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Lewis Acid-Promoted Addition of 1,3-Bis(silyl)propenes to Aldehydes: A Route to 1,3-Dienes

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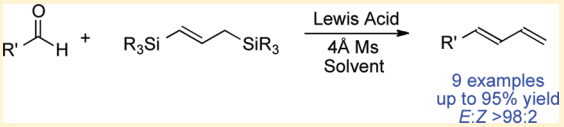
Supporting Information

ABSTRACT: The Lewis acid-promoted addition of 1,3-bis(silyl)-propenes to aldehydes to provide the corresponding (*E*)-1,3-dienes in excellent stereoselectivity and good to excellent yields is reported. The procedure is mild, base-free, and operationally straightforward.



1,3-Dienes are important structural motifs in organic chemistry, as they provide highly suitable platforms for further synthetic elaborations. These valuable synthetic precursors can be readily transformed into a diverse array of functional groups such as carbacycles and heterocycles,[1−3] peroxides,[4] mono-[5] and biscyclopropanes,[6] and β-lactams[7] (Figure 1). Given their broad applicability, it is then not surprising that dienes are valuable intermediates in the total synthesis of natural products.[8] Thus, mild and selective methods for the construction of 1,3-dienes in high diastereoselectivity are essential. Currently existing synthetic methods for producing dienes include reductions of 1,3-diynes or 1,3-enynes,[9] metal-catalyzed cross-coupling reactions of vinyl boronates, halides, or propargylsilanes,[10−13] 1,2- or 1,4-elimination of allylic alcohols,[14] and, perhaps the most common, the Wittig reaction of an unsaturated aldehyde with a phosphonium ylide or an allylic phosphorus ylide.[15,16] However, several of these technologies require strongly basic reaction conditions or provide the diene in an *E*/*Z*-isomeric mixture, which are often not compatible with or desirable in multistep synthesis. Clearly, a simple protocol circumventing these drawbacks is highly desirable. Herein is described a procedure providing a complementary approach to the existing methods for diene construction. It is a mild and operationally straightforward procedure by which (*E*)-1,3-dienes can be obtained in excellent yields and diastereoselectivities by a Lewis acid-promoted addition of 1,3-bis(silyl)propenes to aldehydes.

Recently, we described the use of 1,3-bis(silyl)propenes in a stereoselective [2 + 3]-annulation reaction with α-amino aldehydes yielding the corresponding pyrrolidines (Scheme 1).[17,18] During the course of this investigation it was noted that in some cases diene **3a** was formed in varying amounts together with the desired annulation product **4**. Consequently, we speculated that if the possibility for the intermediate β-silicon-stabilized carbenium ion to be trapped by a nucleophile was removed, then the formation of the diene should be favored.

Initial focus was directed toward the investigation of the influence of the substituents on silicon in bis(silyl)propene **2** (Table 1). It has previously been noted that allyldimethylphenylsilane is, due to steric and electronic effects, less nucleophilic than allyltrimethylsilane,[19,20] and that the $PhMe_2Si$ moiety is also more difficult to eliminate.[21] Changing the bis(silyl) moiety from $PhMe_2Si$ (**2a**) to a trimethylsilyl group (**2b**) indeed increased the yield of the reaction, from 17 to 92%, providing diene **3b** as a single detected stereoisomer (*E*:*Z* > 98:2) (entries 1 and 2). Next the effect of the Lewis acid on the reaction outcome was investigated (entries 2−7), revealing that both $MeAlCl_2$ and $BF_3{\cdot}OEt_2$ are competent in affecting the desired transformation in good yield and excellent diastereoselectivity (*E*:*Z* > 98:2). Interestingly, no reaction occurred when using weaker Lewis acids (entry 5),[22] indicating that the bis(silane) **2b** is a rather poor nucleophile (vide infra). Screening of a few solvents revealed that CH_2Cl_2 was the solvent of choice, yielding the diene in good yields and selectivities, while the use of THF resulted in no conversion and PhMe required considerably longer reaction times.[23]

The addition of **2b** to aldehyde **1c** in the presence of $BF_3{\cdot}OEt_2$ turned out to be capricious and gave varying amounts of diene **3c** together with the homoallylic alcohol **6**, the result of a protodesilylation of **2b** to give allyltrimethylsilane (**5**) followed by the subsequent addition of **5** to the aldehyde (Table 2,

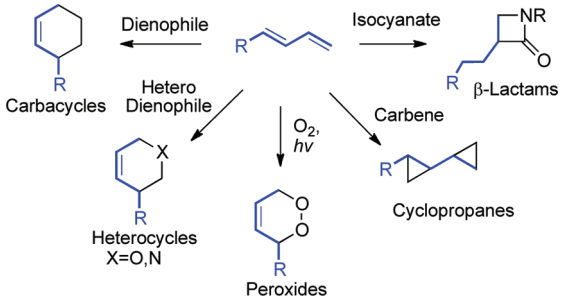


Figure 1. Some key transformations of dienes.

