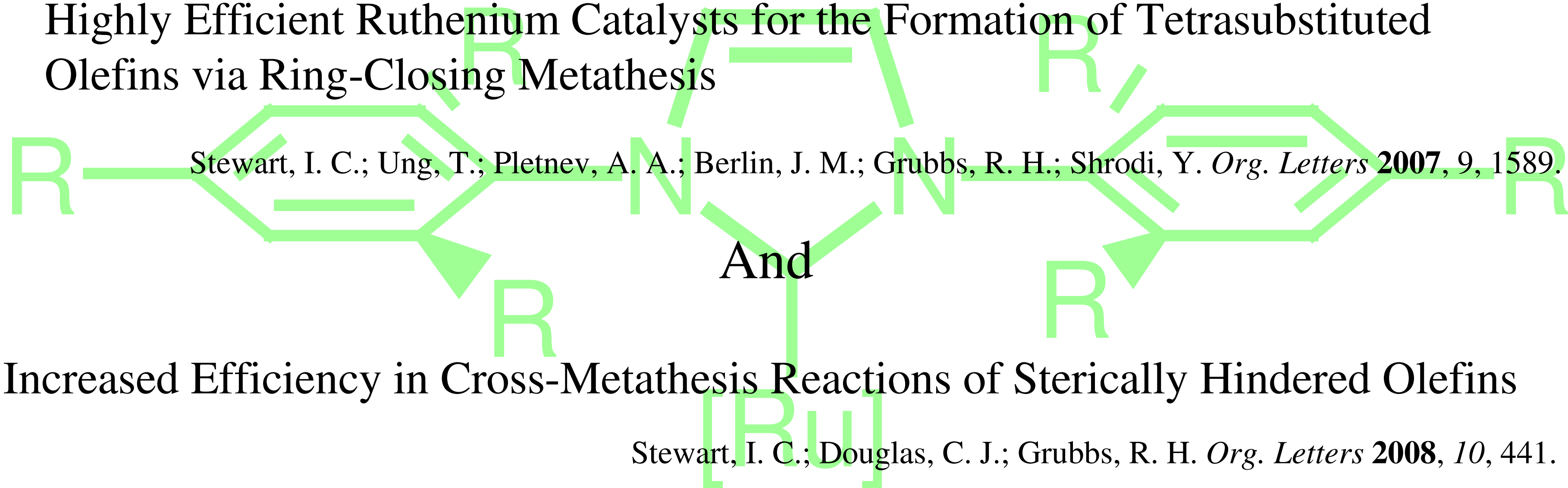
Pushing the Limits of the Metathesis Reaction:

Design of the NHC ligand



Highly Efficient Ruthenium Catalysts for the Formation of Tetrasubstituted Olefins via Ring-Closing Metathesis

Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Shrodi, Y. *Org. Letters* **2007**, 9, 1589.

And

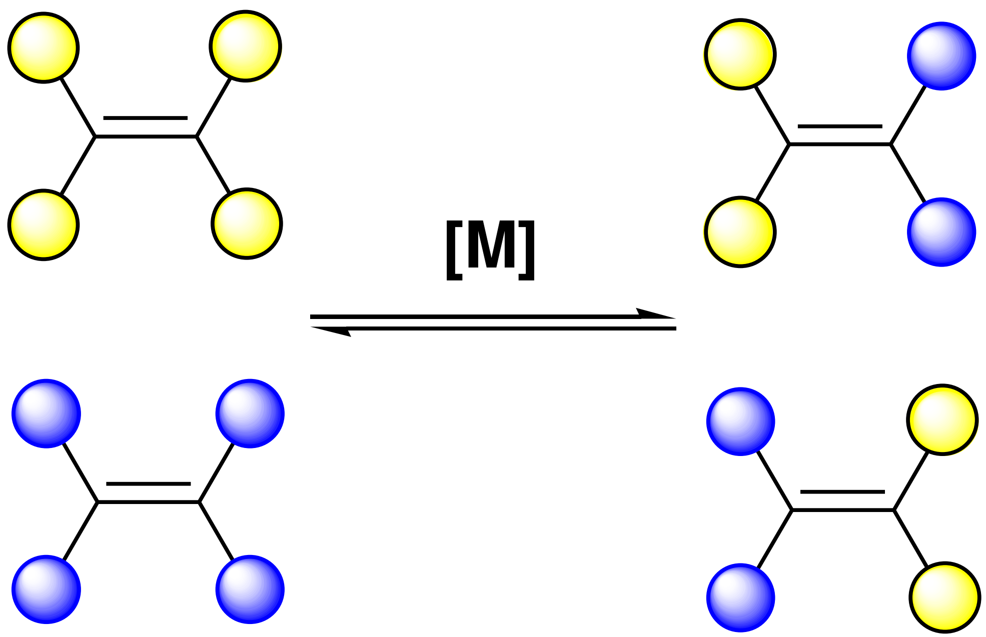
Increased Efficiency in Cross-Metathesis Reactions of Sterically Hindered Olefins

Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Letters* **2008**, *10*, 441.

