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A General Model for Selectivity in Olefin Cross Metathesis

Arnab K. Chatterjee, Tae-Lim Choi, Daniel P. Sanders, and Robert H. Grubbs*

Contribution from the Arnold and Mabel Beckman Laboratories for Chemical Synthesis,
Division of Chemistry and Chemical Engineering, California Institute of Technology,
Pasadena, California 91125

Received December 31, 2002; E-mail: rhg@caltech.edu

Abstract: In recent years, olefin cross metathesis (CM) has emerged as a powerful and convenient synthetic technique in organic chemistry; however, as a general synthetic method, CM has been limited by the lack of predictability in product selectivity and stereoselectivity. Investigations into olefin cross metathesis with several classes of olefins, including substituted and functionalized styrenes, secondary allylic alcohols, tertiary allylic alcohols, and olefins with α-quaternary centers, have led to a general model useful for the prediction of product selectivity and stereoselectivity in cross metathesis. As a general ranking of olefin reactivity in CM, olefins can be categorized by their relative abilities to undergo homodimerization via cross metathesis and the susceptibility of their homodimers toward secondary metathesis reactions. When an olefin of high reactivity is reacted with an olefin of lower reactivity (sterically bulky, electron-deficient, etc.), selective cross metathesis can be achieved using feedstock stoichiometries as low as 1:1. By employing a metathesis catalyst with the appropriate activity, selective cross metathesis reactions can be achieved with a wide variety of electron-rich, electron-deficient, and sterically bulky olefins. Application of this model has allowed for the prediction and development of selective cross metathesis reactions, culminating in unprecedented three-component intermolecular cross metathesis reactions.

Introduction

Olefin cross metathesis (CM) is a convenient route to functionalized and higher olefins from simple alkene precursors. Cross metathesis has recently gained prominence due to the availability of catalysts with varied activities, such as **1**,[1] **2**,[2] and **3**[3] (Figure 1). These catalysts have expanded the variety of functional groups amenable to CM and have demonstrated the ability to prepare highly substituted olefins by CM, often in a stereoselective manner. The installation of structural elements within complex natural products and the synthesis of reagents for further synthetic transformations can now be accomplished by CM using active and functional group tolerant metathesis catalysts. However, cross metathesis remains an underrepresented area of olefin metathesis when compared to ring-opening metathesis polymerizations (ROMP)[4] and ring-closing metathesis (RCM).[5] This has been predominantly a result of several factors: first, low catalyst activity to effect a reaction without a strong enthalpic driving force (such as ring-strain release in ROMP) or the entropic advantage of intramolecular reactions (such as RCM), second, low product selectivity for the CM product, and, third, poor stereoselectivity in the newly formed olefin. While the development of increasingly active catalysts has resolved many of these concerns, the inability to accurately predict selectivity of cross metathesis reactions remains a pertinent issue for the practical application of cross metathesis.

By placing sterically large and electron-withdrawing groups near the reacting olefin, we expected to be able to improve CM product selectivity and stereoselectivity. As a result of our investigations with catalysts **1** and **2**, a significant number of new substrates classes that participate in selective olefin cross metathesis reactions have been discovered.[6] While a descriptive model of selective CM processes had not yet been disclosed,[7] we observed that several different types of olefins could be properly matched to provide highly selective CM reactions.

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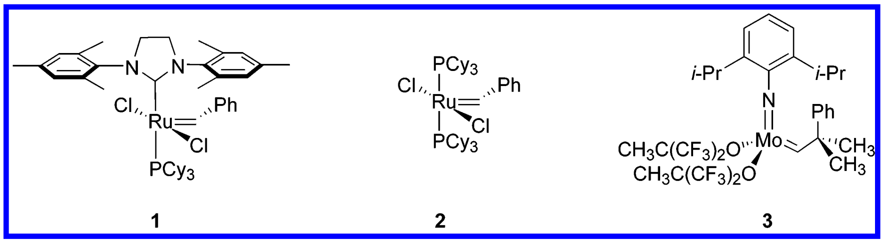
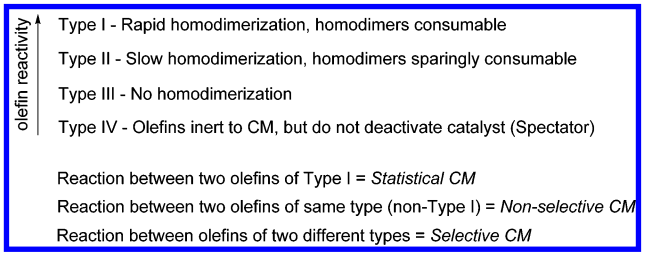


Figure 1. Commonly used olefin metathesis catalysts.



Type I - Rapid homodimerization, homodimers consumable

Type II - Slow homodimerization, homodimers sparingly consumable

Type III - No homodimerization

Type IV - Olefins inert to CM, but do not deactivate catalyst (Spectator)

Reaction between two olefins of Type I = *Statistical CM*

Reaction between two olefins of same type (non-Type I) = *Non-selective CM*

Reaction between olefins of two different types = *Selective CM*

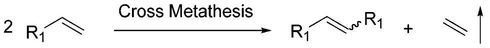
Figure 2. Olefin categorization and rules for selectivity.

These trends from our CM results, in addition to the trends derived from the rapidly expanding body of CM literature, provide the foundation for an empirical model for product selective CM. In this article, we will present a general model based on the categorization of olefin reactivity which can be used to predict both selective and nonselective cross metathesis reactions for a number of commercially available metathesis catalysts with varying activities.

Olefin Reactivity and Product Selectivity in Cross Metathesis. Given the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathways involved in a cross metathesis reaction, it is difficult to accurately predict how the complex interplay of steric and electronic factors will determine the ability of various sets of olefins to participate in selective CM reactions. Due to the multitude of factors influencing olefin reactivity in cross metathesis, a more straightforward, empirical ordering or categorization of olefin reactivity is required. The most convenient way to rank olefin reactivity is to examine their ability to homodimerize (Scheme 1). However, instead of simply looking at the *absolute* ability of an olefin to undergo homodimerization, we looked at its ability to undergo homodimerization *relative* to other olefins and describe olefins on a gradient scale of their propensity to undergo homodimerization, and importantly, the subsequent reactivity of their homodimers. This analysis leads to a general model that comprises four distinct olefin types which can be used to predict both selective and nonselective CM reactions (Figure 2).

