Aza-Wacker-Type Cyclization

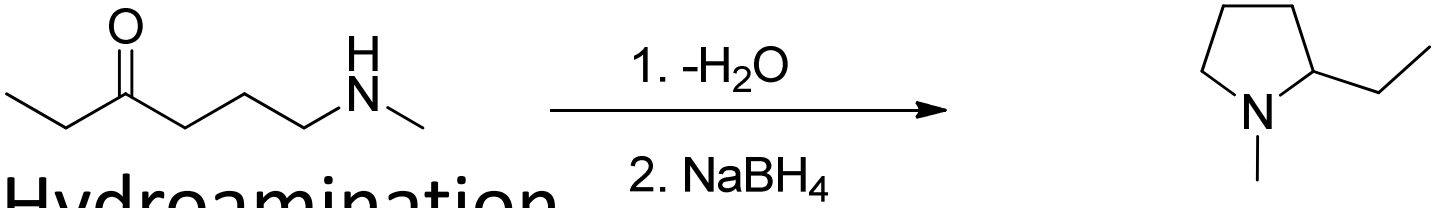
Group Meeting

Tuesday, April 19, 2011

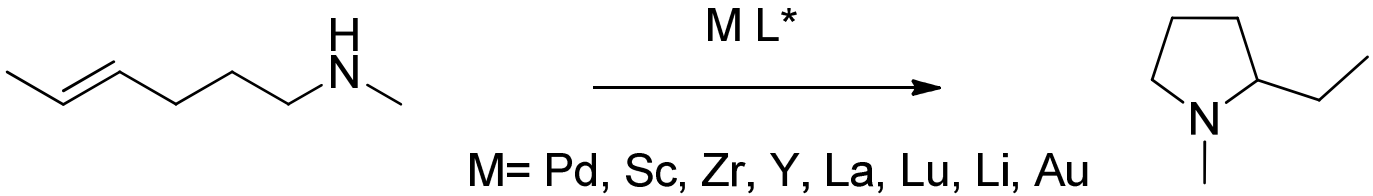
William Kuester

N-heterocylization

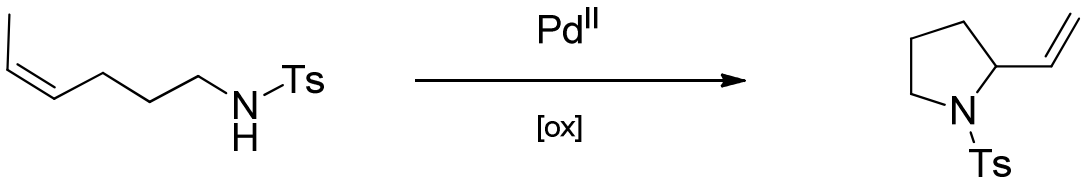
- Reductive Amination



- Hydroamination



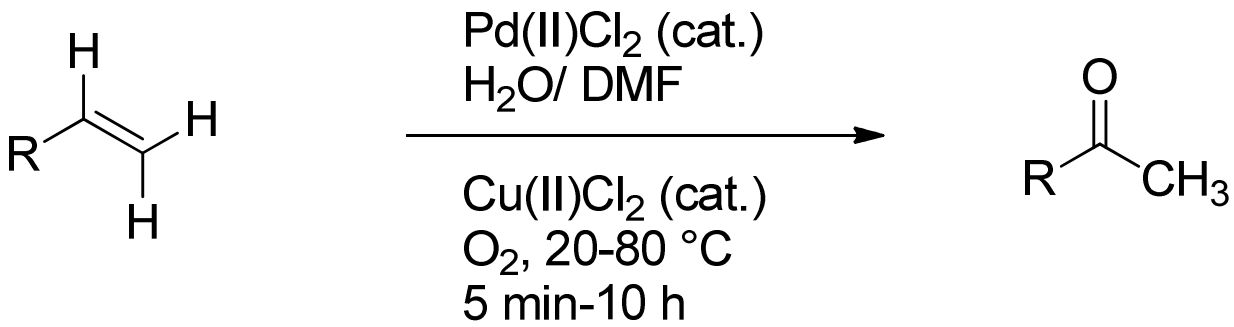
- Oxidative Cyclization



Chemler, S.R. *Org. Biomol. Chem.* **2009**, *7*, 3009-3019.

Wacker Oxidation

- First reported in 1894.

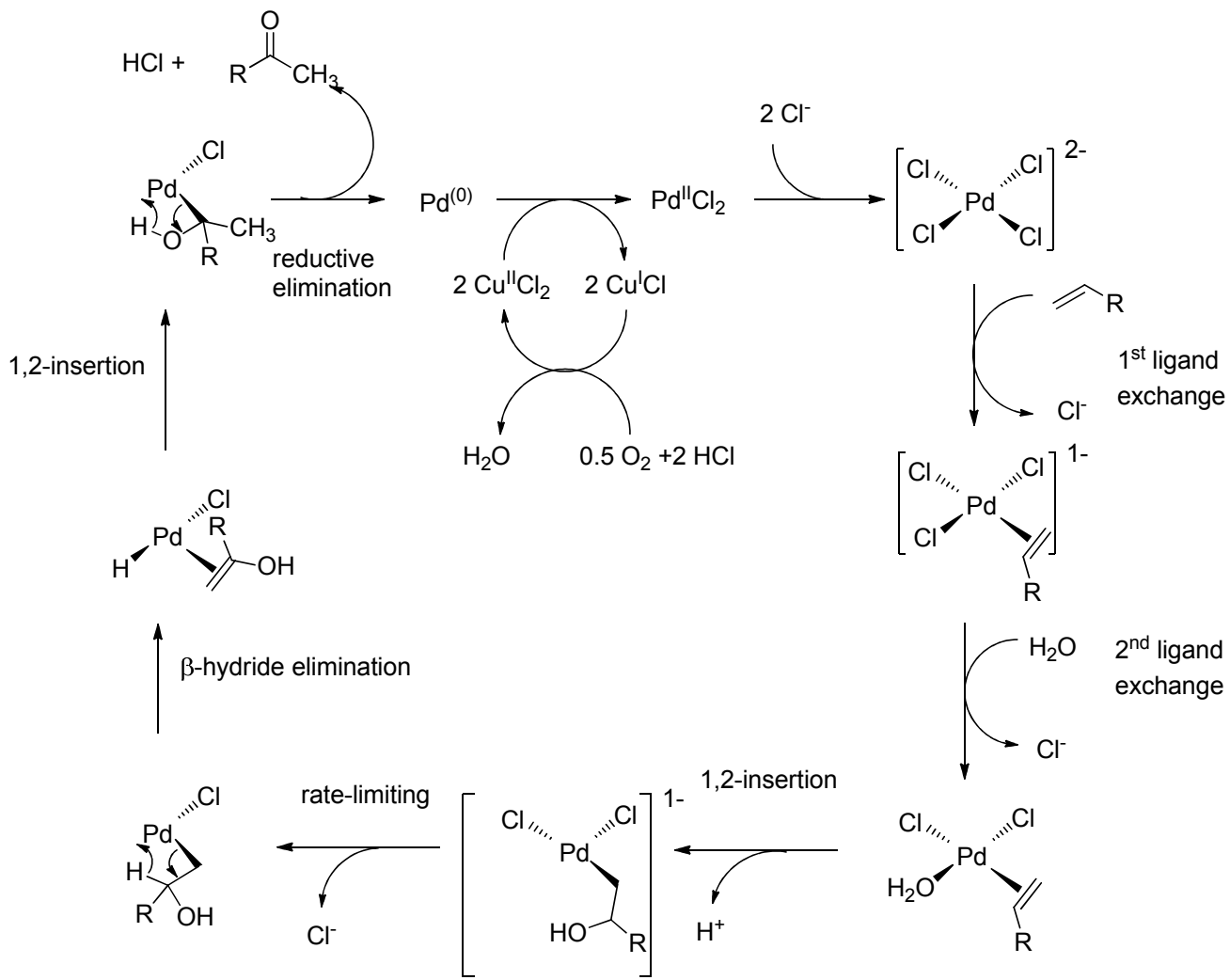


- Developed for the commercial synthesis of acetaldehyde in 1959.

Phillips, F. C. *Am. Chem J.* **1894**, 16,255-277

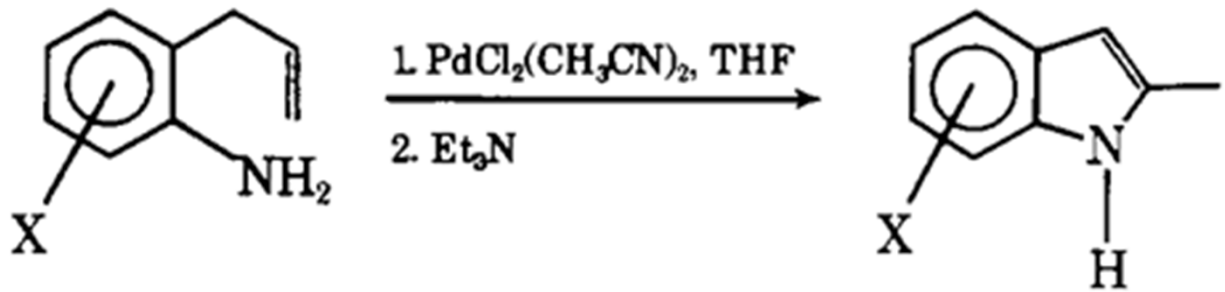
Smidt, J., Hafner, W., Jira, R., Sedlmeier, J., Sieber, R., Ruttinger, R., Kojer, R. *Angew. Chem.* **1959**, 71, 176-182

The Wacker Oxidation Catalytic Cycle



Comas-Vives, A., Stirling, A., Lleds, A., Ujaque, G. *Chem. Eur. J.* **2010**, *16*, 8738-8747.

