# Synthesis of Prenylarenes and Related (Multisubstituted Allyl)arenes from Aryl Halides and Homoallyl Alcohols via Palladium-Catalyzed Retro-Allylation

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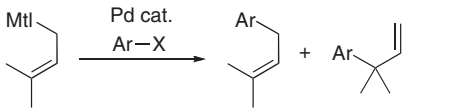
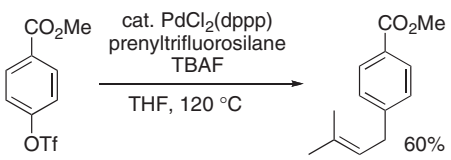
The reactions of aryl halides with 2,3,3-trimethyl-4-penten-2-ol in the presence of a palladium catalyst result in prenyl transfer from the alcohol to aryl halides via retro-allylation, yielding prenylarenes. Other multisubstituted allyl groups such as the 2,3-dimethyl-2-butenyl group are introduced to aromatic rings.

Prenyl-substituted arenes are often found in natural products, most of which show significant biological activities (Figure 1). The synthesis of such biologically interesting compounds has hence been well investigated.[1] However, construction of prenylarene skeletons is usually difficult. For instance, according to a report by Knölker et al. about the synthesis of carquinostatin A,[2] the use of a large excess of nickel complex **1** was essential to afford **3** with satisfactory efficiency and selectivity (Scheme 1). Moreover, a large amount of highly toxic $Ni(CO)_4$ was required for the preparation of **1**, which can be a significant drawback. In most cases, the conventional cross-coupling reactions of aryl halides with prenylmetal reagents provide a mixture of regioisomers (eq 1).[3,4] Exceptionally, prenyltrifluorosilane reacted with aryl triflates under palladium catalysis to afford prenylarenes predominantly (eq 2).[4] However, the reactions were performed in sealed tubes and required a moisture-sensitive prenylmetal. Thus, little is known concerning regioselective and convenient prenylation reactions of aryl halides.




(1)




(2)

Very recently, we have developed the palladium-catalyzed allylation reaction of aryl halides with homoallyl alcohols via palladium-catalyzed retro-allylation.[5] The reaction proceeds with high regiospecificity, providing a variety of allylated arenes. The prenylation of 1-bromonaphthalene with homoallyl alcohol **4** was previously investigated (Scheme 2).[5a,5b] Notably, the prenylation reaction was perfectly regioselective, and none of the regioisomer was obtained.[5b] However, this is the only example of the prenylation reaction in the previous papers. In light of the importance of installing a prenyl moiety to aromatic compounds, we further examined the generality of the prenylation reaction of aryl halides with **4**. We report here the details of the prenylation reaction and related reactions that introduce multisubstituted allyl groups into aryl halides.

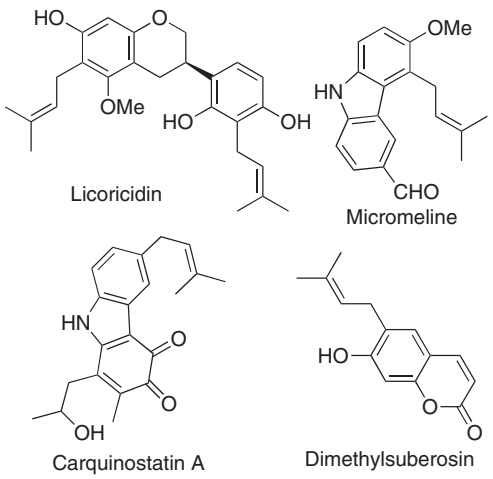
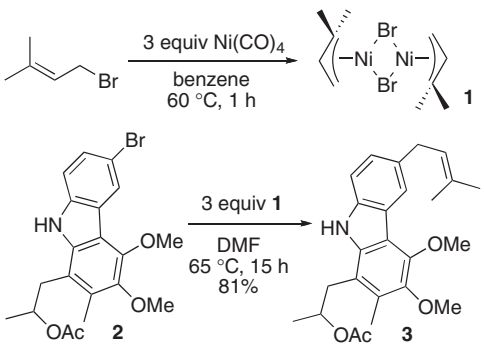