Type I olefins are categorized as those able to undergo a rapid homodimerization and whose homodimers can participate in CM as well as their terminal olefin counterpart. Type II olefins homodimerize slowly, and unlike Type I olefins, their homodimers can only be sparingly consumed in subsequent metathesis reactions. Type III olefins are essentially unable to be homodimerized by the catalyst but are still able to undergo CM with Type I and Type II olefins. Type IV olefins are not able to participate in CM with a particular catalyst but do not inhibit catalyst activity toward other olefins. Outside these categories are olefins that deactivate the catalyst. In general, a reactivity gradient exists from most active type (Type I olefin) to least active Type (Type IV), with sterically unhindered, electron-rich olefins categorized as Type I and increasingly sterically hindered and/or electron-deficient olefins falling into Types II through IV.

Scheme 1. Homodimerization in Cross Metathesis

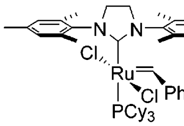
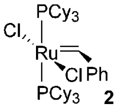
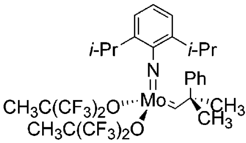


Olefin Categorization for Metathesis Catalysts of Various Activities. Table 1 categorizes all reported CM substrates for catalysts **1**, **2**, and **3** and provides chemists with two basic functions. First, it provides a starting reference point for the design of potentially selective CM reactions. Second, for those working to develop more active metathesis catalysts, it provides a challenging set of olefins that are not active with current catalysts in CM (i.e., Type IV olefins). Up to this point, methodology developed in the area of olefin metathesis has been marked by repeated use of the most active catalyst available. While simple modification of the steric or electronic properties of an olefin (i.e., by choice of protecting groups) is often sufficient to change the reactivity of an olefin and result in a selective reaction, CM selectivity may also be achieved by simply choosing a catalyst with differing activity, as will be shown specifically in the case of styrene CM. Since these catalysts are commercially available, it is straightforward to employ the most selective catalyst. As new types of olefins are used in CM, assigning them an appropriate olefin type will allow them to be used more effectively in selective CM.

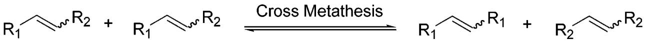
An olefin's general reactivity (as shown in Figure 2) with a given catalyst determines the role of secondary metathesis, that is, subsequent reactions of a product olefin with the propagating catalyst. Predicting the ability (or inability) of the catalyst to perform secondary metathesis on a newly formed CM olefin is important for the development of selective CM reactions. Efficient secondary metathesis occurs when all components in the reaction are readily accessible to the metal alkylidene complex, including homodimers and the CM product. The key to CM reaction selectivity is minimizing the number of undesirable CM side products (such as the homodimers of the starting olefins) either by avoiding their initial formation or by ensuring that they are fully consumed in secondary metathesis events. It is also important that the desired cross product not be redistributed into a statistical product mixture by these same secondary metathesis events.

Throughout this paper, examples of both selective and nonselective CM reactions with combinations of olefins from various types (categorized in Table 1) will be presented to illustrate how the general model shown in Figure 2 accounts for CM selectivity with a wide variety of substrates and how it can be used to predict selectivity in new CM reactions. Specific attention will be paid to how the manipulation of the rates of homodimerization and the role of secondary metathesis in CM through the modification of the steric and electronic properties

Table 1. Olefin Categories for Selective Cross Metathesis

Olefin type	 **1**	 **2**	 **3**
Type I (**fast homodimerization**)	terminal olefins,[6] 1° allylic alcohols, esters,[6h,20] allyl boronate esters,[6f] allyl halides,[6f,6i] styrenes (no large ortho substit.),[6c,d,f,i] allyl phosphonates,[6d] allyl silanes,[25] allyl phosphine oxides,[6h] allyl sulfides,[6h] protected allyl amines[6h]	terminal olefins,[8] allyl silanes,[14,18,19] 1° allylic alcohols, ethers, esters,[8,19,21] allyl boronate esters,[10f] allyl halides[17]	terminal olefins,[11a,b,12,14] allyl silanes[11b]
Type II (**slow homodimerization**)	styrenes (large ortho substit.),[6d,f] acrylates,[6b,i] acrylamides,[6c] acrylic acid,[6c] acrolein,[6b,24] vinyl ketones,[6b] unprotected 3° allylic alcohols,[6f,h] vinyl epoxides,[6b] 2° allylic alcohols, perfluorinated alkane olefins[6b,23]	styrene,[16] 2° allylic alcohols, vinyl dioxolanes,[8] vinyl boronates[8]	styrene,[11a,11b] allyl stannanes[15]
Type III (**no homodimerization**)	1,1-disubstituted olefins,[6a,g] non-bulky trisub. olefins,[6a,g] vinyl phosphonates,[6d] phenyl vinyl sulfone,[22] 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes[16]	3° allyl amines,[14] acrylonitrile[12]
Type IV (**spectators to CM**)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)	1,1-disubstituted olefins,[8] disub. α,β-unsaturated carbonyls, 4° allylic carbon-containing olefins,[8] perfluorinated alkane olefins,[8] 3° allyl amines (protected)[14]	1,1-disubstituted olefins[11a]

Scheme 2. Equilibration of Cross Products



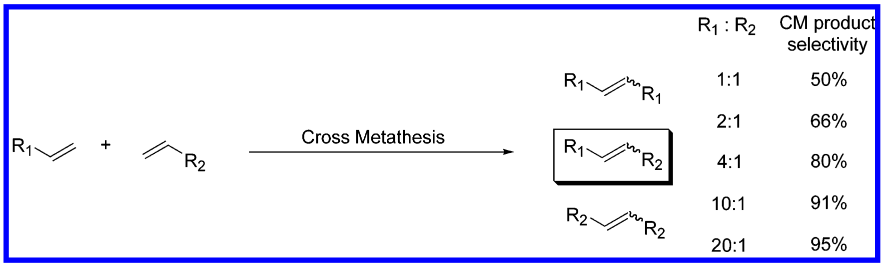
of an olefin or the appropriate choice of catalyst can lead to selectivity in cross metathesis.

