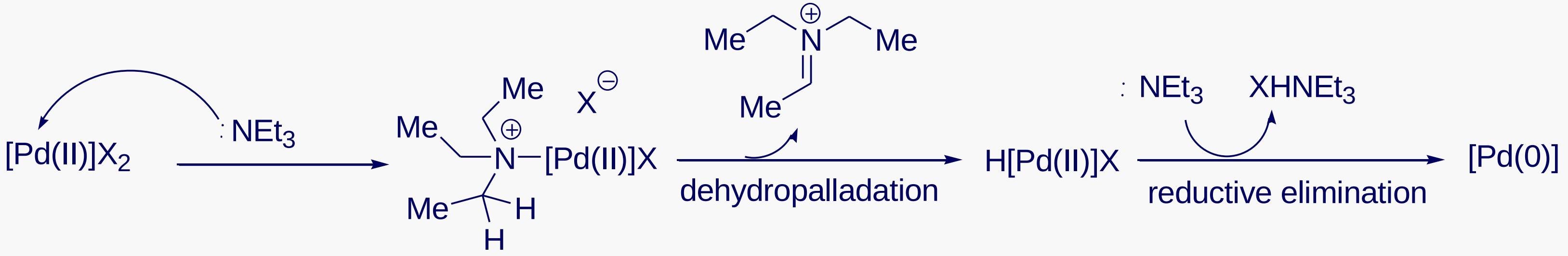
The Catalytic Chemistry of Palladium (0)

$$\mathrm{Pd(0)} \longrightarrow \mathrm{Pd(II)} \longrightarrow \mathrm{Pd(0)}$$

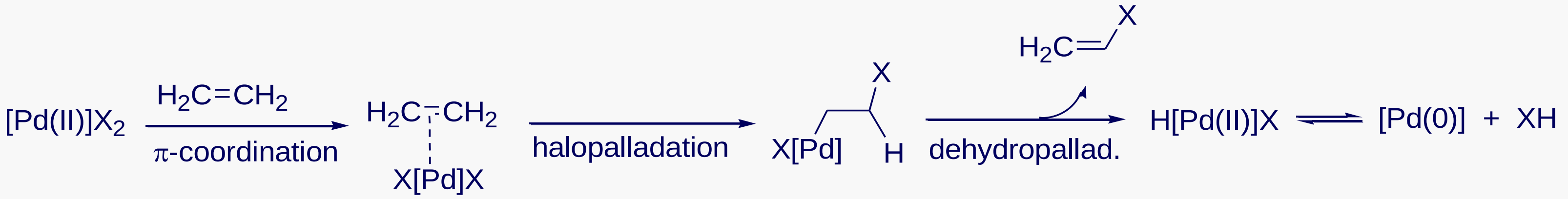
Negishi, E.-i., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**

Pd(0) Sources

Amines

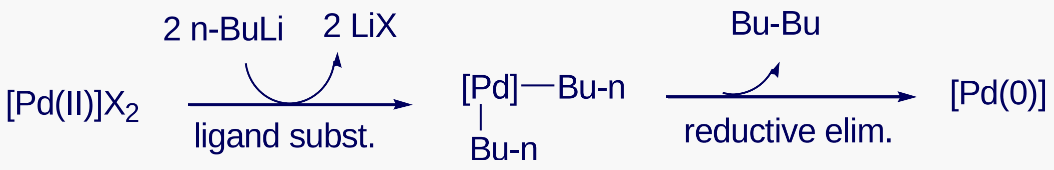


Alkenes



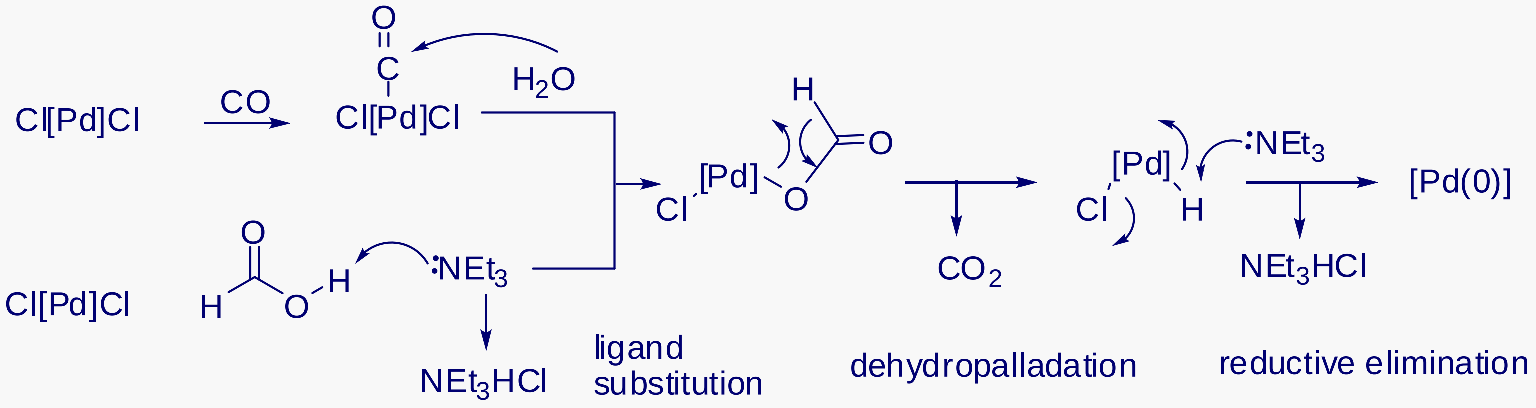
Pd(0) Sources

Organometallics



Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Chem. Eur. J.* **2009**, *15*, 4224

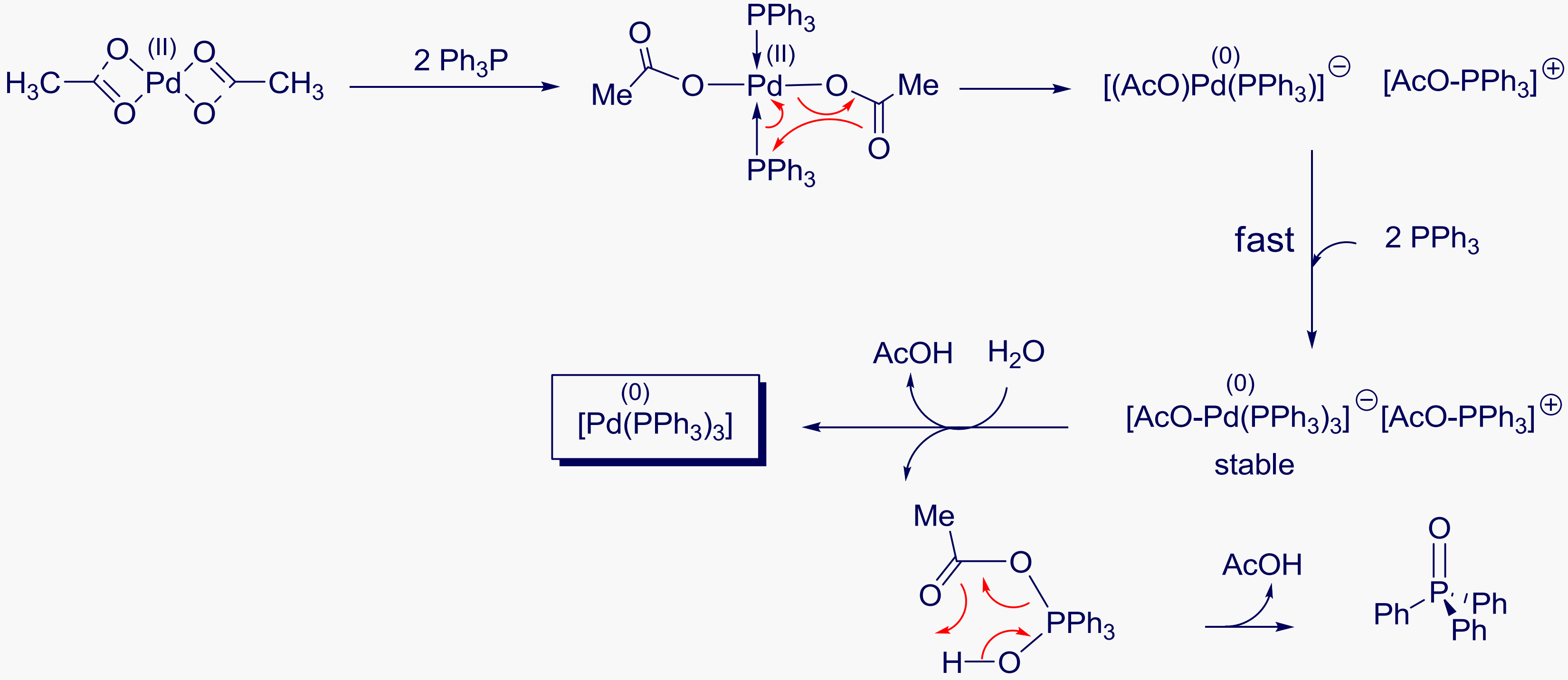
Ammonium formate or CO + H_2O



Pd(0) Sources

Oxidation of a phosphine

$Pd(OAc)_2 + 4\ PPh_3 + H_2O\ \text{----->}\ (PPh_3)_3Pd + O{=}PPh_3 + 2AcOH$



Ozawa, F.; Kubo, A.; Hayashi, T.; *Chem. Lett.* **1992**, 2177

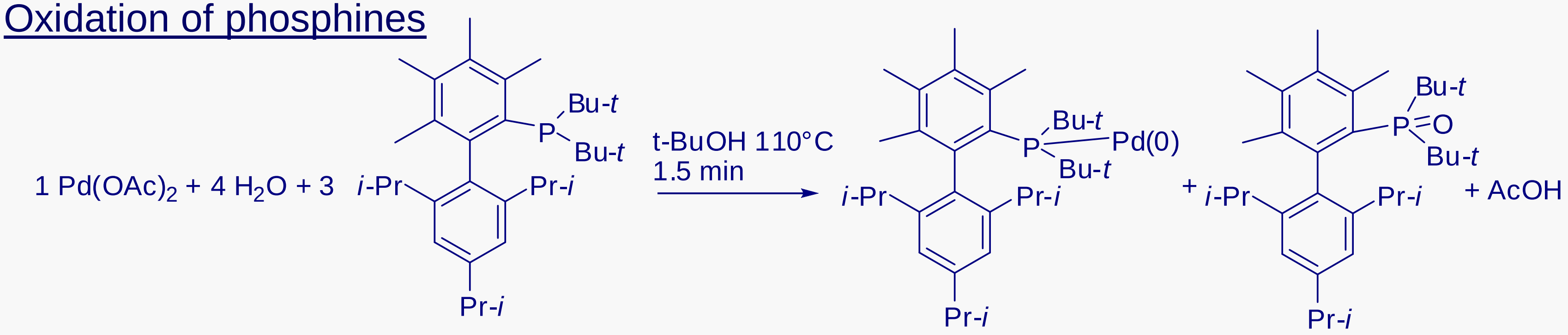
Amatore, C.; Carre, E. Jutand, A.; M'Barke, M.A. *Organometallics*, **1995**, *14*, 1818

G. Poli G. Prestat

Pd(0) Sources

Protocols for forming a highly active Pd(0) catalysts

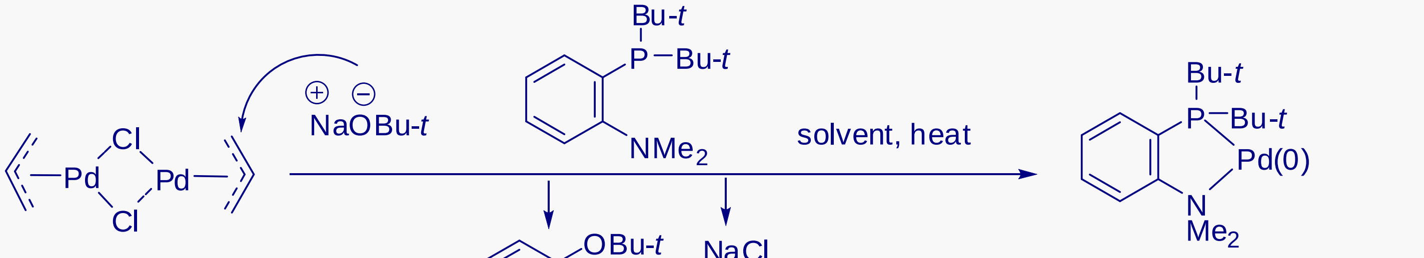
Oxidation of phosphines



probable structure of the very
active Pd(0) catalyst

Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S.L. *Org. Lett.* **2008**,*10*, 3505.

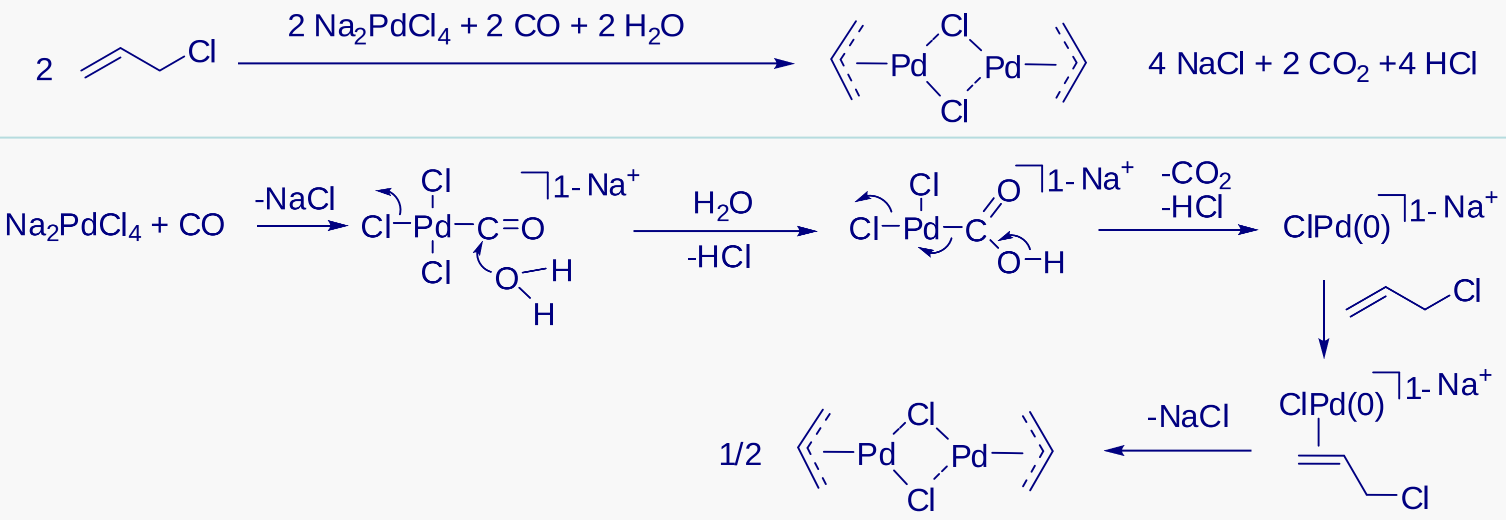
Add of nucleophiles to π-allyl complexes



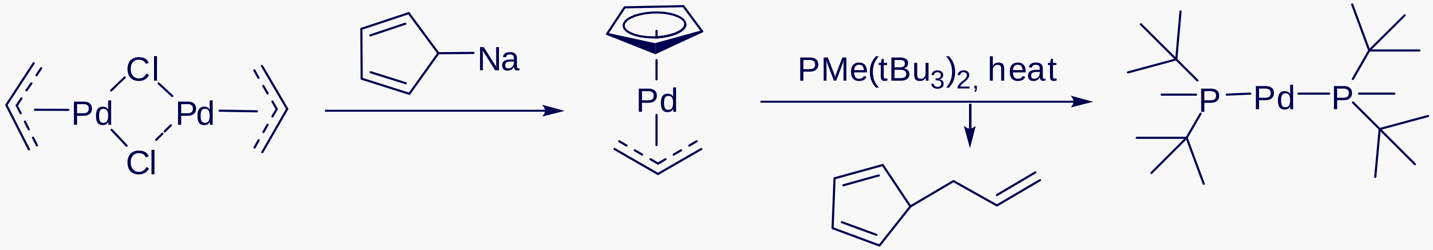
probable structure of the very
active Pd(0) catalyst

Lundgren RJ, Sappong-Kumankumah A, Stradiotto M. *Chem. Eur. J.* **2010**, *16*, 1983

Pd(0) Sources

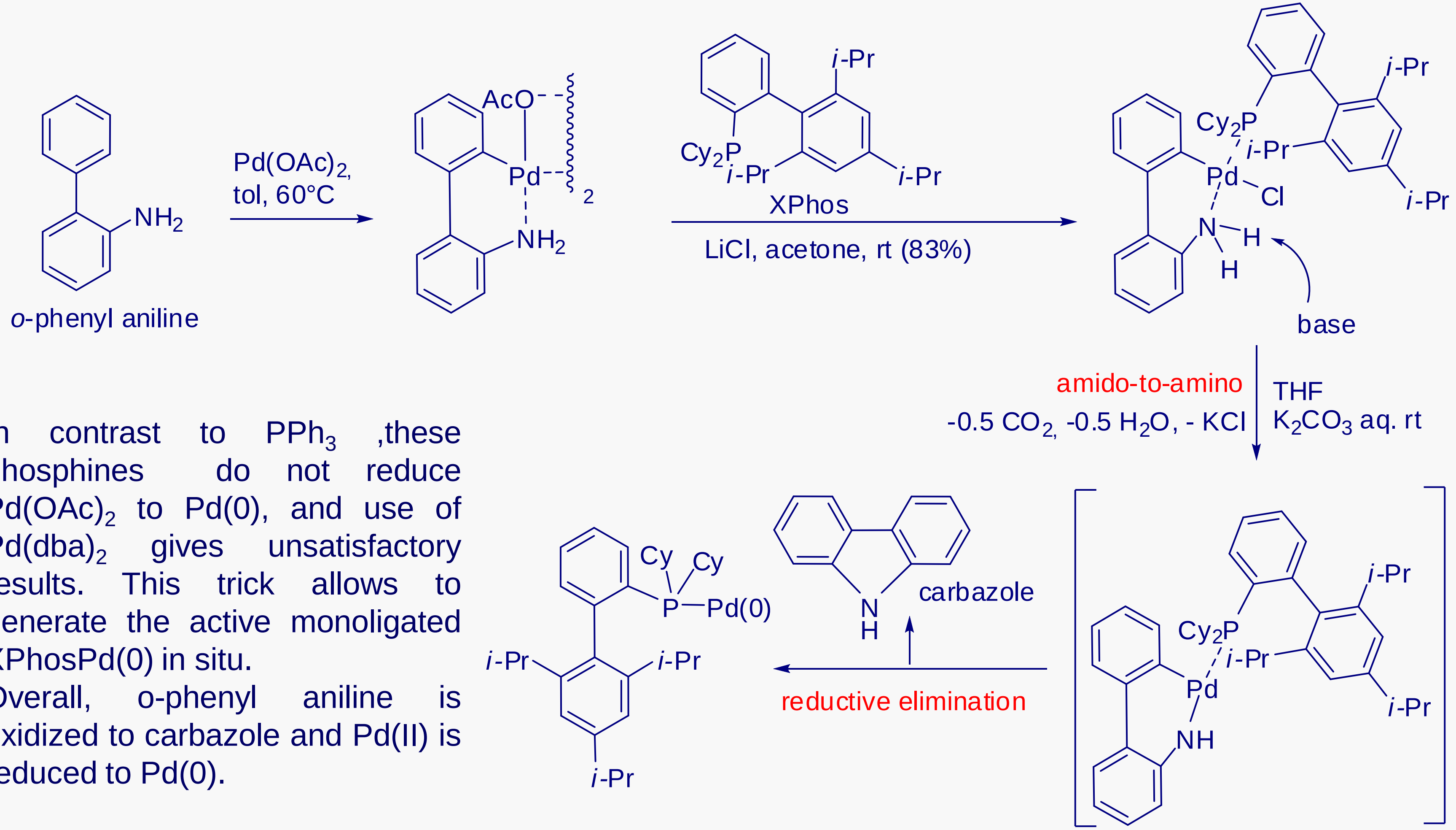


Reductive elimination of Cp(η^{3}-allyl)Pd



Step 1: Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990,** *28***,** 342.
Step 2: Netherton, Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910.