**Figure 1.** Some natural products bearing prenyl groups.




**Scheme 1.** A rare example of selective prenylation of aryl halide.

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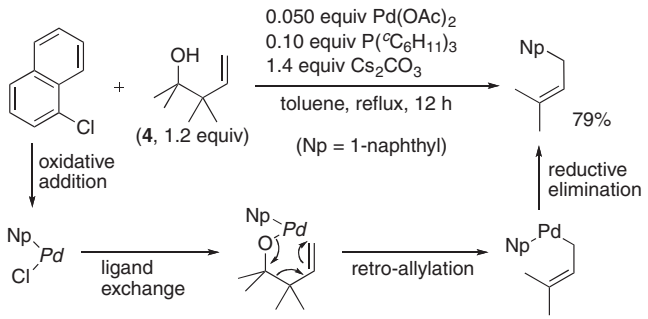



**Scheme 2.**

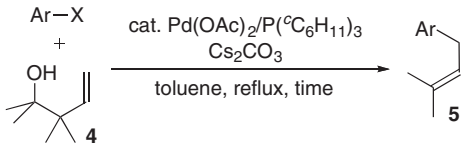
## Results and Discussion

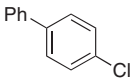
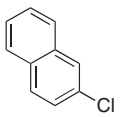
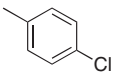
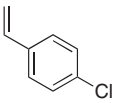
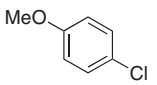
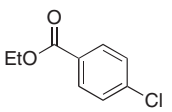
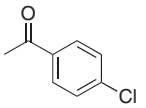
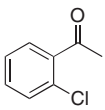
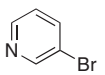
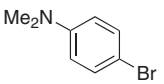
A variety of aryl halides were subjected to the palladium-catalyzed prenylation reaction with **4** (Table 1). Since highly electron-donating tricyclohexylphosphine was used as the ligand, aryl chlorides[6] were able to undergo the prenylation. The reactions of ortho-substituted chloroarenes proceeded with excellent efficiency (Entries 1–3). On the other hand, the prenylation reactions of 2-chloronaphthalene and 4-chlorotoluene were slow, and required 26 h to complete (Entries 5 and 6). Although the reactions of 4-chlorostyrene and 4-chloroanisole were also inefficient at reflux in toluene, a higher temperature under microwave irradiation[7] could accelerate the reaction (Entries 7 and 8). In the reactions of sterically demanding aryl chlorides (Entries 1–3), the retro-allylation step would be accelerated by the steric repulsion around the palladium center. The high temperature could enhance the rate-determining retro-allylation step in the reactions in Entries 7 and 8, where smaller steric repulsion would operate.[5c] Notably, none of the oligomers of 4-chlorostyrene, which could be formed through Mizoroki–Heck reaction,[8] were observed. The reaction conditions were mild enough to leave ester as well as acetyl groups untouched (Entries 9–11). Under the standard conditions, 3-bromopyridine resisted the reaction, and a high temperature was essential to attain a satisfactory result (Entry 12). Both 3-chloropyridine and 2-bromopyridine suffered from very low conversions under several sets of reaction conditions we tested. Unprotected hydroxy and amino groups completely suppressed the reaction. A dimethylamino substituent also retarded the reaction (Entry 13). Attempts to use 1-alkenyl halides resulted in very low yields.

Not only the prenyl group but also a trisubstituted allyl group could be incorporated. The reactions of aryl halides with alcohol **6** provided 2,3-dimethyl-2-butenylarenes **7** through the transposition of the double bond (Scheme 3). The reactions are high-yielding under microwave irradiation at 250 °C, although the reaction of 1-chloronaphthalene with **6** in boiling toluene for 13 h resulted in low conversion, providing **7a** in only 31% yield. Preparation of such tetrasubstituted alkenes by conventional Wittig-type olefination often results in low yields.

