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Olefin Metathesis

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Concise Syntheses of Insect Pheromones Using *Z*-Selective Cross Metathesis**

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The use of insect sex pheromones to limit specifically targeted pest populations has gained increasing popularity as a viable, safe, and environmentally friendly alternative to insecticides. While broad-spectrum insecticides are toxic compounds that have been shown to adversely affect human health,[1] extensive studies have shown that insect pheromones are nontoxic and safe for human consumption at the levels used in pest control practices.[2] Female sex pheromones are mainly employed in pest control in a process termed mating disruption. This involves dispersing pheromones over a large area, overloading the sensory organs of male insects and preventing them from locating and mating with females who are releasing a much smaller amount of the same pheromone blends; this strategy has proven to reduce specific insect populations dramatically.[3] To date, the United States Environmental Protection Agency (EPA) has approved approximately twenty lepidopteran female sex pheromones as active ingredients for pest control.[2]

The lepidopteran order of insects includes extensive families of butterflies and moths whose larvae can devastate critical and valuable crops; it is estimated that insects destroy approximately 13% of food crops in the United States each year.[1] The majority of known lepidopteran sex pheromones are straight-chained hydrocarbon acetates, alcohols, and aldehydes containing one to three double bonds with various olefin geometries. The facile formation of *trans*-olefin-containing pheromones using olefin metathesis has been reported, however the efficient synthesis of *cis*-olefin-containing pheromones has remained a challenge.[4] Current routes to such species involve wasteful processes, including the Lindlar hydrogenation of alkynes and Wittig reactions, among others.[5] Because of difficulty in completely removing the palladium hydrogenation catalyst and the high toxicity of the lead reagent necessary to prevent overreduction, the Lindlar hydrogenation of alkynes is not an optimal route to *Z* olefins. Similarly, the Wittig reaction is not ideal because of the use of stoichiometric reagents and difficulty in removing phosphine oxide by-products.

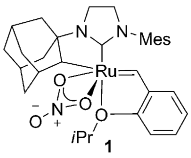

Figure 1. Previously reported chelated catalyst for *Z*-selective olefin metathesis (**1**). Mes = 2,4,6-trimethylphenyl.

A family of functional-group-tolerant, ruthenium-based, *Z*-selective metathesis catalysts was recently disclosed and a monounsaturated *cis*-olefin-containing pheromone was synthesized using the optimized nitrato-type catalyst **1** (Figure 1). Catalyst **1** has been shown to be an improvement over previously reported carboxylate-substituted catalysts in terms of activity, stability, and selectivity.[6] We desired to further demonstrate the efficacy of **1** by synthesizing a set of insect pheromones with diverse functionality, while simultaneously investigating the reactivity of catalyst **1** in more complicated cross metathesis reactions.

Nine lepidopteran female sex pheromones currently approved by the EPA as insecticide alternatives were chosen as synthetic targets, and it was proposed that the chosen species could be formed at ambient temperatures from renewable and commercially available chemicals with a minimal amount of steps and low catalyst loadings of **1**. Alcohol-substituted species were chosen as substrates because simple manipulations, such as acetylation or oxidation, could be subsequently carried out to produce the desired pheromones. It is envisioned that the methods developed could be elaborated to quickly synthesize other well-studied insect pheromones containing *cis* olefins not yet approved by the EPA for pest control.[7]

We proposed that a number of the pheromone targets could be synthesized by the *Z*-selective cross metathesis of various terminal olefins with the seed-oil derivatives oleyl alcohol (**2**) and 11-eicosenol (**4**). These long-chain primary alcohols contain one 1,2-disubstituted *cis* double bond and are obtained by the transesterification and reduction of a number of seed oils, including canola and jojoba oil. The metathesis of seed oils offers new synthetic routes to high-value products from renewable resources with high chemoselectivity.[8] Currently, plant oils are a particularly important renewable raw material for the chemical industry, and products derived from them are used heavily as surfactants, cosmetic products, and lubricants.[9] We envisioned that using these alcohol-substituted starting materials would provide simple, cheap, and renewable routes to high-value insect pheromones.

