The Heck Reaction

Reviews:

Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815–2831.

Belestskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

- Intramolecular:

Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Eds.; Wiley-VCH: New York, **1998**, pp. 231–269.
Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447–471.

- Asymmetric:

McCartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122–5150.

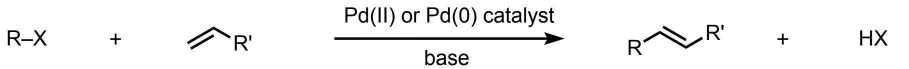
- Solid phase:

Franzén, R. *Can. J. Chem.* **2000**, *78*, 957–962.

- Dehydrogenative:

Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214.

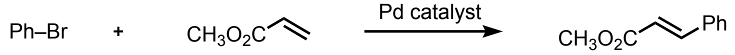
General transformation:

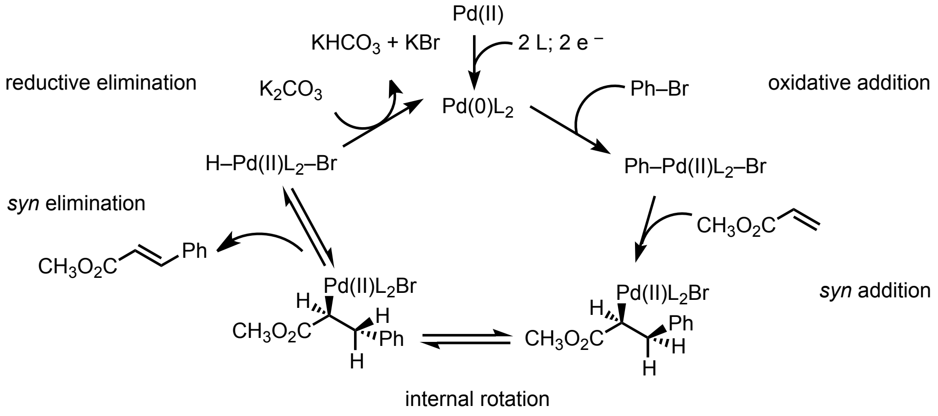


R = alkenyl, aryl, allyl, alkynyl, benzyl X = halide, triflate R' = alkyl, alkenyl, aryl, CO_2R, OR, SiR_3

- Proposed mechanism involving neutral Pd:

Mechanism:





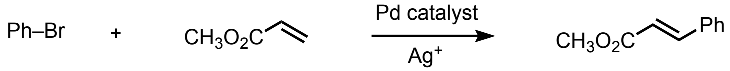
- Pd(II) is reduced to the catalytically active Pd(0) *in situ*, typically through the oxidation of a phosphine ligand.

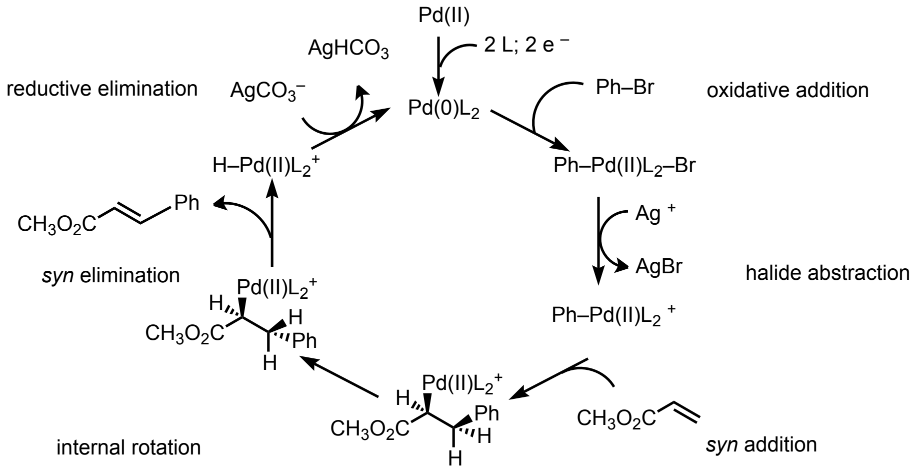
$$Pd(OAc)_2 + H_2O + nPR_3 + 2R'_3N \longrightarrow Pd(PR_3)_{n-1} + O{=}PR_3 + 2R'_3N{\bullet}HOAc$$

Ozawa, F.; Kubo, A.; Hayashi, T. *Chemistry Lett.* **1992**, 2177–2180.

- Ag^+ / Tl^+ salts irreversibly abstract a halide ion from the Pd complex formed by oxidative addition. Reductive elimination from the cationic complex is probably irreversible.

- An example of a proposed mechanism involving cationic Pd:





Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133–4135.

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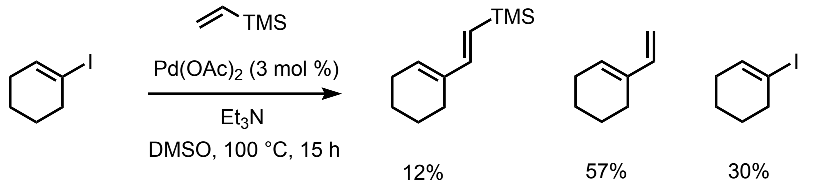
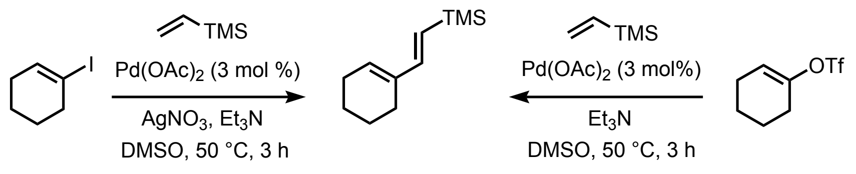
- Reactions with vinyl or aryl triflates often parallel those of the corresponding halides in the presence of silver salts in yields.



12% 57% 30%

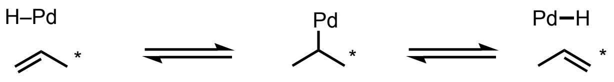
GC yields



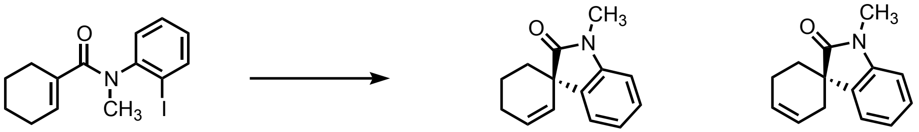
64% 61%

Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909–4914.

- Reversible β-hydride elimination can lead to alkene isomerization.

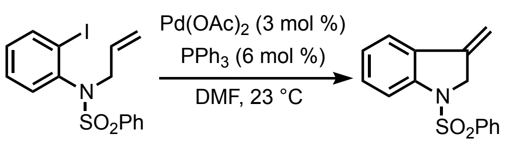


- Use of silver salts can minimize alkene isomerization.



Conditions	
Pd(OAc)$_2$ (1 mol %) PPh$_3$ (3 mol %) Et$_3$N (2 equiv) acetonitrile, 3h, reflux	1 : 1
as above, plus AgNO$_3$ (1 equiv) and 23 °C	26 : 1

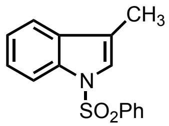
Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133–4135.



Ag$_2$CO$_3$, eq	Time, h	Yield, %
1	24	50
1	48	35
2	5	80

Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1941–1942.

By-product:



- With some ligands, experimental evidence points to a Pd(II)/Pd(IV) catalytic cycle.

Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.

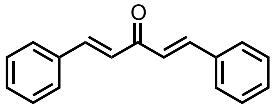
Shaw, B. L.; Perera, S. D.; Staley, E. A. *J. Chem. Soc., Chem. Commun.* **1998**, 1361–1362.

Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S.; *Chem. Rev.* **2010**, *110*, 824–889.

