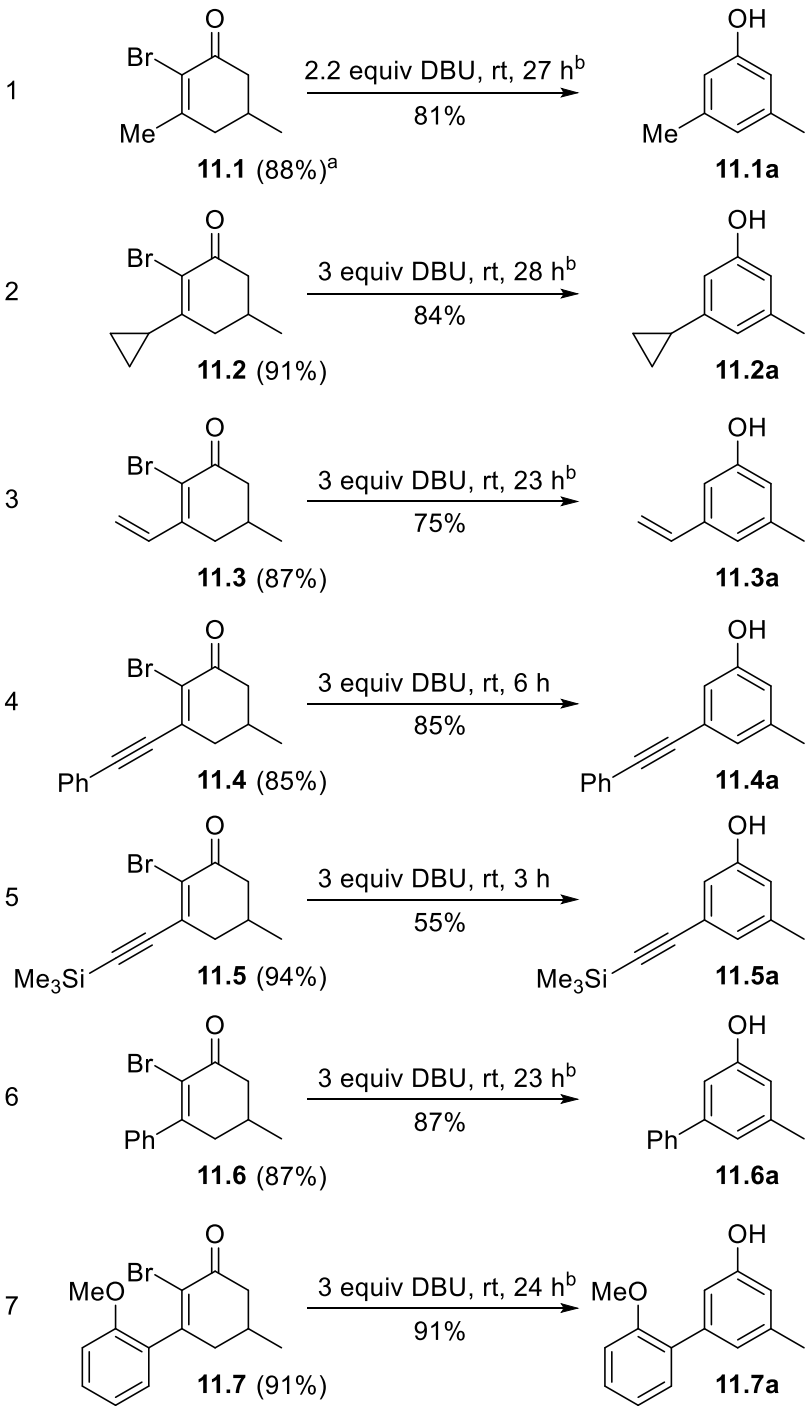
2.2 Aromatization to 3,5-disubstituted phenols

Some of the examples we have studied are listed in Scheme 11. 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 (**10.1**).

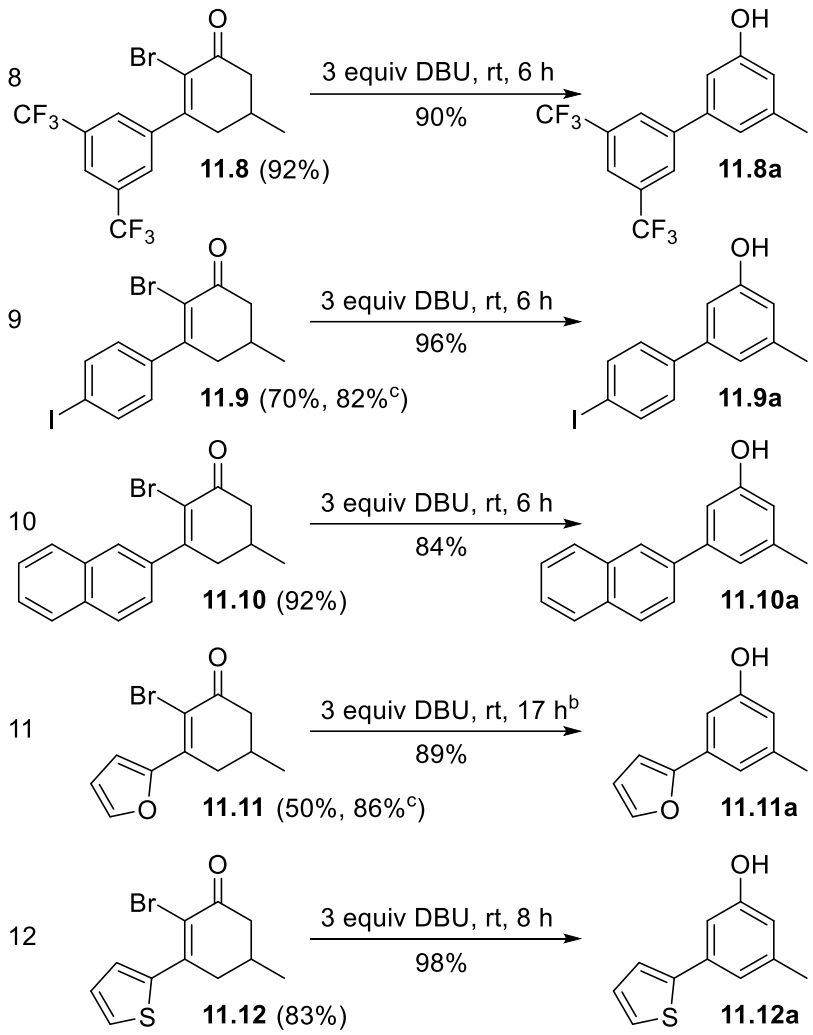


Scheme 10.

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 **11.1**–**11.12**. In the case of entries 9 and 11 a slightly modified procedure was used: silica gel was added to the mixture after organometallic addition, followed by a few drops of 2 N hydrochloric acid. Under these conditions unreacted **10.1** was not hydrolyzed and so the yield of **11.9** and **11.11** could be corrected for the extent of conversion. Treatment of the enones shown in Scheme 11 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.


1
2.2 equiv DBU, rt, 27 h[b]
81%
11.1 (88%)[a]
11.1a
2
3 equiv DBU, rt, 28 h[b]
84%
11.2 (91%)
11.2a
3
3 equiv DBU, rt, 23 h[b]
75%
11.3 (87%)
11.3a
4
3 equiv DBU, rt, 6 h
85%
11.4 (85%)
11.4a
5
3 equiv DBU, rt, 3 h
55%
11.5 (94%)
11.5a
6
3 equiv DBU, rt, 23 h[b]
87%
11.6 (87%)
11.6a
7
3 equiv DBU, rt, 24 h[b]
91%
11.7 (91%)
11.7a

Scheme 11.

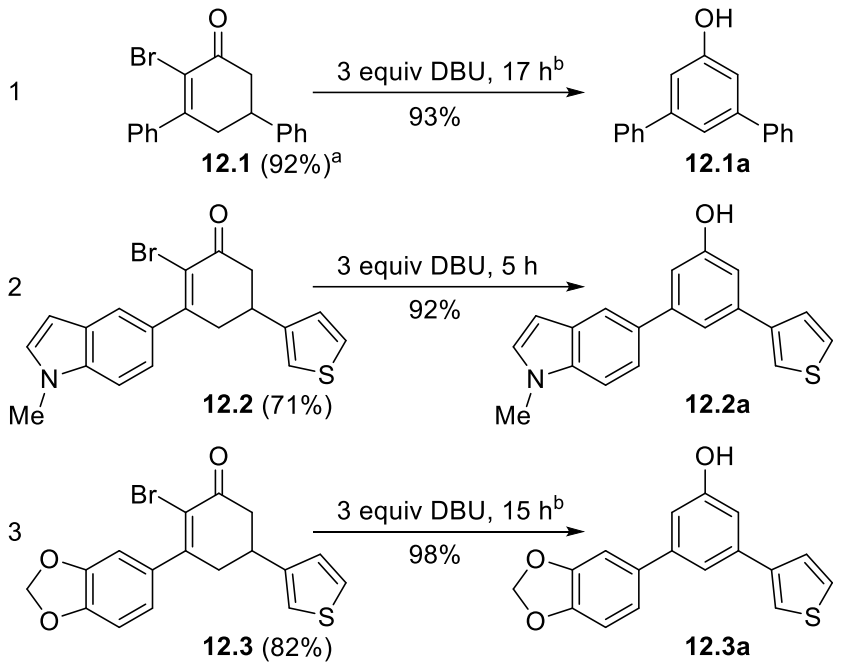


[a]Yield for organometallic addition to **10.1** and acid-induced hydrolysis. [b]Reaction monitored (TLC) for at least 5 h and then left overnight. [c]Yield corrected for recovered **10.1**.

