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Synthesis of Nitrogen-Substituted Methylenecyclopropanes by Strain-Driven Overman Rearrangement of Cyclopropenylmethyl Trichloroacetimidates

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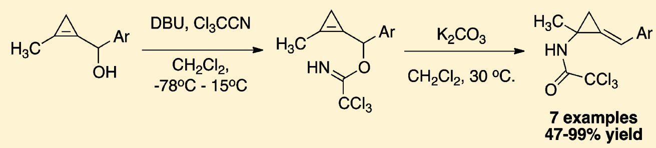
Supporting Information

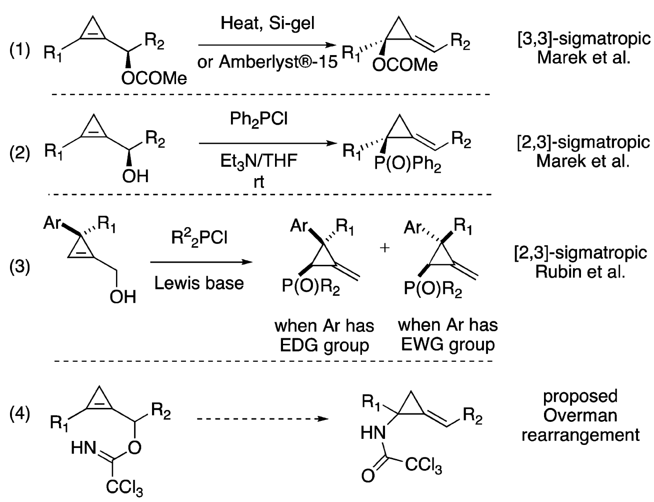
ABSTRACT: Nitrogen-substituted methylenecyclopropanes have been prepared by a strain-driven Overman rearrangement of cyclopropenylmethyl trichloroacetimidates. The reaction proceeds at room temperature and without the need of a transition-metal catalyst. Furthermore, it has been shown that C-3-substituted cyclopropenylmethyl trichloroacetimidates undergo a hydrolytic ring-opening reaction to form allenylcarbinols.



Methylenecyclopropanes are strained, but remarkably stable, unsaturated carbocycles that have attracted significant interest for their strain-driven reactivity.[1−4] Typically, these highly strained systems are susceptible to ring-opening reactions,[5−17] cycloaddition reactions,[18−23] and ring-expansion reactions.[23−28] They have also proved to be precursors for densely functionalized cyclopropanes via ring-retaining C−C[29−37] and C−heteroatom bond-forming reactions to their exocyclic double bond.[38−40]

A range of methods for the synthesis of methylenecyclopropanes exist;[4,41] however, relatively few of these consider the synthesis of heteroatom-substituted structures. Cyclopropenes, bearing an allylic leaving group, can be transformed into methylenecyclopropanes upon nucleophilic attack to the cyclopropene double bond. Such a process is thermodynamically favored due to the relief of strain energy associated with movement of the double bond to the exocyclic position. This approach has been developed for the synthesis of carbon/hydrogen-substituted methylenecyclopropanes[42−47] but is also one of the limited ways to prepare heteroatom-substituted systems. One notable example is the strain-driven [3,3]-sigmatropic rearrangement of cyclopropenylmethyl esters to acetoxy-substituted methylenecyclopropanes by Marek and co-workers (eq 1, Scheme 1).[43] The groups of Marek[43] and Rubin[47] also reported a [2,3]-sigmatropic rearrangement of cyclopropenes to provide methylenecyclopropylphosphine oxides (eq 2 and 3, Scheme 1). Such heteroatom-substituted systems are of interest as phosphorus, oxygen, and nitrogen substituents are ubiquitous in bioactive small molecules. In particular, *N*-substituted methylenecyclopropanes may act as precursors to cyclopropylamines and cyclopropylureas, which are found in a range of bioactive molecules. For example, cyclopropylurea **I** is a kinase inhibitor,[48] **II** displays anti-HIV

Scheme 1. Previous Syntheses of Heteroatom-Substituted Methylenecylopropanes and Proposed Overman Rearrangement of Cyclopropenylmethyl Trichloroacetimidates



activity,[49] and phenylcyclopropylamine **III** is a monoamine oxidase (MAO) inhibitor (Figure 1).[50] As there are no general methods for the synthesis of nitrogen-substituted methylenecyclopropanes there is a need for methodology to allow their preparation. To address this gap, we hypothesized that an allylic trichloroacetimidate rearrangement (Overman rearrangement) of cyclopropenylmethyl trichloroacetimidates (eq 4, Scheme 1)

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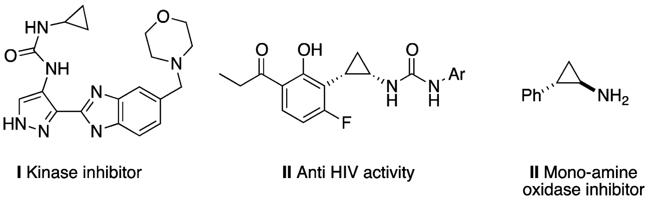


Figure 1. Representative bioactive *N*-substituted cyclopropanes.

should afford 2,2,2-trichloro-*N*-(2-methylenecyclopropyl)-acetamides.

The Overman rearrangement is a powerful method for converting allylic alcohols to allylic amines. Typically, allylic trichloroacetimidates undergo either thermal or Pd(II)-catalyzed rearrangement to allylic trichloroacetamides that may be subsequently transformed into allylic amines by hydrolysis.[51,52] The thermal conditions typically require xylenes at reflux, however, we hypothesized that the strain relief associated with a cyclopropenylmethyl trichloroacetimidate undergoing rearrangement to a 2,2,2-trichloro-*N*-(2-methylene-cyclopropyl)acetamide would allow the reaction to occur without a catalyst and without the need for high temperatures. Herein, we report the successful catalyst-free rearrangement of these systems at ambient temperature.

