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Enantioselective β-Vinylation of α,β-Unsaturated Aldehydes Using a β-Nitroethyl Sulfone as Vinyl Anion Equivalent

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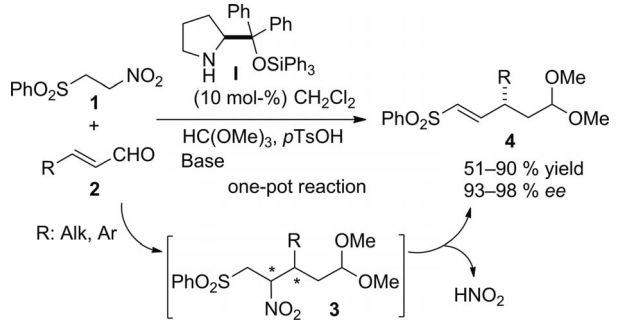
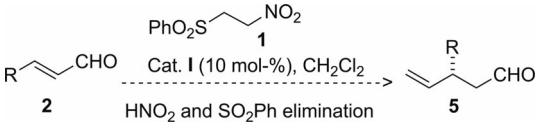
A concise method for the asymmetric β-vinylation of enals is presented. The success of the reaction lies in the stereoselective organocatalyzed addition of β-nitroethyl sulfone **1** to enals and in the ability of Mg to promote the concomitant elimination of the sulfone moiety and the nitrous acid. The method performed in a three-step one-pot operation allows the synthesis of enantioenriched β-vinyl aldehydes and derivatives thereof.

Introduction

The development of methods to allow the rapid assembly of simple starting materials into valuable building blocks with very high chemical and stereochemical efficiency is currently of considerable interest in synthetic organic chemistry.[1,2] Over the last two decades, asymmetric catalysis has provided remarkable results in this area, and several catalytic enantioselective methods based on chiral catalysts are now available for a diversity of carbon–carbon bond-forming reactions.[3–5] Considerable attention has been given to the conjugate addition of nitro compounds, because the nitronate nucleophile may be easily generated by treatment with relatively weak bases,[6–8] and because – after proper functional group manipulation – the diversity of acceptors that may be involved in the reaction allows access to a number of functionalized building blocks.[9] Although the design of chiral catalysts has been the subject of most of these studies, little attention has been paid to exploring nitroalkanes other than nitromethane or nonfunctionalized nitroalkanes as substrates.[10] Recently, we reported an operationally simple method for the stereoselective construction of γ-substituted vinyl sulfones, which involved the conjugate addition of base-sensitive β-nitroethyl sulfones to enals promoted by catalyst **I** (Scheme 1).[11] From this approach, both the carbon–carbon bond and the new stereogenic center are generated concurrently in a single synthetic operation, a notable advantage over traditional methods.[12] In an effort to expand the synthetic utility of β-nitroethyl sulfones,[13] we decided to study the feasibility of carrying out a concomitant elimination of both the sulfone and nitro groups in intermediate **3**, without affecting the stereochemical integrity of the new stereogenic center, to directly produce enantiomerically enriched vinyl-substituted adducts **5** [Equation (1)]. In this way, β-nitroethyl sulfone **1** would act as a masked vinyl anion in the conjugate additions, and the methodology could help to fill the gap of methods for the direct β-vinylation of enals.[14]



Scheme 1. One-pot conjugate addition and nitrous acid elimination to functionalized building blocks.



(1)

Results and Discussion

In a preliminary experiment, the optimized conditions previously described were employed to effect the enantioselective conjugate addition of **1** to enal **2a** (R = Bu). Once the organocatalyzed addition was complete, the aldehyde moiety in the resulting intermediate adduct was acetalyzed,

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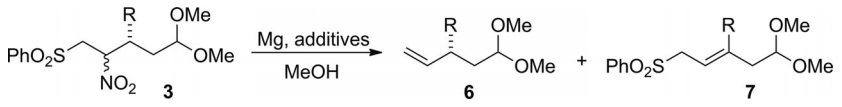
Table 1. Screening of reaction conditions.[a]



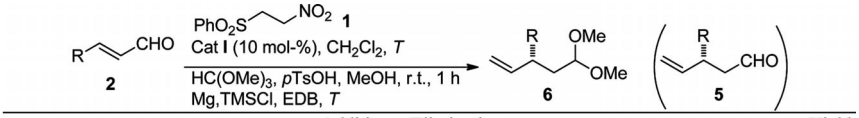
Entry	**3**, R	Mg [equiv.]	Additives [equiv.]	*T* [°C], *t* [h]	Conversion [%][b]	**6**/**7**[b]
1	**3a**, Bu	7.5	*p*-TsOH (0.15)	65, 15	mixture[c]	–
2	**3a**, Bu	7.5	TMSCl, EDB (0.5)	r.t., 4	n.r.[d]	–
3	**3a**, Bu	7.5	TMSCl, EDB (0.5)	65, 15	90	1:0
4	**3a**, Bu	15	TMSCl, EDB (0.5)	65, 2	>95	1:0
5	**3b**, Ph	7.5	TMSCl, EDB (0.5)	65, 15	90	2:1
6	**3b**, Ph	15	TMSCl, EDB (0.5)	65, 3	>95	1:0