Pd(0) Sources



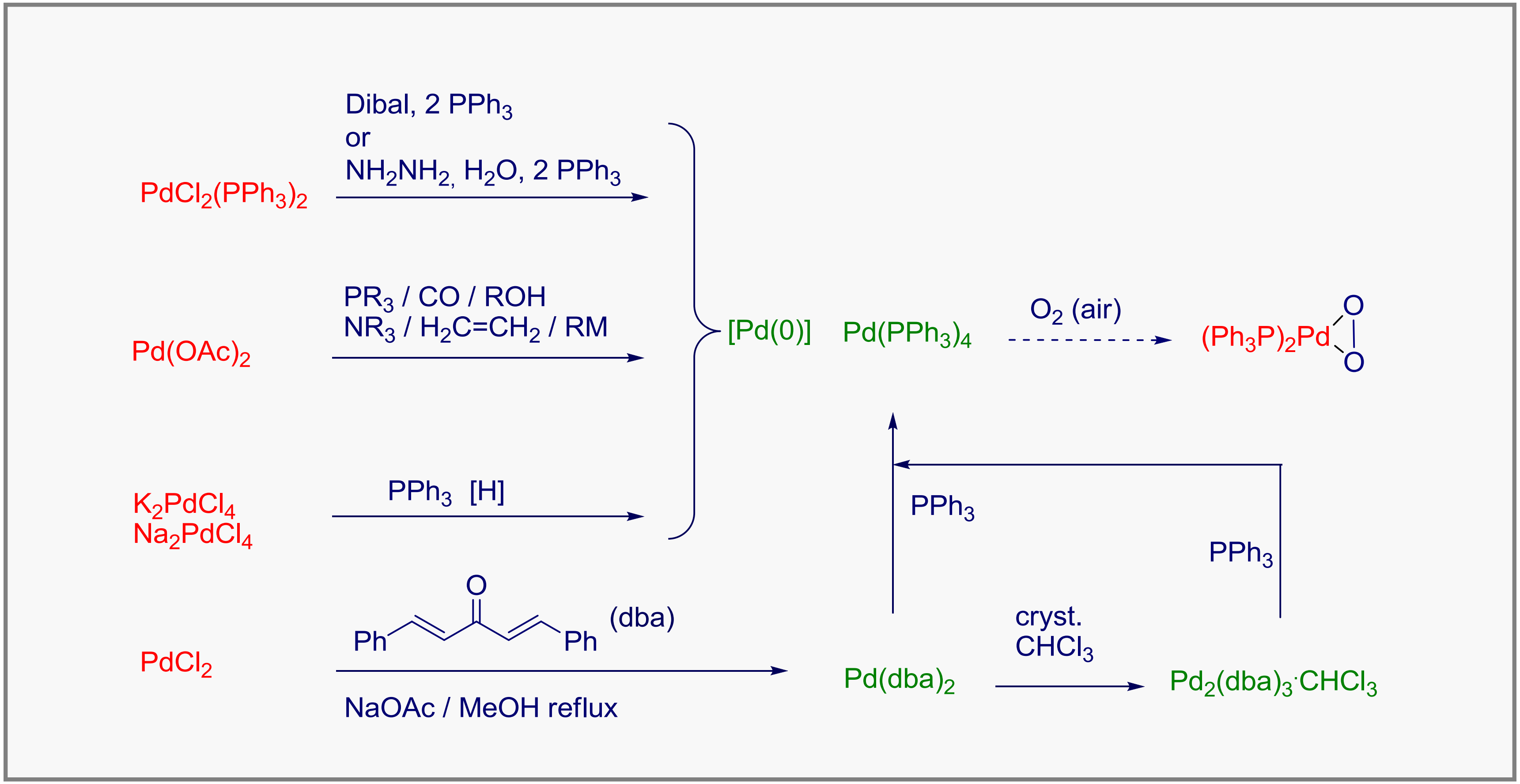
In contrast to PPh_3 ,these phosphines do not reduce $Pd(OAc)_2$ to Pd(0), and use of $Pd(dba)_2$ gives unsatisfactory results. This trick allows to generate the active monoligated XPhosPd(0) in situ.

Overall, o-phenyl aniline is oxidized to carbazole and Pd(II) is reduced to Pd(0).

Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132,* 14073

See also: Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* ***2008,*** *130,* 6686.

Pd(0) Sources



$PdCl_2(PPh_3)_2$ — Dibal, 2 PPh_3 or NH_2NH_2, H_2O, 2 PPh_3

$Pd(OAc)_2$ — PR_3 / CO / ROH; NR_3 / $H_2C{=}CH_2$ / RM

K_2PdCl_4, Na_2PdCl_4 — PPh_3 [H]

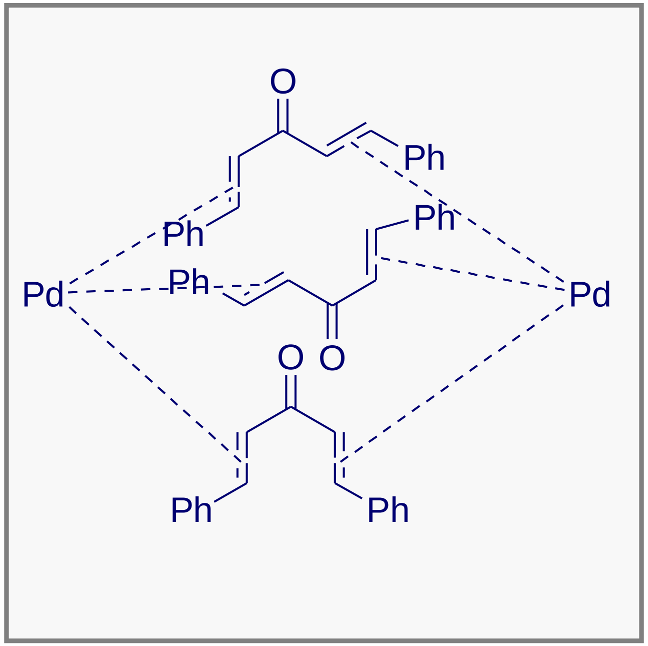
→ [Pd(0)] $Pd(PPh_3)_4$ — O_2 (air) → $(Ph_3P)_2Pd(O_2)$

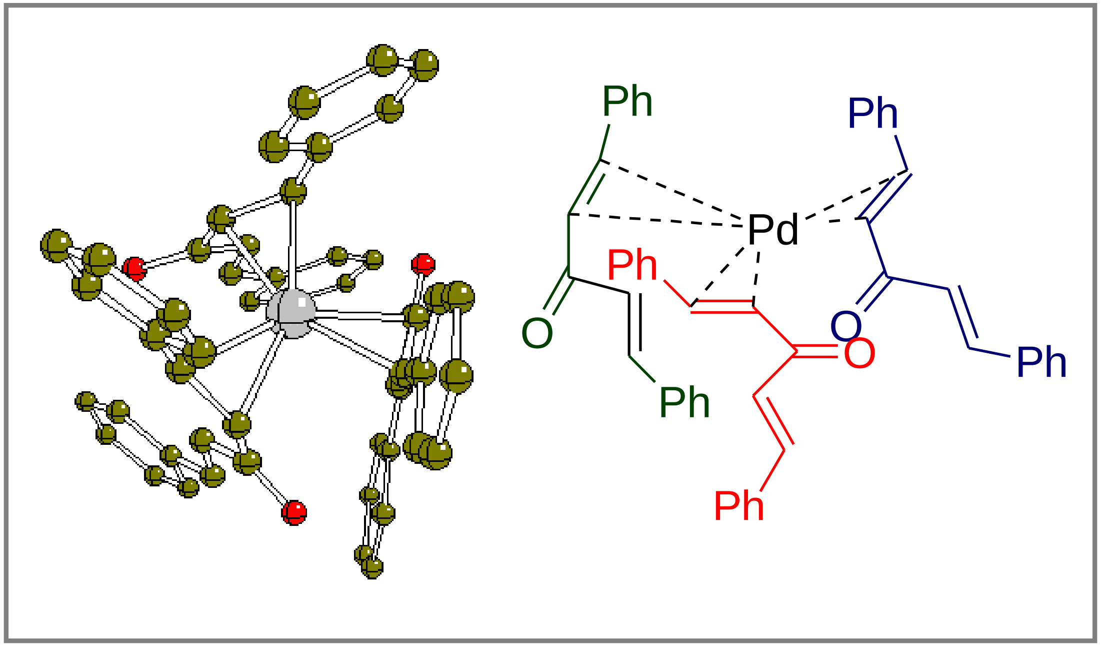
$PdCl_2$ — (dba), NaOAc / MeOH reflux → $Pd(dba)_2$ — cryst. $CHCl_3$ → $Pd_2(dba)_3{\cdot}CHCl_3$

$Pd(dba)_2$ — PPh_3 → $Pd(PPh_3)_4$

$Pd_2(dba)_3{\cdot}CHCl_3$ — PPh_3 → $Pd(PPh_3)_4$

$Pd_2(dba)_3$ and $Pd(dba)_3$





Tris-dibenzylideneacetone dipalladium (0)
$Pd_2(dba)_3$

Tris-dibenzylideneacetone palladium (0)
$Pd(dba)_3$

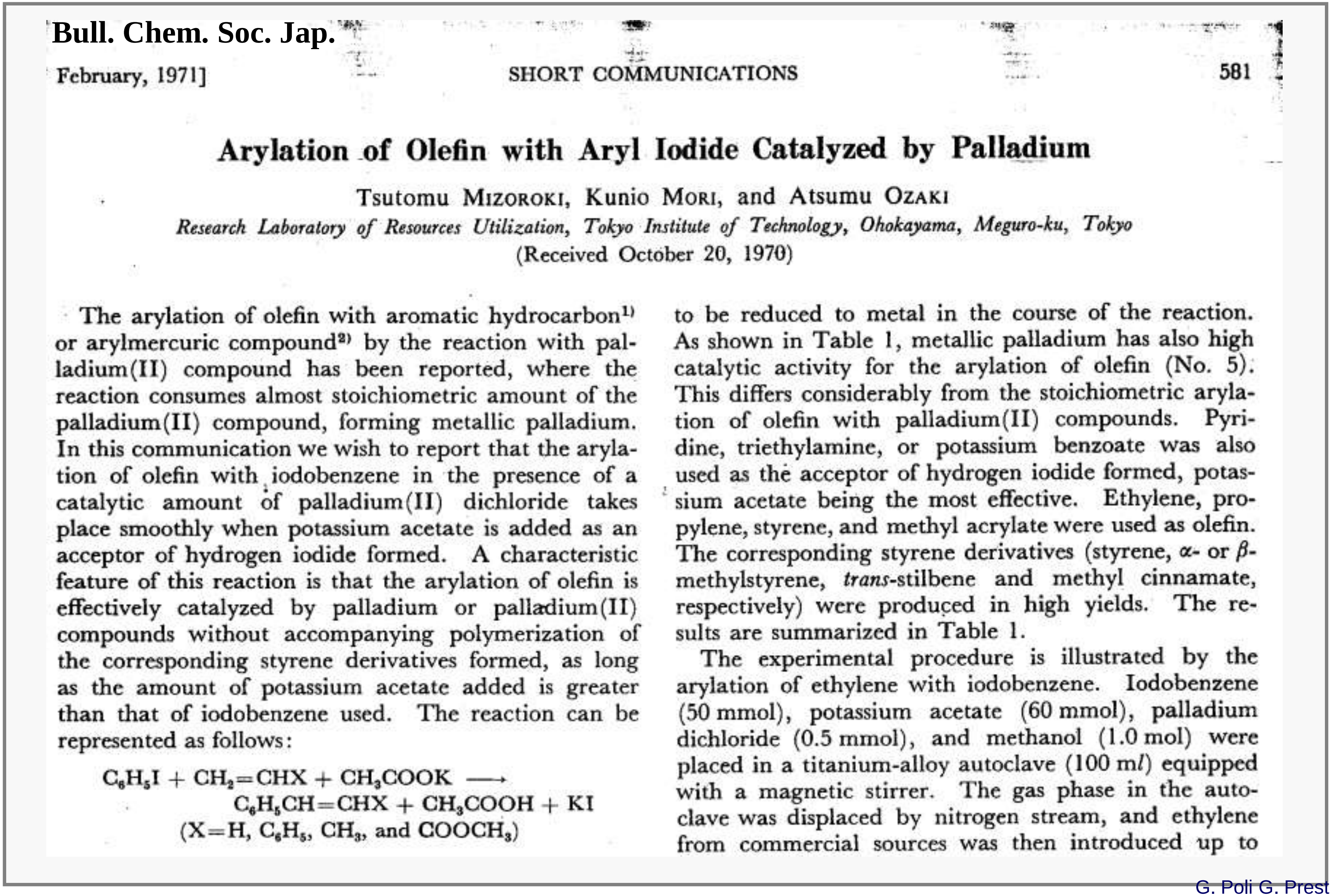
In $Pd(dba)_3$ each dba has one s-cis and one s-trans configured double bond.
Pd is almost in a planar geometry
Only the s-trans double bonds are involved in complexation to Pd

Syn Carbopalladations:

The Mizoroki-Heck Reaction

G. Poli G. Prestat

The Seminal Papers



Bull. Chem. Soc. Jap.

Arylation of Olefin with Aryl Iodide Catalyzed by Palladium

Tsutomu Mizoroki, Kunio Mori, and Atsumu Ozaki
Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo

(Received October 20, 1970)

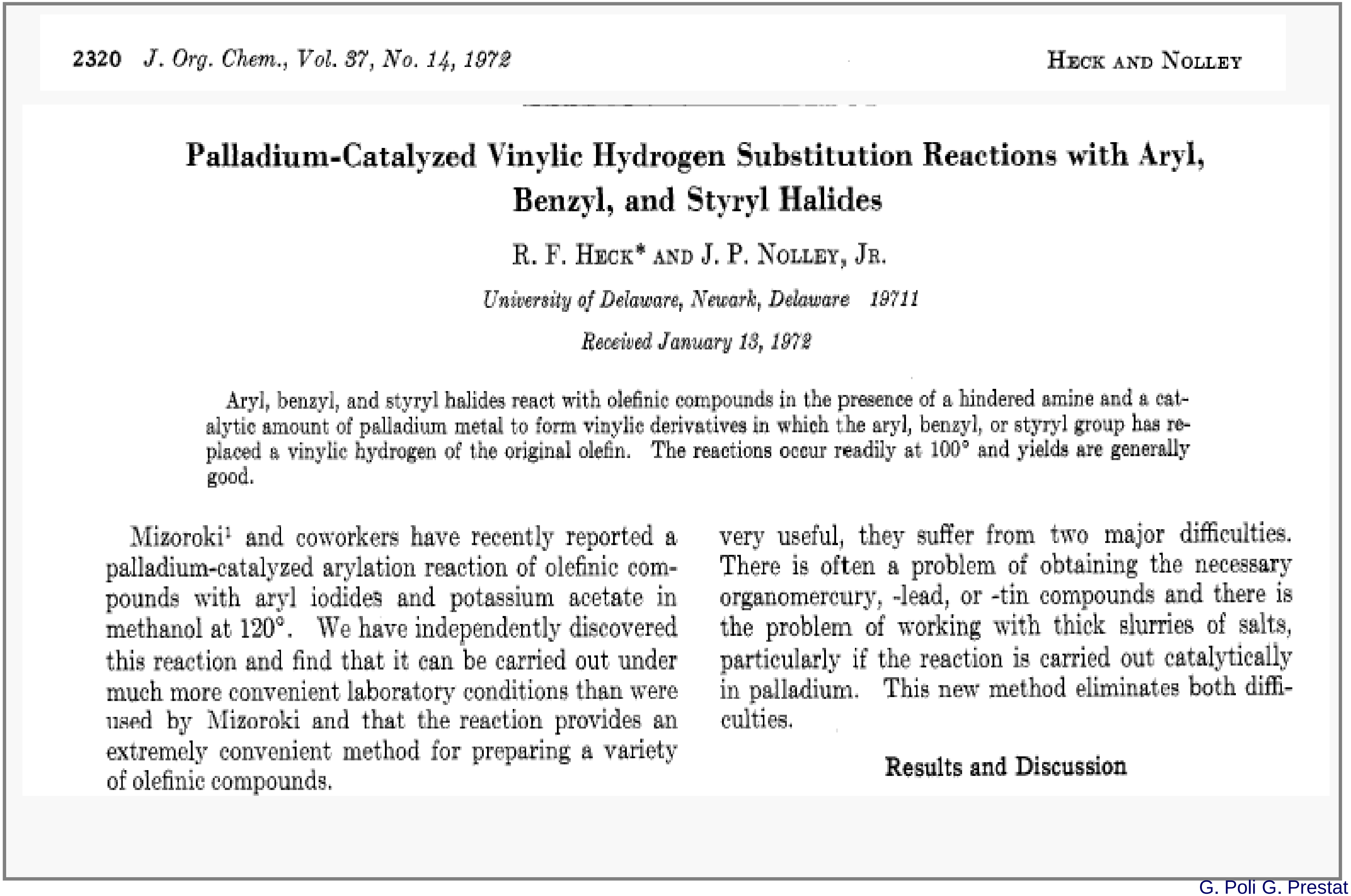
The arylation of olefin with aromatic hydrocarbon[1] or arylmercuric compound[2] by the reaction with palladium(II) compound has been reported, where the reaction consumes almost stoichiometric amount of the palladium(II) compound, forming metallic palladium. In this communication we wish to report that the arylation of olefin with iodobenzene in the presence of a catalytic amount of palladium(II) dichloride takes place smoothly when potassium acetate is added as an acceptor of hydrogen iodide formed. A characteristic feature of this reaction is that the arylation of olefin is effectively catalyzed by palladium or palladium(II) compounds without accompanying polymerization of the corresponding styrene derivatives formed, as long as the amount of potassium acetate added is greater than that of iodobenzene used. The reaction can be represented as follows:

$$C_6H_5I + CH_2{=}CHX + CH_3COOK \longrightarrow$$
$$C_6H_5CH{=}CHX + CH_3COOH + KI$$
$$(X{=}H,\ C_6H_5,\ CH_3,\ \text{and}\ COOCH_3)$$

to be reduced to metal in the course of the reaction. As shown in Table 1, metallic palladium has also high catalytic activity for the arylation of olefin (No. 5). This differs considerably from the stoichiometric arylation of olefin with palladium(II) compounds. Pyridine, triethylamine, or potassium benzoate was also used as the acceptor of hydrogen iodide formed, potassium acetate being the most effective. Ethylene, propylene, styrene, and methyl acrylate were used as olefin. The corresponding styrene derivatives (styrene, α- or β-methylstyrene, *trans*-stilbene and methyl cinnamate, respectively) were produced in high yields. The results are summarized in Table 1.

