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PALLADIUM-CATALYZED TANDEM COUPLING REACTION OF ALKYNE, CONJUGATED DIENE, AND TRIETHYLBORANE

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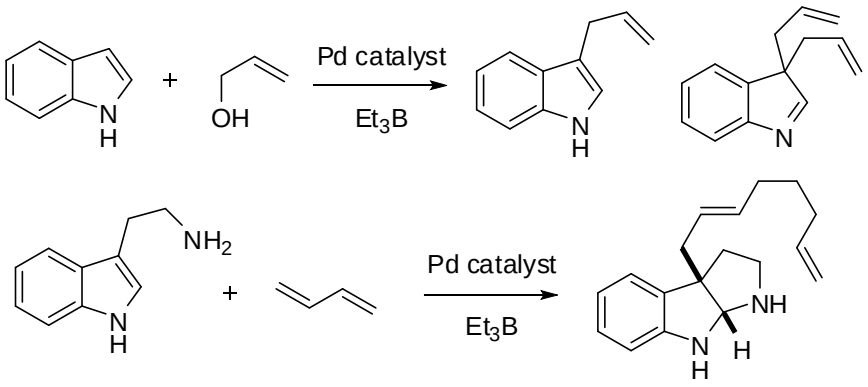
Dedicated to Prof. Dr. Ei-ichi Negishi on the occasion of his 77th birthday.

Abstract – Pd(0) catalyst promotes three-component coupling reactions of allylic alcohols and vinylcyclopropanes with terminal alkynes and triethylborane to provide (*E*)-1-substituted 2-ethyl-1,4-pentadienes and (*E*)-1-substituted 2-ethyl-1,4-heptadienes involving geminal ethylation and allylation at the acetylenic terminal carbon atom with high regio- and stereoselectivities. 1,3-Butadiene and bis-dienes can act as allylating agents to undergo the multi-component coupling reactions, accompanied by dimerization of the diene moieties, to provide 1,4,9-decatrienes and pyrrolidines with excellent regio- and stereoselectivities.

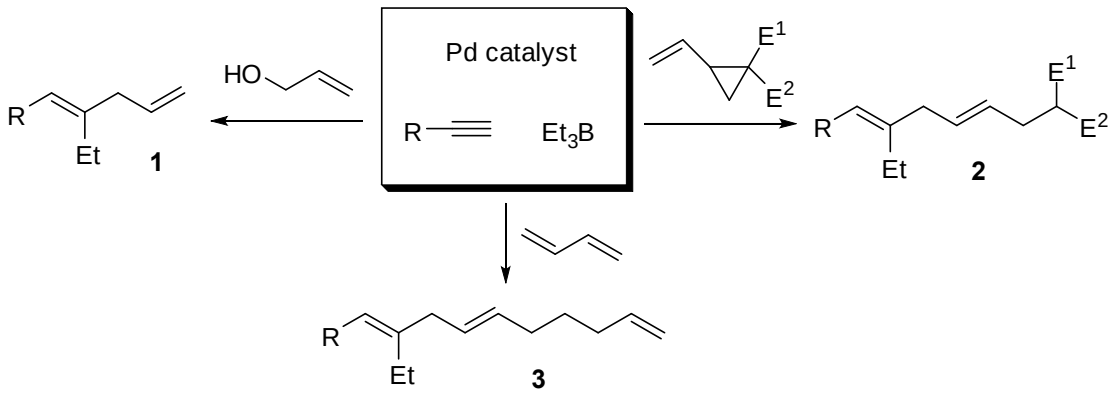
Multi-component coupling reactions are among the most efficient and useful strategies for construction of complex molecules in synthetic chemistry.[1] Specifically, allylic alkylations are convenient and effective methods for transformation of allyl halides and allyl acetates to valuable unsaturated hydrocarbons and fine chemicals. We have previously developed the direct activation of allyl alcohols, promoted by a combination of a Pd catalyst and triethylborane, to form a π–allylpalladium intermediate.[2] This species serves as an allyl cation equivalent for a wide variety of soft nucleophiles, such as amines, polyphenols, and active methylene compounds.[3] Recently, we reported that indole serves as an effective nucleophile toward *C*-allylic alkylation to give 3-allylindole and 3,3-diallylindolenine in excellent yields (Scheme 1).[4] Furthermore, we extended the efficient tandem cyclization to afford pyrroloindole alkaloid frameworks by means of allylic alkylation of tryptamine with 1,3-butadiene via bis-π-allylpalladium key intermediates.