Dr. Laurent Ferrié

Metathesis: Principle

From the Greek *meta*= to change and *thesis* = position



Statistical Distribution of the Olefinic Fragments

Calderon *et al., J. Am. Chem. Soc.* **1968**, *90*, 4133

Metathesis: Principle

<u>In the Greek mythology:</u>

The griffin = eagle + lion

The hippocampus = horse + fish

3

Metathesis: Catalysts

Thermal Metathesis

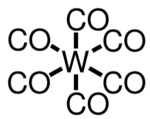
1931

725 °C

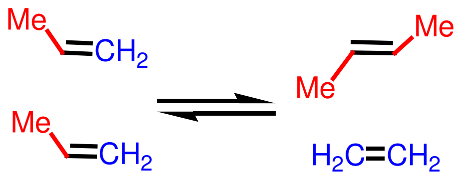
via $W(CO)_5=R_2$

Banks

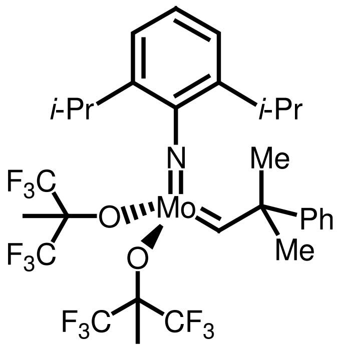
1964



Hetereogenous Catalysis 150 °C

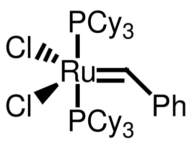


Metathesis Catalysts Used in Organic Chemistry



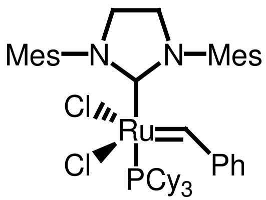
Shrock Catalyst

1990



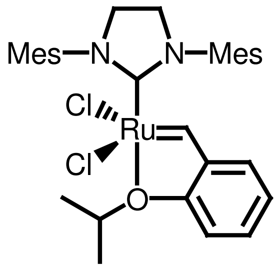
Grubbs Catalyst
1st generation

1995



Grubbs Catalyst
2nd generation

1999

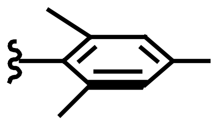


Grubbs-Hoveyda
Catalyst

2000

Cy = Cyclohexyl

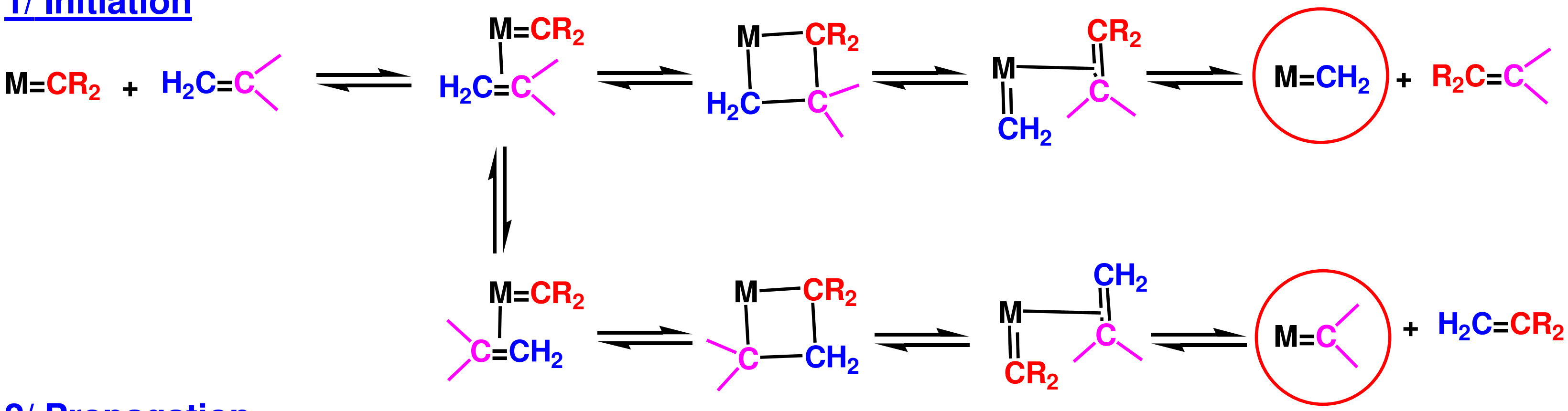
Mes =



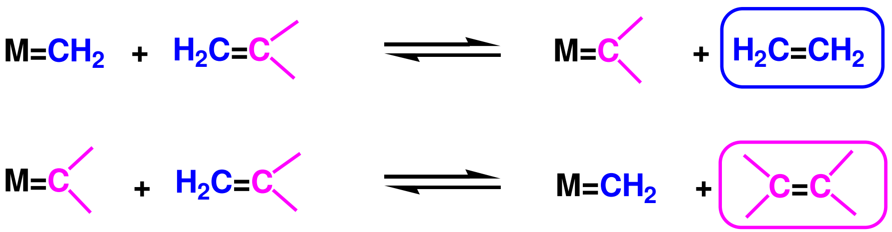
4

Metathesis: Mechanism

1/ Initiation