The experimental procedure is illustrated by the arylation of ethylene with iodobenzene. Iodobenzene (50 mmol), potassium acetate (60 mmol), palladium dichloride (0.5 mmol), and methanol (1.0 mol) were placed in a titanium-alloy autoclave (100 m*l*) equipped with a magnetic stirrer. The gas phase in the autoclave was displaced by nitrogen stream, and ethylene from commercial sources was then introduced up to

The Seminal Papers



2320 *J. Org. Chem., Vol. 37, No. 14, 1972* HECK AND NOLLEY

Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides

R. F. HECK* AND J. P. NOLLEY, JR.

University of Delaware, Newark, Delaware 19711

Received January 13, 1972

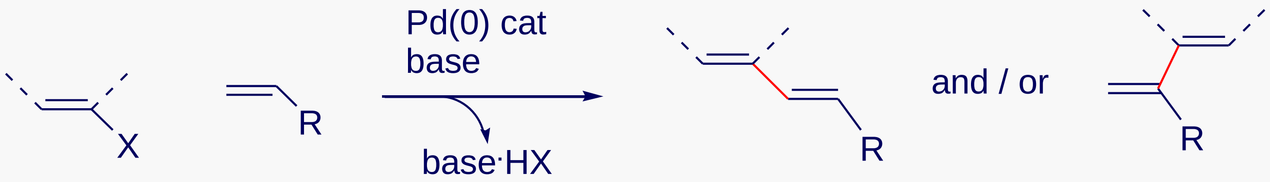
Aryl, benzyl, and styryl halides react with olefinic compounds in the presence of a hindered amine and a catalytic amount of palladium metal to form vinylic derivatives in which the aryl, benzyl, or styryl group has replaced a vinylic hydrogen of the original olefin. The reactions occur readily at 100° and yields are generally good.

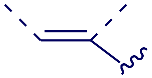
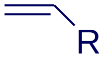
Mizoroki[1] and coworkers have recently reported a palladium-catalyzed arylation reaction of olefinic compounds with aryl iodides and potassium acetate in methanol at 120°. We have independently discovered this reaction and find that it can be carried out under much more convenient laboratory conditions than were used by Mizoroki and that the reaction provides an extremely convenient method for preparing a variety of olefinic compounds.

very useful, they suffer from two major difficulties. There is often a problem of obtaining the necessary organomercury, -lead, or -tin compounds and there is the problem of working with thick slurries of salts, particularly if the reaction is carried out catalytically in palladium. This new method eliminates both difficulties.

Results and Discussion

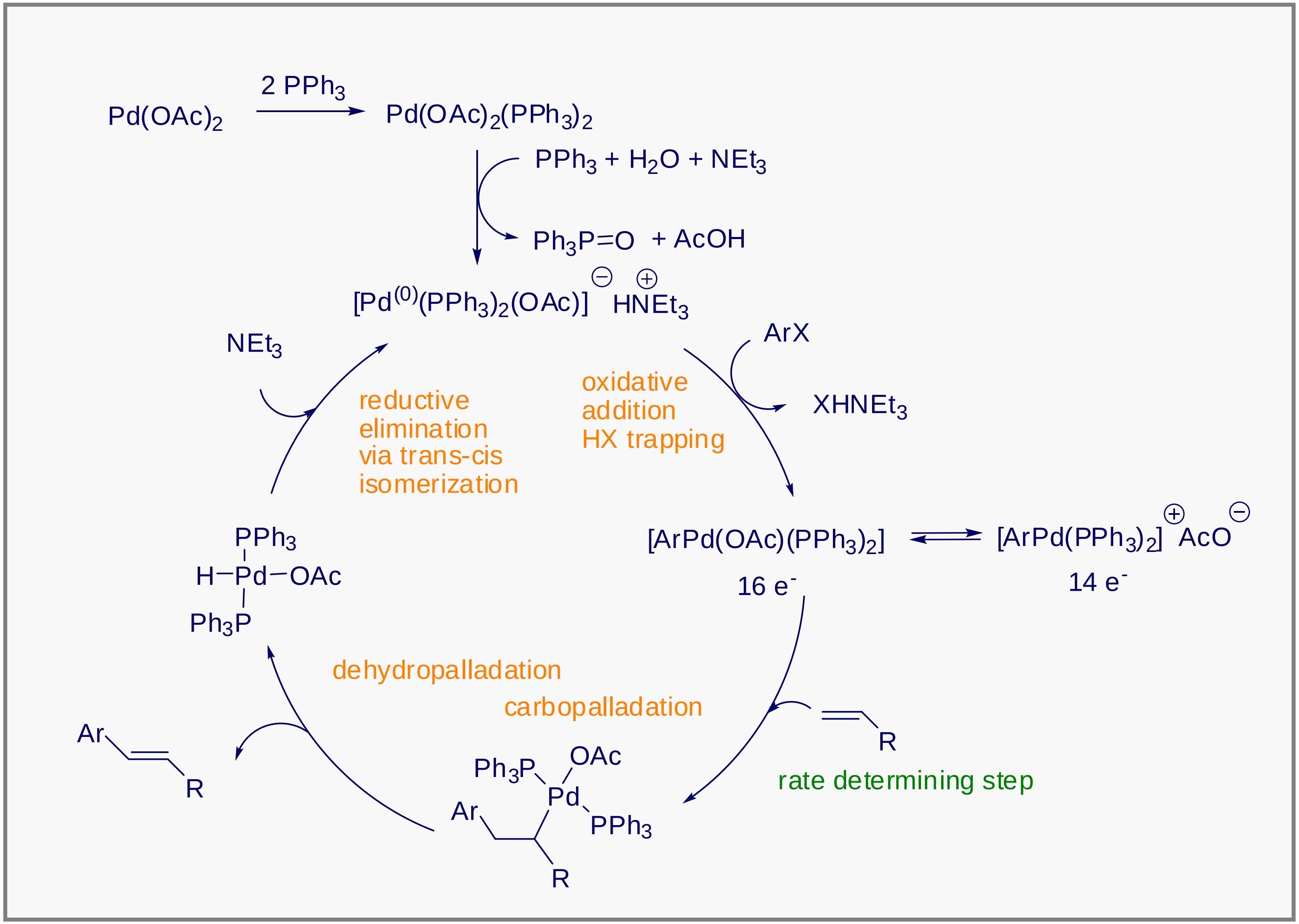
The Mizoroki-Heck Reaction



	aryl, vinyl, benzyl (no β- sp^3 H, otherwise: dehydropalladation !)
X:	N_2BF_4, COCl, I, OTf, Br, Cl
 :	an alkene (neutral, rich, or poor)
Pd cat:	a Pd(0) cat. or a Pd(II) cat. which is reduced in situ to Pd(0)
base:	usually: NEt_3, AcOK, Na_2CO_3...

Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.*, **2000**, 100, 3009; in *Transition Metal Catalyzed Reactions*, Eds Murahashi, S.-I. Davies, S. I. Blackwell Science, Oxford, 1999, p. 29;
Whitecomb, N. J.; Hii, K. K.; Gibson, S.E. *Tetrahedron*, **2001**, 57, 7449.
Martin Oestreich Ed. *The Mizoroki-Heck Reaction*, Wiley, **2009**

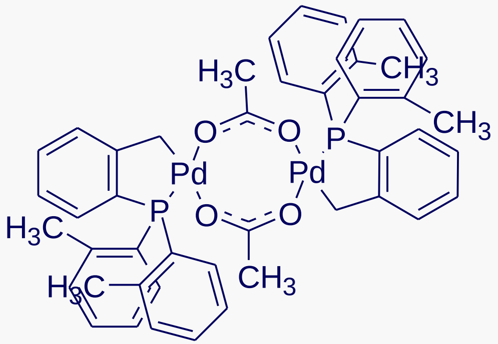
The Mechanism of the Mizoroki-Heck Reaction



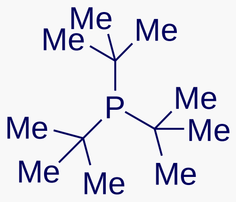
Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314

Choice of the Ancillary Ligand

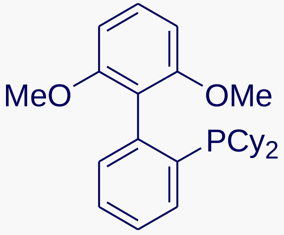
Some special ligands are more expensive than palladium !



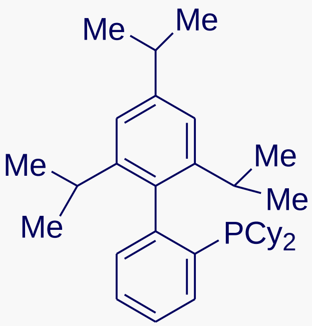
Herrmann's palladacycle



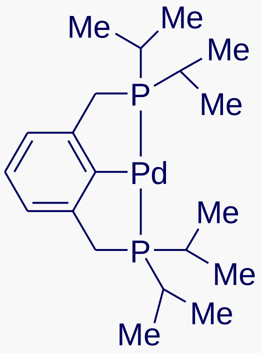
(Fu)



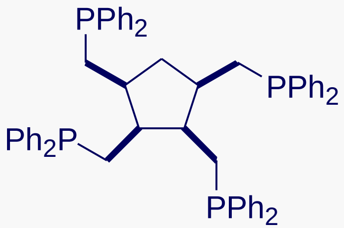
Sphos (Buchwald)



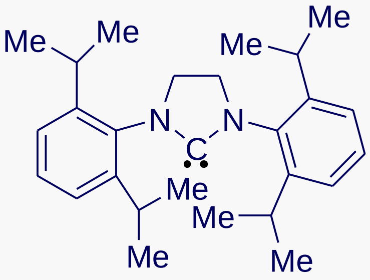
Xphos (Buchwald)



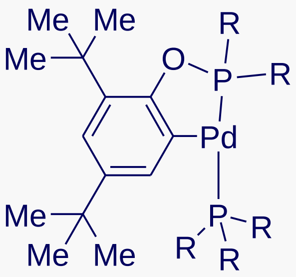
PCP Pincer
(Milstein)



Tedicyp
(Santelli, Parrain)



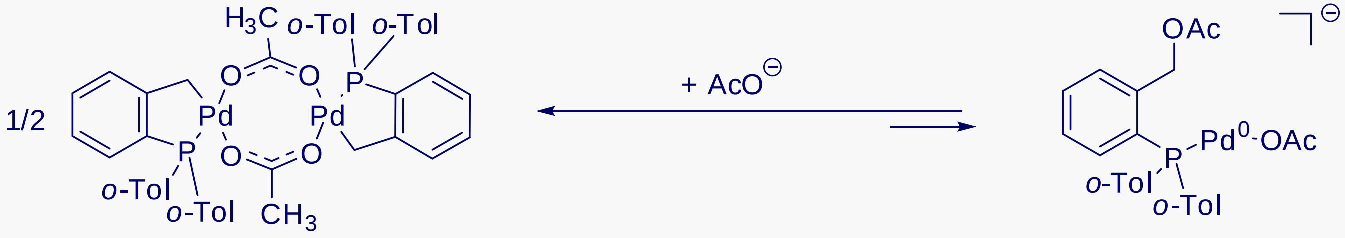
NHC IMes
(Nolan)



(Bedford)

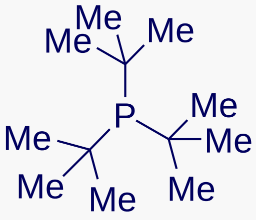
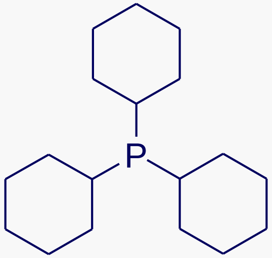
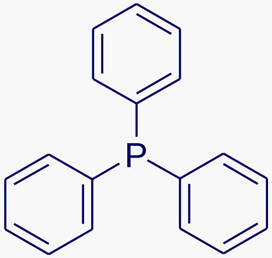
In difficult cases electron-rich and bulky phosphines perform better. Electron richness is expected to favor oxidative addition (with these phosphines the very difficult oxidative addition to aryl chlorides is possible). Bulkiness is expected to favor the reductive elimination (in the cross-coupling reactions). Very reactive iodides, diazonium salts and acyl chlorides can be used without ligands. N-heterocyclic carbenes are known to mimic phosphines. They are very good σ-donors.

Hermann Beller Catalyst



Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. Angew. Chem. Int. Ed. 1995, 34, 1848-1849.
d'Orlyé, F.; Jutand, A. *Tetrahedron* **2005**, *61*, 9670-9678.

Some Useful Corollary Information

	pKa	Cone angle
	11.4	182°
	9.7	170°
	2.7	145°

t-Bu$_3$P is malodorous and pyrophoric. However, it is possible to buy the corresponding tetrafluoborate salt ***t*-Bu$_3$P·HBF$_4$**, and generated the free phosphine *in situ* by addition of a Brønsted base.

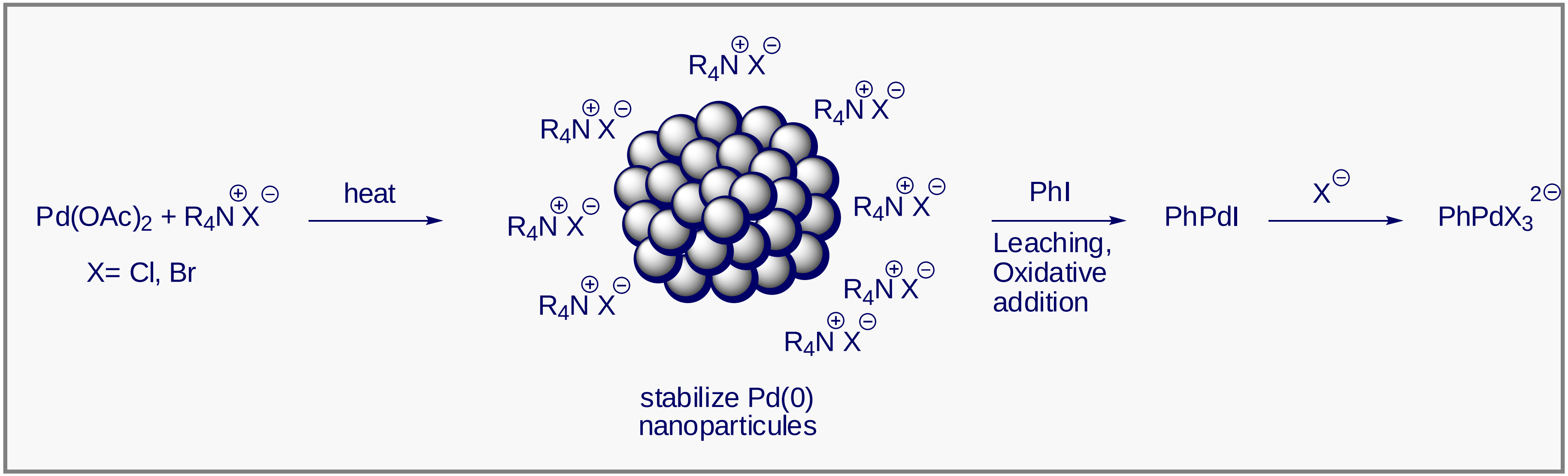
Reviews dealing with ligands in cross-couplings and Heck reactions:
a) Bedford, R. Coord Chem Rev. **2004**, *248*, 2283. b) Littke, A. E.; Fu, G. *Angew. Chem. Int. Ed.*, **2002**, *41*, 4176.

The Ligandless Conditions

Very reactive iodides, diazonium salts and acyl chlorides can be used without ligands.

The system $KHCO_3$ / Bu_4NCl in DMF without ligands is very effective. Under these conditions,[1] known as the Jeffery's ligandless conditions, $R_4N^+X^-$-stabilized Pd colloids are formed and function as active catalysts.[2]

1. Jeffery, T. *Tetrahedron*, **1996**, 52, 10113.
2. Reets, M. T., Westermann, E. *Angew. Chem. Int. Ed.* **2000**, *39*, 165.