Our methods for the Pd/triethylborane system are also useful for nucleophilic allylation toward various kinds of electrophiles. For example, the π-allylpalladium species undergoes an allyl-ethyl exchange reaction with triethylborane, providing allyl diethylborane as an allyl anion equivalent, which reacts with electrophiles such as aldehydes, acetals, and aldimines to provide homoallyl alcohols and homoallylamines.[5] Thus, the Pd/triethylborane system works well for the generation of both allyl cation and allyl anion equivalents directly from allylic alcohols to achieve amphiphilic allylic alkylations.[6]

We report herein that a similar reaction system using a Pd(0) catalyst and triethylborane promotes allylic alcohols and vinylcyclopropanes to undergo coupling reactions with terminal alkynes to provide (*E*)-1-substituted 2-ethyl-1,4-pentadienes and (*E*)-1-substituted 2-ethyl-1,4-heptadienes involving geminal ethylation and allylation at the acetylenic terminal carbon atom with high regio- and stereoselectivities (Scheme 2). It is noteworthy that triethylborane serves not only as an ethylating agent for the coupling reaction but also as an activator for the oxidative addition of allylic alcohols toward Pd(0) catalyst to form the π-allylpalladium intermediate. Furthermore, 1,3-butadiene and bis-dienes can act as allylating agents accompanied by dimerization of the diene moieties to undergo the multi-component coupling reactions, providing 1,4,9-decatrienes and pyrrolidines possessing dienyl and alkenyl side chains in excellent regio- and stereoselectivities.



Scheme 1. Pd-Et_3B Promoted Allylic Alkylation of Indole and Tryptamine with Allyl Alcohol and Butadiene



Scheme 2. Pd-Catalyzed Coupling Reaction of Terminal Alkyne, Allylating Agent, and Et_3B

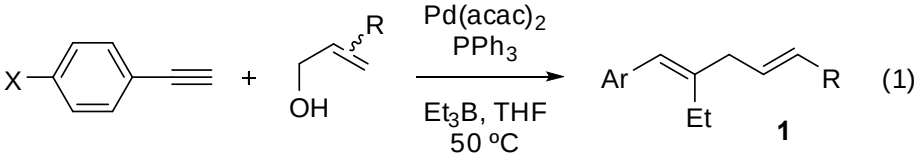
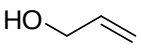
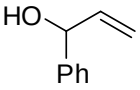
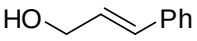
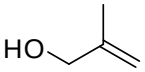
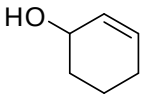
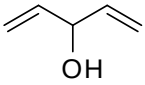
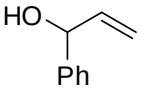
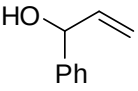
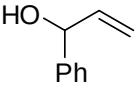


Table 1. Pd-Catalyzed Coupling Reaction of Allylic Alcohol, Alkyne, and Et_3B[a]

run	X	allyl alcohol	yield (%)
1	H		**1a**: 81
2	H		**1b**: 84
3	H		**1b**: 70
4	H		**1c**: 72
5	H		**1d**: 50
6	H		**1e**: 65
7	*p*-OMe		**1f**: 75
8	*p*-Me		**1g**: 71
9	*p*-F		**1h**: 84

[a] The reaction was undertaken in the presence of $Pd(acac)_2$ (0.025 mmol), PPh_3 (0.05 mmol), alkyne (1 mmol), allylic alcohol (2 mmol), and Et_3B (2.4 mmol) in dry THF (0.5 mL) at 50 ºC for 72 h under nitrogen atmosphere.

