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.

~ main stream of her Chemistry ~

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

known as Palladacycle catalystic 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 occur

C-O r.e. from Pd(ii) is rare until 1990’s (and still problematic)

J. F. Hartwig, Acc. Chem. Res. 1998, 52. (Ar(Csp2)-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

< merit >

no FG for further functionalization

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

< trend >

C–H functionalization is somewhat popular in organic rxn. (Ar–H: electrophilic aromatic substitution, ortho lithiation C(sp<sub>3</sub>)–H: free radical, dioxirane etc.) --- selectivity, functional 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<sup>II</sup>) C–H amination (Tanaka(Y)’s-B4 lit.sem.)
Hartwig (Ir<sup>III</sup>/Rh<sup>III</sup>/Ir<sup>IV</sup>) C–H borylation (Shibuguchi san’s D3 lit sem.)
Sanford (Pd<sup>III</sup>/IV) C–H oxygenation

< classification >

1 Inner-sphere

organometallic intermediate (anionic at C)

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

standard transition metal

2 Outer-sphere

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

--- 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.

![Diagram showing C-H activation]

- Thermodynamical stability
- Kinetically favorable orientation
- High selectivity also expected with chelation

(1 eq) (2 mol%)

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


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

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

< method of direct metallation >

< examples >

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

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

@ β-hydrgen (to PdIII) can be compatible in palladacycle

PdCl₂(PPh₃)₂ (100 mol%) gave 5 in 62%

- formed in the course of Heck rxn.
- isolated by column (SiO₂)
- air, moisture stable
- confirmed by X-ray (Pd–N 2.187Å)

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

(Chem. Commun. 2003, 272.)
1-3. Mechanism for palladacycle formation

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

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

cyclometallation mainly occurred from coordinately unsaturated 14e complex [Pd(N-CH(OAc))2] (k1)

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

TABLE II. Equilibrium and Kinetic Parameters of Reaction 17a

<table>
<thead>
<tr>
<th></th>
<th>[Pd(OAc)2][N(CH3)2]</th>
<th>10^6k, M</th>
<th>10^5ΔH°, kJ/mol</th>
<th>10^4ΔS°, J/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH</td>
<td>NaPdCl3(N(CH3)2)</td>
<td>(17a)</td>
<td>(17b)</td>
<td>(17c)</td>
</tr>
<tr>
<td>2,4-(MeO)3C6H4CH2CH2NMMe2</td>
<td>2.0</td>
<td>1.6</td>
<td>1.35</td>
<td>2.0</td>
</tr>
<tr>
<td>4,5-(MeO)2C6H4CH2NMMe2</td>
<td>2.3</td>
<td>1.9</td>
<td>1.55</td>
<td>2.7</td>
</tr>
<tr>
<td>C6H4N(Me2)NMMe2</td>
<td>2.0</td>
<td>1.6</td>
<td>1.55</td>
<td>2.7</td>
</tr>
<tr>
<td>4-MeOC6H4CH2NMMe2</td>
<td>2.0</td>
<td>1.6</td>
<td>1.55</td>
<td>2.7</td>
</tr>
<tr>
<td>4-C6F6C6H4NMMe2</td>
<td>2.0</td>
<td>1.6</td>
<td>1.55</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>19a</th>
<th>19b</th>
<th>19c</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl3</td>
<td>2.7</td>
<td>0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>AcOH (with NaOAc)</td>
<td>2.7</td>
<td>0.14</td>
<td>0.15</td>
</tr>
</tbody>
</table>

But... in AcOH (with NaOAc)

KIE k1(H)/k1(D) = 1.05
· ρ = +1.4 (against σp) --- PdII is no longer a "typical electrophile" in AcOH

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


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

Figure 1. Computed reaction profile (kcal/mol) and key distances (Å) for the cyclometallation 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)

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 for C-C forming reaction.

Key intermediate in total synthesis.


Application of palladacycle in Pd0/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


Acetoanilide + ArSi(OR)₃ (Z. Shi et al. J. Am. Chem. Soc. 2007, ASAP.)

· Ar-N-alkyl-amines + carbonylation


· oxazoline + R₄Sn

(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.)

· Acetoanilide + ArSi(OR)₃ (Z. Shi et al. J. Am. Chem. Soc. 2007, ASAP.)