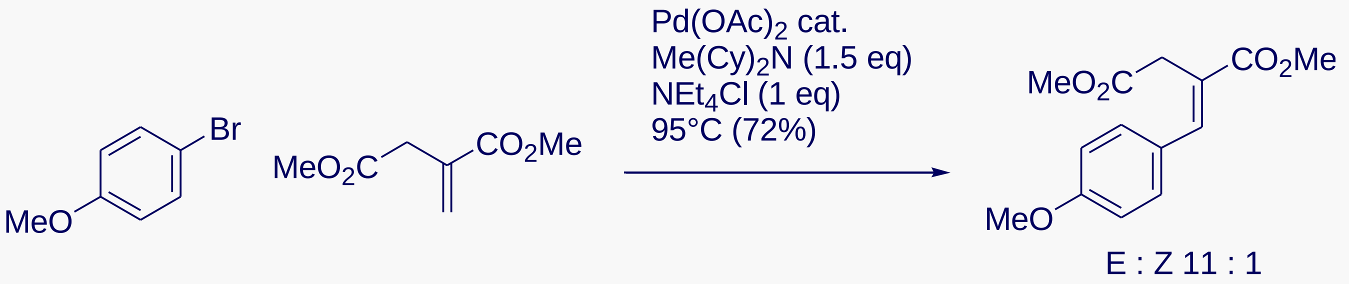
$Pd(OAc)_2 + R_4N^{\oplus}X^{\ominus} \xrightarrow{\text{heat}}$

X= Cl, Br

$\xrightarrow[\text{Leaching, Oxidative addition}]{PhI} PhPdI \xrightarrow{X^{\ominus}} PhPdX_3^{2\ominus}$

stabilize Pd(0) nanoparticules

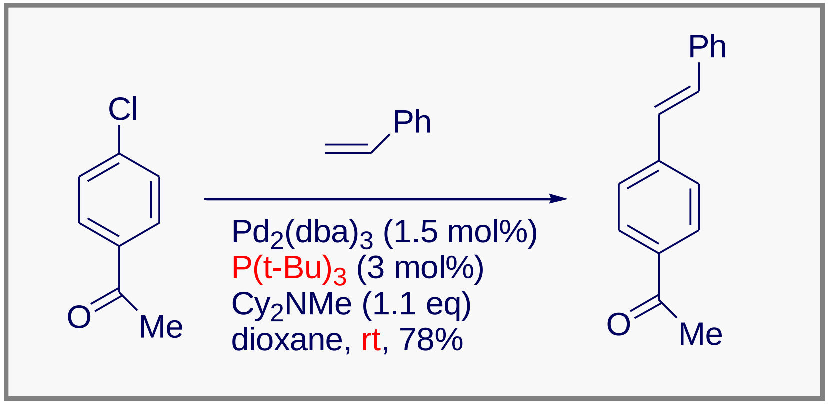
The Ligandless Conditions



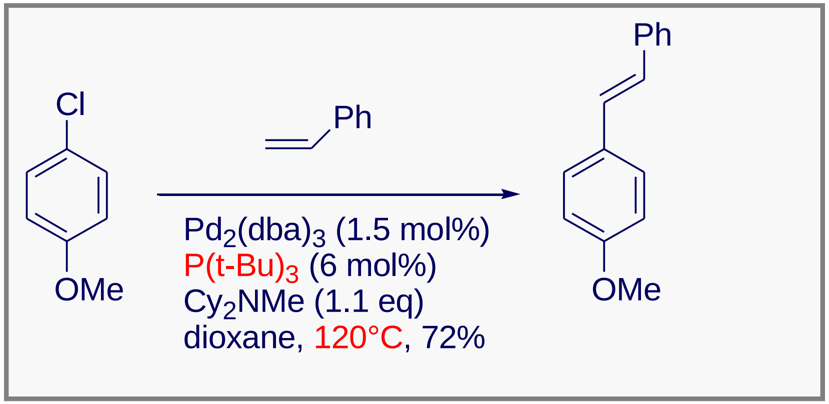
Gürtler, C.; Buchwald, S.L. *Chem. Eur.*, **1999**, *5*, 3107

Halides and Pseudohalides

Iodides react smoothly even in the absence of a ligand, and bromides in the presence or the absence of a phosphine ligand. Chlorides react only in the presence of bulky electron-rich phosphines.

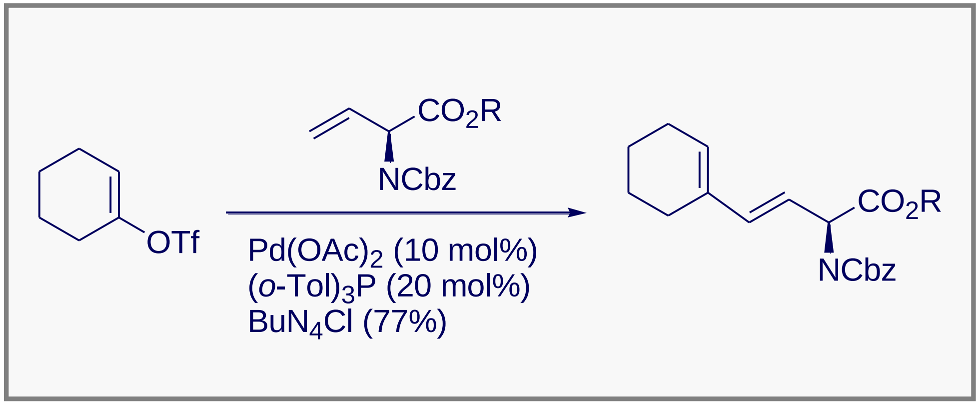


$Pd_2(dba)_3$ (1.5 mol%)
$P(t\text{-}Bu)_3$ (3 mol%)
Cy_2NMe (1.1 eq)
dioxane, rt, 78%



$Pd_2(dba)_3$ (1.5 mol%)
$P(t\text{-}Bu)_3$ (6 mol%)
Cy_2NMe (1.1 eq)
dioxane, 120°C, 72%

Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989



$Pd(OAc)_2$ (10 mol%)
(*o*-Tol)$_3$P (20 mol%)
BuN_4Cl (77%)

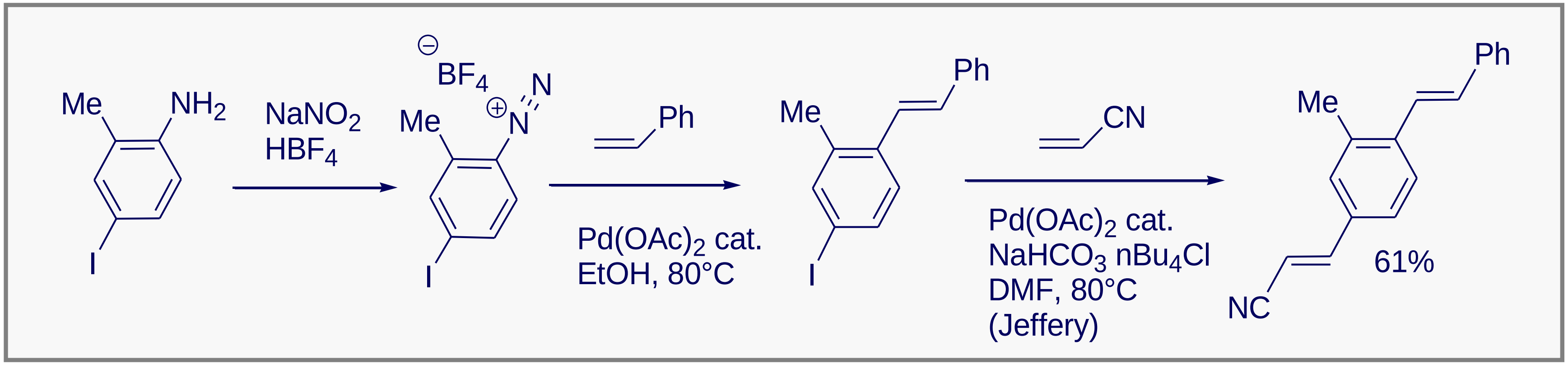
These reactions conditions do not racemize aminoacid derivatives.

Triflates are conveniently obtained from the corresponding ketones or phenols.

Crisp, G. T. *Tetrahedron,* **1992**, *48*, 3541

Halides and Pseudohalides

The diazonium salts are very conveniently obtained from the corresponding anilines (via diazotation), which in turn may derive from the nitro derivatives. The diazonium salts are the most reactive reaction partners. K. Kikukawa, T. Matsuda, Chem. Lett. 1977, 159 – 162; b) K. Kikukawa, K. Nagira, F. Wada, T. Matsuda, Tetrahedron 1981, 37, 31 – 36.

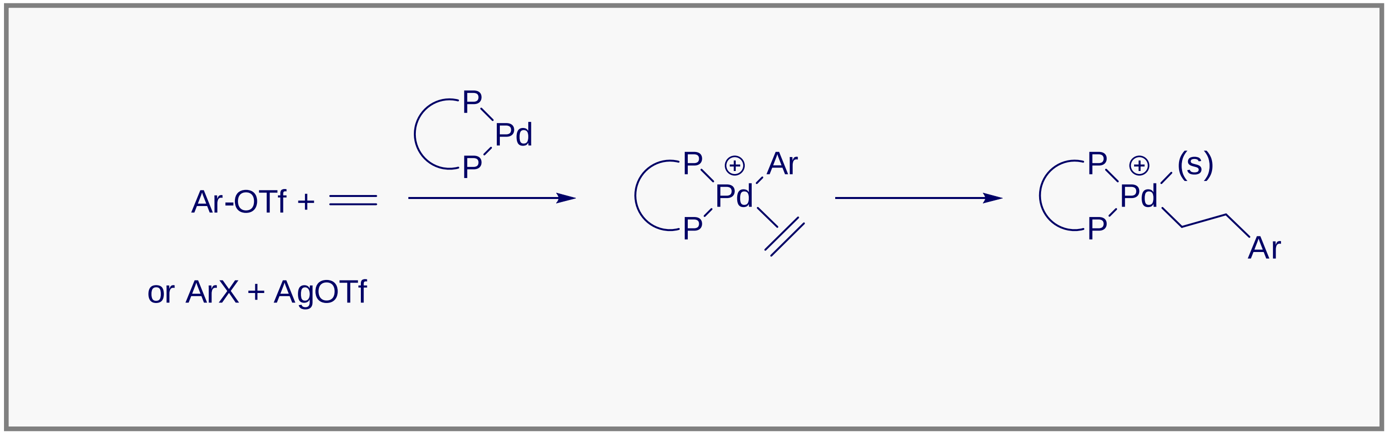


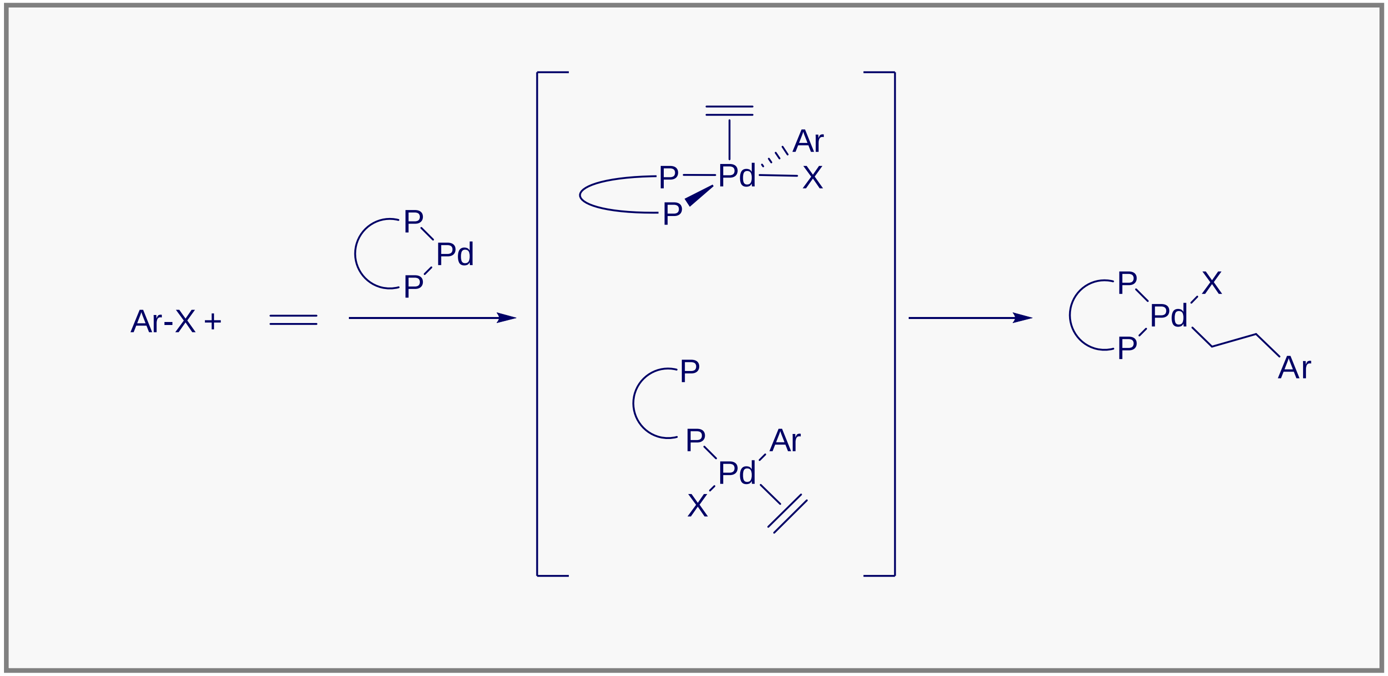
Sengupta, S.; Sadhukhan, S. K.; *Tetrahedron Lett.*, **1998**, *39*, 715

Order of reactivity in the oxidative addition: N_2 >> I >> OTf > Br >> Cl

Jutand, A.; Mosleh, A., *Organometallics*, **1995**, *14*, 1810.

Neutral *vs* Cationic Mechanism

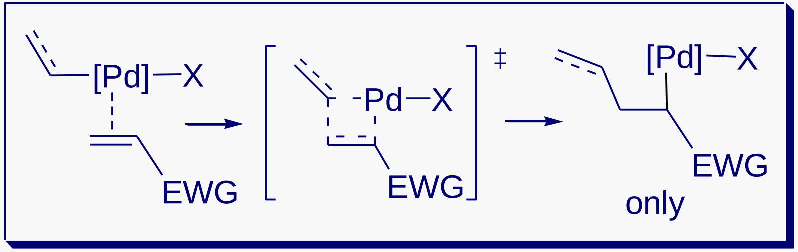




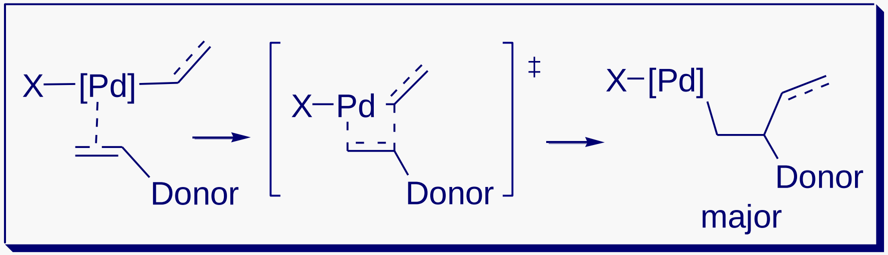
G. Poli G. Prestat

Regioselectivity of the Mizoroki-Heck

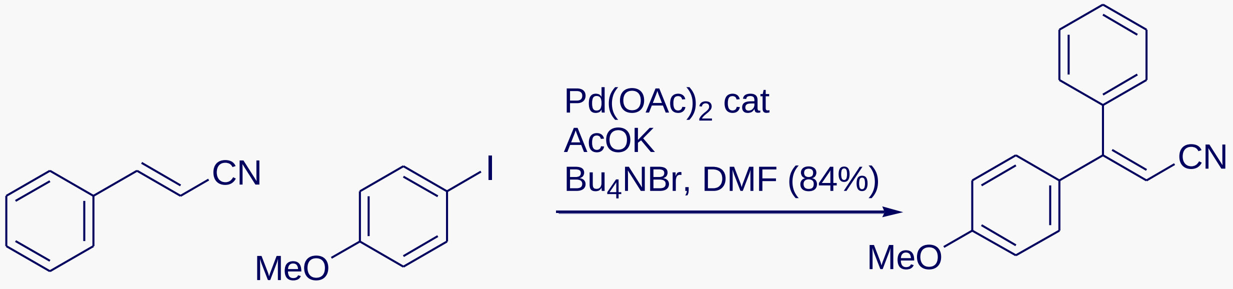
electron poor alkenes



electron rich alkenes

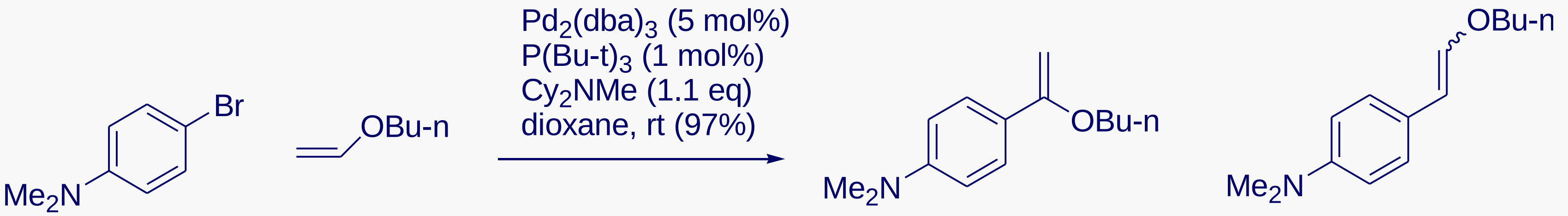


Pd goes to the more electron rich carbon



$Pd(OAc)_2$ cat
AcOK
Bu_4NBr, DMF (84%)

Masllorens, J.; Moreno-Manas, M.; Pla-Quintana, A.; Pleixats, R.; Roglans, A. *Synthesis,* **2002**, *48*, 1903