Scheme 11 (Continued).

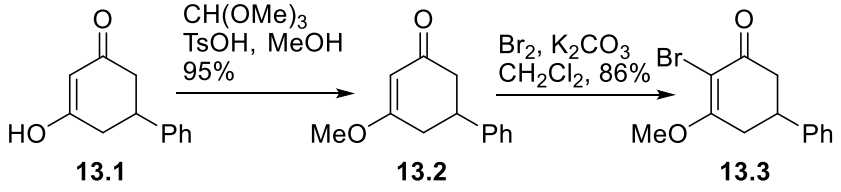
The method is not at all limited to compound **10.1**, and different starting bromoenones having other substituents in place of the C-5 methyl of **10.1** are discussed below (Scheme 12). The required bromoenones for the Grignard

reaction were readily accessible from commercial starting materials by the short sequences summarized in Schemes 13 and 14. This route provides straightforward access to structurally interesting triaryl phenolic compounds.

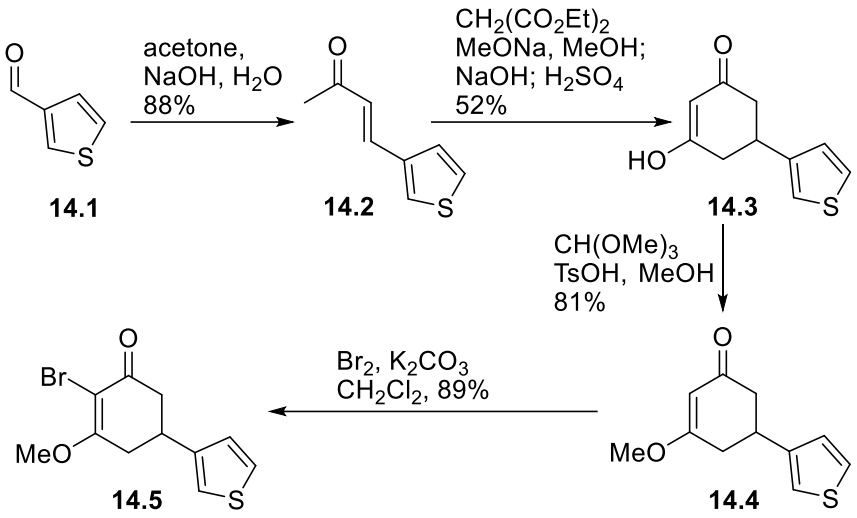


[a]Yield for Grignard addition and acid-induced hydrolysis. [b]Reaction monitored (TLC) for at least 5 h and then left overnight.

Scheme 12.



Scheme 13.

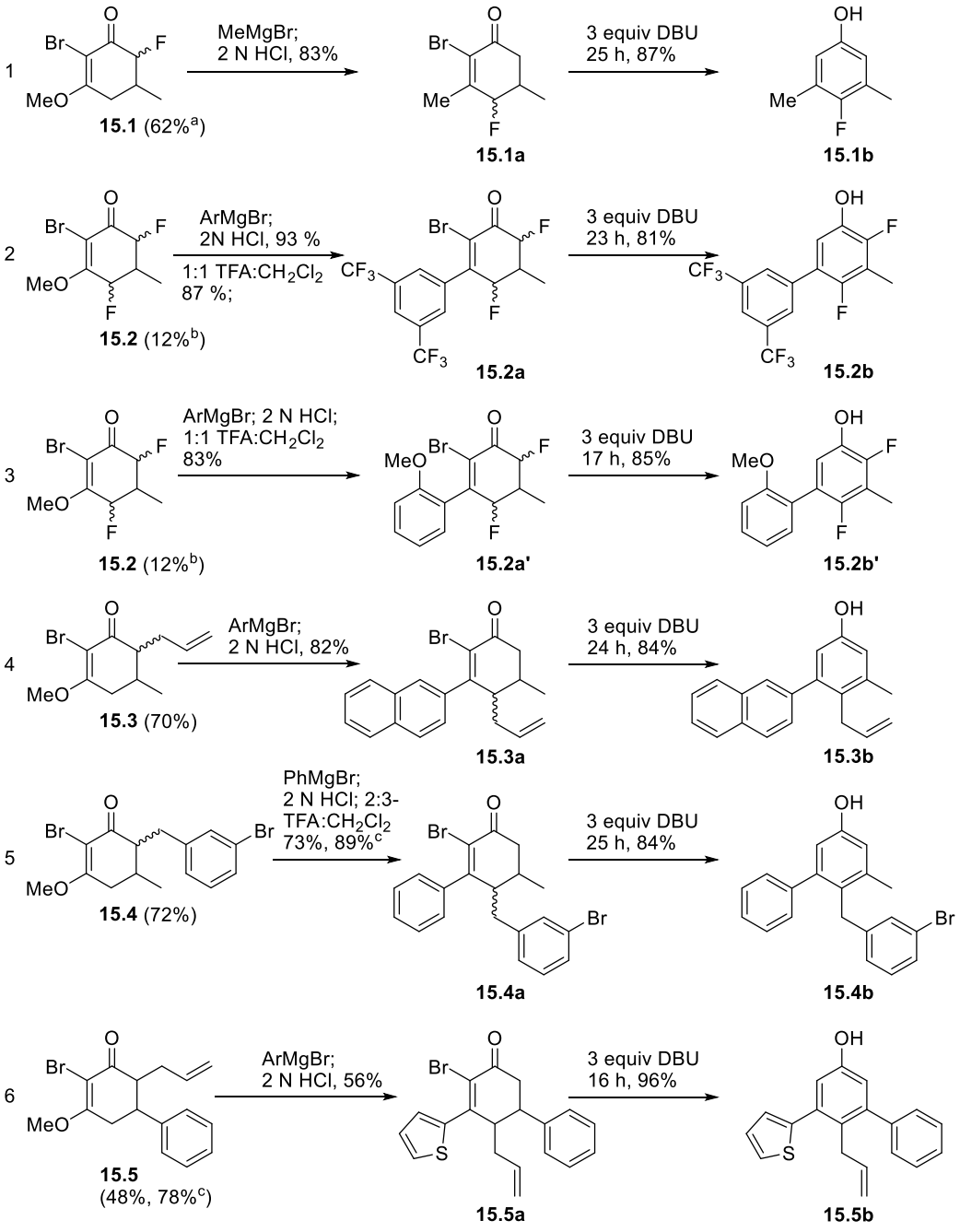


Scheme 14.

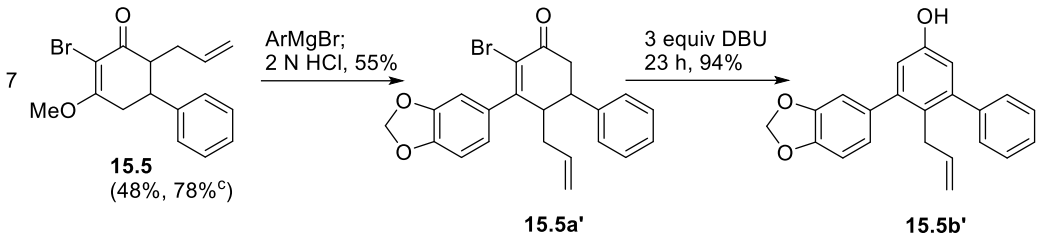
In all three cases (Scheme 12, **12.1**, **12.2** and **12.3**), the reaction with DBU proceeded smoothly giving the expected aromatized materials in high yield (93%, 92% and 98%, respectively) under our standard conditions. Compound **12.3a** is a known intermediate[19] in the synthesis of RO5101576, a leukotriene B4 receptor inhibitor which has been made *inter alia* by transition metal based coupling procedures.[20] The present approach is transition metal free.

