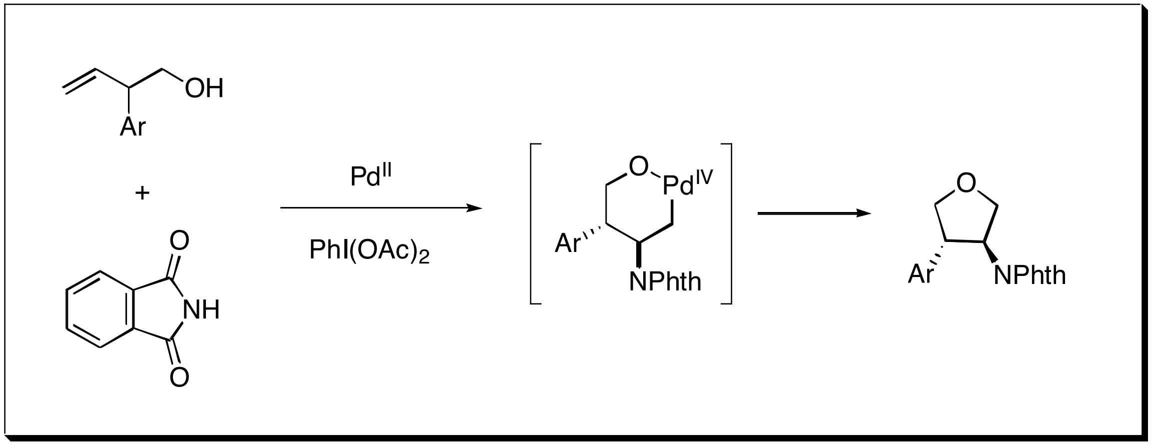
Construction of Tetrahydrofurans by Pd(II)/Pd(IV) - Catalyzed Aminooxygenation of Alkenes

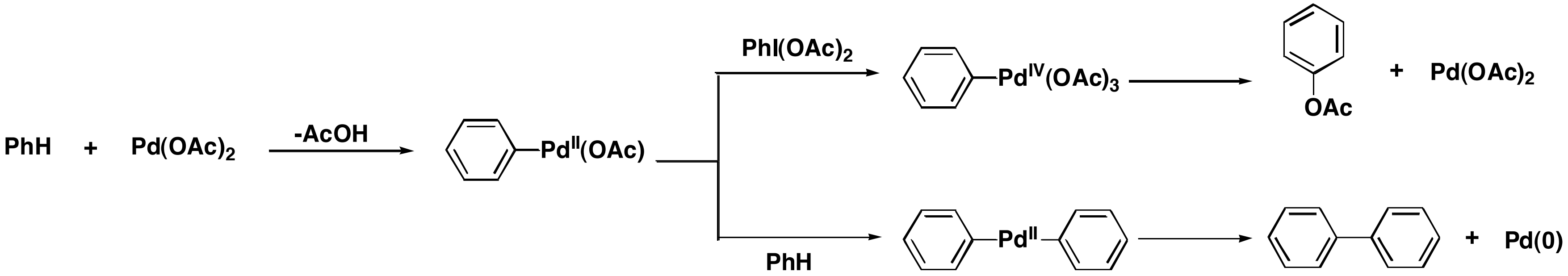
Desai, L.; Sanford, M.S. ***Angew. Chem. Int. Ed.*****, 2007,** ***46*****, 5737-5740.**



Melissa Sprachman

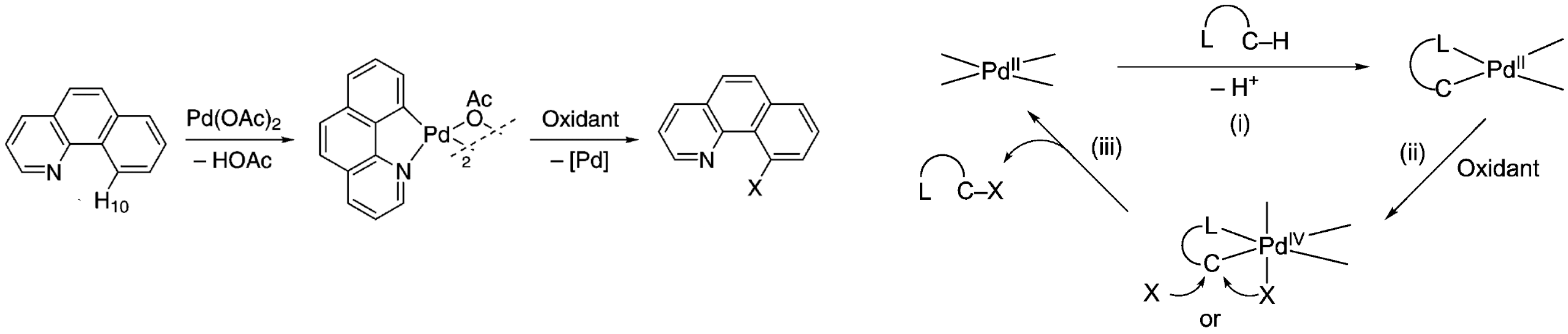
July 28, 2007

Oxidative Functionalization Via Pd^{IV} Intermediates



Yoneyama, T.; Crabtree, R.H. *J. Mol. Catal. A* **1996**, *108*, 35.

