

OLEFIN CROSS METATHESIS

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February 21, 2008

INTRODUCTION

Olefins are important functional groups in organic synthesis. In addition to their prevalence in natural products, olefins can be reliably modified into a great diversity of functional groups with many readily available processes. Among existing olefination methods, cross coupling reactions as a means to form new carbon-carbon bonds have received particular interest. Traditionally these olefination strategies have usually relied on nucleophilic attack on a carbonyl with a carbon nucleophile (Wittig, Horner-Wadsworth-Emmons, Julia) or palladium catalyzed coupling reactions (Suzuki, Stille, Heck). Although many of these reactions are well studied and dependable, there are still many challenges when accessing olefins in a congested or sensitive environment.¹ In addition, these methods are not very efficient because activation of functional groups is generally necessary for both coupling partners. Furthermore, many of these reactions require harsh conditions that are not compatible with other functional groups. Mandatory protection and deprotection of these functional groups adds steps resulting in lower yields and lengthier syntheses. Since its discovery in the 1950s, olefin metathesis, a conceptually different olefination method, has been emerging as a more and more important player in this arena.

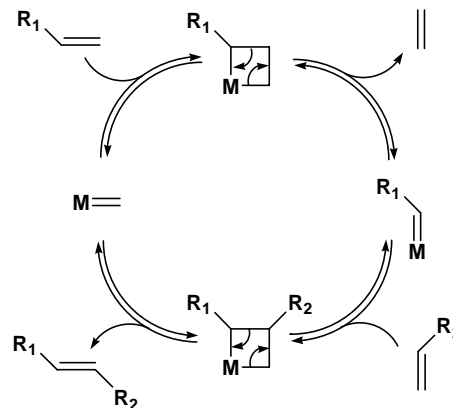
Vast attention has been documented for olefin metathesis, particularly in the past 20 years. Extensive research in this area has resulted in fruitful discoveries in more efficient catalysts and new applications. Several classes of olefin metathesis including ring closing metathesis (RCM), ring opening metathesis polymerization (ROMP) and enyne metathesis (EM) have all become reliable routine methods used widely in both academic and industrial settings.²

Olefin cross metathesis (CM), on the other hand, represents an understudied area. Low yields and unpredictable reaction scope make many chemists reluctant to incorporate CM into a complex, target-oriented synthesis plan, especially as a late stage strategy. Indeed, issues such as alkene stereoselectivity and cross product selectivity associated with CM are inevitable challenges dictated by the unique mechanism of olefin metathesis.³

MECHANISM AND CM SELECTIVITY

Olefin metathesis acts by the redistribution of alkene bonds. The widely accepted mechanism, which was originally proposed by Hérisson and Chauvin in 1971,⁴ proceeds by a [2+2] cycloaddition of

an alkene to a metal alkylidene to form a metallocyclobutane intermediate, which subsequently undergoes a [2+2] cycloreversion to generate ethylene and a substrate-loaded metal carbene (**Scheme 1**). This intermediate reacts with the second olefin in the same fashion to release the product and regenerate the catalyst. The catalytic cycle is a thermodynamically controlled process, and the reaction is driven forward by evolution of ethylene gas.



If two olefins of similar reactivity are subjected to CM conditions, assuming full conversion, a maximum of 50% yield of the desired product will be obtained while 25% of each of the two homocoupling products will be formed. To achieve a synthetically efficient yield of 90%, 10 equivalents of one coupling partner must be used (**Scheme 2**).⁵ The stereoselectivity of product formation further complicates CM. Although the thermodynamically favored

Scheme 2. Cross metathesis selectivity

R1 \ R2		Olefin CM		
R1	R2	R1-CH=CH-R1	R1-CH=CH-R2	R2-CH=CH-R2
1	1	25	50	25
2	1	-	66	33
3	1	-	75	25
4	1	-	80	20
10	1	-	91	9

