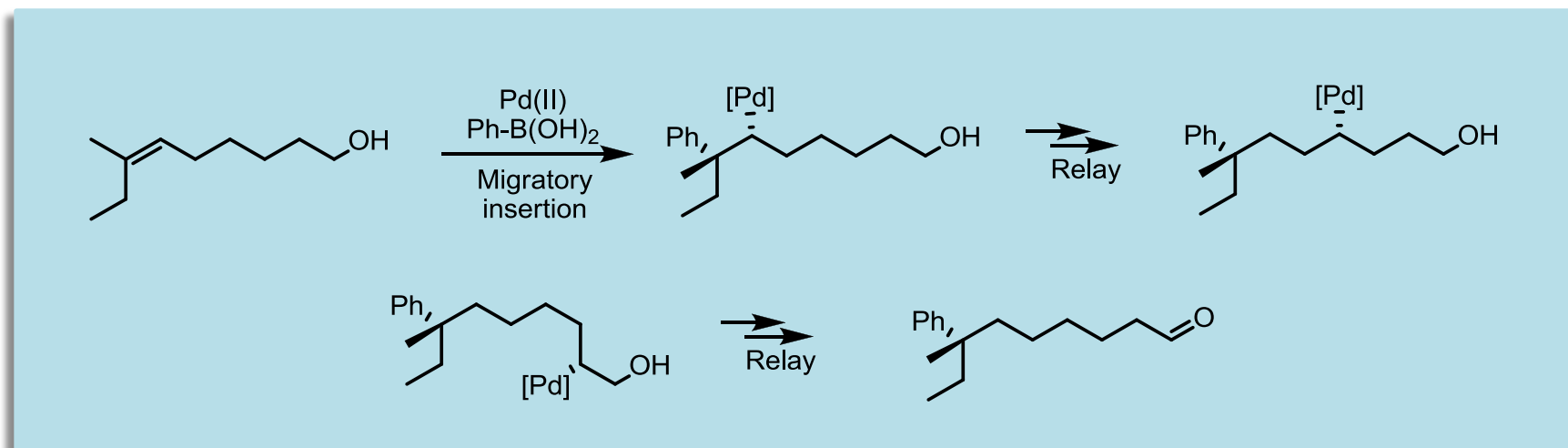


# Redox-Relay Heck Arylations of Acyclic Alkenyl Alcohols

## History and Recent Developments



Qinghe Liu  
Hu Group Meeting  
June 3<sup>rd</sup> 2014

# Contents

## ■ Part 1: history



F. G. A. Stone  
University of Bristol  
University of Baylor



R. F. Heck (Nobel 2010)  
University of Delaware



R. C. Larock  
Iowa State University

## ■ Part 2: recent developments



M. S. Sigman  
Utah University

## ■ Part 3: conclusion

For very useful papers see:

Mei, T.; Sigman, M. S. *Nature* **2014**, 508, 340.

Werner, E. W.; Mei, T.; Burckle, A. J.; Sigman, M. S.  
*Science* **2012**, 338, 1455.

# Contents

## ■ Part 1: history



F. G. A. Stone  
University of Bristol  
University of Baylor



R. F. Heck (Nobel 2010)  
University of Delaware



R. C. Larock  
Iowa State University

## ■ Part 2: recent developments



M. S. Sigman  
Utah University

## ■ Part 3: conclusion

For very useful papers see:

Mei, T.; Sigman, M. S. *Nature* **2014**, 508, 340.

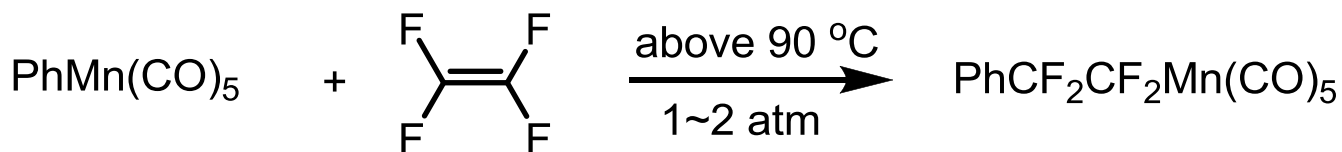
Werner, E. W.; Mei, T.; Burckle, A. J.; Sigman, M. S.  
*Science* **2012**, 338, 1455.

## Early developments

### Addition of Transition Metal Alkyls to Olefins



- 1963: First report of the addition of pentacarbonylphenylmanganese to tetrafluoroethylene without the formation of polymers by F. G. A. Stone.



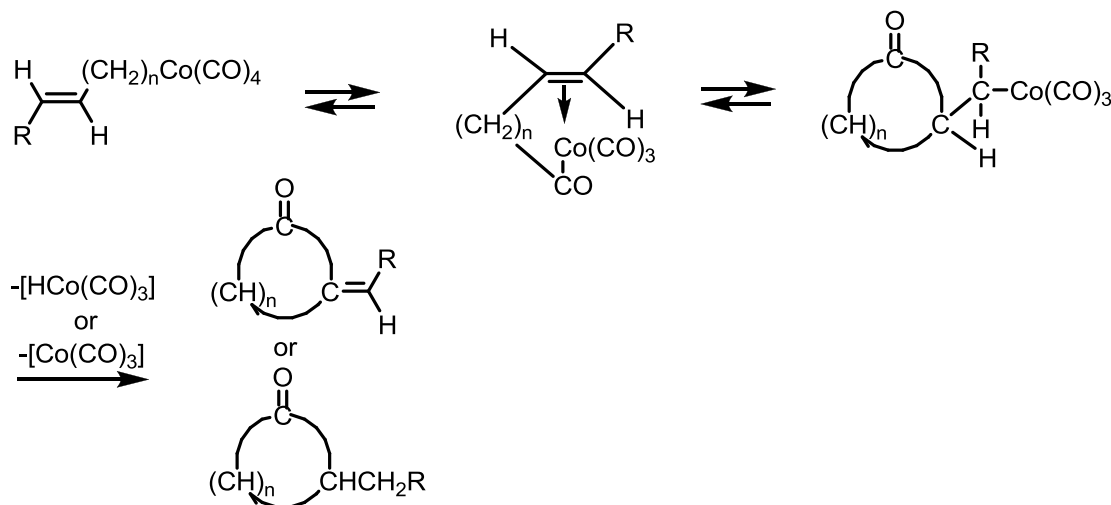
- Two mechanisms may operate in the reactions of these carbonyls with chlorotrifluoroethylene—a free-radical and a four-centre mechanism.

# Early developments

## Addition of Transition Metal Alkyls to Olefins



- 1963: First report of the addition of transition metal alkyls to olefins without the formation of polymers by R. F. Heck.

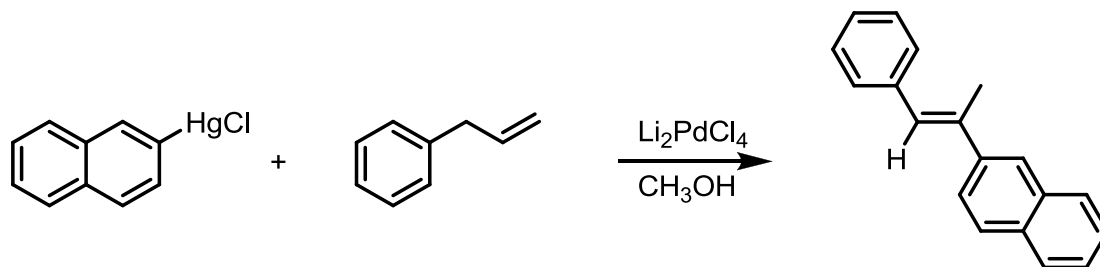


- The most important result is the conclusion that the acylcobalt group can be added across a carbon-carbon double bond.

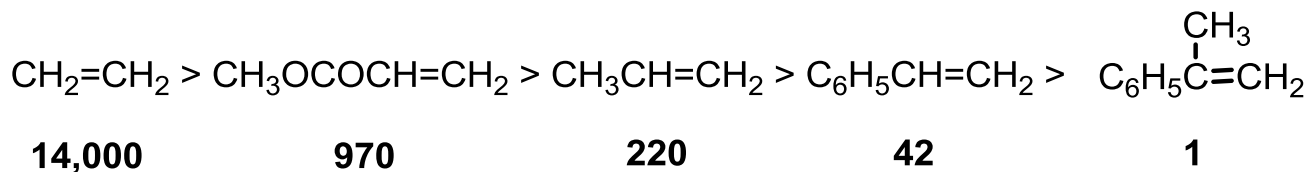
# Early developments

## Arylation of Olefins by Palladium

- 1967: Heck first reported that aryl palladium species react with olefins to produce aryl-substituted olefins, and reduced palladium.



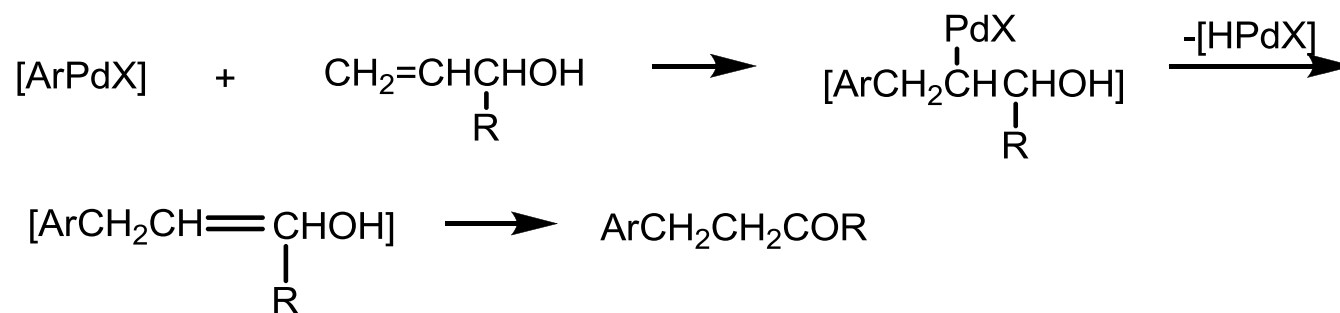
- The olefin arylation reaction is a true organometallic reaction and not a radical or ionic reaction.



# Early developments

## *Arylation of Allylic Alcohols by Palladium*

- 1968: Heck first reported that aryl palladium species react with allylic alcohols to produce aryl-substituted aldehydes and ketones.