[a] Reactions conducted on a 0.5 mmol scale in MeOH (1 mL). [b] Reaction conversion and **6**/**7** ratio determined by ^{1}H NMR spectroscopy. [c] A complex mixture was obtained. [d] No reaction was detected.

as presented in Scheme 1, to prevent side reactions.[15] The initial study focused on the reaction of isolated adduct **3a** (*dr* = 1:1) in the presence of different amounts of Mg and activators in methanol (see Table 1).[16] The best reactivity occurred at refluxing temperature using 15 equiv. of Mg with TMSCl (trimethylsilyl chloride) and EDB (ethylene dibromide) as additives (Table 1, Entry 4). Under these conditions aryl-substituted adduct **3b** behaved similarly (Table 1, Entry 6). The analysis of the reaction mixtures before completion revealed that the nitrous acid elimination, very likely promoted by the presence of $Mg(OMe)_2$,[17] was faster than the reductive sulfone elimination. The large excess amount of metal seemed to accelerate both transformations and helped to avoid the presence of isomerized compounds such as **7** (Table 1, compare Entries 5 and 6). On the other hand, the use of either sodium or aluminum amalgam under a variety of conditions produced complex mixtures in which vinyl adducts **6** could not be detected.

The feasibility of a one-pot reaction for the vinylation of enals was checked by adding the proper amounts of Mg (15 equiv.) and additives (0.5 equiv. of TMSCl and EDB) upon the completion of the addition and protection reactions. To our delight, when these reaction conditions were applied to enal **2b**, vinyl adduct **6b** was produced after 3 h in 60% overall yield (isomerized **7** was not detected) and 99% *ee*.[18] With these reaction conditions in hand, the enal scope of the one-pot vinylation reaction was examined (see Table 2). Under optimized conditions, enals **2a**–**g** were suc-

Table 2. One-pot synthesis of β-vinyl-substituted aldehydes.[a]

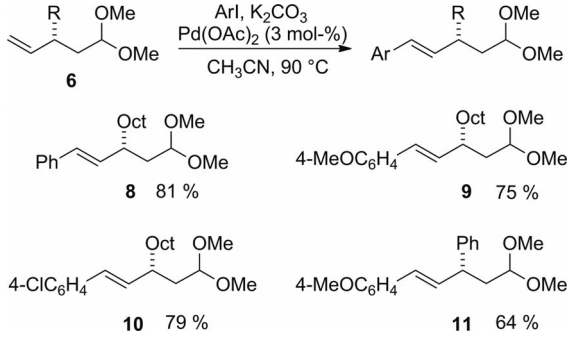


Entry	Enal **2**		Addition *T* [°C], *t* [h]	Elimination *T* [°C], *t* [h]	Product **6** (**5**)		*ee* [%][b]	Yield [%][c]
1	Bu, CHO	**2a**	r.t., 2	65, 2	Bu, OMe, OMe	**6a**	97	85
2	Ph, CHO	**2b**	0, 24	65→r.t., 3	Ph, OMe, OMe	**6b**	99	60
3					Ph, CHO	**5b**	99	51[d]
4	4-Cl-C$_6$H$_4$, CHO	**2c**	0, 24	65→r.t., 3	4-Cl-C$_6$H$_4$, OMe, OMe	**6c**	94	66
5	4-MeO-C$_6$H$_4$, CHO	**2d**	0, 48	65→r.t., 3	4-MeO-C$_6$H$_4$, OMe, OMe	**6d**	98	50
6	Oct, CHO	**2e**	r.t., 2	65, 2	Oct, OMe, OMe	**6e**	97	80
7					Oct, CHO	**5e**	97	60[d]
8	$(CH_2)_4$, CHO	**2f**	r.t., 4	65→r.t., 5	$(CH_2)_4$, OMe, OMe	**6f**	91	50
9	BocHN, $(CH_2)_3$, CHO	**2g**	r.t., 4	65→r.t., 5	BocHN, $(CH_2)_3$, OMe, OMe	**6g**	98	55

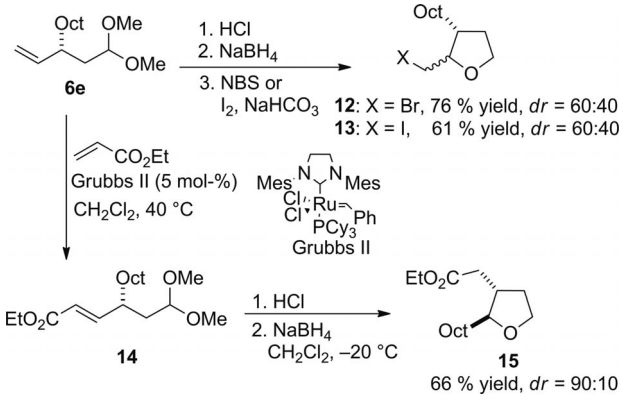
[a] Addition reaction conducted on a 0.75 mmol scale using 1.3–1.5 equiv. of **1** in CH_2Cl_2 (1.5 mL). For the protection step, MeOH (3.75 mL) was added. [b] Determined by chiral HPLC analysis or by NMR analysis using chiral shift reagents (see Supporting Information). [c] Overall yield of isolated product starting from **2**. [d] Aldehydes **5** were obtained by adding 6 N HCl to the reaction mixture and heating at 50 °C (see Experimental Section for details).