Nonselective Cross Metathesis with Two Type I Olefins. When two Type I olefins are used in a CM reaction, the rates of homodimerization are similar and the reactivities of the homodimers and cross products toward secondary metathesis events are high. In these reactions, the desired cross product will be equilibrated with the various homodimers through secondary metathesis reactions (Scheme 2). This will result in a statistical product mixture. For these reactions, one must use nearly 10 equiv of one CM partner to provide 90% of the CM product (Scheme 3). More generally, when two olefins of the same type are combined, nonselective product mixtures are usually obtained. For example, two Type II olefins (such as methyl vinyl ketone and methyl acrylate) can react with each other but will generally undergo nonselective CM, albeit with reduced yields due to the lower overall olefin reactivity.[6e]

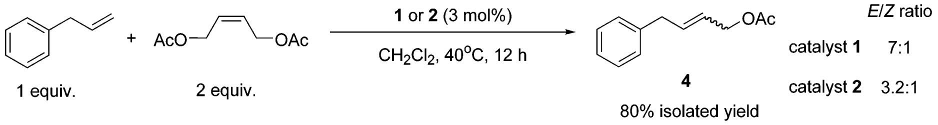
A good example of nonselective CM is the reaction of allylic alcohols using either catalyst **1** or **2** (Scheme 4). The CM reaction between allylbenzene and an allylic alcohol equivalent affords the CM product **4** in 80% isolated yield with either catalyst **1** or **2**, with good to moderate stereoselectivity. Since both reaction partners are Type I olefins, four allyl acetate equivalents are required to provide an 80% yield of the CM product. However, the reaction with catalyst **1** yields a much higher amount of the more thermodynamically favorable trans isomer, presumably due to secondary metathesis on the CM product formed in the reaction. Therefore, the increased trans ratio is simply an effect of the higher activity of catalyst **1** toward the product than catalyst **2**. This brings up the complicated and multifaceted role of secondary metathesis. As will be shown in subsequent sections, in some instances, we observe good product selectivity due to the stability of the cross product toward redistribution by secondary metathesis but poor stereoselectivity due to the inability of the cross product to readily undergo cis/trans isomerization via these same secondary metathesis processes.

Selective Cross Metathesis. To avoid the statistical product distributions produced by these inefficient reactions, one can design selective CM reactions using olefins from two different types, whose rates of dimerization are significantly different and/or slower than CM product formation. The first approach toward selective CM involves the reaction of a Type I olefin with a less reactive Type II or Type III olefin that undergoes homodimerization at a significantly lower rate, if at all. In this reaction, although the Type I olefin may initially homodimerize, the product distribution is driven toward the desired cross product as ethylene is driven from the system (preventing the regeneration of terminal olefins) and the Type I homodimer readily undergoes secondary metathesis with the Type II/III olefin (Scheme 5). This desired cross product will not be

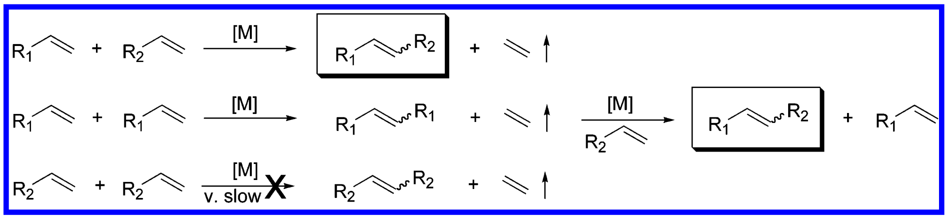
Scheme 3. Statistical Distribution of CM Products



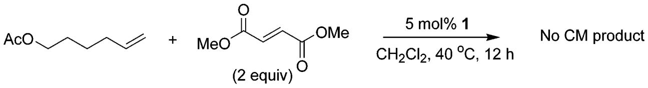
Scheme 4. Nonselective Olefin Cross Metathesis



Scheme 5. Primary Reactions in Cross Metathesis of Type I with Type II/III



Scheme 6. Cross Metathesis of Type I Olefin with Methyl Fumarate



equilibrated to a statistical product mixture due to the inability of the catalyst to efficiently convert the cross product to other products (i.e., the homodimer of the Type II/Type III olefin) via secondary metathesis.

Selective Cross Metathesis of Type I with Type II Olefins. For example, reactions between Type I terminal olefins and Type II olefins such as α,β-unsaturated carbonyl olefins, including acrylates, acrylamides, acrylic acid, and vinyl ketones result in highly selective CM reactions with high stereoselectivity ($E/Z > 20{:}1$).[6b,c] In this case, methyl acrylate is a Type II olefin because it undergoes homodimerization to a small extent under the reaction conditions, allowing for selective reactions with Type I olefins.[6b] To illustrate the low reactivity of the homodimers of these Type II olefins, when methyl fumarate, the trans homodimer of methyl acrylate, is resubjected to catalyst **1** and 5-hexenyl acetate, no CM product is observed (Scheme 6). This is similar to our previously reported results using the homodimer of 2-vinyl-1,3-dioxolane with catalyst **2**.[8]

Secondary allylic alcohols are another class of Type II olefins which can be utilized in CM with moderate to high cross product yields and good stereoselectivity[8] without using large stoichiometric excesses of one reagent (Table 2). It is interesting that the addition of a methyl group at the allylic position leads to much greater trans selectivity, compared to the 7:1 E/Z ratio obtained with a primary allylic alcohol. Similar results were also obtained using catalyst **2**.[8] Interestingly, most of the trans selectivity obtained in entry 1 is retained when a simple α-olefin is used in the reaction (entry 2). We decided to also investigate if protecting groups were required to provide stereoselectivity in this system, similar to our previous work with catalyst **2**.[8] We hypothesized that increasing steric bulk through the addition of protecting groups would decrease CM reactivity but would increase the trans selectivity. Interestingly, although the reactivity trends were as expected, the product stereoselectivity trends were opposite to our hypothesis. Greater selectivity was observed with the unprotected alcohol (entry 3) than with a bulky protecting group, such as a *tert*-butyldiphenylsilyl ether (Entry 5). It is not clear why a smaller protecting group (entry 2 vs entry 5) allows for greater trans selectivity but may in part be due to greater steric accessibility of the cross product with the smaller protecting group to isomerization via secondary metathesis.

