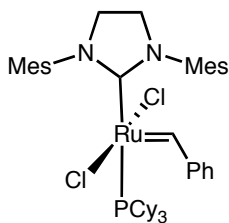
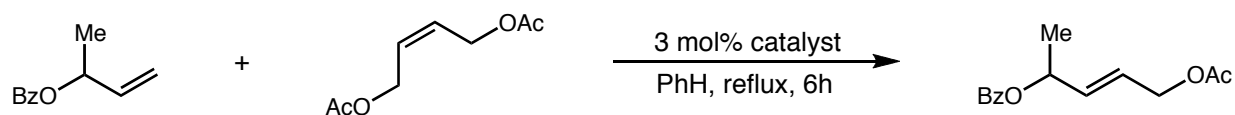


Applications of Non-Commercially Available Metathesis Catalysts

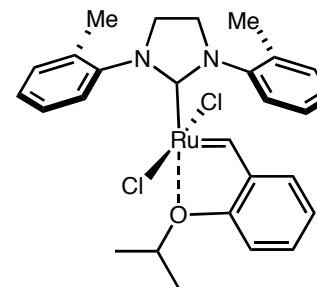
or

A Simple Guide to Optimizing Metathesis Reactions



38%

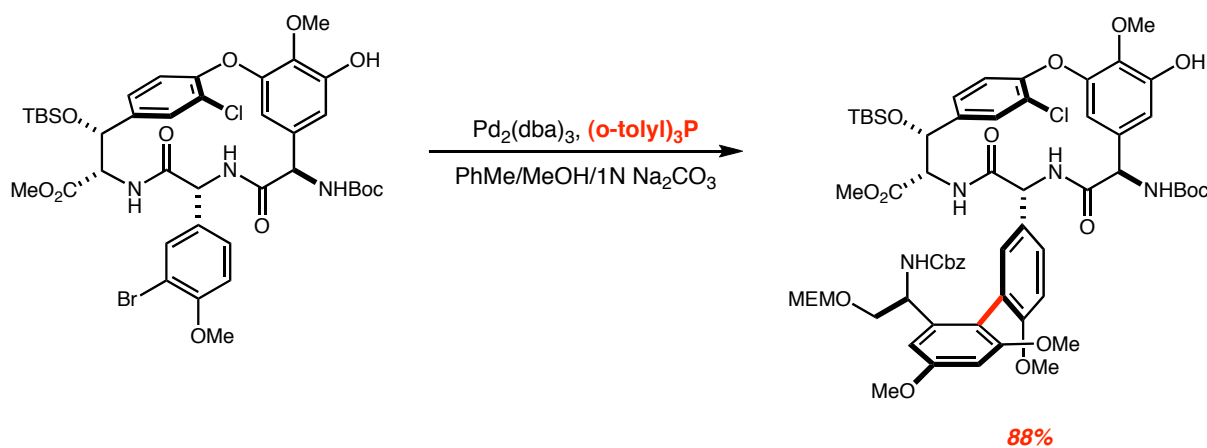
MacMillan Group Meeting
January 16, 2008



87%

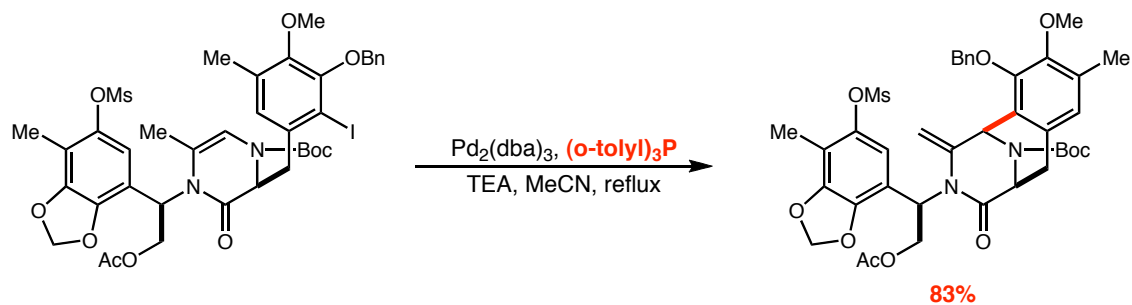
An Alternate Reality

- Consider a situation wherein only four phosphine ligands are commercially available
- PPh_3 , $\text{P}(\text{tBu})_3$, dppe and BINAP would accomplish many, if not most, coupling reactions
- Certain total syntheses would be conspicuously absent

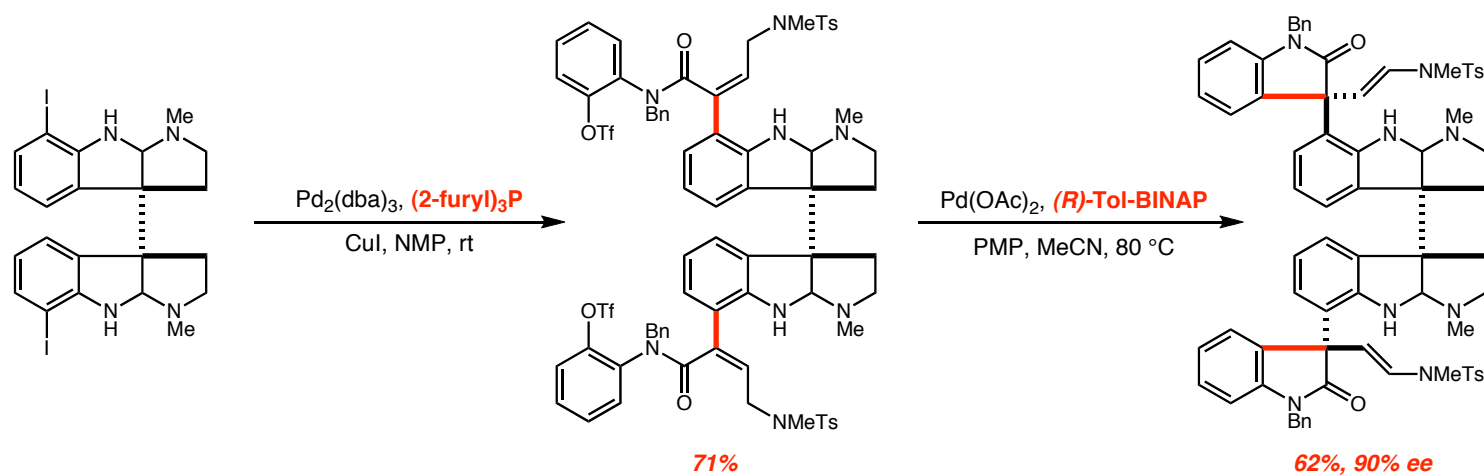


Boger, D. L. *et al. J. Am. Chem. Soc.* **1999**, *121*, 3226.

An Alternate Reality



Fukuyama, T. *et al.* *J. Am. Chem. Soc.* **2002**, *124*, 6552.



Overman, L. E. *et al.* *J. Am. Chem. Soc.* **2002**, *124*, 9008.

Phosphine vs. Catalyst Choice

- Clearly, the commercial availability of a variety of phosphines is key
- Few research groups use 'homemade' phosphine ligands
- Are we justified in also using only commercially available metathesis catalysts?

PHOSPHINE LIGANDS

Widely commercially available

Difficult to synthesize

Few guiding mechanistic principles

METATHESIS CATALYSTS

Few commercially available

Often simple to synthesize

Based strongly on mechanism

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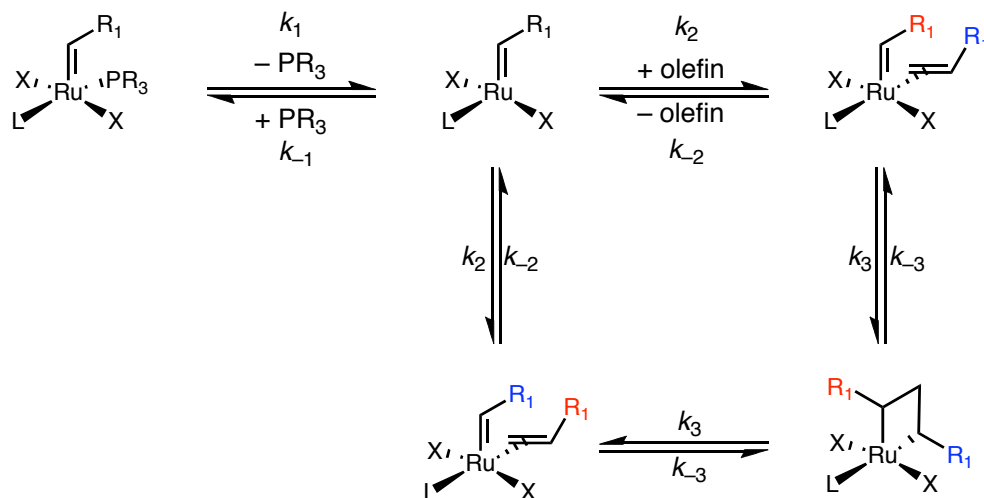
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Based strongly on mechanism

The key to time and fiscal efficiency is selection of the proper catalyst

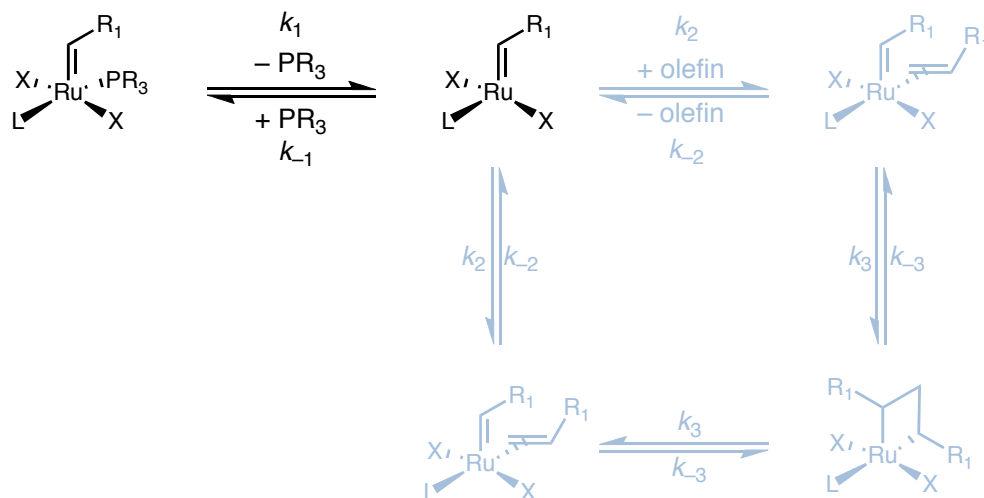
Selection of a Metathesis Catalyst

- First, one should ensure that the substrate has been optimized for commercially available catalysts
- After optimization, a catalyst to be synthesized should be rationally determined
- Both processes require an intimate working knowledge of the mechanism of olefin metathesis



