Directed (Chelated) Catalytic C-H Functionalization with Pd(ii)/Pd(iv) manifold

~ based on Melanie S. Sanford's chemistry ~

Pd catalyzed reaction is one of the most important transformation in organic chemistry.
There are many types of Pd catalyzed reactions such as cross-coupling (Stille, Sonogashira, Suzuki-Miyaura, Negishi, Heck etc.), allylation, oxidation (Wacker) or reduction.

In these cases, we (I) usually think **Pd(0)/Pd(ii)** manifold.

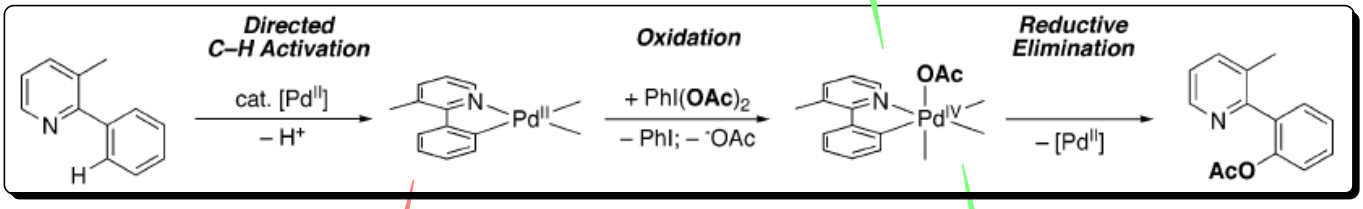
Recently, in the field of catalytic C-H activation, **Pd(ii)/Pd(iv)** cycle becomes to be realized using **some strong terminal oxidant** such as $PhI(OAc)_2$.
Today I will summarize and talk about this trend.

A. J. Canty. *Acc. Chem. Res.* ***1992***, *83.*

(Review(with I^{iii}) : *Inorg. Chem*. **2007**, 46, 1924.)

~ main stream of her Chemistry ~

Pd(iv) complex is not so rare in organometalic field.
(Pd(ii) + MeI etc)



known as Palladacycle
catalytic application is recent trend

assumed more reactive toward r.e. than Pd(ii) complex
C-X (X = O, Cl, Br, **F) forming reductive elim.** can occurr

C-O r.e. from Pd(ii) is rare until 1990's (and still problematic)
J. F. Hartwig. *Acc. Chem. Res.* ***1998***, *852.* ($Ar(Csp_2)$-OR forming only(?), β-hydride elim. of OR)

· Melanie Sanford grew up in Providence, RI.
· She received her undergraduate degree in chemistry from Yale University in 1996 where she worked with Professor Bob Crabtree studying C-F bond functionalization.
· She then moved to Caltech where she worked with Professor Bob Grubbs investigating the mechanism of ruthenium-catalyzed olefin metathesis reactions.
· After receiving her PhD in 2001, she worked with Professor Jay Groves at Princeton University as an NIH post-doctoral fellow studying metalloporphyrin-catalyzed functionalization of olefins.
· Melanie has been an Assistant Professor of Chemistry at the University of Michigan since the summer of 2003.

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1. Directed C-H Activation

1-1. Brief look for C-H activation

(review) M. S. Sanford et al. *Tetrahedron* **2006**, 2439.
D. Sames et al. *Science* **2006**, *312*, 67.
Oka-P san`s *lit.sem.* **2002**

< merit >

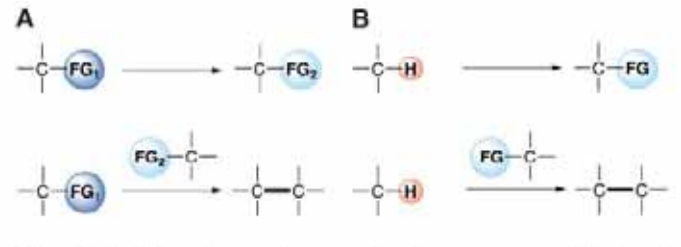


Fig. 2. (**A**) Traditional approach to organic synthesis by means of functional group (FG) transformation. (**B**) Synthesis by means of C–H bond functionalization.

no FG for further functionalization
- atom economy
- structual diversification at later stage

< trend >

C-H functionalization is somewhat popular in organic rxn. (Ar-H: electrophilic aromatic substitution, ortho lithiation $C(sp_3)$-H: free radical, dioxirane etc.) --- selectivity, functinal group compatibility, sometimes problematic

mild, general, and selective *(transition)* ***metal catalyzed*** *methods*

⇨ *have the potential to* ***fundamentally change retrosynthetic approaches*** *to complex molecule synthesis. (like metathesis)*

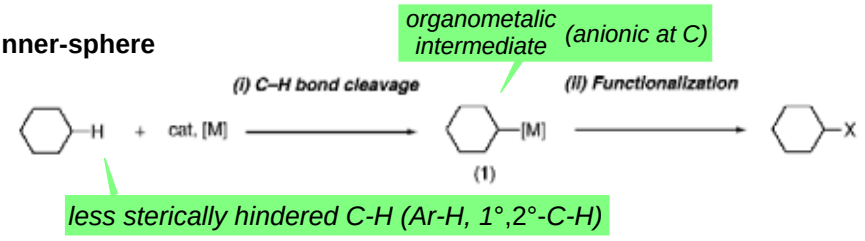
The vast majority of transition metal catalyzed C–H activation/functionalization reactions of complex organic molecules have focused on the transformation of C–H bonds into C–C bonds

Du Bois (Rh^{ii}) C-H amination (Tanaka(Y)`s-B4 lit.sem.)
Hartwig ($Ir^{iii/v}$, $Rh^{iii/v}$) C-H borylation (Shibuguchi san`s D3 lit sem.)
Sanford ($Pd^{ii/iv}$) C-H oxygenation

< classification >

C–H ⟶ C–X

1 Inner-sphere

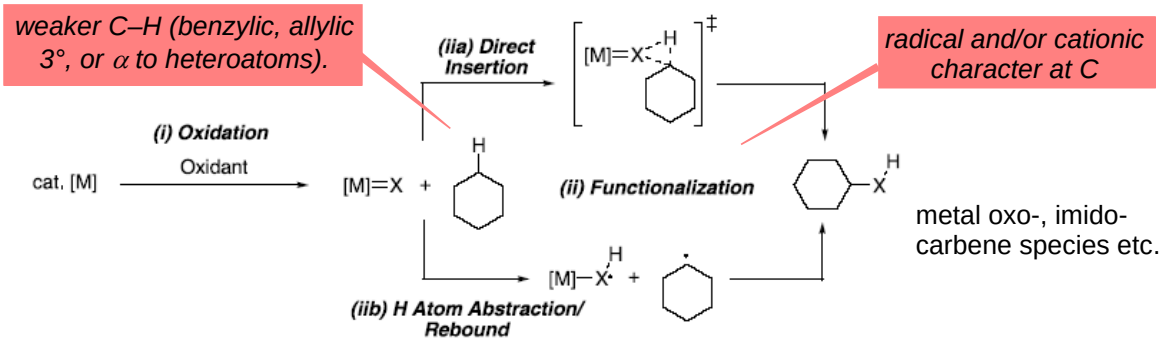


standard transition metal

less sterically hindered C-H (Ar-H, 1°,2°-C-H)

2 Outer-sphere

mimics biological oxidation reactions catalyzed by enzymes (cytochrome P450, methane monooxygenase (MMO))



metal oxo-, imido- carbene species etc.

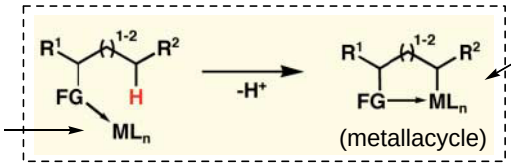
--- substrate does not interact directly with **M** but instead reacts with a coordinated ligand

1-2. Pd-mediated directed C-H activation (palladacycle)

@ directed C-H activation is one reliable approach for C-H bond cleavage by transition metal.

for reactivity

kinetically favorable orientation

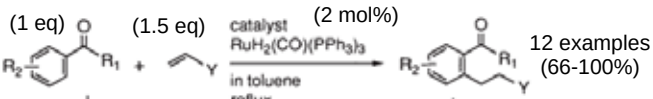


thermodynamical stability

C-M + M-L ≥ C-H (~100 kcal/mol)

high selectivity also expected with chelation

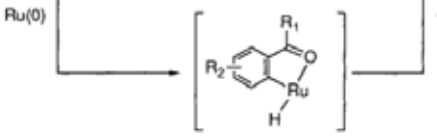
(first(?) successful **catalytic directed** Ar-H functionalization)



12 examples (66-100%)

(S. Murai et al. *Nature* **1993**, *366,* 529.)

speculated via chelation assisted oxidative addition

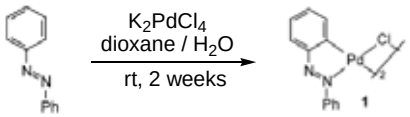


(1,1-disubstituted OK with 5 eq of alkene)

@ In Pd chemistry, this metalation is common (in the preparation of palladacycle)

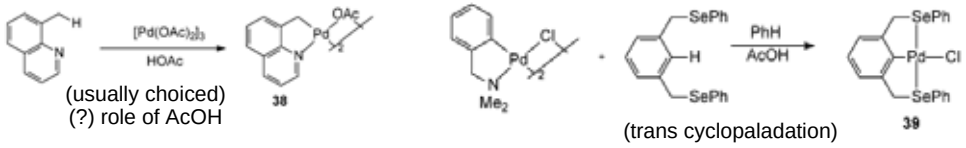
(J. Dupont et al. *Chem. Rev.* ***2005***, *2527.)*

< method of direct metallation >



@ initial work

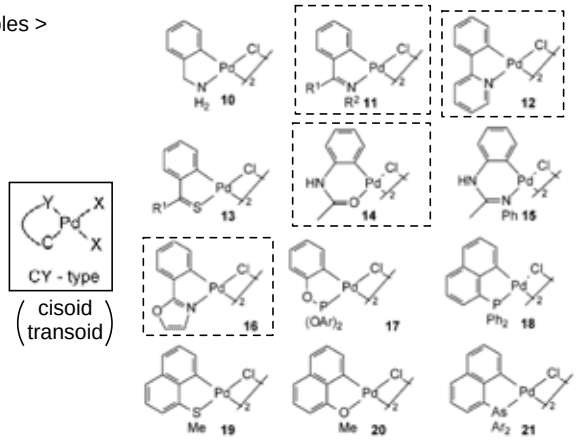
(A. C. Cope et al. *J. Am. Chem. Soc.* ***1965***, *3272.)*

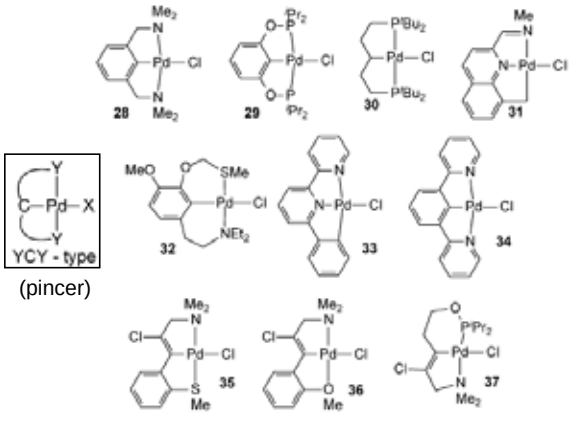


(usually choiced)
(?) role of AcOH

(trans cyclopaladation)

< examples >





(pincer)

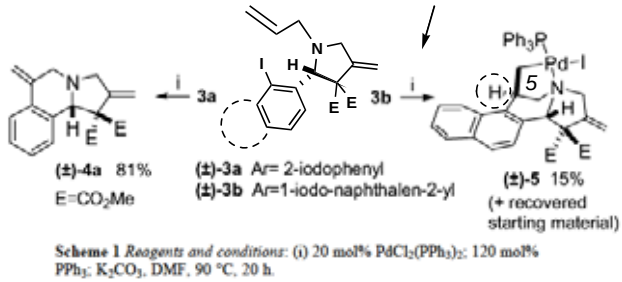
--- applied in cat. rxn.

