Applications of Olefin Cross Metathesis to Commercial Products

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Abstract: In this paper, we will demonstrate the value of olefin cross metathesis as an effective synthetic tool for applications in the agrochemical and pharmaceutical industries. First, we will demonstrate the usefulness of cross metathesis reactions in the efficient synthesis of the major component of the Peach Twig Borer pheromone and the of Omnivorous Leafroller pheromone, insect pheromones are environmentally friendly pest-controlling agents. Second, we will demonstrate highly efficient cross metathesis routes into novel α,β-unsaturated carbonyl intermediates. These novel α,β-unsaturated carbonyl intermediates can be further functionalized into pharmaceutical compounds that are difficult to prepare by the traditional synthetic methodologies. This paper highlights key catalyst-substrate reactivity variations with different ruthenium olefin metathesis catalysts, highlights cross metathesis reactions and techniques and highlights an efficient ruthenium catalyst removal technique.

Keywords: cross metathesis; insect pheromones; organocatalysis; pharmaceuticals; ruthenium catalyst removal

Introduction

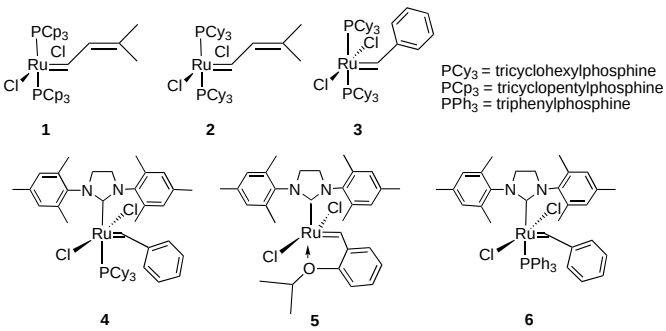
Applications of olefin metathesis in the synthesis of biologically relevant targets are growing rapidly,[1] however, most efforts to date involve ring-closing metathesis as the key synthetic transformation.[2] The exploitation of olefin cross metathesis is just beginning to emerge as a valuable synthetic tool for fine chemical synthesis. For example, cross metathesis methodologies have recently been shown to be highly effective routes in the synthesis of insect pheromones,[3,4] flavor and fragrance compounds,[5] and valuable synthetic intermediates such as novel α,β-unsaturated carbonyl systems.[6,7] In this paper, we will describe several cross metathesis routes to biologically active compounds for agrochemical and pharmaceutical applications.

Results and Discussion

Many of the olefin metathesis catalysts used in this article are available from Materia, Strem, or Aldrich. These catalysts are shown in Scheme 1: dichloro(3-methyl-1,2-butenylidene)bis(tricyclopentylphosphine)-ruthenium(II) (**1**); dichloro(3-methyl-1,2-butenylidene)-bis(tricyclohexylphosphine)ruthenium(II) (**2**); dichloro-(phenylmethylene)bis(tricyclohexylphosphine)ruthenium-(II) (**3**); [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium(II) (**4**); [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium(II) (**5**); [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(triphenylphosphine)ruthenium(II) (**6**).

Insect Pheromones

The use of ruthenium-based metathesis methodology has been of particular success in the synthesis of Lepidopteran insect pheromones.[2,3,4,8,9] Insect pheromones are biologically active compounds used by the same species for communication. The use of the female's sex attractant to confuse the male and disrupt mating is an effective and environmentally friendly technique in controlling insect populations.[10] Lepidopteran insect



Scheme 1. Structures of Materia's olefin metathesis catalysts.

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pheromones are traditionally defined as straight chained alcohols, aldehydes, or acetates containing 10 to 18 carbons and 1 to 3 double bonds. The current worldwide market for insect pheromones is approximately US $250 million and is projected to grow at an annual rate of 11% for the next decade.[11]

The advantages of using olefin metathesis to produce insect pheromones include: most of the starting materials are commodity materials (e.g., seed oils and alpha-olefins), the reactions are run neat, the reactions can provide up to 50% reactor efficiencies, the unreacted starting materials are recycled, very little waste is produced, and the reactions are run under near ambient temperature ranges. These factors make insect pheromones attractive targets for commercialization.

