

The use of Hagemann's Esters to prepare highly functionalized phenols and benzenes[§]

George Majetich* and Scott Allen

Department of Chemistry, University of Georgia, Athens, Georgia USA 30602

E-mail: majetich@chem.uga.edu

Dedicated to "Captain" James M. Cook on the occasion of his 65th birthday[§]

Abstract

Hagemann's esters can be converted into highly functionalized phenols or arenes. The systematic functionalization of Hagemann's ester derivatives permits the preparation of tri- and tetraalkyl-substituted phenols or tetra-, penta-, and hexaalkyl-substituted benzenes. Kotnis's aromatization procedure was found to be solvent dependent, and Suzuki couplings were found to be sensitive to steric hindrance. Wittig olefination and *ortho*-Claisen reactions were reliable means to introduce alkyl substituents at C-4 and/or C-5 positions, respectively. The acid-promoted dehydration of tertiary alcohol **46** to produce enone **47**, followed by its selective alkylation (cf. **48**) is new.

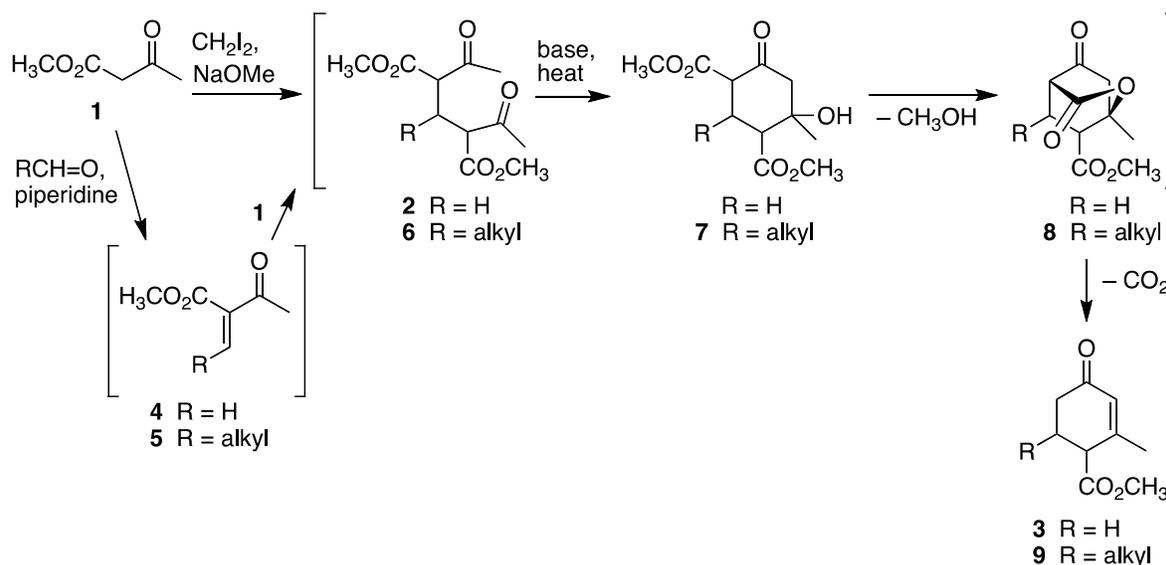
Keywords: Hagemann's ester, tetraalkylphenols, pentaalkylbenzene, Suzuki coupling, regiospecific alkylations, aromatization

Introduction

Many naturally occurring and biologically active compounds contain a highly substituted benzene ring.¹ While functionalization of benzene has been an active area of organic chemistry for more than 150 years, the number of strategies for preparing highly alkylated phenols^{2a-c} and highly alkylated benzenes is limited.^{2d-f}

In 1894, Hagemann^{3a} treated two equivalents of ethyl acetoacetate **1** with one equivalent of diiodomethane and excess sodium methoxide to form glutamate diester **2**; further treatment of **2** with base and heat produced cyclic ester **3** (Scheme 1). Although the initial structure of **3** required revision,^{3b} these cyclohexenone derivatives became known as "Hagemann's esters." One year after Hagemann's synthesis of **3**, Knoevenagel improved its preparation by coupling **1** with formaldehyde to generate Michael acceptor **4** in situ, which reacts with a second molecule of **1** to yield diketone **2**,⁴ which in turn, undergoes intramolecular aldol reaction to produce cyclic alcohol **7**. The mechanism of the formation of Hagemann's ester has been the subject of

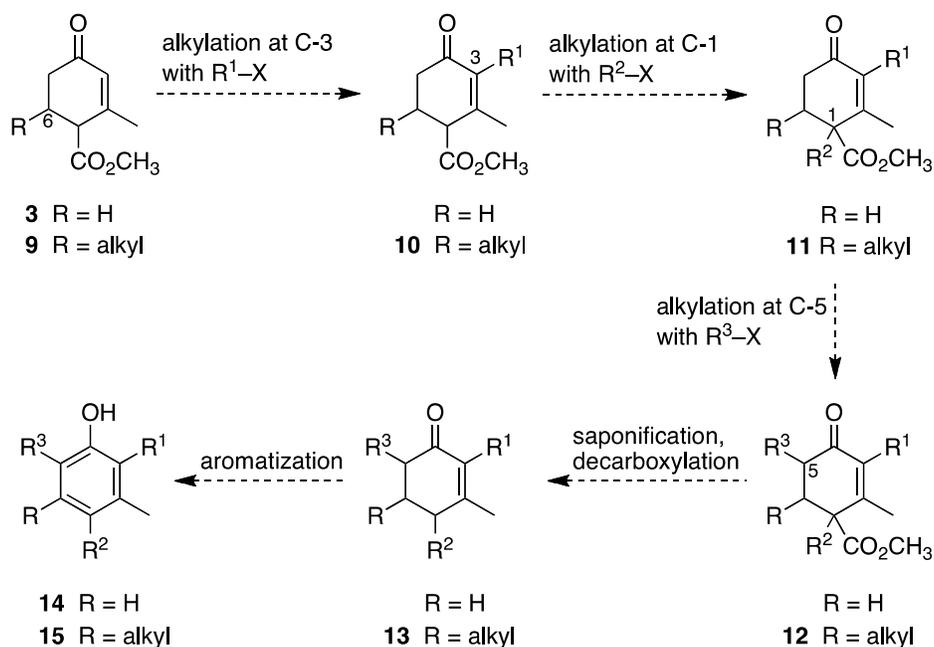
extensive investigation,⁵ but it was not until 1984 when Hoye and co-workers established that aldol **7** forms lactone **8**, which loses carbon dioxide to form ester **3**.⁶ Horning and co-workers developed conditions so that Knoevenagel's modification could be carried out in a single operation;⁷ this one-pot, tandem Knoevenagel/intermolecular Michael addition/intramolecular aldol reaction/intramolecular trans-esterification/decarboxylation sequence represents one of the earliest cascade reactions.⁸ A useful modification of Knoevenagel's general procedure was to employ an aldehyde (or a ketone) in the condensation step,⁹ which introduces one alkyl (or two alkyl) substituent(s) at the C-6 position (cf. **1** → **5** → **6** → **7** → **8** → **9**). A comprehensive review of the synthetic utility and versatility of Hagemann's esters has recently been published.¹⁰



Scheme 1. The intermediates produced during a Hagemann's ester synthesis.

Hagemann's esters can undergo selective alkylation at three sites. In 1943, Smith and Rouvaut reported that **3** undergoes alkylation exclusively at C-3 (cf. **10**, Scheme 2).¹¹ Many syntheses have utilized this alkylation, followed by saponification and decarboxylation, to prepare 2-alkyl-3-methyl-2-cyclohexenones.¹² Once the C-3 position of Hagemann's ester is substituted, Dyier and coworkers found that a second alkyl substituent can be introduced at C-1 in high yield (cf. **11**).¹³ The introduction of an alkyl group at C-5 (cf. **9**) produces enone **12**, which upon saponification and decarboxylation of the C-1 ester produces enone **13** having four different alkyl substituents. Substituted cyclohexenones are easily aromatized using palladium catalyzed dehydrogenation¹⁴ or by introducing a leaving group at C-5 followed by elimination and keto-enol tautomerization.¹⁵ If an alkyl group is introduced at C-6 while preparing the Hagemann's ester, the systematic introduction of alkyl substituents at C-1, C-3, and C-5 produces phenols with five different alkyl substituents (cf. **15**). A structural feature common to all Hagemann's esters is the methyl group at C-2. A project in our labs required the preparation

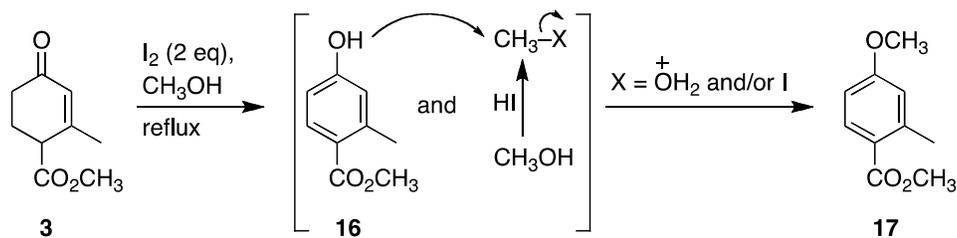
of a pentaalkyl-substituted phenol with a methyl substituent at C-2. This led us to explore the strategy generalized in Scheme 2. The results of this investigation are described herein.



Scheme 2. Our alkylation strategy.