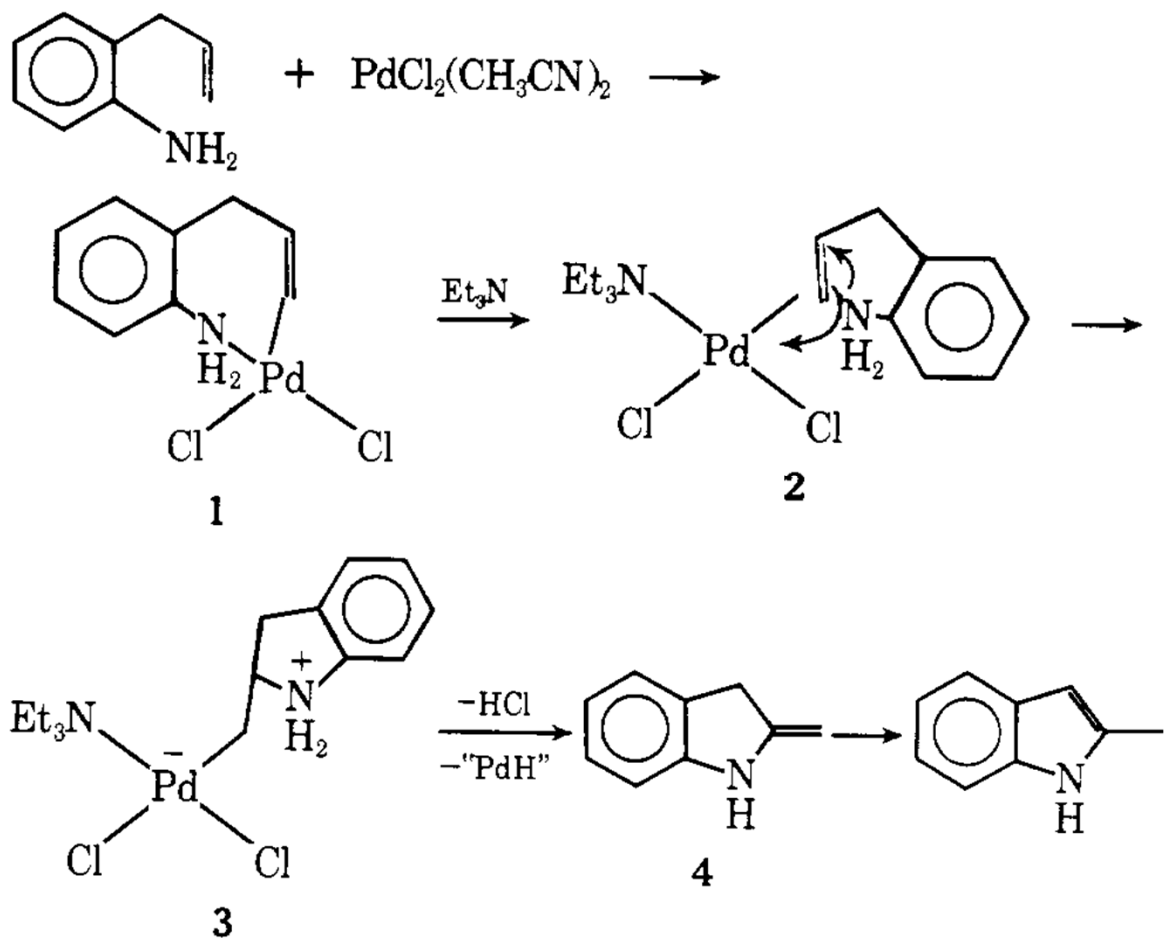
The earliest “Wacker-type” cyclization



X = H[5]	84%
X = 5-Me[6]	76%
X = 5-COOEt[7]	74%
X = 6-OMe[8]	81%

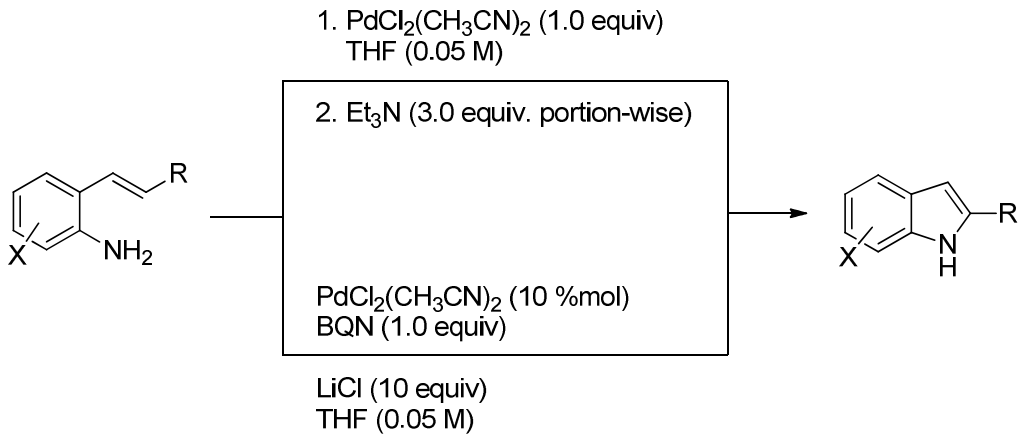
Hegedus, L.S., Allen, G.F., Waterman, E.L. *J. Am. Chem. Soc.* **1976**, 98, 2674-2676.

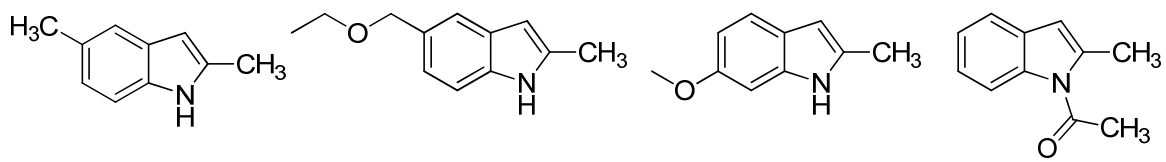
A proposed mechanism for the stoichiometric (in Pd) reaction



Hegedus, L.S., Allen, G.F., Waterman, E.L. *J. Am. Chem. Soc.* **1976**, 98, 2674-2676.

Development of a sub-stoichiometric reaction (in Pd)

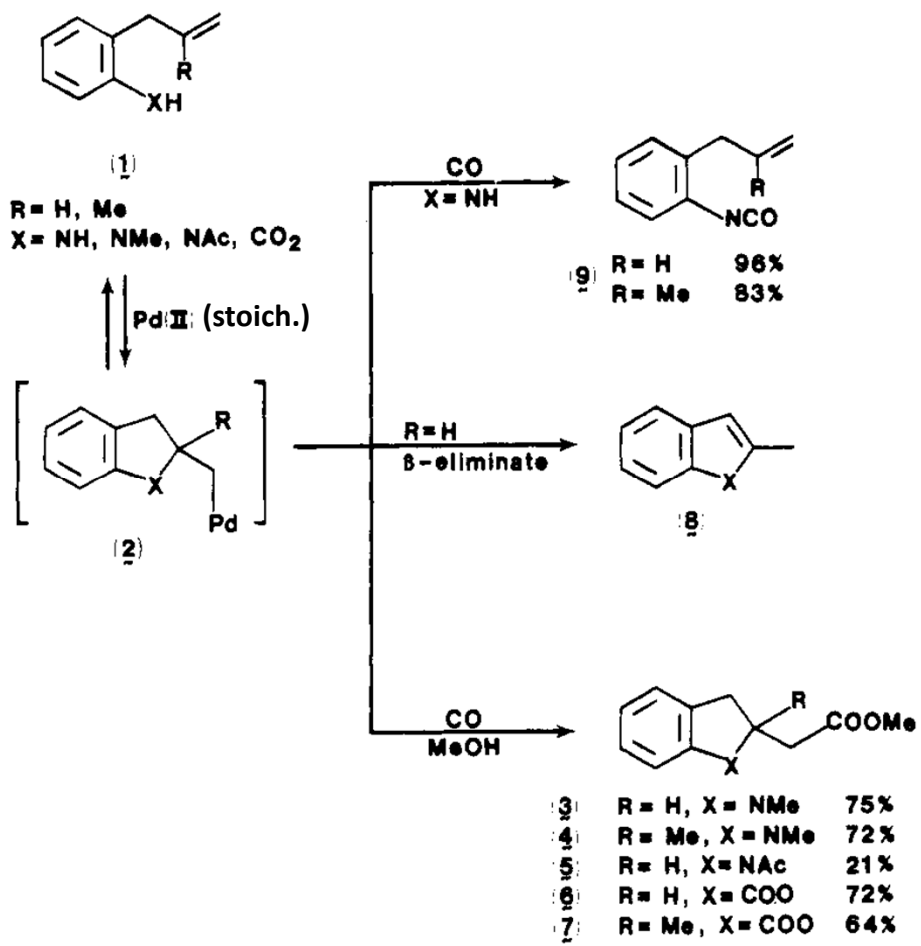




Stoiciometric:	82 %	74	82	27
Catalytic:	0	0	0	71

Hegedus, L.S., Allen, G.F., Bozel, J.J.,Waterman, E.L. *J. Am. Chem. Soc.* **1978**, 100, 5800-5807.

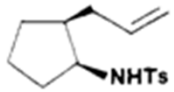
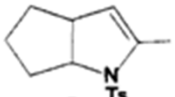
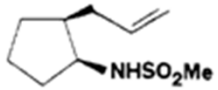
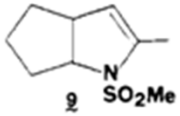
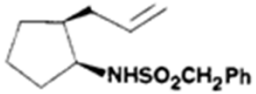
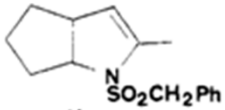
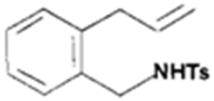
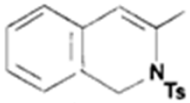
Tandem aminopalladation – CO insertion



Hegedus, L,S., Allen, G.F., Olsen, D.J. *J. Am. Chem. Soc.* **1980**,

Non-aromatic oxidative amination of sulfonamides

Table I

substrate	product	yield,[a] %
 6	 7	85
 8	 9	63
 10	 11	76
 20	 21	84

9 other examples of 5-membered cyclizations 48-99 % yield.

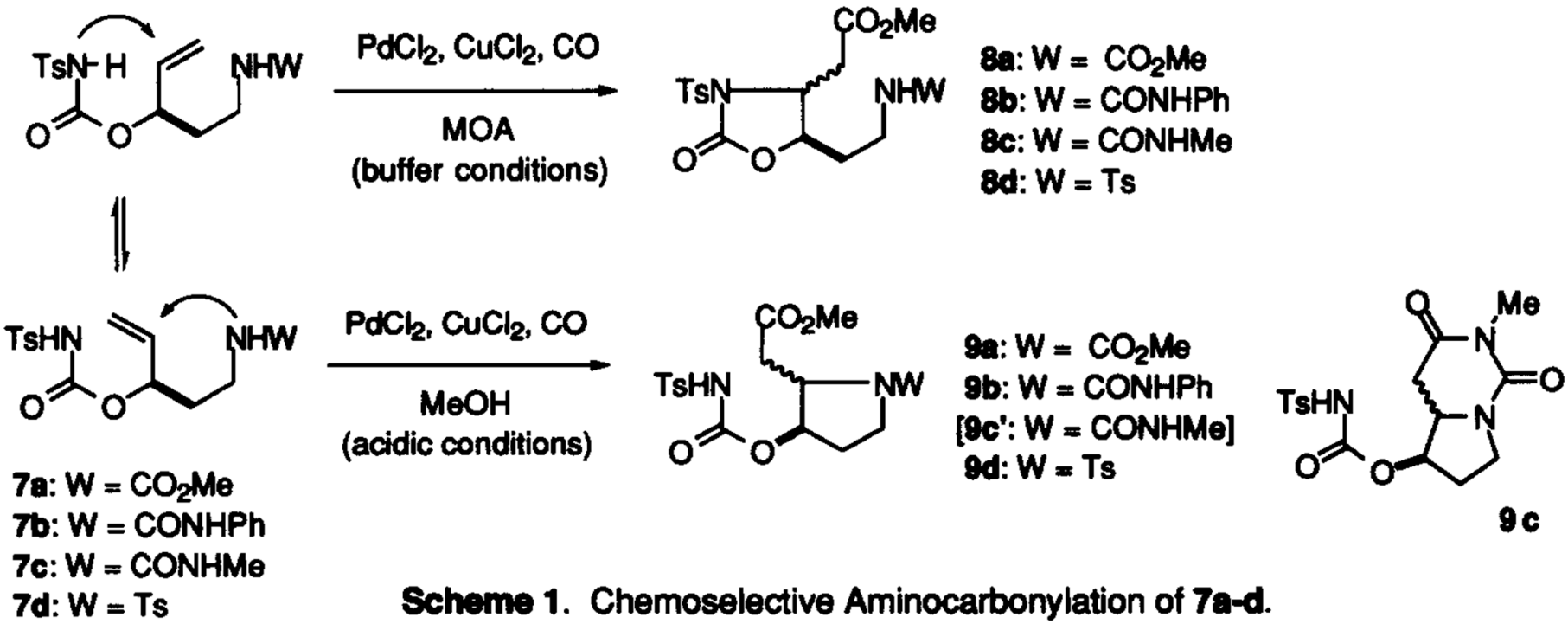
No 4- or 7- membered cyclization observed.