Two attractive pheromone targets are those of the Peach Twig Borer *(Anarsia lineatella)* and Omnivorous Leafroller *(Platynota stultana)*. Peach Twig Borer (PTB) is a pest of peaches, plums, nectarines, and almonds. The PTB pheromone is an 83:17 ratio of (*E*)-5-decenyl acetate (**9**) and (*E*)-5-decenol;[12] modest amounts of the (*Z*)-isomers have no effect on efficacy. Synthesis of **9** has been reported in the patent literature using ruthenium olefin metathesis but these routes are low yielding or difficult to scale up beyond 72-L reaction flasks.[3,13] Our goal was to develop a convenient, high yielding process that could be scaled up into commercial reactors. A key requirement of any synthetic route is the formation of $< 0.1\%$ double bond migrated impurities (i.e., formation of *E*-4-decenyl acetate or *E*-6-decenyl acetate, which are known to be inhibitors in the PTB pheromone to the moths).[14] The reaction sequence to **9** is shown in Scheme 2.

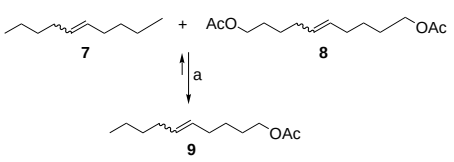
Catalysts **1**, **2**, **3**, **4**, and **6**[15] were screened for the cross metathesis reactions of 5-decene (**7**)[3,16] with 1,10-diacetoxy-5-decene (**8**)[17] to identify the optimal catalyst. Reactions were run with equal molar concentration of **7** and **8** using 0.2 mol % metathesis catalysts, at 45 °C, for 20 hours. Metathesis reactions produce equilibrium mixtures; therefore, using a 1:1 molar ratio of **7**:**8** will produce a maximum yield of 50% of **9**. Unreacted **7** and **8** are readily recovered by vacuum distillation and recycled. Figure 1 depicts the time course of the catalyst screening reactions.

Several interesting observations are seen from the data. First, **4**- and **6**-catalyzed reactions were completed within 10 minutes, while catalysts **1**, **2** and **3** yielded only 10.5% to 33.4% of **9** after 6 hours. Second, **4**- and **6**-catalyzed reactions rapidly formed impurities, 3.4% to 6.5% impurities after 10 minutes, and up to 17.5% impurities after 20 hours.[18]

Several techniques were investigated to maintain the high yield of **9** while keeping the impurity formation to a minimum. Ultimately, running the metathesis reaction at low temperatures proved to be successful. As depicted in Figure 2, cross metathesis of equal moles of **7** and **8**, neat, with 0.2 mol % catalyst **4**, at 5 °C for 18 hours produces a 49% yield of **9** with $< 0.1\%$ double bond migration impurity.

The low-temperature technique has been used in the synthesis of the Omnivorous Leafroller (OLR) pheromone, as described in Scheme 3. OLR is a pest of apples, grapes, pears, peaches, and nectarines. The OLR pheromone is an 82:18 ratio of *E*- to *Z*-11-tetradecenyl acetate (**14**).[19]

The synthesis of OLR pheromone is a particularly attractive target for metathesis because the metathesis reaction produces the pheromone with the desired isomeric (*E* to *Z*) ratio. The two starting materials, 3-hexene (**11**) and 11-eicosenyl acetate (**13**), were derived from commodity materials: **11** was produced by homo-coupling 1-butene (**10**), and **13** was produced from Jojoba oil (**12**). Starting material **12** is a seed oil used in



Scheme 2. Screening metathesis catalysts in the production of **9** by cross metathesis; a) equal molar ratio of **7** and **8**, 0.2 mol % metathesis catalyst, 45 °C, 20 h.

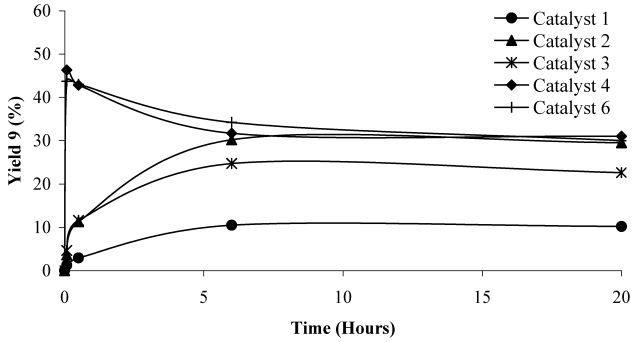


Figure 1. Formation of **9** by cross metathesis of **7**, 1.67 M, and **8**, 1.67 M, in CH_2Cl_2 with 0.2 mol % catalyst at 45 °C.

