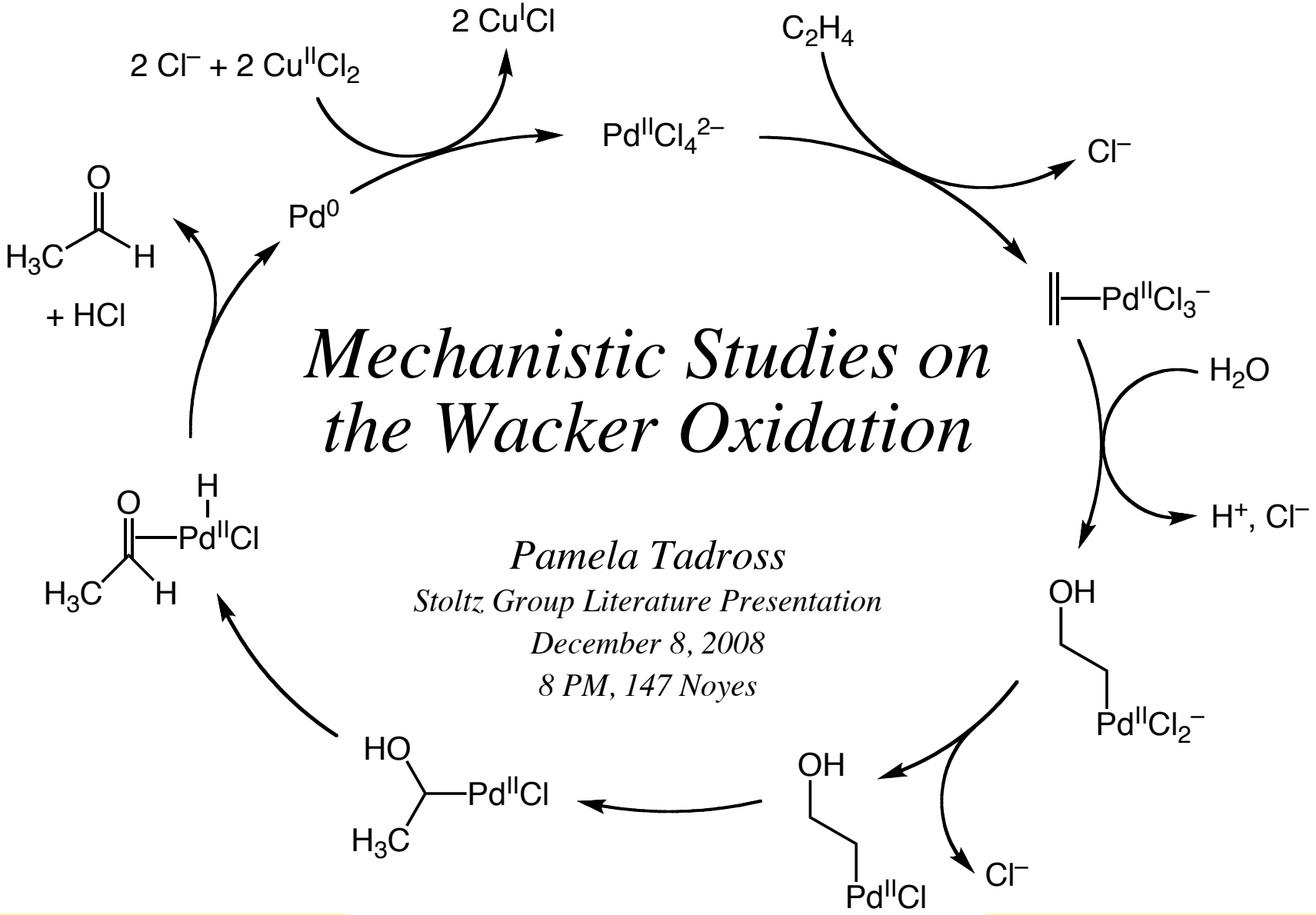


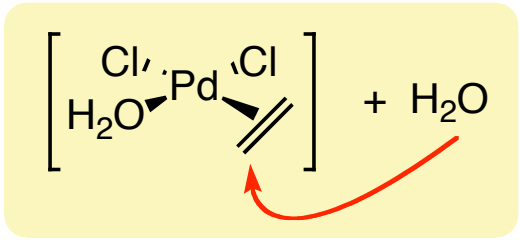
Mechanistic Studies on the Wacker Oxidation

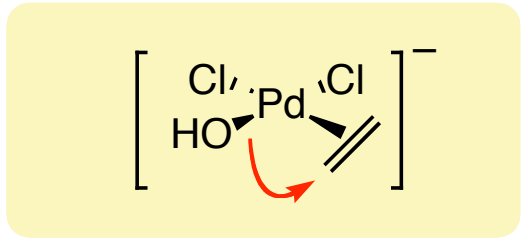
Pamela Tadross

Stoltz Group Literature Presentation

December 8, 2008

8 PM, 147 Noyes





Origins of the Wacker Oxidation

F. C. Phillips, 1894:

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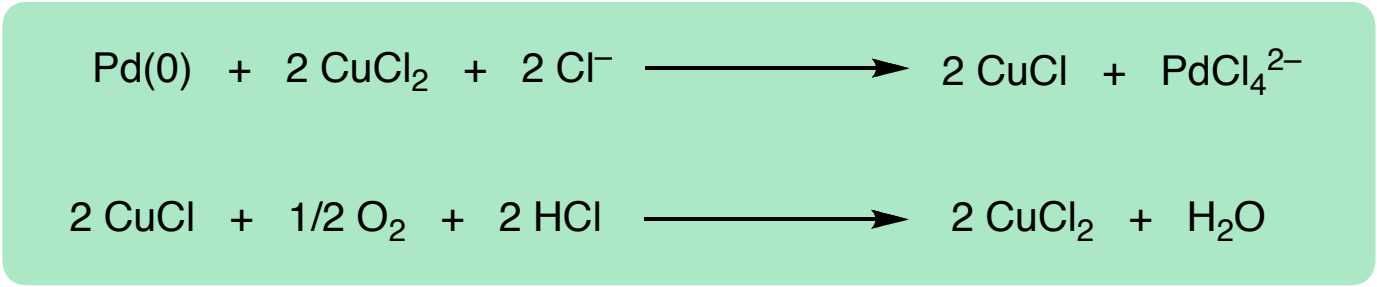
Smidt, Wacker Chemie, 1959:



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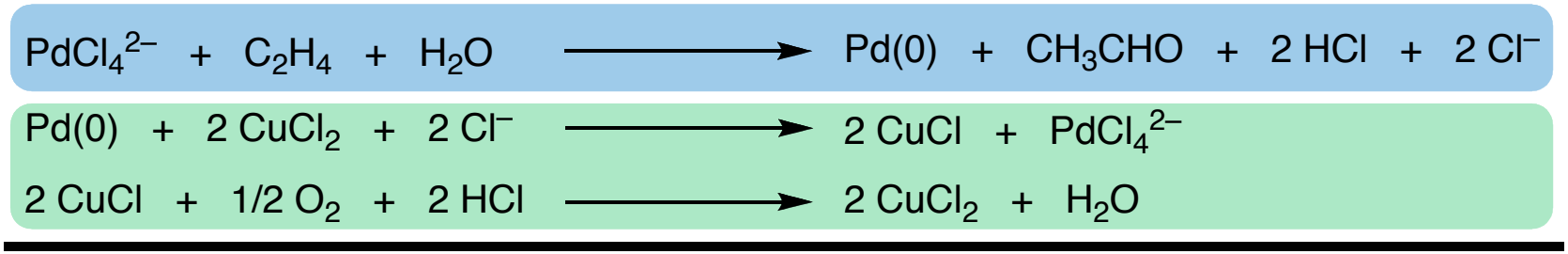

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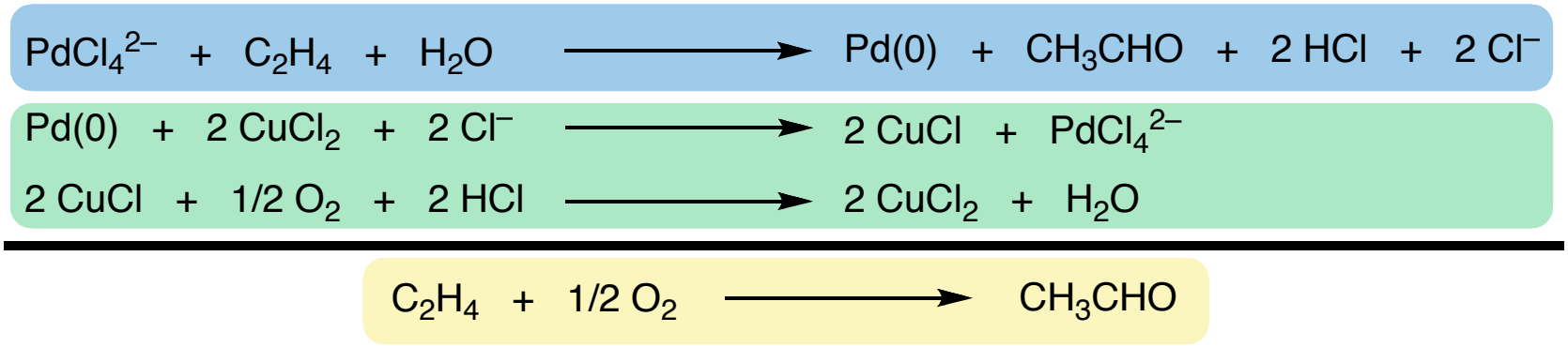

Net Result: Air oxidation of ethylene to acetaldehyde!

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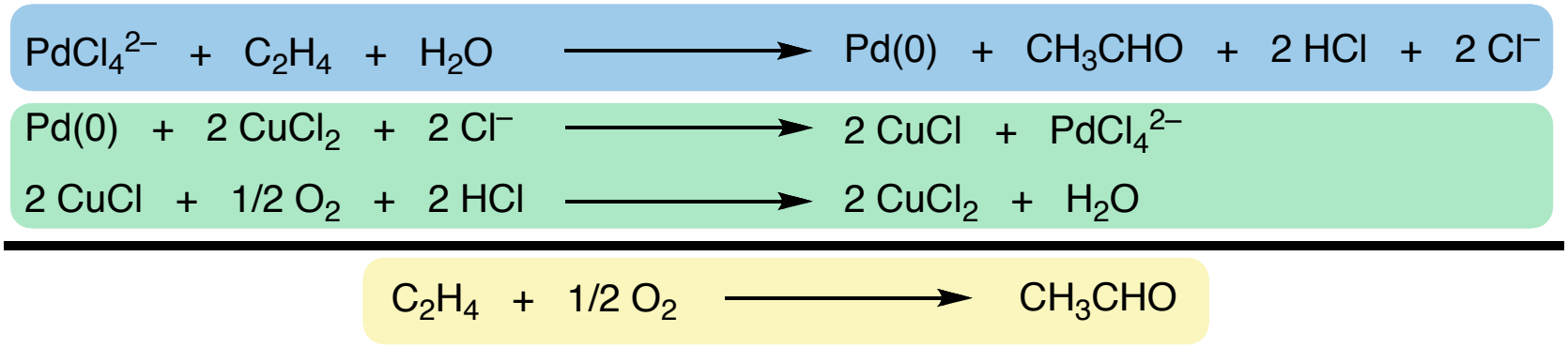

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- First organopalladium reaction applied on industrial scale.
- First rendered commercial in 1960.
- At one point was responsible for the production of over 2 billion pounds per year of acetaldehyde!

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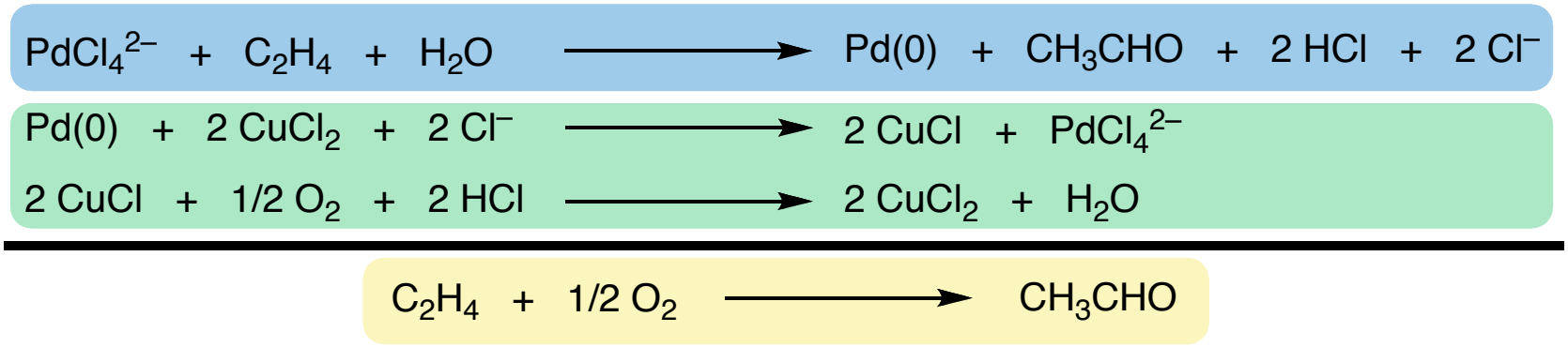

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- First organopalladium reaction applied on industrial scale.
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- At one point was responsible for the production of over 2 billion pounds per year of acetaldehyde!

- Prior acetaldehyde production:
  a) Oxymercuration of acetylene
  b) Dehydrogenation of ethanol
- Wacker process eventually replaced because of more efficient ways of producing acetic acid (i.e. Monsanto process).

Phillips, F. C. *Am. Chem. J.* **1984**, *16*, 255-277. Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, S.; Sabel, A. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 80.

Early Kinetic Studies

Conditions:

$[Pd^{II}]$ = 0.005 - 0.04 M
$[Cl^-]$ = 0.1 - 1.0 M
$[H^+]$ = 0.04 -1.0 M

$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[C_2H_4]}{[Cl^-]^2\,[H^+]}$$

- First order in Pd^{II}
- Second order Cl^- inhibition
- First order acid inhibition

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Early Kinetic Studies

Chloride Inhibition

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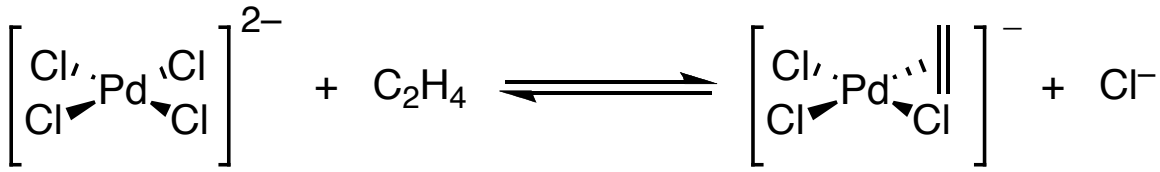
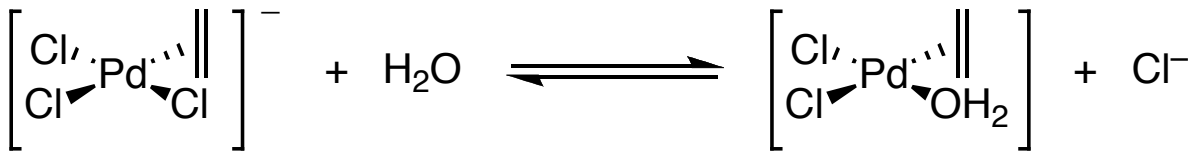
Source of Chloride Inhibition:



$$\frac{1}{[Cl^-]} \text{ inhibition}$$



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Early Kinetic Studies

Proton Inhibition

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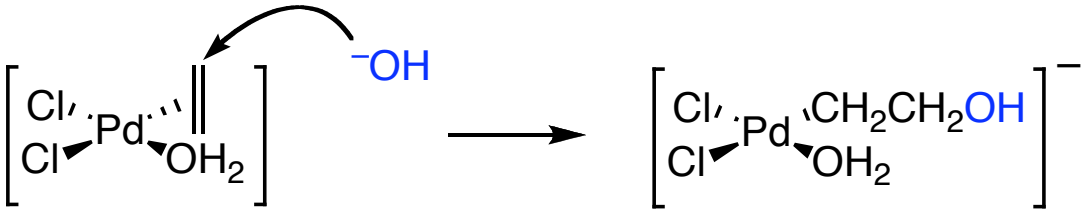

Outer-sphere hydroxide attack: Predicted to be 10^3 times faster than diffusion controlled process

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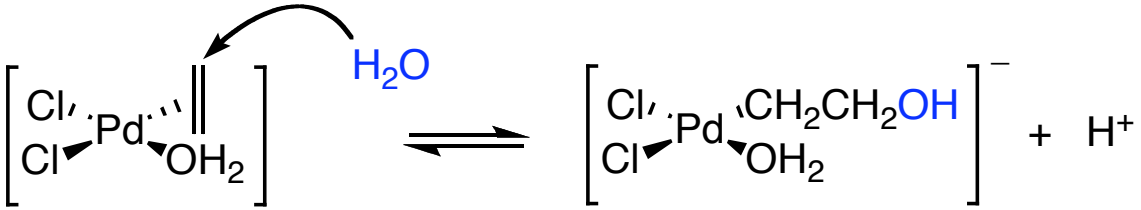

Outer-sphere water attack: Predicted to occur by an anti hydroxypalladation mechanism

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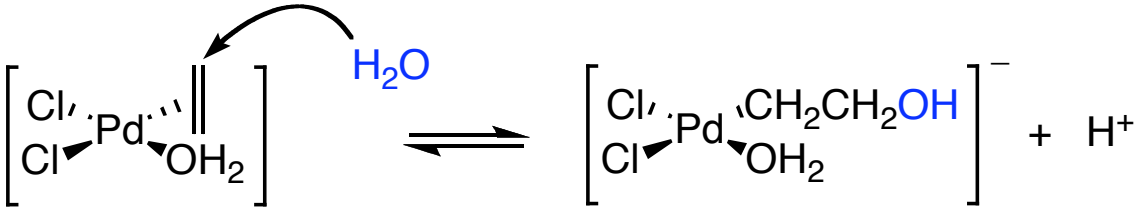

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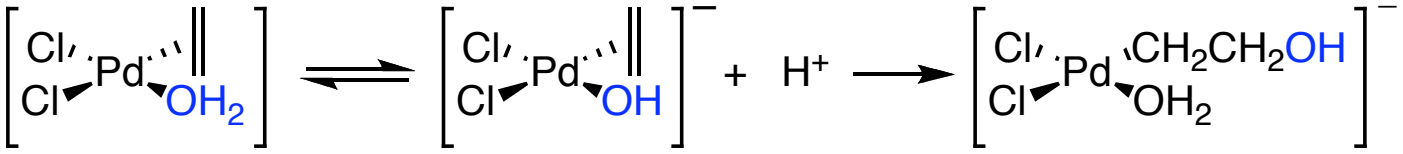

Inner-sphere hydroxyl attack: Predicted to occur by a syn hydroxypalladation mechanism

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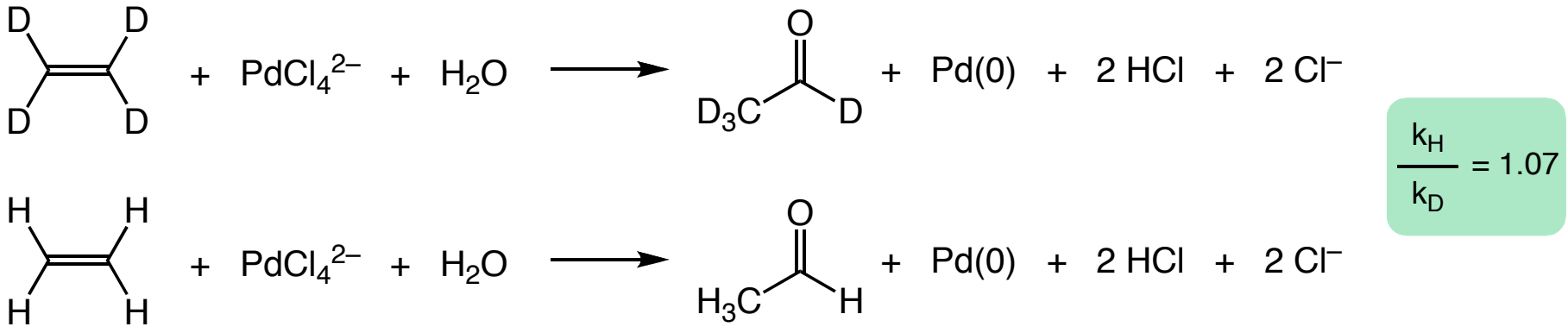
Kinetic Isotope Effects

Early Evidence for an Inner-Sphere Syn Hydroxypalladation Mechanism



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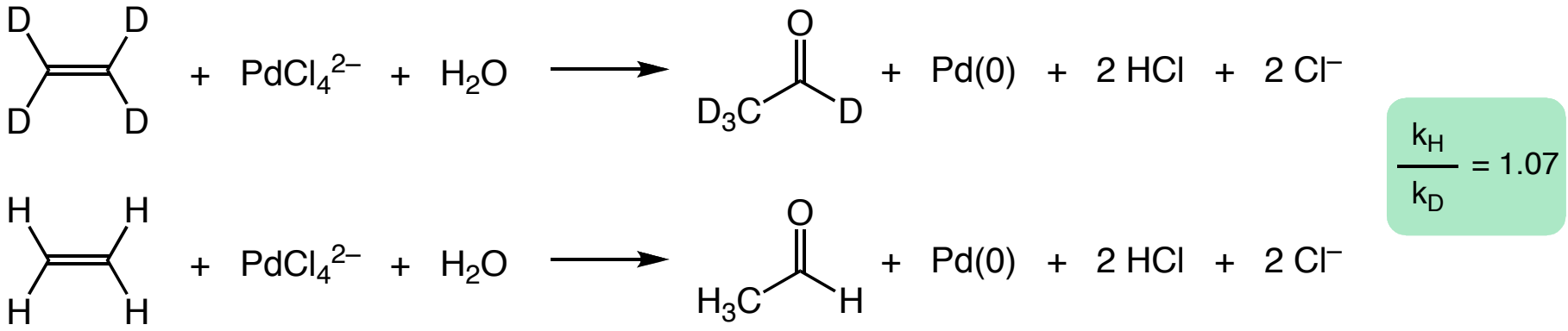
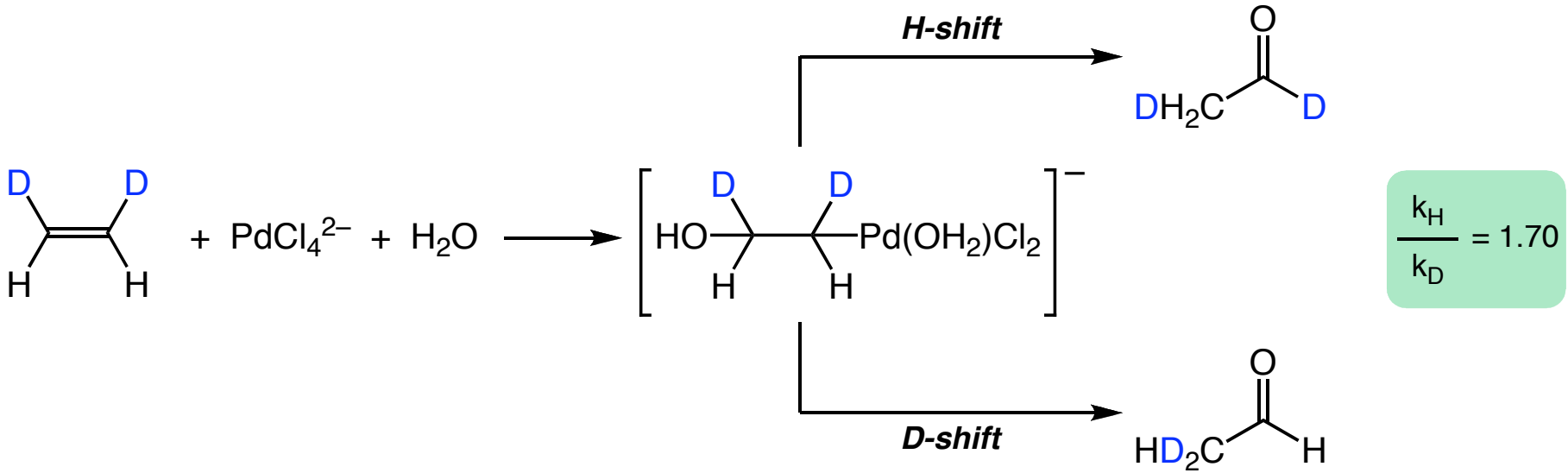


$$\frac{k_H}{k_D} = 1.07$$

KIE for decomposition step determined by competitive isotope effect experiment:



$$\frac{k_H}{k_D} = 1.70$$

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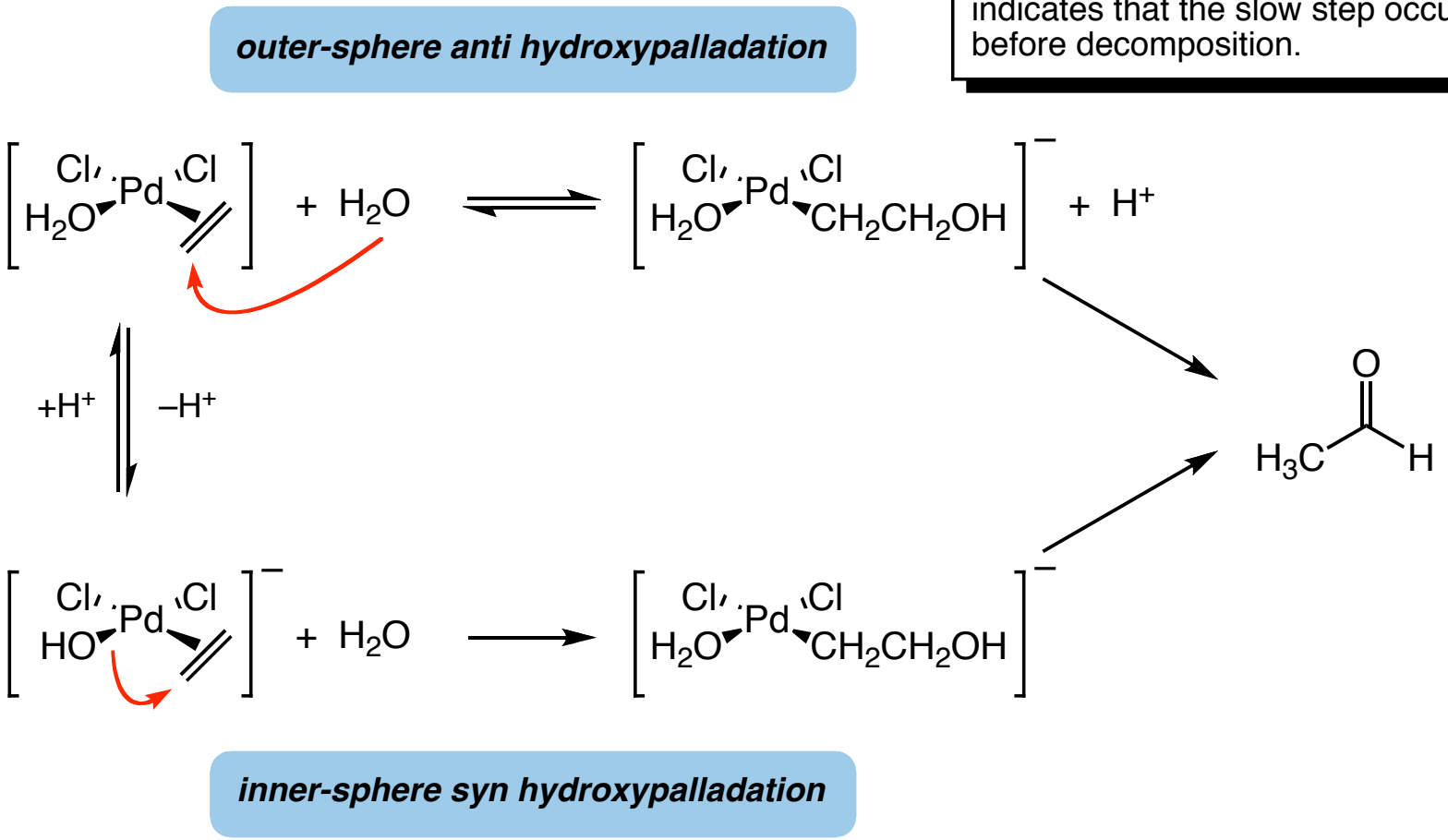
Kinetic Isotope Effects

Early Evidence for an Inner-Sphere Syn Hydroxypalladation Mechanism

KIE 1.07 and competitive KIE of 1.70 indicates that the slow step occurs before decomposition.



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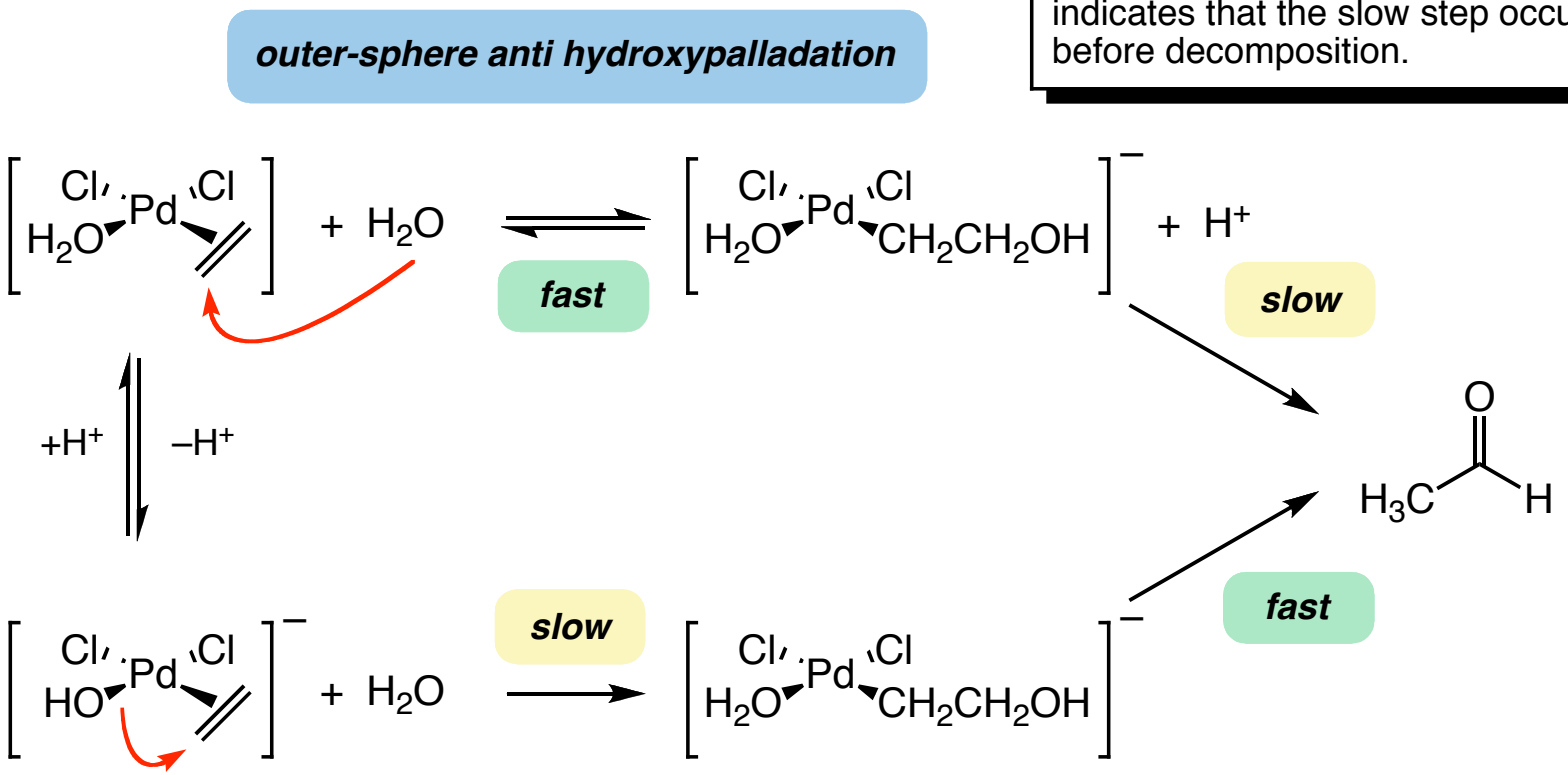

anti pathway has decomposition as the slow step

syn pathway has hydroxypalladation as the slow step

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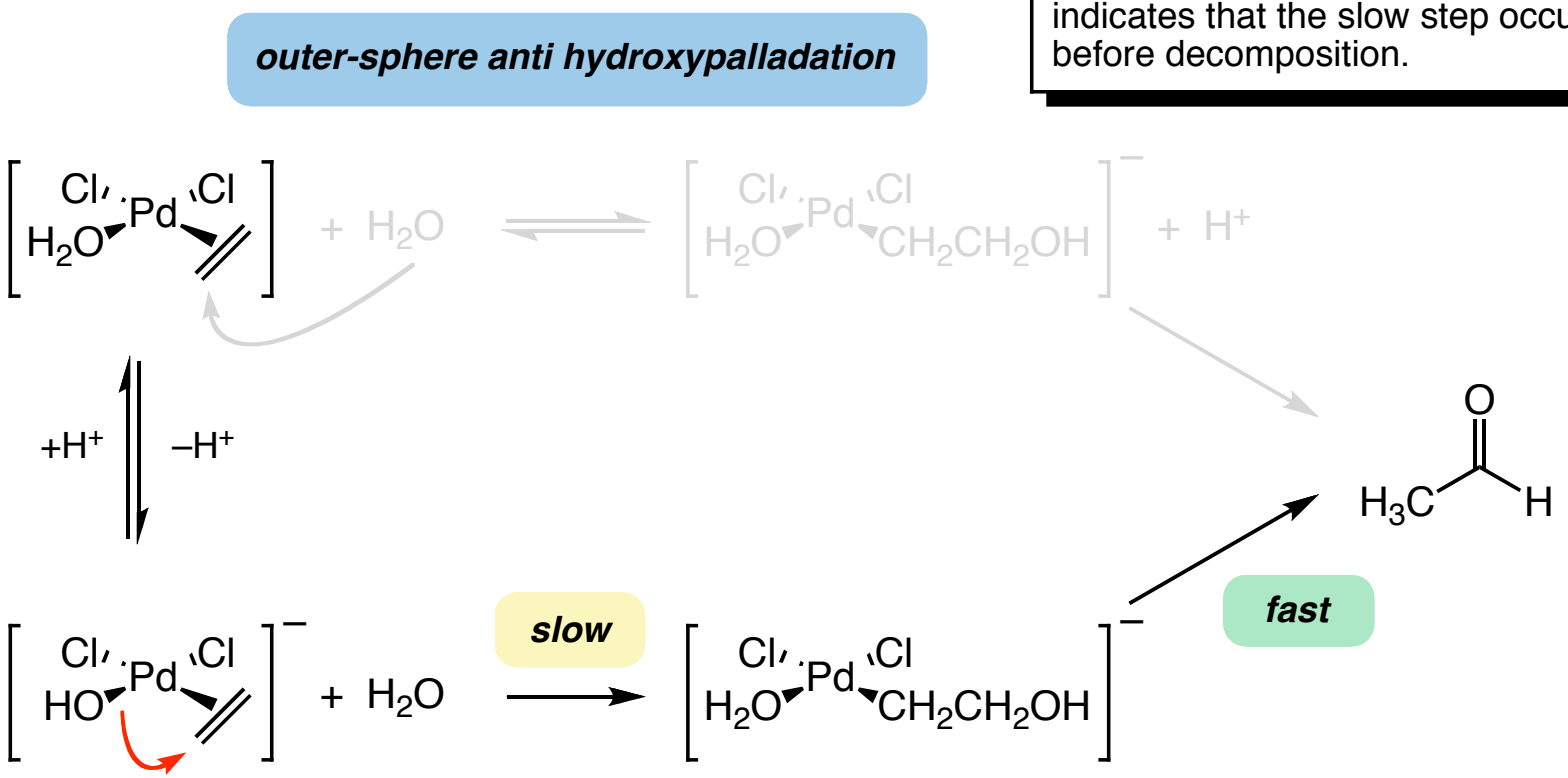

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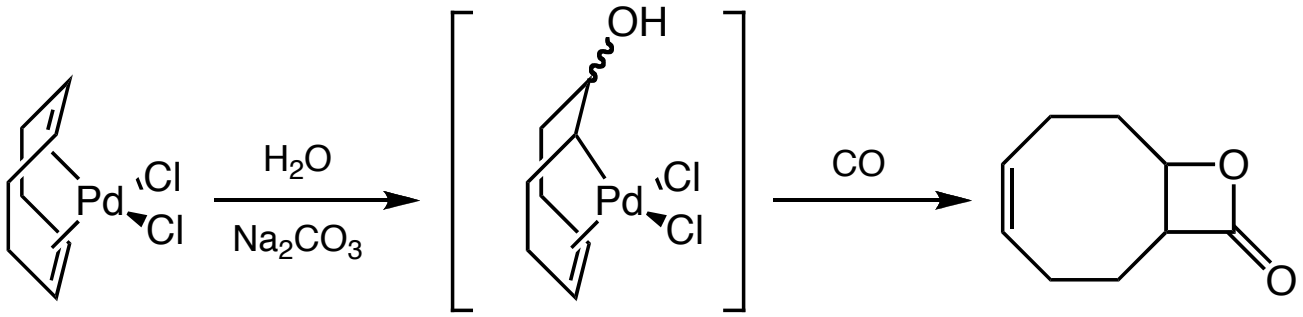
Early Stereochemical Studies

Stille's Work Suggests Anti Hydroxypalladation Mechanism



Key: CO insertion proceeds with retention of stereochemistry at the migrating stereocenter.