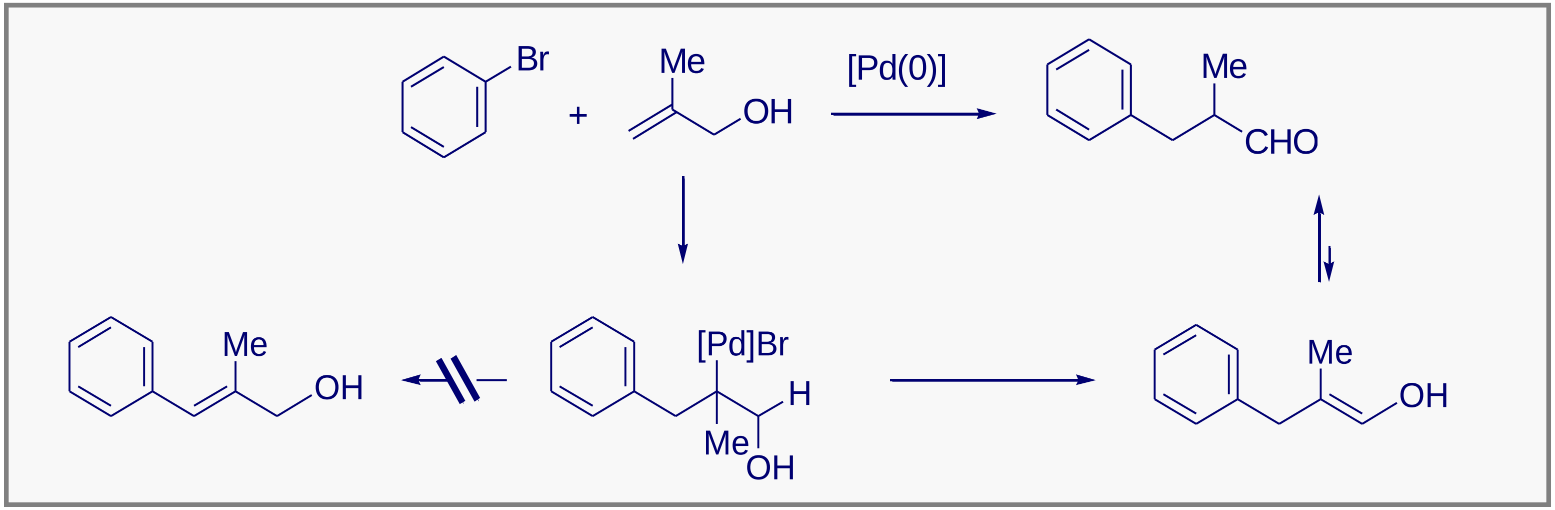
$Pd_2(dba)_3$ (5 mol%)
$P(Bu\text{-}t)_3$ (1 mol%)
Cy_2NMe (1.1 eq)
dioxane, rt (97%)

4 : 1 (E : Z 3 : 1)

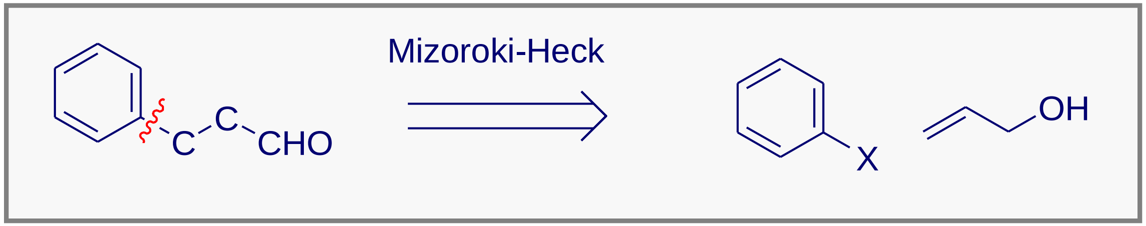
Littke, A. F.; Fu, G. *J. Am. Chem. Soc.*, **2001**, *123*, 6989
Cabri, W. *Acc. Chem. Res.* **1995**, 2-7

Allylic Alcohols as Alkenes

When allylic alcohols are used as alkenes dehydropalladation occurs from an oxygen-bearing carbon. As a result, carbonyl compounds are generated rather than β-arylated allylic alcohols.



Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265. Buntin, S. A.; Heck, R. F. *Org. Synth. Coll. Vol.* **1990**, *7*, 361.

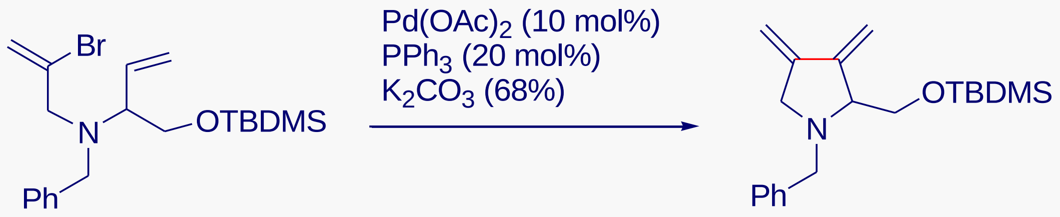


Thus, a dihydrocinnamaldehyde target can be retrosynthetically disconnected via a Mizoroki-Heck reaction.

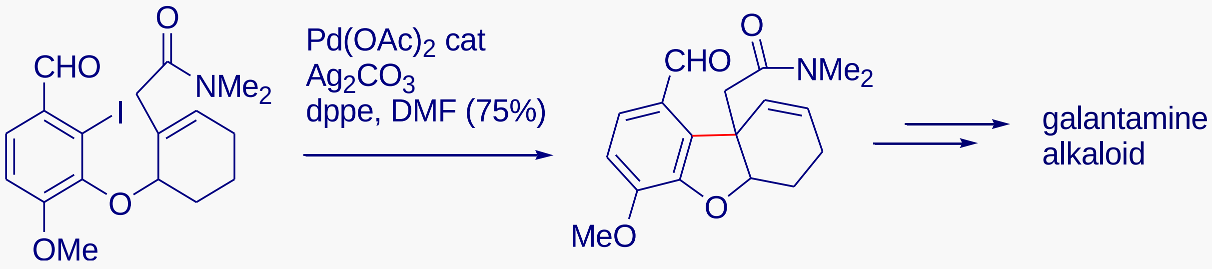
Intramolecular Mizoroki-Heck Reactions

Formation of 5 and 6-Membered Rings

The 5-exo and 6-exo intramolecular variation has been extensively applied in synthesis



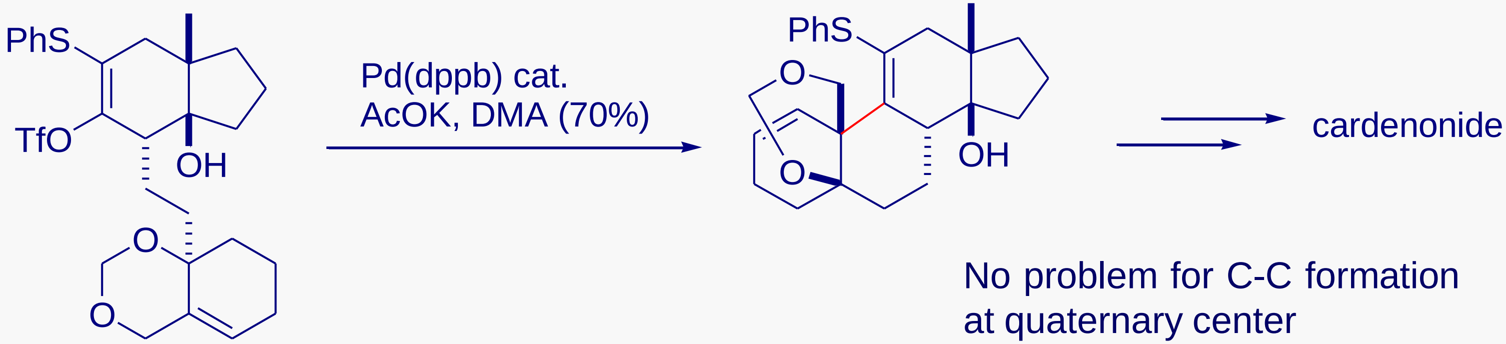
Huwe, C. M.; Blechert, S. *Tetrahedron Lett.*, **1994**, *35*, 9537



Pilger, G. et al. *Synlett*, **2000**, 1163
Parsons, P. J. et al. *Tetrahedron Lett.*, **2001**, *42*, 2209

No problem for C-C formation at quaternary center

Formation of 6-Membered Rings

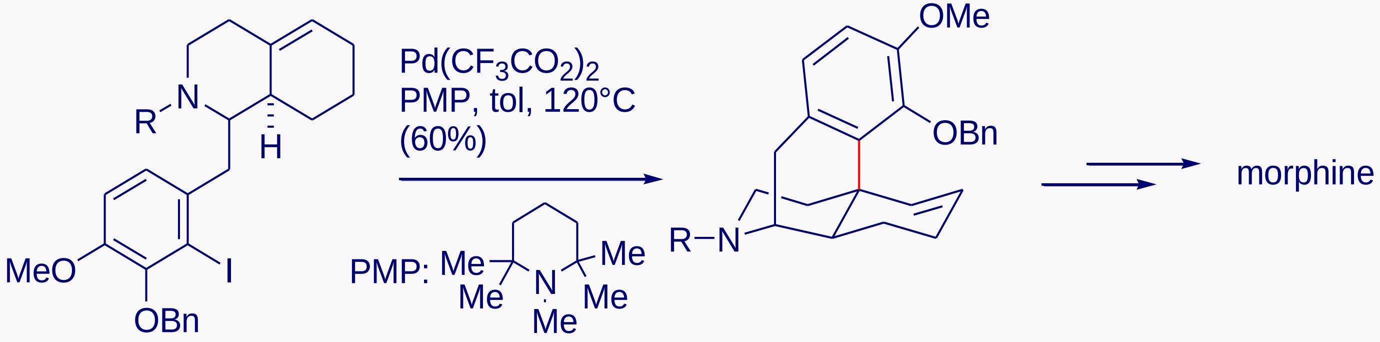


Pd(dppb) cat.
AcOK, DMA (70%)

cardenonide

No problem for C-C formation at quaternary center

Hines, J. Jr; Overman, L. E. Nasser, T.; Rucker, P. V. *Tetrahedron Lett.*, **1998**, *39*, 4647



$Pd(CF_3CO_2)_2$
PMP, tol, 120°C
(60%)

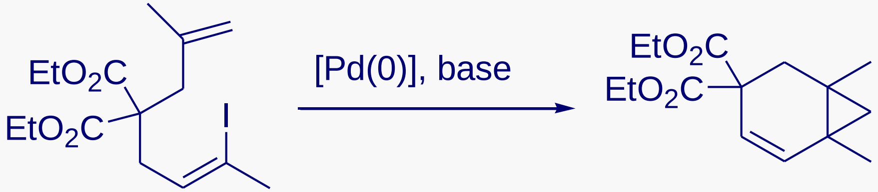
PMP:

morphine

Overman, L. E. et al. *J. Am. Chem. Soc.* **1993**, *115*, 11028

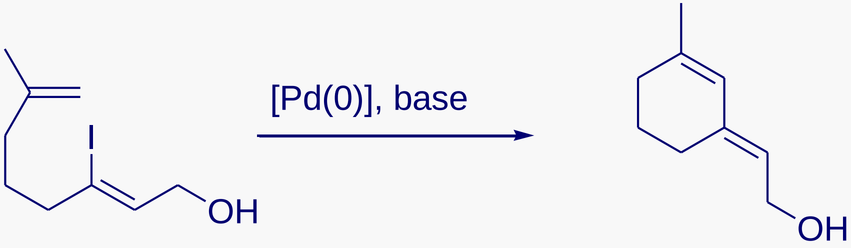
Halo-1,6-Dienes

Type I substrates: 1-halo-1,6-dienes



6-exo cyclization

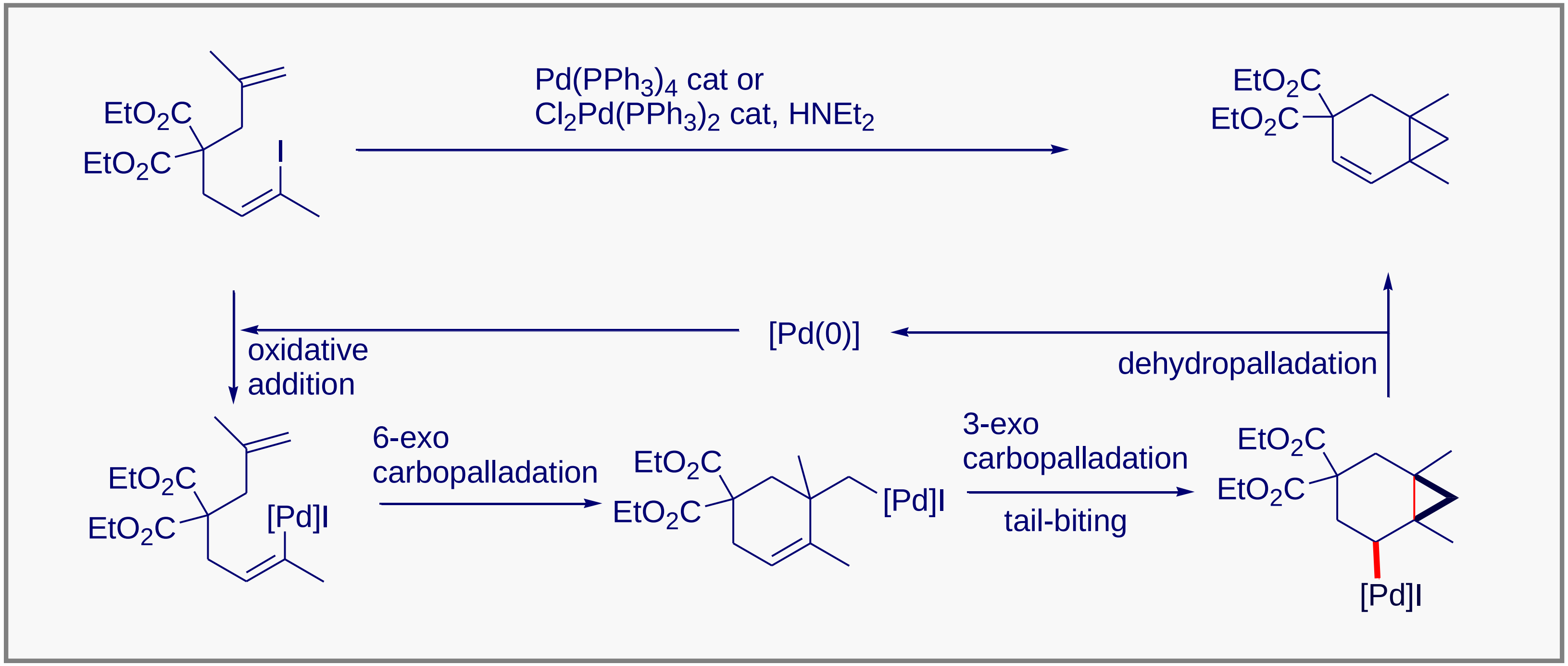
Type II substrates: 2-halo-1,6-dienes



apparent 6-endo cyclization

Owczarczyk, Z.; Lamaty, F.; Vawter, E. J. Negishi, E.-I. *J. Am. Chem. Soc.* **1992**, *114*, 10091

1-Halo-1,6-Dienes



Pd(PPh$_3$)$_4$ cat or
Cl$_2$Pd(PPh$_3$)$_2$ cat, HNEt$_2$

[Pd(0)]

oxidative
addition

dehydropalladation

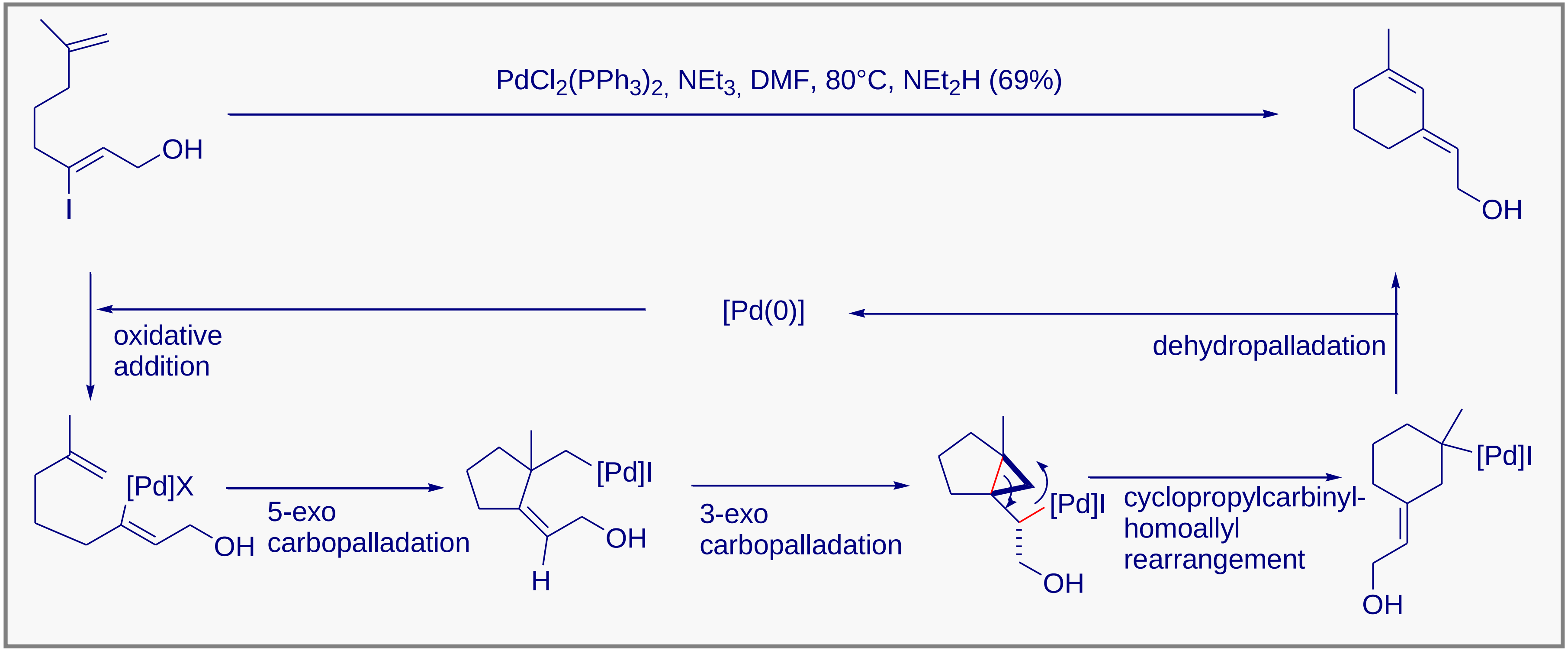
6-exo
carbopalladation

3-exo
carbopalladation

tail-biting

2-Halo-1,6-Dienes

Apparent 6-exo cyclization

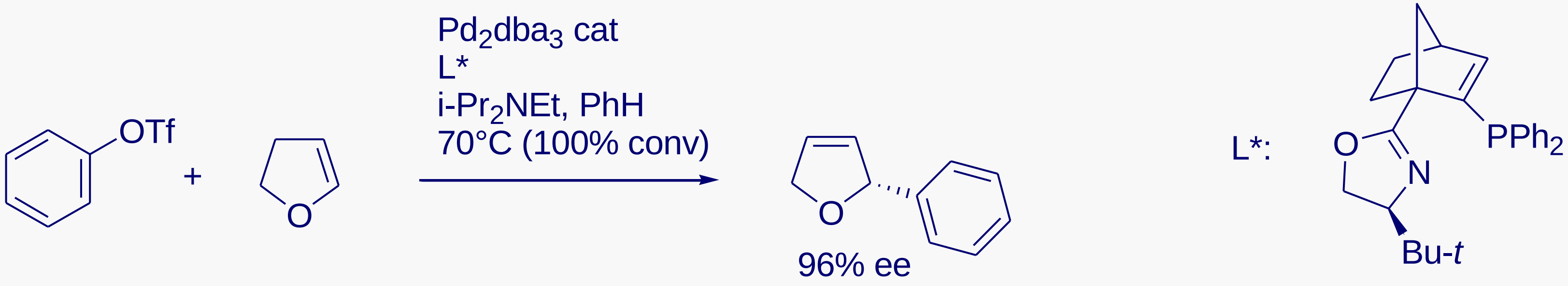


Owing to its mechanism the cyclopropylcarbinyl-to-homoallyl rearrangement can take place only if the two red bonds (C-C and C-Pd) can become syncoplanar. It can be understood as an unusually facile retro-carbopalladation. Notice that the double bond configuration of the final product is reversed with respect to that of the starting material.