Conditions:

• Catalysts:	Pd(OAc)$_2$	Pd$_2$(dba)$_3$
	most common	stable Pd(0) source; useful if substrate is sensitive to oxidation

dba =

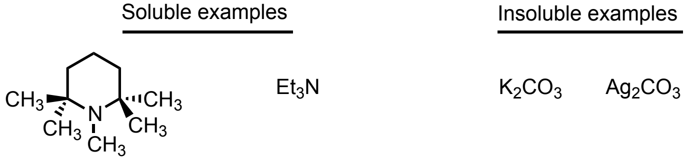


- Ligands: Phosphines (PR$_3$), used to prevent deposition of Pd(0) mirror.

- Solvents: Typically aprotic; a range of polarities.

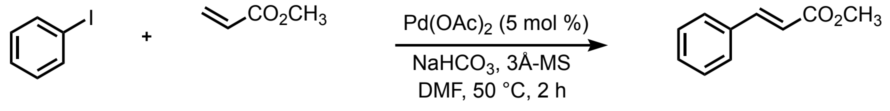
Solvent	toluene	THF	1,1-dichloroethane	DMF
Dielectric constant	2.4	7.6	10.5	38.3

- Bases: both soluble and insoluble bases are used.



1,2,2,6,6-pentamethylpiperidine (PMP)

- Jeffery conditions: The combination of tetraalkylammonium salts (phase-transfer catalysts) and insoluble bases accelerates the rate to the extent that lower reaction temperatures are possible.



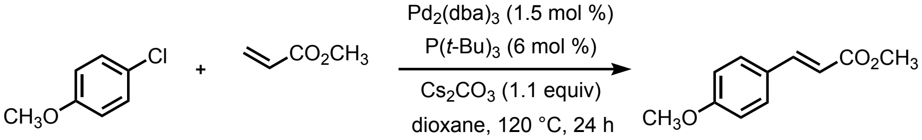
Equiv. of n-Bu_4NCl	GC Yield(%)
0	2
1	99

Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

- One proposed explanation for this rate enhancement is based on the fact that palladium complexes can be stabilized by the coordination of halide ions; thus, the catalyst is less likely to decompose under the Heck reaction conditions.

Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384.

- Conditions for the Heck coupling of aryl chlorides have been developed.

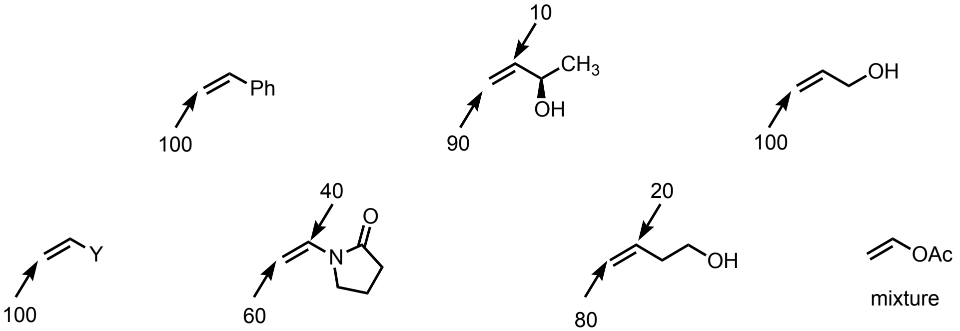


82%

Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.

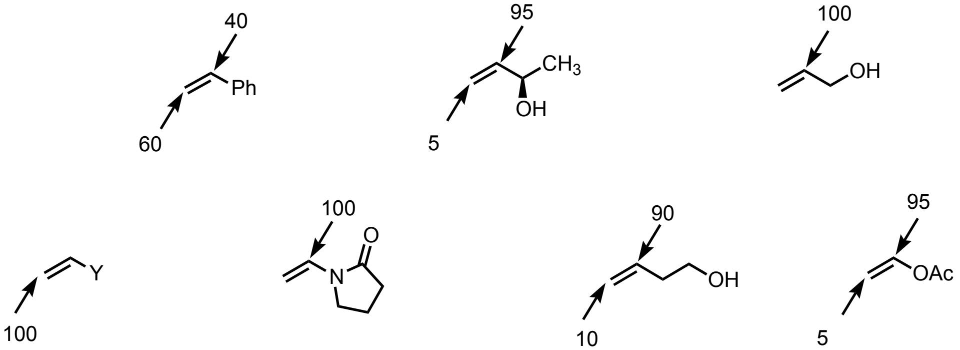
Regiochemistry of addition:

- Neutral Pd complexes: regiochemistry is governed by sterics; position of Ar attachment:



Y = CO_2R
CN
$CONH_2$

- Cationic Pd complexes: regiochemistry is affected by electronics. The cationic Pd complex increases the polarization of the alkene favoring transfer of the vinyl or aryl group to the site of least electron density.



Y = CO_2R
CN
$CONH_2$

Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28,* 2–7.

Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481–1486.

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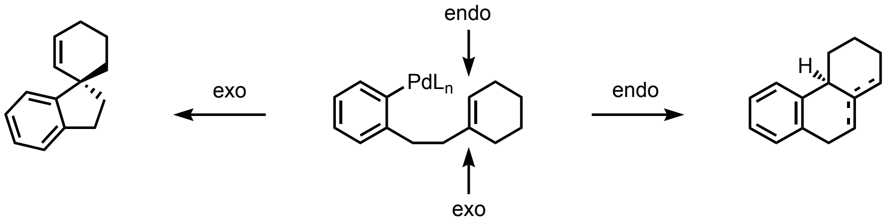
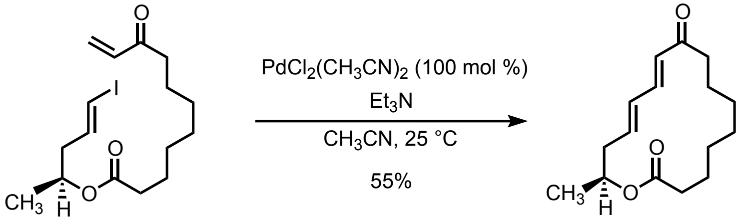
- A major issue in intramolecular Heck reactions is the mode of ring closure, i.e., *exo* versus *endo.*

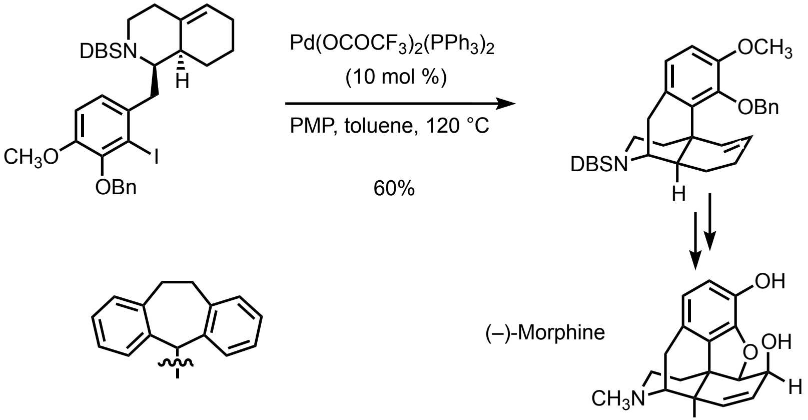


- For large rings, conformational effects can be minimal. If a neutral Pd complex is used, sterics enforce *endo* selectivity.
- The Heck reaction is useful for macrocylization.



Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035–4040.

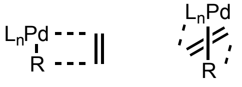
- Five-, six-, and seven-membered ring closures (the most efficient Heck ring closures) give predominantly *exo* products.



