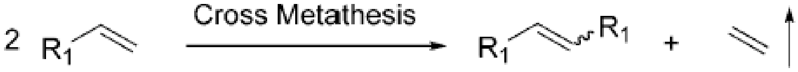
Olefin Cross Metathesis:
A Model in Selectivity

Continuing Discussions of Olefins

Keith Korthals

Scheme 1. Homodimerization in Cross Metathesis



J|A|C|S
ARTICLES
Published on Web 00/00/0000

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

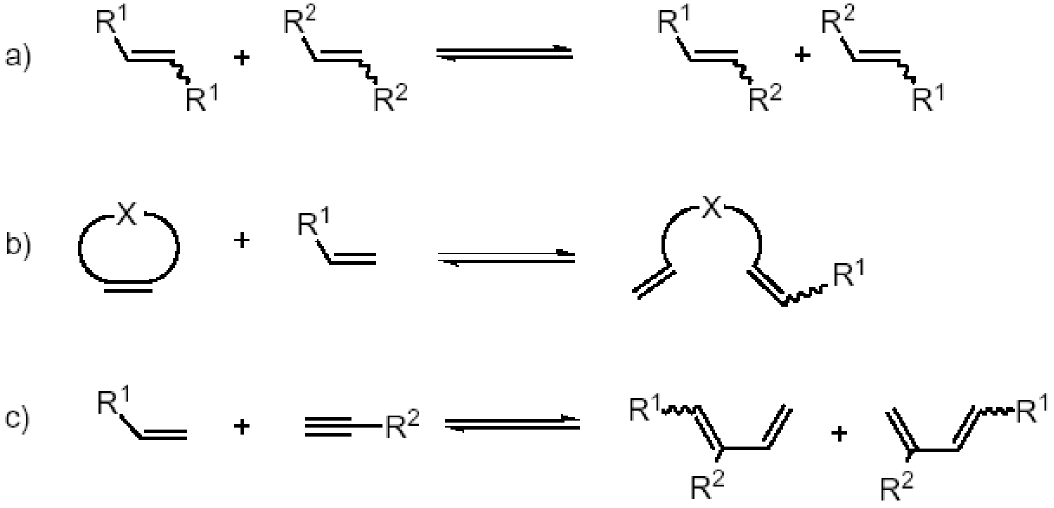
Why Cross Metathesis not used:

- Low catalyst activity to effect a reaction without an enthalipic driving force (ring strain)
  - Newer catalysts have been developed
- Low product selectivity for cross methathesis (lack of a model)
  - Current publication deals with this issue
  - Predict when it can not be predicted
- Low selectivity in the olefin (E and Z)
  - Seems to still be a problem if you want Z

Connon, S.J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923.

Intro. to Cross Metathesis

- Three main variations
  - a) cross-metathesis (only address)
  - b) ring-opening cross-metathesis
  - c) intermolecular enyne metathesis



Connon, S.J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923.

General Mechanism

Scheme 4

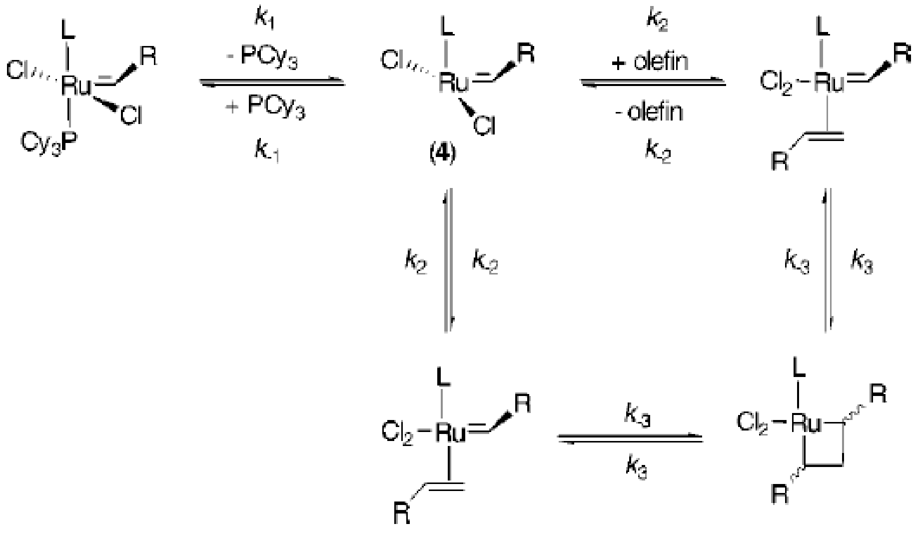


Table 2. Values for the k_{-1}/k_2 Ratio in Catalysts 2 and 1

catalyst	T (°C)	k_1(intercept) (s^{-1})	k_B(predicted) (s^{-1})	k_{-1}/k_2
2	37	0.26	0.16	15300
1	50	0.0031	0.003	1.25

Sanford, M.; Ulman, M.; Gubbs, R. *J. Am. Chem. Soc.* **2001**, *123*, 749-750.

General Mechanism

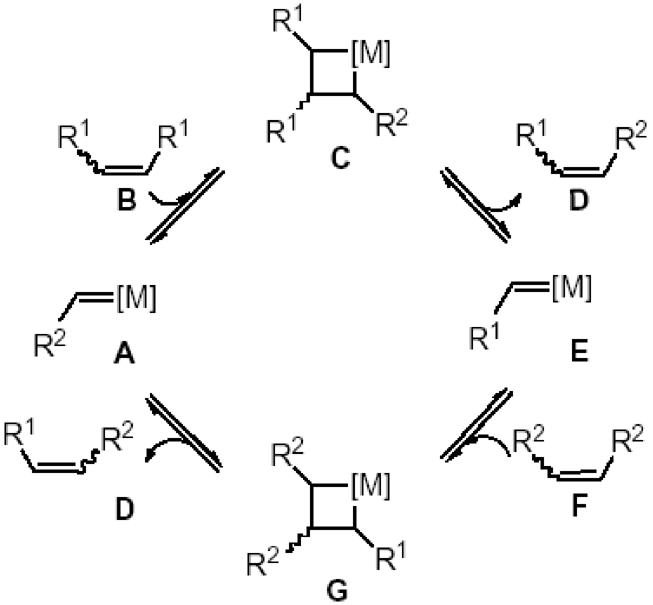
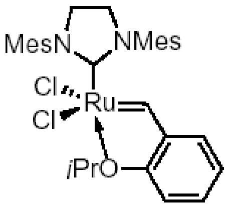


Figure 3. Mechanism of olefin metathesis.