***5~6** membered ring (can vary 3~11 membered)*

*mostly **5,5-system** (5,6- or 6,6- reported)*

@ β-hydrigen (to Pd^{ii}) can be compatible in palladacycle

$PdCl_2(PPh_3)_2$ (100 mol%) gave **5** in 62%



Scheme 1 *Reagents and conditions*: (i) 20 mol% $PdCl_2(PPh_3)_2$, 120 mol% PPh_3, K_2CO_3, DMF, 90 °C, 20 h.

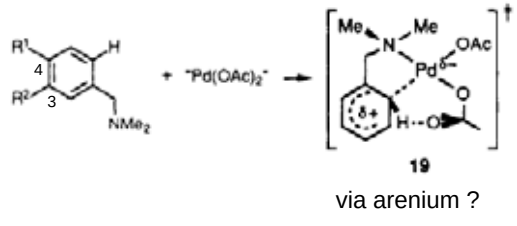
(Chem. Commun. ***2003****, 272.)*

· formed in the course of Heck rxn.
isolated by column (SiO_2)
air, moisture stable
confirmed by X-ray (Pd--N 2.187A)

· the metal is conformationally locked in 5-membered ring and cannot adopt the cisoid conformation toward β-hydrogen.

1-3. Mechanism for palladacycle formation

@ it is thought as electrophilic pathway (for Ar-H: like electrophilic aromatic substitution)



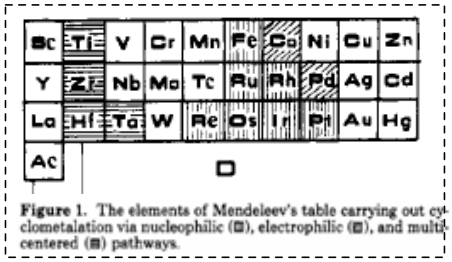
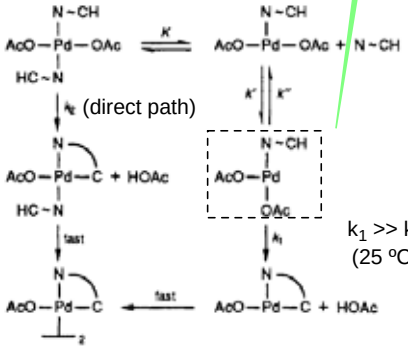


Figure 1. The elements of Mendeleev's table carrying out cyclometalation via nucleophilic (□), electrophilic (□), and multicentered (□) pathways.

--- the result of kinetic investigation was explained in scheme 1

⇩ cyclometallation mainly occurred from coordinately unsaturated 14e complex [Pd(N-CH)(OAc)$_2$] (k_1)

SCHEME I



$k_1 >> k_2$ (25 ºC)

(A. D. Ryabov *Chem. Rev.* ***1990***, 403.)

TABLE II. Equilibrium and Kinetic Parameters of Reaction 17[a]

amine	$[Pd(OAc)_2(N{\sim}CH)_2]$ 298 K 10^3K, M	10^3k_1, s^{-1}	$Na_2Pd_2(OAc)_6$ 323 K 10^4k_{21}, s^{-1}
3,4-$(MeO)_2C_6H_3CH_2NMe_2$	2.7	6.1[b]	4.4
4-$Me_2C_6H_4CH_2NMe_2$	1.5	5.0	4.2
$C_6H_5CH_2NMe_2$	1.35	4.3	7.6
4-$MeOC_6H_4CH_2NMe_2$	2.0	2.7	3.5
4-$ClC_6H_4CH_2NMe_2$	2.9	1.0	14.8

(in $CHCl_3$) (in $CHCl_3$) (**in AcOH** with NaOAc)

- KIE $k_1(H)/k_1(D)$ = 2.2 --- C-H breaking is the rate-limiting
- ρ = -1.6 (against σ_m) --- kinetically electrophilic step
- The activation parameters of the rate-limiting step
  $\delta H^{\ddagger}$ = 11 kJ/mol
  $\delta S^{\ddagger}$ = -0.254 J/mol
  (1 cal = 4.1868 J)

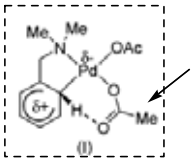
accord with "early", highly ordered transition state **19**, *" 6-membered TS "*

But... **in AcOH** (with NaOAc)
- KIE $k_1(H)/k_1(D)$ = 1.05
- ρ = +1.4 (against σ_p)

Pd^{II} is no longer a "typical electrophile" in AcOH ← still unclear

@ recent computational (DFT) study supports*" 6-membered TS "* (without solvent effect)

(D. L. Davies et al. *J. Am. Chem. Soc.* ***2005***, *13754.)*



electrophilic activation of the arene and intramolecular base for the deprotonation ?

displacement of one arm of the $\eta 2$-OAc by one ortho-C-H

an agostic intermediate (Pd-H) acetate interaction (ortho-H --- O=C) + orientation ideally for H-transfer

the H-acceptor acetate twists away from the new Pd-C bond

with a minimal activation barrier

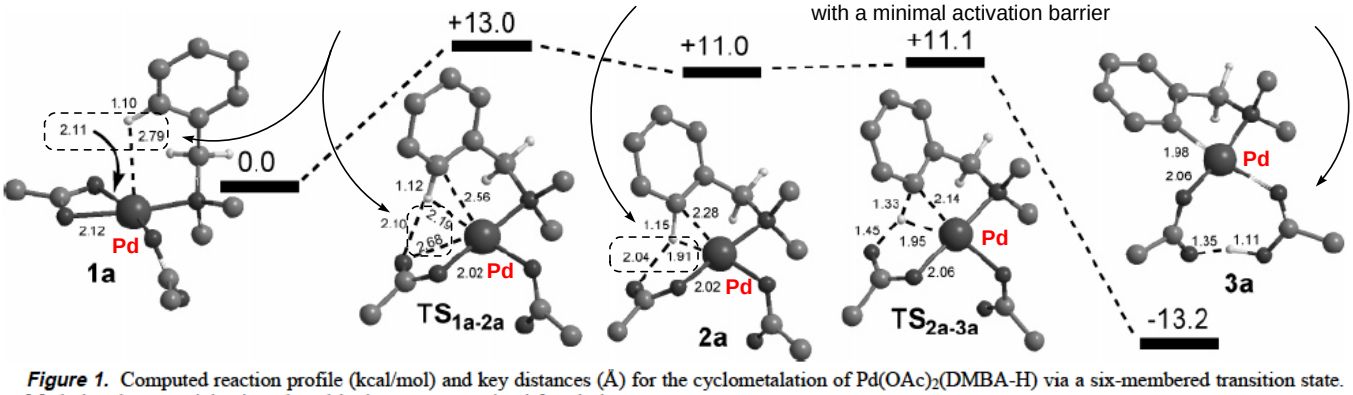


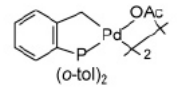
Figure 1. Computed reaction profile (kcal/mol) and key distances (Å) for the cyclometalation of $Pd(OAc)_2$(DMBA-H) via a six-membered transition state. Methyl and nonparticipating phenyl hydrogens are omitted for clarity.

- major changes in atomic charges (**1a** to **TS2a-3a**) occur **only at the activating C-H bond,** C-negative-charge increasing by -0.14, H becomes more positive by +0.09
- the maximum increase of ring-carbons-positive-charge is only +0.05 Pd-positive-charge only slight decrease (from +0.75 to +0.72) ↔ arenium **(1)**
- 4-membered TS (+34.3 kcal/mol), oxidative addition (via 3-centers TS; +25.7 kcal/mol) less accessible

⇨ **6-membered TS** is the most accessible and proceeds via an agostic C-H intermediate rather than arenium

Pd acetate --- electrophilic activation of a C-H bond (agostic), an intramolecular base for the deprotonation

Palladacycle have been utilized as catalyst precursor

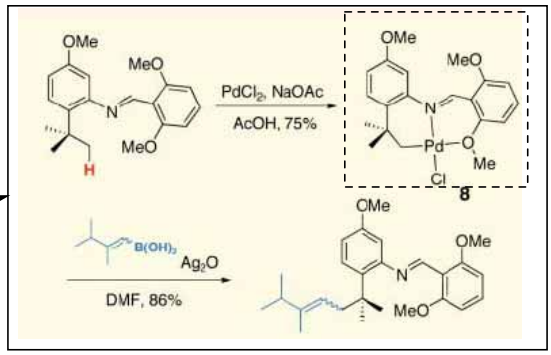


Herrmann-Beller palladacycle

163

key intermediate in total synthesis

(D. Sames et al. *J. Am. Chem. Soc.* **2002**, 11856.)

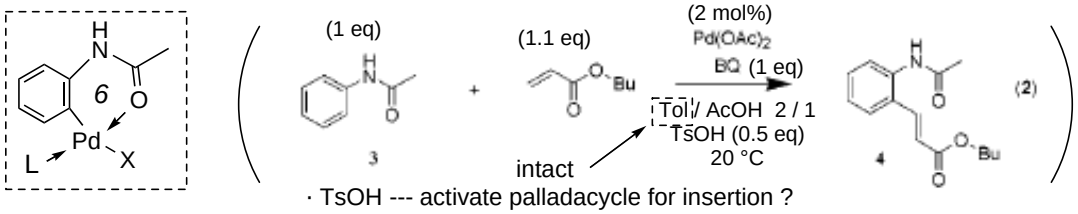


(Ru, Rh: many)

@ Application of palladacycle in $Pd^{0/ii}$ catalytic cycle is also achieved coupled with C-C forming reaction

(oxidant is always speculated to reoxidize Pd(0) → Pd(ii)
classified as C-H directed version of oxidative coupling)

· Acetoanilide + Heck (J. G. de Vries et al. *J. Am. Chem. Soc.* **2002**, 1586.)