Only one 6-membered cyclization observed.

Linear alkene sulfonamides failed to cyclize

Hegedus, L.S., McKearin, J.M. *J. Am Chem. Soc.* **1982**, *104*, 2444-2451

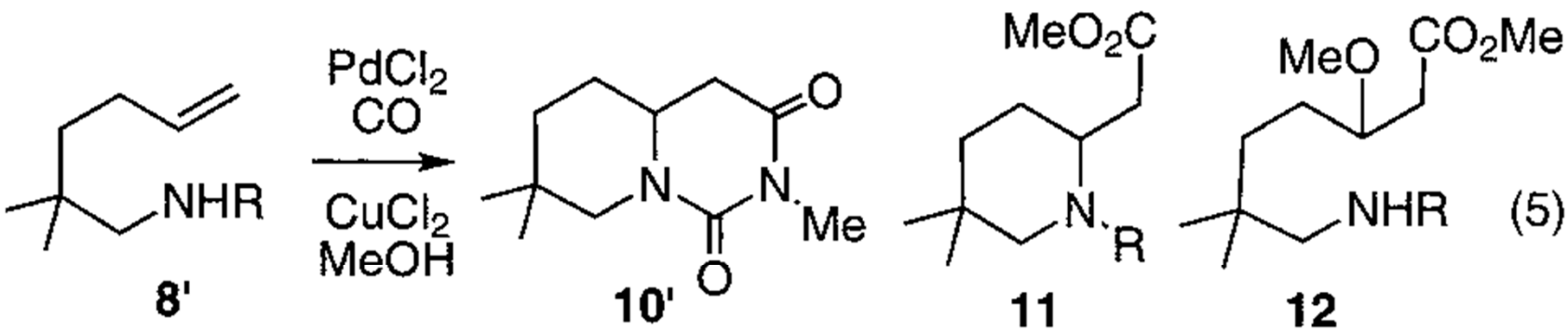
Expansion of scope to *exo*- and *endo*-ureas



Scheme 1. Chemoselective Aminocarbonylation of **7a-d**.

Harayama, H., Tamaru, Y., et. al. *Tet. Lett.* **1996**. 37, 7287-7290.

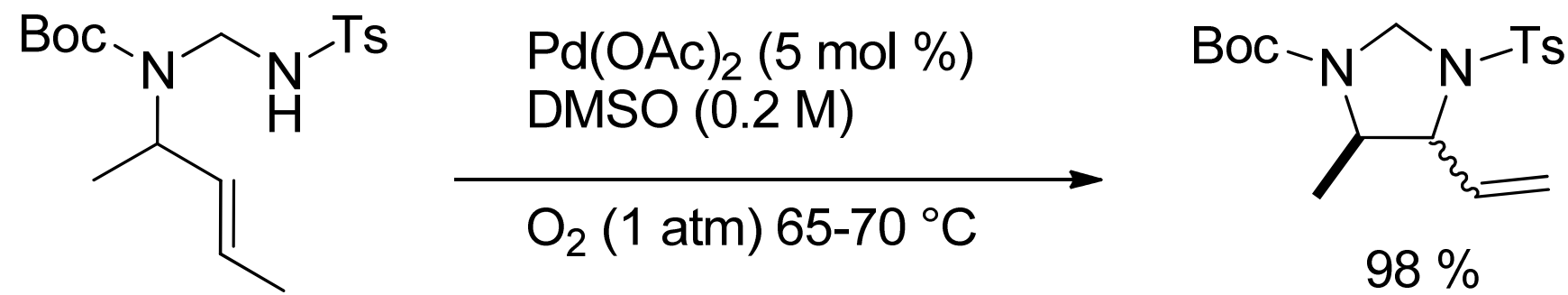
6-membered N-heterocycles

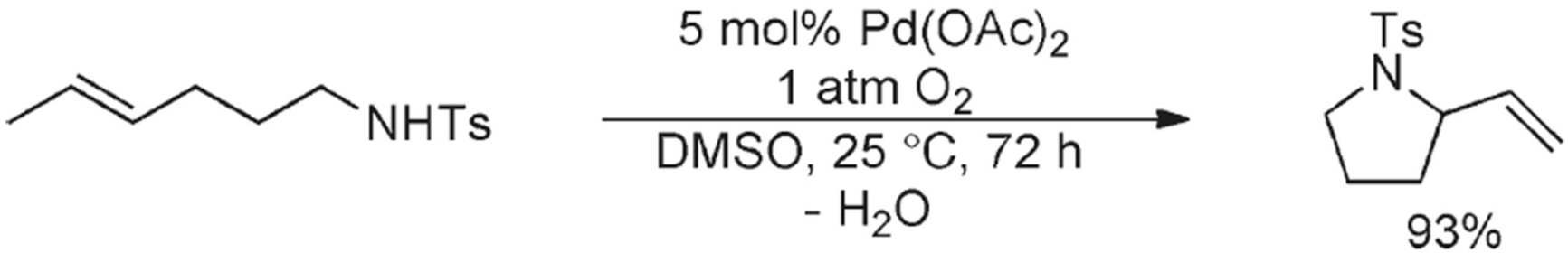


R =	10'	11	12
SO_2Tol	0	58	30
CO_2Me	0	77	16
CONHMe	81	0	0

Tamaru, Y., Kimura, M., *Syn. Lett.* **1997**, 749-757

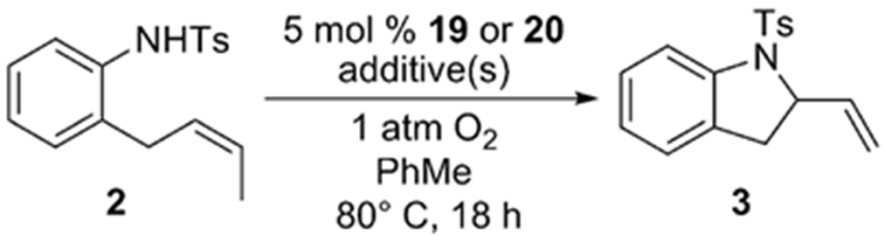
Introduction of O_2 as oxidant



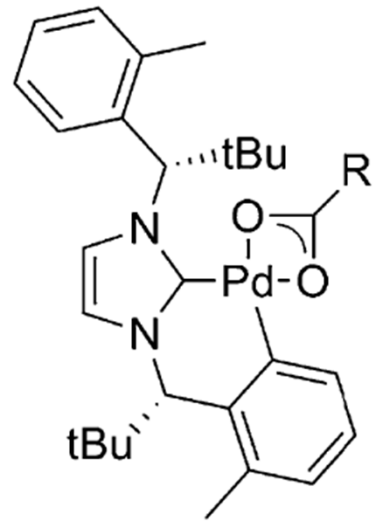


Van Benthem, R.A.T.M., Hiemstra, H. , Longarela, G.R., Speckamp, W.N. *Tet. Lett.* **1994**, *35*, 9281-9284.
Larock, R.C., Hightower, T.R., Hasvold, L.A., Peterson, K.P., *J. Org. Chem.* **1996**, *61*, 3584-3585.

An unsuccessful attempt at asymmetric cyclization



83-96 % yields
0-6 % ee

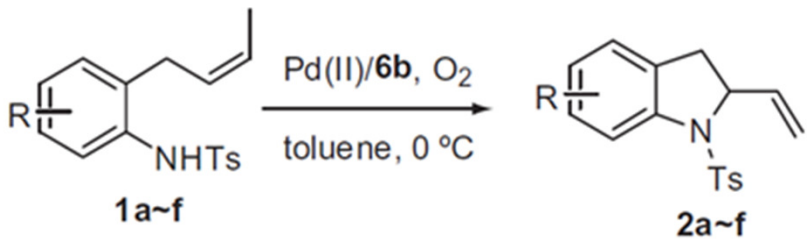


R = CH_3 (**19**)
R = CF_3 (**20**)

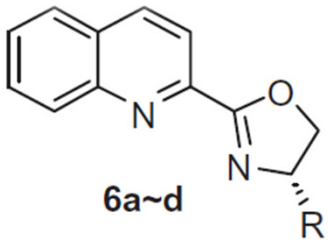
Scarborough, C.C., Bergant, A., Sazama, G.T., Guzei, I.A., Spencer, L.C., Stahl, S.S. *Tetrahedron,* **2009**, 65, 5084-5092.

First successful asymmetric oxidative aminopalladation of an alkene

Aza-Wacker-type cyclization reaction of different substrates with ligand **6b**[a]



Entry	Substrate	Yield[b] (%)	ee[c] (%)
1	**1a** (R = H)	90	69[d]
2	**1b** (R = 4-CH_3)	94	69
3	**1c** (R = 6-CH_3)	37	−8
4	**1d** (R = 4-Cl)	90	68
5	**1e** (R = 6-Cl)	4	−35
6	**1f** (R = 4-OCH_3)	75	74

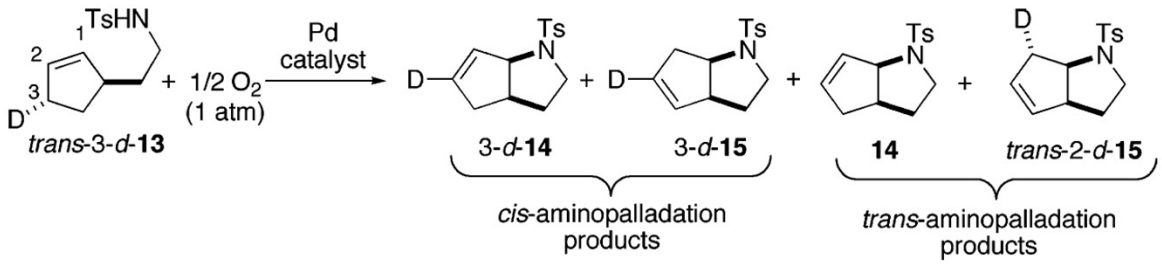


6a~d

6a; R=Ph; **6b**; R=*i*-Pr;
6c; R=Bn; **6d**; R=*t*-Bu; .

Jiang, F., Wu, Z., Zhang, W.B., *Tet. Lett.* **2010**, 51, 5124-5126.