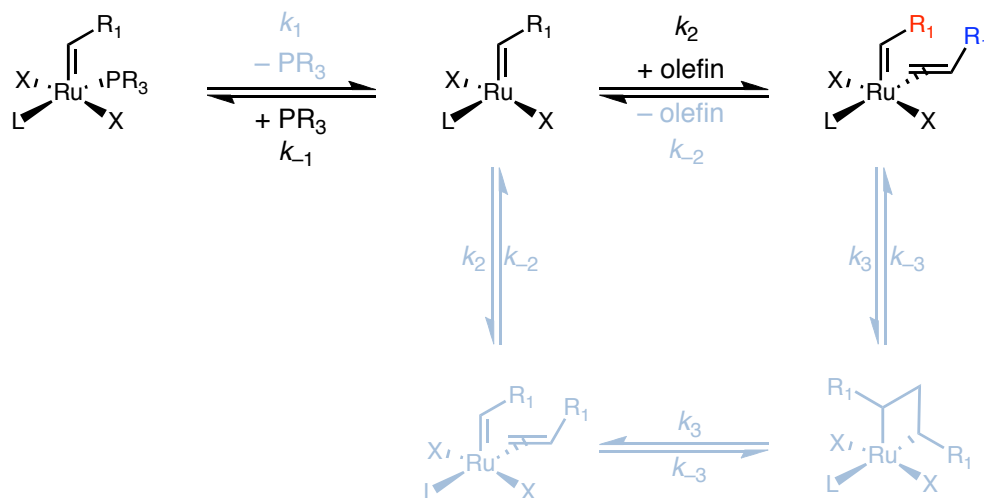
Observations on Phosphine Dissociation

- Surprisingly, 2nd generation catalyst (L = H₂IMES) phosphine dissociation is **100 times less favored**
- Methylidene species (R₁ = H) for either generation catalyst **decompose competitively**
- For all systems investigated, initiation in dichloromethane is 30% faster than in toluene



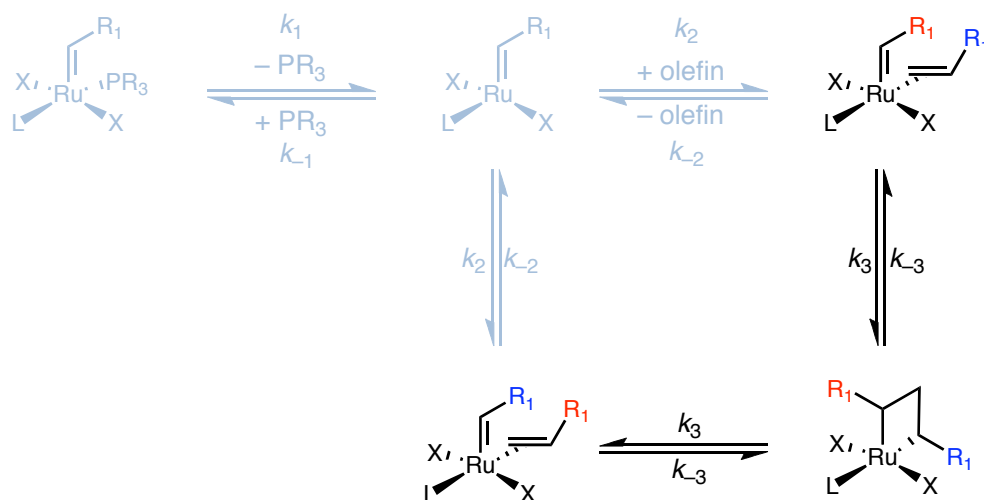
Observations on Olefin Binding

- 2nd generation catalyst (L = H₂IMES) k_{-1}/k_2 is **10000 times lower (in favor of olefin binding)**
- Somewhat surprisingly, is fairly independent of phosphine nature (PCy₃ vs. PPh₃ = factor of 2)
- For comparison, relative rates of phosphine dissociation for PPh₃/PCy₃ differ by 70-fold



Observations on Ruthenacyclobutane

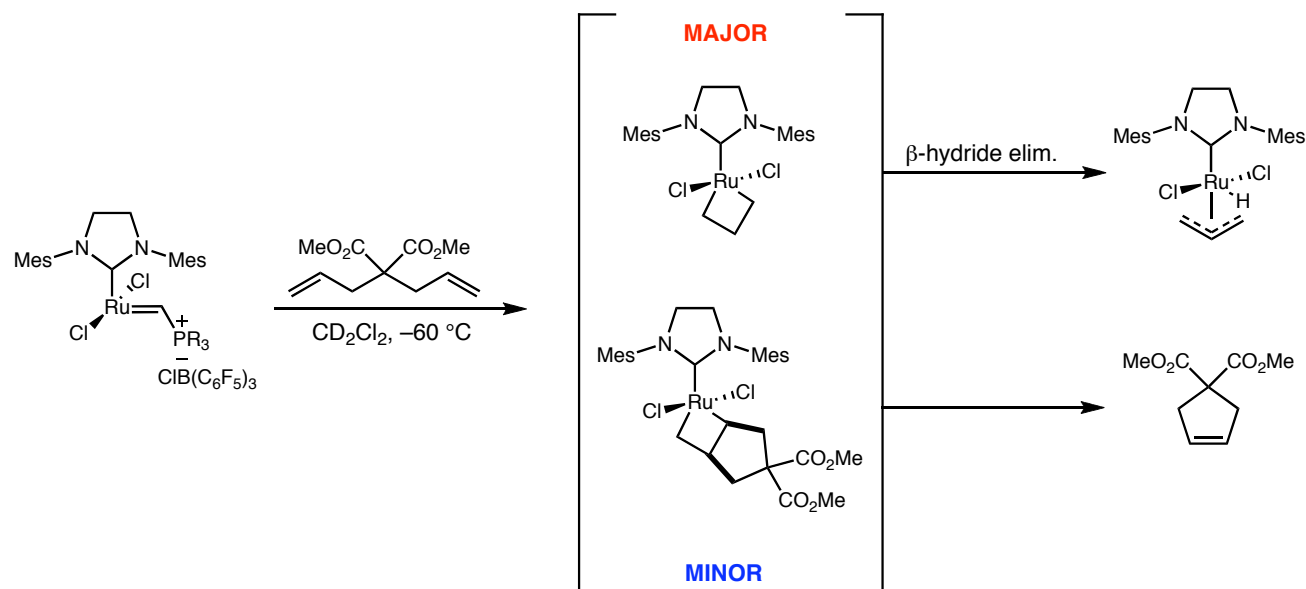
- Use of Piers' catalysts at low (-60 or -78 °C) temperature allow observation of ruthenacyclobutane
- When ethylene is not removed from solution, unsubstituted cyclobutane is dominant Ru species
- Unsubstituted metallacyclobutane is known to decompose to hydride containing species



van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* submitted
 van Rensburg, W. J. *et al. J. Am. Chem. Soc.* **2004**, *126*, 14332.

Observations on Ruthenacyclobutane

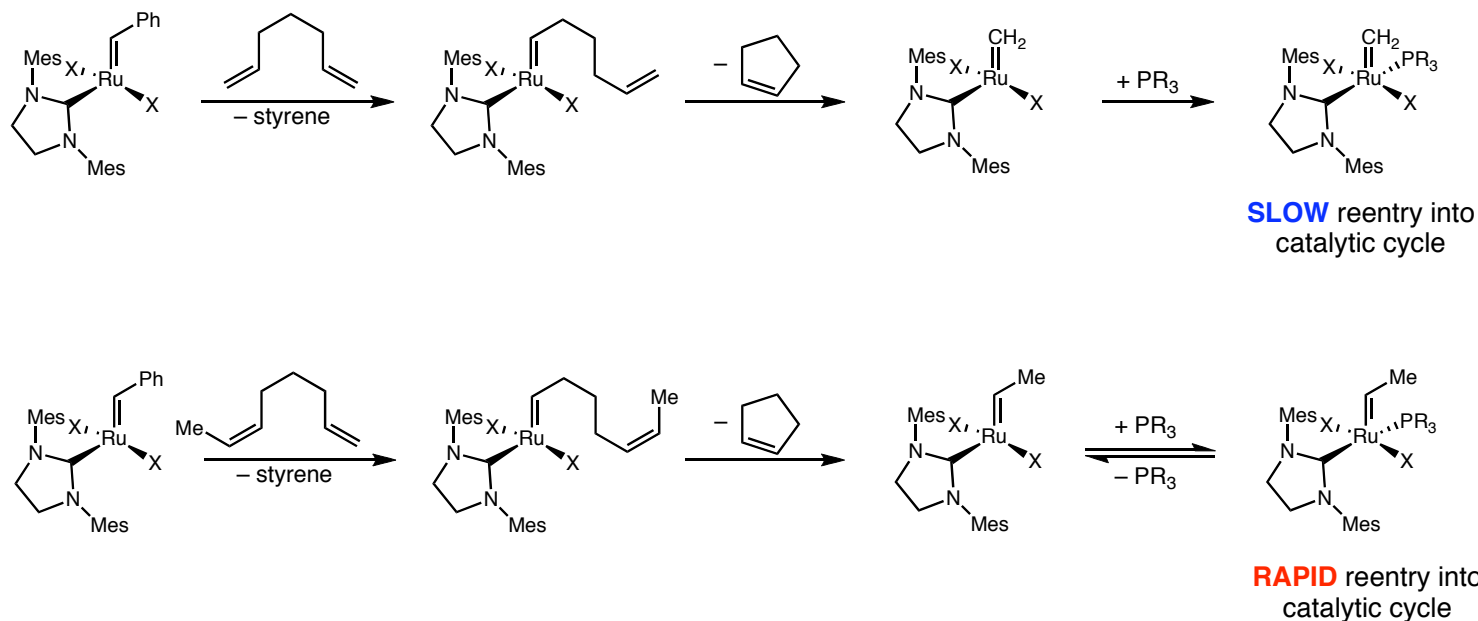
- Use of Piers' catalysts at low (-60 or -78 °C) temperature allow observation of ruthenacyclobutane
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Stage 1: Optimization of Reaction Conditions

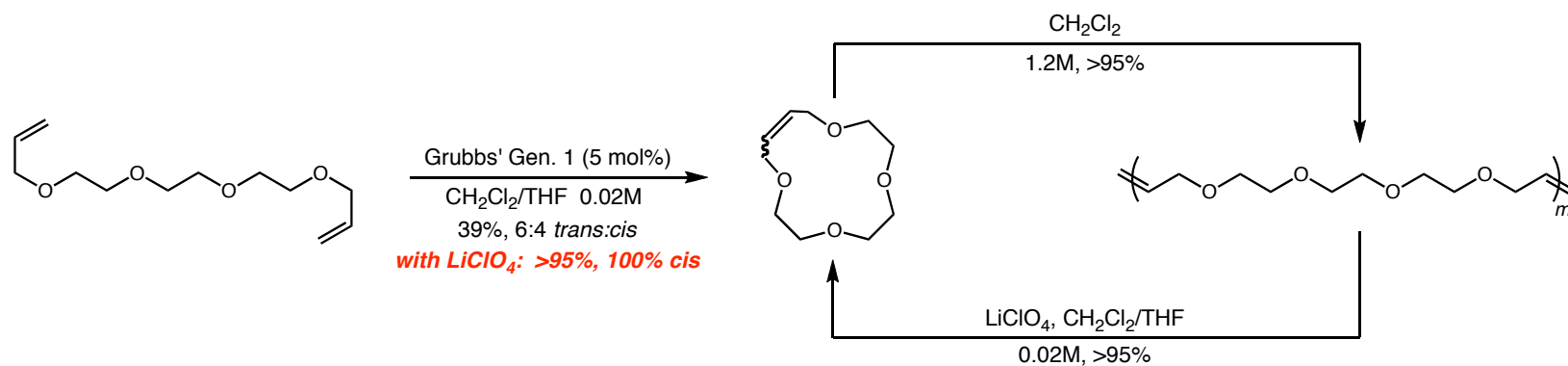
- **Combination of two terminal olefins and phosphine bearing catalyst may be problematic**