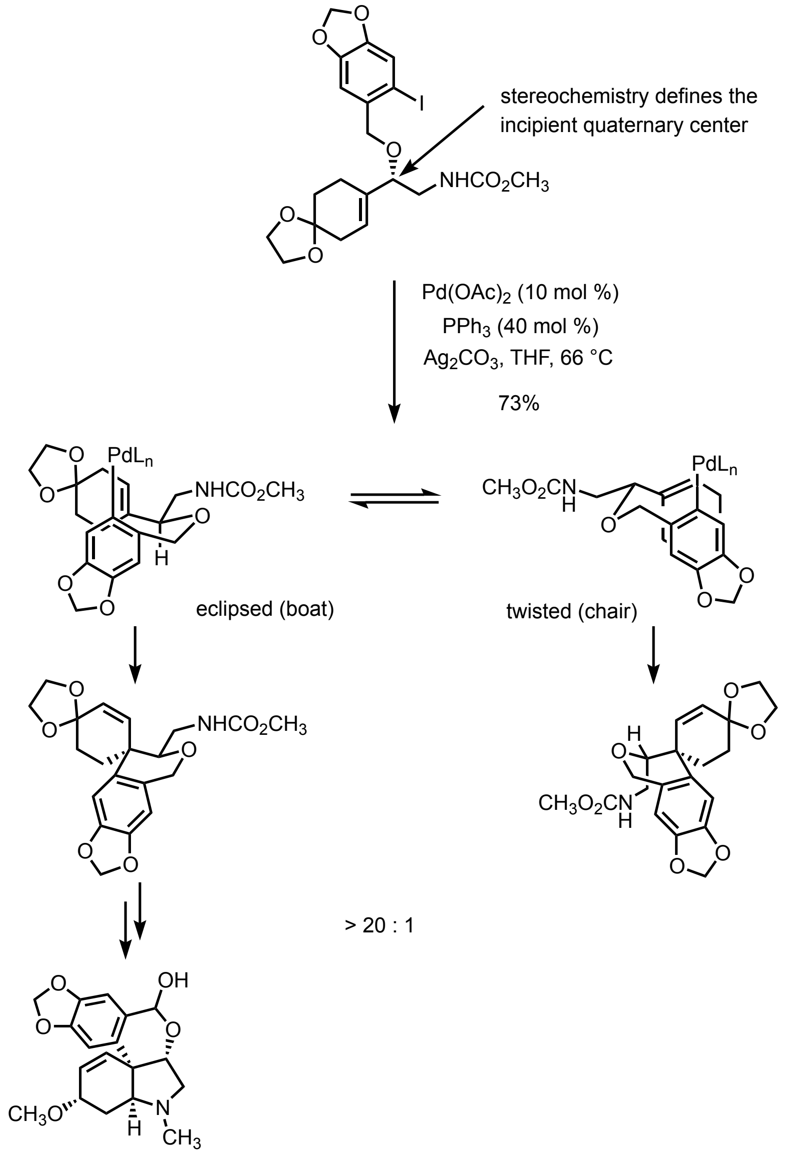
DBS = dibenzosuberyl

Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029.

- Conformational effects are more important when forming smaller rings. The eclipsed orientation is preferred for the reaction, even if this means the rest of the molecule must adopt a less than ideal conformation.



eclipsed twisted



stereochemistry defines the incipient quaternary center

(±)-6a-epipretazettine

Overman, L. E. *Pure & Appl. Chem.* **1994**, *66*, 1423–1430.

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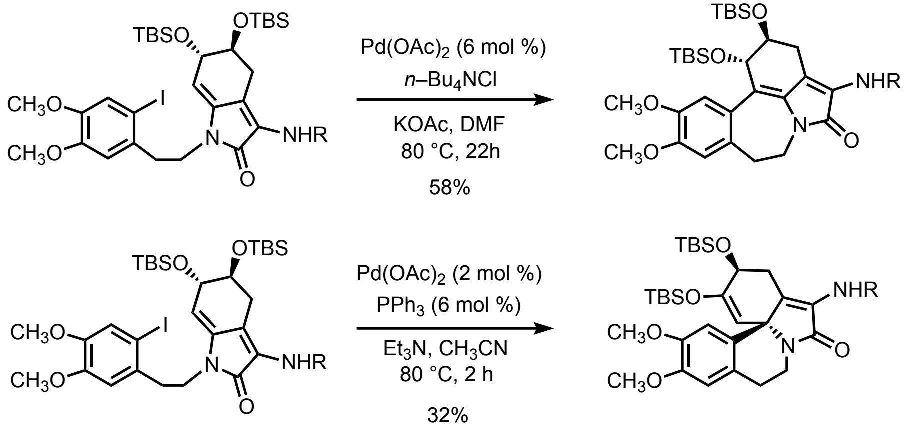
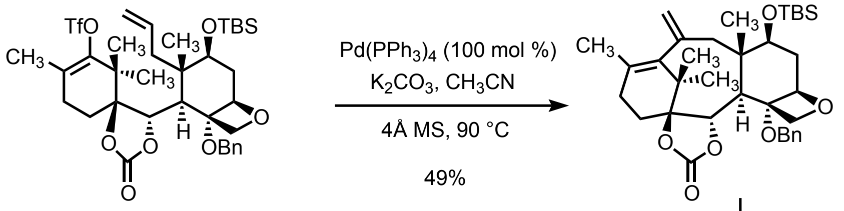
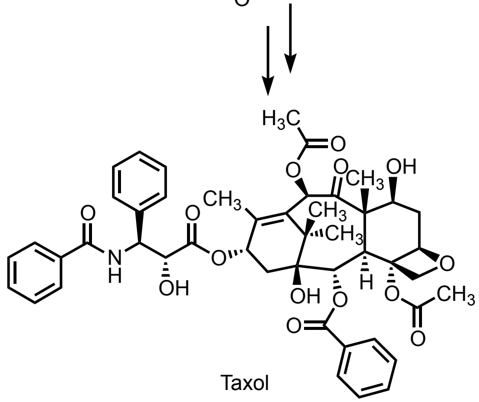
- Variation of reaction conditions can greatly influence *exo* versus *endo* selectivity in small rings.



- The authors' rationale for these results is that under the Jeffery conditions, the coordination sphere of palladium is smaller, and thus the metal can be accommodated at the more substituted alkene site during migratory insertion.

Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835.





Taxol

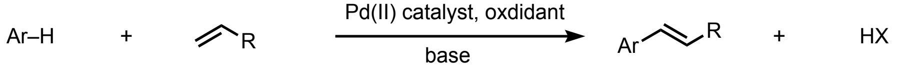
- Steric and electronic effects begin to compete with conformational effects when forming medium–sized rings.

Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723–1726.

Dehydrogenative Process

- It is possible to generate an aryl palladium(II) intermediate for Heck coupling from an arene by C–H insertion.
- An oxidant is required.

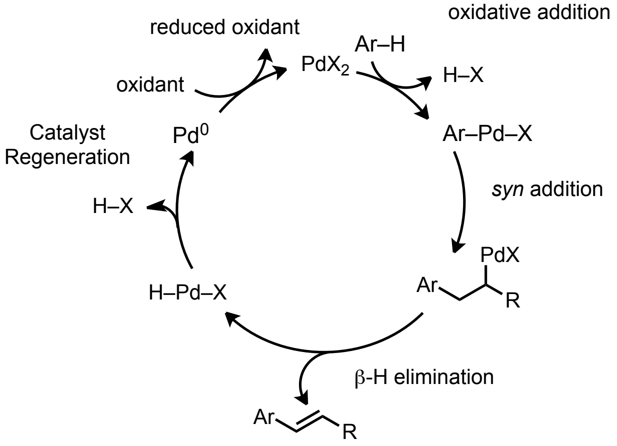
General transformation:



R = alkenyl, aryl, allyl, alkynyl, benzyl X = halide, triflate R' = alkyl, alkenyl, aryl, CO_2R, OR, SiR_3

Mechanism:

- Proposed mechanism:

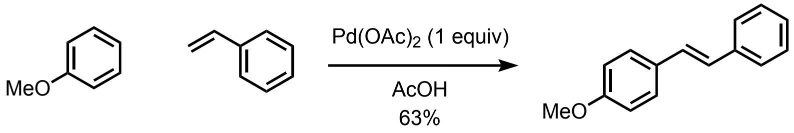


Some oxidants:

O_2, $HPMo_{11}V$, $PhI(OAc)_2$,
benzoquinone, t-BuOOH,
$KMnO_4$, $Na_2S_2O_8$, $Cu(OAc)_2$

Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214.