Cis aminopalladation is preferred

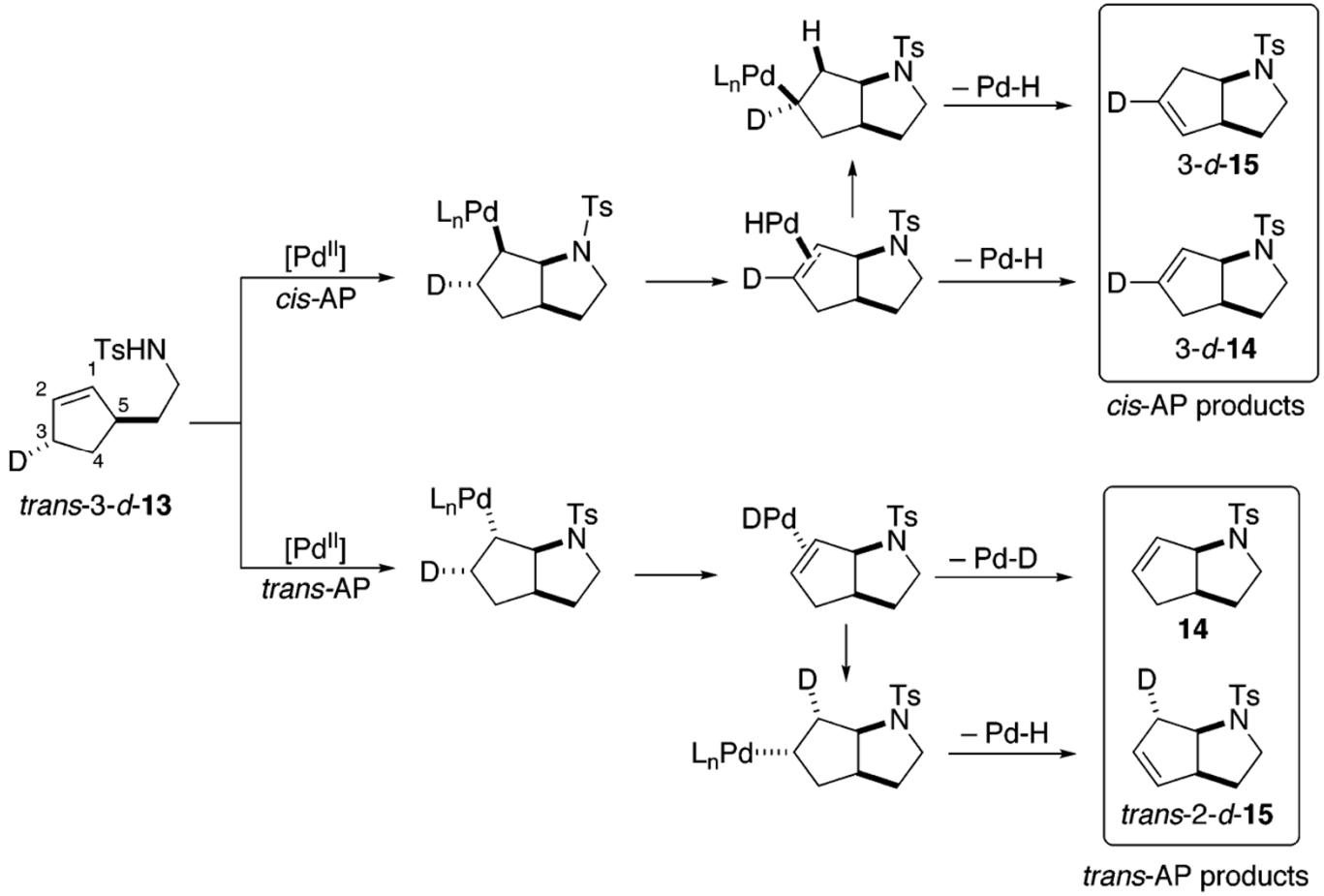


entry	Pd catalysts	time (h)	yield[b] (%)	product ratio[b]	
				cis-AP 3-*d*-**14**/3-*d*-**15**	*trans*-AP **14**/*trans*-2-*d*-**15**
1	$Pd(OAc)_2$/DMSO (**A**)	15	70	100:0	
2	$Pd(OAc)_2$/py (**B**)	15	84	98:2	
3	$Pd(O_2CCF_3)_2$/py (**C**)	15	85	88:12	
4	$Pd(IMes)(O_2CCF_3)_2$/BzOH (**D**)	72	60	43:8	37:12
5	$Pd(O_2CCF_3)_2$/sp (**E**)[c]	72	37[d]	59:41	

[a] All reactions performed at 80 °C; 5 mol % Pd; 0.1 mmol scale. [b]Determined by ^{1}H NMR spectroscopy (internal standard = 1,3,5-trimethoxybenzene). [c]10 mol % Pd. [d]45% starting material recovered.

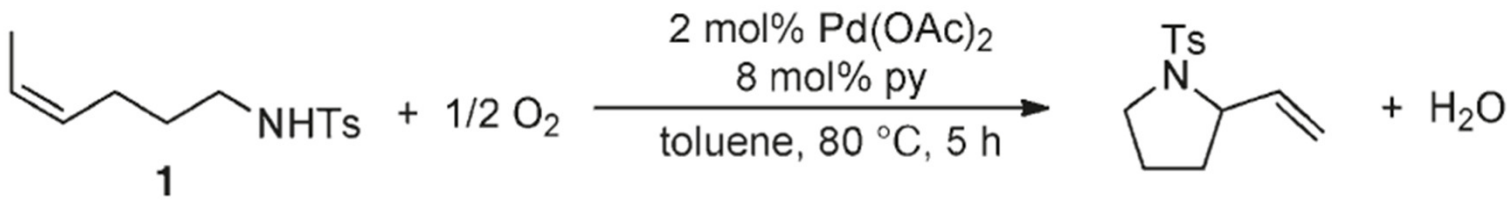
Liu, G.S., Stahl, S.S. *J. Am. Chem. Soc.* **2007**, *129*, 6328-6335

A mechanistic differentiation



Liu, G.S., Stahl, S.S. *J. Am. Chem. Soc.* **2007**, *129*, 6328-6335

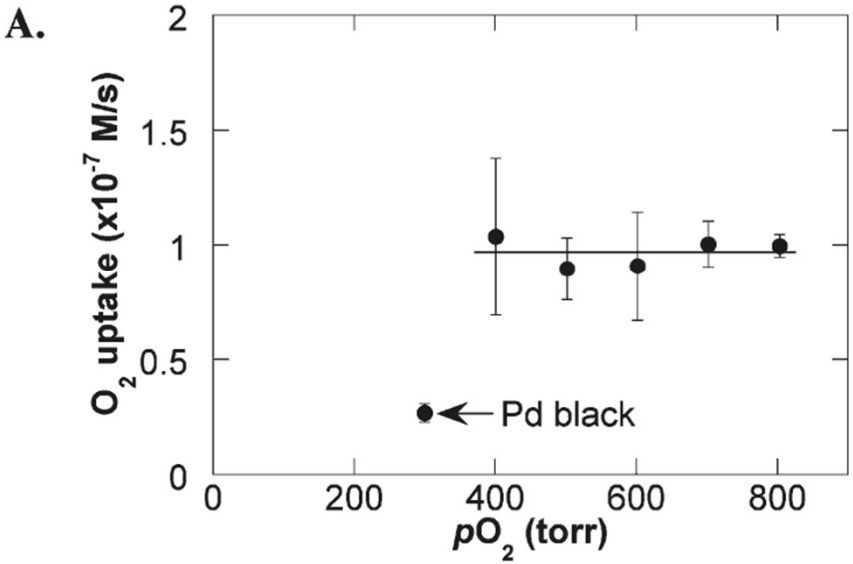
An in-depth mechanistic investigation

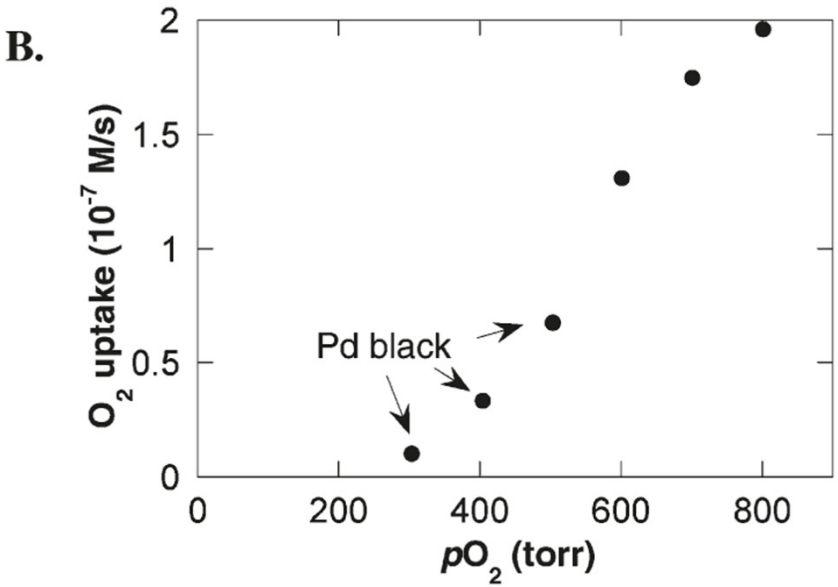


- Goals of this study
  - Determine the dependence on O_2
  - Define the role of pyridine and acetate in ligand exchange on palladium
  - Derive a rate law for the proposed mechanism
  - Use computational methods to model the transition state

Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

O_2 dependence of initial rates



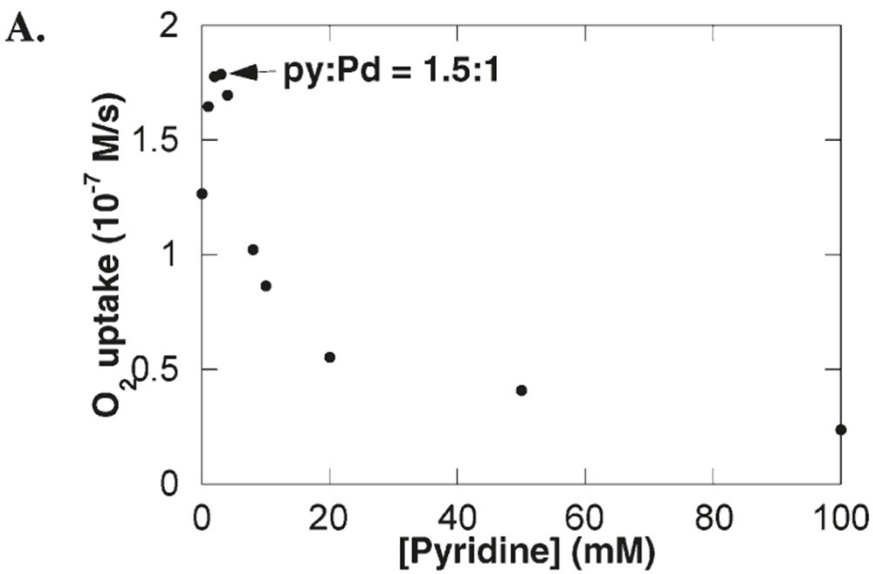


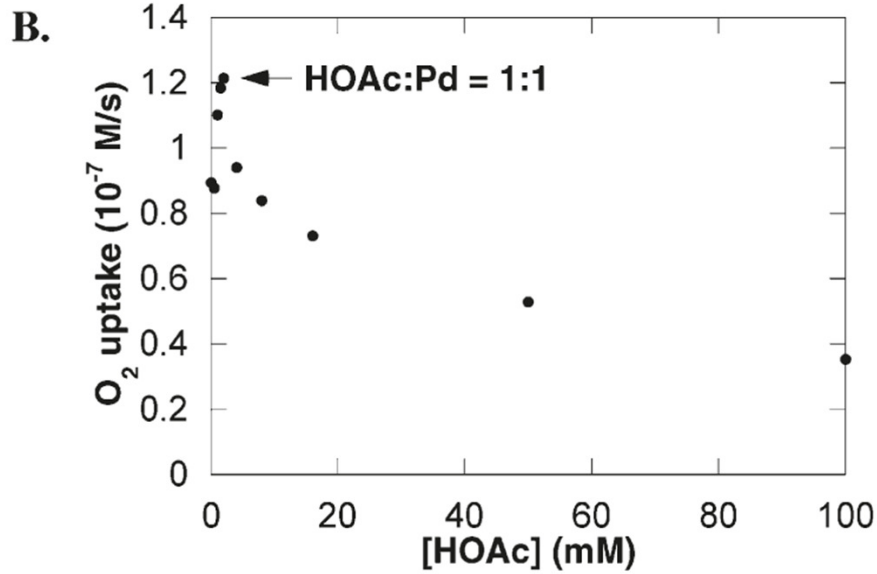
$[Pd(OAc)_2]_o$ = 2.0 mM
$[pyridine]_o$ = **8.0 mM**
$[amide]_o$ = 100 mM
4.0 mL toluene
pO_2 = *300-800 Torr*