cessfully transformed into the corresponding vinyl-substituted adducts. As the results in Table 2 show, products **6a**–**g** were obtained in good yields and with excellent levels of enantioselectivity regardless of the nature of the enal substitution. Thus, α,β-unsaturated aldehydes bearing electron-poor or electron-rich arenes or β-alkyl substituents were tolerated with equal efficiency. The procedure may also be applied to functionalized enals such as **2f** and **2g** to produce, from readily available starting materials, highly functionalized vinyl adducts with high chemical and stereochemical efficiency. If vinyl aldehydes **5** are required for further manipulation, a deprotection step can also be integrated into the process by treatment with acid (see Table 2, Entries 3 and 7).

In addition to the interest in vinyl scaffolds, the distinct functionality of the resulting adducts provides additional versatility to this procedure. For instance (see Scheme 2), a palladium-catalyzed coupling reaction of alkyl and aryl adducts **6** with different aryl halides afforded β-alkenyl-substituted aldehydes in good yields. On the other hand, 2,3-disubstituted tetrahydrofurans would be obtained through a halogen-promoted cyclization[19] after acetal hydrolysis and aldehyde reduction of adducts **6** (see Scheme 3). Transformation of **6e** into the corresponding alcohol, using standard reaction conditions, followed by halocyclization afforded **12** and **13** in good yield, albeit with low diastereoselectivity. Alternatively, **6e** – upon treatment with ethyl acrylate and Grubbs catalyst – provided adduct **14**, which – upon acetal deprotection and subsequent one-pot reduction – afforded **15** in a good diastereomeric ratio, as a result of a concurrent intramolecular oxa-Michael reaction.[20]



Scheme 2. Synthesis of enantioenriched β-alkenyl-substituted enals.



Scheme 3. Synthesis of enantioenriched 2,3-disubstituted tetrahydrofurans.

Conclusions

We have reported an operationally simple protocol for the β-vinylation of α,β-unsaturated aldehydes that consists of an enantioselective conjugate addition to α,β-enals of a β-nitroethyl sulfone, used as a new bench-stable, readily available formal vinyl anion. The method is performed in a one-pot, three-step operation without the need for intermediate isolation[21] and provides a quick entry to attractive building blocks for organic synthesis.

Experimental Section

General Methods: The purification of the reaction products was carried out by flash column chromatography using silica gel (0.040–0.063 mm, 230–400 mesh). Thin layer chromatography was performed on aluminium-backed silica plates. The developed chromatograms were visualized by fluorescence quenching using phosphomolybdic acid. ^{1}H and ^{13}C NMR spectroscopic data were recorded at 300 MHz and 75 MHz, respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26 ppm) for the ^{1}H NMR spectroscopic data and relative to the central resonances of $CDCl_3$ (δ = 77.23 ppm) for the ^{13}C NMR spectroscopic data. HR mass spectra were recorded with an ESI-ion trap mass spectrometer and a TOF (time-of-flight) detector. All solvents were of p.a. (pro analysi) quality and, if necessary, were dried by standard procedures prior to use. Unless otherwise specified, materials were obtained from commercial sources and used without purification. Catalyst **I**, β-nitroethyl sulfone **1**,[11] and α,β-unsaturated aldehydes **2c**,[22] **2e**, and **2f**[23] were prepared according to reported procedures. The absolute configuration was determined by chemical correlation and comparison to literature data[24] (i.e., adduct **6b** was transformed into its corresponding carboxylic acid). The absolute configurations of the remaining compounds were assumed on the basis of a uniform reaction mechanism. Racemic samples of adducts **6a**–**g** were prepared by employing a general procedure using pyrrolidine (20 mol-%) as the catalyst. The enantiomeric excesses for adducts **6a** and **6e** were determined by ^{1}H NMR analysis employing chiral shift reagents. For adducts **6b**, **6c**, and **6d**, the enantiomeric excesses were determined by chiral HPLC analysis of their corresponding carboxylic acids.[25] For adducts **6f** and **6g**, the enantiomeric excesses were determined by chiral HPLC analysis of their corresponding intermediates **4f** and **4g**,[25] as it was previously noted that the *ee* values remain unchanged for vinyl sulfones **4** and their corresponding vinyl adducts.