- Early examples of dehydrogenative processes did not employ oxidants and were stoichiometric in palladium.
- Mechanistic studies suggest a concerted metallation-deprotonation sequence for C–H insertion, facilitated by acetate.



Fujiwara, Y.; Moritani, I.; Asano, R.; Tanaka, H.; Teranishi, S. *Tetrahedron* **1969**, *25*, 4815–4818.
Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

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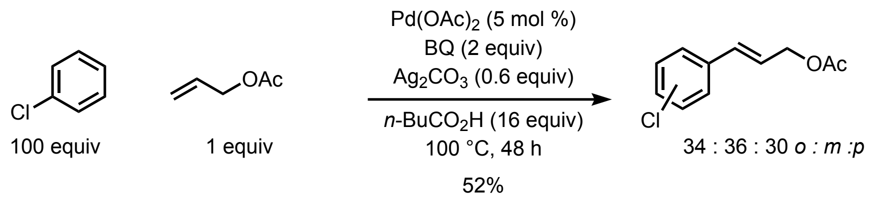
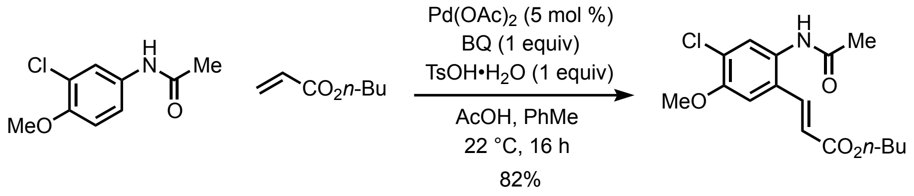
- Control of regioselectivity may be problematic with substituted arenes.
- In the case below, benzoquinone (BQ) was the oxidant and silver carbonate was essential.



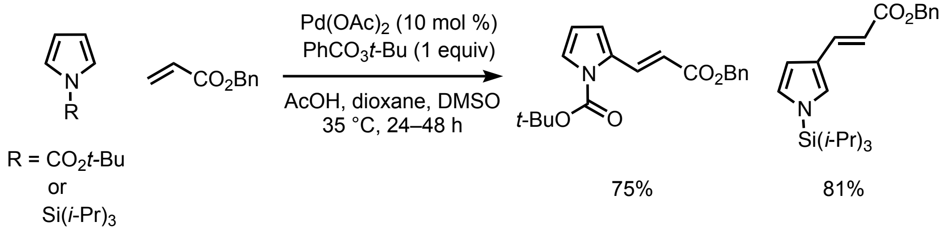
Pan, D.; Yu, M.; Chen, W.; Jiao, N. *Chem. Asian J.* **2010**, *5*, 1090–1093.

- Directing groups may be applied to control the site of reaction.

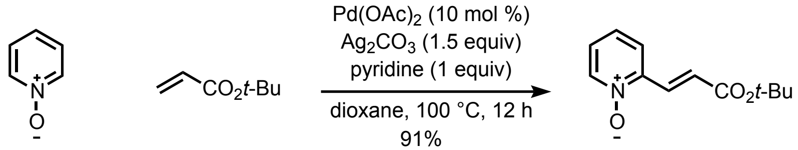


Lee, G. T.; Jian, X.; Prasad, K.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921–1924.

- Various heterocycles are effective substrates, including indoles, thiazoles, oxazoles, pyrroles, furans and activated pyridines.
- Site selectivity with pyrrole substrates can be achieved by the use of directing (carbamate) or blocking (triisopropylsilyl) groups on the nitrogen atom.



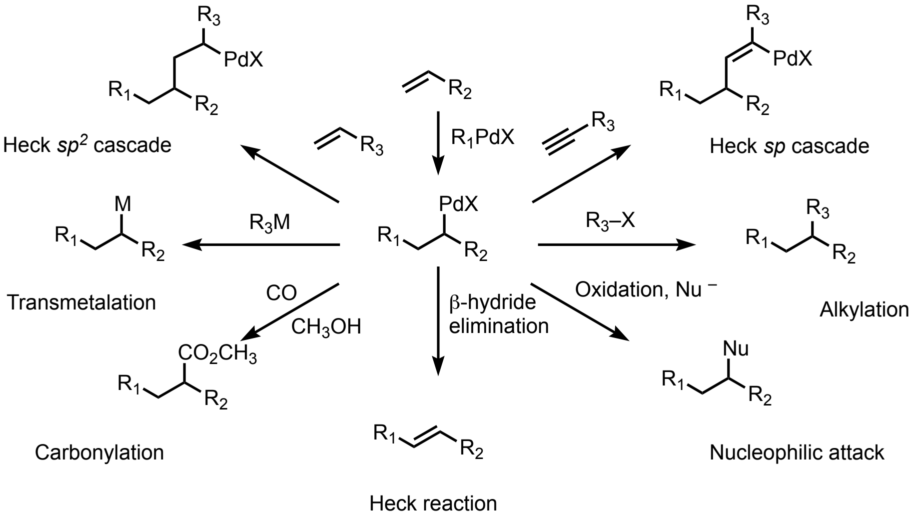
Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529.



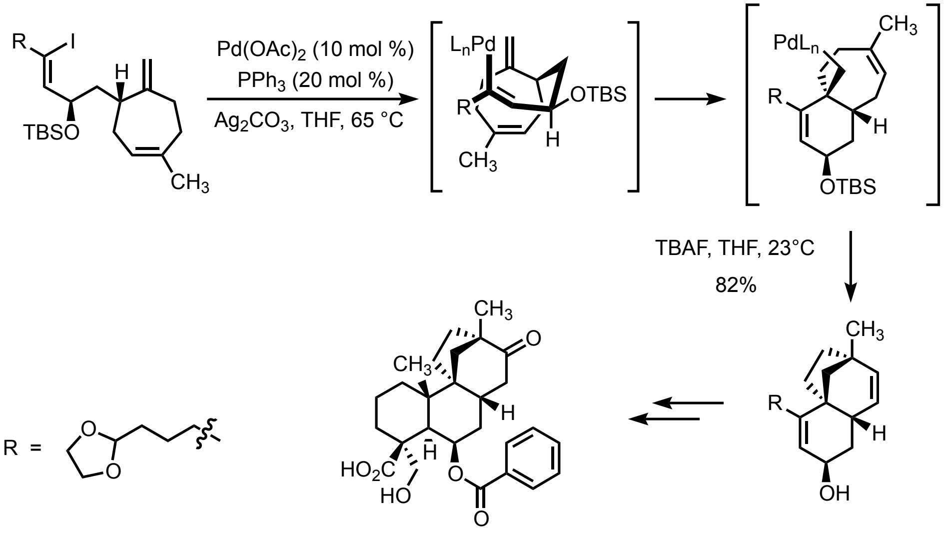
Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256.

Tandem Reaction:

- Additional reaction pathways become available when the initial Pd–C species does not (or can not) decompose via β-hydride elimination.



- Tandem Heck reactions:



Scopadulcic acid A

Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304–5306.

Fox, M. E.; Li, C; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.