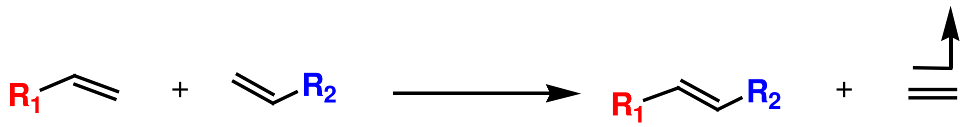
2/ Propagation



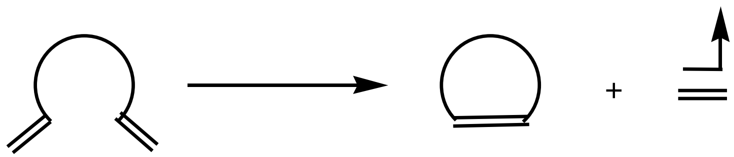
Chauvin Y.; Hérisson, J.-L., *Makromol. Chem.* **1971**, *141*, 161.

Metathesis: Application

1) Cross-Metathesis (CM)



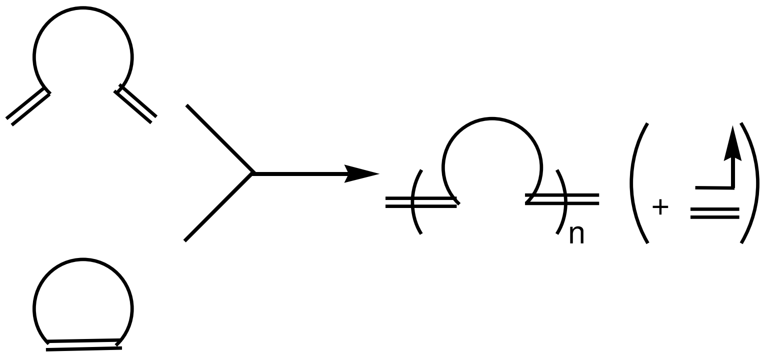
2) Ring-Closing Metathesis (RCM)



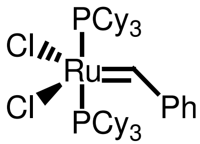
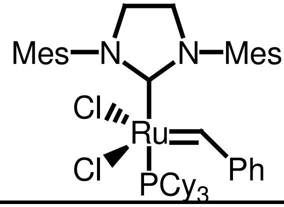
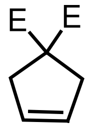
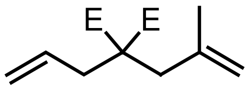
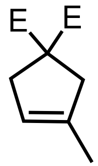
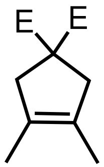
3) Polymerizing Metathesis

(ADMPE)

(ROMP)



Ring-Closing Metathesis: Limitations

Substrate		Product		
			Catalyst: Conversion	
			100%	100%
	5 mol% catalyst → 40℃ DCM		82%	100%
	E= COOEt		0%	40%

Grubbs *et al. Tetrahedron Letters* **1999**, *40*, 2247

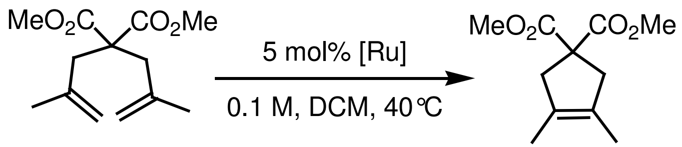
-The obtention of tetrasubstituted olefins by RCM is inefficient

- Phosphine free catalysts (Hoveyda or Grela catalysts) do not give better conversion

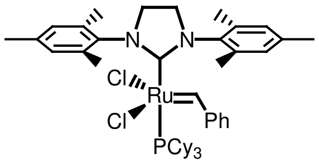
7

Grela, K. *and al., J. Am. Chem. Soc.* **2004**, *126*, 9318.