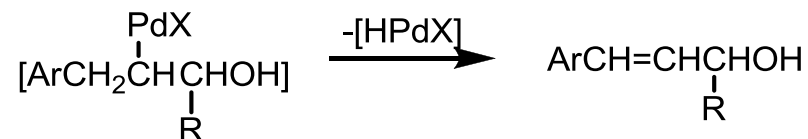


- On the basis of this mechanism, several additional products might be expected.

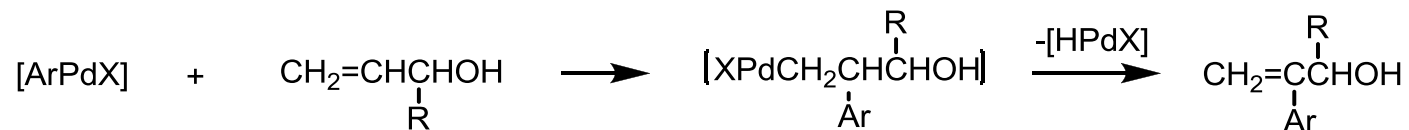
# Early developments

## Arylation of Allylic Alcohols by Palladium

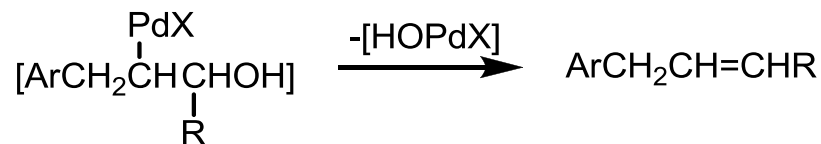
### cinnamyl-type alcohols



### 2-ary-2propen-1-ol derivative



### allylaromatic compound



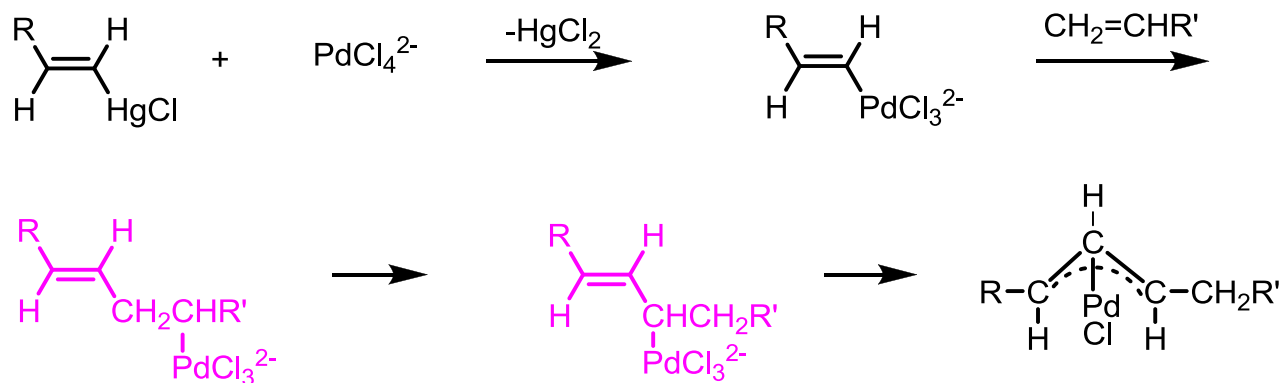


# Early developments

## Palladium Hydride Rearrangement



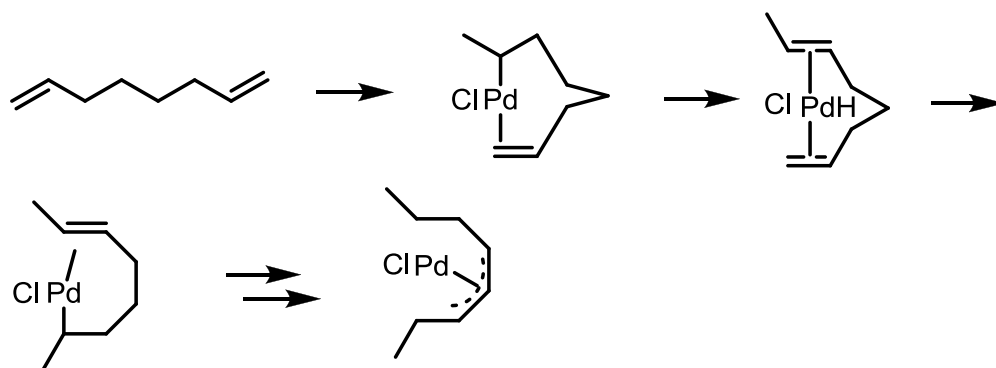
- 1976: first report of palladium hydride rearrangement in the process of  $\pi$ -allylpalladium compound formation by R. C. Larock.



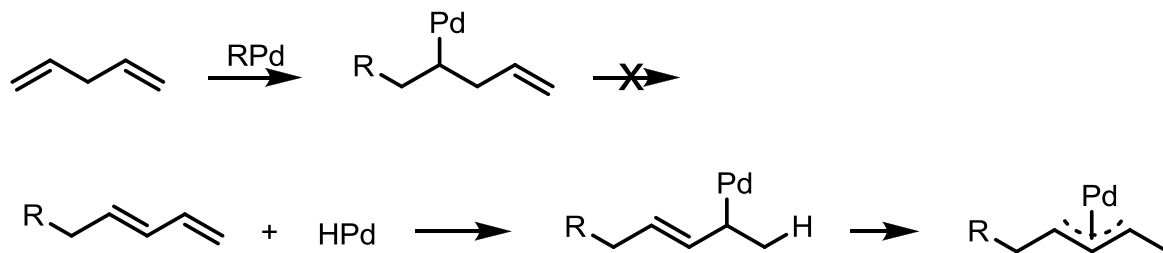
# Early developments

## Remote Migration of Dienes

■ 1983: Larock *et al* demonstrated that organopalladium react with 1,7-dienes to yield  $\pi$ -allylpalladium compounds by remote palladium migration.



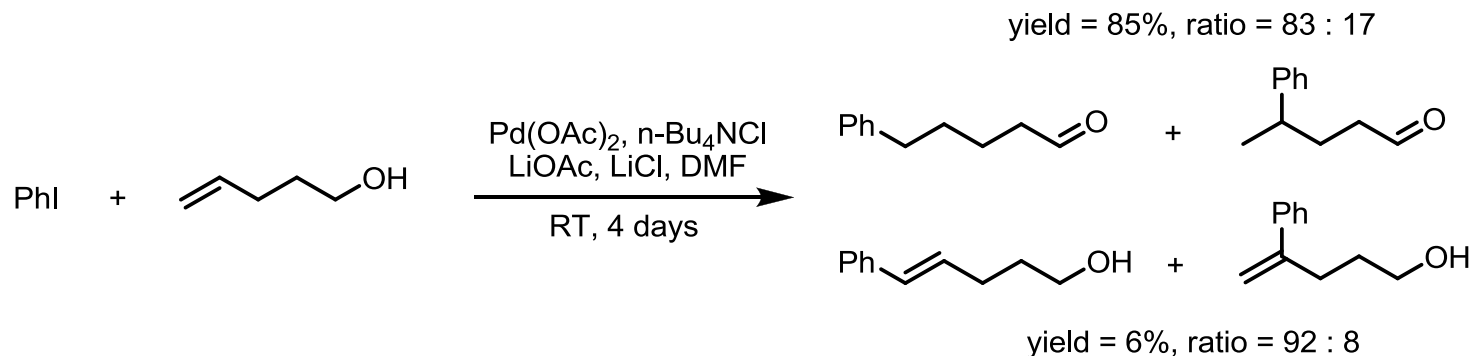
■ The intermediate palladium hydride remains strongly coordinated throughout the reaction to the molecule to which addition originally occurred.



# Early developments

## Redox-relay of Alkenyl Alcohols

■ 1989: Larock *et al* demonstrated that iodobenzene and non-allylic unsaturated alcohols might afford long chain aldehydes or ketones.



- The longer the carbon chain the slower the reaction.
- Need high temperature when separated by more than three carbon.
- The yields increase as one reduces the number of equivalents from 5 to 1.

■ Despite these advances, the field remained relatively inactive for 23 years until a breakthrough discovered by the group of Sigman.

# Contents

## ■ Part 1: history



F. G. A. Stone  
University of Bristol  
University of Baylor



R. F. Heck (Nobel 2010)  
University of Delaware



R. C. Larock  
Iowa State University

## ■ Part 2: recent developments



M. S. Sigman  
Utah University

## ■ Part 3: conclusion

For very useful papers see:

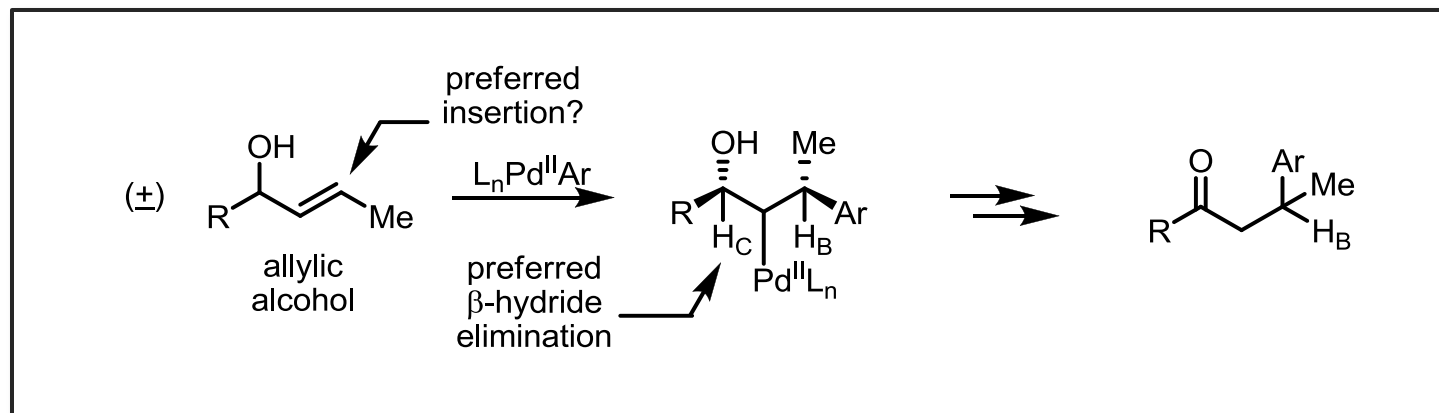
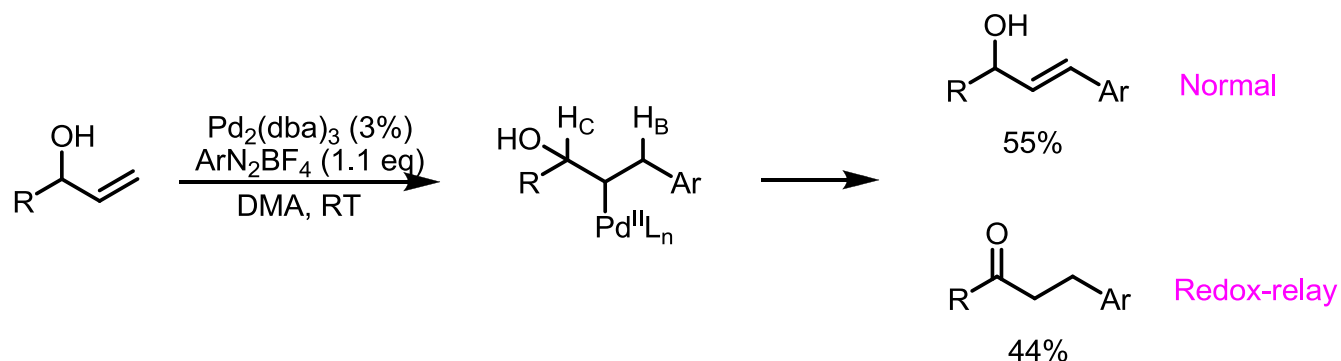
Mei, T.; Sigman, M. S. *Nature* **2014**, *508*, 340.