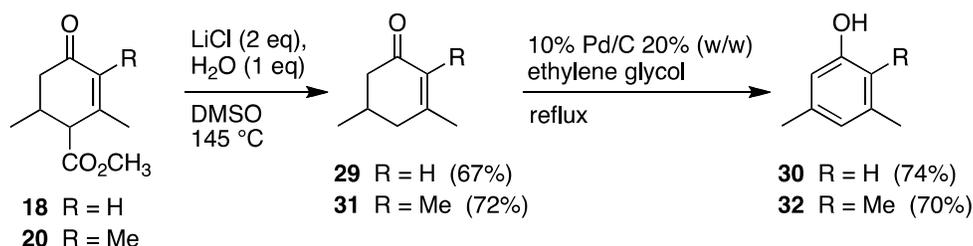
Results and Discussion

In 1990, Kotnis found that Hagemann's esters aromatized on treatment with iodine in refluxing methanol (Scheme 3).¹⁶ While a mechanism has not been proposed for this transformation, it seems reasonable that *p*-hydroxybenzoate **16** was formed by oxidation with one molecule of iodine. This oxidation produces hydrogen iodide in situ, which can protonate the solvent, methanol. The protonated methanol can either act itself as an electrophile in an S_N2-displacement or it can form iodomethane in situ; either electrophilic species leads to *p*-methoxybenzoate **17**.



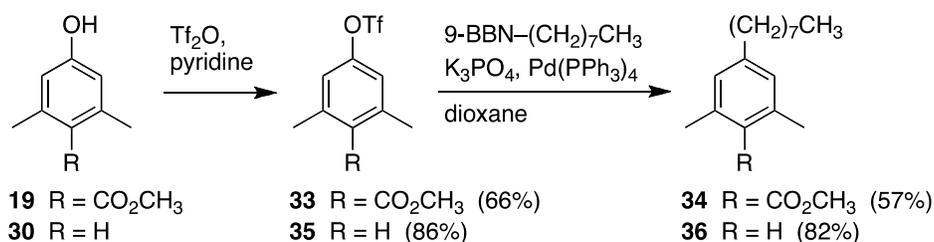
Scheme 3. Kotnis' conversion of Hagemann's ester into a *p*-methoxybenzoate.

moiety present in **18** and **20** is vinylogous to the enone and can undergo decarboxylation using the same conditions that apply to β -keto esters (Scheme 6). Accordingly, heating esters **18** and **20** to 145 °C in moist DMSO containing LiCl gave enones **29** and **31** in good yields. Refluxing enone **29** or **31** in ethylene glycol in the presence of 10% Pd/C (Hornig's aromatization conditions¹⁴) produced phenols **30** or **32**, respectively.



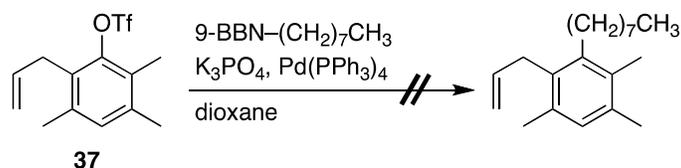
Scheme 6. Preparation of trisubstituted phenols.

Our efforts then turned toward the synthesis of 4-alkyl-substituted benzenes. In the Suzuki coupling reaction alkylboron reagents can be cross-coupled with aryl or vinyl halides^{18a} and triflates^{18b} by using a Pd catalyst. The application of this method to our substrates would allow for highly alkylated phenols to be converted into more functionalized arenes. For example, phenol **21** was converted into triflate **33** using pyridine and triflic anhydride (Scheme 7). Triflate **33** and the alkylborane formed by reacting 9-BBN with 1-octene were treated with Pd(PPh₃)₄, to produce arene **34** in 57% yield. Triflate **35** was generated from phenol **32** in 86% yield. Standard Suzuki coupling conditions gave benzene derivative **36** in 82% yield.



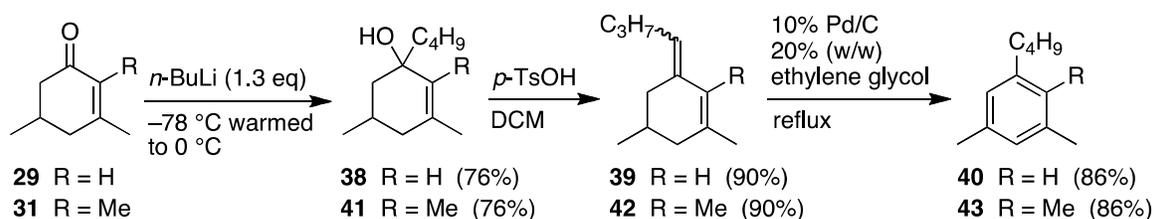
Scheme 7. Preparation of a tetra- or a pentasubstituted benzene.

Interestingly, an attempted Suzuki coupling of triflate **37** failed (Scheme 8), which suggests that substitution at the positions ortho to the triflate generates steric crowding that complicate the Suzuki coupling reaction. A search of the literature failed to find examples of successful Suzuki couplings between an aryl triflate with two ortho substituents under standard Suzuki conditions.



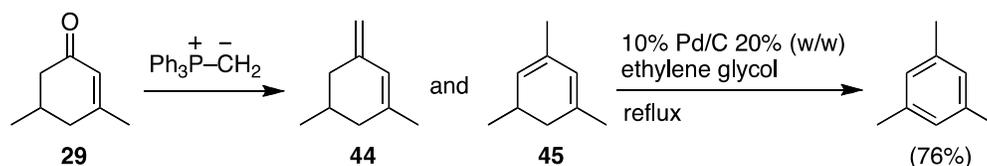
Scheme 8. Failure of the Suzuki coupling with sterically crowded triflates.

Traditional methods to functionalize the C-4 position were also investigated. For example, treatment of enone **29** and **31** with 1.3 equivalents of *n*-butyllithium gave tertiary alcohols **38** and **41**, respectively (Scheme 9). Both alcohols rapidly dehydrated to produce methylenecyclohexenes. The formation of the exocyclic double bond was inconsequential as dienes **39** and **42** aromatized in good yield affording the polyalkyl-substituted benzenes **40** and **43**, respectively.

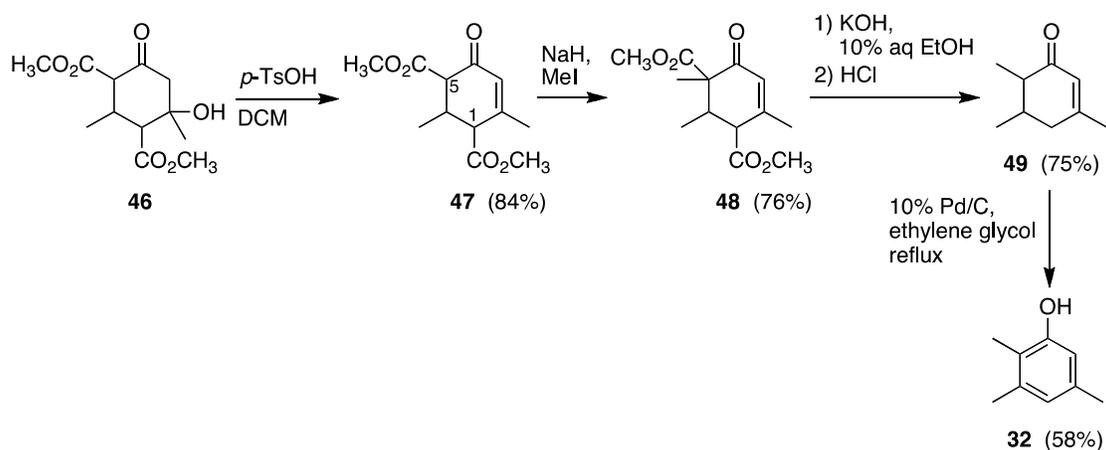


Scheme 9. Preparation of tetrasubstituted alkylbenzenes.

Methylenecyclohexenes similar to **39** and **42** can also be prepared by treating a substituted 2-cyclohexenone with a Wittig reagent. For example, treatment of enone **29** with methylene triphenylphosphonium ylide produced a mixture of methylenecyclohexene **44** and cyclohexa-1,3-diene **45**, which produced mesitylene in 76% yield upon treatment with palladium (Scheme 10).



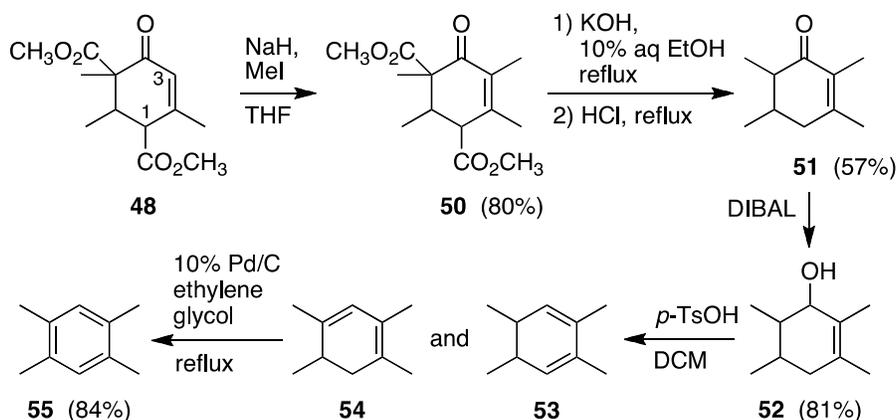
Scheme 10. Functionalization of 2-cyclohexenone using a Wittig/aromatization sequence.



Scheme 11. Preparation of 2,3,5-trimethylphenol **32**.