Initial optimization of both imidate synthesis and subsequent Overman rearrangement utilized *p*-bromobenzaldehyde-derived cyclopropenylcarbinol **1a** (Table 1). The optimum conditions for trichloroacetimidate synthesis involved treating alcohol **1a** with a catalytic amount of DBU in CH_2Cl_2 at −78 °C, followed by addition of trichloroacetonitrile and warming to −15 °C. The imidate **2a** could be identified in the ^{1}H NMR spectrum by the shift of the singlet corresponding to the proton adjacent to oxygen from 5.63 ppm in **1a** downfield to 6.76 ppm for the imidate **2a**. The use of other bases such as NaH and KH gave only recovered starting material. It was found to be important that the imidation reaction with DBU should be left for no longer than 3 h and allowed to warm to a maximum of −15 °C. Longer reaction time or higher temperature led to decomposition and/or lower yield, indicating partial rearrangement to the amide. The imidate could be obtained after rapid removal of all volatile components under reduced pressure and was used directly without further purification.

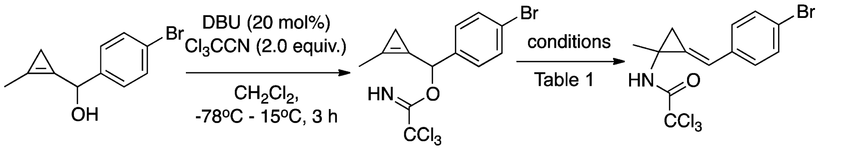
With conditions for the preparation of the imidate in hand, attention was turned toward identifying optimum conditions for the Overman rearrangement. We were delighted to find that imidate **2a** underwent efficient [3,3]-sigmatropic rearrangement under mild conditions (30 °C, CH_2Cl_2, Table 1, entry 1) to yield a single isomer of **3a**. This two-step yield was significantly increased by the addition of K_2CO_3 as a base. However, changing the solvent to DMF resulted in a faster but lower yielding reaction (entry 4, full conversion in 22 h). It also quickly became apparent that catalysis of the rearrangement by $PdCl_2(MeCN)_2$ was inefficient in comparison to the mild thermal conditions (entry 3, Table 1). The Pd catalyst gave only trace product accompanied by significant decomposition. Evidence for methylenecyclopropane formation was indicated by ^{1}H NMR resonance of the proton adjacent to the oxygen of the imidate shifting from a singlet at 6.76 ppm to a triplet at 7.13 ppm corresponding to the alkene.

A range of different aryl-substituted cyclopropenylmethyl trichloroacetimidates was subjected to rearrangement (Table 2). It can be observed that derivatives with electron-rich (**3d,e**) and heterocyclic (**3b**) aryl groups underwent efficient rearrangement. Halogen-substituted phenyl groups were well tolerated (**3a** and **3g**), as was ortho-substitution (**3g**). Highly electron-deficient aryl nitro-substituted systems, however, did not undergo rearrangement at all and only provided recovered starting material. This lack of reactivity is likely due to the electron-deficient aryl groups disfavoring the development of positive charge in the transition state at the oxygen-bearing carbon. This observation, coupled with the higher reactivity of electron-rich aryl groups, suggests the possibility of a transition state with ionic character. Curiously, the dodecyl aldehyde-derived cyclopropenylcarbinol **1j** could not be converted to the corresponding imidate despite extended reaction times and excesses of reagents.[53]

All of the methylenecyclopropanamides were obtained as a single *E*-isomer, suggesting that the reaction likely proceeds through a [3,3] sigmatropic rearrangement mechanism as is normally observed for the Overman rearrangement.[52] The stereochemistry of the rearrangement is assigned on the basis of NOE correlations and is explained by a pseudochair conformation **4** similar to that proposed by Marek and co-workers.[43]

Attempts to reduce or hydrolyze the trichloroacetamides to reveal the free amines were not successful. Conditions investigation included acid hydrolysis (1 M HCl, 0 °C), basic hydrolysis (KOH/EtOH), and reductive cleavage (DIBAL-H or $NaBH_4$); in each case, recovery of starting material along with decomposition was observed. This was attributed to an unstable isocyanate intermediate resulting in the loss of chloroform, as shown by Nishikawa et al.[54] A different course of action was taken, which was to generate the isocyanate intermediate from **3a**/**3f** at −78 °C with Cs_2CO_3 in DMF before capturing it with

Table 1. Optimization of the Overman Rearrangement of 2a To Yield Trichloroacetimidate 3a