Werner, E. W.; Mei, T.; Burckle, A. J.; Sigman, M. S.  
*Science* **2012**, *338*, 1455.

# Redox-relay Heck Arylation

Using Aryldiazonium Salt

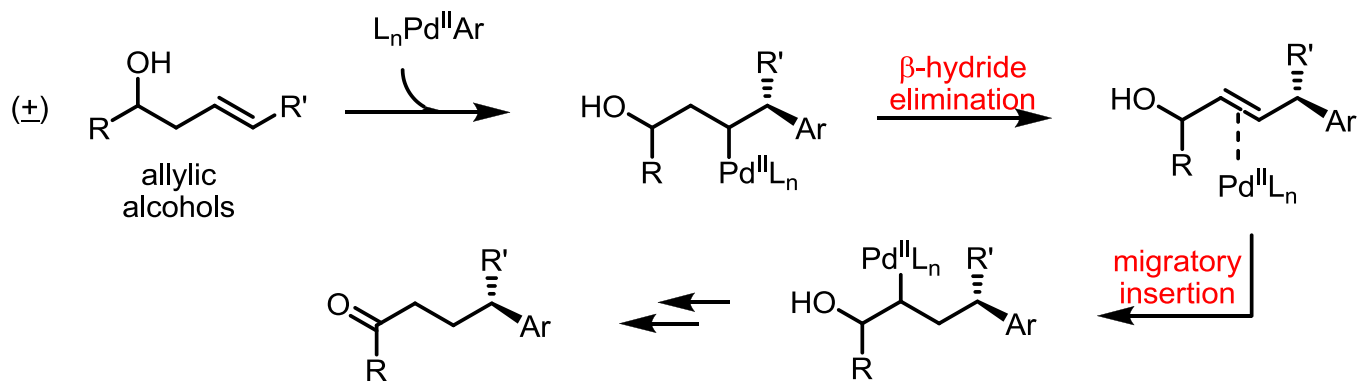
- 2012: Sigman et al first reported the enantioselective Heck arylations of acyclic alkenyl alcohols using a redox-relay strategy.



# Redox-relay Heck Arylation

Using Aryldiazonium Salt

- Proposed migration through the carbon chain using a redox-relay strategy.

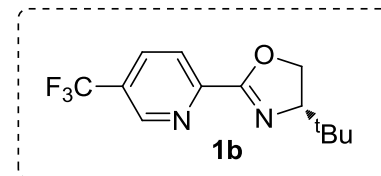
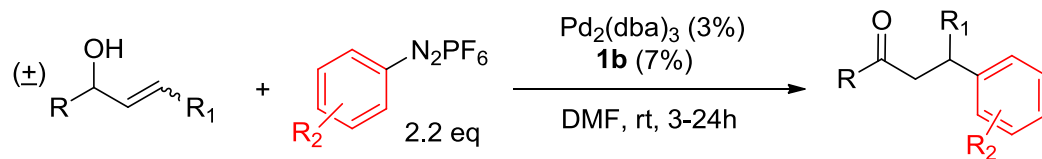


Several problems:

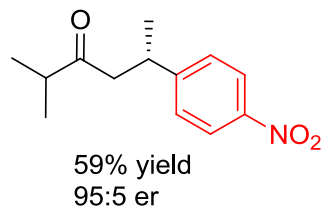
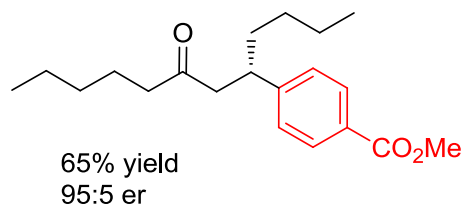
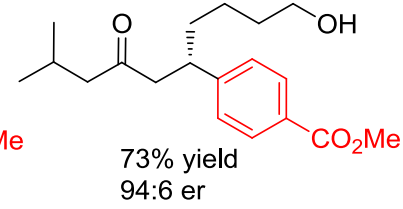
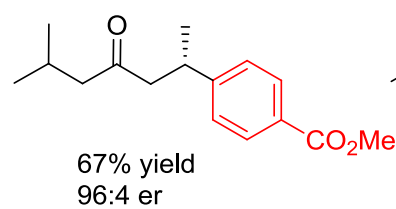
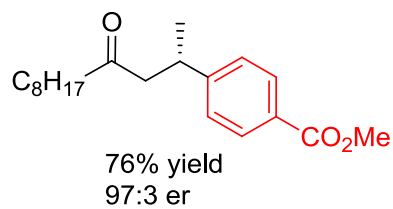
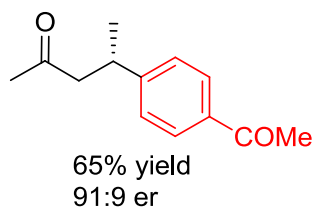
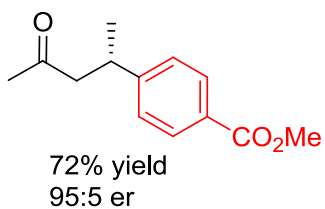
- To favor migration over dissociation of the metal from the alkene: an electrophilic catalyst under mild conditions would be required to promote the binding and insertion.
- High site selectivity and enantioselectivity: require a catalyst sensitive to the subtle electronic differences between the carbons  $\alpha$  and  $\beta$  to the alcohol.

# Redox-relay Heck Arylation

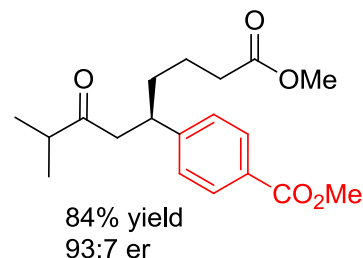
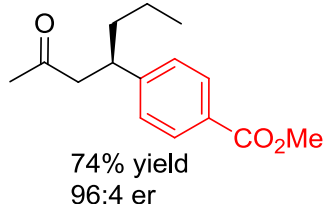
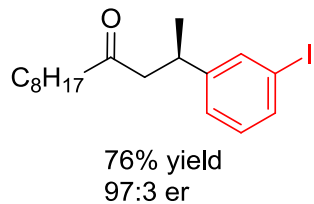
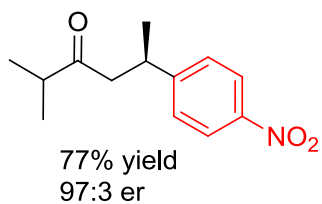
## Allylic Acohols



### using (*E*)-alkenyl substrates

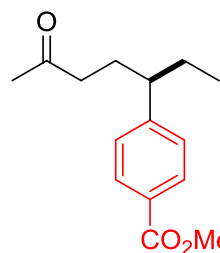
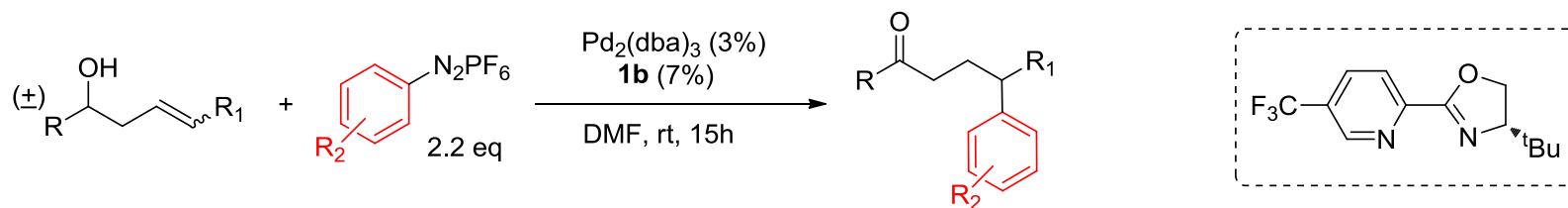