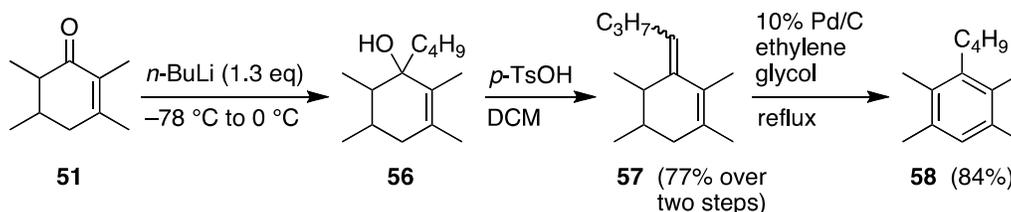
In contrast to the normal one-pot Hagemann's ester synthesis, careful monitoring of the reaction allowed us to stop the cascade of transformations at the tertiary alcohol **46**. Treating **46** with *p*-TsOH produced enone **47**, which retains the C-5 ester. Although both the C-1 and C-5 methine positions are doubly activated, we predicted that the more accessible H-5 would be abstracted preferentially to form the C-4, C-5 enolate. When enone **47** was treated with sodium hydride and methyl iodide, only diester **48** was isolated (Scheme 11). In order to prove this structure, diester **48** was saponified and decarboxylated to give 3,5,6-trimethyl-2-cyclohexenone **49**, which was then aromatized to produce phenol **32**, which was synthesized earlier through a different route.

Another subtle advantage of diester **48** is that it can be alkylated at C-3 (cf. **50**) and then decarboxylated to produce tetrasubstituted enone **51** (Scheme 12). The conversion of **51** into 1,2,4,5-tetramethylbenzene was straightforward. Treatment of enone **51** with DIBAL gave alcohol **52** in 81% yield. Dehydration of **52** using *p*-TsOH in DCM gave an inseparable mixture of isomeric dienes **53** and **54** which were aromatized to give 1,2,4,5-tetramethylbenzene **55**.



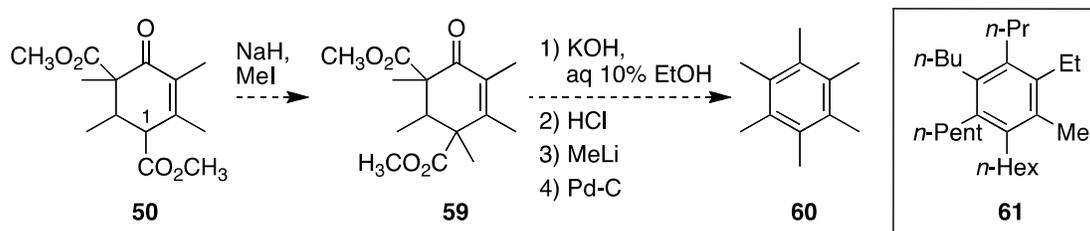
Scheme 12. Preparation of 1,2,4,5-tetramethylbenzene.

The tetrasubstituted enone **51** could give pentasubstituted benzene derivatives (Scheme 13). Treatment of enone **51** with *n*-butyllithium gave tertiary alcohol **56**, which was dehydrated under mildly acidic conditions to give diene **57**. The aromatization of diene **57** was achieved by palladium-catalyzed dehydrogenation¹⁹ to give pentaalkylbenzene derivative **58**.



Scheme 13. Synthesis of 3-butyl-1,2,4,5-tetramethylbenzene **58**.

Scheme 14 shows how hexamethylbenzene **60** could be synthesized based on the findings reported in this paper. The synthesis of whimsical hexasubstituted benzenes, such as **61**, can be envisioned using this methodology.



Scheme 14. The preparation of hexamethylbenzene.

In summary, we have shown that Hagemann's esters can be used to prepare polysubstituted phenols and benzene derivatives in a concise, completely regioselective fashion. In addition, we observed that although Suzuki coupling reactions can be used to convert complex phenols into complex benzene derivatives, triflates with two ortho substituents failed to couple. A substituent can be readily introduced at C-4 by using standard organometallic additions or Wittig reactions.

Experimental Section

General. Routine ¹H NMR spectra were determined in CDCl₃ on either a Bruker AC250 instrument (¹H: 250 MHz; ¹³C: 62.9 MHz) or a Bruker AC300 instrument (¹H: 300 MHz; ¹³C: 75.5 MHz). Chemical shifts are reported relative to TMS. The data reported as integer numbers are accurate to within ±10%. Genuine effort was made to ensure that NMR spectra did not contain any solvent "impurities." All samples were "pure" by ¹H and ¹³C NMR analysis. Infrared

(IR) spectra were recorded as thin films between polished sodium chloride plates on a Perkin-Elmer FT-IR 1600. Electron impact mass spectra (EIMS) were recorded on a Finnigan 4000 spectrometer (70 eV) and are expressed in m/z units.

Anhydrous THF and diethyl ether were prepared by refluxing with, and distillation from sodium/benzophenone under a nitrogen atmosphere in a recycling still. Anhydrous DMF was prepared by refluxing over, and distillation from calcium hydride. All reactions were run under nitrogen using standard laboratory techniques for the exclusion of oxygen and moisture and were monitored by TLC analysis until the starting material was completely consumed. CAS numbers were provided for only a few compounds.

General procedure A. Alkylation of Hagemann's esters

NaH (1.1 molar equiv relative to the ester) was degreased with hexanes and the residual solvent was removed by vacuum. NaH was placed under nitrogen and cooled to $-15\text{ }^{\circ}\text{C}$. Dry THF (10 mL) was added to the NaH. The Hagemann's ester (1.0 eq) in THF (25 mL) was added slowly to the stirred NaH, after which the mixture was stirred at $-15\text{ }^{\circ}\text{C}$ for 1 h. An alkyl halide (1.5 equiv) was then added and the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ether to four times the original volume. The organic layer was washed with water (4 x 25 mL). The aqueous phase was extracted with ether (3 x 10 mL). The organic extracts were combined, washed with brine, dried over anhydrous MgSO_4 , filtered, and then concentrated. The product was isolated by flash chromatography on silica gel.²⁰

General procedure B. Aromatization of alkylated Hagemann's esters

The C-3-alkylated Hagemann ester (cf. **10**) (1 eq) was dissolved in *t*-butyl alcohol (150 mL). Iodine (2 equiv) was added portionwise. The reaction mixture was refluxed, while maintaining the solvent level between 125 mL and 150 mL. The reaction mixture was cooled and the solvent was removed by rotary evaporation. The resulting residue was taken up in ether (200 mL) and washed with water (20 mL), and 10% sodium thiosulfate (3 x 20 mL). The ether layer was concentrated to one-third its original volume and was then extracted with 4% $\text{NaOH}_{(\text{aq})}$ (4 x 15 mL). The basic extract was then cooled to $0\text{ }^{\circ}\text{C}$ using an ice bath and was acidified with 10% $\text{HCl}_{(\text{aq})}$. The acidified layer was then extracted with ether/ethyl acetate 1:1 (3 x 40 mL). The organic extracts were combined, washed with brine, dried over anhydrous MgSO_4 , filtered, and then concentrated.

General procedure C. Synthesis of allyl aryl ethers

The phenol **21** (1.0 equiv) was dissolved in dry DMF (18 mL). Allyl chloride (1.4 equiv), potassium carbonate (2 equiv), and potassium iodide (catalytic amount) were added sequentially and the reaction mixture was stirred for 24 h. The reaction mixture was diluted with ether (125 mL) and washed with water (3 x 30 mL). The aqueous phase was extracted with ether (20 mL), and the ethereal extracts were combined, washed with 10% aqueous cupric sulfate (20 mL) and brine (10 mL). The organic layer was dried over anhydrous MgSO_4 , filtered, and then

concentrated. The Claisen rearrangement precursor was isolated using flash chromatography on silica gel.

General procedure D. *ortho*-Claisen rearrangement

The allyl aryl ether (1.0 equiv) was dissolved in 2 mL of *N,N*-diethylaniline. The reaction mixture was sealed in a thick-walled glass tube equipped with a Teflon screw top (Ace Glass) and was heated at 200 °C for 12 h. The reaction mixture was cooled and diluted with ether to ten times its original volume. The organic phase was washed with cold 5% HCl_(aq) (4 x 5 mL), and brine (5 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and then concentrated. The rearrangement product was isolated by flash chromatography on silica gel.

General procedure E. Synthesis of triflates

The phenol (1.0 equiv) was dissolved in pyridine (0.4 mL). The reaction mixture was cooled to 0 °C. Triflic anhydride (1.1 equiv) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was poured into water (2 mL) and ether (25 mL) was added. The organic layer was washed with water (3 x 3 mL) and brine (3 mL), and dried over anhydrous MgSO₄, filtered, and then concentrated. The crude triflate was isolated via flash chromatography on silica gel.

General procedure F. Suzuki coupling of triflates

To a flask at 0 °C was added 9-BBN (0.5 M solution in THF, 1.1 mmol) and 1-octene (1.1 mmol). The mixture was warmed to room temperature and stirred at room temperature for 3 h. Dioxane (5 mL), K₃PO₄ (1.5 mmol), Pd(PPh₃)₄ (0.025 mmol), and triflate (1.0 mmol) were added and the resulting mixture was heated at 85 °C for 5 h. The residual boron reagent was oxidized with 3 M NaOAc_(aq) (0.5 mL) and 30% H₂O₂ at room temperature for 1 h. The reaction mixture was poured into water (5 mL) and diluted with ether (40 mL). The organic layer was washed with water (3 x 3 mL) and brine (3 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and then concentrated. The coupled aromatic product was purified via flash chromatography on silica gel.