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Scheme 1

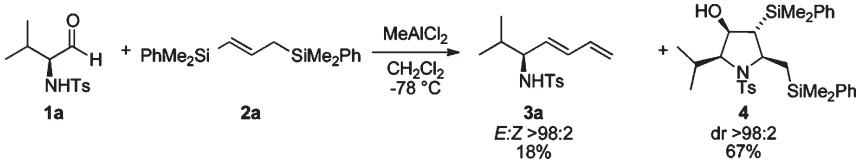
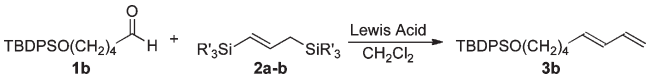


Table 1. Optimization of the Addition of Bis(silane) 2 to Aldehyde 1[a]

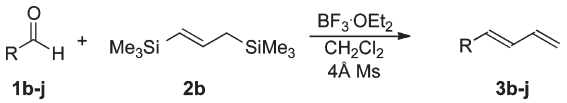


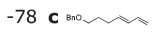
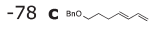
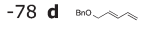
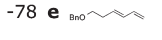
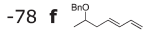
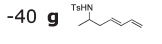
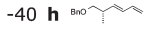
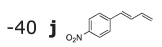
entry	2	R′	LA	3	yield (%)[b]	*E*:*Z*[c]
1	**a**	Me_2Ph	$MeAlCl_2$	**b**	17	>98:2
2	**b**	Me_3	$MeAlCl_2$	**b**	92	>98:2
3	**b**	Me_3	$TiCl_4$	**b**	—[d]	—
4	**b**	Me_3	$SnCl_4$	**b**	—[e]	—
5	**b**	Me_3	$ZnCl_2$	**b**	—[f]	—
6	**b**	Me_3	$BF_3 \cdot OEt_2$	**b**	90	>98:2
7	**b**	Me_3	BBr_3	**b**	—[g]	—

[a] Reaction conditions: To a solution of **2** (2 equiv) and the Lewis acid (2 equiv) in the solvent (1 mL) at −78 °C was added **1** (1 equiv, 0.01 M in the reaction media) dropwise over 1 h, and then the mixture was stirred for an additional 2−36 h. [b] Isolated yield. [c] The *E*:*Z* ratio was determined by ^{1}H NMR spectroscopy. [d] Decomposition of the starting material. [e] Only trimerization of **1b** was detected. [f] No reaction. [g] Trace amounts of **3b** were formed.

entry 2). In a competition experiment it was shown that **5** is more reactive toward the aldehyde than bis(silane) **2b** (Scheme 2), clearly indicating that any formation of **5** must be suppressed. Fortunately, the protodesilylation can be avoided by addition of molecular sieves (4 Å, 100 mg/mL solvent) to the reaction mixture, making the procedure reproducible (entry 3). With optimized reaction conditions in hand, the scope of the reaction was examined (Table 2). The reaction proceeded with good to excellent yield for unhindered aldehydes **1b**,**c** (entries 1, 3), and in all reactions the (*E*)-diene was the only stereoisomer detected by ^{1}H NMR spectroscopy. The addition of bis(silane) **2b** to aldehyde **1d**, having a heteroatom in the α-position, provided diene **3d** in 75% yield (entry 4). The reaction is also compatible with aldehydes containing a heteroatom in the β-position (entries 5−7). However, the reaction with β-sulfonamide-substituted aldehyde **1g** required higher reaction temperatures to reach full conversion, providing diene **3g** as the sole product in 64% yield. The addition to the α-methyl-substituted aldehyde **1h** gave somewhat lower yield, but by increasing the reaction temperature to −40 °C, the diene could be isolated in 55% yield (entry 8). Interestingly, the stereochemistry at the α-center was preserved during the reaction. Aldehyde **1i**, having a quaternary α-carbon, proved to be unreactive, probably reflecting the increased steric hindrance in close proximity to the aldehyde moiety (entry 9). Addition of **2b** to *p*-nitrobenzaldehyde gave the corresponding diene in good yield (entry 10), while addition to electron-rich benzaldehyde derivatives such as *p*-methoxy- and *p*-fluorobenzaldehyde proved unsuccessful.

Table 2. Scope of the Reaction[a]



Entry	1	Aldehyde	T (°C)	3	Diene	Yield (%)[b]	*E*:*Z*[c]
1	**b**		-78	**b**		90	>98:2
2[d]	**c**		-78	**c**		20	>98:2
3	**c**		-78	**c**		80	>98:2
4	**d**		-78	**d**		75	>98:2
5	**e**		-78	**e**		95	>98:2
6	**f**		-78	**f**		78	>98:2
7	**g**		-40	**g**		64	>98:2
8[e]	**h**		-40	**h**		55	>98:2
9	**i**		40	**i**		0	-
10[f]	**j**		-40	**j**		84	>98:2

[a] Reaction conditions: To a solution of **2b** (2 equiv), $BF_3 \cdot OEt_2$ (2 equiv), and 4 Å molecular sieves (100 mg/mL solvent) in 1 mL CH_2Cl_2 at −78 °C was added a 0.01 M solution of **1b**−**j** (1 equiv) and 1-methylnaphthalene (1 equiv) in CH_2Cl_2 dropwise over 1 h. The mixture was stirred for an additional 2−18 h. [b] Yield determined by ^{1}H NMR of the crude reaction mixture using 1-methylnaphthalene as an internal standard. [c] The *E*:*Z* ratio was determined by ^{1}H NMR spectroscopy. [d] The reaction was run without molecular sieves. The major product was the homoallylic alcohol **6** in 69% yield. [e] Er was determined by chiral HPLC (Chiracel OJ column, 0.5% 2-propanol in hexanes, 0.5 mL/min); see Experimental Section. [f] 3 equiv of $BF_3 \cdot OEt_2$ was used.