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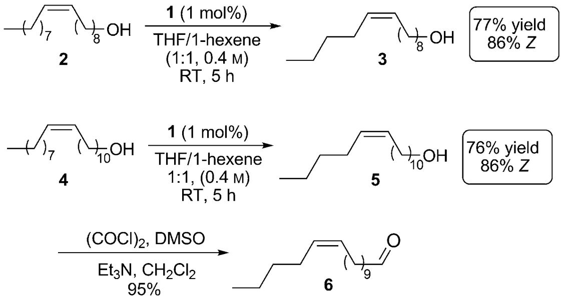


Scheme 1. Syntheses of pheromones **3** and **6**. DMSO = dimethyl sulfoxide.

We found that 1-hexene could be reacted with the aforementioned seed-oil derivatives in the presence of catalyst **1** (1 mol%) to give the desired cross products in good yields with high *cis* selectivity (Scheme 1). The reaction of 1-hexene with oleyl alcohol directly produced **3** in 77% yield and with 86% of the *Z* olefin. The corresponding product (**5**) derived from 11-eicosenol was obtained in 75% yield and with 86% *Z* olefin, and was subsequently oxidized under Swern conditions to provide pheromone **6**. The syntheses reported here are the shortest routes to form pheromones **3** and **6**.[5]

In order to investigate the mechanism of formation of pheromone cross products, the reaction of 1-hexene and oleyl alcohol (**2**) to produce **3** was monitored over time using quantitative ^{13}C NMR spectroscopy (Figure 2).[10] As shown, **2** quickly converts to the terminal olefin, 9-decenol, through an ethenolysis reaction. Formation of a ruthenium methylidene is thus required and we proposed that this species was generated from homodimerization of 1-hexene. The resulting 9-decenol then slowly reacts with 1-hexene to produce the desired pheromone cross product **3**; the *cis*:*trans* ratio of **3** was also monitored and did not change to any appreciable extent over the course of the reaction. It is proposed that internal olefins cannot react directly to produce the desired cross products, but must first be converted to the corresponding terminal olefins through ethenolysis, and only then can they undergo a cross metathesis reaction with another terminal olefin. In order to test this assertion, the internal olefins *cis*-5-decene and **4** were reacted in the presence of catalyst **1** to produce compound **5**. If the proposition was true, since a methylidene cannot be formed because of the absence of ethylene and terminal olefins, there should be no conversion to the desired cross product because the internal olefins cannot be degraded. Indeed, reacting the two internal olefins for up to 19 hours led to no formation of **5**, as monitored by gas chromatography. We believe that this is a general feature of cross metathesis reactions catalyzed by **1** and is possibly a result of the high steric demands associated with forming trisubstituted ruthenacyclobutane intermediates.

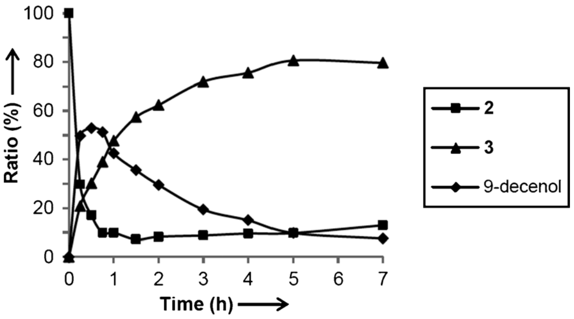
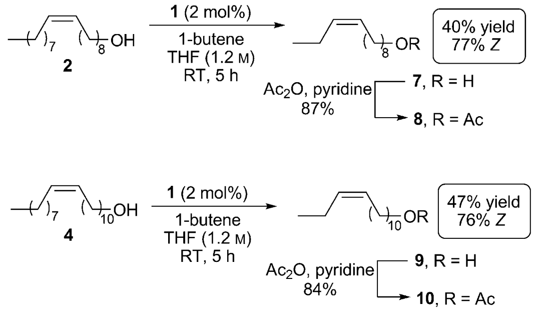