$[Pd(OAc)_2]_o$ = 2.0 mM
$[pyridine]_o$ = **4.0 mM**
$[amide]_o$ = 100 mM
4.0 mL toluene
pO_2 = *300-800 Torr*

Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

“Ligand” dependence of initial rates



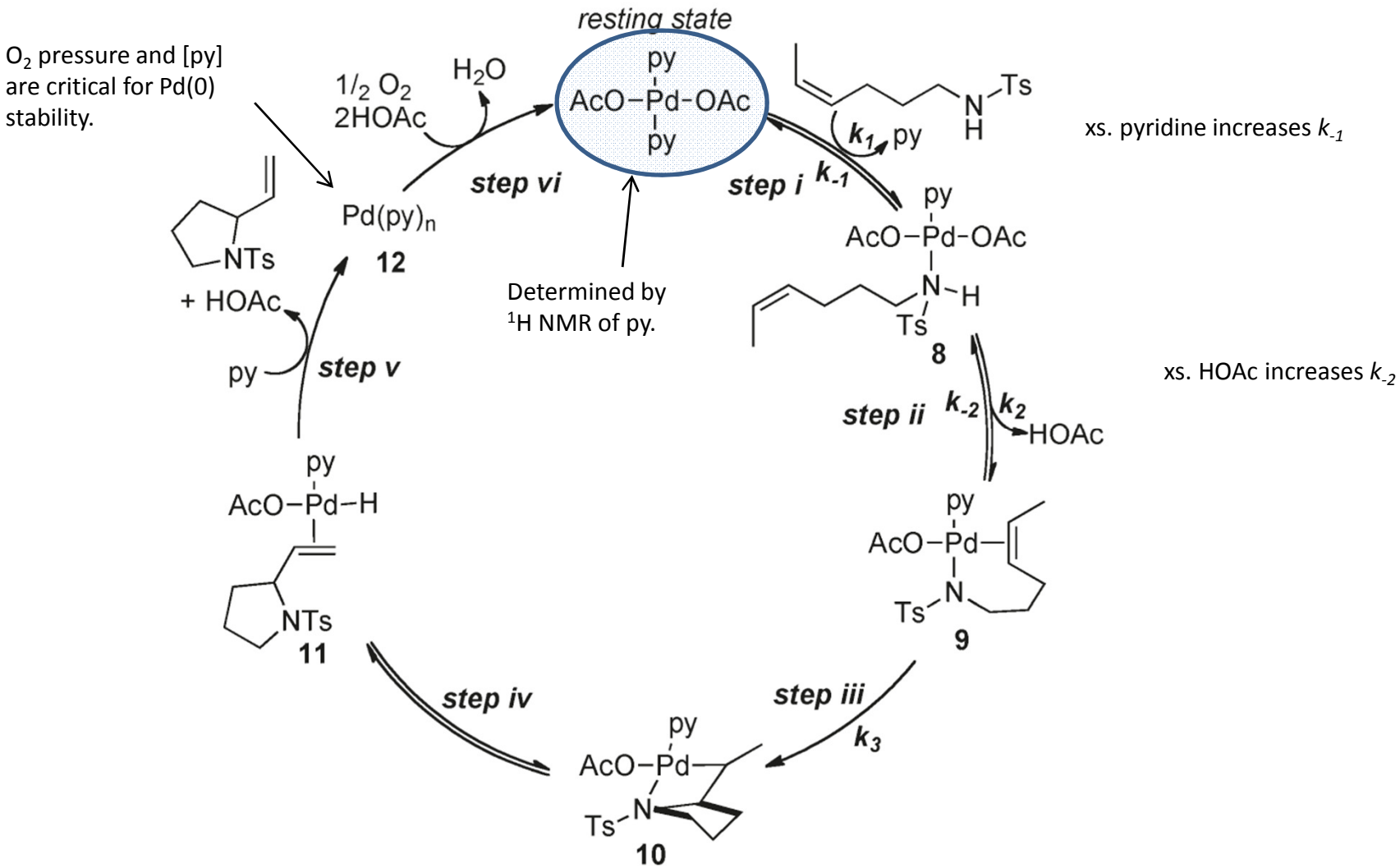


$[Pd(OAc)_2]_o$ = 2.0 mM
$[pyridine]_o$ = *0.0-100 mM*
$[amide]_o$ = 100 mM
4.0 mL toluene
pO_2 = 700 Torr

$[Pd(OAc)_2]_o$ = 2.0 mM
$[pyridine]_o$ = 8.0 mM
$[amide]_o$ = 100 mM
$[HOAC]_o$ = *0-100 mM*
4.0 mL toluene
pO_2 = 700 Torr

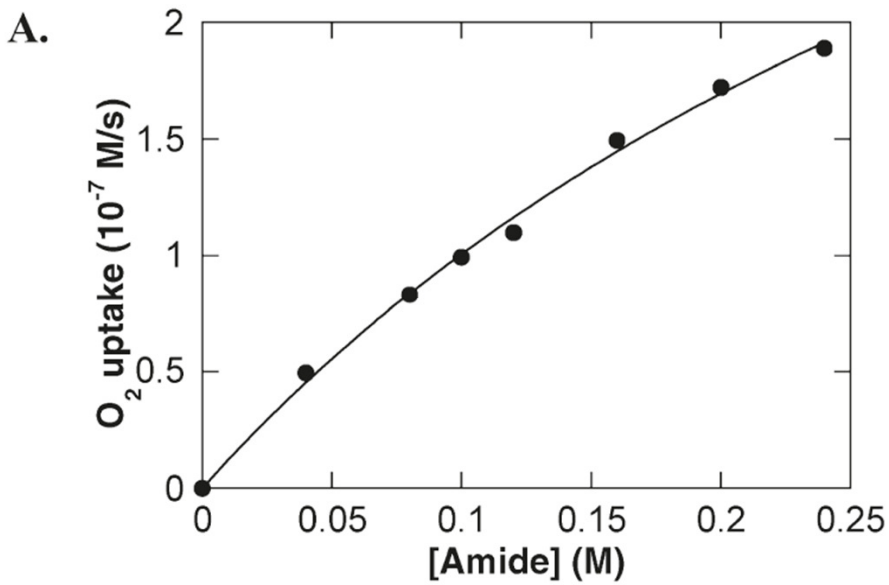
Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