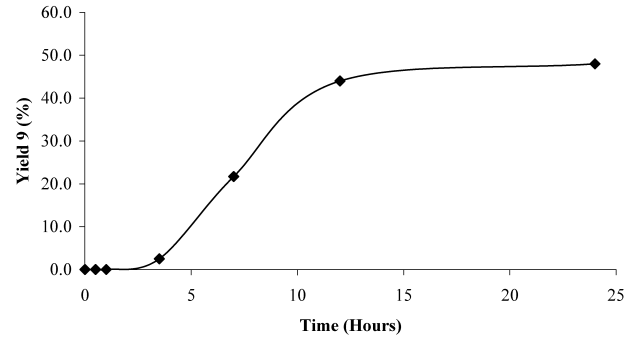
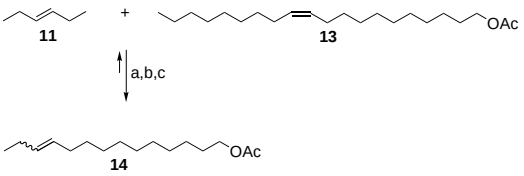
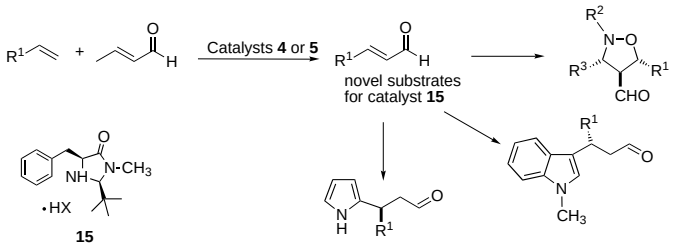


Figure 2. Formation of **9** by cross metathesis of neat **7** and **8** (1:1 mole ratio) with 0.2 mol % catalyst **4** at 5 °C.



Scheme 3. Formation of **14** by cross metathesis: a) 5 °C, 0.2 mol % catalyst **4** to **13**, 4:1 mole ratio of **11:13**, 16 h, 84% conversion; b) TKC, $NaHCO_3$, 70 °C, 20 h; c) vacuum distillation, 50% yield, > 95% purity.



Scheme 4. Efficient cross metathesis routes into novel substrates for **15**.

the cosmetic industry and primarily comprises a mixture of oleyl, eicosenyl and docosenyl esters, with ~60% of the oil being the 11-eicosenyl moiety. Reduction, purification, and acetylation of **12** produce **13** in high yields. Cross metathesis of **11** and **13** (4:1 mole ratio) produced an 84% yield of **14**. The metathesis catalyst was removed by the *in-situ* formation of tris(hydroxymethylphosphine) (THP)[4] from tetrakis(hydroxymethyl)phosphonium chloride (TKC), followed by vacuum distillation of **14** in 50% overall yield and > 95% purity. This methodology has been the basis for the continuing scale-up efforts related to the commercialization of **9** and **14**.

Pharmaceuticals and Intermediates

The demand for chiral intermediates and drugs has grown rapidly over the past several years. Chiral drugs represent almost one third of all drug sales worldwide.[20] The demand for single enantiomer molecules for commercial applications has accelerated the development of asymmetric catalysis. Recently David W.C. MacMillan of Caltech has developed a new and novel class of asymmetric metal-free organic molecules. MacMillan's group has developed imidazolidinone-based chiral organocatalysts that exhibit broad reaction class capabilities and routinely produce chiral products in > 90% ee and > 85% yields.[21] MacMillan's imidazolidinone-based catalysts, (2*S*,5*S*)-2-(*t*-butyl)-3-methyl-5-(phenylmethyl)-4-imidazolidinone (catalyst **15**), trade named OrganoCatalysis™, uses α,β-unsaturated aldehydes as key substrates in these reactions.[21,22,23,24]

Cross metathesis is a powerful tool to produce α,β-unsaturated carbonyl-containing molecules,[6,7] many of which are difficult to prepare by traditional synthetic techniques. Cross metathesis offers complementary technologies to MacMillan's asymmetric organocatalysts, see Scheme 4. Asymmetric metal-free organocatalyst-catalyzed reactions offer several advantages over their transition metal-containing counterparts. Advantages include that the reactions are run under aerobic conditions and in polar protic solvents, they are inexpensive and stable and there is no disposal of toxic metal waste.

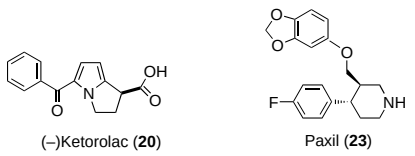
Organocatalysts have been around for over 40 years. In 1960 the first organocatalytic reaction was reported by Pracejus,[25] who described quinuclidine-catalyzed methanolysis of ketenes. In the 1970's Hajos[26] reported proline-catalyzed intramolecular aldol reactions. More recently List[27] and Barbas[28] developed organocatalyst reaction conditions that yield products with up to 97% ee. Numerous groups have developed and examined asymmetric organocatalyst reactions; their work will not be covered here, refer to Dalko[29] for an excellent review of enantioselective organocatalysis. Even though organocatalysts have numerous advantages over their metal-containing counterparts, a major drawback is that they work well for only a relatively small class of substrates. MacMillan's asymmetric imidazolidinone catalyst overcomes this drawback.