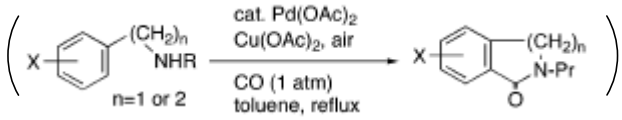


intact

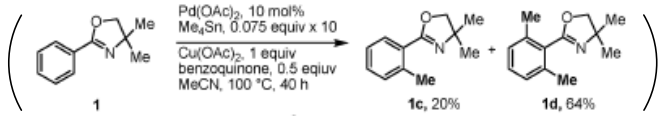
· TsOH --- activate palladacycle for insertion ?

< others (representative) >

· Ar-N-alkyl-amines + carbonylation (K. Orito et al. *J. Am. Chem. Soc.* **2004**, 14342.)

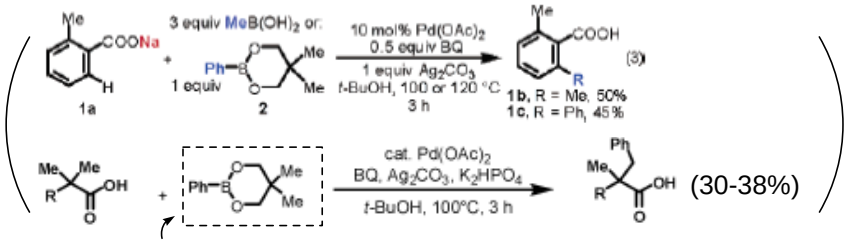


· oxazoline + R_4Sn (J-Q. Yu et al *J. Am. Chem. Soc.* **2006**, 78.)



· Pyridine + $RB(OR)_2$ (J-Q. Yu et al *J. Am. Chem. Soc.* **2006**, 12634.)

· Carboxylic acid + $RB(OR)_2$ (J-Q. Yu et al *J. Am. Chem. Soc.* **2007**, 3510.)



Ar-I also utilized (y. higher (45-70%) although di-Ar products obtained)

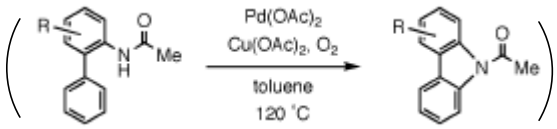
· Acetoanilide + $ArSi(OR)_3$ (Z. Shi et al. *J. Am. Chem. Soc.* **2007**, ASAP.)

directing group? -- sp2 or sp3 C-H? -- coupling partner? -- oxidant?

⇩

⇨ **But analogous catalytic approaches for C-X (-O) forming are rare**

cf) · C-N forming, but intramolecular (S. L. Buchward et al. *J. Am. Chem. Soc.* **2005**, 14560.)



2. Sanford`s work (Pd(ii)/Pd(iv))

2-1. Representative Examples for C-O forming

(For Ar-H)

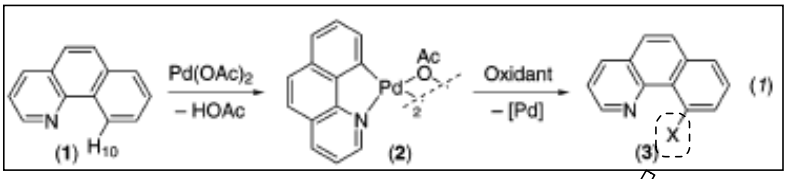
JACS COMMUNICATIONS

A Highly Selective Catalytic Method for the Oxidative Functionalization of C−H Bonds

2004, *126*, 2300−2301

Allison R. Dick, Kami L. Hull, and Melanie S. Sanford*

· Benzo[*h*]quinoline **1** — a single C-H for directed C-H activation; well-known to undergo cyclopalladation



@ extraordinarily high selectivity for C10

@ regioisomeric oxidized products not observed

Table 1. Regioselective Oxidation of Benzo[*h*]quinoline[a]

entry	oxidant	solvent	X (product)	yield[b] (%)
1[c]	$PhI(OAc)_2$	CH_3CN	OAc (**3a**): OH (**3b**)	86[d]
2[c]	$PhI(OAc)_2$	MeOH	OMe (**3c**)	95
3[c]	$PhI(OAc)_2$	EtOH	OEt (**3d**)	80
4[c]	$PhI(OAc)_2$	*i*-PrOH/HOAc	O*i*Pr (**3d**)	72
5[c]	$PhI(OAc)_2$	CF_3CH_2OH	OCH_2CF_3 (**3f**)	71
6[e]	NCS	CH_2CN	Cl (**3g**)	95
7[e]	NBS	CH_3CN	Br (**3h**)	93

[a] 1 equiv of **1** (0.12 M), 1−2 equiv of oxidant, 1−5 mol % $Pd(OAc)_2$ or **2**, 75−100 °C. [b] Isolated yields. [c] 12 h. [d] 11:1 mixture of **3a**:**3b**. [e] 1−3 days.

(**3a**/**3b** 11/1) --- **3b** formed via hydrolysis from **3a**

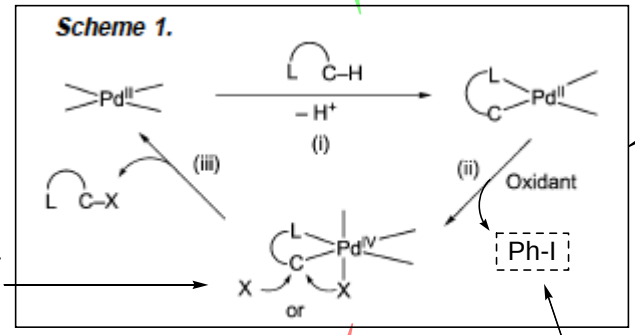
simple modification ! in situ generation of $PhI(OR)_2$?

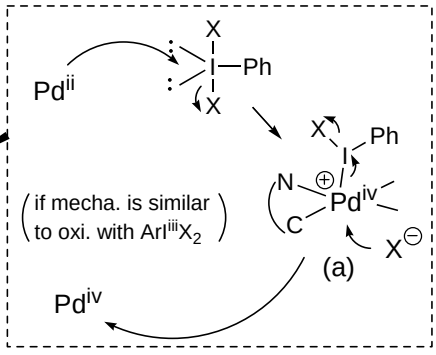
excess LiX + $PhI(OAc)_2$ ~ trace

palladacycle **2** also catalysed rxn.

· high regioselectivity
· high catalytic activity of the isolated palladacycle **2**

Proposed Catalytic Cycle





major drawback

· benzoquinone or $Cu(OAc)_2$
· palladacycle **2** —(solv, heat)→ no products formed

· Pd(II)/Pd(IV) cycles have been implicated in related benzene acetoxylation reactions

(R. H. Crabtree et al. *J. Mol. Cat. A* **1996**, 35.)

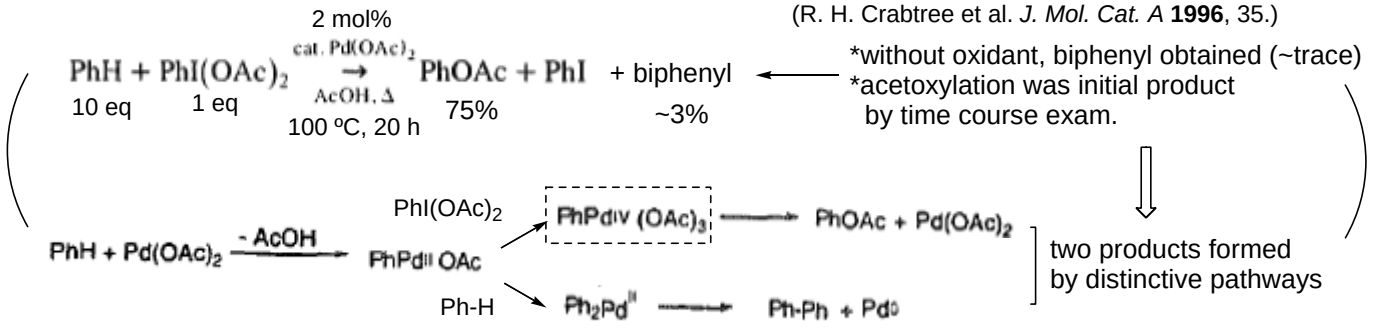


Table 2. Chelate-Directed Oxidation of sp² and sp³ C−H Bonds[a,b]

Entry	Major Product	Yield[c]	Entry	Major Product	Yield[c]
1	(4a)	88%	7	(9)	72%
2	(4b)	77%	8	(10)	52%
3	(5)	80%	9	(11)	83%
4	(6)	62%	10	(12)	78%
5	(7)	54%	11	(13)	58%
6	(8)	47%[d]			

[a] For mono-oxidation: 1 equiv of substrate [0.12 M in AcOH (entries 1, 3, 5), MeOH (entry 2), or CH_3CN (entries 4−8)], 1.1−1.6 equiv of $PhI(OAc)_2$, 1−6 mol % $Pd(OAc)_2$, 100 °C, 12−20 h. [b] For dioxidation: 1 equiv substrate (0.12 M in CH_3CN), 2.3−2.5 equiv of $PhI(OAc)_2$, 6−8 mol % $Pd(OAc)_2$, 100 °C, 12 h. [c] Isolated yields. [d] Yield determined by GC.

sp3-C-H OK

no over-oxidation even at benzylic (steric hindrance)

(in AcOH) (in MeOH) (in AcOH)

8-Me selective

cf) Me → complex mixture

2,2- and 2,5-di-OAc ~15%

2,2-di-OAc ~25%
SM ~25%

2,2-di-OAc 26%

>2eq $PhI(OAc)_2$

not directed by aldehyde

@ exclusion of air/moisture not required

--- rxn. performed in a 20ml vial with a Teflon lined cap

They said...

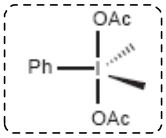
"exceedingly practical method for functional group-directed oxidation of arene C-H bonds"

"attractive alternative to ortho-lithiation/ electrophilic addition procedures"

< $PhI(OAc)_2$? >

表 1　求核置換反応における相対的脱離能

脱離基	脱離能	脱離基	脱離能
Cl	1	CF_3SO_3-	1.4×10^8
I	9.1×10	n-$C_4F_9SO_3$-	2.8×10^8
p-$MeC_6H_4SO_3$-	3.7×10^4	Ph(BF₄)I-	1.1×10^{14}



← Ph(X)I- **hyper leaving group**

< preparation>

PhI —(peroxide; acetic acid/acetic anhydride)→ $PhI(OAc)_2$

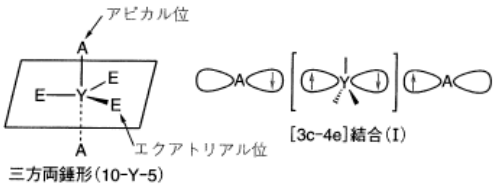


図 12・2　超原子価化合物の構造と電子状態

ハロゲン属元素の中でヨウ素は，サイズが大きく，最も分極しやすい．また，電気陰性度が小さく，酸化されやすいため，容易にその原子価を拡張してオクテット則を超える超原子価有機ヨウ素化合物を形成する．3価や5価の有機ヨウ素化合物はオルガノ-λ^3-およびλ^5-ヨーダン(iodane)とよばれる．

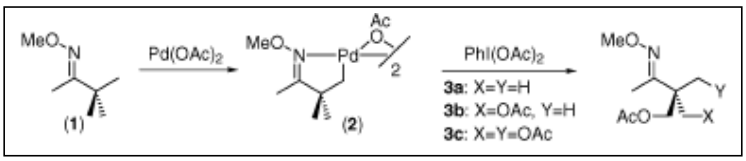
(sp3 C-H)

JACS COMMUNICATIONS
2004, *126*, 9542−9543

Palladium-Catalyzed Oxygenation of Unactivated sp³ C−H Bonds

Lopa V. Desai, Kami L. Hull, and Melanie S. Sanford*

(Highlighted in *Chemical and Engineering News:* 2004, 82(31), 35. and *Lett. Org. Chem.* News and Views Section, 2005, 2(5), 207.)