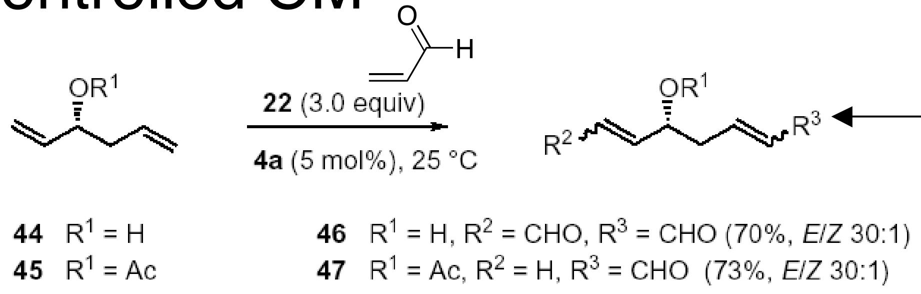
Connon, S.J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923.

Misc. Selectivity

Chelation Controlled CM



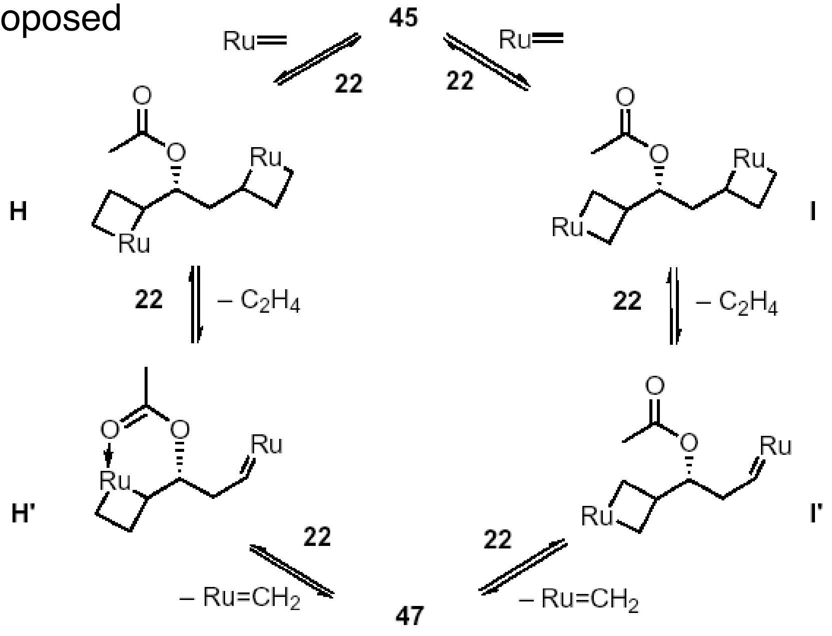
4a



44 R^1 = H
45 R^1 = Ac

46 R^1 = H, R^2 = CHO, R^3 = CHO (70%, *E*/*Z* 30:1) Second addition
47 R^1 = Ac, R^2 = H, R^3 = CHO (73%, *E*/*Z* 30:1) One addition

Proposed

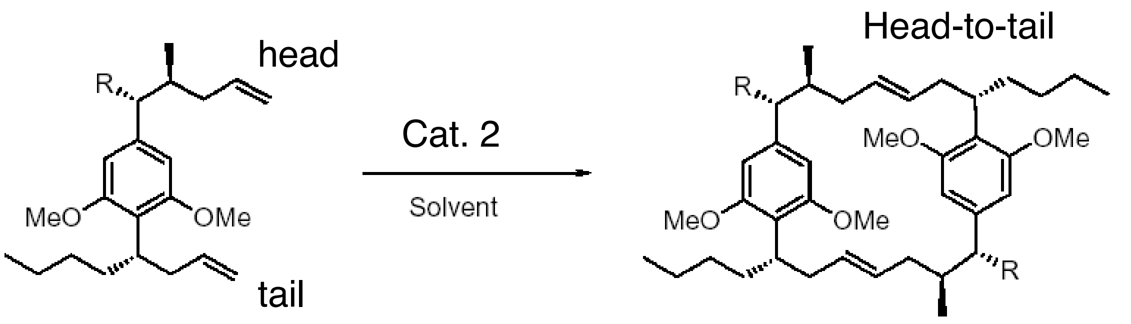


Six member transition state favored

Connon, S.J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923.
BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3(10),* 1451-1454.

