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Pd(II)-catalyzed aliphatic Claisen rearrangements of acyclic allyl vinyl ethers

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ABSTRACT

Palladium (II)-catalyzed [3,3] sigmatropic rearrangement of acyclic allyl vinyl ethers delivers 2,3-*anti* disubstituted pentenal Claisen adducts with high diastereoselectivity. Reaction conditions for circumventing allyl vinyl ether cleavage that had previously plagued catalyzed rearrangement of α-unsubstituted vinyl ether substrates are described. Merging Pd(II) catalysis with the facile access to the Claisen substrates afforded by Ir(I)-catalyzed olefin isomerization provides an expedient procedure for realizing asymmetric *anti*-selective Claisen rearrangements.

1. Introduction

Activating π-bonds through coordination to transition metal complexes constitutes one of the most fundamental mechanisms in catalysis. As a result, catalyzed additions to alkenes are most commonly associated with late transition metal–olefin coordination leading to an activated, electrophilic η^2 complex.[1] This analysis has undoubtedly contributed to the development of [3,3] sigmatropic rearrangements catalyzed by complexation-induced activation of the olefin residues in the ubiquitous 1,5-diene substrates (Fig. 1).[2,3] The ability of Pd(II) complexes to activate olefins toward nucleophilic attack has proven especially useful in developing catalyzed Cope,[4] Claisen,[5] and hetero-Claisen rearrangements.[6] The complementary stereoselectivity exhibited by Pd(II)-catalyzed Claisen variants relative to their thermal counterparts affords unique opportunities to execute *syn*- or *anti*-selective rearrangements from a common substrate. Unfortunately, extending Pd(II) catalysis to diene substrates yielding aldehyde-containing Claisen adducts has yielded limited success.[5a] In pursuit of generally useful, operationally simple aliphatic Claisen rearrangements, we were interested in circumventing these difficulties to realize *anti*-selective Claisen rearrangements to complement the *syn*-selective thermal variants. Toward this goal, this account describes the development of efficient Pd(II)-catalyzed aliphatic Claisen rearrangements of acyclic allyl vinyl ethers affording 2,3-*anti* 4-pentenal products with uniformly high diastereoselection (*anti*/*syn*≥95:5).

2. Background

Transition metal catalysis offers a strategy for accessing [3,3] sigmatropic rearrangements that are stereochemically complementary to their thermal counterparts. Nakai demonstrated that Pd(II)-catalyzed Claisen rearrangements of α-substituted allyl vinyl ethers proceed with high *anti* diastereoselection presumably due to the boat-type transition state enforced by bidentate substrate–catalyst coordination (Eq. 1).[5b] However, van der Baan had previously observed that attempted Pd(II)-catalyzed rearrangement of α-unsubstituted allyl vinyl ethers afforded minor amounts of Claisen adduct **1** and significant quantities of allylic alcohol **2** (Eq. 2).[5a] We have been interested in merging catalyzed olefin isomerization with thermal [3,3] sigmatropic rearrangements as a strategy for developing operationally simple, aliphatic Claisen rearrangements.[7,8] Engaging the allyl vinyl ethers emerging from the Ir(I)-catalyzed olefin isomerization in Pd(II)-catalyzed [3,3] sigmatropic rearrangement offered an attractive strategy for obtaining the stereochemically complementary *anti* Claisen adducts, provided the competing 'hydrolysis' pathway could be circumvented.

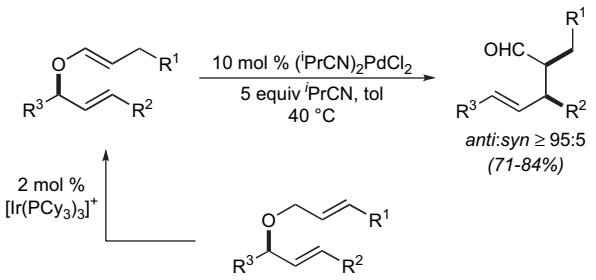

Figure 1. Pd(II)-catalyzed Claisen rearrangements of acyclic allyl vinyl ethers.

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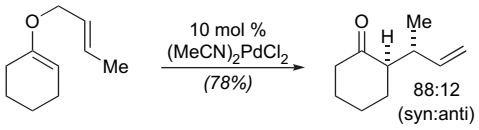
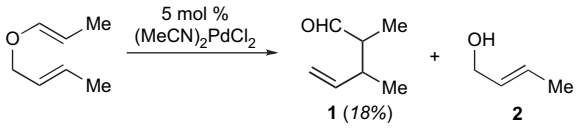


(1)

Nakai *Tetrahedron Lett.* **1987**, *28*, 5879.

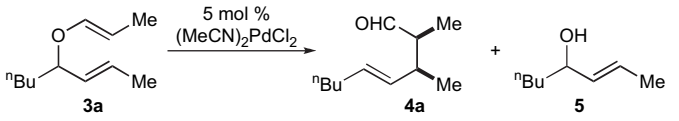


(2)

van der Baan *Tetrahedron Lett.***1986**,*27*, 6267.

3. Results and discussion

Allyl vinyl ether **3a** served as a representative test substrate for evaluating the Pd(II)-catalyzed aliphatic Claisen rearrangements. In accord with van der Baan's observation, reacting **3a** with 5–10 mol % $(MeCN)_2PdCl_2$ afforded a mixture of Claisen adduct **4a** and the allylic alcohol **5** (Eq. 3).[5a] Evaluating reaction efficiency as a function of catalyst structure revealed a strong correlation between product distribution and ligand addend. Specifically, the Pd(II)-catalyzed Claisen rearrangement of α-unsubstituted allyl vinyl ether **3a** proved to be especially responsive to alkyl nitrile additives. Using acetonitrile as solvent or cosolvent in the Claisen rearrangements decreased reaction rates dramatically, presumably due to saturation of the Pd(II) coordination sphere. Nitriles having electronically- or sterically-diminished competency as ligands relative to acetonitrile, however, effectively mitigated the putative hydrolysis side reaction.



Additive	**4a**:**5**	% yield **4a**
none	67:33	43
PhCN (1 equiv)	85:15	58
PhCN (5 equiv)	95:5	69

(3)

Thus, adding 1 equiv of PhCN or ^{i}PrCN to the Pd(II)-catalyzed rearrangement of **3a** further increased the percentage of Claisen adduct (**4a**/**5**=85:15); adding up to 5 equiv of the nitrile affords **4a** contaminated with only 5% of the allylic alcohol (**4a**/**5**=95:5).[9,10]

The nitrile additive was also revealed to have an ancillary benefit beyond limiting allylic alcohol production (Table 1). Claisen rearrangement could be conducted at 40 °C without significant catalyst decomposition and no detectable thermal background reaction leading to significantly decreased reaction times (~96 h at 23 °C→~24 h at 40 °C) (entries a and b).[5f] Reactions conducted at elevated temperature without the nitrile additive led to rapid Pd(0) formation and correspondingly decreased reaction efficiency.