< others (representative) >

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

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

cf) · C-N forming, but intramolecular
2. Sanford’s work (Pd(ii)/Pd(IV))

2-1. Representative Examples for C-O forming

(For Ar-H)

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

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>solvent</th>
<th>X (product)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>PhI(OAc)2</td>
<td>CH3CN</td>
<td>OAc (3a)</td>
<td>86d</td>
</tr>
<tr>
<td>2a</td>
<td>PhI(OAc)2</td>
<td>MeOH</td>
<td>OMe (3c)</td>
<td>95</td>
</tr>
<tr>
<td>3a</td>
<td>PhI(OAc)2</td>
<td>EtOH</td>
<td>OEt (3d)</td>
<td>80</td>
</tr>
<tr>
<td>4a</td>
<td>PhI(OAc)2</td>
<td>4PrOH/HOAc</td>
<td>OPr (3d)</td>
<td>72</td>
</tr>
<tr>
<td>5a</td>
<td>PhI(OAc)2</td>
<td>CF3CH3OH</td>
<td>OCF3CF3 (3f)</td>
<td>71</td>
</tr>
<tr>
<td>6a</td>
<td>NCS</td>
<td>CH3CN</td>
<td>Cl (3g)</td>
<td>95</td>
</tr>
<tr>
<td>7a</td>
<td>NBS</td>
<td>CH3CN</td>
<td>Br (3h)</td>
<td>93</td>
</tr>
</tbody>
</table>

*1 eq of 1, 0.12 eq of oxidant, 1–2 mol % Pd(OAc)2 or 2, 75–100 °C. † Isolated yields. ‡ 11/1 mixture of 3a:3b. § 1–3 days.

@ extraordinarily high selectivity for C10
@ regioisomorphic oxidized products not observed

- high regioselectivity
- high catalytic activity of the isolated palladacycle 2
- palladacycle 2 also catalysed rxn.

For C-0 forming (For Ar-H)

- palladacycle 2 solv, heat → no products formed
- benzoquinone or Cu(OAc)2
- palladacycle 2
- major drawback

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


**without oxidant, biphenyl obtained (~trace)**

2 mol% Pd(OAc)2, 1 eq PhI(OAc)2 + biphenyl

PhI + PhI(OAc)2 + AcOH, 10 eq 1 eq

100 °C, 20 h

75%

PhOAc + PhI + AcOH, 10 eq 1 eq

100 °C, 20 h

~3%

PhOAc + Pd(OAc)2

*acetoxylation was initial product by time course exam.

Ph\((\text{OAc})_2\) ?

--- 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"

@ exclusion of air/moisture not required

--- preparation

Table 2. Chelate-Directed Oxidation of sp\(^2\) and sp\(^3\) C-H Bonds\(^{a,b}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Major Product</th>
<th>Yield(^c)</th>
<th>Entry</th>
<th>Major Product</th>
<th>Yield(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(in AcOH)</td>
<td>68%</td>
<td>7</td>
<td>(9) AcO</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>(in MeOH)</td>
<td>77%</td>
<td>8</td>
<td>(10) AcO</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>(in AcOH)</td>
<td>60%</td>
<td>9</td>
<td>&gt;2eq Ph((\text{OAc})_2) 83%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>complex mixture</td>
<td></td>
<td>10</td>
<td>(12) AcO</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td>2,2-di-OAc ~25%</td>
<td></td>
<td>11</td>
<td>(13) AcO</td>
<td>58%</td>
</tr>
<tr>
<td>6</td>
<td>2,2-di-OAc ~25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) For mono-oxidation: 1 equiv of substrate (0.12 M in AcOH (entries 1, 3, 5), MeOH (entry 2), or CHCN (entries 4–8)). 1.1–1.6 equiv of Ph\((\text{OAc})_2\), 1–6 mol % Pd(OAc)\(_2\), 100 °C, 12–20 h. \(^b\) For dioxidation: 1 equiv substrate (0.12 M in CHCN), 2.3–2.5 equiv of Ph\((\text{OAc})_2\), 6–8 mol % Pd(OAc)\(_2\), 100 °C, 12 h. \(^c\) Isolated yields. \(^d\) Yield determined by GC.