Misc. Selectivity

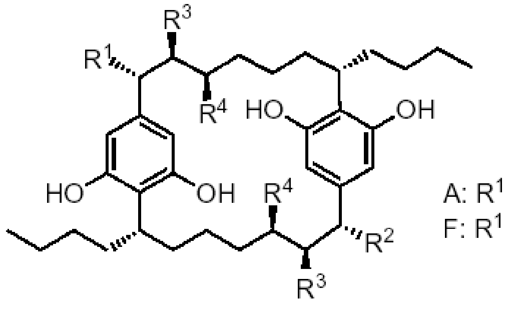
Reversibility of CM



58a R = H
58b R = OTES

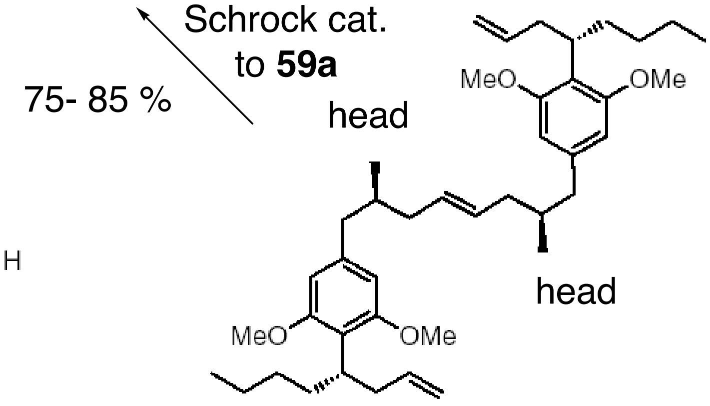
59a R = H (55–72%, *E*/*Z* 100:0)
59b R = OTES 77 %

Most stable thermodynamic product formed by a calculated value of 4.7 kcal/mole (MM2 force field). This gives only the head-to-tail CM dimerization product.



A: R^1 = OH, R^2 = OH, R^3 = Me, R^4 = H
F: R^1 = H, R^2 = H, R^3 = Me, R^4 = H

Figure 9. Cylindrocyclophanes A and F.



61

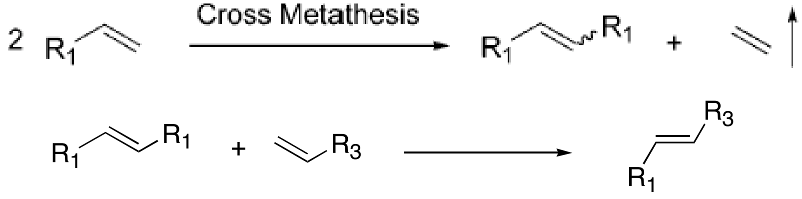
Smith, A.; Adams, C.; Kozmin, S. *J. Am. Chem. Soc.* **2001**, *123*, 990-991.

Connon, S.J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923.
Smith, A.; Kozmin, S; Adams, C.; Paone, D. *J. Am. Chem. Soc.* **2000**, *122*, 4984-4985.

Propensity to Homodimerize

- Relative ability of an olefin to undergo homodimerization was examined

Scheme 1. Homodimerization in Cross Metathesis



olefin reactivity

Type I - Rapid homodimerization, homodimers consumable

Type II - Slow homodimerization, homodimers sparingly consumable

Type III - No homodimerization

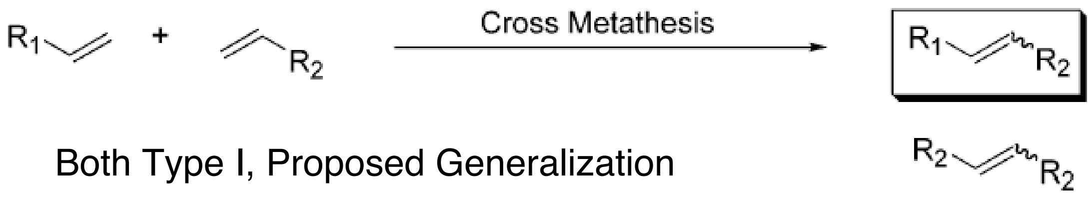
Type IV - Olefins inert to CM, but do not deactivate catalyst (Spectator)

Beyond this, there are olefins that deactivate the catalyst.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

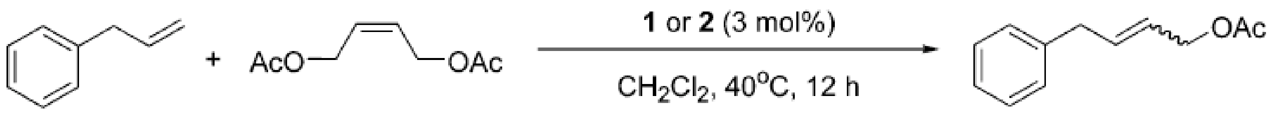
Type I, Statistical Distribution

General Reaction Scheme



$R_1 : R_2$	CM product selectivity
1:1	50%
2:1	66%
4:1	80%
10:1	91%
20:1	95%

Both Type I, Proposed Generalization



1 equiv.

2 equiv.

4

80% isolated yield

	E/*Z* ratio
catalyst **1**	7:1
catalyst **2**	3.2:1

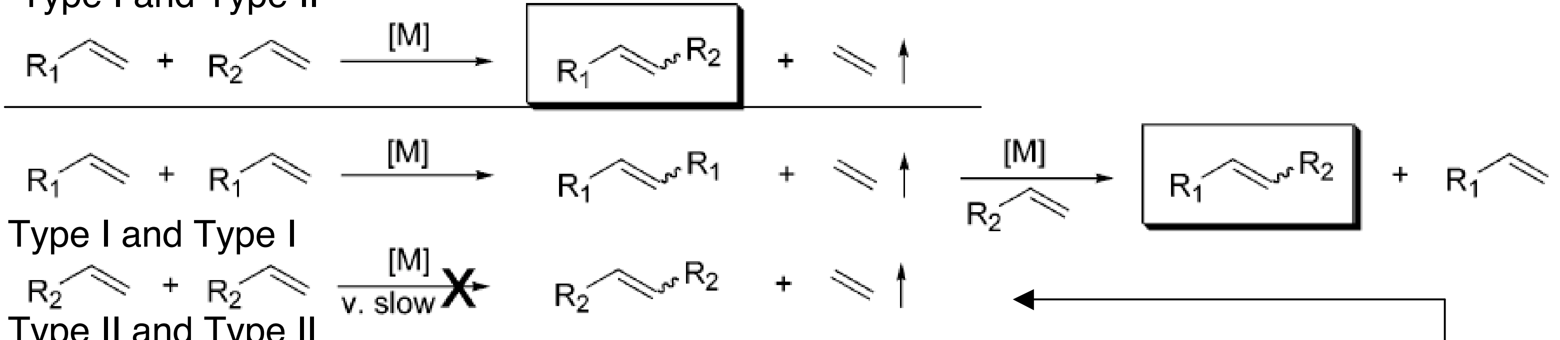
Both Type I or Type I dimer

In order to achieve > 80 % yield of the CM product, excess of the olefin is required.
Essentially non-selective