Table 1
Effect of reaction variables on Claisen rearrangement efficiency[a] (**3a**→**4a**)

Entry	Catalyst	Temperature (°C)	Time (h)	**4a** (% yield)
1	10 mol % $(^{i}PrCN)_2PdCl_2$	23	48	55
2	10 mol % $(^{i}PrCN)_2PdCl_2$	40	24	74
3	10 mol % $(^{i}PrCN)_2PdBr_2$	40	24	70
4	7.5 mol % $(^{i}PrCN)_2PdCl_2$	40	34	68
5	5 mol % $(^{i}PrCN)_2PdCl_2$	40	48	50

[a] Toluene was used as the reaction solvent (0.02 M).

Useful reaction catalysts were generally limited to nitrile complexes of palladium(II) dihalide complexes; the corresponding bis(phosphine) or bis(amine) complexes expressed little or no catalytic activity. Complexes possessing weakly- or non-coordinating counterions (e.g., PdI_2, $Pd(OTf)_2$, $Pd(NO_2)Cl$) afforded extensive substrate decomposition or Claisen adducts with little diastereoselectivity. We had observed a similar phenomenon in thermal Claisen rearrangements where Lewis acidic contaminants promote epimerization of the chiral α-substituted aldehyde Claisen adduct.[7a] Using 7.5–10 mol % of the optimized catalyst system afforded the highest reaction yields; using 5 mol % catalyst led to a measurable decrease in reaction efficiency (Table 1, entry e).

Palladium-catalyzed Claisen rearrangements are generally interpreted according to the mechanism originally enumerated by Nakai (Fig. 2).[5b,d] To rationalize the *anti* diastereoselection emerging from Pd(II)-catalyzed Claisen rearrangements, a Pd(II)–diolefin complex **6** was implicated as an operative intermediate. Substrate chelation of the Pd(II) catalyst favors the boat-type conformation **6** relative to the higher energy chair-type chelate **7**. While this model provides an explanation for the observed *anti* distereoselection, the process by which these Pd(II)-templated diolefin complexes ultimately arrive at the Claisen adduct has not been explicitly defined. Presumably, **6** exists in equilibrium with the σ-bound Pd(II) complex **8** obtained by addition of the electron-rich vinyl ether to the Pd(II) center. Ensuing migratory insertion would deliver oxocarbenium ion **9**, an intermediate common to related transition metal-catalyzed [3,3] sigmatropic rearrangements proceeding via the cyclization-induced rearrangement mechanism.[6] Collapse of **9** via β-elimination of the oxocarbenium ion regenerates the Pd(II) catalyst in delivering the 2,3-*anti* Claisen rearrangement product **10**.

This mechanistic analysis provides a guide for interpreting the ligand-dependent product distribution observed for the Pd(II)-catalyzed rearrangements of aliphatic allyl vinyl ethers.[11] We speculate that addition of an adventitious nucleophile to oxocarbenium ion **9** yields the organopalladium species **11** (Fig. 3, pathway a). Collapse of **9** by $C_{2'}$–C_3 bond fragmentation would generate the allylic alcohol **12** and provide a viable pathway for the apparent substrate hydrolysis observed by van der Bann. Support for this hypothesis was derived from the observation that vinyl ether **13** and allylic ether **14**, substrates that cannot undergo cyclization to generate an oxocarbenium ion intermediate, were immune to ether hydrolysis under the catalyzed Claisen conditions (Eq. 4). This analysis suggested that accelerating the collapse of oxocarbenium ion **9** via C_1–O fragmentation would minimize the putative bimolecular addition believed responsible for allylic alcohol formation (pathway b). Partitioning the competing reaction mechanisms accordingly required Lewis basic additives expressing poor nucleophilicity toward the oxocarbenium ion yet representing strong ligands for Pd(II). The increased electron density at palladium accompanying Lewis base coordination was expected to labilize the Pd–C bond and accelerate the desired collapse of

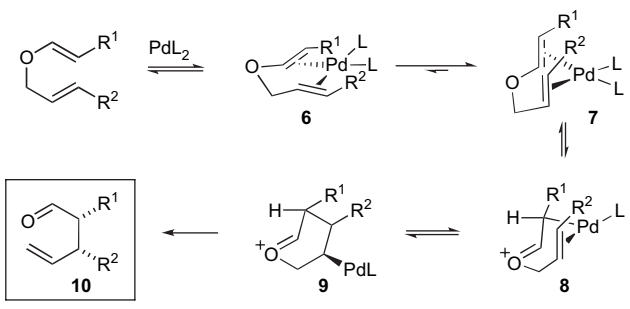


Figure 2. Postulated mechanism for Pd(II)-catalyzed Claisen rearrangements.

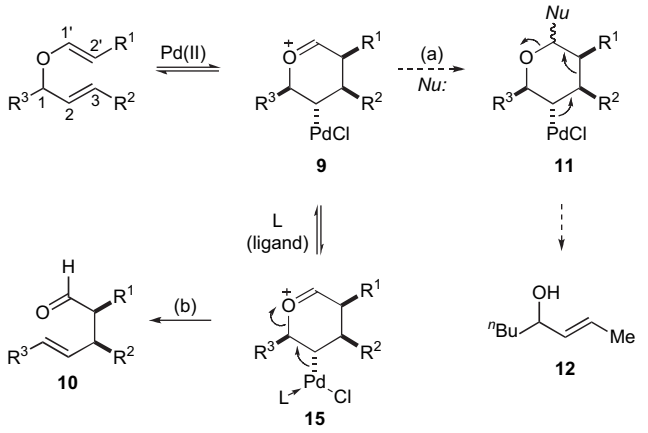
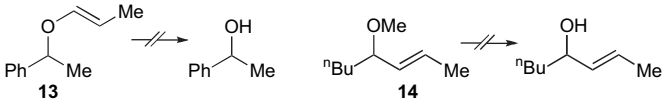


Figure 3. Proposed mechanism for ligand-dependent product distribution in Pd(II)-catalyzed Claisen rearrangements.

oxocarbenium ion **15** (pathway b). Among the Lewis bases satisfying this criterion, alkyl nitriles and alkenes represented good ligands for palladium while offering negligible nucleophilicity.[12]

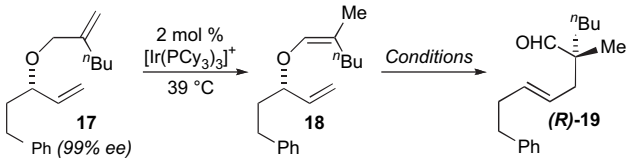


Conditions: 10 mol % $(MeCN)_2PdCl_2$, CH_2Cl_2, 23 °C

(4)