Selective Cross Metathesis of Type I with Type III Olefins. During the course of our earlier studies with catalyst **2**, we found that olefins with 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 (Type IV). However, due to the greater activity of catalyst **1**, CM reactions of quaternary allylic olefins with α-olefins are now possible with excellent stereoselectivity due to their great steric bulk (Table 3). 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 the sterics of 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 terminal olefins (entries 2 and 3). There are several key differences observed when comparing the selectivity of tertiary allylic substrates in CM (Table 2) with quaternary allylic substrates (Table 3). While the steric bulk of tertiary allylic substrates leads to the initial

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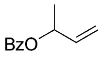
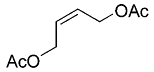
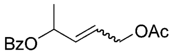
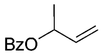
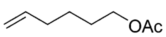
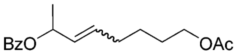
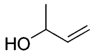
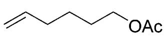
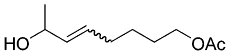
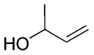
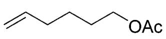
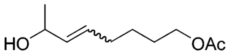
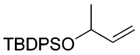
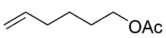
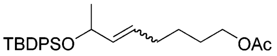
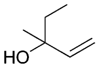
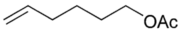
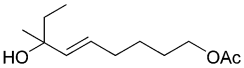
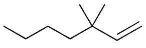
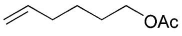
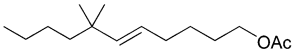
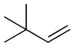
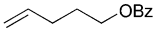
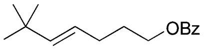
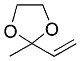
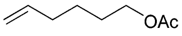
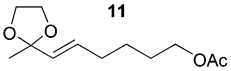
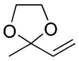
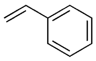
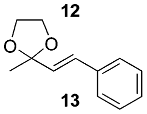
Table 2. Secondary Allylic Alcohol Cross Metathesis

Entry	2° Allylic Alc.	Cross Partner (Equiv)	Product	Iso. Yield (%)	E/Z ratio[a]
1		 (1.8)	 **5**	38	18:1
2		 (2.0)	 **6**	82	10:1
3		 (2.0)	 **7**	92	13:1
4		 (1.0)	 **7**	50 62[b]	14:1 14:1
5		 (0.5)	 **8**	53	6.7:1

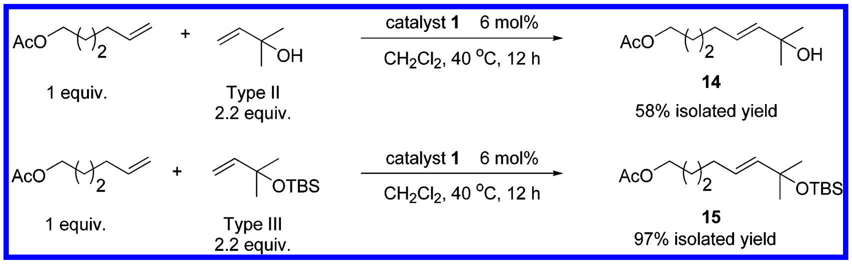
[a] Determined by ^{1}H NMR. [b] Reaction performed at 23 °C.

Table 3. Quaternary Allylic Olefin Cross Metathesis[a]

Entry	4° Allylic Olefin	Equiv.	CM Partner	Product	Isolated Yield[b] (%)
1		2.0		 **9**	93
2		2.0		 **10**	90
3		excess		 **11**	99
4		1.0		 **12**	91
5		2.0		 **13**	70

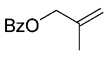
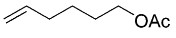
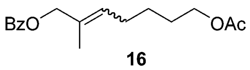
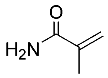
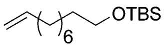
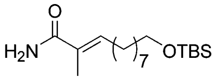
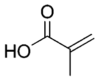
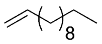
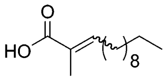
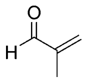
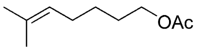
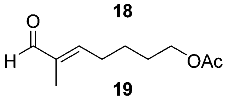
[a] 3−5 mol % of catalyst **1** used, CH_2Cl_2, 40 °C, 12 h. [b] Only *E* isomer observed by ^{1}H NMR.

Scheme 7. Altering Cross Metathesis Selectivity Using Steric Effect



formation of moderately trans product distribution, it also hinders secondary metathesis with the result being moderate trans selectivity. However, the greater steric bulk of the quaternary allylic substrates presumably leads to the initial formation of an exclusively trans product distribution which is unchanged by secondary metathesis events. In addition, the homodimerization of the quaternary allylic olefins is negligible in many cases, allowing for greater CM product selectivity. For example, with 2-methyl-2-vinyl-1,3-dioxolane (Table 3, entries 4 and 5), there was no observation of the dimer of the cyclic ketal, characteristic of a Type III olefin. However, when the tertiary alcohol in entry 1 was used in the CM at 40 °C, there was a background dimerization of the tertiary alcohol. When a similar tertiary alcohol was used, a reduced yield of CM product was observed (Scheme 7). In addition, the independent dimerization of this tertiary allylic alcohol can be performed in excellent yields. However, if this isolated dimer is subsequently reacted with a terminal olefin, no CM product is observed. This indicates that once the dimer is formed, it does not undergo secondary metathesis presumably due to steric bulk. In addition, we found homodimers of olefins with tertiary allylic carbons were not accessible for secondary metathesis either. As a result of these observations, unprotected tertiary allylic alcohols can be considered to be Type II olefins. Interestingly, this undesired dimerization could be suppressed to a large extent by increasing steric bulk via the addition of a silyl protecting group, effectively

Table 4. Cross Metathesis of 1,1-Disubstituted Olefins

Entry	1,1-disub.	CM partner (equiv.)		Product	Isolated Yield (%)	*E/Z* ratio[a]
1			(2.0)	 **16**	80	4:1
2			(1.2)	 **17**	71	>20:1
3			(1.1)	 **18**	23	4:1
4			(1.0)	 **19**	97	>20:1

[a] Determined by ^{1}H NMR, confirmed by ^{1}H NMR NOE experiments.

changing the substrate to a Type III olefin (Scheme 7). This simple substrate modification results in increased CM selectivity by suppressing the unwanted homodimerization side reaction. These reactions represent the control of product and stereoselectivity in CM based purely on steric considerations, which may be manipulated through the judicious choice of protecting groups.