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Heterotypes

Type I homodimers are reactive

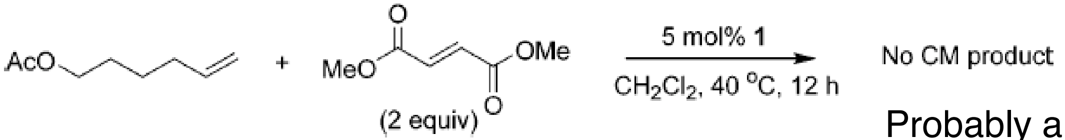


Type I and Type II

Type I and Type I

Type II and Type II

Low Reactivity of Type II homodimers



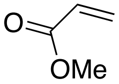
Type I

Type II dimer

Probably all homodimer

[M] Theoretical Product, Reaction very slow
Dimer made by another method.

2 eq.

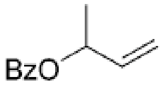
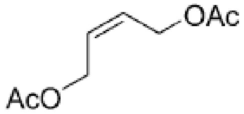
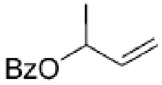
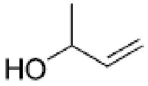
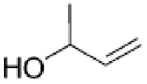
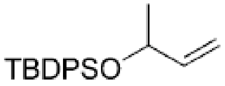


Type II

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Type I and Type II

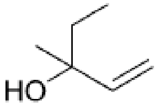
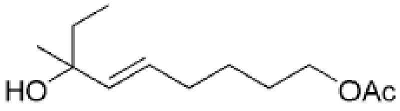
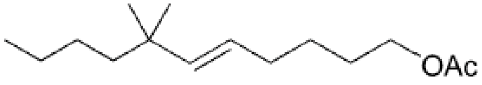
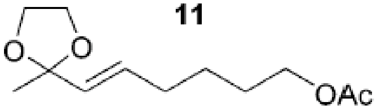
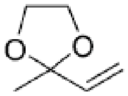
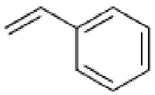
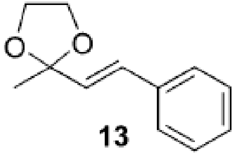
With Cat. 1.

Entry	Type II 2° Allylic Alc.	Cross Partner (Equiv)	Product	Iso. Yield (%)	E/Z ratio[a]
1		 (1.8)	 **5**	38	18:1
2		Type I, homodimer  (2.0)	 **6**	82	10:1
3		Type I  (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.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

4º and Type I CM Partner

Entry	4º 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

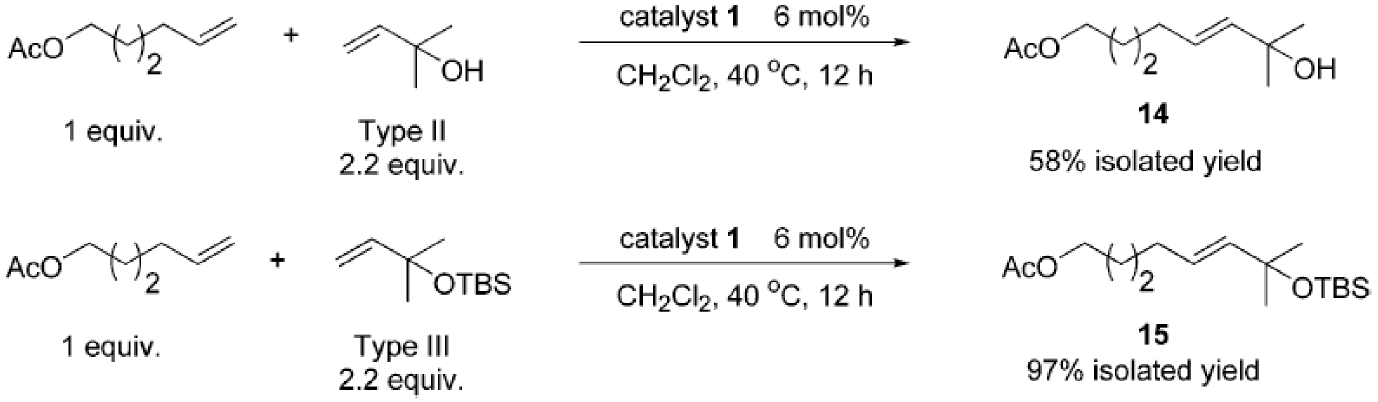
[a] 3−5 mol % of catalyst **1** used, CH_2Cl_2, 40 °C, 12 h. [b] Only *E* isomer observed by ^1H NMR.