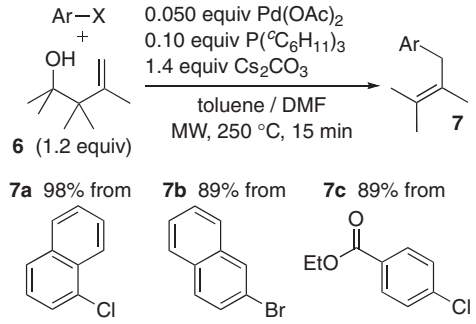
Stereoselective synthesis of trisubstituted alkenes was performed by using **8**, which have two different substituents, methyl and the other bulkier groups at the allylic position (eq 3). Formation of the E isomers of **9** predominated, and the stereoselectivity can be rationalized as outlined in Scheme 4. Upon the retro-allylation reaction of **8**, a chair-like transition state **10a** would be the most favorable because the bulky R group is located at the equatorial position. The other chair-like transition state **10b** has the R group at the axial position, which

**Table 1.** Palladium-Catalyzed Prenylation of Aryl Halides with Homoallyl Alcohol **4**[a]



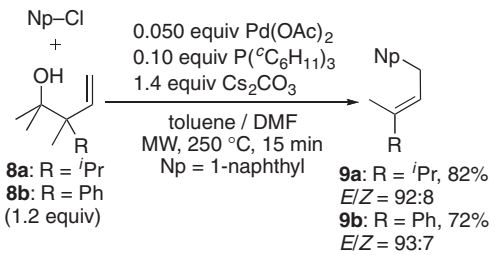

| Entry | Ar–X | Time/h | 5 | Yield/% |
|---|---|---|---|---|
| 1 |  | 17 | **5a** | 100 |
| 2 |  | 10 | **5b** | 98 |
| 3 |  | 10 | **5c** | 86 |
| 4 |  | 15 | **5d** | 80 |
| 5 |  | 26 | **5e** | 93 |
| 6 |  | 26 | **5f** | 84[b] |
| 7 |  | 11 | **5g** | 38 (84)[c] |
| 8 |  | 15 | **5h** | 27 (95)[c] |
| 9 |  | 15 | **5i** | 100 |
| 10 |  | 15 | **5j** | 80 |
| 11 |  | 10 | **5k** | 67 |
| 12 |  | 10 | **5l** | <5 (62)[c] |
| 13 |  | 17 | **5m** | 20 |

a) Conditions: Ar–X (0.50 mmol), alcohol **4** (0.60 mmol), $Pd(OAc)_2$ (0.025 mmol), $P(^cC_6H_{11})_3$ (0.050 mmol), $Cs_2CO_3$ (0.70 mmol), and toluene (2 mL). b) With $Pd(OAc)_2$ (0.050 mmol) and $P(^cC_6H_{11})_3$ (0.10 mmol). c) Performed under microwave irradiation at 250 °C for 15 min.




**Scheme 3.** Synthesis of 2,3-dimethyl-2-butenylarenes.

would render **10b** disfavored. Formation of [(*E*)-alkenyl](naphthyl)palladium **11a** is thus preferred. The intermediate **11a** finally undergoes smooth reductive elimination to yield (*E*)-**9** selectively.




(3)

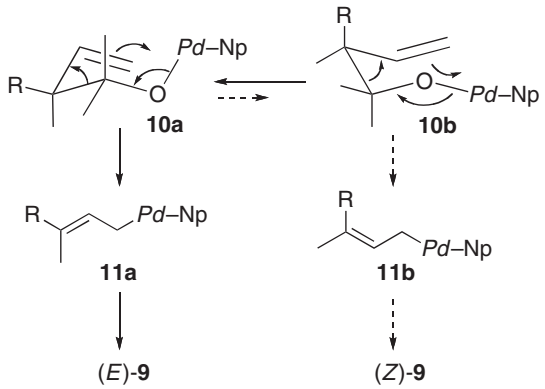
In conclusion, we have disclosed the palladium-catalyzed prenylation and other related allylation of aryl halides that yield (multisubstituted allyl)arenes by using retro-allylation of homoallyl alcohols. The products are not readily available by conventional methods. The present reactions will find applications for the synthesis of biologically intriguing compounds.