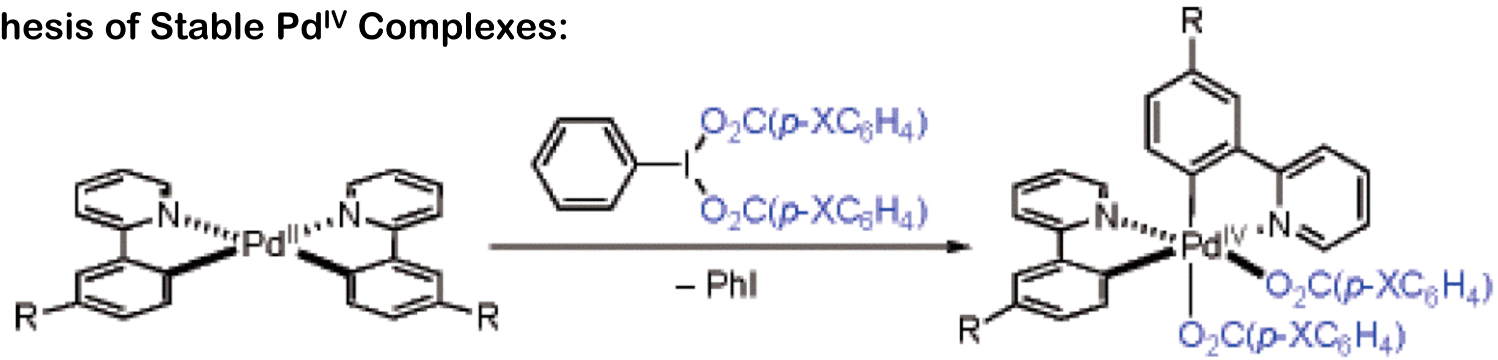
Slide info first found in: Gorin, D. ACS Fellowship essay, Univ. California Berkeley, Berkeley, CA 2006.



Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

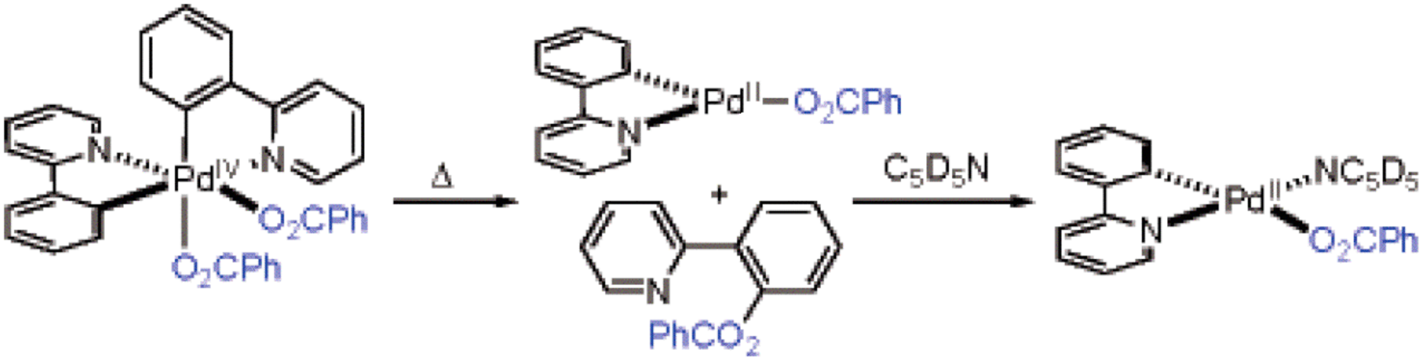
Studies on Isolable Pd^{IV} Complexes

Synthesis of Stable Pd^{IV} Complexes:



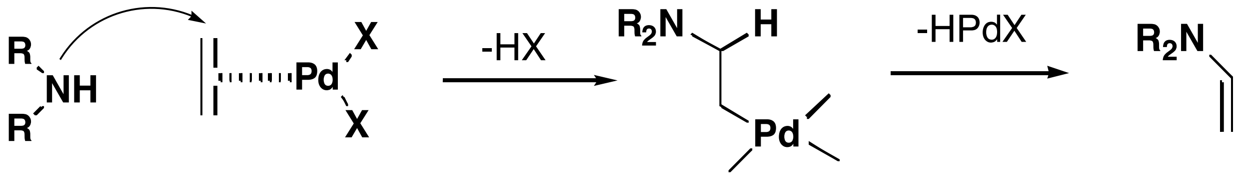
R = H, Me; X = R, Ar, X, NO_2

C-O Bond Forming Reductive Elimination Upon Heating:



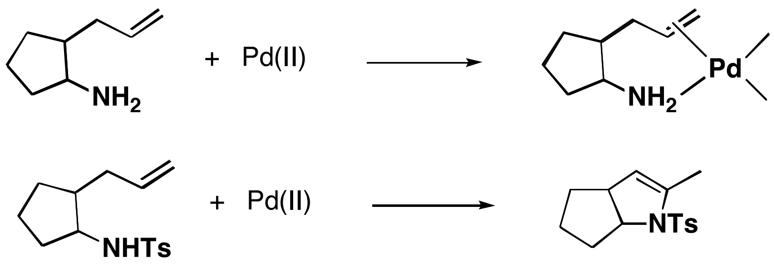
Dick, A.R.; Kampf, J. W..; Sanford, M.S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

Aminopalladation Background

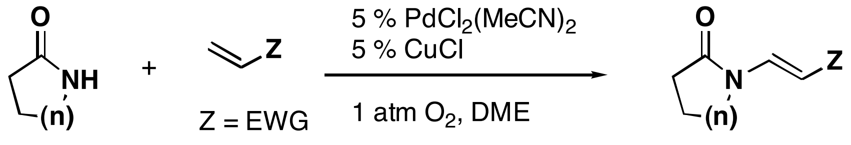


--Aliphatic amines often displace the alkene from the palladium center

--Amides are viable alternatives due to their decreased basicity.

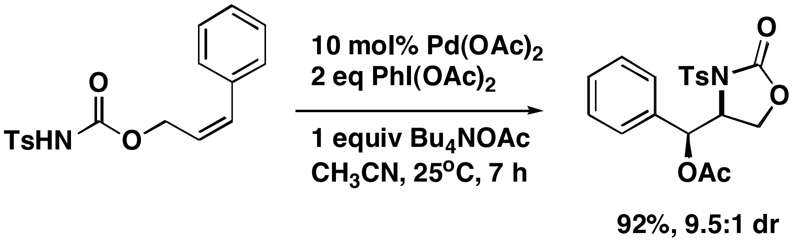


Hegedus, L.S. ***Tetrahedron,*** **1984, *40*, 2415.**



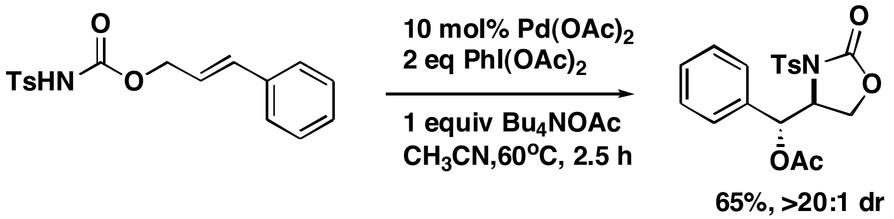
Hosokawa, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*: Negishi, E.-I., Ed.; John Wiley and Sons: New York, 2002, vol 2, pp 2211-2213.

Recent Work in Aminopalladation/Aminoacetoxylation Chemistry



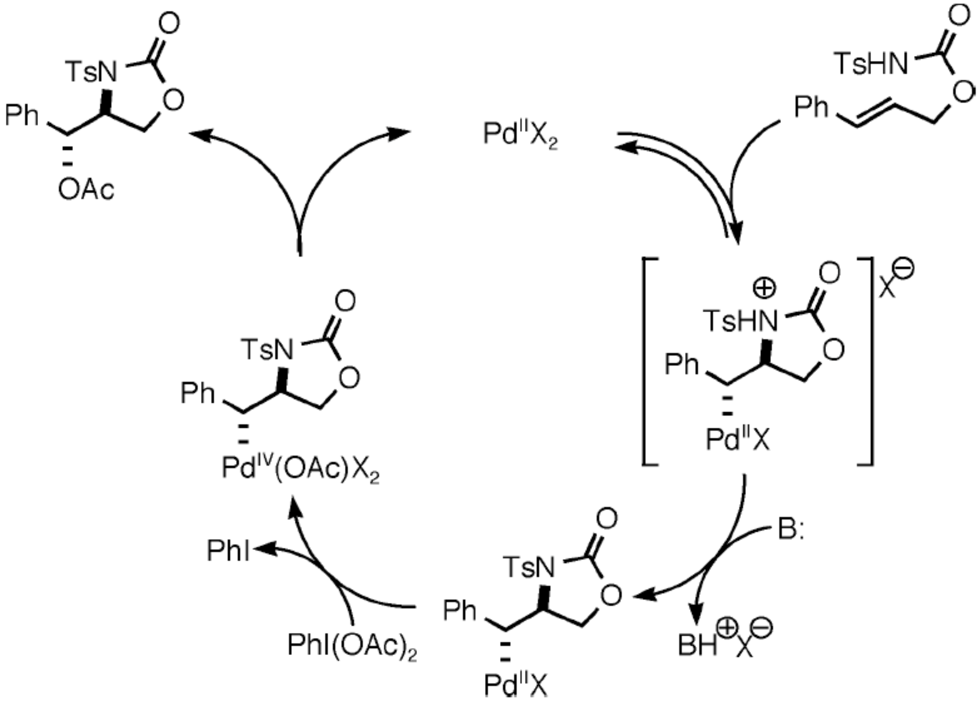
10 mol% $Pd(OAc)_2$
2 eq $PhI(OAc)_2$
1 equiv Bu_4NOAc
CH_3CN, 25°C, 7 h