General procedure G. Aromatization of 2-cyclohexen-1-ones

To a solution of an alkylated 2-cyclohexen-1-one (1.0 equiv) in ethylene glycol (6.0 mL) at room temperature was added 10% Pd/C (100 mg / 1 g of enone). The solution was refluxed for 6 h. The solution was cooled to 50 °C and filtered to remove the catalyst, which was washed with hot ethyl acetate (3 x 15 mL). The organic phases were combined, washed with water (6 x 10 mL) and then concentrated at reduced pressure. The residue was taken up in ether (10 mL) and extracted with 5% NaOH_(aq) (3 x 5 mL). The basic extracts were combined, cooled in an ice bath, and then acidified with 10% HCl_(aq). The aqueous phase was extracted (3 x 15 mL) with ether/ethyl acetate 1:1. The organic phases were combined, washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated.

General procedure H. Decarboxylation of methyl 4-oxo-2-cyclohexenecarboxylates

The substrate (1.0 equiv) was dissolved in DMSO (3.0 mL). Water (2 mL) and LiCl (2 equiv) were added. The reaction mixture was heated at 145 °C on an oil bath for 6 h, and was cooled to room temperature and diluted with ether (10 mL). The organic layer was washed with water (6 x 3 mL) and brine (3 mL), dried over anhydrous MgSO₄, filtered, and then concentrated. The resulting 2-cyclohexenone was purified via flash chromatography.

General procedure I. Decarboxylation of Hagemann diesters

Into a round bottom flask was placed EtOH (4 mL), water (1 mL), and KOH (7 equiv). The diester (1.0 equiv) was dissolved in EtOH (5 mL) and added dropwise to the stirred KOH solution. The reaction mixture was refluxed under nitrogen for 12 h. After cooling, the solution was diluted with water (10 mL) and then concentrated using a rotary evaporator to remove the ethanol. The reaction mixture was acidified with 6 M HCl to pH 2 and refluxed for 2 h. After cooling to room temperature, the reaction mixture was extracted with ether (3 x 10 mL). The organic layer was washed with water (5 mL), and brine (5 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and then concentrated. The product was purified by chromatography on silica gel.

General procedure J. 1,2-Addition of an organolithium reagent to 2-cyclohexenones

Ether (5 mL) was added to a round bottom flask. *n*-BuLi (2.5 M solution in hexanes, 9.05 mmol, 1.25 equiv) was added and the solution was cooled to -78 °C. The substrate (6.96 mmol, 1.0 equiv) dissolved in ether (5 mL) was added dropwise and the resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was poured into cold saturated NH₄Cl_(aq) (20 mL) and extracted with ether (3 x 15 mL). The organic layer was washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated.

General procedure K. Dehydration of tertiary alcohols

The allylic alcohol (1.14 mmol) was dissolved in DCM (2 mL). The resulting solution was cooled to 0 °C. To the stirred solution was added *p*-TsOH (0.3 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with DCM (10 mL) and washed with saturated NaHCO_{3(aq)} solution (2 x 3 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and then concentrated. The resulting diene was isolated via chromatography on silica gel.

General procedure L. Aromatization of dienes using the Horning protocol^{14b,c}

The diene (251 mmol, 1.0 equiv) was dissolved in ethylene glycol (4 mL). To this solution was added 10% Pd/C (15% of the weight of the substrate). The resulting solution was refluxed for 4 h. The reaction mixture was cooled to 50 °C, diluted with hot ethyl acetate (10 mL), and the reaction mixture was filtered to remove the catalyst. The recovered catalyst was washed with hot

ethyl acetate (3 x 10 mL). The organic phases were combined, washed with water (3 x 7 mL) and brine (5 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and then concentrated. The resulting arene was purified by flash chromatography on silica gel.

Methyl 2,6-dimethyl-4-oxo-2-cyclohexenecarboxylate (18). The mixture of ethyl acetate (52.75 g, 454 mmol) and freshly distilled acetaldehyde (9.0 g, 204 mmol) was cooled to -5 °C. Piperidine (348 mg, 4.08 mmol) and ethanol (1.5 mL) were added, and the mixture was swirled. The flask was stoppered with a cork stopper and refrigerated for 24 h. Additional piperidine (348 mg) in ethanol (1.5 mL) was added, the contents swirled, and refrigerated for an additional 24 h. The same amount of piperidine in ethanol was added, and after a total of 26 h of refrigeration, the reaction mixture was allowed to stand unstoppered at room temperature for 24 h. A water-cooled condenser was added to the reaction flask and the reaction mixture was heated to 100 °C on a hot water bath. A distillation apparatus replaced the condenser and ethanol and piperidine were distilled off at atmospheric pressure. The distillation of the residue was continued under high vacuum. Product **18** (32.0 g, 86%), bp 115–120 °C (3 mm Hg), was isolated as an oil and was a mixture of diastereomers of approximately the same R_f = 0.27 (hexanes/ethyl acetate, 4:1). ¹H NMR (300 MHz): δ 1.06–1.09 (m, 3 H), 1.93–19.5 (m, 3 H), 2.07–2.16 (m, 1 H), 2.53–2.61 (m, 2 H), 3.02–3.05 (m, 1 H), 3.73–3.77 (m, 3 H), 5.96–5.97 (m, 1H).

Methyl 2-methyl-4-oxo-6-phenyl-2-cyclohexenecarboxylate (22). Benzaldehyde (1.06 g, 10.0 mmol) and methyl acetoacetate (2.32 g, 20.0 mmol) were mixed in a round bottom flask at room temperature. Piperidine (85 mg, 1 mmol) was added, and the mixture was stirred for 24 h, during which time a solid mass formed. The solid mass was broken up using a spatula and washed with cold 50% aqueous ethanol. The solid was then dissolved in dichloromethane (15 mL/g of solid), and piperidine (425 mg, 5 mmol) was added. The reaction mixture was stirred for 4 d. The reaction mixture was washed with water and brine. The organic layer was dried over anhydrous MgSO₄, filtered, and then concentrated to yield a crude residue (2.31 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 1:1) yielded **22** as a light yellow oil (1.78 g, 73%), which was a mixture of diastereomers of approximately the same R_f = 0.55 (hexanes/ethyl acetate 1:1). ¹H NMR (250 MHz): δ 1.97–1.98 (m, 3 H), 2.55–2.73 (m, 2 H), 3.58–3.70 (m, 5 H), 6.05–6.06 (m, 1 H), 7.18–7.32 (m, 5 H).

Methyl 4-hydroxy-2,6-dimethylbenzoate (19). The reaction followed general procedure B using **18** (1.00 g, 5.50 mmol), *t*-butyl alcohol (30 mL), and iodine (2.79 g, 11.00 mmol). The reaction mixture was refluxed for 3 d. Standard workup furnished a crude residue (650 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 3:2) gave phenol **19** (598 mg, 60%) as an oil, which was homogeneous by TLC analysis, R_f = 0.24 (hexanes/ethyl acetate 4:1). ¹H NMR (300 MHz): δ 2.27 (s, 6 H), 3.89 (s, 3 H), 5.61 (bs, 1 H), 6.48 (s, 2 H). ¹³C NMR (75.5 MHz): δ 170.8, 156.4, 138.0, 114.6, 113.0, 51.9, 20.1. GC-MS: *m/z* (%) 180 (40), 149 (100), 121 (20). IR (film): ν 3299, 1691, 1606, 1300 cm⁻¹.

Methyl 2,3,6-trimethyl-4-oxo-2-cyclohexenecarboxylate (20). The reaction was set up as in general procedure A using methyl 2,6-dimethyl-4-oxo-2-cyclohexenecarboxylate **18** (6.40 g, 35.16 mmol), THF (70 mL), and iodomethane (17.86 g, 70.32 mmol). Standard workup gave a

crude residue (4.83 g). Column chromatography (silica gel, hexanes/ethyl acetate 4:1) afforded product **20** as an oil (4.43 g, 64%), which was a mixture of diastereomers of approximately the same $R_f = 0.36$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 1.01–1.05 (m, 3 H), 1.73–1.79 (m, 3 H), 1.88–1.91 (m, 3H), 2.26–2.68 (m, 3 H), 3.07–3.23 (m, 1 H), 3.71–3.75 (m, 3 H).

Methyl 2,3-dimethyl-4-oxo-6-phenyl-2-cyclohexenecarboxylate (23). The reaction was set up as described in general procedure A using enone **22** (3.65 g, 26.22 mmol), THF (35 mL), and iodomethane (5.58 g, 39.33 mmol). Standard workup furnished a crude residue (3.71 g). Chromatographic separation (silica gel, elution with hexanes/ethyl acetate 3:1) yielded **23** as an oil (2.13 g, 55%), which was a mixture of diastereomers of approximately the same $R_f = 0.41$ (hexanes/ethyl acetate 3:1). $^1\text{H NMR}$ (300 MHz): δ 1.85–2.07 (m, 3 H), 2.56–2.80 (m, 2 H), 3.31–3.64 (m, 5 H), 7.08–7.36 (m, 5 H).

Methyl 4-hydroxy-2,3,6-trimethylbenzoate (21). The reaction was performed as described in general procedure B using **20** (1.23 g, 6.27 mmol), *t*-butyl alcohol (45 mL), and iodine (3.18 g, 12.54 mmol). The reaction mixture was refluxed for 3 d. Standard workup furnished a crude residue (860 mg). Column chromatography (silica gel, DCM/acetone 40:1) yielded phenol **21** as a light yellow oil (799 mg, 65%), which was homogeneous by TLC analysis, $R_f = 0.33$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 2.13 (s, 3 H), 2.20 (s, 3 H), 2.22 (s, 3 H), 3.89 (s, 3 H), 4.82 (s, 1 H), 6.47 (s, 1 H). $^{13}\text{C NMR}$ (75.5 MHz): δ 171.5, 154.2, 135.2, 133.1, 126.9, 120.3, 114.1, 51.9, 19.4, 17.2, 11.2. GC-MS: m/z (%) 194 (40), 163 (100), 135 (20), 91 (20). IR (film): ν 3323, 2915, 1689 cm^{-1} .