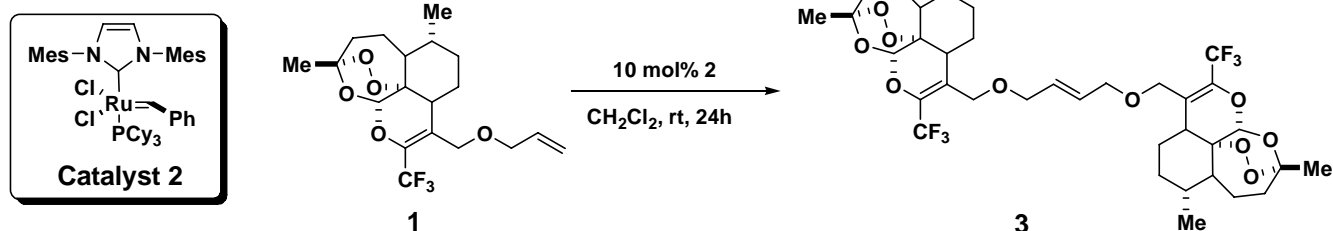
Yields based on R₂

trans olefins are usually the major products, a mixture of *E*, *Z* isomers can be obtained when the energy difference between them is small. On the other hand, CM can be a very efficient way to conjoin two molecules. Studies in this field have developed many creative methods to overcome the limitations presented above.

HOMODIMERIZATION

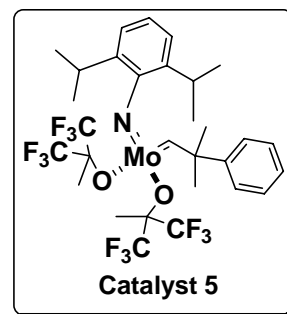
CM of two identical olefins eliminates the question of cross product selectivity, and therefore generally proceeds in good yields.⁶ For instance, artemisinin **1** was successfully dimerized to a more potent antitumor agent **3** via CM by Crousse and Bonnet-Delpon (**Scheme 3**).⁷ Treatment of fluorinated derivative **1** with 10% of catalyst **2**, gave a high yield of the *E* isomer. This dimerization strategy can be recognized as a more efficient alternative to construct symmetric molecules with double functional

Scheme 3. Synthesis of artemisinin dimer

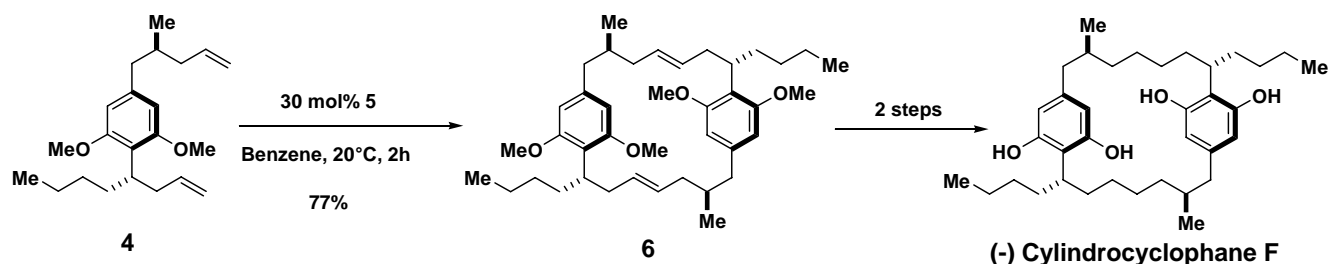


group modification (two-dimensional synthesis).

Another interesting example of this dimerization approach comes from Smith's synthesis of the dimeric natural products (-)-cylindrocyclophane F.⁸ Advanced intermediate **6** was prepared through a thermodynamically controlled double head-to-tail CM (**Scheme 4**). Only the desired *E,E*-olefin isomer was observed in 77% isolated yield from possible three head-to-tail stereo isomers and four head-to-head structural isomers. From **6** only two additional steps were needed to access the natural product.