Other examples of CM with Type III olefins, such as 1,1-disubstituted olefins, using catalyst **1** are shown in Table 4.[6a,b] Even functionalized 1,1-disubstituted olefins are excellent substrates for CM which can give high stereoselectivity (Table 4, entries 2 and 4). Highly active catalyst **1** has also been shown to perform secondary metathesis on trisubstituted prenyl olefins[6g] (Entry 4) allowing for a regio- and stereoselective formal allylic oxidation of one of the terminal methyl groups. The reason methacrylic acid (entry 3) gives relatively poor yield and *E*/*Z* ratio is unclear. The results in Table 4 demonstrate the ability to use olefins with functionalities of several different oxidation states in the CM reactions.

Selective Cross Metathesis of Type II with Type III Olefins. A second approach to selective CM processes utilizes two olefins which *both* dimerize at much slower rates than the formation of productive cross-metathesis product. The inability of Type III olefins to homodimerize allows them to also undergo selective reactions with Type II CM partners. In these reactions, formation of cross product dominates if the rates of homodimerization of Type II olefins and secondary metathesis of the CM products are very slow. For example, most 1,1-disubstituted olefins will readily perform selective CM with terminal (Type I) olefins as well as acrylates[6e] (Type II) and acrolein acetals[6a] (Type II) but will not homodimerize. However, given the low reactivity of some Type III olefins, reduced CM yields may be obtained. Also, since the undesired dimers of Type II olefins are essentially inactive for further CM (unlike Type I dimers), stoichiometric excesses of the less reactive Type III olefin may be required to produce high yields of cross product, such as the CM of acrylates carried out in neat isobutylene.[6g]

In a similar manner, cross metathesis was carried out in neat 3,3-dimethyl-1-butene to drive the CM between the Type III olefin and various Type II olefins (Table 5, entries 1−3). Entries 5 and 6 illustrate the importance of the relative rates of dimerization of the Type II olefins. Even with 4 equiv of 2-methyl-1-heptene (Type III), the rates of dimerization of ethyl acrylate (Type II) and ethyl vinyl ketone (Type II) compete with the CM formation, resulting in a considerable amount of homodimer side products. However, by capping with a β-methyl group, the dimerization is suppressed and higher selectivity toward CM product is obtained. Another strategy is to utilize slow addition of the Type II olefin in order to maintain a low concentration of the more reactive Type II olefin, thereby, minimizing the amount of dimerization (Table 5, entry 7).

Cross Metathesis with Olefins that Bridge Type Categories. While protection of tertiary allylic alcohols has been shown to change their CM behavior leading to enhanced CM selectivity, other olefins, such as styrenes, bridge the broad type categories outlined previously. The CM behavior of styrenes depends strongly on their substitution patterns, providing far more flexibility in terms of functionalization/substitution and catalyst choice in order to achieve selective reactions. Styrenes represent one of the classes of olefins used 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 to good selectivities in CM (Type II). However, catalyst **1** showed a significantly different reactivity and prompted further investigation into this family of CM substrates. For example, with 2.5 mol % of catalyst **1**, the dimerization of styrene to *E*-stilbene was achieved in 94% isolated yield. Consequently, the CM reaction of styrene with a terminal olefin employing catalyst **1** produces a statistical product distribution (Table 6, entry 1) and is different from the results using catalyst **3**, as reported by Crowe and Zhang (entry 2).[11] To confirm that homodimerized styrene can undergo efficient secondary metathesis during CM with catalyst **1**, *E*-stilbene was successfully used as a styrene surrogate in CM with an allylic acetate equivalent (Entry 7). The reaction produced a statistical ratio of CM products. This is unprec-

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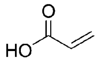
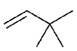
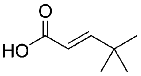
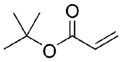
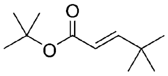
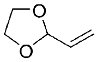
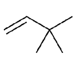
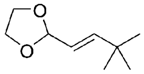
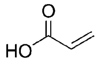
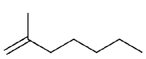
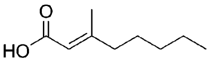
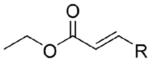
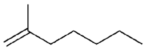
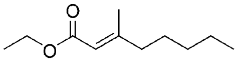
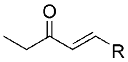
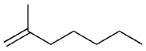
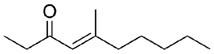
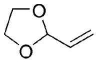
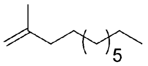
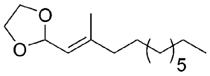
(9) Warwel, S.; Winkelmuller, W. *J. Mol. Catal.* **1985**, *28*, 247.

(10) (a) Feher, F. J.; Soulivong, D.; Eklund, A. G.; Wyndham, K. D. *Chem. Commun.* **1997**, 1186. (b) Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485. (c) Huwe, C. M.; Woltering, T. J.; Jiricek, J.; Weitz-Schmidt, G.; Wong, C.-H. *Bioorg. Med. Chem.* **1999**, 773. (d) Seshadri, H.; Lovely, C. J. *Org. Lett.* **2000**, *2*, 327. (e) Eichelberger, U.; Mansourova, M.; Henning, L.; Findeisen, M.; Giesa, S.; Muller, D.; Welzel, P. *Tetrahedron* **2001**, *57*, 9737. (f) Yammamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128.