The exclusive formation of (*E*)-**3** in these reactions is surprising and is probably the result of a kinetic preference, rather than a thermodynamic reaction outcome. It is proposed that bis(silane) **2** adds to aldehyde **1** through a syn-synclinal transition state, yielding the silicon-stabilized carbenium ion **7** (Scheme 3).[24−26] The decomposition of this intermediate can then proceed through two different reaction manifolds, producing stereoisomeric products. A [1,3]-Brook rearrangement of **7** is expected to give allylsilane **8** (pathway a),[27,28] and a stereoelectronically controlled anti-1,4-elimination of this material is then expected to yield (*E*)-**3**.[29,30] Alternatively, it could be argued that intermediate **7** could eliminate the terminal trialkylsilyl moiety to yield compound **9**. However, a Peterson olefination from **9**, proceeding

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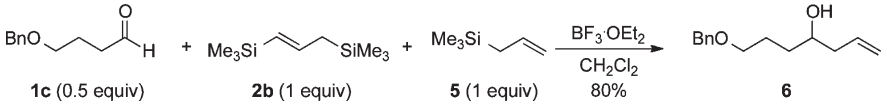
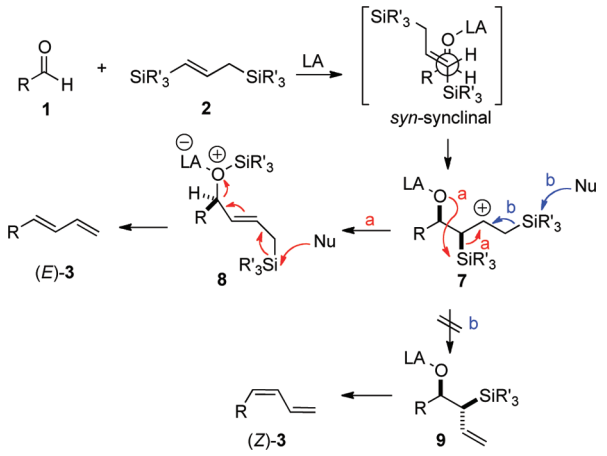
Scheme 2



Scheme 3. Proposed Mechanism for the Formation of (*E*)-1,3-Dienes[a]



[a] LA = Lewis acid, Nu = nucleophile.

through a syn elimination,[31] would give (*Z*)-**3**, which is not observed in the product mixture.[32]

Although we cannot offer an explanation to why the [1,3]-Brook rearrangement/1,4-elimination pathway is preferred, some additional support for this reaction manifold has been obtained (Scheme 4). Reaction of ethyl glyoxalate (**10**) with bis(silane) **2a** in the presence of $SnCl_4$ (0.3 equiv) afforded allylsilane **11**.[33] Subjection of this material to a Lewis acid yielded solely (*E*)-diene **12**, in agreement with the proposed mechanism.

In conclusion, a novel method for the stereoselective synthesis of (*E*)-1,3-dienes under mild and base-free conditions has been developed. The dienes are obtained in good yields as single stereoisomers.

EXPERIMENTAL SECTION

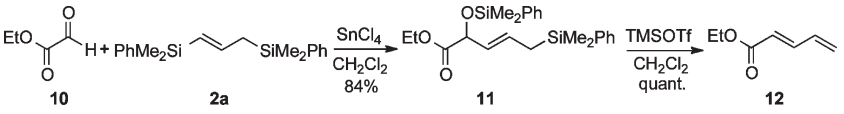
General Methods. Air- and moisture-sensitive reactions were carried out in flame-dried, septum-capped flask under an atmospheric pressure of nitrogen. All liquid reagents were transferred via oven-dried syringes. DMF, CH_2Cl_2, THF and Et_2O were dried using a glass-contour solvent dispensing system. Et_3N, DIPEA were distilled from CaH_2. Analytical thin layer chromatography was performed on silica gel 60 F_{254} plates; the plates were visualized with UV light and a solution of phosphomolybdic acid in ethanol (5 wt %). Flash chromatography was performed using SDS silica gel 60 (35−63 μm). Enantioselectivity was determined by HPLC analysis with a Chiracel OJ column, UV/vis detector, mobile phase: 0.5% 2-propanol in hexanes, 0.5 mL/min, λ 210 nm. Melting points where measured melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz (100 MHz) or 500 MHz (125 MHz) in $CDCl_3$, using the residual peak of $CHCl_3$ (^{1}H NMR δ = 7.26 ppm) and the peak of $CDCl_3$ (^{13}C NMR δ = 77.0 ppm) as internal standards. Chemical shifts are reported in the δ-scale with multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, and m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded, and only the strongest/structurally most important peaks (ν_{max}, cm^{-1}) are listed. The identities of previously characterized substances were established by comparison of ^{1}H NMR data with that in the literature.