Asymmetric Mizoroki-Heck Reactions

Intermolecular Asymmetric Reactions

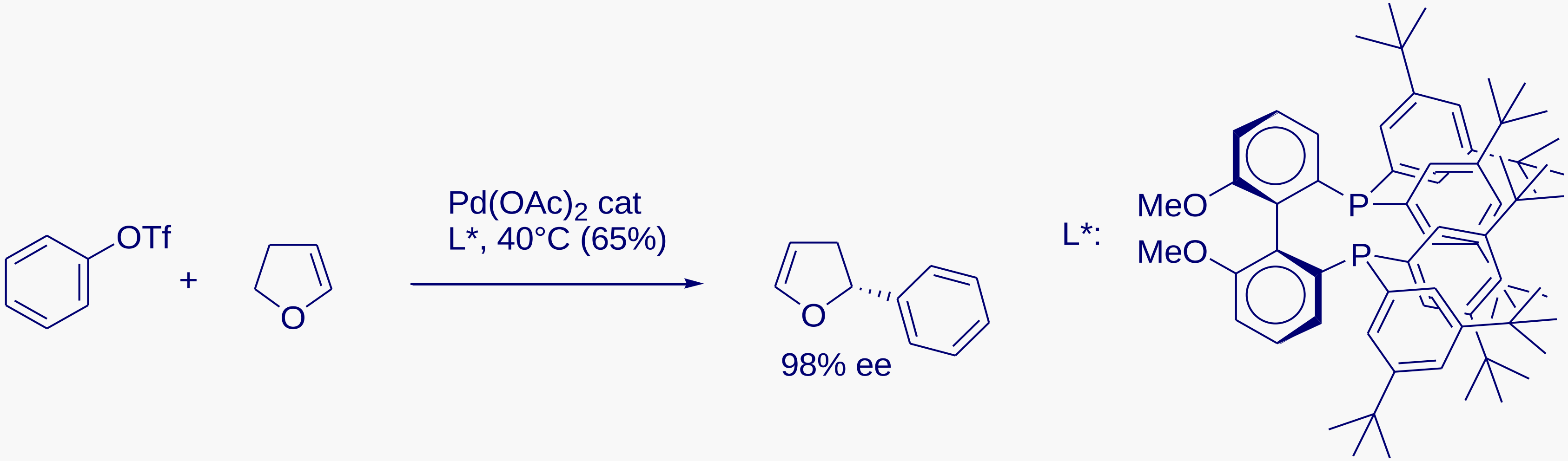
The non-coordinating triflate anion is crucial



Pd_2dba_3 cat
L*
i-Pr_2NEt, PhH
70°C (100% conv)

96% ee

Gilbertson, S. R.; Fu, Z. *Org. Lett*, **2001**, *3*, 161

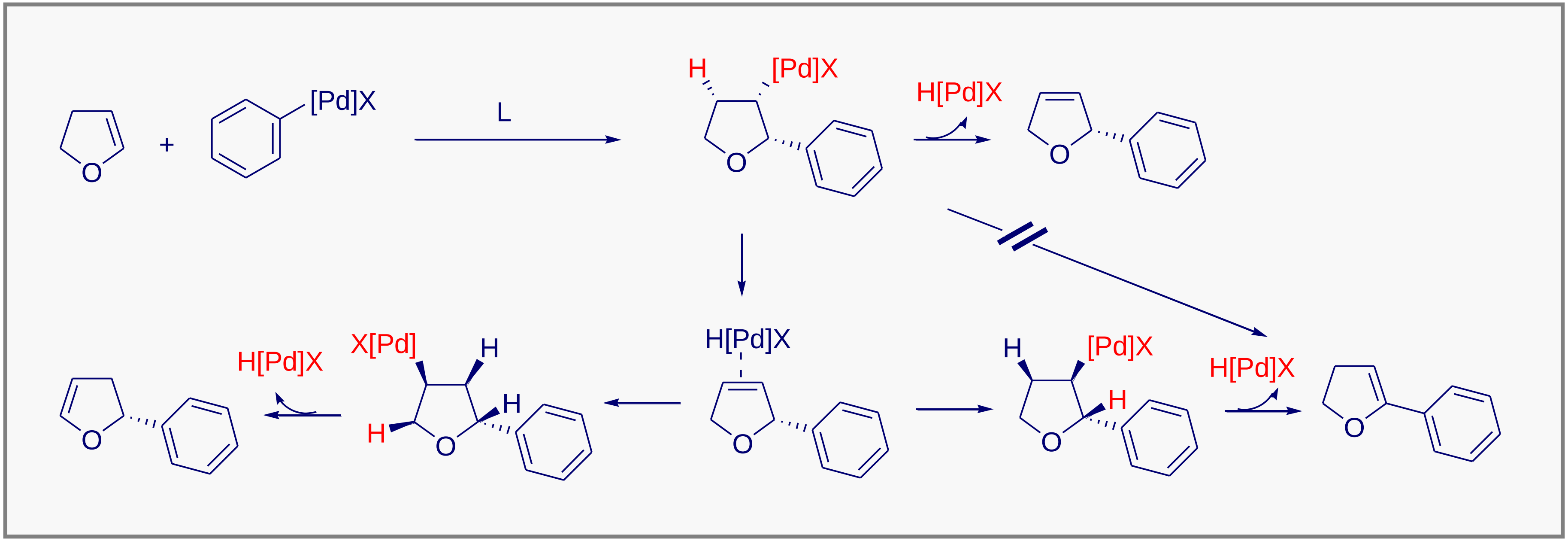


$Pd(OAc)_2$ cat
L*, 40°C (65%)

98% ee

Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315

Intermolecular Asymmetric Reactions

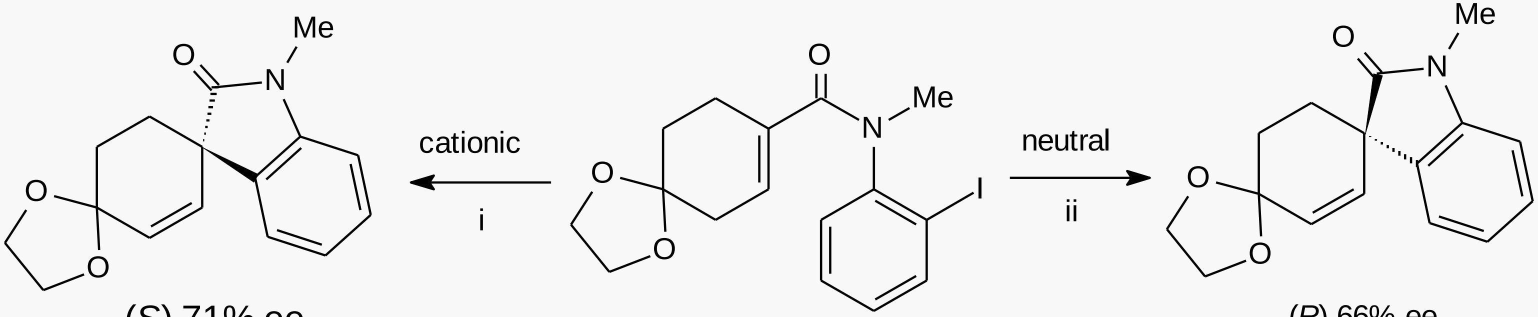


The selectivity of this reaction is highly dependent on the nature of the (pseudo)halide and of the ligand.

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

Intramolecular Asymmetric Reactions

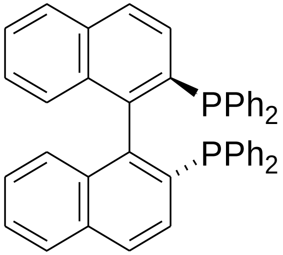
The importance of non-coordinating anions



(*S*) 71% ee

(*R*) 66% ee

i: $Pd_2(dba)_3$ 5%; (*R*)-BINAP 11%; DMA; Ag_3PO_4, 80°C, (81%)
ii: $Pd_2(dba)_3$ 5%, (*R*)-BINAP 11%, DMA; PMP, 110°C (71%)

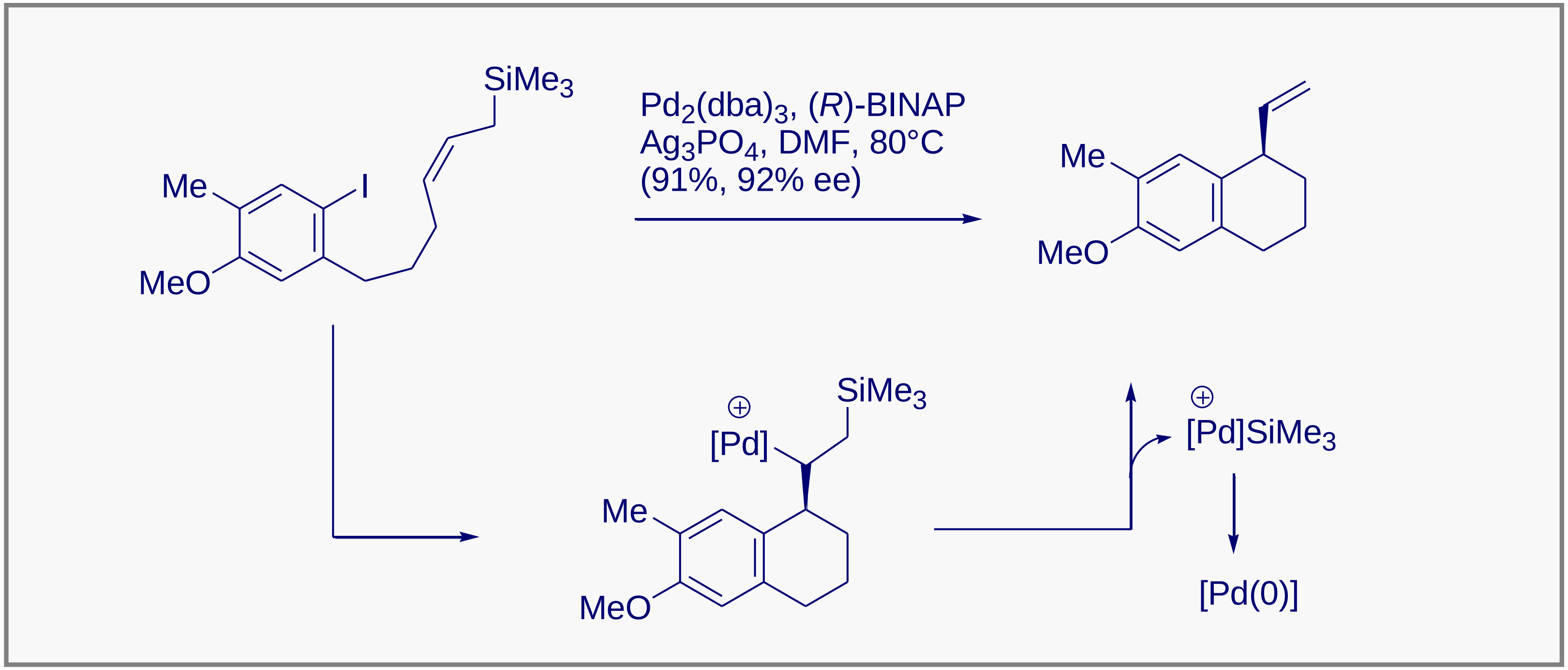


(*R*)-BINAP

Overman, L. E.; Poon, D. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 518

Intramolecular Asymmetric Reactions

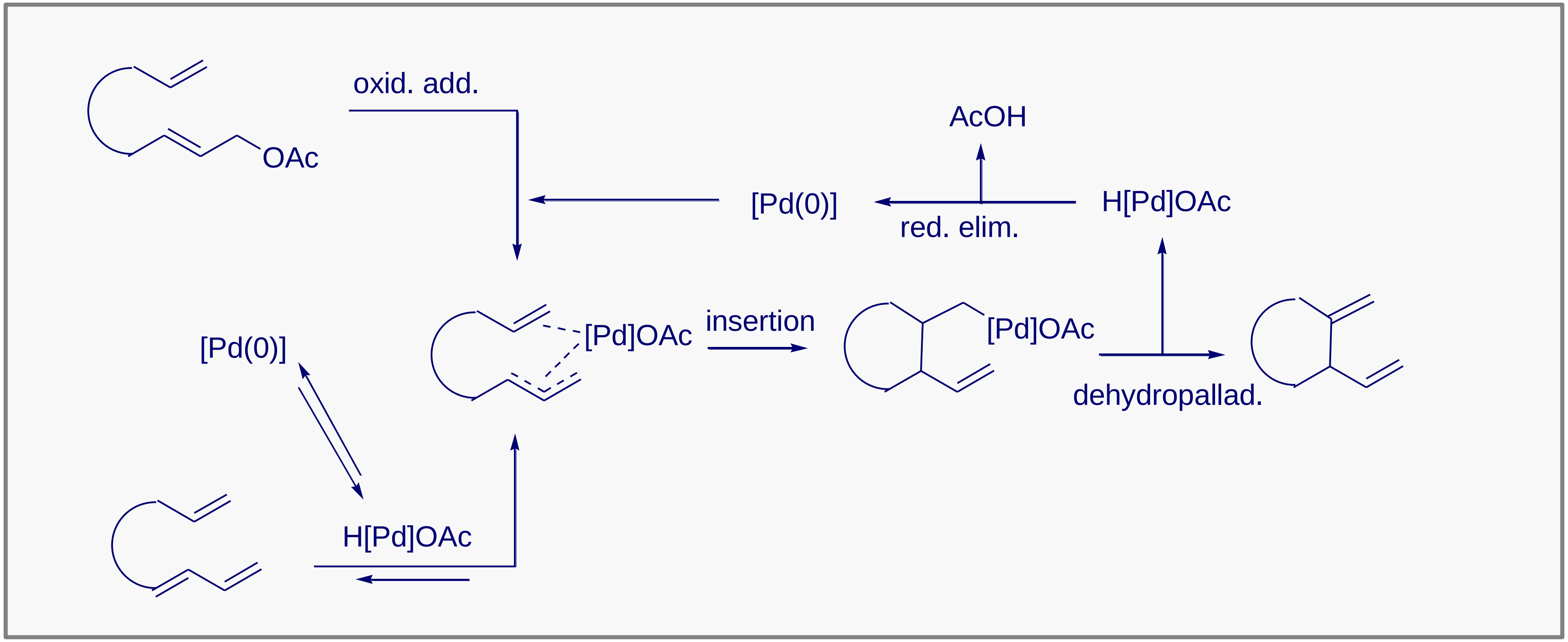
The presence of the silicon atom in the precursor directs the dehydropalladation thereby avoiding β-H elimination from the undesired side.

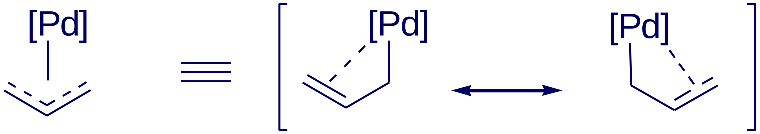


Tietze, L. F.; Schimpf, R. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1089

Related Process Involving Carbopalladations

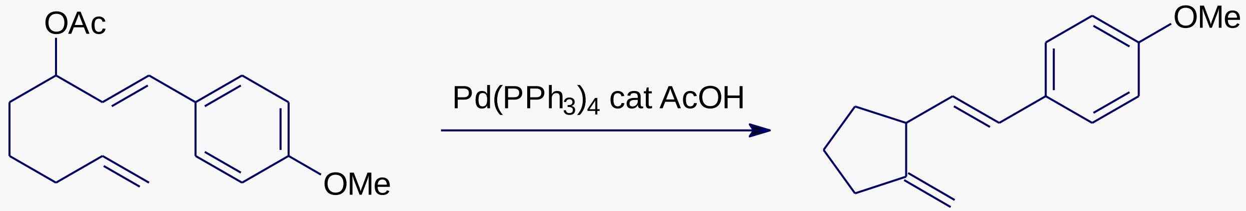
Palladium-ene Cyclizations

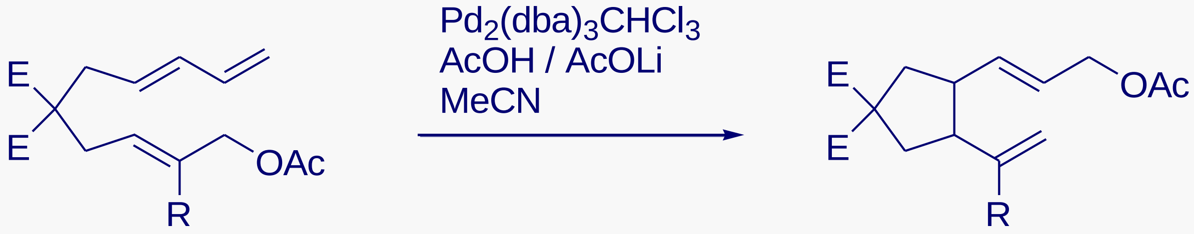




Oppolzer, W. In *Comprehensive Organometallic Chemistry II*, Vol. 12, Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds. Pergamon, Oxford, 1995, p. 905.

