Palladium-Mediated formation of Carbon(Sp^3)-Halogen bonds

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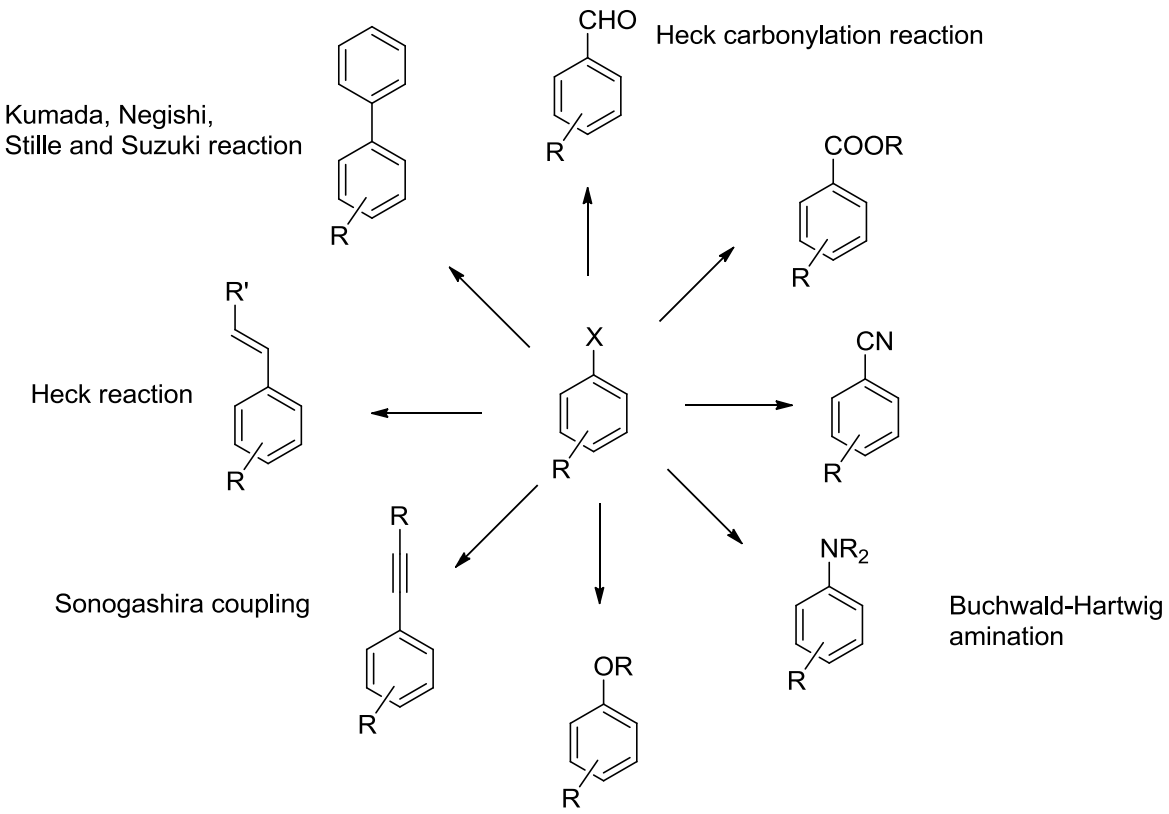
Introduction

- *Forming **C-C** bonds, **C-N** bonds, **C-O** bonds*[1]