< initial >

1 — $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (X eq), 100 °C, 5.5 h

- (X = 1.1) **3a-c** mixture
- (X = 4.5) **3c** 59%
- (without Pd) no rxn.

[a] 1 equiv of substrate (0.12 M), 1.1 equiv of $PhI(OAc)_2$, 5 mol % $Pd(OAc)_2$, 50% AcOH/50% Ac_2O, 100 °C, 1.5−3.5 h. [b] Isolated yields. [c] Isolated as a mixture of oxime *E*/*Z* isomers.

Table 1. Selectivity of Unactivated sp³ C−H Bond Oxidation[a]

Entry	Substrate	Major Product	Yield[b]
1	MeO, N (4)	MeO, N, OAc (9)	74%[c]
2	MeO, N (5)	MeO, N, OAc (10)	78%[c]
3	MeO, N (6)	MeO, N, OAc (11)	39%[c]
4	MeO, N (7)	No Reaction	0%
5	MeO, N (8)	No Reaction	0%

Ac_2O --- prevent hydrolysis

< reactivity >

· OH oxime --- oxidative cleavage (?) to ketone
ketone --- no rxn.

· no α-C-H oxiation despite its higher acidity
cf) in stoichimetric Pd(ii) cases
require fully α-alkylated oxime

· **no β-hydride elim. !**
⇨ regidity of palladacycle

< selectivity >

· 1°-β-C-H selective (ent. 2)
⇨ strong steric preference (1° over 2°) for 5-membered palladacycle (β vs α / γ)

· siginificantly enhanced by α-branching (ent. 1-3)
⇨ required conformation for C-H activation (coplanar between oxime and C-H) is readily accessed

SM —[$Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (X eq), conditions]→ TM

generally, di-OAc not obtained

(X eq)

1.1 AcOH/Ac_2O 1 / 1, 80 °C, 5.5 h
2 — 90 °C, 9 h
1.5 — 100 °C, **1.5 h**
1.1 — 80 °C, **5 min**
3.2 AcOH — 100 °C, 12 h
1.5 CH_2Cl_2
2.1
1.1
1.5 AcOH/Ac_2O 1 / 1, 80 °C, 5.5 h

Table 2. Substrate Scope of sp³ C−H Bond Oxygenation[a]

Entry	Substrate	Product	Yield[b]
1	MeO, N (12)	MeO, N, OAc (22)	61%
2	MeO, N (13)	AcO, MeO, N (23)	75%
3	MeO, N (14)	MeO, N, OAc (24)	81%[c]
4	MeO, N, t-Bu (15)	MeO, N, t-Bu, OAc (25)	86%[c]
5	N (16)	N, OAc, AcO, OAc (26)	63%
6	N (17)	N, OAc (27)	42%
7	N, N (18)	N, OAc, OAc (28)	70%
8	N, O (19)	N, O, OAc (29)	66%
9	N, O (20)	N, O, OAc (30)	44%
10	MeO, N, H, H (21)	MeO, N, H, OAc, H (31)	81%

[b] Isolated yields. [c] Isolated as a mixture of oxime E/Z isomers.

deemed unreactive in stoichiometric cyclopalladation

(conformational effect)
t-Bu locks the 2-Me into coplanarity with the oxime

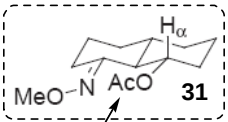
@ Py also effective directing group (ent. 5-9)

might offer mild and selective approach to the dealkylation of ethers/amines

@ 2°-β-C-H also reactive (ent. 9-10)

α to O (electronic)

structual rigidity



eq. selective

? (i) ax.C-H followed by r.e. with inversion
(ii) eq. C-H followed by r.e. with retention ?

2-2. Mechanistic aspects for C-O forming reductive elimination

(Ar(Csp_2)-O)

JACS COMMUNICATIONS
2005, *127*, 12790−12791

Unusually Stable Palladium(IV) Complexes: Detailed Mechanistic Investigation of C−O Bond-Forming Reductive Elimination

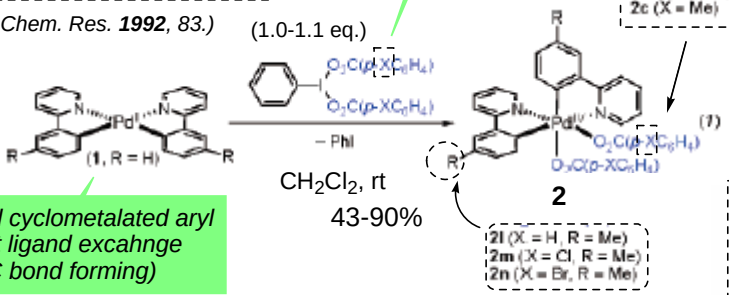
Allison R. Dick, Jeff W. Kampf, and Melanie S. Sanford*

1. oxidation of Pd^{ii} with I^{iii}-oxidant was confirmed by the rational design and isolation of Pd^{iv} complex

Pd^{IV} @ relatively labile @ alkyl ligand can exchange between metal centers

(A. J. Canty. *Acc. Chem. Res.* ***1992***, *83.*)

facile manipulation of electronic parameters



2a (X = H) 2b (X = OMe) 2c (X = Me) 2d (X = OPh) 2e (X = F) 2f (X = Cl) 2g (X = Br) 2h (X = Ac) 2i (X = CF_3) 2j (X = CN) 2k (X = NO_2)

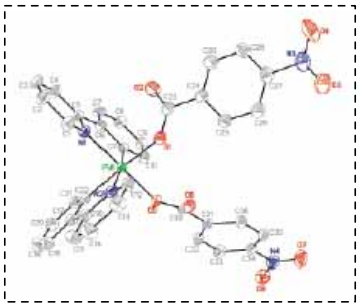
(**2a**: stored in air in solid state at rt for a week)

remarkably in organomet.Pd^{iv} field

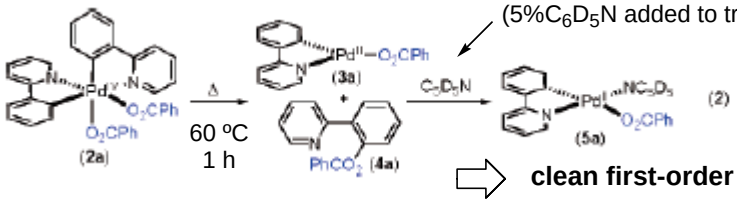
two rigid cyclometalated aryl (prevent ligand excahnge and C-C bond forming)

2l (X = H, R = Me) 2m (X = Cl, R = Me) 2n (X = Br, R = Me)

X-ray ⇨ ***Figure 1.*** ORTEP diagram of **2k**. **(R = H, X = NO_2)**



2. these Pd^{iv} complexes undergo clean C-O bond forming reductive elimination upon themolysis



(5%C_6D_5N added to trap **3a** for facilitating mechanistic studies)
--- standard technique for r.e.study

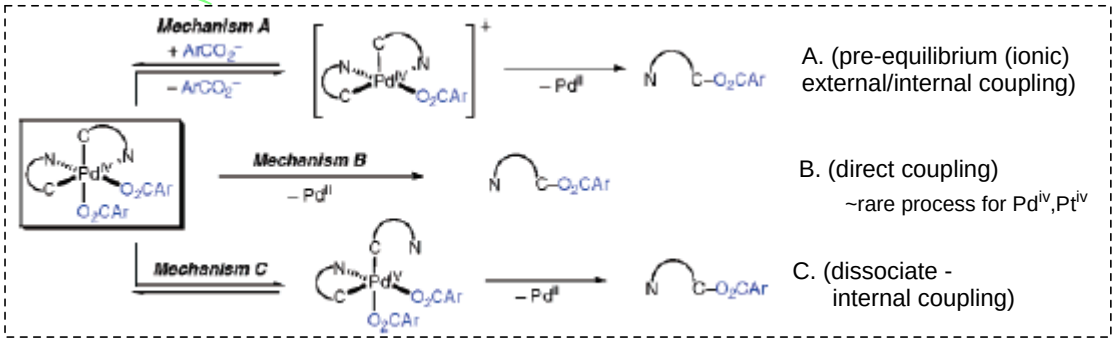
⇨ **clean first-order kinetics**

3. possible mechanisms of C-O bond forming reductive elimination were disscussed

(*Organometallics* ***1988***, *1363.*)

same as Pt^{iv} or (bpy)$Pd^{iv}Me_3I$ case

·1)strong dependence of solvent polarity
·2)highly negative value of **Δ**S* (-13 ~ -39 e.u.) ~ solvent ordering about the charged transition state
·3)ρ ~ +1.4 (for $ArCO_2$)

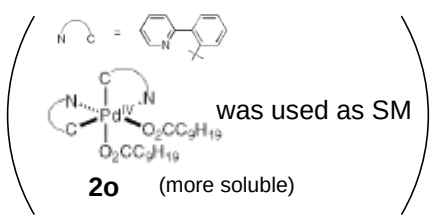


A. (pre-equilibrium (ionic) external/internal coupling)

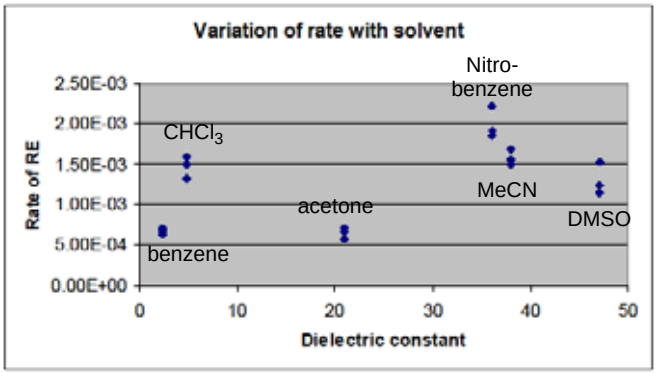
B. (direct coupling)
~rare process for Pd^{iv},Pt^{iv}

C. (dissociate - internal coupling)

@ A is not probable pathway



1) no dependence of solvent polarity ⇨



2) from Eyling analysis for **2c** $\left(\ln(k/T) = -\Delta H^{\ddagger}/RT + \ln(k_B/h) + \Delta S^{\ddagger}/R \right)$

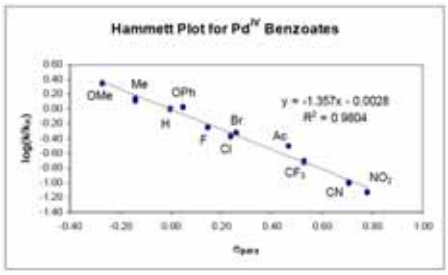
ΔS^{*} { +4.2±1.4 eu (in d_6-DMSO) / -1.4±1.9 eu (in $CDCl_3$) }

(not so charged in transition state ?)