2.3 Aromatization to highly-substituted phenols

We have also studied examples in which the starting bromoenone was kinetically deprotonated at C-6 and treated with an electrophile (Scheme 15).


1
MeMgBr;
2 N HCl, 83%
3 equiv DBU
25 h, 87%
15.1 (62%[a])
15.1a
15.1b
2
ArMgBr;
2N HCl, 93 %
1:1 TFA:CH2Cl2
87 %;
3 equiv DBU
23 h, 81%
15.2 (12%[b])
15.2a
15.2b
3
ArMgBr; 2 N HCl;
1:1 TFA:CH2Cl2
83%
3 equiv DBU
17 h, 85%
15.2 (12%[b])
15.2a'
15.2b'
4
ArMgBr;
2 N HCl, 82%
3 equiv DBU
24 h, 84%
15.3 (70%)
15.3a
15.3b
5
PhMgBr;
2 N HCl; 2:3-
TFA:CH2Cl2
73%, 89%[c]
3 equiv DBU
25 h, 84%
15.4 (72%)
15.4a
15.4b
6
ArMgBr;
2 N HCl, 56%
3 equiv DBU
16 h, 96%
15.5
(48%, 78%[c])
15.5a
15.5b

Scheme 15.



[a]Yield for reaction of 5-substituted 2-bromo-3-methoxycyclohex-2-en-1-one with electrophile. [b]Byproduct from the preparation of **15.1**. [c]Yield corrected for recovered starting material.

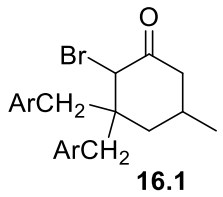
Scheme 15 (Continued).

We used the electrophiles allyl bromide, *meta*-bromobenzyl bromide and *N*-fluorobenzenesulfonimide to prepare compounds **15.1**–**15.5**. In our first example, which was reported in an earlier publication,[16b] we had used $MeSSO_2Tol$ to introduce an SMe group at C-6. Treatment of the C-6 substituted compounds **15.1**–**15.5** with Grignard reagents, followed by exposure to acid, afforded the expected cyclohexenones **15.1a**–**15.5a′** in yields of 55–89%. Once again, the action of DBU at room temperature effected aromatization in high yield.

2.4 Limitations

In addition to the examples shown in Schemes 11, 12 and 15, 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 (**10.1**). With benzylmagnesium chloride or *p*-methoxybenzyl-magnesium chloride the outcome of the addition reaction was unusual[21] as in both experiments a geminally disubstituted cyclohexanone **16.1** (Scheme 16) was formed; 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).



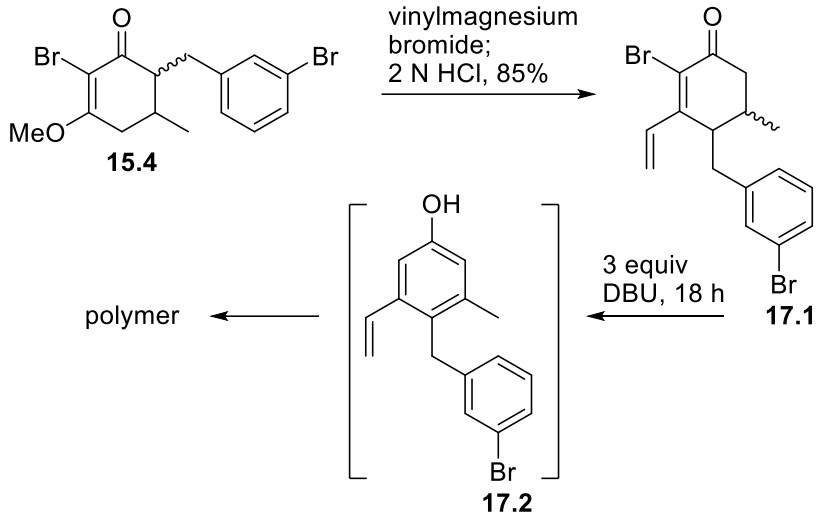
16.1

Scheme 16.

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.[22] A few examples have been reported[23] 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.

Although the reaction of vinylmagnesium bromide with **15.4** proceeded normally to give, after acid treatment, the ketone **17.1** (Scheme 17),

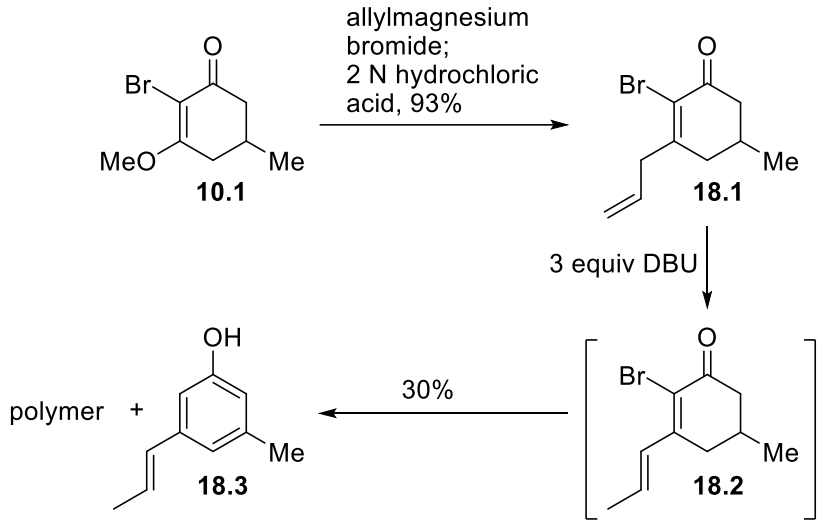
aromatization with DBU appeared to generate a polymer of the desired vinylic phenol in high yield (>90%), this conclusion being based on the MALDI mass spectrum and the ^{1}H NMR spectrum.



Scheme 17.

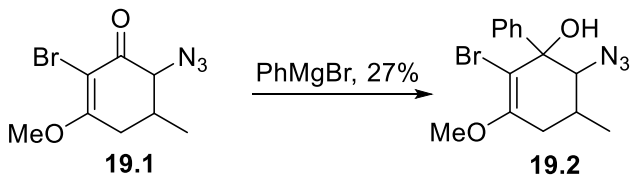
Reaction of allylmagnesium bromide with **10.1**, followed by mild acid treatment (Scheme 18, **10.1**→**18.1**) proceeded normally, but DBU caused double bond migration faster than aromatization, ultimately leading to **18.3**. Consequently, it was possible to isolate some of the intermediate **18.2** and establish the *trans* geometry of the double bond based on a ^3J 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 **18.3** (30% yield) was exclusively *trans*. The MALDI mass spectrum of the crude

product, before isolation of **18.3**, indicated that also in this experiment some polymerization occurred.



Scheme 18.

The last sequence that was problematic involved reaction of azide **19.1** with phenylmagnesium bromide. The intermediate alcohols **19.2** 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 19.

2.5 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 **10.1** 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. Based on 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 intermediate precursor to **15.2a'** 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 intermediate precursor to **15.2a** 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, 87%).

The intermediate precursor to **11.8** 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.

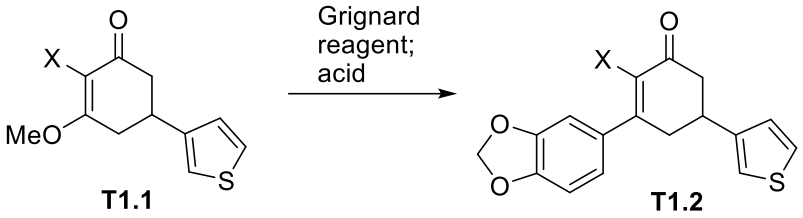
These slow acid hydrolyses reveal that strongly-electron-withdrawing groups exert an appreciable influence on the rate.

The benzyl-substituted compound **15.4a** 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).

2.6 Optimization of reaction conditions

In order to avoid the requirement for an excess of Grignard reagent we carried out several experiments with **T1.1** to optimize the Grignard addition (see Table 1). A change of solvent to Et_2O instead of THF did not offer any improvement; neither did the presence of LiCl in THF.[24] 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 **T1.1** (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 1.



X	T1.1 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]Close TLC monitoring. [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 **T1.1** (X = Cl) as a test case, the Grignard addition (Table 1, last entry) was noticeably faster and the DBU-mediated aromatization proceeded just as smoothly and efficiently (94% yield) as with the bromides.