--- @ exclusion of air/moisture not required

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

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

"attractive alternative to ortho-lithiation/electrophilic addition procedures"
Palladium-Catalyzed Oxygenation of Unactivated sp$^3$ C–H Bonds

Lopa V. Dasoi, Kemi L. Hull, and Melanie S. Sanford*


< initial >

\[
Pd(OAc)_2 \ (5 \text{ mol\%}) \quad \text{PhI(OAc)}_2 (X \text{ eq}) \\
\begin{array}{ccc}
100 ^\circ \text{C}, 5.5 \text{ h} & (X = 1.1) & 3 \text{a-c mixture} \\
\end{array}
\]

\[
(X = 4.5) \quad 3 \text{c} \quad \text{59%} \\
\text{(without Pd)} \quad \text{no rxn.}
\]

Ac$_2$O --- prevent hydrolysis

< reactivity >

- OH oxime --- oxidative cleavage (?) to ketone
  ketone --- no rxn.
- no $\alpha$-C-H oxidation despite its higher acidity
cf) in stoichiometric Pd(ii) cases
  require fully $\alpha$-alkylated oxime

- no $\beta$-hydride elim.!

  $\Rightarrow$ rigidity of palladacycle

< selectivity >

1°-$\beta$-C-H selective (ent. 2)

$\Rightarrow$ strong steric preference (1° over 2°) for
5-membered palladacycle ($\beta$ vs $\alpha$ or $\gamma$)

- significantly enhanced by $\alpha$-branching (ent. 1-3)
  required conformation for C-H activation
  (coplanar between oxime and C-H)
  is readily accessed

  $\Rightarrow$ generally, di-OAc not obtained;

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Major Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me$_2$C=NOH</td>
<td>Me$_2$C=NOAc</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>Me$_2$C=NOH</td>
<td>Me$_2$C=NOAc</td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td>Me$_2$C=NOH</td>
<td>Me$_2$C=NOAc</td>
<td>39%</td>
</tr>
<tr>
<td>4</td>
<td>Me$_2$C=NOH</td>
<td>No Reaction</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Me$_2$C=NOH</td>
<td>No Reaction</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SM</th>
<th>conditions</th>
<th>TM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(OAc)$_2$ (5 mol%)</td>
<td>PhI(OAc)$_2$ (X eq)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Substrate Scope of sp$^3$ C–H Bond Oxygenation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>AcOH/Ac$_2$O 80 °C 5.5 h</td>
<td>12</td>
<td>61</td>
</tr>
</tbody>
</table>
| 2     | 90 °C 9 h | 14 | 81%
| 1.5   | 100 °C 1.5 h | 10 | 63%
| 1.1   | 80 °C 5 min | 12 | 60%
| 3.2   | AcOH 100 °C 12 h | 10 | 66% |
| 1.5   | CH$_2$Cl$_2$ 12 h | 12 | 65%
| 2.1   | 2.1 | 71%
| 1.1   | 1.1 | 75%
| 1.5   | AcOH/Ac$_2$O 80 °C 5.5 h | 10 | 51% |

< initial >

<table>
<thead>
<tr>
<th>SM</th>
<th>conditions</th>
<th>TM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(OAc)$_2$ (5 mol%)</td>
<td>PhI(OAc)$_2$ (X eq)</td>
<td></td>
</tr>
</tbody>
</table>

- deemed unreactive in stoichiometric
cycopalladation

(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°-$\beta$-C-H also reactive (ent. 9-10)

- $\alpha$ to O
  (electronic)

- structural rigidity
eq. selective

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

- Isolated yields. * isolated as a mixture of oxime E/Z isomers.
2-2. Mechanistic aspects for C-O forming reductive elimination

(Ar(Csp2)-O)

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 PdII with III-oxidant was confirmed by the rational design and isolation of PdIV complex

- relatively labile
- alkyl ligand can exchange between metal centers

(1.0-1.1 eq.)

PdIV stored in air in solid state at rt for a week

43-90%

PdIV@ relatively labile
@ alkyl ligand can exchange between metal centers

facile manipulation of electronic parameters

2 rigid cyclometalated aryl (prevent ligand exchange and C-C bond forming)

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

remarkably in organomet.PdIV field

X-ray Figure 1. ORTEP diagram of 2k:
(R = H, X = NO2)

2. these PdIV complexes undergo clean C-O bond forming reductive elimination upon themolysis

(5%C6D5N 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 discussed

same as PtIV or (bpy)PdIVMe3I case

(1) strong dependence of solvent polarity
(2) highly negative value of S* (-13 ~ -39 e.u.)
(3) ρ ~ +1.4 (for ArCO2)

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

B. (direct coupling)

~ rare process for PdIV, PtIV

C. (dissociate - internal coupling)

@ A is not probable pathway

2o (more soluble)

1) no dependence of solvent polarity
2) from Eyling analysis for $2c$

$$\ln(k/T) = -\Delta H^\ddagger/RT + \ln(k_B/b) + \Delta S^\ddagger/R$$

\[ S^* \]

$+4.2 \pm 1.4 \text{ eu (in } \text{d}_6\text{-DMSO})$

$-1.4 \pm 1.9 \text{ eu (in CDCl}_3\text{)}$

(not so charged in transition state?)