3) Electron donor substituents led to moderate rate accelerations

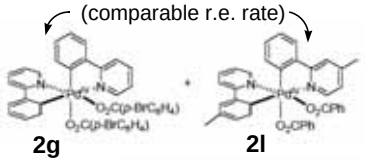
(ρ ~ -1.36±0.04) (for $ArCO_2$)

(benzoate acts as a nucleophilic partner ?)

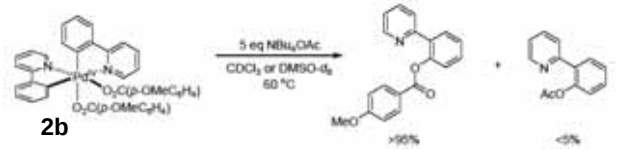


4) no benzoate exchange

(comparable r.e. rate)



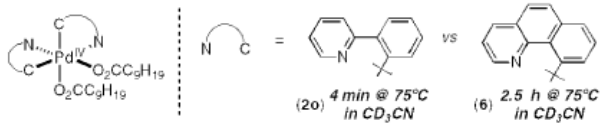
no incorporation of acetate



internal coupling plausible

@ B or C ?

(only preliminary)



(3) added rigidity of the fused ring system is expected to decrease the rate of nitrogen dissociation

⇨ ***mechanism C***

chelate-directed C-O coupling at Pd^{IV} proceeds by a significantly different mechanism than other reductive eliminations from Pd^{IV} or Pt^{IV}.

But there are no conclusion about transition state...

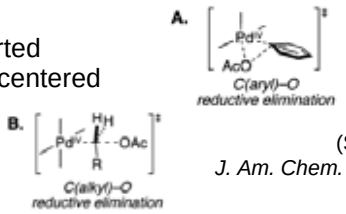
Anyway, from Pd^{iv} complex...

@ for Ar(Csp2)-O bond forming r.e. might be internal ~ concerted

three-centered

@ for C**(sp3)-O bond forming r.e.** ?

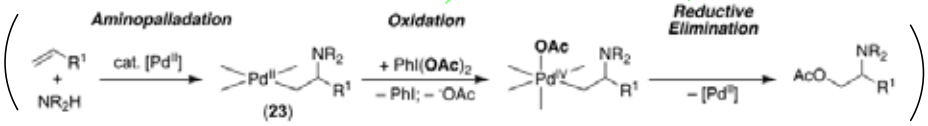
⇒ **S_N2** mechanism was suggested from recent reports (**inversion of stereochemistry**)



(Stahl et al. *J. Am. Chem. Soc.* **2006**, *128*, 7180.)

< oxidative functionalization after palladation >

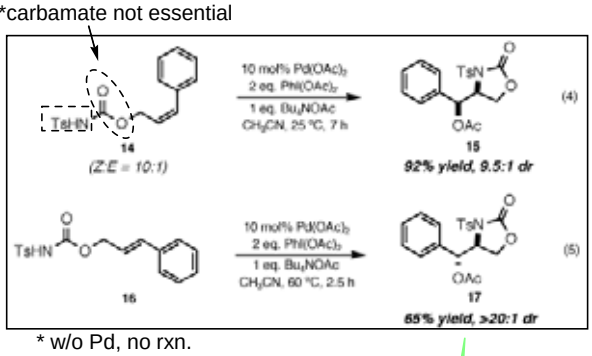
must be faster than competing β-hydride elimination



*** aminoacetoxylation, intramolecular** (Sorensen et al. *J. Am. Chem. Soc.* **2005**, *127*, 7691.)

*carbamate not essential

sulfone amide ↓ prevent cat. poison N-oxi.

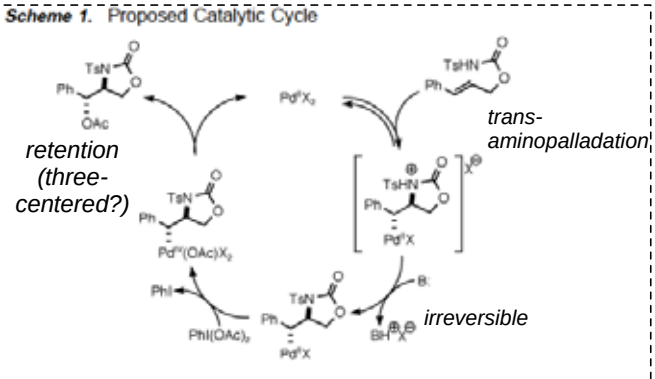


* w/o Pd, no rxn.

* $Cu(OAc)_2$ (2.0 equiv) was ineffective.

stereoselective ***trans alkene difunctionalization***

(net N,O-*anti*-addition)



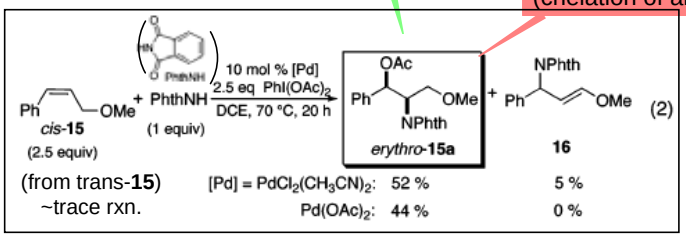
⇨ *trans-aminopalladation;* ***r.e. with retention***

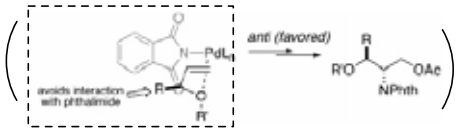
* aminoacetoxylation, intermolecular

(Stahl et al. *J. Am. Chem. Soc.* **2006**, *128*, 7180.)

trans alkene difunctionalization

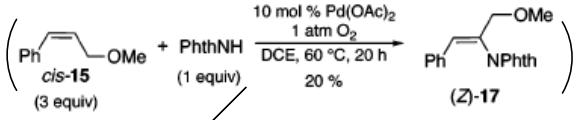
exquisite regioselectivity (chelation of allylic oxygen)



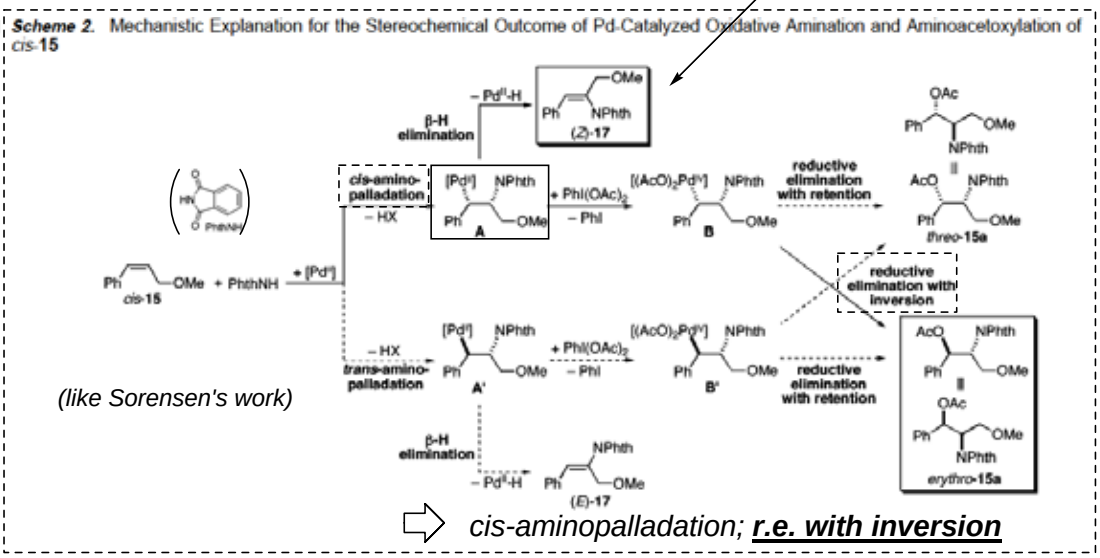


analysis of β-hydride elimination

Pd-black retarted rxn.

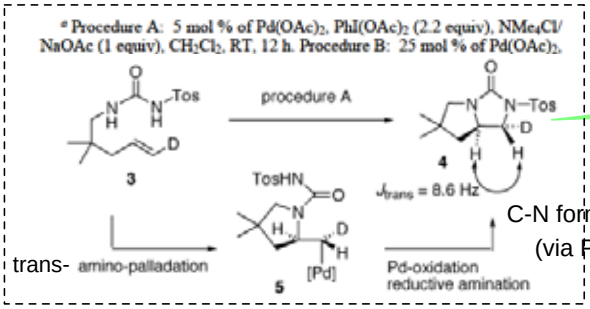


only (allylic) oxygen containing external olefin



* diamination, intramolecular

(Muniz et al. *J. Am. Chem. Soc.* **2005**, *127*, 14586.) → Fujimori's lit. sem. (M1 part)



only the hypervalent iodine reagent $PhI(OAc)_2$ was highly efficient stoichiometric base accelerates rxn.

syn alkene difunctionalization

trans-aminopalladation; ***r.e. with inversion***

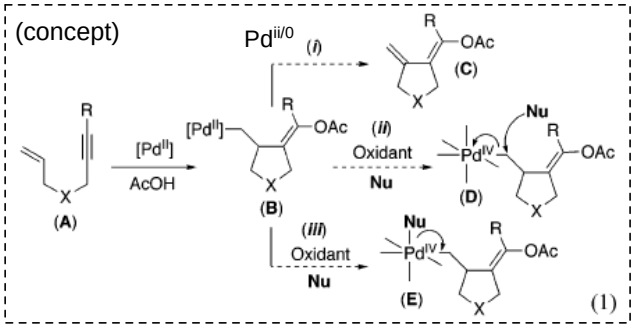
C-N forming r.e. (via Pd^{iv} ?)

● Recent two reports suggests ***r.e. with inversion*** (S_N2) ●

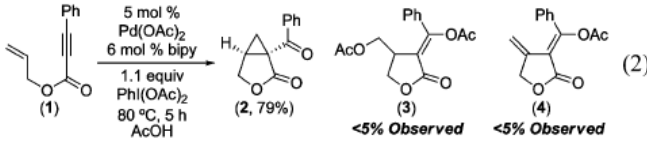
Synthesis of Cyclopropanes via Pd(II/IV)-Catalyzed Reactions of Enynes

Leilani L. Welbes, Thomas W. Lyons, Katie A. Cychosz, and Melanie S. Sanford*

(*J. Am. Chem. Soc.* **2007**, *129*, 5836.)