3 CONCLUSION

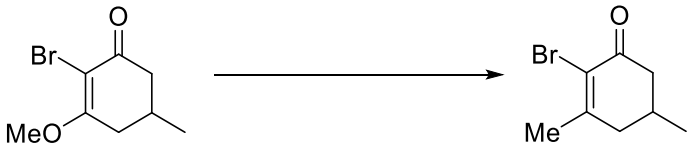
Our route to *meta*-substituted phenols, including those bearing two aryl substituents, is general; it works under mild conditions and the yields are usually very good. No transition metals are required. All but one of our experiments have been done with bromides, but we suspect that use of the corresponding chlorides can be advantageous, as indicated by the reaction of **T1.1** (X = Cl).

The present 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 Scheme 11, entry 9 with an aryl iodide is a case where Pd-mediated aromatization methods would probably cause inappropriate cross coupling. 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 **12.3a** illustrates an application to pharmaceutical chemistry, an area where exclusion of transition metals can be important.

4 EXPERIMENTAL

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. Gradient flash chromatography was done by stepwise small increases in the content of the more polar solvent.

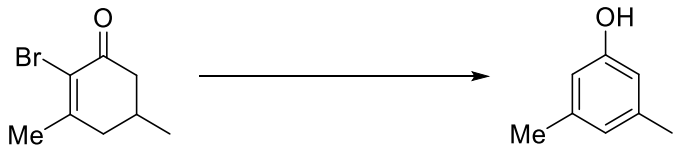
2-Bromo-3,5-dimethylcyclohex-2-en-1-one (11.1).



10.1 **11.1**

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**[16b] (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 **11.1** (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.

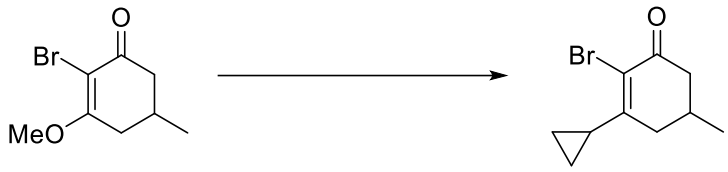
3,5-Dimethylphenol (11.1a).[19]



11.1 **11.1a**

DBU (0.13 mL, 0.83 mmol) was added to a stirred solution of **11.1** (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 **11.1a** (37.5 mg, 81%) as an oil: ^{1}H 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 (11.2).

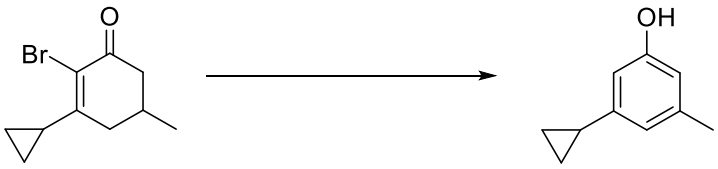


10.1 **11.2**

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 **10.1** (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 **11.2** (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.

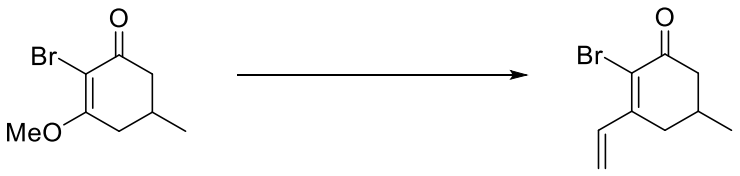
3-Cyclopropyl-5-methylphenol (11.2a).



11.2 **11.2a**

DBU (89 μL, 0.58 mmol) was added to a stirred solution of **11.2** (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 **11.2a** (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.

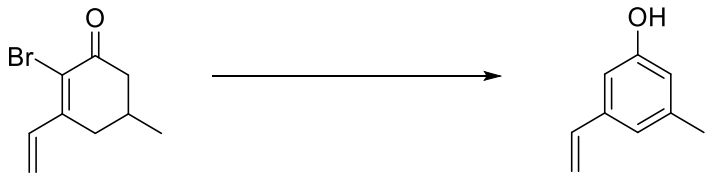
2-Bromo-3-ethenyl-5-methylcyclohex-2-en-1-one (11.3).



10.1 **11.3**

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 **10.1** (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 **11.3** (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 (11.3a).



11.3 **11.3a**

DBU (0.15 mL, 0.99 mmol) was added to a stirred solution of **11.3** (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 **11.3a** (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 (11.4).

10.1 **11.4**

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).[25] Stirring at −78 °C was continued for 1 h. A solution of **10.1** (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 **11.4** (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 (11.4a).

11.4 **11.4a**

DBU (91 μL, 0.60 mmol) was added to a stirred solution of **11.4** (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 **11.4a** (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 (11.5).

10.1 **11.5**

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).[25] Stirring at −78 °C was continued for 2 h. A solution of **10.1** (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 **11.5** (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.

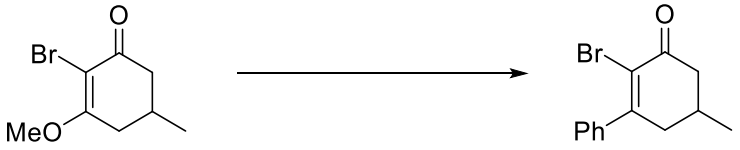
3-Methyl-5-[2-(trimethylsilyl)ethynyl]phenol (11.5a).

11.5 **11.5a**

DBU (0.12 mL, 0.76 mmol) was added to a stirred solution of **11.5** (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 **11.5a** (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 (11.6).

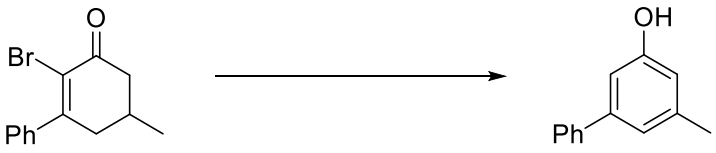


10.1 **11.6**

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 **10.1** (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 **11.6** (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 (11.6a).[19]

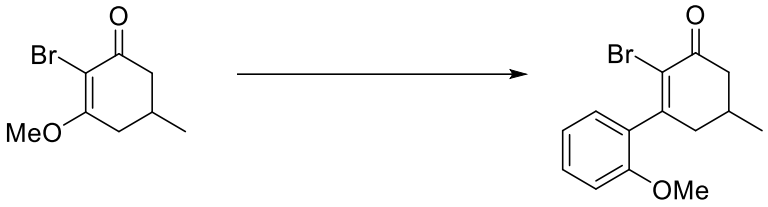


11.6 **11.6a**

DBU (78 μL, 0.51 mmol) was added to a stirred solution of **11.6** (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 **11.6a** (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 (11.7).



10.1 **11.7**

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[26] 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 **10.1** (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 **11.7** (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.

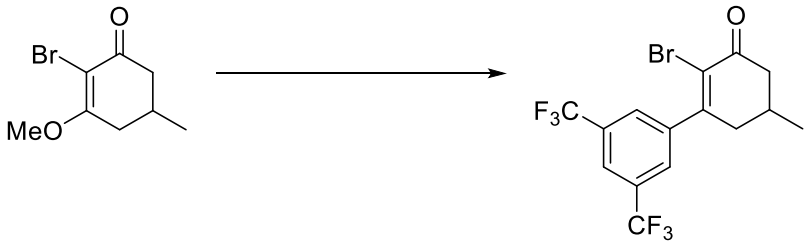
3-(2-Methoxyphenyl)-5-methylphenol (11.7a).[27]

11.7 **11.7a**

DBU (92 μL, 0.60 mmol) was added to a stirred solution of **11.7** (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 **11.7a** (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 (11.8).



10.1 **11.8**

Preparation of the aryl Grignard reagent:[28] 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[26] before use.

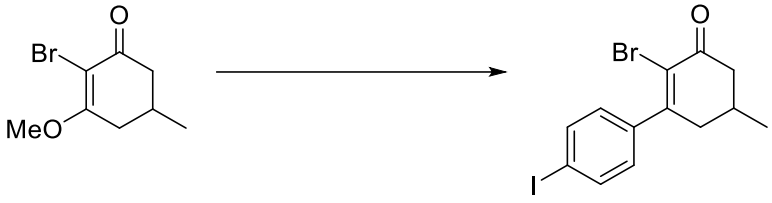
[3,5-Bis(trifluoromethyl)phenyl]magnesium bromide solution (0.58 M in THF, 2.69 mL, 1.56 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **10.1** (115 mg, 0.52 mmol) in THF (4.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 20 min, the ice bath was removed and 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 **11.8** (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 (11.8a).

11.8 **11.8a**

DBU (65 μL, 0.42 mmol) was added to a stirred solution of **11.8** (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 **11.8a** (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 (11.9).