Fully substituted allylic alcohols were not active with cat. 2. They are also exclusive E isomers which are the first examples of exclusively E of an alkyl system.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

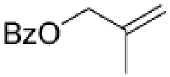
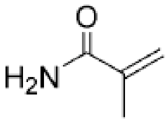
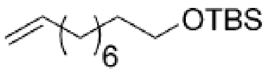
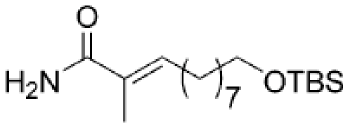
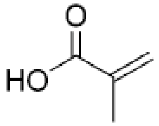
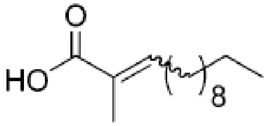
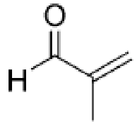
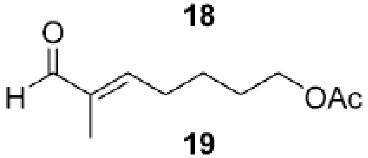
Further Reactivity

Comparing Type II and Type III



Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

1,1-Disubstituted Olefins

Entry	Type III 1,1-disub.	Type I CM partner (equiv.)	With Cat. 1.	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		 Type III (1.0)		 **19**	97	>20:1

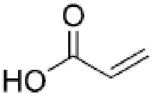
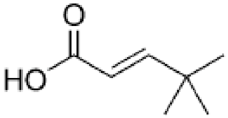
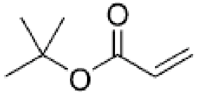
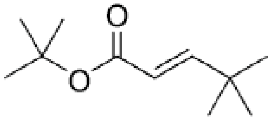
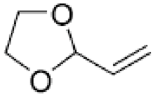
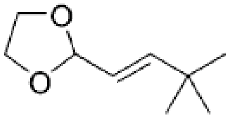
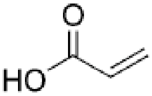
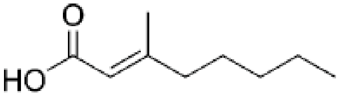
[a] Determined by ^{1}H NMR, confirmed by ^{1}H NMR NOE experiments.

This table shows the ability to use Cat. 1 with a variety of functionality.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Type II and Type III

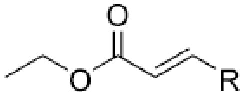
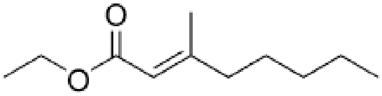
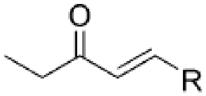
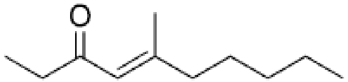
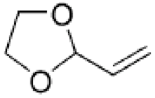
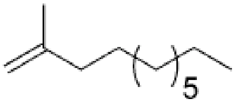
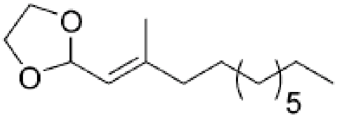
With Cat. 1.

Entry	Type II	Type III (Equiv)		Product	Isolated Yield (%)
1			(neat)		73
2			(neat)		73
3			(neat)		75
4			(4.0)		83[a]

[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.

Type II and Type III

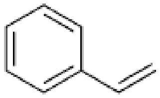
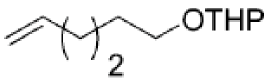
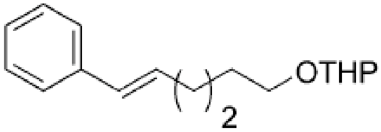
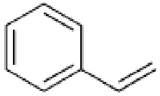
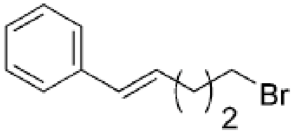
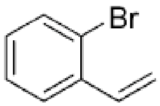
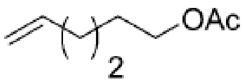
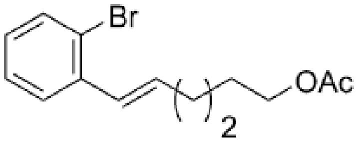
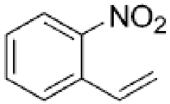
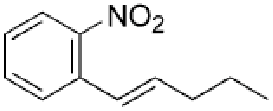
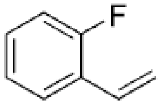
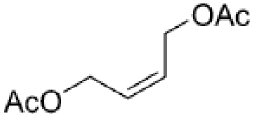
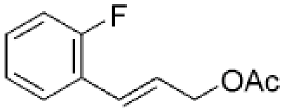
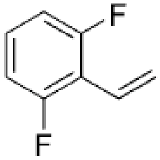
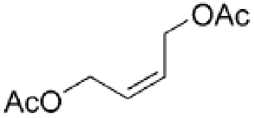
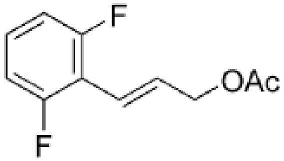
With Cat. 1.

Entry	Type II	Type III (Equiv)	Product	Isolated Yield (%)
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.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Cross Metathesis of Styrenes

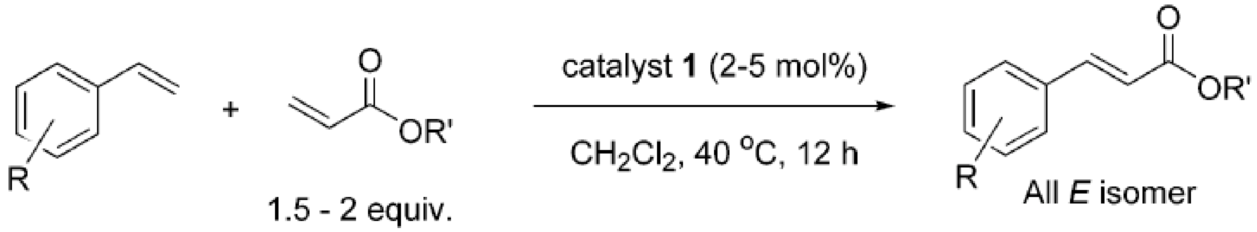
Entry	Catalyst	Aromatic Olefin	Cross-Partner	Aromatic : CM Partner	Product[a]	Isolated Yield (%)
1	**1**			1 : 1 4 : 1		47 71
2	**3**			2 : 1		90
3	**1**			1 : 1 3 : 1		80 98
4	**3**			2 : 1		48
5	**1**			1 : 2		98
6	**1**			1 : 2		50