Palladium-ene Cyclizations

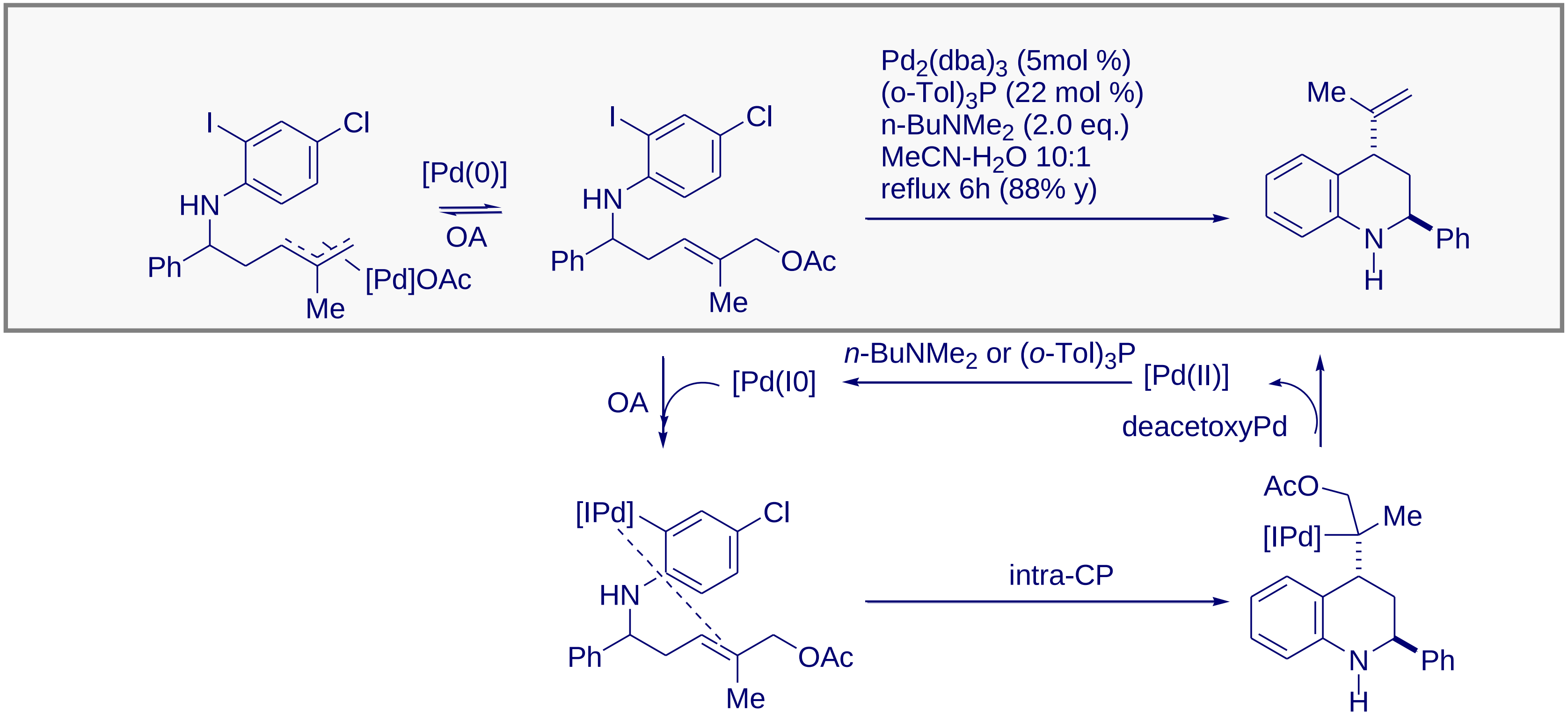




Oppolzer, W.; Swenson, R. E.; Pachinger, W. *Helv. Chim. Acta,* **1989**, *72*, 14
Trost, B. M.; Luengo, J.I. *J. Am. Chem. Soc.* **1988**, *110*, 8239

Reversible *vs* Irreversible Oxidative Addition

oxidative addition / carbopalladation / deacetoxypalladation / Pd(II) reduction

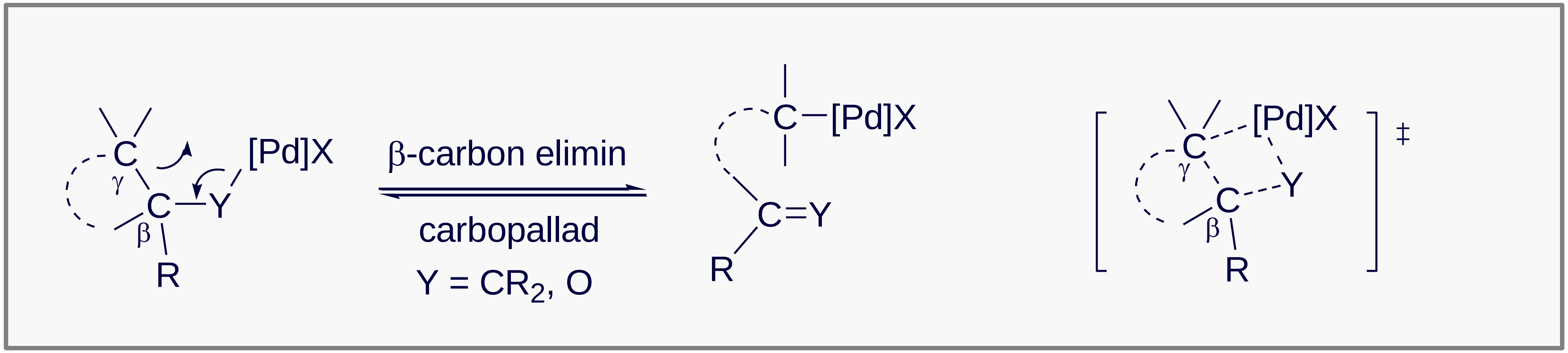


$Pd_2(dba)_3$ (5mol %)
$(o\text{-}Tol)_3P$ (22 mol %)
$n\text{-}BuNMe_2$ (2.0 eq.)
$MeCN\text{-}H_2O$ 10:1
reflux 6h (88% y)

Lautens, M.; Tayama, E.; Herse, C. *JACS,* **2005**, *127*, 72-73
See also: Sinou et al. *Eur. J. Org. Chem.* **2000**, 4071

Pd Catalyzed C-C Cleavage

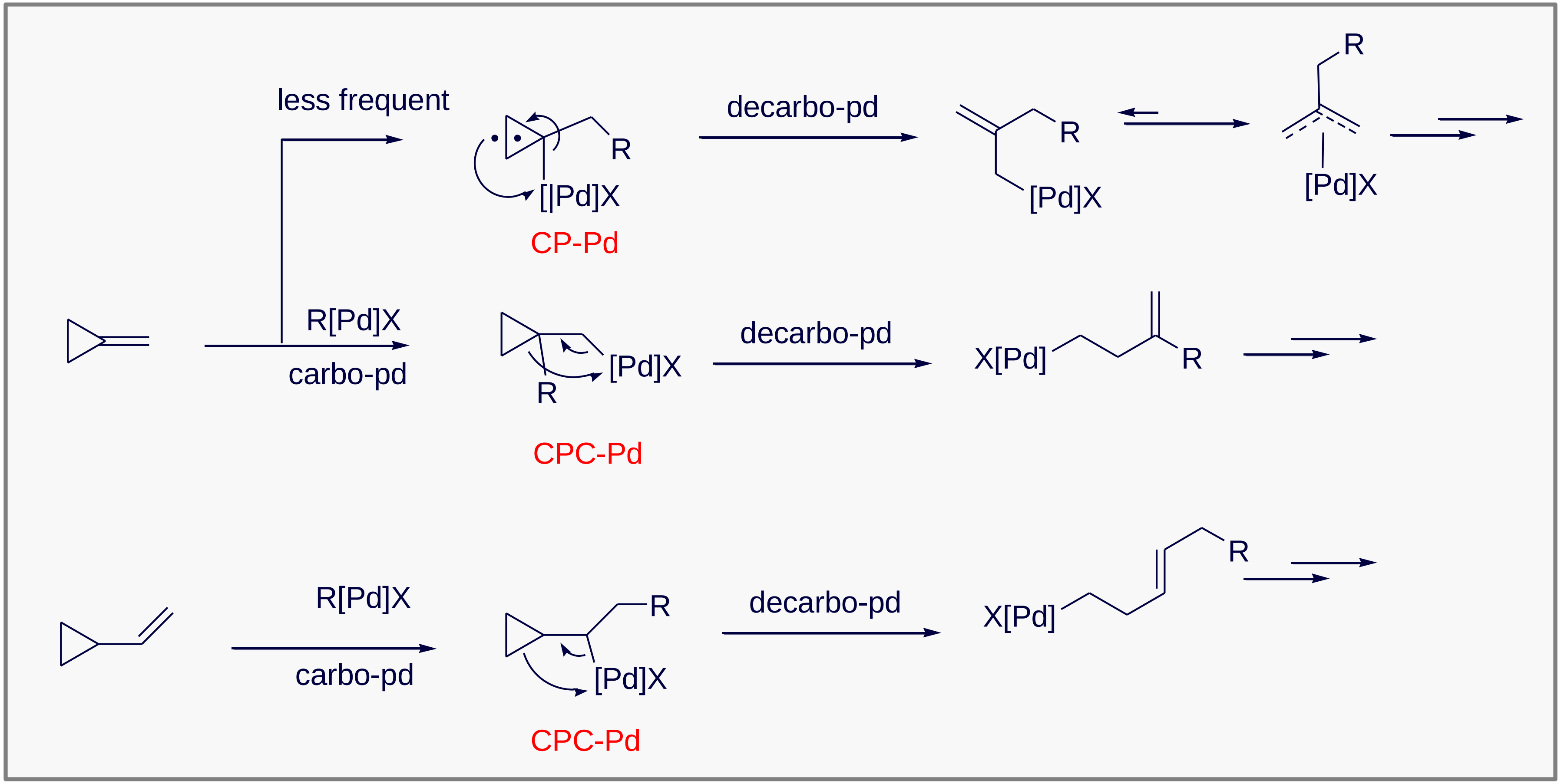
β- Carbon Elimination



Pd β- Carbon elimination is the microscopic reverse reaction of carbopalladation. Although carbopalladation is usually the thermodynamically favored step, some particular cases (*i.e.* strain release and the impossibility of dehydropalladation) may drive the equilibrium in favor of Pd β- Carbon elimination.

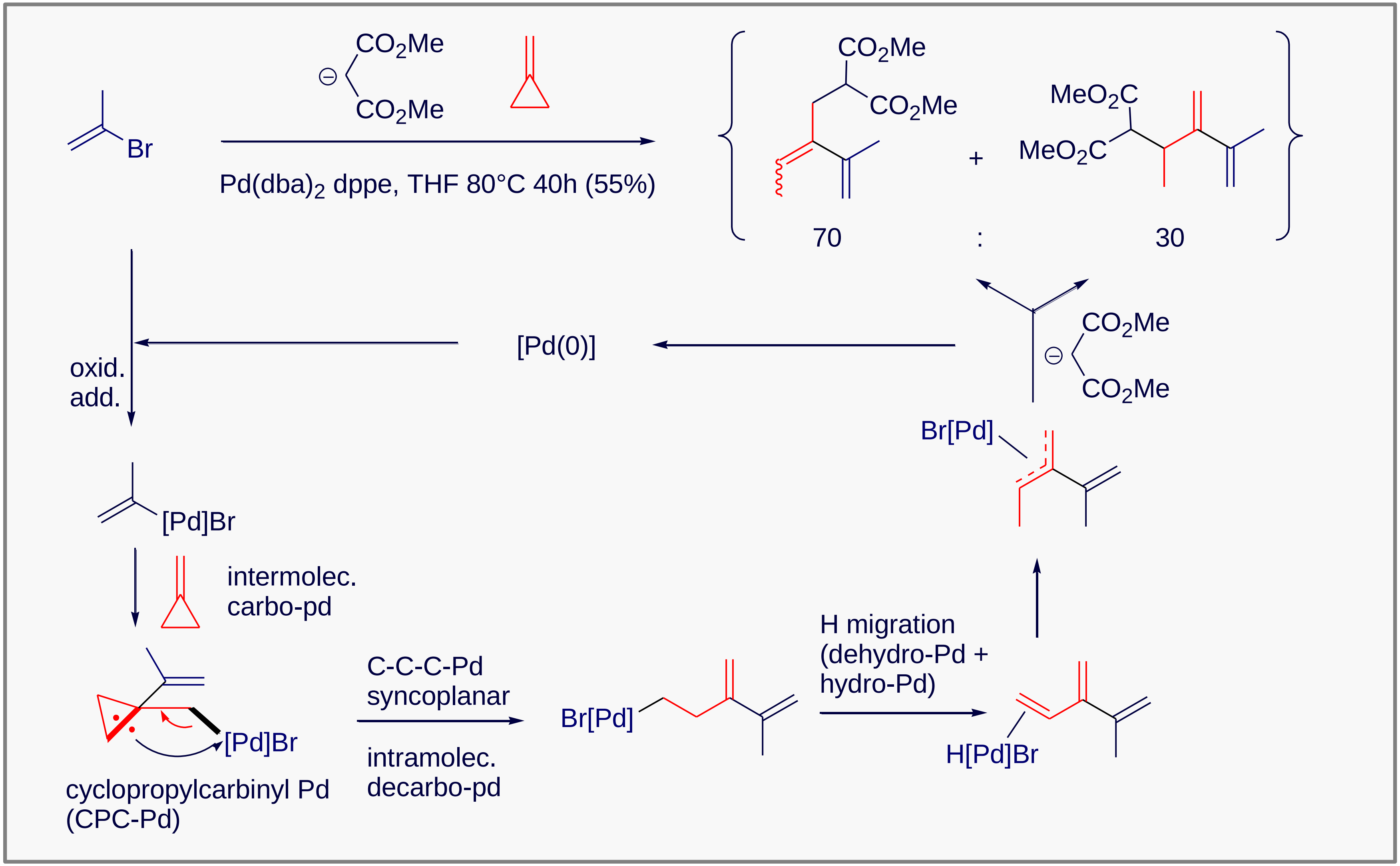
Cleavage of CPC-Pd and CP-Pd

The different modes



CPC-Pd : cyclopropylcarbinylpalladium
CP-Pd : cyclopropylpalladium

From Methylenecyclopropane



CO_2Me ⊖ CO_2Me

Pd(dba)$_2$ dppe, THF 80°C 40h (55%)

70 : 30

[Pd(0)]

oxid. add.

[Pd]Br

intermolec. carbo-pd

cyclopropylcarbinyl Pd (CPC-Pd)

C-C-C-Pd syncoplanar

intramolec. decarbo-pd

Br[Pd]

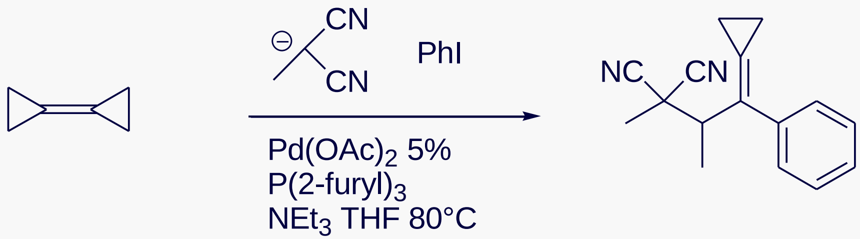
H migration (dehydro-Pd + hydro-Pd)

H[Pd]Br

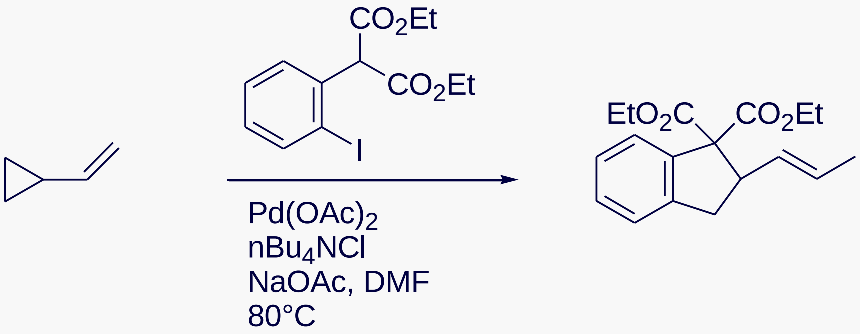
Fournet, G.; Balme, G.; Goré, J. *Tetrahedron*, **1988**, *44*, 5809

Exercices

Propose a plausible mechanism for the following reactions

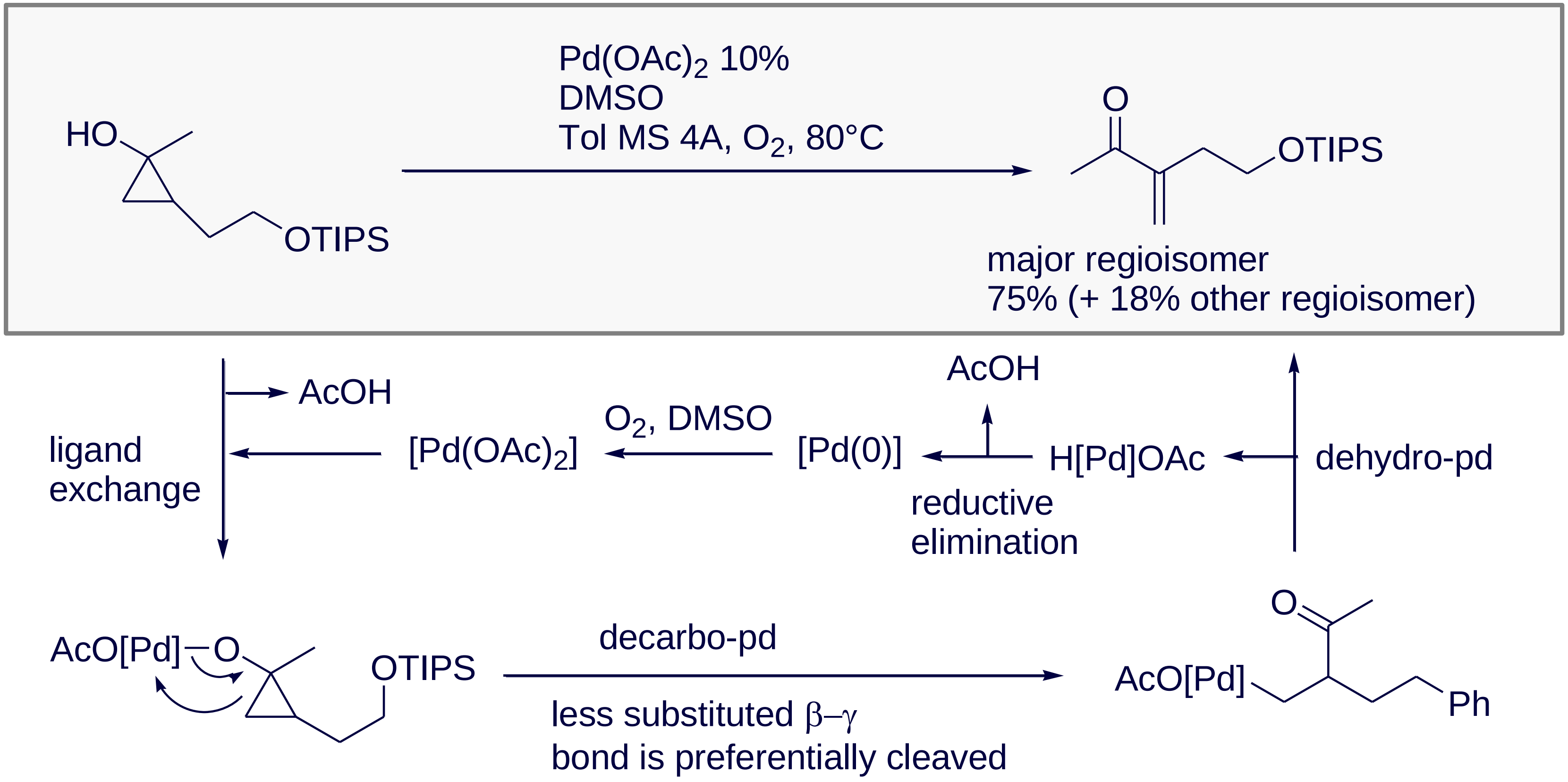


Nuske, H.; Noltemeyer, M.; de Meijere, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3411
de Meijere, A.; Brase, S. *J. Organomet. Chem.* **1999**, *576*, 88.