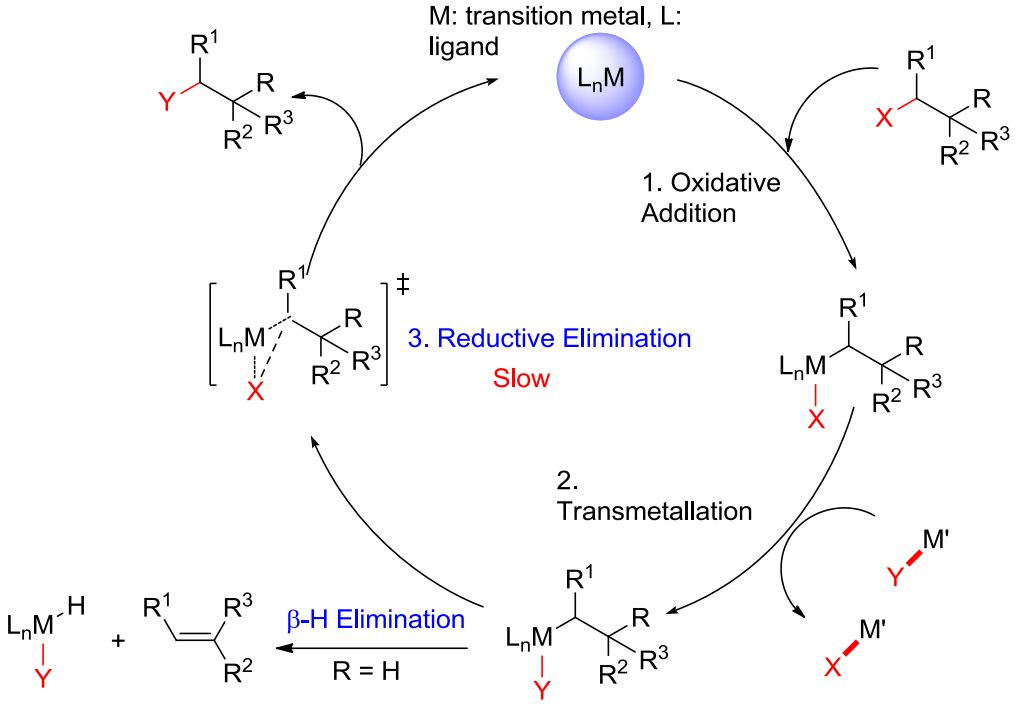


- *Forming **C-X** bonds?*

[1] Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431

Introduction

Challenges in C-X Bond Formation

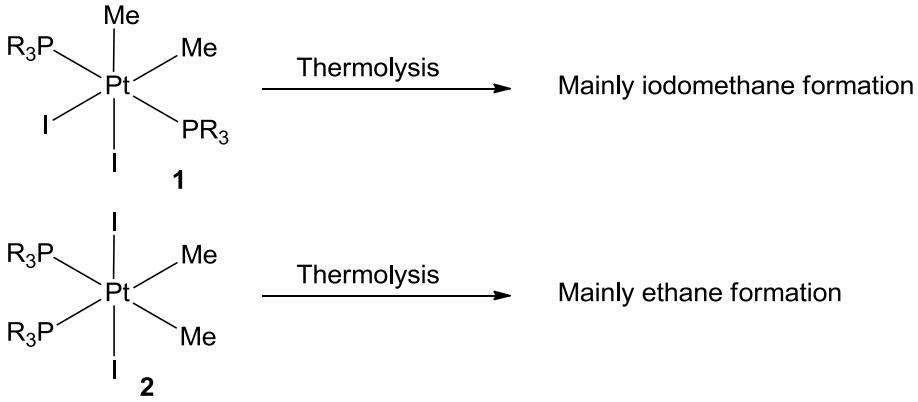


Ease of C-Y reductive elimination

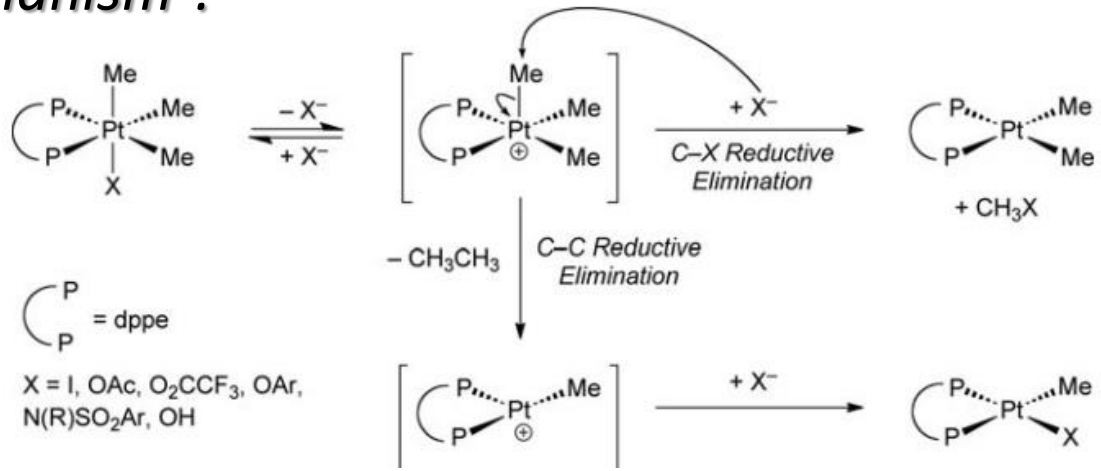
C-I > C-Br > C-Cl > C-F

$C(Sp^3)$-Halide Reductive Elimination From High Valent Metal Centers

- *The First Example of C_{Sp3}-X Bond Formation[1]*



- *The mechanism[2]:*

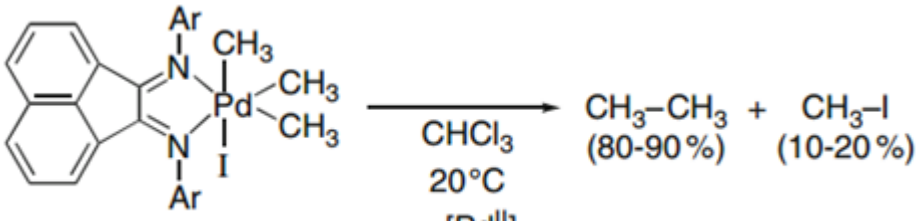


[1] Ruddick, J. D.; Shaw, B. L. *J. Chem. Soc. A* **1969**, 2969