- If **both** terminal olefins cannot be avoided due to substrate synthesis, choose Hovyeda-Grubbs

Stage 1: Optimization of Reaction Conditions

- Substrate templating may offer a solution for cyclization of heteroatom rich macrocycles

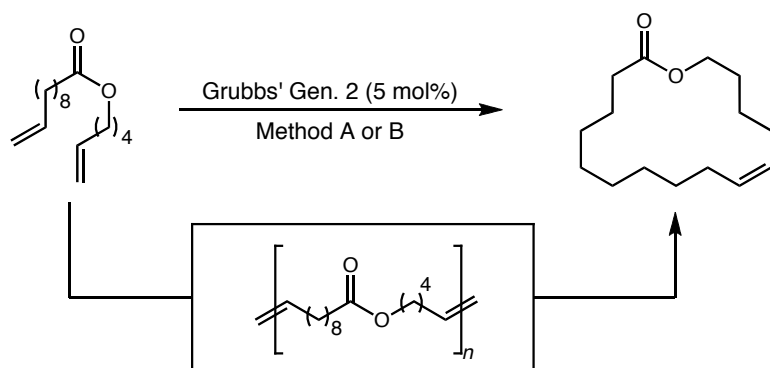


Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1101.

- Cyclodepolymerization is an especially important observation in these systems

Stage 1: Optimization of Reaction Conditions

- Oligomers have been detailed as common intermediates in RCM
- Most efficient macrocyclization strategy may involve polymerization at high concentration followed by dilution and macrocycle formation

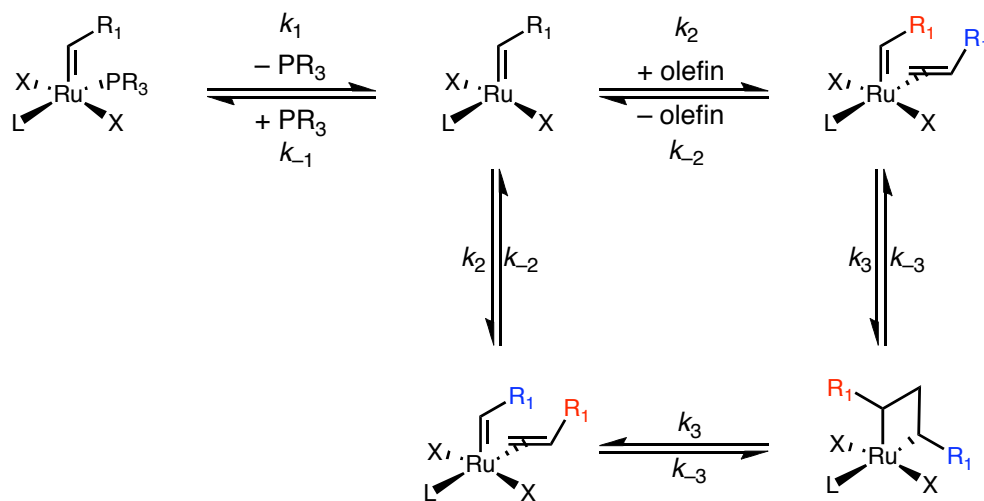


Method A: 0.005M, 9h, 99% conv.

Method B: 0.1M, then dilute to 0.005M, **1h total**, 99% conv.

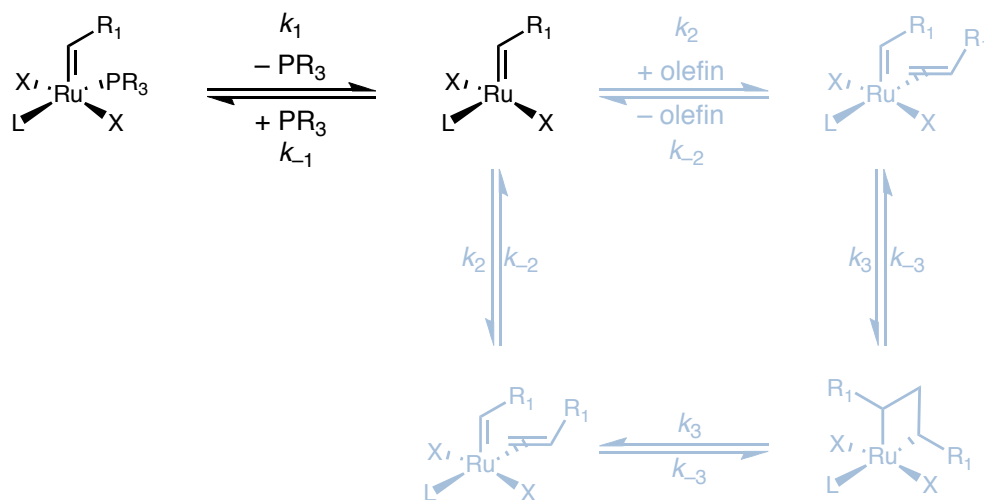
Stage 2: Selection of a Catalyst

- Even perfect substrate/reaction condition optimization may not solve every metathesis problem
- A number of easily synthesized catalysts have been recently reported, based on one of three improvements: rapid initiation, lessened steric demand or improved catalyst lifetime.
- One must identify which of these factors will yield the greatest influence on reaction outcome



Catalysts Based on Rapid Initiation

- The groups of Grubbs, Piers, Grela and Blechert have introduced rapidly initiating catalysts
- Better initiation results in a higher effective concentration of catalyst in solution



Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035.

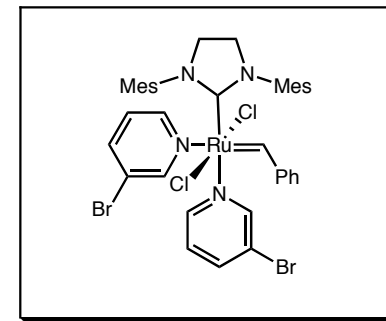
Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038.

Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403.

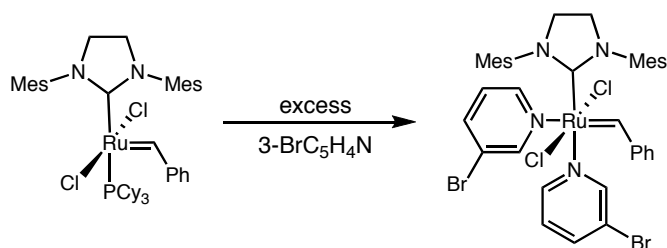
Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6161.

Grubbs' Third Generation

Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, 41, 4035.



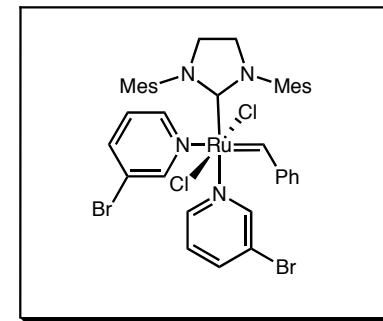
Replacement of phosphine with two 3-bromopyridine ligands yields new precatalyst



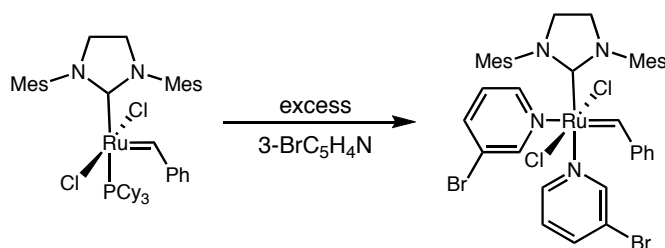
- Ease of synthesis = Exceptional

Grubbs' Third Generation

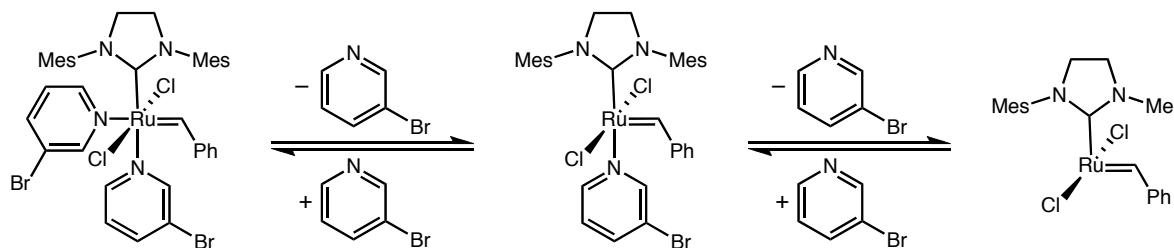
Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, 41, 4035.



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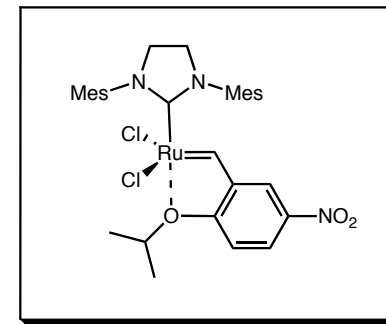
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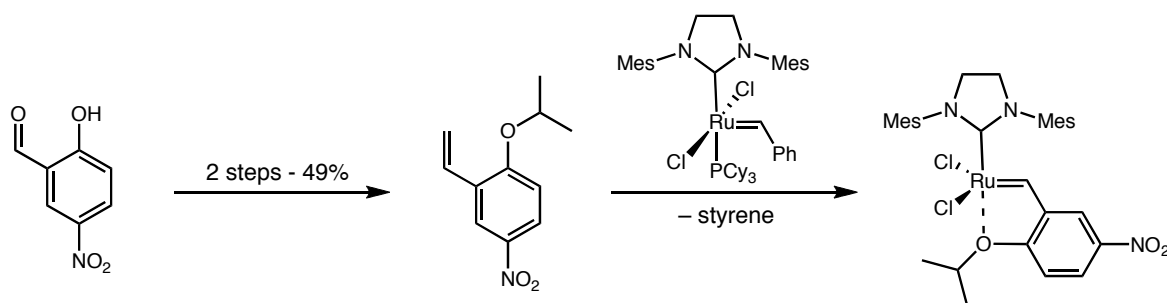
- While the precatalyst is coordinatively saturated, dissociation is rapid

Grela's Nitro-Aryl Catalyst

Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, 41, 4038.