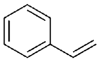
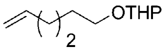
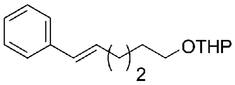
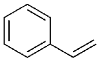
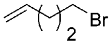
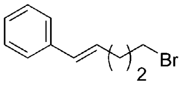
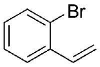
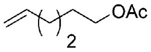
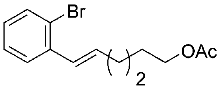
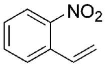
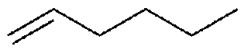
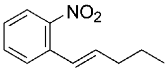
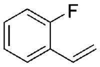
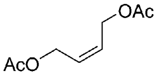
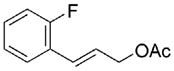
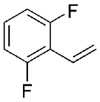
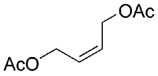
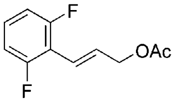
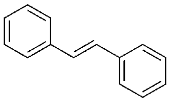
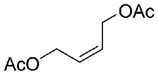
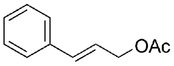
(11) (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998. (b) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117.

Table 5. Cross Metathesis between Type II and Type III Olefins

Entry	Type II	Type III (Equiv)		Product	Isolated Yield (%)
1			(neat)		73
2			(neat)		73
3			(neat)		75
4			(4.0)		83[a]
5			(4.0)		55[a] R=H 83[a] R=Me
6			(4.0)		26[a] R=H 68[a] R=Me
7			(1.0)		67[b]

[a] $E/Z = 2$ determined by ^{1}H NMR, confirmed by ^{1}H NOE experiments. [b] Vinyldioxolane (3 equiv) added slowly in four equal parts over a 6 h period. $E/Z = 3$ determined by ^{1}H NMR, confirmed ^{1}H NOE experiments.

Table 6. Cross Metathesis of Styrenes with Terminal Olefins

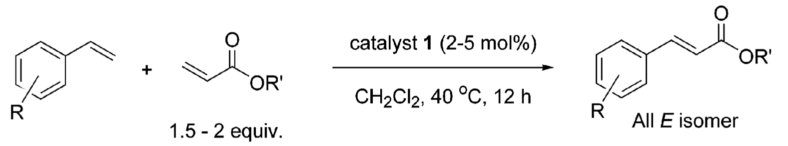
Entry	Catalyst	Aromatic Olefin	Cross-Partner	Aromatic : CM Partner	Product[a]	Isolated Yield (%)
1	**1**			1 : 1 4 : 1		47 71
2	**3**			2 : 1		90
3	**1**			1 : 1 3 : 1		80 98
4	**3**			2 : 1		48
5	**1**			1 : 2		98
6	**1**			1 : 2		50
7	**1**			1 : 1.2		51

[a] Only *E* isomer observed by ^{1}H NMR.

edented since catalysts **2** and **3**, as well as ill-defined catalysts, are not able to efficiently use stilbene as a CM partner, providing another example of the unique reactivity of catalyst **1**. These results clearly indicate that styrene is a Type I olefin for the more active catalyst **1**; however, for catalyst **3** employed by Crowe and Zhang, styrene is a Type II olefin. Styrene CM clearly demonstrates how matching the olefin with an appropriate catalyst (shown in Table 1) can be equally as important as matching olefins in order to achieve selective CM.

In addition to the possibility of using a less active catalyst to

Table 7. Styrene Cross Metathesis with Acrylate Esters



Entry	R	R'	Isolated Yield (%)[a]
1	H	CH_3	92
2	2,4-Dimethyl	CH_2CH_3	87
3	2,4,6-Trimethyl	CH_2CH_3	5[b]
4	2-CF_3	CH_2CH_3	44
5	3,4-Dimethoxy	*n*-Butyl	89
6	4-NO_2	CH_3	89
7	4-CHO	CH_2CH_3	83
8	2-F	CH_2CH_3	72
9	2-Cl	CH_2CH_3	62
10	2-Br	CH_2CH_3	49
11	2,6-Difluoro	CH_2CH_3	15[b]

[a] Only *E* isomer observed by ^{1}H NMR. [b] Determined by ^{1}H NMR.

achieve selectivity, alterations in styrene structure allow for selective CM reactions with terminal olefins using catalyst **1**, by changing styrene from a Type I olefin to a Type II or Type III olefin. 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 substituted styrene, we achieved near quantitative conversion of hexenyl acetate. In the case of 2-bromostyrene, both the steric bulk of the bromine atom and its electron-withdrawing character contribute to make it a Type II olefin. Crowe and Zhang also were able to incorporate *ortho*-substituted styrenes in CM with catalyst **3** 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 efficiently. Due to the higher reactivity of **1**, we only observed reduced activity when *multiple* electron-withdrawing substituents were present. For example, 2,6-difluorobenzene was subjected to CM conditions, and only moderate yields of CM product were isolated (entry 6).

With the differences in reactivity observed with substituted styrenes, we began to investigate CM of styrenes with a variety of non-Type I olefins. We had previously disclosed that a variety of Type II olefins such as α,β-unsaturated esters, amides, ketones, and acids are excellent CM partners with terminal olefins.[6b,c] In addition, it has been demonstrated by Crowe and Goldberg that CM of π-conjugated olefins, such as acrylonitriles, was not compatible with 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 carbonyls, such as acrylates using catalyst **1** (Table 7). This CM complements Wittig or Horner−Wadsworth−Emmons chemistry since unprotected benzaldehydes work well (entry 7). Similar results were also obtained using acrylamides and vinyl phosphonates as the "enone" component.[6c,d,i]

We discovered that the reactivity trends of styrenes were different in these CM reactions when compared to terminal olefin CM in Table 6. While Type I styrenes (Table 7, entries 1 and 6) were excellent CM partners with acrylates, it was observed that *ortho*-substituted styrenes that did not dimerize readily (Type II or Type III olefins) were also not good CM partners with acrylates (entries 3−4, 9−11). Simple *ortho*-alkyl groups did not reduce the reaction yield with acrylates (entry 2); however, when electron-withdrawing functionalities (entry 4) or significant steric bulk (entry 3) was added to the *ortho* position, CM yields fell dramatically due to the low reactivity of both cross partners with the catalyst. Therefore, for proper CM selectivity, the two olefins in CM need to have a difference in rate of reaction with the metal alkylidene complex (e.g., the olefins must be of different types and, preferably, one should be able to readily react with the catalyst to make an active alkylidene).