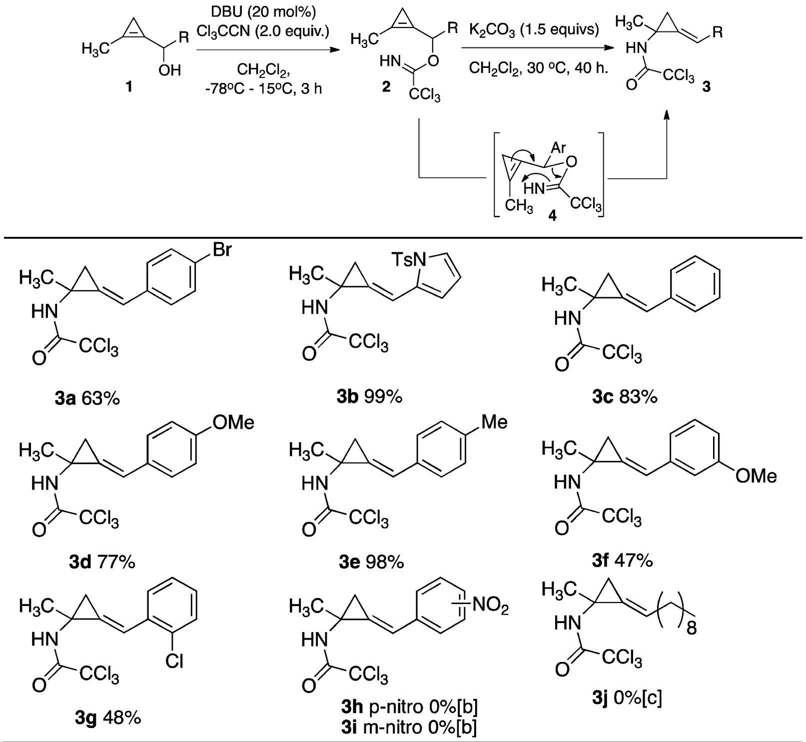


1a **2a** **3a**

entry	additive	conditions	time (h)	yield[a] (%)
1	none	30 °C, CH_2Cl_2	40	21
2	**K_2CO_3 (1 equiv)**	**30 °C, CH_2Cl_2**	**40**	**63**
3	$PdCl_2(MeCN)_2$ (5 mol %)	30 °C, CH_2Cl_2	24	<5
4	K_2CO_3 (1 equiv)	30 °C, DMF	22	53

[a]Isolated yields.

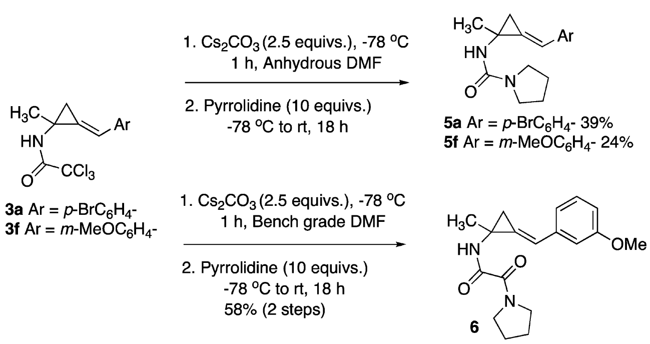
Table 2. Scope of the Overman Rearrangement To Yield 2,2,2-Trichloro-*N*-(2-methylenecyclopropyl)acetamides 3[a]



[a]Isolated yields over two steps, representing a single *E*-isomer of the product. [b]Imidate was formed, but rearrangement did not proceed. [c]Imidate could not be formed.

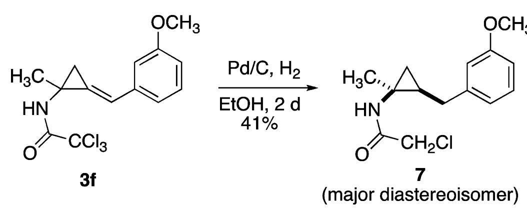
pyrrolidine to successfully yield the desired ureas **5a**/**5f**, respectively (Scheme 2). Cyclopropylureas are valuable targets given their occurrence in a range of bioactive molecules, including kinase inhibitors,[48] epoxide hydrolase inhibitors,[55] and HIV-1 reverse transcriptase inhibitors.[49] Interestingly, when bench-grade DMF, which contained traces of water, was used a 2-oxaacetamide **6** was formed in a moderate yield.[56]

Scheme 2. Manipulation of Methylenecyclopropane 3a/f under Basic Conditions To Yield Ureas 5a/f or Oxaacetamide 6



Given the potential of methylenecyclopropanes **3** as precursors to nitrogen-substituted cyclopropanes, a catalytic hydrogenation was also attempted in order to provide the saturated system. Hydrogenation initially yielded a mixture of reduction products identified as various dehalogenated cyclopropanes. Fortuitously, with extended reaction times, hydrogenation yielded the monochloro amide **7** as a 2.5:1 mixture of diastereoisomers in 41% yield (Scheme 3). Of note is the remaining chloride in **7**, representing a useful handle for further functionalization by substitution or coupling chemistry.

Scheme 3. Catalytic Hydrogenation of Methylenecyclopropane 3f To Yield Saturated Amidocyclopropane 7



We also briefly investigated the Overman rearrangement of cyclopropenylmethyl trichloroacetimidate **9** bearing a *gem*-dimethyl group at C-3. While the trichloroacetimidates **9** could be readily prepared, they underwent rapid hydrolytic ring opening in the presence of silica gel to form allenylcarbinols **10** (Scheme 4). This reaction pathway is highly favored due to the stabilization of the allenyl cation by the *gem*-dimethyl group in conjunction with the relief of ring strain. Indeed, we have previously demonstrated that related cyclopropenylmethyl acetates undergo ring opening to allenyl cations **11** in the presence of $TiCl_4$.[57]

CONCLUSION

In summary, we have developed a method for the preparation of functionalized nitrogen-substituted methylenecyclopropanes via an Overman rearrangement. There are currently no general methods available for these structures, which as we have shown have some potential as precursors to cyclopropylureas. These

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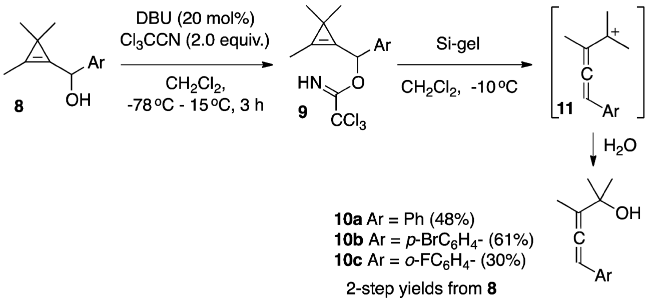
Scheme 4. Formation of Allenylcarbinols 10 by Silica Gel-Induced Hydrolytic Ring Opening of Acetimidate 9 via Allenyl Cation 11



rearrangements occur under very mild conditions by virtue of strain relief and also occur with complete stereoselectivity to give the *E*-methylenecyclopropanes. We have also described initial studies on the manipulation of these systems and divergent reactivity toward the formation of allenyl carbinols when cation-stabilizing groups are present.

■ EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out under an argon or nitrogen atmosphere in dry glassware. Reactions were monitored by TLC using glass-backed silica gel plates or by GC and GC/MS. Compounds were purified using flash column chromatography or by radial chromatography with a Chromatotron. Reaction solvents were obtained from a solvent purification system having passed through anhydrous alumina columns. *n*-BuLi was titrated against diphenylacetic acid prior to use. 1,2,2-Tribromo-1-methylpropane,[58] 1,1,2-tribromo-2,3,3-trimethylcyclopropane,[59] (2-methylcycloprop-1-enyl)(4-bromophenyl)methanol (**1a**),[58] phenyl-(2,3,3-trimethylcycloprop-1-en-1-yl)methanol (**1c**),[60] (2-methylcyclo-prop-1-enyl)(4-methoxyphenyl)methanol (**1d**),[58] 2-methylcycloprop-1-enyl)(4-methylphenyl)methanol (**1e**),[58] phenyl(2,3,3-trimethylcycloprop-1-enyl)methanol (**8a**),[59] and (4-bromophenyl)(2,3,3-trimethylcycloprop-1-enyl)methanol (**8b**)[59] were synthesized and characterized as previously reported. Other reagents were commercially available and used without further purification.

The following abbreviations were used to describe ^{1}H spectra peak splitting patterns: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, dt = doublet of triplets, q = quartets, dq = doublet of quartets, bs = broad singlet, m = multiplet and ad = apparent doublet. IR spectra were recorded as films on NaCl plates (liquids) or in a NaCl solution cells (solids).

General Procedure of the Synthesis of Cyclopropenylcarbinols. In an oven-dried two-neck flask were added 1,2,2-tribromo-1-methylpropane (1.0 equiv) and anhydrous Et_2O (20 mL) before cooling to −78 °C and addition of *n*-BuLi (1.45 M, 1.9 equiv). The resultant solution was warmed to −10 °C for 30 min before cooling to −50 °C and addition of the selected aldehyde. The solution was taken to room temperature after 10 min and allowed to stir for 2 h before quenching with H_2O (20 mL). The mixture was then extracted with Et_2O (3 × 20 mL), dried on Na_2SO_4, and filtered before the solvent was removed under reduced pressure. The crude oil was the purified by means of flash chromatography on silica gel treated with Et_3N (typically ethyl acetate/hexanes).

*(2-Methylcycloprop-1-enyl)[1-(p-toluenesulfonyl)pyrrol-2-yl]-methanol (**1b**).* From *N*-toluenesulfonylpyrrole-2-carboxaldehyde as a yellow oil using 100% CH_2Cl_2 for purification; 179.5 mg, 29% yield. IR (ATR): 3534, 2948, 2869, 1596, 1362, 1173 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, J = 8.4 Hz, 1H), 1.05 (d, J = 8.4 Hz, 1H), 2.09 (d, J = 1.5 Hz, 3H), 2.40 (s, 3H), 2.94 (d, J = 6 Hz, 1H), 5.99 (s, 1H), 6.22−6.25 (m, 2H), 7.26−7.30 (m, 3H), 7.73 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.9, 11.5, 21.7, 62.8, 109.1, 110.8, 111.7, 114.3, 123.8, 126.9, 130.0, 134.9, 136.2, 145.2. HRMS (+EI-Orbitrap): m/z for $C_{16}H_{17}NO_3SNa$ calcd 326.0826, found 326.0821.

*1-(2-Methylcycloprop-1-enyl)dodecan-1-ol (**1d**).* From dodecylaldehyde as a colorless oil using 20% ethyl acetate/hexanes; 345 mg, 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 0.92 (d, $J_{(ab)}$ = 9.0 Hz, 1H), 0.95 (d, $J_{(ab)}$ = 9.0 Hz, 1H), 1.19−1.47 (m, 18H), 1.70 (dd, J = 7.0, 15.0 Hz, 2H), 1.87 (br s, 1H), 2.10 (d, J = 1.5 Hz, 3H), 4.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.2, 11.5, 14.1, 22.7, 25.2, 29.3, 29.5, 29.6, 29.6, 29.6, 31.9, 35.8, 68.0, 108.3, 111.2. IR: 3416 cm^{-1}. HRMS (MMI-TOF) (m/z): (M − H)$^+$ calcd for $C_{16}H_{29}O$ 237.2213, found 237.2214.

*(2-Methylcycloprop-1-enyl)(3-methoxyphenyl)methanol (**1f**).* From 3-methoxybenzaldehyde as pale yellow oil using 20% ethyl acetate/hexanes; 45.5 mg, 20% yield. IR (ATR): 3403, 2943, 2869, 1260 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, J = 8.4 Hz, 1H), 1.06 (d, J = 8.4 Hz, 1H), 2.09 (d, J = 1.2 Hz, 3H), 3.80 (s, 3H), 5.64 (bs, 1H), 6.82−6.86 (m, 1H), 6.96−6.99 (m, 2H), 7.27 (t, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 20.9, 55.3, 112.6, 113.5, 119.9, 121.1, 128.3, 129.7, 138.1, 159.8, 162.3. HRMS (+EI-Orbitrap): m/z for $C_{12}H_{15}O_2$ calcd 191.1072, found 191.1067.