The results of the coupling reactions of various kinds of terminal alkynes, substituted allylic alcohols and triethylborane are summarized in Table 1. Reactions of substituted phenylacetylenes with a wide structural variety of substituted allylic alcohols and triethylborane were conducted in the presence of $Pd(acac)_2$ catalyst and PPh_3 ligand at 50 ˚C under nitrogen atmosphere. Both α-phenylallyl alcohol and cinnamyl alcohol underwent the coupling reactions at the less substituted allylic position to afford the linear type product **1b** as a single product with high regio- and stereoselectivities (runs 2 and 3, Table 1). β-Methallyl alcohol and 2-cyclohexen-1-ol participated in the coupling reaction in a similar manner (runs 4 and 5, Table 1). Divinyl carbinol serves as a 2,4-pentadienyl synthetic equivalent to provide

1,3,6-heptatriene **1e** as a single isomer in reasonable yield (run 6, Table 1). Pd-catalyzed three-component coupling reactions of α-phenylallyl alcohol with several kinds of substituted phenylacetylenes were also conducted. Phenylacetylenes substituted at the *para* positions with electron donating and fluorine groups participated in the coupling reactions without the deterioration of the reactivity and the yield (runs 7-9, Table 1).

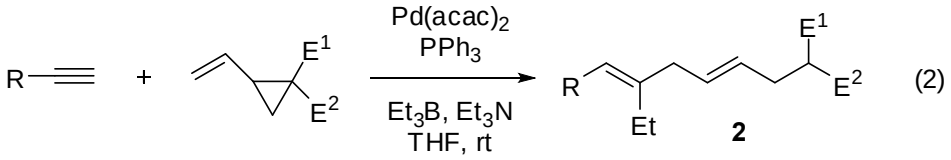
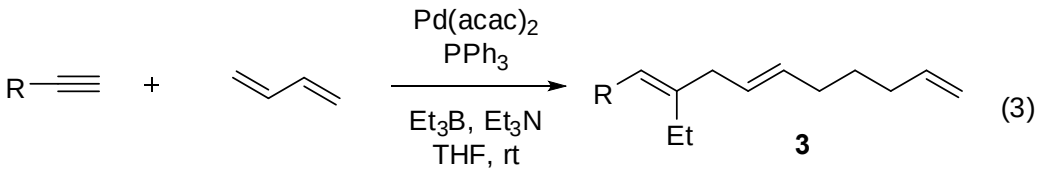


Table 2. Pd-Catalyzed Coupling Reaction of Vinylcyclopropane, Alkyne, and Et_3B[a]

run	R	E^1	E^2	yield (%)
1	Ph	CO_2Me	CO_2Me	**2a**: 74
2	(*p*-F)Ph	CO_2Me	CO_2Me	**2b**: 71
3	*n*-Bu	CO_2Me	CO_2Me	**2c**: 55
4	$BzO(CH_2)_2$-	CO_2Me	CO_2Me	**2d**: 51
5	Ph	CO_2Et	COMe	**2e**: 60
6	Ph	COMe	COMe	**2f**: 40

[a] The reaction was undertaken in the presence of $Pd(acac)_2$ (0.025 mmol), PPh_3 (0.05 mmol), alkyne (1 mmol), cyclopropane (1 mmol), Et_3B (3 mmol), Et_3N (1 mmol) in dry THF (0.5 mL) at room temperature for 72 h under nitrogen atmosphere.

Next, we examined similar coupling reactions of vinylcyclopropanes, which were prepared from dimethyl malonate, β-ketoester, and acetylacetone with 1,4-dichloro-2-butene, in the presence of terminal alkynes, triethylborane, and Pd(0) catalyst at room temperature (eq 2, Table 2).[7] In all cases, triethylamine was indispensable to achieve the coupling reactions. In the absence of triethylamine, the desired reaction did not proceed at all and the vinylcyclopropanes were recovered almost quantitatively. Aromatic and aliphatic substituted terminal alkynes were also useful for the coupling reaction with vinylcyclopropane derived from dimethyl malonate in reasonable to good yields (runs 1-4, Table 2). Vinylcyclopropanes with β-ketoester and β-diketone skeletons reacted with phenylacetylene to give the corresponding coupling products **2e** and **2f**, respectively (runs 5 and 6, Table 2). All of these olefin geometries with respect to the main chain were assigned as *E*-stereoselectivities.