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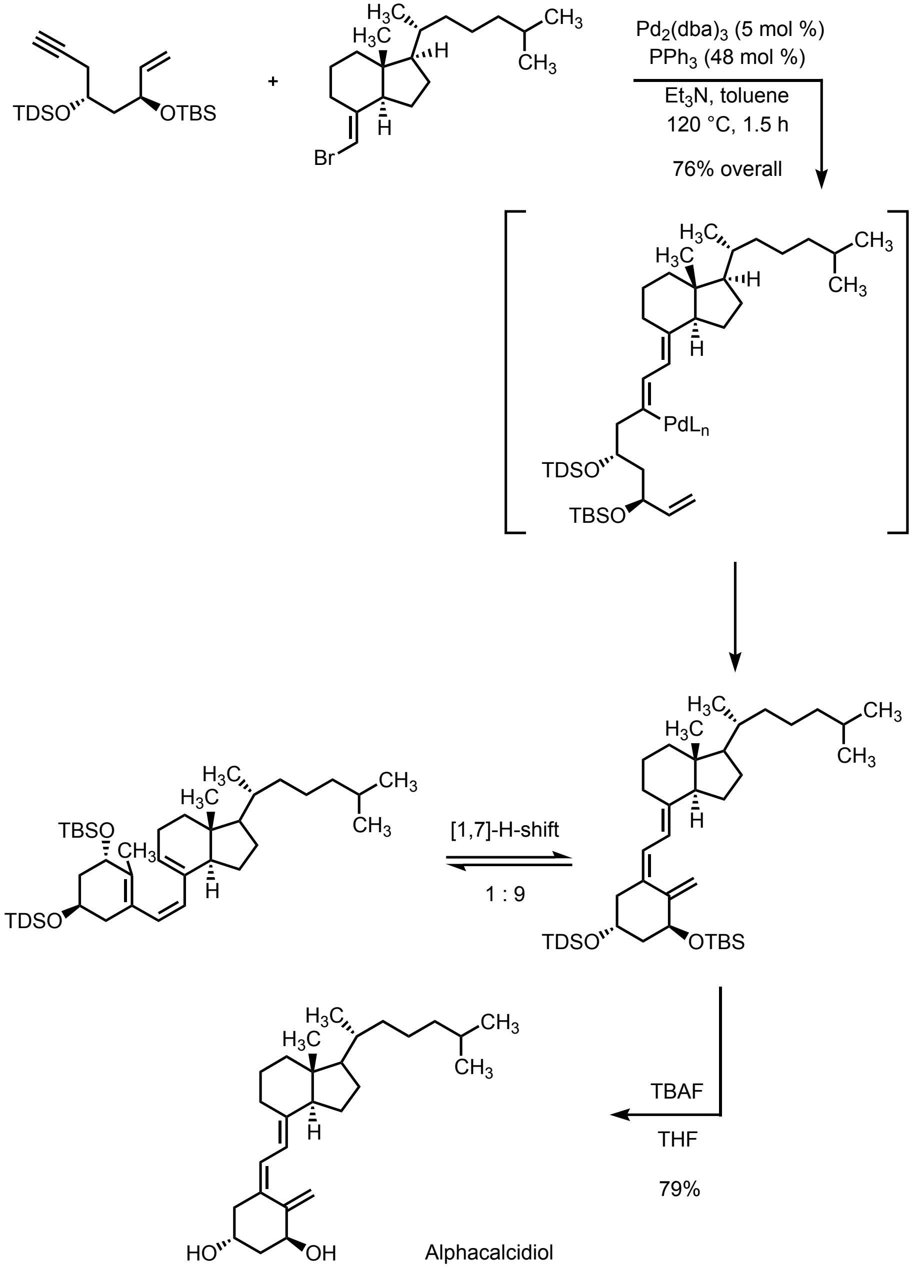
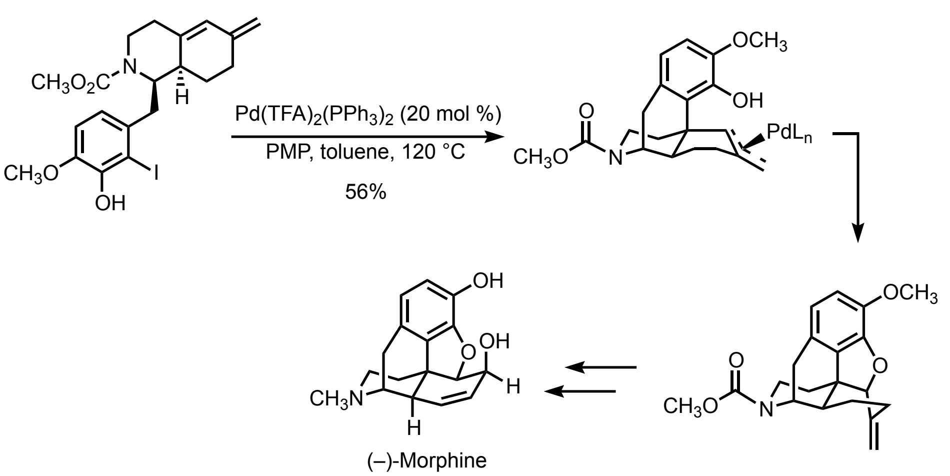
- Tandem Heck reaction, intermolecular



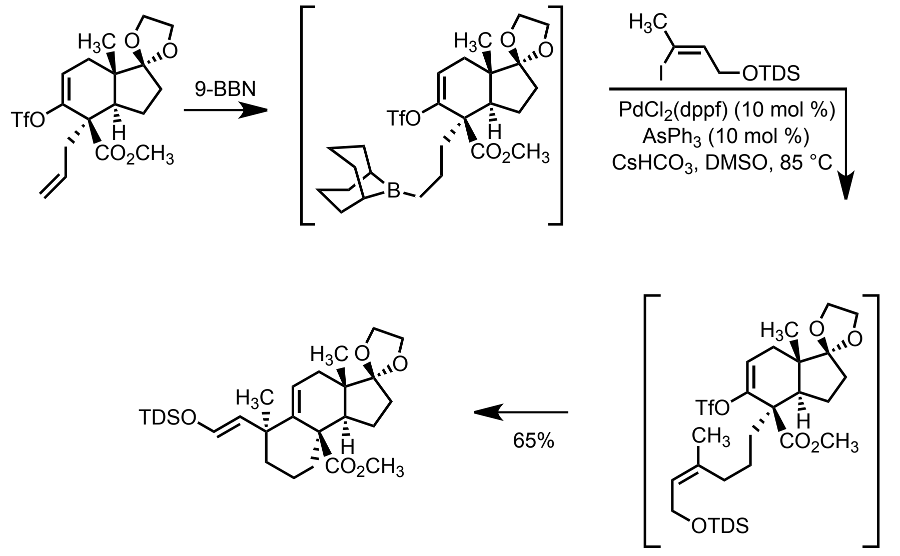
Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845.

- Tandem Heck/π–allylpalladium reactions



Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453–3456.

- Tandem Suzuki/Heck reactions



Kojima, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3455–3458.

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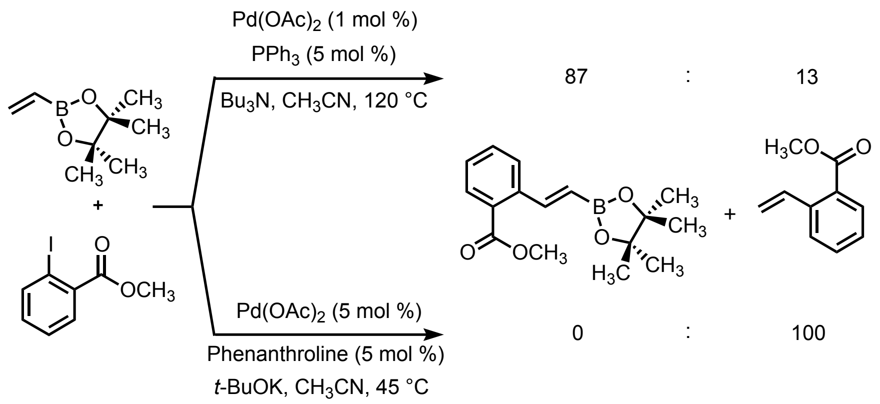
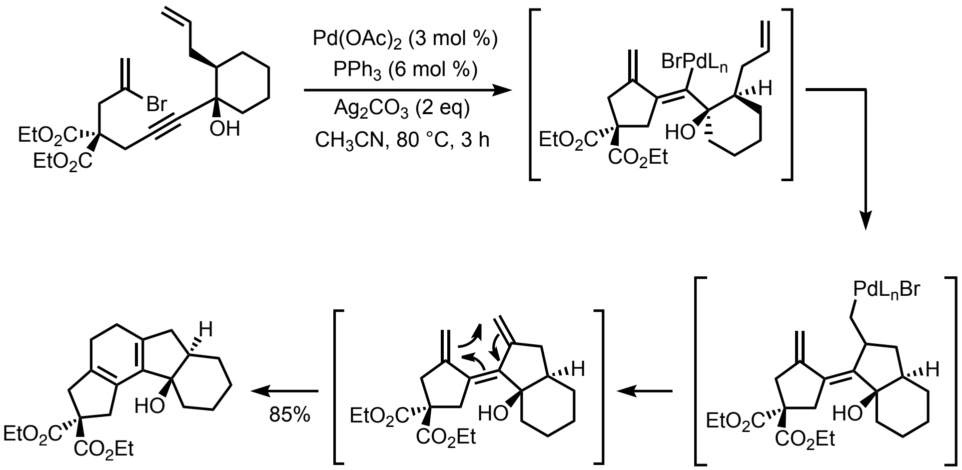
- The ease of reaction (Heck versus Suzuki) is highly dependent upon the reaction conditions:



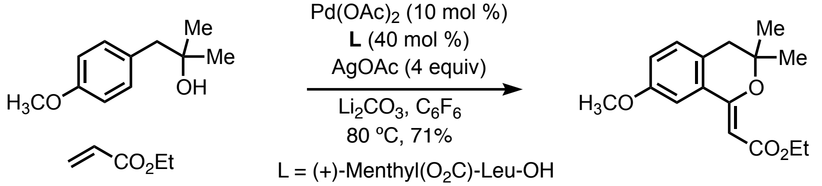
Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.*, **1993**, *34*, 3599–3602.

- Tandem Heck/6π-electrocyclization reactions:



Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11545–11578.

- Tandem dehydrogenative Heck/oxidative cyclization

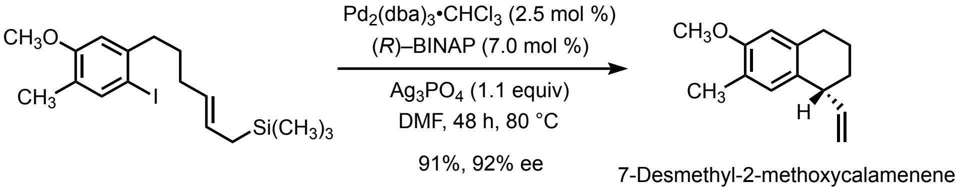


Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc*, **2010**, *132*, 5916–5921.

Enantioselective Heck Reactions:

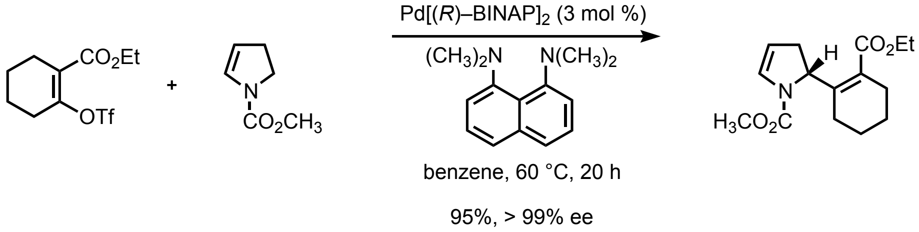
- Typical yields = 50–80%
- Typical ee's = 80–95%

- Formation of tertiary stereocenters:



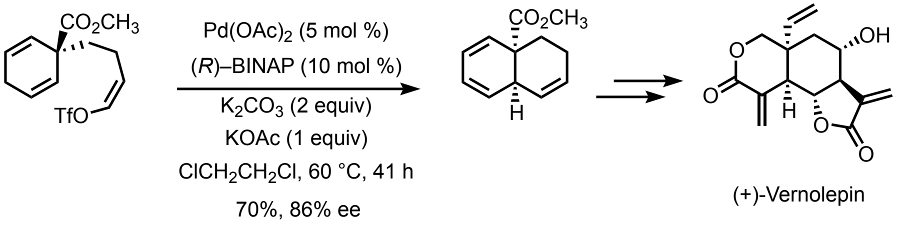
7-Desmethyl-2-methoxycalamenene

Tietze, L. F.; Raschke, T. *Synlett* **1995**, 597–598.

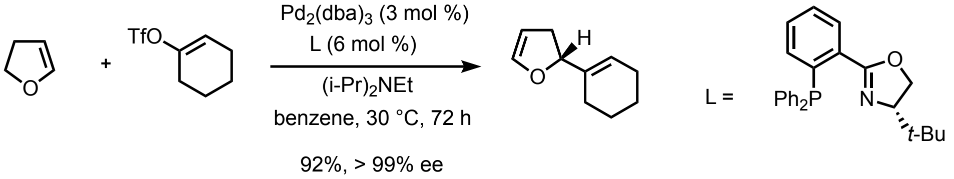


- Note that the alkene within the intially formed pyrrolidine has migrated under the reaction conditions.

Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505–2508.



Ohari, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737–11748.



Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338–1345.

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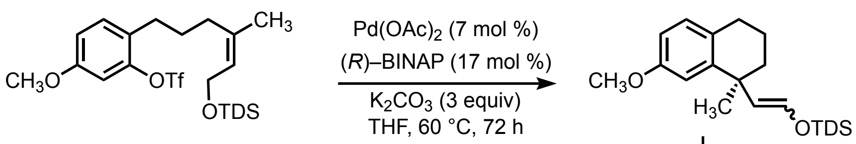
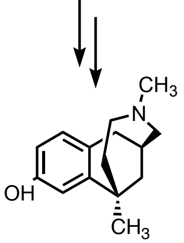
- Formation of quaternary stereocenters:



90%, 90% ee

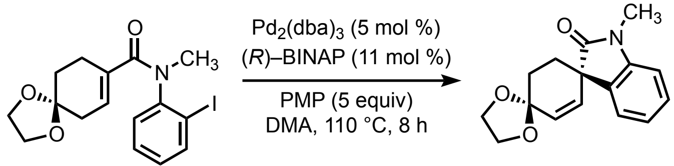


(–)-Eptazocine

Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M.

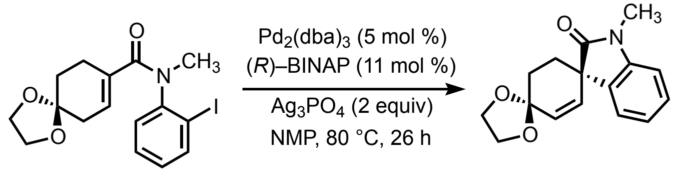
J. Am. Chem. Soc. **1993**, *115*, 8477–8488.

- The choice of base influences whether the Pd complex is neutral or cationic; this in turn can influence the stereochemical outcome.



(S), 71%, 66% ee

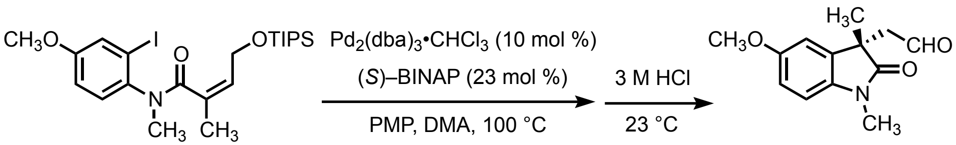
neutral



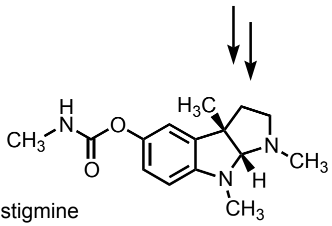
(R), 86%, 70% ee

cationic

Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487.