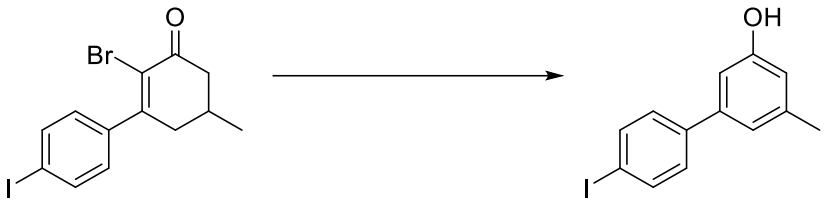


10.1 **11.9**

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[29] was taken up into a syringe and added dropwise to a stirred and cooled (0 °C) solution of **10.1** (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 **11.9** [71 mg, 70%, 82% corrected for recovered **10.1** (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 (11.9a).

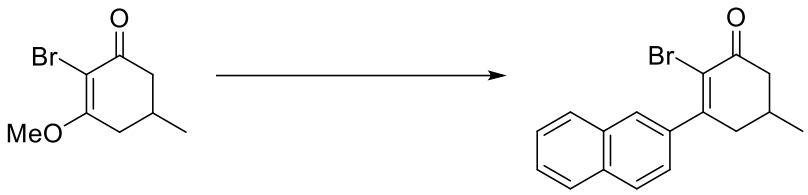


11.9 **11.9a**

DBU (38 μL, 0.25 mmol) was added to a stirred solution of **11.9** (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 **11.9a** (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 (11.10).



10.1 **11.10**

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[30] was titrated according to the literature procedure[26] 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 **10.1** (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 **11.10** (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 (11.10a).

11.10 **11.10a**

DBU (0.11 mL, 0.70 mmol) was added to a stirred solution of **11.10** (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 **11.10a** (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 (11.11).

10.1 **11.11**

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).[31] 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 **10.1** (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 **11.11** [150 mg, 50%, 86% corrected for recovered **10.1** (110 mg)] as a solid: mp 65–66 °C; FTIR ($CDCl_3$, cast) 3115, 2956, 1675, 1267 cm^{-1}; ^1H 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.

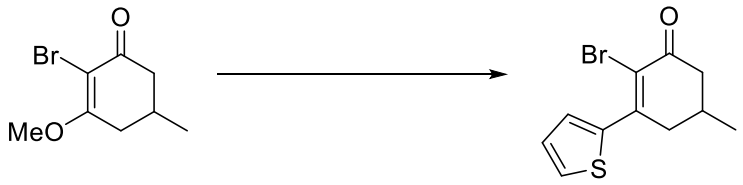
3-(Furan-2-yl)-5-methylphenol (11.11a).[19]

11.11 **11.11a**

DBU (0.10 mL, 0.66 mmol) was added to a stirred solution of **11.11** (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 **11.11a** (34 mg, 89%) as an oil: FTIR ($CDCl_3$, cast) 3372, 3115, 2952, 1604, 1154 cm^{-1}; ^1H 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 (11.12).



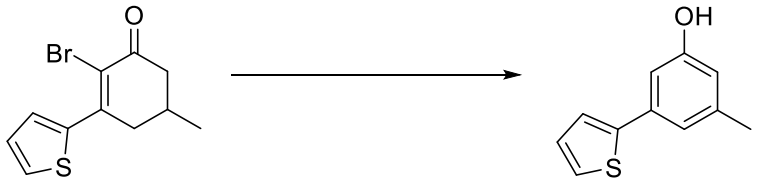
10.1 **11.12**

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[32] was titrated according to the literature procedure[26] before use.

Thien-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 **10.1** (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 **11.12** (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.

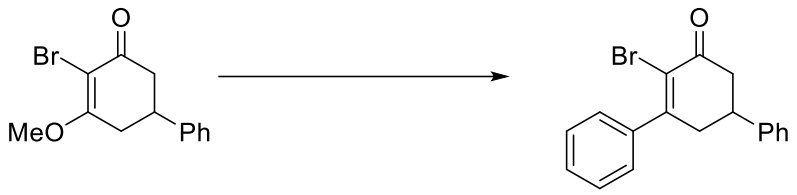
3-Methyl-5-(thiophen-2-yl)phenol (11.12a).[19]



11.12 **11.12a**

DBU (64 μL, 0.42 mmol) was added to a stirred solution of **11.12** (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 **11.12a** (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 (12.1).



13.3 **12.1**

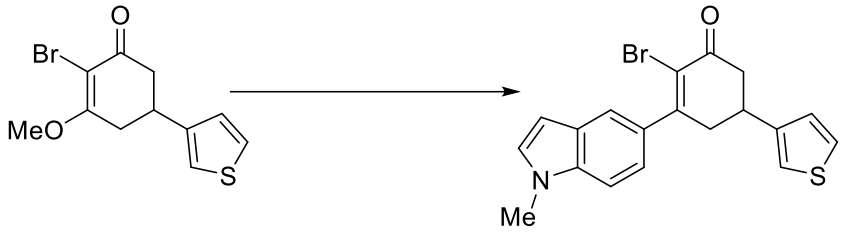
PhMgBr (1.7 M in THF, 0. 23 mL, 0. 38 mmol) was added dropwise over <1 min to a stirred and cooled (0 °C) solution of **13.3** (72 mg, 0.26 mmol) in THF (3.0 mL) (Ar atmosphere). Stirring at 0 °C was continued for 45 min. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirred 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 **12.1** (76.8 mg, 92%) as an oil: FTIR ($CDCl_3$, cast) 3087, 2952, 1684 cm^{-1}; ^1H 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 (12.1a).[33]

12.1 **12.1a**

DBU (0.10 mL, 0.66 mmol) was added to a stirred solution of **12.1** (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 **12.1a** (50.6 mg, 93%) as a solid: mp 92–93 °C (lit.[33] 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 (12.2).



14.5 **12.2**

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).[33] 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[26] 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 **14.5** (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 **12.2** (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.

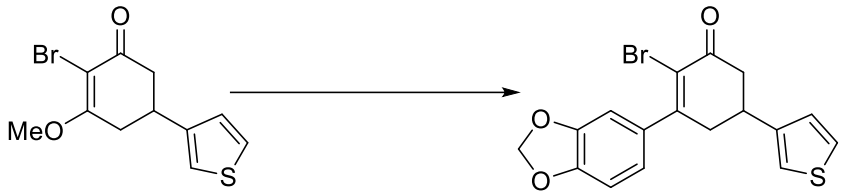
3-(1-Methyl-1*H*-indol-5-yl)-5-(thiophen-3-yl)phenol (12.2a).

12.2 **12.2a**

DBU (53 μL, 0.35 mmol) was added to a stirred solution of **12.2** (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 **12.2a** (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 (12.3).



14.5 **12.3**

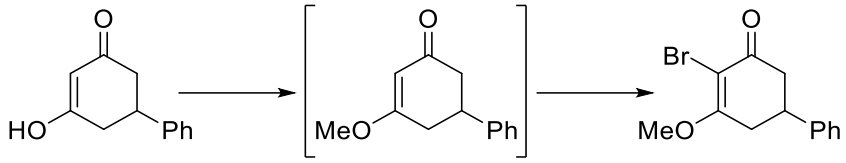
The Grignard reagent was prepared as described before. [(3,4-Methylenedioxy)- phenyl]magnesium bromide (0.66 M in THF, 0.36 mL, 0.24 mmol) was added dropwise over <5 min to a stirred and cooled (0 °C) solution of **14.5** (45 mg, 0.16 mmol) in THF (1.5 mL) (Ar atmosphere). After 2.5 h more Grignard reagent (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 **12.3** (48.4 mg, 82%) a beige solid: 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 (12.3a).[34]

12.3 **12.3a**

DBU (48 μL, 0.32 mmol) was added to a stirred solution of **12.3** (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 **12.3a** (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 (13.3).[35]

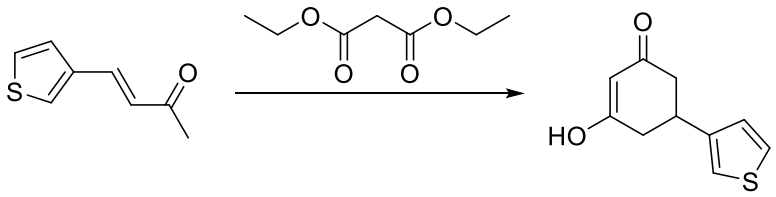


13.1 **13.2** **13.3**

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 **13.1** (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 (**13.2**) (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 **13.3** (2.39 g, 82% over two steps) as a beige solid: mp 162–163 °C (lit.[35] 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 (14.3).[36]

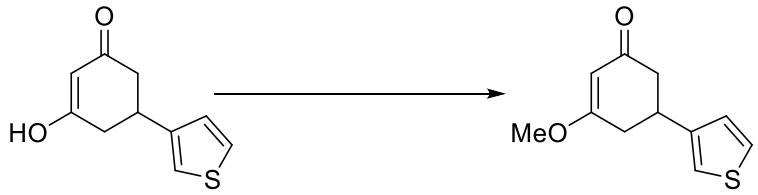


14.2 **14.3**

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 (**14.2**)[37] (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 **14.3** (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 (14.4).