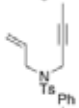


(initial)



*bipy --- sometime effective

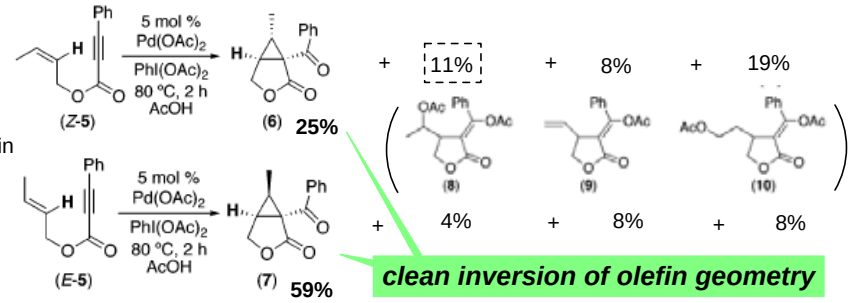
Table 1. Substrate Scope of Oxidative Cyclopropane Formation[a]

entry	substrate	product	substituents	yield[b]
			R R1 R2	
1			H, H, Ph	79%[c]
2			H, H, Me	55%[c]
3			Me, H, Ph	78%[c]
4			Me, H, Me	66%[c]
5			H, CO_2Et, Ph	79%
6				55%
7			X: H	48%[c]
8			CF_3	44%
9			OMe	44%[c]
10				71%[d]
11				47%[c]

[a] Conditions: 5 mol % of $Pd(OAc)_2$, 1.1−4 equiv of $PhI(OAc)_2$, 60−80 °C, 1−16 h. [b] Isolated yields (average of two runs). [c] 6 mol % of bipy added.

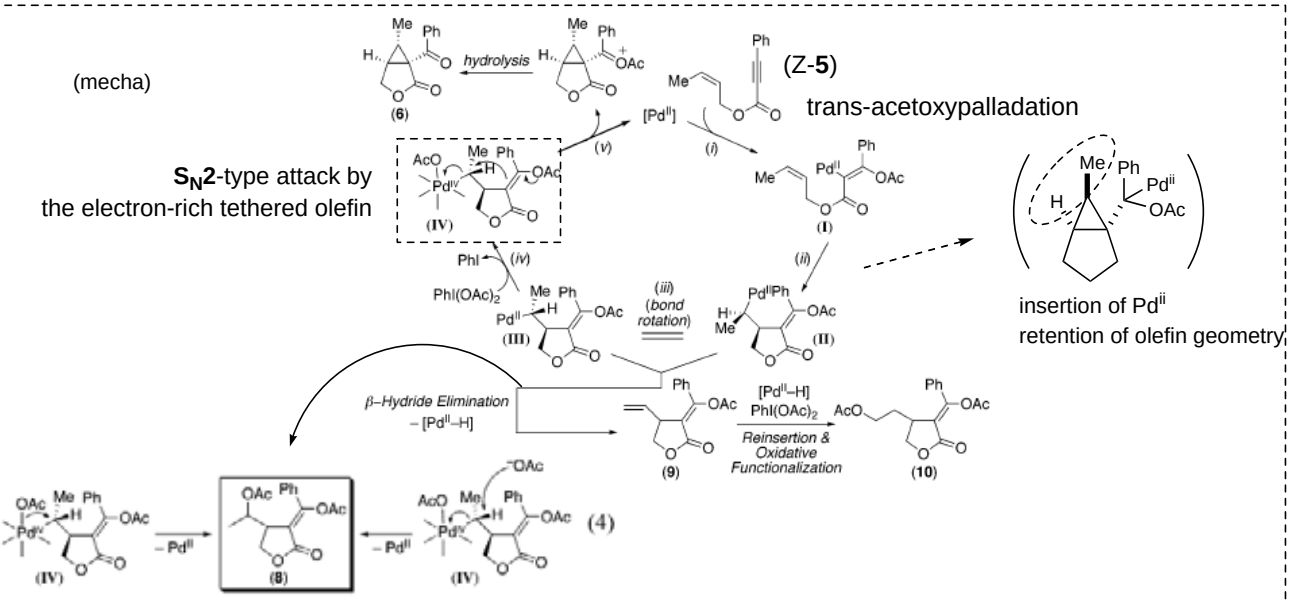
(stereochem)

with 1,2-disubstituted-olefin



clean inversion of olefin geometry

(mecha)



S_N2-type attack by the electron-rich tethered olefin

(from Z-**5**) predominatly one diastereomer, but stereochem could not be established.

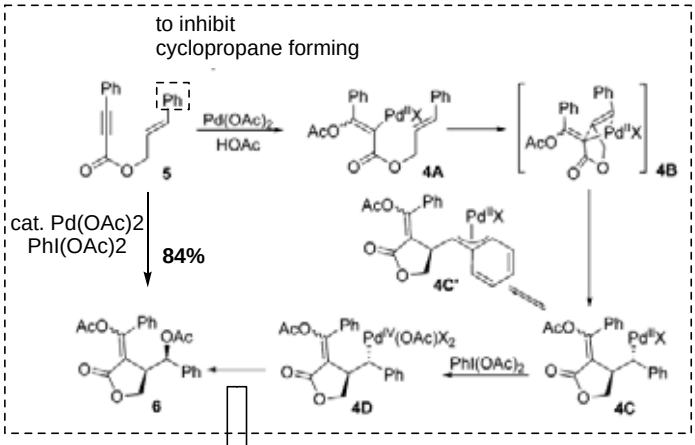
(another group also suggests S_N2 from stereochemistry of this type product)

A Palladium-Catalyzed Cyclization−Oxidation Sequence: Synthesis of Bicyclo[3.1.0]hexanes and Evidence for S_N2 C−O Bond Formation

Xiaofeng Tong,† Matthias Beller,†,‡ and Man Kin Tse*,†,‡

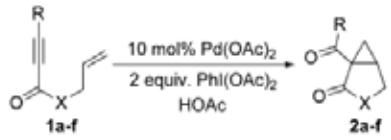
(*J. Am. Chem. Soc.* **2007**, *129*, 4906.)

(quite similar substrate)



r.e. with inversion

Table 1. $Pd(OAc)_2$-Catalyzed Cyclization-Oxidation of **1** in the Presence of $PhI(OAc)_2$[a]



entry	R	X	temp (°C)	time (h)	yield (%)[b]
1	Ph (1a)	O	room temp	60	79
2	Me (1b)	O	room temp	54	83
3	Ph (1a)	O	80	2	0[c]
4	Ph (1a)	O	80	2	63
5	Me (1b)	O	80	2	51
6	*n*-Bu (1c)	O	80	3	75
7	2-MeOC$_6$H$_4$ (1d)	O	80	2	80
8	*n*-Bu (1e)	NTs	80	2	83
9	Ph (1f)	NTs	80	3	77

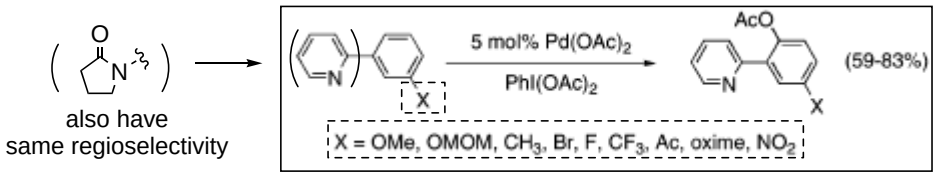
[a] Reaction conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $PhI(OAc)_2$ (0.6 mmol), and HOAc (3 mL). [b] Isolated yield. [c] Without $PhI(OAc)_2$.

They suggested C-O r. e. from the alkyl-Pd(IV) species proceeds by an S_N2 mechanism

2-3. Further development of C-O forming reaction

(About regiochemistry (for Ar(Csp2)-H))

(M. S. Sanford et al. *Org. Lett.* **2005**, *7*, 4149.)

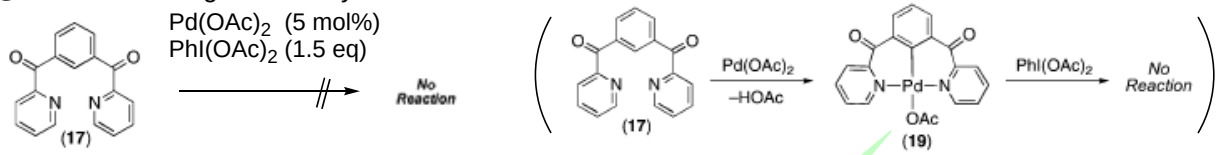


@ tolerate a diverse array of electron-donating and electron-withdrawing meta-substituents

@ **6 :1(X = F) ~ >20 : 1** selectivity for oxygenation of **less sterically hindered** ortho-C-H bond
even when X is secondary chelating group to $Li^{\oplus}$ or Ru^{0}(= OMe, OMOM, F, Cl)
or reported L-type ligands for Pd^{ii} (= ketone, oxime)

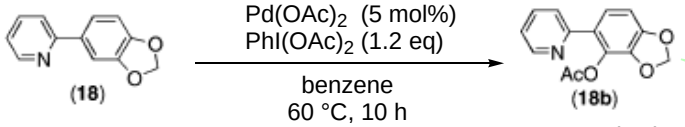
can differentiate two directing group (Py > ketone or oxime)

@ to invert this regioselectivity



tight chelation required to achieve selectivity prevents catalyst turnover.

(only one substrate can chenge this selectivity)



29% (**2**:1)

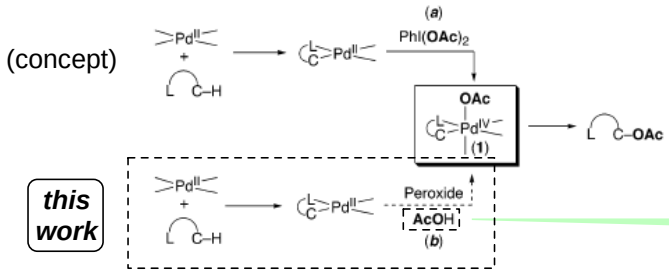
cyclic nature of the ether moiety
{ decreases the effective size and
{ may render the oxygen lone pair more available

⇨ *"complemantaly to ortho-lithiation"* in terms of regioselectivity

---

(Can omit I^{iii} oxidant ?)

(M. S. Sanford et al. *Org. Lett.* **2006**, *8*, 1141.)