Methyl 5-hydroxy-3,4-dimethylbiphenyl-2-carboxylate (24). The reaction was performed as described in general procedure B using **23** (693 mg, 2.68 mmol), *t*-butyl alcohol (20 mL), and iodine (1.36 g, 5.36 mmol). The reaction mixture was refluxed for 5 d. Standard workup gave a crude residue (402 mg). Chromatographic separation (silica gel, elution with hexanes/ethyl acetate 4:1) yielded phenol **24** as an oil (232 mg, 34%), homogeneous by TLC analysis $R_f = 0.32$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 2.20 (s, 3 H), 2.28 (s, 3 H), 3.54 (s, 3 H), 5.33 (s, 1 H), 6.61 (s, 1 H), 7.26–7.37 (m, 5 H). $^{13}\text{C NMR}$ (75.5 MHz): δ 171.1, 154.2, 140.6, 138.7, 135.7, 128.2, 128.0, 127.2, 126.3, 122.1, 113.8, 51.9, 17.11, 11.6. GC-MS: m/z (%) 256 (55), 225 (100), 182 (15). IR (film): $\tilde{\nu}$ 3391, 1698, 1268 cm^{-1} .

Methyl 4-(allyloxy)-2,3,6-trimethylbenzoate (25). The reaction was set up as in the general procedure C using phenol **21** (84 mg, 0.38 mmol), DMF (1 mL), allyl chloride (40.3 mg, 0.53 mmol) and potassium carbonate (74.5 mg, 0.76 mmol). Standard workup provided a crude residue (91 mg). Chromatographic separation (silica gel, elution with hexanes/ethyl acetate 9:1) yielded ether **25** as an oil (80 mg, 79%), homogeneous by TLC analysis, $R_f = 0.68$ (hexanes/ethyl acetate 9:1). $^1\text{H NMR}$ (250 MHz): δ 2.15 (s, 3 H), 2.20 (s, 3 H), 2.27 (s, 3 H), 3.89 (s, 3 H), 4.51–4.53 (m, 2 H), 5.25–5.30 (m, 1 H), 5.38–5.45 (m, 1 H), 5.98–6.12 (m, 1 H), 6.53 (s, 1 H). $^{13}\text{C NMR}$ (62.9 MHz): δ 171.1, 156.8, 134.7, 133.3, 132.9, 127.1, 123.1, 117.0, 110.8, 68.9, 51.8, 19.9, 17.2, 11.5. GC-MS: m/z (%) 234 (100), 203 (85), 161 (90), 133 (75). IR (film): $\tilde{\nu}$ 2914, 1272, 1151 cm^{-1} .

Methyl 5-(allyloxy)-3,4-dimethylbiphenyl-2-carboxylate (27). The reaction was set up as in

the general procedure C using phenol **24** (81 mg, 0.27 mmol) DMF (1 mL), allyl chloride (28.7 mg, 0.38 mmol), and potassium carbonate (53 mg, 0.54 mmol). Standard workup furnished a crude residue (89 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 4:1) yielded ether **27** as a pale oil (75 mg, 80%), homogeneous by TLC analysis, $R_f = 0.72$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 2.24 (s, 3 H), 2.30 (s, 3 H), 3.55 (s, 3 H), 4.56–4.59 (m, 2 H), 5.27–5.31 (m, 1 H), 5.40–5.46 (m, 1 H), 6.04–6.11 (m, 1 H), 6.71 (s, 1 H), 7.32–7.41 (m, 5 H). $^{13}\text{C NMR}$ (75.5 MHz): δ 170.9, 156.8, 141.3, 138.4, 135.3, 133.2, 128.2, 128.1, 127.2, 126.5, 125.0, 117.2, 110.5, 69.0, 51.8, 17.1, 11.8. GC-MS: m/z (%) 296 (100), 265 (50), 195 (80). IR (film): ν 2914, 1723, 1262, 1170 cm^{-1} .

Methyl 3-allyl-4-hydroxy-2,5,6-trimethylbenzoate (26). The reaction was set up as in general procedure D using ether **25** (100 mg, 0.43 mmol) and *N,N*-diethylaniline (100 mg). Standard workup provided a crude residue (100 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 4:1) gave phenol **26** as an oil (89 mg, 89%), homogeneous by TLC analysis, $R_f = 0.41$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 2.14 (s, 3 H), 2.17 (s, 3 H), 2.17 (s, 3 H), 3.40–3.42 (m, 2 H), 3.89 (s, 3 H), 5.01–5.11 (m, 2 H), 5.86–5.97 (m, 1 H). $^{13}\text{C NMR}$ (75.5 MHz): δ 171.8, 152.9, 135.1, 132.2, 130.9, 128.2, 120.9, 120.6, 116.1, 52.0, 30.9, 17.1, 16.6, 11.7. GC-MS: m/z (%) 234 (60), 203 (100), 40 (50). IR (film): ν 2923, 1710, 1196 cm^{-1} .

Methyl 6-allyl-5-hydroxy-3,4-dimethylbiphenyl-2-carboxylate (28). The reaction was set up as in general procedure D using ether **27** (50 mg, 0.16 mmol) and *N,N*-diethylaniline (100 mg, 0.67 mmol). Standard workup furnished a crude residue (50 mg). Chromatographic separation (silica gel, DCM/acetone 90:1) yielded phenol **28** as an oil (41 mg, 82%), homogeneous by TLC analysis, $R_f = 0.42$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 2.22 (s, 3 H), 2.26 (s, 3 H), 3.16–3.19 (m, 2 H), 3.40 (s, 3 H), 5.07–5.17 (m, 2 H), 5.30 (s, 1 H), 5.82–5.91 (m, 1 H), 7.18–7.35 (m, 5 H). $^{13}\text{C NMR}$ (75.5 MHz): δ 170.7, 153.4, 139.1, 137.8, 136.1, 132.8, 129.2, 128.0, 127.8, 127.2, 123.0, 120.1, 116.7, 51.5, 32.3, 17.0, 11.9. GC-MS: m/z (%) 296 (100), 265 (80), 249 (80). IR (film): ν 3522, 1709, 1195 cm^{-1} .

3,5-Dimethylcyclohex-2-enone (29). The reaction was set up as in general procedure H using ester **18** (8.00 g, 4.39 mmol), DMSO (50 mL), water (20 mL), and LiCl (0.37 g, 8.78 mmol). Standard workup produced a crude residue (5.42 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 4:1) yielded enone **29** as an oil (3.67 g, 67%), identical to the known compound, 3,5-dimethyl-2-cyclohexen-1-one [1123-09-7]. $R_f = 0.22$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (250 MHz): δ 1.05 (d, $J = 6$ Hz, 3 H), 1.95 (s, 3 H), 2.00–2.45 (m, 5 H), 5.86 (s, 1 H).

3,5-Dimethylphenol (30). The reaction was set up as in general procedure G using enone **29** (900 mg, 8.18 mmol), ethylene glycol (9.0 mL) and 10% Pd/C (100 mg). Standard workup furnished phenol **30** as an oil (652 mg, 74%), identical to the known compound, 3,5-dimethylphenol [108-68-9]. $R_f = 0.43$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (250 MHz): δ 2.27 (s, 6 H), 6.48 (s, 2 H), 6.59 (s, 1 H).

2,3,5-Trimethylcyclohex-2-enone (31). The reaction was set up as in general procedure H using **20** (509 mg, 2.10 mmol), DMSO (3 mL), water (2 mL), and LiCl (176 mg, 0.42 mmol). Standard workup provided a crude residue (350 mg). Column chromatography (silica gel, hexanes/ethyl

acetate 4:1) yielded enone **31** as an oil (257 mg, 72%), identical to the known compound, 2,3,5-dimethyl-2-cyclohexenone [93445-20-6]. $R_f = 0.34$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (250 MHz): δ 1.00 (d, $J = 6$ Hz, 3 H), 1.74 (s, 3H), 1.90 (s, 3H), 2.01–2.47 (m, 5 H).

2,3,5-Trimethylphenol (32). The reaction was set up as in general procedure G using enone **31** (582 mg, 4.21 mmol), ethylene glycol (6 mL), and 10% Pd/C (60 mg). Following basic extraction, the solvent was removed at reduced pressure to yield phenol **32** as an oil (402 mg, 70%), identical to the known compound, 2,3,5-trimethylphenol [697-82-5]. $R_f = 0.41$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (250 MHz): δ 2.15 (s, 3 H), 2.26 (s, 6 H), 4.60 (s, 1 H), 6.48 (s, 1 H), 6.62 (s, 1 H).

Methyl 2,6-dimethyl-4-(trifluoromethylsulfonyloxy)benzoate (33). The reaction was set up as in general procedure E using phenol **19** (352 mg, 1.13 mmol), pyridine (1.5 mL), and triflic anhydride (261 mg, 1.24 mmol). After standard workup, the solvent was removed at reduced pressure to yield a crude residue (514 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 9:1) yielded triflate **33** as an oil (400 mg, 66%), homogeneous by TLC analysis, $R_f = 0.56$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (250 MHz): δ 2.34 (s, 6 H), 3.93 (s, 3 H), 6.96 (s, 2 H). $^{13}\text{C NMR}$ (62.9 MHz): δ 169.0, 149.4, 138.2, 134.1, 121.2, 120.1, 52.3, 19.8. GC-MS: m/z (%) 312 (50), 281 (100), 91 (70), 69 (99). IR (film): ν 1732, 1421, 1210, 1140 cm^{-1} .