[2] a) Goldberg, K. I.; Yan, J.; Winter, E. L. *J. Am. Chem. Soc.* **1994**, *116*, 1573; b) Goldberg, K. I.; Yan, J.; Breitung, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 6889

$C(Sp^3)$-Halide Reductive Elimination From High Valent Metal Centers

➢ *C_{Sp3}-I Bond Formation reductive elimination from Pd(IV)*



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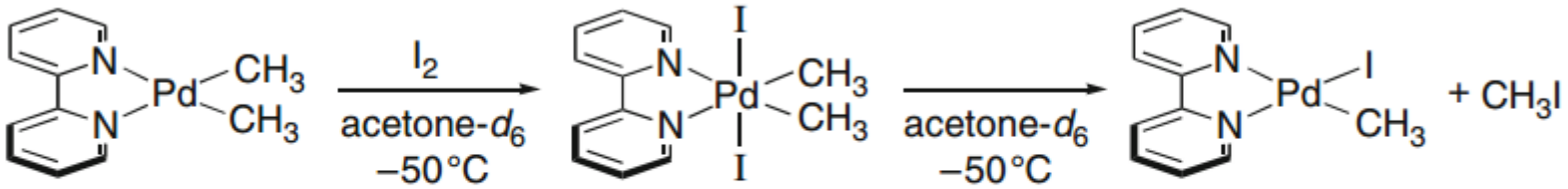


4

5

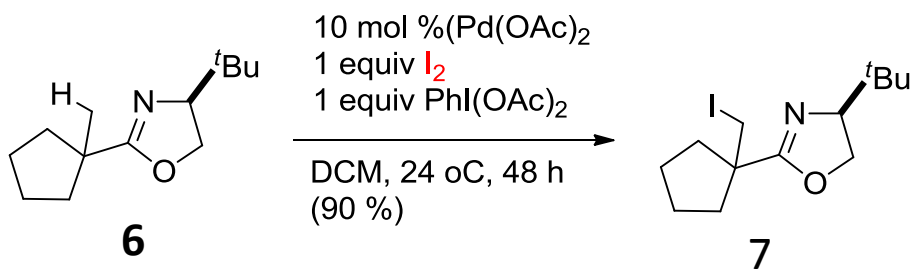
detected by NMR spectroscopy

[1] van, A. R.; Rijnberg, E.; Elsevier, C. J. *Organometallics,* **1994**, 13, 706

[2] Canty, A. J.; Denney, M. C.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 1122