Synthesis of 1,3-Bis(silyl)propene 2b. *(E)-Prop-1-ene-1,3-diylbis(trimethylsilane) (**2b**).*[34] To a stirred solution of allyltrimethylsilane (3.5 mL, 21.9 mmol) in THF (20 mL) were added TMEDA (3.5 mL, 23.0 mmol) and *s*-BuLi (18.8 mL, 1.4 M in hexane) dropwise at −78 °C, and the resultant yellow mixture was stirred 1 h before it was allowed to reach ambient temperature and left overnight. The reaction mixture was cooled to 0 °C, and trimethylsilyl chloride (3.05 mL, 24.1 mmol) was added. After 15 min, the solution was allowed to reach rt and stirred for an additional 1 h. The reaction was quenched by the addition of H_2O (10 mL). The aqueous phase was extracted (Et_2O, 3 × 10 mL), and the combined organic phases were washed (H_2O, 2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane) to give **2b** as a colorless oil in 76% yield (3.11 g, 16.7 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (dt, J = 18.4, 7.8 Hz, 1H), 5.43 (d, J = 18.4 Hz, 1H), 1.62 (d, J = 8.7 Hz, 2H), 0.03 (s, 9H), −0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 128.0, 28.3, −1.0, −2.0.

Synthesis of Aldehydes 1b−c,e-i. *tert-Butyl(hex-5-en-1-yloxy)-diphenylsilane (**16**).*[35] To a stirred suspension of NaH (279 mg, 6.97 mmol) in DMF (15 mL) were added 5-hexen-1-ol (0.7 mL, 5.9 mmol) and TBDPSCl (1.5 mL, 5.81 mmol), and the resultant mixture was stirred at ambient temperature for 5 h. The reaction was quenched by the addition of H_2O (5 mL). The aqueous phase was extracted (Et_2O, 3 × 15 mL), and the combined organic phases were washed (H_2O, 2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give **16** as a colorless oil in 85% yield (1.6 g, 4.93 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.44−7.34 (m, 6H), 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.98 (ddd, J = 17.1, 3.5, 1.7 Hz, 1H), 4.93 (ddt, J = 10.2, 2.1, 1.1 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 1.62−1.55 (m, 2H), 1.52−1.42 (m, 2H), 1.34−1.22 (m, 2H), 1.05 (s, 9H).

*((Pent-4-en-1-yloxy)methyl)benzene (**17**).*[36] To a suspension of NaH (279 mg, 6.97 mmol) in DMF (40 mL) was added 4-penten-1-ol (0.6 mL, 5.81 mmol) at 0 °C. After 5 min, benzyl bromide (0.725 mL, 6.09 mmol) was added dropwise. The resultant mixture was allowed to reach room temperature and stirred for 4 h. The reaction was quenched by addition of NH_4Cl (satd, aq, 5 mL). The aqueous phase was extracted (Et_2O, 3 × 20 mL), and the combined organic phases were washed (H_2O, 2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced

Scheme 4. Formation of the (*E*)-Diene via Allylsilane 11



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pressure. The residue was purified by flash chromatography (pentane:EtOAc, 20:1) to give **17** as a colorless oil in 73% yield (750 mg, 4.26 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.32 (m, 4H), 7.32−7.26 (m, 1H), 5.82 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.06−4.93 (m, 2H), 4.51 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 2.19−2.12 (m, 2H), 1.76−1.68 (m, 2H).

*1-((But-3-enyloxy)methyl)benzene (**18**).*[37] Prepared for commercially available alcohol **15** as described for **17** to afford **18** (398 mg, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.32 (m, 4H), 7.32−7.27 (m, 1H), 5.85 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.15−5.02 (m, 2H), 4.53 (s, 2H), 3.53 (t, J = 6.8 Hz, 2H), 2.39 (qt, J = 6.8, 1.3 Hz, 2H).

*6-((tert-Butyldiphenylsilyl)oxy)hexane-1,2-diol (**19**).*[38] To olefin **16** (920 mg, 2.72 mmol) in MeCN:H_2O:THF (2:2:1, 12.5 mL) were added NMO (382 mg, 3.26 mmol) and OsO_4 (1.75 mL, 20 mg/mL), and the resultant mixture was stirred at rt overnight. The reaction was quenched by addition of sodium sulfite (2 g dissolved in 5 mL of H_2O) and stirred for additional 30 min. The aqueous phase was extracted (Et_2O, 3 × 20 mL), and the combined organic phases were washed (H_2O, 3 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc 2:1) to give **19** as a clear oil in 84% yield (849 mg, 2.28 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 6.6 Hz, 4H), 7.48−7.36 (m, 6H), 3.80−3.62 (m, 4H), 3.44 (dd, J = 10.7, 7.8 Hz, 1H), 2.43 (bs, 1H), 1.91−1.86 (bs, 1H), 1.67−1.50 (m, 4H), 1.46 (dd, J = 14.2, 8.9 Hz, 2H), 1.07 (s, 9H).

*5-(Benzyloxy)pentane-1,2-diol (**20**).* Prepared from **15** as described for **19** to afford **17** (792 mg, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.26 (m, 5H), 4.55 (s, 2H), 3.79−3.70 (m, 1H), 3.65 (ddd, J = 10.4, 6.9, 3.3 Hz, 1H), 3.60−3.53 (m, 2H), 3.48 (ddd, J = 11.0, 7.4, 4.9 Hz, 1H), 3.07 (d, J = 3.8 Hz, 1H), 1.84−1.75 (m, 2H), 1.70−1.60 (m, 2H), 1.54 (ddt, J = 14.1, 8.6, 7.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 128.6, 127.9, 73.3, 72.0, 70.6, 67.0, 31.0, 26.3; IR (film) ν_{max} = 3383(br), 2933, 2862, 1097, 1074 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_3$ (M + H): 211.1334, found: 211.1328.

