Investigations into the Selectivity of Olefin Cross-Metathesis Using Ruthenium Alkylidene Catalysts: Electronic and Steric Matching of Substrates

Thesis by

Arnab Kumar Chatterjee

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This journey at Caltech has been wonderful time in my life, but I feel like I have just started it. Perhaps this is because the spirit of Caltech, its people and surroundings will never leave me. The science comes and goes as I hope my contributions here are quickly overshadowed by even greater advances. However, the experiences from the people here is the most valuable part of my education. I really do consider myself one of the luckiest people alive and appreciate all the support that people here have given me.

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ABSTRACT

Olefin cross-metathesis (CM) is a thermodynamically controlled metathesis reaction that is governed by statistical product distributions and a mixture of olefin stereoisomers. In fact, while the reaction allows for the functionalization of α-olefins under mild conditions, it has not been used widely due to a lack of selective processes. The research effort disclosed here has provided some new solutions to the selectivity issues involved with CM. These include the use of olefins with altered steric and electronic properties allowing for selective olefin functionalization by CM. After an introduction to state-of-the-art CM in Chapter 1, the discussion continues with CM work in earlier generation ruthenium catalyst systems (Chapter 2). The next two chapters reveal new substrate scope in CM using more active ruthenium based catalysts developed in this group, including the synthesis of trisubstituted olefins (Chapter 3) and directly functionalized olefins (Chapter 4). Once discoveries in expanding substrate scope were accomplished, the final chapter outlines an empirical model for understanding the electronic and steric factors in CM selectivity across a variety of olefin metathesis catalysts. This model also provides a method to determine whether selective CM can be performed for target-oriented synthetic efforts. In addition, a better understanding of selectivity issues allows for the discovery of new reaction platforms and expands the synthetic utility of CM is discussed in Chapter 5.

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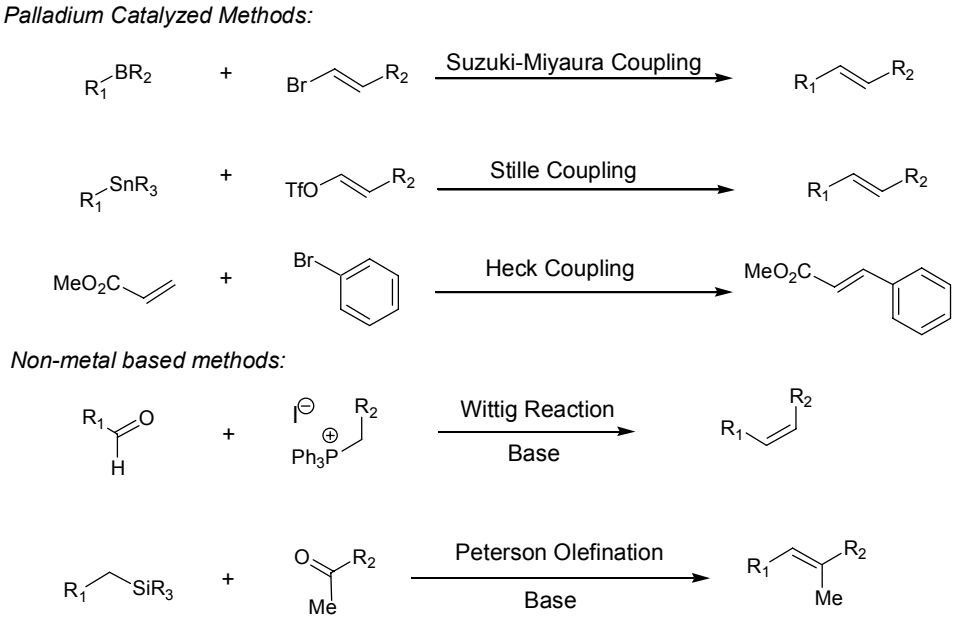
Chapter 1: Introduction to Olefin Cross-Metathesis (CM)

Efficient generation of diverse molecular structures and the efficient interconversion of functional groups are central to advancement of the chemical sciences. Olefins represent a highly versatile functional group that can be readily generated and transformed to other useful functional groups in a reliable manner, including epoxides, aziridines, and diols.[1] Alkenes are also a ubiquitous element in many complex organic molecules, and efficient installation of stereodefined olefins is a formidable challenge. For example, stereodefined tetrasubstituted olefins represent an unsolved problem in organic chemistry.[2] Because of the functional utility of olefins, a variety of intermolecular and intramolecular alkene forming methods exist. For palladium catalyzed methods, an activating group, which requires several steps to install, is usually required for the reaction to proceed (Scheme 1), such as aryl and vinylhalides and

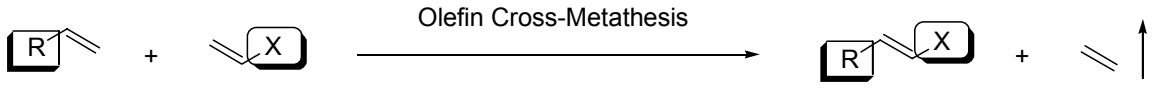


Scheme 1: Olefin Formation by Cross-Coupling

triflates. In addition, non-metal processes frequently employ reactive functional groups,

such as aldehydes and ketones. Once these reactive functionalities are introduced, the subsequent cross-coupling reactions are very reliable alkene C-C bond forming processes. In many cases, however, protective groups are required to mask these functional groups prior to their conversion to olefins, such as carbonyl protective groups. Another drawback to these traditional methods is the use of harsh reagents, such as triflic anhydride and brominating reagents, to prepare cross-coupling reagents. However, a conceptually different approach to olefin formation by cross-coupling would be through the exclusive use of α-olefins, where no change in oxidation state occurs and the only reaction byproduct is ethylene, namely, olefin cross-metathesis (CM).

Olefin cross-metathesis (CM) represents an alternative to the olefination methods described above, where olefins themselves are the reactive functional group (Scheme 2).

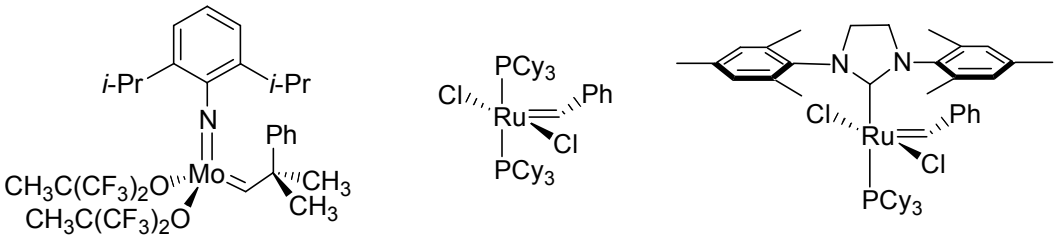


Scheme 2 : Direct Cross-coupling with Olefinic Starting Materials

This is particularly convenient since there are many commercially accessible α-olefin sources. In addition, CM could be used to install natural product relevant alkenes, similar to the ways that ring-closing metathesis (RCM) has been utilized by organic chemists to build naturally occurring carbocycles. However, CM also possesses the ability to append functional groups to olefins that can be used in subsequent reactions. In fact, CM may be able to install the functional groups used in other olefin formation processes described in Scheme 1, such as silyl, stannyl, and boryl functionalities. It is this rapid conversion of a α-olefin to useful functionalized synthons that provides CM with a unique opportunity,

unlike RCM and ring-opening metathesis polymerization (ROMP), to install both structural and functional elements. However, the major limitation of CM is controlling elements of selectivity and this is a formidable challenge for the utility of CM as a reliable synthetic method.

Olefin metathesis is a thermodynamically controlled reaction that has become a highly versatile synthetic method for access to alkene containing compounds. In fact, olefin metathesis chemistry has had a profound impact in several areas of synthetic organic chemistry; including organometallic chemistry,[3] polymer chemistry,[4] and small molecule synthesis.[5] Central to these synthetic accomplishments is the development of single-component transition metal catalysts that exhibit organic functional group tolerance (Figure 1). If selective reactions can be performed by a transition-metal



1 **2** **3**

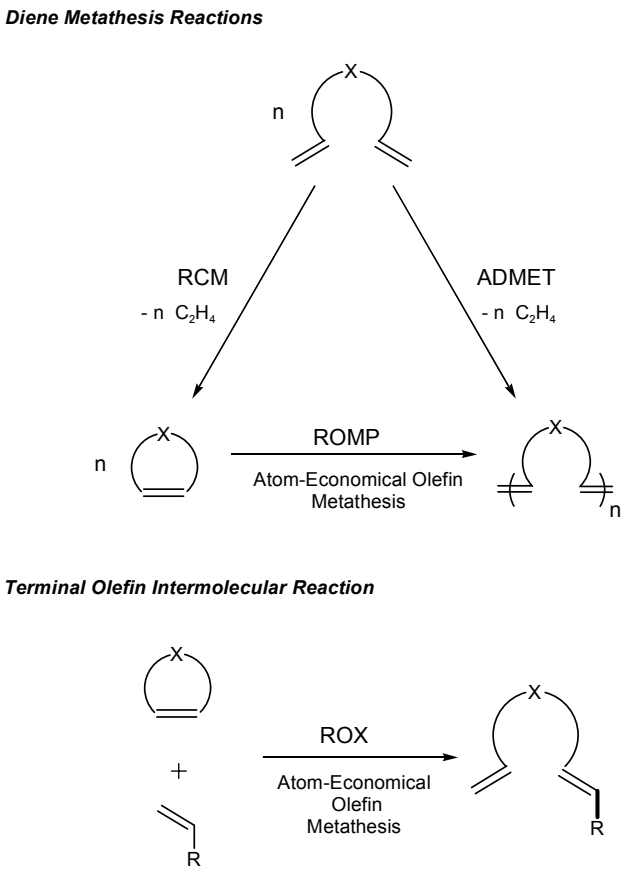
Figure 1 : Commonly Used Olefin Metathesis Catalysts

complex at olefinic sites, then a wide variety of applications are possible. This is a difficult challenge since a variety of metal-catalyzed processes are excellent at converting olefins to other functional groups, including a variety of oxidation processes.[1] The repeated demonstration of functional group tolerance provides synthetic chemists with the confidence to subject highly valuable materials to metathesis conditions. These applications are central to the success of any catalytic transition metal method. Historically, palladium-catalyzed cross-coupling reactions, such as Suzuki,[6] Stille,[7] and

Heck[8] reactions exhibit excellent functional group tolerance and have been rewarded by numerous applications in total synthesis. Fortunately, a diverse set of transition metal catalysts have been employed in functional group tolerant olefin metathesis reactions, with varied degrees of catalytic activity (Figure 1). The catalysts have been prevalent in complex organic synthesis. However, these systems have not been extensively applied to CM due to unresolved problems of selectivity.

Several representative examples of the most commonly used single-component homogeneous olefin metathesis catalysts are those listed in Figure 1. Earlier examples include commercially available alkoxy-amido molybdenum carbene catalyst **1**[9] and ruthenium-based catalyst **2**,[10] both have been used in a variety of metathesis reactions. Interestingly, both of these catalysts have developed a synergistic relationship in the metathesis literature. For example, while **1** has demonstrated greater catalytic activity than **2**, it is more difficult to handle in the presence of air and water, and can be poisoned by certain organic functional groups. Late transition-metal systems, such as catalyst **2**, have had been widely used in a variety of applications in organic chemistry. Even though catalyst **2** exhibits lower metathesis activity to that of **1**, catalyst **2** is less susceptible to decomposition by air, water, and organic functional groups. However, the apparent compromise between functional group compatibility and activity has been overcome with the recent development of catalyst **3**.[11] These imidazoylidene based systems have been discovered due to a more detailed understanding of the initiation of this family of catalysts. While still maintaining the characteristics of ease in handling and functional group compatibility, catalyst **3** possesses greater electron density at the metal center due to σ-donation from the imidazoylidene ligand. This factor, coupled with reduced π-

backbonding in imidazoylidene ligands versus phosphine, leads to greater preference for olefin binding and higher metathesis activity of these systems. This catalyst has been demonstrated to have higher activity in metathesis applications than **1** or **2**, and its use in selective CM is discussed below. All three of these catalysts, and related derivatives,[12] have been widely used in ring-closing metathesis (RCM),[13] ring-opening metathesis



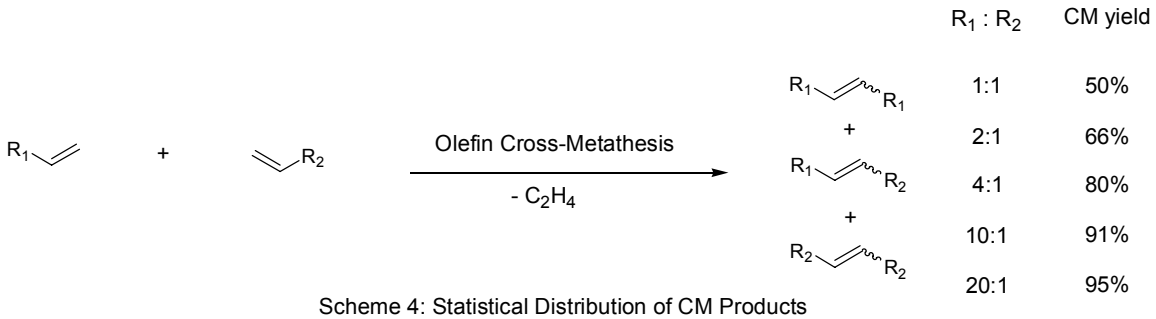
Scheme 3: Processes of Olefin Metathesis to Small and Large Organic Molecules

polymerization (ROMP),[14] acyclic diene metathesis polymerization (ADMET),[15] and ring-opening/cross-metathesis (ROX)[16] (Scheme 3). In addition, asymmetric variants of RCM[17] and ROX[18] have been reported with related ligands sets, illustrating another example of functional group tolerance in the generation of chiral functionalized olefinic compounds. The issues of functional group tolerance in other metathesis processes also

apply to CM, e.g., making olefins preferentially reactive in the presence of other functional groups, such as halides, aldehydes, alcohols. However, the challenge in CM is not merely the tolerance of these functional groups as has been demonstrated in RCM and ROMP synthetic endgames, but the participation of these functionalities in determining CM selectivity. Finally, the fact that CM will be more commonly used early in a synthetic scheme than any other metathesis process requires an efficient method to make functionalized olefins that are useful reagents for subsequent manipulations.

Despite the advances in olefin metathesis for RCM, ROMP, and ROX over the past several decades, CM has received significantly less attention in the literature. In fact, the dimerization of olefins resulting from an unsuccessful RCM reaction is often where the status of CM has been relegated to within the metathesis literature. However, the applicability of CM can not be mistaken, since it allows for the functional homologation of a variety of olefins in a single synthetic step using widely available olefinic precursors. A wide variety of unfunctionalized olefinic precursors are accessible from petrochemical and oleochemical[19] sources. Therefore, the conversion of these unfunctionalized olefins to functionalized ones is of great importance. Unfortunately, because CM is a simple intermolecular reaction governed by thermodynamics, several complications are inherent to the reaction. First, due to low catalytic activity and lack of selectivity in CM, a complex product mixture is often obtained (Scheme 4). For example, combining two olefins in equal stoichiometry that react with the catalyst at similar rates would result in only 50% of the desired CM product. In addition, both undesired homocoupling products would also be obtained as the mass balance in the reaction. For the development of a synthetically efficient reaction, 90% conversion of a

starting material to CM product, nearly 10 equivalents of the CM partner would be necessary. Additional complications arise when low catalytic activities do not



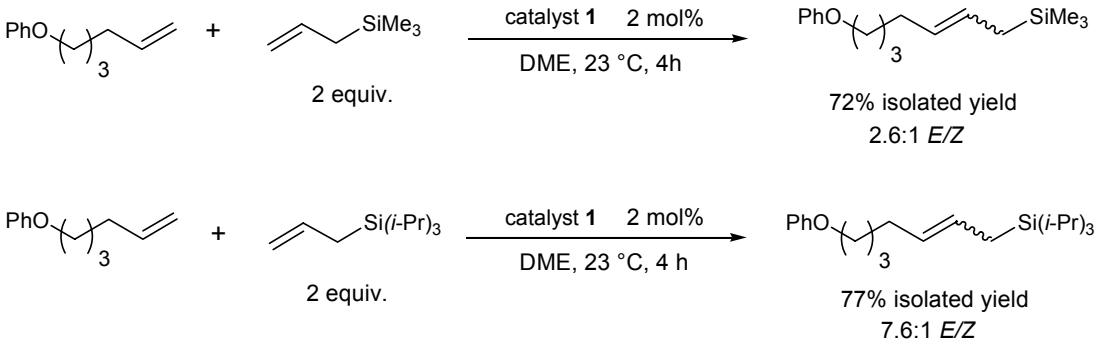
Scheme 4: Statistical Distribution of CM Products

completely consume the terminal olefins in the reaction. These factors make CM reaction even more difficult to execute, requiring the separation of five distinct reaction components. The presence of unreacted starting olefin is partially due to the lower effective catalyst loading in CM than in RCM, since an excess of one CM partner is usually required. In addition, since intermolecular processes are involved, slow reactions rate hamper catalyst activity. Therefore, greater catalyst activity is central to advancing CM methodology by properly consuming all olefinic starting materials and reducing the number of reaction components to three products, two homodimers, and the CM product. In this regard, the high activity of catalyst **3** has been instrumental in providing the reactivity necessary to consume all starting materials to simplify product mixtures and greatly increase the utility of CM.

Another challenge in CM is the mixture of trans and cis isomers that are obtained for each new product in the reaction, and this represents the most striking limitation to selective CM. For example, olefin stereoselectivity is an issue in all metathesis processes, but is only pertinent to RCM of large rings (>8 carbons) and in backbone structure in ROMP polymers. In CM, however, the issue of olefin stereoselectivity is centrally important to the utility of the method. It is these unresolved issues of selectivity

that have made CM a less developed synthetic method compared to ROMP, ROX, and RCM. Development of a selective olefin CM is still in its infancy and will be addressed in the first part of this chapter by investigating three distinct selectivity issues: stereoselective olefin formation, cross-coupling product selectivity by eliminating homodimerization pathways, and olefin chemoselectivity in complex organic molecules. By examining these aspects of selectivity in CM, synthetic chemists have recently become more comfortable in using CM in complex organic molecule synthesis.

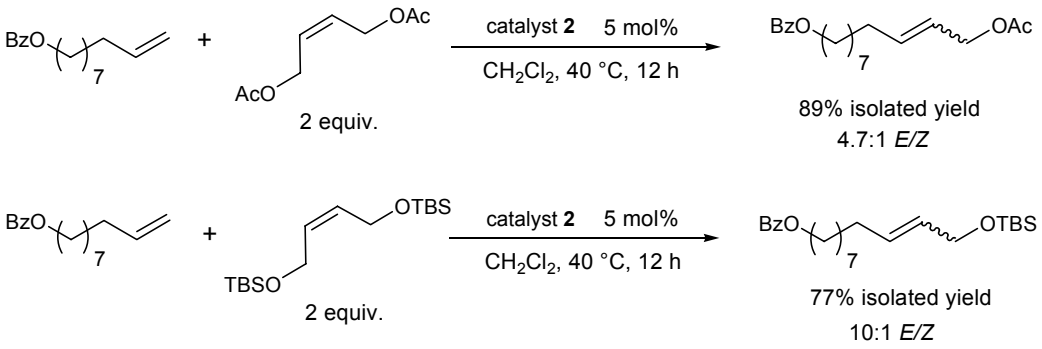
Olefin stereoselectivity is central to any successful CM process. One approach to this problem has been in using removable tethers in RCM as a means to generate cis olefins. It should be noted that there is no general catalyst solution for the formation of cis olefins from a CM reaction. Therefore, several groups have developed RCM as a method to template cis olefins, followed by tether cleavage.[20] However, this does not address generating trans olefins, which is attainable in some stereoselective CM reactions and is discussed below. Therefore, it is hoped that steric perturbations may



Scheme 5: Different Stereoselectivity Based on Allylsilane Substituents

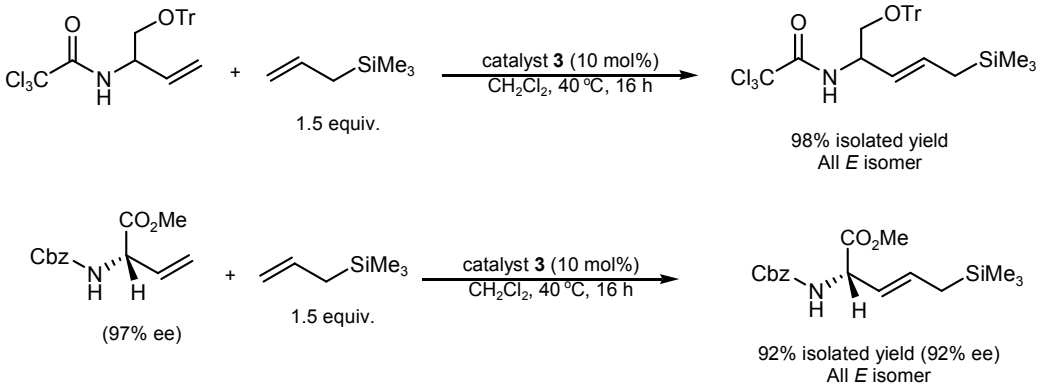
lead to improved trans olefin CM selectivity. The first findings in this area were reported by Crowe *et al.* in regards to allylsilane CM using catalyst **1** (Scheme 5).[21] For example, they observed enhanced trans selectivity with the use of larger silicon substituents where allyltrimethylsilane produces a 2.6:1 *E*/*Z* ratio where the use of allyltriisopropyl silane

results in a 7.6:1 *E*/*Z* ratio with the same terminal olefin CM partner at similar CM yields. Collectively, these results represent the first example of remote stereocontrol in cross-metathesis and have also been demonstrated by this group in simple allylic alcohols protecting group sterics using catalyst **2** (Scheme 6).[22] For example, CM of a α-olefin with allyl acetate equivalent leads to a 4.7:1 *E*/*Z* ratio, where



Scheme 6: Different Stereoselectivity Based on Allyl Protecting Groups

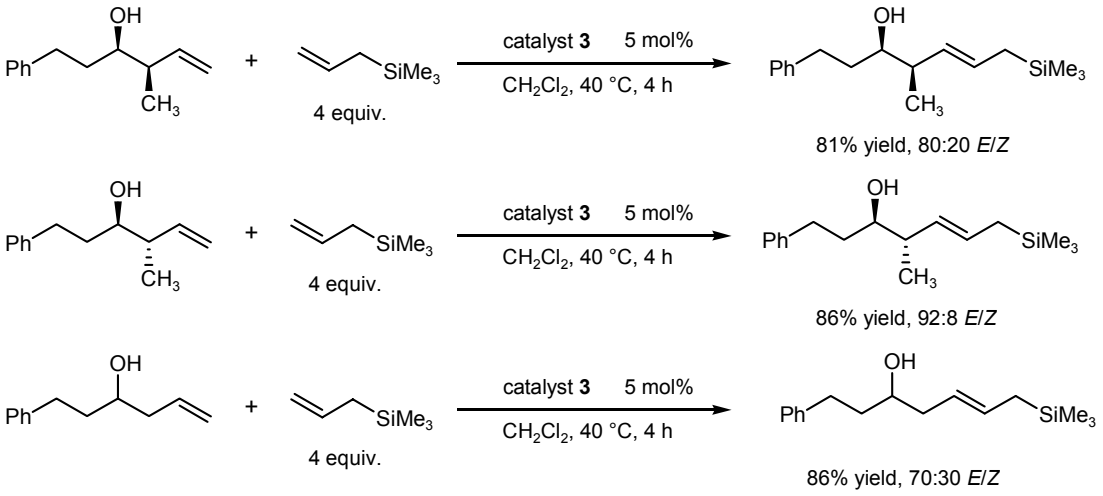
allylic silyl ethers can enrich the trans isomer to a synthetically useful 10:1 *E*/*Z* ratio. In addition, Blechert demonstrated that removing heteroatom substituents from the allylic



Scheme 7: Allylic Substitution Effects on CM Olefin Stereoselectivity

position reduced trans selectivity. Perhaps, the most impressive results of allylic stereocontrol from this work are in regards to substituted allylamines. Using catalyst **1**, Blechert demonstrated the first exclusively trans selective CM reaction using purely steric contributions (Scheme 7).[23] These authors also suggest the possibility of

coordinating groups can affect product and stereoselectivity, but are unable to provide a model for the observed selectivities. Regardless, the installation of a synthetically useful allylsilane under complete stereocontrol is extraordinary. In addition, the functional group tolerance of catalyst **1** is remarkable, since minimal racemization of a highly epimerizable center is observed. This example also demonstrates excellent selectivity for the CM product and the factors contributing to this will be discussed in detail later. In addition, recent work by Taylor and co-workers has demonstrated kinetic CM control in the CM of substituted homoallylic alcohols with allylsilanes using ruthenium catalyst **3** (Scheme 8).[24] These authors demonstrate that secondary metathesis of the



Scheme 8: Relative Stereochemistry Effects on CM Olefin Diastereoselection

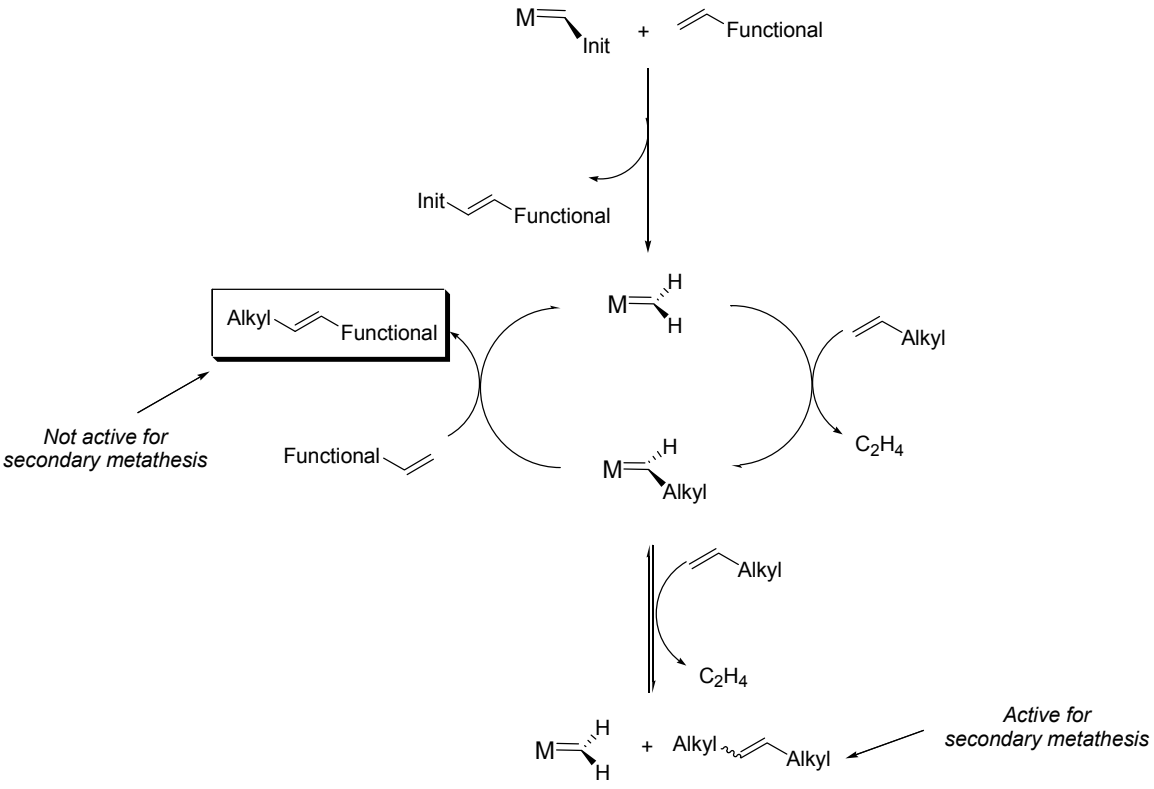
disubstituted CM products was not observed, allowing for selective production of CM product. However, the most surprising result from this work demonstrated that olefin diastereoselection can be governed by relative stereochemistry of substitution at the allylic and homoallylic position. For example, a trans substitution relationship leads to a much higher ratio of the trans olefin isomer. The relay of stereochemistry in the allylic and homoallylic position to the newly formed olefin is unprecedented. In addition,

presence of substituents helps trans selectivity, since the *E*/*Z* ratio falls to 70:30 without any allylic substituents present, similar to what was previously observed by Blechert and our group. These examples show how allylic substitution can assist in the formation of trans olefins.

Another important selectivity issue in CM is product selectivity. Product selectivity in CM revolves around improving the statistical distribution of CM product relative to homodimer formation as described in Scheme 2. Limiting formation of homocoupled product is particularly problematic in CM since there is no inherent orthogonality in the reactive functional groups present, unlike the other cross-coupling methods described in Scheme 1. However, if the statistical distribution of heterocoupled and homocoupled olefin products can be overcome, then the use of simple olefinic starting materials would be extremely useful to synthetic chemists. In addition, limiting the equivalents of CM partners in a selective CM process also reduces the resultant catalysts loading by eliminating unproductive homodimerization pathways. Generally, the two ways to prevent homodimerization of one olefin are by making the olefin electron-deficient or by adding steric bulk.

The underlying implication is that one CM partner would provide a resting state metal carbene, such as an α-olefin. Therefore, the other CM partner would only react in a productive manner to CM product, such as an electron-deficient olefin (Scheme 9). Thereby, the α-olefin can dimerize rapidly and reversibly react with an electron-deficient olefin, forming a CM product that is less accessible to subsequent secondary metathesis reactions. Differences in the rates of these processes allow for selective formation of CM product. There are several important conditions that must be met for successful selective

CM. First, a catalyst system must sufficiently react with an α-olefin and its dimer, on a timescale where productive CM with a second olefin can occur. The extent to which the second functionalized olefin is consumed in CM is typically governed by the rate of

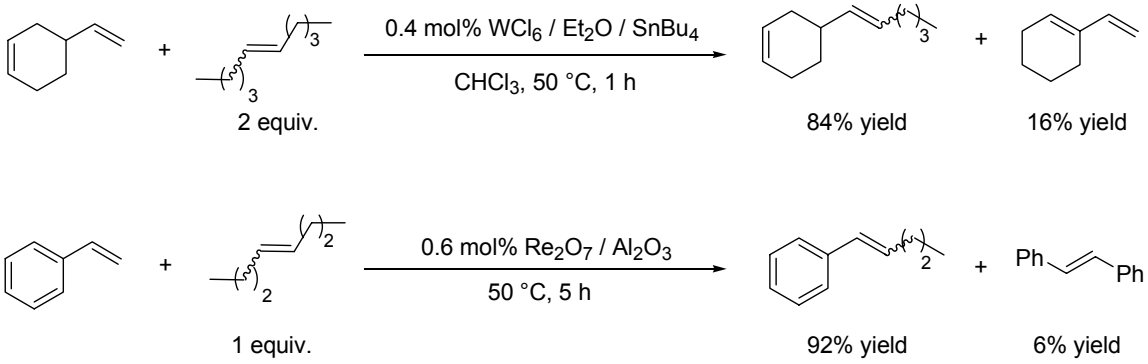


Scheme 9: Proposed Reaction Pathway in Selective Cross-Metathesis

reaction with the catalyst and by how many cycles the α-olefin dimer can react with the catalyst in a degenerative manner. In fact, it is this degenerate scrambling of the α-olefin dimer and the CM product that can reduce catalytic efficiency in simple thermodynamically controlled CM. This is due to propensity of both CM olefins to form stable alkylidenes with a metal carbene catalyst. One way to ascertain the reactivities of alkylidenes is by independent organometallic synthesis of these intermediates. One example of this has been performed on ruthenium-alkylidenes containing electron-withdrawing groups, such as acrylate esters.[25] It was discovered that the (bis)-phosphine

containing ester carbenes were thermodynamically unstable, as were highly reactive initiators with even unstrained olefins, such as cyclohexene. In addition, the formation of carbenes with tertiary or quaternary allylic carbons is not accessible by metathesis, also noting their thermodynamic and kinetic instability.[26] Therefore, these olefins that do not form stable alkylidenes may be excellent partners for CM with α-olefins. This approach is discussed in Chapter 4 as a method to synthesize functionalized olefins.

The second condition is that the functionalized olefin CM partner does not dimerize, or undergoes a slow dimerization relative to formation of CM product. This can be accomplished by adding electron-withdrawing groups on the olefin, decreasing its reactivity to an electrophilic carbene center. Another method to decrease homodimerization is by the addition of steric bulk at the allylic and homoallylic positions. The first report of allylic substituted olefins and the first electron-deficient olefin to participate in selective CM is by Warwel and Winkelmüller in their homologation of terminal olefins with styrene (Scheme 10).[27] They were able to

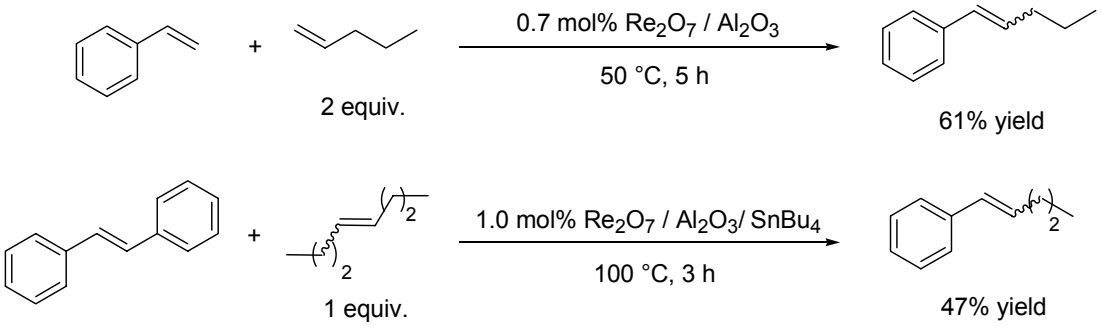


Scheme 10: Selective Styrene CM with Ill-defined catalysts

demonstrate that both electronic (styrene) and sterics (allylic substitution) factors can govern CM product selectivities. Used as intermediates in alkyl benzene synthesis, heterogeneous catalyst systems of Re_2O_7/Al_2O_3 and others were employed in the reaction

of symmetrical unfunctionalized olefins with 4-vinylcyclohexene and styrene. Unfortunately, the catalyst also promoted olefin migration to the isomeric 1-vinylcyclohexene with the homogeneous $WCl_6/SnBu_4$ catalyst system, but did allow for excellent CM efficiencies, beyond simple statistical mixtures. In addition, stereoselectivities of these reactions were not reported, making it unclear what effect a secondary allylic carbon has on olefin stereoselectivity.