Attractive pathways to pharmaceutical intermediates available from cross metathesis and OrganoCatalysis™ include chiral 1,3-nitrone additions, indole alkylations and pyrrole alkylations, as recently described by MacMillan.[19,22] Two attractive targets are the enantiomeric synthesis of (−)Ketorolac (**20**) and Paxil (**23**), which are depicted in Scheme 5.

Compound **20** is a non-steroidal anti-inflammatory drug (NSAID) and is the primary drug used in post-operative pain prevention. [Racemic Ketorolac is marketed in the Unites Stated under the trade names of Acular by Allergan and Toradol IM by Roche.] It is currently marketed as the racemate with the (+)-enantiomer being associated with undesirable gastrointestinal side effects.[30] Therefore an enantiomerically pure synthesis of **20** would be valuable in increasing patient comfort by reducing side effects.

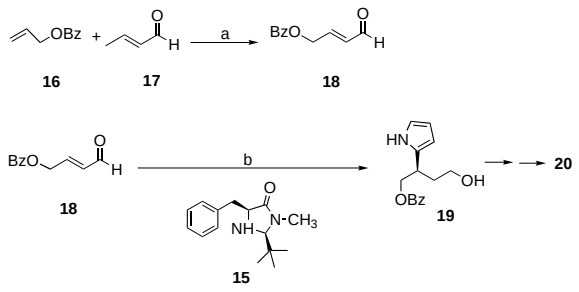
Compound **23**[31] is a selective serotonin (5-HT) reuptake inhibitor with a market value of US $2.4 billion per year. [Paxil (Paroxetine) is marketed in the Unites Stated under the trade name Seroxat by Glaxo Smith Kline.] Having an efficient and enantioselective route to **23** would position one for a share of the generic drug market, when **23** goes off patent.

The key synthetic steps to **20** are depicted in Scheme 6. 4-(Benzoyloxy)-2-butenal (**18**) was produced in 63% yield in 30 minutes by the cross-metathesis of allyl benzoate (**16**) and crotonaldehyde (**17**) with catalyst **5**.[32,33,34] Repeating the experiment with catalyst **4**

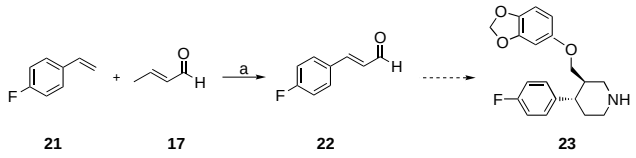


(–)Ketorolac (**20**) Paxil (**23**)

Scheme 5. Structures of (−)Ketorolac (**20**) and Paxil (**23**).



Scheme 6. Synthesis of 4-(benzoyloxy)-3-pyrrole-2-butanol (19). a) 5.0 mol % catalyst 5, RT, 30 min, 68%; b) (i) pyrrole, 20 mol % catalyst 15 dichloroacetic acid; (ii) sodium borohydride, 82% yield, 92% ee.



Scheme 7. Synthesis of **22.** a) 2.5 mol % catalyst **5**, 5 equivalents of **17**, 40 °C, 4 h, 73% isolated yield.

produced < 30% yield of **18** after 6 hours. A metathesis route to **18** was desirable over the conventional synthetic route.[35] Conversion of **18** to (3*S*)-4-(benzoyloxy)-3-pyrrole-2-butanol (**19**) was accomplished by using the dichloroacetic acid salt of (2*S*,5*S*)-5-benzyl-2-*t*-butyl-2-methyl-3-methyl-4-imidazolidinone (catalyst **15**), followed by sodium borohydride reduction (82% yield and 91% ee). Compound **19** has been converted to **20** and will be reported shortly by MacMillan.[36]

Another synthetically useful pharmaceutical target is *p*-fluorocinnamaldehyde (**22**). **22** is a potential key intermediate in the synthesis of Paxil (**23**), see Scheme 7.