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 *ortho*-phenol derivatives form stable benzylidene complexes.[13] However, instead of inhibiting catalyst activity, a variety of protected phenols are active for catalytic CM (Scheme 8). We found that small protecting groups, such as acetate, allowed for excellent CM with acrylates (Type I +

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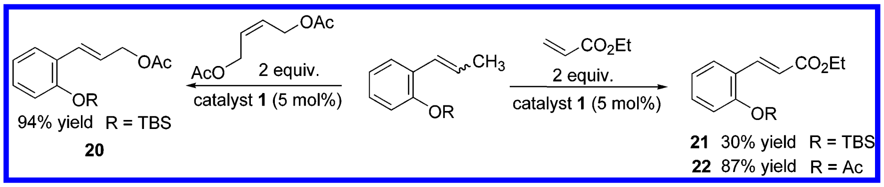
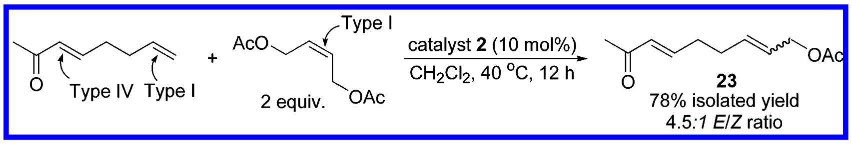
(12) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.

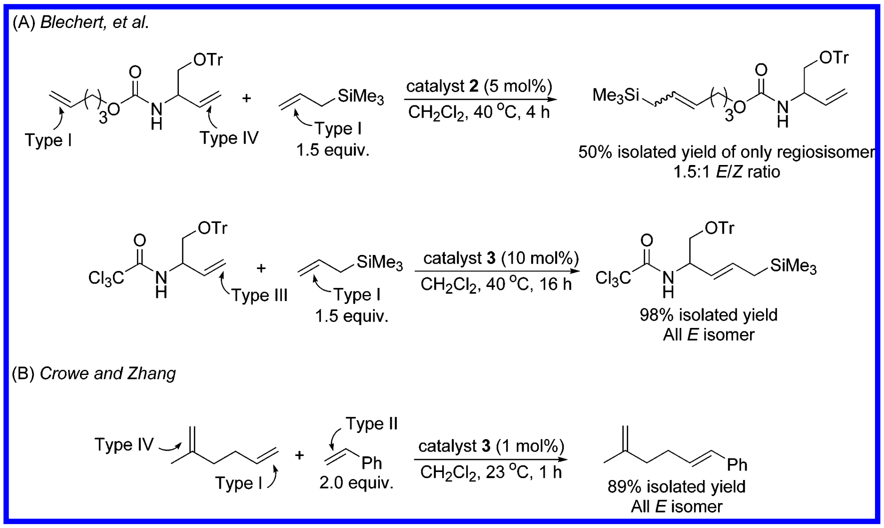
Scheme 8. *ortho*-Phenol Cross Metathesis



Scheme 9. Chemoselective CM Based on Olefin Categorization



Scheme 10. Chemoselective Cross Metathesis Using Catalysts 2 and 3



Type II, respectively). 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, CM of the hindered styrene with acrylate (Type III + Type II, respectively) gives poor yields. In contrast, the reaction provides a very good yield with allyl acetate equivalents (Type III + Type I, respectively). In this case, this substrate reacts like Type III due to steric bulk and is very selective in CM with Type I α-olefins. Collectively, the disclosed work in styrene CM provided an important contribution to the development of the categorization model described in this paper. Both the steric and/or electronic effects of substituents on the styrene, as well as the catalyst choice, can be manipulated to achieve CM selectivity.

Regioselective and Chemoselective Cross Metathesis. The model outlined so far provides a foundation for predicting product selectivity in CM, but it also can be applied to the prediction of chemoselective CM, which is critical for differentiating olefins in the synthesis of complex molecules. The CM of a Type I or Type II olefin in the presence of a Type IV olefin is a good example of this type of chemoselectivity. 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 I olefin (Scheme 9).

Importantly, the CM model outlined in Figure 2 also is consistent with results previously 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 10).[14] Interestingly, in the same report by Blechert, catalyst **3** was used to effect a highly selective CM reaction of that protected allylamine (Type III for catalyst **3**) with allylsilanes (Type I) in excellent yield (Scheme 10). 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 Tables 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**) in the presence of a 1,1-disubstituted olefin (Type IV).[11a] As demonstrated previously in our lab,[6a,g] with the more active catalyst **1**, 1,1-disubstituted olefins are a Type III olefin

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(13) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

(14) Brummer, O.; Ruckert, A.; Blechert, S. *Chem.—Eur. J.* **1997**, *3*, 441.

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(16) (a) Pietraszuk, C.; Marciniec, B.; Fischer, H. *Organometallics* **2000**, *19*, 913. (b) Kujawa-Welten, M.; Pietraszuk, C.; Marciniec, B. *Organometallics* **2002**, *21*, 840.

(17) Blanco, O. M.; Castedo, L. *Synlett* **1999**, 557.

(18) Faure, S.; Piva-Le Blanc, S.; Piva, O. *Tetrahedron Lett.* **1999**, *40*, 6001.

(19) Langer, P.; Holtz, E. *Synlett* **2001**, 110.

(20) Zhang, L.; Herndon, J. W. *Tetrahedron Lett.* **2002**, *43*, 4471.

(21) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paramjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263.

(22) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425.

(23) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692.

(24) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451.

(25) BouzBouz, S.; De Lemos, E.; Cossy, J. *Adv. Synth. Catal.* **2002**, *344*, 627.

Scheme 11. Three Component Olefin Cross Metathesis

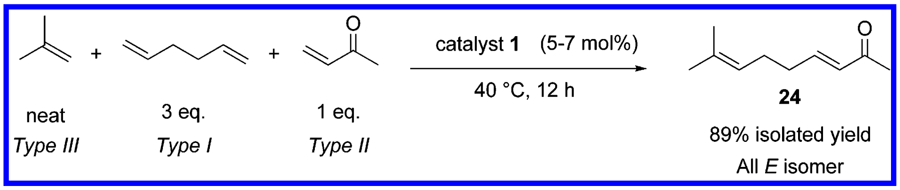
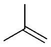
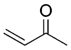
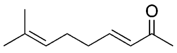
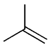
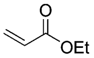
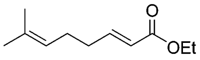
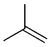
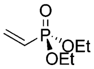
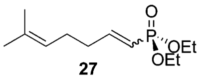
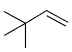
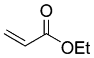
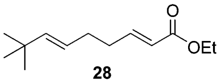
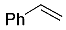
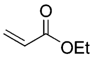
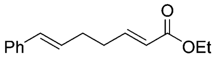
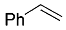
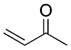
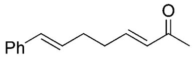