### using (*Z*)-alkenyl substrates

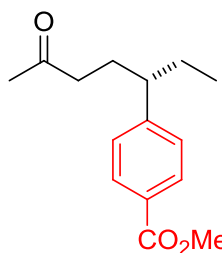


# Redox-relay Heck Arylation

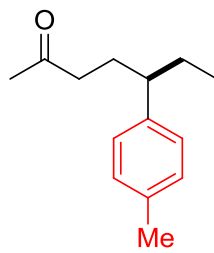
## Homoallylic Alcohols



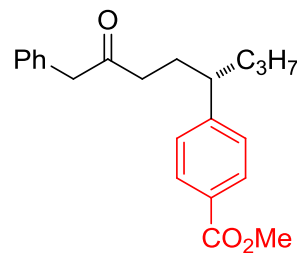
From (Z)-alkene  
79% yield  
96:4 er



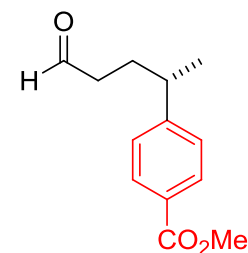
From (E)-alkene  
58% yield  
90:10 er



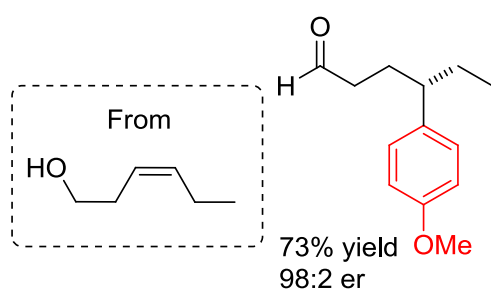
From (Z)-alkene  
72% yield  
97:3 er



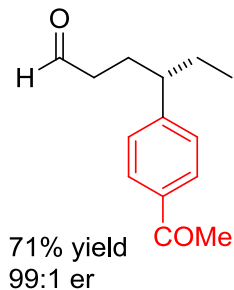
From (E)-alkene  
66% yield  
94:6 er



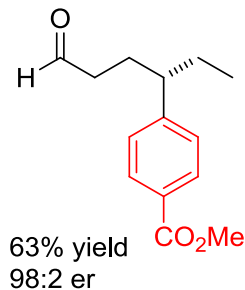
From (E)-alkene  
71% yield  
97:3 er



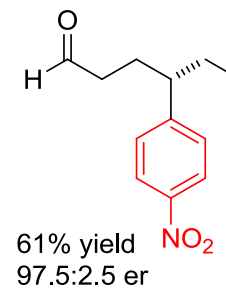
73% yield  
98:2 er



71% yield  
99:1 er



63% yield  
98:2 er



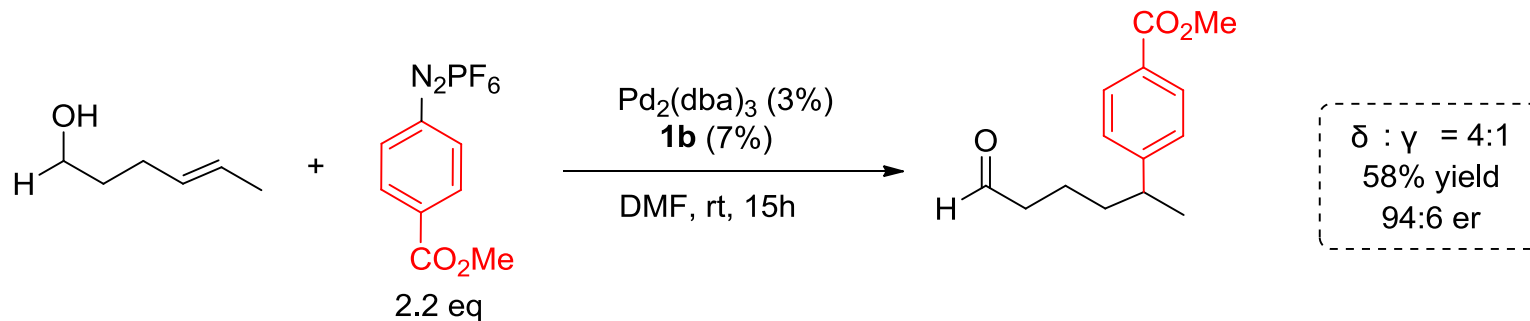
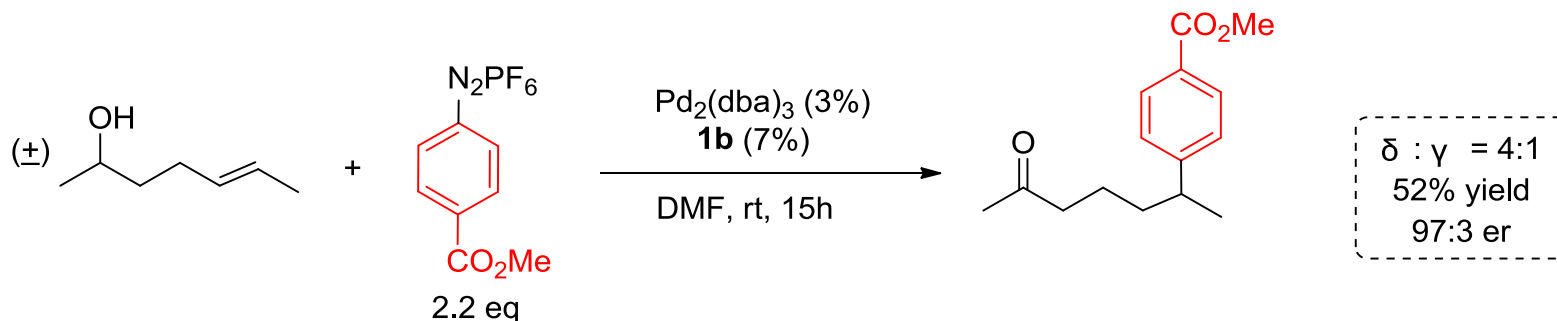
61% yield  
97.5:2.5 er



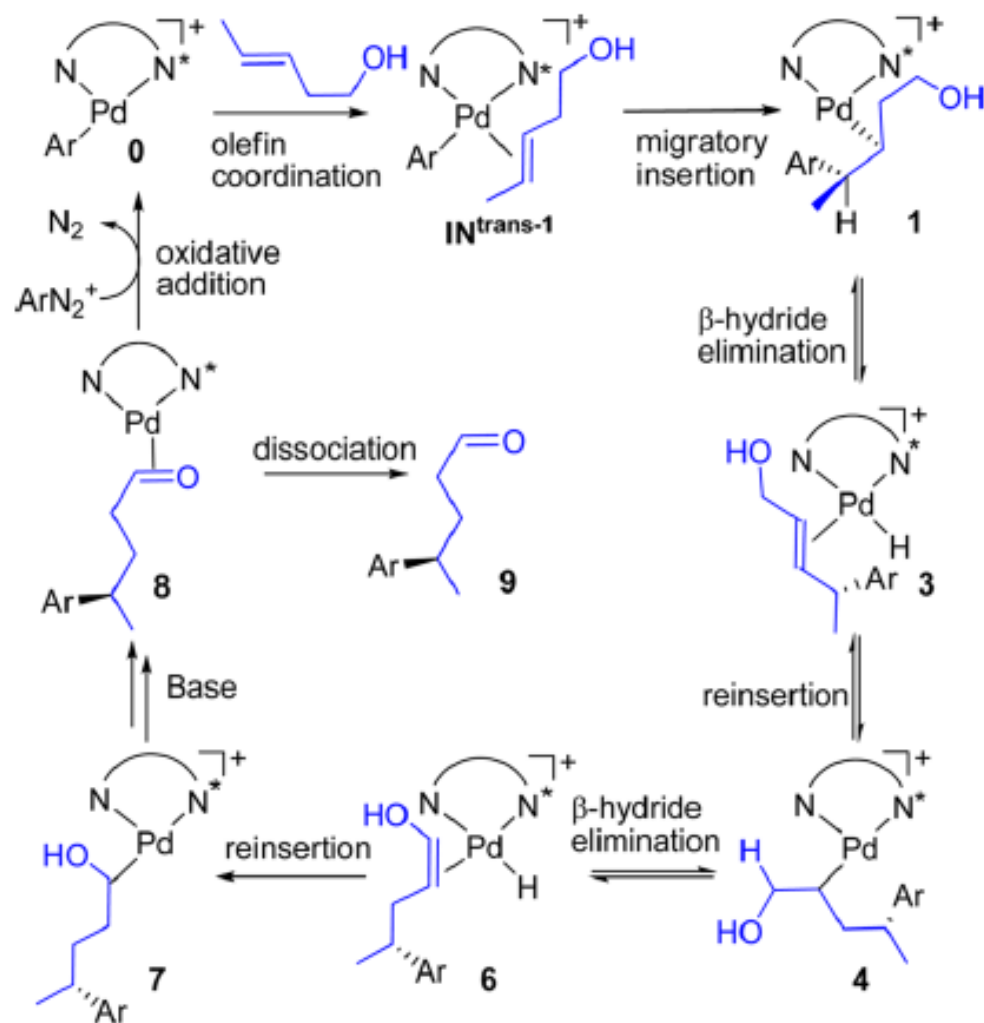
# Redox-relay Heck Arylation

Using Aryldiazonium Salt

- Two substrates wherein the alcohol was an additional carbon away from the alkene.