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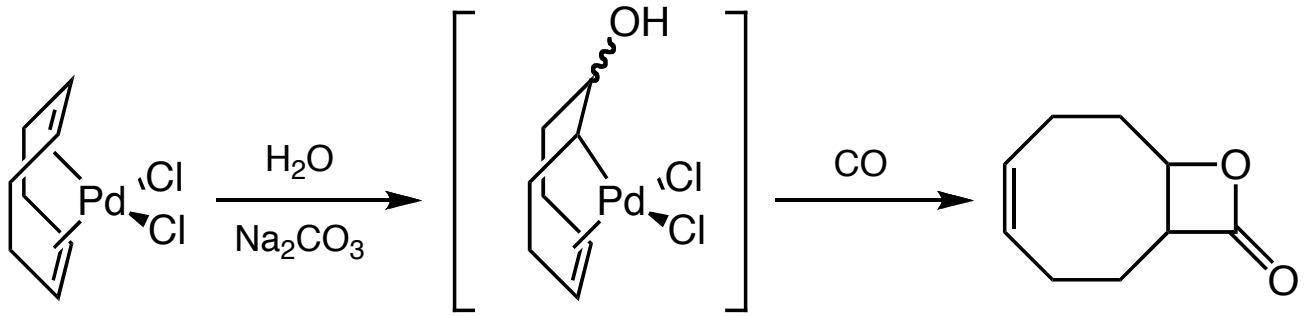

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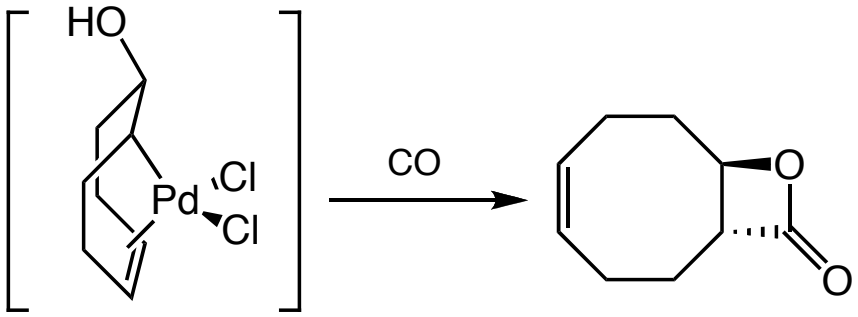
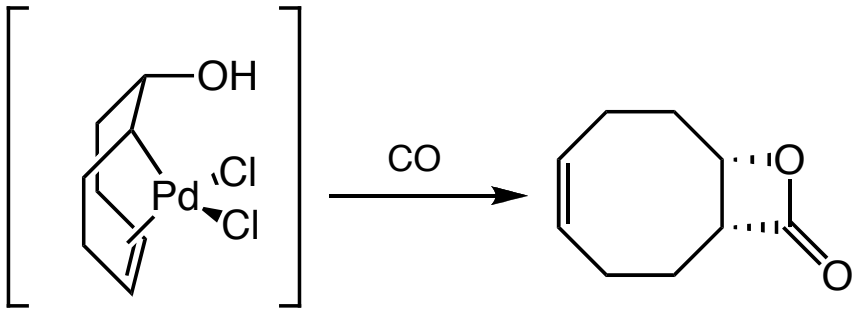


anti hydroxypalladation



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Early Stereochemical Studies

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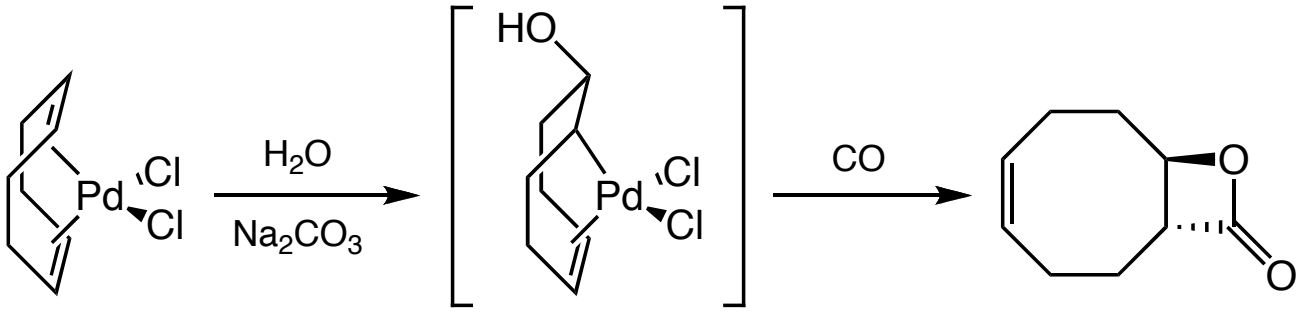

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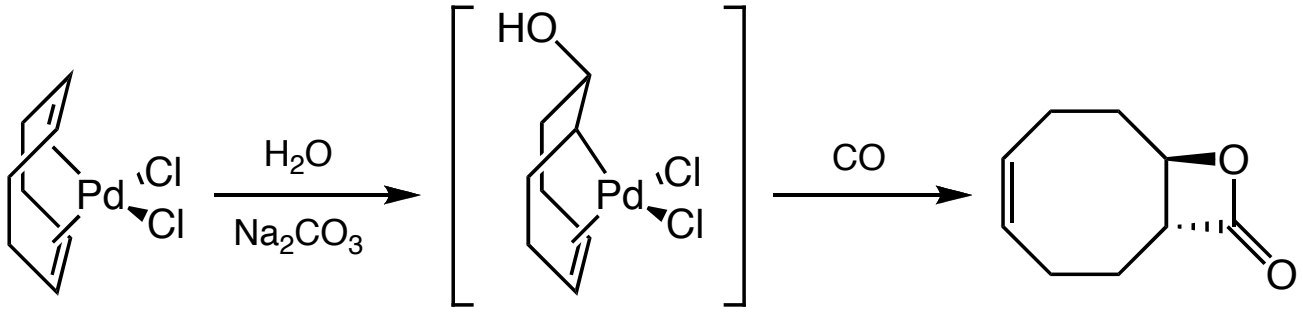

anti hydroxypalladation

Criticism:

- Olefin is unable to rotate into the square plane of the $PdCl_2$ making syn hydroxypalladation impossible
- Ligand exchange to give $Pd(cod)(H_2O)Cl$ would result in a cationic intermediate and is unlikely

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Early Stereochemical Studies

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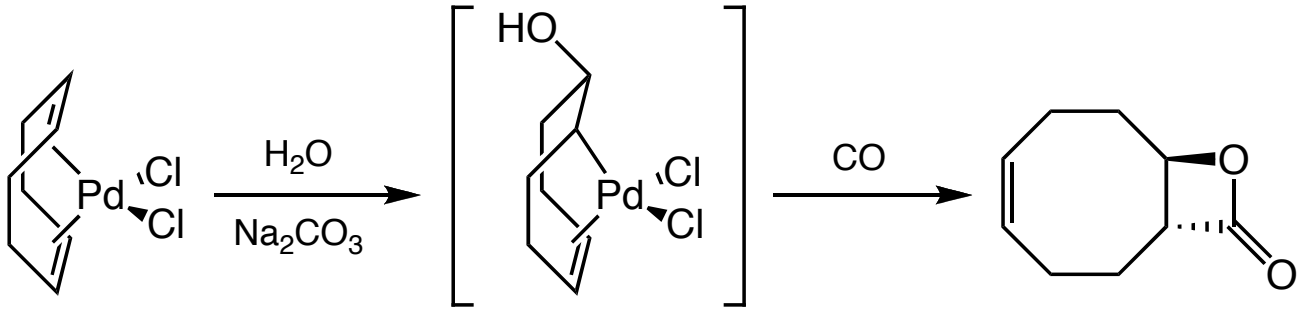

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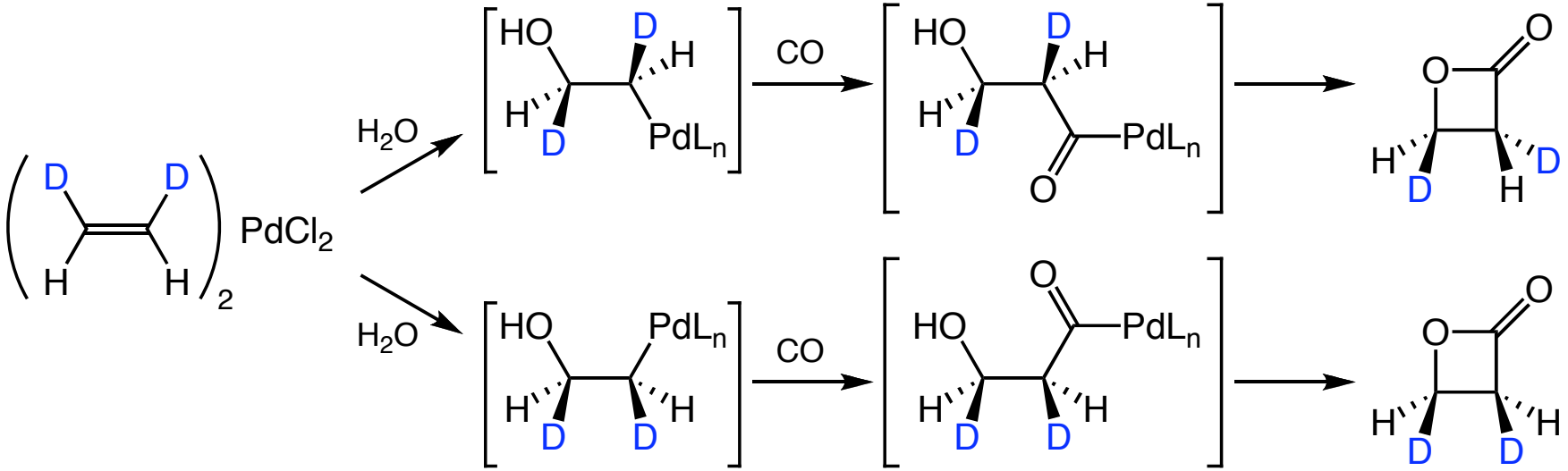

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Early Stereochemical Studies

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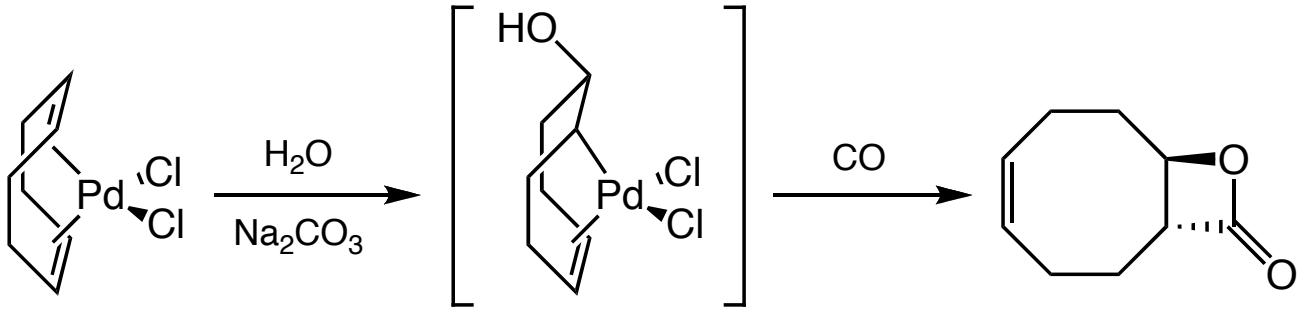

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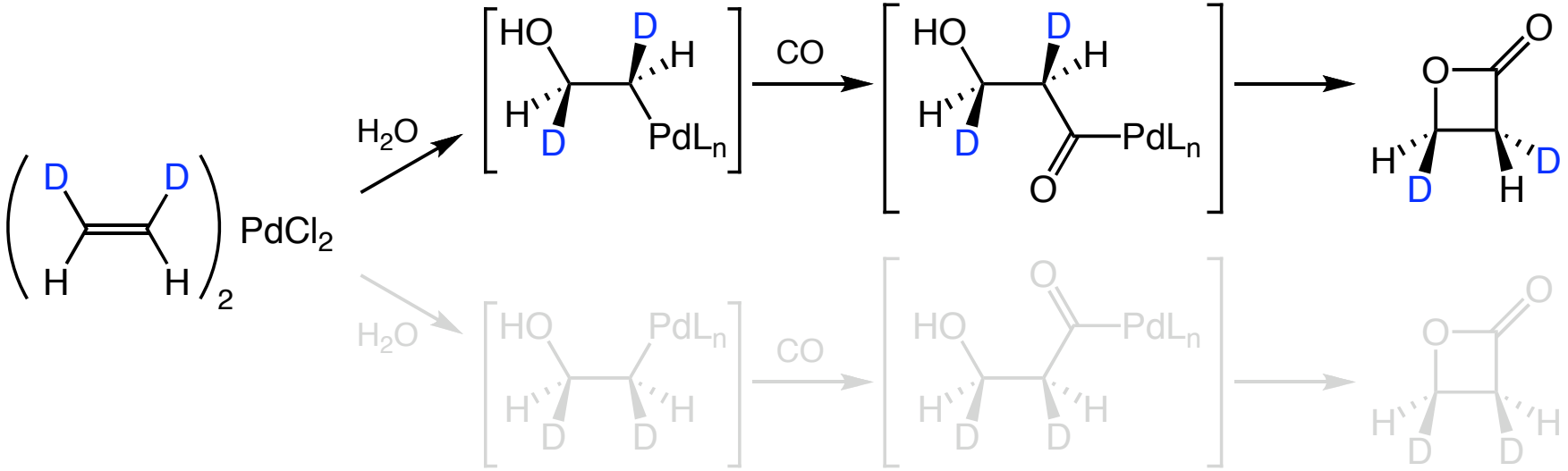

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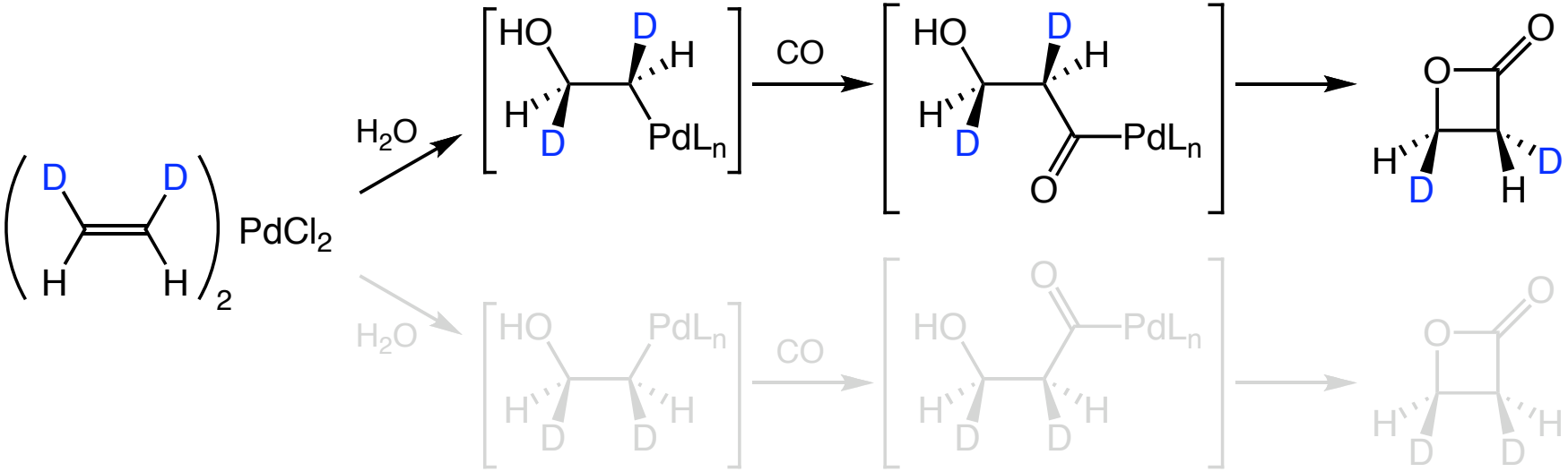
Early Stereochemical Studies

Stille's Work Suggests Anti Hydroxypalladation Mechanism

Criticism:

- Solvent is acetonitrile not water.
- Might proceed through a dimeric Pd complex.
- CO (3 atm) is very coordinating and might occupy coordination sites prohibiting the ligation of water necessary for syn hydroxypalladation.

***anti* hydroxypalladation**



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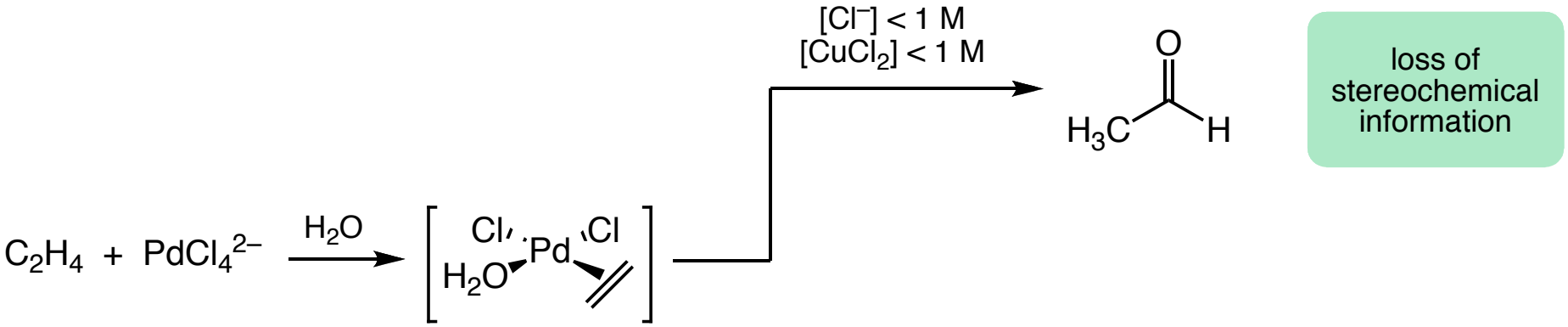
Bäckvall's Stereochemical Studies

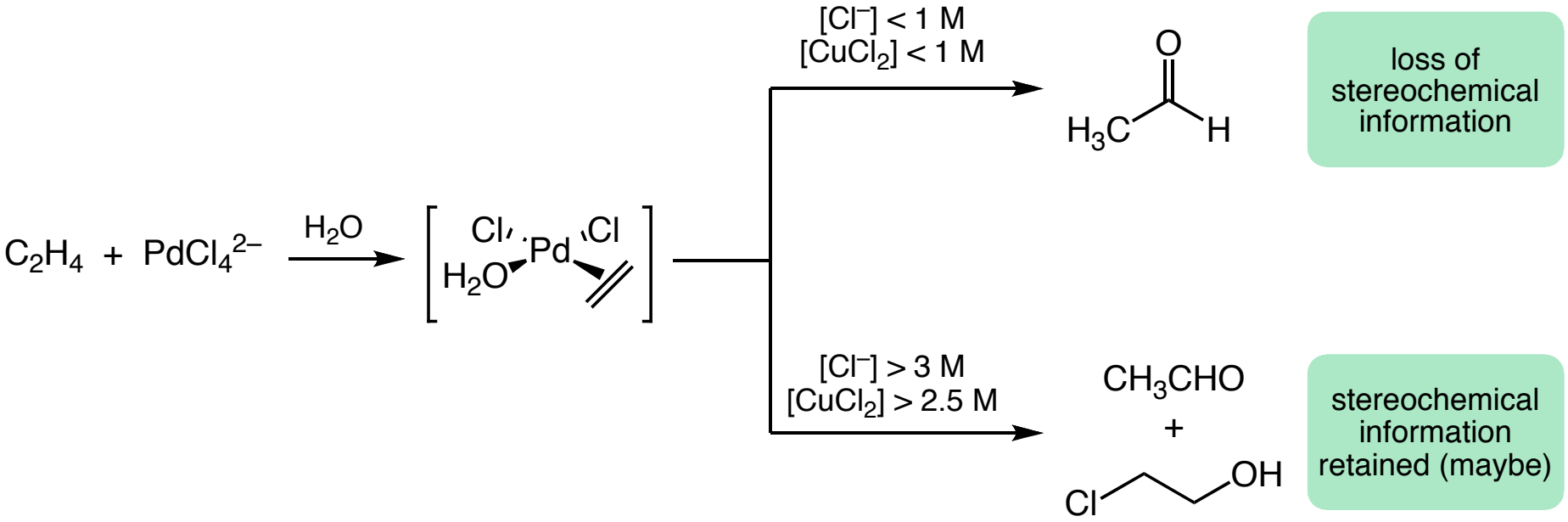
Further (More Convincing) Evidence for Outer-Sphere Anti Hydroxypalladation



Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

Bäckvall's Stereochemical Studies

Further (More Convincing) Evidence for Outer-Sphere Anti Hydroxypalladation



Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

Bäckvall's Stereochemical Studies

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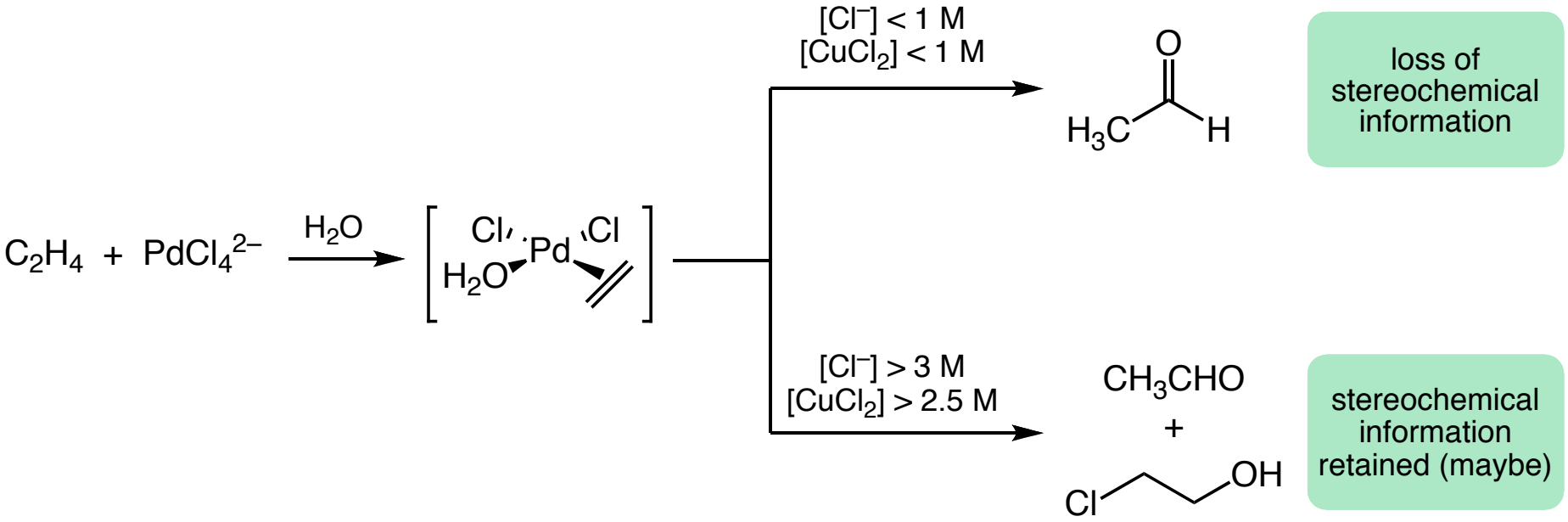

Two Key Assumptions:

- Chlorohydrin and acetaldehyde form from the same intermediate (i.e., $[Pd(CH_2CH_2OH)(H_2O)Cl_2]^-$).
- The steric course of the reaction is not affected by conditions containing high $[Cl^-]$ and high $[CuCl_2]$.

Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

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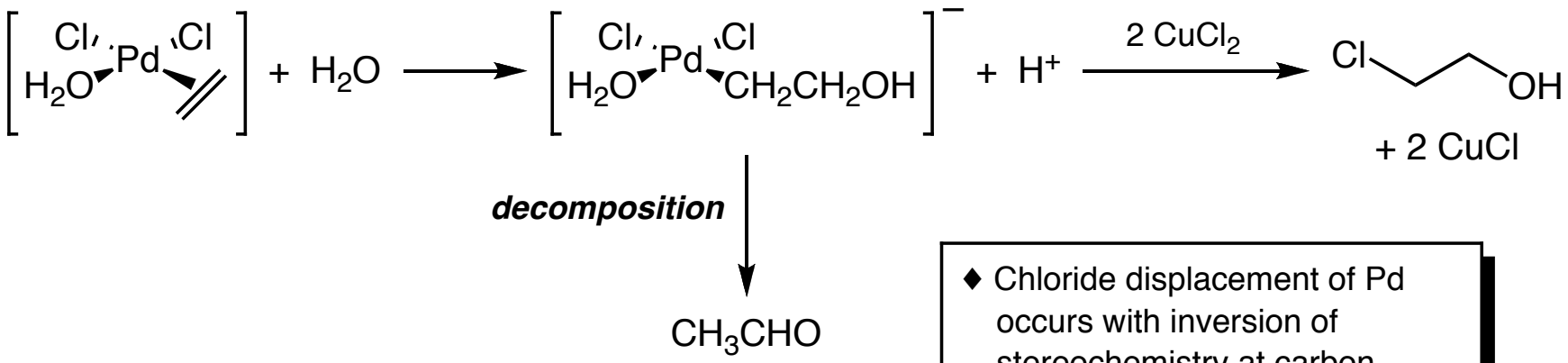

- Chloride displacement of Pd occurs with inversion of stereochemistry at carbon.
- Chlorohydrin formation requires *both* high [Cl^-] and high [$CuCl_2$].

Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

Bäckvall's Stereochemical Studies

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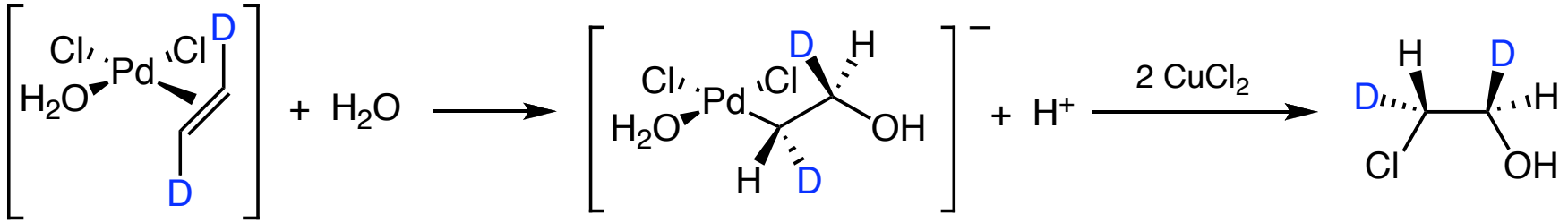

anti hydroxypalladation

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Bäckvall's Stereochemical Studies

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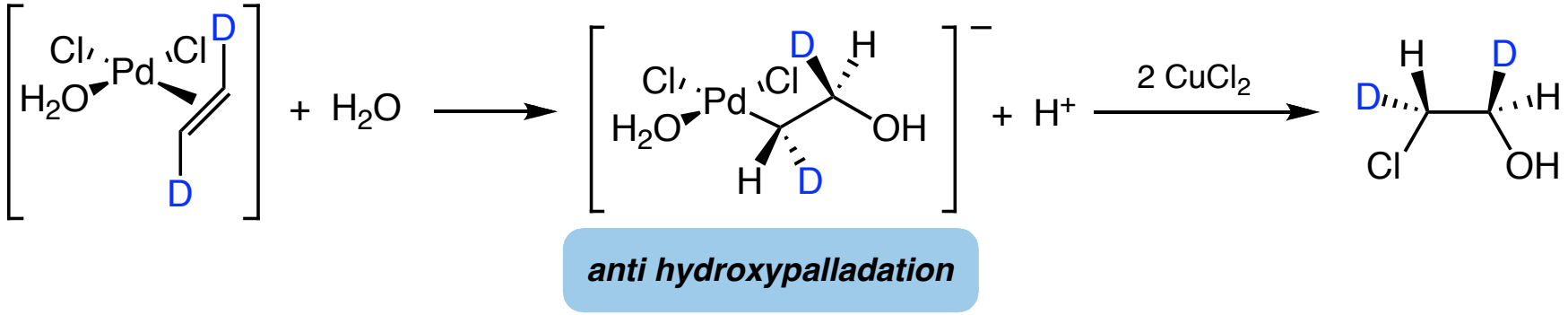
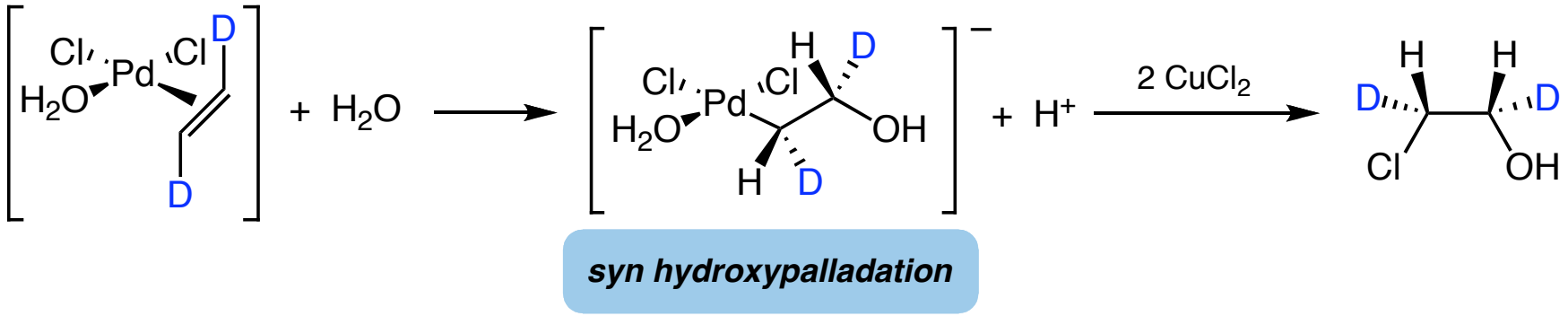


anti hydroxypalladation



syn hydroxypalladation

Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

Bäckvall's Stereochemical Studies

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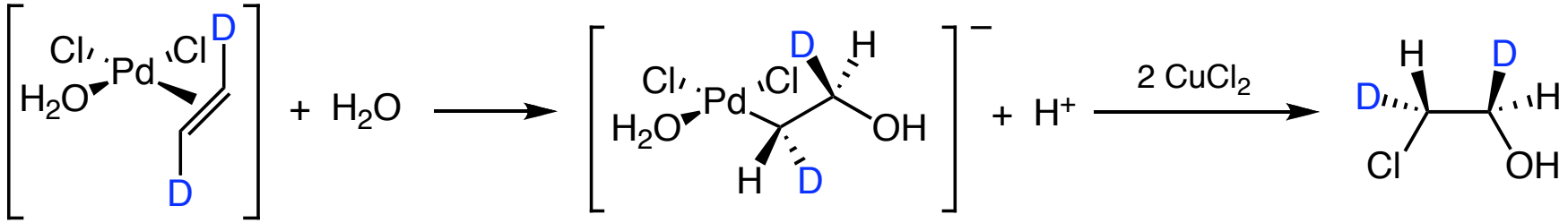


anti hydroxypalladation

syn hydroxypalladation

Control Experiments:

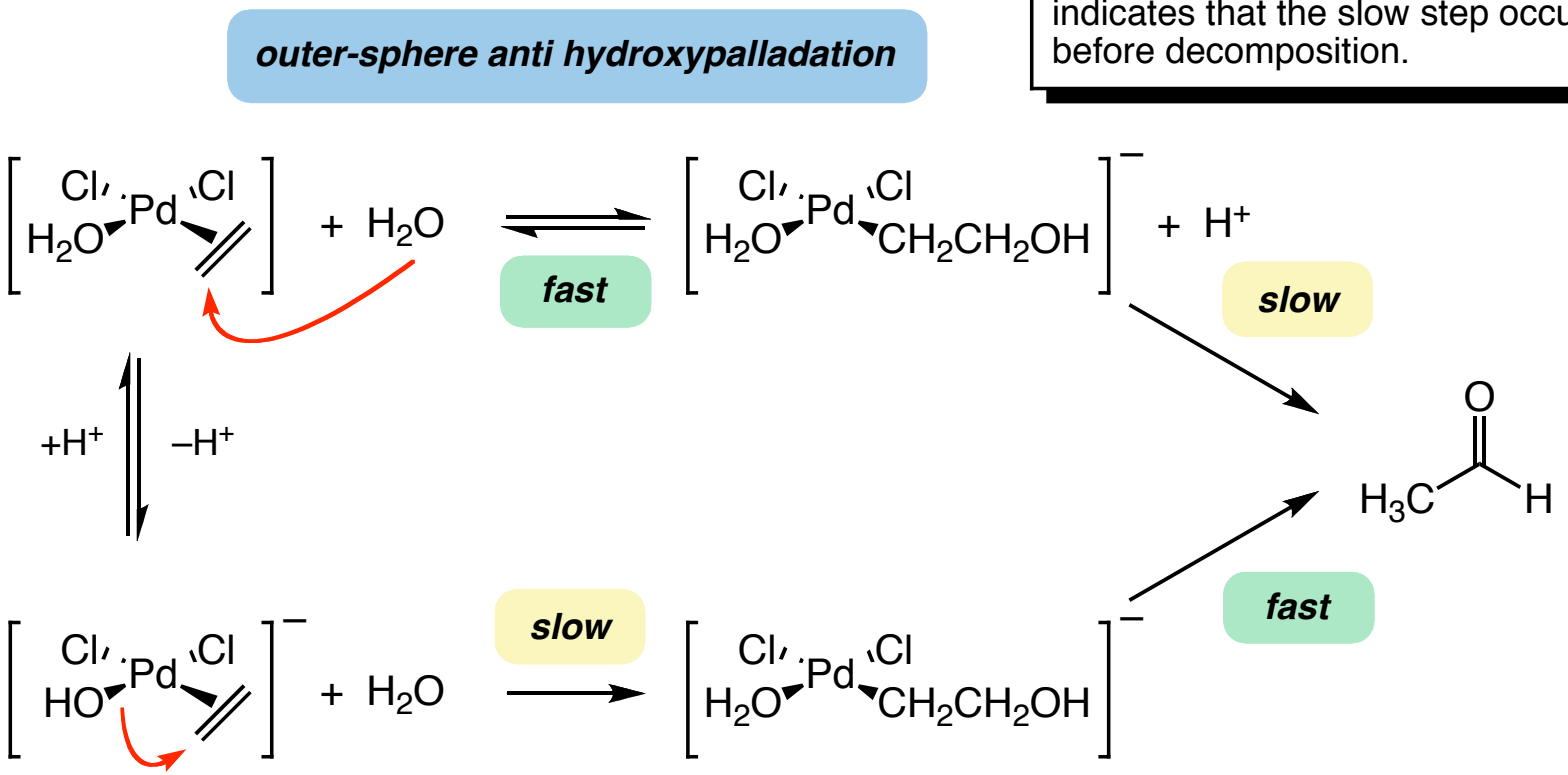
- *Z*/*E* isomerization is < 1% under the reaction conditions.
- Cofirmed that cleavage of C–Pd bond with $CuCl_2$ occurs with inversion at carbon.
- Confirmed that chlorohydrin does not arise from an intermediate epoxide.

Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

Bäckvall's Stereochemical Studies

An Apparent Contradiction with KIE Studies

KIE 1.07 and competitive KIE of 1.70 indicates that the slow step occurs before decomposition.



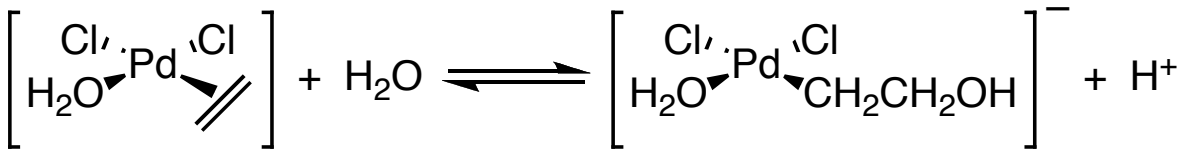
anti pathway has decomposition as the slow step

syn pathway has hydroxypalladation as the slow step

Henry, P. M. *J. Org. Chem.* **1973**, *38*, 2415. Kosaki, M.; Isemura, M.; Kitaura, K.; Schinoda, S.; Saito, Y. *J. Mol. Catal.* **1977**, *2*, 351. Saito, Y.; Schinoda, S. *J. Mol. Catal.* **1980**, *9*, 461.

Bäckvall's Stereochemical Studies

Reconciling Stereochemical Results with Kinetic Data



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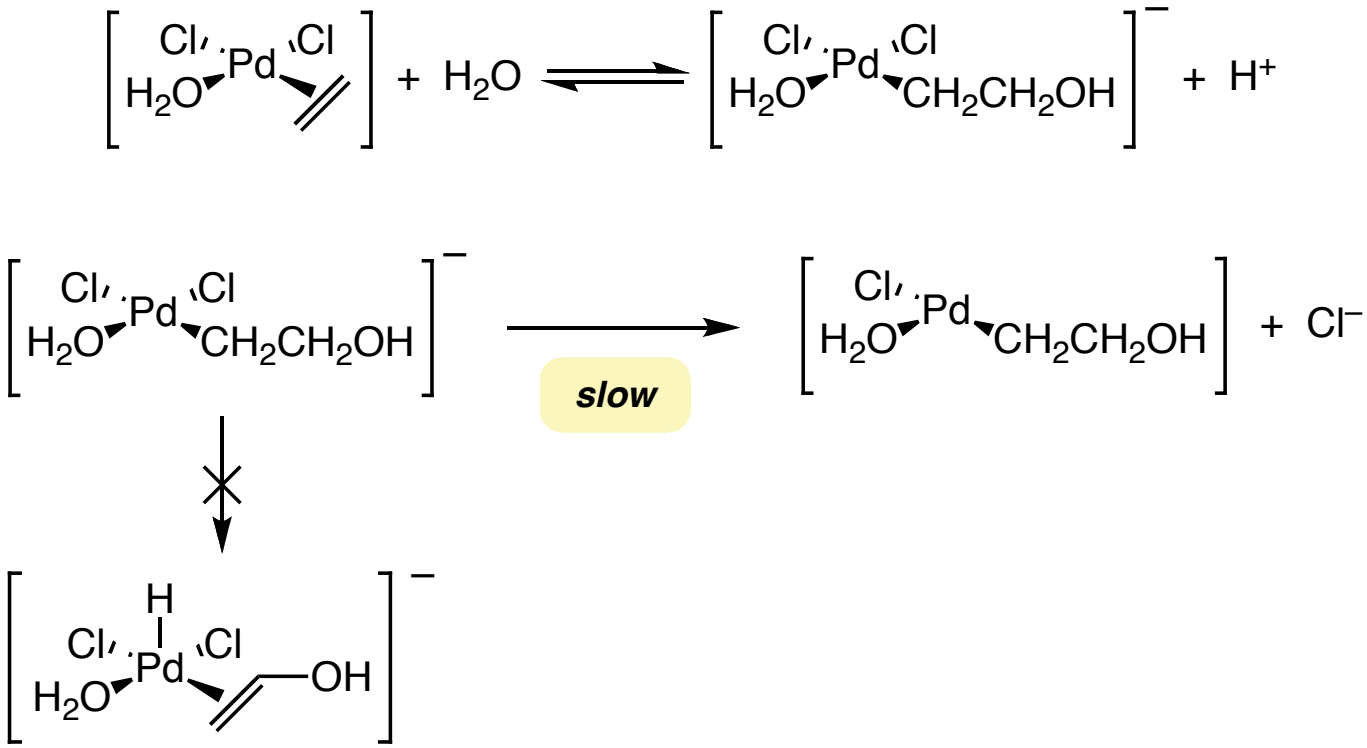

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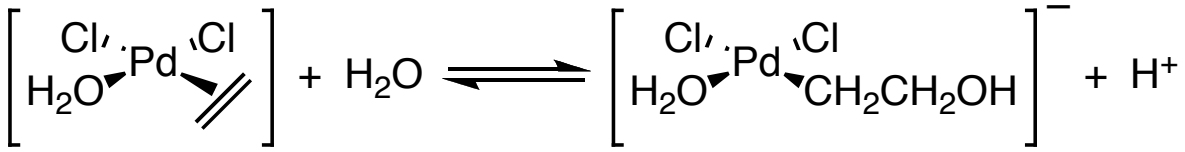
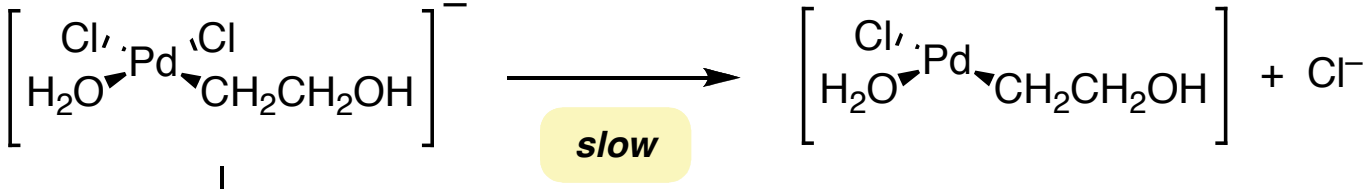
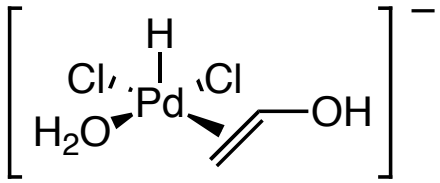
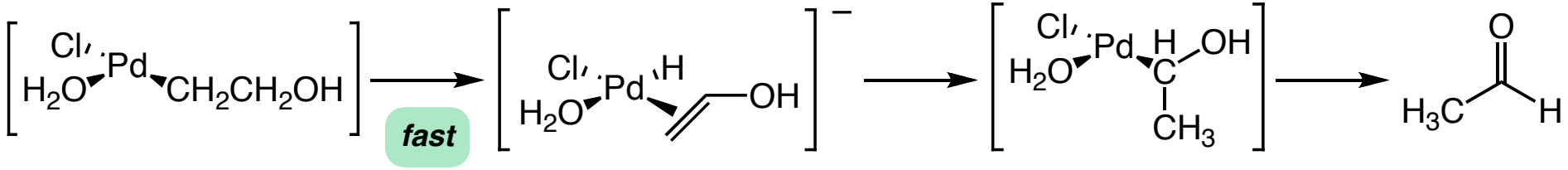






Since decomposition occurs after the rate-limiting step a primary isotope effect would not be predicted.



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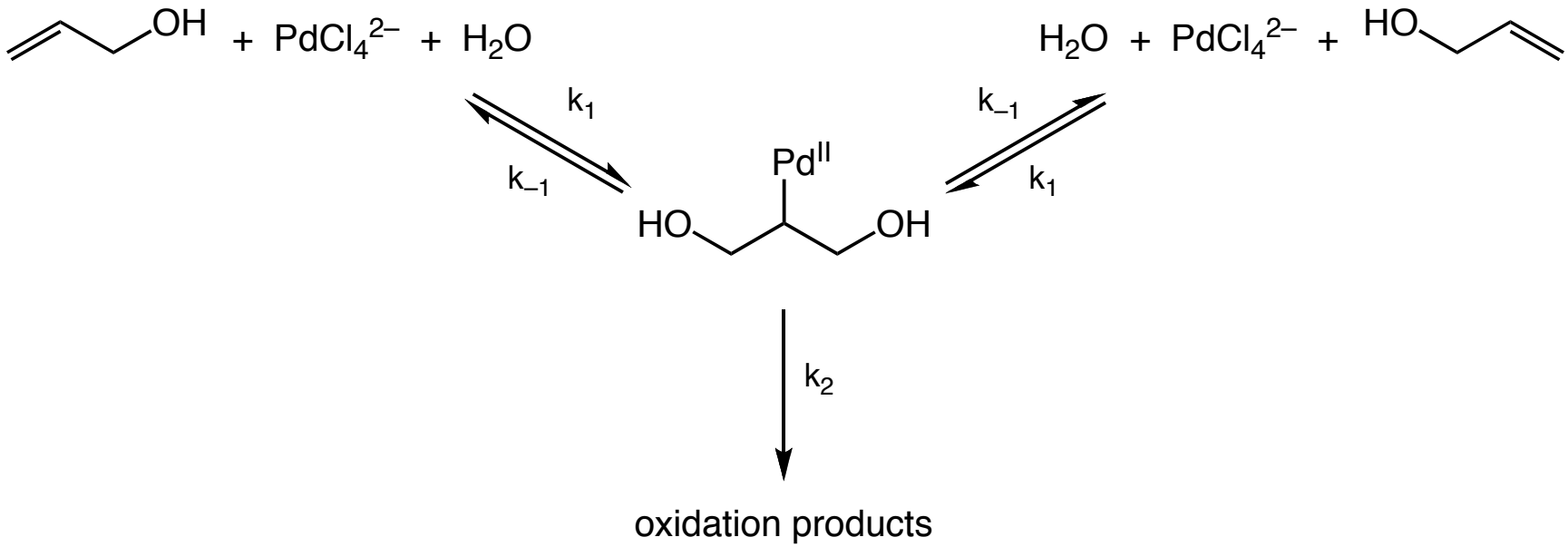
Evidence for Syn Hydroxypalladation

The Isomerization of Allyl Alcohol Under Wacker Conditions



Oxidation of allyl alcohol is directed by the hydroxyl group

Gregor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

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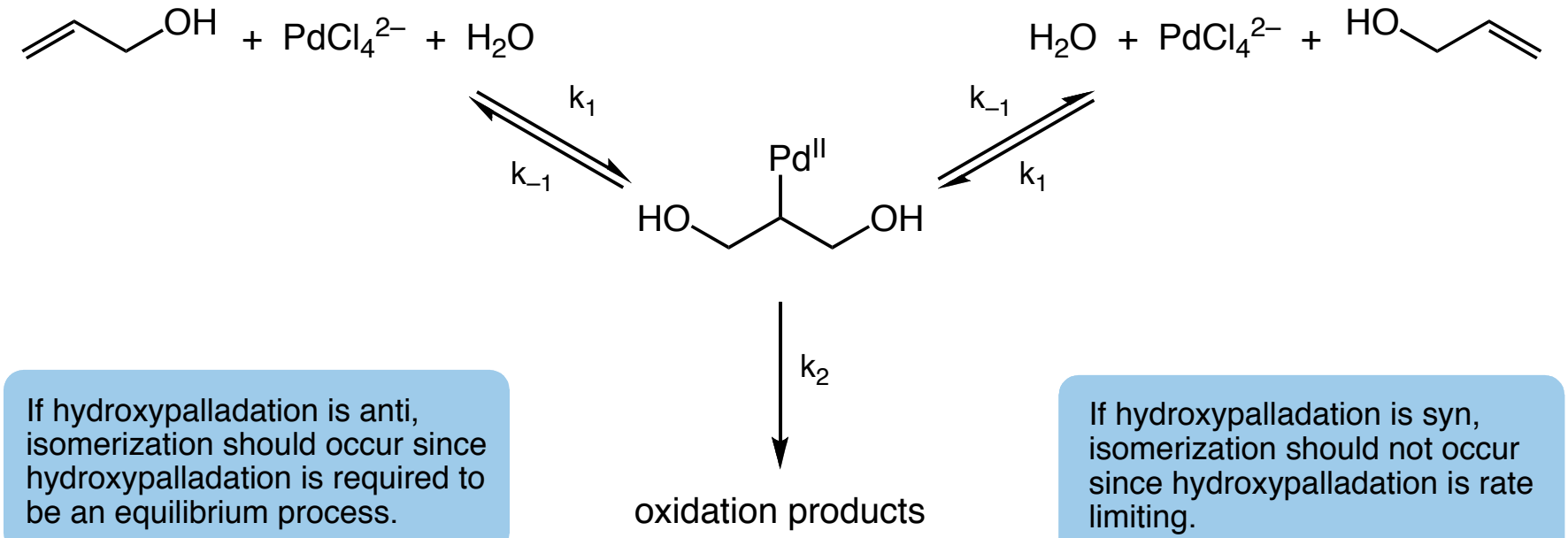

If hydroxypalladation is anti, isomerization should occur since hydroxypalladation is required to be an equilibrium process.

If hydroxypalladation is syn, isomerization should not occur since hydroxypalladation is rate limiting.

Oxidation of allyl alcohol is directed by the hydroxyl group

$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]^2\,[H^+]}$$

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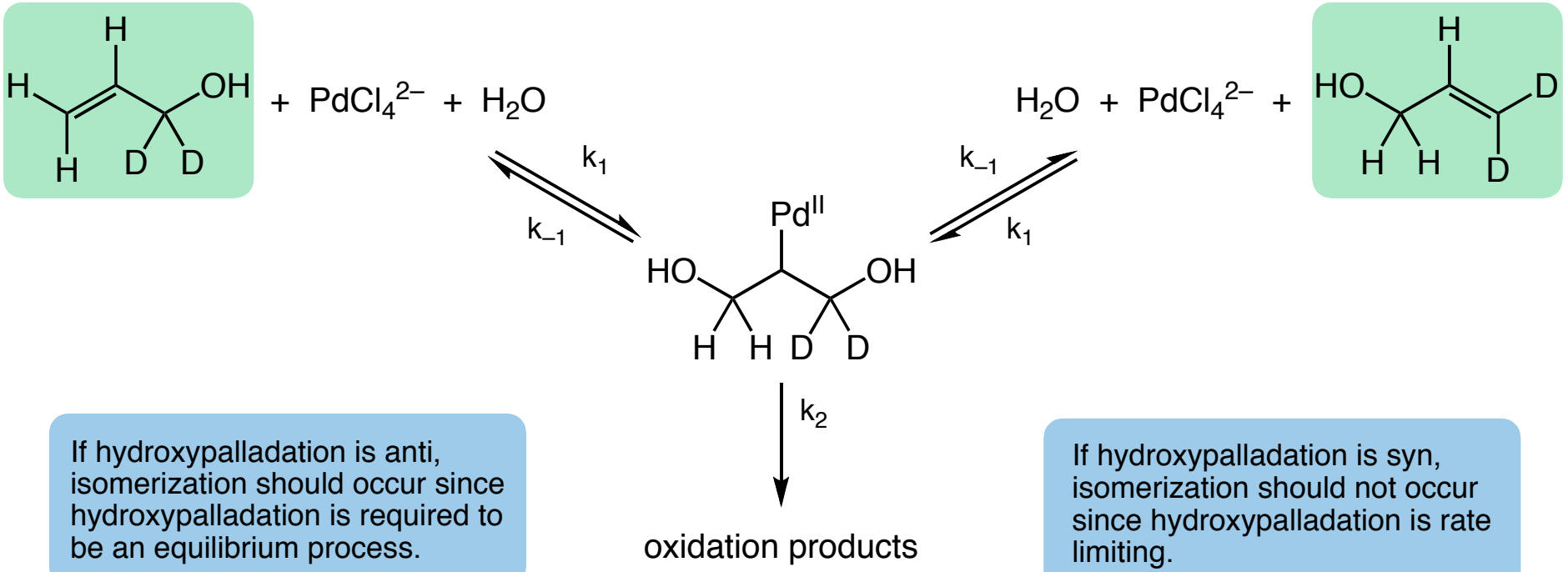

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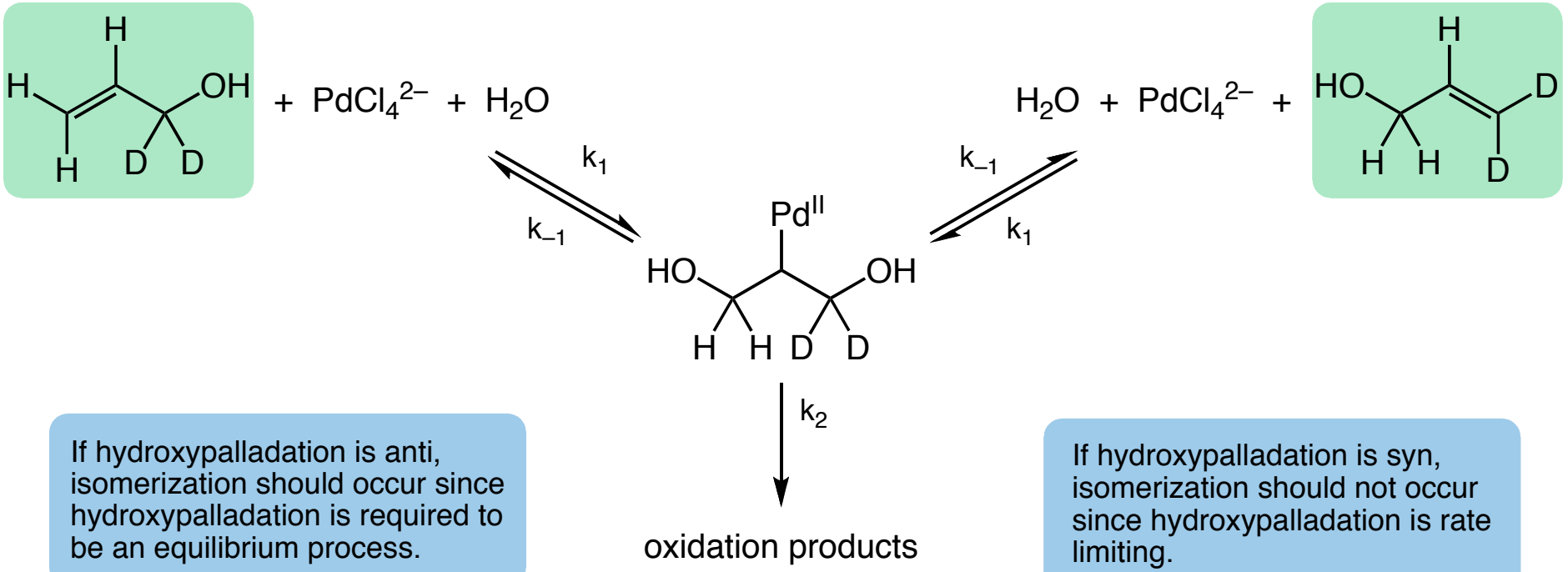


If hydroxypalladation is anti, isomerization should occur since hydroxypalladation is required to be an equilibrium process.

If hydroxypalladation is syn, isomerization should not occur since hydroxypalladation is rate limiting.

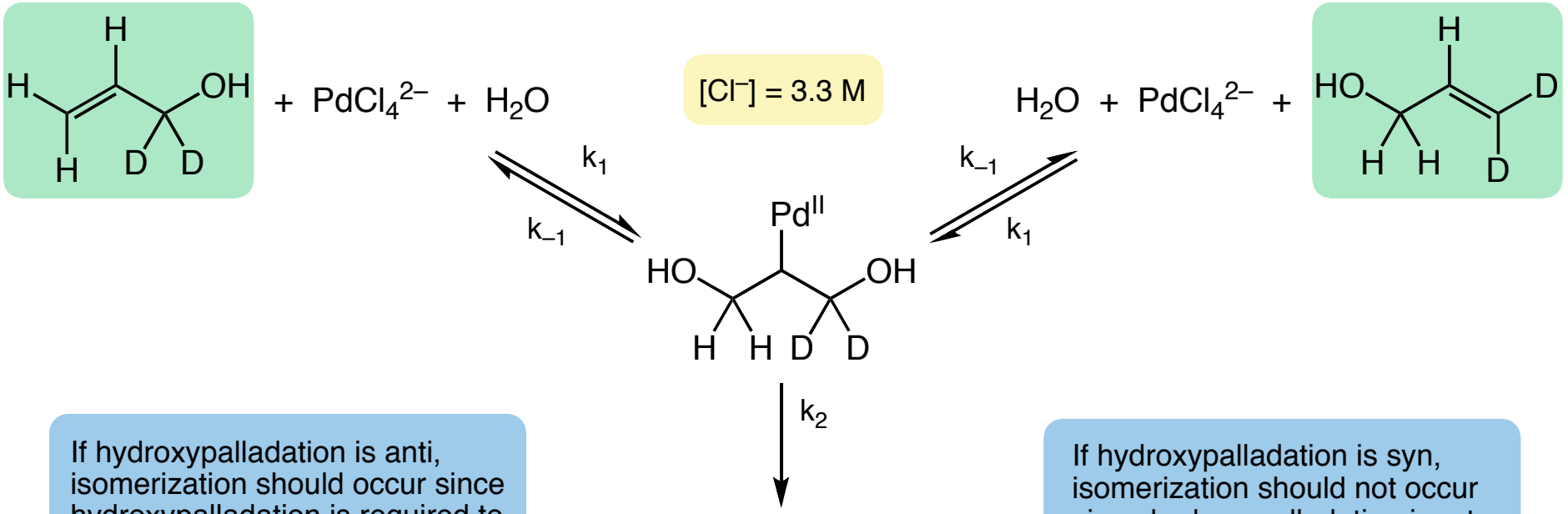
Isomerization product was < 3% of the total deuterated allyl alcohol when the reaction was stopped after one half-life.

Hydroxypalladation is NOT an equilibrium process!

Gregor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

Evidence for Syn Hydroxypalladation

The Isomerization of Allyl Alcohol Under Isomerization Conditions



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$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]}$$

Only isomerization observed.

Gregor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

Evidence for Syn Hydroxypalladation

The Isomerization of Allyl Alcohol Under Isomerization Conditions

Reactions at high and low chloride do not proceed through the same mechanism.

Formation of aldehyde and chlorohydrin does not occur through a common hydroxypalladation intermediate.

If hydrox… isomeriz… hydroxypalladation is required to be an equilibrium process.

…syn, …occur since hydroxypalladation is rate limiting.

oxidation products

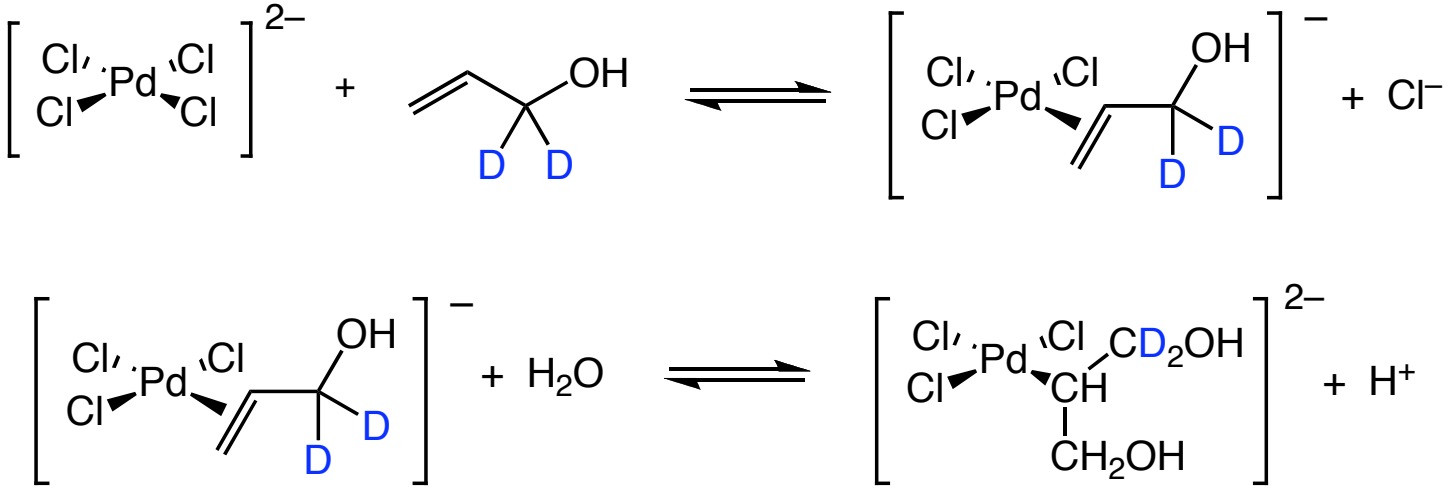
$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]}$$

Only isomerization observed.

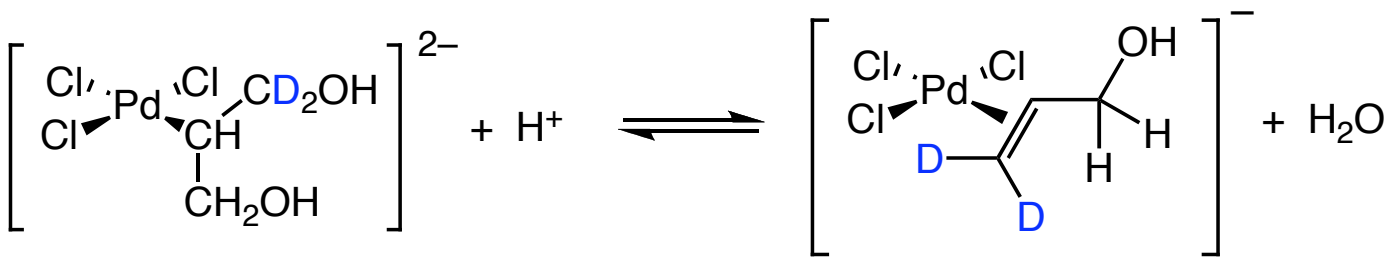
Gregor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

Anti Hydroxypalladation at High [Cl⁻]

Henry's Proposed Pathway



outer-sphere anti hydroxypalladation



Gregor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

Anti Hydroxypalladation at High [Cl⁻]

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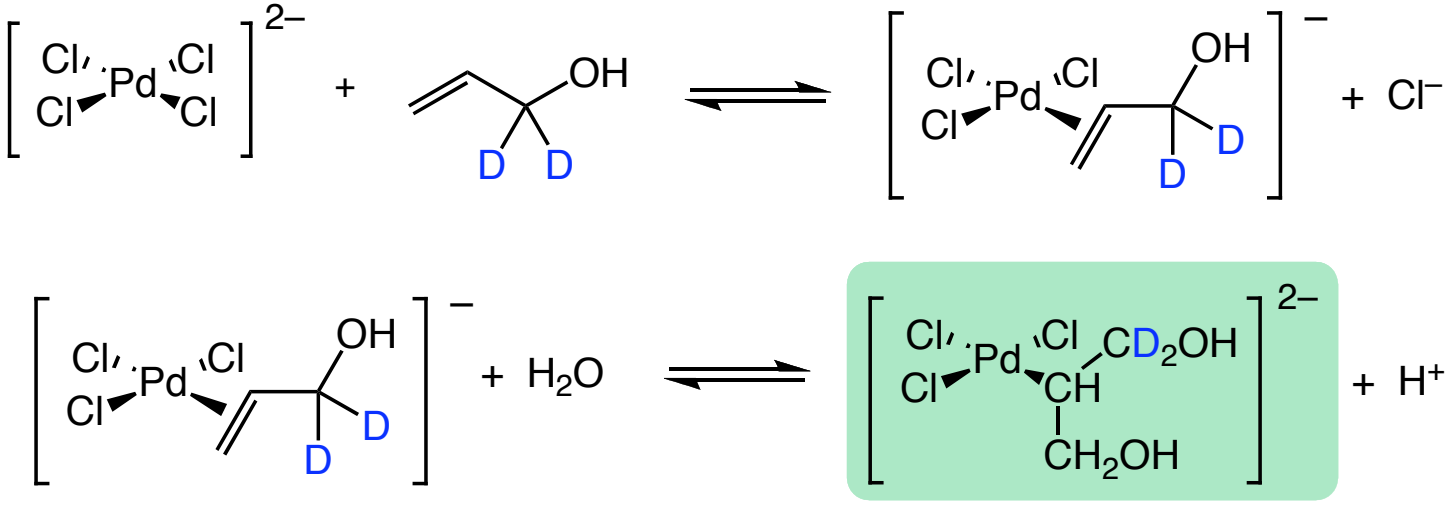

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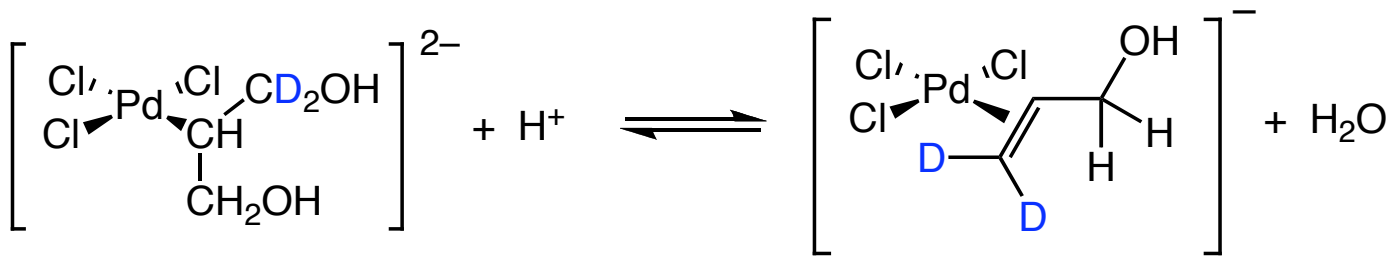
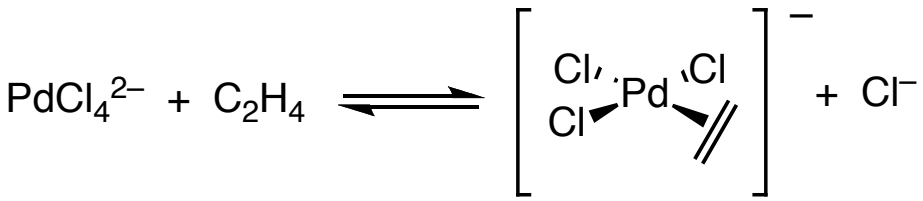


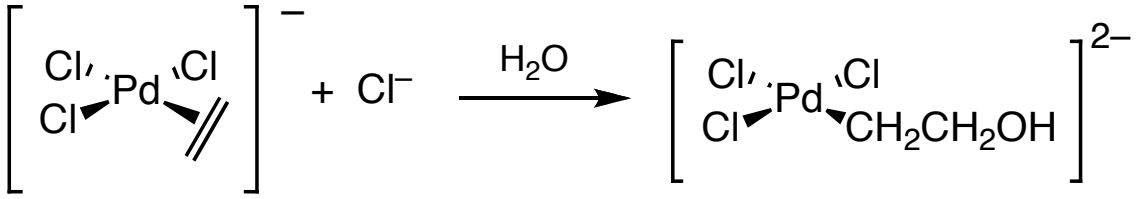
Gregor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

Reinterpreting Bäckvall's Results

Henry's Proposed Pathway

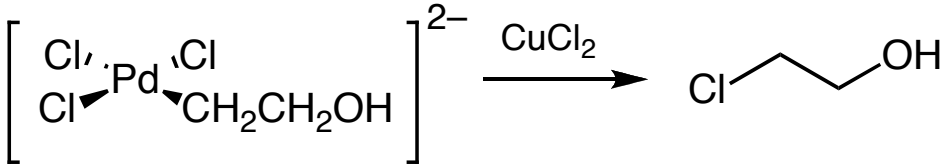


Cl^- ligand loss prevented by high concentration of Cl^-.