Methyl 2,6-dimethyl-4-octylbenzoate (34). The reaction was set up as in general procedure F using 9-BBN (0.5 M solution in THF, 6.71 mmol), 1-octene (751 mg, 6.71 mmol), dioxane (3 mL), K_3PO_4 (193 mg, 0.91 mmol), $\text{Pd}(\text{PPh}_3)_4$ (17 mg, 0.015 mmol), and triflate **33** (191 mg 0.61 mmol). Standard workup gave a crude residue (237 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 9:1) yielded ester **34** as an oil (96 mg, 57%), homogeneous by TLC analysis, $R_f = 0.40$ (hexanes/ethyl acetate 9:1). $^1\text{H NMR}$ (250 MHz): δ 0.88 (t, $J = 7$ Hz, 3 H), 1.22–1.38 (m, 10 H), 1.50–1.61 (m, 2 H), 2.29 (s, 6 H), 2.52 (t, $J = 8$ Hz, 2 H), 3.89 (s, 3 H), 6.84 (s, 2 H). $^{13}\text{C NMR}$ (62.9 MHz): δ 170.7, 144.4, 135.1, 131.0, 127.7, 51.7, 35.6, 31.9, 31.3, 29.4, 29.3, 29.2, 22.6, 19.8, 14.1. GC-MS: m/z (%) 276 (23), 245 (22), 178 (60), 119 (100). IR (film): ν 2923, 1728, 1436, 1267 cm^{-1} .

3,5-Dimethylphenyl trifluoromethanesulfonate (35). The reaction was set up as in general procedure E using 3,5-dimethylphenol **30** (1.00 g, 3.94 mmol), pyridine (5.0 mL), and triflic anhydride (910 mg, 4.33 mmol). Standard workup gave a crude residue (2.03 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 9:1) yielded **35** as an oil (1.78 g, 86%), homogeneous by TLC analysis, $R_f = 0.60$ (hexanes/ethyl acetate 4:1). $^1\text{H NMR}$ (300 MHz): δ 2.35 (s, 6 H), 6.89 (s, 2 H), 7.01 (s, 1 H). $^{13}\text{C NMR}$ (62.9 MHz): δ 149.5, 140.4, 130.0, 121.3, 118.7, 21.2. GC-MS: m/z (%) 254 (42), 175 (20), 121 (100), 77 (54). IR (film): ν 1620, 1587, 1423, 1211 cm^{-1} .

1,3-Dimethyl-5-octylbenzene (36). The reaction was set up as in general procedure F using 9-BBN (430 μL , 0.5 M solution in THF, 2.15 mmol), 1-octene (240 mg, 2.15 mmol), dioxane (8 mL), K_3PO_4 (623 mg, 2.94 mmol), $\text{Pd}(\text{PPh}_3)_4$ (57 mg, 0.05 mmol), and **35** (500 mg, 1.96 mmol). Standard workup provided a crude residue (1.12 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 19:1) yielded arene **36** as an oil (351 mg, 82%), homogeneous by TLC

analysis, $R_f = 0.87$ (hexanes/ethyl acetate 9:1). ^1H NMR (300 MHz): δ 0.92 (t, $J = 7$ Hz, 3 H), 1.25–1.34 (m, 10 H), 1.60–1.65 (m, 2 H), 2.32 (s, 6 H), 2.53–3.58 (t, 2 H, $J = 8$ Hz), 6.84 (s, 3 H). ^{13}C NMR (75.5 MHz): δ 142.9, 137.6, 127.2, 126.2, 35.9, 31.9, 31.7, 29.5, 29.3, 22.7, 21.3, 14.1. GC-MS: m/z (%) 218 (16), 120 (100), 105 (20). IR (film): ν 2923, 1606, 1460 cm^{-1} .

1-Butyl-3,5-dimethylcyclohex-2-enol (38). The reaction was set up as in general procedure J using enone **29** (1.35 g, 12.05 mmol), ether (14 mL), and *n*-BuLi (6.0 mL, 2.5 M solution in hexanes, 15.06 mmol). Standard workup provided a crude residue (1.90 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 4:1) yielded alcohol **38** as an oil (1.51 g, 76%), homogeneous by TLC analysis, $R_f = 0.40$ (hexanes/ethyl acetate 4:1). This compound was too unstable to be characterized further.

1-Butyl-2,3,5-trimethylcyclohex-2-enol (41). The reaction was set up as in general procedure J using enone **31** (962 mg, 7.75 mmol), ether (10 mL), and *n*-BuLi (3.87 mL, 2.5 M solution in hexanes, 9.68 mmol). Standard workup gave a crude residue (1.33 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 6:1) yielded alcohol **41** as an oil (1.05 g, 76%), homogeneous by TLC analysis, $R_f = 0.34$ (hexanes/ethyl acetate 6:1). This compound was too unstable to be characterized further.

(*E,Z*)-3-Butylidene-1,5-dimethylcyclohex-1-ene (39). The reaction was prepared as described in general procedure K using alcohol **38** (1.42 g, 7.89 mmol), DCM (14 mL), and *p*-TsOH (100 mg). After standard workup, the solvent was removed at reduced pressure to yield a crude residue (1.21 g). Chromatographic separation (silica gel, hexanes) yielded diene **39** as an oil (1.15 g, 90%), a mixture of *E* and *Z* isomers with approximately the same $R_f = 0.65$ (hexanes). ^1H NMR (250 MHz): δ 0.86–1.00 (m, 6 H), 1.27–1.42 (m, 4 H), 1.60–1.81 (m, 5 H), 2.00–2.09 (m, 2 H), 2.15–2.45 (m, 1 H), 4.97–5.20 (m, 1 H), 5.81–6.15 (m, 1 H).

(*E,Z*)-3-Butylidene-1,2,5-trimethylcyclohex-1-ene (42). The reaction followed general procedure K using alcohol **41** (1.05 g, 5.83 mmol), DCM (14 mL), and *p*-TsOH (80 mg). Standard workup yielded a crude residue (914 mg). Chromatographic separation (silica gel, hexanes) yielded diene **42** as an oil (895 mg, 90%), homogeneous by TLC analysis, $R_f = 0.62$ (hexanes). ^1H NMR (250 MHz): δ 0.86–0.98 (m, 6 H), 1.27–1.46 (m, 4 H), 1.67–1.81 (m, 8 H), 2.00–2.12 (m, 2 H), 2.50–2.57 (m, 1 H), 3.35–3.39 (m, 1 H). ^{13}C NMR (62.9 MHz): δ 136.9, 130.5, 126.3, 121.7, 41.5, 34.3, 30.0, 28.9, 23.1, 21.7, 20.7, 14.0, 13.9. GC-MS: m/z (%) 178 (45), 149 (100), 121 (38), 107 (67). IR (film): ν 2952, 1451, 1376 cm^{-1} .

1-Butyl-3,5-dimethylbenzene (40). The reaction was set up as in general procedure L using diene **39** (412 mg, 2.54 mmol), ethylene glycol (4.0 mL), and 10% Pd/C catalyst (60 mg). Standard workup furnished a crude residue (389 mg). Chromatographic separation (silica gel, hexanes) yielded arene **40** as an oil (351 mg, 86%), homogeneous by TLC analysis, $R_f = 0.54$ (hexanes). ^1H NMR (300 MHz): δ 0.93–0.98 (t, $J = 7$ Hz, 3 H), 1.30–1.42 (m, 2 H), 1.55–1.63 (m, 2 H), 2.32 (s, 6 H), 2.53–2.58 (t, $J = 7$ Hz, 3 H), 6.83 (s, 3 H). ^{13}C NMR (75.5 MHz): δ 142.8, 137.6, 127.2, 126.2, 35.5, 33.8, 22.5, 21.3, 14.0. GC-MS: m/z (%) 162 (35), 120 (100), 105 (40). IR (film): ν 2924, 1602, 1461 cm^{-1} .

1-Butyl-2,3,5-trimethylbenzene (43). The reaction was set up as in general procedure L using

diene **42** (414 mg, 2.32 mmol), ethylene glycol (4.0 mL), and 10% Pd/C catalyst (50 mg). After standard workup a crude residue (375 mg) was obtained. Chromatographic separation (silica gel, hexanes) yielded arene **43** as an oil (350 mg, 86%), homogeneous by TLC analysis, $R_f = 0.46$ (hexanes). $^1\text{H NMR}$ (300 MHz): δ 1.01 (t, $J = 7$ Hz, 3 H), 1.42–1.61 (m, 4 H), 2.21 (s, 3 H), 2.30 (s, 3 H), 2.32 (s, 3 H), 2.61–2.66 (t, $J = 8$ Hz, 2 H), 6.88 (s, 2 H). $^{13}\text{C NMR}$ (75.5 MHz): δ 140.9, 136.6, 134.5, 131.2, 128.3, 127.6, 33.8, 33.0, 22.9, 20.8, 20.6, 14.5, 14.0, 10.7. GC-MS: m/z (%) 176 (28), 133 (100), 119 (29). IR (film): ν 2932, 1460, 1376, 849 cm^{-1} .