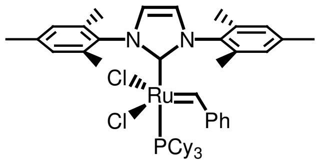
Overcoming the Limitations: Modification of the NHC ligand



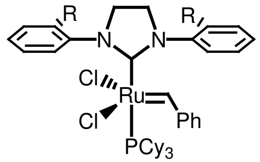
catalyst	time (h)	conv. (%)[a]	time (h)	conv. (%)[a]
1	1	4	24	50
2	1	9	24	40
3	1	0	24	0
4	1	0	20	24
5a	0.25	81	1	86
5b	0.25	62	1	71
5c	0.25	72	1	74
6a	1	45	24	70
6b	1	22	24	59
6c	1	16	24	33



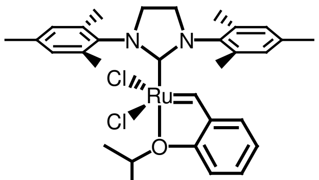
1



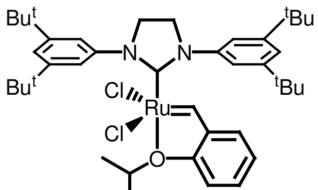
2



5a (R=Me)
5b (R=Et)
5c (R=*i*-Pr)



3



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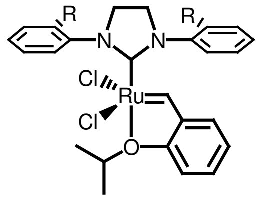
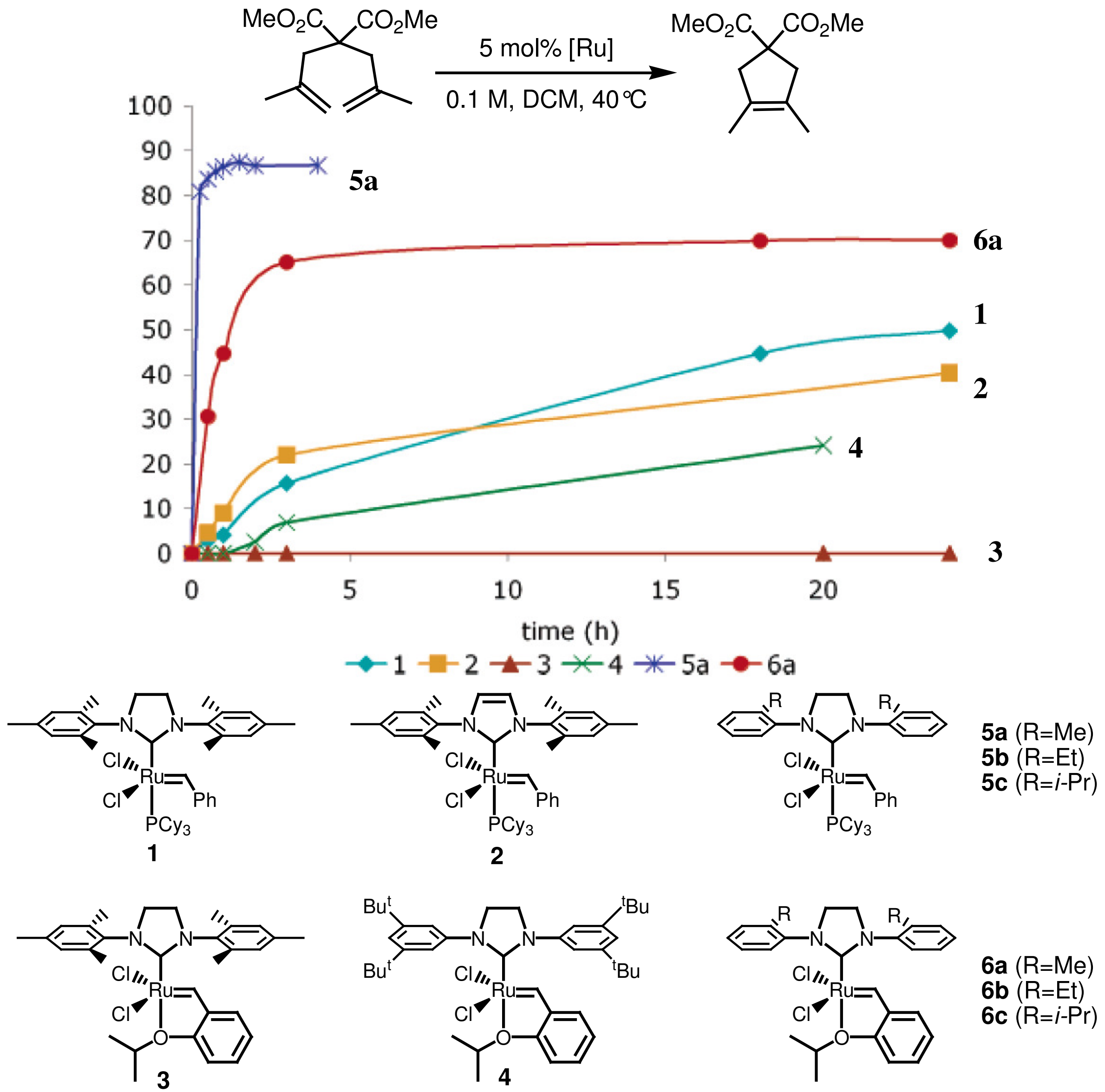