92%, 9.5:1 dr



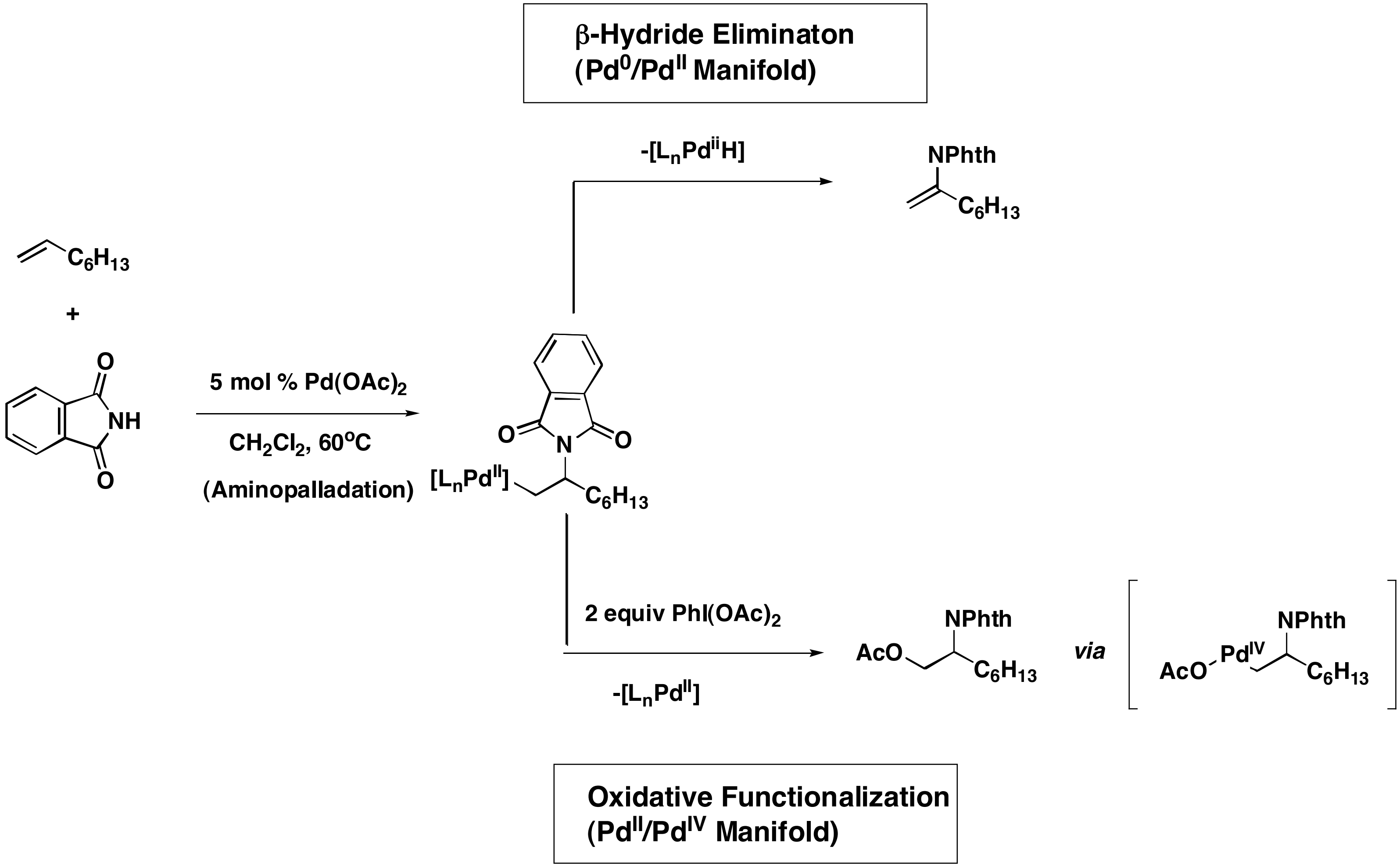
10 mol% $Pd(OAc)_2$
2 eq $PhI(OAc)_2$
1 equiv Bu_4NOAc
CH_3CN,60°C, 2.5 h

65%, >20:1 dr



Alexanian, E. J.; Chulbom, L.; Sorenson, E.J. *J. Am. Chem. Soc.* **2005**, *127*, 7690.