To maximize efficiency and operational simplicity in the Pd(II)-catalyzed Claisen rearrangements, a reaction sequence was developed that utilized easily obtained di(allyl) ethers as precursors to the requisite allyl vinyl ether substrates. The di(allyl) ethers **16** participated in Ir(I)-catalyzed isomerization to the Claisen substrates **3a**–**h** according to the published procedure (Table 2).[7] Allyl vinyl ether products free of metal contaminants were conveniently obtained by filtering hexane (or pentane) solutions of the crude product mixture through Florisil (62–93%). Subjecting the resulting allyl vinyl ethers to the optimized Claisen rearrangement conditions (10 mol % catalyst, 0.1 M toluene, 40 °C) afforded Claisen adducts incorporating various linear or branched alkyl substituents at the allylic (R^2) or vinyl (R^3) positions with uniformly high *anti* diastereoselection (≥95:5).[13] Unlike their thermal counterparts, rigorous control of vinyl ether geometry is not a prerequisite for high diastereoselection in the Pd(II)-catalyzed Claisen rearrangements. Allyl vinyl ethers **3e** and **3f** produced as *E*/*Z* vinyl ether mixture afford the *anti* Claisen adduct with exceptionally high diastereoselectivity (>97:3) with product yields similar to the homogeneous *E*,*E*-allyl vinyl ethers.[14] This observation reveals that vinyl ether geometry is subject to interconversion under the Claisen reaction conditions. The 3-phenyl substrate **3e** suggests that some branching at the R^2 position is tolerated, however, this is not general as substrates incorporating isopropyl or trimethylsilyl substituents at this position are unreactive. Enantioenriched allyl vinyl ethers **3f**–**h** participate in the Pd(II)-catalyzed Claisen rearrangement with only minor erosion of optical purity (entries f–h).

Quaternary carbon stereocenters are also accessible from the Pd(II)-catalyzed Claisen rearrangements. Catalyzed olefin isomerization of the di(allyl) ether precursor **17** proceeds to afford the *Z* vinyl ether **18** without competing isomerization of the terminal olefin (Eq. 5).[15] Reacting **18** with 5 mol % (^{i}PrCN)$PdCl_2$ afforded (*R*)-**19** in excellent yield and with faithful chirality transfer (84%). Steric bulk about the vinyl ether is believed to minimize unproductive Pd coordination at this position, thereby increasing equilibrium concentrations of the Pd(II)–olefin complex leading to cyclization-induced rearrangement and allowing lower catalyst loadings (5 mol %) to be used. In this instance, the Pd(II)-catalyzed Claisen rearrangement is substantially more efficient than the thermal alternative that proceeds in only modest chemical yield and with eroded olefin geometry control.



Conditions	*Result*
5 mol % (^{i}BuCN)$PdCl_2$ 5 equiv ^{i}BuCN, tol	84% **(*R*)-19** (93% ee)
75°C	50% **(*S*)-19** (95% ee) (+ 8% *Z* olefin)

(5)

The Pd(II)-catalyzed Claisen rearrangement protocol provides a highly diastereoselective route to *anti*-2,3-disubstituted-pentenal derivatives. Merging these reactions with Ir(I)-catalyzed isomerization of di(allyl) ethers provides an operationally simple strategy for accessing Claisen rearrangements that are stereochemically complementary to their *syn*-selective thermal counterparts.

4. Experimental

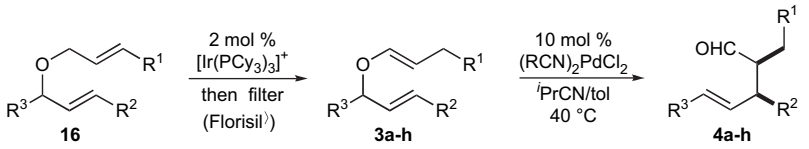
4.1. General information

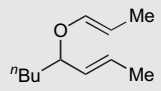
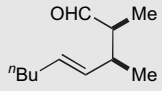
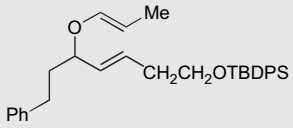
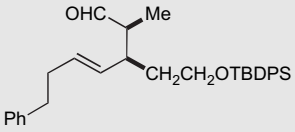
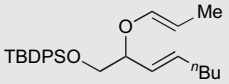
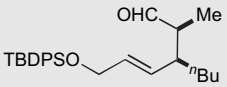
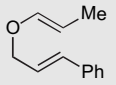
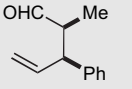
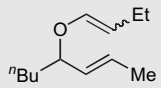
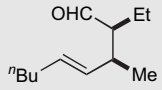
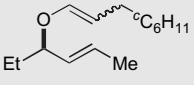
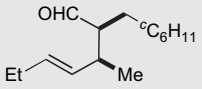
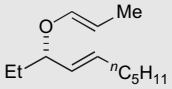
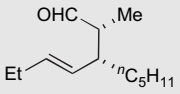
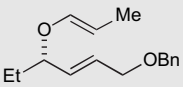
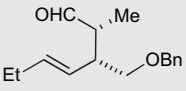
Unless otherwise stated, all reactions were performed in dry glassware under an atmosphere of oxygen-free nitrogen using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents were obtained by passage through successive alumina-packed columns on a solvent purification system. Acetone was distilled from Drierite and stored under dry nitrogen. Isobutyronitrile was distilled from CaH_2. The di(allyl) ethers **16** used in preparing **3a**–**h** and **19** were prepared according to the published procedures.[7] (*S*)-5-Phenylpent-1-en-3-ol (>99% ee) was prepared using the published procedure.[16] $[(^cC_8H_{14})_2IrCl]_2$[17] and PCy_3 were stored and weighed out in a nitrogen-filled glove box. Temperatures for the catalyzed Claisen rearrangements were controlled using an Ika® Werke hotplate/stirrer. Chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra. Flash chromatography was performed as previously described on Iatrobeads 6RS-8060 (pH 7 silica gel), purchased from Shell-USA, or EM silica gel 60 (230–240 mesh).[18,19] Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190–600 nm), using Daicel Chiracel™ columns (250×4.6 mm) (Daicel Inc.).

4.2. General procedure A for isomerization[7a]

A solution of $[(^cC_8H_{14})_2IrCl]_2$ (0.5 mol %, 0.01 equiv Ir) and PCy_3 (3 mol %, 0.03 equiv) in anhydrous CH_2Cl_2 was added to a solution of $NaBPh_4$ (1 mol %, 0.01 equiv) in CH_2Cl_2/acetone (25:1) (0.67 M final concentration in substrate **1**) and the resulting yellow solution stirred for 5 min at ambient temperature. Di(allyl) ether **1** (1.0 equiv) was added and the reaction stirred for 10–60 min at ambient temperature or 0 °C after which the solvent was removed in vacuo. In some cases, PPh_3 (0.03 equiv) was added and the resulting solution stirred for 5 min prior to solvent removal.