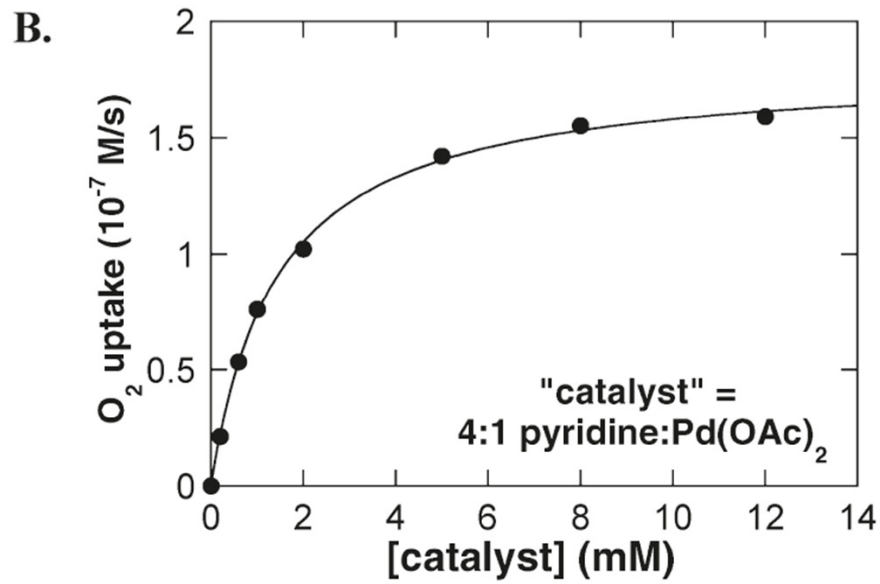
Empirically derived catalytic cycle



Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

Substrate and Catalyst dependence of initial rate



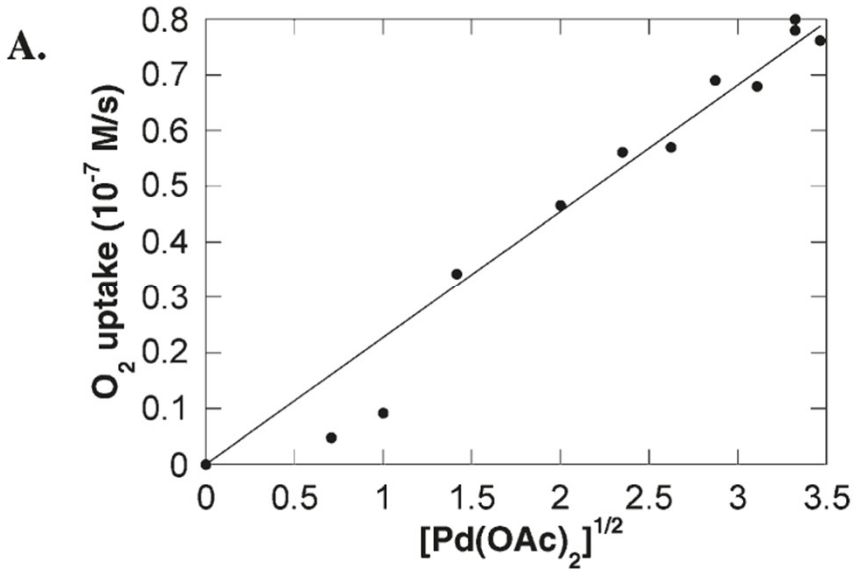


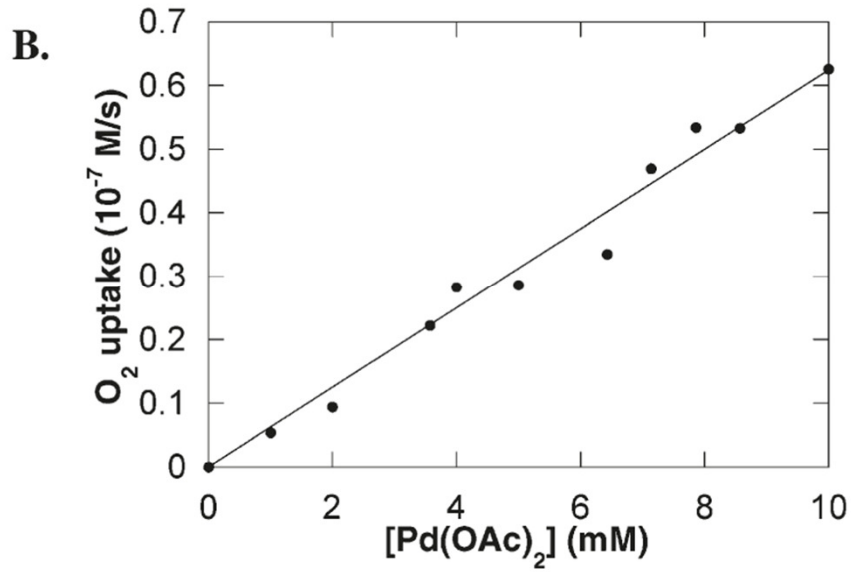
$[Pd(OAc)_2]_o$ = 2.0 mM
$[pyridine]_o$ = 8.0 mM
$[amide]_o$ = *0-240 mM*
4.0 mL toluene
pO_2 = 700 Torr

$[Pd(OAc)_2]_o$ = *0-12 mM*
$[pyridine]_o$ = *0-48 mM*
$[amide]_o$ = 100 mM
4.0 mL toluene
pO_2 = 700 Torr

Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

Influence of Pd concentration upon initial rate in excess pyridine





$[Pd(OAc)_2]_o$ = *0-10 mM*
$[pyridine]_o$ = 120 mM
$[amide]_o$ = 100 mM
4.0 mL toluene
pO_2 = 700 Torr

$[Pd(OAc)_2]_o$ = *0-10 mM*
$[pyridine]_o$ = 8.0 mM
$[amide]_o$ = 100 mM
$[HOAc]_o$ = 5 mM
4.0 mL toluene
pO_2 = 700 Torr

Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

Electronic properties of the turnover-limiting step

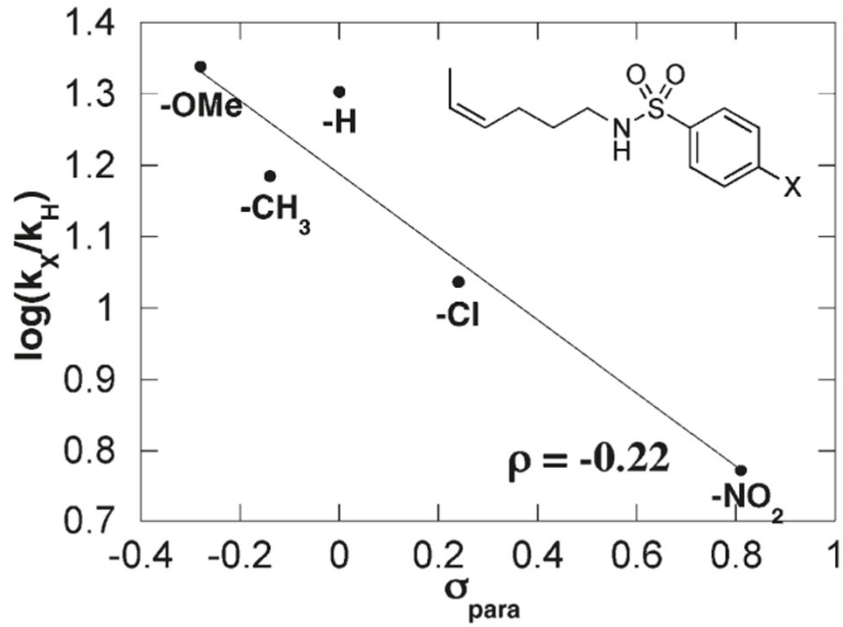
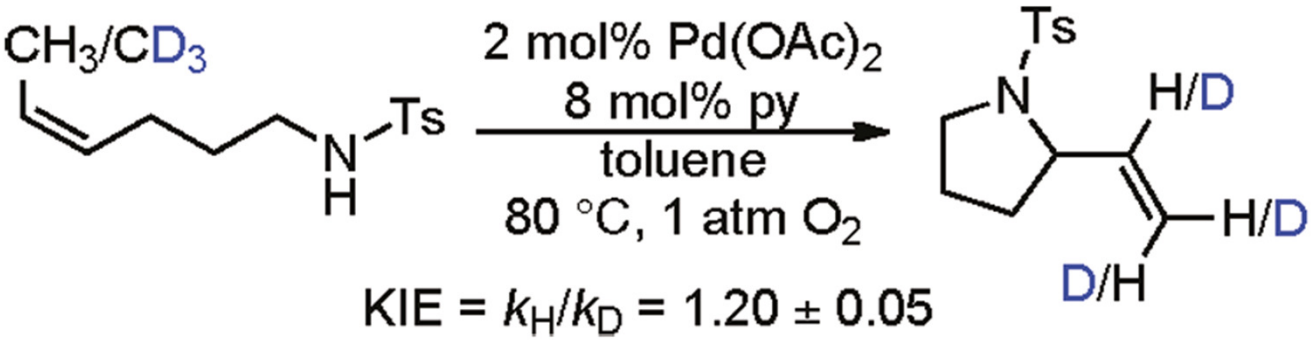


FIGURE 6. Hammett plot derived from the relative initial rates of catalytic oxidative amination conducted with a series of para-substituted benzenesulfonamides. Conditions: $[Pd(OAc)_2]$ = 2.0 mM, [pyridine] = 8.0 mM, [amide] = 100 mM, 4.0 mL of toluene, initial pO_2 = 700 Torr, 80 °C.

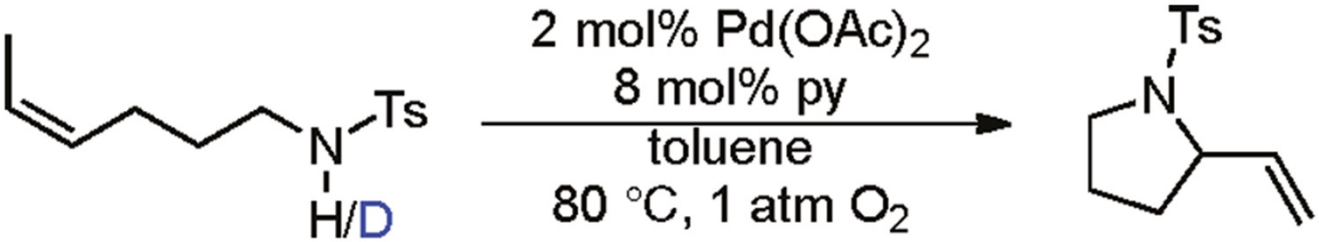
Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

KIE data



(4)

KIE = k_H/k_D = 1.20 ± 0.05

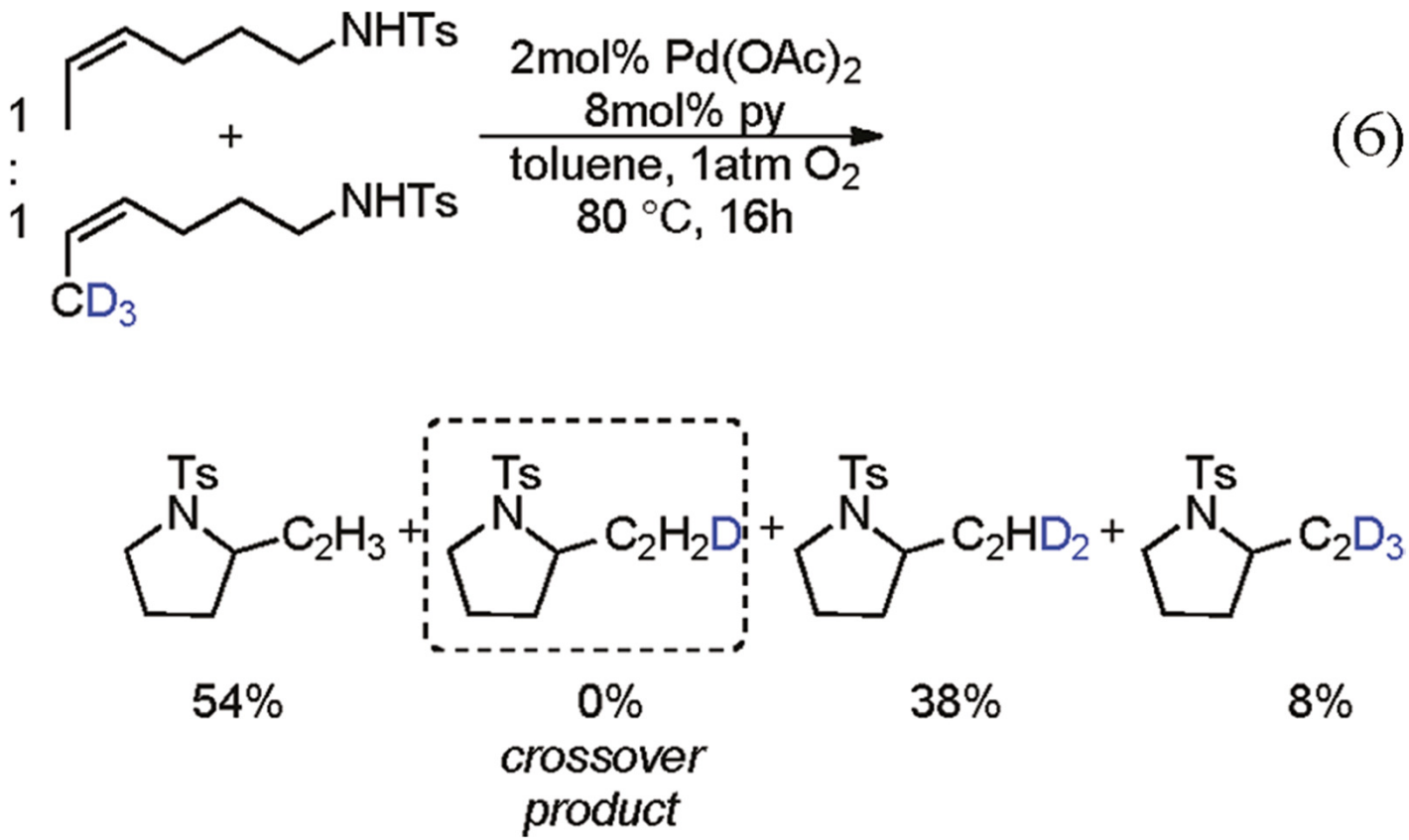


(5)