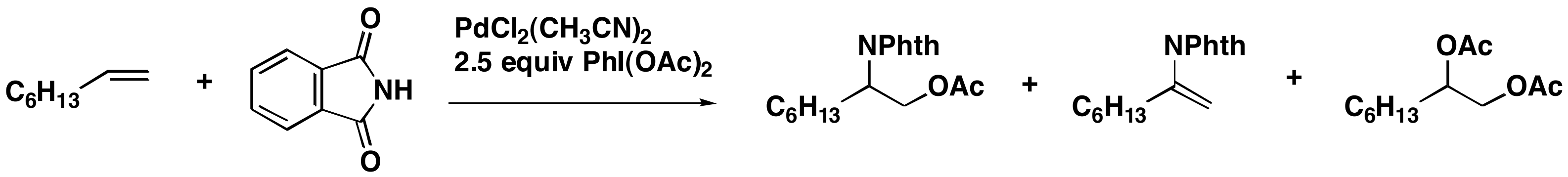
Stahl and Sanford’s Approach to Aminoacetoxylation



β-Hydride Eliminaton (Pd^0/Pd^{II} Manifold)

Oxidative Functionalization (Pd^{II}/Pd^{IV} Manifold)

Intermolecular Pd-Catalyzed Aminoacetoxylation of Alkenes (Stahl)



60 : 19 : 28

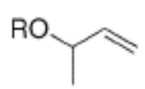
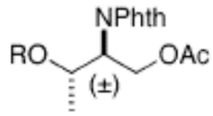
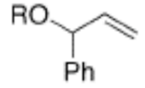
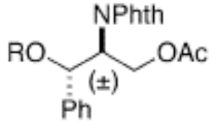
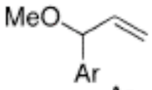
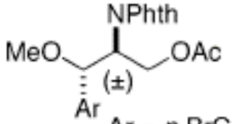
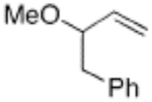
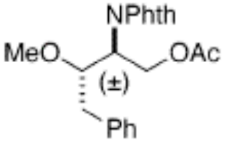
Key Features:

--**Excellent Regioselectivity** (no phthalimide addn at the terminal carbon observed)

--Substantial yields, even for unactivated alkenes

-- Single diastereomers observed by ^{1}HNMR:

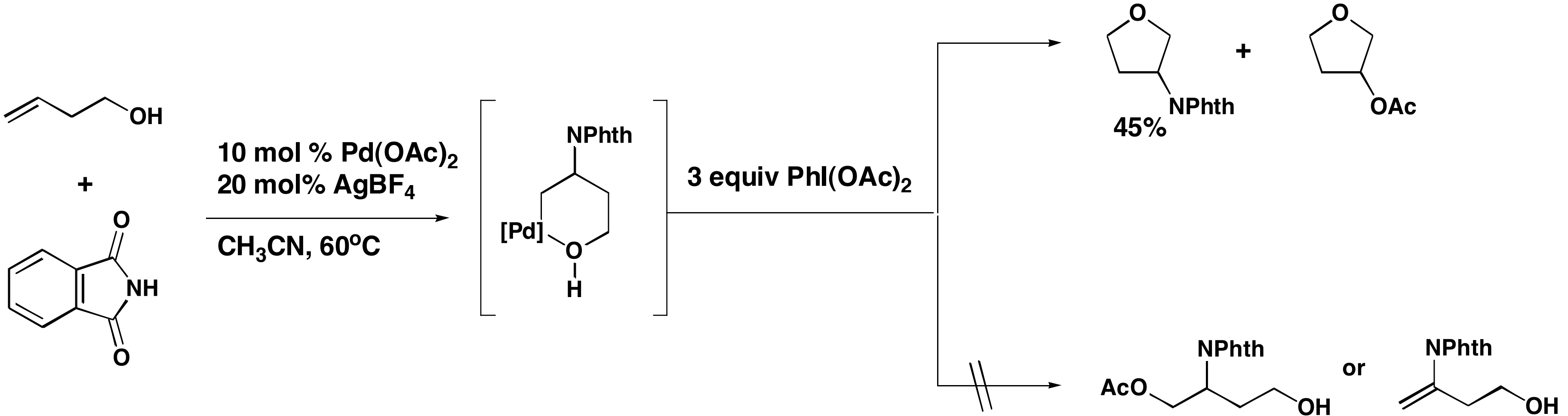
--Favorable yields with allylic Oxygens suggest chelation; Yields drop with vinyl ethers (45%) And homoallylic ethers (30%)