3) Electron donor substituents led to moderate rate accelerations

$(\rho \approx -1.36 \pm 0.04)$ (for ArCO$_2$)

(benzoate acts as a nucleophilic partner?)

4) no benzoate exchange

(comparable r.e. rate)

no incorporation of acetate

\[ @ B \text{ or C?} \]

(only preliminary)

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

| internal coupling plausible |

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...

\[ @ \text{ for Ar(Csp}_2\text{)-O bond forming r.e. might be internal ~ concerted three-centered} \]

\[ @ \text{ for C(sp}_3\text{)-O bond forming r.e.?} \]

\[ \text{S}_2\text{N mechanism was suggested from recent reports} \]

(inversion of stereochemistry)

\[
\begin{align*}
\text{A} & \quad \text{Cayley-O reductive elimination} \\
\text{B} & \quad \text{Chaly-O reductive elimination} \\
\text{(Stahl et al. J. Am. Chem. Soc. 2006, 128, 7180.)} \\
\end{align*}
\]

\[
\begin{align*}
\text{< oxidative functionalization after palladation >} \\
\text{must be faster than competing } \beta-\text{hydride elimination} \\
\end{align*}
\]

\[ ** \text{aminoacetoxylation, intramolecular} \]


\[ *\text{carbamate not essential} \]

\[ \text{sulfone amidine prevents cat. poison N-oxi.} \]

\[ \text{trans-alkene difunctionalization (net N,O-anti-addition)} \]

\[ *\text{w/o Pd, no rxn.} \]

\[ *\text{Cu(OAc)}_2\text{ (2.0 equiv) was ineffective.} \]

\[ \text{trans-aminopalladation; r.e. with retention} \]
**aminoacetoxylation, intermolecular**

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

trans alkene difunctionalization

exquisite regioselectivity (chelation of allylic oxygen)

**diamination, intramolecular**


Fujimori's lit. sem. (M1 part)

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

**Recent two reports suggests** r.e. with inversion (SN2)

Synthesis of Cyclopropanes via Pd(II/V)-Catalyzed Reactions of Enynes
Leilani L. Webes, Thomas W. Lyons, Katie A. Cychoz, and Melanie S. Sanford

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

Table 1. Substrate Scope of Oxidative Cyclopropane Formation

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H, Me</td>
<td>Ph, Ph</td>
<td>78%</td>
</tr>
<tr>
<td>2</td>
<td>H, Me</td>
<td>H, Ph</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>Me, Me</td>
<td>Me, Ph</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>Me, Me</td>
<td>Me, Ph</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>H, Me</td>
<td>Ph, Ph</td>
<td>46%</td>
</tr>
<tr>
<td>6</td>
<td>H, Me</td>
<td>H, Ph</td>
<td>44%</td>
</tr>
<tr>
<td>7</td>
<td>Me, Me</td>
<td>Me, Ph</td>
<td>44%</td>
</tr>
<tr>
<td>8</td>
<td>Me, Me</td>
<td>Me, Ph</td>
<td>44%</td>
</tr>
<tr>
<td>9</td>
<td>Me, Me</td>
<td>Me, Ph</td>
<td>44%</td>
</tr>
<tr>
<td>10</td>
<td>Me, Me</td>
<td>Me, Ph</td>
<td>44%</td>
</tr>
</tbody>
</table>

* Conditions: 5 mol% of Pd(OAc)_2, 1.1 to 4 equiv of PhI(OAc)_2, 60–80 °C, 1–16 h. * Isolated yields (average of two runs). * 6 mol% of bipy added.
clean inversion of olefin geometry

S_{N}2-type attack by the electron-rich tethered olefin

trans-acetoxy palladation

insertion of Pd^{II} retention of olefin geometry

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

(quite similar substrate)

A Palladium-Catalyzed Cyclization-Oxidation Sequence: Synthesis of Bicyclo[3.1.0]hexanes and Evidence for S_{N}2 C-O Bond Formation

Xiaoteng Tong,‡ Mathias Beiler,‡‡ and Man Kin Tse*‡‡

They suggested C-O r. e. from the alkyl-Pd(IV) species proceeds by an S_{N}2 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\(^\text{II}\) or Ru\(^\text{II}\)(= OMe, OMOM, F, Cl) or reported L-type ligands for Pd\(^\text{II}\)(= ketone, oxime)

tight chelation required to achieve selectivity prevents catalyst turnover.