Table 8. Three Component Olefin Cross Metathesis[a]

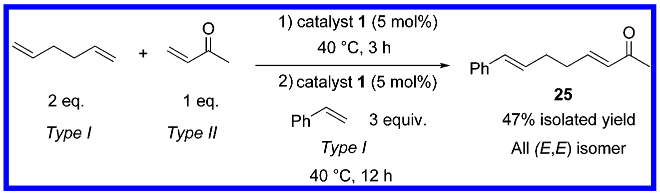
Entry	Method[d]	CM partner Y	CM partner Z	Ratio (Diene:Y:Z)	Product	Isolated Yield (%)
1	A			3:neat:1	 **24**	89
2	A			3:neat:1	 **26**	60
3	A			3:neat:1	 **27**	57[b]
4	A			1:neat:1	 **28**	67[c]
5	B			1:3:1	 **29**	34
6	B			2:3:1	 **25**	47

[a] Using 5−7 mol % of **1** in 0.1−0.2 M refluxing CH_2Cl_2, 12 h. [b] E/Z = 8:1 by ^{1}H NMR. [c] Reaction at 23 °C. [d] Method A = added all components at one time. Method B = added component Z and then added component Y after 4 h.

that is active for CM to form trisubstituted olefins. This shows that while more active catalysts have a larger set of CM active olefins (Type I, II, III), it is useful to identify Type IV olefins for less active catalysts, to help elucidate possible chemoselective CM reactions (Scheme 10). While electronic and steric parameters of olefins account as key 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 can simplistically account for all of these observations in the CM methodology literature.

Three-Component Cross Metathesis Reactions. In addition to describing selectivity in the simple homologation of two olefins in a CM reaction, the olefin classification in Table 1 also provides an opportunity to develop new reactions, such as multicomponent processes. While a three-component reaction has always been theoretically possible, the large mixture of compounds that would form via nonselective processes has made this a challenging method to develop. However, with the current model of selective CM described here, two important concepts have been learned. First, under selective CM conditions, 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 or do so only very slowly, then a third diene-containing olefin can be functionalized at both olefinic sites to provide an unsymmetrical product (Scheme 11).

Scheme 12. One-Pot Three Component Olefin Cross Metathesis



In such a reaction, olefins of three different types may be converted predominantly into one 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 the Type I olefin. In addition, the product olefin from the diene-methyl vinyl ketone CM does not readily undergo secondary metathesis reactions with isobutylene, allowing for a selective reaction.

The formation of a kinetic CM product also allows for chemoselective coupling, where a one-pot sequential CM reaction can occur (Scheme 12). For example, if two CM partners that can react with each other are used in a three-component reaction, such as styrene and methyl vinyl ketone, then a sequential addition strategy is necessary to avoid the unwanted side reaction between these components. Using these two types of three-component CM reactions, a variety of asymmetrically substituted dienes have been prepared (Table 8). These reactions illustrate the use of olefin categorization to effectively predict proper three-component reactivity. In theory, any combination of a Type I diene with a Type II and a Type III olefin would provide a three-component product (Method A, entries 1−4). As mentioned previously, if two Type I olefins need to be coupled, then this coupling must be performed after coupling of the Type II olefin (Method B, entries 5 and 6). The reactions add a new level of complexity to olefin metathesis reactions and are possible due to development of a better understanding of CM reactivity patterns.

Conclusions

In conclusion, a general empirical model for olefin reactivity in cross metathesis has been developed for the prediction of CM selectivity, in terms of olefin product selectivity, regioselectivity, and chemoselectivity. A general ranking of olefin reactivity in CM is achieved by categorizing olefins by their relative ability to undergo homodimerization via cross metathesis and the susceptibility of their homodimers toward secondary metathesis reactions. Product selectivity can be achieved by suppressing the rate of homodimerization of one component and controlling the rate of secondary metathesis on the desired cross product. These rates can be controlled through the choice of olefins with significantly different activities, which can be modified by altering their steric and electronic properties through substituents, functionalities, or protecting groups. In addition, an appropriate choice of olefin metathesis catalyst is critical for product selectivity, regioselectivity, or chemoselectivity. This empirical approach toward understanding cross metathesis selectivity by categorizing the reactivity provides a convenient starting point for the prediction and design of new, selective CM reactions, such as multicomponent CM processes.

Experimental Section

General Information. 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 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.

Representative Procedure. Olefin A (1.0 mmol) and Olefin B (1.0 mmol) were added via syringe to a stirring solution of **2** (0.05 mmol, 5.0 mol %) in CH_2Cl_2 (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with hexane:ethyl acetate (500 mL).

Representative Procedure Using One Olefin as Solvent. Olefin A (0.28 mmol) was added via syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 7.6 mol %) in 3,3-dimethylbutene (1.5 mL, excess) under a nitrogen atmosphere. The flask was stirred under a continuous flow of nitrogen for 12 h at room temperature (23 °C). The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with hexane:ethyl acetate to provide cross product.

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 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 9:1 hexane:ethyl acetate (500 mL). 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 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 9:1 hexane:ethyl acetate (500 mL). Pale oil was obtained (48 mg, 0.19 mmol, 38% yield). Spectra was 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 24. 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 °C. 1,5-Hexadiene (85 μL, 0.72 mmol) and methyl vinyl ketone (20 μL, 0.24 mmol) were 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 °C. After stirring for 12 h, 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 (2 × 10 cm), eluting with 10:1 hexane:ethyl acetate. Clear oil was obtained (32 mg, 0.21 mmol, 89% yield). ^{1}H 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 25. 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 °C with a continuous flow of nitrogen for 3 h. At that point, a solution of styrene (25 mL, 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 °C for an additional 8 h. The resulting solution was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 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). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): d 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 match those of a previously characterized compound; see Johns, A.; Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1989**, *45*, 7835.

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Supporting Information Available: Experimental procedures and nuclear magnetic resonance and mass spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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