General Procedure for the β-Vinylation of Enals: To a solution of catalyst **I** (0.075 mmol, 0.1 equiv.) and enal **2** (0.75 mmol, 1 equiv.) in dry CH_2Cl_2 (1.5 mL) was added β-nitroethyl sulfone **1** (for reaction with aliphatic enals, 0.23 g, 0.98 mmol, 1.3 equiv.; for reaction with aromatic enals, 0.26 g, 1.12 mmol, 1.5 equiv.). The reaction mixture was stirred at the indicated temperature (see Table 2). When the enal was consumed, as detected by ^{1}H NMR spectroscopy, MeOH (3.75 mL), $HC(OMe)_3$ (0.17 mL, 1.5 mmol, 2 equiv.), and *p*-toluensulfonic acid (0.045 g, 0.225 mmol, 0.3 equiv.) were successively added. The reaction mixture was stirred at room temperature, typically for 1 h, and then Mg turnings

(0.27 g, 11.25 mmol, 15 equiv.), TMSCl (for reaction with aliphatic enals, 1.5 equiv.; for reaction with aromatic enals, 0.5 equiv.), and EDB (for reaction with aliphatic enals, 1.5 equiv.; for reaction with aromatic enals, 0.5 equiv.) were added. The flask was equipped with a condenser, and the temperature was mantained at 65 °C or room temperature as indicated in Table 2. When the starting material was consumed, as detected by TLC, Et_2O (10 mL) was added. The resulting mixture was filtered, and the organic solvent was eliminated from the filtrate. The resulting residue was triturated with Et_2O. The ethereal phases were combined, and the solvent was removed at reduced pressure and low temperature (because of the volatility of some of the products) to afford vinyl adducts **6**.

(*R*)-3-(2,2-Dimethoxyethyl)hept-1-ene (6a): Colorless oil (0.119 g, 85%, 97%*ee*). $[\alpha]_D^{25}$ = +4.06 (*c* = 0.66, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.63–5.46 (m, 1 H), 5.01 (s, 1 H), 4.99–4.93 (m, 1 H), 4.39 (dd, *J* = 4.0, 7.7 Hz, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 2.10 (br. s, 1 H), 1.76–1.65 (m, 1 H), 1.52–1.43 (m, 1 H), 1.26 (m, 6 H), 0.87 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 114.9, 103.3, 53.0, 52.8, 40.3, 38.0, 35.1, 29.4, 22.9, 14.2 ppm. HRMS (TOF, CI): calcd. for $C_{10}H_{19}O$ [M + H – $CH_3OH]^+$ 155.1436; found 155.1451.

(*R*)-(5,5-Dimethoxypent-1-en-3-yl)benzene (6b): Colorless oil (0.093 g, 60%, 99%*ee*). $[\alpha]_D^{25}$ = –10.91 (*c* = 0.57, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 2 H), 7.28–7.19 (m, 3 H), 6.06–5.95 (m, 1 H), 5.16–5.04 (m, 2 H), 4.28 (t, *J* = 5.9 Hz, 1 H), 3.48 (q, *J* = 7.6 Hz, 1 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 2.13–1.96 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 141.8, 128.8, 127.8, 126.6, 114.5, 102.9, 52.9, 52.9, 45.7, 38.1 ppm. HRMS (TOF, CI): calcd. for $C_{12}H_{14}O$ [M – $CH_3OH]^+$ 174.1045; found 175.1030.

(*R*)-1-Chloro-4-(5,5-dimethoxypent-1-en-3-yl)benzene (6c): Yellow oil (0.119 g, 66%, 94%*ee*). $[\alpha]_D^{25}$ = –11.60 (*c* = 1.39, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 2 H), 7.18–7.11 (m, 2 H), 5.99–5.85 (m, 1 H), 5.09 (dd, *J* = 2.2, 1.1 Hz, 1 H), 5.04 (dt, *J* = 5.7, 1.3 Hz, 1 H), 4.22 (t, *J* = 5.9 Hz, 1 H), 3.43 (dd, *J* = 15.2, 7.5 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 2.09–1.88 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.2, 141.3, 132.3, 129.2, 128.9, 114.9, 102.8, 53.0, 52.9, 45.0, 38.0 ppm. HRMS (TOF, CI): calcd. for $C_{12}H_{14}OCl$ [M + H – $CH_3OH]^+$ 209.0733; found 209.0718.

(*R*)-1-(5,5-Dimethoxypent-1-en-3-yl)-4-methoxybenzene (6d): Yellow oil (0.089 g, 50%, 98%*ee*). $[\alpha]_D^{25}$ = –5.19 (*c* = 0.58, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.09 (m, 2 H), 6.88–6.82 (m, 2 H), 6.00–5.87 (m, 1 H), 5.08–4.99 (m, 2 H), 4.23 (t, *J* = 5.9 Hz, 1 H), 3.79 (s, 3 H), 3.39 (q, *J* = 7.5 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 2.07–1.88 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 142.5, 135.6, 128.7, 114.2, 114.1, 102.5, 55.8, 53.3, 45.2, 38.2 ppm. HRMS (TOF, CI): calcd. for $C_{13}H_{17}O_2$ [M + H – $CH_3OH]^+$ 205.1229; found 205.1224.