14.3 **14.4**

$TsOH.H_2O$ (39 mg, 0.22 mmol) and $CH(OMe)_3$ (0.99 mL, 8.96 mmol) were added sequentially to a stirred solution of **14.3** (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 **14.4** (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.

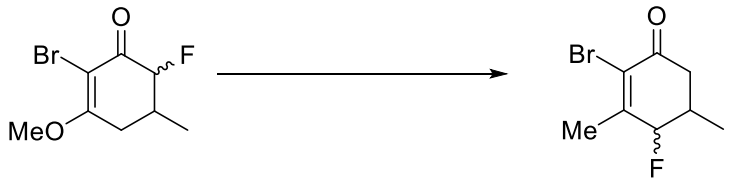
2-Bromo-3-methoxy-5-(thiophen-3-yl)cyclohex-2-en-1-one (14.5).

14.4 **14.5**

K_2CO_3 (1.72 g, 6.7 mmol) was added to a stirred and cooled (0 °C) solution of **14.4** (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 **14.5** (472 mg, 89%) as a solid: mp 148–150 °C; FTIR ($CDCl_3$, cast) 3098, 2951, 1658 cm^{-1}; ^1H 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 (15.1a).



15.1 **15.1a**

MeMgBr (3.0 M in Et_2O, 91 μL, 0.27 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **15.1**[16c] (43.1 mg, 0.18 mmol, a 6:4 mixture of isomers) in THF (2.0 mL) (Ar atmosphere). Stirring was continued for 45

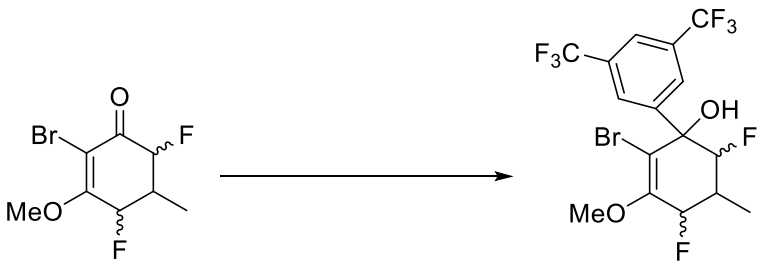
min. The reaction mixture was quenched with hydrochloric acid (2 N, 3 mL) and stirred for 20 min. More hydrochloric acid (2 N, 15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 5% EtOAc–hexanes, gave **15.1a** (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 (15.1b).[38]

15.1a **15.1b**

DBU (46 μL, 0.30 mmol) was added to a stirred solution of **15.1a** (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 **15.1b** (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.

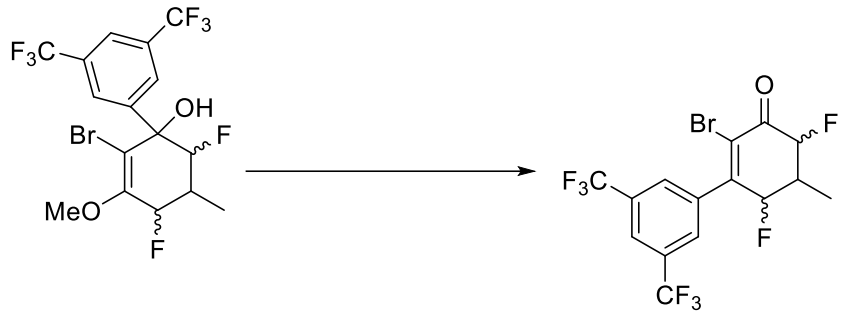
1-[3,5-Bis(trifluoromethyl)phenyl]-2-bromo-4,6-difluoro-3-methoxy-5-methylcyclohex-2-en-1-one (precursor to 15.2a).



15.2 **precursor to 15.2a**

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 **15.2**[16c] (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 **15.2a**, (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-methyl-cyclohex-2-en-1-one (15.2a).

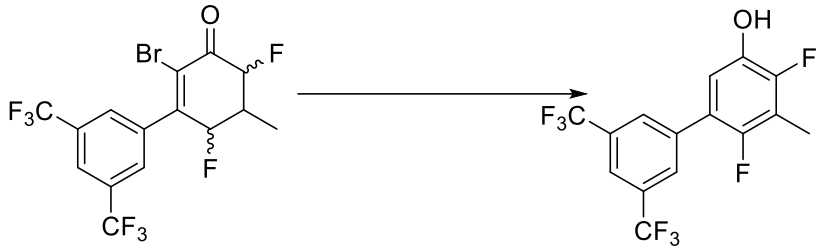


precursor to 15.2a **15.2a**

1-[3,5-Bis(trifluoromethyl)phenyl]-2-bromo-4,6-difluoro-3-methoxy-5-methylcyclohex-2-en-1-ol, the precursor to **15.2a**, (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 **15.2a** (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, $^2J_{H\text{-}F}$ = 59.5, J = 15.0 Hz, 0.5 H), 5.29–5.36 (m, 0.5 H), 5.44 (dd, $^2J_{H\text{-}F}$ = 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 (15.2b).

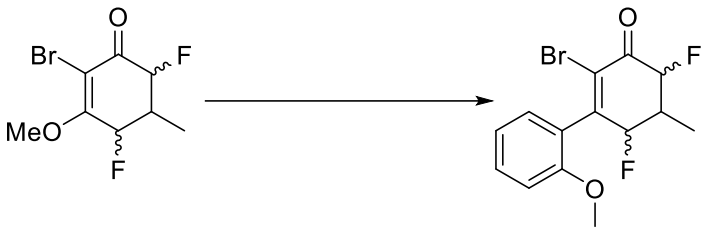


15.2a **15.2b**

DBU (46 μL, 0.30 mmol) was added to a stirred solution of **15.2a** (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 **15.2b** (28.8 mg, 81%) as a solid: mp 68–70 °C; FTIR ($CDCl_3$, cast) 3597, 3432, 3088, 2926, 1626, 1280 cm^{-1}; ^1H 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 (15.2a').

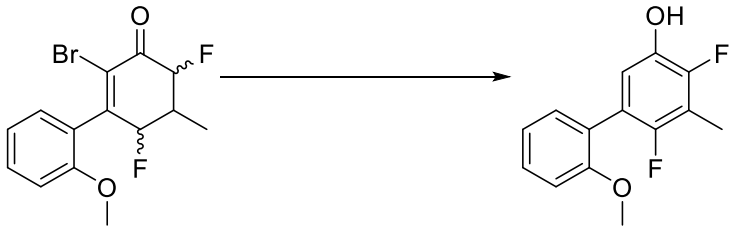


15.2 **15.2a'**

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 **15.2**[16c] (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 **15.2a'** (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 (15.2b').



15.2a' **15.2b'**

DBU (67 μL, 0.44 mmol) was added to a stirred solution of **15.2a'** (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 **15.2b'** (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, $^1J_{C\text{-}F}$ = 235.6, $^3J_{C\text{-}F}$ = 8.3 Hz), 151.8 (dd, $^1J_{C\text{-}F}$ = 239.5, $^3J_{C\text{-}F}$ = 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 (15.3a).

15.3 **15.3a**

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 **15.3**[16b] (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 **15.3a** (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}; ^1H 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 (15.3b).

15.3a **15.3b**

DBU (53 μL, 0.35 mmol) was added to a stirred solution of **15.3a** (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 **15.3b** (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.

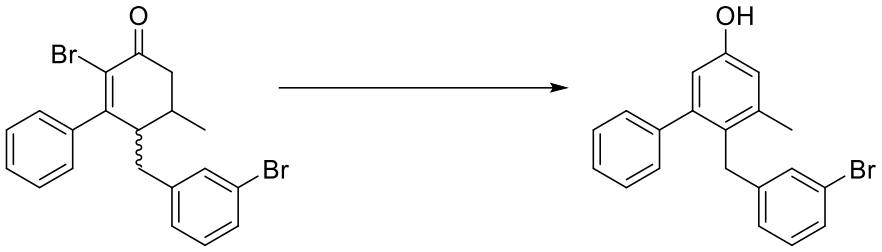
2-Bromo-4-[(3-bromophenyl)methyl]-5-methyl-3-phenylcyclohex-2-en-1-one (15.4a).

15.4 **15.4a**

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 **15.4**[16b] (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 **15.4** (13.7 mg) and a mixture of the intermediates as well as **15.4a**. The intermediates and **15.4a** 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 **15.4a** [66.8 mg, 73%, 89% corrected for recovered **15.4** (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 (15.4b).