Excess Cl^- prevents this intermediate from undergoing decomposition to oxidation products.

outer-sphere anti hydroxypalladation

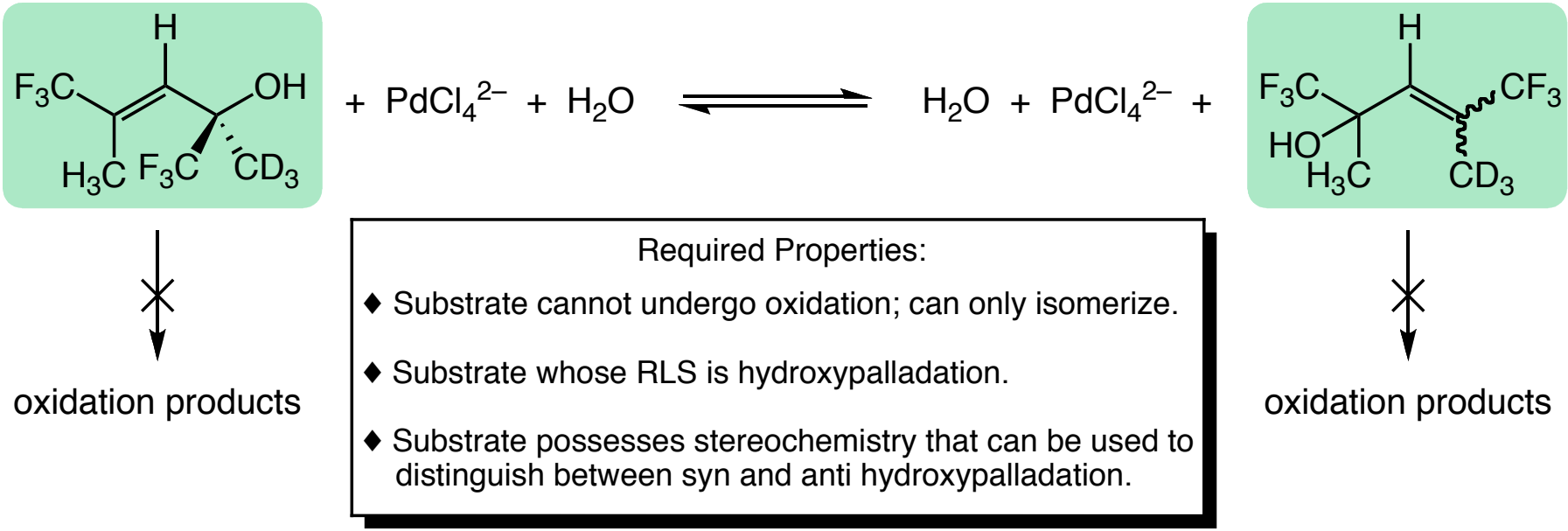


Assumption that oxidation products and chlorohydrin arise from a common intermediate is NOT valid.

Gregor, N.; Zaw, K.; Henry, P. M. *Organometallics* **1984**, *3*, 1251.

Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe



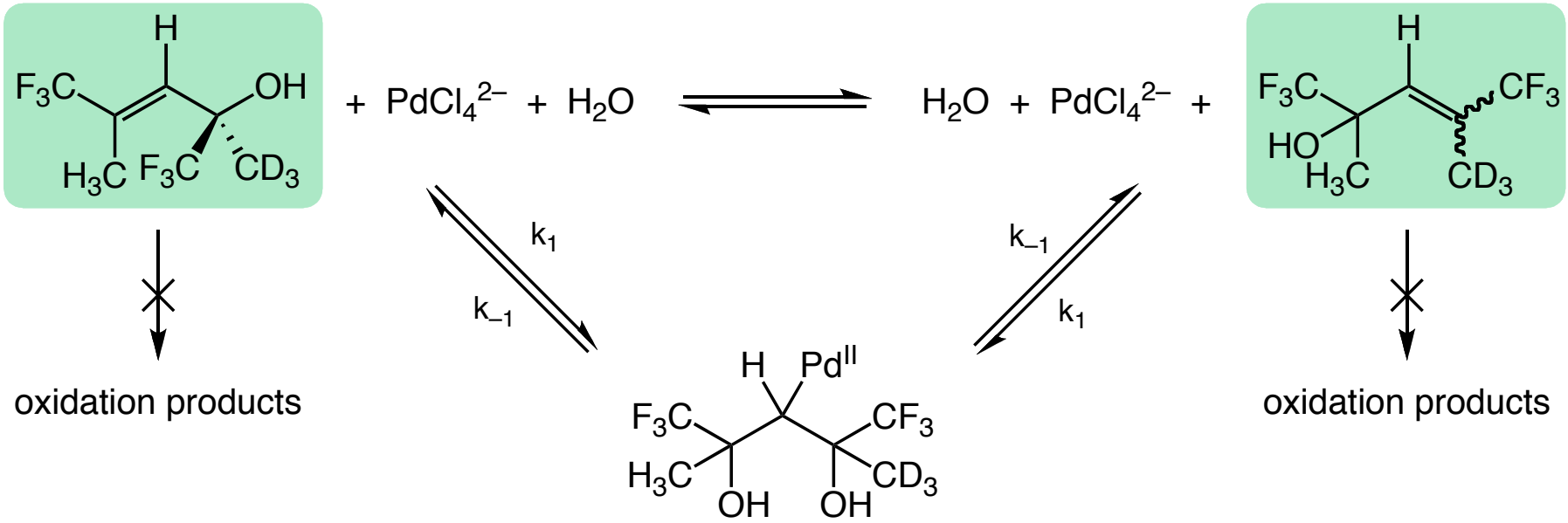
Required Properties:

- Substrate cannot undergo oxidation; can only isomerize.
- Substrate whose RLS is hydroxypalladation.
- Substrate possesses stereochemistry that can be used to distinguish between syn and anti hydroxypalladation.

Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498.

Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe



Exchange is completely symmetric, thus the rate of isomerization depends only on the rate of formation of the hydroxypalladate and not on its equilibrium concentration.

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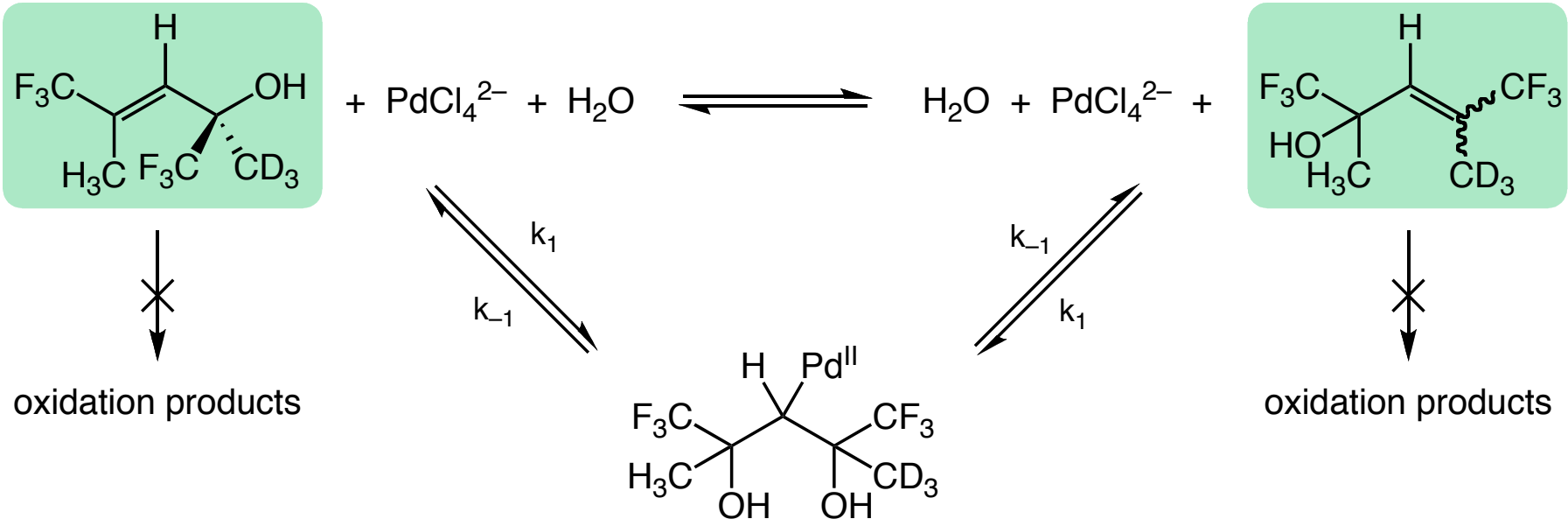
Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe



For syn hydroxypalladation:

$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]^2\,[H^+]}$$

Proton inhibition term must result from an equilibrium that occurs before the rate-limiting hydroxypalladation step.

For anti hydroxypalladation:

$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]}$$

Proton inhibition term does not show up in the exchange rate because it results from this exchange equilibrium.

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Evidence for Syn Hydroxypalladation

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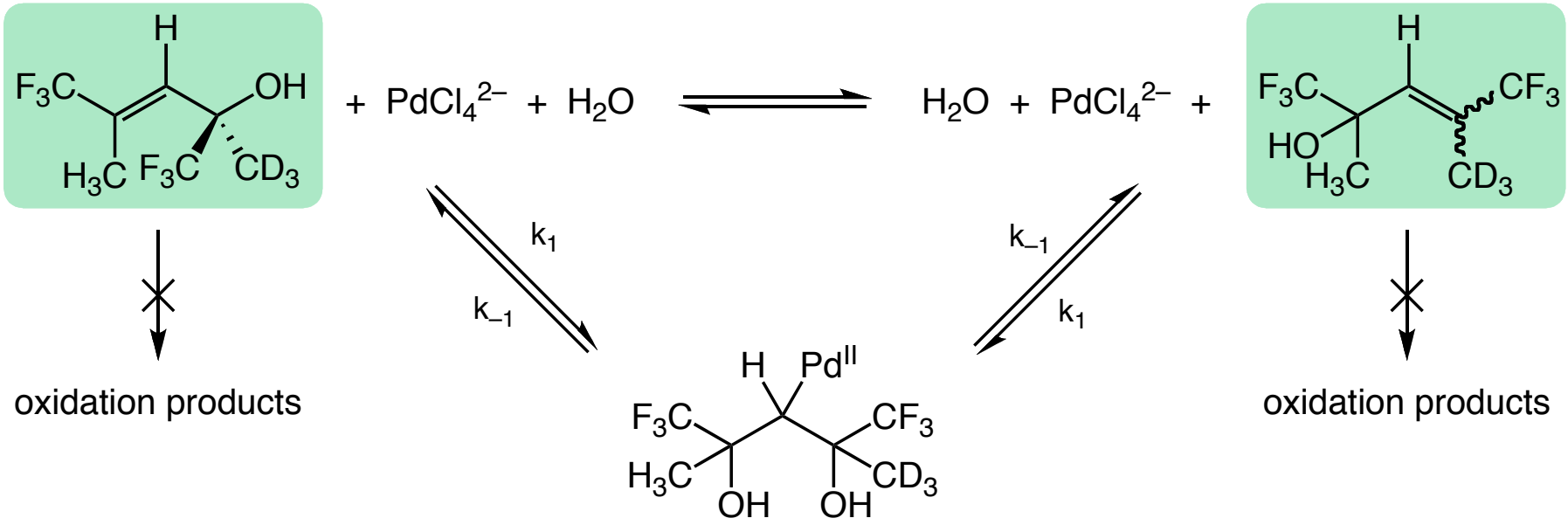

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$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]^2\,[H^+]}$$

Proton inhibition term must result from an equilibrium that occurs before the rate-limiting hydroxypalladation step.

Observed Kinetics under Wacker Conditions:

- Rate expression had a first order proton inhibition term.
- Rate expression was identical to the Wacker rate expression.
- Consistent with syn hydroxypalladation mechanism.

Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498.

Evidence for Syn Hydroxypalladation

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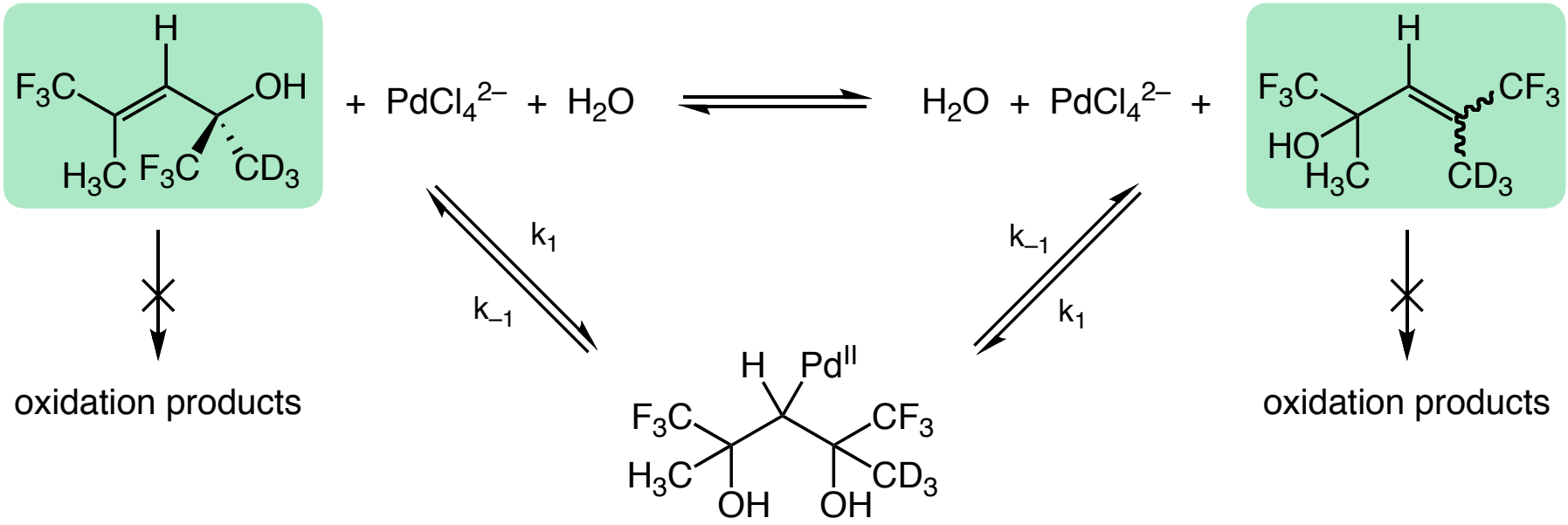


Observed Kinetics under High [Cl^-] Conditions:

- Rate expression had no first order proton inhibition term.
- Rate expression was identical to what Bäckvall observed at high [Cl^-].
- Consistent with anti hydroxypalladation mechanism.

For anti hydroxypalladation:

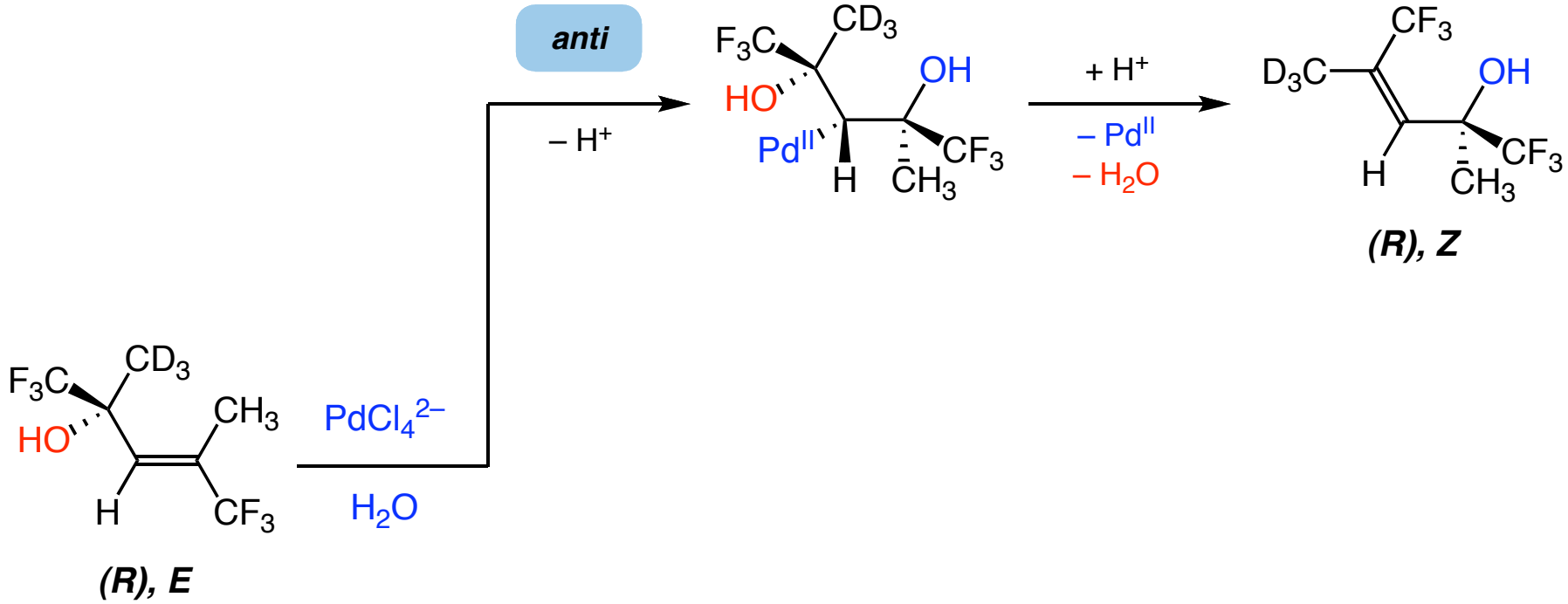
$$\text{Rate} = \frac{-d[C_2H_4]}{dt} = \frac{k\,[PdCl_4^{2-}]\,[\text{olefin}]}{[Cl^-]}$$

Proton inhibition term does not show up in the exchange rate because it results from this exchange equilibrium.

Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498.

Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe



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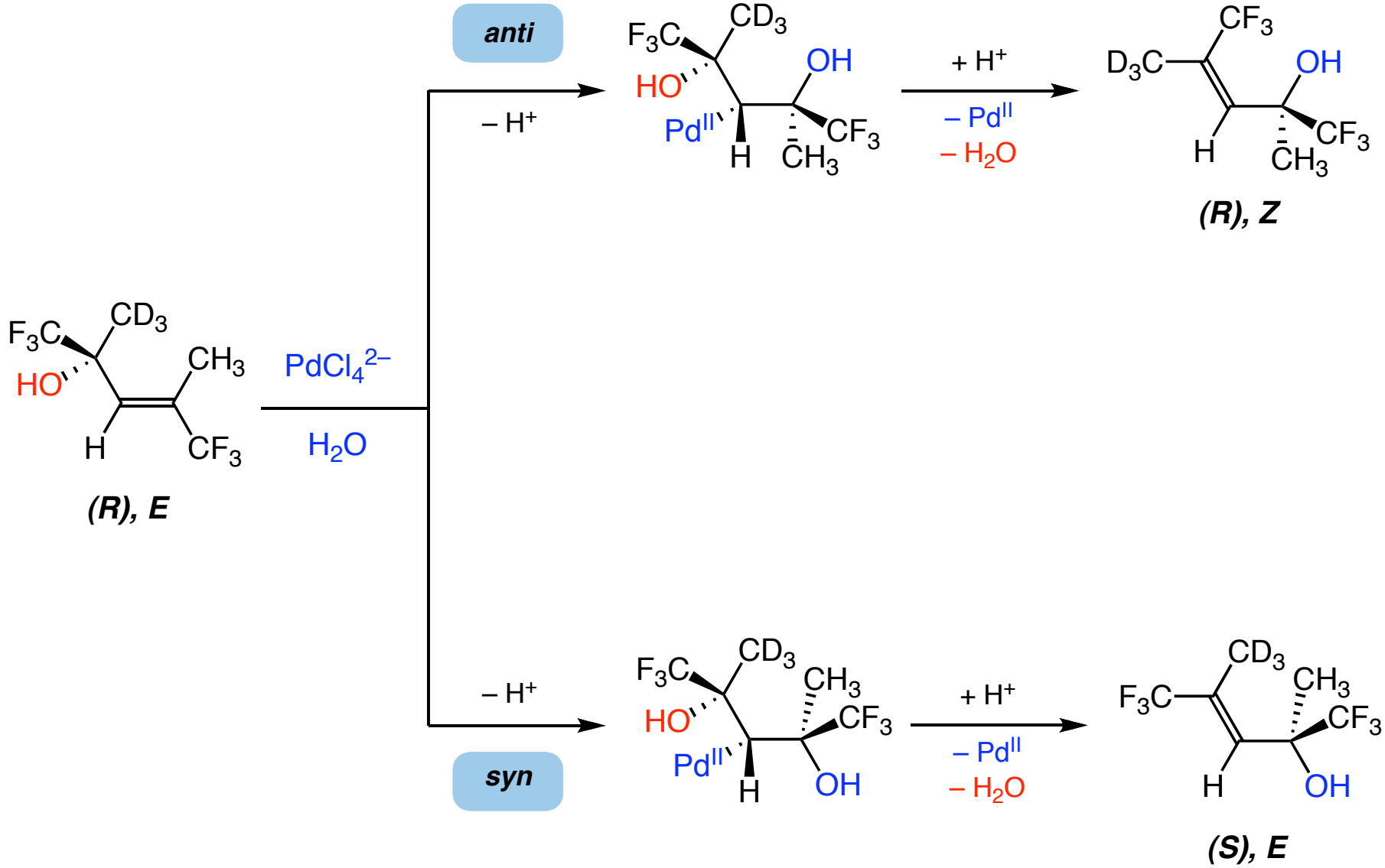

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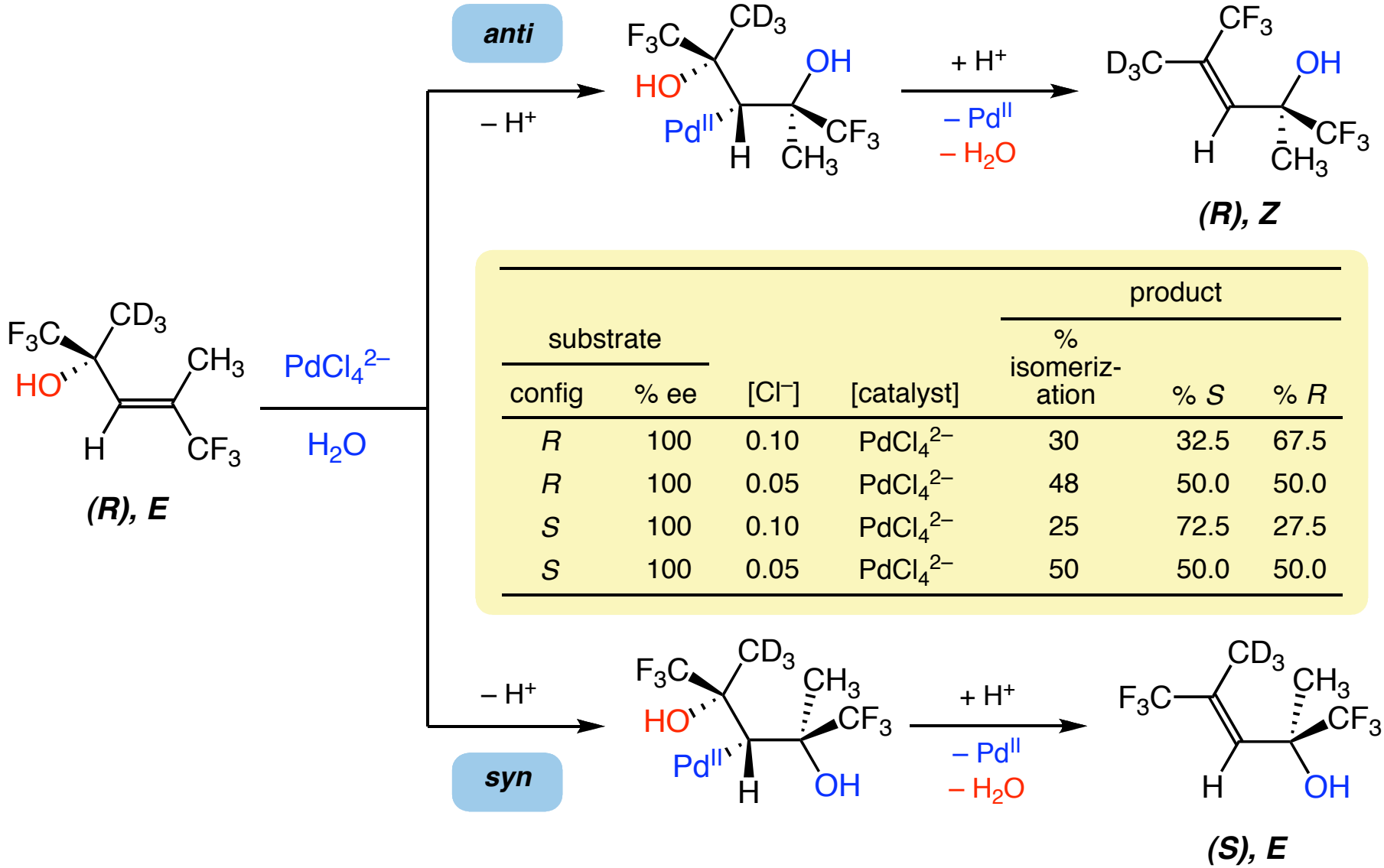
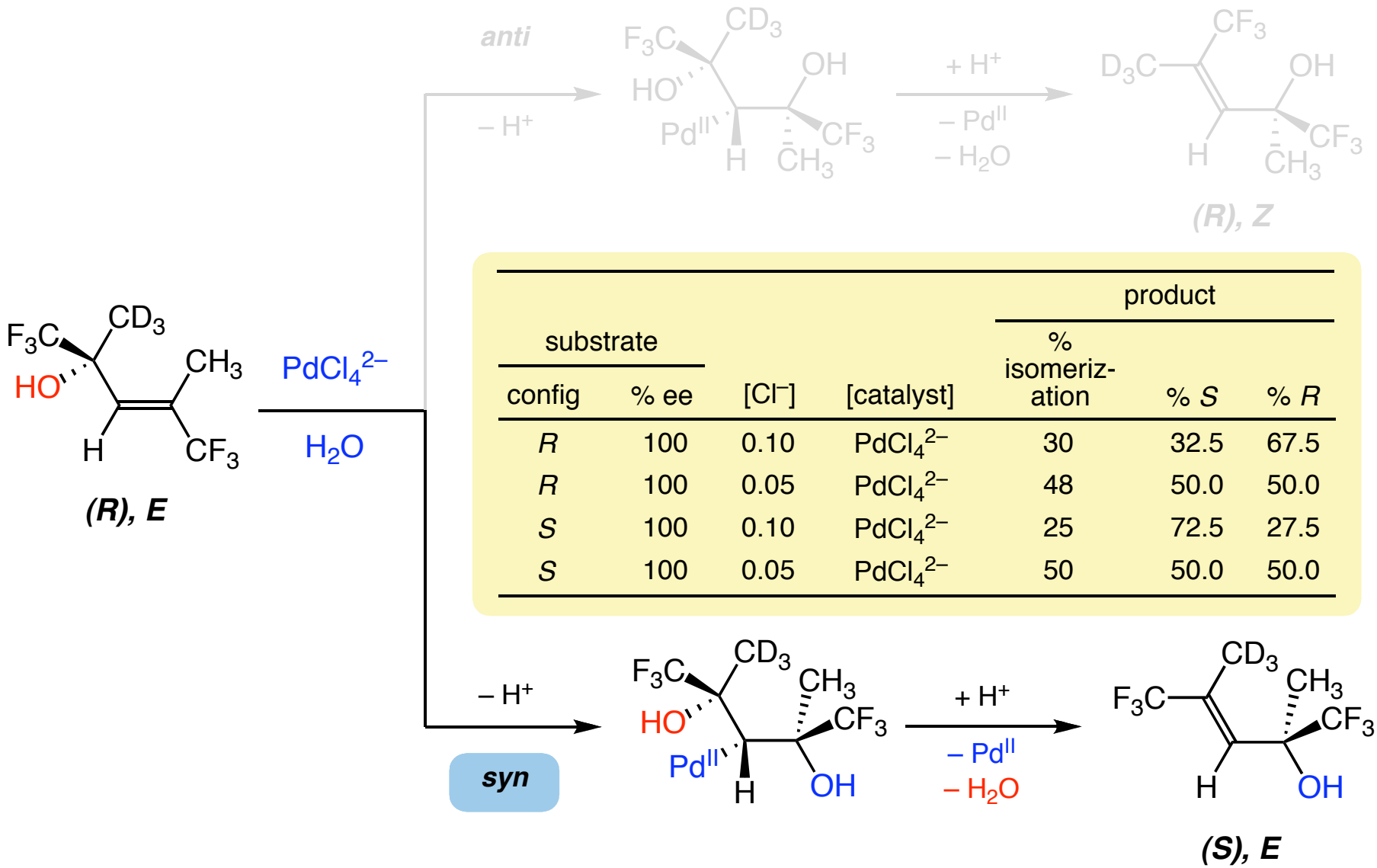


substrate				product		
config	% ee	[Cl⁻]	[catalyst]	% isomerization	% *S*	% *R*
R	100	0.10	$PdCl_4^{2-}$	30	32.5	67.5
R	100	0.05	$PdCl_4^{2-}$	48	50.0	50.0
S	100	0.10	$PdCl_4^{2-}$	25	72.5	27.5
S	100	0.05	$PdCl_4^{2-}$	50	50.0	50.0

Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498.

Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe



substrate				product		
config	% ee	[Cl^-]	[catalyst]	% isomeriz-ation	% *S*	% *R*
R	100	0.10	$PdCl_4^{2-}$	30	32.5	67.5
R	100	0.05	$PdCl_4^{2-}$	48	50.0	50.0
S	100	0.10	$PdCl_4^{2-}$	25	72.5	27.5
S	100	0.05	$PdCl_4^{2-}$	50	50.0	50.0

Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498.

Evidence for Syn Hydroxypalladation

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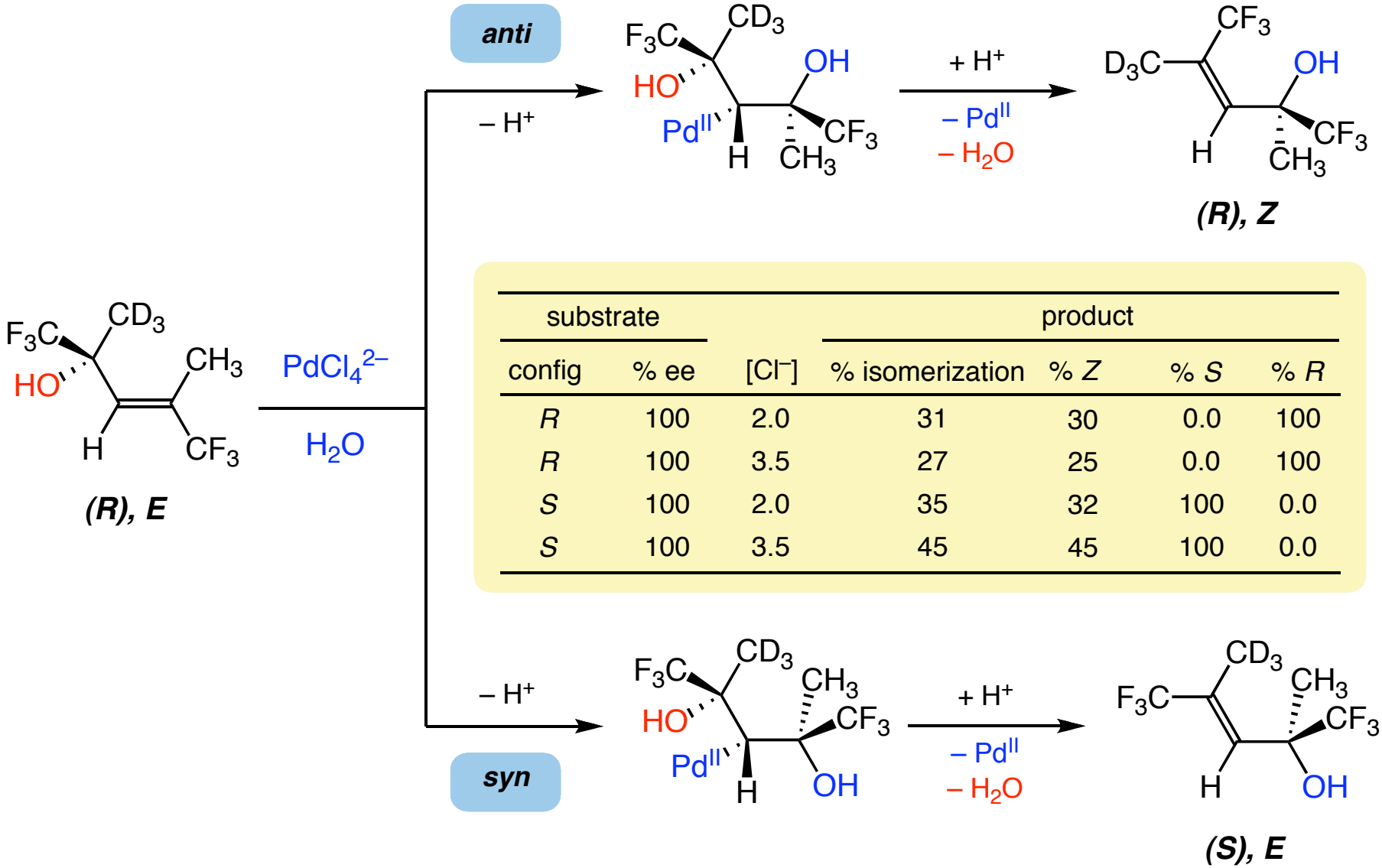
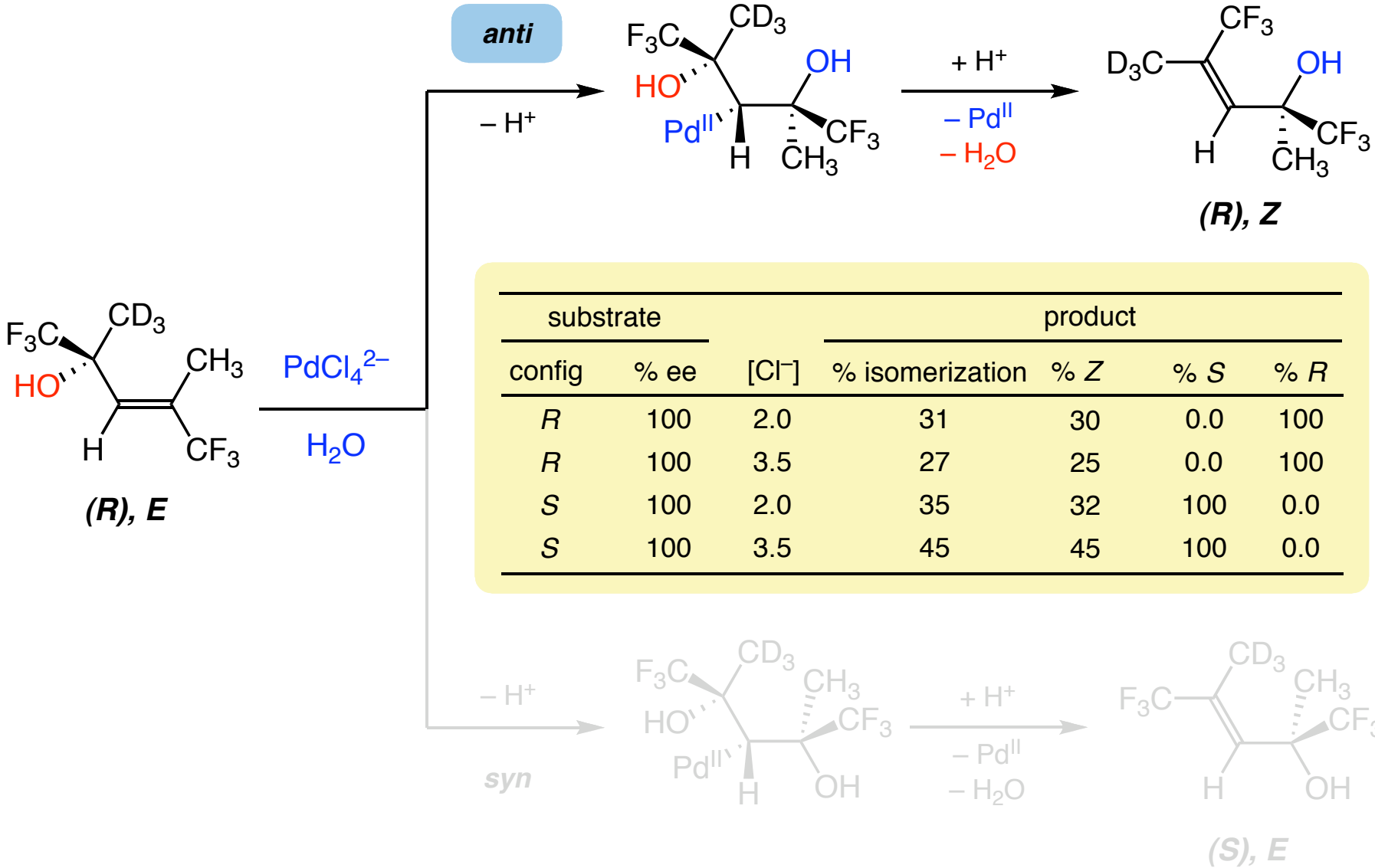


substrate			product			
config	% ee	[Cl⁻]	% isomerization	% *Z*	% *S*	% *R*
R	100	2.0	31	30	0.0	100
R	100	3.5	27	25	0.0	100
S	100	2.0	35	32	100	0.0
S	100	3.5	45	45	100	0.0

Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832.

Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe

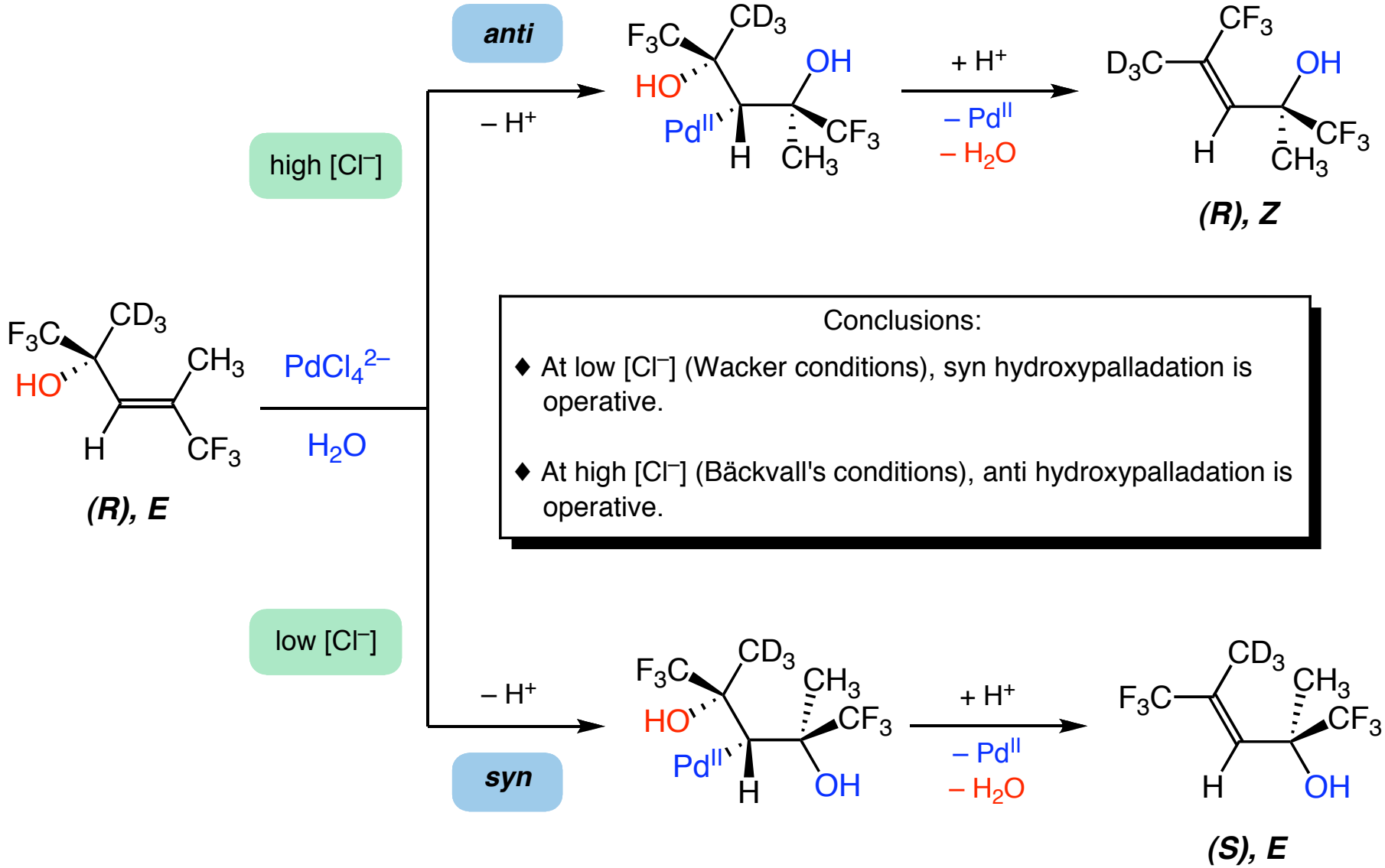


substrate			product			
config	% ee	[Cl⁻]	% isomerization	% *Z*	% *S*	% *R*
R	100	2.0	31	30	0.0	100
R	100	3.5	27	25	0.0	100
S	100	2.0	35	32	100	0.0
S	100	3.5	45	45	100	0.0

Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832.

Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe



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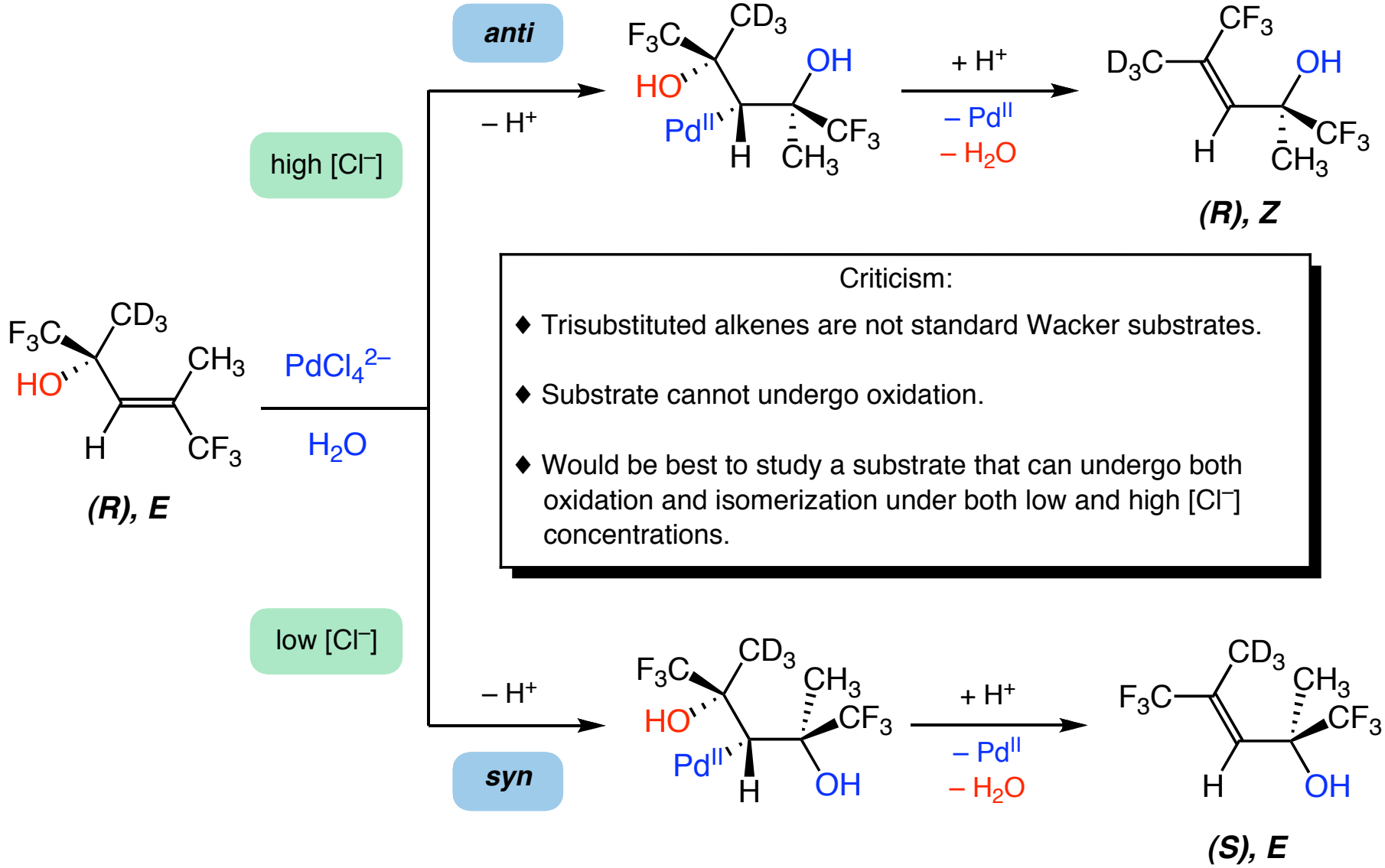
Evidence for Syn Hydroxypalladation

A New Stereochemical and Kinetic Probe

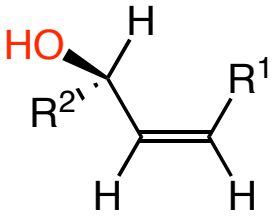


Criticism:

- Trisubstituted alkenes are not standard Wacker substrates.
- Substrate cannot undergo oxidation.
- Would be best to study a substrate that can undergo both oxidation and isomerization under both low and high [Cl⁻] concentrations.

Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498.

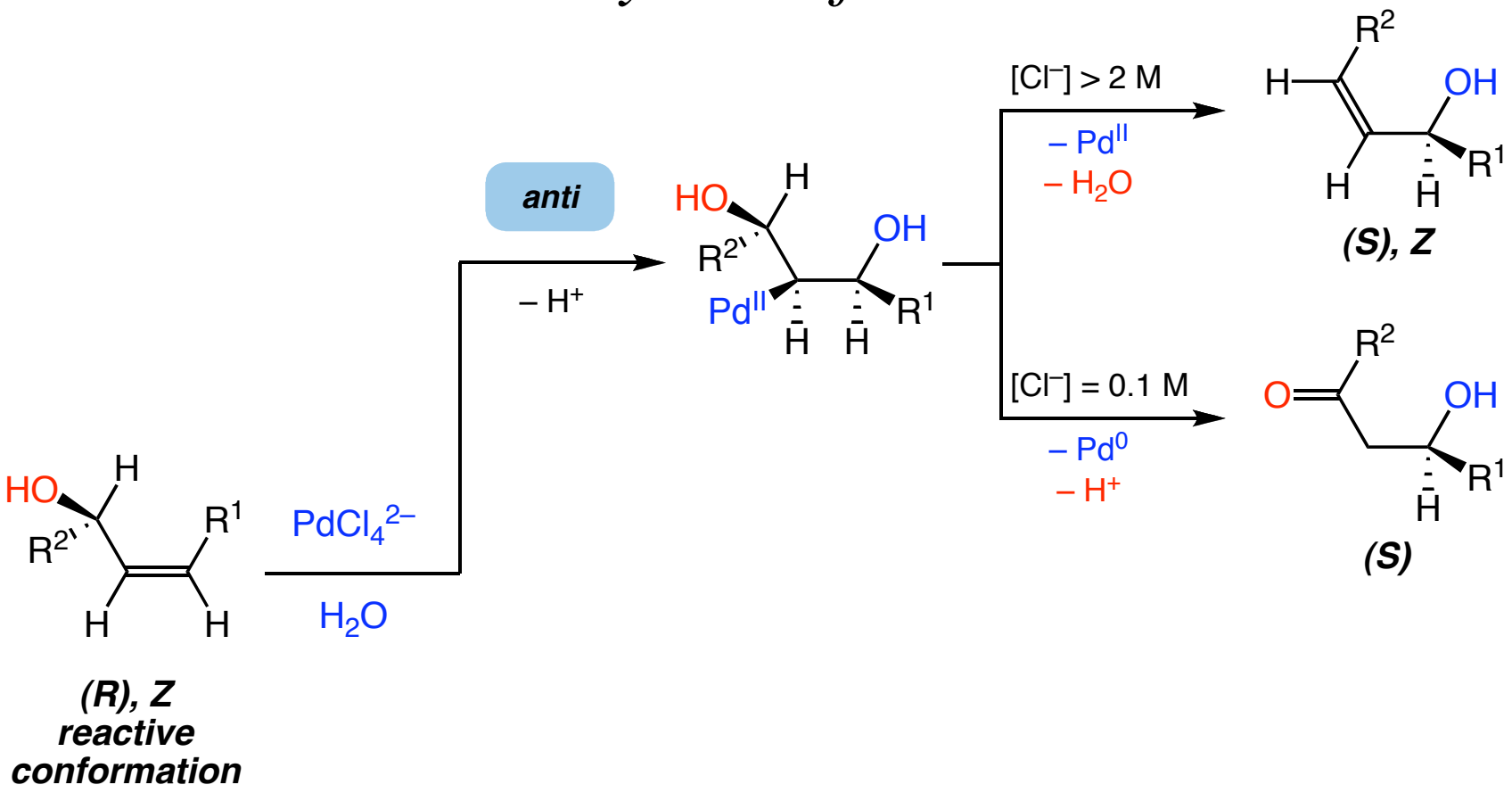
Chirality Transfer Studies



(R), Z reactive conformation

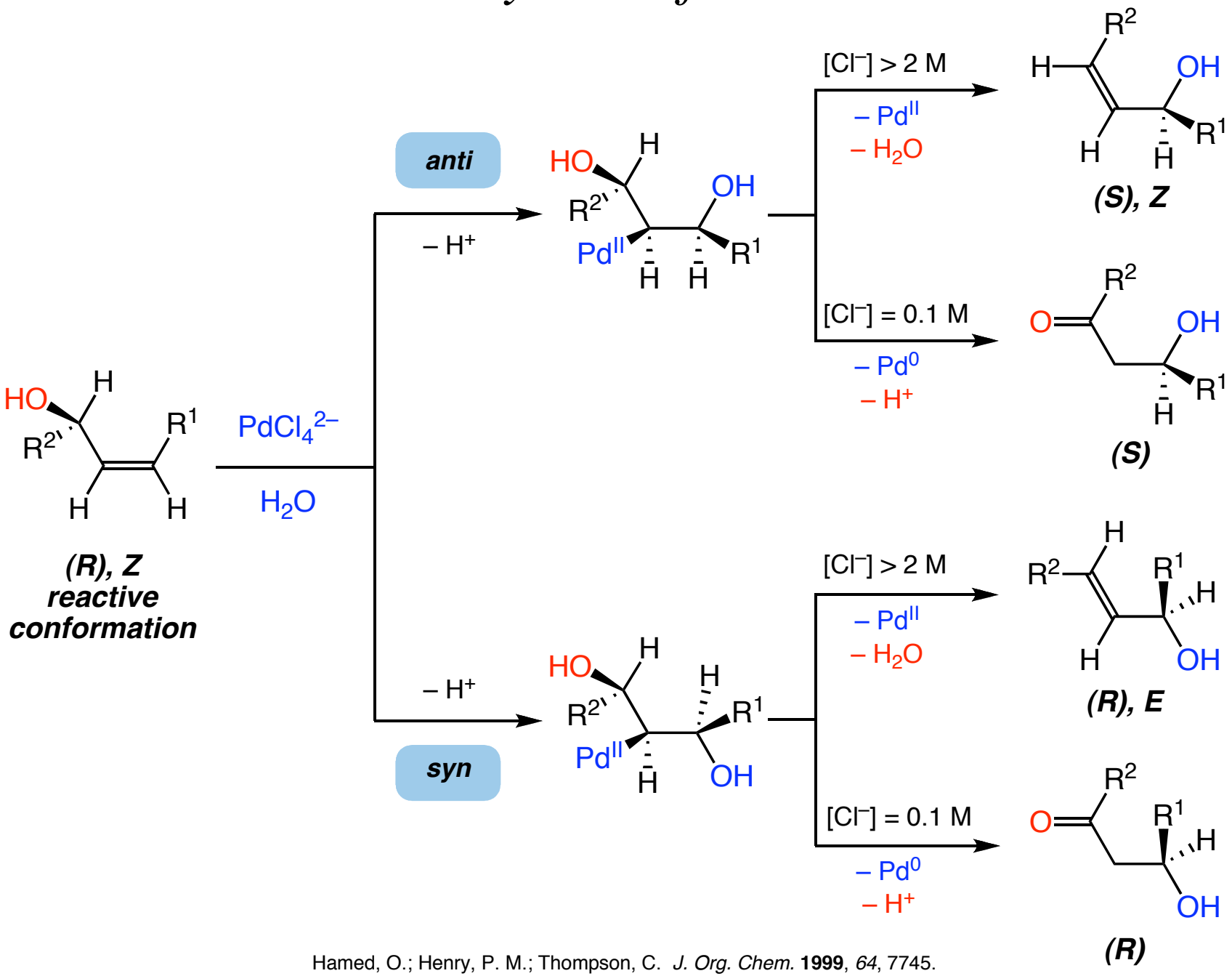
Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



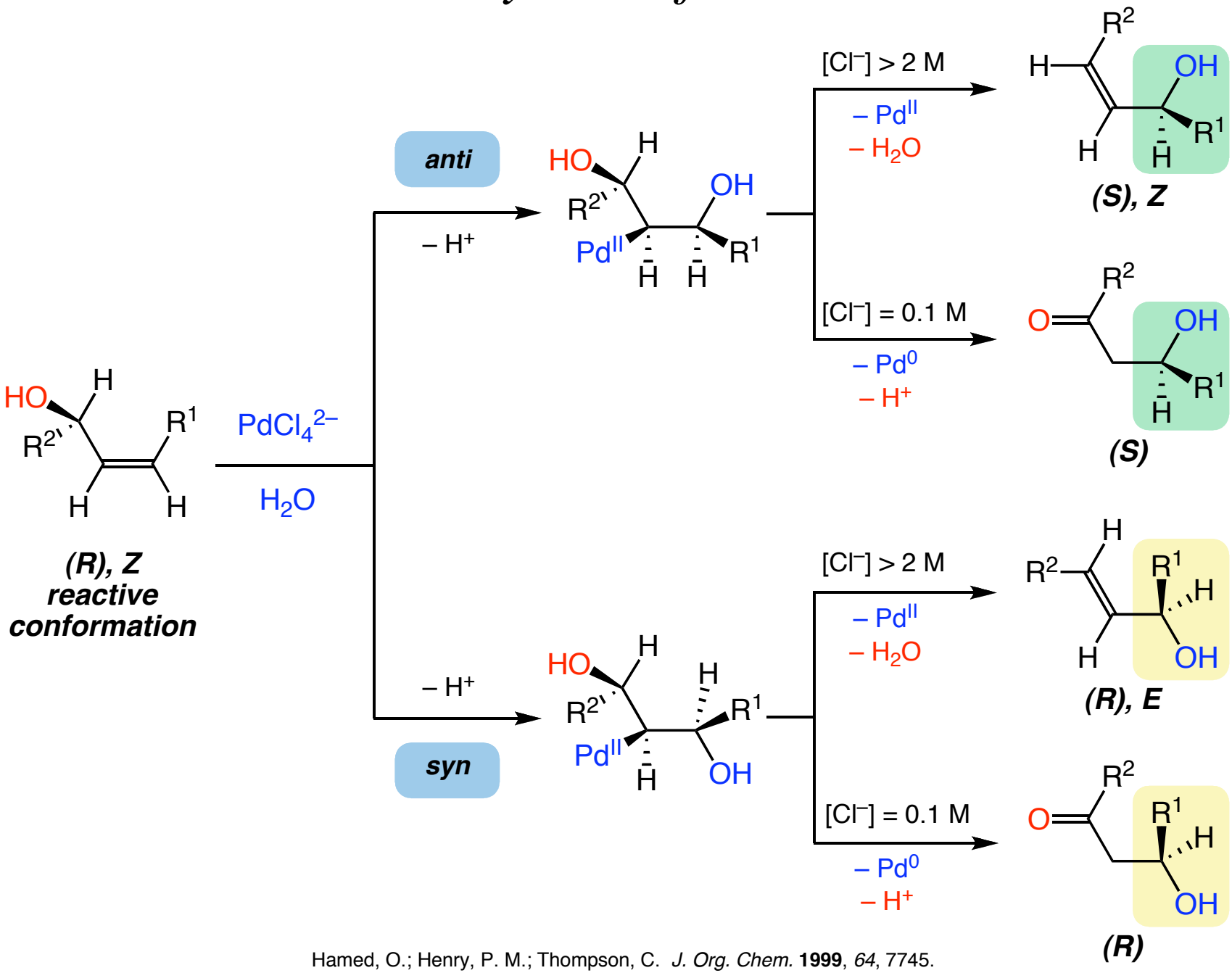
Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



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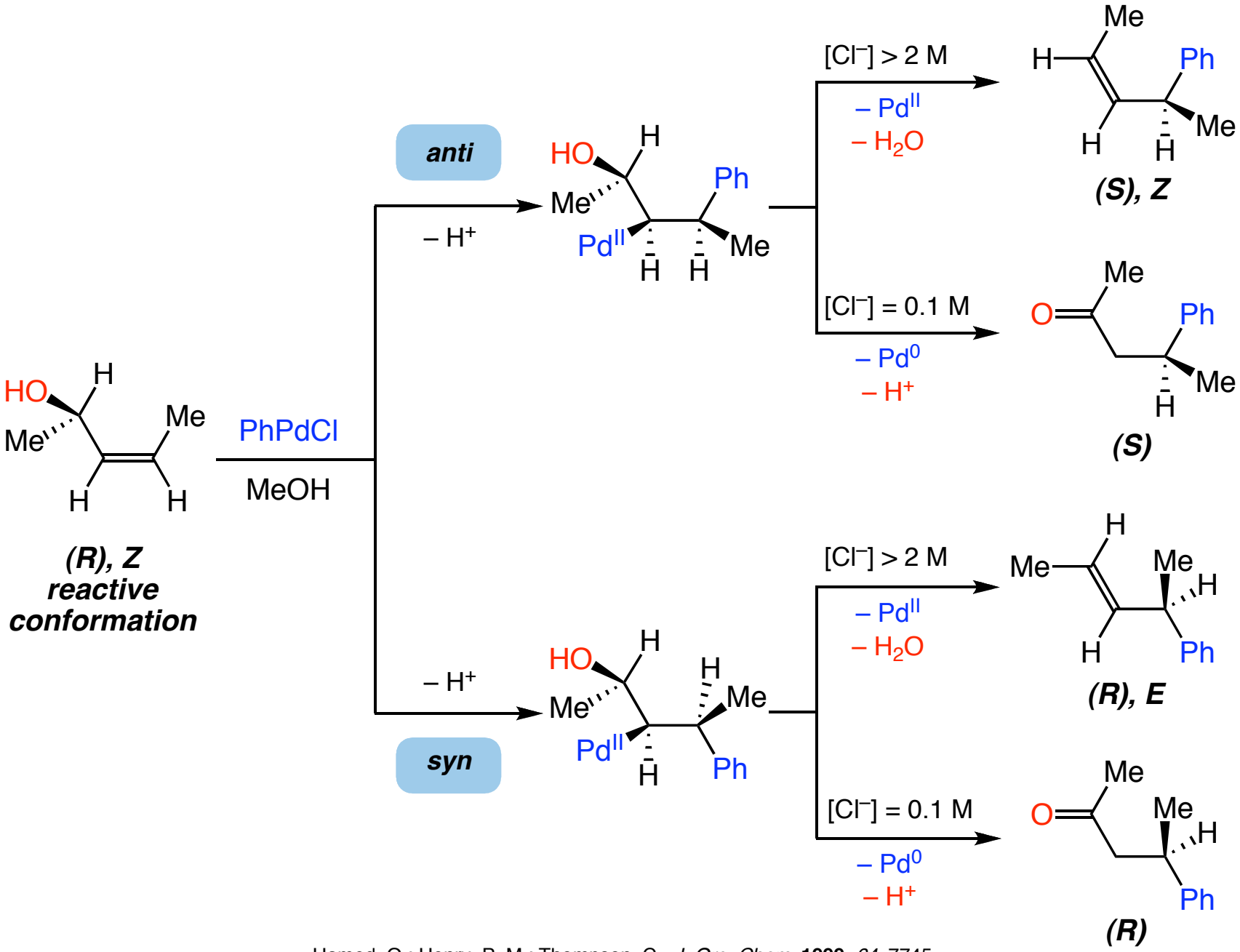
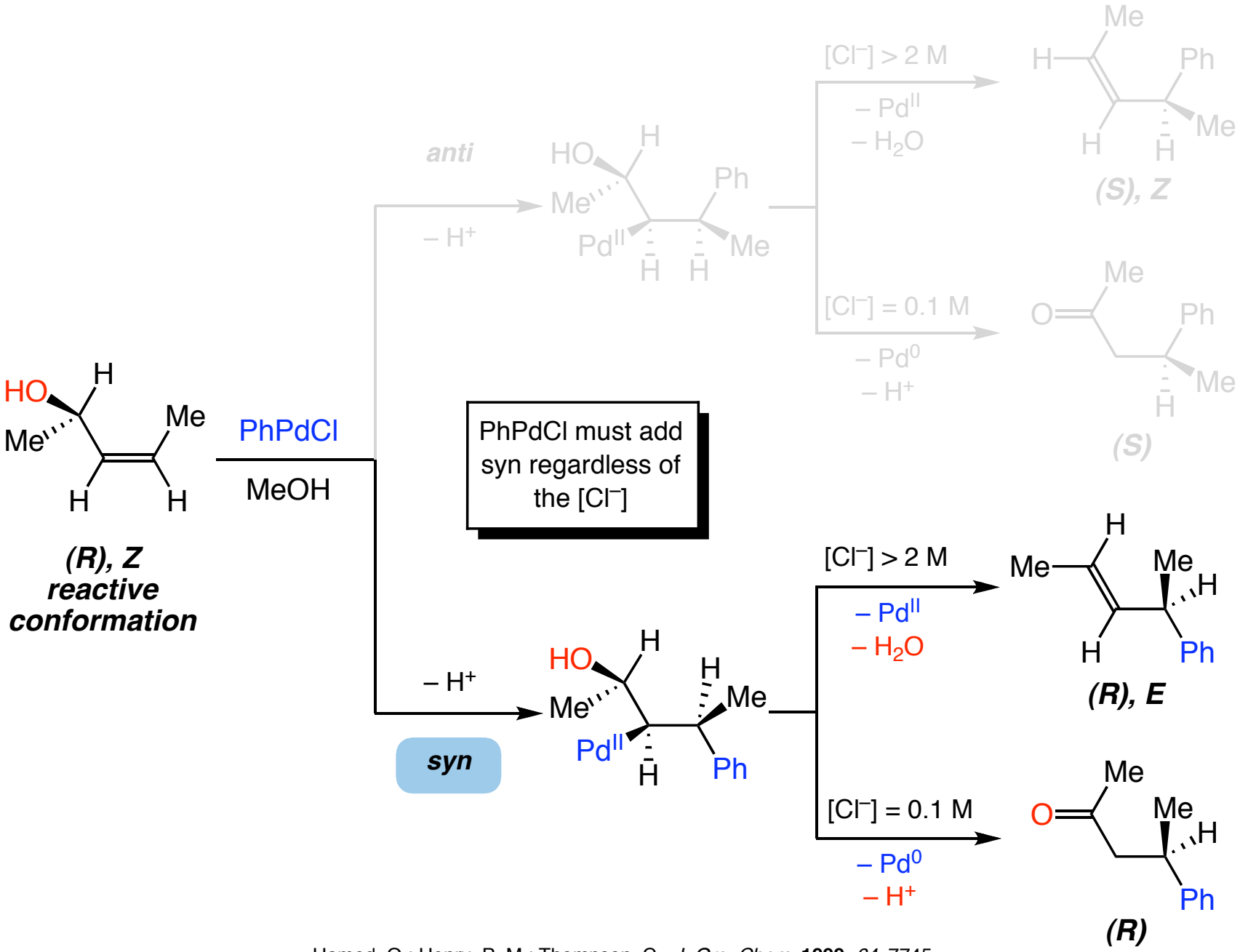
Chirality Transfer Studies



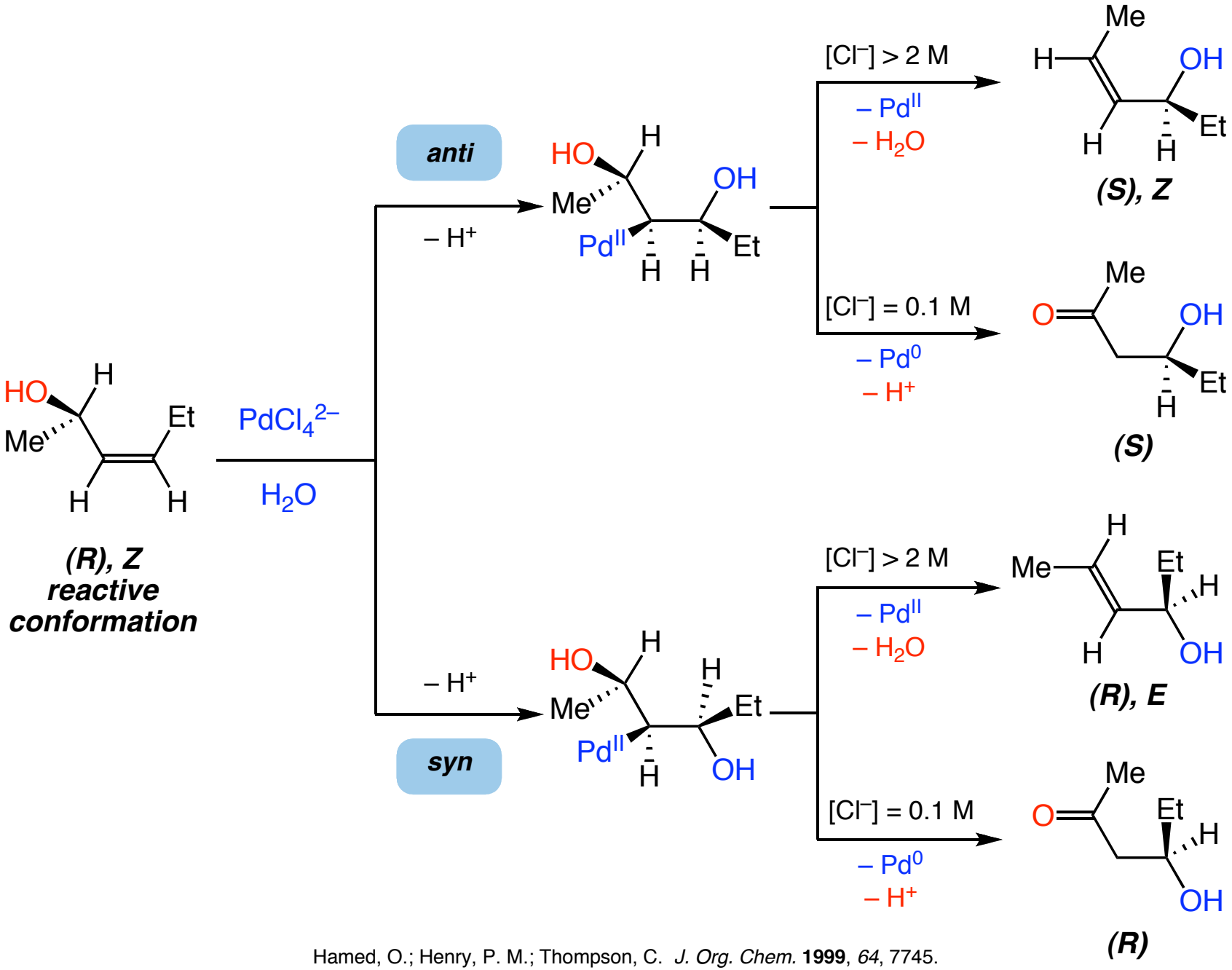
Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