(3)

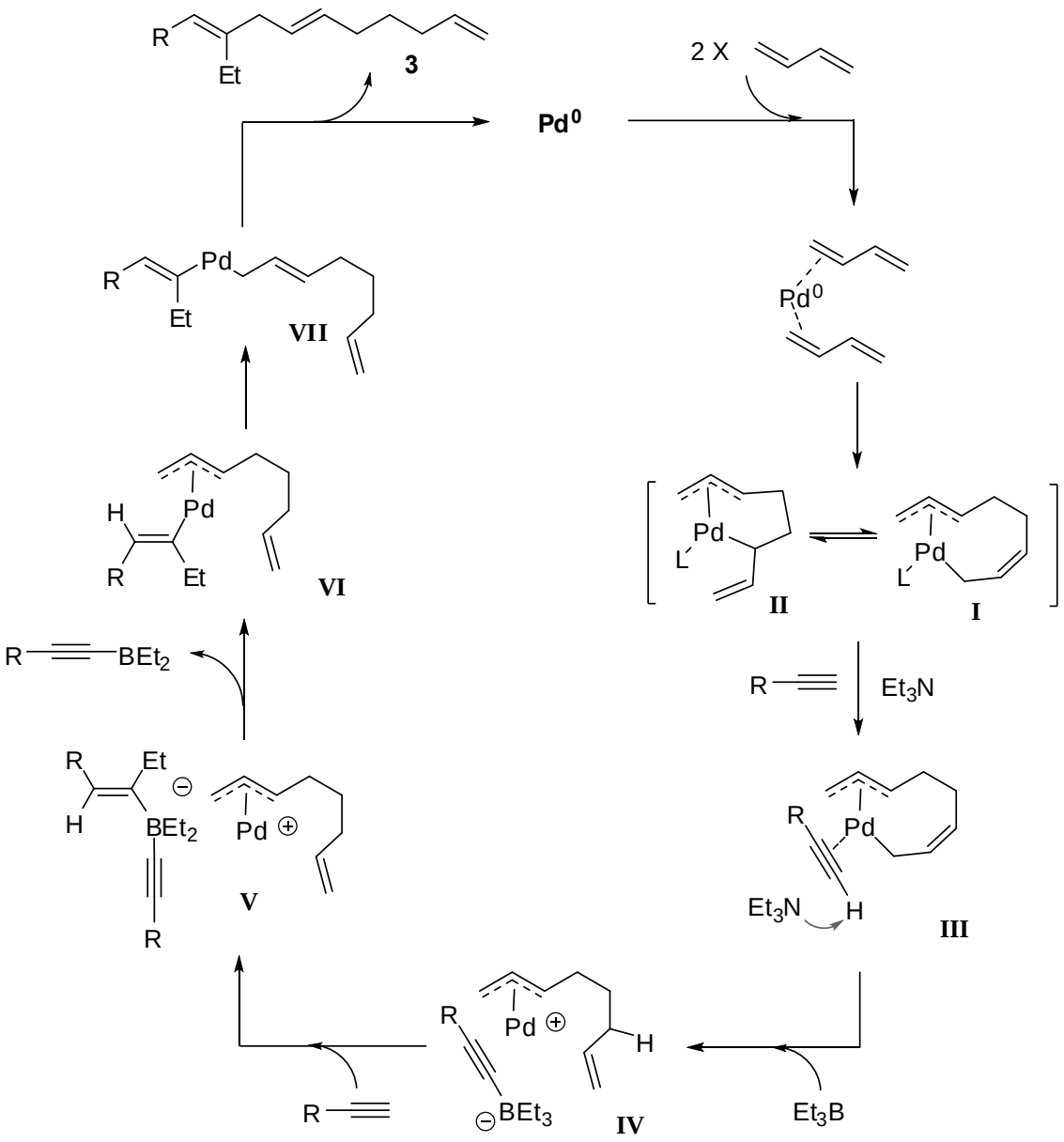
Table 3. Pd-Catalyzed Coupling Reaction of Butadiene, Alkyne, and Et_3B[a]