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

Note: other catalysts were slow to homodimerize, but Cat. 1 was not.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Styrene with Acrylate Esters

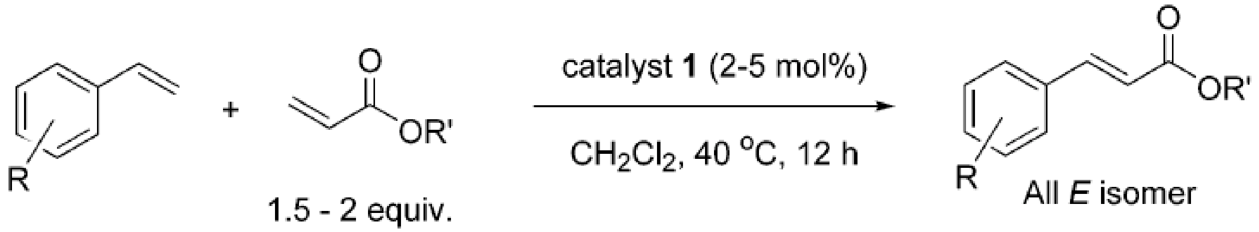


Entry	R	R'	Isolated Yield (%)[a]
1	H	CH_3	92
2	2,4-Dimethyl	CH_2CH_3	87
3	2,4,6-Trimethyl	CH_2CH_3	5[b]
4	2-CF_3	CH_2CH_3	44
5	3,4-Dimethoxy	*n*-Butyl	89
6	4-NO_2	CH_3	89
7	4-CHO	CH_2CH_3	83

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

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Styrene with Acrylate Esters



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]

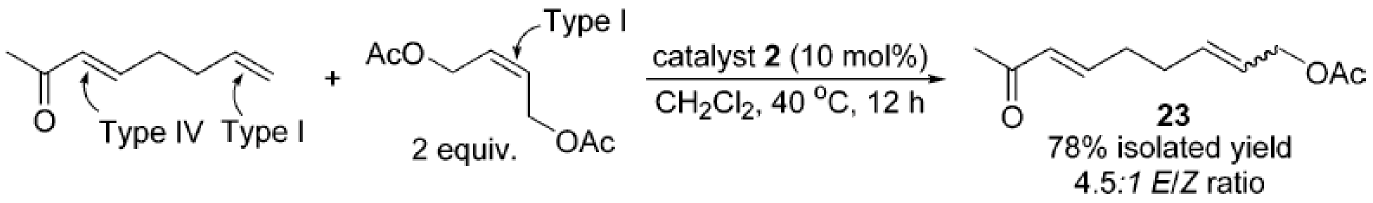
Sterics at the 2,6 positions important

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

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

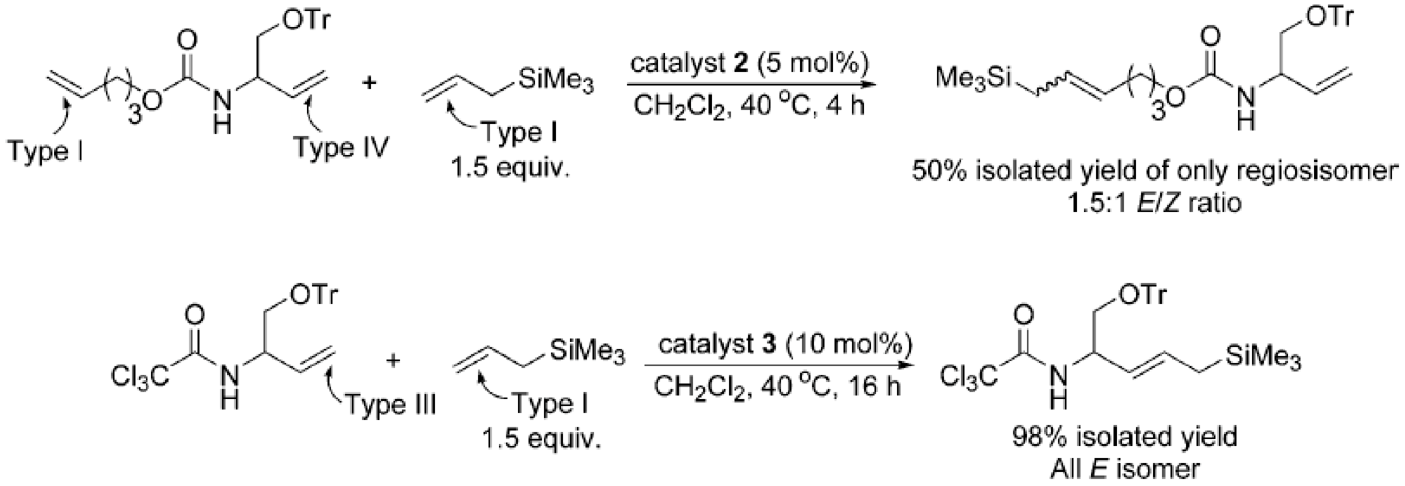
Chemoselective CM

Chemoselective CM Based on Olefin Categorization



Chemoselective Cross Metathesis Using Catalysts 2 and 3

(A) *Blechert, et al.*



Brummer, O.; Ruchert, A.; Blechert, S. *Chem.-Eur. J.* **1997**, *3*, 441
Feng, J.; Schuster, M.; Blechert, S. *Synlett* **1997**, 129.