Scheme 4. Application of CM dimerization in the synthesis of (-) cylindrocyclophane F



Olefin metathesis is a thermodynamically controlled process. The astonishing efficiency and selectivity of the reaction to form **6** is due to the mechanism of CM. Although different isomeric metathesis products could be formed initially, equilibration of the products is promoted by a secondary metathesis, and only the most thermodynamically stable isomer is observed. Subsequently, Monte Carlo

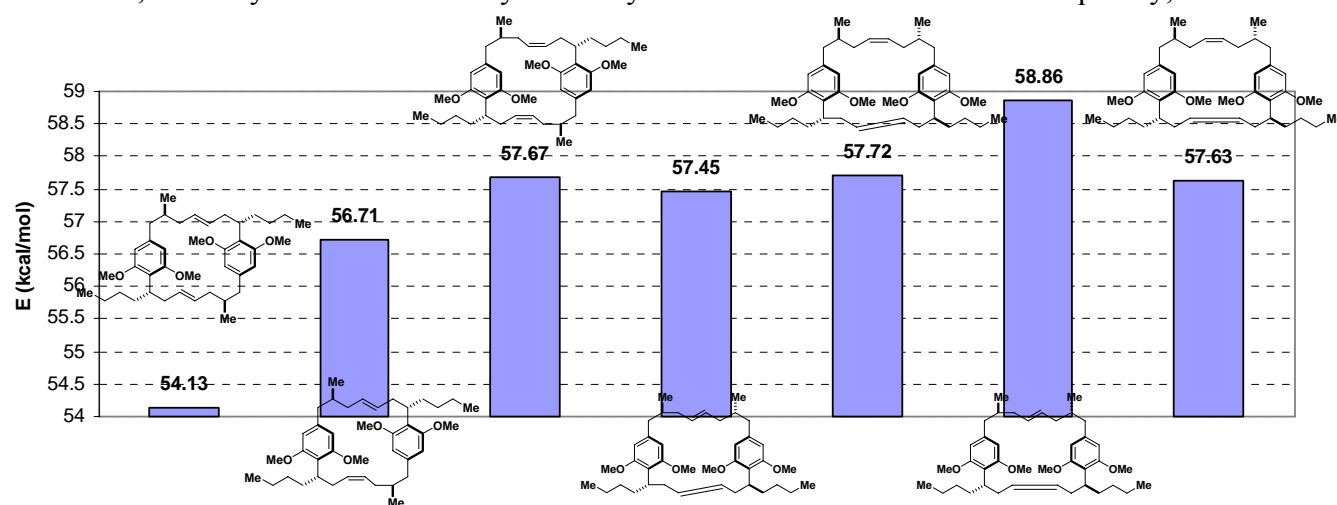


Chart 1. Calculated energy of different isomers

conformational searches utilizing the MM2 force field revealed that the observed product is at least 2.5 kcal/mol lower in energy than other isomers (**Chart 1**). To verify this calculation experimentally, *trans* (**7**) and *cis* (**8**) head-to-head dimers were prepared by the Smith group. Under the same metathesis conditions, the *E,E*-olefin isomer was obtained in 75% and 81% yield respectively, which is almost identical to the yield of the *E,E*-olefin isomer formed from the two monomers (**Scheme 5**).

HETERODIMERIZATION

A model of selectivity

CM of two different olefins has the inevitable challenge of competing homodimerizations, and an approach to improve cross product selectivity is needed. The mechanism of metathesis allows equilibration and the product distribution of a metathesis reaction is governed by the relative energies of product olefins. However, one general observation that has been made is that the activation energy barriers for electronically