Table 2
Olefin isomerization–Claisen rearrangement of 1,1-disubstituted and trisubstituted allyl ethers



Entry	**3** (% yield)[a]	**4** (% yield)[b]	Diastereomer ratio (% ee)[c,d]
a	 (93)	 (74)	95:5 *anti*/*syn*
b	 (93)	 (70)	93:7 *anti*/*syn*
c	 (87)	 (71)	94:6 *anti*/*syn*
d	 (69)	 (71)	96:4 *syn*/*anti*
e	 (92; 1.9:1 *E*:*Z*)	 (71)	>97:3 *anti*/*syn*
f	 (92; 2.6:1 *E*:*Z*) (86% ee)	 (70)	>97:3 *anti*/*syn* (84)
g	 (82, 88% ee)	 (71)	97:3 *anti*/*syn* (86)
h	 (53, 93% ee)	 (59)	97:3 *anti*/*syn* (92)

[a] Allyl vinyl ethers possess *E*,*E* olefin stereochemistry except as noted in entries e and f.
[b] Yields reported for chromatographically purified materials; minor stereoisomers are, generally, inseparable. The major product diastereomers are depicted in the table.
[c] Diastereomer ratios (dr) determined by ^{1}H NMR of crude product mixtures.
[d] Product enantiomeric purity reported in parentheses for reactions employing enantioenriched di(allyl) ethers **16**.

Pentane or hexane was added to the residue and the resulting suspension was loaded onto a 6×2 cm plug of Florisil and eluted with the solvent indicated. Removal of the solvent in vacuo afforded the vinyl ethers as indicated below.

4.3. General procedure B for isomerization[7a]

A solution of $[(^cC_8H_{14})_2IrCl]_2$ (1.0 mol %, 0.02 equiv Ir) and PCy_3 (6.0 mol %, 0.06 equiv) in anhydrous CH_2Cl_2 (1.5 ml) was added to a solution of $NaBPh_4$ (2.0 mol %, 0.02 equiv) in CH_2Cl_2/acetone (25:1) (1.5 ml, 0.67 M final concentration in substrate **16**) and the resulting yellow solution stirred for 5 min at ambient temperature. Di(allyl) ether **16** (1.0 equiv) was added and the reaction stirred for 6–12 h at ambient temperature whereupon the solvent was removed in vacuo. Pentane or hexanes was added and the resulting suspension was loaded onto a 6×2 cm plug of Florisil and eluted with the solvent indicated. Removal of the solvent in vacuo afforded the vinyl ethers as indicated below.

4.3.1. (2E)-4-[(E)-Prop-1-enyloxy]-2-octene (*3a*)

General procedure A was followed employing 1.48 g of (*E*)-4-allyloxy-2-octene (8.80 mmol). Purification by filtration through

Florisil (eluting with pentane) gave 1.37 g (93%) of the title compound as a colorless oil. IR (thin film): 3034, 2933, 2861, 1674, 1657, 1456, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.08 (dq, J=12, 1.6 Hz, 1H), 5.63 (dq, J=15, 6.4 Hz, 1H), 5.36 (ddq, J=15, 6.8, 1.6 Hz, 1H), 4.88 (dq, J=6.7, 12 Hz, 1H), 3.92 (q, J=6.8 Hz, 1H), 1.72 (dd, J=6.7, 1.6 Hz, 3H), 1.53 (dd, J=6.8, 1.6 Hz, 3H), 1.4–1.7 (m, 2H), 1.2–1.4 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 131.6, 128.2, 100.3, 81.4, 35.0, 27.4, 22.6, 17.7, 14.0, 12.5; MS (EI, 70 eV): m/z 111 ($M^+-C_3H_5O$), 69, 55; HRMS m/z calcd for C_8H_{15} ($M^+-C_3H_5O$): 111.1174, found: 111.1171.

4.3.2. (3E)-1-(tert-Butyl)diphenylsilyloxy-5-[(E)-prop-1-enyloxy]-7-phenyl-3-heptene (**3b**)

General procedure A was followed employing 0.399 g of ((*E*)-5-(allyloxy)-7-phenylhept-3-enyloxy)(*tert*-butyl)diphenylsilane (0.822 mmol) at 0 °C for 1 h. After this time, PPh_3 (6.5 mg, 0.025 mmol) was added. Purification by filtration through Florisil (eluting with 5% EtOAc/hexane) gave 0.372 g (93%) of the title compound as a colorless oil. IR (thin film): 3027, 2930, 2858, 1673, 1657, 1428, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 4H), 7.40 (m, 6H), 7.28 (m, 2H), 7.19 (m, 3H), 6.08 (dq, J=12, 1.5 Hz, 1H), 5.68 (dt, J=16, 6.8 Hz, 1H), 5.45 (dd, J=16, 7.3 Hz, 1H), 4.91 (dq, J=12, 6.7 Hz, 1H), 3.96 (dt, J=6.1, 7.0 Hz, 1H), 3.72 (t, J=6.5 Hz, 2H), 2.60–2.76 (m, 2H), 2.32 (dt, J=6.5, 6.5 Hz, 2H), 1.74–2.03 (m, 2H), 1.52 (dd, J=6.8, 1.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 141.8, 135.5, 133.9, 132.0, 130.3, 129.6, 128.5, 128.3, 127.6, 125.7, 100.8, 80.1, 63.5, 36.9, 35.6, 31.4, 26.9, 19.2, 12.5; MS (ESI): m/z 507 (M^++Na); HRMS (ESI) m/z calcd for $C_{32}H_{40}O_2Si$ (M^++Na): 507.2695, found: 507.2719.