(only one substrate can change this selectivity)

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

differentiate two directing group (Py > ketone or oxime) "complementary to ortho-lithiation" in terms of regioselectivity

(Can omit \(\text{I}^{\text{II}}\) oxidant ?)

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

(construct) cf) same strategy was reported in \(\text{Pt}^{\text{IV}}\) chemistry

to prevent OAc hydrolysis external -OAc source possible ?

@ (table 1) oxidants screening

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>of 2a(^*)</th>
<th>entry</th>
<th>oxidant</th>
<th>of 2a(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O₂/urea</td>
<td>10</td>
<td>5</td>
<td>CH₃CO₂H</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>50%aq H₂O₂</td>
<td>11</td>
<td>6</td>
<td>Oxone</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>m-CPBA</td>
<td>14</td>
<td>7</td>
<td>K₂S₂O₈</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>70%aq BuO₂SO₄</td>
<td>18</td>
<td>8</td>
<td>PhO₂(OAc)₂</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^*\) Conditions: 5 mol% Pd(OAc)₂, 2 equiv of oxidant, 0.12 M 2 in AcO/H AcO (50:50), 100 °C, 12 h; 2a isolated as a 5:1 mixture of oxygen 5\% bromine and as a >20:1 mixture of regioisomers. Between 10 and 15% of the difluoroacetylated product was also isolated.

@ (scheme 2) scalability OK

(Kugelrohr distillation) cf) Oxone consists of 2KHSO₅, KHSO₄, K₂SO₄, its active component is KHSO₅ cheap, (formation of dioxirane etc.)

slightly good y. for C(sp3)-H
@ (table 2) \[ \begin{array}{ccc}
\text{entry} & \text{starting material} & \text{major product} & \text{yield} \\
1 & \text{(3)} & \text{NC} & \text{53\%} \\
6 & \text{(8)} & \text{OAc} & \text{57\%} \\
7 & \text{(8)} & \text{OAc} & \text{37\%} \\
12 & \text{(14)} & \text{OAc} & \text{45\%} \\
13 & \text{(15)} & \text{OAc} & \text{63\%} \\
\end{array} \]

@ nearly identical regioselectivities with Ph1(OAc)2 (less hindered \( o-C-H \))

<w/o Ac_2O> improved functional group tolerance

<merit>

<demerit>
comparable or moderately lower yields than with Ph1(OAc)2
N-oxidation of some basic nitrogen containing directing group (pyrazine)

\[\text{Py-type failed? therefore oxime selected?}\]

@ (table 3) \textbf{MeOH} also utilized as external source

\[\text{Conditions}: 10 \text{ \textdegree}C, 3 \text{ equiv of Oxone, 0.12 M in MeOH, 25 \textdegree C to between 40 \text{ and } 85 \textdegree C over 28 \text{ h}. Major regiosomer and oxime E/Z isomer is shown (where relevant).} \]

\[\text{K}_2\text{S}_2\text{O}_8 \text{ used as the oxidant.}\]
2-4. Other C-X forming reaction

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

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

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

@ NXS was used instead of PhI\(_2\) (instability under rxn conditions)

@ So far, good selectivity seems to be only for Ar\((\text{sp}^2)\)-H

@ C\((\text{sp}3)\)-I forming achieved

J-Q Yu et al. \((\text{Angew. Chem. Int. Ed. } 2005, 44, 2112.\)\)

---

**Table 2.** Pd(\(\text{OAc}_2\))-Catalyzed Direct Halogenation of Aromes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>5b-7b</td>
<td>60%</td>
</tr>
</tbody>
</table>

---

**Table 2.** Asymmetric iodination.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14a</td>
<td>14b</td>
<td>83%</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>15a</td>
<td>15b</td>
<td>62%</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>16a</td>
<td>16b</td>
<td>95%</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>17a</td>
<td>17b</td>
<td>98%</td>
<td>99:1</td>
</tr>
</tbody>
</table>

---

*Reaction conditions: Pd(\(\text{OAc}_2\)), (10 mol%), I\(_2\) (1 equiv), PhI(\(\text{OAc}_2\)), (1 equiv), CH\(_3\)Cl, 24°C, 30 h. [a] Entry 1-3. [b] Entry 4-6. [c] 61:39: d.r. (NMR spectroscopy). [d] PdI\(_2\) precipitated at 36-48 h. PhI(\(\text{OAc}_2\)), (1 equiv) was added, and stirring continued for another 48 h.