6a (R=Me)
6b (R=Et)
6c (R=*i*-Pr)

8

Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Shrodi, Y. *Org. Letters* **2007**, 9, 1589.

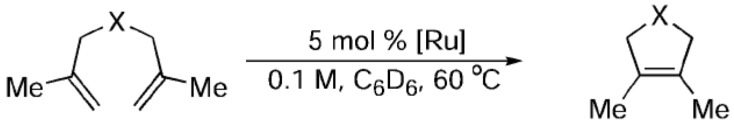
Overcoming the Limitations: Reaction Monitoring

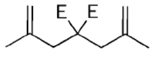
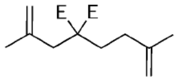
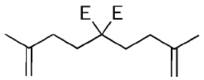
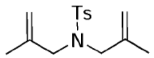
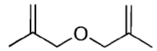
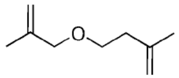
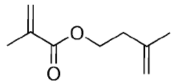
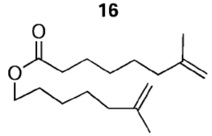


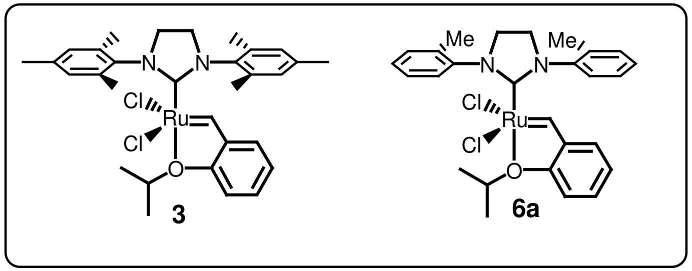
9

Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Shrodi, Y. *Org. Letters* **2007**, 9, 1589.

Application to Different Substrates



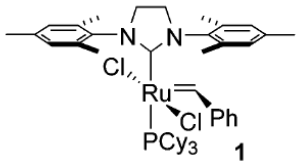
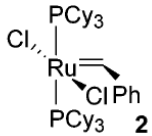
substrate[a]	conv. (%) 3	conv. (%) 6a
 9	30, 24 h	>95, <1 h 100[b]
 11	>95, 24 h	>95, <1 h 100[b]
 12	50, 24 h	87[c], 24 h
 13	85, 24 h	>95, <1 h
 14	>95, 24 h	>95, <1 h
 15	43, 24 h	88, 11 h
 16	n.r.	n.r.
 17	n.r.	n.r.



[a] E = CO_2Et. [b] Isolated yield. [c] Performed in an open system. Conversion in a closed system (NMR tube) was 62%.

Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Shrodi, Y. *Org. Letters* **2007**, 9, 1589.