*4-(Benzyloxy)butane-1,2-diol (**21**).*[39] Prepared from **16** as described for **19** to afford **20** (359 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.54 (s, 2H), 3.96−3.89 (m, 1H), 3.77−3.73 (m, 1H), 3.73−3.66 (m, 2H), 3.64 (ddd, J = 10.5, 6.5, 3.7 Hz, 1H), 3.51 (dt, J = 11.3, 5.5 Hz, 1H), 3.05 (d, J = 2.3 Hz, 1H), 2.14 (s, 1H), 1.90−1.81 (m, 2H), 1.74 (ddt, J = 14.7, 5.8, 3.9 Hz, 1H).

*5-((tert-Butyldiphenylsilyl)oxy)pentanal (**1b**).*[40] To a solution of diol **19** (920 mg, 2.72 mg) in THF (20 mL) was added periodic acid (715 mg, 3.38 mmol) at rt. Percipitants started to form almost immediately, and the resultant solution was stirred for 2 h. The reaction was quenched by addition of H_2O (10 mL). The aqueous phase was extracted (Et_2O, 3 × 15 mL), and the combined organic phases were washed (H_2O, 3 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give **1b** as a colorless oil in 83% yield (635 mg, 1.86 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J = 1.7 Hz, 1H), 7.66 (dd, J = 7.8, 1.3 Hz, 4H), 7.45−7.35 (m, 6H), 3.67 (q, J = 5.8 Hz, 2H), 2.41 (td, J = 7.3, 1.6 Hz, 2H), 1.78−1.68 (m, 2H), 1.64−1.54 (m, 2H), 1.05 (s, 9H).

*4-(Benzyloxy)butanal (**1c**).*[41] Prepared from **20** as described for **1b** to afford **1c** (216 mg, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, J = 1.6 Hz, 1H), 7.38−7.27 (m, 1H), 4.49 (s, 1H), 3.51 (t, J = 6.1 Hz, 1H), 2.55 (td, J = 7.1, 1.6 Hz, 1H), 1.99−1.92 (m, 1H).

*3-(Benzyloxy)propanal (**1e**).*[42] Prepared from **21** as described for **1b** to afford **1e** (143 mg, 99%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.80 (dt, J = 9.2, 1.8 Hz, 1H), 7.40−7.27 (m, 5H), 4.54 (s, 2H), 3.82 (t, J = 6.1 Hz, 2H), 2.70 (tt, J = 9.0, 4.5 Hz, 2H).

Synthesis of Aldehydes 1f. *((Pent-4-en-2-yloxy)methyl)benzene (**23**).*[43] Prepared from commercially available alcohol **22** as described for **17** to afford **25** (1.2 g, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.24 (m, 5H), 5.85 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.12−5.03 (m, 2H), 4.57 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 3.59 (h, J = 6.1 Hz, 1H), 2.39 (dt, J = 14.0, 6.3 Hz, 1H), 2.24 (dt, J = 13.9, 6.8 Hz, 1H), 1.20 (d, J = 6.2 Hz, 3H).

*4-(Benzyloxy)pentane-1,2-diol (**24**).*[43] Prepared from **23** as described for **19** to afford **24** (260 mg, 30%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.66 (dd, J = 21.0, 11.5 Hz, 1H), 4.44 (dd, J = 11.5, 6.5 Hz, 1H), 4.05−3.98 (m, 1H), 3.95−3.82 (m, 1H), 3.64−3.55 (m, 1H), 3.46 (dtd, J = 8.3, 5.6, 3.1 Hz, 1H), 2.98 (d, J = 3.7 Hz, 1H), 2.09 (dt, J = 12.0, 6.3 Hz, 1H), 1.76 (ddd, J = 12.7, 11.9, 6.5 Hz, 1H), 1.64−1.55 (m, 1H), 1.28 (t, J = 5.7 Hz, 3H).

*3-(Benzyloxy)butanal (**1f**).*[44] Prepared from **24** as described for **1b** to afford **1f** (216 mg, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, J = 2.2 Hz, 1H), 7.38−7.24 (m, 6H), 4.61 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.13−4.04 (m, 1H), 2.71 (ddd, J = 16.4, 7.4, 2.5 Hz, 1H), 2.52 (ddd, J = 16.4, 5.0, 1.8 Hz, 1H), 1.30 (d, J = 6.2 Hz, 3H).

Synthesis of Aldehydes 1g. *Ethyl 3-(4-Methylphenylsulfonamido)butanoate (**26**).*[17] To a solution of commercially available β-amino ester **25** (700 mg, 5.3 mmol) in CH_2Cl_2 (15 mL) were added TsCl (967 mg, 5.1 mmol), Et_3N (703 mg, 968 μmol), and DMAP (50 mg, 0.41 mmol) at −15 °C. The resultant mixture was stirred for 2 h. The reaction was quenched by addition of H_2O (5 mL). The aqueous phase was extracted (CH_2Cl_2, 3 × 5 mL), and the combined organic phases were washed (H_2O, 2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give **26** as a colorless oil in 70% yield (1.05 g, 3.69 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.14 (d, J = 8.6 Hz, 1H), 4.12−4.01 (m, 2H), 3.74−3.63 (m, 1H), 2.42 (s, 3H), 2.41 (d, J = 5.3 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.7 Hz, 3H).