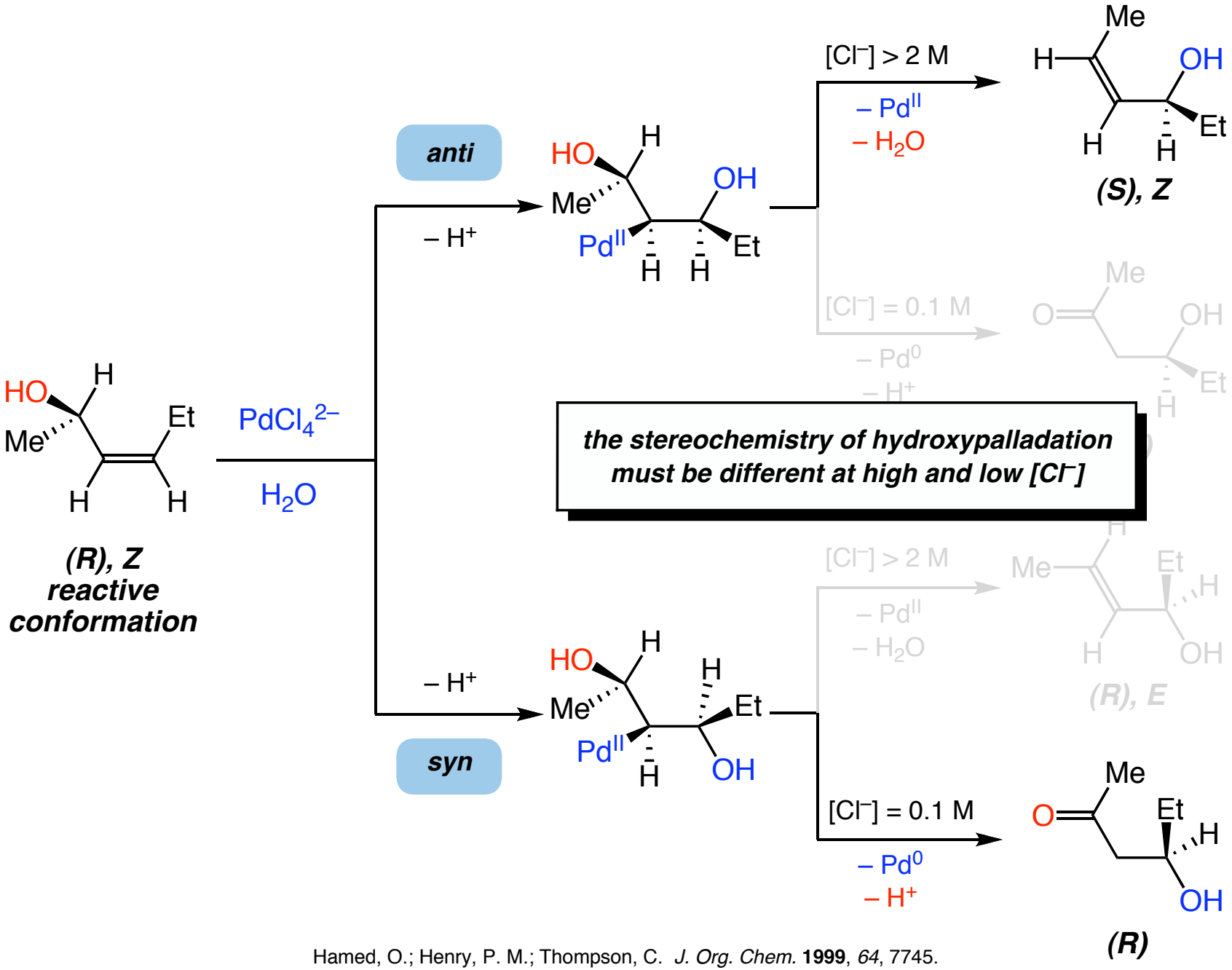
Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



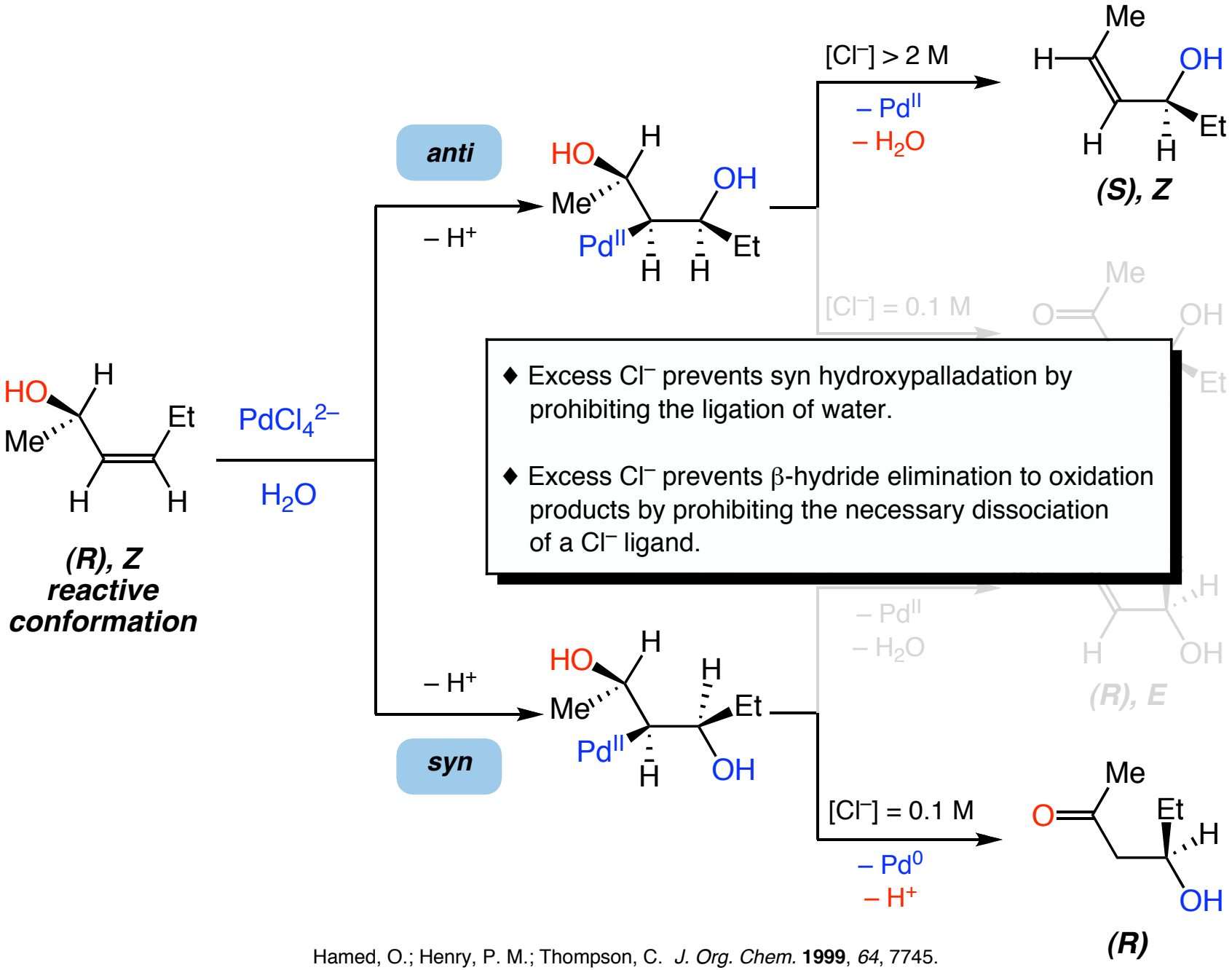
Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



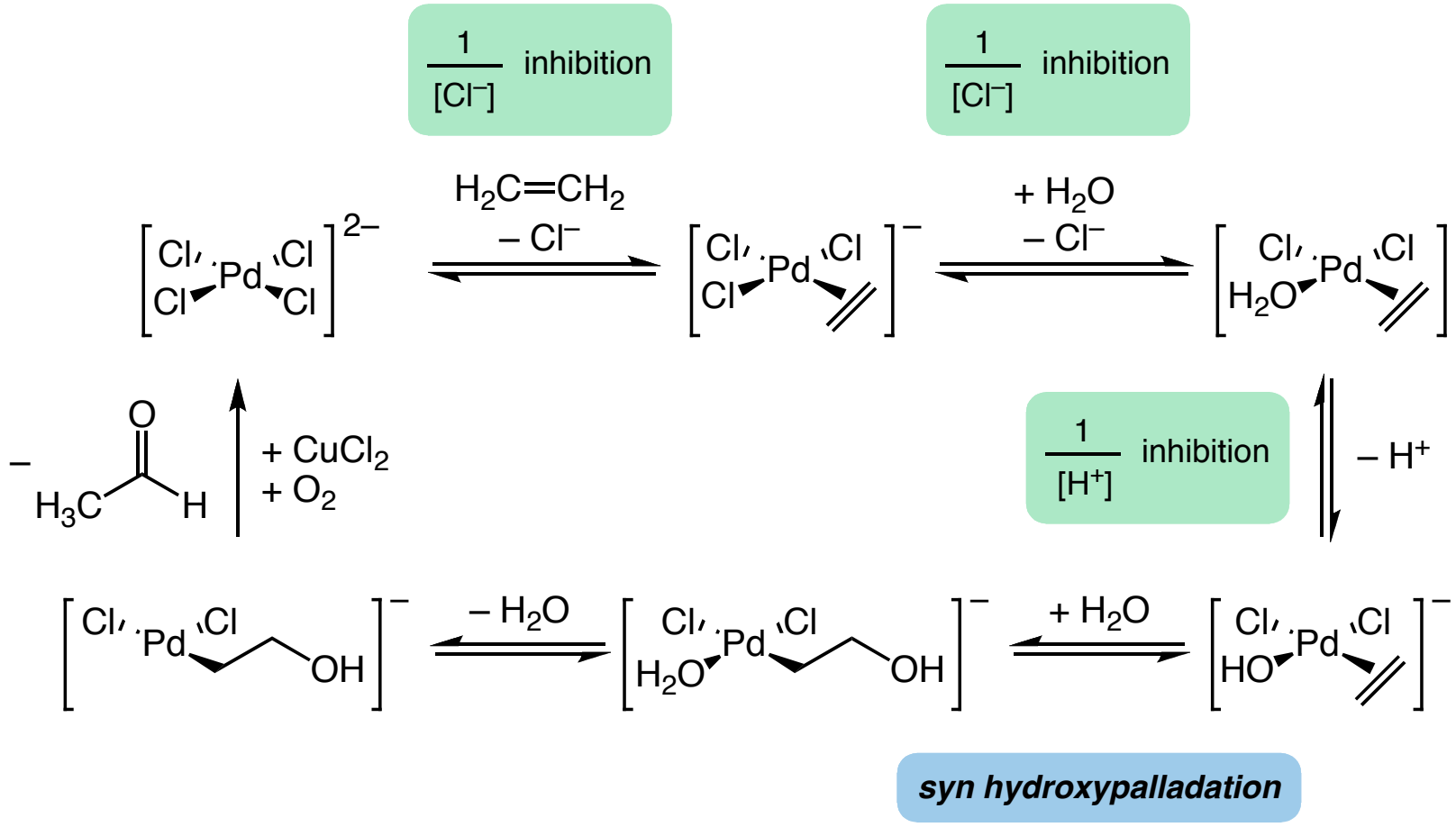
Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Chirality Transfer Studies



Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745.

Mechanism for Oxidation of Olefins under Wacker Conditions



Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 1, p 2119.

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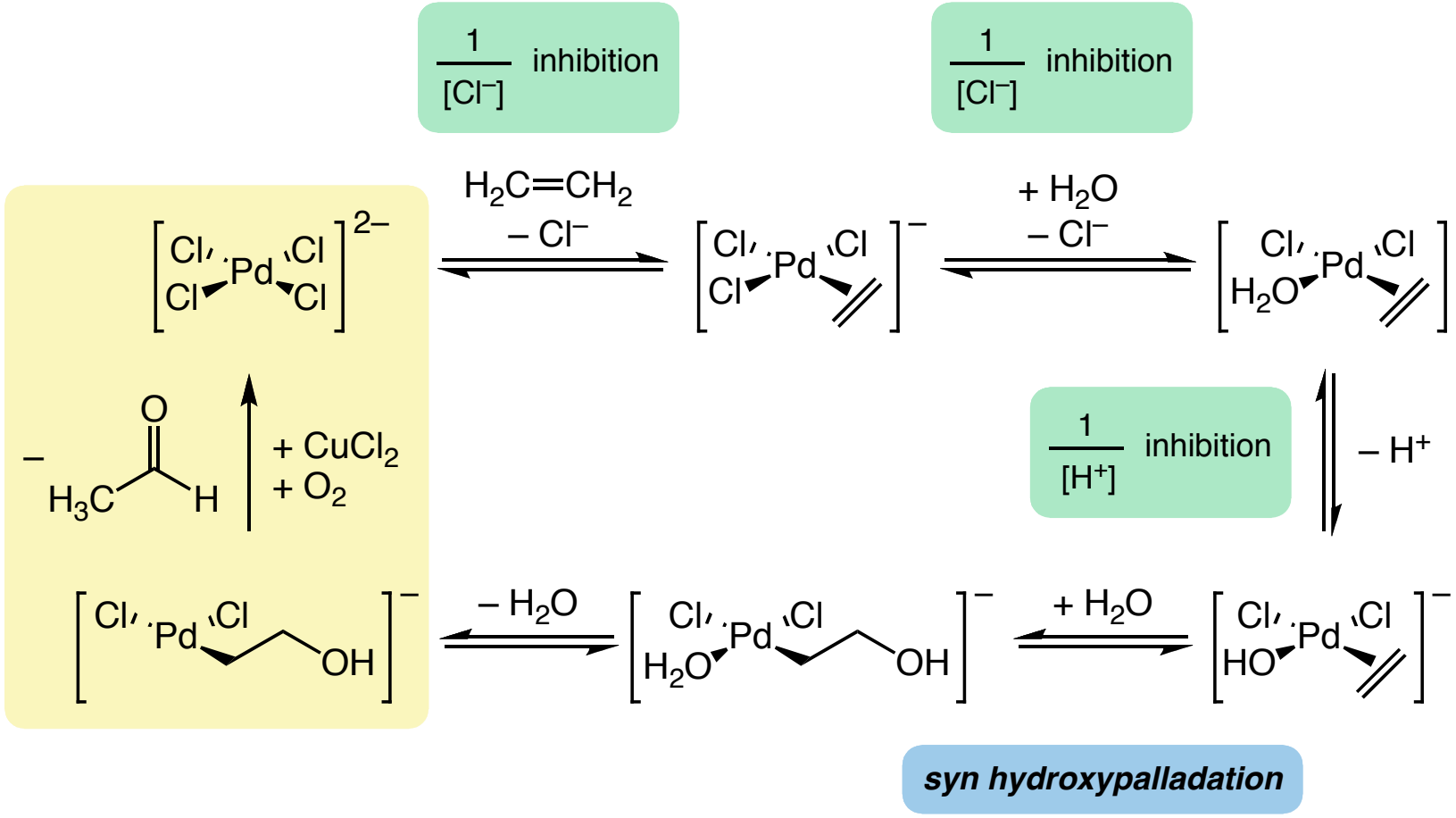
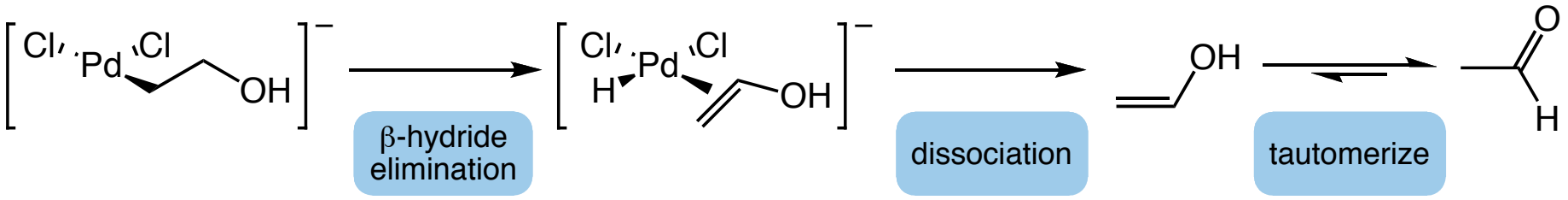


Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 1, p 2119.

Mechanism for Decomposition to Oxidation Products

Moiseev's Mechanism:



Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 80. Moiseev, I. I.; Warhaftig, M. N.; Sirkin, J. H. *Doklady Akad. Nauk UdSSR* **1960**, *130*, 820. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246.

Mechanism for Decomposition to Oxidation Products

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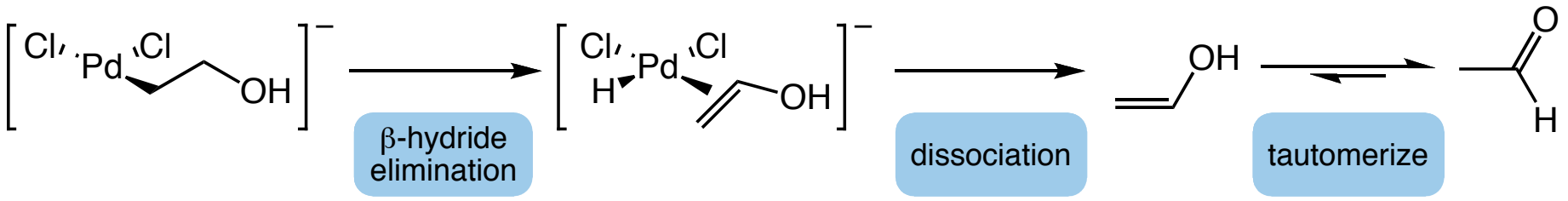
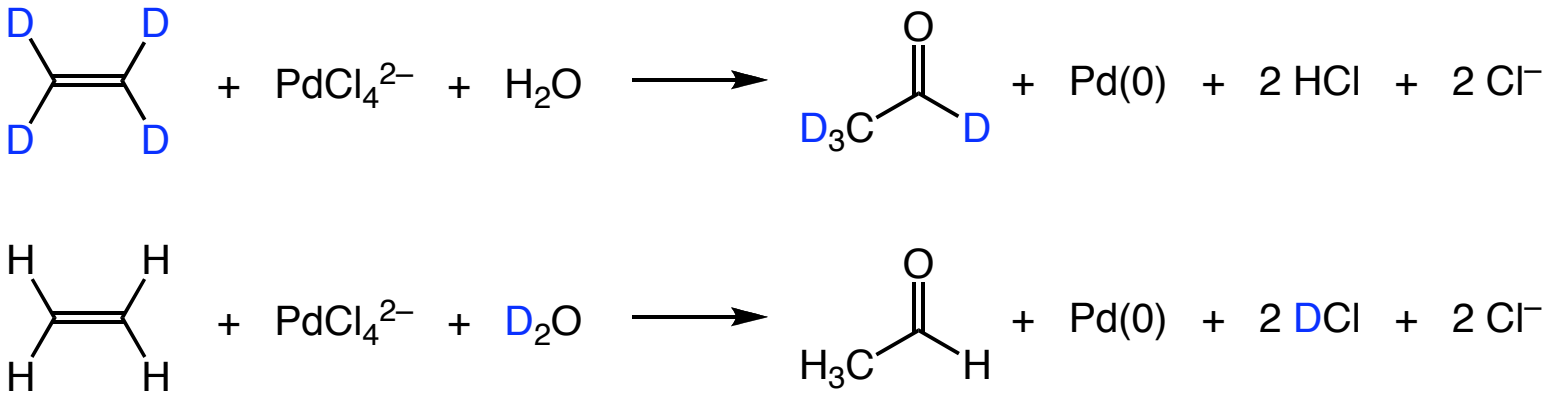


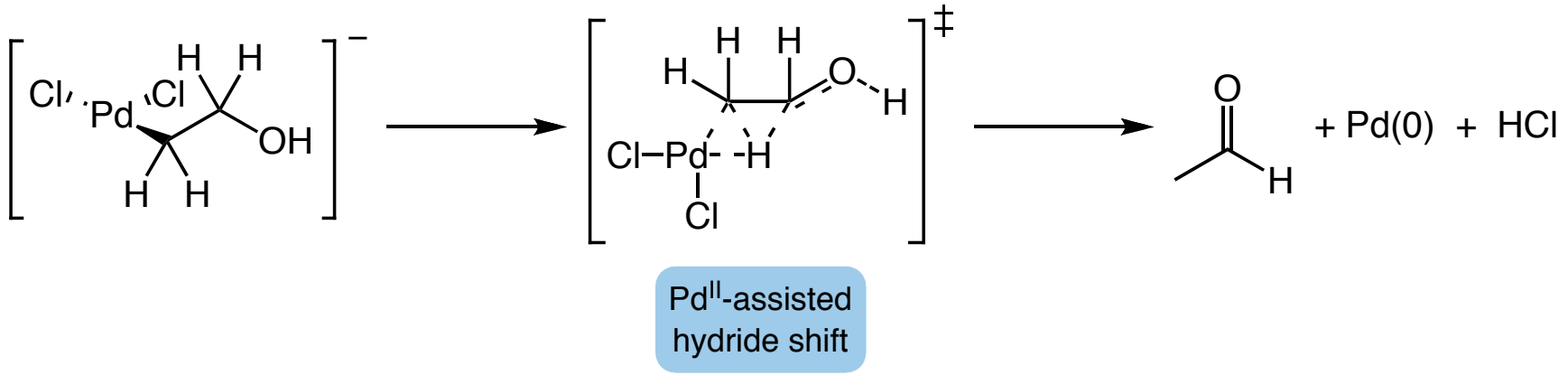


lack of proton incorporation from solvent means that tautomerization mechanism is invalid

Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 80. Moiseev, I. I.; Warhaftig, M. N.; Sirkin, J. H. *Doklady Akad. Nauk UdSSR* **1960**, *130*, 820. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246.

Mechanism for Decomposition to Oxidation Products

Henry's Model



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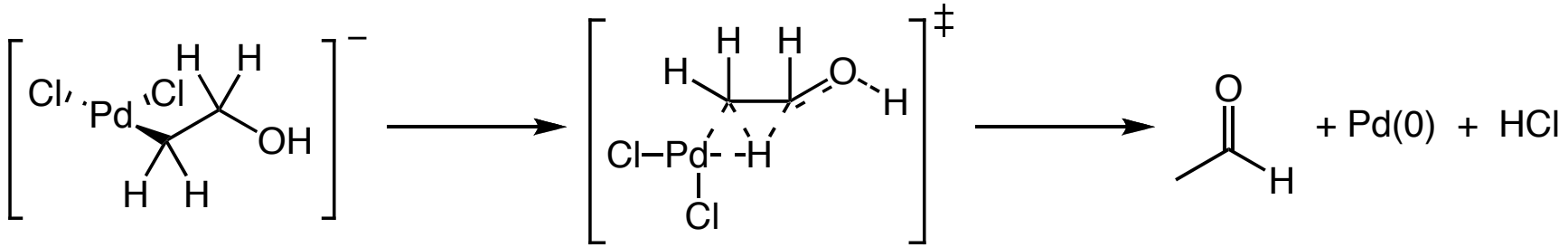
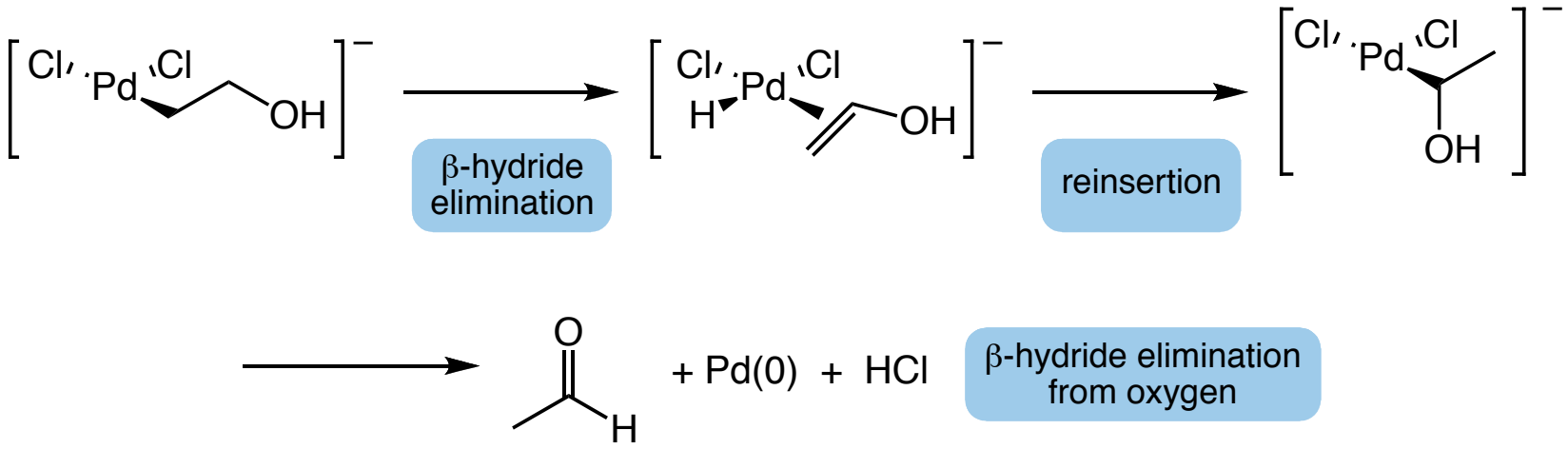


Pd^{II}-assisted hydride shift

Bäckvall's Model



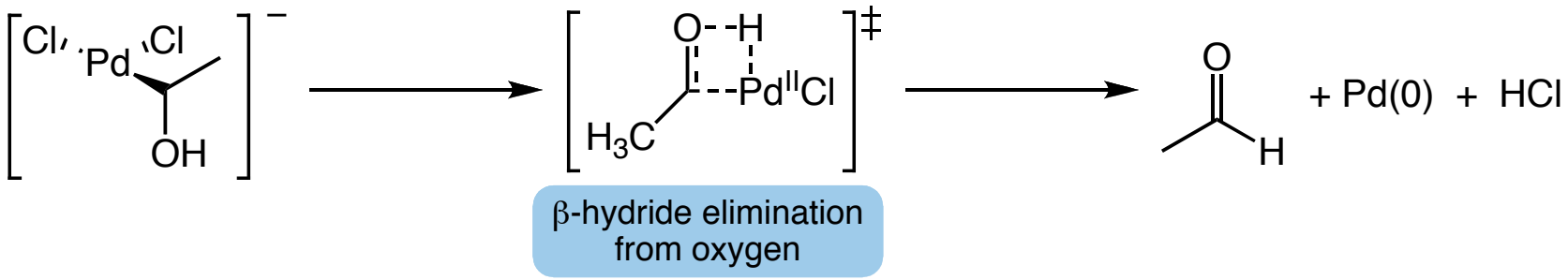
β-hydride elimination from oxygen

Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 80. Moiseev, I. I.; Warhaftig, M. N.; Sirkin, J. H. *Doklady Akad. Nauk UdSSR* **1960**, *130*, 820. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246.

Mechanism for Decomposition to Oxidation Products

Computational Studies

Bäckvall's Model



Goddard's Computations

Keith, J. A.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2006**, *128*, 3132. Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 12342.

Mechanism for Decomposition to Oxidation Products

Computational Studies

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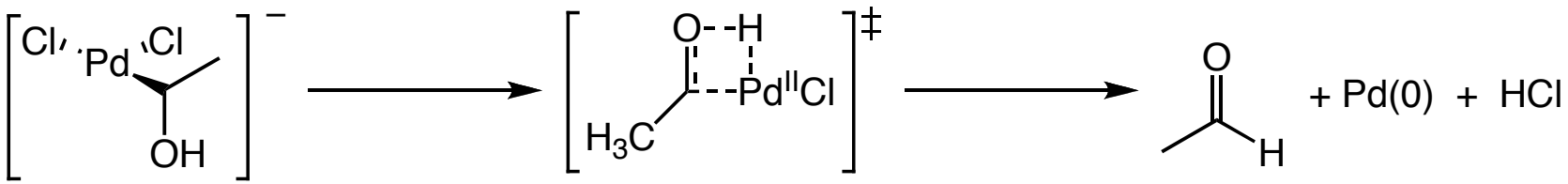

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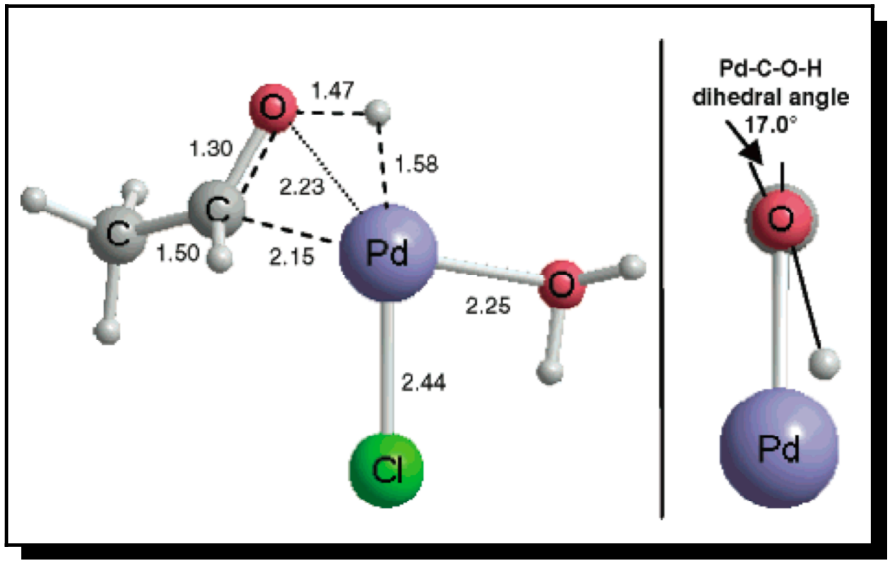

4-membered TS: 36.3 kcal/mol

Keith, J. A.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2006**, *128*, 3132. Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 12342.

Mechanism for Decomposition to Oxidation Products

Computational Studies

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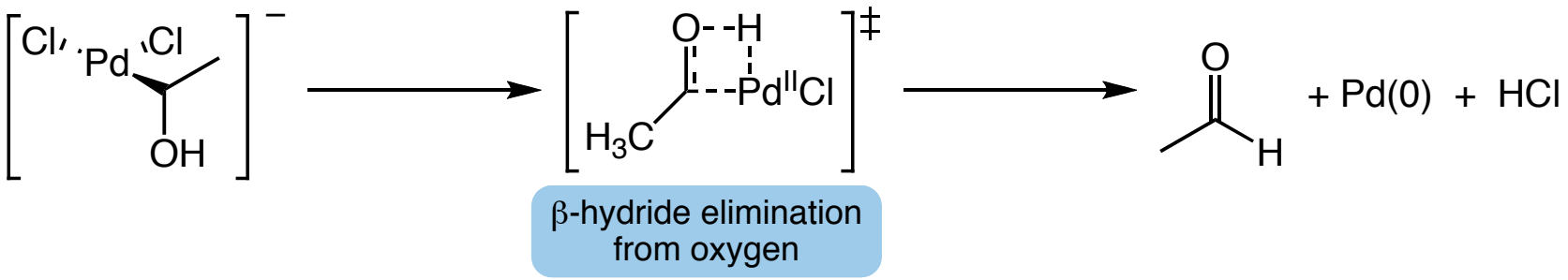
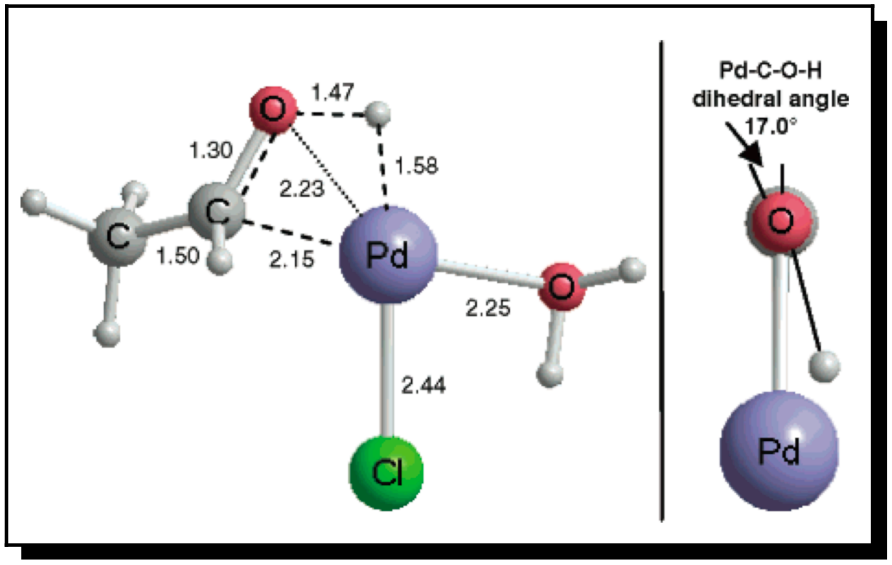
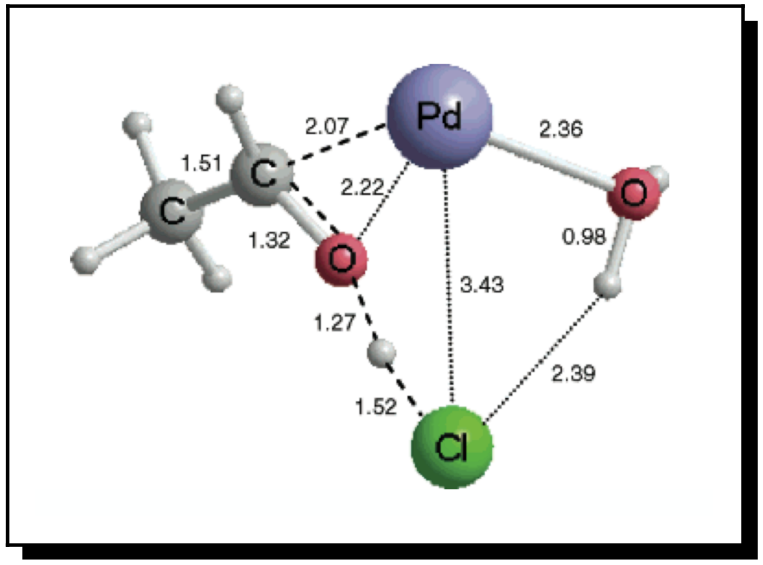


Goddard's Computations



4-membered TS: 36.3 kcal/mol



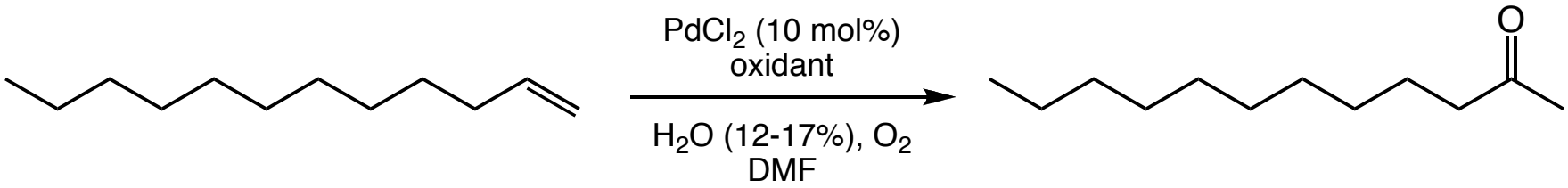
Cl-mediated reductive elimination TS: 18.7 kcal/mol

Keith, J. A.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2006**, *128*, 3132. Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 12342.

From Industrial Process to Synthetic Method

Preparations of Methyl Ketones from Terminal Olefins

Clement, 1964:



oxidant = $CuCl_2 \cdot 2H_2O$ (10 mol%) or *p*-benzoquinone

Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241. Tsuji, J. *Synthesis* **1984**, 369.