## Scheme 2. Catalytic Cycle of the Asymmetric Heck Redox-Relay Reaction



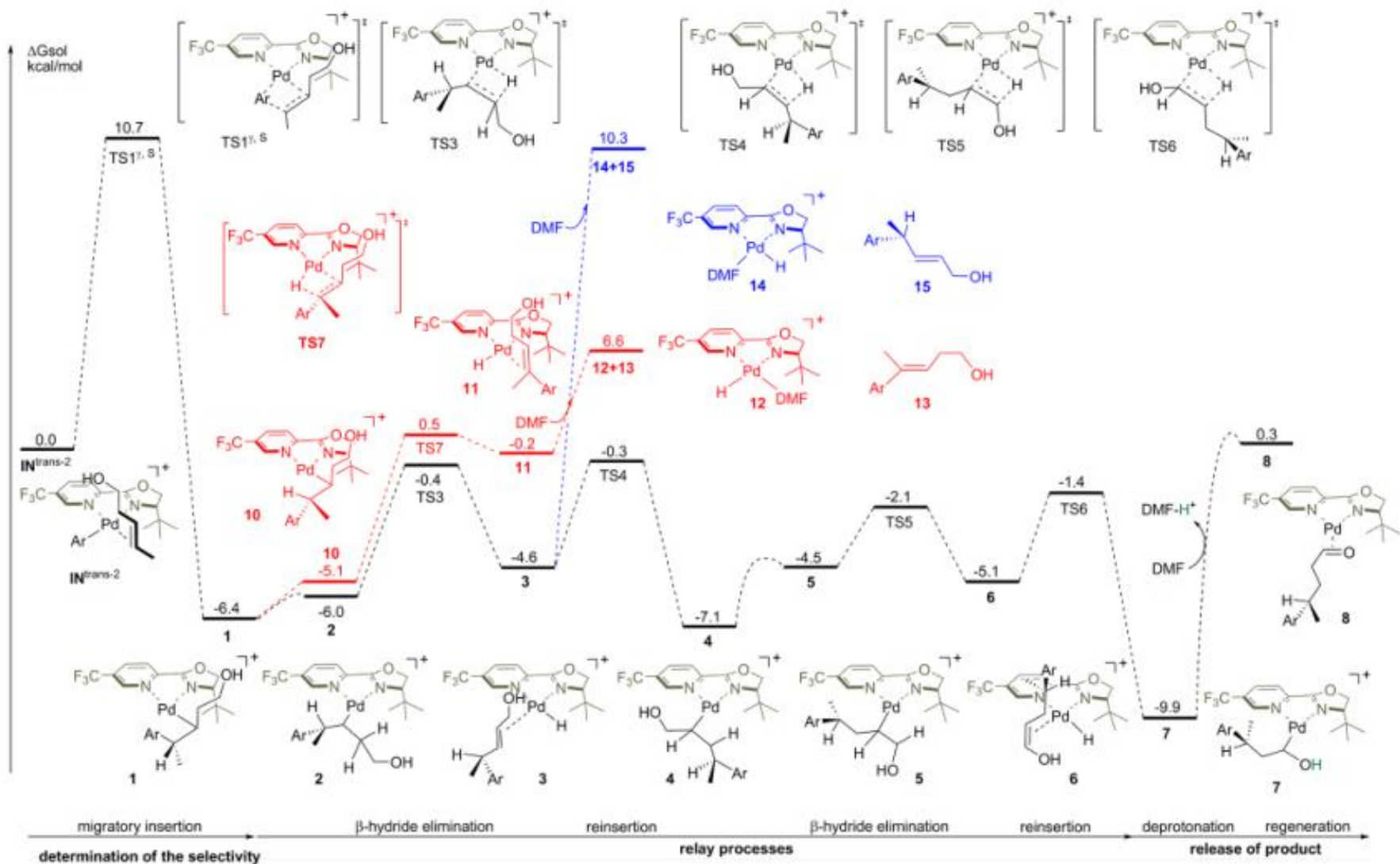
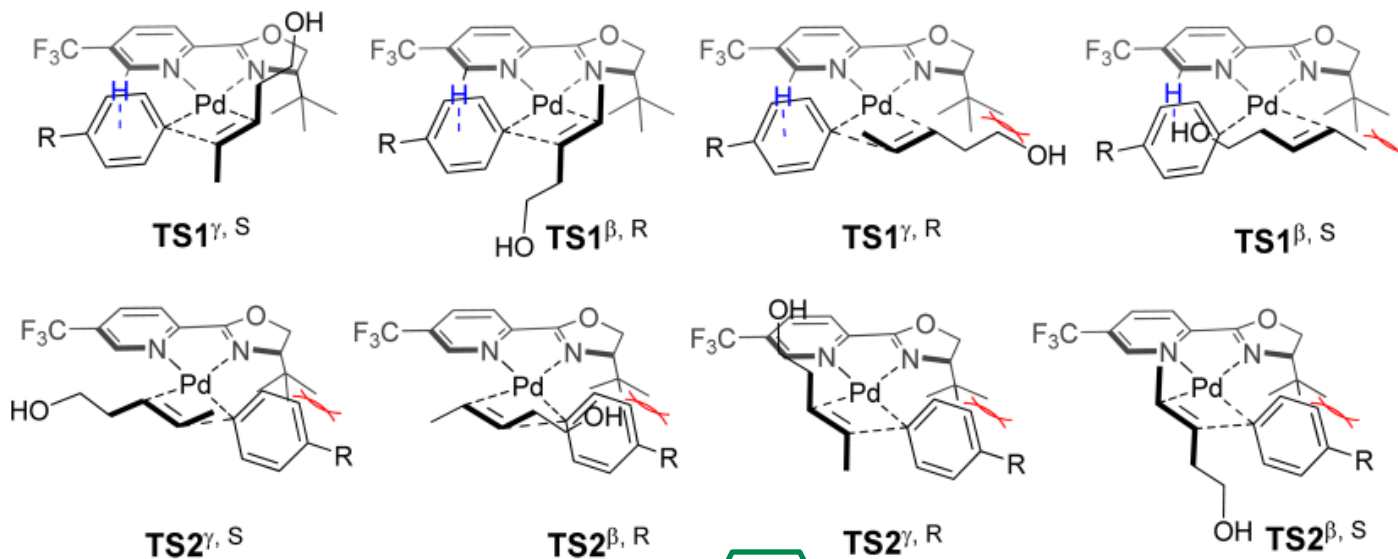


Figure 1. Potential energy surface of the reaction pathway, the alternative conventional Heck reaction pathway (via TS7, shown in red), and the direct alkene dissociation pathway (shown in blue).

# Redox-relay Heck Arylation

## Computational Predictions

Table 1. Structures and Activation Free Energies of Alkene Insertion Step



TS	TS1 $\gamma^S$	TS1 $\beta^R$	TS1 $\gamma^R$	TS1 $\beta^S$
$\Delta G^\ddagger$ (kcal/mol)	10.7	11.7	13.2	15.0
TS	TS2 $\gamma^S$	TS2 $\beta^R$	TS2 $\gamma^R$	TS2 $\beta^S$
$\Delta G^\ddagger$ (kcal/mol)	11.8	12.8	13.0	13.4

# Redox-relay Heck Arylation

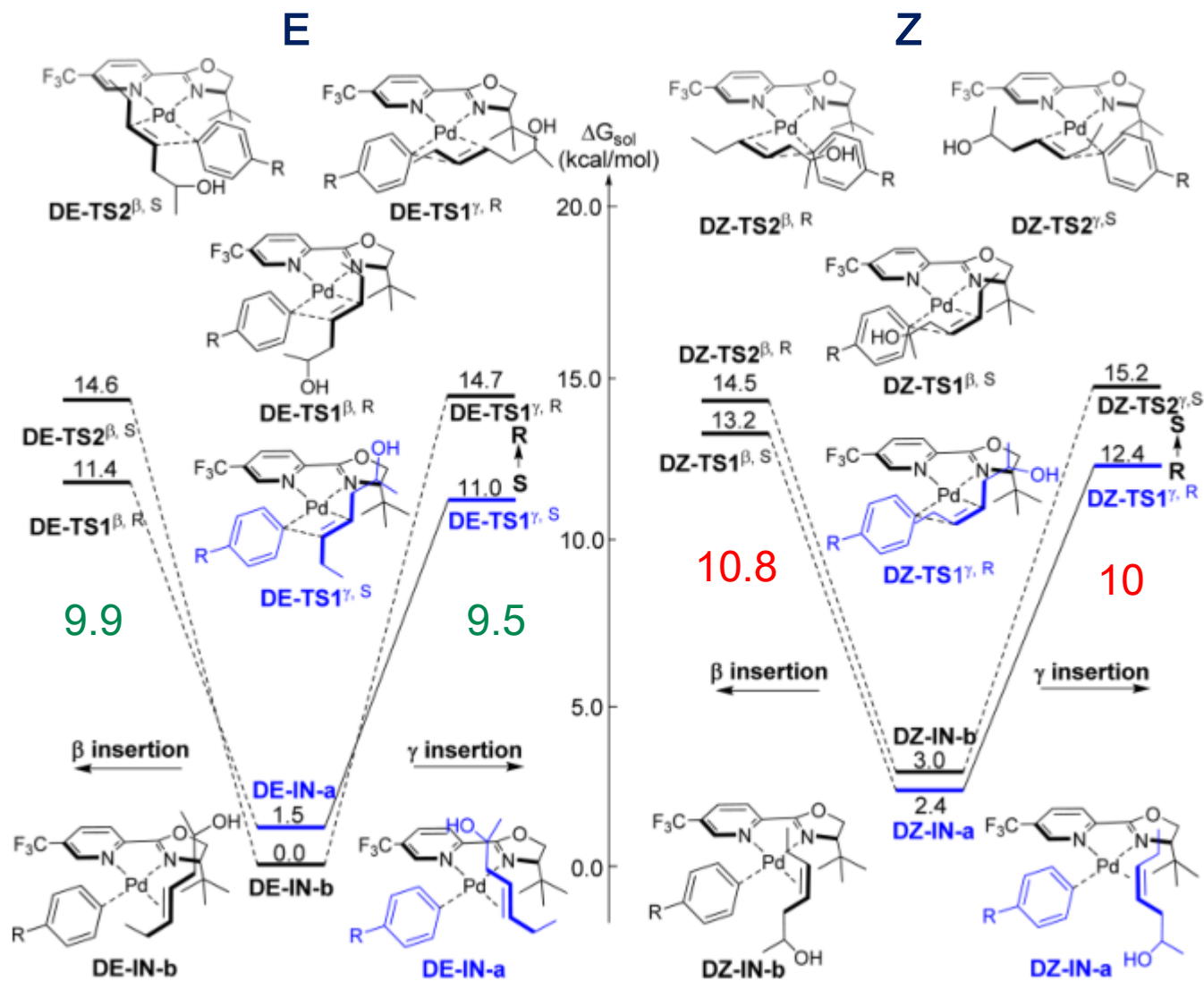
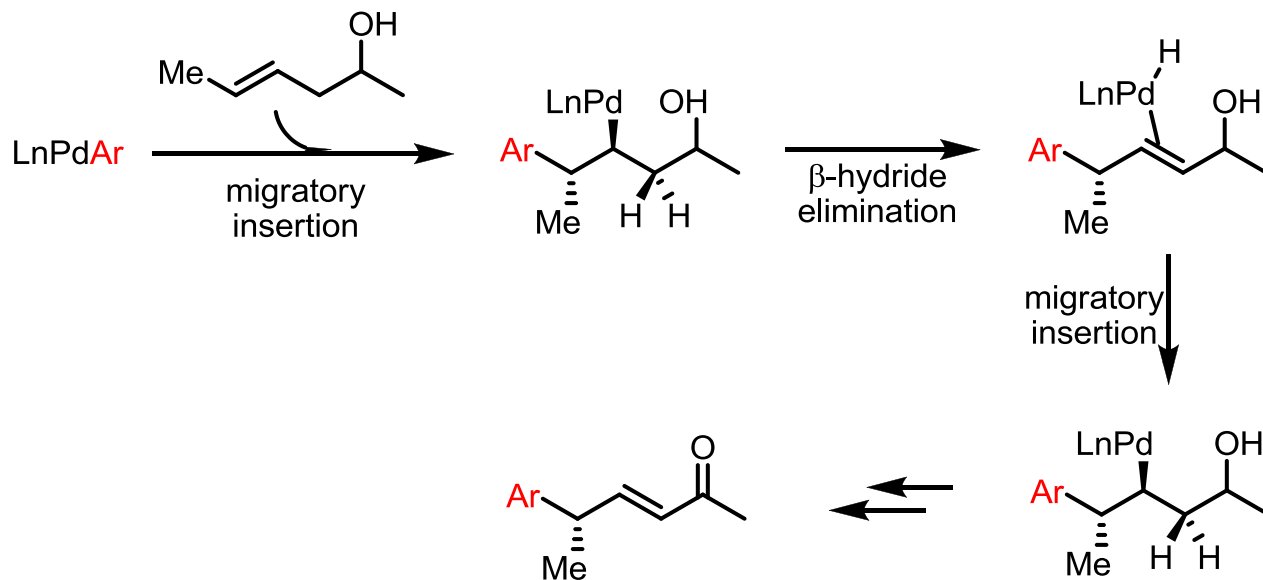