(*R*)-3-(2,2-Dimethoxyethyl)undec-1-ene (6e): Colorless oil (0.145 g, 80%, 97%*ee*). $[\alpha]_D^{25}$ = +5.50 (*c* = 0.34, CH_2Cl_2). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 5.63–5.45 (m, 1 H), 5.01 (s, 1 H), 4.98–4.95 (m, 1 H), 4.39 (dd, *J* = 7.7, 4.0 Hz, 1 H), 3.31 (s, 3 H), 3.29 (s, 3 H), 2.13 (br. s, 1 H), 1.75–1.66 (m, 1 H), 1.52–1.43 (m, 1 H), 1.28 (br. s, 14 H), 0.88 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 114.8, 103.3, 52.9, 52.8, 40.3, 38.0, 35.4, 32.1, 29.9, 29.8, 29.5, 27.2, 22.9, 14.3 ppm. HRMS (TOF, CI): calcd. for $C_{14}H_{27}O$ [M + H – $CH_3OH]^+$ 211.2062; found 211.2067.

(*R*)-3-(2,2-Dimethoxyethyl)nona-1,8-diene (6f): Yellow, pale oil (0.080 g, 50%, 91%*ee*). $[\alpha]_D^{25}$ = +6.20 (*c* = 0.55, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.90–5.73 (m, 1 H), 5.63–5.47 (m, 1 H), 5.02–4.89 (m, 4 H), 4.39 (dd, *J* = 7.7, 4.0 Hz, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 2.12 (br. s, 1 H), 2.03 (dd, *J* = 14.2, 6.7 Hz, 2 H), 1.76–1.65 (m, 1 H), 1.53–1.42 (m, 1 H), 1.41–1.18 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 139.6, 115.1, 114.6, 103.5, 53.2, 53.0, 40.5, 38.2, 35.5, 34.2, 29.5, 27.2 ppm.

(*R*)-*tert*-Butyl 5-(2,2-Dimethoxyethyl)hept-6-enylcarbamate (6g): Yellow, pale oil (0.124 g, 55%, 98%*ee*). $[\alpha]_D^{25}$ = +5.38 (*c* = 0.58, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.59–5.45 (m, 1 H), 5.01 (s, 1 H), 4.99–4.92 (m, 1 H), 4.48 (br. s, 1 H), 4.38 (dd, *J* = 7.7, 4.0 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.08 (dd, *J* = 13.3, 6.4 Hz, 2 H), 2.18–2.03 (m, 1 H), 1.74–1.62 (m, 1 H), 1.53–1.45 (m, 1 H), 1.43 (s, 9 H), 1.36–1.20 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 142.6, 115.1, 103.3, 53.0, 52.7, 40.8, 40.2, 38.0, 35.3, 30.2, 28.6, 27.0, 26.8 ppm. HRMS (TOF, CI): calcd. for $C_{11}H_{18}NO_2$ [M – C_4H_9O – $CH_3OH]^+$ 196.1338; found 196.1353.

Synthesis of Aldehydes 5b and 5e: To directly obtain aldehydes **5**, the previous procedure was applied through to the filtration. Then, HCl (6 M solution, 25 mL) was added to the filtrate, and this mixture was heated to reflux for 8 h. After cooling to room temperature, the ethereal phase was separated and dried with $MgSO_4$, and the solvent was eliminated at reduced pressure and low temperature (because of the volatility of some of the products) to afford crude product **5**, which was purified on silica gel by flash column chromatography (hexane/EtOAc, 98:2).

(*R*)-3-Phenylpent-4-enal (5b): Yellow oil (0.061 g, 51%). $[\alpha]_D^{25}$ = –3.01 (*c* = 1.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.73 (t, *J* = 2.0 Hz, 1 H), 7.37–7.18 (m, 5 H), 6.00 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1 H), 5.16–5.04 (m, 2 H), 3.96 (dd, *J* = 14.3, 7.2 Hz, 1 H), 2.93–2.76 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.4, 142.4, 140.3, 129.4, 128.0, 127.0, 115.3, 48.8, 43.8 ppm. HRMS (TOF, CI): calcd. for $C_{11}H_{13}O$ [M + H]$^+$ 161.0966; found 161.0978.

(*R*)-3-Vinylundecanal (5e): Yellow oil (0.088 g, 60%). $[\alpha]_D^{25}$ = +0.85 (*c* = 0.47, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.75 (t, *J* = 2.4 Hz, 1 H), 5.79–5.55 (m, 1 H), 5.11–5.08 (m, 1 H), 5.07–5.03 (m, 1 H), 2.64 (dd, *J* = 6.0, 13.2 Hz, 1 H), 2.46 (dd, *J* = 0.8, 2.3 Hz, 1 H), 2.44 (t, *J* = 2.6 Hz, 1 H), 1.53–1.14 (m, 14 H), 0.92 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 141.5, 115.6, 49.0, 38.8, 35.2, 32.3, 30.0, 29.7, 27.3, 23.1, 14.5 ppm. HRMS (TOF, CI): calcd. for $C_{13}H_{25}O$ [M + H]$^+$ 197.1905; found 197.1900.