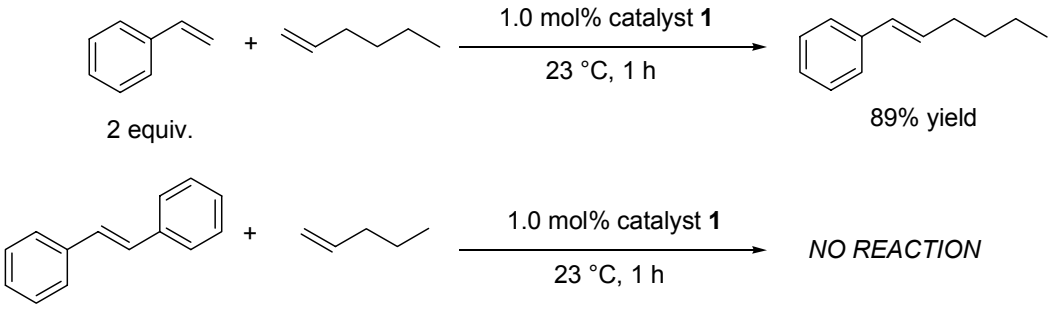
However, the non-statistical product distribution, obtained by Warwel and Winkelmüller favoring heterocoupled product illustrates the first kinetically-controlled CM reaction due to a slow dimerization of styrene to stilbene. These authors demonstrated that stilbene participation in CM with internal olefins required higher catalyst loadings, harsher reaction conditions, and led to lower conversions versus using styrene (Scheme 11). These results demonstrate that resubjecting an isolated



Scheme 11: Internal Olefins in Styrene CM with Ill-defined catalysts

homodimer, such as stilbene, can determine if selective CM is in operation. On the contrary, it was observed that higher yields of CM were obtained using symmetrical internal olefins versus terminal olefin counterparts (92%) versus terminal olefins (61%). The authors conclude that several catalytic cycles were consumed in dimerization of aliphatic olefins rather than in productive CM, leading to lower yields. This work

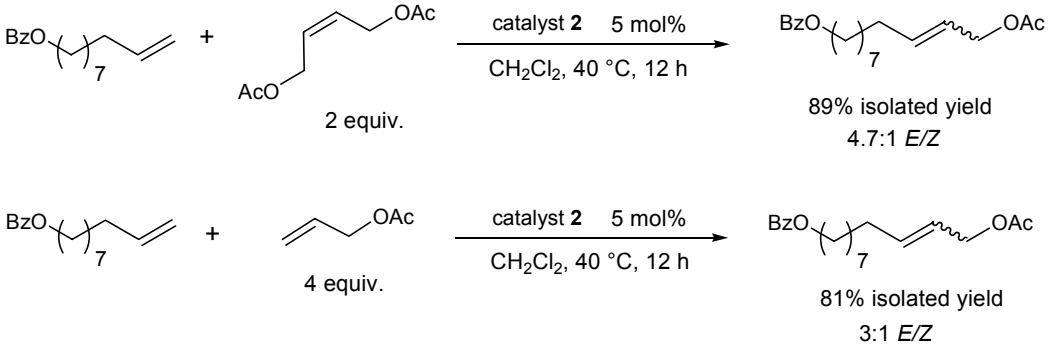
demonstrates the advantages of using certain disubstituted olefinic starting materials rather than their α-olefin counterparts. CM with styrenes has been reinvestigated within the last several years using well-defined homogeneous catalysts. Molybdenum-based catalysts have been particularly useful in these reactions due to their commercial availability and provide different results from those obtained by Warwel. Initially, Schrock *et al.* discovered different rates of styrene dimerization to stilbene using different ligand sets on molybdenum.[28] Crowe and co-workers concurrently demonstrated the kinetic CM between α-olefins with styrenes using catalyst 1, providing stereoselective trans olefins (Scheme 12).[29] This also is a unique



Scheme 12: Styrene CM with Molybdenum Catalyst **1**

reaction since they determined that stilbene was not a good partner for CM. However, the trans stereoselectivity observed here may have also been observed in the earlier work by Warwel, but simply was not reported. Crowe and Zhang also found that the reaction between styrene and an internal olefin dimer exclusively produces the CM product, but not on a timescale relevant to productive CM. These experiments argue that a highly selective process, where neither homodimer is formed, but only the CM product is formed. This is a remarkable reaction, since the elimination of all potential unproductive homodimerizations helps explain such an efficient reaction.

However, the advantageous use of internal olefins in CM, as initially described by Warwel and Winkelmüller, has also been shown to operate in several catalyst systems. For example, concurrent to their work with styrene CM, Banasiak examined the role of internal olefins in insect pheromone synthesis using ill-defined tungsten Fischer carbene complexes.[30] Several important observations were made from this work. For example, it was observed that the removal of ethylene increases catalyst efficiency and trans stereoselectivity by providing an entropic driving force in the reaction. The improved stereoselectivity may be possible due to secondary metathesis of the products leading to the more thermodynamically favorable trans olefin. In addition, it was found that the use of internal olefins, instead of the corresponding α-olefins, allowed for lower catalyst loadings, greater CM product selectivity, and higher trans diastereoselectivity. These results were also corroborated in this group using catalyst **2** and allyl acetate (Scheme 13).[22] The improvement in CM efficiency can be attributed to independent mechanistic



Scheme 13: Terminal Olefin Homologation with Allylic Alcohols

studies that indicated a lower stability of the intermediate methylene carbene relative to alkyl substituted carbenes. The formation of an intermediate methylidene is reduced with the use of one set of symmetrically disubstituted olefins.[26] This also provides an example of the advantage of using single-component catalyst systems in CM. Since intermediate catalytic species can be independently synthesized and studied, the use of single

component homogeneous systems allows for a synergistic relationship between organometallic mechanistic studies and developing efficient synthetic methodology. The increased catalyst stability attained with internal olefins can be attributed to greater secondary metathesis processes that can improve trans stereoselectivity, similar to what Banasiak observed in catalytic reactions in pheromone synthesis with ill-defined catalysts. Therefore, CM product selectivity and olefin stereoselectivity issues must be properly addressed to develop synthetically useful CM processes. While ill-defined catalysts were not very tolerant of functional groups and undergo wanted side reactions (such as olefin isomerization) and do not provide much opportunity for mechanistic studies, they did provide some insights into achieving selective CM processes by judicious choice of CM partners. Many of these observations have been verified with single component catalyst systems.

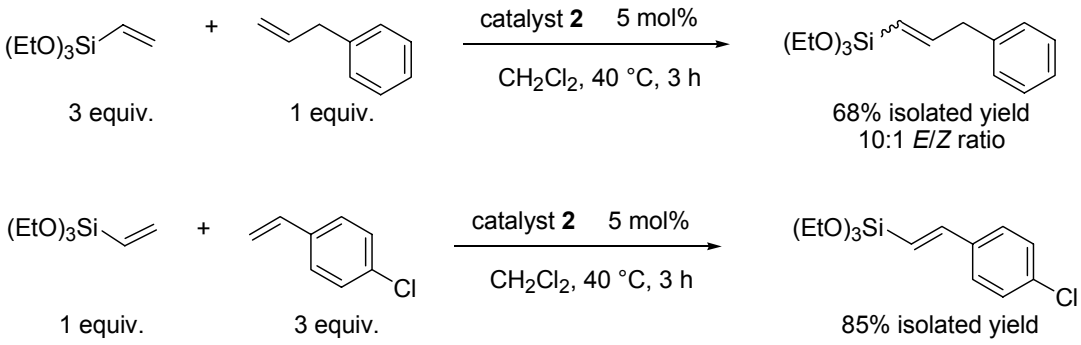
Another area of selective CM reactions involves allylsilane CM. Bespalova and co-workers initially looked at commercially available allyltrimethylsilane in the simple CM with other terminal olefins using ill-defined tungsten catalysts, but did not report olefin stereoselectivities and product selectivity based on CM partner choices.[31] However, several years later, Crowe *et al.* reinvestigated allylsilanes CM with molybdenum carbenes and found that they react analogously as terminal olefins, due to nucleophilic character of these olefins.[21] This allows for selective CM with styrenes and other electrophilic olefins, such as acrylonitriles. In addition, these results demonstrate the first electronic matching in CM, allowing for certain combinations of olefins to furnish CM products in high product selectivity. However, when allylsilane CM is performed with α-olefins, statistical product mixtures are achieved in a modest 2.6-4.9:1

E/*Z* ratio. These results provided a rationale for the observed selectivities based on reactivity patterns of well-defined metal carbene catalysts. In addition, Blechert *et al.* demonstrated that binding one olefin to a polymer support can suppress its homodimerization and increase CM efficiency using catalyst **2**.[32] This can be rationalized based on slow diffusion of polymer-bound olefins, limiting their homodimerization. However, at this point, a general model for product selectivity in CM is missing despite some important discoveries made in the area.

Interestingly, the lack of selectivity in CM led to the initial application of CM in combinatorial chemistry, as a method to introduce structural diversity.[33] While work in developing selective CM methods was still in progress, several groups began applying CM to more functionalized substrates to determine olefin chemoselectivity and functional group tolerance of well-defined homogeneous catalysts. The application of CM has been demonstrated in several arenas, including materials chemistry, bioorganic chemistry, and natural product synthesis. The application of CM to total synthesis has been only recently demonstrated as a means to introduce structurally relevant olefins and in preparing olefinic reagents for subsequent chemistry.

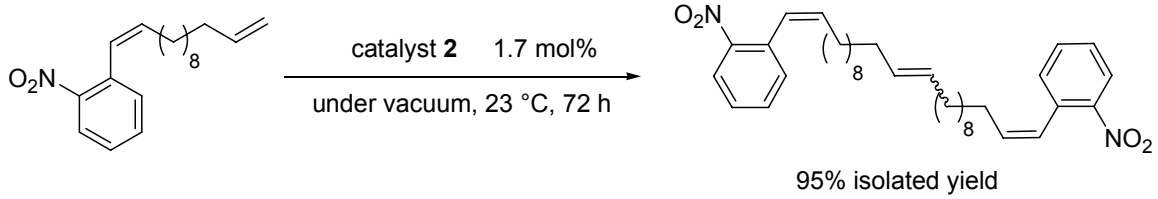
One of the earliest applications of CM was demonstrated by Feher and co-workers in the homologation of vinyl-substituted silsesquioxanes with a variety of terminal olefins in moderate to good yields.[34] These topologically spherical silsesquioxanes have interesting materials properties and CM allows for rapid access to a diverse set of compounds in one synthetic step simply by changing CM partners. Additionally, styrene CM with silsesquioxanes was also demonstrated with ruthenium catalyst **2** and provides excellent trans stereoselectivity. Marciniec and co-workers demonstrated in early CM

work the selective CM between vinylsiloxanes and a variety of terminal olefins, including styrenes (Scheme 14).[35] These reactions demonstrated another family of directly functionalized olefin that can be employed in selective CM. Therefore, the work by Feher and co-workers is an excellent example of CM methods being applied



Scheme 14: Vinylsiloxane CM with Styrene and α-olefins Using Catalyst **2**

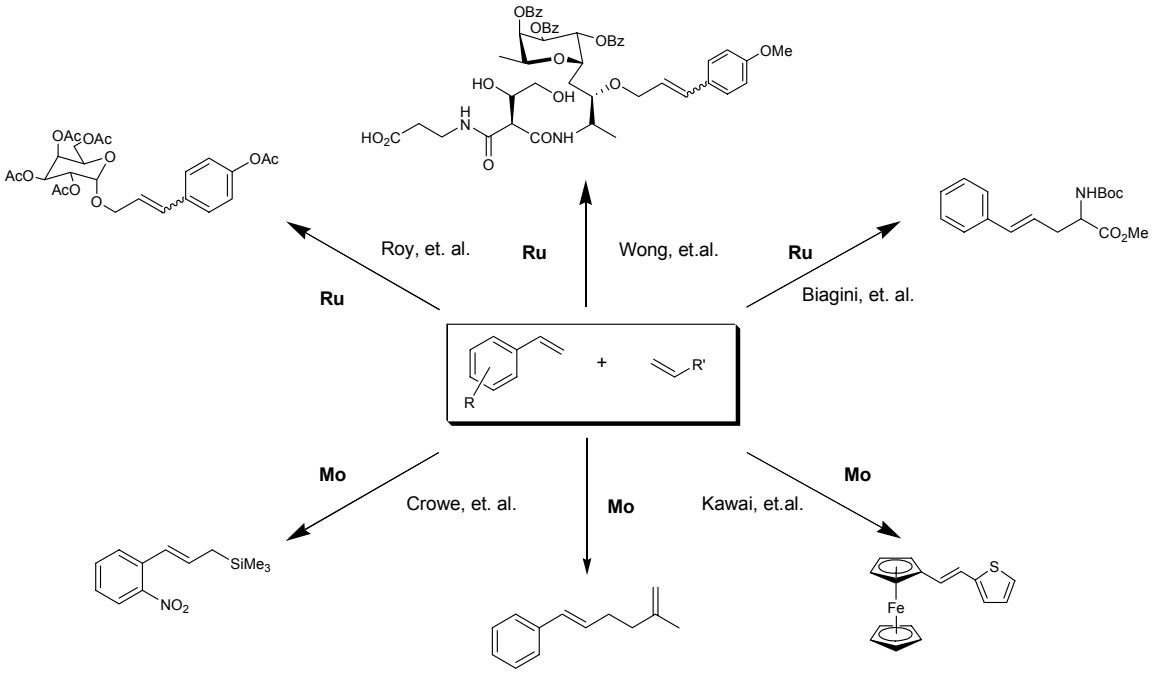
to interesting molecules for materials applications. Another important application of CM to materials science was demonstrated by Duran and Kloeppner.[36] These workers demonstrated one of the first olefin chemoselective CM reactions in their synthetic route to polyalkylanilines. These polyalkylanilines were applied in the formation of ultrathin Langmuir films for application in nonlinear optical materials and electroluminescent materials. Using ruthenium-based catalyst **2**, terminal olefin dimerization was accomplished cleanly in the presence of a cis styrenyl bond (Scheme 15). This demonstrates that chemoselectivity, accomplished here by catalyst choice, is an



Scheme 15 : Chemoselective CM of Terminal Olefin with Styrenyl Bond

important point in CM development. This result is particularly interesting since styrene CM has been widely demonstrated, but is inoperative here due to the nitro withdrawing group. In addition, the cis styrenyl bond was formed by Wittig chemistry, demonstrating the direct orthogonality between CM and Wittig olefination strategies. Styrene CM has been widely applied due to excellent trans selectivity and has been the subject of recent work. For example, Kawai and co-workers have demonstrated the selective CM between styrene derivatives and vinylferrocene using **1** allowing for CM between two electron deficient olefins in moderate yields.[37] Styrene CM has also been demonstrated by Biagini *et al.* using protected homoallylglycine derivatives in albeit low yields, and demonstrates some of the early work in bioorganic chemistry.[38] Wong and co-workers were able to dramatically improve upon styrene CM yields with **2** in their preparation of Silyl Lewis X mimetics.[39] In addition, Roy and co-workers also demonstrated CM styrene with O-allyl glycosides to make extended alkenyl glycosides.[40] Not only do these two studies illustrate the first applications of CM in carbohydrate synthesis, but also demonstrate the wide variety of styrenes employable with catalyst **2** to rapidly generate biologically relevant molecules. In fact, these reports establish much of the functional group tolerance now associated with the catalysts in CM and pushed the limits of CM reactivity with catalyst **2**. With the high degree of stereoselectivity observed in styrene CM, it has been widely used in a variety of applications, and is summarized in Scheme 16. This demonstrates that if a selective process can be discovered, it possesses a broad application in synthetic chemistry. Additional types of selective CM processes are described in detail in the following chapters.

With some work in the area of cross-metathesis begin reported, there was nearly concurrent work in the area of application of CM to bioorganic systems in addition to the styrene examples mentioned above. Much of this work was directed at simple dimerizations, rather than performing cross-coupling. However, Diver and Schreiber accomplished an important application of CM in the dimerization of immunosuppressant FK506.[41] The functional group compatibility was a central highlight to this work with the use of ruthenium catalyst **2** albeit in moderate yields. The lack of protecting groups employed and presence of other olefins inert to the reaction conditions is a remarkable feature of this work and is one of the first chemoselective CM reactions. In addition, work by Roy and co-workers has exploited CM both in a variety of areas, including early work glycoside dimerizations[42] and heterocoupling reactions with styrenes (Scheme 16).[40] Perhaps one of the most unique applications of CM in carbohydrate chemistry has

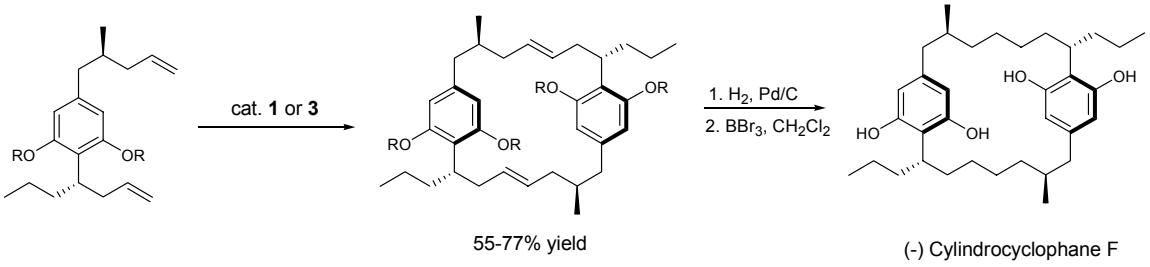


Scheme 16: Styrene Homologation by CM

been in the work of Seeberger and co-workers with regards to their automated oligosaccharide synthesizer.[43] This work demonstrates the unique orthogonality of olefin

metathesis in respect to many standard carbohydrate reactions in the context of complex synthesis of up to dodecomer oligosaccharides. As well precedented before in non-carbohydrate systems, Seeberger and co-workers used metathesis in the release of the oligosaccharide from solid support by ethylenolysis, without interruption of complex carbohydrate functionalities. Finally, similar work has been demonstrated in the nucleic acid area with simple dimerization of allylnucleosides[44] and cross-metathesis between vinylphosphonate containing nucleotides with vinylnucleosides to generate "dimeric" nucleotides.[45] In summary, there are a rich amount of applications of CM in bioorganic chemistry and these applications provided new avenues in understanding peptides and carbohydrates through biologically stable C-C bonds.

Finally, with the use of CM in method development stages and in biological applications, the utilization of CM by synthetic organic community has been somewhat more obscure. Until very recently, unlike its intramolecular variant (RCM), CM has not been used in a complex target-oriented synthesis. However, recent reports in the area have been focused on two classes of CM utility: dimerization strategies and chain elongation. One of the first examples of the dimerization approach has been work done by Smith and co-workers in their synthesis of (-)-cylindrocyclophanes A and F (Scheme 17).[46] In their synthesis of this class of dimeric natural products, a thermodynamically

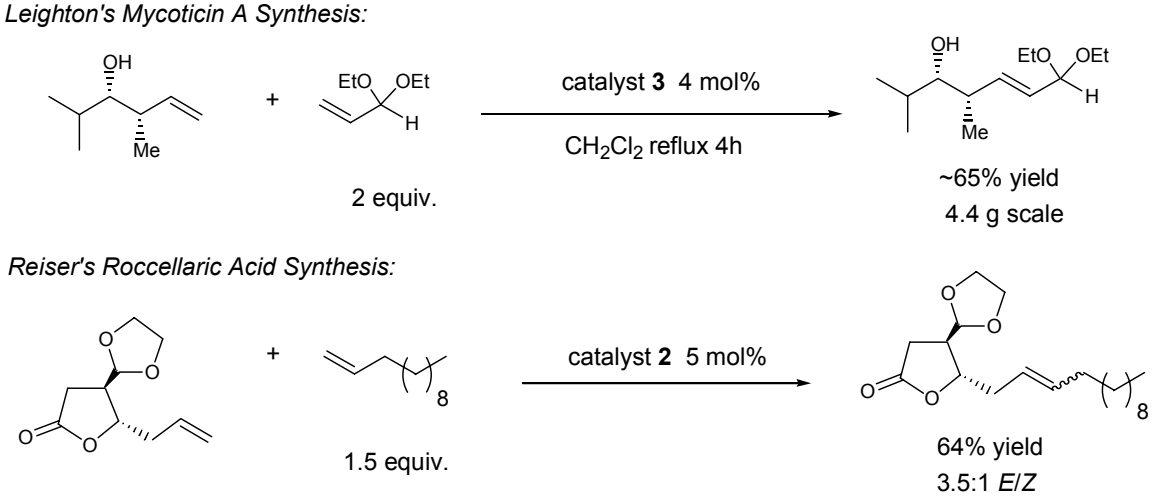


Scheme 17: CM Dimerization Strategy in Cylindrocyclophane Synthesis

controlled head-to-tail CM reaction, and subsequent ring-closure was used to construct a 22-member cyclophane exclusively as the *E*,*E*-isomer. Perhaps the most interesting part of this work is the excellent olefin stereocontrol achieved with remote olefinic substitutions in the homoallylic position. Smith and co-workers also demonstrated that subjecting an independently synthesized head-to-head dimer to the metathesis conditions leads to the same head-to-tail dimer [7,7]-cyclophane product. In addition to this work, Corey and co-workers have reported another interesting dimerization strategy in the synthesis of the squalenoid Glabrescol and its meso diastereomers.[47] One of the remarkable features is the amenability of catalyst **1** toward vinyl epoxide functionality and other substituted olefins in the farnesyl acetate derived substrate. The dimerization approaches described to date have highlighted CM as a functional group tolerant method to rapidly regenerate thermodynamically favored products in excellent yield.

Second, several examples of chain elongation by CM have been recently disclosed, requiring efficient cross-coupling of differing functionalities. Zercher *et al.*, in their formal synthesis of the natural product FR-900848, have demonstrated a chain elongation approach in polycyclopropane synthesis.[48] As previously described in our group, a two-step CM approach was utilized in this synthesis.[22] An initial dimerization of a vinyl cyclopropane provided a homodimer that was used in excess with another different vinylcyclopropane CM partner, to generate the heterocoupled product in excellent yield with moderate stereoselectivity. Interestingly, the CM reaction utilized provided a higher than statistically predicted CM yield, but an explanation for this selectivity was not described. In addition, Itoh and co-workers performed a similar CM with fluorinated vinylcyclopropanes, and demonstrated that while the direct dimerization

of certain substituted vinylcyclopropanes proceeds in low yield, they provide exclusive trans olefin formation, which was unprecedented.[49] These examples from the target-oriented synthetic literature corroborate independent results where the use of allylic alcohol protecting groups limits homodimerization and provides enhanced trans diastereoselection. Finally, Leighton and co-workers have applied a recent example of CM allylic stereocontrol to their synthesis of mycoticin A (Scheme 18).[50] As an early



Scheme 18 : Total Synthesis Applications of Terminal Olefin Homologation by CM

step in their formal synthesis of their target, they applied an acrolein acetal CM[22] in excellent stereocontrol to a substrate with both allylic and homoallylic substitution, derived from a crotylation reaction. The imidazoylidene containing ruthenium catalyst **3** was employed and demonstrated an excellent method for chain elongation with a masked aldehyde source. In the Leighton synthesis, CM was demonstrated early in a synthesis due to its efficiency in generating a highly functionalized acyclic synthetic precursor; however, there is also a recent example of CM employed as an endgame in synthesis. Reiser *et al.* perform a late-stage CM with 1-dodecene in their synthesis of (-)-Roccellaric acid, a member of the γ-butyrolactone family of natural products (Scheme 18).[51] By

performing a cross-metathesis reaction at the end of their synthesis, a wide variety of side-chains can be introduced to generate diversity, since several members of the γ-butyrolactones family of natural products have exhibited antibiotic and antitumor properties. The use of CM by the synthetic organic community in both early and late steps represents the viability of CM to make important bond constructions stereoselectively and in a high yield. CM has also been employed in generating diversity through the use of readily available olefinic cross-partners.

In conclusion, the use of olefin cross-metathesis has started garnering attention as a viable tool in organic synthesis. Many fundamental studies on the functional group tolerance, electronic factors, and steric parameters required for stereoselective synthesis have been investigated with a variety of catalysts systems. In fact, some of the most exciting work is related to the kinetic CM product formation by slowing the homodimerization of one olefin partner. Simultaneously, CM has been applied to total synthesis and in biological area generating rigid alkenyl C-C bond constructions. In fact, the central challenges in CM still center on the elimination of homocoupling products, generating products with good stereoselectivity, and increasing substrate scope. In addition, extensive organometallic work to improve overall catalyst activity will allow for low catalyst loadings and efficient preparation of bulk starting materials. These challenges represent challenges unique to CM from those in endgame RCM and ROMP applications. The following discussion will address selective CM reactions recently discovered and a model to assist in understanding product selective CM processes and their applications to new reaction platforms.

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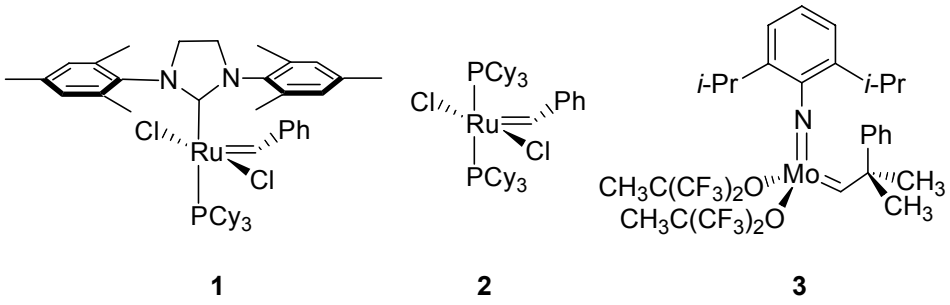
Chapter 2: Ruthenium (bis)-phosphine Catalysts in CM

The formation of carbon-carbon bonds in an efficient and stereoselective manner is a central part of synthetic chemistry. The ability to build complex molecules from accessible precursors provides the intermediates for complex synthesis. One such approach for carbon-carbon bond formation is through the olefin metathesis reaction. The olefin metathesis reaction is a metal alkylidene catalyzed reaction that exchanges olefin substituents via metallocyclobutane intermediates.[1] Two applications of this reaction have been in ring-opening metathesis polymerization[2] (ROMP) and ring-closing



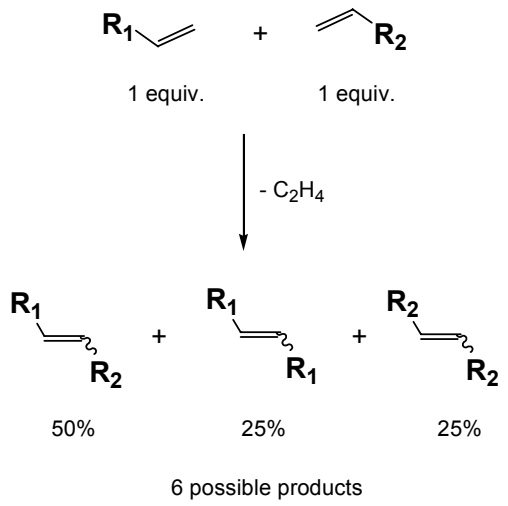
1 **2** **3**

Figure 1 : Commonly Used Olefin Metathesis Catalysts

metathesis (RCM) of acyclic dienes.[3] With the recent advent of a new family of metathesis catalysts with dihydroimidazolylidene catalyst **1**,[4] the scope of olefin metathesis has been greatly expanded. The commercial availability of **1** and other well defined homogeneous catalysts, such as the parent ruthenium benzylidene catalyst **2**,[5] the molybdenum alkoxy-imido alkylidene **3** developed by Schrock *et al.*[6] has made the olefin metathesis reaction practical for small molecule synthesis (Figure 1).

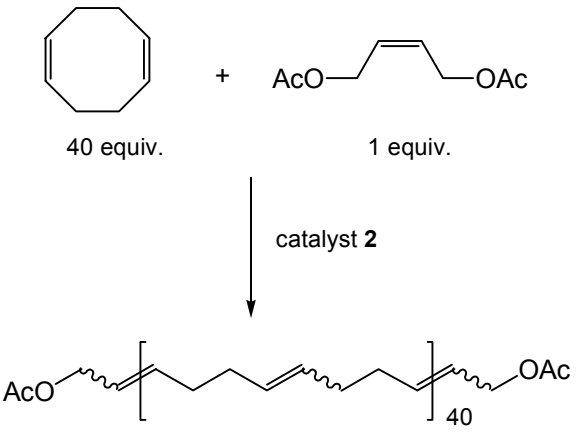
The amount of work in RCM and ROMP has overshadowed work in the intermolecular variant of olefin metathesis, olefin cross-metathesis (CM). This is largely due to the mixture of products and low stereoselectivity of the products obtained in the

reaction, limiting its synthetic practicality (Scheme 1). Six possible products can be



Scheme 1: Complex Mixture Obtained in Cross-Metathesis (CM)

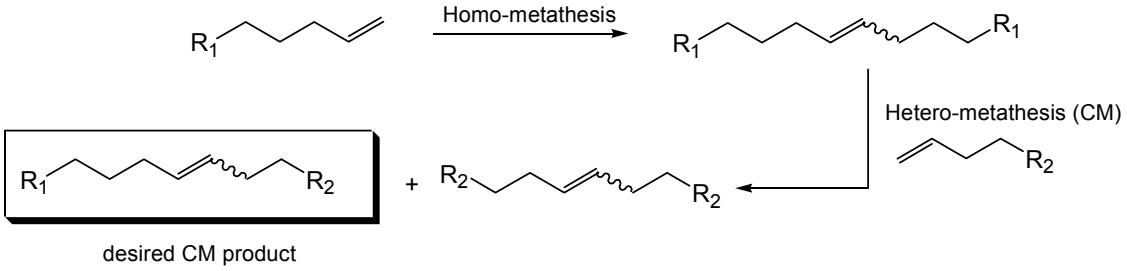
obtained including unreacted starting material. The lack of olefin stereoselectivity, as well as low product selectivity limits the utility of CM. However, CM has recently been reinvestigated in the Grubbs group and began with the use of disubstituted olefins as chain transfer agents in the formation of telechelic polymers in a tandem ROMP/CM process (Scheme 2).[7] The use of this chain transfer agents allows for excellent control of



Scheme 2: Telechelic Polymer by ROMP/CM

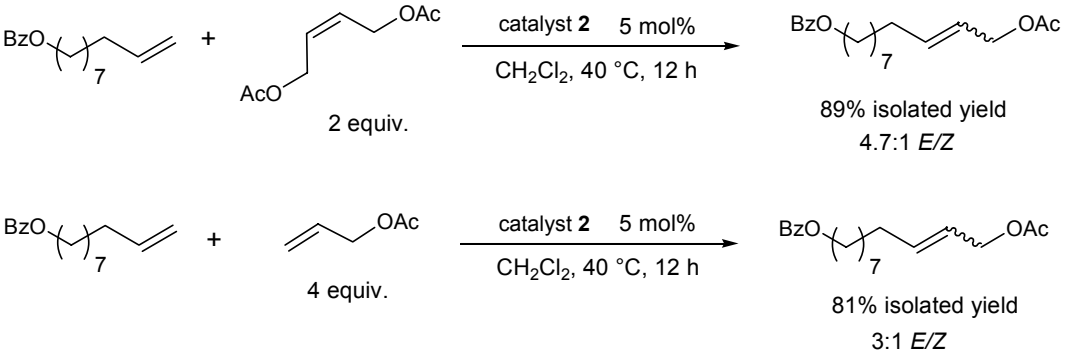
molecular weight as well as furnishing functional groups that can be used in the synthesis of block co-polymers.[8] This inspired the use of disubstituted olefins in CM to limit the

number of side products formed in the reaction and demonstrate the interplay between polymer and small molecule chemistry in olefin metathesis. The use of allylic alcohols (or protected equivalents) also allowed for a systematic investigation into alkene stereoselectivity and CM product selectivity. This approach allows for selective formation of CM product via a two step process (Scheme 3).[9] This protocol offers the



Scheme 3: Two-step CM Protocol Limits Side-Products

advantage of reducing the mixture of products in the reaction by using an excess of the symmetrical (R_1) dimer. In addition, it was found that the use of an internal olefin is most efficient due to catalytic intermediates involved (Scheme 4). For example, the use

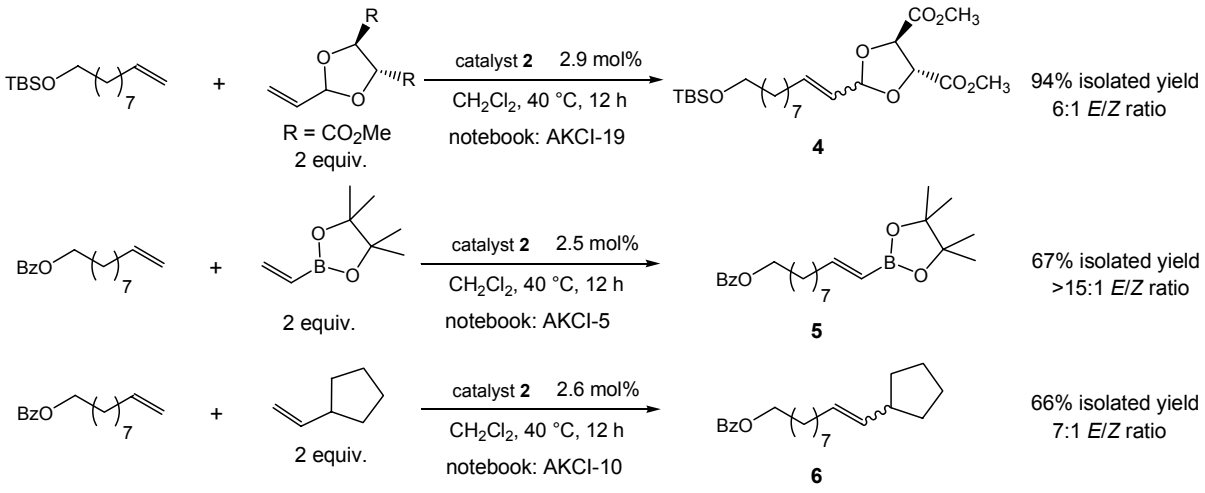


Scheme 4: Terminal Olefin Homologation with Allylic Alcohols

of *cis*-2-butene-1,4-diacetate provides greater CM yields and higher trans selectivity than using the same number of equivalents of allyl acetate. It has been speculated that the first reaction provides a higher yield due to greater catalyst lifetime, by reducing the amount of a terminal ruthenium methylidene ($M{=}CH_2$) produced in the reaction. It was previously shown in mechanistic studies that the ruthenium methylidene is unstable and

is not readily active for reentry into the catalytic cycle.[10] This may account for the difference in yields, and increase in trans selectivity due to secondary metathesis of the resultant CM product to the more thermodynamically favorable trans olefin isomer.

The goal of our initial work with catalyst **2** was to expand the substrate scope of olefins that can be used in selective CM reactions. In addition, we wished to employ substrates that provided high trans stereoselectivity in the CM reaction, since most CM reactions between α-olefins lead to stereoselectivities that are not synthetically useful (3-4:1 *E*/*Z*). With the discovery that vinyl dioxolanes were selective CM partners with α-olefins provided products with good stereoselectivities,[11] other isosteric vinyl dioxolanes were investigated. Tartrate acetals, vinyl cyclopentane, and vinyl boronate[12] (Scheme 5) were found to be excellent substrates for CM with catalyst **2**. For example, the tartrate acetal of acrolein participates in a highly selective CM reaction with a α-olefin to provide product **4** in excellent yield. This allows easy access to a protected α,β-unsaturated aldehyde in one step from olefinic precursors. In addition,

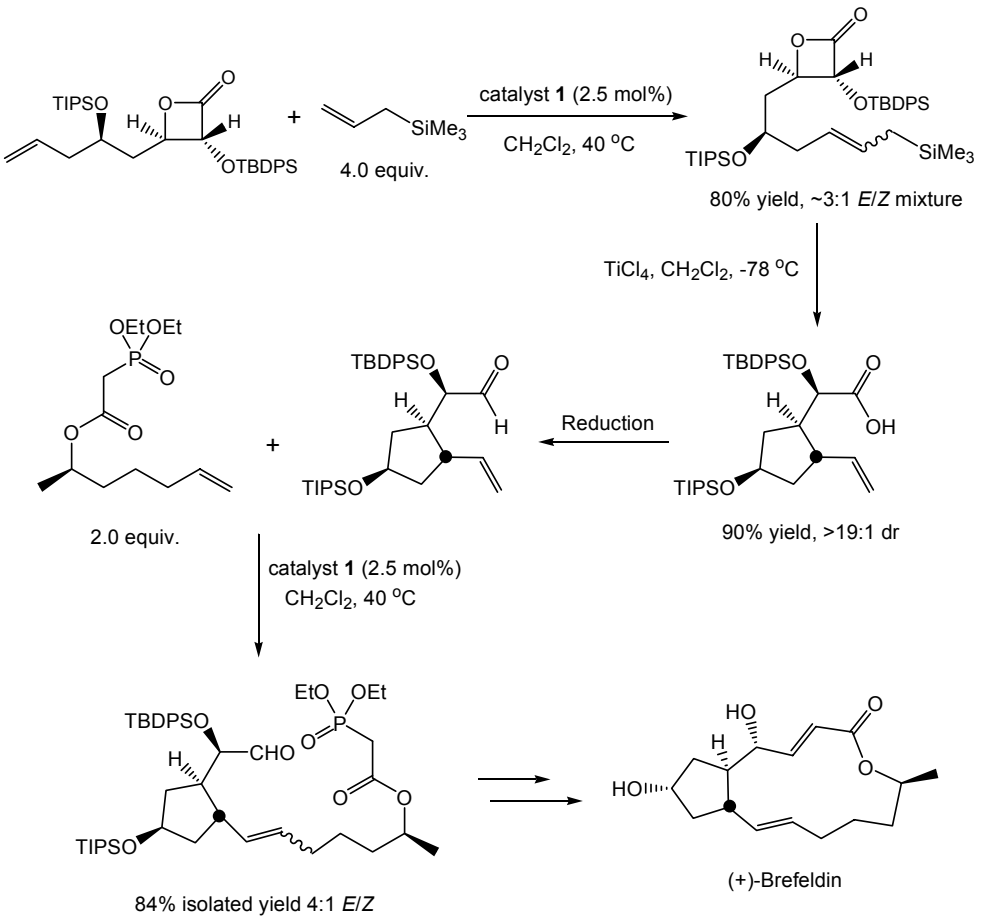


Scheme 5: Selective Terminal Olefin CM with Vinyl Dioxolane Isosteres

the facile formation of product **5** is noteworthy, which can be further manipulated in Suzuki coupling chemistry.[13] In fact, this reaction is a simple way to homologate olefins to Suzuki synthons without requiring the use of more reactive alkyne functionality and subsequent hydroboration. With the high trans stereoselectivity achieved, this reaction can be viewed as a formal C-H activation of an olefinic proton and subsequent conversion to a boronate ester. This demonstrates an example of using CM not only to build C-C bonds of structural importance, but also to make useful reagents for further synthetic transformations. Finally, in the all carbon analog of the acrolein acetal, vinylcyclopentane also furnished the CM product in good yield; however, the selectivity for the CM product is near statistical ratios in providing product **6**. The enhanced trans product of the reaction may be due to steric factors of the constrained ring.