1,5-Dimethyl-3-methylene-1-cyclohexene (44) and 1,3,5-trimethylcyclohexa-1,3-diene (45). Methyltriphenylphosphonium bromide (4.75 g, 13.3 mmol) was suspended in ether (60 mL). The mixture was cooled to 0 °C. *n*-BuLi (1.87 M solution in hexanes, 12.09 mmol) was added dropwise. The resulting solution was stirred at room temperature for 3 h. A solution of enone **29** (500 mg, 4.03 mmol) in ether (40 mL) was added. The reaction mixture was allowed to stir for 12 h. The ether was distilled off while simultaneously adding THF until the reaction solvent was mostly THF. The reaction mixture was refluxed for 6 h. After cooling to room temperature, the solution was diluted with water (80 mL) and extracted with ether (3 x 100 mL). The organic layer was washed with water (2 x 70 mL), 5% $\text{HCl}_{(\text{aq})}$ (50 mL), water (50 mL), and brine (40 mL). The organic layer was dried over anhydrous MgSO_4 , filtered, and then concentrated to yield a crude residue (350 mg). Chromatographic separation (silica gel, hexanes) yielded a mixture (237 mg, 48%) of 3-methylene-1-cyclohexene **44** and cyclohexa-1,3-diene **45**, which was aromatized without characterization.

Mesitylene. The mixture of 3-methylene-1-cyclohexene **44** and cyclohexa-1,3-diene **45** (127 mg, 1.04 mmol) was mixed with ethylene glycol (1 mL) and placed in a thick-walled glass tube equipped with a Teflon screw cap (Ace Glass). To this mixture was added 10% Pd/C catalyst (15 mg). The mixture was placed under nitrogen and the tube was sealed. The reaction mixture was heated at 190 °C for 4 h. After cooling to 50 °C, the reaction mixture was filtered to remove the catalyst, which was washed with hot ethyl acetate (3 x 3 mL). The organic phases were combined, washed with water (3 x 1.5 mL), and brine (1 mL). The organic phase was dried over anhydrous MgSO_4 , filtered, and then concentrated to furnish a crude oily residue (117 mg). Column chromatography (silica gel, hexanes) yielded mesitylene [108-67-8] (95 mg, 76%), $R_f = 0.52$ (hexanes). $^1\text{H NMR}$ (250 MHz): δ 2.30 (s, 9 H), 6.83 (s, 3H).

Dimethyl 4-hydroxy-2,4-dimethyl-6-oxocyclohexane-1,3-dicarboxylate (46). Methyl acetoacetate (160.00 g, 1.37 mol) and freshly distilled acetaldehyde (27.62 g, 626 mmol) were mixed together and cooled to -5 °C. Piperidine (1.03 g, 12 mmol) in ethanol (2 mL) was added and the mixture was swirled. The reaction mixture was stoppered with a cork stopper and placed in a refrigerator for 24 h. Additional piperidine (1.03 g) in ethanol was added, swirled, and refrigerated for 24 h. The same amount of piperidine in ethanol was added, and after a total of 36 h of refrigeration, the reaction mixture was allowed to stand unstoppered at room temperature for 24 h. The solid mass that formed was collected with a Buchner funnel and washed with cold ethanol (20 mL). The residual solvent was removed at reduced pressure to yield **46** as a white solid (72.32 g, 45%), homogeneous by TLC analysis, $R_f = 0.31$

(hexanes:ethyl acetate, 1:1). ^1H NMR (250 MHz): δ 0.97 (d, $J = 6$ Hz, 3 H), 1.25 (s, 3 H), 2.35 (d, $J = 14$ Hz, 1 H), 2.54–2.60 (m, 2 H), 2.80–2.92 (m, 1 H), 3.06 (d, $J = 12$ Hz, 1 H), 3.75 (s, 3 H), 3.78 (s, 3 H). ^{13}C NMR (62.9 MHz): δ 201.7, 175.0, 169.1, 72.7, 63.2, 56.9, 52.4, 52.1, 33.9, 28.4, 18.6. GC-MS: m/z (%) 140 (15), 112 (37), 69 (46), 40 (100). IR (film): ν 3487, 1742, 1709, 1357 cm^{-1} .

Dimethyl 2,4-dimethyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (47). Tertiary alcohol **46** (64.50 g, 0.250 mol) was dissolved in DCM (250 mL). To this solution was added *p*-TsOH (61.70 g, 0.324 mol). The reaction mixture was stirred at room temperature for 4 d. The reaction mixture was diluted with DCM (300 mL) and washed with saturated $\text{NaHCO}_3(\text{aq})$ (3 x 50 mL). The organic layer was dried over anhydrous MgSO_4 , filtered and then concentrated to yield a crude residue (59.36 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 2:1) yielded **47** as a white solid (50.55 g, 84%), a mixture of diastereomers of approximately the same $R_f = 0.26$ (hexanes/ethyl acetate 4:1). ^1H NMR (250 MHz): δ 0.98–1.26 (m, 3 H), 1.91–2.01 (m, 3 H), 2.50–3.50 (m, 3 H), 3.63–3.76 (m, 6 H), 5.85–5.98 (m, 1 H).

Dimethyl 1,2,4-trimethyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (48). The reaction followed general procedure A using diester **47** (25.1 g, 0.104 mol), THF (a total of 300 mL), and iodomethane (22.15 g, 0.156 mol). Standard workup gave a crude residue (24.94 g). Column chromatography (silica gel, hexanes/ethyl acetate 4:1) yielded **48** as an oil (20.1 g, 76%), homogeneous by TLC analysis, $R_f = 0.32$ (hexanes/ethyl acetate 4:1). ^1H NMR (300 MHz): δ 1.04–1.06 (m, 3 H), 1.41 (s, 3 H), 1.89 (s, 3 H), 2.32–2.38 (m, 1 H), 3.49–3.52 (m, 1 H), 3.63 (s, 3 H), 3.76 (s, 3 H), 5.98 (s, 1 H). ^{13}C NMR (75.5 MHz): δ 194.8, 173.0, 170.7, 156.3, 126.9, 61.2, 55.9, 53.0, 52.2, 40.7, 21.8, 18.6, 14.6. GC-MS: m/z (%) 223 (6), 163 (8), 140 (58), 112 (100). IR (film): ν 2951, 1733, 1667, 1249 cm^{-1} .

3,5,6-Trimethylcyclohex-2-enone (49). The reaction applied general procedure I using diester **48** (692 mg, 2.72 mmol), ethanol (9 mL), water (1 mL), and KOH (647 mg, 19.0 mmol). Standard workup furnished a crude residue (340 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 9:1) gave an oil **49** (282 mg, 75%), a mixture of diastereomers of approximately the same $R_f = 0.42$ (hexanes/ethyl acetate 4:1). ^1H NMR (250 MHz) δ 0.91–1.26 (m, 6 H), 1.91 (s, 3 H), 1.92–2.39 (m, 4 H), 5.78–5.83 (m, 1 H).

2,3,5-Trimethylphenol (32). The reaction was carried out as in general procedure G using enone **49** (175 mg, 1.26 mmol), ethylene glycol (2 mL), and 10% Pd/C (200 mg). Following basic extraction, the solvent was removed at reduced pressure to yield phenol **32** as an oil (99 mg, 58%), identical to the known compound, 2,3,5-trimethylphenol [697-82-5]. $R_f = 0.41$ (hexanes/ethyl acetate 4:1). ^1H NMR (250 MHz): δ 2.15 (s, 3 H), 2.26 (s, 6 H), 4.60 (s, 1 H), 6.48 (s, 1 H), 6.62 (s, 1 H).

Dimethyl 1,2,4,5-tetramethyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (50). The reaction applied general procedure A using diester **48** (16.72 g, 62.38 mmol), THF (175 mL), and iodomethane (13.28 g, 93.57 mol). Standard workup provided a crude residue (17.18 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 4:1) gave diester **50** as an oil (14.22, 80%), a mixture of diastereomers of approximately the same $R_f = 0.38$ (hexanes/ethyl

acetate 4:1). ^1H NMR (300 MHz): δ 0.89–1.06 (m, 3 H), 1.38–1.42 (m, 3 H), 1.77–1.90 (m, 6 H), 2.12–2.28 (m, 1 H), 3.46–3.50 (m, 1 H), 3.62–3.75 (m, 6 H).

2,3,5,6-Tetramethylcyclohex-2-enone (51). The reaction followed general procedure I using diester **50** (8.25 g, 30.78 mmol), ethanol (125 mL), water (15 mL), and KOH (7.33 g, 215.4 mmol). Standard workup provided a crude residue (4.32 g). Chromatographic separation (silica gel, hexanes/ethyl acetate 9:1) gave enone **51** as a light yellow oil (2.68 g, 57%), a mixture of diastereomers of approximately the same $R_f = 0.53$ (hexanes/ethyl acetate 4:1). ^1H NMR (250 MHz): δ 0.89–1.14 (m, 6 H), 1.74 (s, 3 H), 1.89 (s, 3 H), 1.89–2.46 (m, 4 H).

2,3,5,6-Tetramethylcyclohex-2-enol (52). Diisobutylaluminum hydride (1.0 M in toluene, 4.53 mmol) was added to a round bottom flask and cooled to $-78\text{ }^\circ\text{C}$. Enone **51** (276 mg, 1.81 mmol) dissolved in ether (2 mL) was added dropwise. After stirring at $-78\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was poured into ice-cold saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ solution (5 mL). The aqueous layer was extracted with ether (3 x 10 mL). The organic extracts were combined, washed with 5% $\text{HCl}_{(\text{aq})}$ (3 x 7 mL), water (7 mL), and brine (7 mL). The organic phase was dried over anhydrous MgSO_4 , filtered, and then concentrated to yield a crude residue (278 mg). Chromatographic separation (silica gel, hexanes/ethyl acetate 4:1) gave alcohol **52** (227 mg, 81%) as a yellow oil, homogeneous based on TLC analysis, $R_f = 0.40$ (hexanes/ethyl acetate 4:1). This compound was too unstable to be characterized.