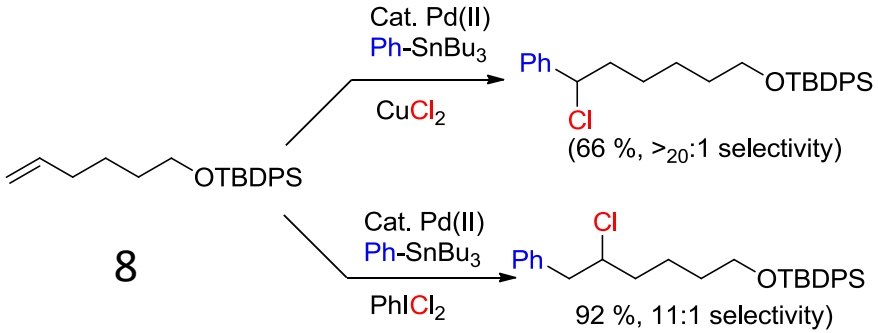
$C(Sp^3)$-Halide Reductive Elimination From High Valent Metal Centers

➢ Catalytically C_{Sp3}-I Bond Formation[1]



$PhI(OAc)_2$ contribute to C-H activation;
I_2 contribute to forming Pd(IV) complex.

➢ Catalytically C_{Sp3}-Cl Bond Formation[2]



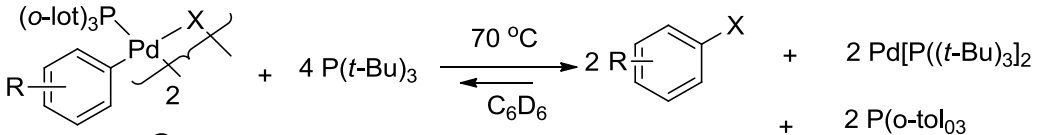
Different reactive electrophilic chlorinating reagent

High reactive iodine(III) oxidants such as PhICl2 might be effective at surpressing β –hydride elimination.

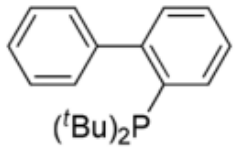
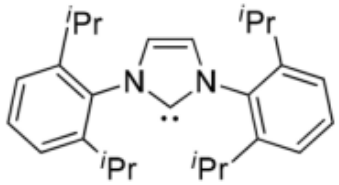
[1] Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2005**, *44,* 2112
[2] Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130,* 2150

C(Sp^3)-Halide Reductive Elimination From Pd(II) Species

- *Sterically hindered Phosphine ligands could promote the reductive elimiation*



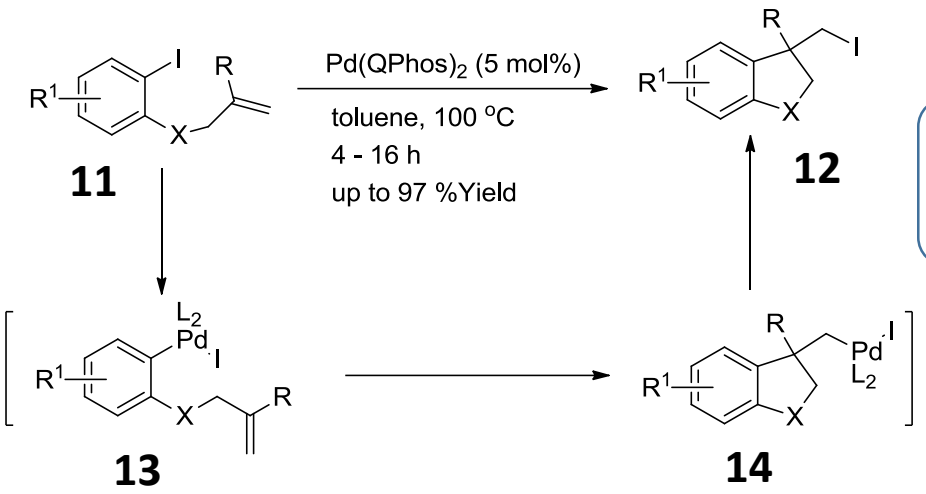
9 **10**

L	yield	L	yield
$P(^tBu)_3$	70% Ar-Cl 70% Ar-Br 39% Ar-I	$PFc(^tBu)_2$	0
$PCy(^tBu)_2$	10% Ar-Cl 15% Ar-Br		0
$P(1\text{-Ad})(^tBu)_2$	69% Ar-Cl 81% Ar-Br		0
Q-phos	52% Ar-Cl 42% Ar-Br		

(a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2001**, *123*, 1232;
(b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2003**, *125*, 13944;
(c) Roy, A. H.; Hartwig, J. F. *Organometallics*, **2004**, *23*, 1533