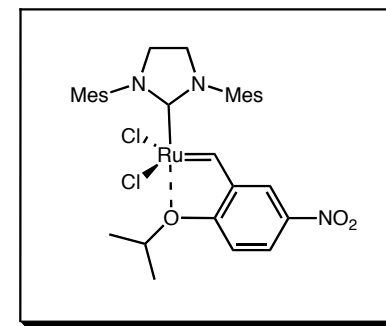
Electronic deactivation of isopropoxy-donor is key design feature



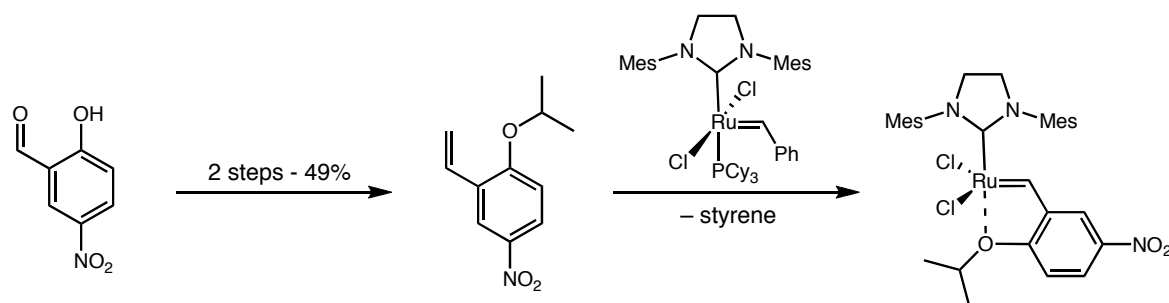
- Ease of synthesis = Very Good

Grela's Nitro-Aryl Catalyst

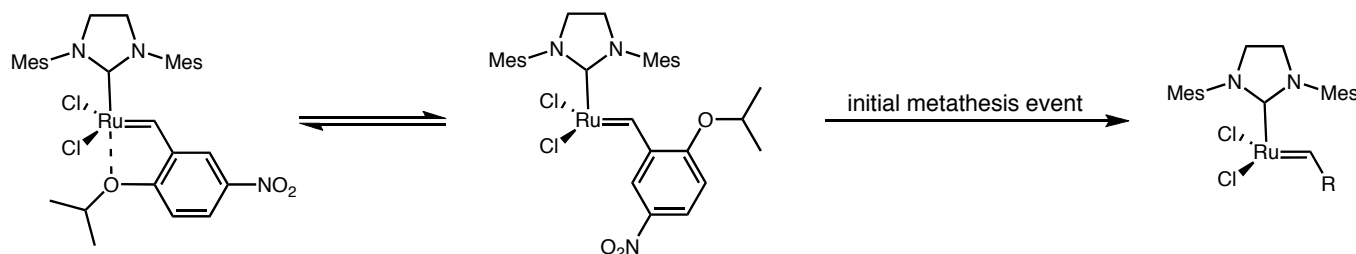
Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, 41, 4038.



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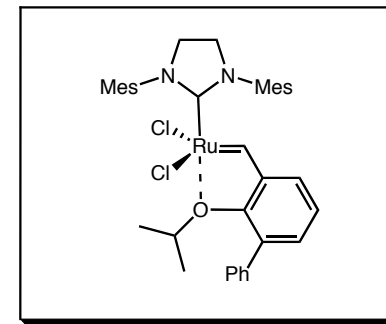
- Ease of synthesis = Very Good



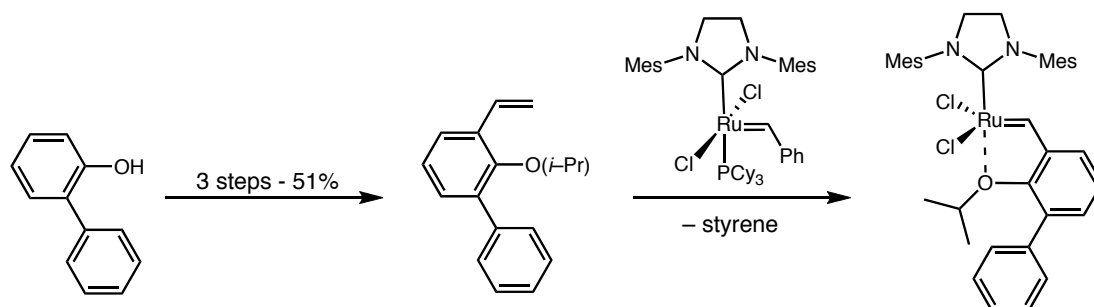
- Nitro group renders the isopropoxy donor less Lewis basic, thus more labile

Blechert's Biphenyl Catalyst

Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403.



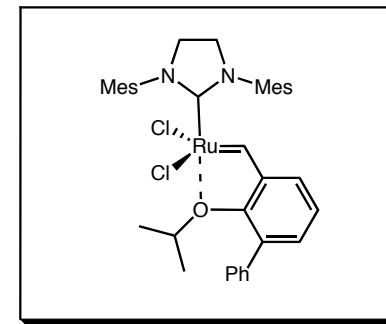
Steric interaction between *ortho* substituents disfavors chelation



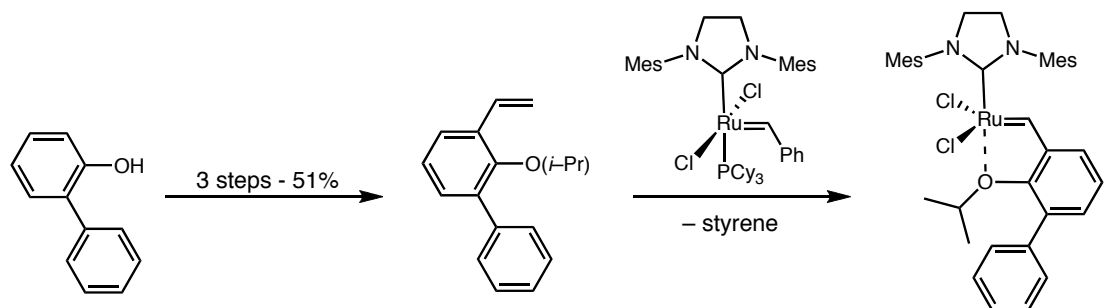
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Blechert's Biphenyl Catalyst

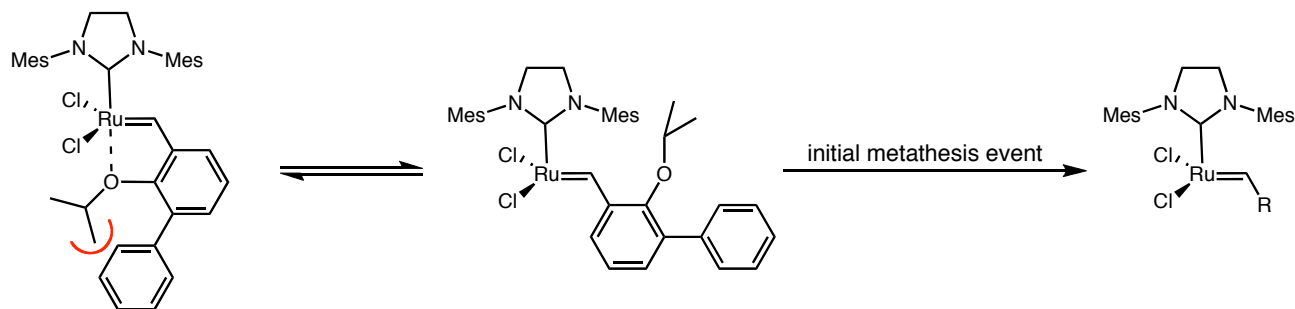
Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403.



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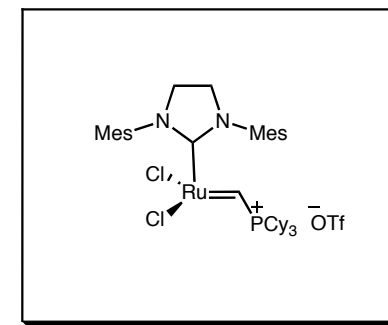
• Ease of synthesis = Very Good



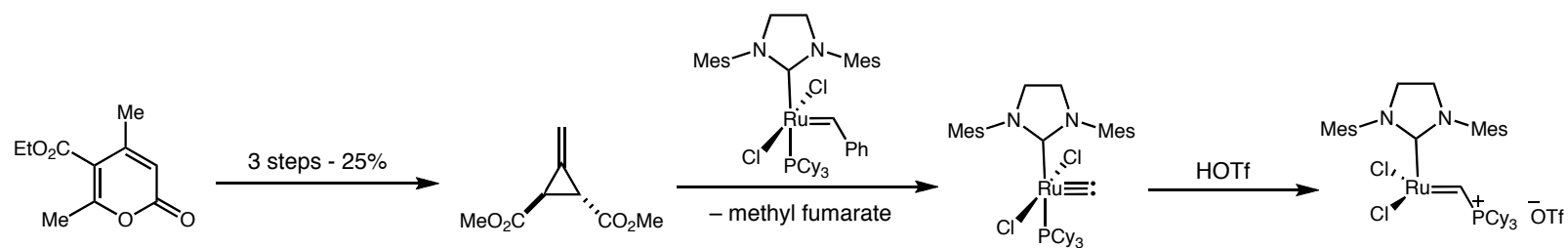
• Steric interaction in planar chelate disfavors coordination

Piers' Phosponium Catalyst

Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, 43, 6161.



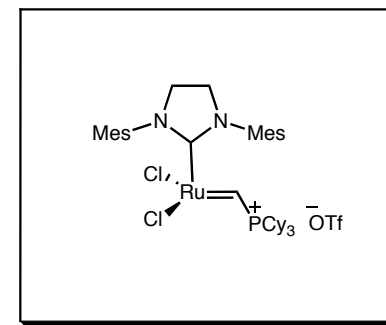
Phosphine donor is removed as vinylphosponium species



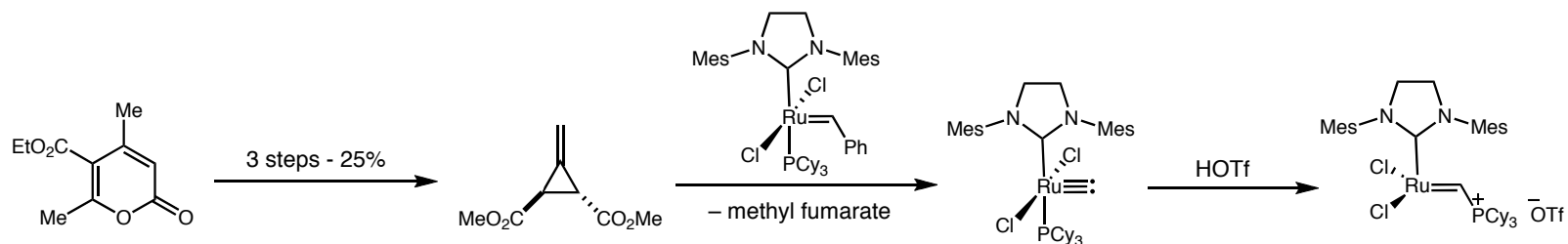
- Ease of synthesis = Good

Piers' Phosphonium Catalyst

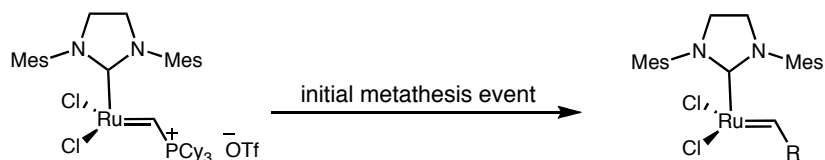
Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, 43, 6161.