Cross-Metathesis: General Model and Limitations

Olefin type	 1	 2
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]
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]
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]
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]

Grubbs, R. H. *et al. J. Am. Chem. Soc.* **2003**, *125*, 11360

<u>Cross-Metathesis:</u>

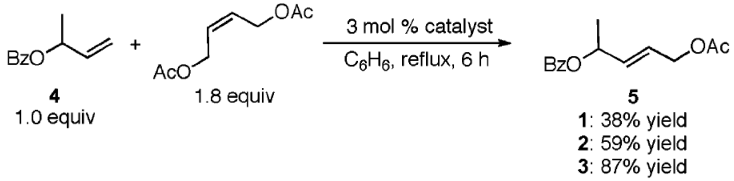
Type I + Type I: statistic mixture, good yields

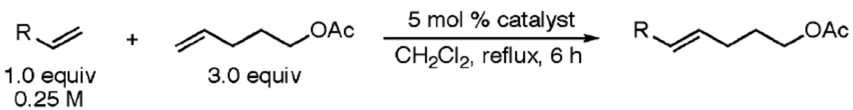
Type I + Type II: good yields

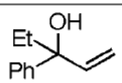
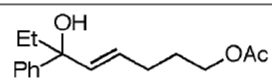
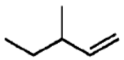
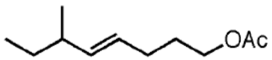
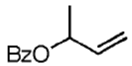
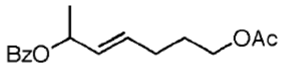
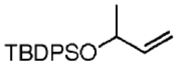
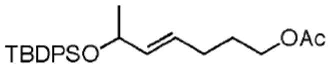
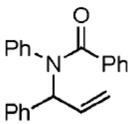
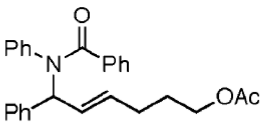
Type I + type III: moderate to low yields

Type II + type III: generally low yields

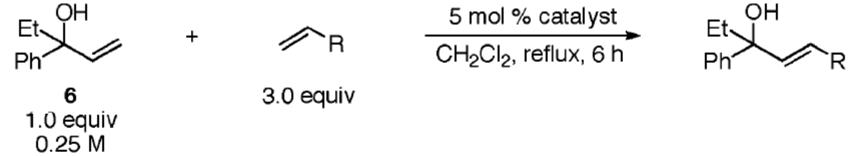
Cross-Metathesis: Use of Modified NHC Ligands

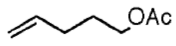
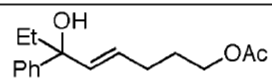
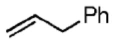
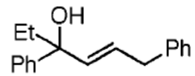
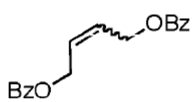
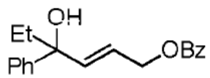
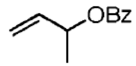
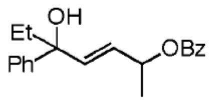




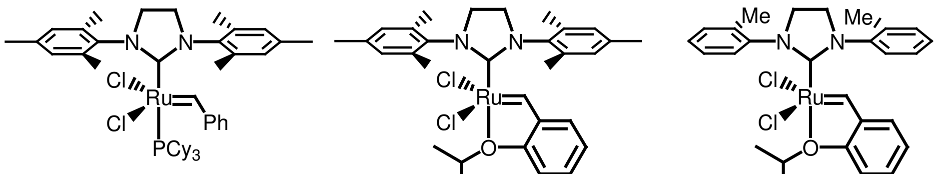
entry	reactant	product[a]	yield (%)[b] 2	yield (%)[b] 3
1			70	89
2			85	98
3			82	93
4			68	91
5			19	30

[a] *E/Z* > 20:1 in all cases. [b] Isolated yields.



entry	reactant	product[a]	yield (%)[b] 2	yield (%)[b] 3
1			70	89
2			64	91
3			81	98
4[c]			50	66

[a] *E/Z* > 20:1 in all cases. [b] Isolated yields. [c] Isolated as a 3:2 mixture of diastereomers.



1 2 3

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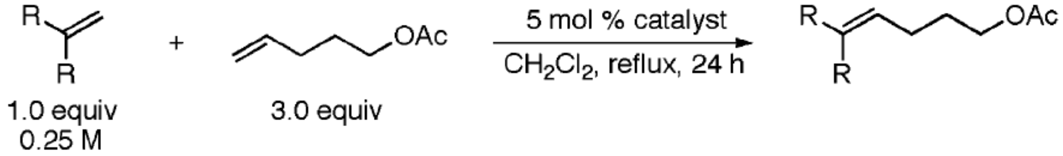
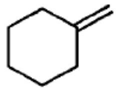
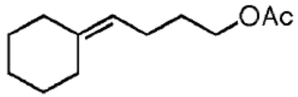
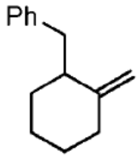
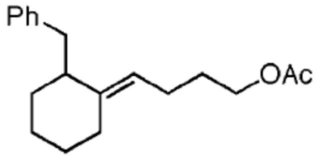
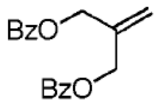
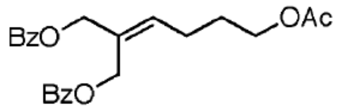
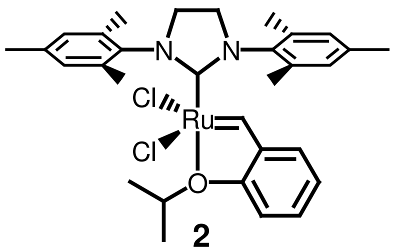
Cross-Metathesis: Formation of Trisubstituted Olefins by CM