(S), 84%, 95% ee

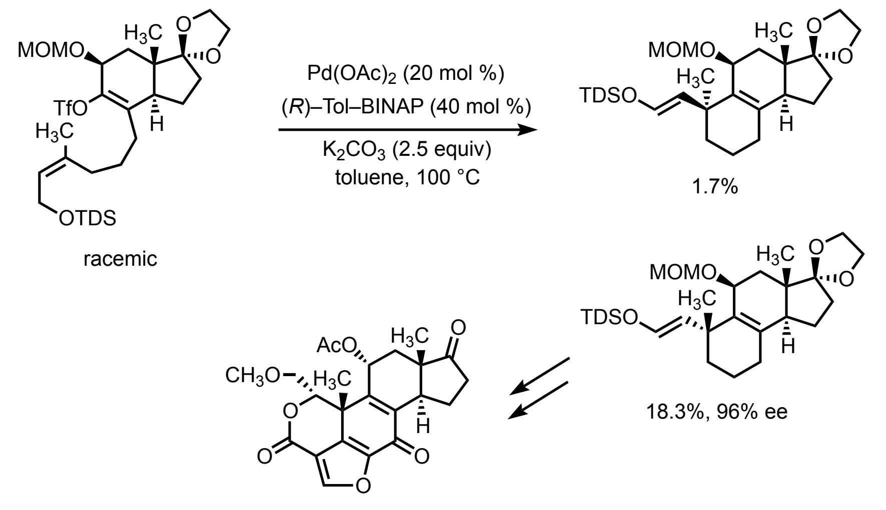


(–)-Physostigmine

Matsuura, T.; Overman, L. E.; Poon, D. J.

J. Am. Chem. Soc. **1998**, *120*, 6500–6503.

- Kinetic Resolution:



racemic

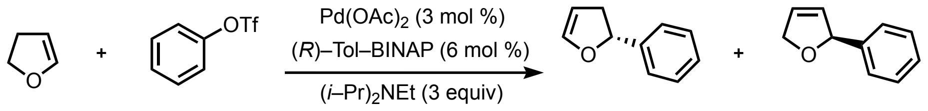
1.7%

18.3%, 96% ee

(+)-Wortmannin

- The enantiomer of the major product not observed. Instead, a complex mixture of products was formed.

Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311–314.

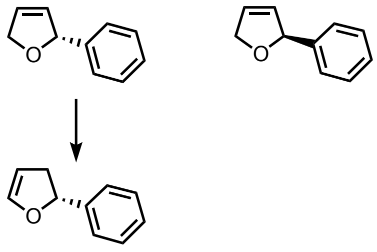


(R), 71%, 93% ee

(S), 7%, 67% ee

- Initial products are 2,5 dihydrofurans:

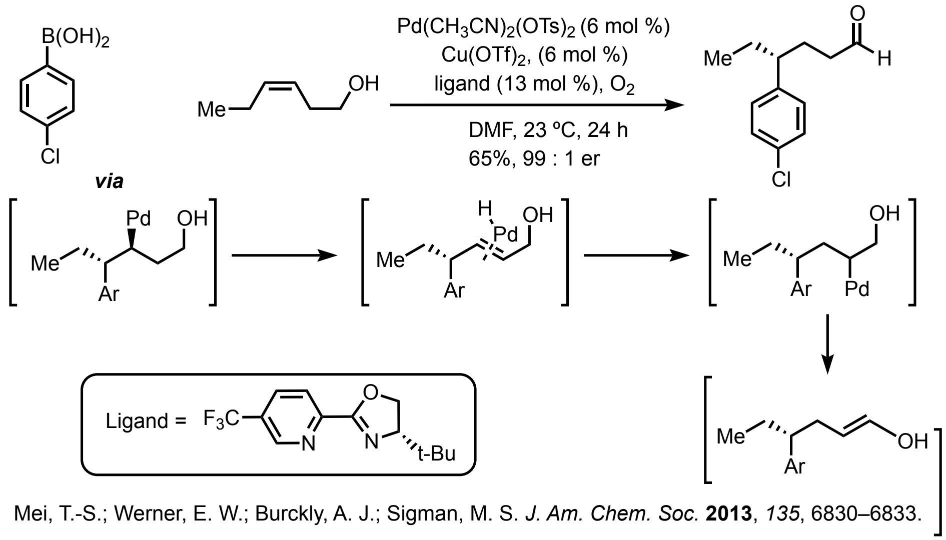
- Only the (R) isomer can isomerize due to the asymmetric environment of the ligand.



Ozawa, F.; Kubo, F.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188–4196.

Andrew Haidle

- An Enantioselective redox-relay Heck process was achieved by a regioselective Heck coupling followed by isomerization of the transient allylic double bond to generate the aldehyde shown:

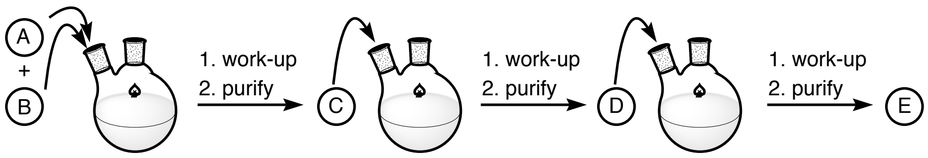


Mei, T.-S.; Werner, E. W.; Burckly, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830–6833.

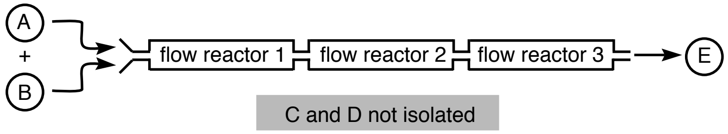
Heck Reactions in Continuous Flow:

- Continuous flow techniques have become an increasingly popular approach to streamlining multi-step syntheses. A comparison between traditional and continuous flow multi-step synthesis is shown below (Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.):

Traditional Multi-Step Synthesis:



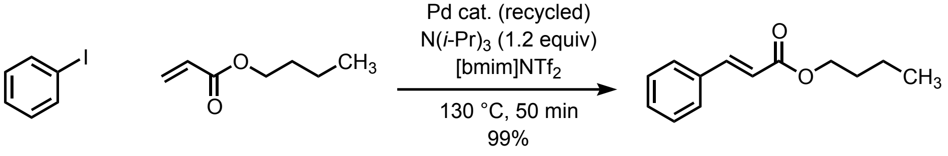
Continuous Flow Multi-Step Synthesis:



- Advantages of continuous flow:
  - Improved control over mixing and temperature.
  - Improved safety: reactions are "scaled out" instead of "scaled up"; if more material is needed, the process is performed for a longer time. As a result, large amounts of chemicals or reaction volumes are avoided, which decrease the likelihood of accidents.
  - Inline work-up and purification are possible, increasing the overall efficiency of the process.

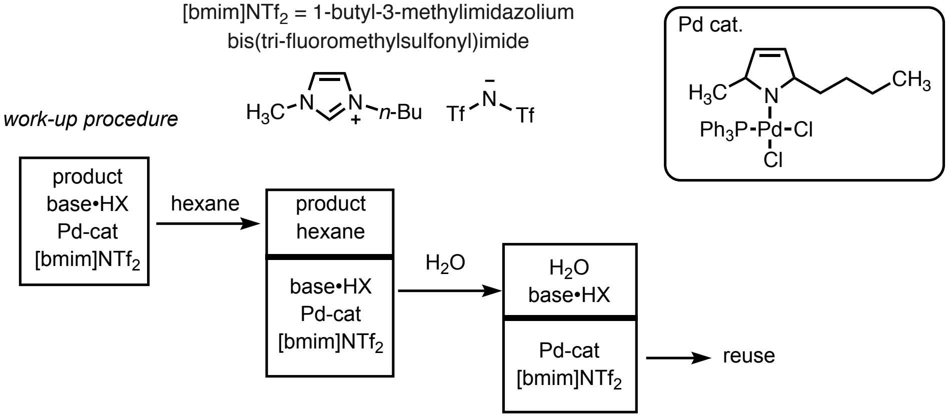
Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.
Webb D.; Jamison, T. F. *Org. Lett.* **2012** *14*, 568–571.