This reaction has been recently applied to the synthesis of (+)-brefeldin by Wang and Romo.[14] These workers were able to use two CM reactions in their synthetic route, demonstrating one of the first examples of CM as a key step in total synthesis. In an early step in their synthesis, they were able to install an allylsilane moiety by CM, followed by addition into the β-lactone to provide a highly diastereoselective synthesis of the vinylcyclopentane core (Scheme 6). An additional CM reaction was used in an extremely convergent manner to install one of the two olefins in the natural product. The CM piece was used in a two fold excess, but did provide a higher yield of CM product than the statistical distribution. Although the stereoselectivity in the cross-metathesis is moderate (4:1 *E*/*Z*), the convergent nature of the synthesis and the mild reaction

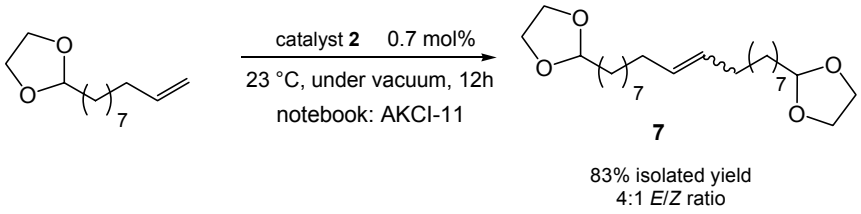
conditions of the CM step provide a nice application of vinylcyclopentane CM



Scheme 6 : Selective CM Reactions in the Synthesis of (+)-Brefeldin

methodology. The authors also noted that the dimerization of the substituted vinylcyclopentane is slower, and illustrates that subtle steric differences can increase CM efficiency. This example also demonstrates the excellent functional group orthogonality between olefin CM and Horner-Wadsworth-Emmons olefination. Finally, even though we demonstrated that catalyst **2** could use vinylcyclopentane as the CM partner, these authors required the use of more active catalyst **1** to afford useful yields of the CM product. However, the participation of vinylcyclopentanes has been nicely applied to complex synthesis.

In addition to the CM reactions described above, we also wanted to optimize the homodimerization conditions of α-olefins. The homodimerization of olefinic compounds is well precedented. In pioneering work by Diver and Schreiber, the immunosuppressant FK506 was homodimerized by olefin metathesis to probe cellular function.[15] In addition, recent work has been done in generating novel compounds for biological application in the dimerization of sphingolipids[16] and nucleosides.[17] It is particularly noteworthy that these applications of CM predate those in natural product synthesis. However, many of these reactions are performed at elevated temperature with high catalyst loadings. Therefore, we wished to investigate a mild, solvent-free method to accomplish homodimerization. For example, dimerization of undecenylic aldehyde acetal proceeded in 83% isolated yield (4:1 *E*/*Z*) to the symmetrical dimer (Scheme 7).



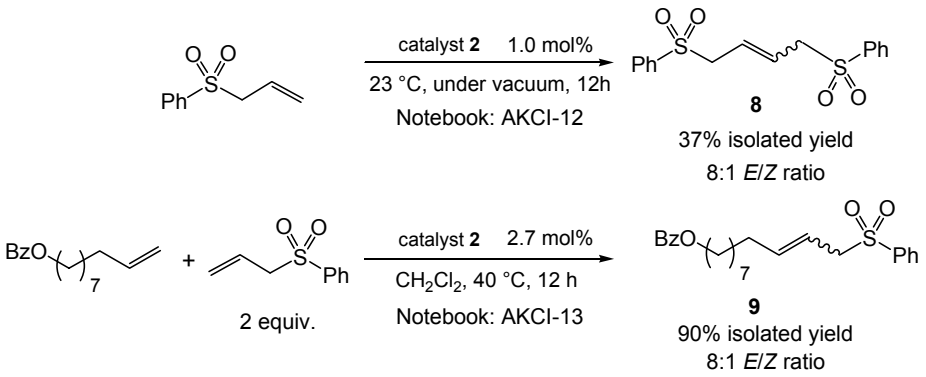
7

83% isolated yield
4:1 *E*/*Z* ratio

Scheme 7 : Solvent-free Homodimerization by Cross-Metathesis

This reaction has the added advantage of not requiring solvent and being performed under ambient temperatures by simply applying gentle vacuum to assist in the removal of ethylene. The efficiency of the CM reaction under such low catalyst loadings is also of significance. Another substrate that was investigated for dimerization was phenyl allyl sulfone. We were interested in this substrate, as a method to install sulfur functionality by metathesis (Scheme 8). It has been previously shown that the participation of reduced sulfur functional groups, such as allyl sulfides was not compatible with late transition metal catalysts, such as **2**.[18] Initially, we discovered that the dimerization of phenyl allyl

sulfone could be achieved using **2**, albeit in low yields (Scheme 8). However, when the



Scheme 8 : Selective Terminal Olefin CM with Allylic Sulfones

CM reaction with a α-olefin was conducted, an excellent yield of CM product was obtained, beyond a simple statistical outcome. This result, as well as the reaction with the tartrate dioxolane in Scheme 5, provided the first evidence of selective CM reactions where the relative dimerization rates of CM partners are significantly different leading to non-statistical product distributions. In addition to achieving good product selectivity, we discovered that a variety of olefins also provide moderate trans olefin stereoselectivity, making these reactions synthetically useful. In conclusion, these results began to provide some insight into reactivity patterns of olefins in CM using catalysts **1** and **2** and will be discussed in subsequent chapters.

Experimental Section.

General Experimental Section. NMR spectra were recorded on either a JEOL GX-400 or GE-300 NMR. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless

stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-resolution mass spectra (EI and FAB) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.[19]

Compound 4. Acrolein-(L)-methyltartrate acetal (215 μl, 1.0 mmol) and 9-decen-1(*tert*-butyldimethylsilane)-yl (165 μl, 0.5 mmol) were simultaneously added *via* syringe to a stirring solution of **2** (12 mg, 0.014 mmol, 2.9 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 5:1 hexane:ethyl acetate. A clear oil was obtained (214 mg, 94% yield, 9:1 trans/cis as determined by ^{13}C relative intensities of peaks at 125.3 and 124.8). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 6.00 (1H, m), 5.55 (2H, m), 4.82 (1H, d, J = 3.7 Hz), 4.73 (1H, d, J = 3.7 Hz), 3.80 (6H, s), 3.57 (2H, t, J = 6.6 Hz), 2.07 (2H, m), 1.50-1.21 (12H, m), 0.87 (9H, s), 0.02 (6H, s) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 170.6, 170.2, 141.1, 125.3, 124.8, 108.1, 102.7, 63.8, 53.4, 53.3, 33.4, 32.6, 30.0, 29.9, 29.7, 29.0, 26.5, 26.3, 18.9, 14.8. R_f = 0.23 (9:1 hexane:ethyl acetate); HRMS (FAB) calcd for

$C_{23}H_{42}O_7Si$ $[M+H]^+$ 459.2778, found 459.2776. Elemental analysis Calcd: C: 60.23, H: 9.23; Found: C: 59.98, H: 9.15.

Compound 5. 2-Ethenyl-4,5-tetramethyl-1,3,2-dioxaborolane[20] (130 μl, 1.0 mmol) and 9-decen-1-yl benzoate (145 μl, 0.5 mmol) were simultaneously added *via* syringe to a stirring solution of **2** (11 mg, 0.013 mmol, 2.5 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. A pale yellow oil was obtained (127 mg, 67% yield, only trans isomer detected in ^{1}H-NMR spectra). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (2H, d, J = 6.9 Hz), 7.54 (1H, t, J = 7.4 Hz), 7.43 (2H, t, J = 7.6 Hz), 6.62 (1H, dt, J = 6.9, 6.4 Hz) 5.39-5.28 (1H, broad m), 4.30 (2H, t, J = 6.7 Hz), 2.14 (2H, m), 1.75 (2H, q, J = 6.8 Hz), 1.50-1.05 (22H, broad m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.2, 155.3, 133.3, 130.1, 128.9, 83.5, 65.7, 36.4, 29.9, 29.7, 29.3, 28.7, 26.6, 25.3. R_f = 0.26 (20:1 hexane:ethyl acetate); HRMS (FAB) calcd for $C_{23}H_{35}BO_4$ $[M+H]^+$ 387.2711, found 387.2699.

Compound 6. Vinylcyclopentane (140 μl, 1.0 mmol) and 9-decen-1-yl benzoate (140 μl, 0.5 mmol) were simultaneously added *via* syringe to a stirring solution of **2** (11 mg, 0.013 mmol, 2.5 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate. A clear oil was obtained (110 mg, 66% yield, 7:1 trans/cis as

determined by integration of peaks at 5.38 and 5.34 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 8.05 (2H, d, J = 7.3 Hz), 7.54 (1H, m), 7.44 (2H, t, J = 7.5 Hz), 5.38 (2H, m), 4.32 (2H, t, J = 6.7 Hz), 2.48-2.32 (1H, m), 1.98-1.21 (22H, broad m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 167.2, 135.9, 135.6, 133.3, 130.1, 129.0, 128.9, 65.7, 43.9, 34.4, 33.8, 33.1, 30.2, 30.0, 29.8, 29.6, 29.3, 26.6, 25.7. R_f = 0.61 (10:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{22}H_{32}O_2$ $[M]^+$ 328.2402, found 328.2400.

Compound 7. Undecylinic aldehyde acetal (0.6611 g, 3.0 mmol) was added *via* syringe to a flask containing **2** (18 mg, 0.021 mmol, 0.7 mol %). The flask was fitted with a vacuum adapter and placed under vacuum (100 mtorr) for 12 hours. The reaction mixture was then purified directly on a silica gel column (2x10 cm), eluting with 15:1 hexane:ethyl acetate. A white solid was obtained (0.5112 g, 83% yield, 4:1 trans/cis as determined by ^{1}H integration of peaks at 5.45 and 5.28 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.45-5.28 (2H, m), 4.30 (2H, t, J = 6.6 Hz), 4.05-3.83 (8H, m), 1.97 (4H, broad m), 1.60 (4H, broad m), 1.50-1.25 (24H, broad m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 130.8, 105.2, 65.3, 34.4, 33.1, 30.1, 30.0, 29.8, 29.7, 29.6, 24.6. R_f = 0.19 (15:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{24}H_{43}O_4$ $[M - H]^+$ 395.3161, found 395.3164.

Compound 8. Allyl phenyl sulfone (1.0881 g, 6.0 mmol) was added *via* syringe to a flask containing **2** (51 mg, 0.062 mmol, 1.0 mol %). The flask was fitted with a vacuum adapter and placed under vacuum (100 mtorr) for 12 hours. The reaction mixture was then purified directly on a silica gel column (2x10 cm), eluting with 2:1 hexane:ethyl

acetate. A white solid was obtained (.3725 g, 37% yield, 8:1 trans/cis as determined by ^{1}H integration of peaks at 5.77 and 5.61 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.84-7.80 (4H, m), 7.69-7.52 (6H, m), 5.61-5.57 (2H, m), 3.76 (4H, dd, J = 1.9 Hz) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 138.8, 134.6, 129.9, 129.6, 129.0, 128.9, 126.9, 60.1. R_f = 0.20 (2:1 hexane:ethyl acetate); HRMS (FAB) calcd for $C_{22}H_{32}O_2$ $[M+ H]^+$ 337.0576, found 337.0568. Elemental analysis Calcd: C: 57.12, H: 4.79; Found: C: 56.88, H: 4.95.

Compound 9. Allyl phenyl sulfone (155 μl, 1.0 mmol) and 9-decen-1-yl benzoate (145 μl, 0.5 mmol) were simultaneously added *via* syringe to a stirring solution of **2** (12 mg, 0.014 mmol, 2.7 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 2:1 hexane:ethyl acetate. A clear oil was obtained (196 mg, 90% yield, 8:1 trans/cis as determined by integration of peaks at 5.60 and 5.46). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 8.03 (2H, d, J = 7.3 Hz), 7.83 (2H, d, J = 7.3 Hz), 7.63-7.41 (6H, m), 5.50-5.34 (2H, m), 4.30 (2H, t, J = 6.6 Hz), 3.72 (2H, d, J = 6.9 Hz), 1.95 (2H, m), 1.72 (2H, m), 1.43-1.08 (10H, broad m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 167.2, 142.3, 134.1, 133.4, 130.0, 129.6, 129.5, 129.1, 128.9, 116.4, 115.7, 65.6, 60.7, 55.8, 33.0, 29.8, 29.7, 29.6, 29.4, 29.3, 29.2, 27.8, 26.6. R_f = 0.42 (2:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{22}H_{32}O_2$ $[M+H]^+$ 415.1943, found 415.1953. Elemental analysis Calcd: C: 69.54, H: 7.29; Found: C: 69.72, H: 6.95.

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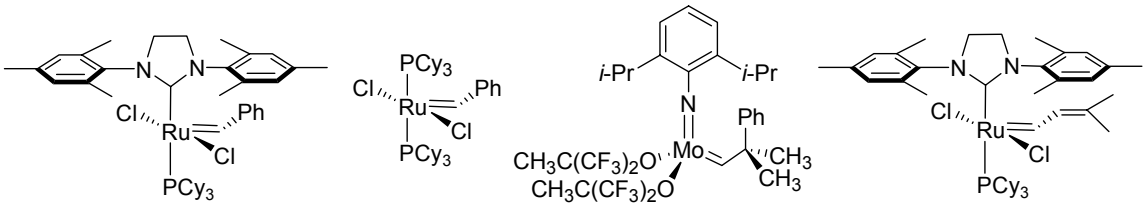
Chapter 3: Synthesis of Trisubstituted Olefins by CM

Trisubstituted carbon-carbon double bonds are a recurring motif in a diverse array of organic molecules. Therefore, new stereoselective methods for generating trisubstituted olefins remain an ongoing challenge in the area of synthetic organic chemistry. A wide variety of organic methodologies have been investigated to date, including intramolecular Claisen rearrangments,[1,2] Wittig olefination,[3] Julia couplings,[4] Peterson olefination,[5] alkylation of sulfonyl hydrazones,[6] and direct methods for the preparation of flourinated trisubstituted alkenes.[7] Transition metal mediated routes, including hydromagnesization,[8] hydrozirconation,[9] and the use of organocuprates,[10] has also been reported, but often suffer from use of harsh stoichiometric reagents. Therefore, a mild and catalytic method of preparing trisubstituted olefins will be synthetically useful, such as olefin cross-metathesis (CM) by employing a variety of commercially-available olefin metathesis catalysts (Figure 1).

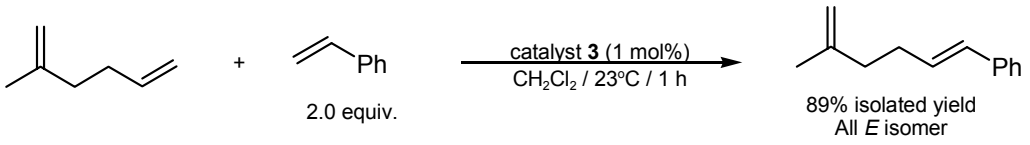


1 **2** **3** **4**

Figure 1: Commonly Used Olefin Metathesis Catalysts

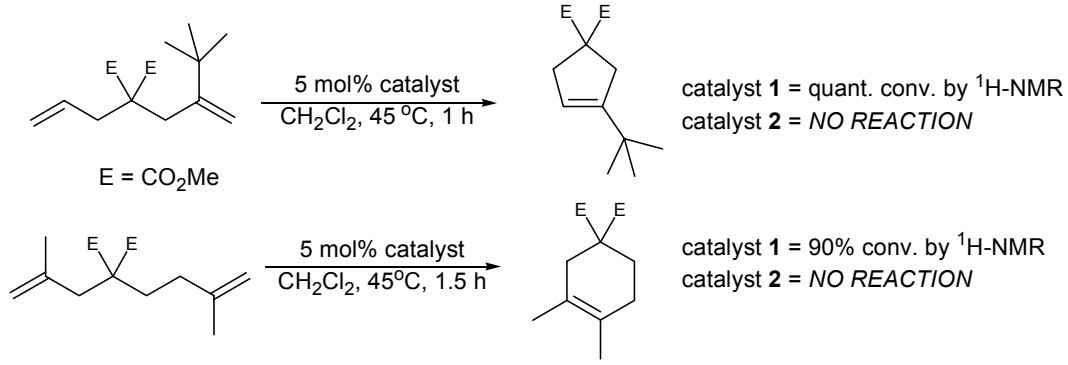
While a variety of trisubstituted olefins have been synthesized by ring-closing metathesis (RCM), the intermolecular CM reaction had not been reported. Wagner *et al.* reported the ADMET polymerization of 2-methyl-1,5-hexadiene with catalyst **3** to polymers of moderate molecular weight that had trisubstituted olefins in the polymer backbone (Scheme 1).[11] In addition, the polymer exhibits perfect 1,4 architecture in the polyisoprene structure. Previously, Crowe *et al.* reported that 1,1-disubstituted olefins

were unreactive CM partners with styrene using catalyst **3** (Scheme 1).[12] For example, in



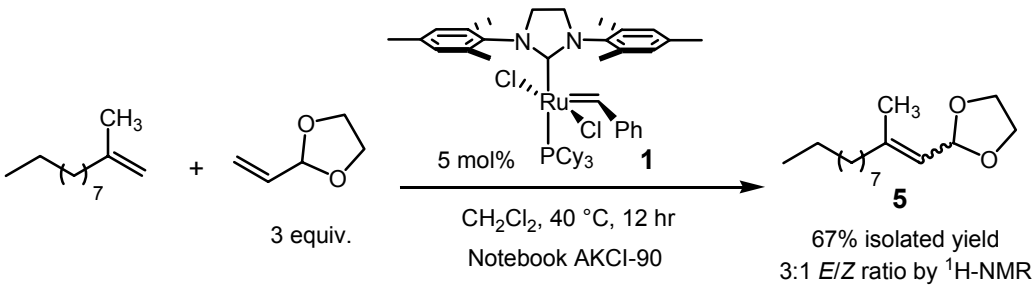
Scheme 1: Gem-disubstituted Olefins Inert to Catalyst **3**

the presence of a 1,1-geminally disubstituted diene only the α-olefin is active for metathesis. However, the highly active ruthenium-based olefin metathesis catalyst **1** containing 4,5-dihydro-imidazol-2-ylidene ligands has been reported to catalyze the RCM of a wide variety of highly substituted dienes (Scheme 2).[13] The high activity of



Scheme 2: Higher Susbtituted Olefins by RCM using Catalyst **1**

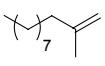
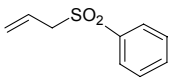
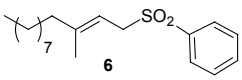
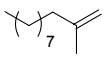
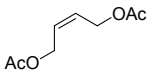
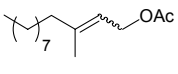
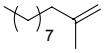
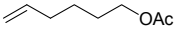
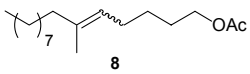
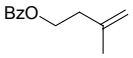
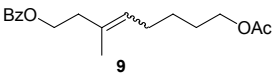
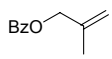
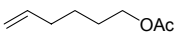
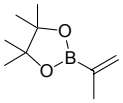
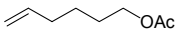
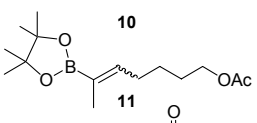
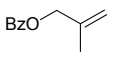
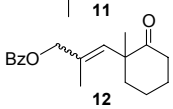
these catalysts for RCM prompted the investigation of their potential application in cross-metathesis of 1,1-disubstituted olefins. We were able to accomplish the first example of intermolecular CM between geminal disubstituted olefins and α-olefins to generate trisubstituted olefinic products.[14] Our studies began with the use of 2-methyl-1-undecene as an unfunctionalized geminal disubstituted olefin for CM with vinyl dioxolanes (Scheme 3). This provides direct access to a protected trisubstituted α,β-unsaturated aldehyde in moderate yields. In this reaction, the vinyldioxolane component (3 equivalents) was added in four equal parts over a six hour period. This maintained a low concentration of dioxolane homodimer and increased the isolated yield of cross-



Scheme 3: Synthesis of Trisubstituted Olefins by Cross-Metathesis

metathesis product by 10 percent. We found that certain homodimers, such as this dioxolane homodimer, were not as active for subsequent CM as the terminal dioxolane equivalent. Therefore, a low concentration of α-olefin reduces the formation of an unreactive homodimer and increases the yield of CM product. A variety of geminally-disubstituted olefins participate in CM with a variety of α-olefins and their equivalents (Table 1, Entry 3-6). Unlike the case of vinyldioxolane as the CM partner, these α-olefin

Table 1. Trisubstituted Olefins by Cross-Metathesis using Catalyst **1**

Entry	1,1-Geminal Olefin	α-Olefin (2 equiv.)	Product	Isolated Yield	*E*/*Z* ratio[b]	Notebook
1			 **6**	87	3.4:1	AKCI-59
2			 **7**	53	2.5:1	AKCI-61
3			 **8**	60	2.3:1	AKCI-68
4			 **9**	80	2.8:1	AKCI-80
5			 **10**	81	4:1	AKCI-87
6			 **11**	72	8.2:1	AKCI-185
7			 **12**	53[a]	3:1	AKCI-95

[a] Catalyst **4** was used [b] Determined by NMR

cross-partners can interchangeably use their homodimerized counterparts in similar

yields. In addition, coupling to allyl sulfone (Entry 1)**,** and 1,4-diacetoxy-*cis*-2,3-butene (Entry 2) can be achieved in good yields with moderate trans stereoselectivity. We were surprised to observe the excellent CM reactivity of allyl sulfone (87% isolated yield, Table 1, Entry 1) since other sulfur-containing functionalities are known to deactivate late-transition metal catalysts.[15] We had previously demonstrated the CM of allyl sulfones with α-olefins using catalyst **2**.[16] Functionalized disubstituted olefins (Table 1, Entries 4 and 5) also proved excellent substrates for this reaction, and showed improved yields relative to purely alkyl substituted examples in Entries 1-3. We observe that the benzoate ester functionality may increase reactivity of the geminal olefins with the catalytic ruthenium species, but the reason why is unclear. We were also interested in incorporating functional groups that could be incorporated by CM. For example, 1,1-disubstituted vinyl boronates participate in CM with α-olefins with improved *E*/*Z* selectivity (Table 1, Entry 6). In fact, the cis and trans isomers obtained are separable by column chromatography. These products are useful for the synthesis of a variety of trisubstituted olefins by Suzuki couplings. This reaction is also advantageous to performing hydroboration of the corresponding alkyne, where a mixture of regioisomers would be obtained.[17] The regiospecificity of CM is important to note, since the choice of CM partners allows one to access either desired regioisomer. Unfortunately, using a 1,1-disubstituted vinylboronate containing a homoallylic silyl ether did not provide appreciable amounts of CM product, so the reaction seems sensitive to steric bulk beyond methyl groups as the other geminal substituent. Finally, we also are able to incorporate quaternary allylic carbons as shown in Entry 7. This provides a trisubstituted olefin with a fully substituted allylic carbon in moderate yield and stereoselectivity. This reaction

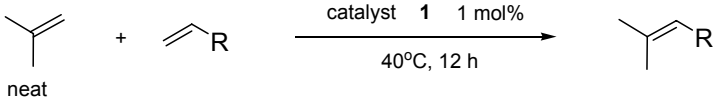
then allows for contiguous stereocenters to be installed by a simple CM reaction. The utility of allylic substitution in CM selectivity will be discussed in subsequent chapters. Finally, it should be noted that in all these reactions, the disubstituted olefin does not undergo homodimerization, enabling quantitative recovery of unreacted starting material. These represent the first examples of cross-metathesis reactions between geminal disubstituted olefins and α-olefins employing ruthenium alkylidenes **1** and **4**. Protected homoallylic and allylic alcohols under these reaction conditions have shown the best conversion to CM product so far.

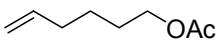
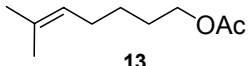
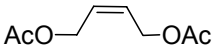
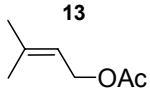
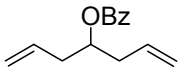
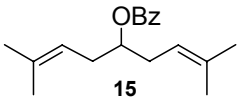
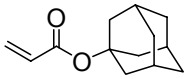
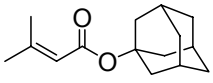
However, we were relatively disappointed with the olefin diastereoselectivity and moderately high catalyst loadings and reaction temperatures required in these reactions. Therefore, we wanted to investigate the use of symmetrical 1,1-geminally disubstituted olefins. Another reason why we wished to investigate these olefins was to increase substrate scope, since only methyl groups as the second geminal substituent are used in Table 1. We anticipated that the use of identical substituents on the geminal carbon would expand the substrate scope, without being complicated by the issue of poor stereoselectivity. In fact, we have been able to affect the convenient CM of symmetrical 1,1-disubstituted olefins with a variety of CM partners. Of particular interest is an isoprenoid synthetic route by the homologation of α-olefins with isobutylene or 2-methyl-2-butene using catalyst **1**.[18] The reactions of a variety of olefins with isobutylene provide excellent CM yields. We were particularly pleased with these reactions since the prenyl groups generated are a ubiquitous structural element in a variety of natural products. Conventional methods to install this structural unit involve Wittig olefinations of an aldehyde or Claisen rearrangement of tertiary allyl ethers. However, the ability for

CM to use exclusively olefinic starting materials to generate trisubstituted olefins, instead of using more reactive aldehyde functionalities, such as those employed in Wittig chemistry will be useful. In fact, since both of these reactions use orthogonal functional groups, this opens avenues for two-directional synthesis using CM and Wittig olefination.

Our initial work in 1,1-symmetrically disubstituted olefins began with the cross-metathesis of isobutylene with α-olefins (Table 2). These reactions offer a convenient

Table 2. Cross Metathesis with Isobutylene using catalyst **1**

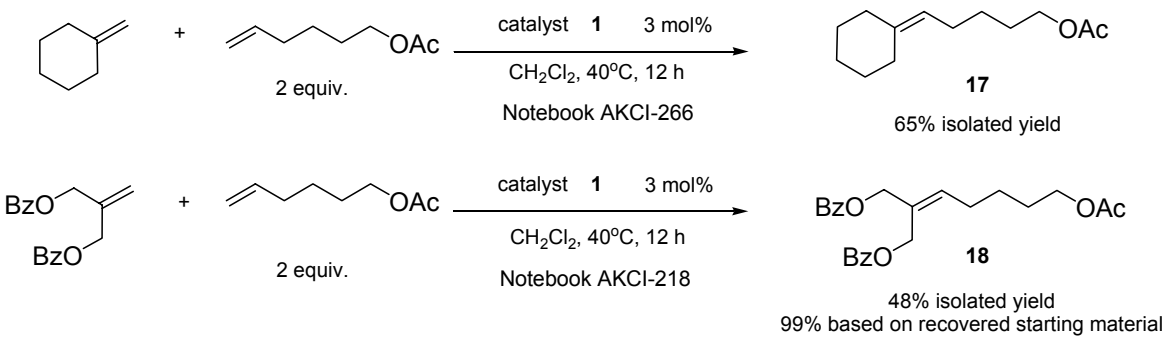


Entry	Metathesis Partner	Product	Isolat. yield	Notebook
1		 **13**	97	AKCII-88
2		 **14**	88	AKCI-231
3		 **15**	96	AKCII-94
4[a]		 **16**	83	DPSI-278

[a] Reaction performed by Daniel P. Sanders, Grubbs Group

alternative to the use of $Ph_3P{=}C(CH_3)_2$ and the corresponding aldehyde to form prenyl functionality. Prenyl groups are a ubiquitous structural element in many natural products and are also frequently employed in ene chemistry. For example, the reaction works well with simple α-olefins (Entry 1) as well as with 1,2-disubstiuted olefin starting materials (Entry 2). In addition the reactions tolerate substrates that could ring close as demonstrated in the homoallylic hepatadiene case (Entry 3). Senecioic acid derivations are also readily available from the CM reaction with the corresponding acrylate ester,

demonstrating the use of electron-deficient olefins (Entry 4). In all of these cases, the



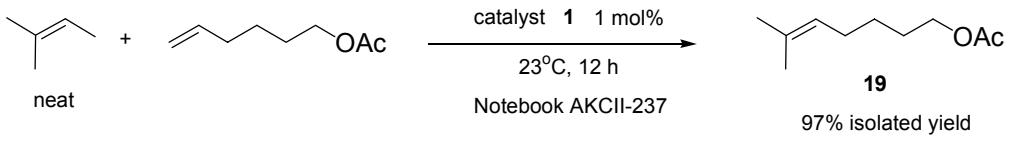
Scheme 4: CM of Symmetrical Disubstituted Olefins

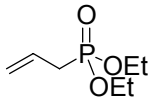
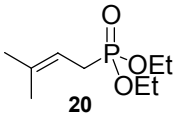
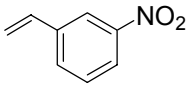
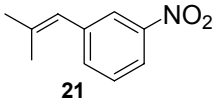
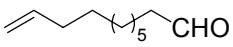
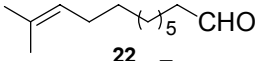
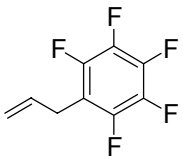
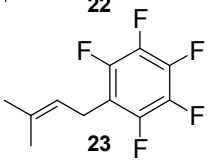
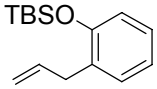
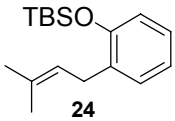
workup is straightforward where the excess isobutylene (bp -6.9 °C) is allowed to evaporate leaving catalyst and CM product. With these results in hand, we investigated other symmetrically substituted olefins and found that both methylene cyclohexane and 2-methylene-1,3-dibenzoate work well as CM partners with 5-hexenyl acetate (Scheme 4). Even though the yields are lower, these reactions offer a straightforward method to homologate olefins without the use of ketone precursors. In addition, since the 1,1-disubstituted olefin does not dimerize, it can be fully recovered and recycled in subsequent CM reactions. These substrates have also been used in this group for homologation to allylboronates[19] and α,β-unsaturated carbonyl containing olefins,[20] thereby demonstrating good substrate scope.

Interestingly, we did observe a small background dimerization of a small amount of isobutylene to tetramethylethylene (<15%), but this did not affect the CM efficiency. The CM efficiency is surprising since the catalyst loadings are very low relative to the amount of bulk olefin in the reaction, with an effective catalyst loading of 0.0001 mol%. The inability of the 1,1-disubstituted olefin to readily homodimerize allows it to serve as both a reaction solvent and as an effective cross partner. These factors allow for selective CM to the trisubstituted olefinic product in excellent yield. However, the background

dimerization of isobutylene to tetramethylethylene prompted us to investigate the use of tetramethylethylene as a more convenient CM partner, since it is a liquid at room temperature (bp 73 ^{o}C). Unfortunately, this did not provide a synthetically useful amount of CM product, but we were able to use 2-methyl-2-butene (bp 35-38 ^{o}C) as a useful CM partner where the entropic driving force is the loss of propene. In fact, we were surprised to see very efficient CM with this substrate at 35 ^{o}C and room temperature (Table 3). This reaction represents the first CM reaction that involves the productive CM of trisubstituted olefins with α-olefins to generate useful products. Our previous results

Table 3. Cross Metathesis with 2-Methyl-2-butene using **1**



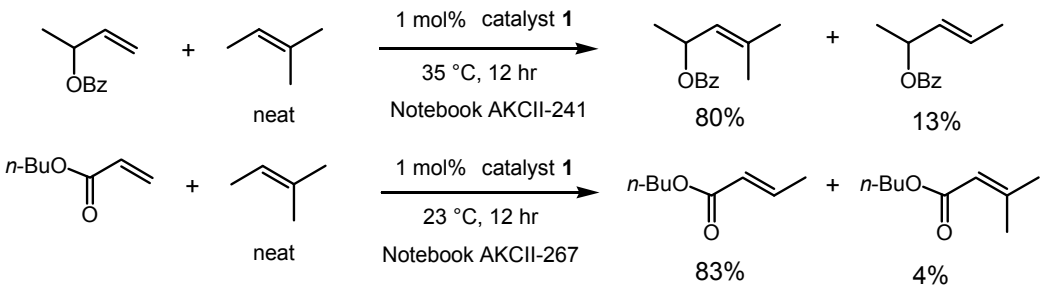
Entry[a]	CM partner	Product	Isolat. Yield	Notebook
1		 **20**	97	AKCII-222
2		 **21**	95	AKCII-232
3		 **22**	91	AKCII-235
4		 **23**	91	AKCII-233
5		 **24**	99	AKCII-242

[a] Reactions performed at 35 ^{o}C

required higher catalyst loadings (5 mol%) and refluxing CH_2Cl_2 to get productive CM yields. One general note is the ease in performing these reactions, where no solvent is

required, all reagents were handled on the bench, and only ambient temperatures are needed to afford CM products in excellent yield. The substrate scope in these CM is quite general, including allylphosphonates (Entry 1), which allows for an efficient synthesis of prenyl diene reagents from commercially available starting materials. In addition to amenability of an electron-deficient styrene (Entry 2), unprotected aldehydes work well, allowing direct orthogonality to Wittig methods (Entry 3). Substituted allylbenzenes (Entry 4 and 5) are also well tolerated in the reaction. Particularly interesting is the CM of phenolic allylbenzene (Entry 5), where CM is a convenient alternative to aromatic Claisen chemistry that would initially require the synthesis of tertiary phenoxy ether. In fact, we were pleased to find that this method has been applied in an allyl to prenyl conversion in the synthesis of the core of Garsubellin A.[21] In all of these reactions in Table 3, we were able to detect a small amount of the methyl CM product, but observed that this material is consumed in the course of the reaction to furnish the more thermodynamically stable trisubstituted olefin. Therefore, we wanted to see if there were olefin CM partners that would not readily perform metathesis on a methyl terminated product. For example, in the reaction of *n*-butyl-acrylate with 2-methyl-2-butene, we were able to detect only a small amount (< 5%) of the senecioic acid derivative, but observed the majority of material converted to *n*-butyl-crotonate (Scheme 5). In this case, the propagating species of catalyst **1** was unable to perform secondary metathesis of the initial CM product. Additionally, in the CM reaction of a secondary allylic benzoate with 2-methyl-2-butene furnishes a mixture of methyl and dimethyl capped products that can not be converted to more thermodynamically stable

trisubstituted olefin even upon re-subjecting the mixture to fresh catalyst and 2-methyl-2-



Scheme 5. Product Distribution by ^{1}H-NMR of Challenging CM Substrates

butene. These results lead to three important points about the differences in the use of isobutylene and 2-methyl-2-butene in CM reactions to install prenyl groups. First, despite the ease of the 2-methyl-2-butene reaction, the substrate scope in isobutylene CM is greater because it can perform CM on sterically challenging and electron-deficient olefins. Second, that 2-methyl-2-butene can be a useful method to install either methyl *or* dimethyl groups based on the reactivity characteristics of the CM partner, i.e. the ability of the methyl terminated product to undergo secondary metathesis. Finally, these reactions can be used to determine the reactivity of new CM substrates, specifically the extent of secondary metathesis of initial CM products. This has an important impact on determining product selectivity in CM and will be discussed in the following chapters.