2,3,5,6-Tetramethylcyclohexa-1,3-diene (53) and 1,2,4,5-tetramethylcyclohexa-1,3-diene (54). The reaction was carried out as in general procedure K using alcohol **52** (100 mg, 0.65 mmol), DCM (1 mL), and *p*-TsOH (10 mg). Standard workup provided a crude residue (90 mg). Chromatographic separation (silica gel, hexanes) gave a mixture of cyclohexa-1,3-dienes **53** and **54** (72 mg, 82%), $R_f = 0.76$ (hexanes).

1,2,4,5-Tetramethylbenzene (55). The reaction was carried out as in general procedure L using the mixture of cyclohexa-1,3-dienes **53** and **54** (55 mg), ethylene glycol (1.0 mL), and 10% Pd/C (40 mg). Standard workup provided **55** as an oil (35 mg, 61%), identical to the known compound, 1,2,4,5-tetramethylbenzene [95-93-2]. $R_f = 0.47$ (hexanes). ^1H NMR (250 MHz): δ 2.21 (s, 12 H), 6.92 (s, 2 H).

1-Butyl-2,3,5,6-tetramethylcyclohex-2-enol (56). The reaction followed general procedure J using enone **51** (252 mg, 1.65 mmol), ether (2 mL) and *n*-BuLi (825 μL , 2.5 M solution in hexanes, 2.06 mmol). Standard workup provided alcohol **56** as an oil (233 mg), homogeneous by TLC analysis, $R_f = 0.32$ (hexanes/ethyl acetate 9:1). This compound was too unstable to be characterized.

3-Butylidene-1,2,4,5-tetramethylcyclohex-1-ene (57). The reaction was prepared as in general procedure K using cyclohexenol **56** (233 mg, 1.12 mmol), DCM (3 mL), and *p*-TsOH (15 mg). Standard workup provided a crude residue (178 mg). Chromatographic separation (silica gel, hexanes) yielded cyclohexene **57** (148 mg; 77% from **51**), homogeneous by TLC analysis, $R_f = 0.73$ (hexanes).

3-Butyl-1,2,4,5-tetramethylbenzene (58). The reaction was carried out as in general procedure L using **57** (45 mg, 0.23 mmol), ethylene glycol (0.5 mL), and 10% Pd/C (40 mg). Standard

workup provided a crude residue (43 mg). Chromatographic separation (silica gel, hexanes) yielded **58** as an oil (37 mg, 84%), homogeneous by TLC analysis, $R_f = 0.58$ (hexanes). $^1\text{H NMR}$ (250 MHz): δ 0.97–1.03 (m, 3 H), 1.44–1.49 (m, 4 H), 2.22 (s, 3 H), 2.25 (s, 3 H), 2.64–2.70 (m, 2 H), 6.86 (s, 1 H). $^{13}\text{C NMR}$ (62.9 MHz): δ 139.4, 133.6, 131.9, 129.2, 31.8, 30.0, 23.3, 20.6, 15.4, 14.0. GC-MS: m/z (%) 190 (21), 147 (100), 133 (13); IR (film). $\tilde{\nu}$ 2955, 2923, 1456 cm^{-1} .

Acknowledgements

The principal author thanks Dr. Rajendra Kumar Singh, then a doctoral candidate, for introducing him to the fascinating chemistry of Hagemann's ester as part of his undergraduate research experience at *Carnegie-Mellon University* (Fall and Spring Semesters 1973/1974).

References

[§]Taken in part from the MS thesis of Scott Allen, University of Georgia, **1997**.

[§]Professor James M. Cook is not related to the legendary Captain James Cook of His Majesty's Royal Navy, who discovered Hawaii in 1778. But on July 27, 2006 Professor James M. Cook **captained** the *Academic All-Stars* to a 5-2 victory over the *Industrial All-Stars* in a softball game held at the 55th Gordon Research Conference on Natural Products.

1. Scott, A. I.; Devon, T. K. *Handbook of Naturally Occurring Compounds*, Academic Press: New York, 1972.
2. *Tetrasubstituted phenols*: (a) Ramachary, D. B.; Narayana, V. V.; Prasad, M. S.; Ramakumar, K. *Org. Biomol. Chem.* **2009**, 7, 3372. (b) Covarrubias-Zuniga, A.; Rios-Barrios, E. *J. Org. Chem.* **1997**, 62, 5688. (c) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, 127, 4578. *Pentasubstituted arenes*: (d) Paulsen, H.; Antons, S.; Brandes, A.; Logers, M.; Müller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuss, J. *Angew. Chem., Int. Ed.* **1999**, 38, 3373. *Hexasubstituted arenes*: (e) Kiprof, P.; Li, J.; Renish, C. L.; Kalombo, E. K.; Young, V. G. *J. Organometallic Chem.* **2001**, 620(1–2), 113. (f) Brandenburg, J.; Beckert, R.; Fehling, P.; Doering, M.; Goeris, H. *J. Prakt. Chem./Chem.-Ztg.* **1996**, 338, 430.
3. (a) Hagemann, C. *Ber. Dtsch. Chem. Ges.* **1893**, 26, 876. (b) Hagemann, C. *Ber. Dtsch. Chem. Ges.* **1893**, 26, 2300.
4. Knoevenagel, E. *Liebigs Ann. Chem.* **1894**, 281, 25.
5. (a) Rabe, P.; Rahn, R.; Elze, F. *Liebigs Ann. Chem.* **1904**, 332, 1. (c) Rabe, P.; Spence, D. *Liebigs Ann. Chem.* **1905**, 342, 328. (c) Dieckmann, W. *Ber.* **1912**, 45, 2689. (e) Dieckmann, W. *Ber. Dtsch. Chem. Ges.* **1912**, 45, 2967.
6. Hoye, T. R.; Magee, A. S.; Rosen, R. E. *J. Org. Chem.* **1984**, 49, 3224.

7. (a) Horning, E. C.; Denekas, M. O.; Field, R. F. *J. Org. Chem.* **1944**, *9*, 548. (b) Horning, E. C.; Field, R. E. *J. Am. Chem. Soc.* **1946**, *68*, 384.
8. Tietze, L. F.; Brashe, G.; Gericke, K. M. *Domino Reactions in Organic Chemistry*, Wiley-VCH, 2006, Weinheim.
9. (a) Aniliker, R.; Lindsey, A. S.; Nettelton, D. E., Jr.; Turner, R. B. *J. Am. Chem. Soc.* **1957**, *79*, 220. (b) Mongrainn, M.; Lafontaine, J.; Belanger, A.; Deslonghamps, P. *Can. J. Chem.* **1970**, *48*, 3273. (c) McCurry, P. M., Jr.; Singh, R. K. *Synth. Commun.* **1976**, *6*, 75.
10. Pollini, G. P.; Benetti, S.; Risi, C. D.; Zanirato, V. *Tetrahedron* **2010**, *66*, 2775.
11. Smith, L. I. Rouault, G. F. *J. Am. Chem. Soc.* **1943**, *65*, 631.
12. (a) Hogg, J. A. *J. Am. Chem. Soc.* **1948**, *70*, 161. (b) Hogg, J. A. *J. Am. Chem. Soc.* **1949**, *71*, 1918. (c) Edgar, A. J. B.; Harper, S. H.; Kazi, M. A. *J. Chem. Soc.* **1957**, 1837. (d) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408. (e) Nasipuri, D.; Sarkar, G.; Guha, M.; Roy, R. *Tetrahedron Lett.* **1966**, *9*, 927. (f) McAndrews, B. A. *J. Chem. Soc., Perkin Trans. I.* **1979**, *7*, 1837. (g) White, J. D.; Sung, W. L. *J. Org. Chem.* **1974**, *39*, 2323. (h) Ziegler, F. E.; Kloek, J. *Tetrahedron*, **1977**, *33*, 373. (i) Battiste, M. A.; Streckowski, L. Paryzek, Z. *Org. Process. Res. Devel.* **1977**, *1*, 222. (j) Sakan, K.; Smith, D. A.; Babirad, S. A.; Fronczek, F. R.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 2311.
13. Dyier, F. J.; Kidd, D. A. A.; Walker, J. J. *J. Chem. Soc., Perkin Trans. I* **1952**, 4778.
14. (a) Mosettig, E.; Duvall, H. M. *J. Am. Chem. Soc.* **1937**, *59*, 367. (b) Horning, E. C.; Horning, M. G. *J. Am. Chem. Soc.* **1947**, *69*, 1359. (c) Horning, E. C.; Horning, M. G.; Walker, G. N. *J. Am. Chem. Soc.* **1949**, *71*, 169.
15. (a) Tietze, L.; Kiedrowski, G.; Berger, B. *Tetrahedron Lett.* **1982**, *23*, 51. (b) Al-Hassan, M. I. *Gazz. Chim. Ital.* **1987**, *117*, 187. (c) Tamura, Y.; Yoshimoto, Y.; Suzuki, M.; Terashima, M. *Chem. Ind.* **1970**, 1410. (d) Tamura, Y.; Yoshimoto, Y. *Chem. Ind.* **1980**, 888.
16. Kotnis, A. S. *Tetrahedron Lett.* **1990**, *31*, 481.
17. Tarbell, D. S. *Org. React.* **1944**, *2*, 1.
18. (a) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221.
19. Tsai, M.; Friend, C. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1982**, *104*, 2539.
20. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.