General Procedure for the Synthesis of Compounds 8–11: To a mixture of olefin **6** (0.25 mmol) and the aryl iodide (0.75 mmol, 3 equiv.) in CH_3CN (2 mL) were added K_2CO_3 (0.052 g, 0.375 mmol, 1.5 equiv.), nBu$_4$NOAc (0.151 g, 0.50 mmol, 2 equiv.), and KCl (0.019 g, 0.25 mmol, 1 equiv.) under nitrogen. Then, $Pd(OAc)_2$ (3 mol-%, 0.002 g, 7.5 mmol) was added, and the resulting mixture was heated to reflux at 85 °C for 2 h. After cooling to room temperature, the solvent was evaporated, and the residue was suspended again in Et_2O (5 mL). The mixture was washed with H_2O (3 × 2 mL). Then, the ethereal layer was dried with $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (hexane/EtOAc, 98:2).

(*R*,*E*)-[3-(2,2-Dimethoxyethyl)undec-1-enyl]benzene (8): Yellow oil (0.064 g, 81%). $[\alpha]_D^{25}$ = –3.00 (*c* = 0.49, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.13 (m, 5 H), 6.39 (d, *J* = 15.8 Hz, 1 H), 5.99 (dd, *J* = 9.2, 15.8 Hz, 1 H), 4.44 (dd, *J* = 3.7, 7.4 Hz, 1 H), 3.35 (s, 3 H), 3.32 (s, 3 H), 2.32 (dd, *J* = 4.4, 8.5 Hz, 1 H), 1.82 (dd, *J* = 6.6, 14.6 Hz, 1 H), 1.64–1.53 (m, 1 H), 1.45–1.22 (m, 14 H), 0.90 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.7, 134.6, 130.1, 128.5, 126.9, 126.0, 103.0, 52.7, 52.7, 39.5, 38.2, 35.6, 31.9, 29.7, 29.6, 29.3, 27.2, 22.7, 14.1 ppm. HRMS (TOF, CI): calcd. for $C_{20}H_{31}O$ [M + H – $CH_3OH]^+$ 287.2375; found 287.2375.

(*R*,*E*)-1-[3-(2,2-Dimethoxyethyl)undec-1-enyl]-4-methoxybenzene (9): Yellow oil (0.065 g, 75%). $[\alpha]_D^{25}$ = –4.17 (*c* = 0.96, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 6.34 (d, *J* = 15.8 Hz, 1 H), 5.84 (dd, *J* = 9.2, 15.7 Hz, 1 H), 4.44 (dd, *J* = 3.7, 7.6 Hz, 1 H), 3.83 (s, 3 H), 3.35 (s, 3 H), 3.32 (s, 3 H), 2.34–2.23 (m, 1 H), 1.87–1.75 (m, 1 H), 1.69–1.52 (m, 1 H), 1.50–1.18 (m, 14 H), 0.90 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 132.7, 130.8, 129.7, 127.4, 114.2, 103.4, 55.6, 53.0, 52.9, 39.7, 38.6, 36.0, 32.1, 30.0, 29.8, 29.6, 27.4, 22.9, 14.4 ppm. HRMS (TOF, CI): calcd. for $C_{21}H_{33}O_2$ [M + H – CH_3OH]$^+$ 317.2481; found 317.2485.

(*R*,*E*)-1-Chloro-4-[3-(2,2-dimethoxyethyl)undec-1-enyl]benzene (10): Yellow oil (0.070 g, 79%). $[\alpha]_D^{25}$ = –3.34 (*c* = 1.10, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.10 (m, 4 H), 6.34 (d, *J* = 15.8 Hz, 1 H), 5.97 (dd, *J* = 9.2, 15.8 Hz, 1 H), 4.42 (dd, *J* = 3.9, 7.3 Hz, 1 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 2.40–2.30 (m, 1 H), 1.61–1.57 (m, 1 H), 1.89–1.78 (m, 1 H), 1.47–1.23 (m, 14 H), 0.90 (t, *J* = 6.7 Hz, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.4, 135.2, 132.4, 128.8, 127.2, 102.9, 52.7, 52.5, 39.5, 38.1, 35.6, 31.8, 29.7, 29.5, 29.3, 27.2, 22.7, 14.1 ppm. HRMS (TOF, CI): calcd. for $C_{20}H_{29}OCl$ [M – CH_3OH]$^+$ 320.1907; found 320.1922.

(*R*,*E*)-1-(5,5-Dimethoxy-3-phenylpent-1-enyl)-4-methoxybenzene (11): Yellow oil (0.050 g, 64%). $[\alpha]_D^{25}$ = +6.42 (*c* = 1.06, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.18 (m, 7 H), 6.96–6.88 (m, 2 H), 6.51–6.29 (m, 2 H), 4.33 (t, *J* = 5.9 Hz, 1 H), 3.84 (s, 3 H), 3.62 (q, *J* = 7.5 Hz, 1 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 2.24–1.99 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 137.7, 135.9, 133.9, 129.5, 128.8, 128.7, 127.3, 126.4, 114.3, 103.0, 55.5, 53.0, 52.9, 44.1, 38.7 ppm. HRMS (TOF, CI): calcd. for $C_{20}H_{25}O_3$ [M + H]$^+$ 313.1804; found 313.1819.