Chemoselective CM

(B) *Crowe and Zhang*

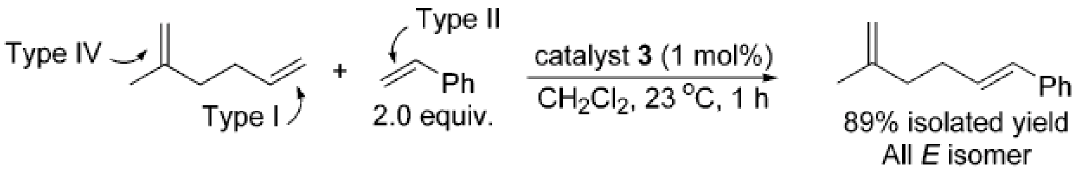
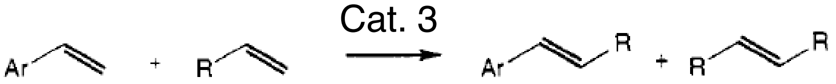


Table I. Cross-Metathesis Reactions[a]



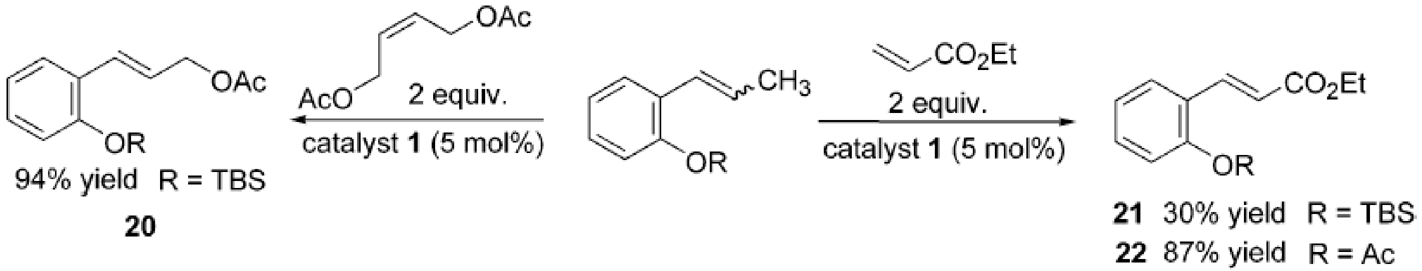
entry	Ar	R	ArCH=CHR (%)[b]	RCH=CHR (%)
1	Ph	*n*-hexyl	89	2
2	Ph	$CH_2CH_2C(=CH_2)CH_3$	86	2
3	Ph	cyclohex-4-enyl	60	15
4	Ph	$CH_2CH_2CH_2Br$	90	4
5	Ph	$CH_2CH_2CH(Br)CH_3$	84	8
6	Ph	CH_2CH_2Br	50	42
7	Ph	$CH_2CH_2COCH_3$	0 (11)[c]	*e*
8	Ph	$CH_2CH_2C(=CH_2)OTMS$	22 (66)[c,d]	*e*
9	Ph	$CH_2CH_2CO_2CH_2Ph$	67	20
10	Ph	$CH_2CH_2CH_2OCH_2Ph$	85	2
11	*p*-$MeOC_6H_4$	*n*-hexyl	88	2
12	*m*-$O_2NC_6H_4$	*n*-hexyl	48	39

[a] Reactions were run with 2 equiv of styrene and 1 mol % catalyst. The amount of stilbene formed in most cases is less than 4%. [b] Only the trans isomer was detected by ^1H NMR. [c] The yield in parentheses is for a reaction using 5 mol % catalyst. [d] Isolated as the ketone. [e] Yield was not determined.

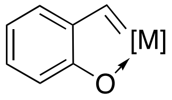
Crowe, W. E.; Zhang, Z. *J. Am. Chem. Soc.* **1993**, *115*, 10998.

Chelation/Three Component Olefin CM

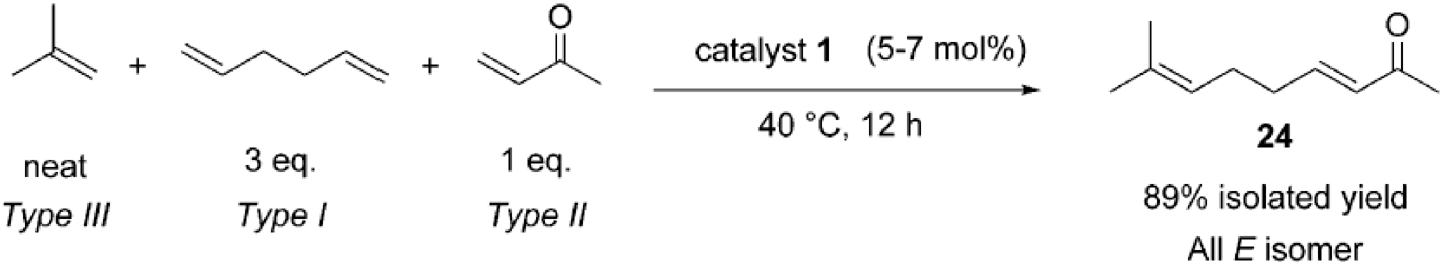
Ortho-substituted phenols



Phenol requires protection due to chelation with the catalyst.

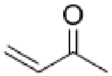
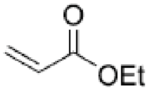
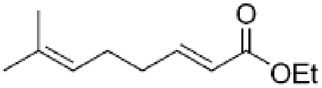
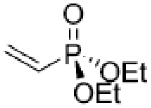
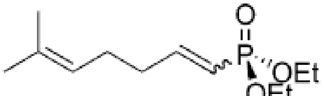
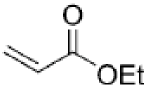
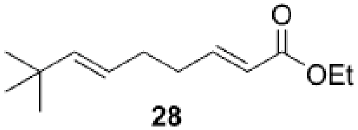
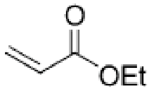
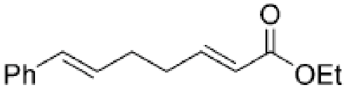
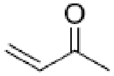