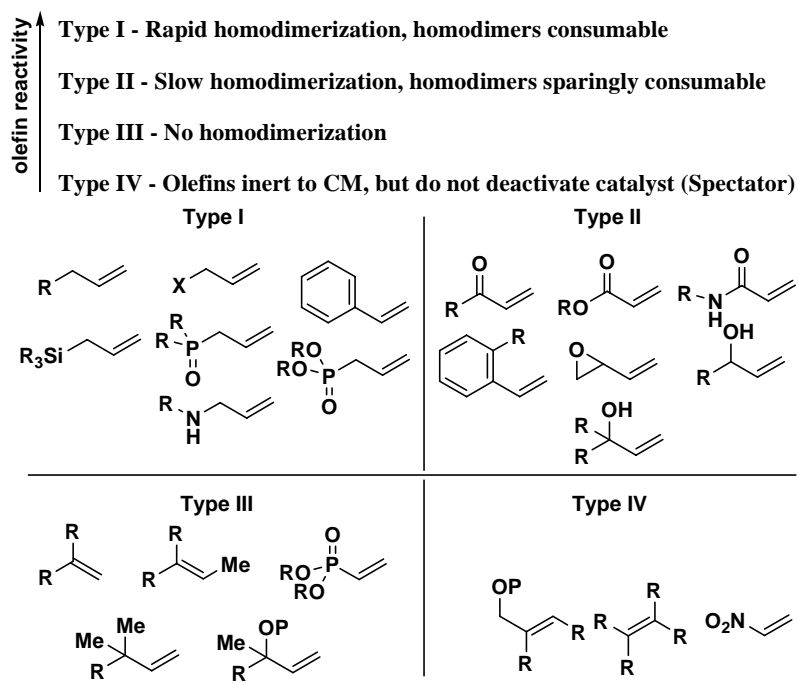
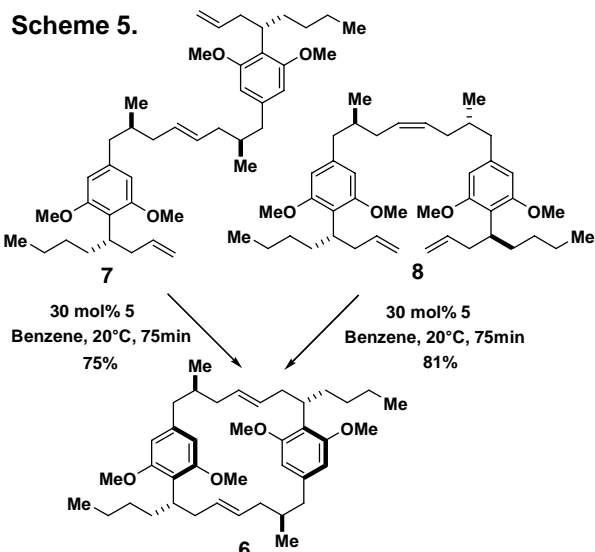
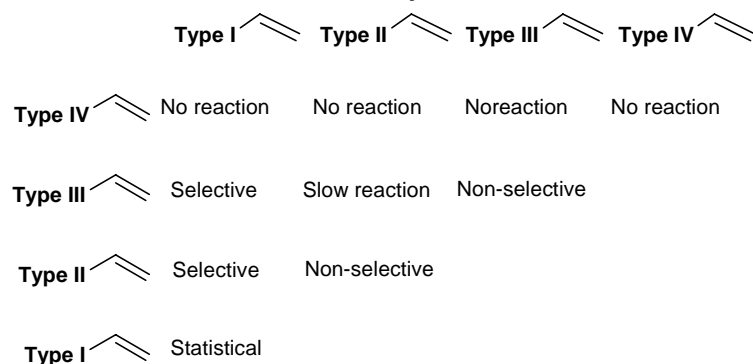


Figure 1. Olefin categorization for catalyst 2

Scheme 6. CM mode of selectivity



deactivated and sterically hindered olefins are high, often resulting in diminished reactivity towards metathesis. If the desired olefin product is kinetically trapped and does not undergo a secondary metathesis, a higher yield can be anticipated as long as undesired products undergo secondary metathesis. Therefore a systematic survey of functionalized olefin reactivity should serve as a guideline for researchers to plan synthetic routes. This model of olefin selectivity was first proposed by Grubbs, who categorized olefins into four groups (Figure 1).⁵

Type I olefins undergo rapid dimerization and the resulting homodimers will participate in secondary metathesis. Type II olefins homodimerize and the homodimers are Type IV olefins. Type III olefins are active in metathesis but do not