4.3.3. (3E)-1-(tert-Butyl)diphenylsilyloxy-2-[(E)-prop-1-enyloxy]-3-octene (**3c**)

A modification of general procedure A was followed employing 0.218 g of ((*E*)-2-(allyloxy)oct-3-enyloxy)(*tert*-butyl)diphenylsilane (0.515 mmol). The substrate was added at 0 °C and stirred at this temperature for 1 h followed by addition of PPh_3 (4.1 mg, 6 mol %). Purification by filtration through Florisil (eluting with 5% Et_2O/pentane) gave 0.189 g (87%) of the title compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.72 (m, 4H), 7.33–7.45 (m, 6H), 6.12 (dq, J=12, 1.5 Hz, 1H), 5.67 (dtd, J=16, 6.7, 0.7 Hz, 1H), 5.35 (ddt, J=16, 7.1, 1.4 Hz, 1H), 4.87 (dq, J=13, 6.2 Hz, 1H), 4.11 (dt, J=6.0, 6.3 Hz, 1H), 3.74 (dd, J=11, 6.4 Hz, 1H), 3.63 (dd, J=11, 5.1 Hz, 1H), 2.03 (dt, J=6.5, 6.6 Hz, 2H), 1.51 (dd, J=6.8, 1.5 Hz, 3H), 1.25–1.40 (m, 4H), 1.05 (s, 9), 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 135.7, 135.0, 133.6, 133.5, 129.6, 127.6, 126.9, 100.3, 81.7, 66.5, 32.0, 31.1, 26.8, 22.2, 19.2, 13.9, 12.5; MS (EI, 70 eV): m/z 422 (M^+), 365, 307, 267, 239, 199, 183, 135, 109, 75, 67; HRMS m/z calcd for $C_{27}H_{38}O_2Si$ (M^+): 422.2641, found: 422.2628.

4.3.4. (E)-3-[(E)-Prop-1-enyloxy]propenylbenzene (**3d**)

General procedure A was followed employing 0.800 g of *E*-3-allyloxypropenylbenzene (4.59 mmol) for 1 h. Purification by filtration through Florisil (gradient elution with pentane to 2.5% Et_2O/pentane) gave 0.549 g (69%) of the title compound as a colorless oil. IR (thin film): 3027, 2923, 2858, 1675, 1656, 1267, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.44 (m, 5H), 6.66 (d, J=16.0 Hz, 1H), 6.28–6.38 (m, 2H), 4.85–4.96 (m, 1H), 4.36 (dd, J=5.9, 1.2 Hz, 2H), 1.61 (dd, J=6.7, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.0, 136.4, 132.5, 128.4, 127.7, 126.4, 124.9, 99.3, 69.7, 12.4; MS (EI, 70 eV): m/z 174 (M^+), 131, 118, 117, 115, 104, 91, 89; HRMS (EI) m/z calcd for $C_{12}H_{14}O$ (M^+): 174.1045, found: 174.1041.

4.3.5. (2E)-4-[(E)-But-1-enyloxy]-2-octene (**3e**)

General procedure B was followed employing 0.995 g of (2*E*)-4-((*E*)-but-2-enyloxy)oct-2-ene (5.46 mmol). Purification by filtration through Florisil (eluting with pentane) gave 0.918 g (92%) of the title compound as a colorless oil and a 1.9:1 *E*/*Z* mixture of butenyl group isomers. IR (thin film): 3035, 2960, 2861, 1669, 1456, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.08 (dt, J=12, 1.4 Hz, 1H), 5.63 (dqd, J=15, 6.4, 0.8 Hz, 1H), 5.36 (ddq, J=14, 7.6, 1.6 Hz, 1H), 4.91 (dt, J=12, 7.1 Hz, 1H), 3.92 (dt, J=14, 7.6 Hz, 1H), 1.92 (ddq, J=15, 7.3, 1.4 Hz, 2H), 1.71 (ddd, J=6.4, 1.5, 0.4 Hz, 3H), 1.38–1.75 (m, 2H), 1.30 (m, 4H), 0.95 (t, J=7.4 Hz, 3H), 0.88 (m, 3H); signals observed for the (*Z*)-isomer: 5.94 (dt, J=6.3, 1.4 Hz, 1H), 4.30 (dt, J=13, 7.1 Hz, 1H), 3.88 (dt, J=14, 7.0 Hz, 1H), 2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 142.96 (*Z*), 131.9 (*Z*), 131.7, 128.0, 127.9 (*Z*), 108.4 (*Z*), 108.0, 82.2 (*Z*), 81.2, 35.0, 27.3, 22.6, 21.0, 17.5, 17.4 (*Z*), 15.1, 14.4 (*Z*), 13.9; MS (EI, 70 eV): m/z 154 ($M^+-C_2H_5$), 139, 125, 110, 81, 69, 55; HRMS m/z calcd for $C_{12}H_{22}O$ (M^+): 182.1671, found: 182.1676.

4.3.6. (3R,4E)-3-[(E)-3-Cyclohexyl-1-prop-1-enyloxy]-4-hexene (**3f**)

General procedure B was followed employing 0.704 g of ((1*E*)-3-((*R*,*E*)-hex-4-en-3-yloxy)prop-1-enyl)cyclohexane (3.16 mmol). Purification by filtration through Florisil (eluting with pentane) gave 0.648 g (92%) of the title compound as a colorless oil and a 2.6:1.0 *E*/*Z* mixture of cyclohexyl-1-propenyl group isomers. IR (thin film): 3036, 2921, 2852, 1670, 1448, 1288, 1164 cm^{-1}; $[\alpha]_D$ −7.9 (*c* 3.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.03 (dt, J=12.3, 1.1 Hz, 1H), 5.99 (dt, J=6.4, 1.4 Hz, 1H, *Z*-isomer), 5.57–5.72 (m, 1H), 5.31–5.41 (m, 1H), 4.86 (dt, J=12.3, 7.8 Hz, 1H, *E*-isomer), 4.31 (dt, J=7.4, 6.4 Hz, 1H, *Z*-isomer), 3.87 (dt, J=7.0, 6.7 Hz, 1H, *E*-isomer), 3.82 (dt, J=7.8, 6.7 Hz, 1H, *Z*-isomer), 1.94–2.00 (m, 1H), 1.45–1.78 (m, 11H), 1.07–1.28 (m, 4H), 0.79–0.98 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 143.8 (*Z*), 131.5 (*Z*), 131.2, 128.5, 128.2 (*Z*), 105.0 (*Z*), 104.6, 83.5 (*Z*), 82.5, 38.6, 38.3, 35.5, 33.1, 33.0, 32.9, 32.9, 31.7, 28.2, 28.1, 26.6, 26.4, 26.3, 17.7, 9.6; MS (EI, 70 eV): m/z 222 (M^+), 204, 193, 179, 140, 126, 122, 111, 96, 83; HRMS (EI) m/z calcd for $C_{15}H_{26}O$ (M^+): 222.1984, found: 222.1988.