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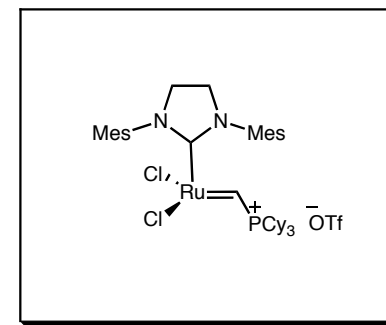
• Ease of synthesis = Good



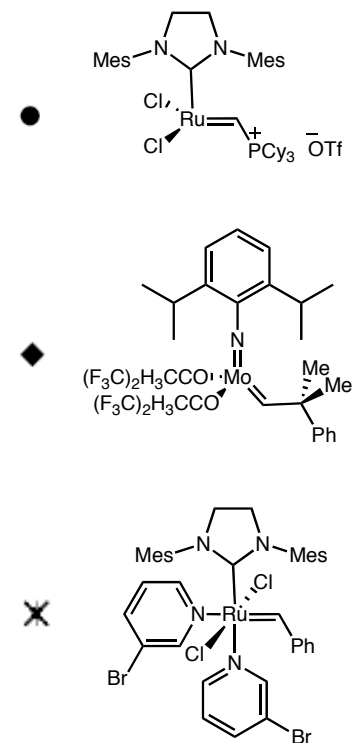
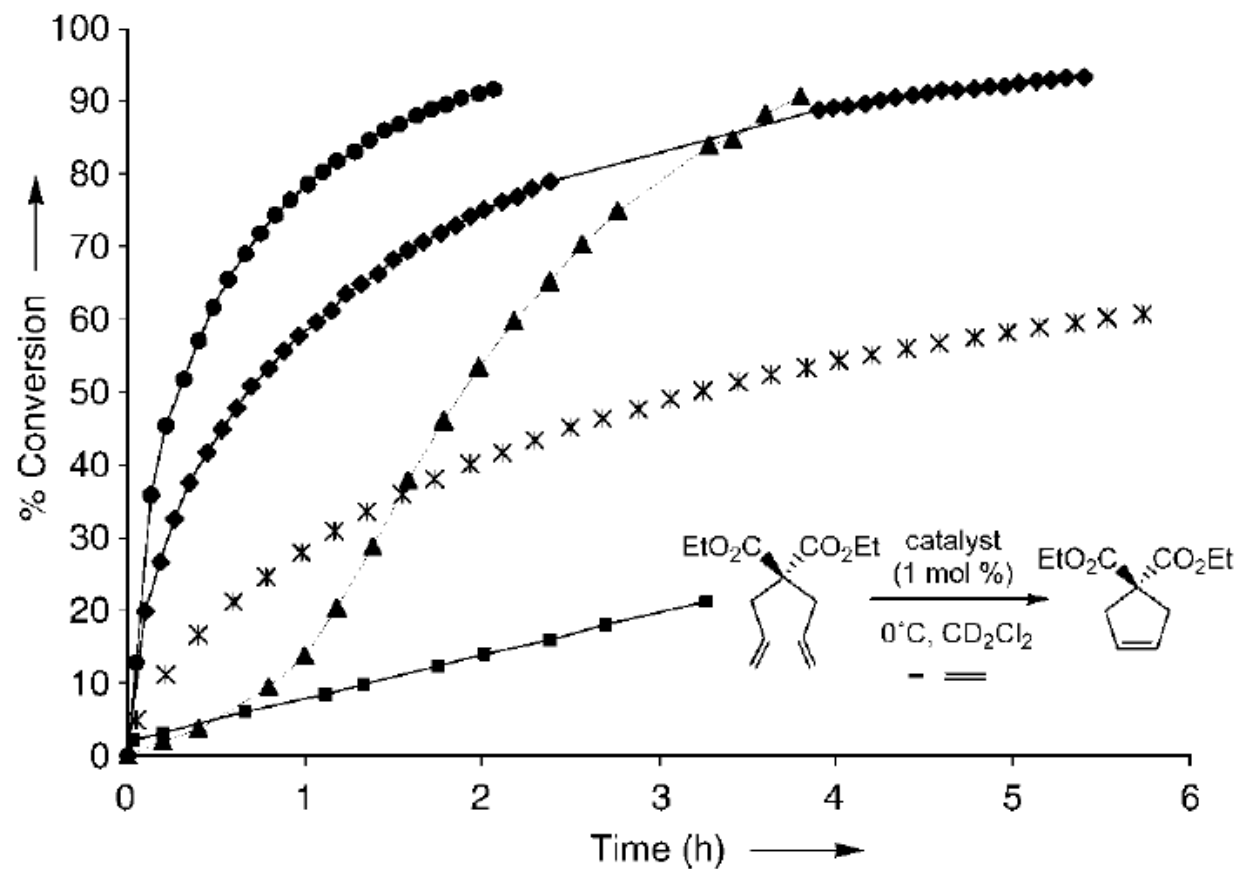
- No preequilibrium event before metathesis can begin
- Re-metathesis of vinylphosphonium salt essentially not possible

Piers' Phosphonium Catalyst

Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6161.

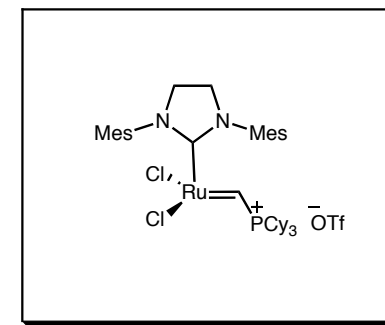


Phosphine donor is removed as vinylphosphonium species



Piers' Phosponium Catalyst

Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, 43, 6161.

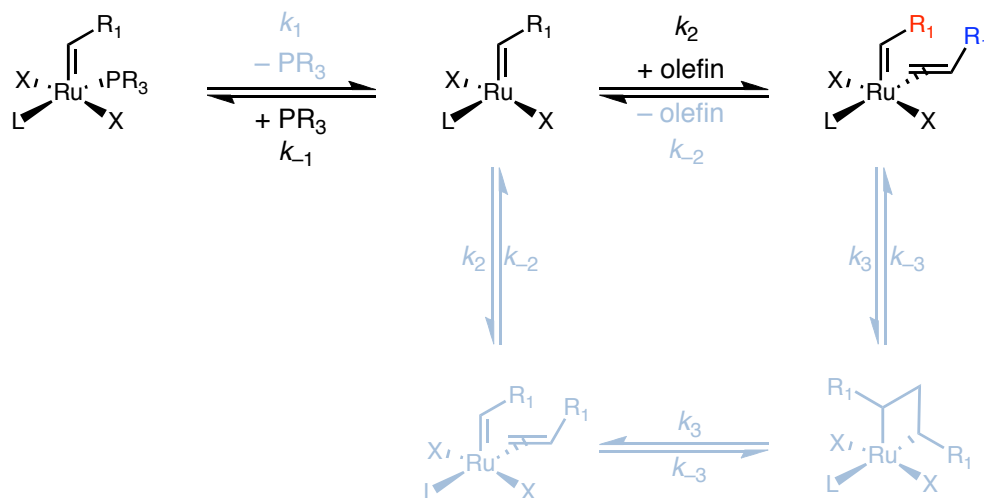


Phosphine donor is removed as vinylphosponium species

Substrate	Product	R	Catalyst Loading	time (min)	Conversion (%)
		H	1.0 mol%	<2	100
		H	0.1 mol%	30	100
		Me	1.0 mol%	<10	100
		H	1.0 mol%	<10	100
		Me	1.0 mol%	60	98
		–	5.0 mol%	<10	85

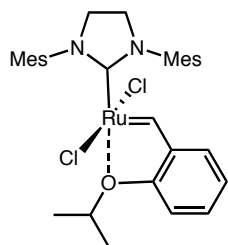
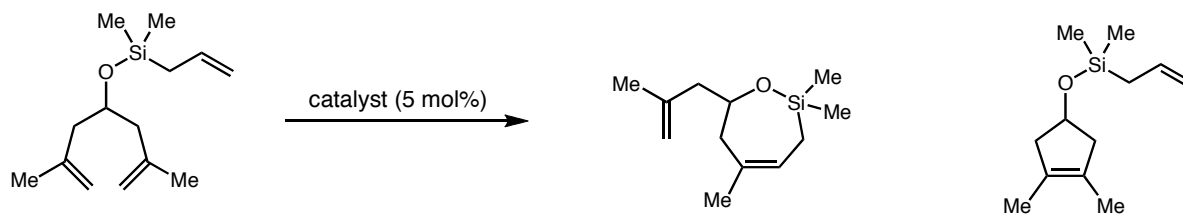
Catalysts Based on Improved Olefin Binding

- Replacement of PR_3 by a carbene donor markedly improved selectivity for olefin binding
- Could further alteration of the NHC donor provide further improvement?

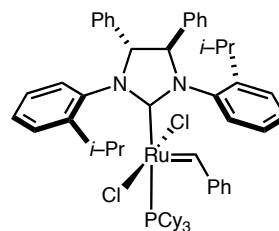


Grubbs' Serendipitous Observations

- While attempting to develop an asymmetric catalyst, production of highly substituted olefins is observed



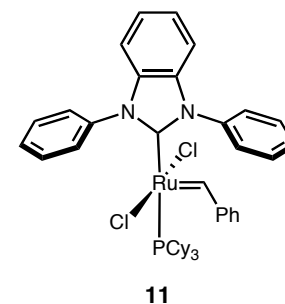
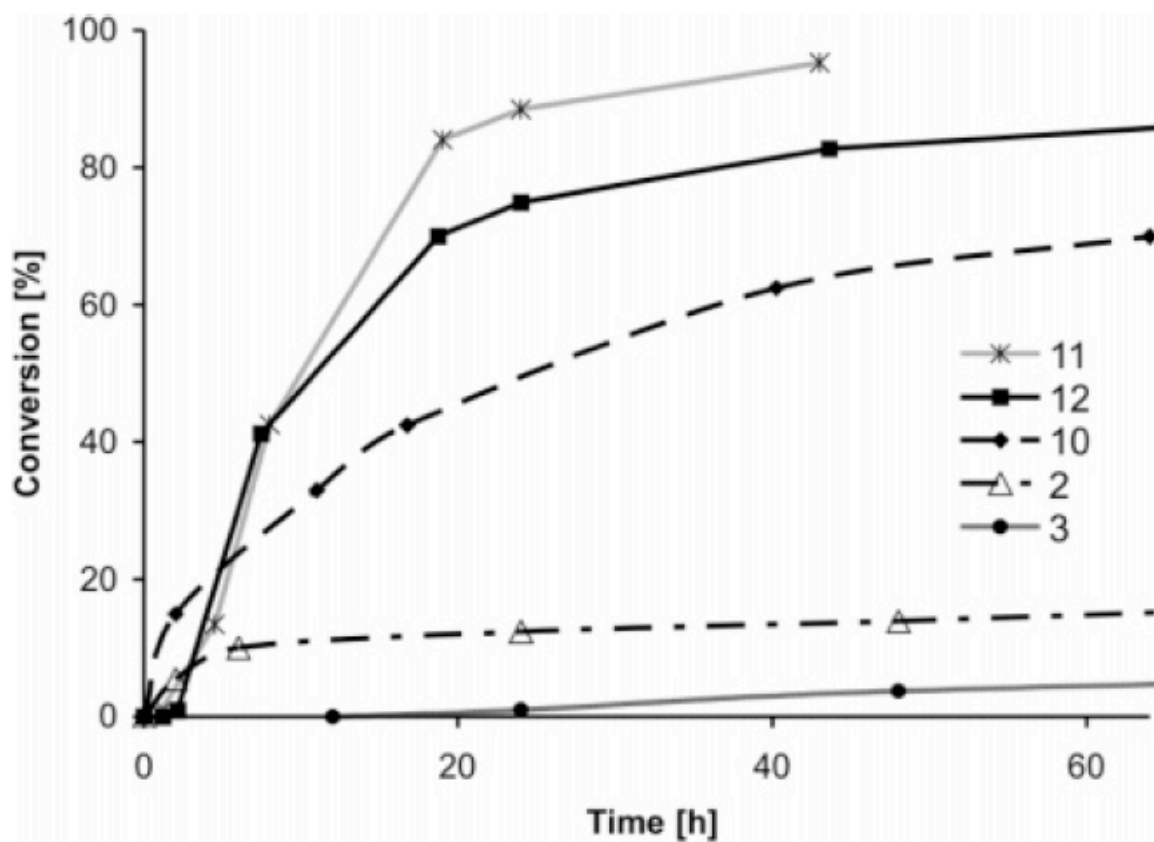
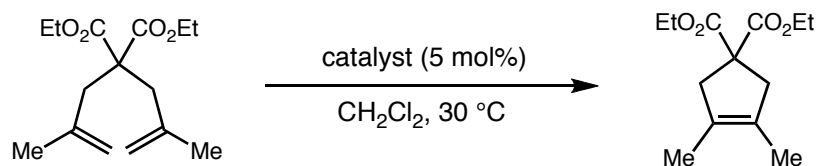
> 95% trisubstituted olefin