Three Component Olefin Cross Metathesis



Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Three Component Olefin CM

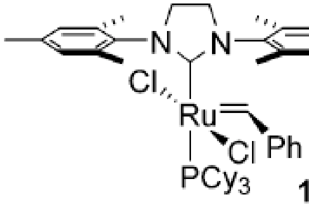
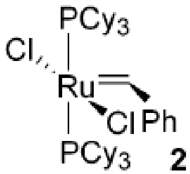
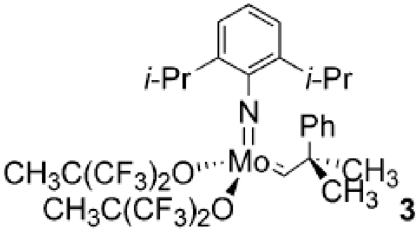
Entry	Method[d]	CM partner Y	CM partner Z	Ratio (Diene:Y:Z)	Product	Isolated Yield (%)
1	A			3:neat:1	 **24**	89
2	A			3:neat:1	 **26**	60
3	A			3:neat:1	 **27**	57[b]
4	A			1:neat:1	 **28**	67[c]
5	B			1:3:1	 **29**	34
6	B			2:3:1	 **25**	47

[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.

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

The Proposed Rules (Guidelines)

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]

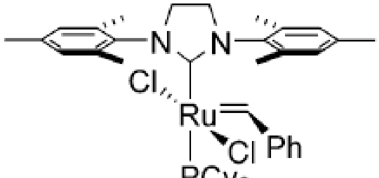
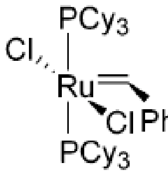
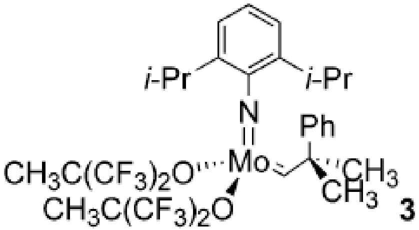
Reaction between two olefins of Type I = *Statistical CM*

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

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

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

The Proposed Rules (Guidelines)

Olefin type	 1	 2	 3
Type III **(no homodimerization)** Low reactivity	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)** Low reactivity	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]

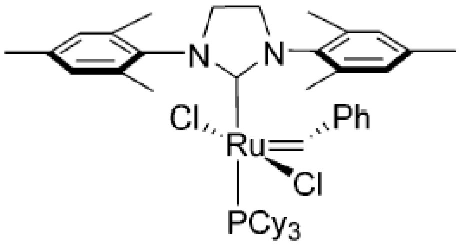
Reaction between two olefins of Type I = *Statistical CM*

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

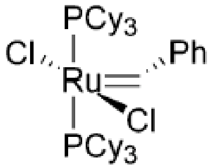
Reaction between olefins of two different types = *Selective CM*

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

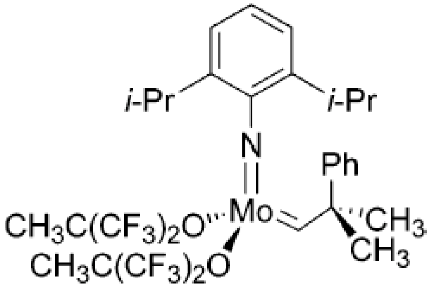
Useful information



1



2



3

Figure 1. Commonly used olefin metathesis catalysts.

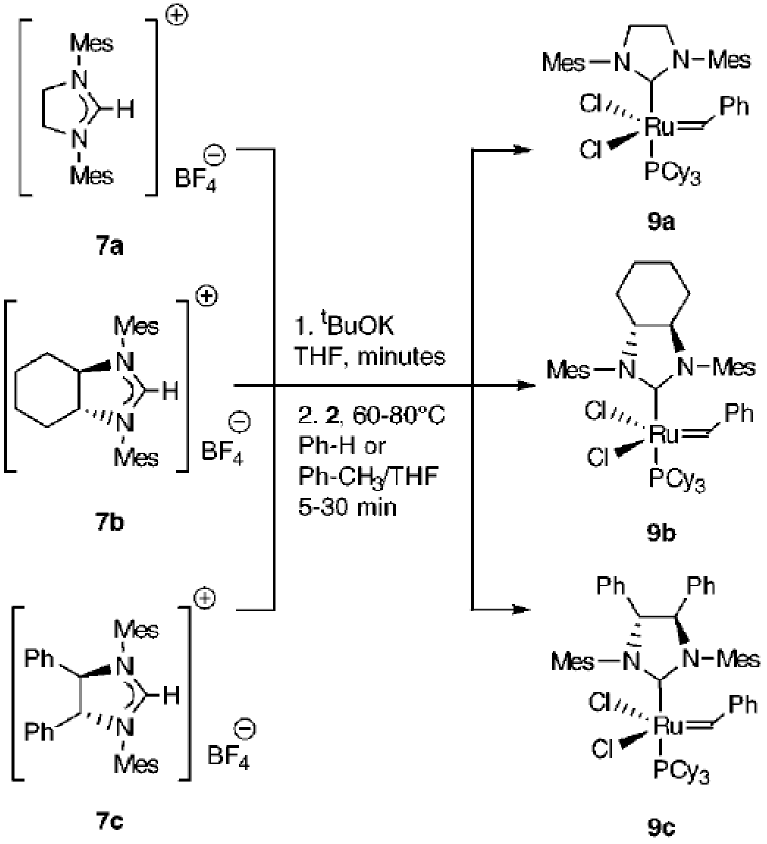
olefin reactivity ↑

- 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)

Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* XXXX, XXX,

Appendix A

Grubbs generation two preparation



Air and water tolerant complex

Scholl, M.; Ding, S.; Lee, C.; Grubbs, R. *Org. Lett.* **1999**, *1 (6*), 953-956.

The End