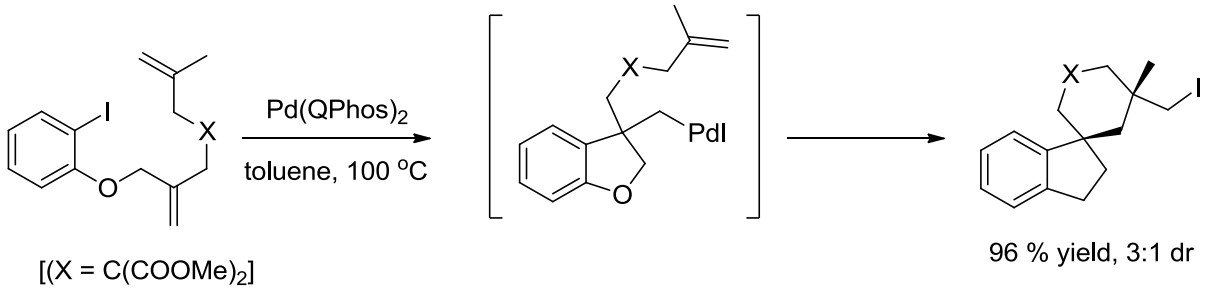
$C(Sp^3)$-Halide Reductive Elimination From Pd(II) Species

- *Pd(0) mediated C--X Bond Formation*[1]



TEMPO did not inhibit the reaction

- *Domino synthesis of polycyclic alkyl iodide*[2]



[(X = C(COOMe)$_2$]

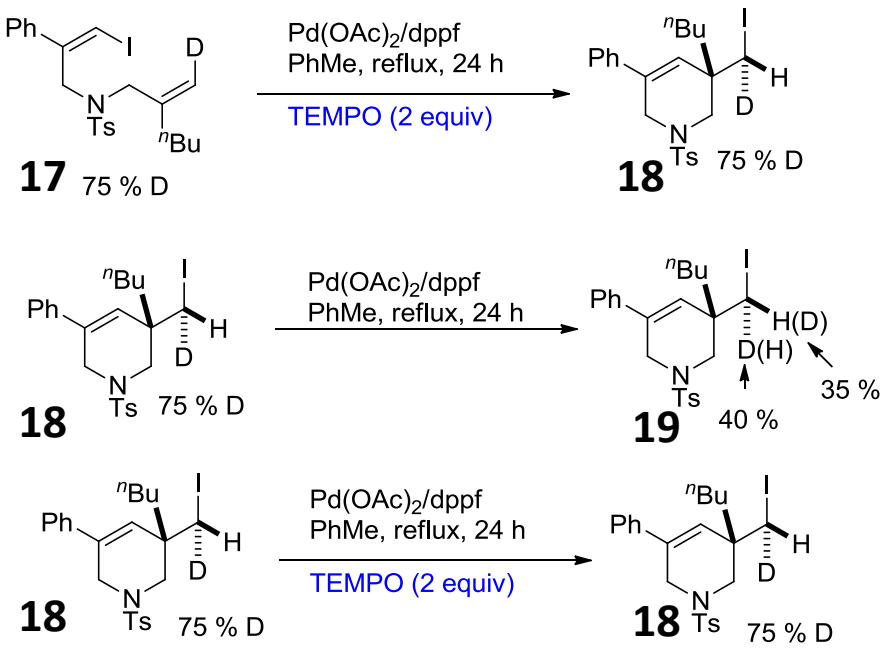
15 **16**

[1] Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.*, **2011**, *133*, 1778

[2] Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.*, **2011**, *133*, 4916