Initial Step for the Synthesis of 2,3-Disubstituted Tetrahydrofurans 12 and 13: To a solution of **5e** (0.175 g, 0.89 mmol) in CH_2Cl_2 (2 mL) was added a dispersion of $NaBH_4$ (0.035 g, 1.80 mmol, 2 equiv.) in EtOH (1 mL) at 0 °C. The resulting suspension was stirred at this temperature for 20 min, and then H_2O (1 mL) was added. The organic layer was separated, washed with H_2O (1 mL), dried with $MgSO_4$, and concentrated to afford the alcohol as a yellow oil (0.160 g, 91%), which was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.61 (dd, *J* = 9.0, 27.2 Hz, 1 H), 5.07 (dt, *J* = 1.3, 4.8 Hz, 1 H), 5.03–5.00 (m, 1 H), 3.82–3.63 (m, 3 H), 2.21–2.08 (m, 1 H), 1.56–1.45 (s, 2 H), 1.36–1.22 (m, 14 H), 0.92 (t, *J* = 6.7 Hz, 5 H) ppm.

(3*R*)-2-(Bromomethyl)-3-octyltetrahydrofuran (12): In a darkened vessel was placed a solution of the alcohol (0.050 g, 0.25 mmol) in CH_3CN (1.5 mL). To this solution was added *N*-bromosuccinimide (0.053 g, 0.3 mmol, 1.2 equiv.), and the reaction mixture was stirred for 12 h and then quenched by the addition of a saturated solution of $Na_2S_2O_3$/$NaHCO_3$ (1:1). The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product **12**, which was purified by silica gel chromatography (hexane/EtOAc, 95:5) to afford a yellow oil (0.053 g, 76%) as a 60:40 mixture of diastereomers. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.24–4.10 (m, 1 H, minor), 4.09–3.96 (m, 1 H, major), 3.96–3.89 (m, 2 H, major), 3.88–3.81 (m, 1 H, minor), 3.80–3.73 (m, 1 H, minor), 3.56–3.50 (m, 1 H, minor), 3.44 (dd, *J* = 5.5, 10.9 Hz, 2 H, major), 3.37–3.32 (m, 1 H, minor), 2.76–2.66 (m, 1 H, minor), 2.35–2.25 (m, 1 H, major), 2.20–2.02 (m, 2 H, major and minor), 1.80–1.57 (m, 2 H, major and minor), 1.43–1.19 (m, 28 H, major and minor), 0.99–0.84 (m, 6 H, major and minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.4 (major), 81.3 (minor), 67.7 (major), 67.0 (minor), 45.0 (major), 42.0 (minor), 33.2 (major), 32.9 (minor), 31.9 (major), 30.9 (minor), 29.7 (major), 29.5 (major), 29.3 (major), 28.4 (minor), 28.2 (minor), 28.0 (minor), 22.7 (major), 14.1 (minor), 10.5 (major), 6.1 (minor) ppm.

(3*R*)-2-(Iodomethyl)-3-octyltetrahydrofuran (13): In a darkened vessel was placed a solution of the alcohol (0.050 g, 0.25 mmol) in CH_2Cl_2 (1.5 mL). To this solution was added iodine (0.178 g, 0.7 mmol, 2.8 equiv.) and a saturated solution of $NaHCO_3$ (1.5 mL). The reaction mixture was stirred for 12 h and then quenched by the addition of a saturated solution of $Na_2S_2O_3$/$NaHCO_3$ (1:1). The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give crude **13**, which was purified by flash column silica gel chromatography (hexane/EtOAc, 95:5) to afford a yellow oil (0.049 g, 61%) as a 60:40 mixture of diastereomers. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.17–4.13 (m, 1 H, minor), 4.06–3.97 (m, 1 H, major), 3.92 (dd, *J* = 5.5, 7.6 Hz, 2 H, major), 3.88–3.80 (m, 1 H, minor), 3.52 (dd, *J* = 5.8, 11.0 Hz, 1 H, minor), 3.39 (dd, *J* = 4.7, 10.3 Hz, 1 H, minor), 3.25 (dd, *J* = 5.6, 10.2 Hz, 1 H, minor), 3.19 (dd, *J* = 5.6, 6.8 Hz, 2 H, major), 2.32–2.22 (m, 1 H, minor), 2.22–2.02 (m, 2 H, major and minor), 2.01–1.92 (m, 1 H, major), 1.82–1.59 (m, 2 H, major and minor), 1.44–1.23 (m, 28 H, major and minor), 0.92 (t, *J* = 4.7 Hz, 6 H, major and minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.8 (major), 81.8 (minor), 68.1 (major), 67.4 (minor), 45.5 (major), 42.4 (minor), 33.7 (major), 33.4 (minor), 32.3 (major), 31.4 (minor), 30.1 (major), 29.9 (major), 29.7 (major), 28.8 (minor), 28.6 (minor), 28.5 (minor), 23.1 (major), 14.5 (minor), 10.9 (major), 6.5 (minor) ppm. HRMS (TOF, CI): calcd. for $C_{13}H_{26}IO$ [M + H]$^+$ 325.1028; found 325.1041.