Figure 3. Selectivity-determining transition states for the ethyl-substituted homoallylic secondary alcohols.<sup>57</sup>

# Redox-relay Heck Arylation

Using Boronic Acids

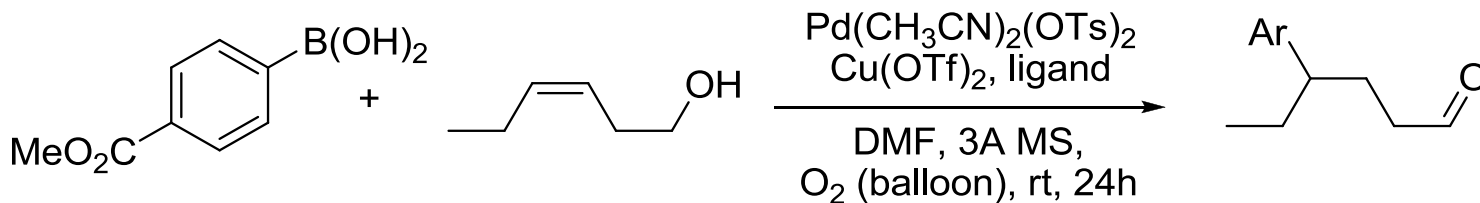


- expand to oxidative variant (boronic acids)? .
- how about the site-selectivity (i.e.,  $\gamma$  vs  $\beta$ )

# Redox-relay Heck Arylation

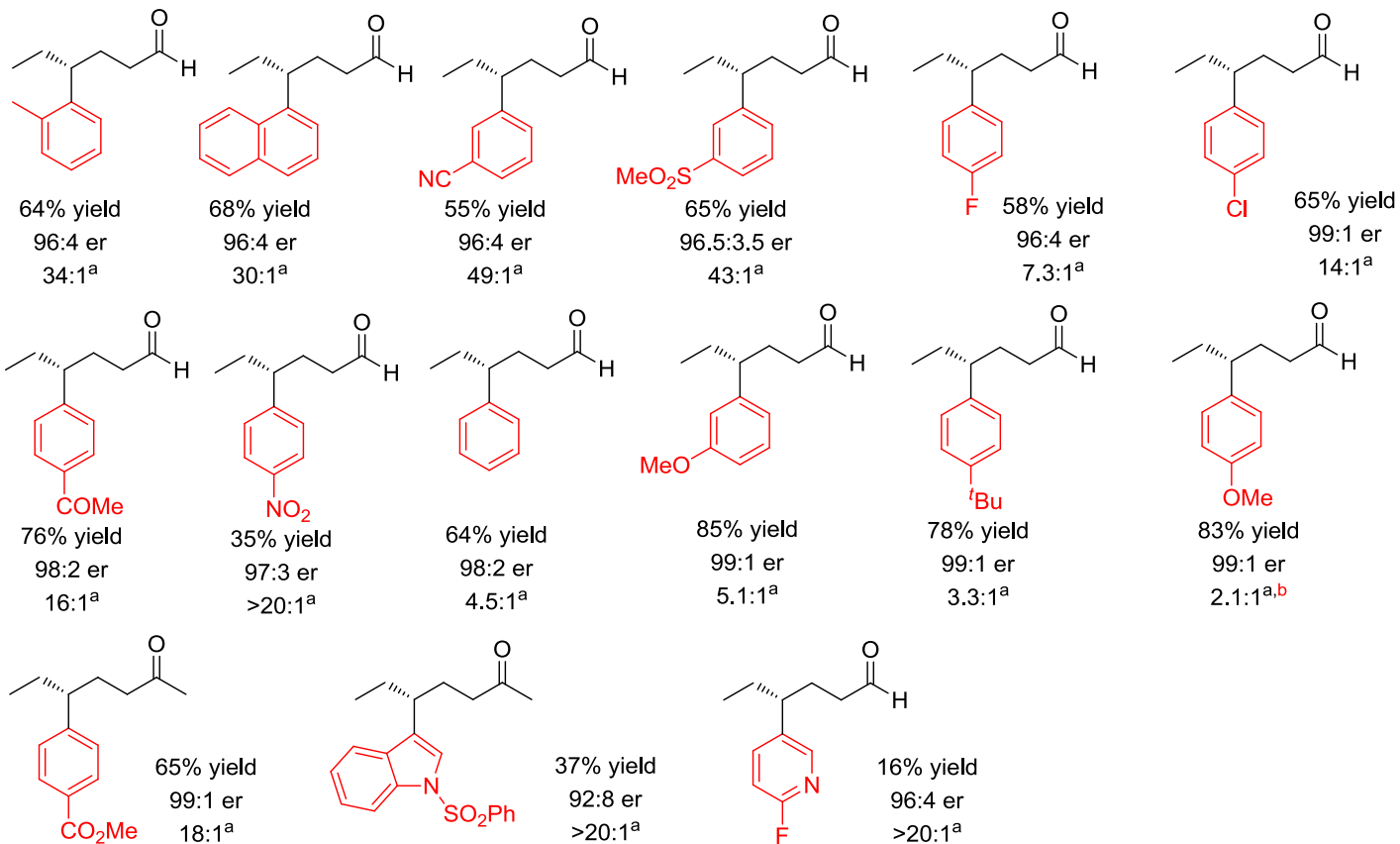
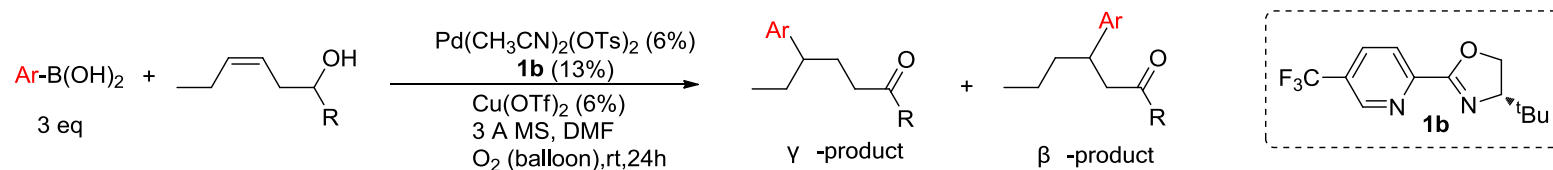
Using Boronic Acids

## ■ Reaction Optimization.



entry	Pd/Cu/ligand (mol %)	boronic acid (equiv)	3 A MS (mg/mmol)	conv. (%)	yield (%)
1	5/5/11	2	-	17	15
2	5/5/11	2	40	58	50
3	5/5/11	2	150	80	70
4	5/5/11	2	400	78	67
5	5/5/11	3	150	>90	82 (99:1 er)

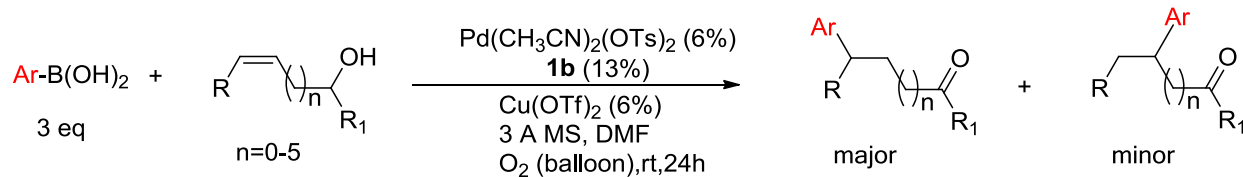
## Scope of the enantioselective redox-relay Heck reaction.



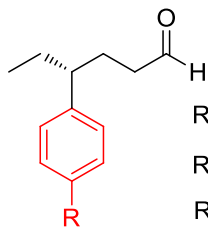
from *rac*-2° alcohol



## Evaluation of various alkenol substrates.



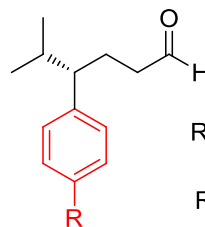
### Alkene substitution effects



R = OMe; 72% yield; ( $\gamma$  :  $\beta$  = 1.2:1); 98.5:1.5 er for  $\gamma$  ; 94:6 for  $\beta$

R = F; 55% yield; ( $\gamma$  :  $\beta$  = 2:1); 98:2 er for  $\gamma$  ; 94:6 for  $\beta$

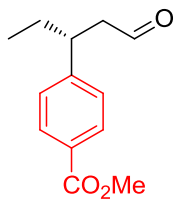
R = CO<sub>2</sub>Me; 50% yield; ( $\gamma$  :  $\beta$  = 6:1); 98:2 er for  $\gamma$



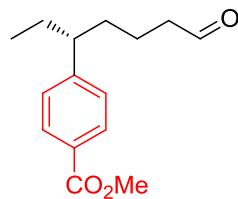
R = OMe; 57% yield; ( $\gamma$  :  $\beta$  = 3.7:1); 97:3 er for  $\gamma$

R = CO<sub>2</sub>Me; 65% yield; ( $\gamma$  :  $\beta$  = 27:1); 99:1 er for  $\gamma$

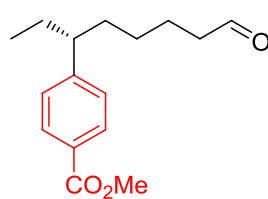
### Chain-length effects



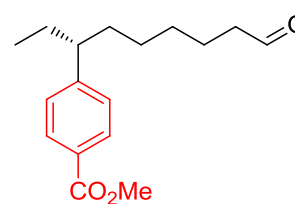
63% yield  
97:3 er  
 $\beta$  :  $\alpha$  =>20:1



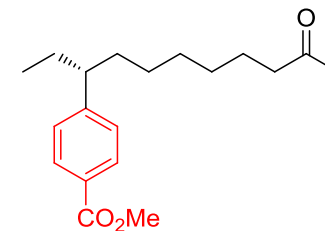
59% yield  
97:3 er for  $\delta$   
 $\delta$  :  $\gamma$  = 7:1