- Continuous flow techniques have been applied in the Heck reaction.
- Using flow microsystems, shorter reaction times are possible due to improved mixing.
- By immobilizing the catalyst in an ionic liquid, [bmim]NTf$_2$, the catalyst and product can be easily separated from the reaction media.



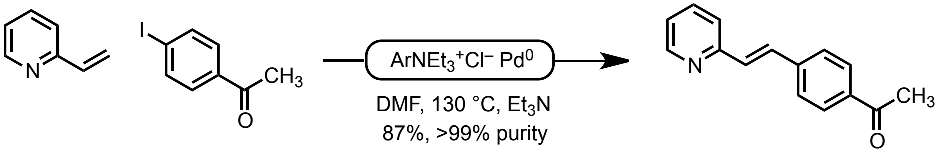
[bmim]NTf$_2$ = 1-butyl-3-methylimidazolium bis(tri-fluoromethylsulfonyl)imide

work-up procedure



Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Proc. Res. Dev.* **2004**, *8*, 477–481.

- Supported Pd^0 nanoparticles have also been employed as catalysts in flow Heck reactions and can be reused.
- Reactions are performed ligand-free under "Jeffery-like" conditions.
- No additional purification is required as 100% conversion is achieved.

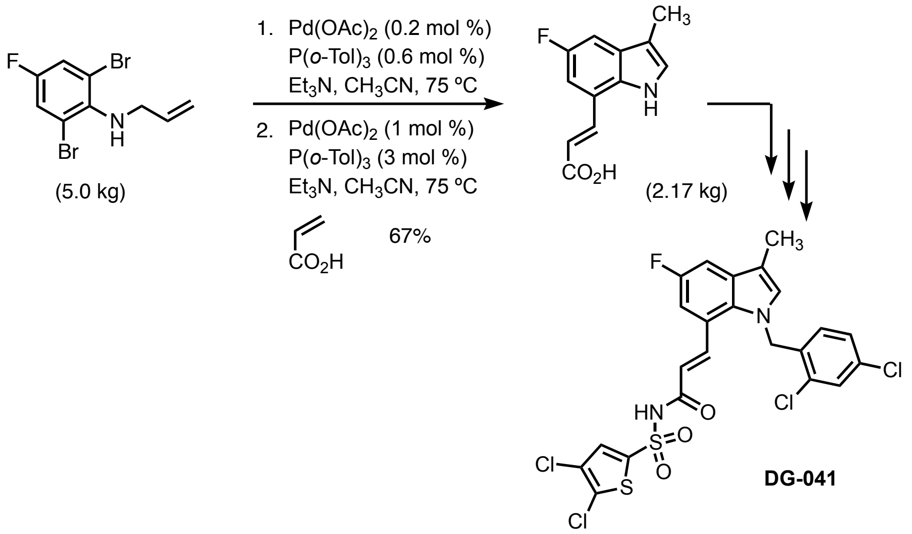


Nikbin, N.; Ladlow, M.; Ley, S.V. *Org. Proc. Res. Dev.* **2007**, *11*, 458–462.

James Mousseau, Fan Liu

Selected Applications in Industry:

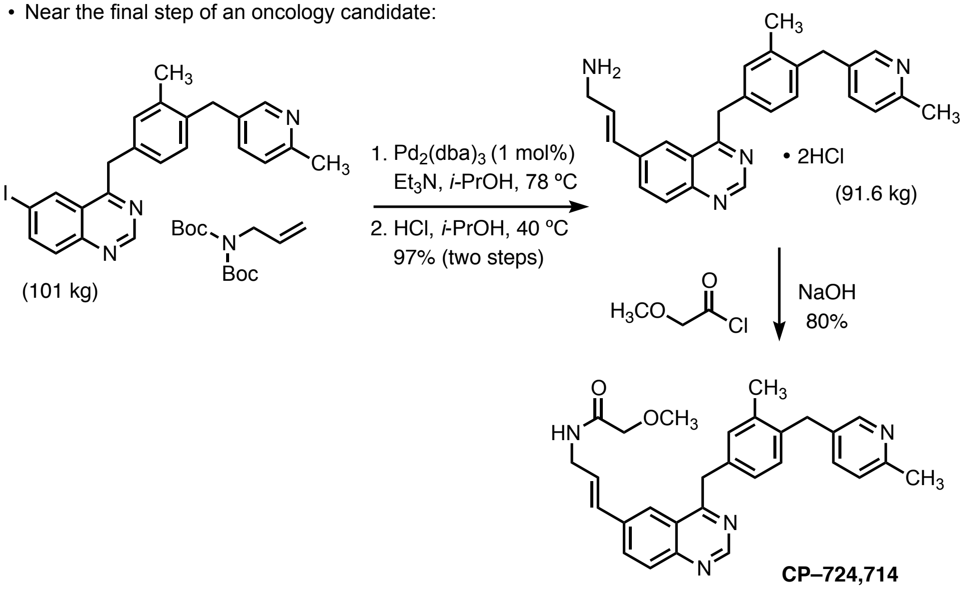
- Synthesis of an EP3 receptor antagonist via a double Heck cyclization reaction:



DG-041

Zegar, S.; Tokar, C.; Enache, L. A.; Rajagopol, V.; Zeller, W.; O'Connell, M.; Singh, J.; Muellner, F. W.; Zembower, D. E. O*rg. Proc. Res. Dev.* **2007,** *11*, 747–753.

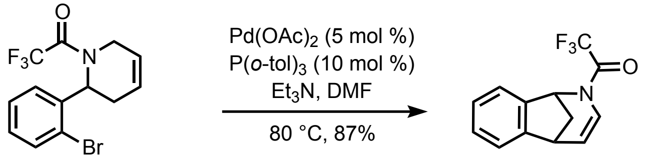
- Near the final step of an oncology candidate:



CP–724,714

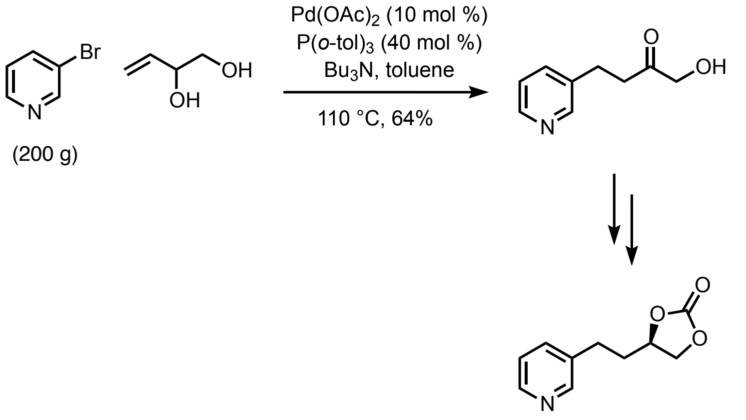
Ripin, D.H. B.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M.; Vetelino, M. G.; Wei, L.O*rg. Proc. Res. Dev.* **2005,** *9*, 440–450.

- Application to the synthesis of the anti-smoking drug, Chantix®:

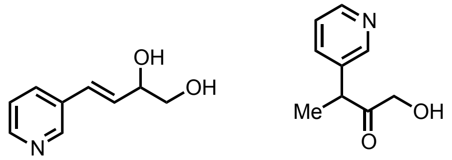


Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Bashore, C. G.; Bianco, K.; Flick, A. C. *Tetrahedron Lett.* **2011**, *52*, 953–954.

- Application in the manufacturing route of 1-hydroxy-4-(3-pyridyl)butan-2-one:
  - Reaction was optimized to limit the formation of the by-products depicted below.



Possible by-products (not observed):



Ainge, D.; Vaz, L-M. *Org. Proc. Res. Dev.* **2002**, *6*, 811.

James Mousseau