From Industrial Process to Synthetic Method

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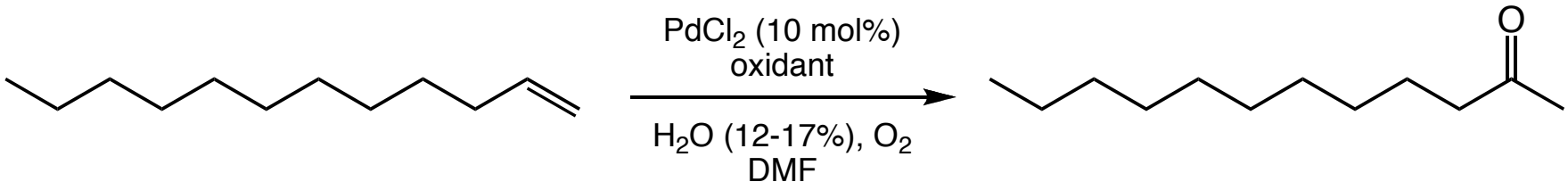

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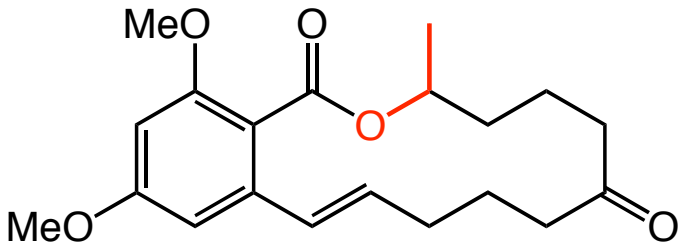
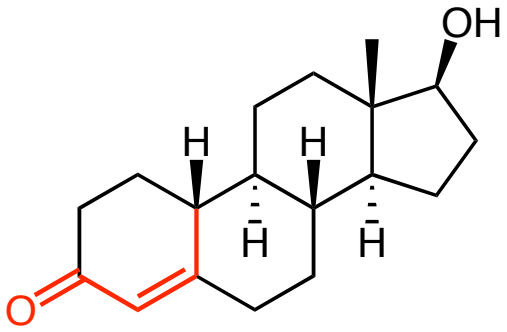
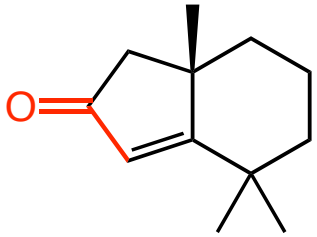


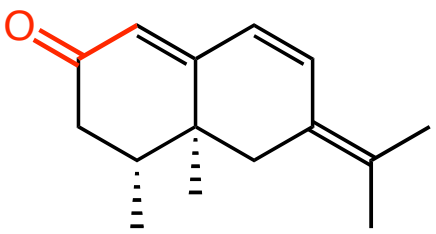
Zearalenone



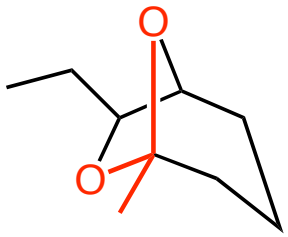
19-Nortestosterone



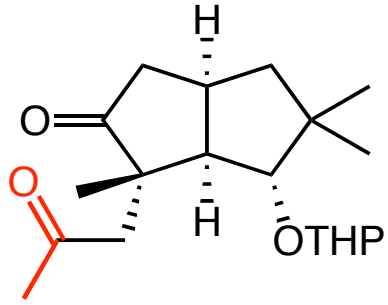
intermediate to Dichroanone



Nootkatone



Brevicomin



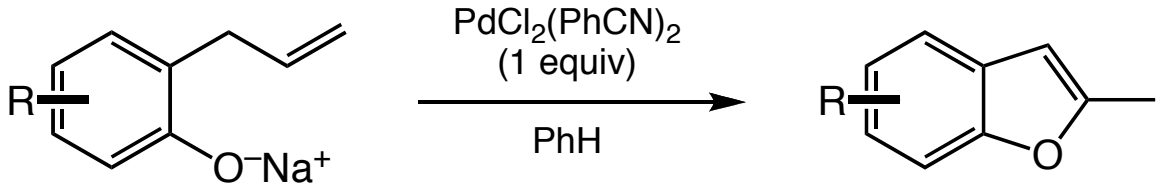
intermediate to Coriolin

Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241. Tsuji, J. *Synthesis* **1984**, 369.

From Industrial Process to Synthetic Method

Oxidative Cyclizations Give Access to Heterocyclic Compounds

Moritani, 1973:



Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett.* **1973**, *10*, 739.

From Industrial Process to Synthetic Method

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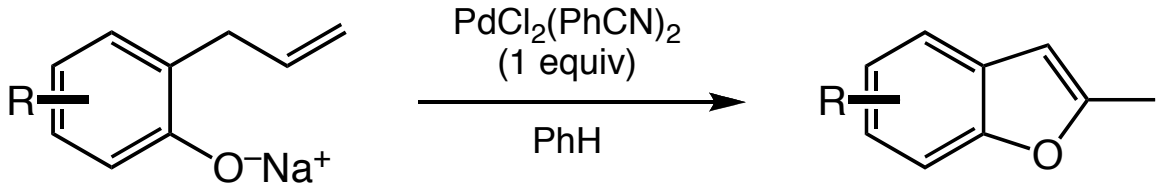

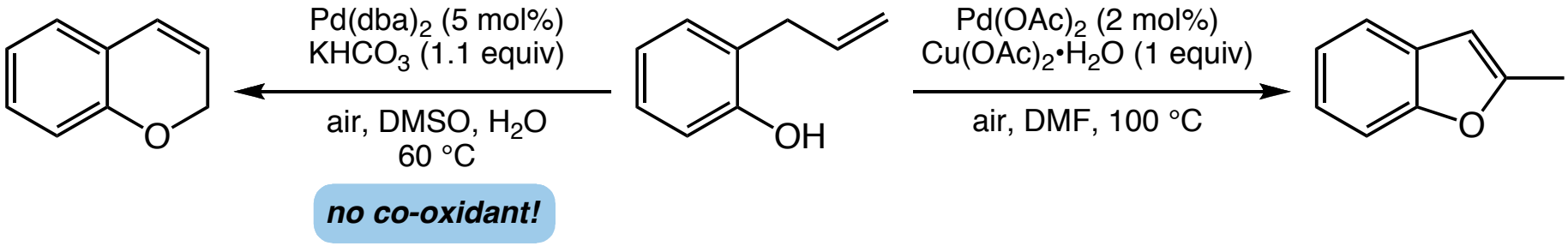

no co-oxidant!

Roshchin, A. I.; Kel'chevski, S. M.; Bumagin, N. A. *J. Organomet. Chem.* **1998**, *560*, 163. Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522.

From Industrial Process to Synthetic Method

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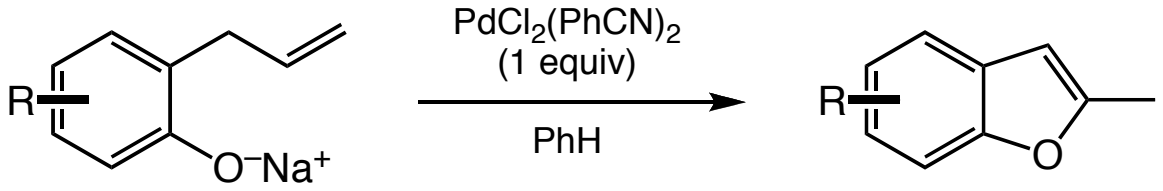
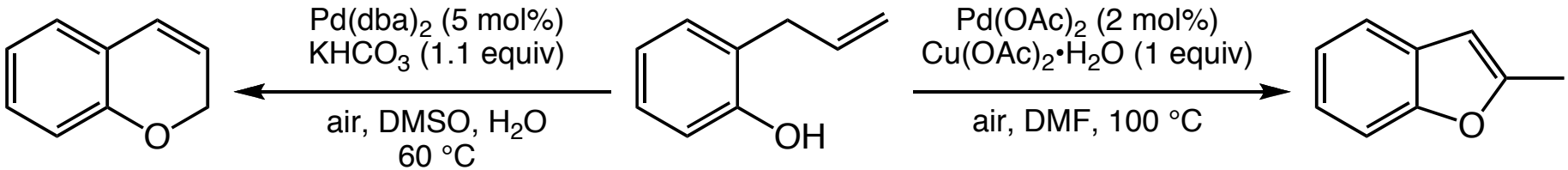
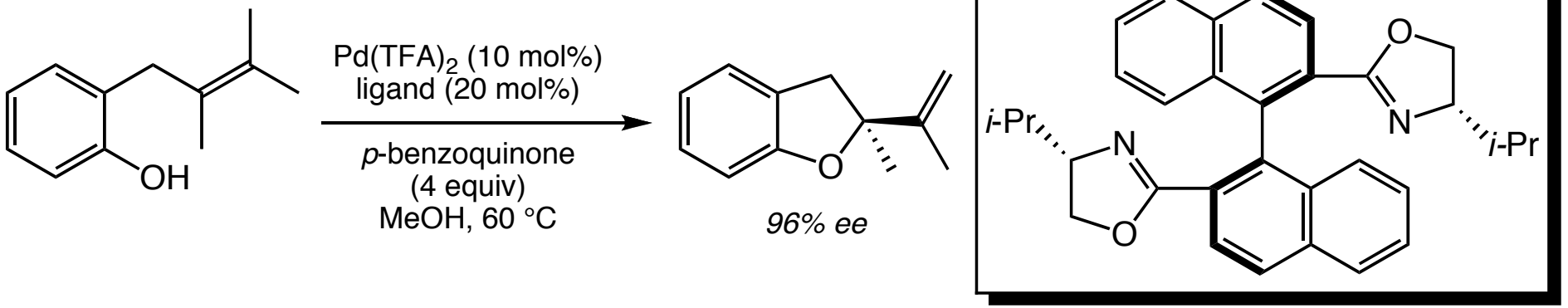
Moritani, 1973:





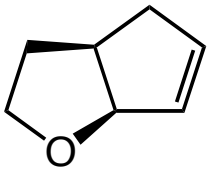
no co-oxidant!

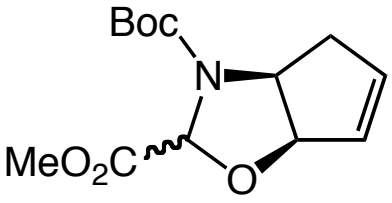


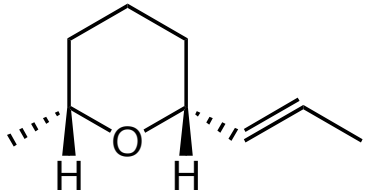
Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071.

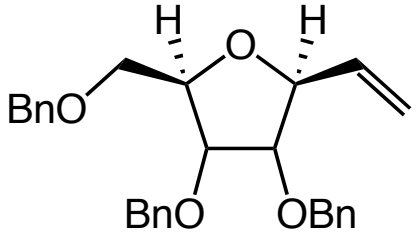
From Industrial Process to Synthetic Method

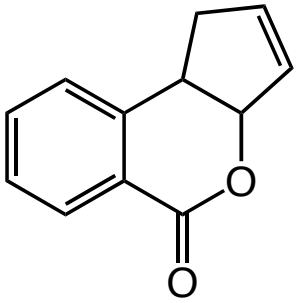
Oxidative Cyclizations Give Access to Heterocyclic Compounds

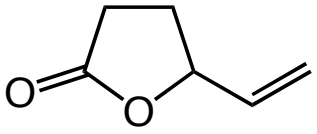


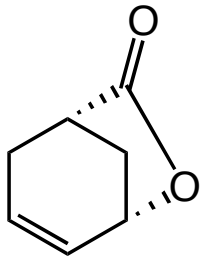


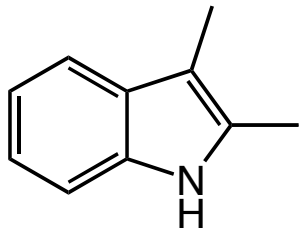


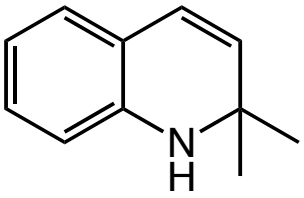


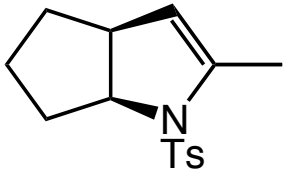


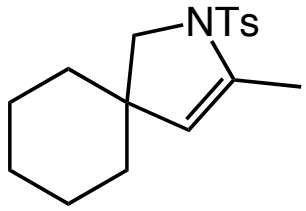


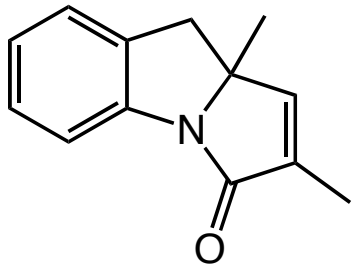






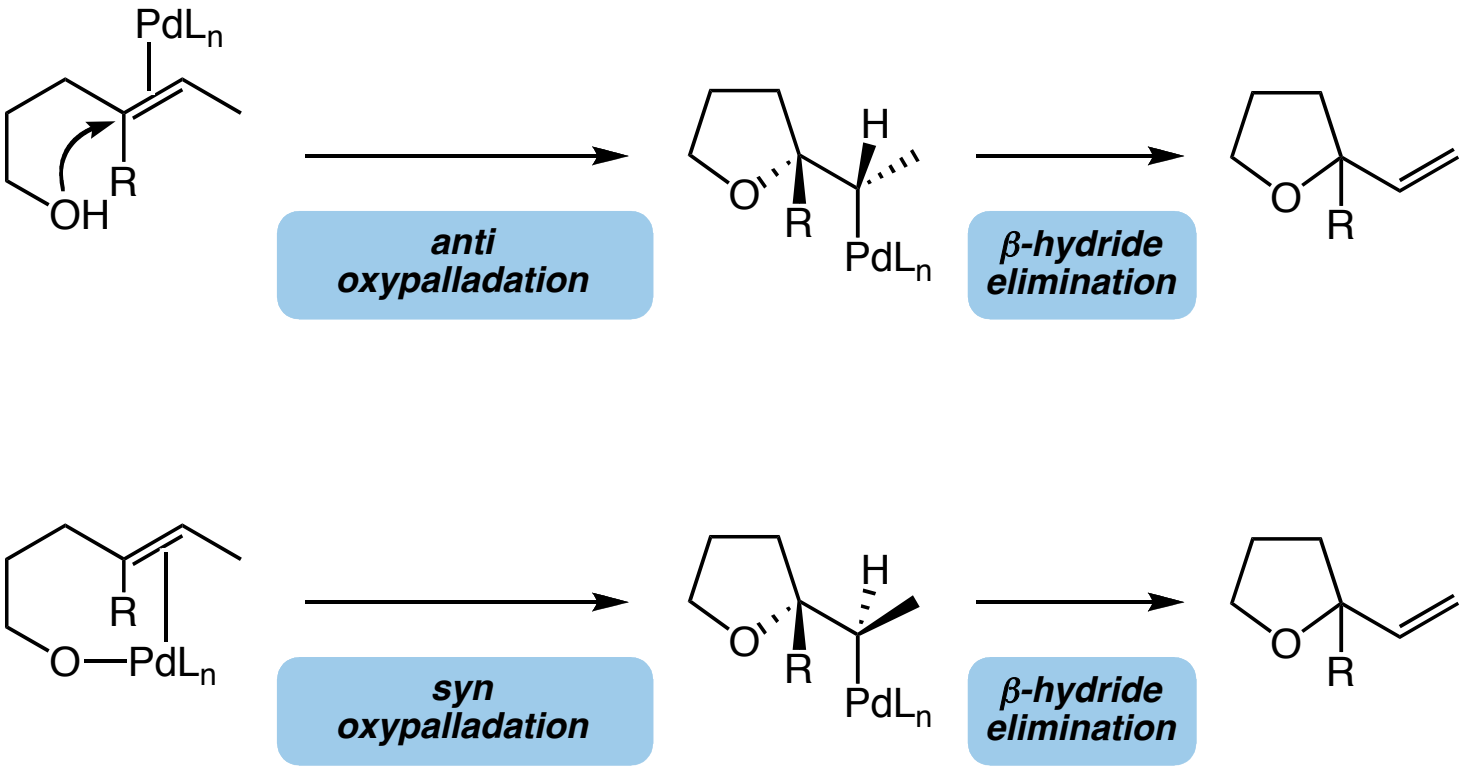






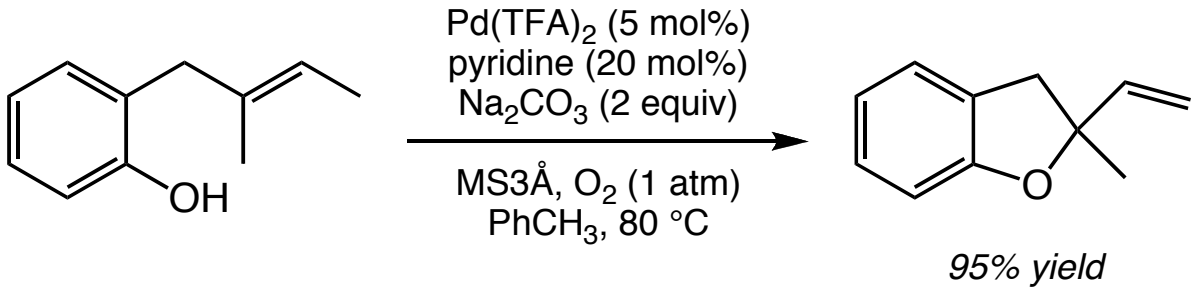
Hosokawa, T.; Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons: New York, 2002; Vol. 2, pp 2169-2192.

Stereochemistry of Oxidative Cyclizations



Stereochemistry of Oxidative Cyclizations

Stoltz Group Studies

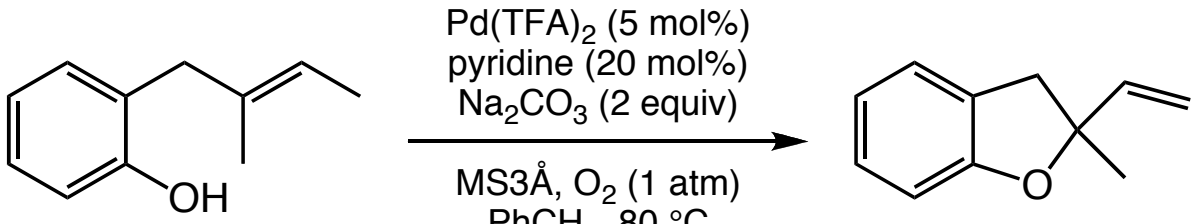


95% yield

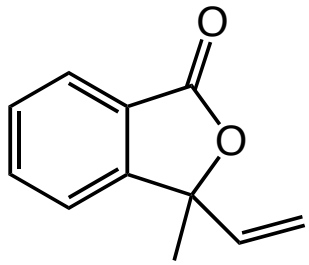
Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2892.

Stereochemistry of Oxidative Cyclizations

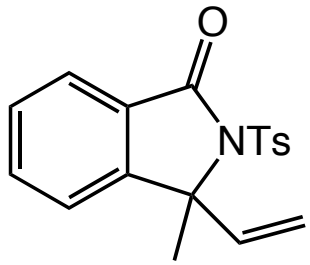
Stoltz Group Studies



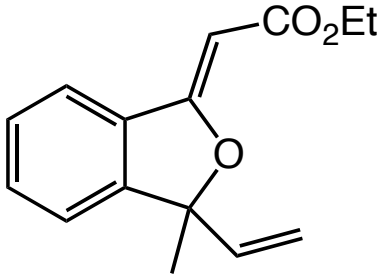
95% yield



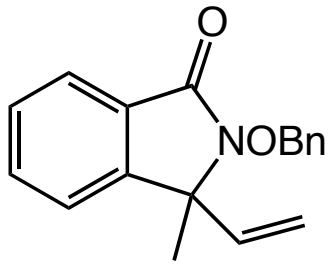
90% yield



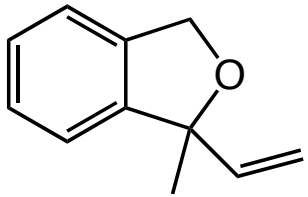
88% yield



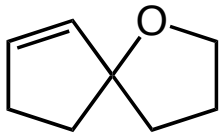
63% yield



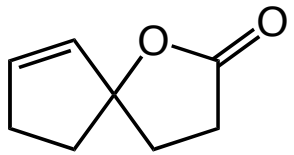
82% yield



87% yield



93% yield

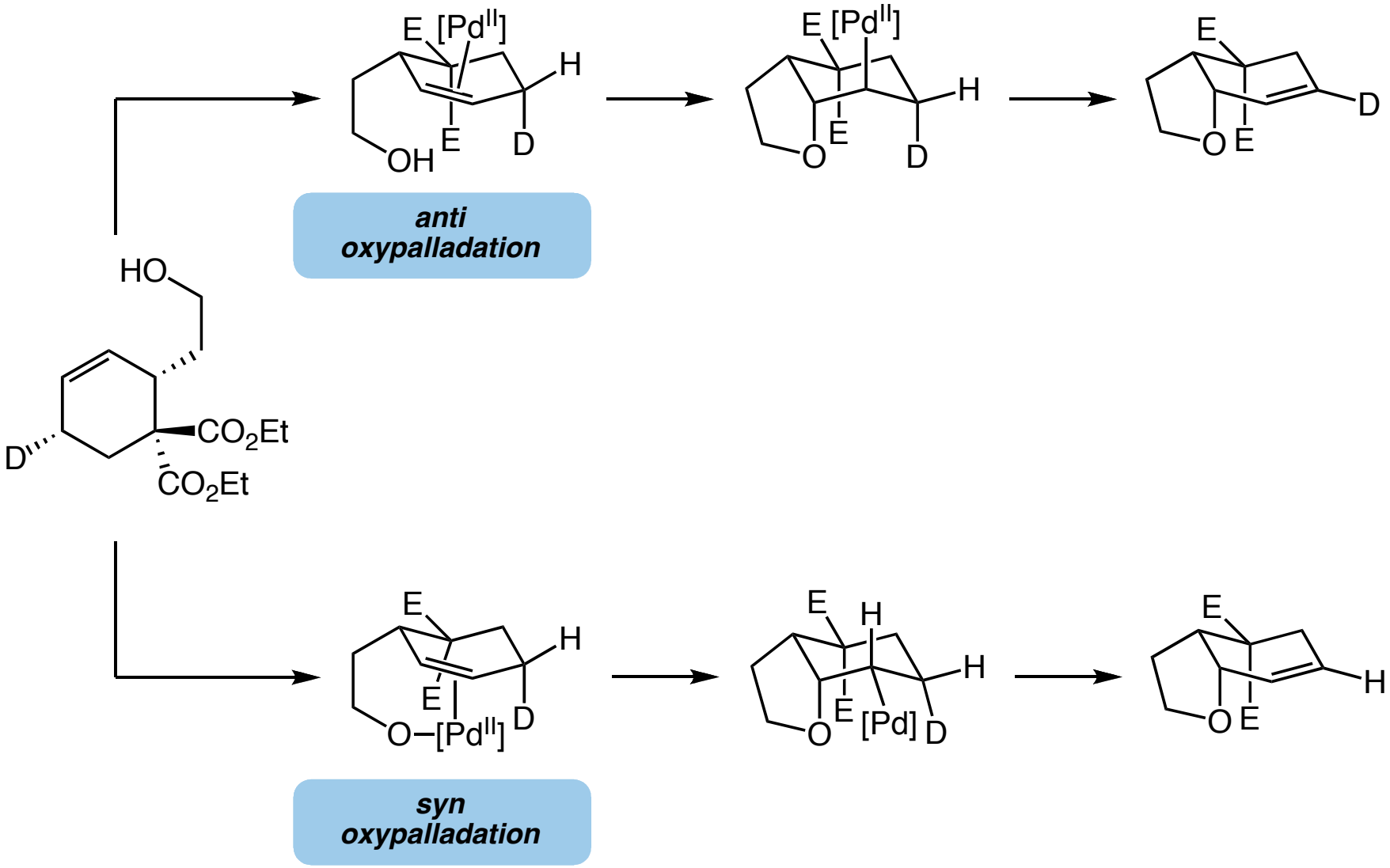


62% yield

Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2892.

Stereochemistry of Oxidative Cyclizations

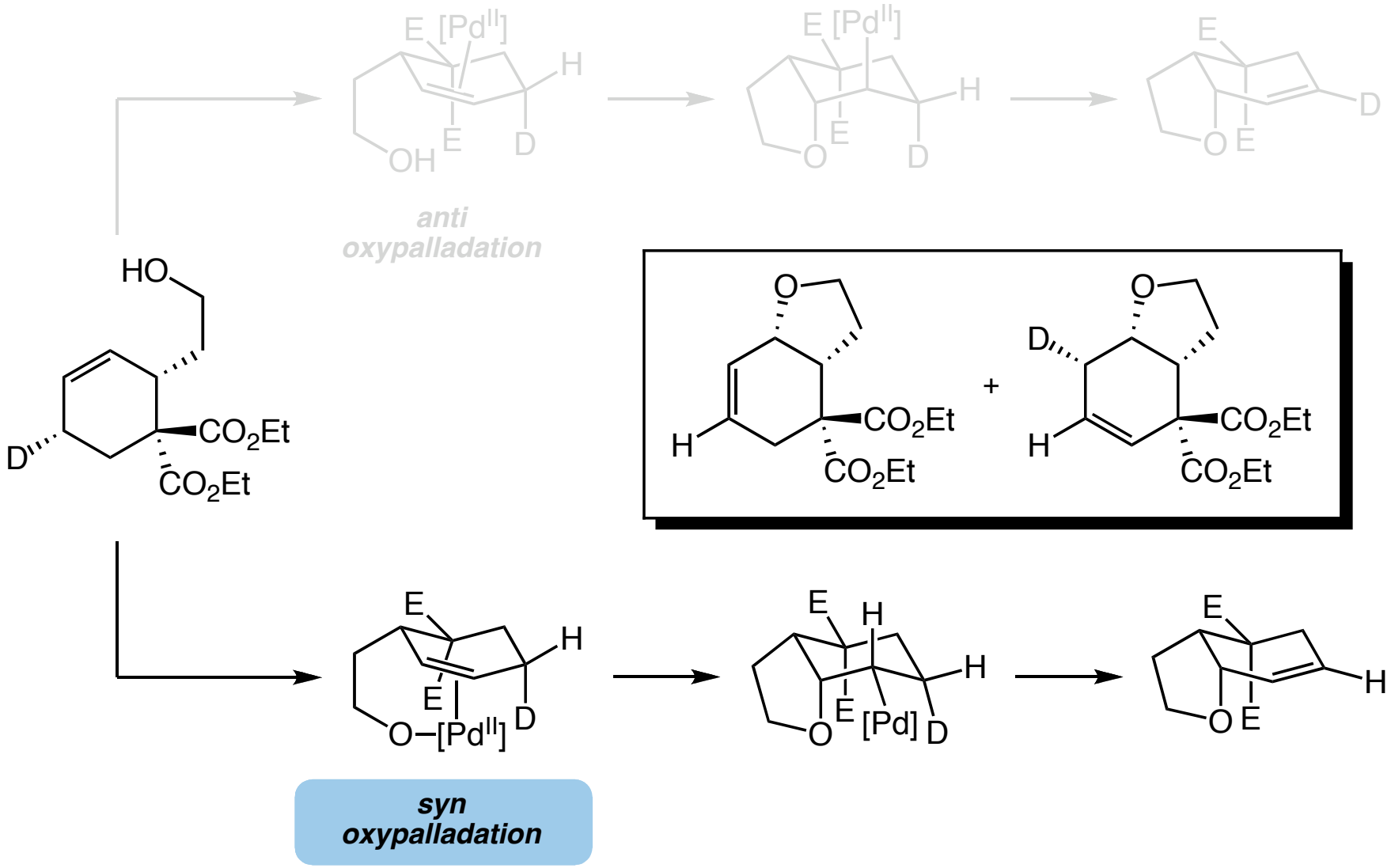
Stoltz Group Studies



Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

Stereochemistry of Oxidative Cyclizations

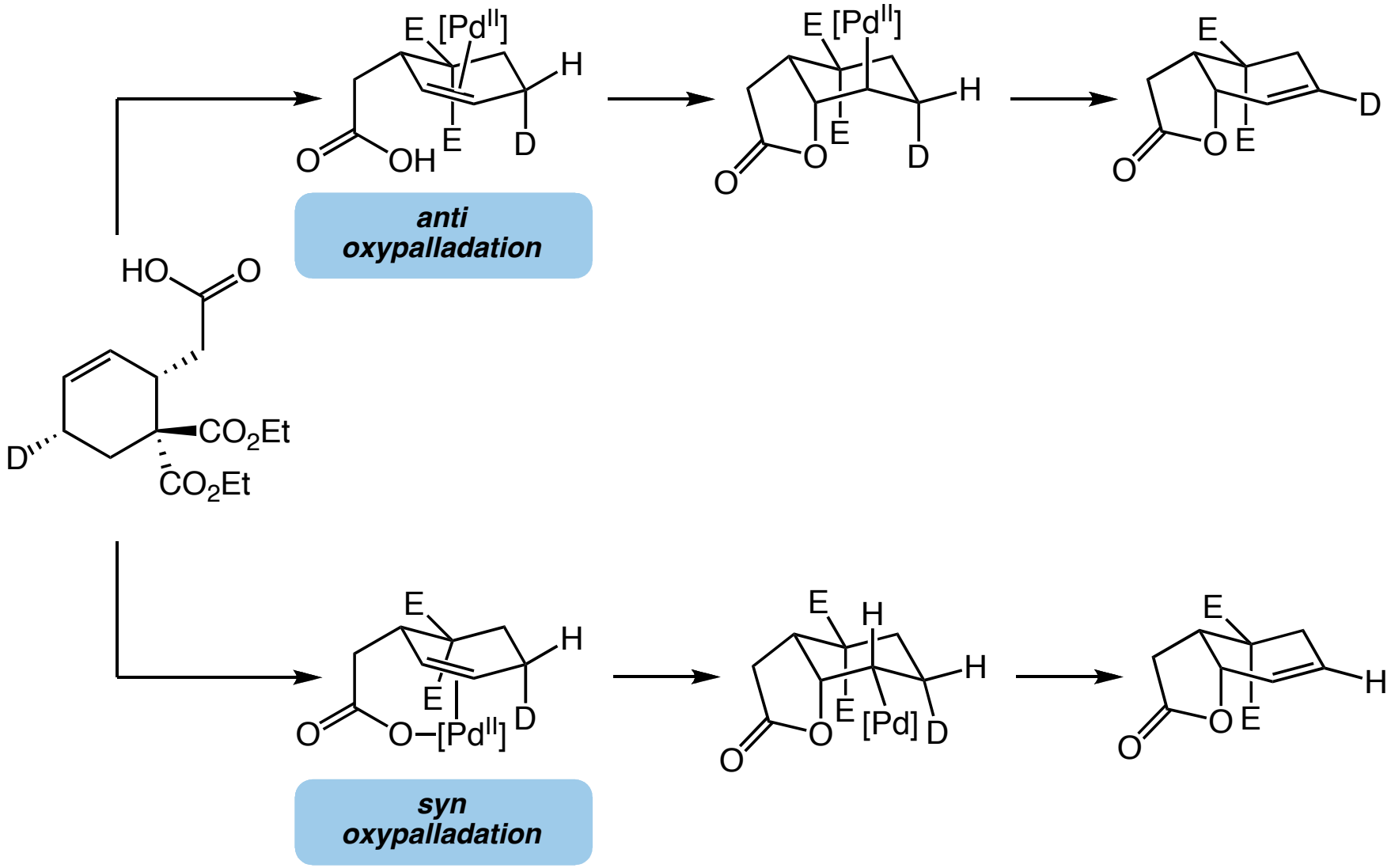
Stoltz Group Studies



Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

Stereochemistry of Oxidative Cyclizations

Stoltz Group Studies



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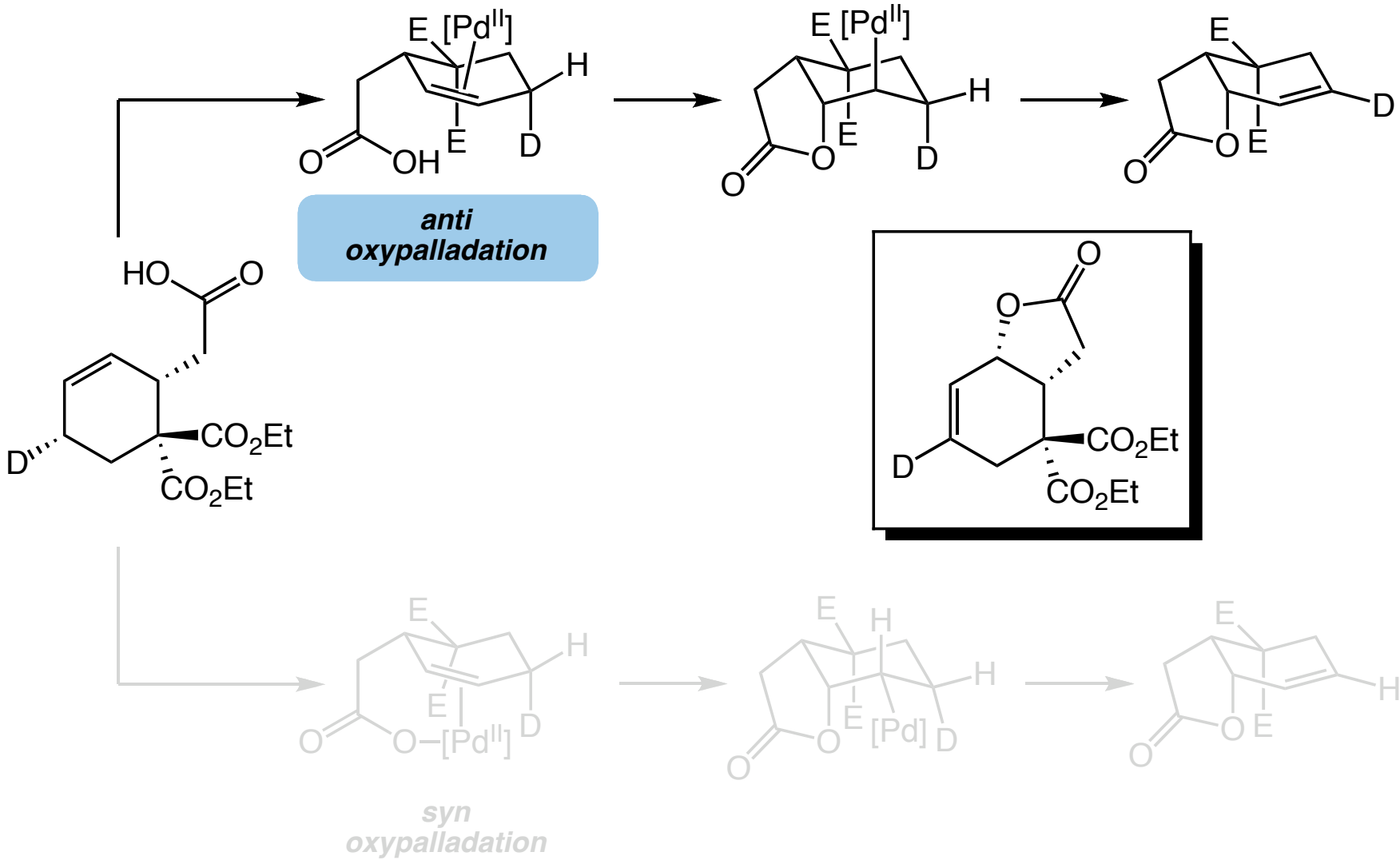
Stereochemistry of Oxidative Cyclizations