*(2-Methylcycloprop-1-enyl)(2-chlorophenyl)methanol (**1g**).* From 2-chlorobenzaldehyde as a clear oil using 20% ethyl acetate/hexanes; 184.8 mg >99% yield. IR (ATR): 3357, 2964, 2871, 1441 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 2H), 2.06 (s, 3H), 2.59 (bs, 1H), 6.03 (bs, 1H), 7.22−7.28 (m, 2H), 7.30−7.37 (m, 1H), 7.50−7.53 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.1, 11.4, 67.2, 109.7, 110.6, 127.1, 127.9, 128.9, 129.6, 132.3, 138.7. HRMS (+EI-Orbitrap): m/z for $C_{11}H_{12}ClO$ calcd 195.0571, found 195.0569.

*2-Methylcycloprop-1-enyl)(4-nitrophenyl)methanol (**1h**).* From 4-nitrobenzaldehyde as a yellow semisolid using 50% Et_2O/pentane; 335.1 mg, 94% yield. IR (ATR): 3594, 3054, 2986, 1268 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, $J_{(ab)}$ = 8.3 Hz, 1H), 1.08 (d, $J_{(ab)}$ = 8.3 Hz, 1H), 2.11 (d, J = 1.4 Hz, 3H), 5.80 (s, 1H), 7.61 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 11.4, 69.2, 110.0, 111.6, 123.8, 127.0, 148.4. HRMS (MMI-TOF): m/z for (2 M + NH_4)$^+$ calcd for $C_{22}H_{26}N_3O_6$ 428.1822, found 428.1828.

*(2-Methylcycloprop-1-enyl)(3-nitrophenyl)methanol (**1i**).* From 3-nitrobenzaldehyde as an off-white semisolid without need for purification by column; 309.2 mg, 88% yield. IR (ATR): 3583, 2857, 1529, 1350 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J = 8.3 Hz, 1H), 1.08 (d, J = 8.3 Hz, 1H), 2.11 (d, J = 1.4 Hz, 3H), 5.79 (s, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.81−7.72 (m, 1H), 8.14−8.18 (m, 1H), 8.29−8.31 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.1, 11.4, 69.1, 109.9, 111.5, 121.4, 122.8, 129.5, 132.5, 143.4, 189.9. HRMS (+EI-Orbitrap): m/z for $C_{11}H_{11}NO_3Na$ calcd 228.0636, found 228.0631.

*(2-Fluorophenyl)(2,3,3-trimethylcycloprop-1-en-1-yl)methanol (**8c**).* From 2-fluorobenzaldehyde as a clear oil using 20% ethyl acetate/hexanes for purification; 610.5 mg, 20% yield. IR (ATR): 3447, 2957, 1610, 1487, 1454, 1032, 1032, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 3H), 2.10 (3, 3H), 1.63 (bs, 1H), 1.97 (s, 3H), 5.93 (s, 1H), 7.03 (app t, J = 8.7 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.26−7.28 (m, 1H), 7.47 (t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6, 22.2, 25.3, 25.6, 65.1 (d, J = 4.6 Hz), 115.3 (d, J = 21.8 Hz), 124.6 (d, J = 13.8 Hz), 124.9 (d, J = 3.5 Hz), 128.5 (d, J = 4.6 Hz), 129.9 (d, J = 8.1 Hz), 159.9 (d, J = 245.1 Hz). HRMS (ASAP-TOF): m/z for $C_{13}H_{15}FO$ + H − H_2O calcd 189.1080, found 189.1071.

General Procedure for the Synthesis of Nitrogen-Substituted Alkylidenecyclopropanes. To a stirred solution of cyclopropenylcarbinol (1 equiv) in CH_2Cl_2 (∼0.1 M) was added DBU (0.15 equiv) followed by trichloroacetonitrile (1.5 equiv) at −78 °C. The resulting solution was allowed to warm to −10 °C over a period of 2 h before the reaction mixture was evaporated to dryness under reduced pressure. The resulting oil was in most cases identified as the intermediate imidate by NMR of the crude reaction mixture and was used directly in the rearrangement step. Where the ^{1}H NMR of the crude imidate was clean a listing of the signals is provided below. A solution of crude imidate (1 equiv) and K_2CO_3 (1.5 equiv) in CH_2Cl_2 (1 mL) was allowed to stir at 30 °C for 40 h. After this time, the solution was filtered before removal of solvent by evaporation under reduced pressure. The crude semisolid was purified by means of flash chromatography on a neutral alumina column (ethyl acetate/hexanes) to yield the alkylidenecyclopropane.

*1-[(E)-2-(4-Bromophenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3a**).* From **1a** as an off-white semisolid after purification with 20% ethyl acetate/hexanes; 51 mg, 63% yield over two steps. **Imidate.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, *J* = 8.3 Hz, 1H), 1.14 (d, *J* = 8.3 Hz, 1H), 2.09 (d, *J* = 1.5 Hz, 3H), 6.76 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 8.43 (s, 1H). **3a.** IR (ATR): 3289, 2922, 2850, 1694, 1506 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.76 (dd, *J* = 10.9, 2.6 Hz, 1H), 1.83 (dd, *J* = 10.9, 2.6 Hz, 1H), 7.07 (s, 1H), 7.13 (t, *J* = 2.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 20.9, 29.9, 120.3, 121.8, 128.7, 128.8, 131.8, 135.6, 162.3. HRMS (+EI-Orbitrap): *m/z* for $C_{13}H_{11}BrCl_3NONa$ calcd 403.8987, found 403.8982.

*1-[(E)-2-[[1-(p-Tolylsulfonyl)-1H-pyrrol-2-yl]methylidene]-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3b**).* From **1b** as a yellow oil after purification with 100% CH_2Cl_2; 275 mg, >99% yield over two steps. IR (ATR): 3364, 2969, 2027, 1713, 1494, 1367, 1174 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (s, 3H), 1.55−1.59 (m, 1H), 1.62 (dd, *J* = 11.1, 2.7 Hz, 1H), 2.36 (s, 3H), 6.27 (t, *J* = 3.9 Hz, 1H), 6.52−6.52 (m, 1H), 6.99 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.64 (t, *J* = 2.7 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CHCl_3$): δ 19.6, 21.0, 21.7, 31.4, 110.5, 112.5, 112.7, 123.1, 127.1, 128.5, 130.1, 131.9, 135.9, 145.1, 161.98. HRMS (+EI-Orbitrap): *m/z* for $C_{18}H_{17}Cl_3N_2O_3S$ + H calcd 447.0103, found 447.0098.