---

Scheme 1. Proposed catalytic cycle of C-H bond activation.
**<C-F forming>**


* No Pd, no fluorinated product.

* Microwave accelerates reaction dramatically.

* Formation of 1b is not Pd-catalyzed reaction.

**Table 1. Palladium-Catalyzed Fluorination of 8-Methylequinoline**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant Source</th>
<th>Yield of 1a+1b+1c</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF3·Et2O</td>
<td>82% (36%)</td>
<td>57% (75%)</td>
</tr>
<tr>
<td>2</td>
<td>BF3·Et2O</td>
<td>25% (0%)</td>
<td>37% (15%)</td>
</tr>
<tr>
<td>3</td>
<td>BF3·Et2O</td>
<td>24% (22%)</td>
<td>19% (16%)</td>
</tr>
<tr>
<td>4</td>
<td>BF3·Et2O</td>
<td>25% (12%)</td>
<td>6% (3%)</td>
</tr>
<tr>
<td>5</td>
<td>PhPO2Cl</td>
<td>19% (9%)</td>
<td>15% (9%)</td>
</tr>
</tbody>
</table>

*Conditions: 110 °C, 18 h.*

*3* was optimal F⁺ source for phenylpyridine type.

< C-C forming >


cf) Pd⁰/ii approach (see page 5).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Product</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
<tr>
<td>7</td>
<td>C≡N</td>
<td>F-CN</td>
<td>65%</td>
</tr>
</tbody>
</table>

*Conditions: 1 equiv of substrate, 1.1-2.5 equiv of [Ph3]BF4, 3 mol% Pd(OAc)₂ in AcOH, Ac2O, AcO, or toluene 100 °C, 1-24 h.*

*With 2 equiv of substrate, 1.8 equiv of [Ph3]BF4, NaHCO₃ (1.5-2.5 equiv) added.*

< C-C forming >
<div class="markdown-body">

Iodonium reagents have been used as highly reactive coupling partners for Pd<sup>0/II</sup> catalyzed reaction. 

**Mechanism**

- **Negative for Pd<sup>IV</sup>**
  - [Iodonium] reagents have been used as highly reactive coupling partners for Pd<sup>0/II</sup> catalyzed reaction
  - (i) oxidation to Pd<sup>IV</sup> by [Ph<sub>2</sub>I]<sub>BF<sub>4</sub></sub> then C-C forming reaction (without a change of oxidation state at the metal).
  - (ii) direct electrophilic cleavage of the Pd<sup>II</sup>-C by [Ph<sub>2</sub>I]<sub>BF<sub>4</sub></sub> (still unclear)

- **Positive for Pd<sup>IV</sup>**
  - more electron-rich Ar is generally transferred selectively
  - more electron-deficient favor

---

**Summary**

What is the key for Sanford's success?

**Future**

- asymmetric variant (monodentate ?, trinuclear-Pd ?)
- further functionalities (N, S, CF<sub>3</sub> ?)
- toward more complex molecule

---

**Table 2. Functionalization of 1 with Diverse Aryl Substituents Using [Mes–I–Ar]<sub>BF<sub>4</sub></sub>**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar (Product)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[16]</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>[1b]</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>[1c]</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>[1d]</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>[1e]</td>
<td>84%</td>
</tr>
<tr>
<td>6</td>
<td>[1f]</td>
<td>72%</td>
</tr>
<tr>
<td>7</td>
<td>[1g]</td>
<td>87%</td>
</tr>
</tbody>
</table>

*Conditions: substrate 1 (0.12 M), [Mes–I–Ar]<sub>BF<sub>4</sub></sub>(1.1–1.3 equiv). Pd(OAc)<sub>2</sub> (5 mol%), AcOH, 12 h, 100 °C. *Reaction carried out at 120 °C.*

---

**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.)

---

**Combined Palladacycle and Pd<sup>IV</sup> chemistry**

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