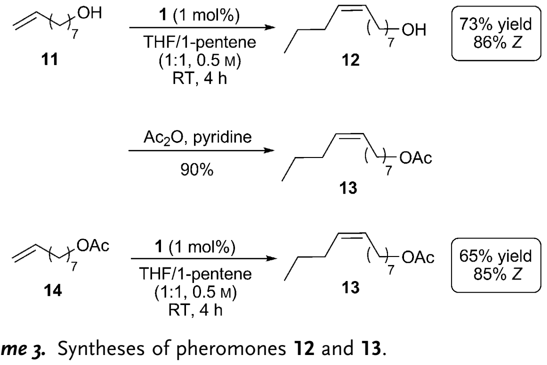
Figure 2. Time–course experiment monitoring relative amounts of **2**, 9-decenol, and the desired pheromone **3**.

Cross metathesis of the same seed-oil derivatives with 1-butene proved to be more difficult than with 1-hexene (Scheme 2). As with all reactions presented in this study, generated ethylene must be allowed to escape in order to obtain reasonable conversions, so a fixed amount of the gaseous substrate was not used. The optimal conditions involved slow bubbling of 1-butene into the reaction solution and slightly higher catalyst loading of **1** (2 mol%). Reaction with oleyl alcohol and 11-eicosenol followed by acetylation of the cross products led to formation of pheromones **8** and **10** in modest yields (40–47%) and slightly reduced *cis* selectivity (76–77%).[11] A significant amount of the corresponding terminal olefins derived from ethenolysis of **2** and **4** were detected, suggesting that the lower yields are a result of the inability of 1-butene to efficiently react with the terminal olefins under the conditions tested.[12]



Scheme 2. Syntheses of pheromones **8** and **10**.

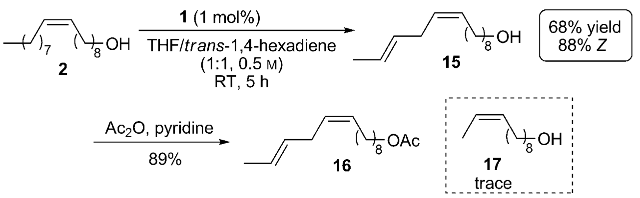
Cross metathesis of the terminal olefins 8-nonenol and 1-pentene led to formation of pheromone **12** in good yield (73%) with high *cis* selectivity (86%; Scheme 3). Subsequent



Scheme 3. Syntheses of pheromones **12** and **13**.

acetylation of **12** provided pheromone **13** in 90 % yield. Compound **13** was alternatively synthesized by the direct reaction of 8-nonenyl acetate and 1-pentene, proceeding in analogous overall yields ($\approx 65\%$) and *Z* selectivities ($\approx 85\%$) when compared to the above two-step sequence. The reaction of 1-pentene with 8-nonenol resulted in slightly higher yields compared to the reaction with 8-nonenyl acetate, which is likely a result of the higher selectivity that alcohol-containing substrates exhibit for formation of the desired cross products.[13] Regardless, it has been demonstrated that *Z* olefins with acetate functionality can be easily prepared using catalyst **1**. The successful use of functionalized terminal olefins in this methodology is attractive because of the wide variety of commercially available α-olefins that contain alcohol and acetate functional groups.