run	R	yield (%)
1	Ph	**3a**: 74
2	(*p*-Me)Ph	**3b**: 71
3	(*p*-F)Ph	**3c**: 60
4	*n*-Hept	**3d**: 56

[a] The reaction was undertaken in the presence of $Pd(acac)_2$ (0.025 mmol), PPh_3 (0.05 mmol), alkyne (1 mmol), butadiene (2 mmol), Et_3B (2.4 mmol), Et_3N (3 mmol) in dry THF (0.5 mL) at room temperature for 72 h under nitrogen atmosphere.

1,3-Butadiene undergoes dimerization to serve as a bis-π-allylpalladium complex under the Pd(0) catalytic system.[8] The results of the coupling reaction with aromatic and aliphatic terminal alkynes, 1,3-butadiene, and triethylborane in the presence of Pd catalyst are presented in Table 3. Triethylamine was required to complete the multi-component coupling reaction. Irrespective of the kinds of terminal alkynes, the reaction proceeded smoothly at room temperature to give (1*E*,4*E*)-1,4,9-decatrienes **3** as a single isomer.

A plausible reaction mechanism for the multi-component coupling reaction with an alkyne, triethylborane, and 1,3-butadiene is proposed in Scheme 3. Pd(0) catalyst promotes the dimerization of butadiene to afford η^1,η^3-bis-allylpalladium intermediates **I** and **II** serving as Lewis acids to increase the acidity of the coordinated terminal alkynes.[9] The abstraction of the activated acetylenic terminal proton by triethylamine proceeds to generate π-allylpalladium alkynylborate intermediate **IV**, which would undergo [1,2] ethyl group transfer from the B atom to the acetylide carbon atom to form π-allylpalladium vinyldiethylborate complex **V** with excellent regio- and stereoselectivities. Allylvinylpalladium **VI** would be formed through the transmetallation of complex **V**, and decatriene **3** would be formed with the liberation of Pd(0) catalyst via reductive elimination.



Scheme 3. Plausible Reaction Mechanism for Tandem Coulping Reaction

A series of these reaction systems were applied to the coupling reaction of a bis-diene tethered by tosylamide for the efficient synthesis of pyrrolidines via tandem cyclizations. The coupling reactions of the bis-diene, various kinds of terminal alkynes, and triethylborane were carried out in the presence of Pd catalyst in THF at room temperature (eq 4). Regardless of the aromatic and aliphatic substituents on the terminal alkynes, the pyrrolidine frameworks were constructed successfully (Table 4). It is also significant that triethylamine accelerated the multi-component coupling reaction involving tandem cyclization of the diene moiety giving rise to *trans*-3-allyl-4-pentadienyl pyrrolidine **4** in a 7:1 ratio with exclusive *trans* selectivities (entries 2 and 4, Table 4). This method might be one of the most useful and convenient strategies for the highly efficient regio- and stereocontrolled synthesis of heterocyclic compounds.