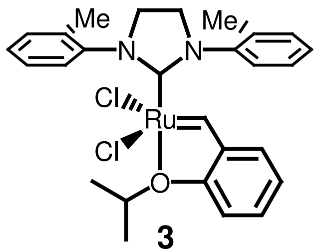


entry	reactant	product	yield (%)[a] 2	yield (%)[a] 3
1			78	60
2			17	0
3			73	54

[a] Isolated yields.



2



3

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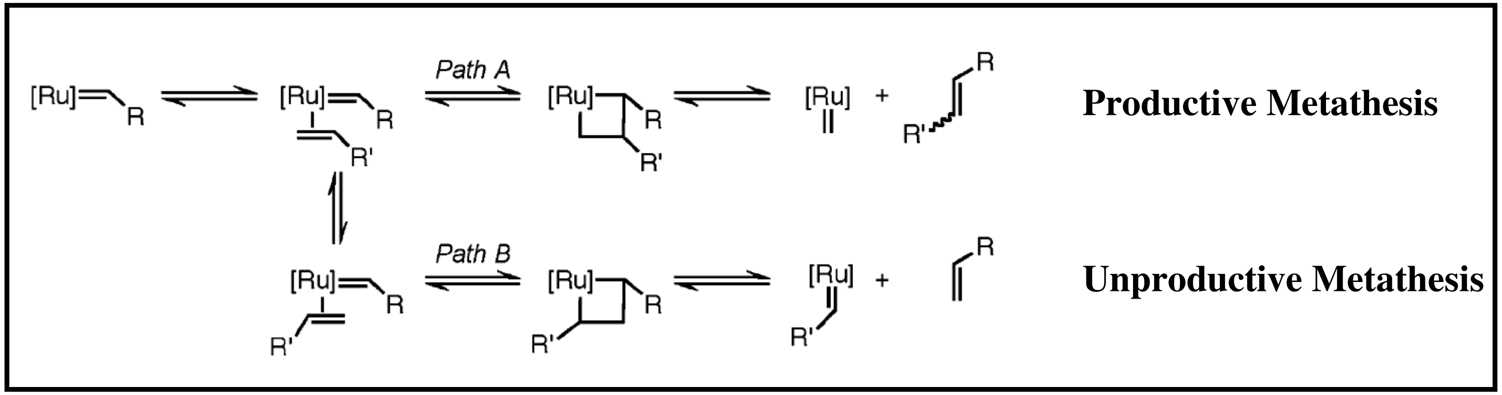
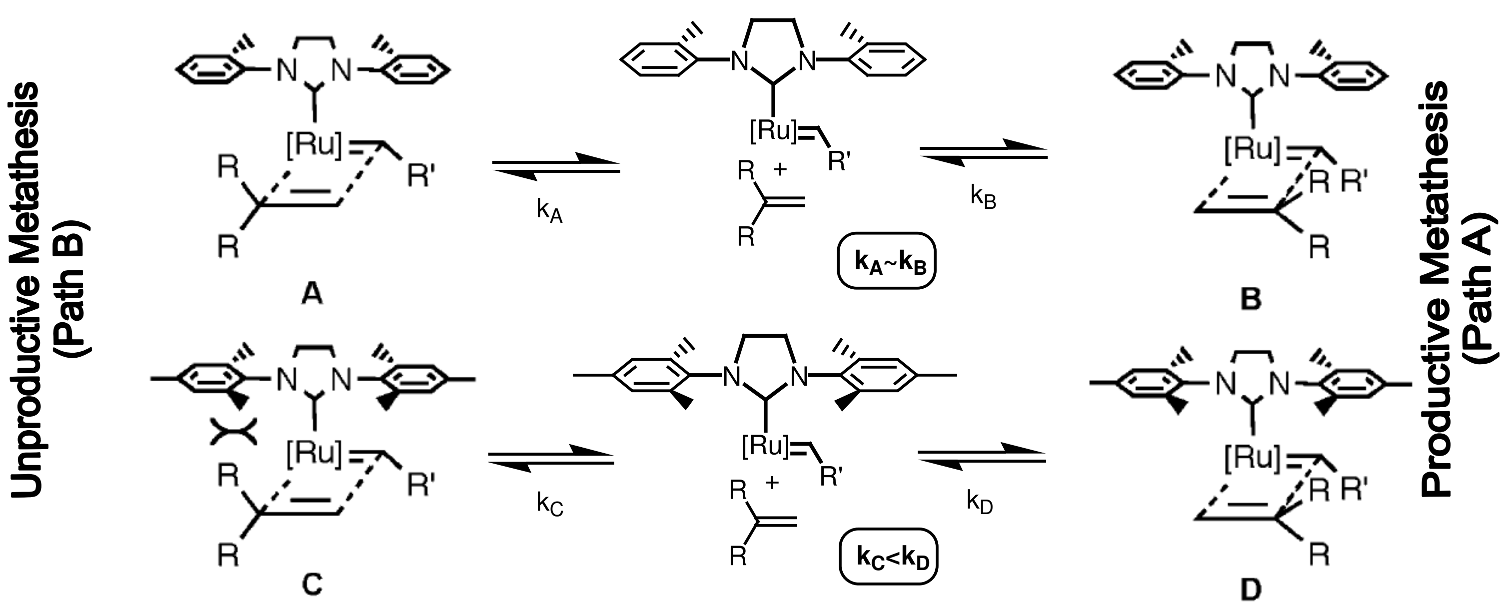
Productive and Unproductive Metathesis: Mechanistic Aspect