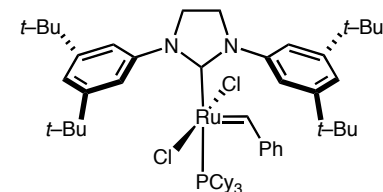
70% trisubstituted olefin

30% tetrasubstituted olefin

NHC-Ligand Optimization



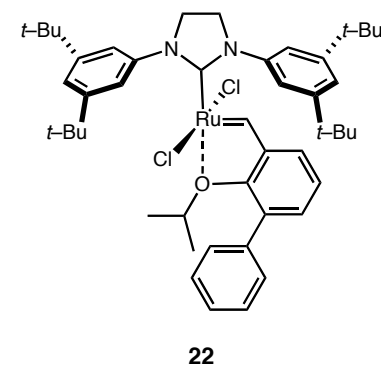
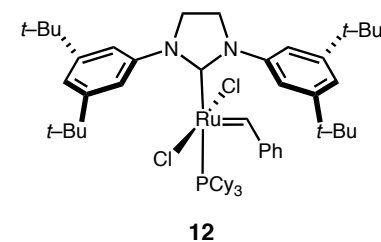
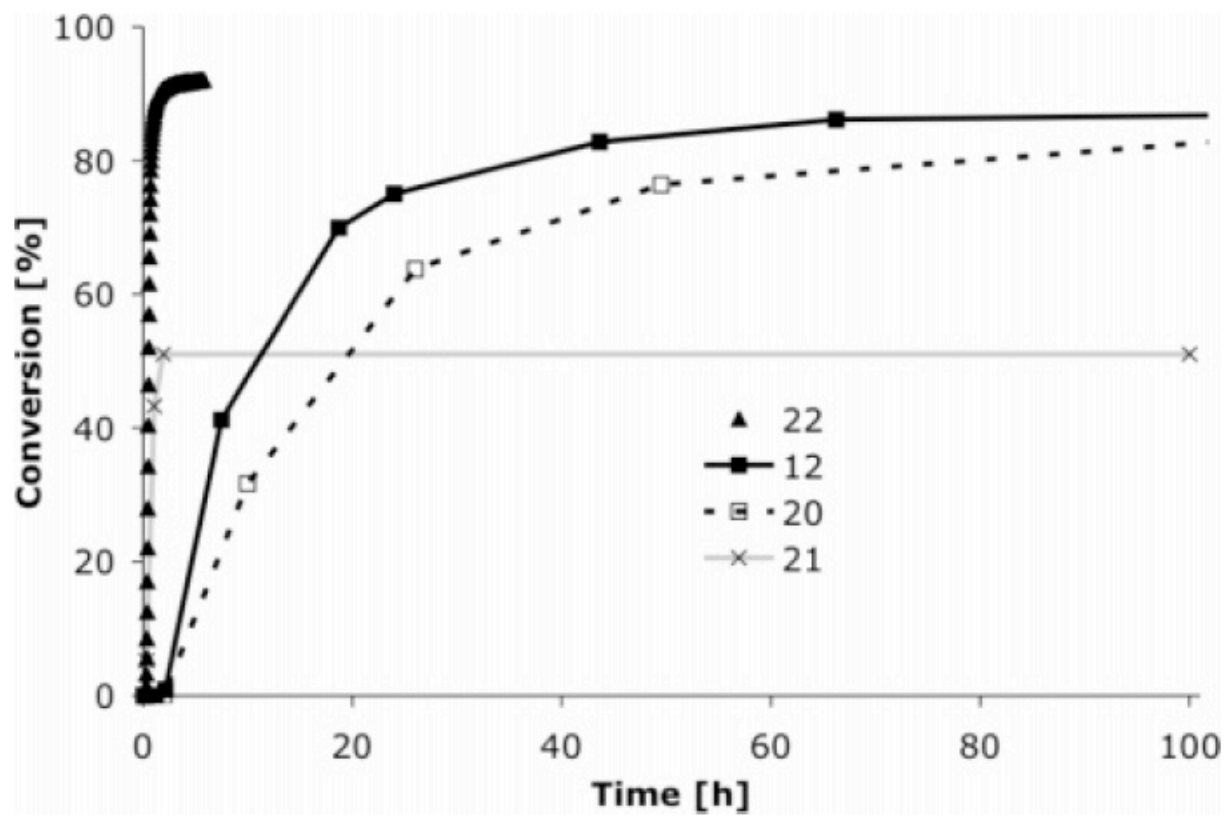
11



12

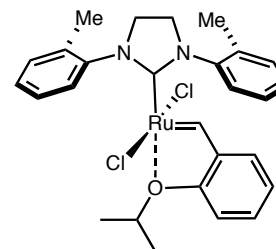
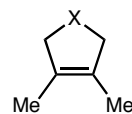
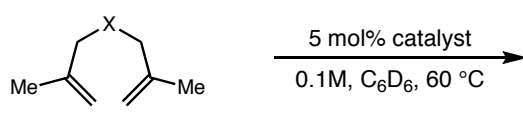
NHC-Ligand Optimization

- Applying the Blechert modification produces a highly active catalyst for the formation of tetrasubstituted olefins



NHC-Ligand Optimization

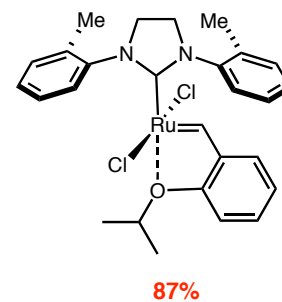
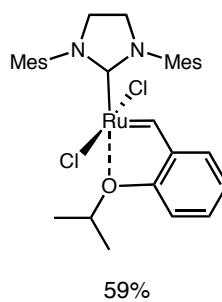
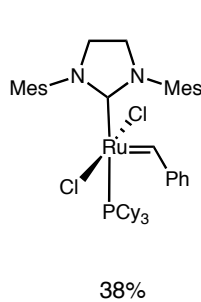
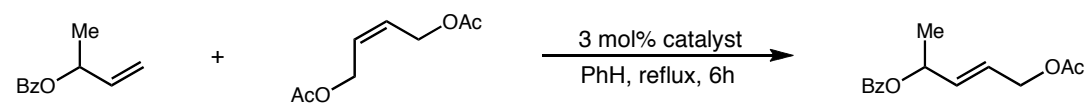
- Most recently reported modification involves the tolyl-substituted NHC ligand



Substrate	Product	Yield	Substrate	Product	Yield
		>95%			>95%
		>95%			>95%
		87%			88%

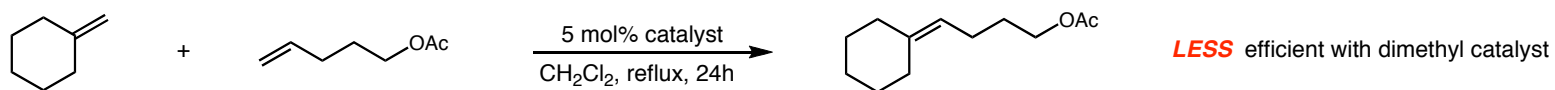
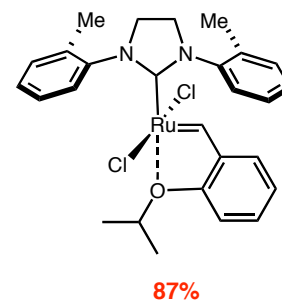
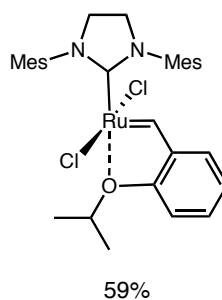
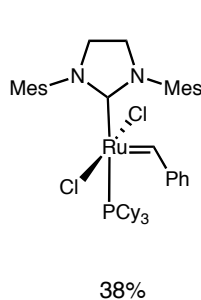
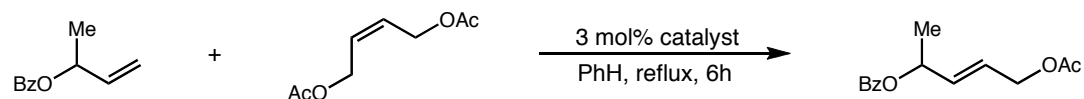
Hindered Cross-Metathesis Reactions

- Further ligand optimization has allowed for difficult cross-metathesis reactions to be successfully performed



Hindered Cross-Metathesis Reactions

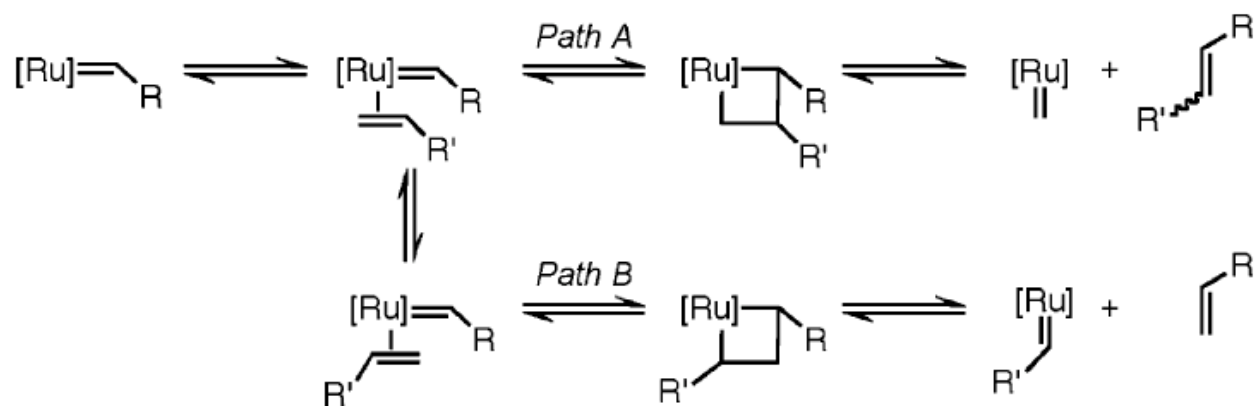
- Further ligand optimization has allowed for difficult cross-metathesis reactions to be successfully performed