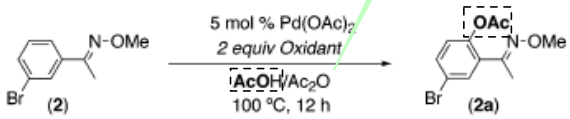


cf) same strategy was reported in Pt^{iv} chemistry

external -OAc source possible ?

to prevent OAc hydrolysis

@ *(table 1) oxidants screening*



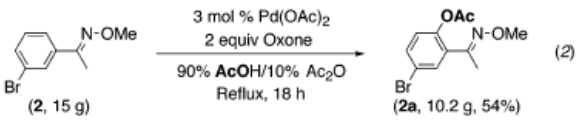
entry	oxidant	isolated yield (%) of 2a[a]	entry	oxidant	isolated yield (%) of 2a[a]
1	H_2O_2·urea	10	5	CH_3CO_3H	34
2	50% aq H_2O_2	11	6	Oxone	68
3	*m*-CPBA	14	7	$K_2S_2O_8$	76[b]
4	70% aq *t*-BuOOH	18	8	$PhI(OAc)_2$	81[b]

[a] Conditions: 5 mol % $Pd(OAc)_2$, 2 equiv of oxidant, 0.12 M **2** in AcOH/Ac_2O (50:50), 100 °C, 12 h; **2a** isolated as a 5:1 mixture of oxime *E*/*Z* isomers and as a >20:1 mixture of regioisomers. [b] Between 10 and 15% of the di-*o*-acetoxylated product was also isolated.

comparable

slightly good y. for C(sp3)-H

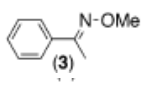
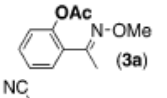
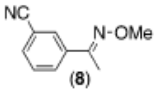
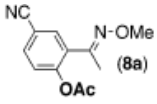
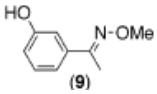
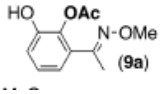
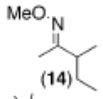
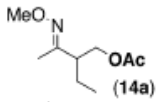
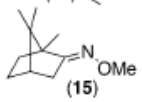
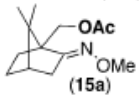
@ *(scheme 2)* ***scalability*** *OK*



(Kugelrohr distilation)

cf) Oxone
consists of $2KHSO_5$, $KHSO_4$, K_2SO_4;
its active component is $KHSO_5$
cheap, (formation of dioxirane etc.)

@ (table 2)

entry	starting material	major product	yield (Peroxide)[a]	yield (PhI(OAc)$_2$)[b]
1	 (3)	 (3a)	53%	73%
6	 (8)	 (8a)	57%[c]	66%
7	 (9)	 (9a)	37%	<5%
12	 (14)	 (14a)	45%[c]	75%
13	 (15)	 (15a)	63%[c]	75%

@ nearly identical regioselectivities with $PhI(OAc)_2$ (less hindered o-C-H)

(w/o Ac_2O) → improved functional group tolerance

‖

<merit>

↕

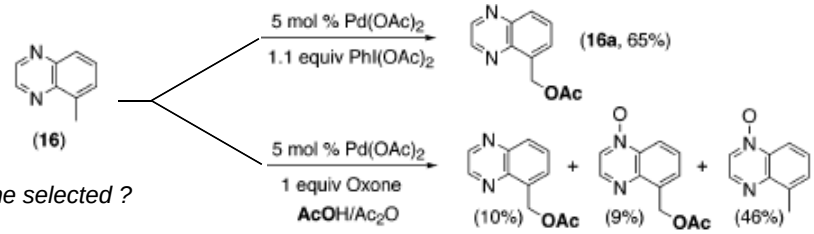
<demerit>

- comparable or moderately lower yields than with $PhI(OAc)_2$
- N-oxidation of some basic nitrogen containing directing group (pyrazine)

1°-β-C-H selective

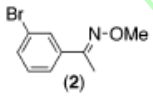
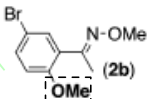
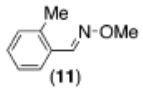
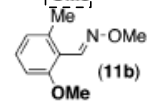
free radical pathways are negligible (well-precedented with $K_2S_2O_8$)

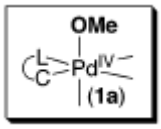
([c] $K_2S_2O_8$ used as the oxidant)



Py-type failed ?
therefore oxime selected ?

@ (table 3) ***MeOH*** *also utilized as external source*

entry	starting material	major product	yield[a]
1	 (2)	 (2b)	70%
2	 (11)	 (11b)	59%



might be genarated

[a] Conditions: 5–10 mol % $Pd(OAc)_2$, 2–3 equiv of Oxone, 0.12 M in MeOH, 25 °C to between 40 and 80 °C over 48 h. Major regioisomer and oxime *E*/*Z* isomer is shown (where relevant). [b] $K_2S_2O_8$ used as the oxidant.

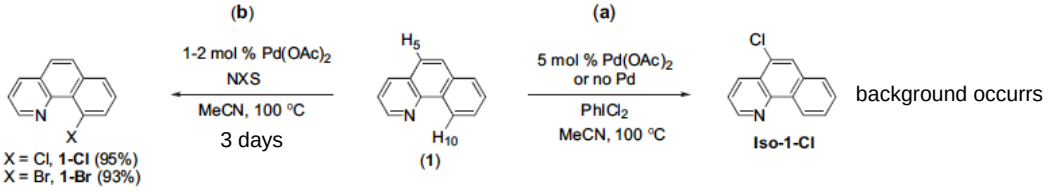
2-4. Other C-X forming reaction

< C-(Cl, Br, I) forming >

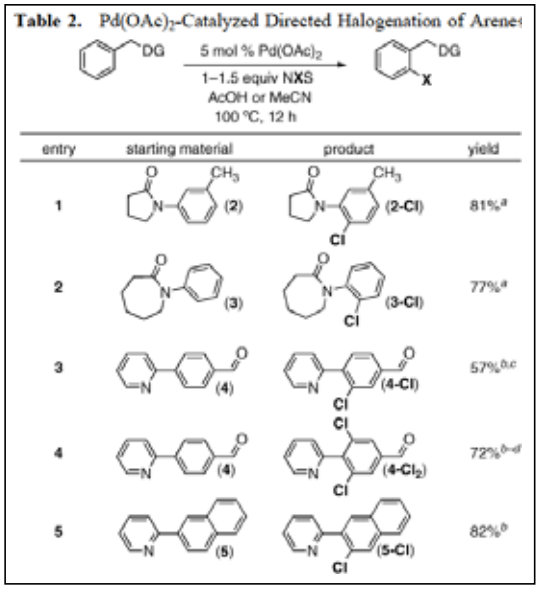
M. S. Sanford et al. { (*Org. Lett.* **2006**, *8*, 2523.) (*Tetrahedron.* **2006**, *62*, 11483.)

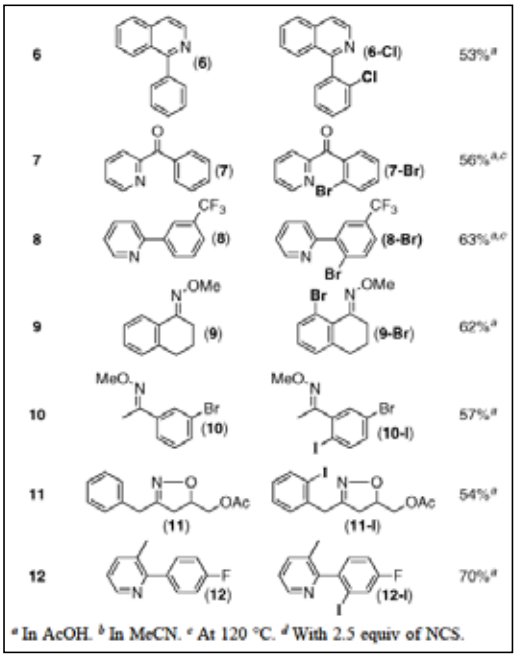
*C-halogen forming r. e. is thermodynamically disfavored relative to o. a. at most metal centers.
(K_{eq} for r. e. of Ar-X from Pd^{II} : ~10^{-5}(for Ar-I), ~10^{-2}(for Ar-Cl))

@ NXS was used instead of $PhIX_2$ (instability under rxn conditions)

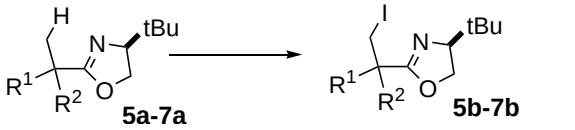


@ So far, good selectivity seems to be only for Ar(sp_2)-H



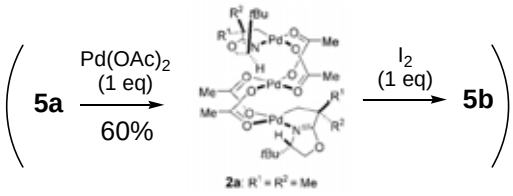


@ C(sp3)-I forming achieved J-Q Yu et al. (*Angew. Chem. Int. Ed.* **2005**, 44, 2112.)



Entry		Substrate	Yield [%]
1	**5a**	$R^1 = R^2 = Me$	92
2	**6a**	$R^1 = Me$; $R^2 = Et$	91[d]
3	**7a**	$R^1 = R^2 = Et$	88[e]

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 48–72 h. [b] Entries 1–3. [c] Entries 4–6. [d] 63:37 d.r. (NMR spectroscopy). [e] PdI_2 precipitated at 36–48 h, $PhI(OAc)_2$ (1 equiv) was added, and stirring continued for another 48 h.



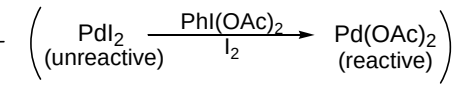
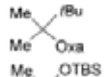
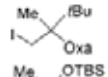
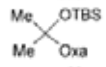
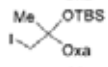
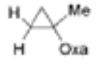
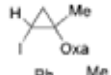
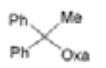
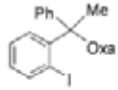
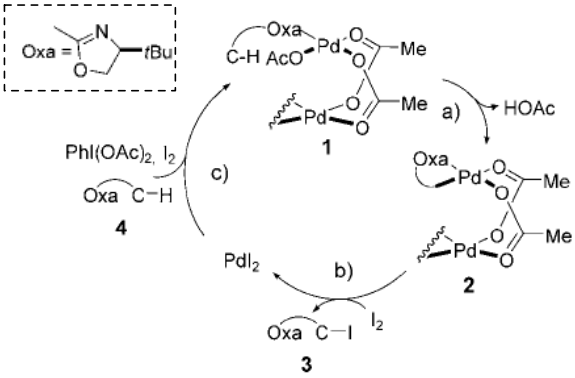


Table 2: Asymmetric iodination.[a]

Entry	Substrate		Product		Yield [%]	d.r.
1	**14a**		**14b**		83[b]	91:9
2	**15a**		**15b**		62[c]	93:7
3	**16a**		**16b**		65[d]	99:1
4	**17a**		**17b**		98[e]	99:1

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2. [b] 24 °C, 30 h. [c] 50 °C, 48 h. [d] 24 °C, 96 h. [e] 24 °C, 13 h. TBS = *tert*-butyldimethylsilyl.



Scheme 1. Proposed catalytic cycle of C–H-bond activation.