4.3.7. (3S,4E)-3-[(E)-Prop-1-enyloxy]-4-decene (**3g**)

General procedure A was followed employing 0.900 g of (3*S*)-(*E*)-3-(allyloxy)dec-4-ene (4.59 mmol) for 15 min at ambient temperature. Purification by filtration through Florisil (eluting with pentane) gave 0.738 g (82%) of the title compound as a colorless oil. IR (thin film): 3038, 2960, 2927, 2858, 1675, 1657, 1459, 1173 cm^{-1}; $[\alpha]_D$ +0.66 (*c* 2.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.09 (dq, J=12.3, 1.6 Hz, 1H), 5.61 (dt, J=15.4, 6.4 Hz, 1H), 5.31 (ddt, J=15.4, 7.6, 1.4 Hz, 1H), 0.88 (t, J=7.5 Hz, 3H), 4.87 (dq, J=12.3, 6.8 Hz, 1H), 3.86 (dt, J=6.9, 6.8 Hz, 1H), 2.04 (dt, J=6.8, 6.5 Hz, 2H), 1.44–1.71 (m, 2H), 1.52 (dd, J=6.8, 1.6 Hz, 3H), 1.22–1.43 (m, 6H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 134.1, 129.9, 100.4, 82.7, 32.2, 31.3, 28.8, 28.2, 22.4, 14.0, 12.5, 9.6; MS (EI, 70 eV): m/z 196 (M^+), 167, 138, 109, 97, 83, 69; HRMS (EI) m/z calcd for $C_{13}H_{24}O$ (M^+): 196.1827, found: 196.1820.

4.3.8. (4S,2E)-1-Benzyloxy-4-[(E)-prop-1-enyloxy]-2-hexene (**3h**)

General procedure A was followed employing 0.431 g of (4*S*)-(*E*)-4-allyloxy-1-benzyloxyhex-2-ene (1.75 mmol) for 10 min at ambient temperature. After this time, PPh_3 (13.8 mg, 0.053 mmol) was added. Purification by filtration through Florisil (gradient elution with hexane to 2.5% Et_2O/pentane) gave 0.228 g (53%) of the title compound as a colorless oil. IR (thin film): 3031, 2933, 2857, 1674, 1656, 1454, 1170 cm^{-1}; $[\alpha]_D$ −3.8 (*c* 2.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H), 6.10 (dq, J=12.3, 1.6 Hz, 1H), 5.78 (dt, J=15.7, 5.5 Hz, 1H), 5.64 (dd, J=15.7, 6.7 Hz, 1H), 4.90 (dq, J=12.3, 6.8 Hz, 1H), 4.05 (dd, J=5.5, 0.5 Hz, 2H), 4.52 (s, 2H), 3.97 (dt, J=6.5, 6.4 Hz, 1H), 1.57–1.75 (m, 2H), 1.53 (dd, J=6.8, 1.5 Hz, 3H), 0.92 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 138.1, 133.0, 128.9, 128.3, 127.7, 127.5, 100.8, 81.6, 71.9, 69.9, 28.0, 12.4 9.5; MS (EI, 70 eV): m/z 246 (M^+), 189, 171, 91, 77, 69; HRMS (EI) m/z calcd for $C_{16}H_{22}O_2$ (M^+): 246.1620, found: 246.1619.

*4.3.9. (3R)-3-[(Z)-2-Methylhex-1-enyloxy]-5-phenyl-1-pentene (**13**)*

General procedure B was followed employing 0.500 g of (3*R*)-[3-(2-butyl-allyloxy)-pent-4-enyl]-benzene (1.94 mmol) for 11 h. Purification by filtration through Florisil (elution with hexane) gave 0.225 g (45%) of the title compound as a colorless oil. IR (thin film): 3027, 2956, 2858, 1682, 1455, 1152 cm^{-1}; $[\alpha]_D$ 5.4 (*c* 2.29, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.32 (m, 5H), 5.72–5.83 (m, 2H), 5.15–5.27 (m, 2H), 3.92 (dt, *J*=6.7, 6.2 Hz, 1H), 2.63–2.81 (m, 2H), 2.07–2.20 (m, 2H), 1.78–2.03 (m, 2H), 1.53 (d, *J*=1.4 Hz, 3H), 1.30–1.44 (m, 4H), 0.93 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 138.7, 138.6, 128.4, 128.3, 125.8, 116.5, 114.4, 81.0, 36.8, 31.3, 29.6, 28.7, 22.5, 17.3, 14.0; MS (EI, 70 eV): *m*/*z* 258 (M^+), 144, 129, 114, 91, 71; HRMS (EI) *m*/*z* calcd for $C_{18}H_{26}O$ (M^+): 258.1984, found: 258.1979.

4.3.10. Preparation of (^{i}BuCN)$_2$PdCl$_2$

A suspension of 2.00 g of $PdCl_2$ (11.3 mmol) in ^{i}BuCN (20 ml) was heated at 100 °C overnight. The resulting solution was filtered while warm and rinsed through the filter with a small amount of CH_2Cl_2. Hexane was added to the filtrate and the resulting precipitate was filtered, washed with hexanes, and dried under vacuum for 30 min to afford 3.44 g (96%) of the catalyst as a yellow/orange solid, which was stored in a desiccator.

4.4. General procedure C for palladium-catalyzed Claisen rearrangements

The vinyl ether **2** (1.0 equiv) was added to a solution of (^{i}BuCN)$_2$PdCl$_2$ (0.05–0.10 equiv) in toluene/^{i}BuCN (5 equiv) (0.1 M final concentration of substrate) and the reaction stirred at 40 or 50 °C. After the indicated time, hexane was added to the reaction mixture and the resulting mixture was purified by flash chromatography on Iatrobeads 6RS-8060 silica gel.[21] The column was initially flushed with 150–200 ml hexane prior to elution of desired product with pentane/diethyl ether as specified below.

*4.4.1. (E)-anti-2,3-Dimethylnon-4-enal (**4a**)*

General procedure C (10 mol% catalyst, 40 °C, 24 h) was followed employing 0.20 g of ether **3a** (1.19 mmol). Purification by flash chromatography (2.5% Et_2O/pentane) on Iatrobeads gave 0.148 g (74%) of the title compound as a colorless oil (*anti*/*syn*=95:5). IR (thin film): 2961, 2929, 2873, 1728, 1456, 1378, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.63 (d, *J*=2.3 Hz, 1H), 5.46 (dt, *J*=15, 6.7 Hz, 1H), 5.25 (dd, *J*=15, 7.9 Hz, 1H), 2.57 (m, 1H), 2.26 (dqd, *J*=14, 6.8, 2.2 Hz, 1H), 2.00 (m, 2H), 1.2–1.4 (m, 4H), 1.06 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=7.0 Hz, 3H), 0.89 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3, 131.5, 131.4, 51.5, 37.4, 32.1, 31.5, 22.1, 18.4, 13.8, 10.4; MS (EI, 70 eV): *m*/*z* 168 (M^+), 153, 139, 127, 111, 83, 69, 55; HRMS *m*/*z* calcd for $C_{11}H_{20}O$ (M^+): 168.1514, found: 168.1512.