54% yield  
99:1 er for  $\epsilon$   
99:1 er for  $\delta$   
 $\epsilon$  :  $\delta$  = 3.5:1



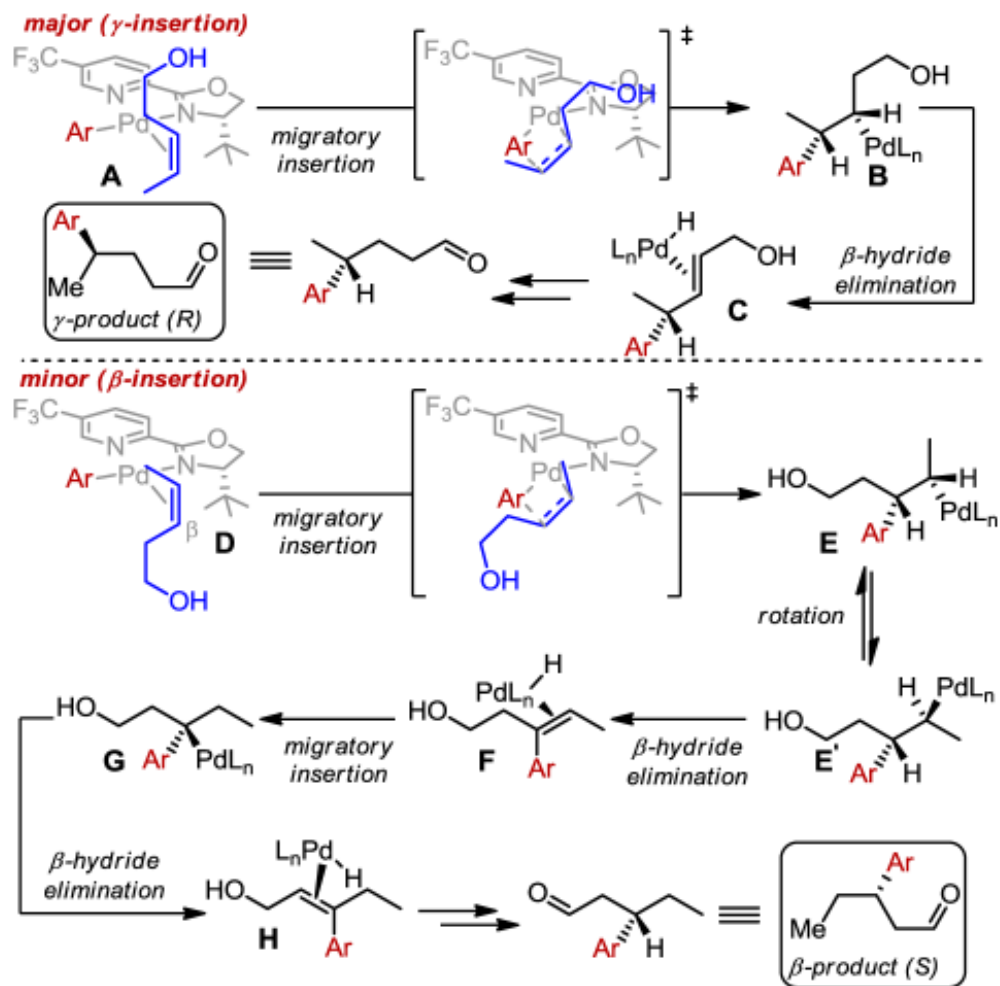
63% yield  
97:3 er for  $\zeta$   
99:1 er for  $\epsilon$   
 $\zeta$  :  $\epsilon$  = 3.2:1



51% yield  
94:6 er for  $\eta$   
96:4 er for  $\zeta$   
 $\eta$  :  $\zeta$  = 2.8:1

# Redox-relay Heck Arylation

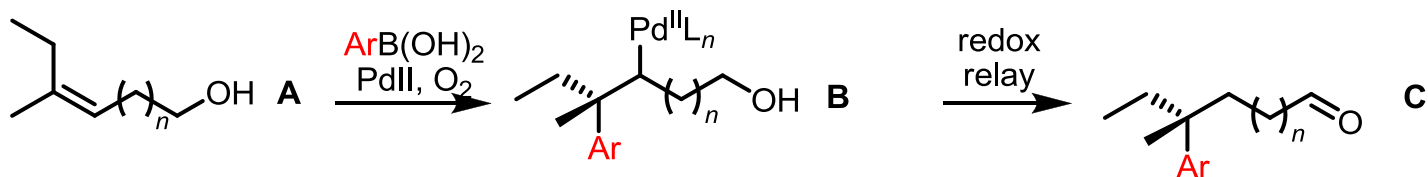
Using Boronic Acids



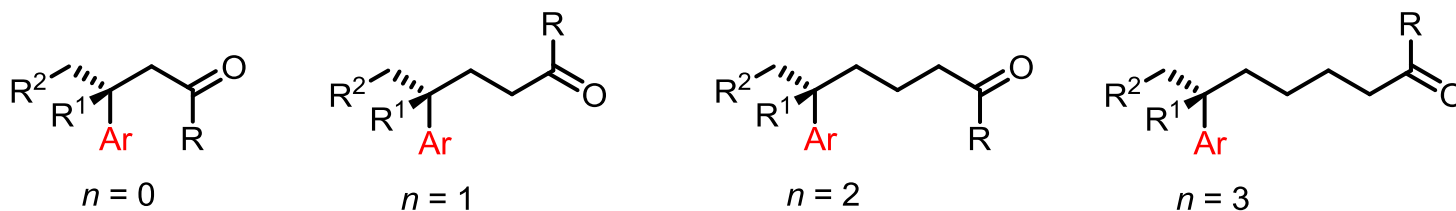
# Redox-relay Heck Arylation

Using Boronic Acids

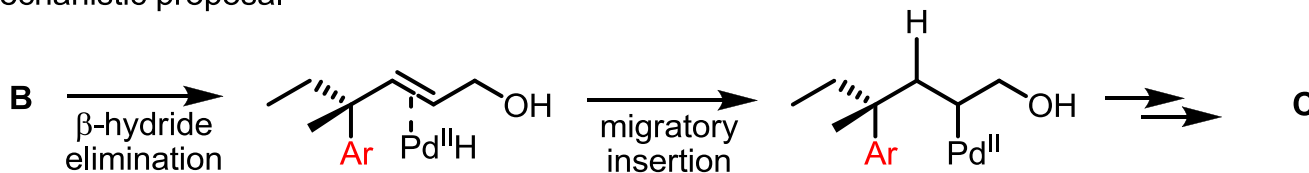
- Proposed modular strategy using trisubstituted alkenes.



accessible products



mechanistic proposal

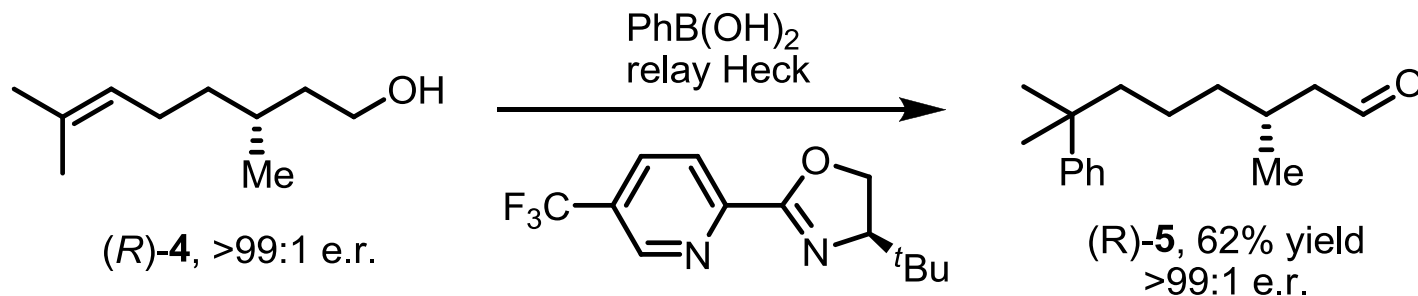
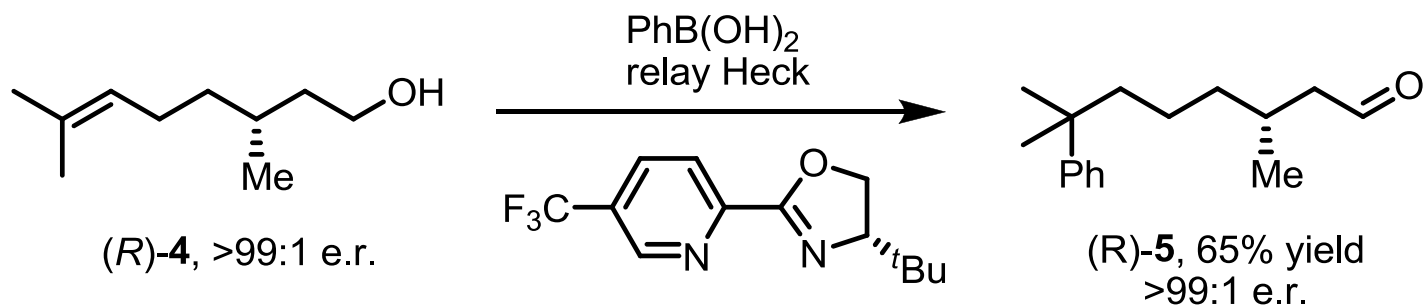


- reactivity?
- site selectivity?
- enantioselectivity?