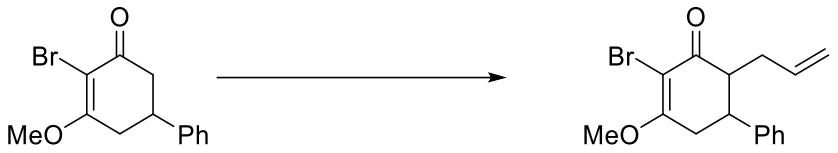


15.4a **15.4b**

DBU (55 μL, 0.36 mmol) was added to a stirred solution of **15.4a** (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 **15.4b** (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 (15.5).



13.3 **15.5**

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 **13.3** (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 **13.3** 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 **15.5** [129 mg, 48%, 70% corrected for recovered **13.3** (76 mg)] as a solid: mp 184–185 °C; FTIR ($CDCl_3$, cast) 3073, 2946, 1651 cm^{-1}; ^1H 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 (15.5a).

15.5 **15.5a**

The Grignard reagent was prepared as described before. Thien-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 **15.5** (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 **15.5a** (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 **15.5a** (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 (15.5b).

15.5a **15.5b**

DBU (26 μL, 0.17 mmol) was added to a stirred solution of **15.5a** (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 **15.5b** (16.2 mg, 96%) as an oil: FTIR ($CDCl_3$, cast) 3373, 3100, 2975, 1588 cm^{-1}; ^1H 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 (15.5a').

15.5 **15.5a'**

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).[32] 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[26] 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 **15.5** (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 **15.5a'** (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.

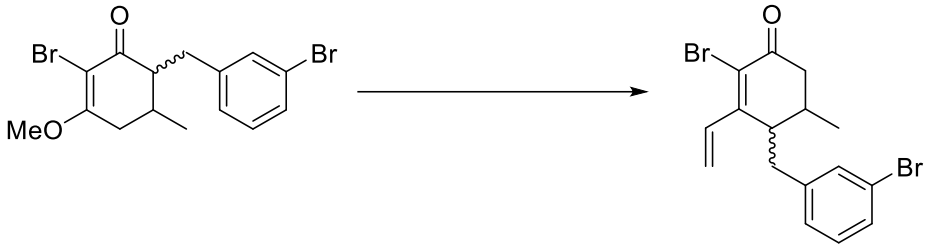
3-(2*H*-1,3-Benzodioxol-5-yl)-5-phenyl-4-(prop-2-en-1-yl)phenol (15.5b').

15.5a' **15.5b'**

DBU (34 μL, 0.23 mmol) was added to a stirred solution of **15.5a'** (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 **15.5b'** (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 (17.1).

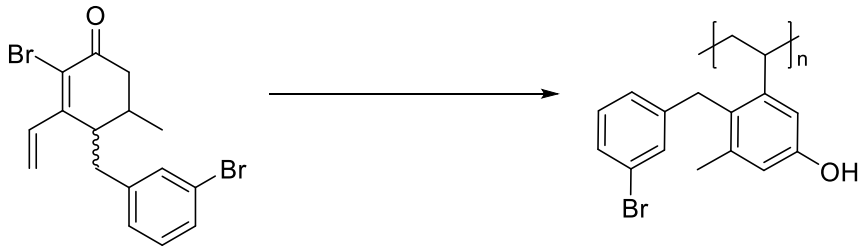


15.4 **17.1**

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 **15.4**[16c] (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 **17.1** (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}; ^{1}H 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

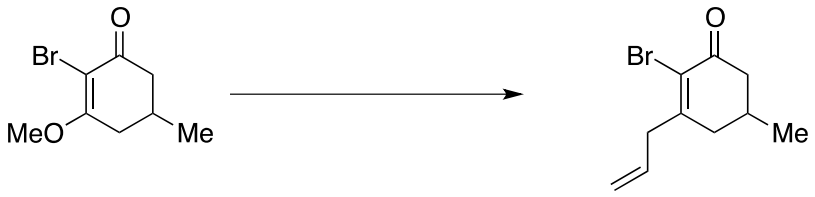


17.1 **Polymer of 17.1**

DBU (62 μL, 0.41 mmol) was added to a stirred solution of **17.1** (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 **17.1** (40.4 mg, 97% crude yield) as an oil.

2-Bromo-5-methyl-3-(prop-2-en-1-yl)cyclohex-2-en-1-one (18.1).

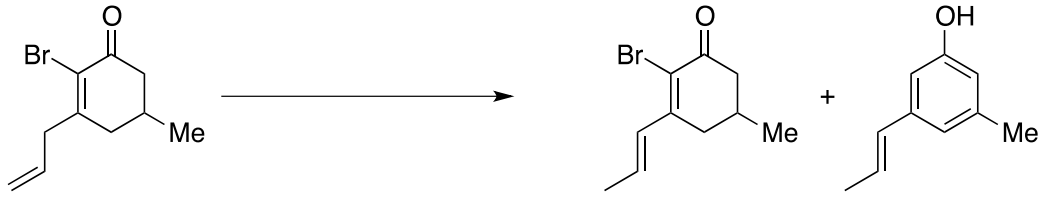


10.1 **18.1**

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 **10.1** (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 **18.1** (159 mg, 93%) as an oil: FTIR ($CDCl_3$, cast) 3307, 2957, 1685 cm^{-1}; ^1H 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 (18.2).

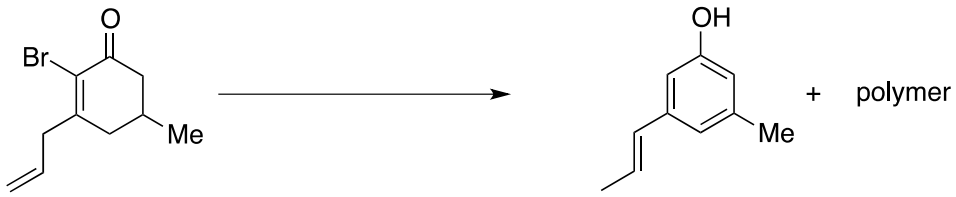


18.1 **18.2** **18.3**

DBU (0.10 mL, 0.67 mmol) in THF (0.5 mL) was added dropwise to a stirred solution of **18.1** (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 **18.2** (8.0 mg, 11%) as a white solid and **18.3** (12.8 mg, 27%) as a colorless oil. Compound **18.2** 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 **18.3** had: FTIR ($CDCl_3$, cast) 3343, 3024, 2957, 1591 cm^{-1}; ^{1}H 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 148.0888.

3-Methyl-5-[(1E)-prop-1-en-1-yl]phenol (18.3).

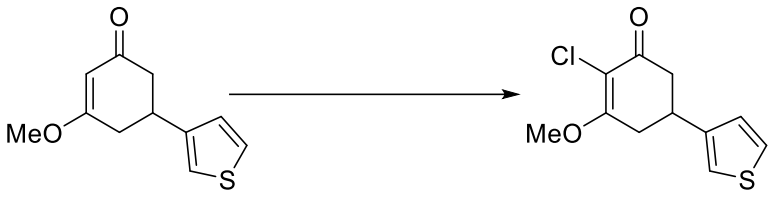


18.2 **18.3**

DBU (0.22 mL, 1.47 mmol) was added to a stirred solution of **18.2** (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 **18.3**. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% EtOAc-hexane, gave **18.3** (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 (T1.1, X = Cl).

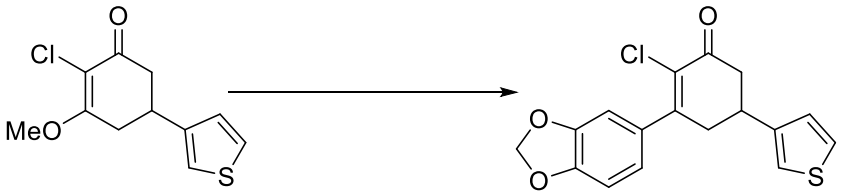


14.4 **T1.1, X = Cl**

NCS (120 mg, 0.88 mmol) in THF (2 mL) was added dropwise to a stirred and cooled (0 °C) solution of **14.4** (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 **T1.1** (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 (T1.2, X = Cl).



T1.1, X = Cl **T1.2, 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 **T1.1** (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 **T1.2** (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 (12.3a) from T1.2 (X = Cl).[34]

T1.2 (X = Cl) **12.3a**

DBU (86 μL, 0.56 mmol) was added to a stirred solution of **T1.2** (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 **12.3a** (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); ^{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.