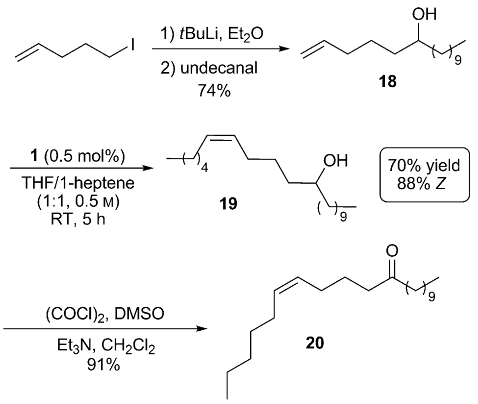
We next attempted to synthesize a pheromone containing an unconjugated diene and found that the *Z*-selective cross metathesis of oleyl alcohol and *trans*-1,4-hexadiene using catalyst **1** led to selective formation of compound **15**, which was subsequently acetylated to give pheromone **16** (Scheme 4). Previously reported syntheses of **16** require at least six steps from commercially available starting materials.[14] We were able to form **16** starting from renewable and commercially available reagents in two steps with good overall yield (60 %) and high *cis* selectivity (88 %). It should be noted that only trace amounts of products derived from metathesis of the internal double bond of the *trans*-1,4-hexadiene starting material, such as compound **17**, were detected. Despite significant research efforts, the selective synthesis of unconjugated and conjugated dienes using previous generations of metathesis catalysts has remained difficult.[15] This is the first example of the cross metathesis of an unconjugated diene that exhibits chemoselectivity based on olefin geometry.[16] The observed chemoselectivity suggests that this strategy could be a powerful and general tool to construct (*E*,*Z*) dienes. The selective formation of **15** over **17** seems to be a consequence of the inability of **1** to react with 1,2-disubsituted *trans* olefins. Because it has been proposed that all internal olefins must first undergo an ethenolysis reaction before they can react further, the observation that *trans* olefins are unreactive suggests that catalyst **1** could be a capable *Z*-selective ethenolysis catalyst.[17]



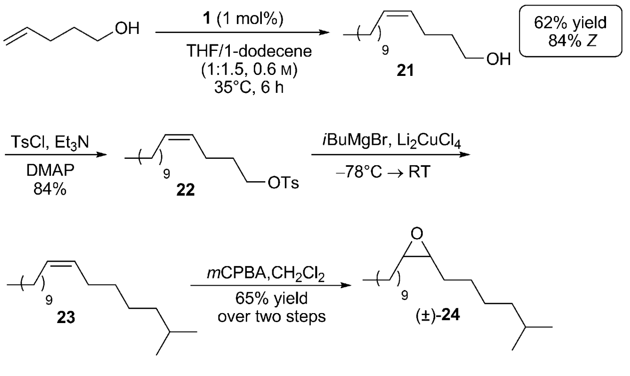
Scheme 4. Synthesis of pheromone **16**.

Two of the synthetic targets do not follow the general definition of lepidopteran insect pheromones; the major component pheromone (**20**) of the Douglas fir tussock moth contains ketone functionality, while the gypsy moth pheromone disparlure (**24**) contains an epoxide. We proposed that both pheromones would require more involved syntheses compared to the above compounds, but could be readily accessible using *Z*-selective metathesis methodology.

A number of syntheses of **20** have been reported using as few as four steps, however, construction of the *cis* olefin was predominantly achieved by the semireduction of alkynes with a Lindlar catalyst, or the Wittig reaction.[18] Our synthesis of **20** was carried out as shown in Scheme 5. Secondary alcohol **18**, which was formed by addition of 4-pentenyl lithium to 10-undecenal, was reacted with 1-heptene in a *Z*-selective cross metathesis reaction with 0.5 mol % catalyst loading of **1** to give **19** in good yield (70 %) with high *Z* selectivity (88 %). Compound **19** was then oxidized to the desired ketone-containing pheromone **20** using a Swern reaction. Pheromone **20** was thus obtained in three steps from commercially available starting materials, in 47 % overall yield and 88 % of the *Z* olefin.



Scheme 5. Synthesis of pheromone **20**.



Scheme 6. Synthesis of pheromone (±)-**24**. DMAP = 4-dimethylaminopyridine, *m*CPBA = *meta*-chloroperbenzoic acid, Ts = 4-toluenesulfonyl.