## Experimental

**General.** $^1$H NMR (300 and 500 MHz) and $^{13}$C NMR (75.3 and 125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts ($\delta$) are in parts per million relative to tetramethylsilane at 0.00 ppm for $^1$H and relative to $CDCl_3$ at 77.0 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60$F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

The reactions under microwave irradiation were carried out using a focused microwave unit (Biotage Initiator$^{TM}$). The maximum irradiation power is 400 W. Each reaction was run in a 5-mL glass pressure vial, which is a commercially available vial specifically for the Biotage Initiator$^{TM}$. It took 6 min to reach 250 °C. After reaching the indicated temperatures, controlled microwave irradiation started and continued for 15 min, keeping the reaction temperature constant.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and DMF were purchased from Wako Pure Chemical Co. Toluene was stored over slices of sodium. DMF was used as received. Tri(*p*-tolyl)phosphine and cesium carbonate were purchased from Wako Pure Chemical Co. Palladium acetate and tricyclohexylphosphine




**Scheme 4.** Origin of stereoselectivity.

were obtained from TCI and Acros, respectively. The homoallyl alcohol **4** was prepared according to the literature.[5b]

**Typical Procedure.** The reaction of Entry 1 in Table 1 is representative. Cesium carbonate (0.23 g, 0.72 mmol) was placed in a 30-mL two-necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo by heating with a hair dryer for 2 min. Palladium acetate (5.6 mg, 0.025 mmol) was added to the reaction flask. The flask was then filled with argon by using standard Schlenk technique. Tricyclohexylphosphine (0.50 M in toluene, 0.10 mL, 0.050 mmol) and toluene (0.50 mL) were added and the resulting mixture was stirred for 10 min at room temperature. Toluene (1.5 mL), homoallyl alcohol **4** (73 mg, 0.60 mmol), and *o*-chlorotoluene (**2a**, 58 μL, 0.50 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 17 h. After the mixture was cooled to room temperature, water (20 mL) was added. The product was extracted with hexane (20 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification with hexane as an eluent gave 2-(3-methyl-2-butenyl)toluene (**5a**, 0.080 g, 0.50 mmol) in 100% yield.

**Characterization Data.** Spectral data for **4**,[5b] **5e**,[9] **5h**,[10] **5i**,[11] **5j**,[12] and **7b**[13] are found in the literature.

**2-(3-Methyl-2-butenyl)toluene (5a):** IR (neat) 2971, 1490, 1451, 1377 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.72 (s, 3H), 1.74 (s, 3H), 2.29 (s, 3H), 3.30 (d, $J = 7.0$ Hz, 2H), 5.22–5.26 (m, 1H), 7.08–7.14 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.84, 19.46, 25.73, 32.16, 122.49, 125.87, 125.93, 128.56, 130.01, 132.36, 136.12, 139.92. Found: C, 89.75; H, 9.94%. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06%.

**1,3-Dimethyl-2-(3-methyl-2-butenyl)benzene (5b):** IR (neat) 2977, 1472, 1376, 1099 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.69 (s, 3H), 1.78 (s, 3H), 2.30 (s, 6H), 3.33 (d, $J = 6.5$ Hz, 2H), 4.97–5.01 (m, 1H), 7.01 (s, 3H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.93, 20.01, 25.63, 28.78, 121.94, 125.65, 128.00, 131.63, 136.25, 138.51. Found: C, 89.43; H, 10.42%. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41%.

**2-(3-Methyl-2-butenyl)biphenyl (5c):** IR (neat) 2973, 1479, 1010 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.51 (s, 3H), 1.68 (s, 3H), 3.28 (d, $J = 7.0$ Hz, 2H), 5.17–5.21 (m, 1H), 7.21–7.62 (m, 9H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.69, 25.69, 31.98, 123.64, 125.67, 126.70, 127.42, 127.98, 129.25, 129.33, 129.94, 131.94, 139.23, 141.74, 141.81. Found: C, 91.94; H, 8.26%. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16%.