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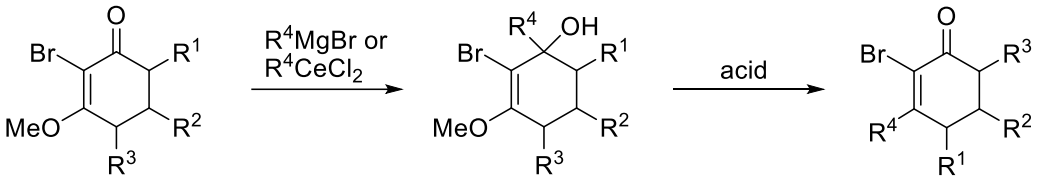
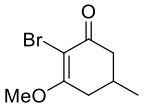
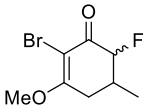
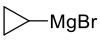
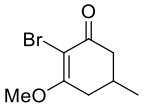
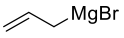
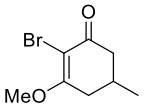
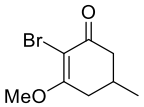
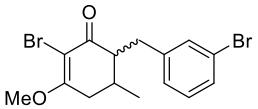
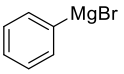
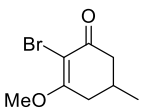
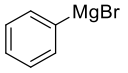
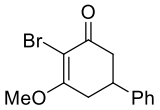
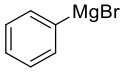
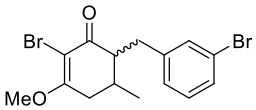
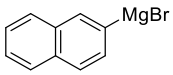
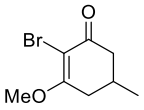
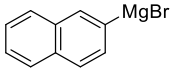
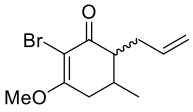
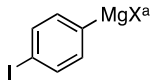
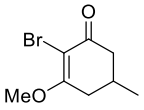
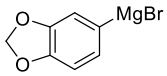
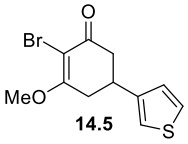
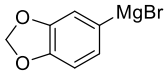
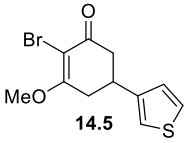
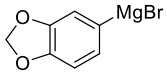
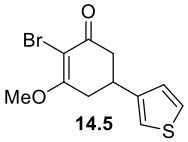
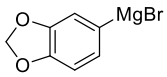
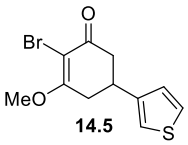
6 APPENDIX

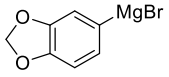
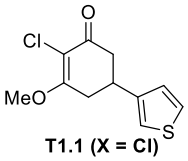
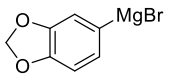
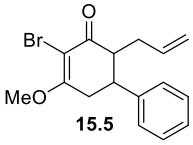
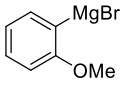
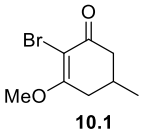
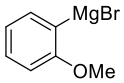
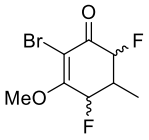
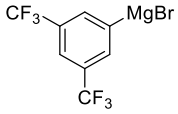
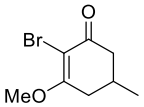
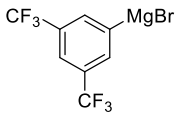
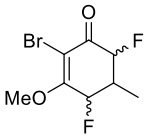
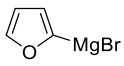
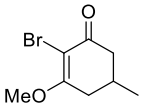
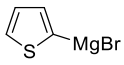
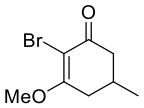
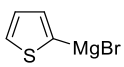
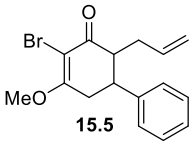
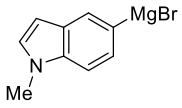
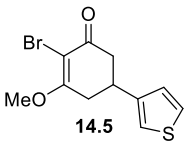
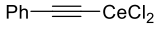
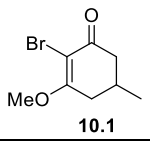
Attached here is a global summary of the conditions of an organometallic reagent addition to an enone and following acid treatment and the overall yield.

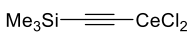
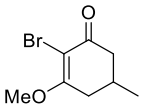
Table 2. Organometallic addition, acid hydrolysis conditions and yield.



Organometallic reagent	Substrate	Addition conditions	Hydrolysis conditions	Overall yield (%)
MeMgBr	 **10.1**	1.3 equiv, 0 °C, 2.5 h	2 N HCl, rt, 15 min	88%
MeMgBr	 **15.1**	1.5 equiv, 0 °C, 45 min	2 N HCl, rt, 20 min	83%
	 **10.1**	2 equiv, 0 °C to rt over 2.5 h; 4 equiv, rt, 21 h	2 N HCl, rt, 20 min	91%
	 **10.1**	1 equiv, 0 °C, 30 min	2 N HCl, rt, 5 min	93%
	 **10.1**	1.5 equiv, 0 °C, 2.5 h	2 N HCl, rt, 30 min	87%
	 **15.4**	3 equiv, 0 °C, 2 h	2 N HCl, rt, 20 min	85%
	 **10.1**	1.5 equiv, 0 °C, 50 min, rt, 50 min	2 N HCl, rt, 15 min	87%

	 **13.3**	1.5 equiv, 0 °C, 45 min	2 N HCl, rt, 2 h	92%
	 **15.4**	3 equiv, 0 °C, 3 h, rt, 2 h; 1.5 equiv, rt, 1 h	2 N HCl, rt, 30 min, column, then TFA:CH_2Cl_2 (2:3), rt, 28 h	73% or 89%[b]
	 **10.1**	1.5 equiv, 0 °C to rt over 1 h; 1 equiv, rt, 1 h	2 N HCl, rt, 5 min	92%
	 **15.3**	3 equiv, 0 °C to rt over 2.5 h, rt 16 h	2 N HCl, rt, 1.5 h	82%
	 **10.1**	6 equiv, 0 °C, 30 min, rt, 16 h	silica gel plus several drops of 2 N HCl, rt, 30 min	70% or 82%[b]
	 **14.5**	(a) 1.5 equiv, 0 °C, 2.5 h; 1 equiv, 0 °C to rt over 3 h	2 N HCl, rt, 30 min	82%
	 **14.5**	(b) 1.25 equiv, 0 °C, 4 h, rt, 43 h	2 N HCl, rt, 30 min	76%, starting concentration twice that of experiment (a)
	 **14.5**	(c) 1.25 equiv, 0 °C, 4 h, rt, 48 h	silica gel, column, then 2 N HCl and acetone, rt, 1 h	47% or 70%[b], this experiment done in Et_2O-THF.
	 **14.5**	(d) 1.25 equiv, 0 °C, 4 h, rt, 65 h	silica gel, column, then 2 N HCl and THF, rt, 2 h	56% or 69%[b], the Grignard step done in THF with addition of LiCl.

	 T1.1 (X = Cl)	(e) 1.5 equiv, 0 °C, 2 h	2 N HCl, rt, 30 min	89%
	 15.5	3 equiv, 0 °C to rt over 4 h, rt, 21 h; 3 equiv, rt, 42 h	2 N HCl, rt, 5 h	55%
	 10.1	1.1 equiv, 0 °C, 30 min, rt, 1 h; 0.5 equiv, rt, 30 min	2 N HCl, rt, 20 min	91%
	 15.2	2.5 equiv, 0 °C, 2.5 h	2 N HCl, rt, 2 h; TFA:CH_2Cl_2 (1:1), rt, 1 h	83%
	 10.1	3 equiv, 0 °C, 20 min, rt, 2 h	2 N HCl, rt, overnight	92%
	 15.2	3 equiv, 0 °C, 4 h	TFA-CH_2Cl_2 (1:1), rt, 45 h	81% (93% for addition, 87% for hydrolysis)
	 10.1	1.5 equiv, 0 °C, 20 min, rt, 19 h	silica gel plus several drops of 2 N HCl, rt, 20 min	50% or 86%[b]
	 10.1	1.5 equiv, 0 °C to rt over 3 h; 1.5 equiv, rt, 5 h; 3 equiv, rt, 12 h	2 N HCl, rt, 2.5 h	83%
	 15.5	3 equiv, 0 °C to rt over 4 h, recooled, 3 equiv, 0 °C to rt over 15 h	2 N HCl, rt, 3 h	56%
	 14.5	3 equiv, 0 °C, 1 h, rt, 5 days	2 N HCl, rt, 20 min	71%
	 10.1	5 equiv, –78 °C, 4 h	2 N HCl, rt, 15 min	85%

	 **10.1**	5 equiv, –78 °C to 0 °C over 4 h	2 N HCl, rt, 15 min	94%

Footnote: [a]Generated from 1,4-diiodobenzene and *i*-PrMgCl. [b]Corrected for recovered starting material.