- Why does the less bulky catalyst show lower reactivity when forming a trisubstituted olefin

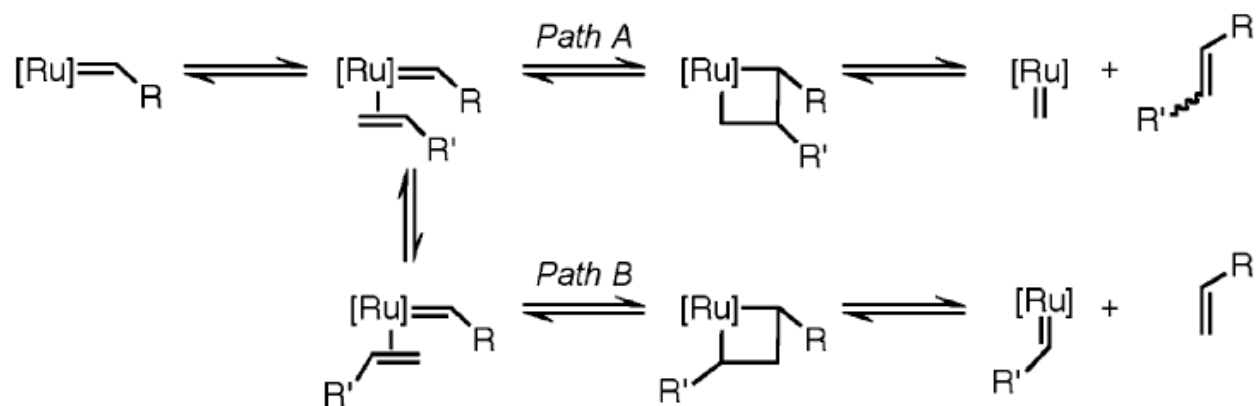
Hindered Cross-Metathesis Reactions

- The less sterically demanding catalyst may be performing rapid, but non-productive metathesis reactions

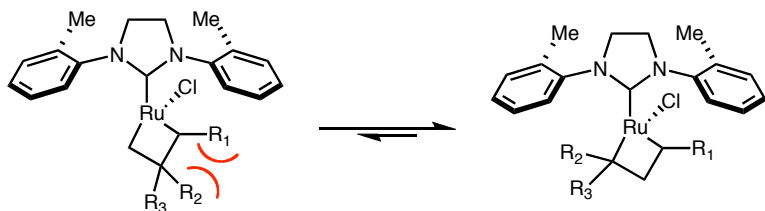


Hindered Cross-Metathesis Reactions

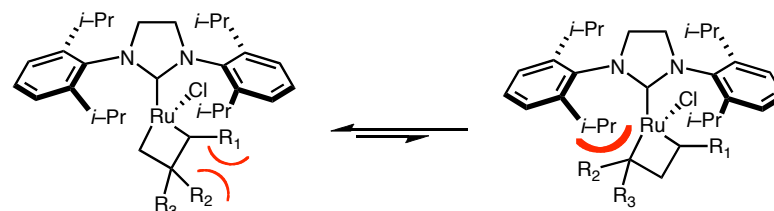
- The less sterically demanding catalyst may be performing rapid, but non-productive metathesis reactions



- Could *increasing* the steric demand of the NHC ligand force desired olefin termini into contact?



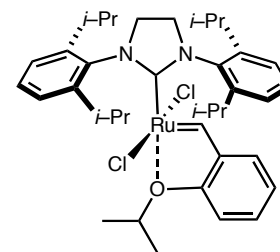
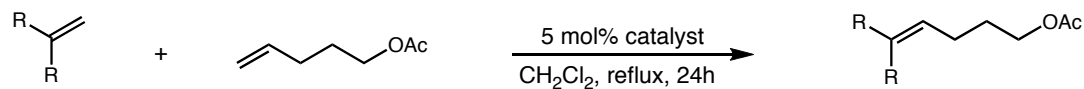
Steric interaction between substituted carbon atoms dominates



Steric interaction with *ortho* ligand substituents dominates

Hindered Cross-Metathesis Reactions

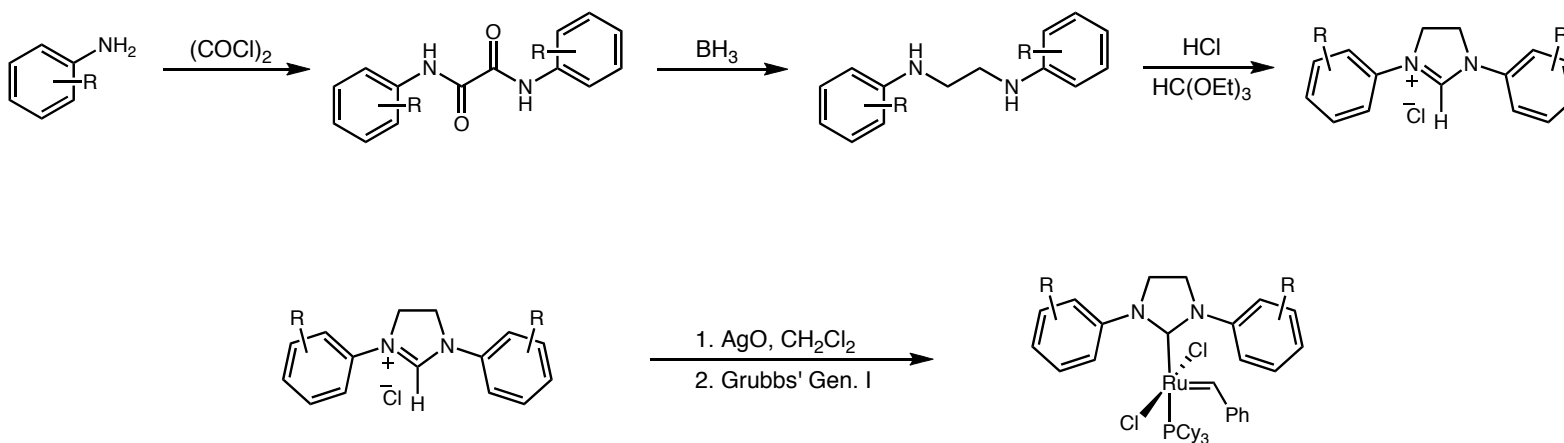
- The application of a carbene ligand with bulky groups in the *ortho* aryl positions results in efficient formation of trisubstituted olefins, but with some limitations.



Substrate	Product	Yield
		98%
		96%
		7%

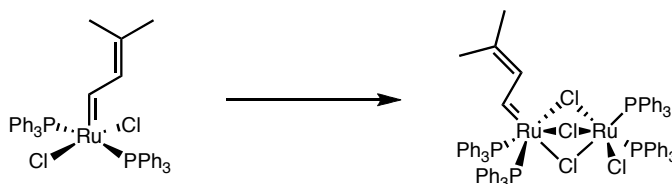
General NHC Synthetic Scheme

- Three step synthesis transforms aniline into corresponding NHC
- Silver is typically used as a carbene transfer agent

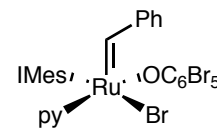
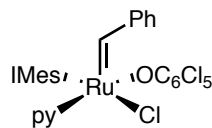
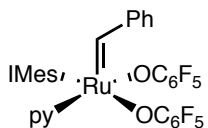


Other Catalyst Decomposition Pathways

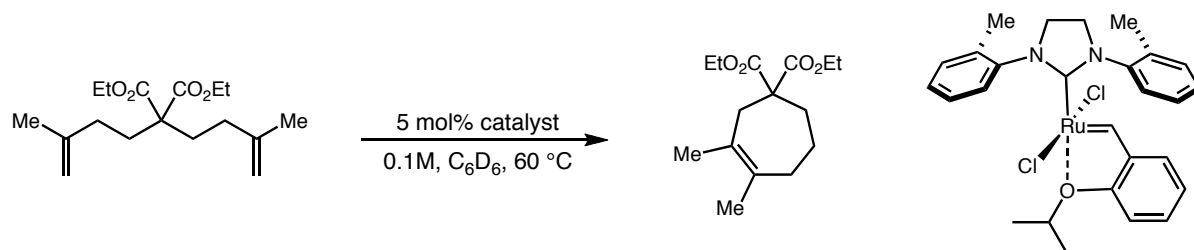
- An increase in catalyst lifetime will positively influence any metathesis reaction
- Fogg group observes formation of triply chloride-bridged ruthenium species as a deactivation pathway



- Substitution with pseudo-halide ligands yields efficient catalysts
- Currently, however, the syntheses of these catalysts is prohibitive

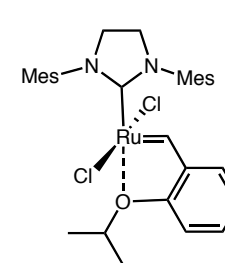
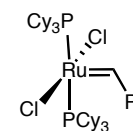
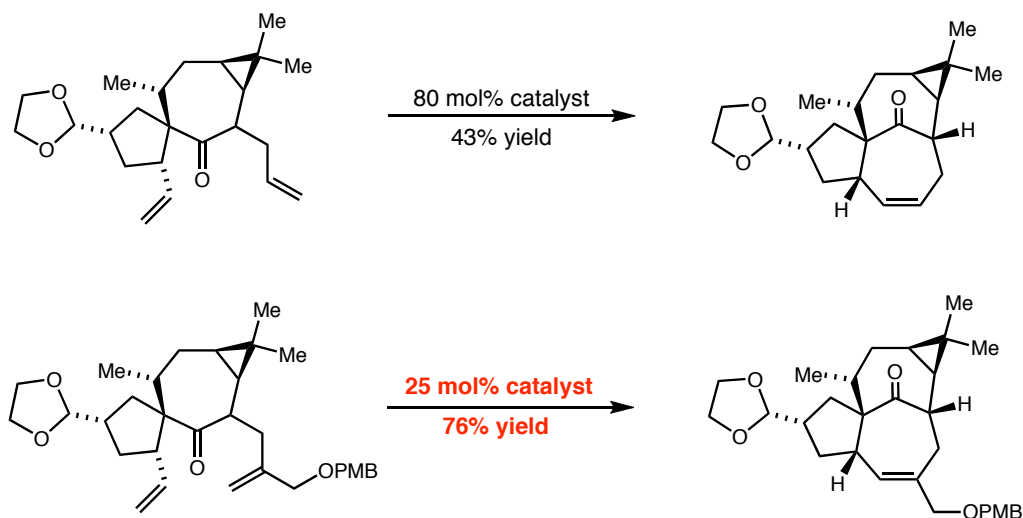


Real World Examples (A Positive Sense)



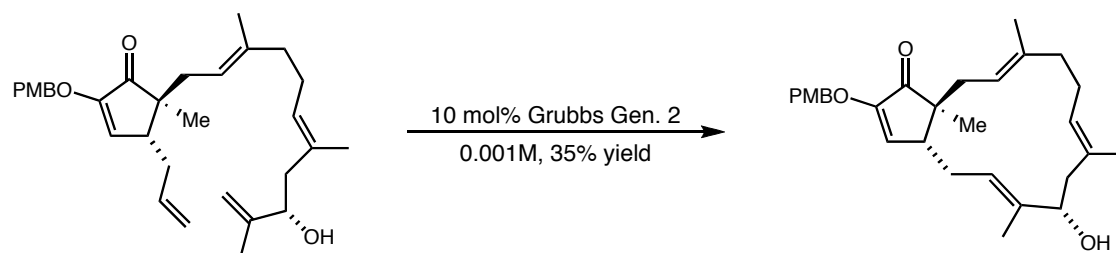
Sealed tube: 62%
Open vessel (remove C₂H₄): **87%**

Stewart, I. C. *et al J. Am. Chem. Soc.* **2007**, *9*, 1589.