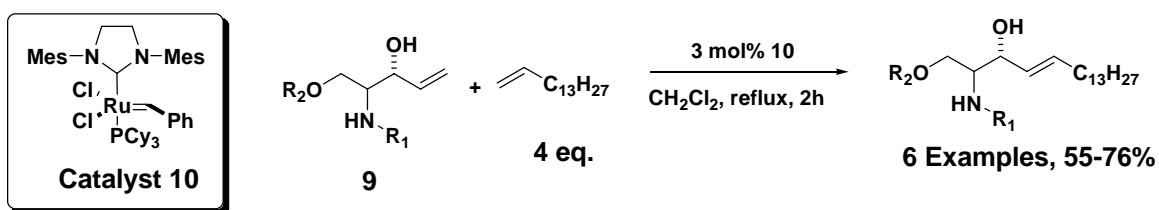
homodimerize. Type IV olefins are not reactive towards metathesis. It should be noted that different catalysts require different definitions of olefin types. In all cases, however, steric bulk and electronic deficiency are both deactivating factors for olefin metathesis. As it is summarized in **Scheme 6**, CM between two Type I olefins gives a statistical distribution of hetero- and homo-dimers. CM between two olefins of the same type (other than Type I) is typically non-selective, and CM between two different olefin types is generally selective and the cross product can be formed favorably over homodimers.

Statistical CM

Statistically, increasing the equivalents of one olefin in CM will decrease the formation of homodimer of the other olefin. The yield of the reaction is improved by sacrificing the former coupling olefin and increasing the conversion of the latter. This is a viable technique for olefin functionalization in target-oriented synthesis since many α -olefins are commercially available or readily prepared.⁹ In this report, a statistical CM is defined as the equivalence ratio of the two coupling olefins exceeding **2.5:1**, while a selective CM has a less than **2.5:1** ratio of the two substrate olefins.

One application of statistical CM is olefin chain elongation. CM reaction conditions are mild and tolerate most carbonyl and protic functional groups, making this protocol advantageous over other olefin functionalization methods. For instance, in Katsumura's synthesis of sphingolipid derivatives, CM of 1-pentadecene and amino alcohol **9** was employed as a key step to access diversified derivatives.¹⁰ The reaction proceeded smoothly to yield the *E*-alkene as a single isomer in moderate to high yields, even in the presence of a free allylic alcohol (**Scheme 7**).

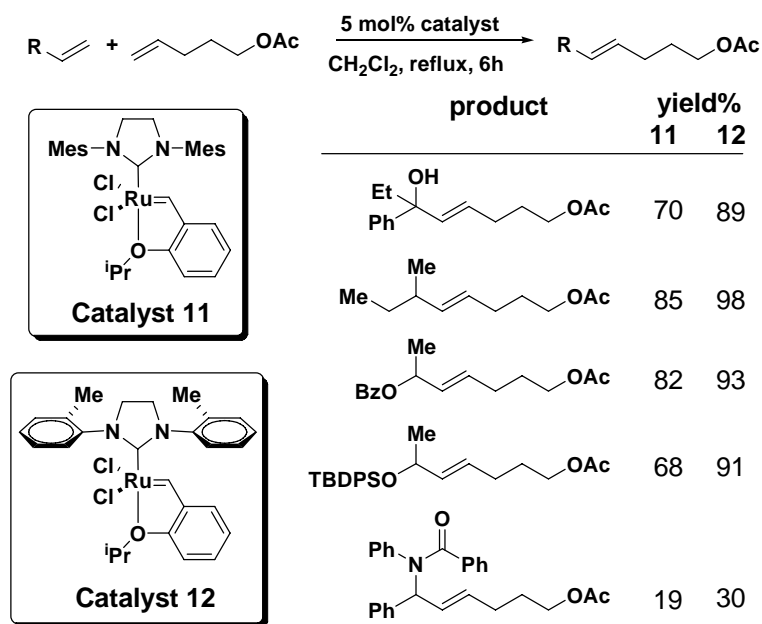
Scheme 7. Key CM in the synthesis of sphingolipids derivatives



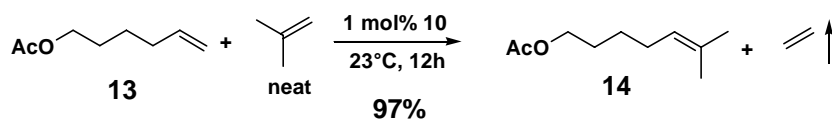
CM of congested olefins generally proceeds in high *E:Z* selectivity but low yields. Grubbs recently reported a new type of ruthenium metathesis catalyst **12** that is especially effective for this type of CM.¹¹ Reducing the steric bulk on the *N*-heterocyclic carbene ligand from *N*-mesityl (catalyst **11**) to *N*-tolyl (catalyst **12**), resulted in a significant improvement in catalyzing metathesis reactions of sterically hindered alkenes (**Scheme 8**). Universally improved yields were achieved with broad substrate scope and complete stereoselectivity for *E* alkenes. This latest advancement in catalyst activity will certainly enhance the utility of CM.