In conclusion, the cross-metathesis reactions between symmetrical disubstituted olefins and terminal olefins employing ruthenium alkylidenes **1** and **4** have been presented. These reactions allow for the selective functionalization of α-olefins to trisubstituted olefins. Even though there are limitations in terms of sterics on the 1,1-disubstituted component, these reactions do tolerate a wide variety of functionalities and substitutions including those that are used in alternative olefination methods. Of particular synthetic interest is the convenient conversion of terminal olefins to prenyl

groups. This method allows for an efficient one-step formation of trisubstituted olefins under mild reaction conditions and low catalyst loadings and further demonstrates the utility of olefin metathesis in organic synthesis.

Experimental Section.

General Experimental Section. NMR spectra were recorded on either a JEOL GX-400, GE-300 NMR, or Varian Mercury NMR. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-resolution mass spectra (EI and FAB) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.[22]

Compound 5. 2-Methyl-1-undecene (110 μl, 0.5 mmol) and 2-vinyl-1,3-dioxolane (100 μl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (12 mg,

0.015 mmol, 2.9 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. Pale yellow oil was obtained (60 mg, 67% yield, 3:1 *E*/*Z* based on relative intensities of ^{13}C peaks at 122.1, 121.2 ppm). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 5.48 (1H, m), 5.22 (1H, m), 4.00 (2H, app t), 3.87 (2H, app t), 1.96 (2H, m), 1.75 (3H, s), 1.46-1.25 (17H, m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 122.1, 121.2, 101.0, 100.6, 65.4, 40.1, 32.4, 32.1, 30.1, 30.0, 29.9, 27.9, 27.7, 23.2, 14.6. R_f = 0.26 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{15}H_{28}O_2$ $[M]^+$ 240.2083, found 240.2089.

Compound 6. 2-Methyl-1-undecene (110 µl, 0.50 mmol) and allylphenylsulfone (155 µl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (30 mg, 0.035 mmol, 7 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. Clear oil was obtained (139 mg, 87% yield, 3.4:1 *E*/*Z* based on relative intensities of ^{13}C peaks at 110.6, 111.0 ppm). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.84-7.80 (2H, m), 7.69-7.52 (3H, m), 5.64 (1H, m), 3.76 (2H, d, J = 6.9 Hz), 1.96 (2H, m), 1.75 (3H, s), 1.46-1.25 (14H, m), 0.87 (3H, t, J = 6.3 Hz) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 147.3, 139.9, 129.5, 129.1, 111.0, 110.6, 56.7, 56.5, 40.2, 32.4, 32.3, 30.1, 30.0, 29.9, 29.8, 28.1, 24.0, 23.2, 16.6, 14.6. R_f = 0.53 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{19}H_{30}O_2S$ $[M + H]^+$ 323.2045, found 323.2046. Elemental analysis Calcd: C: 70.76, H: 9.38; Found: C: 70.66, H: 9.43.

Compound 7. 2-Methyl-1-undecene (110 μl, 0.50 mmol) and *cis*-2-butene-1,4-diacetate (160 μl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (21 mg, 0.025 mmol, 5 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. Clear oil was obtained (63 mg, 53% yield, 2.5:1 *E*/*Z* based on integrations of ^{1}H peaks at 4.57, 4.66 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.32 (1H, m), 4.57 (2H, d, J = 6.9 Hz), 2.07-1.96 (5H, m), 1.75 (3H, s), 1.46-1.25 (14H, m), 0.87 (3H, t, J = 6.3 Hz) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.6, 118.6, 110.0, 62.0, 40.1, 32.6, 32.4, 30.1, 29.8, 28.1, 24.0, 23.2, 21.6, 16.6, 14.6. R_f = 0.53 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{15}H_{28}O_2$ $[M]^+$ 240.2085, found 240.2089.

Compound 8. 2-Methyl-1-undecene (110 μl, 0.50 mmol) and 5-hexenyl-1-acetate (170 μl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (20 mg, 0.024 mmol, 4.8 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. Clear oil was obtained (83 mg, 60% yield, 2.3:1 *E*/*Z* based on relative intensities of ^{13}C peaks at 125.0, 124.2 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.06 (1H, m), 4.04 (2H, t, J = 6.9 Hz), 2.03 (3H, obs s), 2.08-1.91 (4H, m), 1.69-1.57 (2H, m), 1.57 (3H, obs s), 1.47-1.05 (16H, m), 0.87 (3H, t, J = 6.3 Hz) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.7, 136.7, 125.0, 65.1, 40.2, 32.5, 32.4, 30.2, 30.1, 29.9, 28.8,

28.5, 28.0, 26.7, 23.2, 21.5, 16.6, 14.6. R_f = 0.35 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{18}H_{34}O_2$ $[M]^+$ 282.25556, found 282.25588. Elemental analysis Calcd: C: 76.54, H: 12.13; Found: C: 75.96, H: 12.15.

Compound 9. 1-Benzyloxy-3-methyl-3-butene (95 μl, 0.50 mmol) and 5-hexenyl-1-acetate (170 μl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 4.3 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Clear oil was obtained (121 mg, 80% yield, 2.8:1 *E*/*Z* based on integration of ^{1}H peaks at 2.49, 2.43 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (2H, d, *J* = 6.9 Hz), 7.54 (1H, t, *J* = 7.4 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 5.26-5.20 (1H, m), 4.38 (2H, t, *J* = 6.6 Hz), 4.00 (2H, t, J = 6.3 Hz), 2.51-2.41 (2H, m), 2.06-1.99 (5H, m), 1.68 (3H, s), 1.58 (2H, m), 1.36 (2H, m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.8, 167.1, 133.4, 132.0, 131.0, 128.9, 127.5, 65.0, 64.0, 39.3, 31.8, 28.1, 26.5, 24.2, 21.6, 16.6. R_f = 0.52 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{18}H_{24}O_4$ $[M]^+$ 304.1674, found 304.1686. Elemental analysis Calcd: C: 71.03, H: 7.95; Found: C: 70.67, H: 7.92.

Compound 10. 1-Benzyloxy-2-methyl-2-propene (90 μl, 0.51 mmol) and 5-hexenyl-1-acetate (170 μl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (21 mg, 0.026 mmol, 5.0 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then

reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate (500 ml) and then elute with 9:1 hexane:ethyl acetate. Clear oil was obtained (120 mg, 81% yield, 4:1 *E*/*Z* based on integration of ^{1}H peaks at 5.41, 5.63 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (2H, d, *J* = 6.9 Hz), 7.54 (1H, t, *J* = 7.4 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 5.63 (1H, m), 4.67 (2H, s), 4.00 (2H, t, *J* = 6.3 Hz), 2.18-2.01 (5H, m), 1.97 (3H, s), 1.61 (2H, m), 1.43 (2H, m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.3, 166.6, 133.0, 130.7, 130.6, 130.5, 129.7, 129.3, 128.5, 70.7, 64.5, 28.4, 25.8, 21.6, 14.2. R_f = 0.43 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{17}H_{22}O_4$ $[M + H]^+$ 291.1596, found 291.1589. Elemental analysis Calcd: C: 70.32, H: 7.64; Found: C: 69.89, H: 7.76.

Compound 11. 5-Hexenyl-1-acetate (170 μl, 1.0 mmol) was added *via* syringe to a stirring solution of **1** (21 mg, 0.026 mmol, 5.0 mol %) and 2-isopropenyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane[23] (84 mg, 0.50 mmol) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500 ml). Clear oil was obtained (101 mg, 72% yield, 8.2:1 *E*/*Z* based on integration of ^{1}H peaks of isolated compounds at 6.25, 6.03 ppm). ^{1}H NMR of *E* isomer (300 MHz, $CDCl_3$, ppm): δ 6.25 (1H, t, *J* = 6.8 Hz), 4.00 (2H, t, *J* = 6.3 Hz), 2.12 (2H, m), 1.97 (3H, s), 1.80-1.60 (5H, m), 1.51-1.41 (2H, m), 1.26 (12H, s). HRMS (EI) calcd for $C_{17}H_{25}BO_4$ $[M]^+$ 282.2005, found 282.2011. R_f = 0.41 (9:1 hexane:ethyl acetate), minor isomer (*Z*) R_f = 0.50. Spectra match those of a

related known compound, see: Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett.* **1999**, 1069.

Compound 12. 1-Benzyloxy-2-methyl-2-propene (82 μl, 0.51 mmol) and 2-vinyl-2-methylcyclohexanone (135 μl, 1.0 mmol) were simultaneously added *via* syringe to a stirring solution of **4** (30 mg, 0.036 mmol, 7.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500mL). Light brown oil was obtained (76 mg, 53% yield, 3:1 *E*/*Z* based on integration of ^{1}H peaks at 5.63, 5.41 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (2H, d, J = 6.9 Hz), 7.54 (1H, t, J = 7.4 Hz), 7.42 (2H, t, J = 7.6 Hz), 5.63 (1H, m), 4.67 (2H, s), 2.47-2.23 (2H, m), 1.95-1.81 (9H, m), 1.04 (3H, m). R_f = 0.57 (9:1 hexane:ethyl acetate).

Compound 13. To an oven dried, 100 mL Fischer-Porter bottle with Teflon stir bar, ruthenium metathesis catalyst **1** (21.0 mg, 0.025 mmol, 3.7 mol%) was added. The bottle was capped with a rubber septum and flushed with dry nitrogen and cooled to -78 ^{o}C. 5-Hexenyl-1-acetate (110 μL, 0.66 mmol) was injected into the bottle. Once the substrate was frozen, a pressure regulator was attached to the bottle. The bottle was evacuated and backfilled with dry nitrogen 3 times. Subsequently, isobutylene (5 mL, 50 equiv.) was condensed into the bottle. The bottle was backfilled to ~2 psi with nitrogen, sealed, and allowed to slowly warm to room temperature, at which time it was transferred to an oil bath at 40 ^{o}C. After stirring for 12 hours, the bottle was removed from the oil bath and

allowed to cool to room temperature. The isobutylene was slowly vented off at room temperature until the pressure apparatus could be safely disassembled. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate (500mL). Clear oil was obtained (108 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.08 (1H, m), 4.03 (2H, t, J = 6.9 Hz), 2.02 (3H, s), 2.00 (2H, obs q, J = 7.2 Hz), 1.67 (3H, s), 1.63-1.56 (5H, m), 1.41-1.31 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.2, 131.9, 124.2, 64.8, 28.5, 27.8, 26.3, 26.0, 21.3, 18.0. R_f = 0.43 (9:1 hexane:ethyl acetate).

Compound 14. To an oven dried, 100 mL Fischer-Porter bottle with Teflon stir bar, ruthenium metathesis catalyst **1** (21.0 mg, 0.025 mmol, 5.0 mol%) was added. The bottle was capped with a rubber septum and flushed with dry nitrogen and cooled to -78 ^{o}C. *cis*-2-butene-1,4-diacetate (80 μL, 0.51 mmol) was injected into the bottle containing 2.5 mL CH_2Cl_2 (it was later found that this is not necessary for the reaction to proceed). The bottle was evacuated and backfilled with dry nitrogen 3 times. Subsequently, isobutylene (2 mL) was condensed into the bottle. The bottle was backfilled to ~2 psi with nitrogen, sealed, and allowed to slowly warm to room temperature, at which time it was transferred to an oil bath at 40 ^{o}C. After stirring for 12 hours, the bottle was removed from the oil bath and allowed to cool to room temperature. The isobutylene was slowly vented off at room temperature until the pressure apparatus could be safely disassembled. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate (500mL). Clear oil was obtained (108 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.34 (1H, m), 4.55

(2H, d, J = 7.2 Hz), 2.04 (3H, s), 1.75 (3H, broad s), 1.70 (3H, broad s). R_f = 0.66 (9:1 hexane:ethyl acetate). Spectra matches that of previously reported characterization, see: Vani, P. V. S. N.; Chida, A. S.; Srinivasan, R.; Chandrasekharam, M.; Singh, A. K. *Synth. Commun.* **2001**, *31*, 219.

Compound 15. To an oven dried, 100 mL Fischer-Porter bottle with Teflon stir bar and containing 4-Benzyloxy-1,6-heptadiene (200 mg, 0.66 mmol), ruthenium metathesis catalyst **1** (13.3 mg, 0.016 mmol, 1.7 mol%) was added. The bottle was capped with a rubber septum and flushed with dry nitrogen and cooled to -78 ^{o}C. Once the substrate was frozen, a pressure regulator was attached to the bottle. The bottle was evacuated and backfilled with dry nitrogen 3 times. Subsequently, isobutylene (10 mL) was condensed into the bottle. The bottle was backfilled to ~2 psi with nitrogen, sealed, and allowed to slowly warm to room temperature, at which time it was transferred to an oil bath at 40 ^{o}C. After stirring for 12 hours, the bottle was removed from the oil bath and allowed to cool to room temperature. The isobutylene was slowly vented off at room temperature until the pressure apparatus could be safely disassembled. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate (500mL). Clear oil was obtained (241 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.05 (2H, d, J = 7.2 Hz), 7.53 (1H, t, J = 7.2 Hz), 7.42 (2H, t, J = 7.6 Hz), 5.19 (2H, t, J = 7.2 Hz), 5.10 (1H, q, J = 6.0 Hz), 2.42-2.36 (4H, m), 1.69 (6H, s), 1.63 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.0, 134.2, 132.4, 129.8, 128.0, 119.7, 75.0, 32.7, 26.0, 18.0. R_f = 0.76 (9:1 hexane:ethyl acetate).

Compound 17. 5-Hexenyl-1-acetate (167 μL, 1.0 mmol) and 2-methylenecyclohexane (60 μL, 0.50 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (19 mg, 0.023 mmol, 4.6 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Clear oil was obtained (68 mg, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.04 (1H, t, J = 7.2 Hz), 4.05 (2H, t, J = 6.3 Hz), 2.11-1.97 (9H, m), 1.69-1.31 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.4, 128.7, 120.9, 64.9, 37.5, 29.0, 28.9, 28.5, 28.2, 27.3, 26.9, 26.8, 21.4. R_f = 0.68 (9:1 hexane:ethyl acetate).

Compound 18. 5-Hexenyl-1-acetate (170 μL, 1.0 mmol) was added *via* syringe to a stirring solution of **1** (15 mg, 0.018 mmol, 3.3 mol %) and 2-methylenepropane-1,4-dibenzoate (163 mg, 0.55 mmol) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500mL) and then elute with 4:1 hexane:ethyl acetate. Clear oil was obtained (109 mg, 48% yield) as well as (94 mg, 0.31 mmol) of and 2-methylenepropane-1,4-dibenzoate starting material. CM product ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (4H, d, J = 6.9 Hz), 7.54 (2H, t, J = 7.4 Hz), 7.42 (4H, t, J = 7.6 Hz), 5.92 (1H, t, J = 7.5 Hz), 4.99 (2H, s), 4.92 (2H, s), 4.05 (2H, t, J = 6.3 Hz), 2.29 (2H, q, J = 7.5 Hz), 2.01 (3H, s), 1.69-1.64 (2H, m), 1.53-1.45 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.3, 166.5, 136.8, 133.2, 133.1, 130.2, 130.1, 129.8, 128.5, 128.4, 67.7, 64.5, 60.8, 28.6, 27.8, 26.1, 21.4. R_f = 0.13 (9:1 hexane:ethyl acetate).

Compound 19. 2-Methyl-2-butene (3.0 mL) (Aldrich Chem. Co.) and 5-hexenyl-1-acetate (230 μL, 1.47 mmol) were added simultaneously *via* syringe to a stirring solution of catalyst **1** (11 mg, 0.013 mmol, 0.85 mol%) under a nitrogen atmosphere. The flask was allowed to stir at room temperature for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 25:1 hexane:ethyl acetate to provide the cross metathesis product (244 mg, 1.43 mmol, 97% yield) as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.08 (1H, m), 4.03 (2H, t, J = 6.9 Hz), 2.02 (3H, s), 2.00 (2H, obs q, J = 7.2 Hz), 1.67 (3H, s), 1.63-1.56 (5H, m), 1.41-1.31 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.2, 131.9, 124.2, 64.8, 28.5, 27.8, 26.3, 26.0, 21.3, 18.0. R_f = 0.43 (9:1 hexane:ethyl acetate).

Compound 20. 2-methyl-2-butene (3.0 mL) (Aldrich Chem. Co.) was added *via* syringe to a stirring solution of catalyst **1** (15 mg, 0.018 mmol, 2.8 mol%) and diethylallylphosphonate (100 μL, 0.62 mmol) under a nitrogen atmosphere. The flask was fitted with a condenser and heated to 35 ^{o}C under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 10:1 ethyl acetate:hexanes (500 mL) followed by 20:1 ethyl acetate:hexanes (300 mL) to provide the cross metathesis product (123 mg, 0.60 mmol, 97% yield) as a viscous oil. ^{1}H NMR (300 MHz, CDCl3, ppm): δ 5.15 (1H, m), 4.06 (4H, m), 2.47 (2H, dd, J = 21.9, 7.8 Hz), 1.67 (3H, d, J = 5.4 Hz), 1.58 (3H, d, J = 4.2 Hz), 1.24 (6H, J = 6.9 Hz) and matches that of a previous characterization, see:

Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572. R_f = 0.29 (1:1 hexane:ethyl acetate).

Compound 21. 2-methyl-2-butene (3.2 mL) (Aldrich Chem. Co.) and 3-nitrostyrene (190 μL, 1.36 mmol) were added simultaneously *via* syringe to a stirring solution of catalyst **1** (11 mg, 0.013 mmol, 1.0 mol%) under a nitrogen atmosphere. The flask was fitted with a condenser and heated to 35 ^{o}C under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate to provide the cross metathesis product (229 mg, 1.29 mmol, 95% yield) as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.16-7.99 (2H, m), 7.61-7.40 (2H, m), 6.42-6.28 (1H, m), 1.93 (3H, s), 1.87 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.8, 134.8, 131.8, 129.4, 129.1, 123.4, 121.4, 120.8, 27.1, 19.7. R_f = 0.41 (9:1 hexane:ethyl acetate). Spectra matched those previously reported, see: Wan, P.; Davis, M. J.; Teo, M.-A. *J. Org. Chem.* **1989**, *54*, 1354.

Compound 22. 2-methyl-2-butene (3.2 mL) (Aldrich Chem. Co.) and undecylinic aldehyde (270 μL, 1.30 mmol) were added simultaneously *via* syringe to a stirring solution of catalyst **1** (11 mg, 0.013 mmol, 1.0 mol%) under a nitrogen atmosphere. The flask was fitted with a condenser and heated to 35 ^{o}C under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate to provide the cross metathesis product (231 mg, 1.18 mmol, 91% yield) as a clear oil. ^{1}H NMR (300 MHz,

$CDCl_3$, ppm): δ 9.74 (1H, s), 5.10 (1H, m), 2.42 (2H, m), 1.96 (2H, m), 1.68-1.50 (8H, m), 1.47-1.30 (10H, m). R_f = 0.31 (9:1 hexane:ethyl acetate).

Compound 23. 2-methyl-2-butene (3.2 mL) (Aldrich Chem. Co.) and pentafluoroallylbenzene (225 μL, 1.47 mmol) were added simultaneously *via* syringe to a stirring solution of catalyst **1** (13 mg, 0.015 mmol, 1.0 mol%) under a nitrogen atmosphere. The flask was fitted with a condenser and heated to 35 ^oC under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate to provide the cross-metathesis product (316 mg, 1.34 mmol, 91% yield) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 5.13 (1H, m), 3.37 (2H, m), 2.42 (2H, m), 1.75 (3H, s), 1.65 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 134.9, 119.1, 25.9, 21.7, 17.9. R_f = 0.93 (9:1 hexane:ethyl acetate).

Compound 24. 2-methyl-2-butene (3.0 mL) (Aldrich Chem. Co.) was added *via* syringe to a stirring solution of catalyst **1** (13 mg, 0.015 mmol, 1.0 mol%) and 2-vinyl-1-*tert*-butyldimethylsilyloxyphenol (263 mg, 1.06 mmol) under a nitrogen atmosphere. The flask was fitted with a condenser and heated to 35 ^oC under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate to provide the cross metathesis product (290 mg, 1.05 mmol, 99% yield) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.31-6.86 (4H, m), 5.40 (1H, m), 3.45 (2H, d, J = 7.2 Hz), 1.87 (3H, s), 1.82 (3H, s), 1.15 (9H, s), 0.37 (6H, s). R_f = 0.89 (9:1 hexane:ethyl acetate). Compound

spectra match those of the methyl ether analog, see: Strunz, G.; Ya, L. *Can. J. Chem.* **1992**, *70*, 1317.

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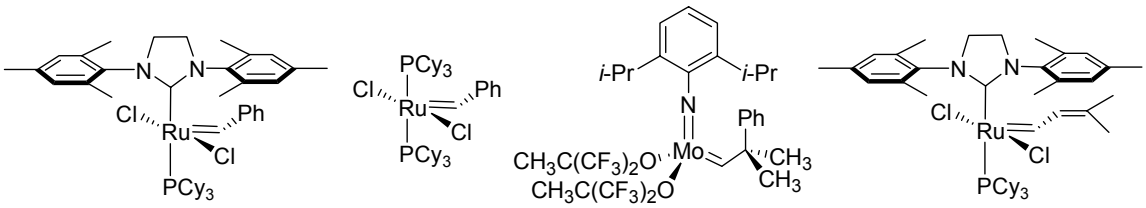
Chapter 4: Synthesis of Functionalized Olefins by CM

The generation of olefins with electron-withdrawing functionality, such as α,β-unsaturated aldehydes, ketones, and esters, remains an important transformation in organic chemistry. The most common approach to these compounds is by use of the Horner-Wadsworth-Emmons (HWE) reaction of stabilized phosphonium ylides with aldehydes and ketones. Other approaches include metal-catalyzed cross-coupling reactions, such as the Heck reaction.[1] These compounds are highly versatile in a variety of reactions, including a variety of conjugate addition reactions.[2] Therefore, the ability to rapidly generate these compounds is highly advantageous. One possible method to synthesize these products may be through the use of olefin cross-metathesis (CM) using commercially available catalysts **1** - **4** (Figure 1). This would be particularly useful, since ethylene would be the only byproduct in the reaction and a wide variety of commercially

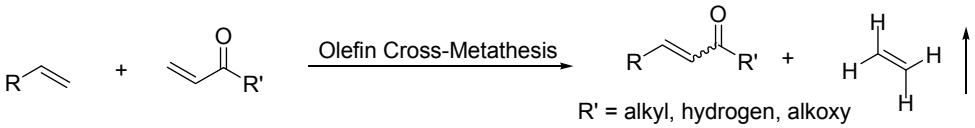


1 **2** **3** **4**

Figure 1: Commonly Used Olefin Metathesis Catalysts

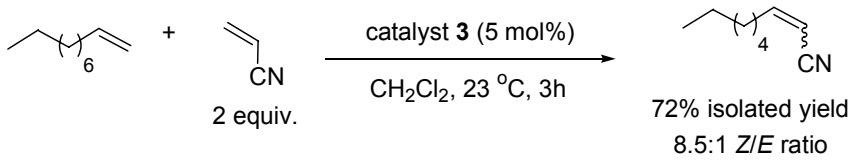
available acrylates and vinyl ketones could be used in the reaction (Scheme 1). However, the use of electron-deficient olefins in CM has been met with limited success. One of the initial reports, by Crowe and Goldberg,[3] showed that acrylonitrile participated in a cross-metathesis reaction with a variety of terminal olefins using catalyst **3** (Scheme 2).

However, other α,β-substituted olefins such enones and enoic esters, were



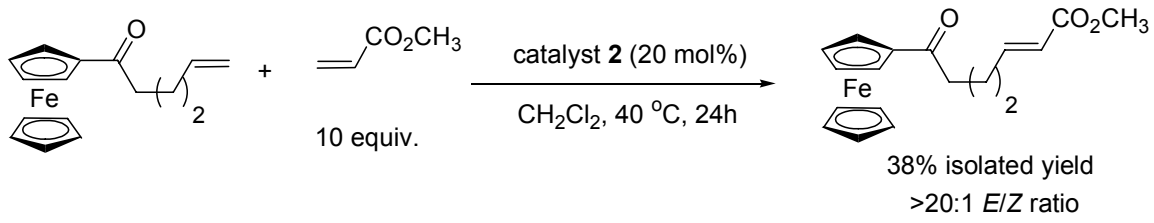
Scheme 1: Proposed α,β-Unsaturated Carbonyl CM with Olefinic Starting Materials

not compatible with molybdenum alkylidene **3** making the methodology strictly limited to acrylonitriles. However, ruthenium alkylidenes **1** and **4** bearing N-heterocyclic carbene ligands displayed unique new activity in CM



Scheme 2: Acrylonitrile CM with Molybdenum-based catalysts

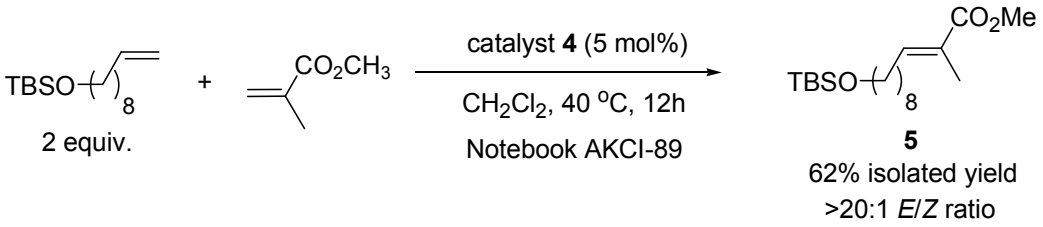
towards previously metathesis inactive substrates with catalyst **2** and **3**, such as 1,1-geminally disubstituted olefins as described in the previous chapter. Therefore, we decided to investigate CM of α,β-unsaturated carbonyl containing olefins. There had been one report of CM of acrylate esters with catalyst **2** at the same time as this work, but the yield is low and requires high catalyst loadings (Scheme 3).[4] In addition, a large



Scheme 3: Previous Acrylate CM with Ruthenium bis-phosphine catalysts

excess of acrylate was required to provide any measurable amount of CM product. However, the homologation of terminal olefins with α,β-unsaturated carbonyls has been efficiently accomplished using ruthenium alkylidenes **1** and **4**. The reaction exhibits excellent selectivity in terms of product selectivity and stereoselectivity.[5]

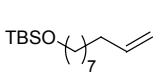
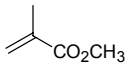
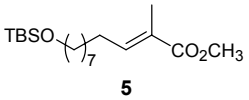
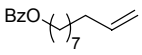
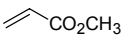
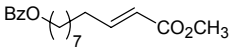
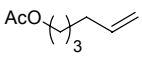
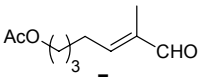
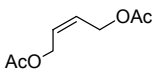
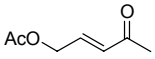
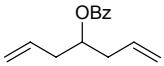
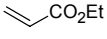
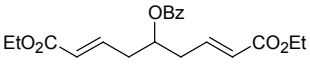
In exploring a variety of geminally disubstituted olefins in cross-metathesis (vide infra), we discovered that methyl methacrylate participates in a cross-metathesis reaction with α-olefins to generate the trisubstituted enoic ester **5** in moderate yield with excellent stereoselectivity (Scheme 4). This led to the investigation of a variety of α,β- carbonyl



Scheme 4: Initial Acrylate CM with Ruthenium imidazolylidene catalysts

containing compounds in CM (Table 1). Particularly notable are the excellent yields attained with aldehydes (Table 1, Entry 3) where the desired oxidation state can be

Table 1. Cross-Metathesis Reactions with Unsaturated Esters, Aldehydes and Ketones[a]

Entry	CM Partner	Unsaturated Carbonyl	Equiv.	Product	Isolated Yield	*E*/*Z*[b]	Notebook
1			0.5	 **5**	62	>20:1	AKCI-89
2			2.0	 **6**	91	>20:1	AKCI-110
3			0.5	 **7**	92[c]	>20:1	JPM
4			0.5	 **8**	81	>20:1	AKCI-203
5			4.0	 **9**	76	>20:1	AKCII-93

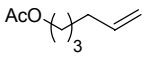
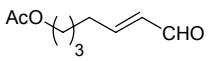
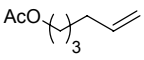
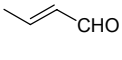
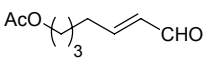
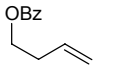
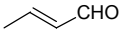
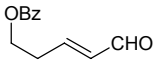
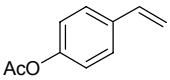
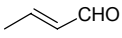
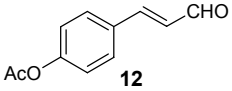
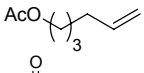
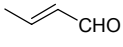
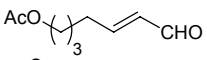
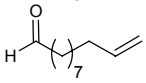
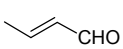
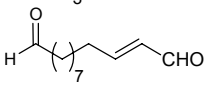
[a]Reactions with 3-5 mol% of **1** or **4** [b]Ratio based on ^{1}H-NMR spectra [c]Reaction performed by J.P. Morgan, Grubbs Group

directly accessed; unlike using HWE chemistry where the ester needs to be initially formed followed by reduction.[6] In addition, the CM reaction between an allyl alcohol and vinyl ketone work well, demonstrating that α-olefins bearing functionality at the allylic position can be used (Entry 4). Finally, a double CM reaction can be performed

on a homoallylic benzoate (Entry 5). This substrate may be susceptible to base-promoted eliminate under Wittig conditions, but is completely amenable to CM conditions with an excess of the acrylate partner. It should be noted that acrylic amides and acids have also been applied by this group in similar CM reactions and demonstrated good substrate scope.[7] In addition, the reactions are all trans selective, making them synthetically useful. In summary, these discoveries opened new possibilities for the use of CM as an efficient and highly stereoselective carbon-carbon bond forming reaction.

In the reactions using acrolein as the CM partner, an interesting trend developed as the reaction was optimized. For example, we observed a decrease in CM efficiency as the ratio of acrolein to catalyst increased. We imagined that the commercial purity of

Table 2. Cross-Metathesis Reactions with Acrolein versus Crotonaldehyde[a]

Entry	CM Partner	Unsaturated Carbonyl	Equiv.	Product	Isolated Yield	*E*/*Z*[b]	Notebook
1			2.0	 **10**	62[c]	>20:1	JPM
2			2.0		95[d]	>20:1	AKCII-23
3			2.1	 **11**	56	>20:1	AKCII-34
4			2.0	 **12**	89	>20:1	AKCII-30
5			1.0		77	>20:1	AKCII-25
6			2.2	 **13**	98	>20:1	AKCII-28

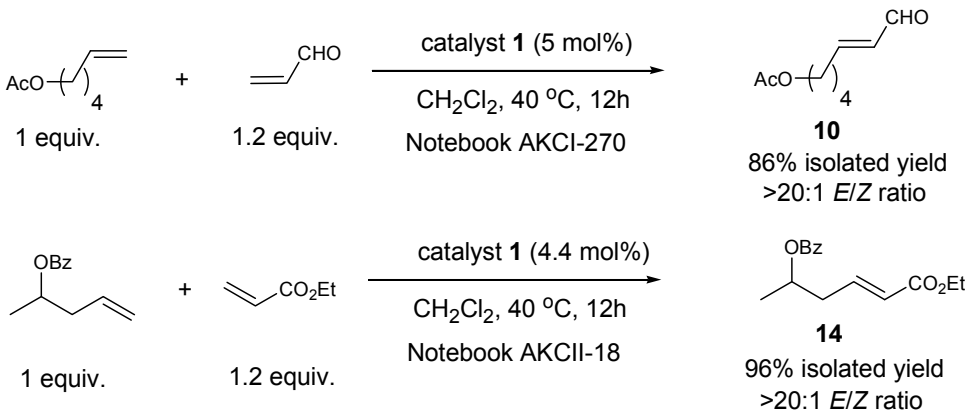
[a]Reactions with 3-5 mol% of **1** or **4** [b]Ratio based on ^{1}H-NMR spectra [c]Reaction performed by J.P. Morgan, Grubbs Group [d] Yield determined by NMR

acrolein may have been inhibiting catalyst activity. Therefore, many of the reactions that were not efficient reactions with acrolein proceeded in good yields when crotonaldehyde was used as the aldehyde source, since it is available in greater than 99% purity from

Aldrich. There was a significant increase in yield under identical reaction conditions (Table 2, Entries 1 and 2). This reaction optimization allowed for a variety of new α,β-unsaturated aldehydes to be prepared, including ones that could eliminate under HWE conditions, such as homoallylic benzoate (Entry 3). The crotonaldehyde CM method also provides access to a variety of cinnamaldehydes that can be prepared by CM, such as 4-acetoxycinnamaldehyde **12** (Entry 4). This is an important result since almost 700 styrenes are commercially available, while there are only 20 cinnamaldehydes are available. It is also important to note that many of these reactions are highly selective CM processes, where 1:1 stoichiometry provides more that 50% CM product (Entry 5) and is discussed below in detail. In addition, the functional group tolerance of the catalyst allows for the installation a α,β-unsaturated aldehyde in the presence of an aliphatic aldehyde (Entry 6). In all of these reactions, exclusive formation of the trans olefin isomer is observed, as it is formed as the kinetic product in the reaction and not a result of secondary metathesis to the more thermodynamically favored product. For example, the productive CM formation of a trans-cinnamate is on a faster timescale than the metathesis-based isomerization of a cis-cinnamate to the trans-cinnamate. It is not clear why the trans olefin is the initial product, since there are no direct analogies between the metallocyclobutane intermediates involved in this reaction and oxophosphatane intermediates invoked in stereocontrol in Horner-Wadsworth-Emmons chemistry. Regardless, the stereoselectivities observed make these reactions useful for further synthetic manipulations.[8]

Next, we wished to further investigate the level of product selectivities in these reactions. Our hypothesis was that by using electron-deficient olefins, dimerization of

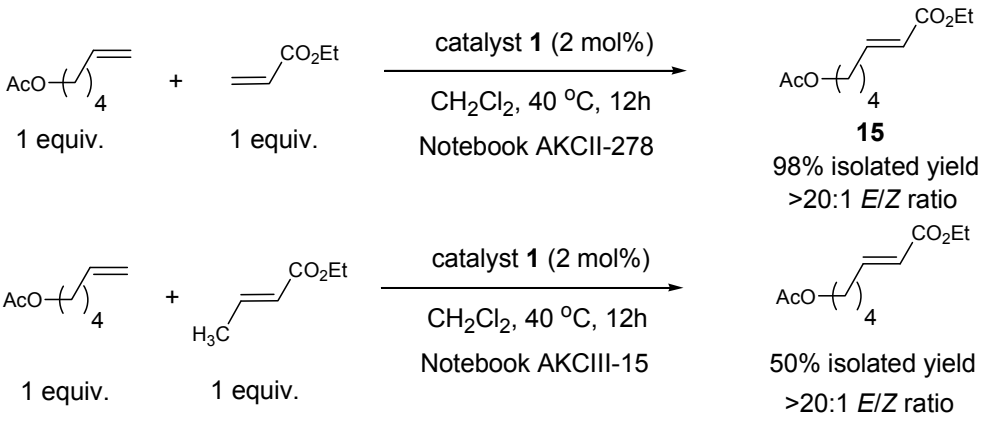
these olefins should be slow relative to productive CM formation. We were able to test this by using a 1:1 stoichiometry in the CM reactions (Scheme 5). For example, the need for an excess of one of the CM substrates is required in all previous examples of CM, since homodimerization of both olefin partners is unavoidable or incomplete reaction of



Scheme 5: Product Selective CM with Ruthenium Imidazolylidene Catalysts

the electron-deficient olefin. However, we found that both acrolein and acrylates could be used in slight excess to provide excellent CM yield. Again, in the acrylate CM reaction, base sensitive homoallylic substrates are excellent partners for CM. We became interested in understanding what factors were responsible to such unprecedented selectivity in CM. For example, we knew that under certain reaction conditions, the acrylate dimerization was quite efficient, but was much slower that acrylate CM with α-olefins.[9] It was previously shown by Blechert *et al.* that propensity for dimerization is not the proper measurement for determining a candidate for selective CM with α-olefins, since certain olefins that can individually dimerize also participate in selective CM.[10] We wished to investigate if the CM products obtained in these selective reaction were accessible for secondary metathesis.