Wood, J. L. *et al J. Am. Chem. Soc.* **2004**, *126*, 16300.

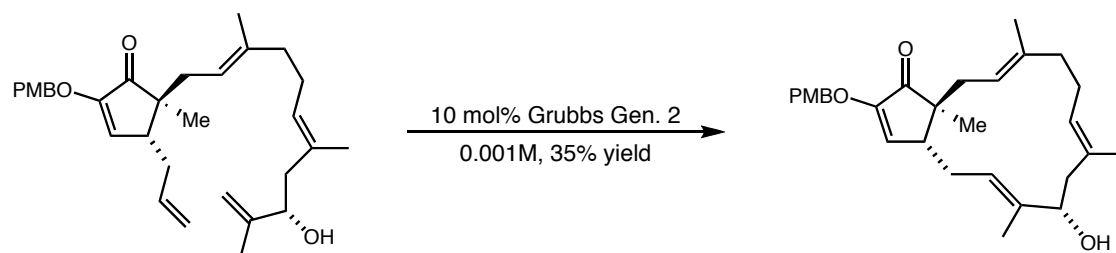
An Example with Room for Improvement



Trost, B. M.; Guangbin, G.; Vance, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4540.

- What three modifications would you make to this procedure as an attempt to improve yield?

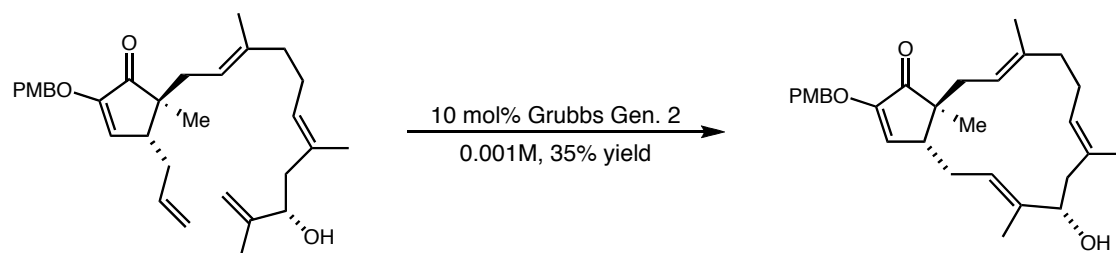
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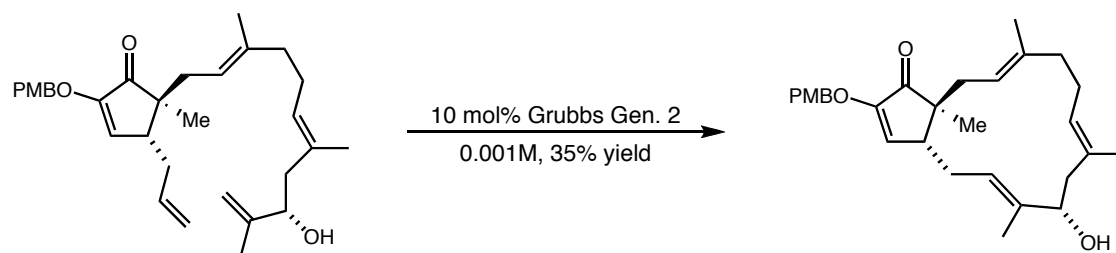
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An Example with Room for Improvement

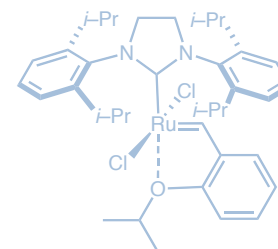
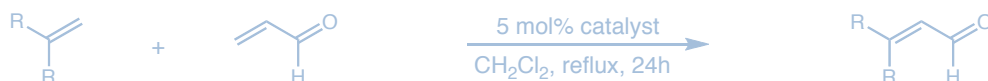


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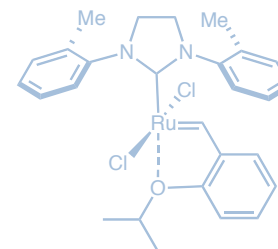
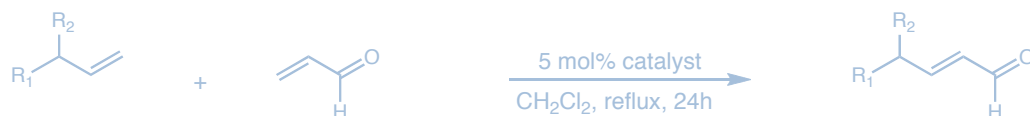
- What three modifications would you make to this procedure as an attempt to improve yield?
- First, run the reaction briefly at high concentration, followed by dilution to 0.001M
- Next, try a phosphine-free commercial catalyst (i.e., Hoyveda-Grubbs) at these conditions
- Finally, if the reaction only slowly yields product, look to a more active catalyst (Blechert, Piers)

Applications in the MacMillan Laboratory

- Formation of tetrasubstituted olefins is a significant extension for natural product synthesis
- Cross metathesis to form trisubstituted unsaturated aldehydes for Hantzsch reduction may benefit from use of diisopropyl substituted catalyst



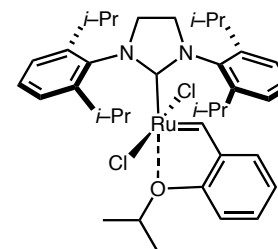
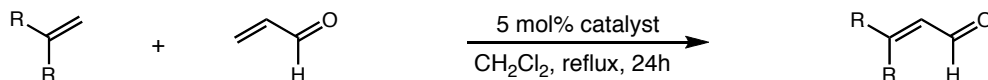
- Formation of complicated disubstituted unsaturated aldehydes may also benefit from the use of an altered NHC catalyst



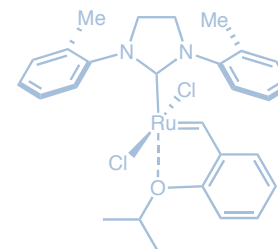
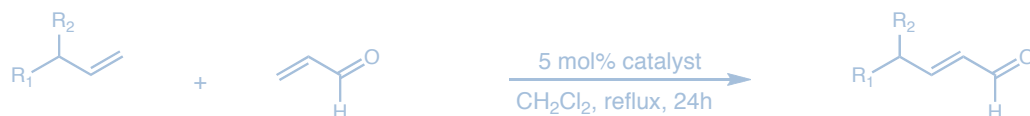
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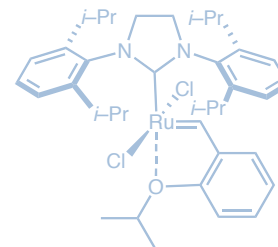
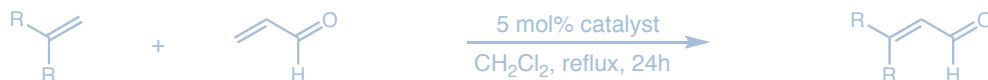
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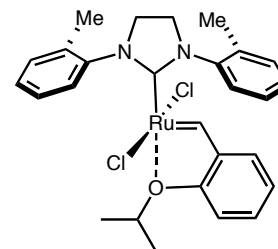
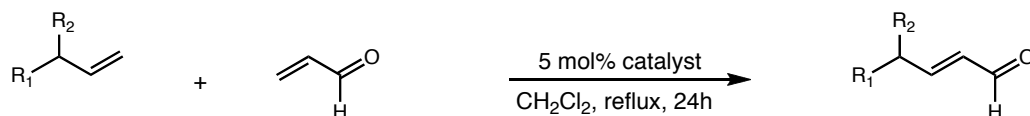
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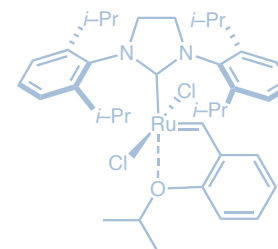
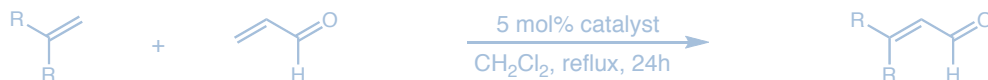
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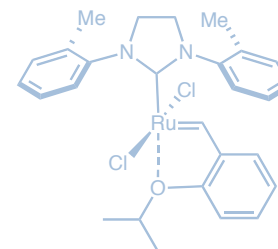
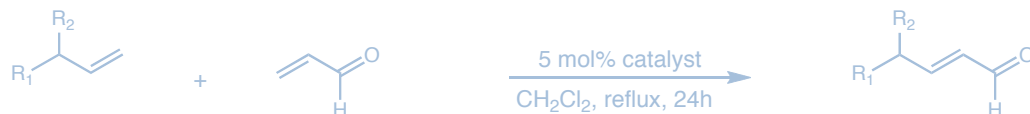
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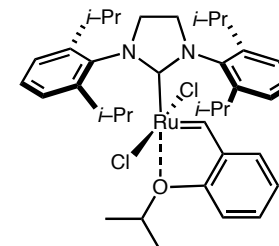
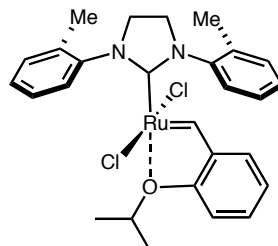
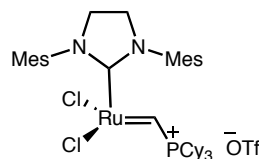
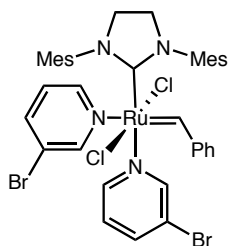
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Metathesize Smarter, not Harder

- Slight changes to substrate structure and reaction conditions may yield significant gains
- Many recently reported catalysts are easily synthesized
- Careful consideration of each specific metathesis challenge can guide investigations



Don't be afraid to use cutting edge metathesis technology