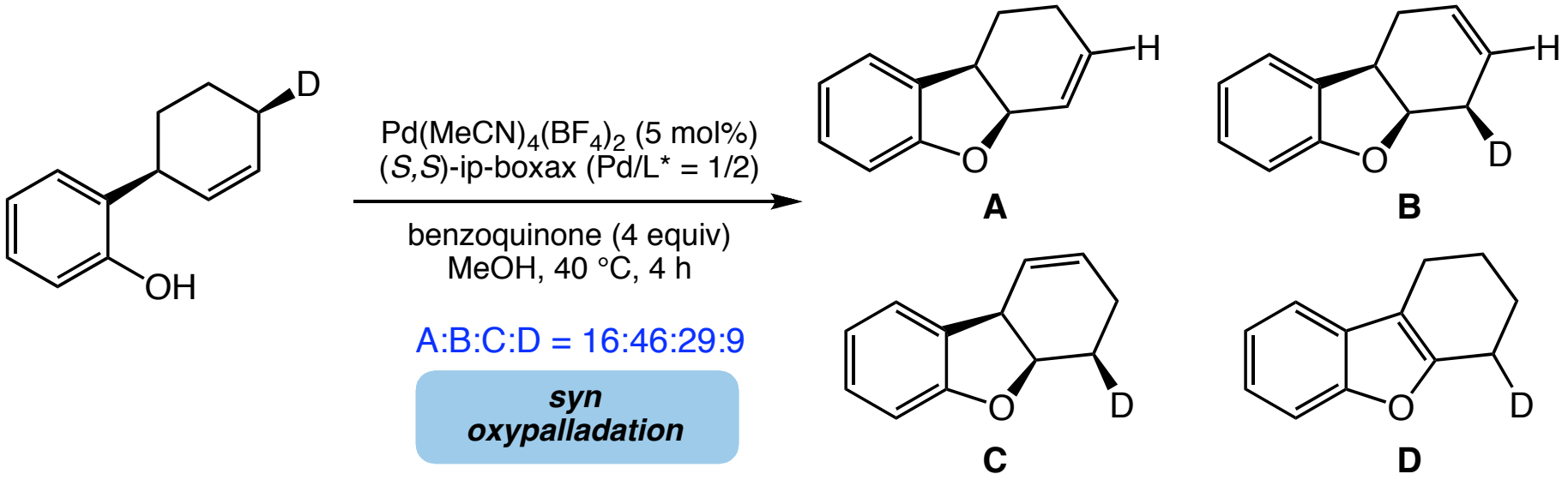
Stoltz Group Studies



Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

Stereochemistry of Oxidative Cyclizations

Hayashi Group Studies



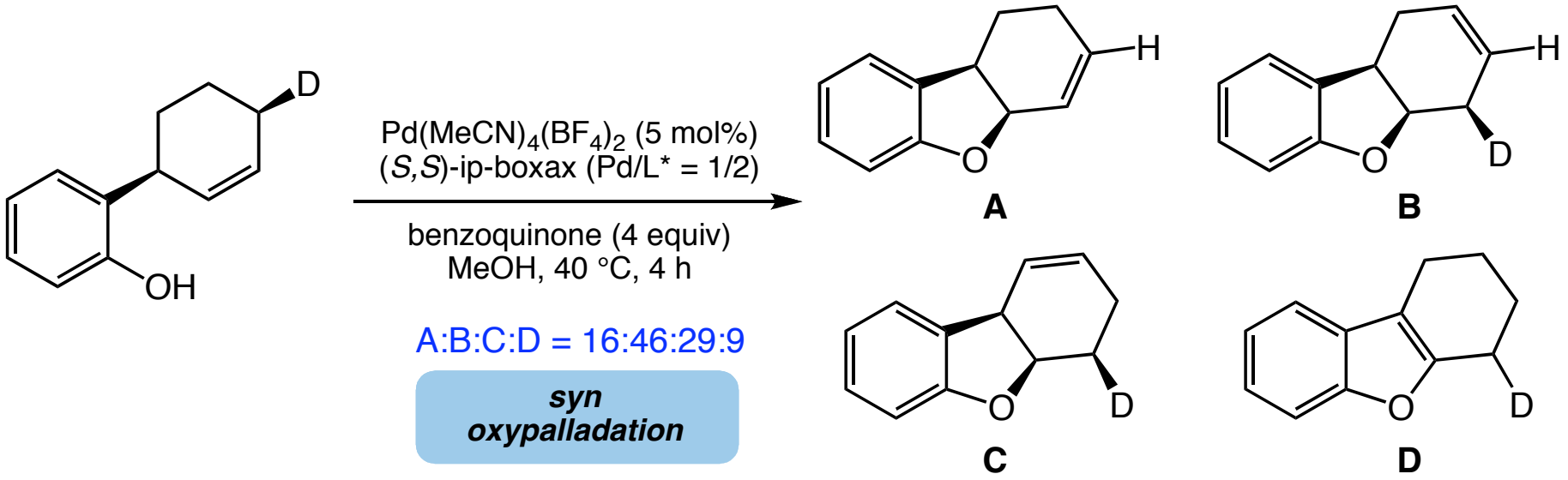
A:B:C:D = 16:46:29:9

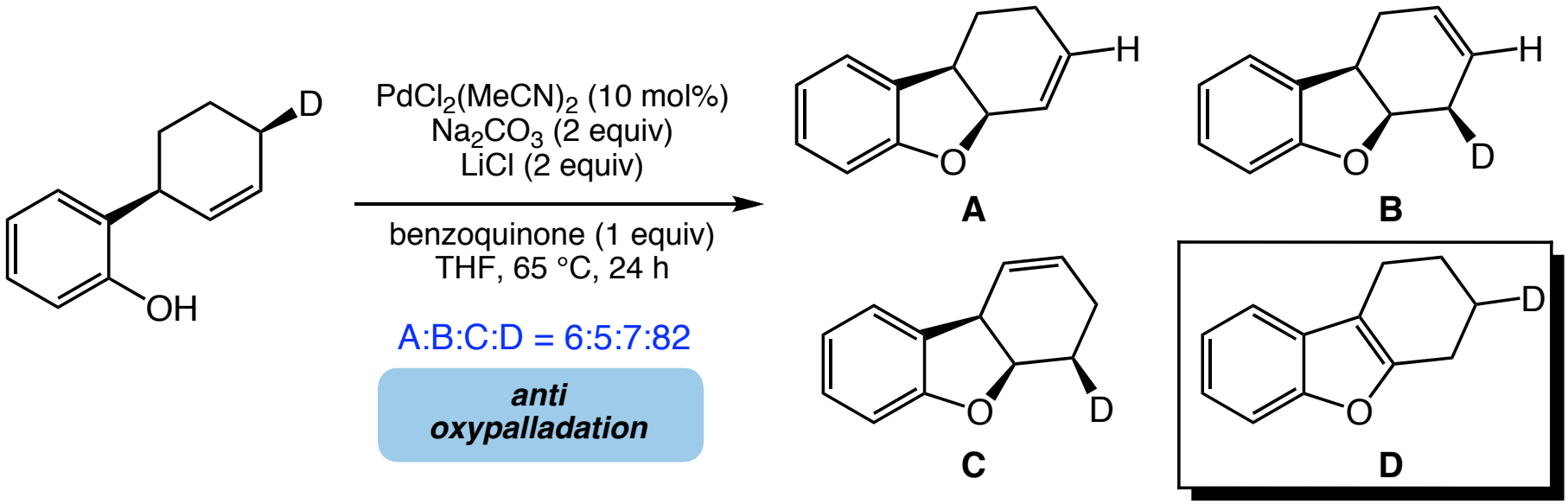
***syn* oxypalladation**

Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036.

Stereochemistry of Oxidative Cyclizations

Hayashi Group Studies

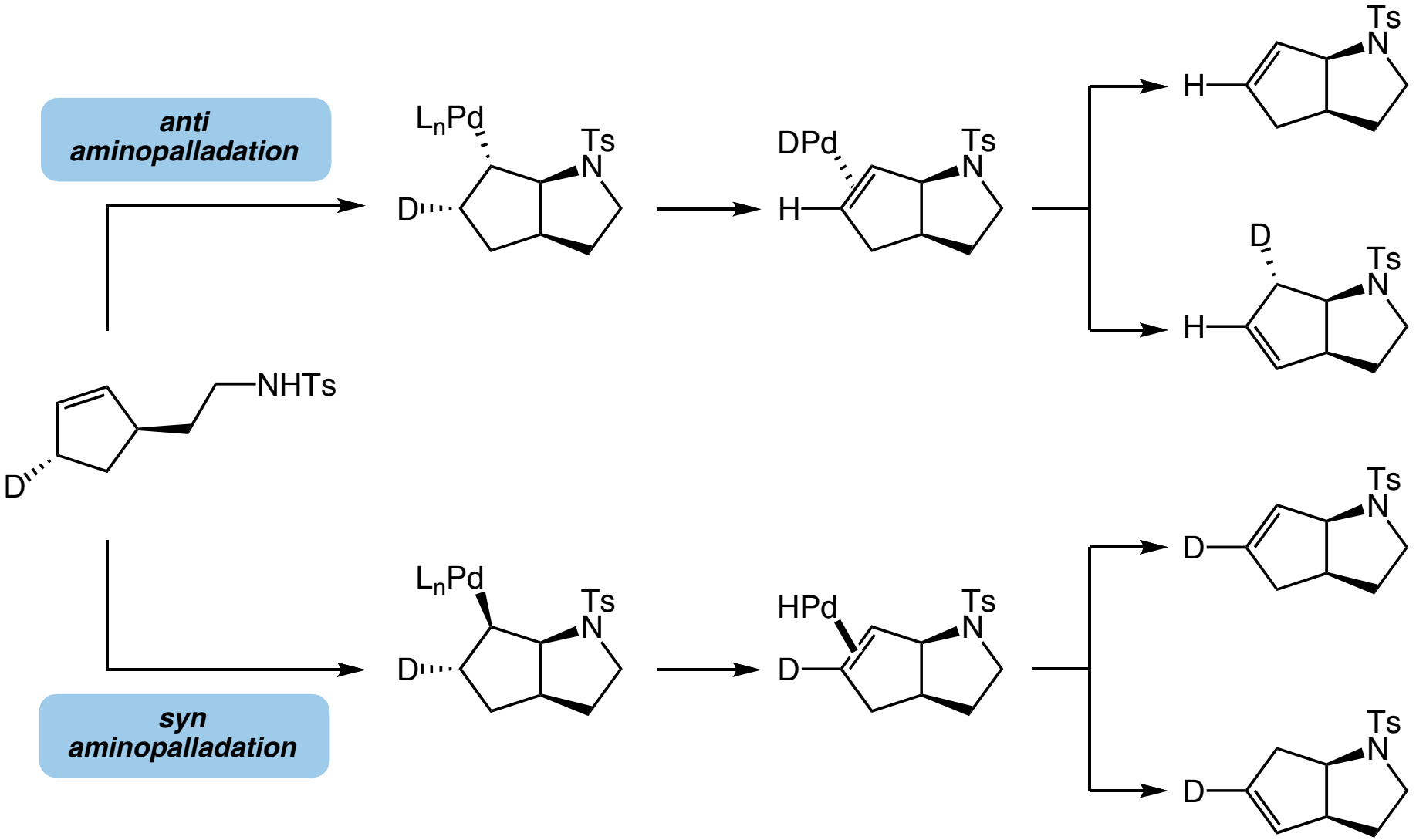




Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036.

Stereochemistry of Oxidative Cyclizations

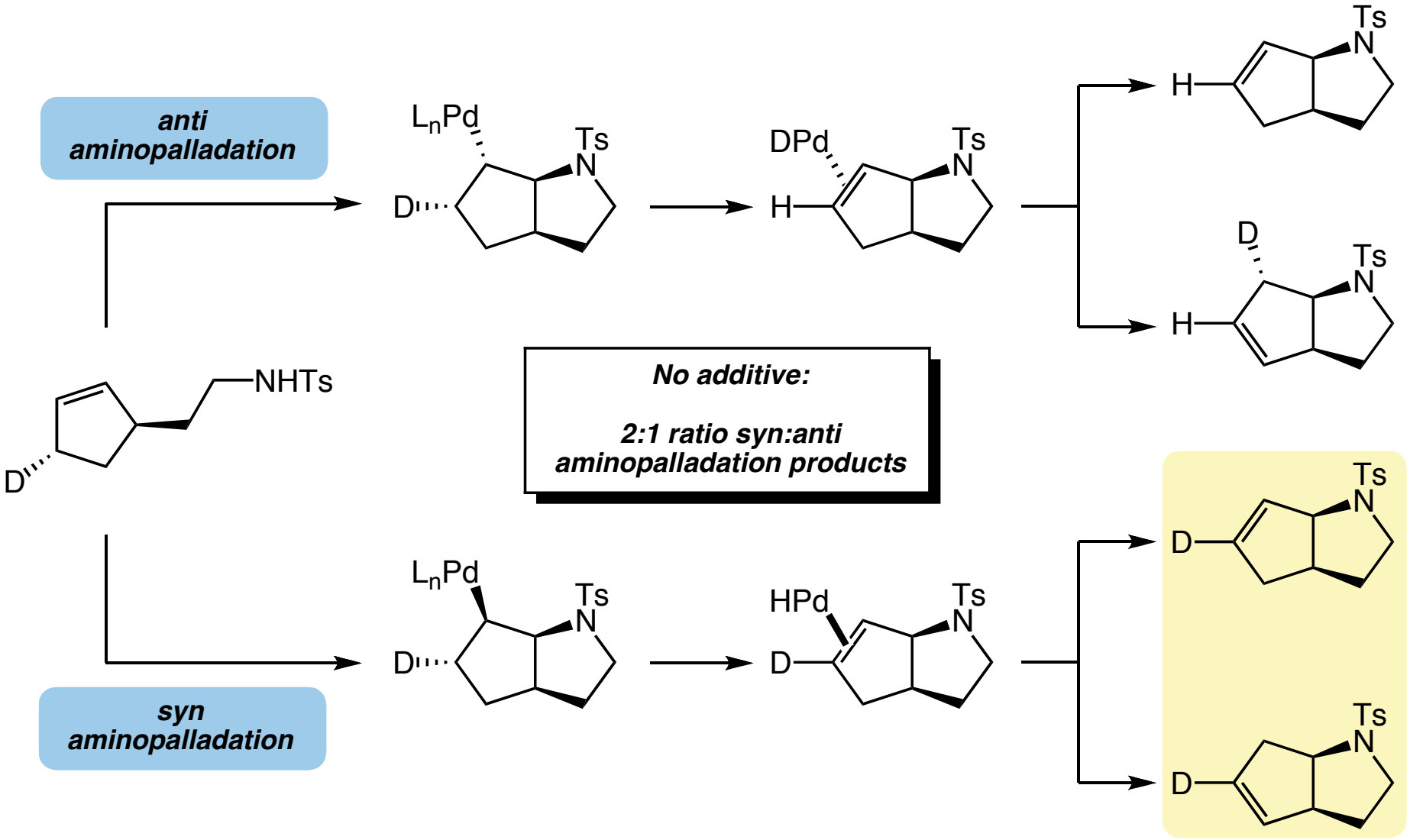
Stahl Group Studies



Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

Stereochemistry of Oxidative Cyclizations

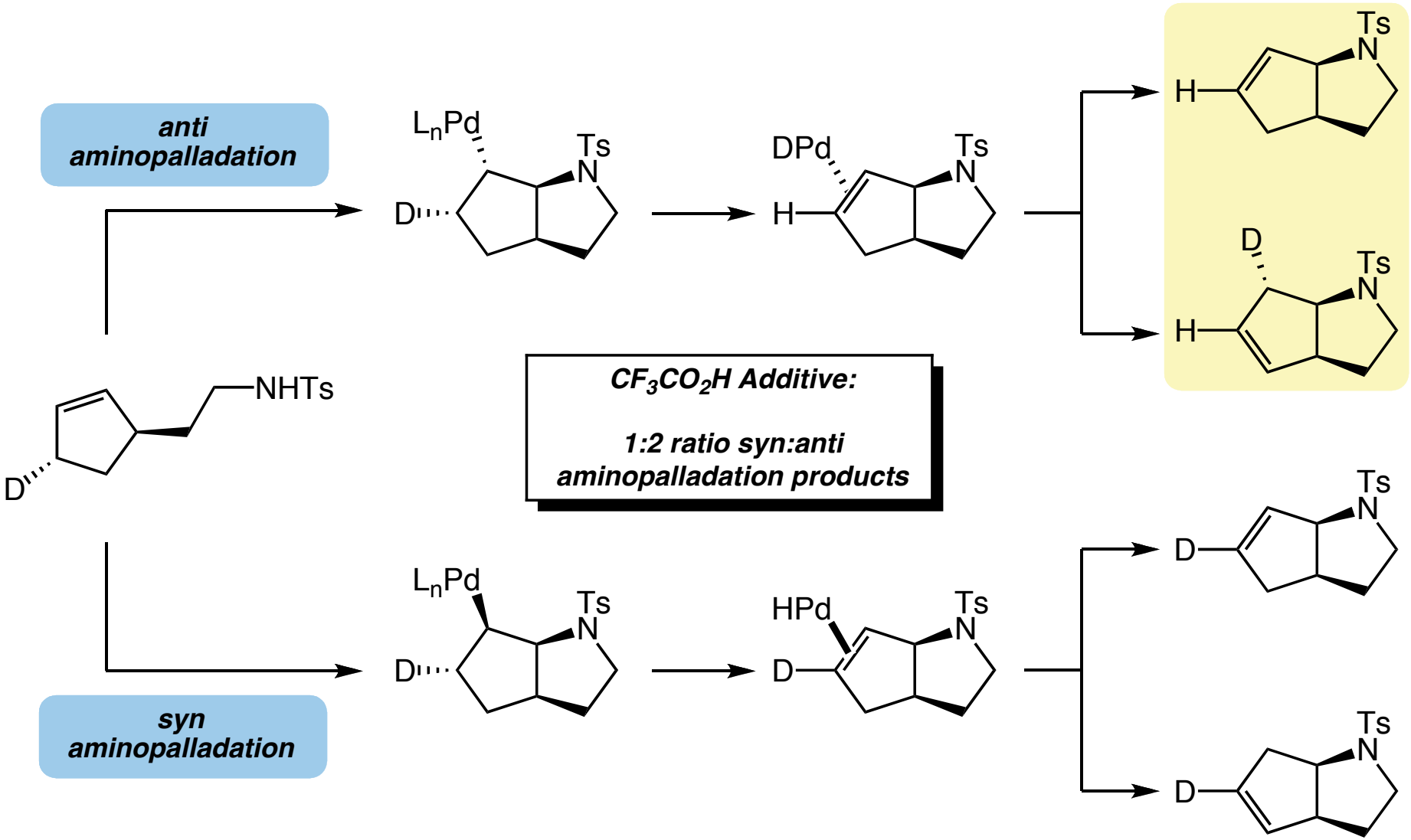
Stahl Group Studies



Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

Stereochemistry of Oxidative Cyclizations

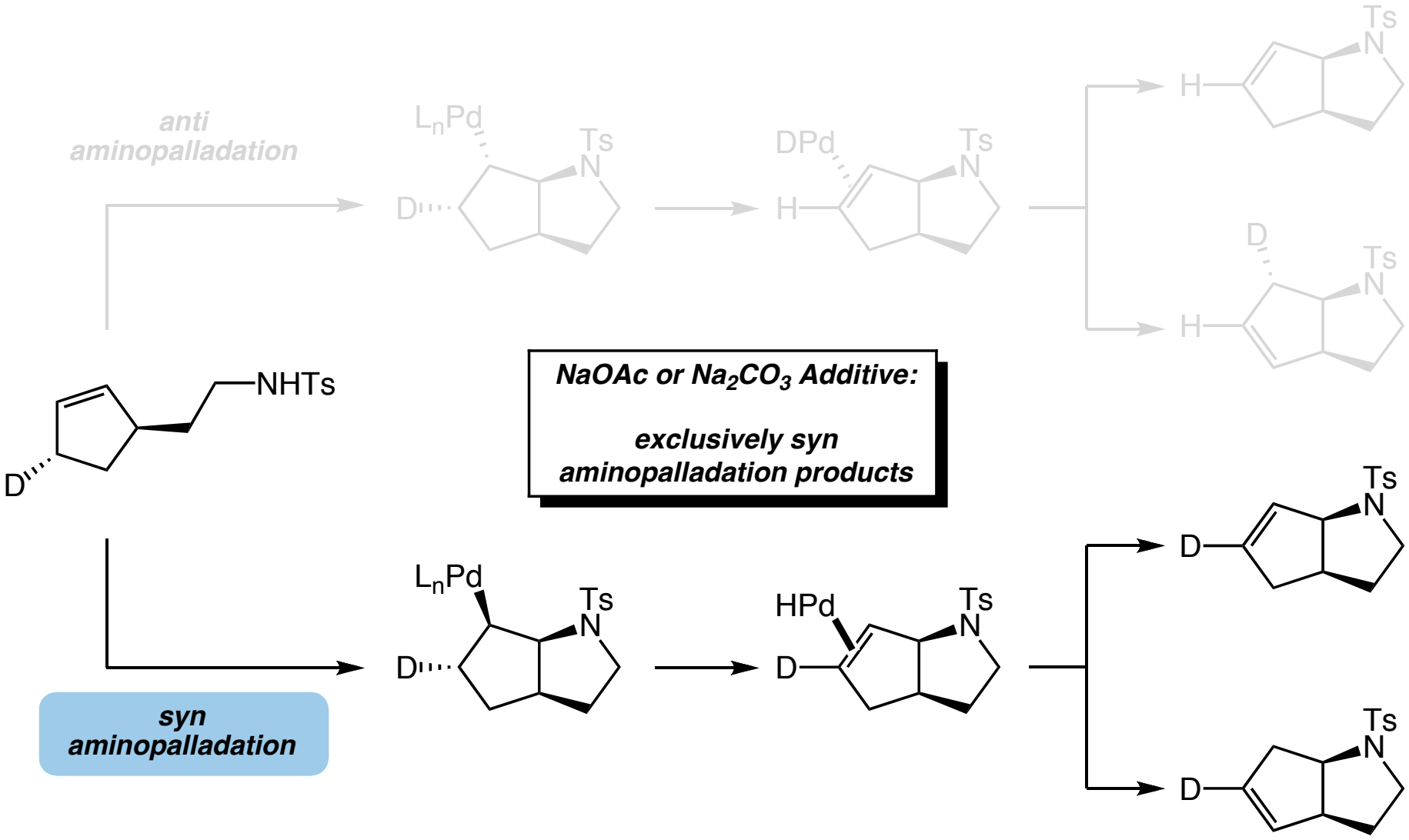
Stahl Group Studies



Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

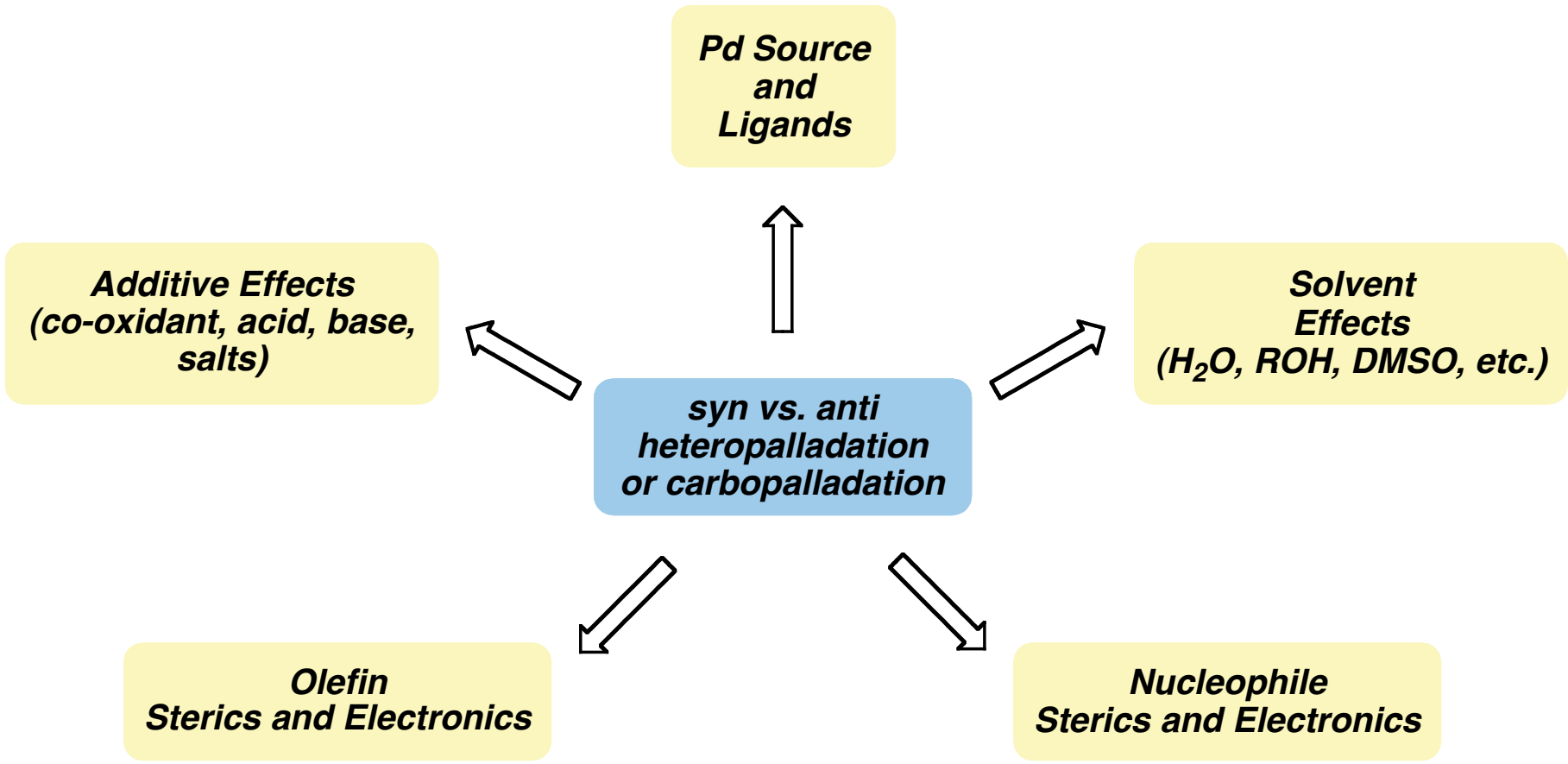
Stereochemistry of Oxidative Cyclizations

Stahl Group Studies



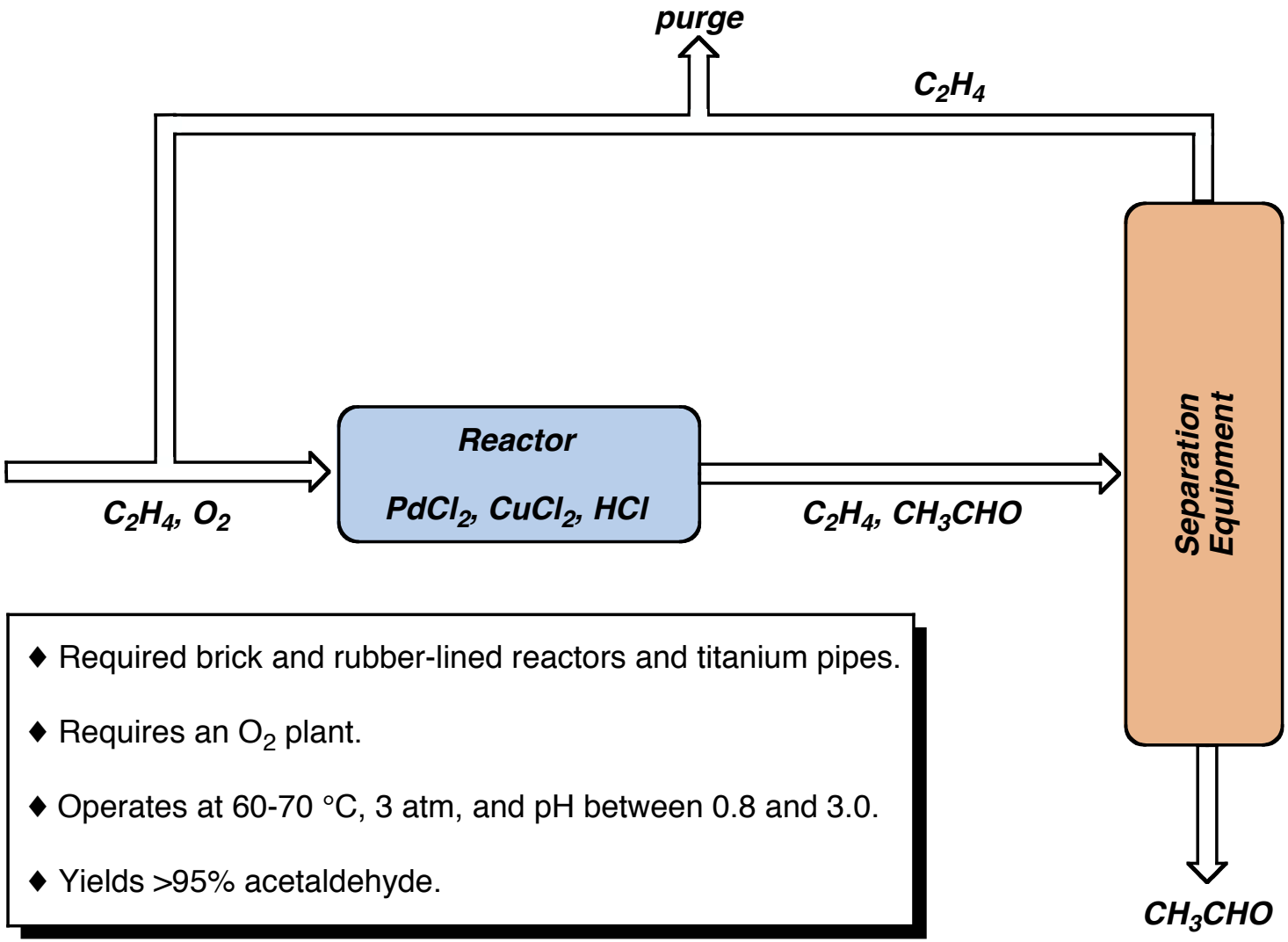
Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

Conclusions



The Wacker Oxidation

One-Stage Process



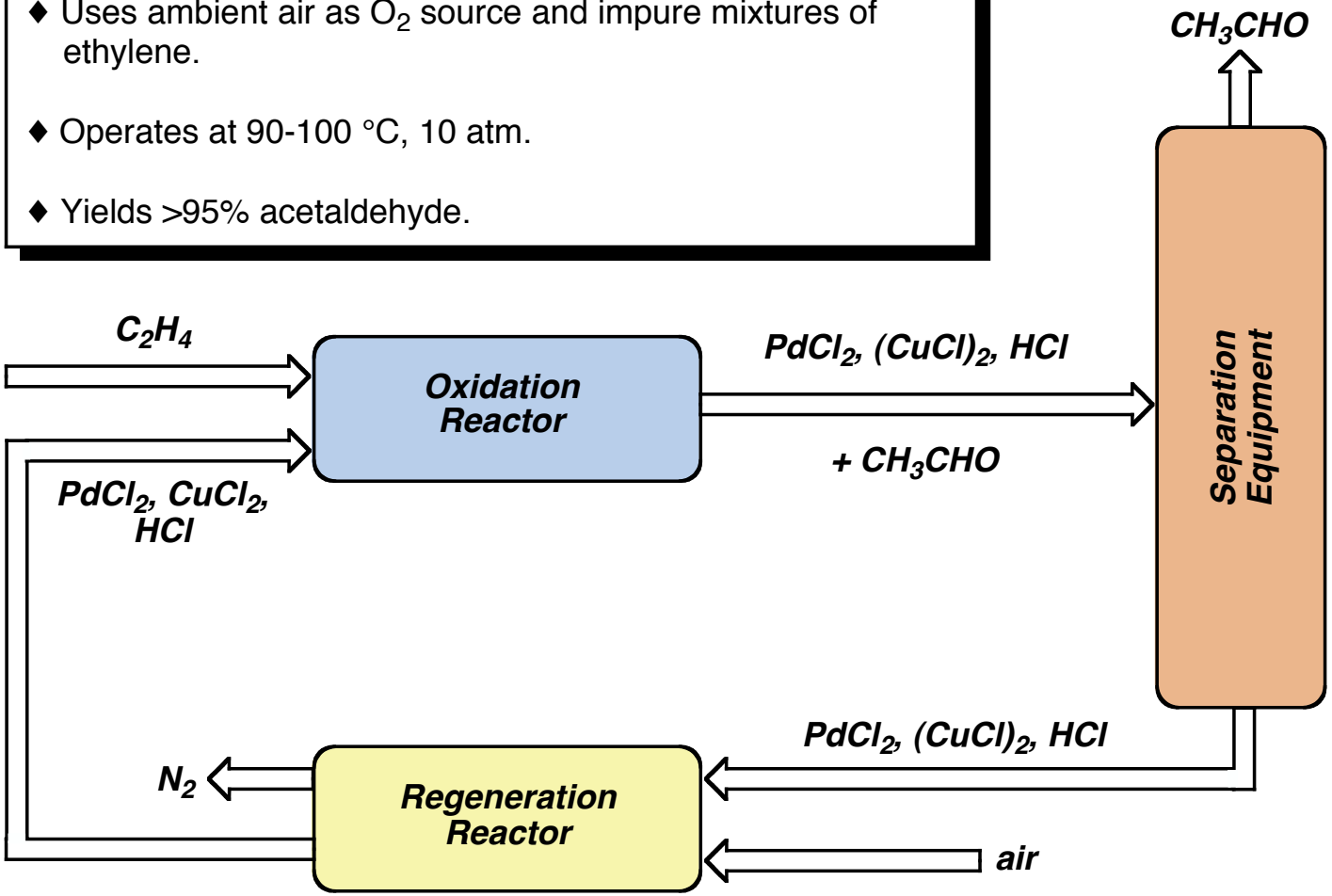
- Required brick and rubber-lined reactors and titanium pipes.
- Requires an O_2 plant.
- Operates at 60-70 °C, 3 atm, and pH between 0.8 and 3.0.
- Yields >95% acetaldehyde.

Wiseman, P. *Introduction to Industrial Organic Chemistry;* 2nd Ed.; Applied Science Publishers: London, 1979; pp. 116-120.

The Wacker Oxidation

Two-Stage Process

- Required brick and rubber-lined reactors and titanium pipes.
- Uses ambient air as O_2 source and impure mixtures of ethylene.
- Operates at 90-100 °C, 10 atm.
- Yields >95% acetaldehyde.



Wiseman, P. *Introduction to Industrial Organic Chemistry;* 2nd Ed.; Applied Science Publishers: London, 1979; pp. 116-120.