*4-Methyl N-(4-Oxobutan-2-yl)benzenesulfonamide (**1g**).*[17] To a solution of **26** (1.1 g, 3.7 mmol) in CH_2Cl_2 (10 mL) was added DIBAL (4.4 mL, 1.0 M in hexane) dropwise at −78 °C. The resultant mixture was stirred for 45 min. The reaction was allowed to reach ambient temperature, quenched by addition of MeOH (5 mL), and poured onto Rochelle salt. The aqueous phase was extracted (CH_2Cl_2, 2 × 10 mL), and the combined organic phases were washed (H_2O, 2 × 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 2:1→1:1) to afford **1g** (426 mg, 48%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.76 (d, J = 8.4 Hz, 1H), 3.79−3.70 (m, 1H), 2.71−2.57 (m, 2H), 2.43 (s, 3H), 1.13 (d, J = 6.8 Hz, 3H).

Synthesis of Aldehydes 1h. *(R)-Methyl 3-(Benzyloxy)-2-methylpropanoate (**28**).*[45] To a solution of commercially available β-hydroxyester **27** (500 mg, 4.23 mmol) in cHex:CH_2Cl_2 (2:1, 9 mL) were added benzyl trichloroacetimidate (1.28 mg, 5.08 mmol) and trifluoromethanesulfonic acid (42 μL, 48 μmol) at 0 °C. Precipitates started to form after a couple of minutes, and the reaction mixture was allowed to warm up to rt and stirred overnight. The reaction was filtered, and the filtrate was washed with $NaHCO_3$ (aq satd, 20 mL) and H_2O (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give **28** as a colorless oil in 72% yield (634 mg, 3.05 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.25 (m, 5H), 4.57 (t, J = 9.6 Hz, 1H), 4.52 (d, J = 1.7 Hz, 1H), 3.70 (s, 3H), 3.66 (dd, J = 9.1, 7.3 Hz, 1H), 3.50 (dd, J = 9.1, 5.9 Hz, 1H), 2.83−2.75 (m, 1H), 1.18 (d, J = 7.1 Hz, 3H).

*(R)-3-(Benzyloxy)-2-methylpropanal (**1h**).*[46] To a solution of **28** (500 mg, 2.40 mmol) in CH_2Cl_2 (6 mL) was added DIBAL (2.88 mL, 1.0 M in hexane) dropwise at −78 °C. After 1 h, the reaction was quenched by addition of MeOH (5 mL) and poured onto Rochelle salt. The aqueous was extracted (CH_2Cl_2, 2 × 10 mL), and the combined organic phases were washed (H_2O, 2 × 15 mL), dried ($MgSO_4$), and

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concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give **1h** as a colorless oil in 61% yield (261 mg, 1.46 mmol). 90:10 er determined by HPLC analysis (Chiralcel OD-J, 0.5% 2-propanol in hexanes, 0.5 mL/min, λ = 210 nm, *R* isomer 46.2 min, *S* isomer 43.534 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, J = 1.5 Hz, 1H), 7.38−7.27 (m, 5H), 4.53 (s, 2H), 3.67 (ddd, J = 14.7, 9.4, 6.0 Hz, 2H), 2.72−2.62 (m, 1H), 1.14 (d, J = 7.1 Hz, 3H).

Synthesis of Aldehydes 1i. *3-((tert-Butyldiphenylsilyl)oxy)-2,2-dimethylpropan-1-ol (**30**).*[47] To a suspension of NaH (86 mg, 2.88 mmol) in THF (12 mL) was added commercial available diol **29** (300 mg, 2.88 mmol) in small portions at rt. The resultant mixture was stirred for 1 h before TBDPSCl (1 mL, 2.9 M in THF) was added dropwise during 1 h. The reaction was stirred overnight and quenched by addition of H_2O (10 mL). The aqueous phase was extracted (Et_2O, 3 × 10 mL), and the combined organic phases were washed (H_2O, 2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 8:1) to give **30** as a colorless oil in 77% yield (759 mg, 2.21 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.48−7.37 (m, 6H), 3.51 (d, J = 6.0 Hz, 2H), 3.48 (d, J = 4.8 Hz, 2H), 2.36 (t, J = 6.0 Hz, 1H), 1.06 (d, J = 2.9 Hz, 9H), 0.89 (s, 6H).

*3-((tert-Butyldiphenylsilyl)oxy)-2,2-dimethylpropanal (**1i**).*[47] To a solution of alcohol **30** (287 mg, 838 μmol) in CH_2Cl_2 (2 mL) was added TEMPO (1.3 mg, 838 μmol) at rt. After 5 min, KBr (100 mg) dissolved in aqueous $NaHCO_3$ (5% w/w, 5.7 mL) was added. The resultant mixture turned apricot and was cooled to 0 °C prior to dropwise addition of sodium hypochlorite (10% active Cl^-, 1.2 mL) until the color of the solution stayed red. The mixture was then stirred for an additional 1 h. The aqueous phase was extracted (CH_2Cl_2, 3 × 5 mL), and the combined organic phases were washed with $NaHCO_3$ (satd aq, 10 mL) and brine (satd aq, 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give **1i** as a colorless oil in 49% yield (139 mg, 407 μmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.66−7.59 (m, 4H), 7.45−7.36 (m, 6H), 3.64 (s, 2H), 1.06 (d, J = 5.2 Hz, 6H), 1.03 (s, 9H).