*1-[(E)-2-Phenylmethylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3c**).* From **1c** as an off-white semisolid after purification with 20% ethyl acetate/hexanes; 80.1 mg, 83% yield over two steps. **Imidate.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, *J* = 8.4 Hz, 1H), 1.15 (d, *J* = 8.4 Hz, 1H), 2.09 (d, *J* = 1.4 Hz, 3H), 6.82 (s, 1H), 7.32−7.40 (m, 3H), 7.45−7.48 (m, 2H), 8.42 (s, 1H). **1c.** IR (ATR): 3415, 3054, 2986, 1719, 1492, 1421, 1265, 895 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 3H), 1.80 (dd, *J* = 10.8, 2.6 Hz, 1H), 1.86 (dd, *J* = 10.8, 2.6 Hz, 1H), 7.06 (bs, 1H), 7.19 (t, *J* = 2.6 Hz, 1H), 7.27−7.38 (m, 3H), 7.45−7.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 21.0, 29.9, 121.2, 127.2, 127.9, 128.0, 128.7, 136.6, 162.3. HRMS (MMI-TOF) *m/z*: (M + H)$^+$ calcd for $C_{13}H_{13}NOCl_3$ 304.0063, found 304.0057.

*1-[(E)-2-(4-Methoxyphenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3d**).* From **1d** as an off-white semisolid after purification with 30% ethyl acetate/hexanes; 145.6 mg, 77% yield over two steps. **Imidate.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (dd, *J* = 23.7, 8.4 Hz, 2H), 2.09 (d, *J* = 1.5 Hz, 3H), 3.79 (s, 3H), 6.75 (s, 1H), 6.85−6.92 (m, 2H), 7.38 (d, *J* = 8.7, 2H), 8.38 (s, 1H). **3d.** IR (ATR): 3423, 3054, 2986, 1717, 1512, 1421, 1265, 705 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.75 (dd, *J* = 8.6, 2.4 Hz, 1H), 1.81 (dd, *J* = 10.7, 2.8 Hz, 1H), 3.81 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CHCl_3$): δ 19.8, 21.0, 29.9, 55.3, 114.1, 120.5, 125.5, 128.4, 129.4, 159.4, 162.3. HRMS (MMI-TOF) *m/z*: (M + H$^+$) calcd for $C_{14}H_{15}NO_2Cl_3$ 334.0170, found 334.0157.

*1-[(E)-2-(4-Methylphenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3e**).* From **1e** as an off-white semisolid after purification with 30% ethyl acetate/hexanes; 281 mg, 98% yield over two steps. **Imidate.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, *J* = 8.4 Hz, 1H), 1.14 (d, *J* = 8.4 Hz, 1H), 2.10 (d, *J* = 1.5 Hz, 3H), 2.36 (s, 3H), 6.78 (s, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 8.39 (s, 1H). **3e.** IR (cm^{-1}): 3417, 3050, 3030, 2971, 2929, 2864, 1715, 1513, 1489, 1236, 821, 711. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.77 (dd, *J* = 10.6, 2.6 Hz, 1H), 1.83 (dd, *J* = 10.7, 2.6 Hz, 1H), 2.35 (s, 3H), 7.01 (bs, 1H), 7.11−7.19 (m, 3H), 7.44 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 23.1, 21.5, 30.0, 121.1, 126.9, 127.2, 129.5, 134.0, 138.0, 162.4. HRMS (MMI-TOF) *m/z*: (M + H)$^+$ calcd for $C_{14}H_{15}NOCl_3$ 318.0221, found 318.0214.

*1-[(E)-2-(3-Methoxyphenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3f**).* From **1f** an off-white semisolid after purification with 30% ethyl acetate/hexanes; 38 mg, 47% yield over two steps. **3f.** IR (cm^{-1}): 3443, 2957, 1600, 1511, 1249, 1170, 1030. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.79 (dd, *J* = 10.9, 2.6 Hz, 1H), 1.86 (dd, *J* = 10.9, 2.6 Hz, 1H), 3.82 (s, 3H), 6.81−6.86 (m, 1H), 7.06 (s, 1H), 7.09 (t, *J* = 2.4 Hz, 1H), 7.12 (ap, 1H), 7.15−7.16 (m, 1H), 7.27 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 20.9, 29.9, 55.3, 92.6, 112.6, 113.5, 119.9, 121.1, 128.3, 129.7, 138.1, 159.8, 162.3. MS: *m/z* 356 (M+Na, 100), 213 (17). HRMS (+EI-Orbitrap): *m/z* for $C_{14}H_{14}Cl_3NO_2$ + Na calcd 355.9987, found 355.9982.

*1-[(E)-2-(2-Chlorophenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (**3g**).* From **1g** as an off-white semisolid after purification with 20% ethyl acetate/hexanes; 88.8 mg, 48% yield over two steps. **Imidate.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, *J* = 8.4 Hz, 1H), 1.26 (d, *J* = 8.4 Hz, 1H), 2.08 (d, *J* = 1.5 Hz, 3H), 7.15 (s, 1H), 7.25−7.32 (m, 2H), 7.38−7.41 (m, 1H), 7.53−7.56 (m, 2H), 8.46 (s, 1H). **3g.** IR (ATR): 3317, 2968, 1695, 1495 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 3H), 1.81 (dd, *J* = 11.1, 2.6 Hz, 1H), 1.88 (dd, *J* = 11.1, 2.6 Hz, 1H), 7.10 (bs, 1H), 7.18−7.25 (m, 2H), 7.38 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.58 (t, *J* = 2.6 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CHCl_3$): δ 20.1, 20.9, 30.0, 117.1, 126.8, 127.2, 129.0, 129.9, 130.7, 133.6, 134.2, 162.2. HRMS (+EI-Orbitrap): *m/z* for $C_{13}H_{11}Cl_4NO$ + Na calcd 359.9492, found 359.9487.