< C-F forming >

M. S. Sanford et al. (*J. Am. Chem. Soc.* **2006**, *128*, 7134.)

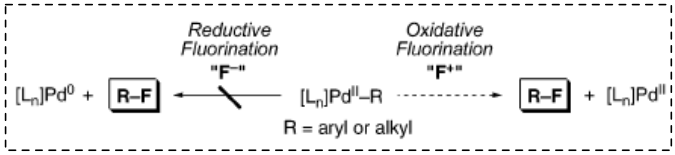
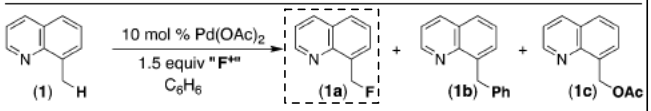
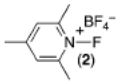
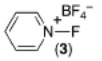
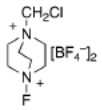
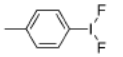
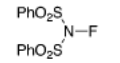


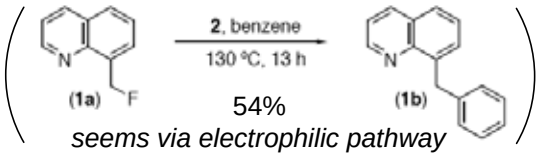
Table 1. Palladium-Catalyzed Fluorination of 8-Methylquinoline



entry	"F⁺" source	yield of 1a+1b+1c (yield 1a) Thermal[a]	yield of 1a+1b+1c (yield 1a) μwave[b]
1	 (2)	82% (36%)	**97% (75%)**
2	 (3)	25% (0%)	37% (15%)
3		24 % (22%)	19% (16%)
4		25% (12%)	8% (3%)
5		19% (9%)	15% (9%)

[a] Conditions: 110 °C, 18 h. [b] Conditions: 110 °C, 1 h, 200 W; yields of **1a**, **1b**, and **1c** were determined by GC using naphthalene as an internal standard.

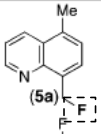
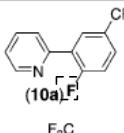
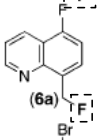
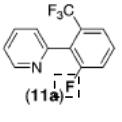
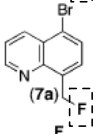
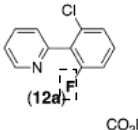
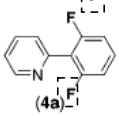
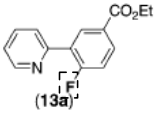
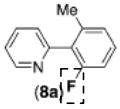
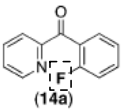
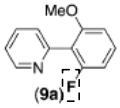
* **microwave** accelerates rxn dramatically.
* No Pd, no fluorinated product.
* formation of **1b** is not Pd-catalyzed reaction.



54%

seems via electrophilic pathway

Table 2. Substrate Scope of Pd-Catalyzed C–H Bond Fluorination

entry	oxidant	product	isolated yield	entry	oxidant	product	isolated yield
1	2	 (5a)	57%[a]	7	3	 (10a)	75%[b]
2	2	 (6a)	49%[a]	8	3	 (11a)	59%[b]
3	2	 (7a)	53%[a]	9	3	 (12a)	50%[b]
4	3	 (4a)	62%[b]	10	3	 (13a)	54%[b]
5	3	 (8a)	52%[b]	11	3	 (14a)	52%[b]
6	3	 (9a)	33%[b]	12	3	 (15a)	60%[b]

[a] Conditions: 7–10 mol % of $Pd(OAc)_2$, 1.5–2 equiv of **2**, C_6H_6, microwave (1–4 h, 100–110 °C, 200–250 W). [b] Conditions: 10 mol % of $Pd(OAc)_2$, 2.5–4.5 equiv of **3**, 0.12–0.5 mL of CH_3CN, $CF_3C_6H_5$, microwave (1.5–2 h, 150 °C, 300 W).

* **3** was optimal F^+ source for phenylpyridine type. (ent 4-12)
* Ar-Br is often not tolerated under $Pd^{0/ii}$ (ent 3)

< C-C forming >

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cf) $Pd^{0/ii}$ approach (see page 5) ..

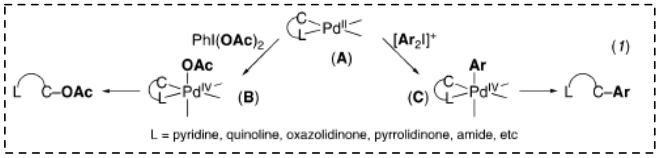
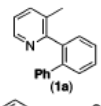
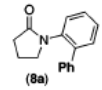
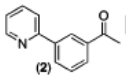
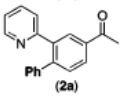
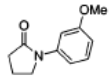
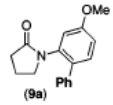
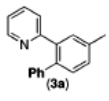
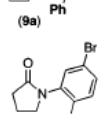
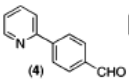
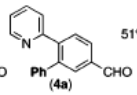
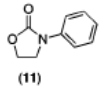
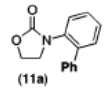
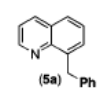
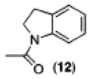


Table 1. Palladium-Catalyzed Phenylation of C–H Bonds[a]

Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	 (1)	 (1a)	88%	8	 (8)	 (8a)	75%[c]
2	 (2)	 (2a)	91%	9	 (9)	 (9a)	84%[c]
3	 (3)	 (3a)	74%	10	 (10)	 (10a)	78%
4	 (4)	 (4a)	51%[e]	11	 (11)	 (11a)	83%[c]
5	 (5)	 (5a)	72%[b]	12	 (12)	(12a)	49%[e]
6	(5a)	(6a)	60%[d]	13	(13)	(13a)	67%
7	(7)	(7a)	58%[e]				

[a] Conditions: 1 equiv of substrate, 1.1–2.5 equiv of $[Ph_2I]BF_4$, 5 mol % $Pd(OAc)_2$ in AcOH, AcOH/Ac_2O, C_6H_6, or toluene, 100 °C, 8–24 h. [b] With 2 equiv of substrate, 1.0 equiv of $[Ph_2I]BF_4$. [c] $NaHCO_3$ (1.5–2.0 equiv) added. [d] Approximately 16% of **6a** was formed in the absence of $Pd(OAc)_2$. [e] The balance of material was starting material (**12**) and/or starting material and diarylated product (**4** and **7**).

⇨ not involve Pd^0 ?

<diverse Ar group>

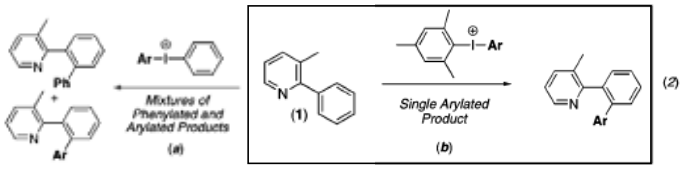


Table 2. Functionalization of **1** with Diverse Aryl Substituents Using $[Mes-I-Ar]BF_4$[a]

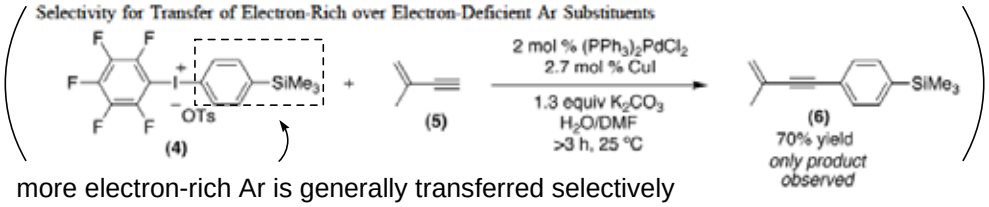
Entry	Ar (Product)	Yield	Entry	Ar (Product)	Yield
1	(1a)	85%	5	CH_3 (1e)	84%
2	CF_3 (1b)	87%	6	(1f)	72%
3	F (1c)	88%			
4	Cl (1d)	83%	7	OCH_3 (1g)	81%[b]

[a] Conditions: substrate **1** (0.12 M), $[Mes-I-Ar]BF_4$ (1.1−1.3 equiv), $Pd(OAc)_2$ (5 mol %), AcOH, 12 h, 100 °C. [b] Reaction carried out at 120 °C.

@ Mechanism { (i) oxidation to Pd^{IV} by $[Ph_2I]BF_4$ then C-C forming r. e.
(ii) direct electrophilic cleavage of the Pd^{II}-C by $[Ph_2I]BF_4$ (without a change of oxidation state at the metal). ***still unclear***

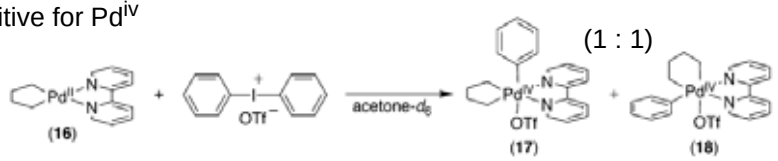
· negative for Pd^{iv}

I^{iii} [iodonium] reagents have been used as highly reactive coupling partoner for $Pd^{0/ii}$ catalyzed reaction



more electron-rich Ar is generally transferred selectively

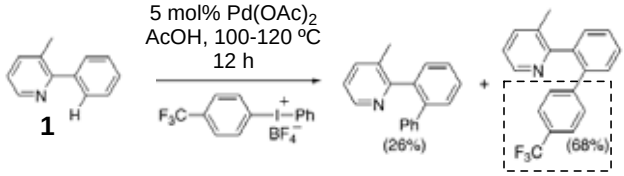
· positive for Pd^{iv}



A. J. Canty et al. (*Organometallics* **2004**, *23*, 3466.)

-50 ºC, ^1H NMR

· ?



more electron-defficient favor

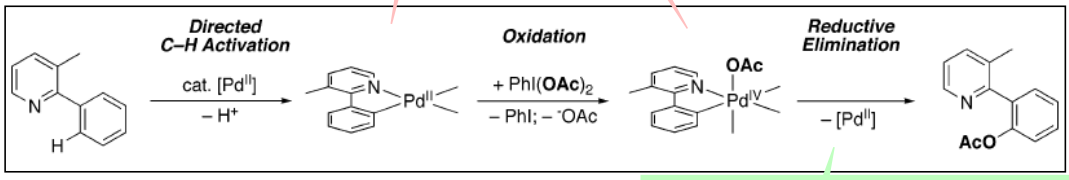
< other reports for C-C forming >

(for oxiditive coupling between two C-H) (*J. Am. Chem. Soc.* **2006**, *128*, 14047.)

(for 2-Ar of indole) (*J. Am. Chem. Soc.* **2006**, *128*, 4972.)

< Summary > ⇨ What is the key for Sanford's success ?

combined Palladacycle and Pd^{iv} chemistry



extended to many type of C-X forming
(X = OR, OAc, Cl, Br, I, F, C, N)

< Future > { @ asymmetric variant (monodentate ?, trinuclear-Pd ?)
@ futher functionalities (N, S, CF_3 ?)
@ toward more complex molecule