The prenyl functionality is a ubiquitous moiety in natural products, particularly in terpenoids. Initial work by Grubbs and coworkers has shown that treating terminal olefins in neat isobutene with the second generation ruthenium catalyst **10** affords good to excellent yields. One such example is presented in **Scheme 9**.¹² One notable advantage of this reaction is operational simplicity. No solvent is required, all reagents are stable for benchtop handling and the only workup is the evaporation of isobutene. This procedure was further modified by replacing gaseous isobutene with 2-isopentene, which has a boiling point of 35-38 °C.¹² In this case, exclusive formation of the thermodynamic product 1,1-dimethyl olefin **14** (**Scheme 10**) was observed with excellent yield. The new protocol was adopted by Porco in his

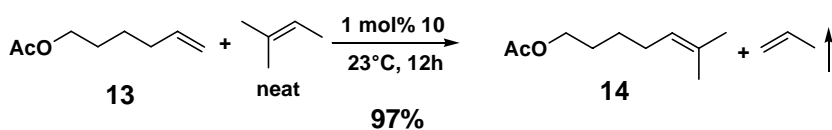
Scheme 8. Chain elongation with newer generation catalyst



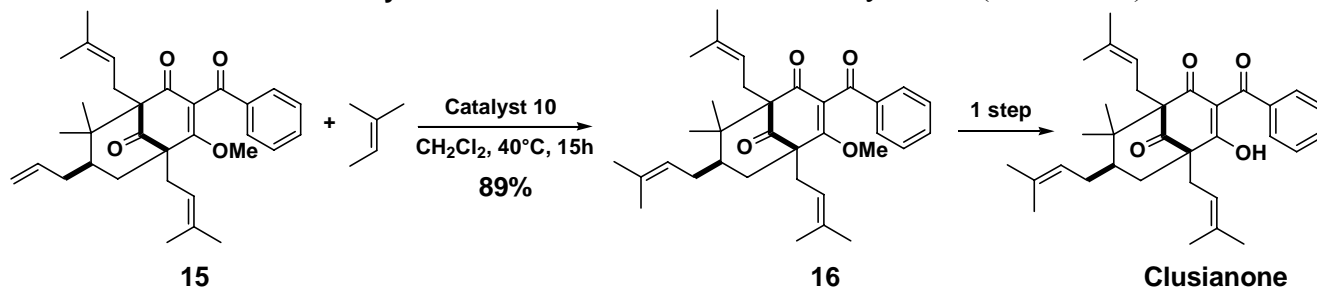
Scheme 9. CM with isobutene



Scheme 10. CM with 2-isopentene



Scheme 11. CM towards the synthesis of Clusianone

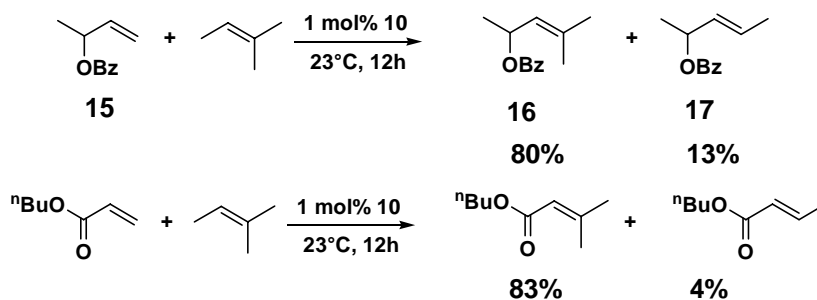


This reaction works well for straight chain terminal olefins (Type I). However, product selectivity of sterically hindered and electron deficient olefins, is difficult to predict. For example, the reaction of secondary allylic benzoate **15** and 2-isopentene produced 80% of 1,1,2-trisubstituted olefin

synthesis of the polyprenylated natural product clusianone as an end game strategy.¹³ With the second generation Grubbs catalyst **10**, advanced intermediate **16** was obtained in excellent yield. Subsequent one step nucleophilic demethylation completed the synthesis (**Scheme 11**).

and 13% of 1,2-disubstituted olefin.¹² Resubjecting the mixture to fresh catalyst and 2-isopentene did not give any further conversion to the more thermodynamically stable olefin, proving severely hindered and electronically deactivated olefins (Type IV) can be inert to metathesis. (Scheme 12).