The concept of secondary metathesis is critical in developing efficient CM processes. For example, in polymerization reactions, molecular weight distributions and polymer backbone architecture are affected by the ability of a given catalyst to scramble newly formed olefins. Similarly, for selective CM secondary metathesis of productive CM product needs to be significantly reduced or eliminated. This insures that homodimers of α-olefins, for example, are funneled to the CM product. In addition, by using an α-olefin that rapidly forms a dimer that is completely accessible to secondary metathesis, one can enhance the quantity of CM product by reacting with any available functionalized olefin (such as an acrylate). Therefore, the removal of ethylene from the system from the functionalized olefin can only occur by reacting in a productive manner with an α-olefin to form CM product. In addition, we tested the ability for catalyst to perform secondary metathesis on acrylate CM products by resubjecting them to the metathesis conditions. We found that these reactions did not scramble the productive CM reactions. To further illustrate this important point, we carried out the reaction of ethyl

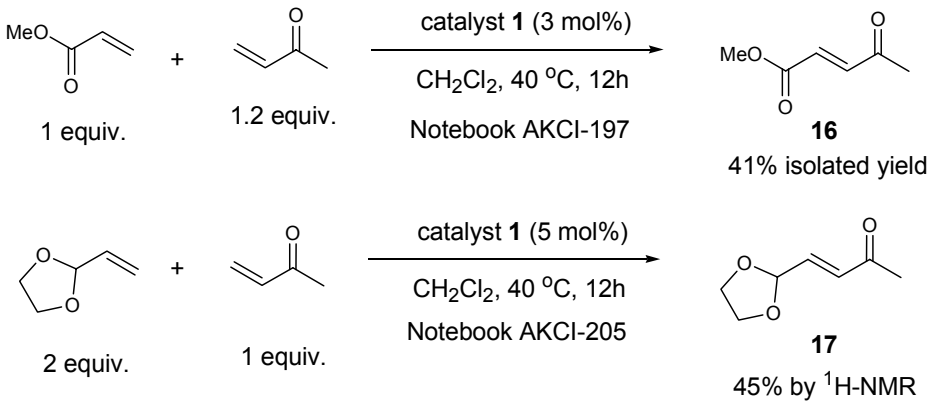


Scheme 6: Acrylate versus Crotonate in CM with Ruthenium Imidazolylidene Catalysts

crotonate under the optimized reaction conditions for acrylate CM and found the CM reaction efficiency was dramatically lower (Scheme 6). Even though the entropically

driven loss of a volatile gas (propylene) exists for crotonate CM partners, we found that this reduced the yield of CM product by 50%. Therefore, the 1,2-disubstituted α,β-unsaturated carbonyl containing olefin formed in these reactions is not readily accessible for secondary metathesis. Fortunately, this kinetic formation of CM products does not lead to low olefin stereoselectivity. This is surprising since many metathesis catalysts often provide *cis*-substituted olefins as a kinetic product.

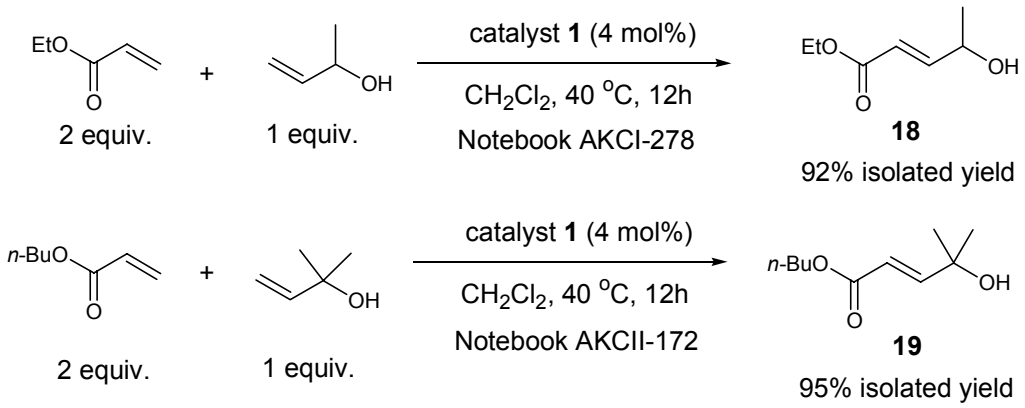
As the range of substrates for CM was being expanded, we also became interested in using more challenging α-olefins as the CM partner. In fact, since these α,β-unsaturated compounds are useful synthons in organic chemistry, we wished to make some challenging substrates by CM and the results are outlined in Scheme 7 and 8. For



Scheme 7: CM between Two Functionalized Olefins

example, the ability to do CM between two enones is possible, although the yields are modest (Scheme 7). However, the ability to produce a molecule with a α,β-unsaturated ketone in the presence of a protected α,β-unsaturated aldehyde is useful. Traditional routes to these types of compounds involve lengthy protective group manipulations. However, the yields of these reactions are lower, since they involve electron deficient components that may not react well with an electrophilic metal center. In the case of vinyl dioxolane CM with methyl vinyl ketone, the steric bulk of the substrate probably

lowers its direct reaction with the catalyst. At the same time, we were also interested in CM reactions of unprotected alcohols with catalyst **1** (Scheme 8). While unprotected alcohols are well tolerated by ruthenium-based catalyst systems, they do lower reaction efficiencies, particularly allylic alcohols. In addition, there was no prior work that

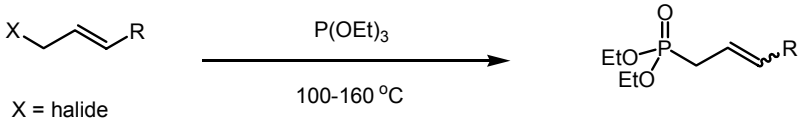


Scheme 8: Acrylate CM with Subsitituted Allylic Alcohols

described the CM of highly substituted secondary and tertiary allylic alcohols. Therefore, we investigated the CM of acrylates with substituted allylic alcohols and the results are summarized in Scheme 8. We were gratified to find these substrates work well with catalyst **1**, even though a two fold excess of the acrylate component is required for high CM conversions. In summary, these reactions allow for highly functionalized olefin to be synthesized by stereoselective CM.

At this point, with the unique reactivity trends of catalyst **1** and **4** in providing highly selective CM products, we became interested in expanding the substrate scope of these reactions beyond α,β-unsaturated carbonyl functionalities. For example, we began the investigation of α,β-unsaturated phosphonates as potential CM partners. Olefins that contain phosphonate functionality are used extensively in synthetic organic chemistry. For example, allylic phosphonates are employed in the preparation of dienes and

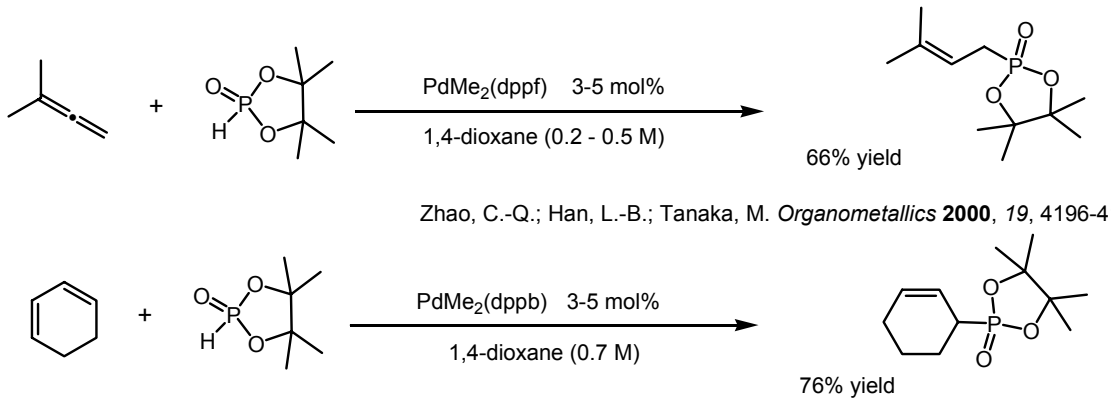
polyenes by Horner-Emmons olefination, providing products with improved stereoselectivity as compared to the corresponding phosphonium salts.[11] The reaction of organic halides with trialkyl phosphites (Michaelis-Arbuzov reaction) is used primarily for the synthesis of allylphosphonates (Scheme 9).[12] However, elimination and/or loss of olefin stereochemical integrity are often competitive with product formation under the



Bhattacharya, A. K.; Thyagarjan, G. *Chem. Rev.* **1981**, *81*, 415.

Scheme 9: Synthesis of Allylphosphonates by Michaelis-Arbuzov Reaction

reaction conditions. Palladium catalyzed cross-coupling of hydrogen phosphonates to conjugated dienes and allenes has also been developed, but requires high reaction temperatures and provides low regioselectivity in highly substituted phosphonates products (Scheme 10).[13] In addition, these methods require the use of highly reactive



Zhao, C.-Q.; Han, L.-B.; Tanaka, M. *Organometallics* **2000**, *19*, 4196-4198.

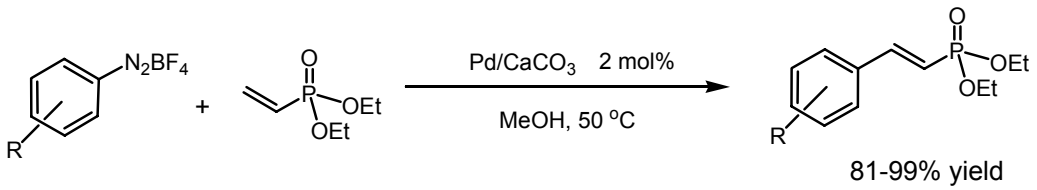
Mirzaei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* **2001**, 42, 297-299.

Scheme 10: Synthesis of Allylphosphonates by Hydrophosphorylation Reactions

functional groups, such as allenes, dienes, and alkyl halides, so the use of simple olefinic precursors would be advantageous.

Vinylphosphonates are important synthetic intermediates[14] and have been investigated as biologically active compounds.[15] Vinylphosphonates have been used as

intermediates in stereoselective synthesis of trisubstituted olefins[16] and in heterocycle synthesis.[17] The synthesis of vinylphosphonates has also been widely examined and a variety of non-catalytic approaches have been described in the literature.[18] Recent metal-catalyzed methods include, alkyne hydrozirconation,[19] palladium catalyzed cross-coupling,[20] and Heck coupling of aryldiazonium salts (Scheme 11) with vinyl phosphonates,[21] but are limited by the requirement of highly reactive functional groups in the substrates. Therefore, a mild, general and stereoselective method for the synthesis of

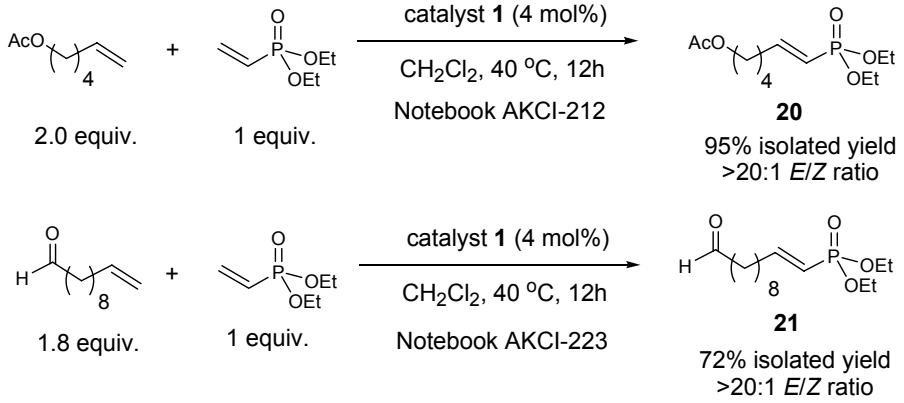


Brunner, H.; Le Cousturier de Courcy, N.; Genet, J.-P. *Synlett* **2000**, 201-204.

Scheme 11: Synthesis of Vinylphosphonates by Heck Coupling of Diazonium salts

vinyl and allylphosphonates using commercially available starting materials would be valuable, and may provide an additional degree of orthogonality to the previously reported syntheses. This also allows for the application of selective CM to install both phosphonate structural elements as well as provide a method for the synthesis of useful reagents. We have been able to apply catalyst **1** to the CM of vinyl and allylphosphonates using commercially available precursors.[24] Previously, phosphorus-containing α,ω-dienes, such as allylphosphonates and allylphosphoramides, have been utilized as RCM substrates by Hanson and co-workers using catalyst **2**.[22] In addition, Gouverneur and co-workers have demonstrated the intramolecular RCM of allylic phosphine oxides, phosphinates, and phosphoboranes using **2** and an unsaturated analog of **1**.[23] However, the intermolecular CM reaction of phosphonates has not been previously reported and was the focus of this work.

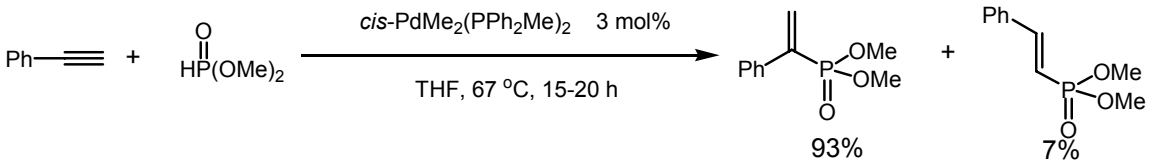
Olefins couple efficiently with diethylvinylphosphonate to generate α,β-unsaturated phosphonates in excellent yield using catalyst **1**. Terminal olefins were reacted with commercially available diethyl vinylphosphonate and after column chromatography, a 95% yield of CM product **20** was obtained exclusively as the (*E*) isomer (Scheme 12) with 5-hexene-1-acetate. Importantly, no dimerization of the



Scheme 12: CM of Vinylphosphonates with α-olefins

vinylphosphonate was detected by ^{1}H-NMR allowing for selective CM. Unprotected aldehyde functionality is well tolerated with the ruthenium catalyst **1** to provide **21** in good yield**.** For example, compound **21** is properly functionalized for a subsequent intramolecular reaction, demonstrating the orthogonality of CM and Horner-Emmons chemistry. In addition, CM provides a unique method to synthesize these compounds directly from olefins demonstrating the utility of this method. In addition, vinylphosphonic acids are compatible with the catalyst and can also provide the CM product in good yields, even though their solubility in CH_2Cl_2 is low. A wide variety of other CM partners for vinylphosphonates were included in our initial report in literature.[24] In fact, a report shortly after this work was able to couple vinylphosphonates to nucleosides using CM.[25] Finally, these reactions by ruthenium-catalyzed CM offer a choice of regioselectivity by choice of CM partners, while palladium-catalyzed

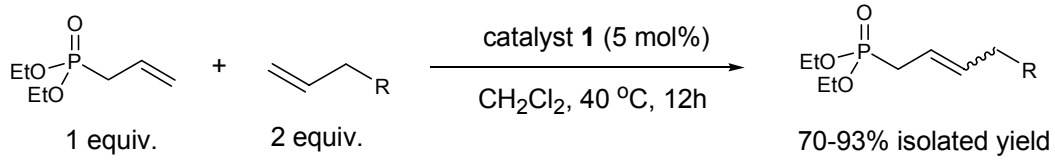
hydrophosphorylation provides the more substituted 1,1-geminal product predominantly and provides a mixture in other cases (Scheme 13).[26]



Han, L.-B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571-1572.

Scheme 13: Alternate Regiochemistry in Hydrophosphorylation Routes to Vinylphosphonates

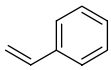
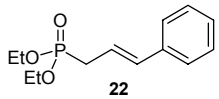
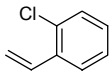
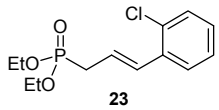
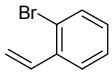
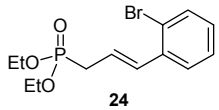
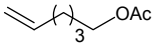
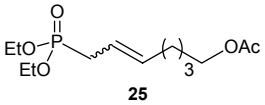
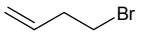
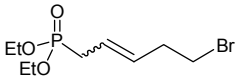
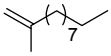
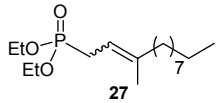
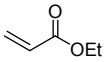
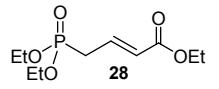
Second, diethylallylphosphonate was investigated as a potential CM partner. This was a particularly interesting substrate for CM reactions because of the variety of dienes that can be synthesized from substituted allylphosphonates (Scheme 14). In addition,



Scheme 14: CM of Vinylphosphonates with α-olefins

since diethylallylphosphonate is commercially available, one can easily gain access to these diene synthons. It has been previously demonstrated that some allylic functional groups improve cross-coupling selectivity and disfavor homodimerization by creating an electronic or steric match. We attempted to take advantage of this to improve CM efficiency and stereoselectivity. It is particularly important to have good stereoselectivity in these reactions since olefin stereochemistry is usually transferred to a newly formed olefin in the Horner-Emmons reaction. As summarized in Table 3,

Table 3. Synthesis of Allylphosphonates by CM[a]

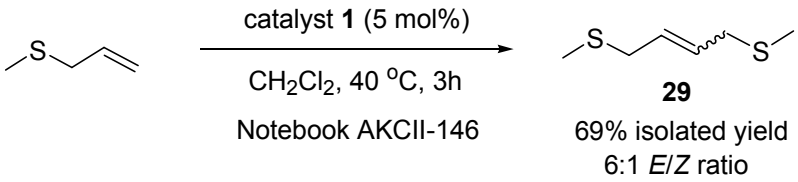
Entry	CM Partner (2 equiv.)	Product	Isolated Yield	E/Z ratio[b]	Notebook
1		 **22**	70%	>20:1	AKCII-36
2		 **23**	93%	>20:1	AKCII-42
3		 **24**	73%	>20:1	AKCII-43
4		 **25**	74%[c]	4:1	AKCI-245
5		 **26**	85%[c]	3.3:1	AKCII-41
6		 **27**	90%	2.5:1	AKCII-35
7		 **28**	87%[c]	>20:1	AKCII-210

[a] 3-7mol% of catalyst **1** used [b] Determined by ^{1}H and ^{31}P-NMR [c] 1 equiv. of allylphosphonate and 2 equiv. of α-olefin used

allylphosphonates are viable CM partners, providing slightly enhanced CM ratios relative to the predicted statistical mixture. For example, in the reaction between styrene and the allylphosphonate, equal stoichiometry leads to a 56% yield of CM which is close to the 50% statistical yield. However, both homodimers can be recovered and recycled in the reaction. In addition, some challenging styrenes are excellent CM partners (Table 3, Entry 2 and 3) and provide the *E*-isomer exclusively. In these cases, the CM selectivities are higher because of the slower dimerization of these styrenes to their stilbenes. An alkyl bromide can be installed (Entry 5) showing orthogonality to Arbuzov chemistry and a trisubstituted allylphosphonates is also produced in excellent yield with modest stereoselectivity (Table 3, Entry 6). Finally, the reaction of allylphosphonates with ethyl acrylate is also an efficient reaction to get to diene esters synthons. All CM products

were easily separated from their respective homodimers by column chromatography. We continued to investigate a variety of other substrates that were inactive olefins for CM using other ruthenium-based catalyst systems to study activity and selectivity in more detail.

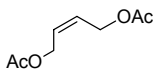
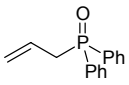
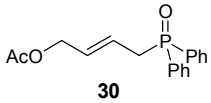
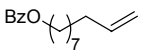
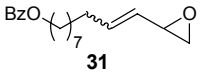
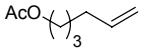
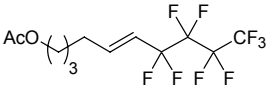
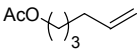
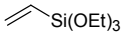
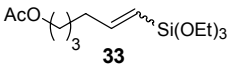
At this point, mechanistic work in understanding why imidazoylidene-based catalyst systems are more active than their parent bis-phosphine catalyst **2** was undertaken. By detailed mechanistic analysis, it was discovered that the preference for olefin binding in catalyst **1** was over ten thousand times greater than in catalyst **2**.[27] This is particularly interesting, since the competing pathway in these systems is rebinding a basic phosphine ligand. In addition, this work also demonstrated the upper limit of rate of binding olefin is nearly *equivalent* to binding phosphine in systems such as **1**. With this in mind, we decided to investigate olefins that contain potentially good ligands for ruthenium metal centers. This is perhaps the true test or functional group tolerance in olefin metathesis, where an olefin is preferentially chosen by the catalyst rather than a potential ligand. One objective in this chemistry is to make ligands for other metal centers by performing a selective CM with catalyst **1**. For example, reduced oxidation states of sulfur are notoriously good ligands for late transition metal centers due to soft-soft compatibility.[28] It was previously demonstrated that sulfides are only tolerated with earlier transition-metal catalyst systems, such as **3**.[29] However, we were able to effect the dimerization of methylallyl sulfide in moderate yields with good stereoselectivity



Scheme 15: Allylmethylsulfide Dimerization with Catalyst **1**

(Scheme 15). Other functional groups at the vinylic position were also investigated in cross-metathesis, and the results are summarized in Table 4. We were particularly

Table 4. Cross-Metathesis Reactions with Functionalized Olefins

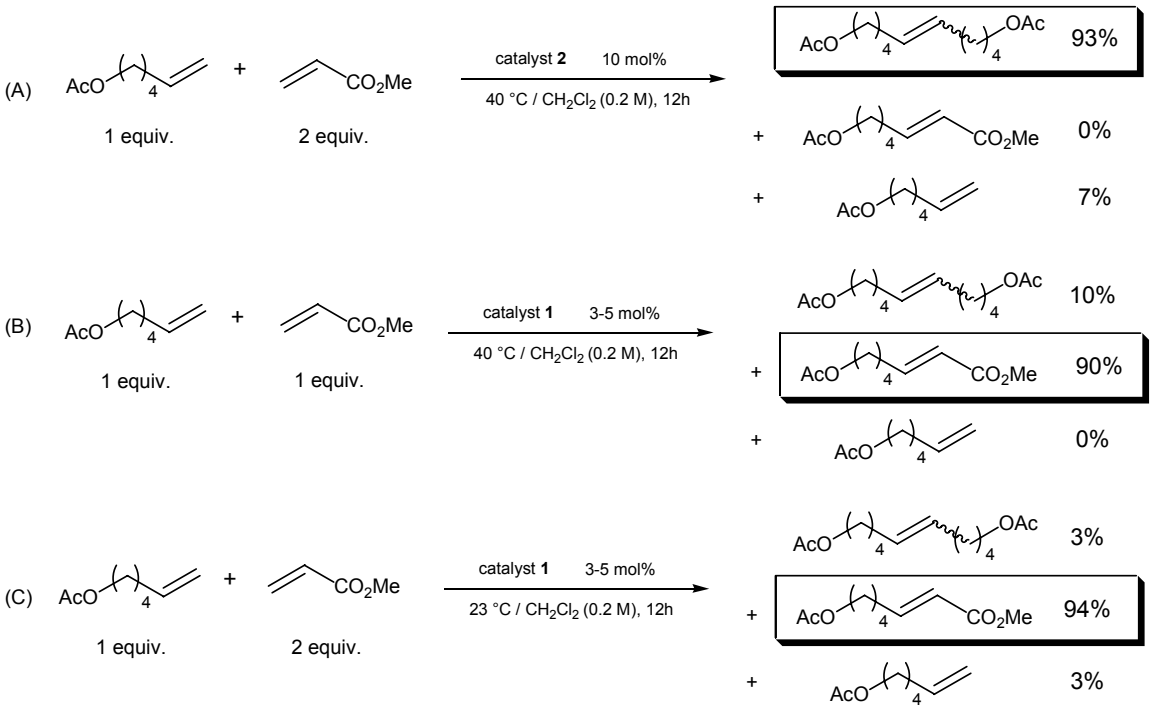
Entry	CM Partner	Functionalized Olefin	Equiv.	Product	Isolated Yield	*E/Z*[b]	Notebook
1			0.5	 **30**	90	>20:1	AKCII-160
2			4.0	 **31**	55[c]	5:1	AKCI-110/125
3			2.0	 **32**	34	>20:1	AKCI-122
4			2.0	 **33**	81	11:1	AKCI-127

[a]Reactions with 4-7 mol% of **1** or **4** [b]Ratio based on ^{1}H-NMR spectra [c] Added over a 12 hr. period

surprised to observe the reaction of phosphine oxides with catalyst **1** proceeded in excellent yields considering that phosphines are good ligands for ruthenium-based catalysts (Entry 1). In addition, the olefins stereoselectivity in a CM with an allyl acetate equivalent is excellent, increasing the utility of the method. It is even possible to use these products from a metal-catalyzed reaction as ligands for other metal systems. We were also interested in using functional groups that are highly reactive with other late-transition metals. For example, butadiene monoxide (Entry 2) participates in cross-metathesis with catalyst **4** in moderate yields. This reaction allows for the simple homologation of olefins with vinyl epoxides, and the products are highly versatile synthons due to their inherent ring-strain. It is surprising that olefins with direct functional groups on them, such as epoxides, are well tolerated by catalyst **1**. The vinyl epoxide methodology has been recently applied in the CM of two different vinyl epoxides in the synthesis of ABC ring systems of Thyrsiferol and Venustatriol.[30] We found that the slow addition of butadiene monoxide over a 12 hour period substantially

increased the conversion due to maintaining an appreciable amount of terminal epoxide available for CM. In addition, we found that an electron-deficient fluorinated alkene (Entry 3) also participates in CM with terminal olefins with excellent stereoselectivities. After this report, an expanded set of substrates with fluorinated alkanes in CM has been reported with a related catalyst system.[31] Similar to the CM of vinyl boronic esters with terminal olefins employing ruthenium benzylidene **2** (*vide infra*), vinyl siloxanes are also very good CM partners using **4** (Table 4, Entry 4), but yielded only 36% of cross-product with ruthenium benzylidene **2.** These siloxanes are useful synthons for further manipulation, such as Suzuki-type aryl halide cross-couplings.[32] It has recently been reported that vinyl siloxane CM is also catalyzed by **2**,[33] but it appears that in this system, catalyst **4** provides considerably higher yields of the CM product.

In summary, these reactions with functionality directly on the olefin have opened several new avenues for the application of CM in organic synthesis. Particularly, these reactions provided the opportunity for highly selective CM both in terms of product selectivity and olefin stereoselectivity. A dramatic difference in activities is observed between catalyst **2** and catalysts **1** and **4**. For example, in the chemistry of α,β-unsaturated esters with terminal olefins, catalyst **2** simply performs the dimerization of the α-olefin component (Scheme 16A). Catalyst **2** is not inactivated upon the addition of a α,β-unsaturated ester (such as ethyl acrylate), but simply does not incorporate this olefin. This is quite different from catalyst **3**, which is poisoned for any metathesis upon addition of acrylates.[3] Crowe and Goldberg explain this in terms of a possible heteroatom coordination of the acrylate to the molybdenum center. However, when catalyst **1** or **4** is used in the same reaction, then a highly selective CM reaction between



Scheme 16: Catalyst and Temperature Effect Product Distribution in Acrylate CM

the two olefins in equal stoichiometry occurs with exclusive trans olefin stereoselectivity under refluxing methylene chloride conditions (Scheme 16B). However, this reaction does contain a background dimerization of the acrylate component that accounts for the other 10% of the material in the reaction. This occurs due to secondary metathesis of the productive CM product and by a direct acrylate dimerization. However, both of these processes are slower that productive CM, so they are small byproducts in the reaction. Upon the optimization of the reaction, we hypothesized that using a lower reaction temperature may assist in CM product selectivity. In fact, when we performed the CM at room temperature, there was no acrylate dimerization product and a higher yield of the CM product (Scheme 16C). This procedure is advantageous since all of the side products in the reaction (starting acrylate, α-olefin, and α-olefin dimer) can all be recycled in subsequent CM reactions. However, where an acrylate dimer is formed, it can not be efficiently recycled in a subsequent CM. In conclusion, when such a large difference in

activity is discovered in any catalytic system, one needs to survey the landscape of substrate compatibility. With this surveillance complete, we began to develop a model and contextual method to use CM in selective organic synthesis and is discussed in the final chapter.

Experimental Section.

General Experimental Section. NMR spectra were recorded on either a JEOL GX-400 or GE-300 NMR. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-resolution mass spectra (EI and FAB) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.[34]

Compound 5. 9-Decen-1(*tert*-butyldimethylsilane)-yl (330 μL, 1.0 mmol) and methyl methacrylate (55 μl, 0.51 mmol) were added simultaneously *via* syringe to a stirring

solution of **4** (21 mg, 0.026 mmol, 5.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A viscous oil was obtained (110 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.75 (1H, m), 3.71 (3H, s), 3.57 (2H, t, J = 6.3 Hz), 2.14 (2H, m), 1.81 (3H, app s), 1.50–1.05 (12H, broad m), 0.87 (9H, s), 0.02 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.2, 143.2, 143.1, 128.0, 63.8, 52.1, 33.4, 30.0, 29.8, 29.2, 29.1, 26.5, 26.3, 18.9. 12.9. R_f = 0.81 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{19}H_{38}O_3Si$ $[M+ H]^+$ 343.2668, found 343.2677. Elemental analysis Calcd: C: 66.61, H: 11.18; Found: C: 66.47, H: 11.03.

Compound 6. 9-Decen-1-yl benzoate (145 μl, 0.52 mmol) and methyl acrylate (90 μl, 1.0 mmol) were added simultaneously *via* syringe to a stirring solution of **4** (17 mg, 0.022 mmol, 4.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A white crystalline was obtained (151.4 mg, 91% yield, >20:1 E/Z by olefinic ^{1}H coupling constants). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.01 (2H, app d, J = 7.2 Hz), 7.50 (1H, m), 7.45 (2H, m), 6.93 (1H, dt, J = 15.9 Hz, 6.9 Hz), 5.78 (1H, app d, J = 15.9 Hz), 4.28 (2H, t, J= 6.6 Hz), 3.68 (3H, s), 2.15 (2H, m), 1.74 (2H, p, J = 6.6 Hz), 1.49–1.05 (10H, broad m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.5, 167.1, 150.0, 133.3, 131.1, 130.0, 128.8, 121.5, 65.5, 51.8, 32.7, 29.8, 29.5, 29.2, 28.5, 26.5. R_f = 0.40

(9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{19}H_{26}O_4$ $[M+ H]^+$ 319.1909, found 319.1914. Elemental analysis Calcd: C: 71.67, H: 8.23; Found: C: 71.31, H: 8.24.

Compound 8. *cis*-2-butene-1,4-diacetate (145 μl, 0.95 mmol) and methyl vinyl ketone (40 μl, 0.48 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (15 mg, 0.018 mmol, 3.7 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained (55 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.75 (1H, dt, J = 15.9, 4.8 Hz), 6.23 (1H, dt, J = 16.2, 2.1 Hz), 4.75 (2H, dd, J = 4.8, 2.1 Hz), 2.26 (3H, s), 2.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 197.8, 170.5, 140.0, 131.1, 62.9, 27.6, 21.0. R_f = 0.38 (9:1 hexane:ethyl acetate).

Compound 9. Ethyl acrylate (220 μl, 2.03 mmol) was added *via* syringe to a solution of 4-benzyloxy-1,6-heptadiene (109 mg, 0.50 mmol) and catalyst **1** (14 mg, 0.016 mmol, 3.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 5:1 hexane:ethyl acetate. The product was obtained (137 mg, 76% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.00 (2H, d, J = 7.2 Hz), 7.55 (1H, t, J = 7.2 Hz), 7.42 (2H, t, J = 7.8 Hz), 6.91 (2H, dt, J = 15.6, 7.2 Hz), 5.91 (2H, d, J = 15.6 Hz), 5.92 (1H, quint, J = 6.0 Hz), 4.15 (4H, q, J = 7.2 Hz), 2.61 (4H, t, J = 6.9 Hz), 1.24 (6H, t, J = 7.2 Hz) ^{13}C NMR (75 MHz,

$CDCl_3$, ppm): δ 165.9, 165.7, 142.5, 133.3, 129.8, 129.7, 128.5, 124.9, 71.5, 60.6, 36.4, 14.4. R_f = 0.40 (3:1 hexane:ethyl acetate).

Compound 10 (Table 2, Entry 5). *trans*-crotonaldehyde (44 μl, 0.53 mmol) and 5-hexenyl-1-acetate (85 μl, 0.51 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (20 mg, 0.024 mmol, 4.7 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 4:1 hexane:ethyl acetate + 2% Et_3N. A clear oil was obtained (66 mg, 0.39 mmol, 77% yield). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 9.46 (1H, app d, J = 7.5 Hz), 6.83 (1H, dt, J = 6.8, 15.6 Hz), 6.10 (1H, qt, J = 1.5, 8.1 Hz), 4.05 (2H, t, J = 6.3 Hz), 2.34 (2H, q, J = 6.9 Hz), 2.00 (3H, s), 1.67-1.52 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 194.0, 171.2, 157.9, 133.4, 64.2, 32.5, 28.4, 24.6, 22.6, 21.3. HRMS (EI) calcd. for $C_9H_{14}O_3$ $[M]^+$ 170.0943, found 170.0878. R_f = 0.23 (9:1 hexane:ethyl acetate).

Compound 11. *trans*-crotonaldehyde (88 μl, 1.06 mmol) was added *via* syringe to a solution of 1-benzyloxy-3-butene (89 mg, 0.50 mmol) and catalyst **1** (15 mg, 0.018 mmol, 3.5 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 4:1 hexane:ethyl acetate. The product was obtained (58 mg, 0.28 mmol, 56% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.54 (1H, d, J = 7.5 Hz), 8.01 (2H, d, J = 8.0 Hz), 7.56 (1H, t, J = 7.8 Hz), 7.44 (2H, dt, J = 7.2 Hz), 6.90 (1H, dt, J = 15.9, 6.6 Hz), 6.24

(1H, ddd, J = 15.9, 7.8, 1.2 Hz), 4.50 (2H, t, J = 6.3 Hz), 2.81 (2H, q, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 193.6, 166.4, 153.3, 134.8, 133.3, 129.8, 129.6, 128.6, 62.6, 32.3. R_f = 0.09 (9:1 hexane:ethyl acetate).

Compound 12. *trans*-Crotonaldehyde (87 µl, 1.05 mmol) and 4-acetoxystyrene (80 µl, 0.50 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (17 mg, 0.020 mmol, 4.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 4:1 hexane:ethyl acetate. A white solid was obtained (85 mg, 0.45 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.70 (1H, d, J = 7.5 Hz), 7.61-7.49 (3H, m), 7.20-7.03 (2H, m), 6.70 (1H, dd, J = 15.6, 7.5 Hz), 2.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 193.5, 169.1, 152.8, 151.6, 131.8, 129.8, 128.8, 127.5, 122.5, 121.9, 21.5. R_f = 0.17 (9:1 hexane:ethyl acetate).