*4.4.2. (E)-anti-3-(tert-Butyldiphenylsilyloxyethyl)-2-methyl-7-phenylhept-4-enal (**4b**)*

General procedure C (10 mol% catalyst, 50 °C, 26 h) was followed employing 0.10 g of ether **3b** (0.206 mmol). Purification by flash chromatography (gradient elution with hexane to 5% EtOAc/hexanes) on Iatrobeads gave 0.070 g (70%) of the title compound as a colorless oil (*anti*/*syn*=93:7). IR (thin film): 2930, 1726, 1454, 1428, 1390, 1111, 973 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.53 (d, *J*=2.1 Hz, 1H), 7.65 (m, 5H), 7.35–7.45 (m, 5H), 7.1–7.3 (m, 5H), 5.42 (dt, *J*=15, 6.7 Hz, 1H), 5.06 (dd, *J*=15, 9.2 Hz, 1H), 3.64 (m, 2H), 2.67 (m, 2H), 2.60 (m, 2H), 2.23 (m, 3H), 1.43–1.73 (m, 2H), 1.05 (s, 9H), 0.94 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2, 141.7, 135.5, 133.8, 132.5, 129.9, 129.6, 128.4, 128.2, 127.6, 125.8, 61.5, 50.2, 39.3, 35.8, 35.4, 34.2, 26.8, 19.2, 10.1; MS (ESI): *m*/*z* 507 (M^++Na); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{40}O_2Si$ (M^++Na): 507.2695, found: 507.2715.

*4.4.3. (E)-anti-3-n-Butyl-2-methyl-6-(tert-butyldiphenylsilyloxy)hex-4-enal (**4c**)*

General procedure C (10 mol% catalyst, 40 °C, 15 h) was followed employing 0.177 g of ether **3c** (0.420 mmol). Purification by flash chromatography (5% Et_2O/pentane) on Iatrobeads gave 0.125 g (71%) of the title compound as a colorless oil (*anti*/*syn*=94:6). ^1H NMR (300 MHz, $CDCl_3$): δ 9.60 (d, *J*=2.2 Hz, 1H), 7.67 (dd, *J*=7.0, 1.0 Hz 4H), 7.33–7.45 (m, 6H), 5.58 (dt, *J*=15, 4.6 Hz, 1H), 5.42 (ddt, *J*=15, 9.0, 1.4 Hz, 1H), 4.17 (dd, *J*=4.6, 1.4 Hz, 2H), 2.46 (m, 1H), 2.33 (dqd, *J*=14, 6.9, 2.2 Hz, 1H), 1.15–1.45 (m, 6H), 1.05 (s, 9H), 1.01 (d, *J*=6.9 Hz, 3H), 0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.0, 135.4, 133.7, 131.3, 130.2, 129.6, 127.6, 64.0, 50.2, 42.7, 32.4, 29.5, 26.7, 22.5, 19.2, 14.0, 10.1; MS (ESI): *m*/*z* 445 (M^++Na); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{38}O_2Si$ (M^++Na): 445.2539, found: 445.2555.

*4.4.4. (E)-anti-2-Methyl-3-phenylpent-4-enal (**4d**)*

General procedure C (10 mol% catalyst, 50 °C, 38 h) was followed employing 0.200 g of ether **3d** (1.148 mmol). Purification by flash chromatography (gradient elution with hexane to 2.5% Et_2O/pentane) on Iatrobeads gave 0.142 g (71%) of the title compound as a colorless oil (*anti*/*syn*=96:4). IR (thin film): 2978, 2932, 1724, 1724, 1493, 1453, 994, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.54 (d, *J*=2.4 Hz, 1H), 7.20–7.41 (m, 5H), 5.91–6.02 (m, 1H), 5.16 (s, 1H), 5.12 (d, *J*=5.5, 1H), 3.59 (app t, *J*=8.7 Hz, 1H), 2.77–2.86 (m, 1H), 1.13 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 141.3, 138.0, 128.7, 127.7, 126.7, 116.8, 51.4, 50.4, 11.8; MS (EI, 70 eV): *m*/*z* 174 (M^+), 159, 145, 117, 91; HRMS *m*/*z* calcd for $C_{12}H_{14}O$ (M^+): 174.1045, found: 174.1039.

*4.4.5. (E)-anti-2-Ethyl-3-methylnon-4-enal (**4e**)*

General procedure C (10 mol% catalyst, 40 °C, 24 h) was followed employing 0.200 g of ether **3e** (1.10 mmol). Purification by flash chromatography (2.5% Et_2O/pentane) on Iatrobeads gave 0.142 g (71%) of the title compound as a colorless oil (*anti*/*syn*=>97:3). IR (thin film): 2961, 2873, 2703, 1724, 1460, 1380, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.56 (d, *J*=3.7 Hz, 1H), 5.44 (dtd, *J*=15, 6.6, 0.7 Hz, 1H), 5.25 (ddt, *J*=15, 8.1, 1.3 Hz, 1H), 2.45 (m, 1H), 1.92–2.07 (m, 2H), 1.47–1.65 (m, 2H), 1.22–1.37 (m, 4H), 1.00 (d, *J*=6.9 Hz, 3H), 0.90 (m, 3H), 0.87 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7, 132.2, 131.3, 59.0, 36.9, 32.1, 31.6, 22.1, 19.8, 18.6, 13.9, 11.9; MS (EI, 70 eV): *m*/*z* 182 (M^+), 167, 153, 126, 111, 97, 81, 69, 55; HRMS *m*/*z* calcd for $C_{12}H_{22}O$ (M^+): 182.1671, found: 182.1667.

*4.4.6. (E,2S,3S)-anti-2-Cyclohexylmethyl-3-methylhept-4-enal (**4f**)*

General procedure C (10 mol% catalyst, 50 °C, 24 h) was followed employing 0.200 g of ether **3f** (84% ee; 0.899 mmol). Purification by flash chromatography (gradient elution with pentane to 1.5% Et_2O/pentane) on Iatrobeads gave 0.140 g (70%) of the title compound as a colorless oil (*anti*/*syn*=>97:3). Separation of the enantiomers of the derived *p*-tosylhydrazones by chiral HPLC Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 3% ^{i}PrOH, 97% hexanes, t_R 15.7 and 19.2 provided the enantiomer ratio: 90.6:9.4 (84% ee). IR (thin film): 2963, 2924, 2852, 1726 cm^{-1}; $[\alpha]_D$ −26.3 (*c* 2.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.54 (d, *J*=3.9 Hz, 1H), 5.48 (dt, *J*=15, 6.3 Hz, 1H), 5.23 (ddt, *J*=15, 8.1, 1.4 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 2.01 (m, 2H), 1.58–1.78 (m, 6H), 1.50 (m, 1H), 1.26 (m, 1H), 1.18 (m, 4H), 1.00 (d, *J*=6.8 Hz, 3H), 0.97 (t, *J*=7.4 Hz, 3H), 0.72–1.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 132.8, 131.2, 54.7, 37.4, 35.6, 34.2, 34.0, 32.6, 26.4, 26.2, 26.0, 25.4, 18.4, 13.8; MS (EI, 70 eV): *m*/*z* 221 (M^+), 204, 193, 179, 165, 125, 111, 95, 93, 67, 55; HRMS *m*/*z* calcd for $C_{15}H_{26}O_2$ (M^+): 222.1984, found: 222.1981.