Many routes to enantiopure **24** have been reported, and have led to the determination that (+)-**24** is significantly more active than (−)-**24** as a chemical attractant. Despite this observation, the racemic form (±)-**24** has been shown to disrupt mating as effectively as (+)-**24** and is extensively employed in pest control practices.[19] Multiple reported syntheses of (±)-**24** exist and require no fewer than four steps.[5h,20] Our synthesis was carried out as shown in Scheme 6. First, cross metathesis of 4-pentenol and 1-

dodecene afforded **21** in moderate yield (62%) and high *Z* selectivity (84%).[21] Alcohol **21** was tosylated and reacted with isobutylmagnesium bromide to produce the desired alkyl intermediate **23**.[22] Subsequent epoxidation of **23** with *m*CPBA gave (±)-**24** in four steps from commercially available starting materials.

Current industrial syntheses of (±)-**24** similarly proceed through epoxidation of alkyl intermediate **23**, which can be formed either by Wittig or acetylenic routes.[5h] Use of the Wittig reaction on an industrial scale is generally difficult because of the large amount of phosphine oxide by-products that must be removed, and problems cooling the reaction mixture enough to promote adequate *cis* selectivity. Still, (±)-**24** can be formed in five steps with 60% overall yield and 88% *Z* olefin using this route. The industrial-scale synthesis of (±)-**24** using the poisoned hydrogenation of a disubstituted acetylene can be completed in four overall steps with 98% *Z* olefin. However, on an industrial scale, forming disubstituted acetylenes can be expensive and requires the use of large amounts of liquid ammonia. In addition, temperature control can be a problem and lead to incomplete reduction, and migration of double bonds and isomerization can occur, thus leading to impurities. The use of metathesis as the key step to form (±)-**24** is attractive because cheap α-olefins can be used, unreacted starting material can be recycled, and all reactions can be run at mild temperatures. It is envisioned that all of the synthetic routes outlined above can be adapted for large-scale syntheses.

In summary, the facile synthesis of nine lepidopteran female sex pheromones has been achieved using ruthenium-based *Z*-selective olefin metathesis. These pheromones are approved by the EPA as pest control agents, however, it is conceived that other analogous pheromones can be synthesized in a similar manner, further promoting their use as insecticide alternatives. The synthesis of these compounds provides valuable insight into the reactivity and selectivity of catalyst **1**, which is markedly distinct from previous generations of metathesis catalysts. The development of new *Z*-selective catalysts and operating on a larger scale should make this methodology even more selective and efficient. Compounds containing a variety of functional groups, including alcohols, acetates, aldehydes, ketones, and epoxides were easily prepared in a minimal number of steps from commercial sources, including several seed-oil derivatives; the syntheses of all pheromones described above are the most concise to date. It has been demonstrated that ruthenium-based *Z*-selective metathesis provides an attractive route to form complex internal olefins in good yields with high *cis* selectivity, and could emerge as a viable alternative to other popular methods used to form *cis* olefins, such as the partial hydrogenation of alkynes and the Wittig reaction.

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[10] See the Supporting Information for NMR conditions.

[11] Alternative methods, including pressurization of the reaction vessel with 1-butene, and a slow stream of 1-butene into the headspace of the reaction vessel, resulted in highly reduced yields and *Z* selectivity. The cause of this reduced *Z* selectivity is not known, but will be investigated in due course.

[12] A small amount of terminal olefin products derived from ethenolysis of the seed-oil derivatives was generated during the corresponding reaction with 1-hexene as well. The reaction of 9-decenol with 1-butene to produce **7** produced analogous yields and *Z* selectivities when compared to the reaction of oleyl alcohol and 1-butene.

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[21] The moderate yield is not surprising, given that the homodimerization of 4-pentenol has proven to be a difficult reaction. See Ref. [6c].

[22] It should be noted that species **23** resembles a number of monounsaturated, unfunctionalized hydrocarbon pheromones, and this synthetic route should enable facile access to such species. For an example, see: D. A. Carlson, M. S. Mayer, D. Z. Sihacek, *Science* **1971**, *176*, 174.