Compound 13. *trans*-Crotonaldehyde (87 µl, 1.05 mmol) and undecylinic aldehyde (104 µl, 0.48 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (14 mg, 0.016 mmol, 3.3 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 5:1 hexane:ethyl acetate + 2% Et_3N. A yellow oil was obtained (91 mg, 0.46 mmol, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.72 (1H, t, J = 1.8 Hz), 9.46 (1H, d, J = 8.1

Hz), 6.82 (1H, t, J = 15.6, 6.9 Hz), 6.07 (1H, ddt, J = 15.6, 7.5, 1.8 Hz), 2.39 (2H, dt, J = 7.2, 1.8 Hz), 2.29 (2H, app q, J = 6.6 Hz), 1.60-1.44 (4H, m), 1.28 (8H, s). R_f = 0.12 (9:1 hexane:ethyl acetate).

Compound 14. Ethyl acrylate (65 µl, 0.60 mmol) and 2-benzyloxy-4-pentene (100 µl, 0.49 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 4.4 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A pinkish oil was obtained (130 mg, 0.47 mmol, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.01 (2H, d, J = 8.0 Hz), 7.56 (1H, t, J = 7.8 Hz), 7.44 (2H, app t, J = 7.2 Hz), 6.95 (1H, dt, J = 15.6, 7.2 Hz), 5.90 (1H, dt, J = 15.9, 1.5 Hz), 5.24 (1H, quint, J = 6.3 Hz), 4.14 (2H, q, J = 7.2 Hz), 2.67-2.50 (2H, m), 1.35 (3H, d, J = 6.3 Hz), 1.24 (3H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.0, 165.8, 143.4, 132.9, 130.3, 129.5, 128.3, 124.3, 69.9, 60.4, 38.6, 19.9, 14.4. R_f = 0.36 (9:1 hexane:ethyl acetate).

Compound 15. Ethyl acrylate (130 µl, 1.20 mmol) and 5-hexenyl-1-acetate (200 µl, 1.20 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (20 mg, 0.024 mmol, 2.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained (253 mg, 1.18 mmol, 98% yield). ^{1}H NMR (300 MHz,

$CDCl_3$, ppm): δ 6.80 (2H, dt, *J* = 15.3, 7.2 Hz), 5.69 (1H, dt, *J* = 15.3, 1.8 Hz), 4.08 (2H, q, *J* = 7.2 Hz), 3.89 (2H, t, *J* = 6.3 Hz), 2.14 (2H, q, *J* = 6.9 Hz), 1.89 (3H, s), 1.62-1.42 (4H, m), 1.16 (3H, t, *J* = 6.9 Hz). R_f = 0.42 (9:1 hexane:ethyl acetate).

Compound 16. Methyl acrylate (90 μl, 1.00 mmol) and methyl vinyl ketone (40 μl, 0.48 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (13 mg, 0.016 mmol, 3.2 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500 mL) followed by 3:1 hexane:ethyl acetate (1000 mL). An oil was obtained (25 mg, 0.20 mmol, 41% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.03 (1H, d, *J* = 16.2 Hz), 6.65 (1H, d, *J* = 16.2 Hz), 3.80 (3H, s), 2.36 (3H, s). R_f = 0.37 (3:1 hexane:ethyl acetate). Compound matched spectra of previously characterized compound: Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857.

Compound 17. Methyl vinyl ketone (40 μl, 0.48 mmol) and 2-vinyl-1,3-dioxolane (100 μl, 1.00 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (14 mg, 0.017 mmol, 3.4 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. An oil (25 mg) was obtained as a mixture of desired product to vinyldioxolane homodimer in 1:2 molar ratio. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) of CM

product: δ 6.56 (1H, dd, *J* = 15.9, 4.8 Hz), 6.33 (1H, dd, *J* = 15.9, 0.9 Hz), 5.44 (1H, dd, *J* = 4.8, 0.9 Hz), 4.02-3.92 (4H, m), 2.36 (3H, s). R_f = 0.30 (9:1 hexane:ethyl acetate).

Compound 18. Ethyl acrylate (110 μl, 1.02 mmol) and *rac*-3-butene-2-ol (43 μl, 0.50 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 4.3 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 4:1 hexane:ethyl acetate. An clear oil (66 mg, 0.46 mmol, 92%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) of CM product: δ 6.94 (1H, dd, *J* = 15.6, 4.8 Hz), 6.00 (1H, dd, *J* = 15.6, 1.5 Hz), 4.48 (1H, m), 4.18 (2H, q, *J* = 6.9 Hz), 2.06 (1H, broad s), 1.32 (3H, d, *J* = 6.6 Hz), 1.28 (3H, t, *J* = 7.2 Hz), R_f = 0.21 (3:1 hexane:ethyl acetate). The compound matches a previous report, see: Morikawa, T.; Washio, Y.; Harada, S.; Hanai, R.; Kayashita, T.; Nemoto, H.; Shiro, M.; Taguchi, T. *J. Chem. Soc. Perkin Trans. 1* **1995**, 271.

Compound 19. *n*-Butyl acrylate (55 μl, 0.38 mmol) and 2-methyl-3-butene-2-ol (20 μl, 0.19 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (6 mg, 0.007 mmol, 3.7 mol%) in CH_2Cl_2 (1 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 8:1 hexane:ethyl acetate (500 ml) followed by 4:1 hexane:ethyl acetate (300 ml). A clear oil (34 mg, 0.18 mmol, 95%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.97 (1H, d, *J* = 15.6

Hz), 5.98 (1H, d, *J* = 15.6 Hz), 4.12 (2H, t, *J* = 6.6 Hz), 1.95 (1H, broad s), 1.62 (2H, quint, *J* = 6.9 Hz), 1.35 (6H, obs s), 1.44-1.32 (2H, m), 0.91 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.1, 154.7, 118.0, 71.0, 64.6, 30.9, 29.5, 19.4, 14.0. R_f = 0.39 (3:1 hexane:ethyl acetate). Elemental analysis Calcd: C: 64.49, H: 9.74; Found: C: 64.33, H: 9.98. The compound matches a previous report of the methyl ester, see: van Haard, P. M. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1975**, 803.

Compound 20. Diethylvinylphosphonate (80 μl, 0.52 mmol) and 5-hexenyl-1-acetate (170 μl, 1.01 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (16 mg, 0.019 mmol, 3.6 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:1 hexane:ethyl acetate (500 ml) followed by ethyl acetate (500 ml). A clear oil (138 mg, 0.50 mmol, 95%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.65 (1H, ddt, J = 23.7, 15.3, 6.6 Hz), 5.56 (1H, ddt, *J* = 20.7, 17.1, 1.5 Hz), 4.03-3.88 (6H, m), 2.20-2.12 (2H, m), 1.94 (3H, s), 1.57-1.40 (4H, m), 1.21 (6H, *t*, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.1, 153.1 (d, *J* = 4.3 Hz), 117.4 (d, *J* = 187 Hz), 64.2, 61.8 (d, *J* = 5.6 Hz), 34.0, 33.7, 28.3, 24.5, 21.2, 16.7, 16.6. ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 20.2. R_f = 0.18 (1:1 hexane:ethyl acetate). HRMS (EI) calcd. for $C_{12}H_{23}O_5P$ $[M + H]^+$ 279.1361, found 279.1358. Spectra correspond to a previously characterized compound, see: Zhong, P.; Xiong, Z. X.; Huang, X. *Synth. Commun.* **2000**, *30*, 273.

Compound 21. Diethylvinylphosphonate (80 μl, 0.52 mmol) and undecylinic aldehyde (200 μl, 0.96 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (18 mg, 0.022 mmol, 4.2 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 2:1 hexane:ethyl acetate (500 ml) followed by 1:1 hexane:ethyl acetate (700 ml). A clear oil (114 mg, 0.37 mmol, 72%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.76 (1H, s), 6.77 (1H, m), 5.62 (1H, m), 4.06 (4H, m), 2.41 (2H, dt, J = 7.5, 1.8 Hz), 2.21-2.17 (4H, m), 1.60-1.20 (16H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 178.1, 154.6 (d, J = 4.2 Hz), 116.3 (d, J = 187 Hz), 62.1 (d, J = 5.7 Hz), 34.4, 34.3, 29.3, 29.2, 29.1, 27.9, 25.1, 16.7, 16.6. ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 19.6. R_f = 0.28 (1:1 hexane:ethyl acetate). HRMS (EI) calcd. for $C_{15}H_{29}O_4P$ $[M - H]^+$ 303.1725, found 303.1718.

Compound 22. Diethylallylphosphonate (65 μl, 0.36 mmol) from Acros Organics and styrene (85 μl, 0.74 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (13 mg, 0.015 mmol, 4.2 mol%) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:1 hexane:ethyl acetate (300 ml) followed by 2:1 hexane:ethyl acetate (500 ml), then with 1:1 hexane:ethyl acetate and finally 200mL of ethyl acetate. A brown oil (65 mg, 0.26 mmol, 70%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.40-7.20 (5H, m), 6.52 (1H, dd, J = 15.9, 5.4 Hz), 6.15 (1H, m), 4.20-4.00 (4H, m), 2.75 (2H, ddd, J = 22.2, 7.5, 1.2 Hz), 1.32 (6H, t, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ

136.9 (d, J = 3.5 Hz), 134.8 (d, J = 15 Hz), 128.7 (d, J = 0.6 Hz), 127.7 (d, J = 0.9 Hz), 126.4 (d, J = 2.0 Hz), 126.3, 119.0 (d, J = 11.7 Hz), 62.2 (d, J = 6.6 Hz), 31.2 (d, J = 138.9 Hz), 16.7 (d, J = 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 28.0. R_f = 0.22 (1:1 hexane:ethyl acetate). Spectra correspond to a previously characterized compound, see: Kiddle, J. J.; Babler, J. H. *J. Org. Chem*. **1993**, *58*, 3572.

Compound 23. Diethylallylphosphonate (70 μl, 0.39 mmol) from Acros Organics and 2-chlorostyrene (100 μl, 0.78 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (13 mg, 0.015 mmol, 3.9 mol%) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 1:1 hexane:ethyl acetate (400 ml) followed by 1:4 hexane:ethyl acetate (500 ml). A brown oil (105 mg, 0.36 mmol, 93%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.47 (1H, dd, J = 7.8, 1.8 Hz), 7.27 (1H, m), 7.20-7.11 (2H, m), 6.86 (1H, d, J = 15.9, 5.1 Hz), 6.18-6.06 (1H, m), 4.15-4.02 (4H, m), 2.77 (2H, ddd, J = 22.2, 7.8, 1.2 Hz), 1.28 (6H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 134.8 (d, J = 3.6 Hz), 132.6 (d, J = 2.6 Hz), 130.9 (d, J = 15.0 Hz), 129.6, 128.6, 126.8, 126.7, 121.9 (d, J = 11.7 Hz), 62.2 (d, J = 6.5 Hz), 31.2 (d, J = 138.9 Hz), 16.6 (d, J = 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 27.4. R_f = 0.33 (1:1 hexane:ethyl acetate). Spectra correspond to a similar previously characterized compound, see: Kiddle, J. J.; Babler, J. H. *J. Org. Chem*. **1993**, *58*, 3572.

Compound 24. Diethylallylphosphonate (70 μl, 0.39 mmol) from Acros Organics and 2-bromostyrene (100 μl, 0.77 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (12 mg, 0.015 mmol, 3.8 mol%) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 1:1 hexane:ethyl acetate (400 ml) followed by 1:3 hexane:ethyl acetate (500 ml). A brown oil (98 mg, 0.29 mmol, 75%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.48 (2H, td, J = 8.1, 1.0 Hz), 7.23 (1H, app t, J = 7.2 Hz), 7.06 (1H, app t, J = 7.5 Hz), 6.83 (1H, dd, J = 15.6, 5.1 Hz), 6.16-6.03 (1H, m), 4.17-4.00 (4H, m), 2.78 (2H, ddd, J = 22.2, 7.5, 1.2 Hz), 1.30 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.6 (d, J = 3.4 Hz), 133.4 (d, J = 15.0 Hz), 132.9, 128.9, 127.6, 127.1 (d, J = 2.3 Hz), 123.3 (d, J = 2.9 Hz), 122.1 (d, J = 11.7 Hz), 62.3 (d, J = 6.5 Hz), 31.2 (d, J = 138.9 Hz), 16.7 (d, J = 6.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 27.4. R_f = 0.36 (1:1 hexane:ethyl acetate). Spectra correspond to a previously characterized compound, see: Kiddle, J. J.; Babler, J. H. *J. Org. Chem*. **1993**, *58*, 3572.

Compound 25. Diethylallylphosphonate (175 μl, 0.98 mmol) from Acros Organics and 5-hexene-1-acetate (85 μl, 0.51 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (17 mg, 0.021 mmol, 4.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:1 hexane:ethyl acetate (500 ml) followed by 1:1 hexane:ethyl acetate (500 ml), and finally 2:1 ethyl acetate/hexane. An yellow oil (110 mg, 0.38 mmol, 74%)

was obtained as a 4:1 *E*/*Z* ratio by ^{1}H peak integration at 2.41 and 2.54 ppm. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.58-5.26 (2H, m), 4.05-3.03 (6H, m), 2.45 (2H, dd, *J* = 21.6, 7.2 Hz), 2.02-1.94 (2H, m), 1.94 (3H, s), 1.58-1.29 (2H, m), 1.39-1.31 (2H, m), 1.21 (6H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.1, 135.5 (d, *J* = 14.5 Hz), 119.2 (d, *J* = 11.0 Hz), 64.5, 62.0 (d, *J* = 6.6 Hz), 36.2, 30.7 (d, *J* = 139 Hz), 27.2, 25.3, 16.7, 16.6. ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 28.2. R_f = 0.18 (3:1 hexane:ethyl acetate). HRMS (EI) calcd. for $C_{13}H_{25}O_5P$ $[M]^+$ 292.1439, found 292.1436. Spectra correspond to a previously characterized compound, see: Balczewski, P.; Mikolajczyk, M. *Synthesis* **1995**, 392.

Compound 26. Diethylallylphosphonate (85 μl, 0.48 mmol) from Acros Organics and 4-bromo-1-butene (25 μl, 0.24 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (8 mg, 0.009 mmol, 3.9 mol%) in CH_2Cl_2 (1.25 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 1:1 hexane:ethyl acetate (400 ml) followed by 1:4 hexane:ethyl acetate (500 ml). A clear oil (58 mg, 0.20 mmol, 85%) was obtained as a 3.3:1 *E*/*Z* ratio by ^{13}C peak heights at 132.3 and 130.8. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.44-5.65 (2H, m), 4.11-4.02 (4H, m), 3.35 (2H, *t*, *J* = 6.9 Hz), 2.62-2.49 (4H, m), 1.28 (6H, t, *J* = 7.2 Hz). ^{13}C (75 MHz, CDCl3, ppm): δ 132.1 (d, *J* = 14.5 Hz), 130.7 (d, *J* = 14.0 Hz), 62.1 (d, *J* = 6.6 Hz), 36.0, 32.3, 30.7 (d, *J* = 139 Hz), 27.2, 16.7 (d, *J* = 6.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 28.2. R_f = 0.30 (1:1 hexane:ethyl acetate).

Compound 27. Diethylallylphosphonate (100 μl, 0.56 mmol) from Acros Organics and 2-methyl-1-undecene (220 μl, 0.98 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (17 mg, 0.020 mmol, 3.6 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:2 hexane:ethyl acetate (500 ml) followed by 1:1 hexane:ethyl acetate (200 ml). A brown oil (137 mg, 0.43 mmol, 77%) was obtained as a 2.5:1 *E*/*Z* ratio by ^{1}H peak integration at 1.69 and 1.60 ppm. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.17-5.10 (1H, m), 4.10-4.00 (4H, m), 2.52 (2H, dd, J = 21.6, 7.8 Hz), 2.02-1.95 (2H, m), 1.60 (3H, d, J = 3.6 Hz), 1.34-1.22 (20H, m), 0.84 (3H, t, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 140.6 (d, J = 14.2 Hz), 112.2 (d, J = 10.8 Hz), 61.9 (d, J = 6.6 Hz), 39.9 (d, J = 2.6 Hz), 32.1, 29.9, 29.8, 29.6, 29.5, 28.0, 27.4, 25.6, 23.7, 22.9, 16.7, 16.7, 16.4, 14.3. ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 29.9. R_f = 0.28 (3:1 hexane:ethyl acetate). Spectra matches those found in a previous characterization, see: Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron* **1996**, *52*, 14543.

Compound 28. Diethylallylphosphonate (45 μl, 0.25 mmol) from Acros Organics and ethyl acrylate (55 μl, 0.51 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (14 mg, 0.017 mmol, 6.5 mol%) in CH_2Cl_2 (2 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 2:1 hexane:ethyl acetate. A clear oil (55 mg, 0.22 mmol, 87%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.91-6.78 (1H, m), 5.92 (1H, dd, J = 15.3,

4.8 Hz), 4.20-4.04 (6H, m), 2.71 (2H, dd, J = 23.1, 8.1 Hz), 1.32-1.23 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.6, 137.4 (d, J = 11.2 Hz), 125.9 (d, J = 13.3 Hz), 62.4 (d, J = 6.8 Hz), 60.7, 30.8 (d, J = 138 Hz), 16.6 (d, J = 6.0 Hz), 14.5. ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 25.5. R_f = 0.13 (1:1 hexane:ethyl acetate). Spectra matches those found in a previous characterization, see: Beckström, P.; Jacobsson, U.; Norin, T.; Unelius, C. R. *Tetrahedron* **1988**, *44*, 2541.

Compound 29. Allylmethyl sulfide (30 μl, 0.27 mmol) was added *via* syringe to a stirring solution of **1** (12 mg, 0.014 mmol, 5.1 mol%) in CH_2Cl_2 (1.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil (14 mg, 0.09 mmol, 69%) was obtained as a mixture of 6:1 *E*/*Z* as assigned by relative ^{1}H integration at 5.51 and 5.62 ppm. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.53-5.49 (2H, m), 3.10 (4H, dd, J = 4.5, 2.1 Hz), 2.02 (6H, s). R_f = 0.74 (9:1 hexane:ethyl acetate). Spectra matches those found in a previous characterization, see: Caserio, M. C.; Fisher, C. L.; Kim, J. K. *J. Org. Chem.* **1985**, *50*, 4390.

Compound 30. *cis*-2-butene-1,4-diacetate (70 μl, 0.44 mmol) was added *via* syringe to a stirring solution of Allyldiphenylphosphine oxide (53 mg, 0.22 mmol) and **1** (14 mg, 0.017 mmol, 7.5 mol%) in CH_2Cl_2 (1.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 2:1

hexane:ethyl acetate. A white semi-solid (62 mg, 0.20 mmol, 90%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.80-7.40 (10H, m), 5.79-5.55 (2H, m), 4.40 (2H, m), 3.10 (2H, dd, *J* = 14.1, 7.2 Hz), 1.92 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.7, 132.1 (d, *J* = 2.9 Hz), 131.1 (d, *J* = 9.4 Hz), 130.4 (d, *J* = 11.4 Hz), 128.8 (d, *J* = 11.4 Hz), 124.0 (d, *J* = 9.0 Hz), 64.4 (d, *J* = 2.0 Hz), 34.8 (d, *J* = 67.8 Hz), 21.1. ^{31}P NMR (121 MHz, $CDCl_3$, ppm): δ 31.0. R_f = 0.13 (1:1 hexane:ethyl acetate). Spectral data matches those reported in a previous characterization, see: Clayden, J.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2913.

Compound 31. 9-Decen-1-yl benzoate (145 μl, 0.52 mmol) and butadiene monoxide (160 μl, 1.98 mmol) and was added simultaneously *via* syringe to a stirring solution of **4** (21 mg, 0.027 mmol, 5.0 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. A clear oil was obtained (95 mg, 55% yield, 5:1 trans/cis as determined by relative integrations of ^{1}H peaks at 5.94 and 5.75 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03 (2H, app d, *J* = 7.2 Hz), 7.55 (1H, m), 7.44 (2H, m), 5.94 (1H, dt, *J* = 15.3 Hz, 6.9 Hz), 5.12 (1H, dd, *J* = 8.7 Hz, 6.3 Hz), 4.31 (2H, t, *J*= 6.6 Hz), 3.30 (1H, m), 2.63 (1H, m), 2.03 (1H, m) 1.76 (2H, m), 1.51-1.22 (10H, broad m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.2, 137.8, 137.6, 133.3, 130.1, 128.9, 128.1, 65.6, 53.0, 49.3, 32.9, 29.9, 29.7, 29.6, 29.4, 29.3, 26.6. R_f = 0.38 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{19}H_{26}O_3$ $[M+ H]^+$ 303.1960, found 303.1960.

Compound 32. 2,2,3,3,4,4,5,5,6,6,6-Nonaflouro-1-hexene (175 µl, 1.0 mmol) and 5-Hexenyl-1-acetate (85 µl, 0.51 mmol) were added simultaneously *via* syringe to a stirring solution of **4** (17 mg, 0.022 mmol, 4.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. An amber oil was obtained (62 mg, 34% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 6.40 (1H, m), 5.65 (1H, m), 4.07 (2H, t, J = 6.3 Hz), 2.10 (2H, m), 2.05 (3H, app s), 1.72 (2H, m), 1.53 (2H, m) ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 171.6, 143.2, 143.0, 118.2, 117.8, 117.5, 64.5, 32.1, 32.0, 28.5, 25.0, 23.2, 21.4, 14.6. R_f = 0.72 (9:1 hexane:ethyl acetate).

Compound 33. Vinyltriethoxysilane (190 µl, 1.0 mmol) and 5-hexenyl-1-acetate (85 µl, 0.51 mmol) were added simultaneously *via* syringe to a stirring solution of **4** (21 mg, 0.027 mmol, 5.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate. A clear oil was obtained (126 mg, 81% yield, 11:1 trans/cis as determined by integration of ^{1}H NMR peaks at 5.40 and 5.28 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.38 (1H, dt, J = 18.9 Hz, 6.3 Hz), 5.41 (1H, app d, J = 18.9 Hz), 4.03 (2H, t, J = 6.3 Hz), 3.79 (6H, q, 6.9 Hz), 2.16 (2H, m), 2.02 (3H, s), 1.59 (2H, m), 1.47 (m, 2H), 1.20 (9H, t, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.6, 153.4, 120.3, 64.8, 64.4, 58.9, 58.8, 36.5, 36.3, 28.8, 28.6, 25.2, 24.4, 18.7. R_f = 0.31 (10:1

hexane:ethyl acetate). HRMS (FAB) calcd for $C_{14}H_{28}O_5Si$ $[M+ H]^+$ 305.1784, found 305.1770.

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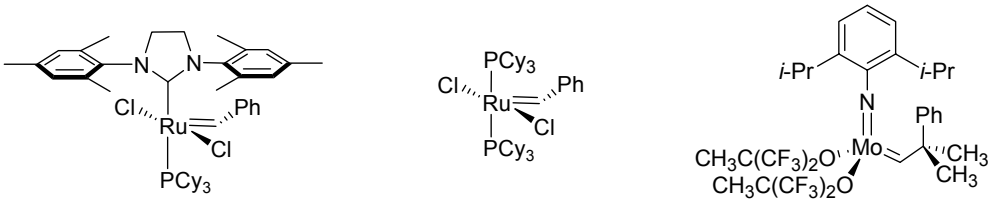
Chapter 5: A Model for Selectivity in CM

Olefin cross-metathesis (CM) is a convenient route to functionalized and higher olefins from simple alkene precursors, but has been an underrepresented area of olefin metathesis when compared to ring-opening metathesis polymerizations (ROMP)[1] and ring-closing metathesis (RCM).[2] This is in large part due to several factors: first, low catalyst activity to affect a reaction where no enthalpic driving force exists (such as ring-strain release in ROMP polymerizations) or the entropic advantage of intramolecular reactions (such as RCM); second, low product selectivity for the CM product; and third, low stereoselectivity in the newly formed olefin. However, work in CM has recently gained prominence due to the availability of catalysts with varied activities, such as **1**,[3] **2**,[4] and **3**[5] (Figure 1). This has opened new avenues for selective reactions, both in



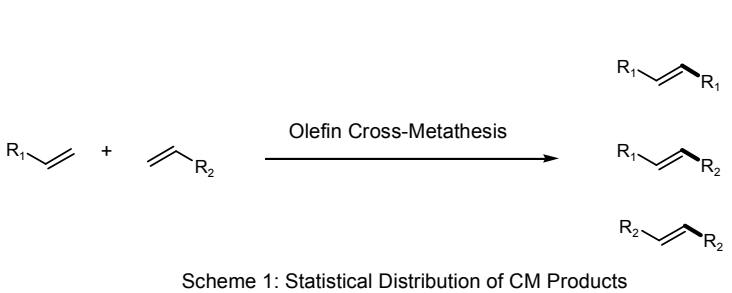
1 **2** **3**

Figure 1: Commonly Used Olefin Metathesis Catalysts

terms of offering stereoselective reactions, expanding the variety of functional groups amenable to CM, and installing highly substituted olefins by CM. The formation of structural elements in natural products by CM and synthesizing reagents by CM for further synthetic transformations can now be accessed by using active and functional group tolerant metathesis catalysts. At this stage of CM development, a manner to classify and predict reaction efficiencies is important to make CM a useful synthetic method.

Central to CM reaction efficiency is to the use of two olefins that dimerize at

different rates. If the dimerization rate of each olefin by CM is similar and completely reversible, then the reaction will be governed by statistics (Scheme 1). For these



R_1 : R_2	CM yield
1:1	50%
2:1	66%
4:1	80%
10:1	91%
20:1	95%

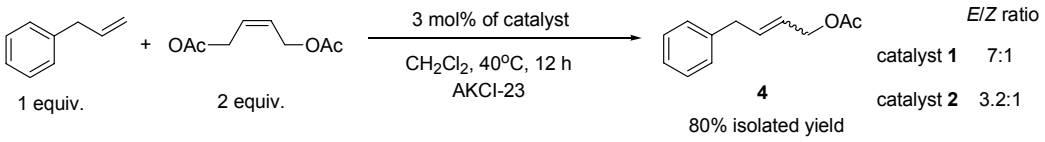
Scheme 1: Statistical Distribution of CM Products

reactions, one would have to use nearly 10 equivalents of one CM partner to provide 90% of CM product. Not only is this an inefficient reaction, it also requires high catalyst loadings since many metathesis cycles are consumed in unproductive homodimerization events and secondary metathesis of these homodimerization products. Therefore, improvements in product selectivity should improve efficiency and lower catalyst loading. The underlying principal necessary to improve CM efficiency is the use of one olefin that dimerizes at a significantly slower rate than the formation of cross-metathesis product. Another scenario arises where two olefins *both* dimerize at much slower rates than formation of productive cross-metathesis product. However, it is difficult to independently study all the factors that determine where selective CM occurs. Therefore, the development of a model based on empirical data that categorizes olefins based on the reactivities in CM will allow for predictability in the design of selective cross-metathesis reactions.

Our investigations began with the utilization of catalyst **1** and **2** with a variety of substrates that have not been previously used in CM reactions. Our intention was that by placing sterically large and electron-withdrawing groups near the reacting olefin, we could improve cross-metathesis efficiency, by disfavoring homodimerization and trans stereoselectivity by steric congestion. Under these conditions, we not only wanted functional groups to be tolerated by the catalyst, but

wanted the functional groups to direct CM selectively. This is a salient point since currently olefin metathesis catalysts are largely judged by functional group tolerance in complex synthesis. As a result of our investigations, a significant number of new substrate classes that participate in selective olefin cross-metathesis reactions have been discovered.[6] While a descriptive model of selective CM processes has not been yet been disclosed, we noticed that several different types of olefins could be properly matched to provide highly selective CM yields.[7] These observations provide the foundation for a model that combines our work in CM with those from other groups to provide a working model for selective CM. By developing this model, we have been able to access new reaction platforms, such as a three-component CM reaction.

Our investigations in exploring CM selectivity started with primary allylic alcohols. For example, catalyst **1** and **2** are able to incorporate allylic alcohols with good to moderate stereoselectivity (Scheme 2). The CM reaction between



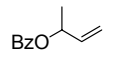
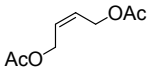
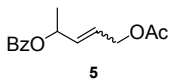
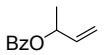
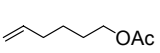
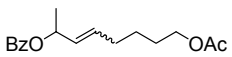
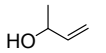
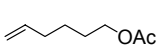
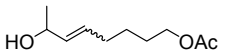
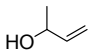
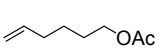
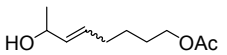
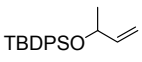
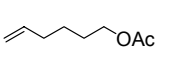
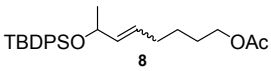
Scheme 2: Olefin Isomerization by Secondary Metathesis Processes

allylbenzene and an allylic alcohol equivalent provides the CM product in 80% isolated yield with both catalyst **1** and **2**. The yields are based on statistics since four equivalents of allyl acetate is used in the reaction and provides 80% CM product (Scheme 1). However, the reaction with catalyst **1** provides a much higher amount of the trans olefins isomer, presumably due to the catalyst reacting with the CM product formed in the reaction, a phenomena known as secondary metathesis. Efficient secondary metathesis occurs when all components in the reaction are equally accessible to the metal alkylidenes complex, including homodimers and the CM product. Therefore, the increased trans ratio is simply an effect of the higher activity

of catalyst **1** toward the product than catalyst **2**. Secondary metathesis of the CM product provides a metathesis-based isomerization to the more thermodynamically favorable trans isomer. By this account, secondary metathesis processes account for the different stereoselectivities observed. Therefore, trans selective metathesis processes will actually involve non productive selective reactions, so accomplishing both of these goals may be difficult. As will be described below, eliminating secondary metathesis of the CM product allows for product selective CM to occur by making homodimers reactive to the catalyst, but not the CM product. In addition, these reactions may also provide better trans olefin selectivity due to sterics, even with reduced secondary metathesis reactions.

Our studies in the investigation of the inherent stereoselectivity of secondary allylic alcohols in CM (Table 1) provided some important initial results in the role of sterics in selective CM. Investigations in this area began with 3-5 mol% of catalyst **1** in CH_2Cl_2 and heated to 40 ^oC for 12 hours. Excellent

Table 1. Secondary Allylic Alcohol CM

Entry	2^o Allylic Alc.	Cross Partner (Equiv)	Product	Iso. Yield (%)	E/Z ratio[a]	Notebook
1		 (1.8)	 **5**	38	18:1	AKCI-177
2		 (2.0)	 **6**	82	10:1	AKCI-180
3		 (2.0)	 **7**	92	13:1	AKCI-188
4		 (1.0)		50 62[b]	14:1 14:1	AKCII-276 AKCII-282
5		 (0.5)	 **8**	53	6.7:1	AKCII-24

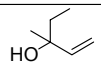
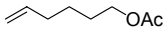
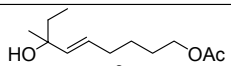
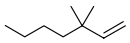
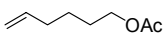
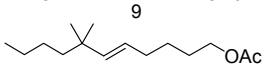
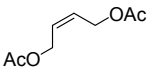
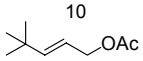
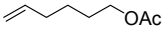
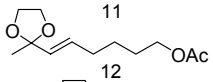
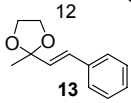
[a] Determined by ^{1}H-NMR [b] Reaction performed at 23 ^oC

stereoselectivity was observed, but the CM product was obtained in low yields in CM with another allylic alcohol (Table 1, Entry 1). We were pleased to find that our hypothesis of the addition of a methyl group at the allylic position leads to much greater trans selectivity, compared to a 7:1 *E*/*Z* ratio obtained with a primary alcohol

(Scheme 2). Similar results were also obtained using catalyst **2** demonstrating a general trend in reactivity that is not catalyst specific.[8] Next, we investigated the reaction of these secondary allylic alcohols with simple α-olefins. We were also intrigued to find that most of the trans selectivity obtained by Entry 1 is retained when a simple α-olefin is used in the reaction (Entry 2), but with much higher CM yields. We also decided to investigate if protecting groups were required to obtain stereoselectivity in this system. We hypothesized that the addition of protecting groups would increase sterics and lead to decrease CM reactivity, but with greater trans selectivity. Interestingly, the reactivity trends were as we expected, but the stereoselectivities obtained were surprising. In fact, we observe greater trans selectivity with the unprotected alcohol (Entry 3) to provide CM product, than using a bulky protecting group, such as a *tert*-butyldiphenylsilyl ether (Entry 5). In addition, we performed the reaction at room temperature in equal stoichiometry and found a slight preference for the CM product (62% vs. 50%) while not dimerizing the secondary alcohol component (Entry 4). It is not clear why a smaller protecting group allows for greater trans selectivity, but may in part be due to greater secondary metathesis of the CM products. The presence of small protecting groups, therefore, allows for greater access to secondary metathesis based isomerization similar to the reactions outlined in Scheme 2. These results provided some early results into the role of sterics into product selectivity and olefin diastereoselectivity in CM.

During the course of our earlier studies with catalyst **2**, we found that fully substituted allylic carbons/quaternary centers did not participate in CM.[8] They did not eliminate activity of the catalyst, but simply did not participate in the reaction. Therefore, with greater activity observed with catalyst **1**, we began to investigate the reaction of quaternary allylic olefins with α-olefins. We hypothesized that we could get excellent stereoselectivity in CM with these substrates (Table 2) due to sterics.

Table 2. Quarternary Allylic Olefin Cross-Metathesis[a]

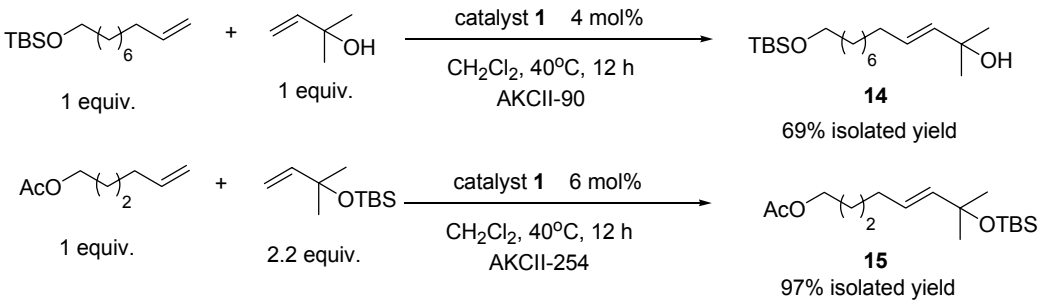
Entry	4° Allylic Olefin	Equiv.	CM Partner	Product	Yield	Notebook Reference
1		2.0		 9	93	AKCI-178
2		2.0		 10	90	AKCII-269
3		excess		 11	93[b]	AKCII-175
4		1.0		 12	91	AKCI-294
5		2.0		 **13**	70	AKCI-277

[a] 3-5 mol% of catalyst **1** used, CH_2Cl_2, 40 °C, 12h [b] Reaction performed at 23 °C

These reactions are useful because they are able to install highly substituted carbons in a stereodefined manner. We were pleased to discover that these reactions are the first example of exclusive trans olefin selectivity in CM based solely on alkyl substituents. For example, an unprotected tertiary alcohol (Entry 1) provides an excellent yield of the CM product with only the trans isomer observed by ^{1}H-NMR. Alkyl substituents have also been explored in the reaction and work quite nicely with catalyst **1** with a variety of α-olefins or equivalents (Entry 2 and 3). Entry 3 provides a convenient method to homologate terminal olefins with a *tert*-butyl group. Finally, the homologation of a α-olefin with the cyclic acetal of methyl vinyl ketone can provide the CM product in excellent yield in 1:1 stoichiometry (Entry 4). In addition, styrene can be used as a CM partner with the cyclic ketal, with the balance of the cyclic ketal recovered as starting material (Entry 5). These represent the unique control of product and stereoselectivity in CM based purely on steric considerations.