*4.4.7. (E,2R,3R)-anti-2-Methyl-3-pentylhept-4-enal (**4g**)*

General procedure C (8 mol% catalyst, 50 °C, 24 h) was followed employing 0.247 g of ether **3g** (88% ee; 1.258 mmol). Purification by

flash chromatography (elution with 2.5% Et_2O/pentane) on Iatrobeads gave 0.175 g (71%) of the title compound as a colorless oil (*anti*/*syn*=97:3). Separation of the enantiomers of the derived *p*-tosylhydrazones by chiral HPLC Daicel Chiracel™ AD column, flow rate 1.0 ml/min, 3% ^{i}PrOH, 97% hexanes, t_R 23.2 and 25.7 provided the enantiomer ratio: 93.2:6.8 (86% ee). IR (thin film): 2960, 2928, 2857, 2699, 1728, 1458, 1377, 971 cm^{-1}; $[\alpha]_D$ −23.8 (*c* 4.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.59 (d, *J*=2.2 Hz, 1H), 5.47 (dt, *J*=15.2, 6.3 Hz, 1H), 5.09 (ddt, *J*=15.3, 9.0, 1.4 Hz, 1H), 2.34–2.48 (m, 1H), 2.34–2.24 (m, 1H), 2.08–1.93 (m, 2H), 1.16–1.43 (m, 8H), 1.00 (d, *J*=6.9 Hz, 3H), 0.95 (t, *J*=7.4 Hz, 3H), 0.87 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 134.7, 128.7, 50.4, 43.1, 32.8, 31.6, 26.9, 25.5, 22.5, 14.0, 13.9, 10.0; MS (EI, 70 eV): *m*/*z* 196 (M^+), 181, 167, 153, 139, 125, 111, 97, 83, 69; HRMS *m*/*z* calcd for $C_{13}H_{24}O$ (M^+): 196.1827, found: 196.1823.

*4.4.8. (E,2R,3R)-anti-3-Benzyloxymethyl-2-methylhept-4-enal (**4h**)*

General procedure C (10 mol % catalyst, 50 °C, 30 h) was followed employing 0.10 g of ether **3h** (93% ee; 0.406 mmol). Purification by flash chromatography (elution with 2.5% Et_2O/pentane) on Iatrobeads gave 0.059 g (59%) of the title compound as a colorless oil (*anti*/*syn*=97:3). Separation of the enantiomers by chiral HPLC Daicel Chiracel™ OD-H column, flow rate 0.8 ml/min, 0.2% ^{i}PrOH, 99.8% hexanes, t_R 12.9 and 15.1 provided the enantiomer ratio: 4.2:95.8 (92% ee). IR (thin film): 2963, 2932, 2872, 1724, 1454, 1363, 1100, 972 cm^{-1}; $[\alpha]_D$ 11.8 (*c* 2.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, *J*=2.2 Hz, 1H), 7.25–7.50 (m, 5H), 5.59 (dt, *J*=15.4, 6.3 Hz, 1H), 5.18 (ddt, *J*=15.4, 8.8, 1.5 Hz, 1H), 4.48 (s, 2H), 3.50 (dd, *J*=9.3, 5.2 Hz, 1H), 3.39 (app t, *J*=8.5 Hz, 1H), 2.75–2.87 (m, 1H), 2.50–2.60 (m, 1H), 1.96–2.06 (m, 2H), 1.01 (d, *J*=7.0 Hz, 3H), 0.96 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 138.1, 136.0, 128.3, 127.6 (2C overlap), 125.3, 73.0, 71.7, 47.9, 43.6, 25.6, 13.7, 10.1; MS (EI, 70 eV): *m*/*z* 247 (M+1), 246 (M^+), 188, 158, 125, 91; HRMS *m*/*z* calcd for $C_{16}H_{22}O_2$ (M^+): 246.1620, found: 246.1613.

*4.4.9. (E,2R)-2-Butyl-2-methyl-7-phenylhept-4-enal (**R-14**)*

To a solution of (^{i}PrCN)$_2$PdCl$_2$ (5.5 mol %, 17 mg, 55 μmol) and ^{i}PrCN (5 equiv to **6**, 5 mmol, 31 μl) in toluene (10 ml, 0.1 M final concentration of **12**) was added vinyl ether **12** (259 mg, 1 mmol; 99% ee). The resulting solution was stirred at 40 °C for 12.5 h. After cooling to ambient temperature, the reaction mixture was transferred directly to a Iatrobeads (neutral silica gel)-packed flash column and eluted with 100% hexanes (100 ml) then 2% Et_2O in pentane to afford 217 mg (84%) of the title compound as a colorless oil. The enantiomers of the primary alcohol obtained by ^{i}Bu$_2$AlH reduction of ***R*-13** were separated by chiral HPLC (Daicel Chiracel™ AD column, flow rate 1.0 ml/min, 2% ^{i}PrOH, 98% hexanes, t_R 11.1 and 12.2) to provide the enantiomer ratio: 3.7:96.3 (93% ee). $[\alpha]_D$ −1.2 (*c* 1.35, $CHCl_3$); IR (film): 2958, 2931, 2859, 1726, 1454, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.42 (s, 1H), 7.16–7.31 (m, 5H), 5.50 (dt, *J*=15.2, 6.6 Hz, 1H), 5.31 (dt, *J*=15.1, 7.3 Hz, 1H), 2.68 (t, *J*=7.3 Hz, 2H), 2.34 (dt, *J*=7.6, 7.1 Hz, 2H), 2.08–2.22 (m, 2H), 1.07–1.55 (m, 6H), 0.97 (s, 3H), 0.90 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 141.7, 133.4, 128.4, 128.2, 125.7, 125.1, 49.1, 38.5, 35.8, 34.9, 34.2, 26.1, 23.3, 18.3, 13.9; MS (EI, 70 eV): *m*/*z* 258 (M^+), 240, 202, 183, 167, 154, 98, 91; HRMS *m*/*z* calcd for $C_{12}H_{14}O$ (M^+): 258.1984, found: 258.1979.

4.5. Proof of stereochemistry

The relative stereochemistry of **4a**[20] and **4d**[21] was assigned based on correlation to literature compounds. The relative stereochemistry of **4g** and **4h** was assigned based on comparison to the corresponding *syn* diastereomers.[7b] The relative stereochemistry for all other compounds was assigned by analogy to the above examples.

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