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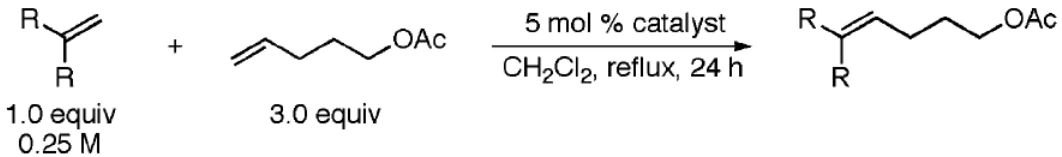
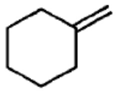
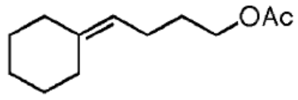
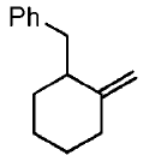
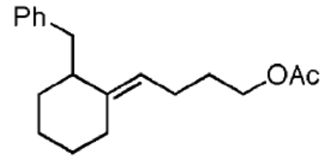
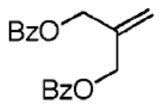
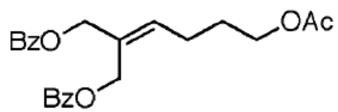
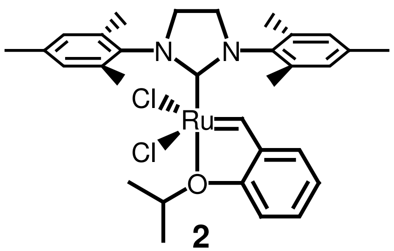
Wagener, K. B. *and al. J. Organomet. Chem.,* **2006**, *691*, 585.

Improvement in the Formation of Trisubstituted Olefins by Using Bulky NHC Ligands

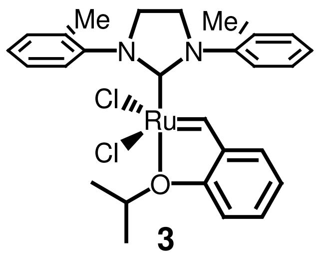


entry	reactant	product	yield (%)[a] 2	3	7
1			78	60	98
2			17	0	7
3			73	54	96

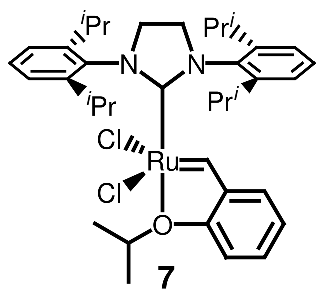
[a] Isolated yields.



2



3



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Conclusion

- The design of the NHC ligands in the Ruthenium metathesis catalysts demonstrated significant improvements to difficult processes in both RCM and CM reactions

- *o*-Tolyl NHC ligand, by decreasing steric bulk, allows efficient formation of tetrasubtituted cyclic olefins by RCM.

- *o*-Tolyl NHC ligand, by decreasing steric bulk, enhances the CM with substituted terminal olefins but are not effective for the CM with 1,1 disubstituted olefins.

- Bulky NHC ligands, are the most effective for the CM with 1,1 disubstituted olefins likely due to a selectivity of productive versus unproductive pathways.