C(Sp^3)-Halide Reductive Elimination From Pd(II) Species

➢ *Studies with deuterium-labeled vinyl iodides*

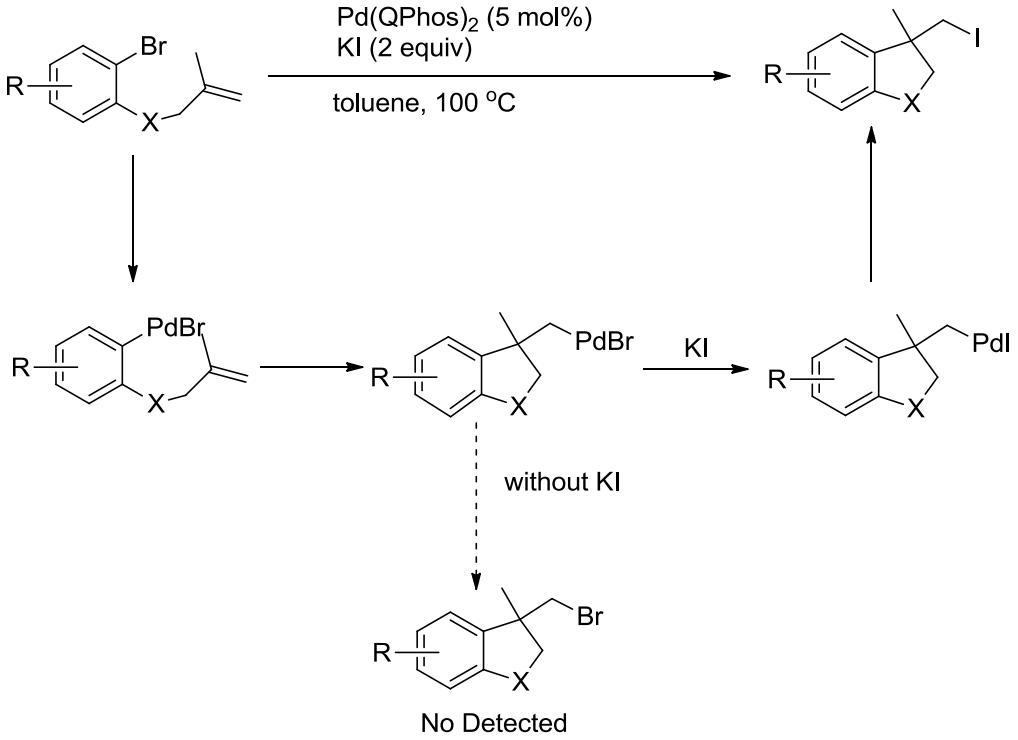


- The Palladium catalyzed carboiodination reaction is a stereospecific process.
- Pd/dppf system initiated radical process after the formation of the product.

Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146

$C(Sp^3)$-Halide Reductive Elimination From Pd(II) Species

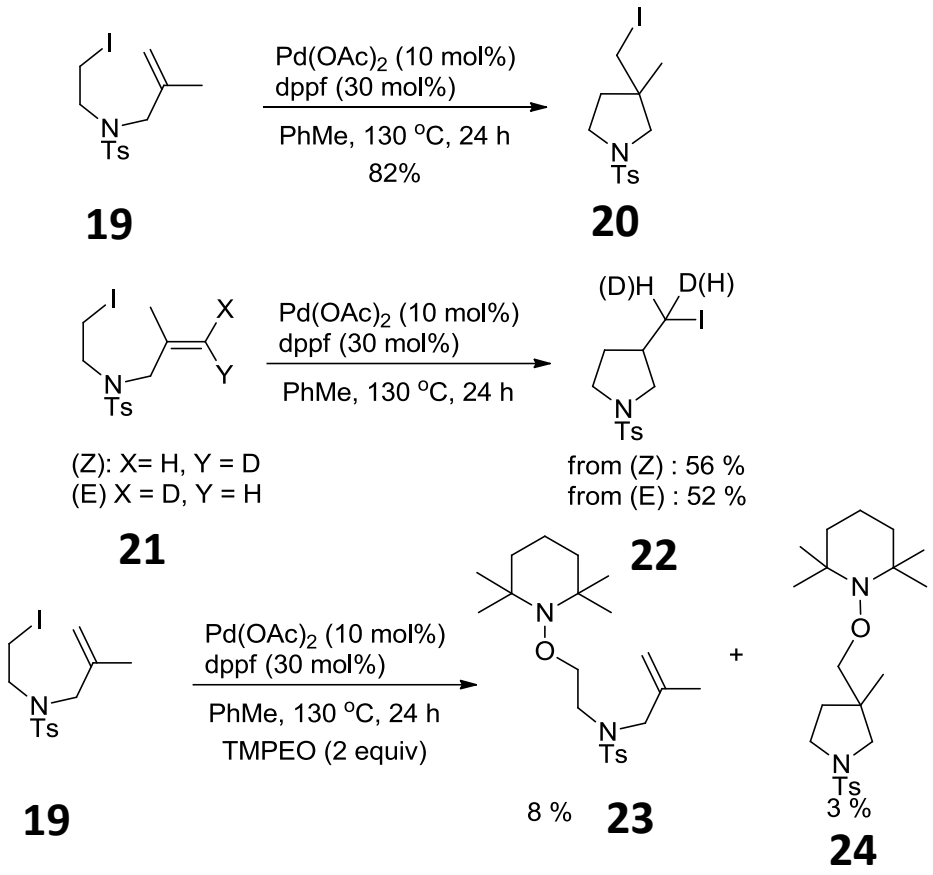
- *Carboiodination of aryl bromides (more useful)*



Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916.

Other Reaction Types

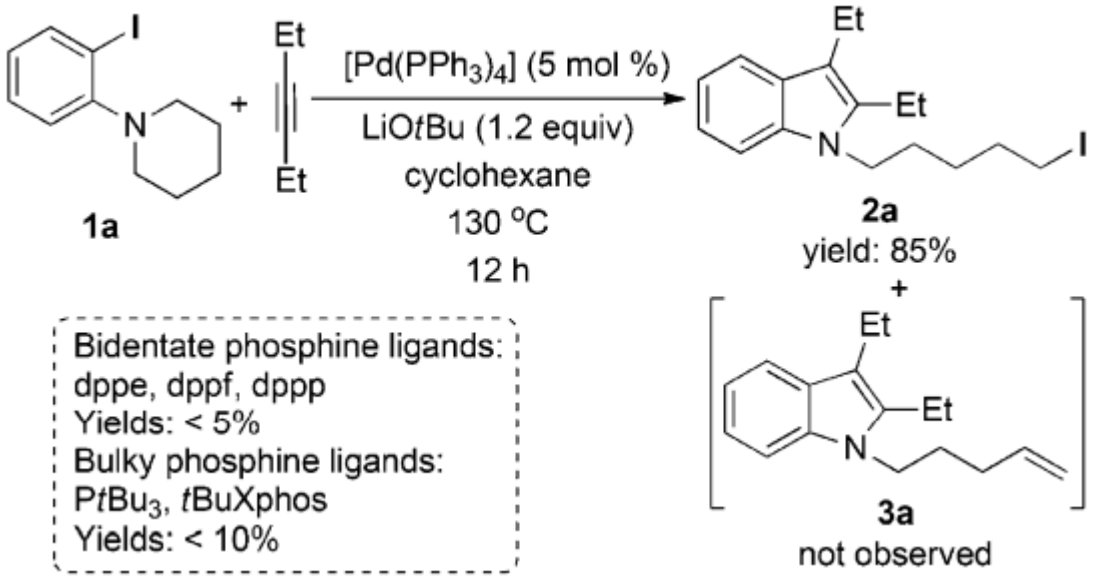
- *Reaction with Radical intermediate*



Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* , **2012**, *10*, 7274

New Strategy