KIE = k_H/k_D = 1.15 ± 0.05

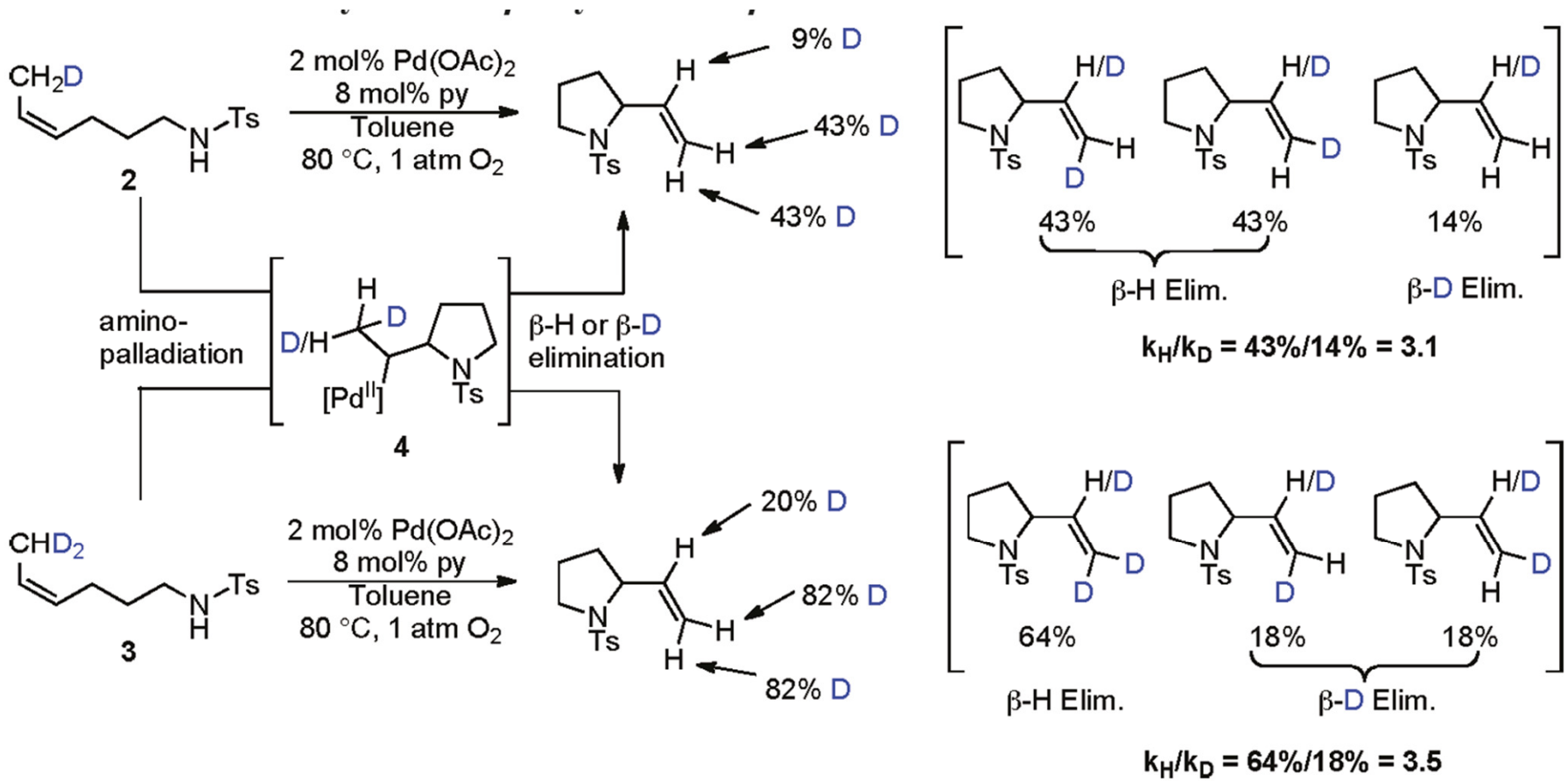
Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

Results of a crossover experiment



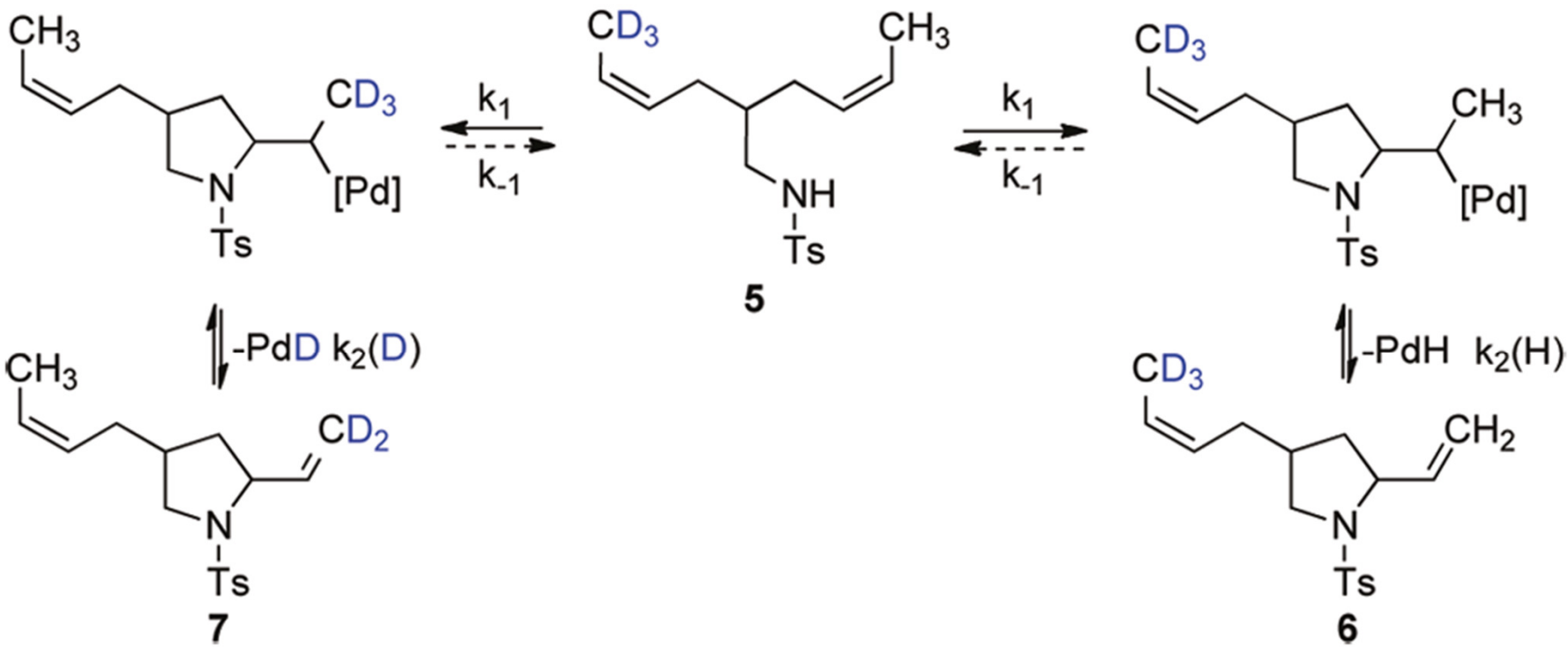
Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

β-H v. β-D elimination



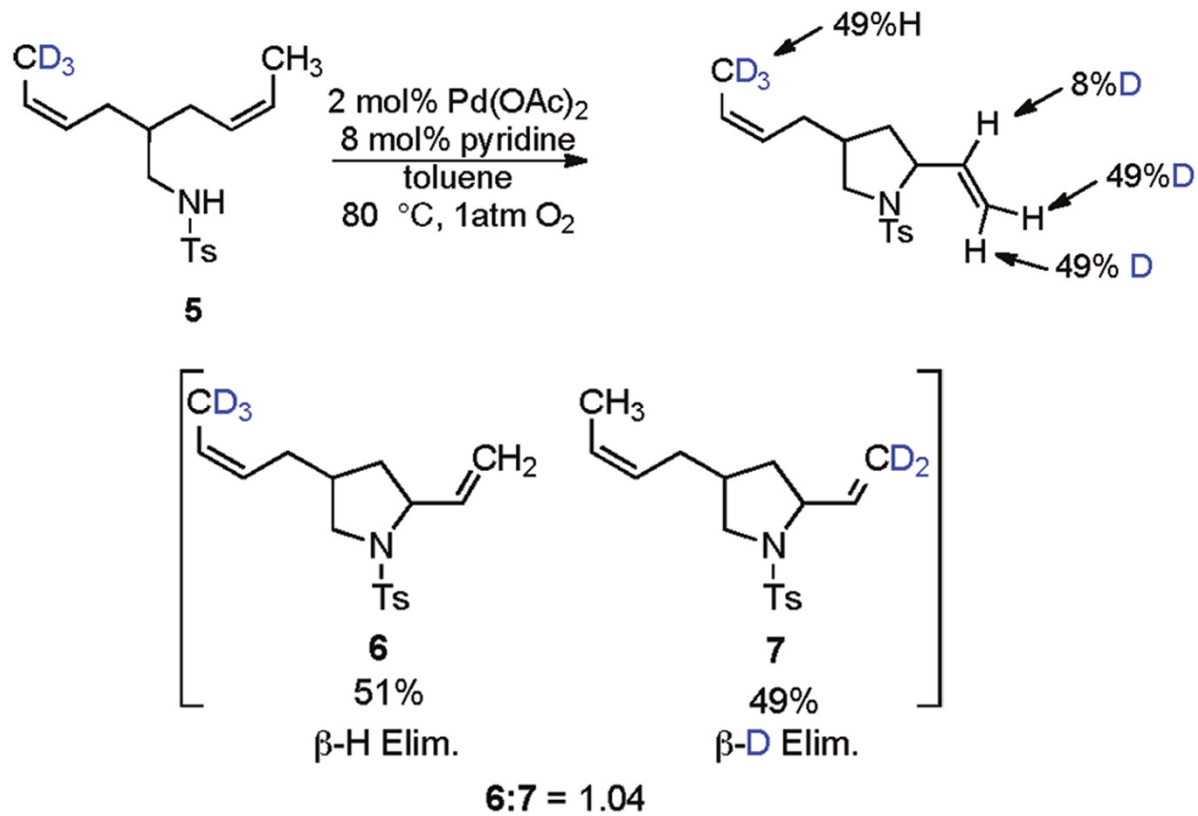
Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