# Redox-relay Heck Arylation

Using Boronic Acids

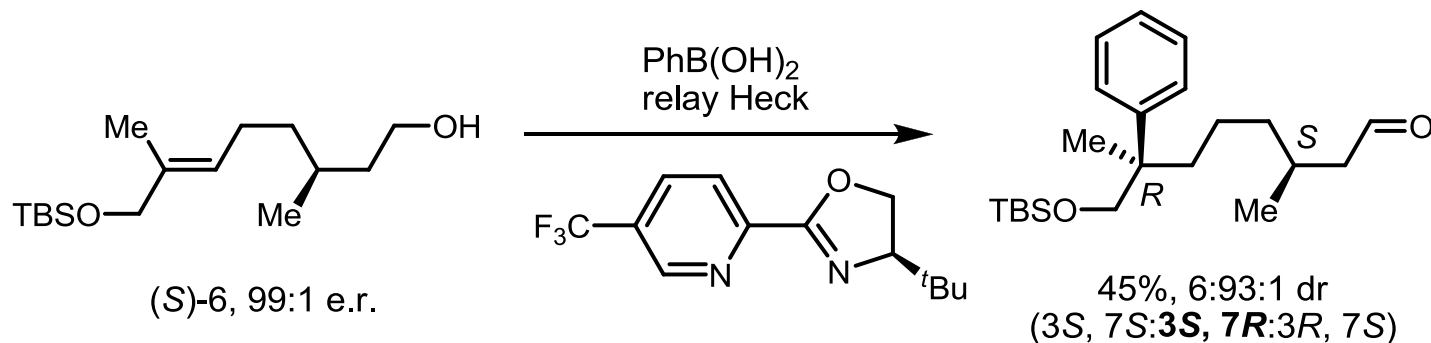
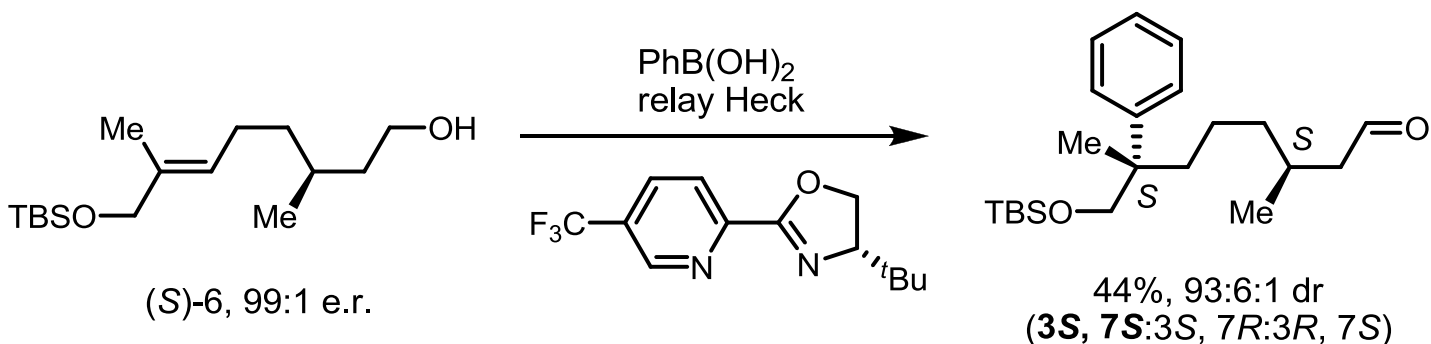
## ■ Preservation of preinstalled stereocentre.



# Redox-relay Heck Arylation

Using Boronic Acids

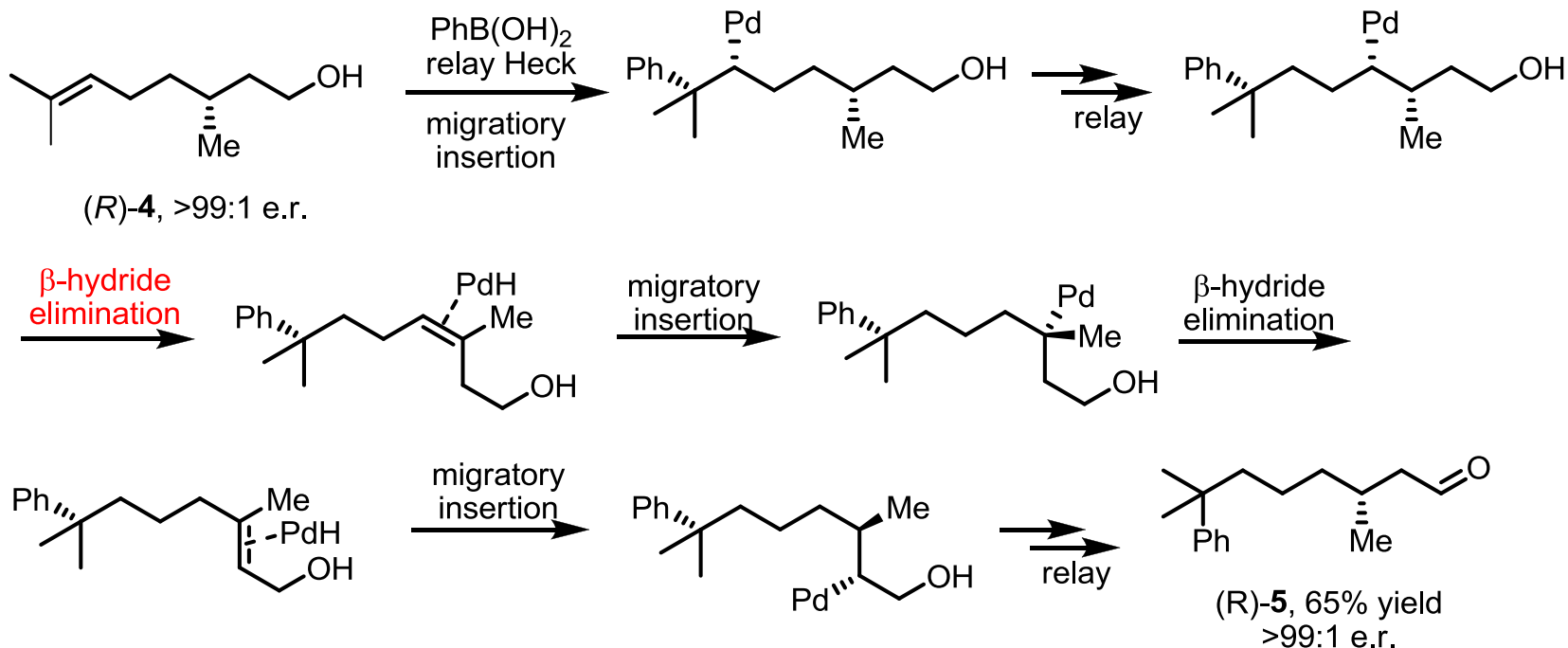
## ■ Control of two remote chiral centres.



# Redox-relay Heck Arylation

Using Boronic Acids

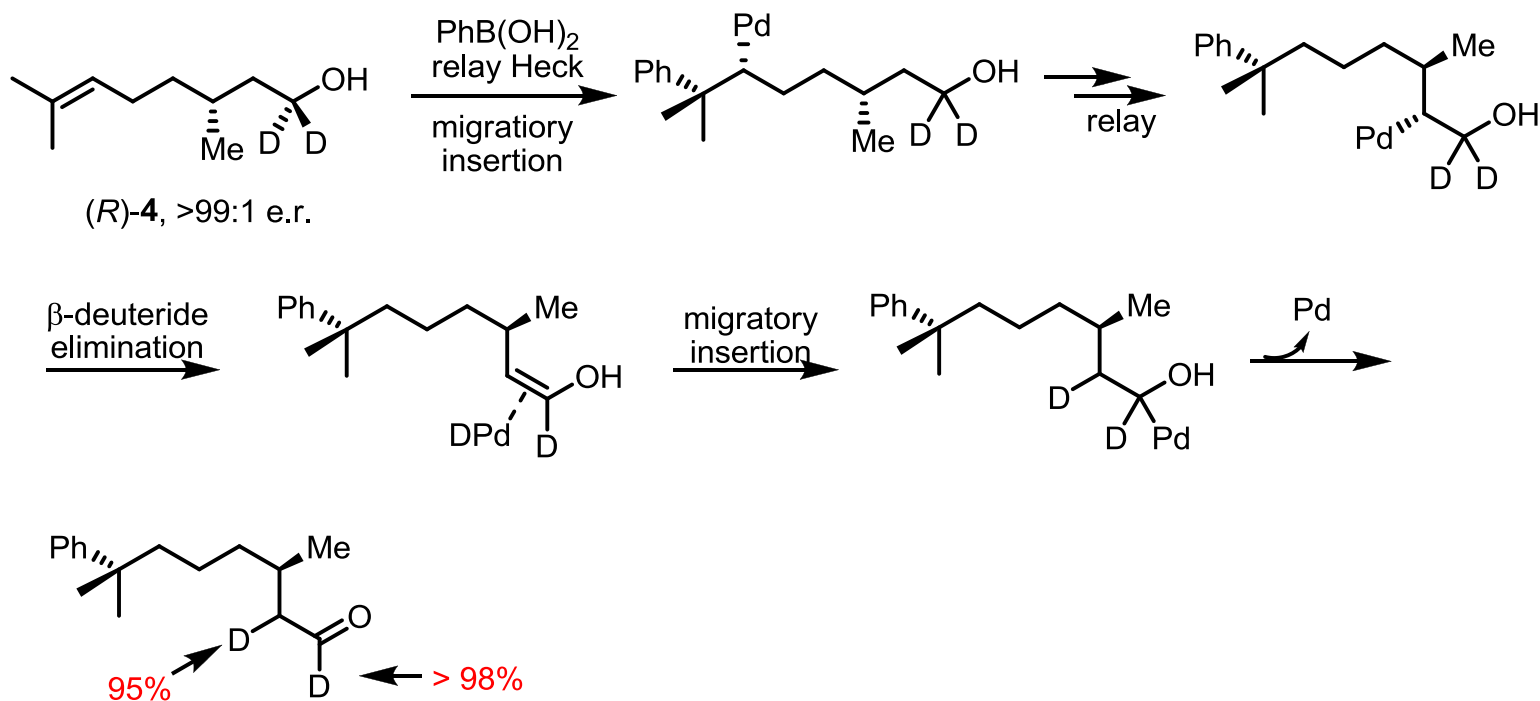
## ■ Mechanistic analysis for the formation of **5**.



# Redox-relay Heck Arylation

Using Boronic Acids

## ■ Isotopic labelling experiment.



# Contents

## ■ Part 1: history



F. G. A. Stone  
University of Bristol  
University of Baylor



R. F. Heck (Nobel 2010)  
University of Delaware



R. C. Larock  
Iowa State University

## ■ Part 2: recent developments



M. S. Sigman  
Utah University

## ■ Part 3: conclusion

For very useful papers see:

Mei, T.; Sigman, M. S. *Nature* **2014**, 508, 340.

Werner, E. W.; Mei, T.; Burckle, A. J.; Sigman, M. S.  
*Science* **2012**, 338, 1455.



## *Summary and Outlook*

- To develop an oxidative variant of the enantioselective redox-relay Heck reaction using substrates else besides aryldiazonium salts and boronic acids.
- It is necessary to develop new chiral ligands and cheap catalysts to be used in the enantioselective redox-relay Heck reaction.
- To probe the organometallic mechanistic questions, apply these methods to synthetic endeavors, and expand the concept of redox-relay Heck reactions to new reaction types.



*Thank  
you*