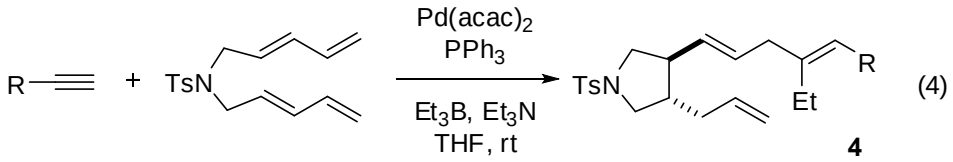


Table 4. Pd-Catalyzed Tandem Reaction of Bis-diene, Alkyne, and Et_3B[a]

run	R	yield (%) [ratio]
1	(*p*-Me)Ph	**4a**: 86 [7:1]
2	(*p*-F)Ph	**4b**: 86 [7:1]
3	(*p*-Br)Ph	**4c**: 41 [single]
4	*n*-Propyl	**4d**: 50 [single]
5	*n*-Bu	**4e**: 41 [single]
6	*c*-Propyl	**4f**: 63 [single]
7	$(CH_2)_2OTHP$	**4g**: 70 [single]

[a] The reaction was undertaken in the presence of $Pd(acac)_2$ (0.025 mmol), PPh_3 (0.05 mmol), alkyne (1 mmol), bis-diene (0.5 mmol), Et_3B (2.4 mmol), Et_3N (3 mmol) in dry THF (0.5 mL) at room temperature for 72 h under nitrogen atmosphere.

In summary, Pd(0) catalyst promotes three-component coupling reactions of allylic alcohols and vinylcyclopropanes with terminal alkynes and triethylborane to provide (*E*)-1-substituted 2-ethyl-1,4-pentadienes and (*E*)-1-substituted 2-ethyl-1,4-heptadienes involving geminal ethylation and allylation at the acetylenic terminal carbon atom with high regio- and stereoselectivities. Under similar conditions, Pd-catalyzed three-component coupling reactions of 1,3-butadiene, terminal alkynes, and triethylborane involving dimerization of butadiene gave (1*E*,4*E*)-deca-1,4,9-triene with excellent regio- and stereoselectivities. Furthermore, a bis-diene undergoes the tandem coupling reaction accompanied by intramolecular dimerization of the diene moiety via bis-π–allylpalladium to afford *trans*-3-allyl-4-pentadienylpyrrolidiene with excellent regio- and stereoselectivities. Applications of the multi-component coupling reaction for the efficient synthesis of physiologically active molecules such as prostanoids are being pursued in our laboratory.

ACKNOWLEDGEMENTS

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7. General procedure for the Pd-catalyzed multi-component coupling reaction (run 1, Table 2): A 25 mL of two-necked round-bottomed flask, equipped with a rubber septum and an air condenser at the top of which is attached a three-way stopcock fitted a nitrogen balloon, is charged with $Pd(acac)_2$ (7.6 mg, 0.025 mmol) and PPh_3 (13.1 mg, 0.05 mmol). The apparatus is purged with nitrogen and the flask is charged with freshly distilled THF (0.5 mL). Into this solution, phenylacetylene (102 mg, 1 mmol), vinylcyclopropane (184 mg, 1 mmol), triethylamine (140 μL, 1 mmol), and Et_3B (3.0 mL of 1 M hexane solution; 3.0 mmol) are successively added while stirring the solution with a magnetic stirrer. The stirring is continued for 72 h at room temperature. After the reaction completes, the reaction mixture is diluted with ethyl acetate (20 mL). The organic phase is washed with sat. $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), and then dried over magnesium sulfate,

filtered, and concentrated. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, which was subjected to column chromatography over silica gel (hexane/EtOAc = 20/1, v/v) to give **2a** (234 mg, 74%, R_f = 0.51; hexane/EtOAc = 4/1, v/v).

Dimethyl 2-[(2*E*,5*E*)-5-benzylidenehept-2-enyl]malonate (**2a)**: IR (neat) 3022 (w), 2962 (s), 2875 (w), 1736 (s), 1647 (w), 1599 (w), 1435 (s), 1197 (s), 1153 (s), 1028 (m), 920 (w), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, J = 7.6 Hz, 3 H), 2.21 (q, J = 7.6 Hz, 2 H), 2.65 (t, J = 7.0 Hz, 2 H), 2.84 (d, J = 6.8 Hz, 2 H), 3.46 (t, J = 7.0 Hz, 1 H), 3.72 (s, 6 H), 5.48 (dt, J = 15.4, 6.8 Hz, 1 H), 5.60 (dt, J = 15.4, 7.0 Hz, 1 H), 6.20 (s, 1 H), 7.15-7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8, 23.8, 31.8, 39.7, 51.8, 52.3, 125.1, 125.7, 126.9, 127.7, 128.2, 131.3, 138.0, 142.9, 168.9. High-resolution MS, calcd for $C_{19}H_{24}O_4$: 316.1675. Found *m/z* (relative intensity): 316.1678 (M^+, 100), 317 (24), 285 (11).