Alkene	Product	Yield ^{1}H NMR (isolated)
 R = Bn Bz		78 (71) 67 (62)
 R = Me Bn		75 (74) 68 (65)
 Ar = p-BrC$_6$H$_4$	 Ar = p-BrC$_6$H$_4$	65 (64)
		73 (71)

Reactions with $PdCl_2(CH_3CN)_2$ and $PhI(OAc)_2$

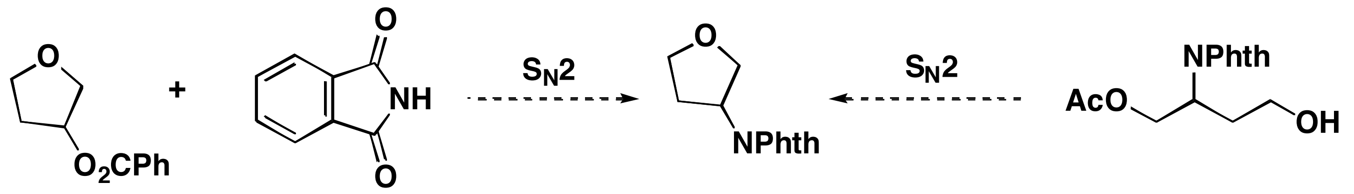
Liu, G.; Stahl, S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.

Sanford: Suppression of β-Hydride Elimination Using Tethered Alcohols



--Coordination of the alcoholic oxygen to Pd slows β-hydride elimination

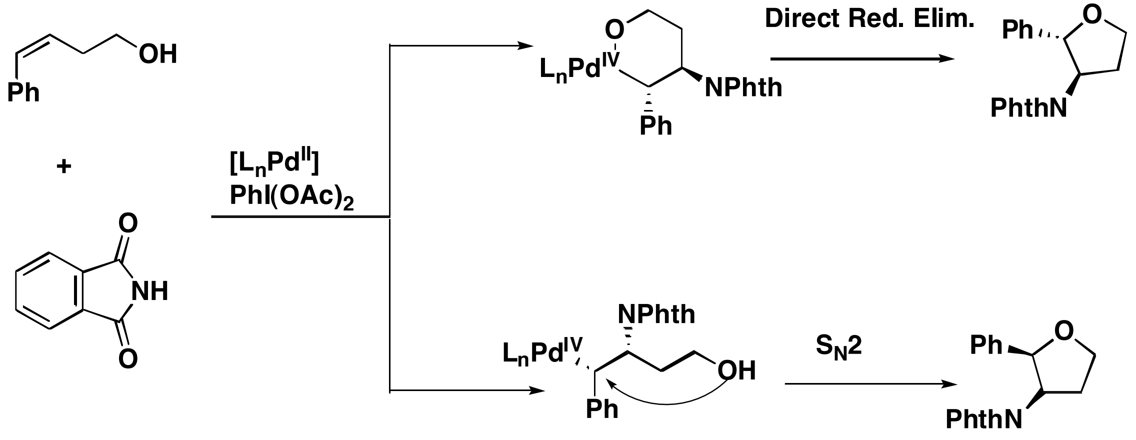
Possible S_N2 Mechanisms for Aminooxygenation:



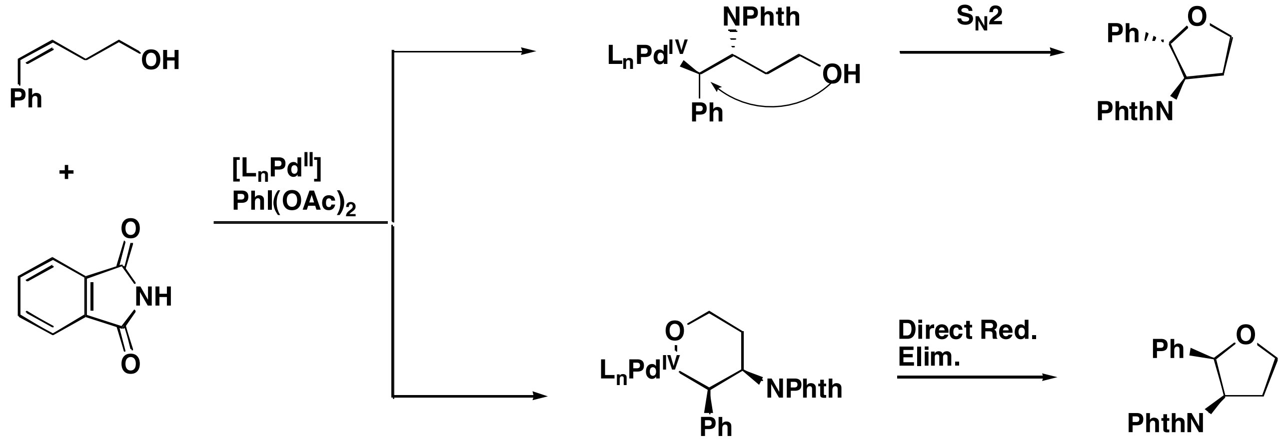
--Subjection of authentic samples of either substrate did not yield amidated THF products