General Procedures for Diene Formation. To a solution of (*E*)-1,3-bis(trimethylsilyl)prop-1-ene **2b** (2 equiv), $BF_3 \cdot OEt_2$ (2 equiv), and 4 Å molecular sieves (100 mg/mL solvent) in CH_2Cl_2 (1 mL/150 μmol aldehyde) at −78 °C was added a 0.01 M solution of **1b**−**j** (1 equiv) and 1-methylnaphthalene (1 equiv) in CH_2Cl_2 dropwise over 1 h. The mixture was stirred for an additional 2−18 h. The reaction was monitored by TLC and quenched by addition of NH_4Cl (satd aq, 1.5 mL/150 μmol aldehyde). The aqueous phase was extracted (CH_2Cl_2, 2 × 2 mL/150 μmol aldehyde), dried ($MgSO_4$), and concentrated under reduced pressure to give the product.

*(E)-tert-Butyl(octa-5,7-dien-1-yloxy)diphenylsilane (**3b**).*[48] Prepared according to the general procedure using aldehyde **1b** (43 mg, 126 μmol). Reaction time: 2 h. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 6.6 Hz, 4H), 7.40 (dq, J = 14.1, 7.1 Hz, 6H), 6.30 (dt, J = 17.2, 10.3 Hz, 1H), 6.03 (dd, J = 15.6, 10.3 Hz, 1H), 5.72−5.64 (m, 1H), 5.08 (d, J = 16.7 Hz, 1H), 4.95 (d, J = 10.6 Hz, 1H), 3.66 (t, J = 6.3 Hz, 2H), 2.07 (dd, J = 14.5, 7.2 Hz, 1H), 1.63−1.43 (m, 2H), 1.05 (s, 9H).

*(E)-((Hepta-4,6-dien-1-yloxy)methyl)benzene (**3c**).* Prepared according to the general procedure using aldehyde **1c** (100 mg, 560 μmol). Reaction time: 12 h. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.23 (m, 4H), 7.23−7.18 (m, 1H), 6.23 (dt, J = 17.0, 10.3 Hz, 1H), 5.98 (dd, J = 15.2, 10.4 Hz, 1H), 5.67−5.58 (m, 1H), 5.01 (d, J = 16.8 Hz, 1H), 4.89 (d, J = 10.2 Hz, 1H), 4.42 (s, 2H), 3.40 (t, J = 6.5 Hz, 2H), 2.11 (q, J = 7.2 Hz, 2H), 1.69−1.60 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 137.2, 134.5, 131.3, 128.3, 127.6, 127.5, 114.9, 72.9, 69.6, 29.2, 29.1; IR (film) ν_{max} = 2937, 2854, 1454, 1105, 1004 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}O$ (M + H): 203.1430, found: 203.1432.

*(E)-((Penta-2,4-dien-1-yloxy)methyl)benzene (**3d**).*[49] Prepared according to the general procedure using commercially available aldehyde **1d** (20 mg, 130 μmol). Reaction time: 12 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 6.42−6.25 (m, 2H), 5.88−5.79 (m, 1H), 5.25−5.20 (m, 1H), 5.13−5.08 (m, 2H), 4.55 (d, J = 18.4 Hz, 2H), 4.08 (d, J = 6.0 Hz, 2H). ^{1}H NMR analysis on the crude reaction mixture.

*(E)-((Hexa-3,5-dien-1-yloxy)methyl)benzene (**3e**).*[50] Prepared according to the general procedure using aldehyde **1e** (40 mg, 240 μmol). Reaction time: 3 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.27 (m, 7H), 6.32 (dt, J = 17.0, 10.3 Hz, 1H), 6.12 (dd, J = 15.3, 10.4 Hz, 1H), 5.77−5.69 (m, 1H), 5.11 (d, J = 17.0 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 4.52 (s, 2H), 3.53 (t, J = 6.8 Hz, 2H), 2.42 (q, J = 6.6 Hz, 2H) ^{1}H NMR analysis on the crude reaction mixture.

*(E)-((Hepta-4,6-dien-2-yloxy)methyl)benzene (**3f**).* Prepared according to the general procedure using aldehyde **1f** (20 mg, 110 μmol). Reaction time: 12 h. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.23 (m, 4H), 7.22−7.16 (m, 1H), 6.24 (dt, J = 17.0, 10.3 Hz, 1H), 6.02 (dd, J = 15.2, 10.4 Hz, 1H), 5.64 (dt, J = 15.0, 7.3 Hz, 1H), 5.03 (d, J = 17.0 Hz, 1H), 4.91 (d, J = 10.1 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.42 (d, J = 11.8 Hz, 1H), 3.54−3.46 (m, 1H), 2.36−2.29 (m, 1H), 2.19 (dt, J = 14.1, 6.9 Hz, 1H), 1.12 (d, J = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 137.1, 133.2, 131.0, 128.3, 127.6, 127.4, 115.3, 74.6, 70.4, 39.6, 19.6; IR (film) ν_{max} = 2970, 1092, 1005 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}O$ (M + H): 203.1430, found: 203.1429.