Larock, R.C.; Yum, E. K. *Tetrahedron*, **1996**, *52*, 2743

From Tertiary Cyclopropanols [Pd(II)]



$Pd(OAc)_2$ 10%
DMSO
Tol MS 4A, O_2, 80°C

major regioisomer
75% (+ 18% other regioisomer)

AcOH

ligand exchange

$[Pd(OAc)_2]$

O_2, DMSO

[Pd(0)]

AcOH

reductive elimination

H[Pd]OAc

dehydro-pd

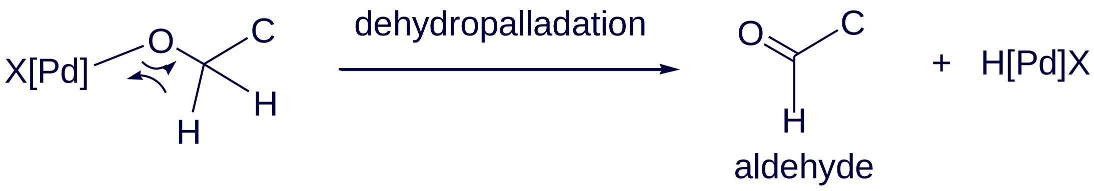
decarbo-pd

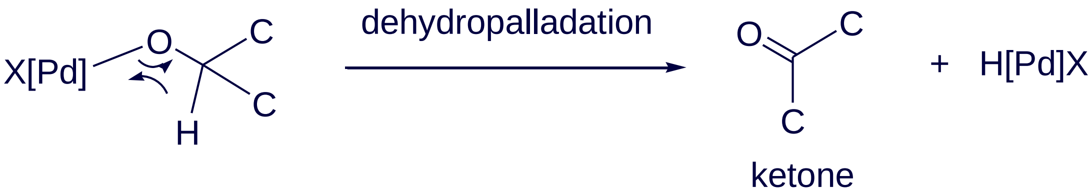
less substituted β–γ bond is preferentially cleaved

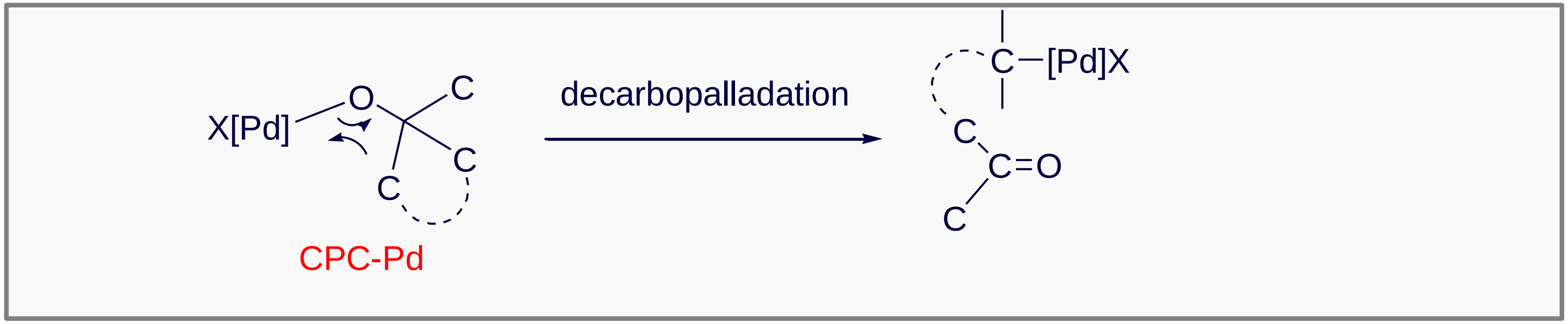
CPC-Pd

Park, S-.B.; Cha, J. K.; *Org. Lett.* **2000**, 2, 147

Dehydropalladation *versus* Decarbopalladation

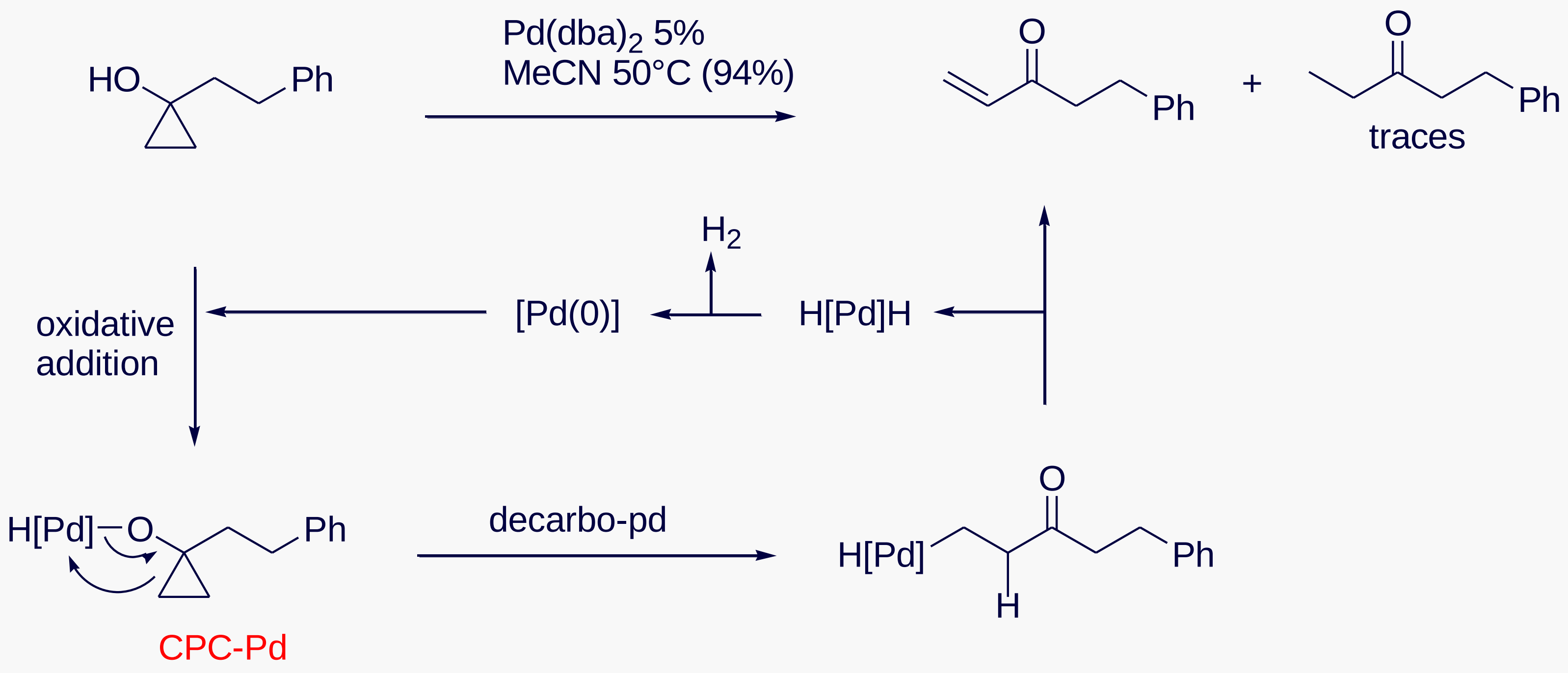






To obtain decarbopalladation, competitive dehydropalladation must be forbidden in the substrate (tertiary substituent) and strain release must operate. Indeed, dehydropalladation of oxypalladium intermediates is a key step in Pd-mediated oxidations.

From Tertiary Cyclopropanols [Pd(0)]



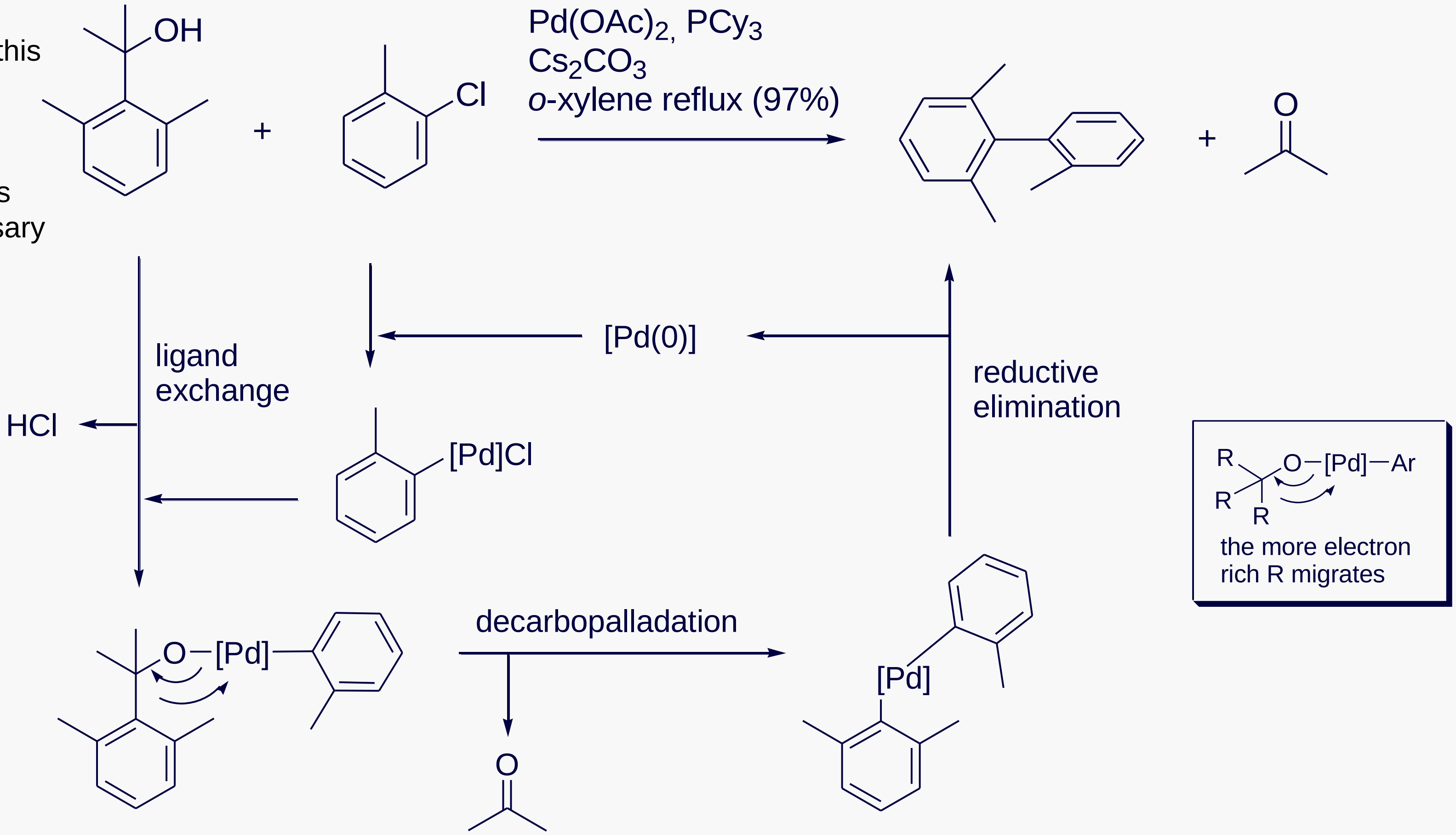
Okumoto, H.; Jinnai, T.; Shimizu, H.; Harasa, Y.; Mishima, H.; Suzuki, A. *Synlett*, **2000**, 629

G. Poli G. Prestat

Arylative Fragmentation α,α -Disubstituted Arylmethanols

No strain release in this case

Bulky phosphines are necessary



$Pd(OAc)_2$, PCy_3
Cs_2CO_3
o-xylene reflux (97%)

[Pd(0)]

ligand exchange

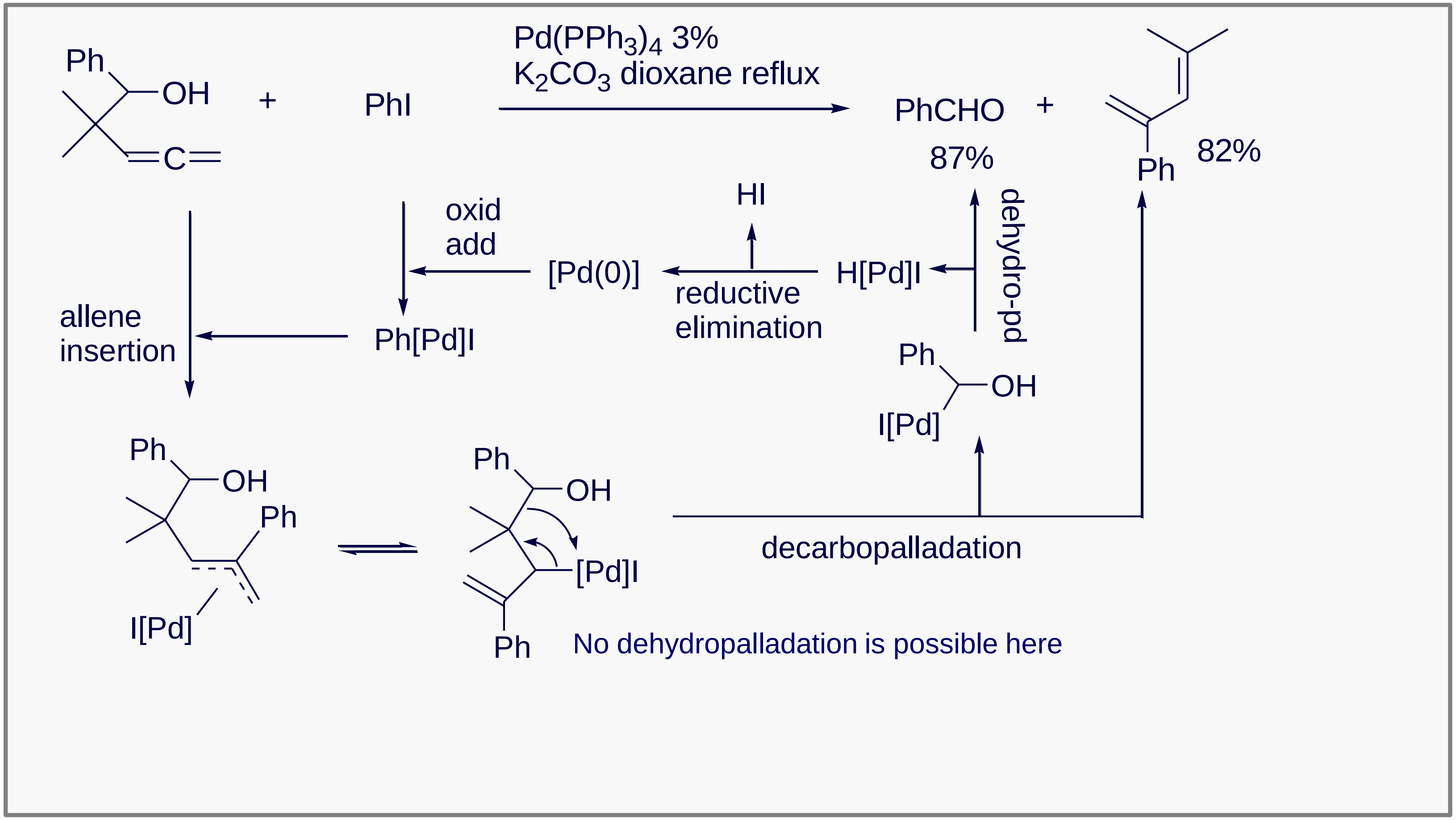
reductive elimination

decarbopalladation

the more electron rich R migrates

Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M.; *J. Am. Chem. Soc.* **2001**, *123*, 10407
Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, *J. Org. Chem.* **2003**, 68, 5236

Arylative Fragmentation of 2,2-Disubstituted 3-Allen-1-ols



No dehydropalladation is possible here

Oh, C. H.; Jung, S. H.; Bang, S. Y.; Park, D. I. *Org. Lett.* **2002**, *4*, 3325