Unsatisfactory yields of **22** were obtained by a conventional synthetic methodology.[37] But **22** was synthesized efficiently by the cross metathesis of *p*-fluorostyrene (**21**) with 5 equivalents of **17** in 73% yield, using catalyst **5**. Under the same conditions, the use of catalyst **4** produced mainly *p,p'*-difluorostilbene (52% yield). Work is under way to complete the synthesis of **23** from **22**. Other groups have also reported similar reactivity variations between catalyst **4** and **5**.[38] The differences in the catalyst specificities are presumed to be associated with the presence of the tricyclohexylphosphine, which inhibits productive metathesis of certain electron-poor olefins.

Conclusion

In this paper we have described the efficient syntheses of several agrochemical and pharmaceutical compounds *via* olefin cross metathesis methodology. The syntheses of insect pheromones **9** and **14** were demonstrated without solvent from the cross metathesis of commodity starting materials. We also described low-temperature reaction conditions that prevent impurity formation (arising from double-bond migrations) and the use of an efficient metathesis catalyst removal agent. We further demonstrated improved syntheses of two important pharmaceutical intermediates by tandem cross metathesis and organocatalysis reactions. This combination of techniques greatly reduces the number of steps required to directly produce chiral pharmaceutical intermediates, typically without the need for a chiral resolution step. These examples demonstrate that olefin cross metathesis is a powerful synthetic tool to produce carbon-carbon double bonds. In the past decade, olefin metathesis has had a huge influence on the field of organic chemistry and rarely has a new catalyst technology been so eagerly accepted and used. It will be exciting to see what another decade of olefin metathesis will yield.

Experimental Section

The following materials were used without further purification: 5-hexen-1-ol was purchased from CreaNova, 5-hexen-1-ol was converted to 5-hexen-1-yl acetate under standard acetylation conditions, 1-hexene was purchased from BP Amoco, **10** was purchased from Aeriform, Ester X [also known as sodium bis(2-methoxyethoxy)aluminum hydride] was purchased from Rohm and Haas, TKC was purchased from Cytec and **12** was purchased from Desert King International.

5-Decenyl Acetate (9)

To a 3-L flask was added 1.00 kg (3.8 mol, 97%) **8**, 0.53 kg (3.8 mol) **7**[4] and 100 mg of BHT. The solution was cooled to 5 °C and sparged with argon for 20 minutes. Catalyst **4** (6.44 g, 7.6 mmol, 0.2 mol %) was added, the flask was sealed with a rubber septa and stirring was continued for 20 hours. GC analysis indicated a 49% yield of **9** with < 0.1% double bond migrated impurities. The metathesis catalyst was removed with THP as described below. Compound **7** was removed by rotovap under high vacuum,[16] the remaining solution was flashed distilled followed by packed bed vacuum distillation using a 2 in × 36 in distillation column packed with 0.16 in stainless Pro-Pak™ distillation packing. Product **9** (677 g, 3.42 mol, 45% isolated yield in > 98% chemical purity) was collected at 0.20 mmHg over a boiling point range of 75 °C to 78 °C, in an 84:16 *E:Z* isomeric ratio.[39] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3H, C<u>H</u>$_3$), 1.34 (m, 6H, C<u>H</u>$_2$), 1.58 (m, 2H, C<u>H</u>$_2$), 1.97 (m, 4H, =CH-C<u>H</u>$_2$), 2.02 (s, 3H, C<u>H</u>$_3$), 4.02 (t, 2H, -OC<u>H</u>$_2$), 5.38 (m, 2H, -C<u>H</u>=).

Metathesis Catalyst Removal Procedure: Synthesis of 1 M Solution of Tris(hydroxymethyl)phosphine (THP) in Isopropyl Alcohol

The metathesis catalyst was removed by complexing with THP[3,40] and extracting the metathesis catalyst-THP complex with water. To a 2-L round-bottomed flask was added 245 g (1.03 mol) tetrakis(hydroxymethyl)phosphonium chloride (TKC) and 500 mL isopropyl alcohol (IPA). This mixture was degassed with nitrogen for 20 minutes, potassium hydroxide (64 g, 1.03 mol, 90% purity, Aldrich) was added slowly over 30 minutes to the vigorously stirring solution, while under a nitrogen atmosphere (reaction is exothermic!). A white precipitate (KCl) forms immediately. After the potassium hydroxide has been added, the reaction was stirred for an additional 30 minutes. The content of the flask was diluted to 1 L by the addition of IPA. The THP mixture was stored in the refrigerator or used in the next step without further purification.

To a metathesis reaction was added at least 25 mole equivalents of THP per mole of ruthenium metathesis catalyst and stirred vigorously at 60 °C to 70 °C for 18 to 24 hours, under nitrogen. The color of the reaction will go from dark brown to faint yellow or colorless after 18 hours.