*1-[(E)-2-[(4-Bromophenyl)methylidene]-1-methylcyclopropylamino](1-pyrrolidinyl)formaldehyde (**5a**).* To a solution of **3a** (62 mg, 0.16 mmol) in anhydrous DMF (2 mL) under nitrogen was added Cs_2CO_3 (140 mg, 0.43 mmol) at −78 °C. The mixture was allowed to stir for 1 h before the slow addition of pyrrolidine (140 μL, 120 mg, 1.69 mmol), which was subsequently allowed to warm to room temperature over 18 h. After this time, the mixture was diluted with 50% ethyl acetate in hexanes and washed with water. The crude mixture was dried on Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude oil was purified by means of flash chromatography with 100% ethyl acetate to afford **5a** as a yellow oil in a 39% yield (21.0 mg, 0.06 mmol). IR (ATR): 3252, 2970, 1689, 1489, 1383, 1161 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H), 1.74−1.77 (m, 4H), 2.02 (s, 3H), 2.41−2.47 (m, 2H), 2.68−2.72 (m, 2H), 6.65 (bs, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 23.9, 24.5, 46.2, 77.9, 122.1, 129.7, 130.3, 131.0, 131.5, 158.5, 171.7. HRMS (+EI-Orbitrap): *m/z* for $C_{16}H_{19}BrN_2O$ + H calcd 335.0759, found 335.0754.

*1-[(E)-2-[(3-Methoxyphenyl)methylidene]-1-methylcyclopropylamino](1-pyrrolidinyl)formaldehyde (**5f**).* To a solution of **3f** (88.1 mg, 0.26 mmol) in anhydrous DMF (2 mL) under nitrogen was added Cs_2CO_3 (214.5 mg, 0.75 mmol) at −78 °C. The mixture was allowed to stir for 1 h before the slow addition of pyrrolidine (130 μL, 112 mg, 1.57 mmol), which was subsequently allowed to warm to room temperature over 18 h. After this time, the mixture was diluted with 50% ethyl acetate in hexanes and washed with water. The crude mixture was dried on Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude oil was purified by means of flash chromatography with 30% ethyl acetate/hexanes to afford **5f** as a yellow oil in a 24% yield (18.3 mg, 0.06 mmol). IR (ATR): 3222, 2964, 2834, 1689, 1600, 1578 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 3H), 1.75−1.78 (m, 4H), 2.03 (s, 3H), 2.42−2.47 (m, 2H), 2.69−2.74 (m, 2H), 3.82 (s, 3H), 6.54 (bs, 1H), 6.86−6.89 (m, 1H), 7.01−7.03 (m, 2H), 7.32 (t, *J* = 8.4 Hz, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 11.8, 23.9, 24.5, 46.7, 55.3, 77.7, 113.7, 114.9, 121.8, 129.3, 130.7, 132.7, 158.2, 159.5, 172.1. HRMS (+EI-Orbitrap): *m/z* for $C_{17}H_{22}N_2O_2$ + H calcd 287.1759, found 287.1754.

*1-[(E)-2-[(m-Methoxyphenyl)methylidene]-1-methylcyclopropylamino]-2-(1-pyrrolidinyl)-1,2-ethanedione (**6**).* To a solution of **3f** (19.8 mg, 0.06 mmol) in DMF (1 mL, bench grade) under nitrogen was added pyrrolidine (50 μL, 43 mg, 0.6 mmol) followed by Cs_2CO_3 (45.0 mg, 0.14 mmol) at −78 °C. The mixture was subsequently allowed to warm to room temperature over 18 h. After this time, the mixture was diluted with 50% ethyl acetate in hexanes (5 mL) and washed with water (5 × 5 mL). The crude mixture was dried on Na_2SO_4 and filtered and had the solvent removed under reduced pressure. The crude oil was purified by means of flash chromatography with 30% ethyl acetate/hexanes to afford **6f** as a yellow oil in 58% yield (10.8 mg, 0.03 mmol). IR (ATR): 3297, 2969, 1687, 1623, 1428 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H), 1.76 (dq, J = 10.8, 2.8 Hz, 2H), 1.83 (p, J = 6.6 Hz, 2H), 1.95 (p, J = 6.6 Hz, 2H), 3.52 (t, J = 6.8 Hz, 2H), 4.00 (dt, J = 6.8, 3.6 Hz, 2H), 6.79−6.82 (m, 1H), 7.07−7.12 (m, 3H), 7.25 (t, J = 8.0 Hz, 1H), 7.9 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 21.5, 23.5, 26.9, 28.5, 48.0, 48.8, 55.3, 112.4, 113.3, 119.9, 120.4, 129.6, 129.7, 138.6, 159.3, 159.9, 161.4. HRMS (+EI-Orbitrap): m/z for $C_{18}H_{22}O_3N_2$ + Na calcd 337.1528, found 337.1523.