Synthesis of 2,3-Disubstituted Tetrahydrofuran 15: For step 1, to a solution of olefin **6e** (0.242 g, 1 mmol, 1 equiv.) in dry CH_2Cl_2 (5 mL) were added ethyl acrylate (0.32 mL, 3 mmol, 3 equiv.) and a solution of Grubbs II catalyst (10 mol-%, 0.085 g) in CH_2Cl_2 (1 mL) under argon. The reaction mixture was heated at 40 °C and stirred for 20 h. Then, the reaction mixture was concentrated under reduced pressure to give the crude product, which was purified before the next step by flash column chromatography (hexane/EtOAc, 95:5) to afford olefin **14** as a yellow oil (0.211 g, 67%). Data for (*R*,*E*)-ethyl 4-(2,2-dimethoxyethyl)dodec-2-enoate (**14**): $[\alpha]_D^{25}$ = –2.54 (*c* = 0.94, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.78 (dd, *J* = 9.4, 15.6 Hz, 1 H), 5.84 (dd, *J* = 0.7, 15.6 Hz, 1 H), 4.36 (dd, *J* = 4.4, 7.4 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 2.43–2.25 (m, 1 H), 1.87–1.75 (m, 1 H), 1.67–1.54 (m, 1 H), 1.34–1.25 (m, 14 H), 0.91 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 153.0, 121.8, 103.1, 60.7, 53.2, 53.2, 39.1, 37.7, 35.0, 32.3, 30.0, 29.9, 29.7, 27.4, 23.1, 14.7, 14.5 ppm. HRMS (TOF, CI): calcd. for $C_{17}H_{31}O_3$ [M + H – CH_3OH]$^+$ 283.2273; found 283.2281. For step 2, to a solution of olefin **14** (0.175 g, 0.5 mmol, 1 equiv.), obtained from the previous step, in Me_2CO (2.5 mL) was added HCl (2 M solution, 2 mL). This mixture was stirred at room temperature for 1 h, and then Me_2CO was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The organic layer was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the pure unprotected olefin as a yellow oil (0.123 g, 92%). $[\alpha]_D^{25}$ = –2.26 (*c* = 1.04, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, *J* = 1.6 Hz, 1 H), 6.83 (dd, *J* = 8.6, 15.7 Hz, 1 H), 5.87 (dd, *J* = 15.7 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 2.93–2.74 (m, 1 H), 2.55 (dd, *J* = 1.2, 6.2 Hz, 2 H), 1.70–1.14 (m, 14 H), 0.92 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7, 166.3, 150.5, 121.9, 60.4, 48.0, 36.5, 34.5, 31.8, 29.5, 29.4, 29.2, 27.0, 22.6, 14.2, 14.1 ppm. HRMS (TOF, CI): calcd. for $C_{16}H_{29}O_3$ [M + H]$^+$ 269.2117; found 269.2127. For step 3, to a solution of the aldehyde

(0.054 g, 0.2 mmol, 1 equiv.), obtained in the previous step, in CH_2Cl_2 (1 mL) was added a dispersion of $NaBH_4$ (6.0 mg, 0.15 mmol, 0.75 equiv.) in EtOH (1 mL) at –10 °C. The resultant suspension was stirred for 48 h at this temperature, and then H_2O (1 mL) was added. The organic layer was separated, washed with H_2O (1 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (hexane/EtOAc, 95:5) to afford **15** (yellow oil, 0.036 g, 66%) as a 90:10 mixture of diastereomers. For characterization, an analytical sample of the major diastereomer was isolated by preparative chromatography. Data for ethyl 2-[(2*S*,3*S*)-2-octyltetrahydrofuran-3-yl]acetate (*trans*-**15**): $[\alpha]_D^{25}$ = +4.12 (*c* = 0.72, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (q, *J* = 7.1 Hz, 2 H), 3.88 (dd, *J* = 4.5, 7.7 Hz, 1 H), 3.84 (dd, *J* = 6.1, 7.7 Hz, 2 H), 2.54 (dd, *J* = 4.5, 15.0 Hz, 1 H), 2.47 (dd, *J* = 8.1, 15.0 Hz, 1 H), 2.43–2.38 (m, 1 H), 2.09 (dt, *J* = 6.1, 13.8 Hz, 1 H), 1.86–1.78 (m, 1 H), 1.61–1.53 (m, 2 H), 1.32–1.24 (m, 15 H), 0.89 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 80.7, 67.2, 60.5, 44.6, 40.2, 32.8, 32.5, 31.9, 29.8, 29.5, 29.3, 28.3, 22.6, 14.2, 14.1 ppm. HRMS (TOF, CI): calcd. for $C_{16}H_{31}O_3$ $[M + H]^+$ 271.2273; found 271.2271.

Supporting Information (see footnote on the first page of this article): HPLC spectra, assignment of the relative configuration of **15**, and copies of ^{1}H and ^{13}C NMR spectra.

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