Nitrogen-degassed water (typically ~150 mL of water/L reaction mixture) was added and vigorously stirred for 10 minutes. Stirring was stopped and the phases separated. The bright orange aqueous phase was removed and 150 mL water again were added and stirred vigorously for 10 minutes. Again the phases separated and the aqueous phase was removed. This procedure was repeated until the aqueous phase was colorless, usually 2 to 3 washings. The organic phase was washed with 50 mL of 2.0 M HCl for 5 minutes (pH <1) and removed, followed by washing with 50 mL of sodium bicarbonate saturated water for 5 minutes (pH >7), removed and washed with brine. The solution is dried with anhydrous sodium sulfate.

3-Hexene (11)

A 5-L jacketed 3-necked flask was equipped with a magnetic stir bar, gas feeding tube and a packed bed column containing a dry ice condenser. Catalyst **4** (2.97 g, 0.0035 mol, 0.023 mol % based on **10** added) and toluene (240 g) were added. The flask was sparged with argon for 15 min, while being cooled to 15 °C. Compound **10** (gas) (841 g, 15.0 mol) was added by bubbling into the toluene solution over 10.5 hours. The rate of addition was such that the reaction temperature remained above 10 °C. After 10.5 hours, the packed bed column and the dry ice condenser were replaced with a Friedrich condenser. The Friedrich condenser was circulated with 0 °C coolant. The reaction flask was cooled to 10 °C. An argon purge with a flow rate of ~1 L/minute was maintained for 12 hours.[41]

The metathesis catalyst was removed by the *in-situ* generation of THP. TKC (80% purity, 20.80 g, 25 equivalent to catalyst) and $NaHCO_3$ (7.35 g, 25 equivalent to catalyst) were added to the solution. The chiller/heater controlling the jacketed flask was set to 40 °C and stirred for 18 hours. The reaction was cooled to 10 °C and washed with water (500 mL) and brine (500 mL) and dried over anhydrous Na_2SO_4. Compound **11** was isolated in 52% overall yield, (443 g, 5.27 mol, >99% purity) by atmospheric distillation (bp 66 °C to 71 °C) under argon, through a 2 in $\times$ 36 in Pro-Pak™ packed distillation column. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.98 (t, 6H, C<u>H</u>$_3$), 2.05 (m, 4H, C<u>H</u>$_2$-CH=), 5.44 (m, 2H, C<u>H</u>=C<u>H</u>).

11-Eicosenyl Acetate (13)

Refined grade **12** (5.3 kg, 8.7 mol) was placed in a 12-liter flask equipped with an overhead stirrer. A 70% solution of Ester X (2.8 kg, 9.6 mol) was slowly added into the reactor at a rate that kept the pot temperature below 50 °C. After complete addition of Ester X, the reaction was stirred for an additional two hours and then quenched with 4.0 L of 50% aqueous sulfuric acid. The organic layer was separated from the aqueous, washed with water and dried over sodium sulfate. GC analysis[42] showed the reaction mixture to be composed of 57.5% 11-eicosenol, 29.6% 13-docosenol, and 5.7% 9-octadecenol, with the remainder being trace amounts of smaller and larger fatty alcohols. 11-Eicosenol was purified by vacuum distillation (0.20 mmHg) using a 3-in $\times$ 36 in distillation column packed with 0.24 in stainless Pro-Pak™ distillation packing. 11-Eicosenol was collected over a boiling point range of 155 °C to 160 C. The chemical purity of 11-eicosenol by GC was determined to be >95%; yield: 2.7 kg (8.7 mol).

11-Eicosenol (2.7 kg, 8.7 mol) and acetic acid, (33 g, 0.55 mol) were warmed to 80 °C in a 12-L round-bottom flask. Acetic anhydride (931 g, 9.1 mol) was slowly added to the flask while the solution was vigorously stirred. On completion, the solution was heated to 100 °C, under nitrogen, for an additional 2 hours and then cooled to room temperature. GC analysis indicated >99% conversion to **13**.[42] The solution was washed twice with 2 L of water, once with 2 L of a saturated aqueous sodium bicarbonate solution and dried with anhydrous sodium sulfate, and filtered to yield 3.0 kg (8.5 mol) of **13** (80–95% yield based on eicosenyl fraction). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, 3H, C<u>H</u>$_3$), 1.28 (m, 26H, C<u>H</u>$_2$); 1.60 (m, 2H, C<u>H</u>$_2$), 1.97 (m, 4H, C<u>H</u>$_2$), 2.01 (s, 3H, C<u>H</u>$_3$), 4.05 (t, 2H, C<u>H</u>$_2$-O), 5.38 (m, 2H, -C<u>H</u>=). This material was used in the metathesis reaction without further purification.