With the vinyl ketone used in Table 2, Entry 4 and 5, there was no observation of the dimer of the cyclic acetal. However, when a tertiary alcohol in Entry 1 was used in the CM at 40 °C, there was a background dimerization of the tertiary alcohol. Therefore, when a similar substrate was used in 1:1 stoichiometry, a

reduced yield of CM product was observed (Scheme 3). The dimerization of a

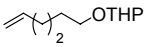
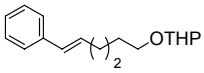
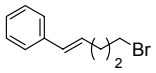
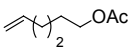
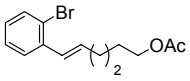
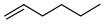
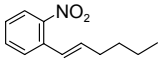
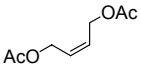
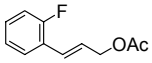
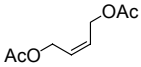
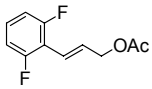
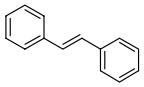
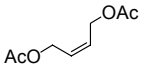
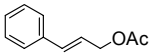


Scheme 3: Alter CM Selectivity by Steric Factors

tertiary allylic alcohol can be performed in excellent yields. If the dimer is resubjected under the same reaction with a α-olefin, then no CM product is observed. This indicates that once the dimer is formed in a CM reaction, it does not undergo secondary metathesis presumably due to steric bulk of the dimer. In addition, we found homodimers of olefins with tertiary allylic carbons were not accessible for secondary metathesis either. Interestingly, this undesired dimerization can be suppressed to a large extent by using a silyl protecting group (Scheme 3). This provides higher CM selectivity due to steric contributions of the protecting group. This demonstrates the use of steric bulk to alter reactivity patterns in CM and provides a way to alter selectivity in CM. At this point, we also wished to investigate the electronic parameters required for selective CM in addition to the effects of sterics described above.

Styrenes represent one of the classes of olefins used in widely in CM with ill-defined catalyst systems,[9] as well as **2,**[10] and **3**,[11] because of high *trans* selectivity in the CM product. In all these cases the dimerization of styrene to stilbene was reported to be slow, allowing for moderate selectivities in CM. However, with catalyst **1** we saw a significantly different reactivity. For example, with 2.5 mol% of catalyst **1**, the dimerization of styrene to stilbene was achieved in 94% isolated yield. Consequently, the CM reactions of styrene with terminal olefins (Table 3) is governed

Table 3. Cross-Metathesis of Styrenes with Terminal Olefins

Entry	Catalyst	Aromatic Olefin	Cross-Partner	Aromatic : CM Partner	Product[b]	Isolated Yield	Notebook
1	1			1 : 1		47%	TLC[a]
2	3			2 : 1		90%	Ref. 10a
3	1			1 : 1 3 : 1		80% 98%	AKCII-104 AKCII-97
4	3			2 : 1		48%	Ref. 10a,b
5	1			1 : 2		98%	AKCI-297
6	1			1 : 2		50%	AKCII-51
7	1			1 : 1.2		51%	AKCI-299

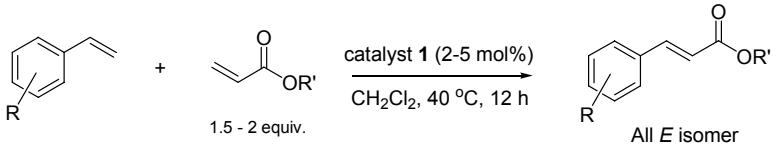
[a] Reaction performed by Tae-Lim Choi, Grubbs group [b]Only E isomer observed

by statistical product distributions (Entry 1) unlike reactions using catalyst **3**, as reported by Crowe and Zhang (Entry 2).[11] Interestingly, alterations in styrene structure allows for selective CM reactions with terminal olefins. For example, the use of 2-bromostyrene as the CM partner leads to selective formation of the CM product (Entry 3). By simply using an excess of this styrene, near quantitative conversion of α-olefin and full recovery of starting material without any stilbene formation was achieved. We believe that 2-bromostyrene is an optimized case with terminal olefins, where both the steric bulk of the bromine atom and its electron-withdrawing character also contribute to its selective CM with α-olefins. Crowe and Zhang also were able to incorporate *ortho*-substituted styrenes in CM with catalyst **2**, but found that their reactivity is low with terminal olefins (Entry 4).[11] This may be due to low catalyst activity toward electronic-deficient styrene substrates, since the accompanying terminal olefin was dimerized. We observed a similar trend only when multiple electron-withdrawing substituents are present. For example, 2,5-

difluorobenzene was subjected to CM conditions and only moderate yields of CM product were isolated (Entry 6). This is a particularly noticeable difference since 2-fluorostyrene was a nearly quantitative CM reaction (Entry 5). Finally, as a method to determine if the parent styrene reaction is completely reversible, *trans*-stilbene was successfully used as a styrene surrogate in CM with allylic acetate CM partners (Entry 7) to yield a statistical product ratio. This is unprecedented since ill-defined catalysts, **2**, and **3** are not able to efficiently use stilbene as a CM partner, providing another example of the unique reactivity of catalyst **1**.

With the differences in reactivity observed with styrenes, we investigated CM of styrenes with olefins that did not behave like terminal olefins. We had previously disclosed that a variety of α,β-unsaturated esters, amides, ketones, and acids are excellent CM partners with terminal olefins.[6c,h] In addition, it has been demonstrated by Crowe and Goldberg that CM of π-substituted olefins, such as acrylonitriles, were not compatible in CM with styrenes using catalyst **3** because they possessed similar electronic properties. They suggested that CM required matching of a more nucleophilic, electron-rich olefin with either styrene or acrylonitrile.[12] However, in contrast to Crowe's work with catalyst **3**, we found that styrenes are excellent CM partners with electron-deficient α,β-unsaturated carbonyl, such as acrylate esters using catalyst **1** (Table 4). We discovered that the reactivity trends of styrenes were different in these CM reactions when compared to α-olefins CM in Table 3. It was observed that *ortho*-substituted styrenes that did not dimerize readily, were also not good CM partners with acrylates (Entries 3, 9-11). In addition, styrenes that readily dimerized to stilbene were excellent CM partners with acrylates, such as styrene (Entry 1) and 4-nitrostyrene (Entry 6). In addition, the CM method allows for direct orthogonality to Wittig chemistry since unprotected benzaldehydes work well (Entry 7). Similar results were also obtained using vinyl phosphonates as

Table 4. Styrene Cross-Metathesis with Acrylate Esters

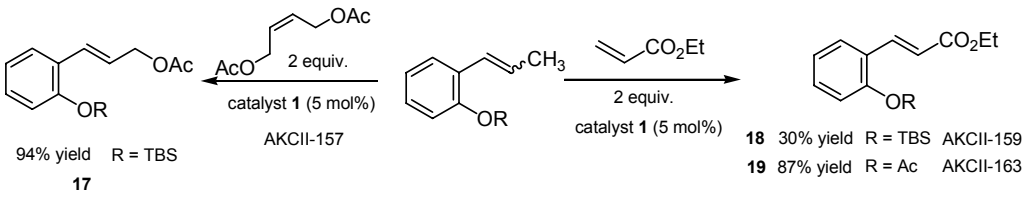


Entry	R	R'	Isolated Yield	Notebook
1	H	CH_3	92	AKCI-190
2	2,4-Dimethyl	CH_2CH_3	87	AKCI-247
3	2,4,6-Trimethyl	CH_2CH_3	5[a]	AKCI-285
4	2-CF_3	CH_2CH_3	44	AKCII-216
5	3,4-Dimethoxy	*n*-Butyl	89	AKCII-78
6	4-NO_2	CH_3	89	AKCI-215
7	4-CHO	CH_2CH_3	83	AKCI-257
8	2-F	CH_2CH_3	72	AKCI-284
9	2-Cl	CH_2CH_3	62	AKCI-286
10	2-Br	CH_2CH_3	49	AKCI-283
11	2,6-Difluoro	CH_2CH_3	19	AKCI-254

[a] Determined by ^{1}H-NMR

the "enone" component.[6d] It was also interesting that simple *ortho*-alkyl groups did not reduce styrene dimerization, since 2,4-dimethylstyrene was also able to react in good yield acrylate esters (Entry 2), but that electron-withdrawing functionality at the *ortho* position, such as 2-trifluoromethyl styrene (Entry 4) plays a large role in determining CM efficiency. In addition, two methyl groups at the ortho position completely destroy CM reactivity with acrylates (Entry 3). Therefore, for proper CM selectivity, the two olefins in CM need to have a difference in rate of reaction with the metal alkylidene complex.

As additional evidence for alteration in styrene reactivity based on substitution patterns, we investigated *ortho*-phenol styrene derivatives. These are interesting substrates for catalytic reactions, since several derivatives form stable benzylidene complexes.[13] However, instead of inhibiting catalyst activity, a variety of protected phenols are active for catalytic CM (Scheme 4).



Scheme 4: *ortho*-Phenol Cross-Metathesis

We found that small protecting groups, such as acetate, allowed for excellent CM with acrylates. The balance of the material in this reaction was recovered as the stilbene dimer. This protection pattern is similar to other unhindered styrenes in Table 4. However, when a larger protecting group is employing, such as *tert*-butyldimethylsilyl, then CM with acrylates gives poor yields, in contrast the reaction provides very good yield with allyl acetate equivalents. In this case, this substrate reacts like 2-bromostyrene due to steric bulk and is very selective in CM with α-olefins. This suggests that CM with allylic esters and acrylate esters may proceed by different reaction pathways, and that small changes in protecting groups can affect CM selectivity.

With these observations with styrene CM, we began to formulate a reactivity model to describe these results and others observed in CM. Instead of simply looking at *absolute* homodimerization as a measure of an olefin's ability to participate in selective CM, we looked at *relative* homodimerization and describe olefins on a gradient scale of their propensity to undergo homodimerization to determine certain matched cases for selective CM. In addition, not only is ability to dimerize a contributing factor, but also the ability to perform secondary metathesis on the homodimerized products. Accounting for these factors, leads to a model that comprises four distinct olefin types which predicts product selectivity in CM (Figure 2). For example, Type I olefins are ones that undergo a rapid homodimerization, and

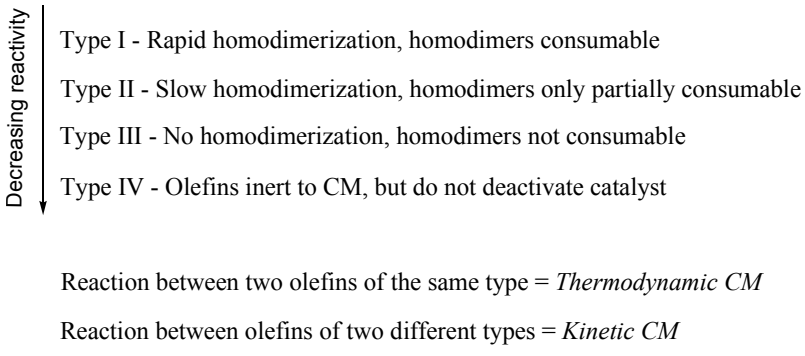
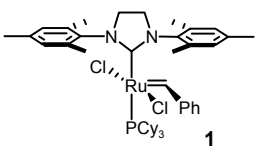
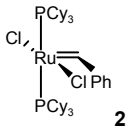
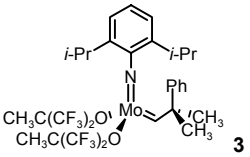


Figure 2. Olefin Categorization and Rules for Selective CM

where their homodimers equally participate in CM as well as their terminal olefin counterpart. It is this ability (or inability) to perform secondary metathesis on a newly formed CM olefin that is essential to understand in predicting selective CM. For example, when two Type I olefins are used in a CM reaction, they will react in a manner to provide a statistical product mixture, or thermodynamic CM. As seen in the case of catalyst **1**, styrenes without large electron-withdrawing ortho-substituents, as well as primary allylic alcohols (and protected derivatives) are Type I olefins, as seen in Table 3, Entry 1. Therefore, when two olefins of the same type are combined, statistical mixtures are usually obtained. For example, when two Type II olefins are combined, such as in Table 4 Entry 10, non-selective CM yields are obtained. Table 5 summarizes all known CM substrates reported in the literature as well as our work disclosed here. When two olefins of different types are reacted; a second reaction pathway is possible.

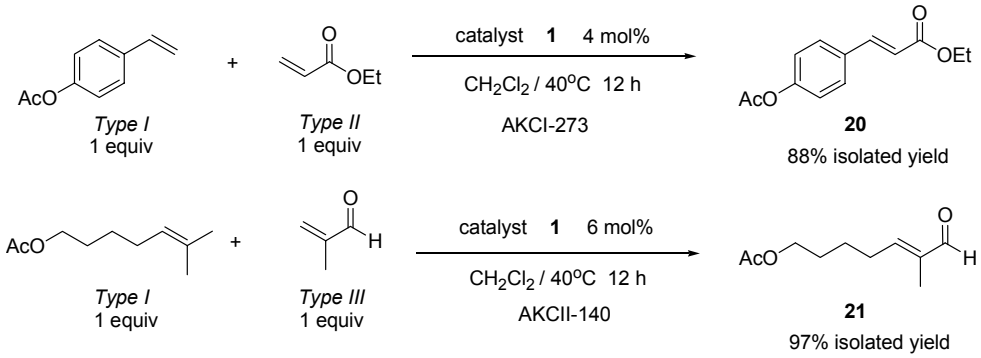
A second CM reaction pathway leads to non-statistical or kinetically controlled CM reactions, where the CM product predominates with respect to

Table 5. Olefin Categories for Selective CM

Olefin type	 1	 2	 3
Type 1 (fast homodimerization)	Terminal olefins,[6] 1° allylic alcohols, esters[6g,20] Allylboronate esters,[6f] Allylic halides[6f,6h] Styrenes (no large ortho substit.)[6c,d,f,h] Allylphosphonates,[6d] phosphine oxides,[6g] sulfides,[6g] protected amines[6g] Allylsilanes[25]	Terminal olefin[8] Allylsilanes[14,18,19] 1° allylic alcohols, ethers, esters[8,19,21] Allylboronate esters[10f] Allylhalides[17]	Terminal olefins[11a,b,12,14] Allylsilanes[11b]
Type 2 (slow homodimerization)	Styrenes (large ortho substit.)[6d,f] Acrylate esters,[6b,h] amides,[6c] acids,[6c] aldehydes,[6b,6d,24] ketones,[6b] unprotected 3° allylic alcohols,[6g,6f] vinyl epoxides[6b] 2° allylic alcohols Perfluorinated alkane olefins[6b,23]	Styrene[9,16] 2° allylic alcohols, vinyl dioxolanes[8] Vinyl boronates[8]	Styrene[11a,11b] Allylstannanes[15]
Type 3 (no homodimerization)	1,1-Disubstituted olefins[6a] Vinylphosphonates[6d] Phenyl Vinyl Sulfone[22] 4° allylic carbons (all alkyl substituents) 3° allylic alcohols (protected)	Vinylsiloxanes[16]	Tertiary allylamines[14] Acrylonitrile[12]
Type 4 (spectators to CM)	Vinyl nitro olefins Trisubstituted allylic alcohols (protected)	1,1-disubstituted olefins disubstit. α,β-unsaturated carbonyls 4° allylic carbon containing olefins[8] Perfluorinated alkane olefins[8] 3° allylamines (protected)[14]	1,1-disubstituted olefins[11a]

homodimers. The formation of a kinetic CM product also greatly limits secondary metathesis processes that would scramble productive CM products, as well as allow for unwanted homodimers to be converted to CM product. Conversely, reactions between Type I olefins, leading to thermodynamically controlled reactions are accessible to secondary metathesis. Kinetic CM reactions are mediated by olefins where the rates of dimerization are significantly different and/or slower that CM product formation. Kinetic CM requires the reaction of olefins from two different types. For example, in a reaction between a Type I olefin, such as α-olefins, and acrylate esters (Type II), highly selective reactions are possible in nearly 1:1 stoichiometry (Scheme 5). In this case, the acrylate esters are Type II olefin that undergoes homodimerization to a small extent under the reaction conditions allowing for selective reactions with olefins of the Type I (4-acetoxystyrene) in 1:1 stoichiometry. Additionally, there is also the case where one of olefins in CM does not dimerize at all (Type III olefin), such as methacrolein, allowing for selective CM

in equal stoichiometry as shown in Scheme 5.[6i] In the methacrolein reaction, the entropic driving force of isobutylene loss allows for

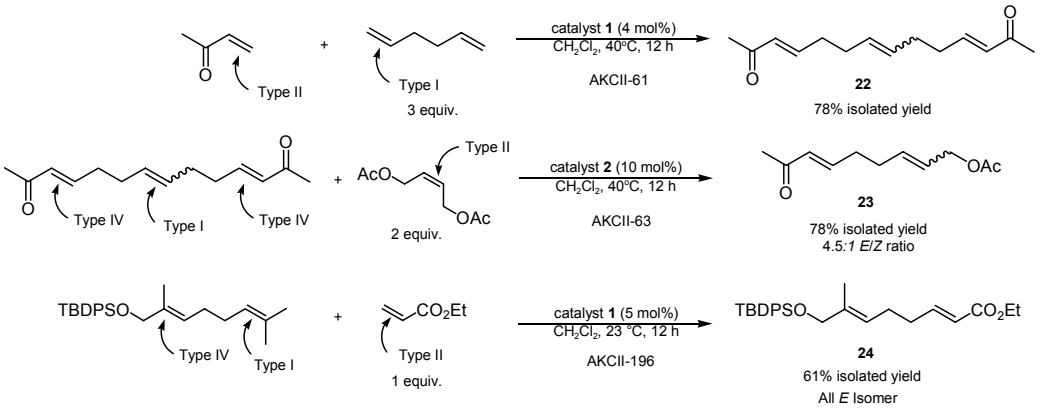


Scheme 5: Olefin Cross-Metathesis Mediated by Equal Stoichiometry

a regio- and stereoselective formal allylic oxidation of one of the terminal methyl groups. It is important to distinguish between Type II and Type III olefins because Type II homodimers are formed, but are not significantly active in subsequent metathesis reactions. The inability of Type III olefins to homodimerize allows it to also undergo selective reactions with Type II CM partners. For example, most 1,1-disubstituted olefins will readily perform selective CM with α-olefins as well as acrylate esters[6e] (Type II) and acrolein acetals[6a] (Type II), but will not homodimerize with itself. However, two Type II olefins (such as methyl vinyl ketone and methyl acrylate) can react with each other but will generally undergo non-selective CM.[6e] Therefore, it is important to use olefins from two different types to achieve selective, or kinetic, CM.

A fourth olefin type is one that is not affected by a particular catalyst, but does not inhibit catalyst activity toward other olefins. This provides a foundation for chemoselective CM, which is critical for differentiating between olefins in the synthesis of complex molecules. To a first approximation, this can be determined by the CM of a Type I or Type II olefin in the presence of a Type IV olefin. For example, using catalyst **2,** a disubstituted α,β-unsaturated carbonyl containing olefin (Type IV) is not affected, allowing for selective reactions between a Type I olefin

dimer and a Type II olefin (Scheme 6). Interestingly, the Type IV olefin for catalyst **2** is formed in a kinetic TypeI/Type II CM using catalyst **1**. An additional demonstration of a Type IV olefin involves recent work in our group also demonstrated a selective reaction of geraniol at one of its trisubstituted olefin (Type I since it can be made by a thermodynamic CM reaction) in the presence of another trisubstituted olefin that contains a bulky allylic protecting group, a Type IV olefin (Scheme 6).[6i] This allows for the conversion of natural

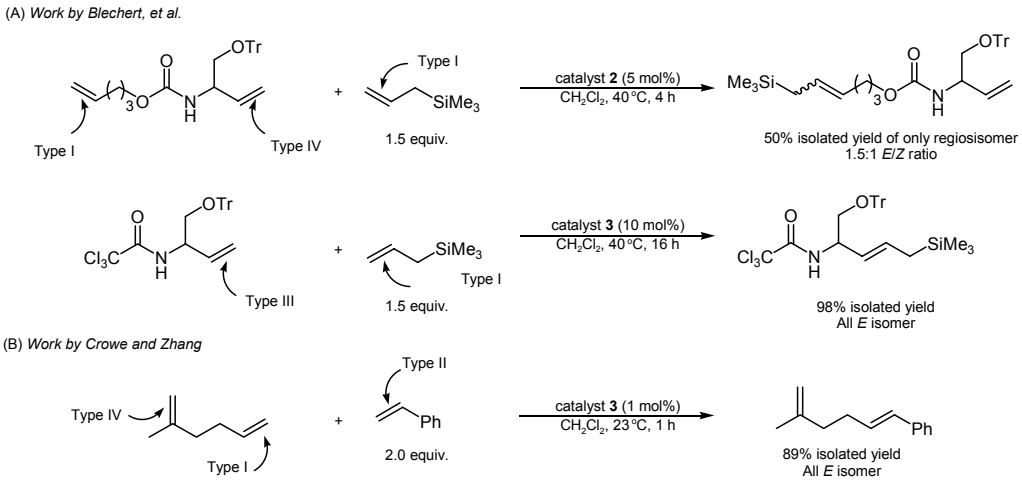


Scheme 6: Chemoselective CM based on Olefin Categorization

olefinic sources such as geraniol and nerol to other synthetically useful compounds and is an interesting application of selective CM processes.

This model for CM outlined in Figure 2 also explains results reported by other groups. For example, Blechert *et al.* used steric constraints and heteroatom functionality to demonstrate that a highly substituted allylamine (Type IV for catalyst **2**) could be benign to CM in the presence of two Type I olefins (Scheme 7).[14] Interestingly, in the same report by Blechert, catalyst **3** was used to effect a highly selective CM reaction of that same allylamine (Type III for catalyst **3**) with allylsilanes (Type I) in excellent yield (Scheme 7). In addition, this is one of the first examples of using steric bulk at the allylic carbon to obtain high olefin stereoselectivity and is comparable to the results we observed in Table 1 and 2 with catalyst **1**. Similarly, Crowe and Zhang performed a selective CM between a Type I

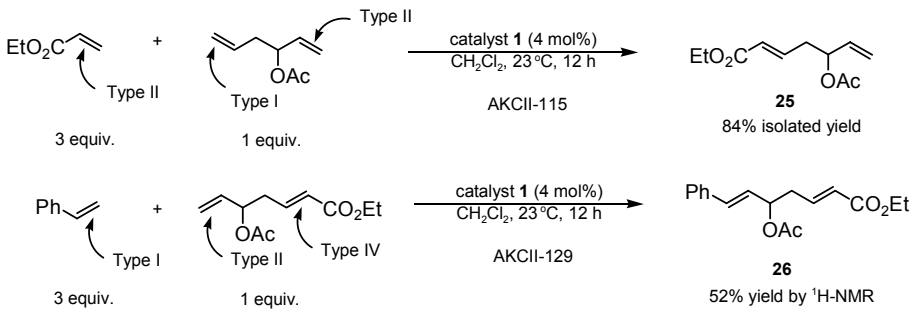
terminal olefin and styrene (Type II for catalyst **3**) and conducted in the presence of a 1,1-disubstituted olefin (Type IV).[11] As demonstrated previously in our lab,[6a] with the more active catalyst **1**, 1,1-disubstituted olefins are a Type III olefin that is active



Scheme 7: Chemoselective Cross-Metathesis using Catalysts **2** and **3**

for CM to form trisubstituted olefins. This shows that while more active catalysts will have a larger set of CM active olefins (Type I, II, III) it is useful to understand Type IV olefins for all catalysts, in order to determine possible chemoselective CM reactions. While electronic and steric parameters of olefins account as contributing factors in ways olefins are classified, other factors are often implied in determining selectivity, including chelating ability of certain functional groups to metal catalysts. For example, the effects of carbonyl groups, such as acetate protecting groups, and allylic heteroatoms have been implied to alter reactivity in CM. It is for these reasons that a comprehensive empirical model is necessary that account for all of these observations all of the methodology that exists in CM with different catalysts. Therefore, an olefin classification system for CM allows for the straightforward interpretation of efficient CM reactions (Scheme 5) as well as chemoselective CM reactions (Scheme 6 and 7). Table 5 represents all reported CM substrates for catalysts **1**, **2**, and **3** and provides chemists with two basic functions. First, it

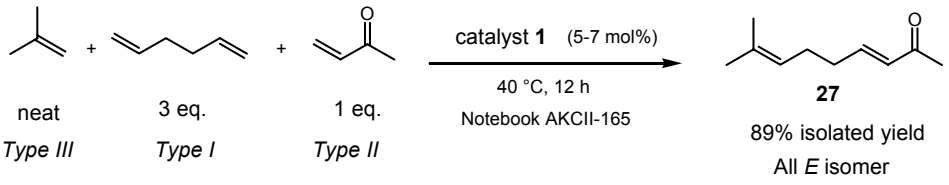
provides a reference point for synthetic chemists to utilize/design a potential selective CM reaction. Second, for those working to develop more active metathesis catalysts, it provides a set of olefins not currently active for CM (i.e., Type IV olefins) for new catalysts to attempt to use and place into the metathesis active Types (I, II, III). Up to this point, methodology developed in the area of olefin metathesis has been marked by repeated use of the most active catalyst available. However, where advantages in selective CM are presented with less active catalysts, then the utility of CM can be truly materialized. For example, in styrene CM with α-olefins, the use of catalyst **2** or **3** provides better selectivity that using the most active catalyst for that olefin, namely catalyst **1**. In addition, since these catalysts are commercially-available reagents, it is easy to employ the most selective catalyst without much effort. In addition, as new olefins are active for CM, placing them in an appropriate olefin type will allow them to be used more effectively in selective CM. Finally, the olefin categorization allows chemists to predict highly chemo and regioselective reactions. For example, as shown in Scheme 8, it is possible to have an unsymmetrical diene react differently based on its CM partners. For example, a Type II (acrylate)/Type I (homoallylic alcohol) coupling occurs at room temperature while leaving the Type II olefin (secondary allylic alcohol) unreacted. Subsequently, this Type II olefin undergoes a selective CM reaction with a Type I olefin (unsubstituted styrene) while not performing secondary metathesis on the previous



Scheme 8: Regioselective CM based on Olefin Categorization

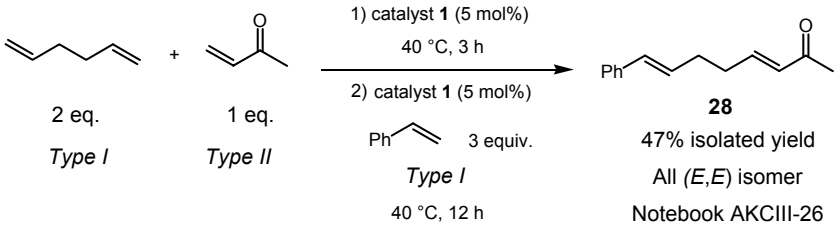
kinetic CM olefin product. These examples demonstrate that defining selectivity patterns in CM not only effects reaction stoichiometries, but also provides a method to construct complex molecules with multiple olefinic sites.

In addition to describing selectivity in the simple homologation of two olefins in a CM reaction, the olefin classification in Table 5 also provides an opportunity to discover new reactions, such as multi-component processes. While a three component reaction is theoretically possible, the large mixture of compounds from non-selective processes has made this an unattractive method to develop. However, with the current model of selective CM described here, two important things have been learned. First, that under kinetic CM control, secondary metathesis of the resulting olefins can be significantly slower than productive CM. Second, by using two olefins that do not perform CM with each other, then a third diene containing olefin can be functionalized at both olefinic sites to provide an unsymmetrical product (Scheme 9). In such a reaction, olefins of three different types are converted to one



Scheme 9: Three Component Olefin Cross-Metathesis

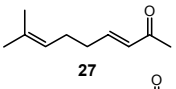
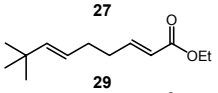
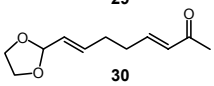
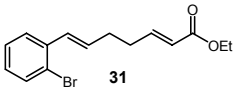
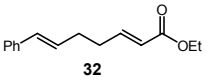
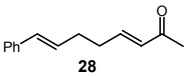
main product as a single stereoisomer. This reaction is successful because the Type III and Type II olefins react at a much slower rate with each other than their respective reactions with a Type I olefin. In addition, the products from these individual reactions do not undergo secondary metathesis, allowing for selective reactions. The formation of a kinetic CM product also allows for chemoselective coupling, where a one-pot sequential CM reaction can occur (Scheme 10). For example, if two CM



Scheme 10: One-pot Three Component Olefin Cross-Metathesis

partners are used in a three-component reaction that can perform efficient CM with each other, such as styrene and methyl vinyl ketone, then a sequential addition strategy avoids the unwanted side reaction. Therefore, by categorizing olefins and predicting their reactivity patterns, a variety of unsymmetrically substituted dienes can be prepared (Table 6). These reactions allow for a way to use olefin categorization to effectively predict proper three-component reactivity. In theory, any combination of a Type I, II, and III can be combined to provide a three-

Table 6. Three Component Olefin Cross-Metathesis[a]

Entry	Method	CM partner A	CM partner B	Ratio	Product	Isolated Yield	Notebook Reference
1	A			3:neat:1	 **27**	89	AKCII-165
2	A			1:neat:1	 **29**	67[b]	AKCII-298
3	A			1:3:1	 **30**	51[c]	AKCII-304
4	A			2:5:1	 **31**	51	AKCIII-14
5	B			1:3:1	 **32**	34	AKCIII-3
6	B			2:3:1	 **28**	47	AKCIII-26

[a] Using 5-7mol% of **1** in 0.1-0.2M refluxing CH_2Cl_2, 12h [b] Reaction at 23 °C [c] Determined by ^{1}H-NMR
Method A = Added all components at one time, Method B = Added one component, then added second component after 4 hours

component product (Method A). In addition, if two Type I olefins need to be coupled, then one kinetic CM olefin needs to be formed first, followed by a second CM reaction (Method B). The reactions add a new level of complexity to olefin metathesis reactions, and are possible due to development of stereoselective CM and a

better understanding of CM reactivity patterns.

In conclusion, a model for reactivity patterns of olefins in CM is described. This model is able to account for all known CM reactions. In most cases, the classification of an olefin can predict its product selectivity patterns. In conjunction with our discovery of stereoselective CM with sterically encumbered olefins and electron-deficient olefins, we have been able to address both product and stereoselective reactions. In addition, by understanding the inherent reactivity of olefins in CM with a variety of catalysts, one can access new reaction platforms, such as multi-component CM reactions. These findings should allow for the application of CM to the synthesis of complex organic molecules and increase the utility of olefin metathesis in organic chemistry in general.

Experimental Section.

General Procedure:

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich or TCI America and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use. Catalyst **1** and **2** were stored and manipulated on the bench. NMR spectra were recorded on a Varian Mercury 300 MHz NMR.

Compound 4. *cis*-2-butene-1,4-diacetate (160 μl, 1.0 mmol) and allylbenzene (55 μL, 0.50 mmol) were added simultaneously via syringe to a stirring solution of **2** (11 mg, 0.014 mmol, 2.7 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then

reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500mL). Pale oil was obtained (76 mg, 80% yield, trans/cis as determined by integration of peaks at 4.73 and 4.55 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.34-7.17 (5H, m), 5.92 (1H, m), 5.65 (1H, m), 4.55 (2H, app d), 3.41 (2H, d, J = 3.3 Hz), 2.06 (3H, unresolved s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.4, 135.1, 134.0, 129.2, 129.1, 126.8, 125.8, 65.5, 60.8, 39.2, 21.6. R_f = 0.53 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{12}H_{14}O_2$ $[M-H]^+$ 189.0916, found 189.0916.

Compound 5. *cis*-2-butene-1,4-diacetate (160 μl, 0.9 mmol) and 2-benzyloxy-3-butene (90 μL, 0.51 mmol) were added simultaneously via syringe to a stirring solution of **1** (11 mg, 0.015 mmol, 2.8 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500mL). Pale oil was obtained (48 mg, 0.19 mmol, 38% yield). Spectra compared to reported compound, see: Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 58. R_f = 0.36 (9:1 hexane:ethyl acetate).

Compound 6. 5-Hexenyl-1-acetate (170 μl, 1.0 mmol) and 2-benzyloxy-3-butene (90 μL, 0.51 mmol) were added simultaneously via syringe to a stirring solution of **1** (15 mg, 0.018 mmol, 3.5 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:1 hexane:ethyl acetate (500mL). Clear oil was obtained (121 mg, 0.42

mmol, 82% yield, 10:1 *E*/*Z* determined by relative ^{13}C peak heights at 71.9 and 68.0 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.02 (2H, t, *J* = 7.2 Hz), 7.51 (1H, t, *J* = 7.2 Hz), 7.40 (2H, t, *J* = 7.8 Hz), 5.80-5.70 (1H, m), 5.61-5.51 (2H, m), 4.02 (2H, t, *J* = 6.6 Hz), 2.09-1.98 (5H, m), 1.65-1.55 (2H, m), 1.47-1.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.2, 165.9, 132.9, 132.8, 130.9, 130.2, 129.7, 128.4, 71.9, 64.6, 32.1, 28.4, 25.6, 21.4, 20.9. HRMS (EI) calcd for $C_{17}H_{22}O_4$ $[M + H]^+$ 291.1596, found 291.1601. R_f = 0.50 (3:1 hexane:ethyl acetate).

Compound 7. 5-Hexenyl-1-acetate (170 μl, 1.0 mmol) and 3-butene-2-ol (45 μL, 0.52 mmol) were added simultaneously via syringe to a stirring solution of **1** (12 mg, 0.014 mmol, 2.7 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500mL) followed by 3:1 hexane:ethyl acetate (500mL). Brown oil was obtained (89 mg, 92% yield, 13:1 *E*/*Z* determined by relative ^{1}H integrations at 4.62 and 4.24 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.66-5.40 (2H, m), 4.22 (1H, quint, *J* = 7.8 Hz), 4.02 (2H, t, *J* = 7.8 Hz), 2.09-1.98 (5H, m), 1.65-1.55 (3H, m), 1.47-1.38 (2H, m), 1.32 (3H, app d). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.2, 134.7, 130.2, 69.7, 64.2, 32.1, 28.4, 25.6, 22.4, 20.9. R_f = 0.26 (3:1 hexane:ethyl acetate). Compound spectra match those of previously characterized (*Z*) compound, see: Bratt, K.; Garavelas, A.; Perlmutter, P.; Westman, G.. *J. Org. Chem.* **1996**, *61*, 2109

Compound 8. 5-Hexenyl-1-acetate (85 μl, 0.51 mmol) and 2-*tert*-butyldiphenylsilyl-3-butene (300 μL, 1.07 mmol) were added simultaneously via syringe to a stirring solution of **1** (23 mg, 0.027 mmol, 5.3 mol%) in CH_2Cl_2 (2.5 ml).

The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Brown oil was obtained (115 mg, 0.27 mmol, 53% yield, 7:1 *E*/*Z* determined by relative ^{1}H integrations at 4.58 and 4.28 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.73-7.68 (4H, m), 7.42-7.36 (6H, m), 5.58-5.45 (1H, m), 5.40-5.32 (1H, m), 4.28 (1H, quint, *J* = 6.0 Hz), 4.05 (2H, t, *J* = 6.9 Hz), 2.06 (3H, s), 1.96 (2H, q, *J* = 6.9 Hz), 1.63-1.53 (2H, m), 1.41-1.34 (2H, m), 1.17 (3H, d, J = 6.3 Hz), 1.08 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.3, 136.1, 136.0, 135.2, 135.1, 135.0, 134.8, 134.6, 129.7, 129.0, 127.9, 127.7, 127.6, 127.5, 70.6, 64.8, 31.9, 28.4, 27.4, 27.3, 25.8, 25.0, 24.9, 21.4, 19.6. R_f = 0.56 (9:1 hexane:ethyl acetate). Compound spectra match those of previously characterized (*Z*) compound, see: Bratt, K.; Garavelas, A.; Perlmutter, P.; Westman, G.. *J. Org. Chem.* **1996**, *61*, 2109.