Alternative Routes Considered

***cis* Aminopalladation/oxidation**

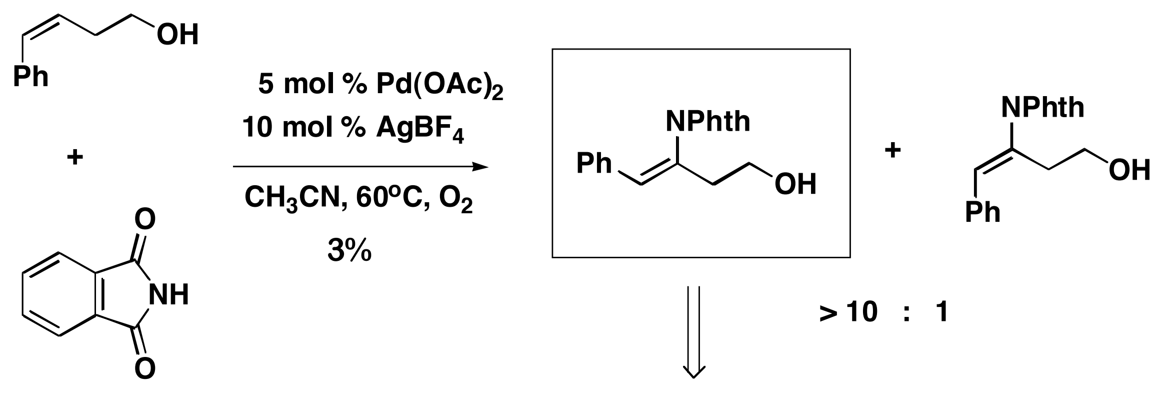


***trans* Aminopalladation/oxidation**



Only the *trans* THF products were observed.

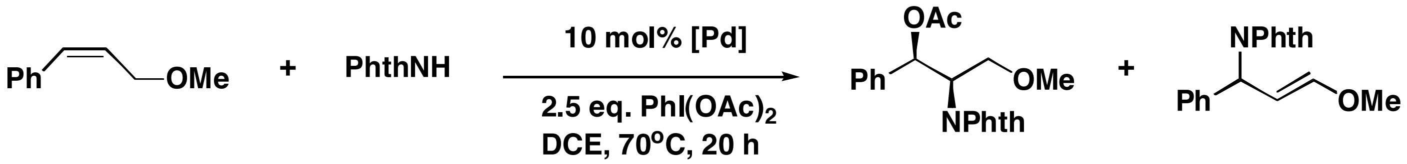
Determination of the Stereochemistry of Aminopalladation



From *cis* aminopalladation

Liu, G.; Stahl, S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.

Support from Stahl's Work:



[Pd] = PdCl$_2$(CH$_3$CN)$_2$:	52%	5%
Pd(OAc)$_2$:	44%	0%

Possible routes:

A) *trans*-aminopalladation followed by oxidative Pd-C cleavage with retention

B) *cis*-aminopalladation followed by oxidative Pd-C cleavage with inversion

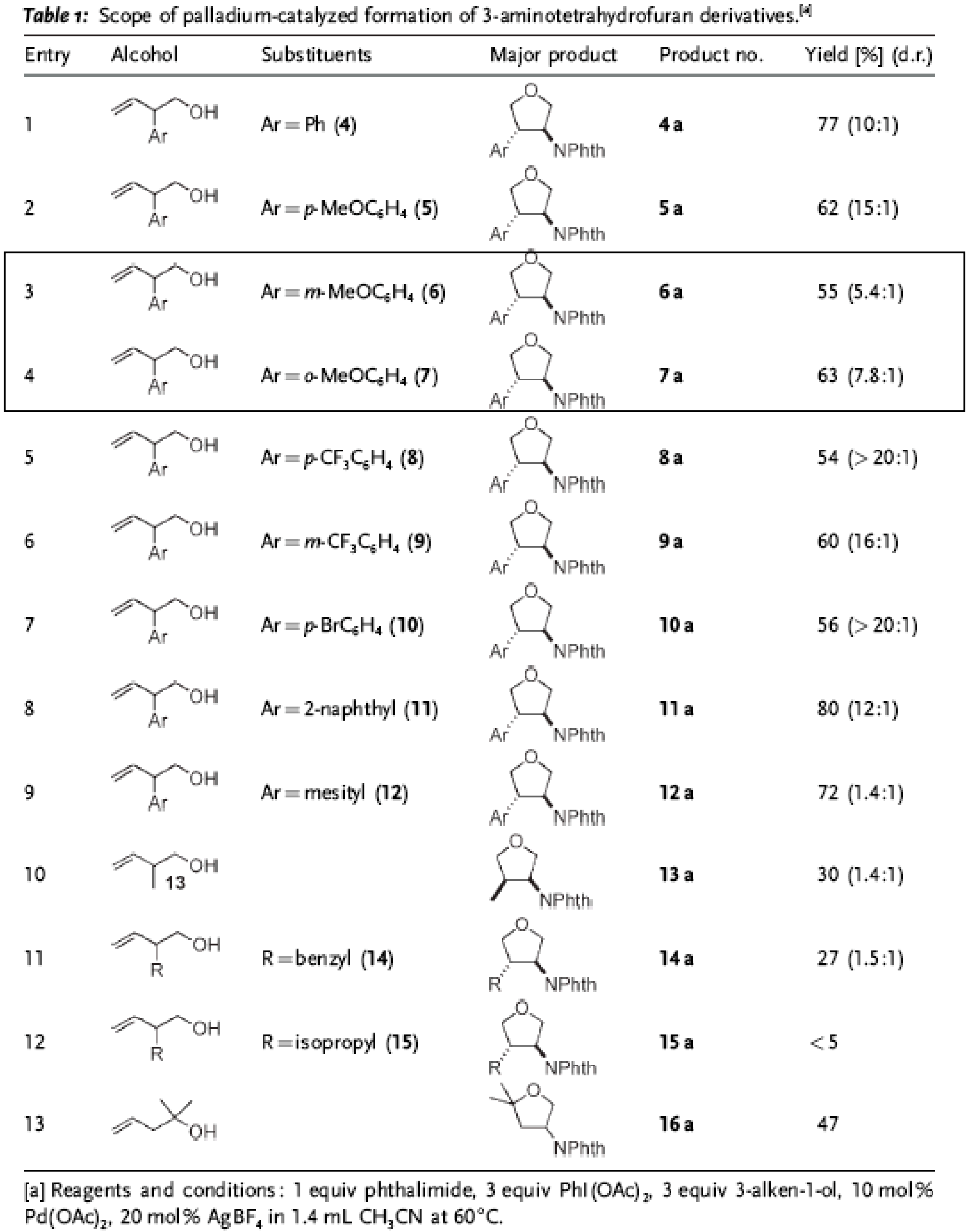


Table 1: Scope of palladium-catalyzed formation of 3-aminotetrahydrofuran derivatives.[a]

Entry	Alcohol	Substituents	Major product	Product no.	Yield [%] (d.r.)
1		Ar = Ph (**4**)		**4a**	77 (10:1)
2		Ar = *p*-MeOC$_6$H$_4$ (**5**)		**5a**	62 (15:1)
3		Ar = *m*-MeOC$_6$H$_4$ (**6**)		**6a**	55 (5.4:1)
4		Ar = *o*-MeOC$_6$H$_4$ (**7**)		**7a**	63 (7.8:1)
5		Ar = *p*-CF$_3$C$_6$H$_4$ (**8**)		**8a**	54 (> 20:1)
6		Ar = *m*-CF$_3$C$_6$H$_4$ (**9**)		**9a**	60 (16:1)
7		Ar = *p*-BrC$_6$H$_4$ (**10**)		**10a**	56 (> 20:1)
8		Ar = 2-naphthyl (**11**)		**11a**	80 (12:1)
9		Ar = mesityl (**12**)		**12a**	72 (1.4:1)
10	13			**13a**	30 (1.4:1)
11		R = benzyl (**14**)		**14a**	27 (1.5:1)
12		R = isopropyl (**15**)		**15a**	< 5
13				**16a**	47

[a] Reagents and conditions: 1 equiv phthalimide, 3 equiv PhI(OAc)$_2$, 3 equiv 3-alken-1-ol, 10 mol% Pd(OAc)$_2$, 20 mol% AgBF$_4$ in 1.4 mL CH$_3$CN at 60°C.

Decreased diastereoselectivities were observed with substituents in the *meta* and *para* positions

Conclusions

-3 aminotetrahydofurans were unexpectedly synthesized in Sanford and coworkers' attempts to suppress the beta-hydride elimination pathway of an aminopalladation/oxidation sequence.

-Evidence from experiments by Stahl and Sanford supports *cis*-aminopalladation of alkenes.

-The promising diastereoselectivities and consequent mechanistic elucidation may lay the framework for the development of enantioselective Pd^{II}/Pd^{IV} reactions.