*2-Chloro-1-[2-[(m-methoxyphenyl)methyl]-1-methylcyclopropylamino]-1-ethanone (**7**).* Under an atmosphere of H_2, **3f** (88.9 mg, 0.26 mmol) was stirred in ethanol (10 mL) for 2 days with Pd/C (8.0 mg) at room temperature. After this time, the mixture was passed through a short plug of Celite before the solvent was removed under reduced pressure to reveal a brown oil which was subsequently purified be means of flash chromatography with 30% ethyl acetate/hexanes to reveal **7** as a slightly yellow oil in a 41% yield (30.3 mg, 0.11 mmol). IR (ATR): 3292, 3096, 2959, 1663, 1489, 1251 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.57 (t, J = 6.0 Hz, minor isomer), 0.68 (t, J = 6.0 Hz, major isomer), 1.01 (dd, J = 9.0, 6.0 Hz, 1H, major isomer), 1.05 (dd, J = 10.0, 6.0 Hz, 1H, minor isomer), 1.20−1.28 (m, 1H, major isomer), 1.28−1.34 (m, 1H, major isomer), 1.44 (s, 3H, major isomer), 1.49 (s, 3H, minor isomer), 2.51 (dd, J = 15.0, 8.0 Hz, 1H, minor isomer), 2.62 (dd, J = 15.0, 8.0 Hz, 1H, major isomer), 2.83 (dd, J = 15.0, 7.0 Hz, 1H, major isomer), 2.93 (dd, J = 15.0, 6.0 Hz, 1H, minor isomer), 3.83 (s, 3H, major isomer), 3.83 (s, 3H, minor isomer), 3.99 (s, 2H, minor isomer), 4.03 (s, 2H, major isomer), 6.78−6.90 (m, 3H, minor and major isomer), 7.25 (t, J = 8.0 Hz, 1H, major isomer), 7.25 (t, J = 8.0 Hz, 1H, major isomer). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 20.4, 20.6, 23.6, 25.4, 26.2, 33.3, 33.5, 35.0, 35.3, 42.8, 42.9, 55.3, 55.3, 111.4, 111.5, 114.1, 114.3, 120.6, 120.8, 129.5, 129.7, 142.7, 142.9, 159.8, 159.9, 166.0, 166.8. HRMS (+EI-Orbitrap): m/z for $C_{14}H_{18}ClNO_2$ + Na calcd 290.0923, found 290.0918.

General Procedure for the Synthesis of Allenylcarbinols 10. To a stirred solution of the appropriate cyclopropenylcarbinol **8** (1 equiv) in CH_2Cl_2 (∼0.1 M) was added DBU (0.15 equiv) followed by trichloroacetonitrile (1.5 equiv) at −78 °C. The resulting solution was allowed to warm to −10 °C over a period of 2 h before the reaction mixture was evaporated to dryness under reduced pressure. The resulting oil was in most cases identified as the intermediate imidate by crude ^{1}H NMR and was also used directly in the allene-formation step. The crude imidate (1 equiv) was dissolved in reagent-grade CH_2Cl_2 (∼0.01 M) and cooled to −10 °C, and silica gel (500 mg per 0.1 mmol of imidate) was added. The reaction was stirred vigorously and allowed to warm to room temperature. After consumption of the starting material (typically about 3 h), the reaction was filtered, evaporated to dryness, and purified by flash column chromatography (15% ethyl acetate/hexanes) to yield the pure allenyl carbinol.

*2,3-Dimethyl-5-phenylpenta-3,4-dien-2-ol (**10a**).* From **8a** as a pale yellow oil after filtration and evaporation to dryness and purification with 15% ethyl acetate/hexanes; 14.1 mg, 48% yield. IR (ATR): 3593, 3054, 2986, 1421, 1265, 896, 733, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 6H), 1.90 (d, J = 2.9 Hz, 3H), 6.21 (q, J = 2.9 Hz, 1H), 7.18−7.33 (m, 5H). ^{13}C (100 MHz, $CDCl_3$) δ 14.5, 29.0, 29.3, 71.7, 96.5, 111.9, 126.6, 126.9, 128.7, 135.2, 200.6. HRMS (MMI-TOF): m/z for $C_{13}H_{16}O$ − H calcd 187.1201, found 187.1258.

*5-(2-Bromophenyl)-2,3-dimethylpenta-3,4-dien-2-ol (**10b**).* From **8b** as a pale orange viscous oil after purification with 15% ethyl acetate/hexanes; 22 mg, 61% yield over two steps. **Imidate.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.29 (s, 3H), 2.16 (s, 3H), 7.27 (3, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 8.0, 1.5 Hz, 1H), 7.81 (d, J = 8.0, 1.5 Hz, 1H), 8.67 (s, 1H). IR (ATR): 3313, 2977, 1953, 1492, 1235 cm^{-1}. **10b.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 6H), 1.88 (d, J = 2.0 Hz, 3H), 6.62 (d, J = 2.0 Hz), 7.01 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 8.0, 1.5 Hz, 1H), 7.50 (d, J = 8.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6, 29.2, 29.3, 71.8, 95.5, 112.2, 122.6, 127.6, 128.3, 128.3, 133.3, 134.7, 201.9. HRMS (ASAP-TOF): m/z for $C_{13}H_{15}BrO$ + H calcd 267.0385, found 267.0378.

*5-(2-Fluorophenyl)-2,3-dimethylpenta-3,4-dien-2-ol (**10c**).* From **8c** as a clear oil after purification with 20% ethyl acetate/hexanes; 38.6 mg, 30% yield. IR (ATR): 3313, 2977, 1953, 1492, 1235 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 6H), 1.89 (d, J = 2.5 Hz), 6.40 (s, 1H), 7.01 (t, J = 10 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 7.13−7.18 (m, 1H), 7.31 (dt, J = 7.5, 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4, 28.9, 29.0, 71.5, 88.8, 111.5, 115.6 (d, J = 20.9 Hz), 122.7 (d, J = 11.5 Hz), 124.1, 128.0, 128.1, 159.8 (d, J = 246.0 Hz), 201.5. HRMS (ASAP-TOF): m/z for $C_{13}H_{15}FO$ + H − H_2O calcd 189.1080, found 189.1051.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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