**4-(3-Methyl-2-butenyl)biphenyl (5d):** Amorphous solid. IR (nujol) 2982, 1734, 1558, 1489 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.76 (s, 3H), 1.78 (s, 3H), 3.40 (d, $J = 7.5$ Hz, 2H), 5.36–5.40 (m, 1H), 7.25–7.28 (m, 2H), 7.32–7.35 (m, 1H), 7.41–7.45 (m, 2H), 7.51–7.54 (m, 2H), 7.57–7.60 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.85,

25.78, 33.99, 123.01, 126.96, 127.01, 127.12, 128.68, 128.70, 132.71, 138.71, 140.94, 141.15. HRMS (EI) Found: 222.1404 [$M^+$]; Calcd for $C_{17}H_{18}$: 222.1409.

**4-(3-Methyl-2-butenyl)toluene (5f):** IR (neat) 2975, 1516, 1104 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.76 (s, 3H), 1.78 (s, 3H), 2.36 (s, 3H), 3.35 (d, $J = 7.0$ Hz, 2H), 5.34–5.38 (m, 1H), 7.12 (s, 4H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.77, 20.96, 25.74, 33.91, 123.48, 128.16, 129.03, 132.20, 135.10, 138.73. HRMS (EI) Found: 160.1254 [$M^+$]; Calcd for $C_{12}H_{16}$: 160.1252.

**4-(3-Methyl-2-butenyl)styrene (5g):** IR (neat) 1684, 1558 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.77 (s, 3H), 1.80 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.23 (d, $J = 11.0$ Hz, 1H), 5.35–5.39 (m, 1H), 5.75 (d, $J = 18.0$ Hz, 1H), 6.74 (dd, $J = 18.0$, 11.0 Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.79, 25.73, 34.07, 112.85, 122.99, 126.21, 128.42, 132.58, 135.16, 136.67, 141.53. Found: C, 90.38; H, 9.58%. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36%.

**Methyl 2-(3-Methyl-2-butenyl)phenyl Ketone (5k):** IR (neat) 1684, 1253 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.70 (s, 3H), 1.72 (s, 3H), 2.56 (s, 3H), 3.58 (d, $J = 7.0$ Hz, 2H), 5.22–5.26 (m, 1H), 7.24–7.29 (m, 2H), 7.37–7.40 (m, 1H), 7.59 (dd, $J = 7.5$, 1.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.90, 25.73, 29.96, 32.31, 123.02, 125.68, 128.62, 130.62, 131.27, 132.75, 138.33, 141.35, 202.61. HRMS (EI) Found: 188.1195 [$M^+$]; Calcd for $C_{13}H_{16}O$: 188.1201.

**3-(3-Methyl-2-butenyl)pyridine (5l):** IR (neat) 2977, 1576, 1423, 1027 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.72 (s, 3H), 1.75 (s, 3H), 3.34 (d, $J = 7.5$ Hz, 2H), 5.27–5.30 (m, 1H), 7.19–7.21 (m, 1H), 7.47–7.49 (m, 1H), 8.42–8.44 (m, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.85, 25.69, 31.50, 121.76, 123.29, 129.79, 133.76, 135.77, 147.11, 149.82. HRMS (EI) Found: 147.1046 [$M^+$]; Calcd for $C_{10}H_{13}N$: 147.1048.

**2,3,3,4-Tetramethyl-4-penten-2-ol (6):** IR (neat) 3447, 2978, 1377 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.13 (s, 6H), 1.19 (s, 6H), 1.87 (s, 3H), 4.86 (s, 1H), 5.01 (s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 23.57, 23.72, 25.88, 45.67, 74.27, 113.47, 151.58. HRMS (EI) Found: 125.1334 [$M - OH]^+$; Calcd for $C_9H_{17}$: 125.1330.

**1-(2,3-Dimethyl-2-butenyl)naphthalene (7a):** IR (neat) 1505, 1380, 1202 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.66 (s, 3H), 1.81 (s, 3H), 1.84 (s, 3H), 3.78 (s, 2H), 7.26–7.27 (m, 1H), 7.41–7.44 (m, 1H), 7.49–7.55 (m, 2H), 7.73–7.75 (m, 1H), 7.88–7.90 (m, 1H), 8.07–8.09 (m, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 18.67, 20.57, 20.71, 36.95, 123.56, 125.05, 125.35, 125.46, 125.61, 125.65, 126.39, 126.65, 128.64, 132.58, 133.73, 136.18. Found: C, 91.41; H, 8.75%. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63%.