*(E)-N-(Hepta-4,6-dien-2-yl)-4-methylbenzenesulfonamide (**3g**).*[17] Prepared according to the general procedure using aldehyde **1g** (50 mg, 210 μmol). Reaction time: 12 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (t, J = 10.7 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.17 (dt, J = 17.0, 10.3 Hz, 1H), 5.97 (dd, J = 15.2, 10.4 Hz, 1H), 5.38 (dt, J = 15.1, 7.5 Hz, 1H), 5.10 (d, J = 17.0 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 4.37 (d, J = 7.4 Hz, 1H), 3.42−3.31 (m, 1H), 2.43 (s, 3H), 2.14 (t, J = 6.8 Hz, 2H), 1.09 (d, J = 6.6 Hz, 3H).

*(S,E)-(((2-Methylhexa-3,5-dien-1-yl)oxy)methyl)benzene (**3h**).* Prepared according to the general procedure using aldehyde **1h** (46 mg, 260 μmol). Reaction time: 12 h. Colorless oil. 88:12 er determined by HPLC analysis (Chiralcel OD-J, 1% 2-propanol in hexanes, 0.5 mL/min, λ = 210 nm, *R* isomer 14.9 min, *S* isomer 16.6 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.24 (m, 4H), 7.24−7.18 (m, 1H), 6.24 (dt, J = 16.9, 10.2 Hz, 1H), 6.03 (dd, J = 15.3, 10.4 Hz, 1H), 5.61 (dd, J = 15.4, 7.2 Hz, 1H), 5.05 (dd, J = 17.0, 1.2 Hz, 1H), 4.92 (dd, J = 10.1, 1.1 Hz, 1H), 4.44 (s, 2H), 3.31 (dd, J = 9.1, 6.5 Hz, 1H), 3.24 (dd, J = 9.1, 6.8 Hz, 1H), 2.48 (hept, J = 6.7 Hz, 1H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 137.4, 137.3, 130.5, 128.3, 127.6, 127.5, 115.4, 75.0, 73.0, 36.8, 16.9; IR (film) ν_{max} = 2856, 1095, 1004 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}O$ (M + H): 203.1430, found: 203.1428.

*(E)-1-(Buta-1,3-dien-1-yl)-4-nitrobenzene (**3j**).* Prepared according to the general procedure in darkness using commercially available aldehyde **1j** (50 mg, 330 μmol). Reaction time: 12 h. White solid, mp: 77.6−78.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21−8.14 (m, 2H), 7.52 (t, J = 5.6 Hz, 2H), 6.92 (dd, J = 15.7, 10.5 Hz, 1H), 6.60 (d, J = 15.7 Hz, 1H), 6.53 (dt, J = 16.9, 10.3 Hz, 1H), 5.47 (d, J = 16.9 Hz, 1H), 5.34 (d, J = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 143.6, 136.4, 134.0, 130.4, 126.8, 124.0, 120.9; IR (film) ν_{max} = 1516, 1344, 1003 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}O_2N$ (M + H): 176.0706, found: 176.0706.

Synthesis and Spectral Data of Homolylic Alcohol 6. *7-(Benzyloxy)hept-1-en-4-ol (**6**).* To (*E*)-1,3-bis(trimethylsilyl)prop-1-ene (105 mg, 561 μmol), allyltrimethylsilane (64 mg, 561 μmol), and $BF_3 \cdot OEt_2$ (138 μL, 1.12 mmol) in CH_2Cl_2 (1 mL) in the precense of 4 Å Ms (50 mg) were added aldehyde **1c** (50 mg, 281 μmol) and 1-methylnaphthalene (78 μL, 281 μmol) dissolved in CH_2Cl_2 (1 mL) dropwise (1 mL/h) at −40 °C. The reaction was monitored by TLC and quenched by addition of NH_4Cl (satd aq, 2 mL). The aqueous phase was extracted (CH_2Cl_2, 2 × 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give **6** as a colorless oil in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.23 (m, 4H), 7.21 (ddd, J = 11.9, 5.8, 2.7 Hz, 1H),

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5.81−5.71 (m, 1H), 5.08−5.01 (m, 2H), 4.45 (s, 2H), 3.63−3.55 (m, 1H), 3.44 (t, J = 6.1 Hz, 2H), 2.30 (d, J = 3.4 Hz, 1H), 2.24−2.17 (m, 1H), 2.11 (dt, J = 14.0, 7.6 Hz, 1H), 1.74−1.62 (m, 2H), 1.62−1.54 (m, 1H), 1.43 (dtd, J = 14.3, 8.1, 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 135.0, 128.4, 127.7, 127.6, 117.7, 73.0, 70.5, 70.4, 42.0, 34.0, 26.2; IR (film) ν_{max} = 3410(br), 2927, 2858, 1099 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{21}O_2$ (M + H): 221.1536, found: 221.1535.

■ ASSOCIATED CONTENT

Supporting Information. Solvent screening, ^{1}H NMR for all synthesized compounds, and ^{13}C NMR spectra for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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