11-Tetradecenyl Acetate (14)

Compounds **11** (443 g, 5.27 mol) and **13** (466 g, 1.32 mol) were added to a 2-L round-bottomed flask. The mixture was flushed with nitrogen for 15 minutes and cooled to 5 °C. Catalyst **4** (2.23 g, 2.6 mmol) was added and the mixture was stirred for 20 hours. GC analysis showed an 84% yield of **14** with <0.1% double bond migrated impurities.[43]

The metathesis catalyst is removed as described above for product **11**, except the reaction was heated to 60 °C for 20 hours. Product **14** was purified by packed-bed vacuum distillation (0.50 mmHg), collecting material over the boiling point range of 122 °C to 124 °C to yield 168 g (0.66 mol, 50% overall yield) chemical purity by GC was >95%, with an isomeric ratio of 82.6% *E*-**14** and 17.4% *Z*-**14**.[43] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (t, 3H, C<u>H</u>$_3$), 1.42 (m, 14H, C<u>H</u>$_2$), 1.81 (m, 2H, C<u>H</u>$_2$), 1.96 (m, 4H, C<u>H</u>$_2$), 2.01 (s, 3H, C<u>H</u>$_3$), 4.16 (t, 2H, C<u>H</u>$_2$-O), 5.62 (m, 2H, -C<u>H</u>=).

4-(Benzoyloxy)-2-butenal (18)

To a 50-mL round-bottomed flask was added 1.0 g (0.20 mmol) **16**, 5.1 mL (6.20 mmol) **17** and 10 mL dry toluene. The reaction mixture was sparged with argon for 10 minutes. Catalyst **5** (19 mg, 0.03 mmol) was added and stirred at room temperature for 30 minutes to afford **18** in 68% yield by GC, 9% crotonyl benzoate, and 7% **16**. The reaction was concentrated under reduced pressure and purified by silica gel chromatography (25% ethyl acetate in hexane) to yield 730 mg (3.85 mmol) of **18**.[35] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.11$ (d, 2H, C$\underline{H}_2$-O), 6.40 (dd, 1H, OHC-C$\underline{H}$=), 6.95 (dq, 1H, CH=C$\underline{H}$-CH$_2$), 7.48 (m, 2H, *meta*-H), 7.62 (m, 1H, *para*-H), 8.09 (d, 2H, *ortho*-H), 9.65 (d, 1H, C$\underline{H}$O).

4-(Benzoyloxy)-3-pyrrole-2-butanol (19)

To a 100-mL round-bottom flask equipped with a magnetic stir bar was added catalyst **15** (246.35 mg, 1.00 mmol, 0.2 equiv. based on **18**) and chloroacetic acid (94.5 mg, 1.0 mmol, 1.0 equiv. based on **15**). The two solids were dissolved in 8.05 mL of purified diethyl ether and 0.975 mL of water. The solution was stirred at −30 °C for 5 minutes, pyrrole (1.74 mL, 25.05 mmol, 5.0 equiv. to **18**, freshly distilled from CaH_2) was added *via* a syringe. The reaction was stirred for another 5 minutes to bring the solution back to −30 °C. Aldehyde **18** (951 mg, 5.0 mmol, 1 equiv.) was added by syringe as a solution in 0.5 mL of diethyl ether. The reaction was stirred at −30 °C and monitored by TLC (70% hexane, 30% ethyl acetate, *p*-anisaldehyde stain) until **18** was consumed. The reaction was warmed to 0 °C and approximately 25 mL of absolute ethanol were added, followed by $NaBH_4$ (812 mg, 0.756 mmol, 0.38 equiv.). The reaction was stirred at 0 °C for 15 minutes. The mixture was added to a separatory funnel and water saturated $NaHCO_3$ was added until gas evolution ceased (about 30 mL total). The product was extracted with 4 × 25 mL of CH_2Cl_2. The organic phases were combined and washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to give the crude product. Column chromatography (70% hexane/30% ethyl acetate) gave **19** as an oil which solidified on standing to a white solid (1.03 g, 80% yield, 92% ee).[36] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.0$ (m, 2H, C$\underline{H}_2$-CH$_2$OH), 3.38 (m, 1H, chiral proton), 3.65 and 3.75 (2H, m, C$\underline{H}_2$OH), 4.5 (2H, s, C$\underline{H}_2$-OBz), 6.05 (1H, m, pyrrole C-$\underline{H}$), 6.05 (1H, m, pyrrole C-$\underline{H}$), 6.15 (1H, m, pyrrole C-$\underline{H}$), 6.70 (1H, m, pyrrole C-$\underline{H}$), 7.45 (2H, m, aromatic), 7.55 (1H, m, aromatic) 8.00 (2H, m, aromatic), 8.45 (1H, bs, pyrrole N-$\underline{H}$). Enantiomeric excess was determined by normal phase HPLC using a Chiracel OD 0.46 cm ID × 25 cm column, mobile phase was 10% 2-propanol in *n*-hexane. The retention times were 19.086 min (minor enantiomer) and 20.727 min (major enantiomer).