Compound 9. 5-Hexenyl-1-acetate (170 μl, 1.02 mmol) and 3-methyl-1-penten-3-ol (60 μL, 0.51 mmol) were added simultaneously via syringe to a stirring solution of **1** (20 mg, 0.024 mmol, 4.8 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:1 hexane:ethyl acetate. Brown oil was obtained (100 mg, 0.47 mmol, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.58 (1H, dt, *J* = 15.6, 6.6 Hz), 5.46 (1H, d, *J* = 15.6 Hz), 4.02 (1H, t, *J* = 6.6 Hz), 2.06-1.92 (5H, m), 1.61-1.35 (6H, m), 1.18 (3H, s), 0.81 (3H, t, *J* = 6.9 Hz). R_f = 0.40 (3:1 hexane:ethyl acetate).

Compound 10. 5-Hexenyl-1-acetate (50 μl, 0.30 mmol) and 3,3-Dimethyl-1-hexene (95 μL, 0.61 mmol) were added simultaneously via syringe to a stirring solution of **1**

(12 mg, 0.014 mmol, 4.7 mol%) in CH_2Cl_2 (1.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Clear oil was obtained (61 mg, 0.27 mmol, 90% yield, only one olefin isomer observed by ^{1}H-NMR). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.38-5.18 (2H, m), 4.04 (2H, t, J = 6.6 Hz), 2.04 (3H, obs s), 2.01 (2H, q, J = 6.9 Hz), 1.67-1.57 (2H, m), 1.43-1.37 (2H, m), 1.20 (4H, app d, J = 3.3 Hz), 0.93 (6H, s), 0.87-0.82 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.3, 140.1, 125.2, 64.8, 46.0, 36.0, 32.6, 29.3, 28.3, 27.7, 26.3, 21.3, 18.1, 15.2. R_f = 0.68 (5:1 hexane:ethyl acetate).

Compound 11. *cis*-2-butene-1,4-diacetate (50 μl, 0.32 mmol) was added via syringe to a stirring solution of **1** (10 mg, 0.012 mmol, 3.8 mol%) in 3,3-Dimethyl-1-butene (2 mL, 15.52 mmol). The flask was fitted with a condenser and stirred under nitrogen for 12 hours at room temperature (23 ^{o}C). The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 50:1 hexane:ethyl acetate. Clear oil was obtained (92 mg, 0.60 mmol, 93% yield, only one olefin isomer observed by ^{1}H-NMR). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.75 (1H, dt, J = 15.6, 1.2 Hz), 5.45 (2H, dt, J = 15.3, 6.6 Hz), 4.50 (2H, dd, J = 6.3, 1.2 Hz), 2.05 (3H, s), 1.01 (9H, s). R_f = 0.62 (9:1 hexane:ethyl acetate).

Compound 12. 5-Hexenyl-1-acetate (81 μl, 0.48 mmol) and 2-methyl-2-vinyl-1,3-dioxolane (50 μL, 0.48 mmol) were added simultaneously via syringe to a stirring solution of **1** (14 mg, 0.017 mmol, 3.7 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel

column (2x10 cm), eluting with 5:1 hexane:ethyl acetate. Clear oil was obtained (100 mg, 0.44 mmol, 91% yield, only one olefin isomer observed by ^{1}H-NMR). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.77 (1H, dt, *J* = 15.3, 6.9 Hz), 5.42 (1H, dt, *J* = 15.6, 1.5 Hz), 4.05 (2H, t, J = 6.6 Hz), 3.96-3.82 (4H, m), 2.14-1.98 (5H, m), 1.55-1.45 (2H, m), 1.42-1.35 (5H, m). R_f = 0.31 (9:1 hexane:ethyl acetate). Spectra match those of known compounds that are related, see: Camps, J.; Font, J.; de March, P. *Tetrahedron* **1981**, *37*, 2499.

Compound 13. Styrene (32 μl, 0.28 mmol) and 2-methyl-2-vinyl-1,3-dioxolane (63 μL, 0.55 mmol) were added simultaneously via syringe to a stirring solution of **1** (7 mg, 0.008 mmol, 3.0 mol%) in CH_2Cl_2 (1.3 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Clear oil was obtained (37 mg, 0.19 mmol, 70% yield, only *E* olefin isomer observed by ^{1}H-NMR). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.42-7.25 (5H, m), 6.71 (1H, d, *J* = 15.9 Hz), 6.15 (1H, d, *J* = 15.9 Hz), 4.05-3.92 (4H, m), 1.57 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.3, 129.9, 128.8, 128.1, 126.9, 107.9, 64.9, 30.0, 25.6. Elemental analysis Calcd: C: 75.76, H: 7.42; Found: C: 75.47, H: 7.63. R_f = 0.41 (9:1 hexane:ethyl acetate).

Compound 14. 1-*tert*-butyldimethylsilyloxy-9-decene (190 μl, 0.57 mmol) and 3-methyl-3-buten-2-ol (55 μL, 0.54 mmol) were added simultaneously via syringe to a stirring solution of **1** (17 mg, 0.020 mmol, 4.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained

(121 mg, 0.37 mmol, 69% yield) and only one olefin isomer detected in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.60-5.58 (2H, m), 3.58 (2H, t, *J* = 6.6 Hz), 2.01-1.96 (2H, m), 1.54-1.47 (4H, m), 1.36-1.24 (14H, m), 0.89 (9H, s), 0.03 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 137.9, 127.4, 70.8, 63.5, 33.1, 32.4, 31.9, 30.1, 29.7, 29.6, 29.5, 29.4, 26.3, 26.1, 22.9, 18.7, 14.4, -4.9 ppm. R_f = 0.23 (9:1 hexane:ethyl acetate).

Compound 15. 5-hexenyl-1-acetate (40 μL, 0.24 mmol) was added via syringe to a stirring solution of **1** (12 mg, 0.014 mmol, 6.0 mol%) and 2-*tert*-butyldimethylsilyloxy-2-methyl-3-butene (106 mg, 0.53 mmol) in CH_2Cl_2 (1.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate (500 ml) followed by 3:1 hexane:ethyl acetate (300 ml). A clear oil was obtained (73 mg, 0.23 mmol, 97% yield) and only one olefin isomer detected in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.60-5.50 (2H, m), 4.05 (2H, t, *J* = 6.6 Hz), 2.04-1.99 (5H, m), 1.70-1.58 (2H, m), 1.47-1.40 (2H, m), 1.26 (6H, s), 0.85 (9H, s), 0.03 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.3, 139.6, 125.9, 73.1, 64.7, 32.1, 30.9, 28.5, 26.2, 26.0, 21.4, 18.4, -1.66 ppm. R_f = 0.18 (9:1 hexane:ethyl acetate).

Compound in Table 3, Entry 3. 5-hexenyl-1-acetate (70 μL, 0.45 mmol) and 2-bromostyrene (170 μL, 1.36 mmol) were added simultaneously via syringe to a stirring solution of **1** (19 mg, 0.021 mmol, 4.8 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. A light brown oil was

obtained (130 mg, 0.44 mmol, 98% yield) and only one olefin isomer detected in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.52-7.43 (2H, m), 7.29-7.02 (2H, m), 6.70 (1H, d, *J* = 15.9 Hz), 6.13 (1H, dt, *J* = 15.9, 6.9 Hz), 4.09 (2H, t, *J* = 6.6 Hz), 2.28 (2H, app q), 2.04 (3H, s), 1.74-1.53 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.3, 139.6, 133.4, 132.9, 129.3, 128.4, 127.5, 126.9, 126.2, 64.6, 32.8, 28.4, 25.8, 21.4 ppm. HRMS (EI) for $C_{14}H_{17}BrO_2$: Calcd 296.0412, Found 296.0403. R_f = 0.34 (9:1 hexane:ethyl acetate).

Compound in Table 3, Entry 5. *cis*-2-butene-1,4-diacetate (75 μL, 0.48 mmol) and 2-fluorostyrene (24 μL, 0.20 mmol) were added simultaneously via syringe to a stirring solution of **1** (8 mg, 0.009 mmol, 5.0 mol%) in CH_2Cl_2 (1.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate. A brown oil was obtained (38 mg, 0.20 mmol, 97% yield) and only one olefin isomer detected in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.48-7.42 (1H, m), 7.24-7.19 (1H, m), 7.12-7.00 (2H, m), 6.79 (1H, d, *J* = 16.2 Hz), 6.36 (1H, dt, *J* = 15.9, 6.3 Hz), 4.74 (2H, dd, *J* = 6.3, 1.2 Hz), 2.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.8, 162.0, 158.7, 129.5 (d, *J* = 8.3 Hz), 127.6 (d, *J* = 3.5 Hz), 126.4 (d, *J* = 3.8 Hz), 125.9 (d, *J* = 5.2 Hz), 124.2 (d, *J* = 3.7 Hz), 115.8 (d, *J* = 21.9 Hz), 65.3, 21.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ -118.2 (t, *J* = 5.9 Hz). R_f = 0.34 (9:1 hexane:ethyl acetate).

Compound in Table 3, Entry 6. *cis*-2-butene-1,4-diacetate (160 μL, 1.01 mmol) and 2,5-difluorostyrene (62 μL, 0.50 mmol) were added simultaneously via syringe to a stirring solution of **1** (13 mg, 0.015 mmol, 3.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The

reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A dark brown oil was obtained (53 mg, 0.25 mmol, 50% yield) and only one olefin isomer detected in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.42-7.10 (2H, m), 6.90-6.80 (2H, m), 6.71-6.55 (1H, m), 4.75 (2H, app d), 2.11 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 162.7, 159.4, 134.3, 130.5, 128.8, 120.0, 123.3, 111.8, 65.6, 21.3. R_f = 0.48 (9:1 hexane:ethyl acetate). HRMS(EI) for $C_{11}H_{10}F_2O_2$ Calcd: 212.0649, Found: 212.0644.

Compound in Table 3, Entry 7. *cis*-2-butene-1,4-diacetate (24 μL, 0.15 mmol) was added via syringe to a stirring solution of **1** (4 mg, 0.015 mmol, 3.0 mol%) and *trans*-stilbene (23 mg, 0.13 mmol) in CH_2Cl_2 (1.3 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear yellow oil was obtained (23 mg, 0.13 mmol, 51% yield) and only one olefin isomer detected in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.42-7.26 (5H, m), 6.65 (1H, d, J = 15.9 Hz), 6.29 (1H, dt, J = 15.9, 6.3 Hz), 4.75 (2H, app d), 2.11 (3H, s) ppm. R_f = 0.41 (9:1 hexane:ethyl acetate). Compound spectra match that of *trans*-cinnamyl acetate in Aldrich compound library.

Compound in Table 4, Entry 1. Methyl acrylate (90 μL, 1.00 mmol) and styrene (60 μl, 0.52 mmol) were added simultaneously via syringe to a stirring solution of **1** (20 mg, 0.024 mmol, 4.5 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. A white crystalline solid was obtained (78

mg, 0.48 mmol, 92% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.64 (1H, d, *J* = 15.6 Hz), 6.40 (1H, d, *J* = 15.9 Hz), 3.83 (3H, s). R_f = 0.53 (9:1 hexane:ethyl acetate). Compound spectra match that of *trans*-methyl cinnamate in Aldrich compound library.

Compound in Table 4, Entry 2. Ethyl acrylate (110 μL, 1.02 mmol) and 2,4-dimethylstyrene (75 μl, 0.51 mmol) were added simultaneously via syringe to a stirring solution of **1** (10 mg, 0.012 mmol, 2.4 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. A clear oil was obtained (91 mg, 0.45 mmol, 87% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.95 (1H, d, *J* = 15.9 Hz), 7.48-7.45 (1H, m), 7.02-7.00 (2H, m), 6.33 (1H, d, *J* = 16.2 Hz), 4.26 (2H, q, *J* = 6.9 Hz), 2.41 (3H, s), 2.33 (3H, s), 1.34 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.3, 142.2, 140.3, 137.7, 131.6, 127.2, 126.4, 118.2, 60.6, 21.6, 20.0, 14.6. HRMS (EI) for $C_{13}H_{16}O_2$: Calcd 204.1150, Found 204.1155. Elemental analysis Calcd: C: 76.44, H: 7.90; Found: C: 76.07, H: 8.05. R_f = 0.70 (9:1 hexane:ethyl acetate).

Compound in Table 4, Entry 4. Ethyl acrylate (75 μL, 0.69 mmol) and 2-trifluoromethylstyrene (50 μl, 0.34 mmol) were added simultaneously via syringe to a stirring solution of **1** (15 mg, 0.018 mmol, 5.1 mol%) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A brown oil was obtained

(37 mg, 0.15 mmol, 44% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.05 (1H, app d), 7.70-7.31 (4H, m), 6.43 (1H, app d), 4.20 (2H, q, J = 6.9 Hz), 1.31 (3H, app t). R_f = 0.70 (9:1 hexane:ethyl acetate). Compound matches spectra previously reported of the methyl ester, see: Vallgårda, J.; Appelberg, U.; Csöregh, I.; Hacksell, U. *J. Chem. Soc. Perkin Trans. 1* **1994**, 461.

Compound in Table 4, Entry 5. Ethyl acrylate (81 μL, 0.56 mmol) and 3,4-dimethoxystyrene (56 μl, 0.38 mmol) were added simultaneously via syringe to a stirring solution of **1** (13 mg, 0.015 mmol, 4.0 mol%) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained (96 mg, 0.36 mmol, 96% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.62 (1H, d, *J* = 15.9 Hz), 7.10 (1H, dd, *J* = 8.4, 2.0 Hz), 7.05 (1H, d, *J* = 2.1 Hz), 6.85 (1H, d, *J* = 8.1 Hz), 6.30 (1H, d, *J* = 15.9 Hz), 4.20 (2H, t, *J* = 6.6 Hz), 3.91 (6H, s), 1.73-1.62 (2H, m), 1.50-1.38 (2H, m), 0.96 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.5,151.2, 149.3, 144.6, 127.6, 122.8, 116.1, 111.2, 109.7, 64.6, 56.2, 56.1, 31.1, 19.5, 14.1. R_f = 0.24 (9:1 hexane:ethyl acetate).

Compound in Table 4, Entry 6. Methyl acrylate (90 μL, 1.00 mmol) and 4-nitrostyrene (75 μl, 0.51 mmol) were added simultaneously via syringe to a stirring solution of **1** (10 mg, 0.012 mmol, 2.3 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel

column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A white crystalline solid was obtained (93 mg, 0.45 mmol, 89% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.25 (1H, dd, J = 7.2, 2.1 Hz), 7.74-7.66 (4H, m), 6.55 (1H, d, J = 16.2 Hz), 3.84 (3H, app s). R_f = 0.30 (9:1 hexane:ethyl acetate). Spectra match those of previously characterized compound, see: Huang, X.; Xie, L.; Wu, H. *J. Org. Chem.* **1988**, *53*, 4862.

Compound in Table 4, Entry 7. Ethyl acrylate (110 μL, 1.02 mmol) and 4-vinylbenzaldehyde (75 μl, 0.49 mmol) were added simultaneously via syringe to a stirring solution of **1** (16 mg, 0.019 mmol, 3.8 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 pentane:ethyl acetate. A dark yellow oil was obtained (85 mg, 0.42 mmol, 83% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.00 (1H, s), 7.90-7.64 (4H, m), 6.52 (1H, d, J = 15.9 Hz), 4.26 (2H, q, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz). R_f = 0.28 (9:1 hexane:ethyl acetate). Spectra match those of previously characterized compound, see: Syper, L.; Mlochowski, J. *Synthesis* **1984**, 747.

Compound in Table 4, Entry 8. Ethyl acrylate (110 μL, 1.02 mmol) and 2-fluorostyrene (60 μl, 0.50 mmol) were added simultaneously via syringe to a stirring solution of **1** (12 mg, 0.014 mmol, 2.8 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained (70 mg, 0.36 mmol, 72% yield) and only *E* olefin isomer detected (by coupling

constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.80 (1H, d, *J* = 16.2 Hz), 7.55-7.49 (1H, m), 7.35-7.30 (1H, m), 7.17-7.05 (2H, m), 6.52 (1H, d, *J* = 16.2 Hz), 4.26 (2H, q, *J* = 6.9 Hz), 1.33 (3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ166.9, 137.3, 133.8, 131.9, 129.2, 124.6, 121.1, 121.0, 116.5, 61.0, 14.7. R_f = 0.39 (9:1 hexane:ethyl acetate). Spectra match those of previously characterized compound, see: Houghton, R. P.; Voyle, M.; Price, R. *J. Organomet. Chem.* **1983**, *259*, 183.

Compound in Table 4, Entry 9. Ethyl acrylate (96 μL, 0.89 mmol) and 2-chlorostyrene (57 μl, 0.44 mmol) were added simultaneously via syringe to a stirring solution of **1** (19 mg, 0.022 mmol, 5.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate. A clear oil was obtained (58 mg, 0.27 mmol, 62% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.07 (1H, d, *J* = 15.9 Hz), 7.62-7.59 (1H, m), 7.42-7.26 (3H, m), 7.17-7.05 (2H, m), 6.43 (1H, d, *J* = 15.9 Hz), 4.26 (2H, q, *J* = 6.9 Hz), 1.33 (3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ166.6, 140.5, 133.8, 132.9, 131.2, 130.3, 127.8, 127.2, 121.1, 61.6, 14.7. R_f = 0.63 (9:1 hexane:ethyl acetate). Spectra match those of previously characterized compound, see: Berrier, C.; Gesson, J. P.; Jacquesy, J. C.; Renoux, A. *Tetrahedron* **1983**, *40*, 4973.

Compound in Table 4, Entry 10. Ethyl acrylate (73 μL, 0.67 mmol) and 2-bromostyrene (42 μl, 0.33 mmol) were added simultaneously via syringe to a stirring solution of **1** (22 mg, 0.026 mmol, 7.7 mol%) in CH_2Cl_2 (2.5 ml). The flask was

fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate. A clear oil was obtained (42 mg, 0.17 mmol, 49% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.07 (1H, d, *J* = 15.9 Hz), 7.62-7.59 (2H, m), 7.35-7.22 (2H, m), 6.39 (1H, d, *J* = 15.9 Hz), 4.26 (2H, q, *J* = 6.9 Hz), 1.33 (3H, *J* = 7.2 Hz). R_f = 0.60 (9:1 hexane:ethyl acetate). Spectra match those of previously characterized compound, see: Dyker, G.; Grundt, P. *Helv. Chim. Acta.* **1999**, *82*, 588.

Compound in Table 4, Entry 11. Ethyl acrylate (110 μL, 1.02 mmol) and 2,5-difluorostyrene (60 μl, 0.48 mmol) were added simultaneously via syringe to a stirring solution of **1** (16 mg, 0.019 mmol, 4.0 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 pentane:ethyl acetate. An oil was obtained (19 mg, 0.09 mmol, 19% yield) and only *E* olefin isomer detected (by coupling constants) in ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.75 (1H, d, *J* = 15.9 Hz), 7.53-7.37 (1H, m), 6.97-6.90 (2H, m), 6.75 (1H, d, *J* = 15.9 Hz), 4.26 (2H, q, *J* = 6.9 Hz), 1.33 (3H, *J* = 7.2 Hz). R_f = 0.52 (9:1 hexane:ethyl acetate).

Compound 17. *cis*-2-butene-1,4-diacetate (95 μl, 0.60 mmol) was added via syringe to a stirring solution of **1** (15 mg, 0.018 mmol, 5.7 mol%) and 2-propene-*tert*-butyldimethylsilyloxy-phenol (76 mg, 0.31 mmol) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel

column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Clear oil was obtained (88 mg, 0.29 mmol, 94% yield) and all trans olefin by coupling constants in ^{1}H spectra . ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.45 (1H, dd, *J* = 7.5, 1.2 Hz), 7.14 (1H, app t, *J* = 7.5 Hz), 7.02-6.90 (2H, m), 5.80-5.70 (1H, dd, *J* = 8.1, 1.2 Hz), 6.22 (1H, dt, *J* = 16.2, 6.0 Hz), 4.73 (2H, dd, *J* = 6.0, 1.5 Hz), 2.10 (3H, s), 1.03 (9H, s), 0.21 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.8, 153.0, 129.0, 128.9, 127.7, 126.6, 123.0, 121.5, 119.7, 65.6, 26.1, 21.3, 18.6, -3.9. R_f = 0.51 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{17}H_{26}SiO_3$ $[M]^+$ 306.1651, found 306.1648. R_f = 0.51 (9:1 hexane:ethyl acetate).

Compound 18. Ethyl acrylate (65 μl, 0.60 mmol) was added via syringe to a stirring solution of **1** (13 mg, 0.015 mmol, 5.0 mol%) and 2-propene-*tert*-butyldimethylsilyloxy-phenol (75 mg, 0.30 mmol) in CH_2Cl_2 (1.7 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate. Clear oil was obtained (28 mg, 0.09 mmol, 30% yield) and all trans olefin by coupling constants in ^{1}H spectra. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.09 (1H, d, *J* = 16.2 Hz), 7.55 (1H, dd, *J* = 7.8, 1.5 Hz), 7.28-7.22 (1H, m), 6.99-6.82 (2H, m), 6.37 (1H, d, *J* = 16.5 Hz), 4.24 (2H, q, *J* = 7.2 Hz), 1.32 (3H, app t, J = 7.2 Hz), 1.03 (9H, s), 0.22 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.3, 154.7, 140.0, 131.4, 127.4, 126.1, 121.7, 120.1, 117.9, 60.5, 26.1, 18.6, 14.6, -3.9. R_f = 0.45 (9:1 hexane:ethyl acetate).

Compound 19. Ethyl acrylate (95 μl, 0.88 mmol) was added via syringe to a stirring solution of **1** (13 mg, 0.015 mmol, 3.4 mol%) and 2-propene-acetoxyphenol (78 mg, 0.44 mmol) in CH_2Cl_2 (2.0 ml). The flask was fitted with a condenser and

refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 20:1 hexane:ethyl acetate (300 ml) followed by 3:1 hexane:ethyl acetate (500 ml). Clear oil was obtained (90 mg, 0.38 mmol, 87% yield) and all trans olefin by coupling constants by ^{1}H-NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.73 (1H, d, *J* = 15.9 Hz), 7.62 (1H, dd, *J* = 7.8, 1.5 Hz), 7.39 (1H, td, *J* = 7.8, 1.5 Hz), 7.27-7.22 (1H, m), 7.11 (1H, dd, *J* = 7.8, 1.2 Hz), 6.43 (1H, d, *J* = 16.2 Hz), 4.25 (2H, q, *J* = 7.2 Hz), 2.37 (3H, app s), 1.32 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.2, 166.7, 149.3, 137.9, 131.1, 127.7, 127.2, 126.4, 123.2, 120.4, 60.8, 21.2, 14.5. R_f = 0.20 (9:1 hexane:ethyl acetate). Elemental analysis Calcd: C: 66.66, H: 6.02; Found: C: 66.54, H: 6.07.

Compound 20. Ethyl acrylate (54 μl, 0.50 mmol) and 4-acetoxystyrene (77 μl, 0.48 mmol) were added simultaneously via syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 4.2 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. Clear oil was obtained (99 mg, 0.43 mmol, 88% yield) and all trans olefin by coupling constants in ^{1}H spectra. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.62 (1H, d, *J* = 15.9 Hz), 7.52-7.49 (2H, m), 7.11-7.08 (2H, m), 6.36 (1H, d, *J* = 15.9 Hz), 4.23 (2H, q, J = 7.2 Hz), 2.27 (3H, s), 1.31 (3H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.2, 166.9, 152.2, 143.6, 132.2, 129.3, 122.3, 118.6, 60.8, 21.5, 14.7. R_f = 0.21 (9:1 hexane:ethyl acetate). Elemental analysis Calcd: C: 66.66, H: 6.02; Found: C: 66.54, H: 6.07.

Compound 21. Methacrolein (10 μl, 0.12 mmol) was added via syringe to a stirring

solution of **1** (6 mg, 0.007 mmol, 6.3 mol%) and 1-Acetoxy-5-methyl-2-hexene (19 mg, 0.11 mmol) in CH_2Cl_2 (1.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. Clear oil was obtained (20 mg, 0.1086 mmol, 97% yield) and all trans olefin by ^1H and ^{13}C spectra. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 9.41 (1H, s), 6.51 (1H, app t), 4.02 (2H, t, J = 6.9 Hz), 2.37 (2H, q, J = 7.2 Hz), 2.04 (3H, app s), 1.74-1.54 (7H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 195.2, 171.2, 153.9, 139.8, 64.2, 28.8, 28.5, 25.1, 21.3, 9.6. R_f = 0.11 (9:1 hexane:ethyl acetate). Spectra matches those of previously characterized compound by J. P. Morgan, Grubbs group.

Compound 22. Methyl vinyl ketone (22 μl, 0.30 mmol) and 1,5-hexadiene (105 μL, 0.88 mmol) was added simultaneously via syringe to a stirring solution of **1** (11 mg, 0.013 mmol, 4.3 mol%) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 3:1 hexane:ethyl acetate. Clear oil was obtained (29 mg, 0.23 mmol, 78% yield) and all trans olefin by ^1H spectra. This compound is a mixture of terminal olefin and its corresponding dimer. R_f = 0.32 (9:1 hexane:ethyl acetate).

Compound 23. *cis*-2-butene-1,4-diacetate (25 μL, 0.16 mmol) was added via syringe to a stirring solution of **2** (4 mg, 0.005 mmol, 9.0 mol%) and compound **22** (9 mg, 0.054 mmol) in CH_2Cl_2 (1.0 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with

4:1 hexane:ethyl acetate. Yellow oil was obtained (10 mg, 0.23 mmol, 78% yield) as a 4.5:1 *E*/*Z* olefin mixture by ^{1}H NMR integration at 4.60 and 4.51 ppm. R_f = 0.50 (3:1 hexane:ethyl acetate).

Compound 24. Ethyl acrylate (25 μL, 0.16 mmol) was added via syringe to a stirring solution of **1** (16 mg, 0.019 mmol, 3.9 mol%) and *tert*-butyldiphenylsilyloxy geraniol (193 mg, 0.054 mmol) in CH_2Cl_2 (2.5 ml). The flask was stirred under nitrogen at 23 ^{o}C for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 15:1 hexane:ethyl acetate. A clear oil was obtained (131 mg, 0.30 mmol, 61% yield). R_f = 0.54 (9:1 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.76-7.64 (4H, m), 7.45-7.35 (6H, m), 6.96 (1H, dt, *J* = 15.6, 6.6 Hz), 5.84 (1H, dt, J = 15.9, 1.5 Hz), 5.44-5.39 (1H, m), 4.25-4.05 (4H, m), 2.32-2.12 (4H, m), 1.45 (3H, s), 1.29 (3H, t, *J* = 6.9 Hz), 1.06 (9H, s).

Compound 25. Ethyl acrylate (115 μL, 1.06 mmol) and 3-acetoxy-1,5-hexadiene were (55 μl, 0.36 mmol) were added simultaneously via syringe to a stirring solution of **1** (16 mg, 0.019 mmol, 5.1 mol%) in CH_2Cl_2 (2.0 ml). The flask was stirred under nitrogen at 23 ^{o}C for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained (64 mg, 0.30 mmol, 84% yield). R_f = 0.28 (9:1 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.85 (1H, dt, *J* = 15.9, 7.2 Hz), 5.87 (1H, dt, *J* = 15.6, 1.5 Hz), 5.85-5.72 (1H, m), 5.38-5.19 (3H, m), 4.17 (2H, q, *J* = 7.2 Hz), 2.56-2.51 (1H, m), 2.06 (3H, s), 1.28 (3H, t, *J* = 6.9 Hz).

Compound 26. Styrene (30 μL, 0.26 mmol) was added via syringe to a stirring

solution of **1** (7 mg, 0.008 mmol, 10.0 mol%) and compound **25** (19 mg, 0.08 mmol) in CH_2Cl_2 (1.0 ml). The flask was stirred under nitrogen at 23 ^oC for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 5:1 hexane:ethyl acetate. A clear oil was obtained (16 mg) as a 3.4:1 mixture of compound **25** and **26** (calculated 13 mg, 0.041 mmol, 52% yield). R_f = 0.28 (9:1 hexane:ethyl acetate). ^1H NMR of Compound **26** (300 MHz, $CDCl_3$, ppm): δ 7.40-7.26 (5H, m), 6.98-6.82 (1H, m), 6.65 (1H, d, *J* = 15.6 Hz), 6.20-6.08 (1H, dd, *J* = 15.6 Hz, 6.6 Hz), 5.85-5.72 (1H, m), 5.58-5.51 (1H, m), 4.17 (2H, q, *J* = 7.2 Hz), 2.68-2.61 (2H, m), 2.06 (3H, s), 1.28 (3H, t, *J* = 6.9 Hz).

Compound 27. To an oven dried, 100 mL Fischer-Porter bottle with Teflon stir bar, ruthenium metathesis catalyst **1** (14 mg, 0.017 mmol, 7.0 mol%) was added. The bottle was capped with a rubber septum and flushed with dry nitrogen and cooled to -78 ^oC. 1,5-Hexadiene (85 μL, 0.72 mmol) and methyl vinyl ketone (20 μL, 0.24 mmol) was injected into the bottle. Once the substrates were frozen, a pressure regulator was attached to the bottle. The bottle was evacuated and backfilled with dry nitrogen 3 times. Subsequently, isobutylene (10 mL) was condensed into the bottle. The bottle was backfilled to ~2 psi with nitrogen, sealed, and allowed to slowly warm to room temperature, at which time it was transferred to an oil bath at 40^oC. After stirring for 12 hours, the bottle was removed from the oil bath and allowed to cool to room temperature. The isobutylene was slowly vented off at room temperature until the pressure apparatus could be safely disassembled. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate. Clear oil was obtained (32 mg, 0.21 mmol, 89% yield). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (1H, dt, *J* = 15.9, 6.6 Hz), 6.07 (1H, dt, *J* = 15.9, 1.5 Hz), 5.12-5.06 (1H, m), 2.26-

2.14 (7H, m), 1.69 (3H, s), 1.60 (3H, s). R_f = 0.53 (9:1 hexane:ethyl acetate). Spectra matches that of a previous characterization, see: Coxon, J. M.; Garland, R. P.; Hartshorn, M. P. *Aust. J. Chem.* **1972**, *25*, 353.

Compound 28. 1,5-Hexadiene (70 μL, 0.59 mmol) and methyl vinyl ketone (25 μL, 0.30 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 7.1 mol %) in CH_2Cl_2 (2.0 ml) under a nitrogen atmosphere. The flask was fitted with a reflux condenser stirred at 40 ^oC with a continuous flow of nitrogen for 3 hours. At that point, a solution of styrene (25 μL, 0.30 mmol) and catalyst **1** (16 mg, 0.019 mmol, 6.2 mol%) in CH_2Cl_2 was cannula transferred. The reaction mixture was stirred at 40 ^oC for an additional 8 hours. The resulting solution was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 15:1 hexane:ethyl acetate to provide cross product (R_f = 0.33 in 9:1 hexane:ethyl acetate) as a clear oil (28 mg, 0.14 mmol, 47% yield). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.35-7.21 (5H, m), 6.87-6.79 (1H, m), 6.42 (1H, d, *J* = 15.9 Hz), 6.27-6.10 (2H, m), 2.41 (4H, app s), 2.26 (3H, s). Spectra matches that of a previously characterized compound, see: Johns, A.; Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1989**, *45*, 7835.

Compound 29. 1,5-Hexadiene from (33 μL, 0.28 mmol) was added *via* syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 7.6 mol %) and ethyl acrylate (30 μL, 0.28 mmol) in 3,3-Dimethylbutene (1.5 mL, excess) under a nitrogen atmosphere. The flask was stirred under a continuous flow of nitrogen for 12 hours at room temperature (23 ^oC). The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 8:1 hexane:ethyl acetate to provide cross product (R_f = 0.39 in 5:1 hexane:ethyl acetate) as a viscous oil

(39 mg, 0.19 mmol, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.95 (1H, dt, *J* = 15.9, 6.6 Hz), 5.80 (1H, dt, *J* = 15.9, 1.5 Hz), 5.50-5.40 (1H, m), 5.27 (1H, dt, *J* = 15.3, 6.6 Hz), 4.05 (2H, q, *J* = 6.6 Hz), 2.26-2.12 (4H, m), 1.28 (3H, t, *J* = 7.2 Hz), 0.98 (9H, s).

Compound 30. 1,5-Hexadiene from (40 μL, 0.34 mmol) was added *via* syringe to a stirring solution of **1** (14 mg, 0.017 mmol, 5.0 mol %), ethyl vinyl ketone (33 μL, 0.33 mmol) and 2-vinyl-1,3-dioxolane (100 μl, 1.00 mmol) and CH_2Cl_2 (2.0 ml) under a nitrogen atmosphere. The flask was fitted with a reflux condenser stirred at 40 ^oC with a continuous flow of nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 8:1 hexane:ethyl acetate to provide cross product (R_f = 0.34 in 3:1 hexane:ethyl acetate) as a viscous oil (41 mg, 0.19 mmol, 51% calculated yield) which consists of a mixture of CM product and vinyl dioxolane dimer. ^{1}H NMR of compound **31** (300 MHz, $CDCl_3$, ppm): δ 6.77 (1H, dt, *J* = 15.9, 6.6 Hz), 6.09 (1H, dt, *J* = 15.9, 1.5 Hz), 5.96-5.85 (1H, m), 5.56-5.45 (1H, m), 5.16 (1H, d, *J* = 6.0 Hz), 4.06-3.72 (4H, m), 2.52 (2H, q, *J* = 6.6 Hz), 2.40-2.20 (4H, m), 1.04 (3H, t, *J* = 7.2 Hz).

Compound 31. 1,5-Hexadiene (70 μL, 0.59 mmol) was added *via* syringe to a stirring solution of **1** (25 mg, 0.030 mmol, 10.0 mol %), ethyl acrylate (32 μL, 0.30 mmol) and 2-bromostyrene (185 μl, 1.48 mmol) and CH_2Cl_2 (1.5 ml) under a nitrogen atmosphere. The flask was fitted with a reflux condenser stirred at 40 ^oC with a continuous flow of nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 15:1 hexane:ethyl acetate to provide cross product (R_f = 0.31 in 9:1 hexane:ethyl

acetate) as a viscous oil (47 mg, 0.15 mmol, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.54-7.45 (2H, m), 7.27-7.22 (1H, m), 7.10-6.98 (2H, m), 6.75 (1H, d, *J* = 16.2), 6.12 (1H, m), 5.88 (1H, d, *J* = 16.2 Hz), 4.10 (2H, q, *J* = 6.6 Hz), 2.40 (4H, app s), 1.15 (3H, t, *J* = 7.2 Hz).

Compound 32. 1,5-Hexadiene (63 μL, 0.53 mmol) and ethyl acrylate (58 μL, 0.53 mmol) were added simultaneously *via* syringe to a stirring solution of **1** (22 mg, 0.026 mmol, 5.2 mol %) in CH_2Cl_2 (2.5 ml) under a nitrogen atmosphere. The flask was fitted with a reflux condenser stirred at 40 ^oC with a continuous flow of nitrogen for 1.5 hours. At that point, styrene (180 μL, 1.57 mmol) was added via syringe. The reaction mixture was stirred at 40 ^oC for an additional 11 hours. The resulting solution was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2x10 cm), eluting with 10:1 hexane:ethyl acetate to provide cross product (R_f = 0.38 in 9:1 hexane:ethyl acetate) as a clear oil (41 mg, 0.18 mmol, 34% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.35-7.21 (5H, m), 7.04-6.96 (1H, m), 6.47-6.40 (1H, m), 6.24-6.16 (1H, m), 5.86 (1H, d, *J* = 15.6 Hz), 4.08 (2H, q, *J* = 6.6 Hz), 2.41 (4H, app s), 1.31 (3H, app t). Spectra matches that of a previously characterized methyl ester, see: Johns, A.; Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1989**, *45*, 7835.

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