**Ethyl 4-(2,3-Dimethyl-2-butenyl)benzoate (7c):** IR (neat) 1718, 1275, 1106 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.38 (t, $J = 7.0$ Hz, 3H), 1.58 (s, 3H), 1.74 (s, 3H), 1.78 (s, 3H), 3.50 (s, 2H), 4.36 (q, $J = 7.0$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.94 (d, $J = 8.0$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.35, 18.39, 20.61, 20.70, 40.19, 60.71, 125.58, 126.55, 128.03, 128.36, 129.55, 146.62, 166.72. Found: C, 77.41; H, 8.71%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

**2,3-Dimethyl-3-(1-methylethyl)-4-penten-2-ol (8a):** IR (neat) 3566, 2979, 1373 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.83 (d, $J = 6.5$ Hz, 3H), 0.96 (s, 3H), 0.98 (d, $J = 6.5$ Hz, 3H), 1.19 (s, 3H), 1.23 (s, 3H), 1.90 (m, 1H), 5.03 (d, $J = 17.5$ Hz, 1H), 5.26 (d, $J = 11.0$ Hz, 1H), 5.88 (dd, $J = 17.5$, 11.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 11.86, 19.27, 20.23, 26.24, 27.30, 32.37, 49.70, 74.84, 114.51, 144.53. HRMS (EI) Found: 139.1489 [$M - OH]^+$; Calcd for $C_{10}H_{19}$: 139.1487.

**2,3-Dimethyl-3-phenyl-4-penten-2-ol (8b):** IR (neat) 3566, 2981, 1373 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.13 (s, 3H), 1.18 (s, 3H), 1.54 (s, 3H), 5.14 (d, $J = 17.5$ Hz, 1H), 5.25 (d, $J = 11.0$ Hz, 1H), 6.74 (dd, $J = 17.5$, 11.0 Hz, 1H), 7.20–7.24 (m, 1H), 7.29–7.33 (m, 2H), 7.46–7.48 (m, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.14, 25.84, 26.05, 51.18, 74.50, 114.43, 126.14, 127.65, 128.47, 143.58, 144.99. HRMS (FAB) Found: 189.1280 [$M - H]^+$; Calcd for $C_{13}H_{17}O$: 189.1279.

**(*E*)-1-(3,4-Dimethyl-2-pentenyl)naphthalene (9a):** IR (neat) 2961, 1506 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.03 (d, $J = 6.5$ Hz, 6H), 1.77 (s, 3H), 2.29–2.34 (m, 1H), 3.79 (d, $J = 7.0$ Hz, 2H), 5.04–5.44 (m, 1H), 7.33–7.35 (m, 1H), 7.39–7.42 (m, 1H), 7.47–7.53 (m, 2H), 7.71–7.73 (m, 1H), 7.85–7.87 (m, 1H), 8.02–8.04 (m, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.65, 21.45, 31.46, 36.82, 120.34, 124.05, 125.41, 125.47, 125.61, 125.64, 126.51, 128.62, 132.13, 133.81, 137.86, 142.25. HRMS (EI) Found: 224.1566 [$M^+$]; Calcd for $C_{17}H_{20}$: 224,1565.

**(*E*)-1-(3-Phenyl-2-butenyl)naphthalene (9b):** IR (neat) 3054, 1507 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.25 (s, 3H), 4.01 (d, $J = 7.0$ Hz, 2H), 6.04–6.08 (m, 1H), 7.21–7.26 (m, 1H), 7.29–7.34 (m, 2H), 7.40–7.44 (m, 4H), 7.49–7.56 (m, 2H), 7.75–7.77 (m, 1H), 7.88–7.90 (m, 1H), 8.07–8.09 (m, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 16.06, 32.51, 123.94, 125.54, 125.63, 125.71, 125.80, 125.89, 126.61, 126.74, 126.84, 128.17, 128.71, 132.06, 133.88, 135.78, 137.03, 143.47. HRMS (EI) Found: 258.1404 [$M^+$]; Calcd for $C_{20}H_{18}$: 258.1409.

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