1-[(1*E*,4*E*)-2-Ethyldeca-1,4,9-trienyl]benzene (**3a)**: IR (neat) 3022 (w), 2966 (s), 2930 (s), 2856 (s), 1641 (m), 1599 (m), 1493 (s), 1443 (m), 970 (s), 912 (s), 698 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, J = 7.6 Hz, 3 H), 1.49 (quint, J = 7.4 Hz, 2 H), 2.04–2.09 (m, 4 H), 2.25 (q, J = 7.6 Hz, 2 H), 2.85 (d, J = 5.5 Hz, 2 H), 4.94 (d, J = 10.2 Hz, 1 H), 5.00 (d, J = 17.1 Hz, 1 H), 5.42–5.56 (m, 2 H), 5.81 (ddt, J = 17.1, 10.2, 6.7 Hz, 1 H), 6.24 (s, 1 H), 7.12-7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9, 23.8, 28.8, 32.0, 33.2, 40.1, 114.3, 124.9, 125.8, 127.9, 128.1, 132.0, 138.4, 143.8. High-resolution MS, calcd for $C_{18}H_{24}$: 240.1878, Found *m/z* (relative intensity): 240.1867 (M^+, 100), 211 (73), 241 (45).

(3*R,4*R**)-3-Allyl-4-[(1*E*,4*E*)-4-ethyl-7-(tetrahydro-2*H*-pyran-2-yloxy)hepta-1,4-dienyl]-1-tosyl-pyrrolidine** (**4g**): IR (neat) 3076 (w), 2939 (s), 2872 (s), 2359 (s), 2341 (s), 1641 (s), 1599 (s), 1441 (m), 1346 (s), 1163 (s), 1032 (s), 814 (m), 667 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.6 Hz, 3 H), 1.49-1.57 (m, 6 H), 1.79-1.85 (m, 2 H), 1.99 (q, J = 7.6 Hz, 2 H), 2.22 (br dd, J = 9.6, 6.5 Hz, 1 H), 2.24 (t, J = 8.5 Hz, 1 H), 2.30 (q, J = 7.1 Hz, 2 H), 2.44 (s, 3 H), 2.67 (d, J = 6.8 Hz, 2 H), 2.88 (dd, J = 9.8, 8.5 Hz, 1 H), 2.94 (t, J = 9.8 Hz, 1 H), 3.36 (t, J = 9.6 Hz, 2 H), 3.47-3.51 (m, 2 H), 3.68 (dt, J = 16.8, 7.3 Hz, 1 H), 3.85 (td, J = 15.1, 7.3 Hz, 1 H), 4.58 (t, J = 6.8 Hz, 1 H), 4.95 (d, J = 10.5 Hz, 1 H), 4.98 (d, J = 17.1 Hz, 1 H), 5.09 (dd, J = 15.2, 8.5 Hz, 1 H), 5.13 (t, J = 7.1 Hz, 1 H), 5.40 (dt, J = 15.2, 6.8 Hz, 1 H), 5.62 (ddd, J = 17.1, 10.5, 7.8 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.70 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0, 19.6, 21.5, 23.2, 25.5, 28.4, 30.7, 35.5, 39.7, 44.0, 47.5, 52.6, 53.0, 62.3, 67.2, 98.7, 116.5, 121.0, 127.4, 129.5, 131.9, 134.1, 135.4, 141.2, 143.1. High-resolution MS, calcd for $C_{28}H_{41}NO_4S$: 487.2756. Found *m/z* (relative intensity): 487.2759 (M^+, 100).

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