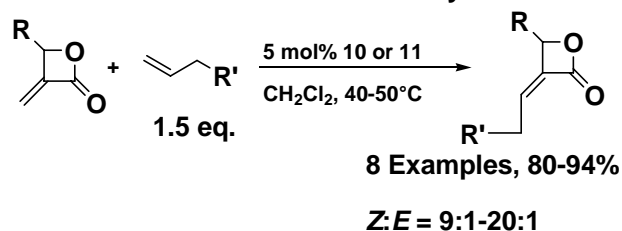
Scheme 12. CM of deactivated olefins



Selective CM

The low selectivity of CM can be attenuated by coupling olefins of different types. By carefully pairing CM olefins, improved selectivity for cross product over homodimers can be accomplished. Good CM yields can then be achieved with low stoichiometric ratios of two olefins. For instance, CM of methylenexetanone (Type III) and a terminal olefin (Type I) gave alkylideneoxetanones in high *Z:E* ratios and reliable yields.¹⁴ Either second generation Grubbs catalyst **10** or Hoveyda-Grubbs catalyst **11** was successfully employed in promoting this reaction. Remarkable functional group tolerance of CM has been demonstrated on these highly strained substrates. A more striking observation is that only 1.5 equivalents of the coupling partner was needed to produce up to 94% isolated yield of the cross product, exceeding the 60% theoretical yield predicted by statistics (Scheme 13). This observation could be explained by the Grubbs model of olefin selectivity. CM of a Type I olefin and a Type III olefin proceeds selectively and gives an improved cross product yield than would be predicted from statistics.¹⁵⁻¹⁷

Scheme 13. CM with strained exocyclic enones



On the other hand, the model of CM selectivity does not apply in all cases. In Williams's synthesis towards fungal metabolites stephacidins A and B, the key intermediate **19** was needed.¹⁸ Direct CM of Type I olefin **18** and Type III olefin 3-chloroisobutene yielded nothing but recovered starting material **18** (Scheme 14). It is unclear that the null yield was due to α -chloride deactivating 3-chloroisobutene to a Type IV olefin or α -chloride's poisonous effect to the catalyst. An alternative CM to redeem this failed reaction was carried out between **18** and methylacrolein. Terminal olefin **18** is a Type I olefin and methylacrolein is a Type II olefin for catalyst **10**. Type I and Type II olefins react selectively in CM, and as predicted, the reaction between **18** and methylacrolein smoothly afforded 65% of enone **20** and 15% recovered **18**. Reduction and chlorination of **20** gave access to **19**. Although the

reactivity of CM can be unpredictable even with the assistance of Grubbs' model of selectivity, CM usually enables an efficient synthetic plan in which a bypass can often be developed to circumvent the problems encountered.

CONCLUSION

Olefin cross metathesis is an efficient and tolerant method to make carbon-carbon double bonds. Nevertheless, it has received less attention compared to other olefin metathesis reactions due to poor control of reaction selectivity. Methods have been introduced to overcome the shortcomings, and many creative applications of CM have been developed in recent years. In addition, by categorizing olefins into different types by their reactivity, a general model of selectivity of CM has been developed. The discovery of new catalysts has made CM more efficient and more open to a broader substrate scope.

Despite these recent achievements, CM is not a perfect technique. Reactivity of different types of olefins is still somewhat unpredictable and can result in low reaction yields. However, the superb efficiency CM brings to a synthetic route very often outweighs difficulties, and further advancement in this area will surely make CM a fundamental process in modern organic chemistry.

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Scheme 14. Preparation of allylic chloride with CM