A probe of the Reversibility of the Aminopalladation Step



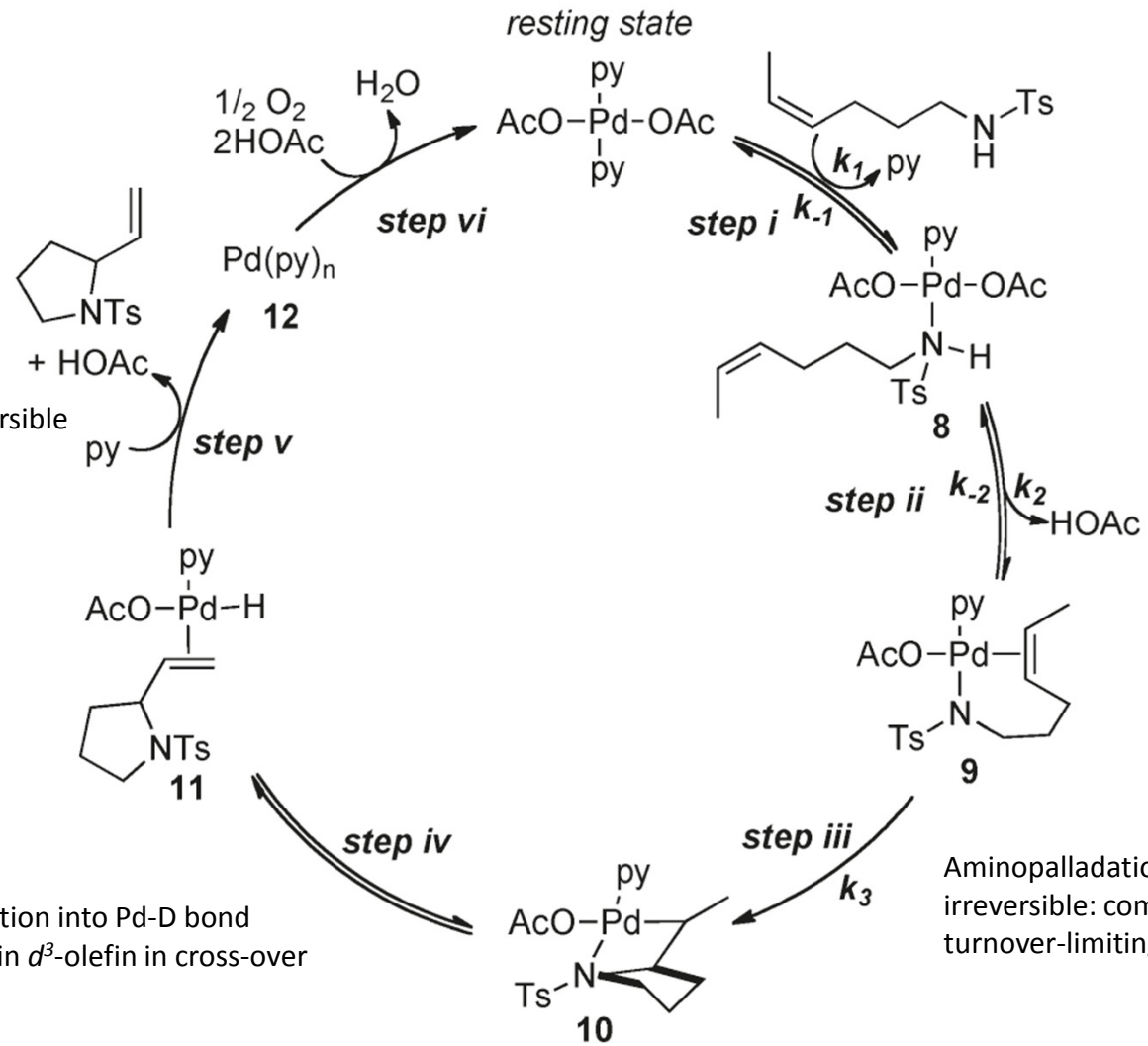
Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

Aminopalladation is irreversible



Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

The catalytic cycle revisited



Reductive elimination
cross-over study: irreversible

Reinsertion into Pd-D bond
results in d^3-olefin in cross-over

Aminopalladation
irreversible: competition experiment
turnover-limiting: Hammet plot

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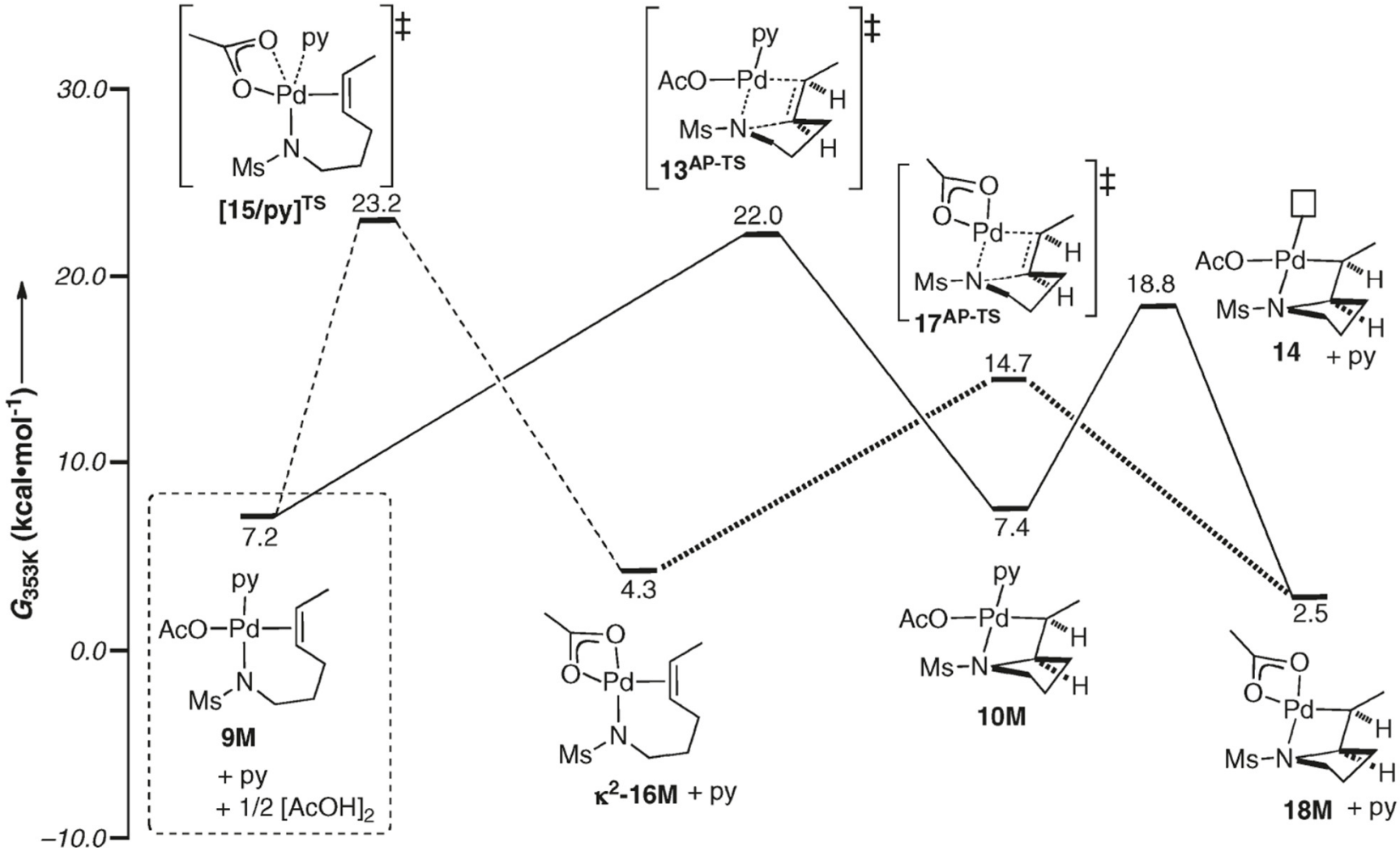
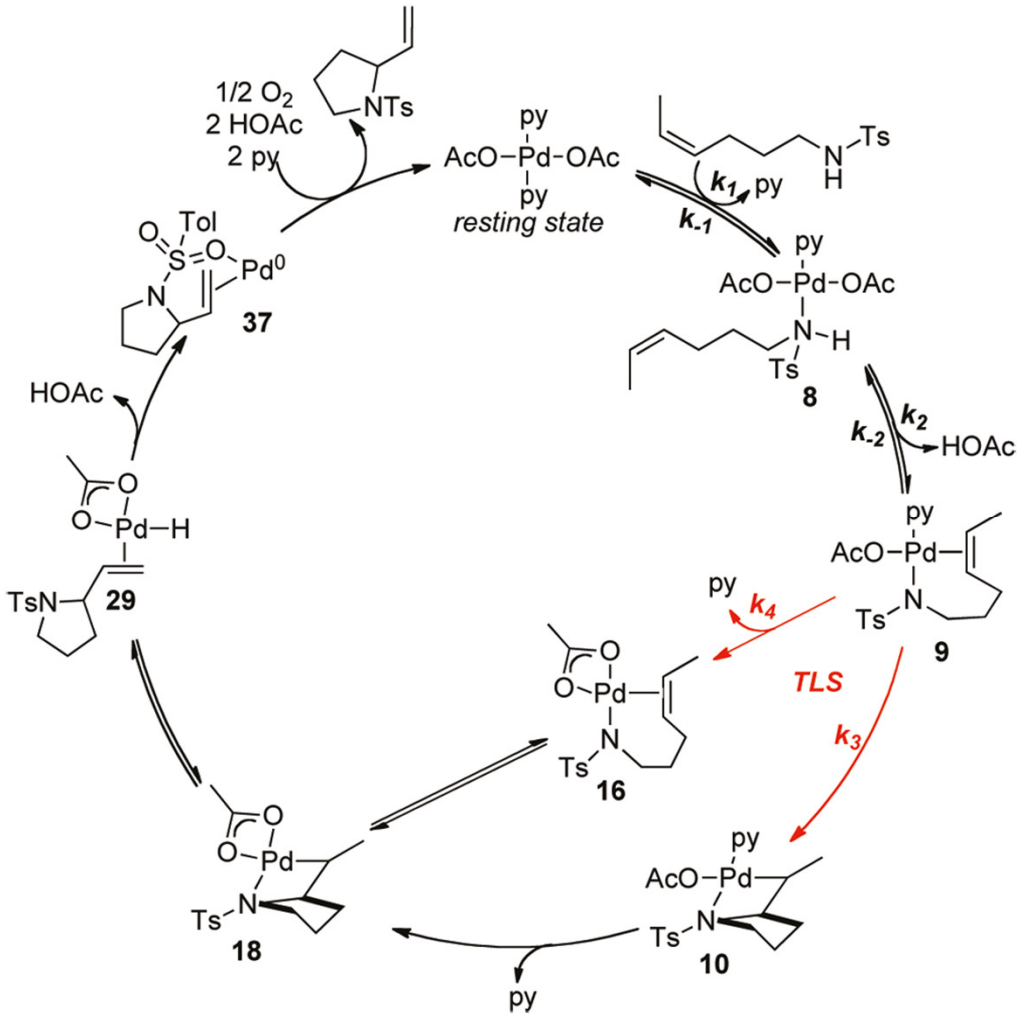
Two possible energy landscapes



Ye, X., Liu, G., Popp, B. V., Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031-1044.

Revised Catalytic Cycle



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Conclusions

- Oxidative aminopalladocyclization is a useful pathway to functionallized N-heterocycles.
- The mechanism proceeds through the steady-state formation of a Pd^{II}-amidate-alkene intermediate.
- The alkene insertion into the Pd-N bond is both turnover-limiting and irreversible.
- Two pathways including a pyridine-ligated and pyridine dissociative are energetically accessible through the catalytic cycle