p-Fluorocinnamaldehyde (22)

To a 50-mL round-bottomed flask was added 1.22 g (10.0 mmol) **21**, 3.4 g (48.6 mmol) **17** and 20 mL methylene chloride. The reaction mixture was sparged with argon for 15 minutes. Catalyst **5** (0.156 g, 0.25 mmol, 2.5 mol %) was added and stirred at 40 °C for 4 hours. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (15% of ethyl acetate in hexane) to yield 1.09 g (7.30 mmol) **22** in 73% yield and 98% purity. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.61$ (dd, 1H, =C$\underline{H}$-CHO), 7.03 (t, 2H, *meta*-H), 7.48 (d, 1H, Ph-C$\underline{H}$=), 7.54 (dd, 2H, *ortho*-$\underline{H}$), 9.65 (d, 1H, C$\underline{H}$O); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 116.53$ (*meta*-carbons, $J_{CCF} = 22.0$ Hz; 128.48 (C$\underline{H}$=CHO), 130.45 (*epi*-carbons), 130.64 (*ortho*-carbons), 151.53 (Ph-C$\underline{H}$=), 164.50 ($J_{CF} = 251.0$ Hz), 193.56 (C$\underline{H}$O).

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[16] **7:** bp 31 °C to 32 °C at 1.0 mmHg, isolated in 60% to 70% yields; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, 6H, $C\underline{H}_3$), 1.26 (m, 8H, $C\underline{H}_2$), 2.05 (m, 4H, $C\underline{H}_2$-CH=), 5.38 (m, 2H, C<u>H</u>=C<u>H</u>).
[17] Compound **8** was produced by homocoupling neat 5-hexenyl acetate with 0.2 mol % catalyst **2** or **3** under 30 mmHg vacuum, heated to 35 °C for 18 hours. The metathesis catalyst was removed as described in the synthesis of **9**. Product **8** was purified by vacuum distillation, bp 106 °C to 108 °C at 0.30 mmHg, 80% to 85% isolated yields, as a 4:1 mixture of *E:Z* isomers (see ref.[39] for GC conditions and results). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (m, 4H, =CH-CH_2-C$\underline{H}_2$-), 1.56 (m, 4H, =CH-C$\underline{H}_2$-CH_2-), 1.95 (m, 4H, -C$\underline{H}_2$-CH_2-O), 1.98 (s, 6H, $C\underline{H}_3$), 3.98 (overlapping triplets, 4H, -C$\underline{H}_2$-O), 5.32 (m, 2H, =C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.61$, 25.60, 25.76, 26.53, 27.86, 27.99, 31.88, 63.95, 63.98, 129.28, 129.83, 170.29.
[18] The major impurities were *E,Z*-4-decenyl acetate, *E,Z*-6-decenyl acetate, *E,Z*-4-nonenyl acetate, *E,Z*-5-nonenyl acetate, *E,Z*-5-undecenyl acetate and *E,Z*-6-undecenyl acetate. These impurities were synthesized and co-injected to verify compounds or characterized by GC-MS.
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[41] This set-up allows **10** to be removed with $< 10\%$ loss of **11**.
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nute; ramp rate 25 °C/minute to 240 °C, hold 10 minutes. Oleyl alcohol Rt 6.103 min; 11-eicosenol Rt 6.920 min; 13-docosenol 8.007 min; oleyl acetate Rt 6.548 min; **13** Rt 7.499 min; 13-docosenyl acetate 8.249 min.

[43] GC analysis with FID detector and J&W DB-225™ column 30 m × 0.25 mm (ID) × 0.25 μm film thickness. GC conditions: Initial temperature 100 °C, hold 0 minute; ramp rate 25 °C/minute to 200 °C, hold 15 minutes. **11** (*E*-isomer) Rt 8.24 min and **11** (*Z*-isomer) Rt 8.38 min.