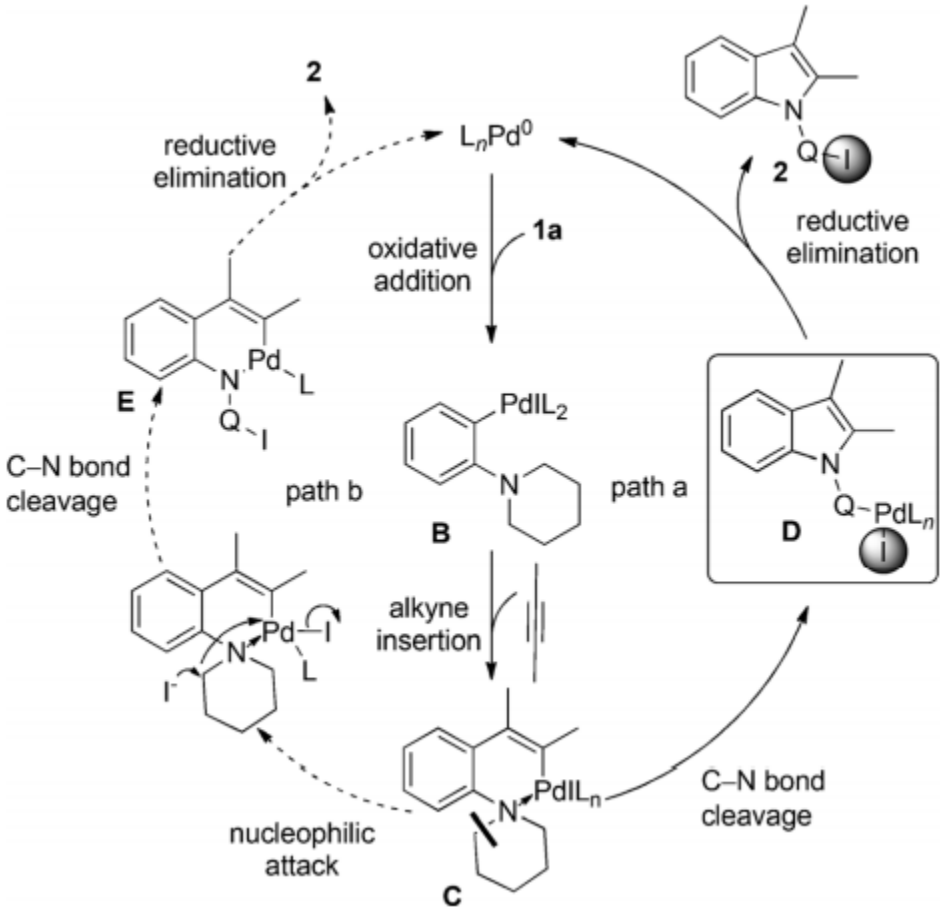
- *R.E. from Alkylpalladium Halides containing syn-β-hydrogen atoms*



DOI: 10.1002/anie.201408341

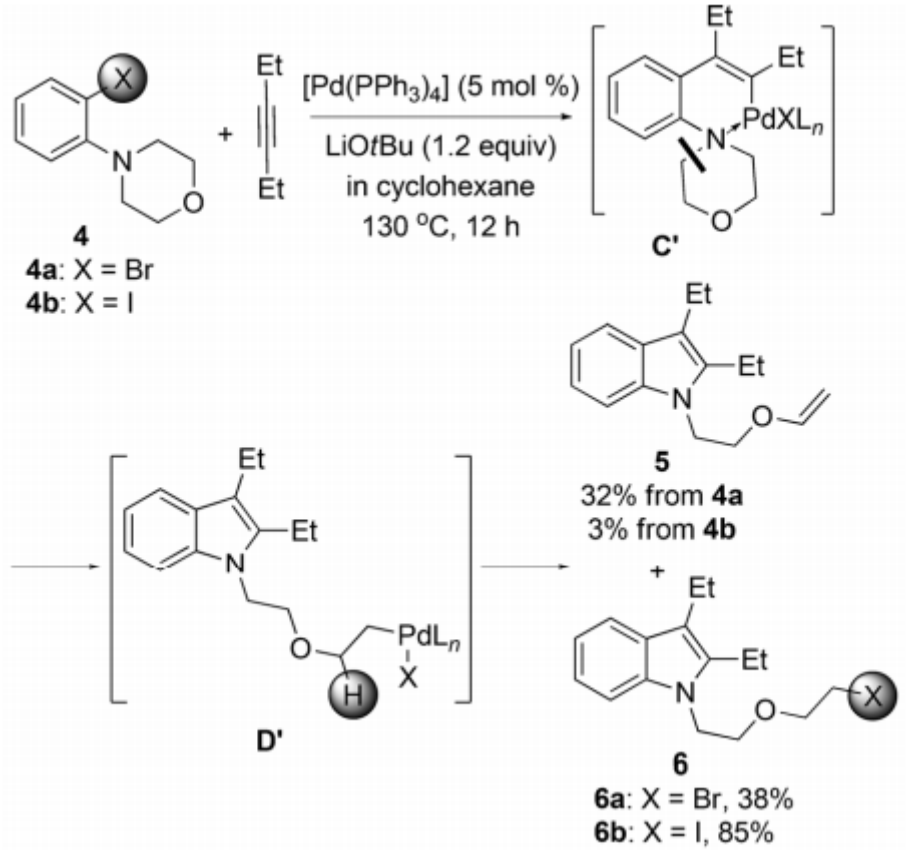
New Strategy

- *Proposed Catalytic Cycle:*



New Strategy

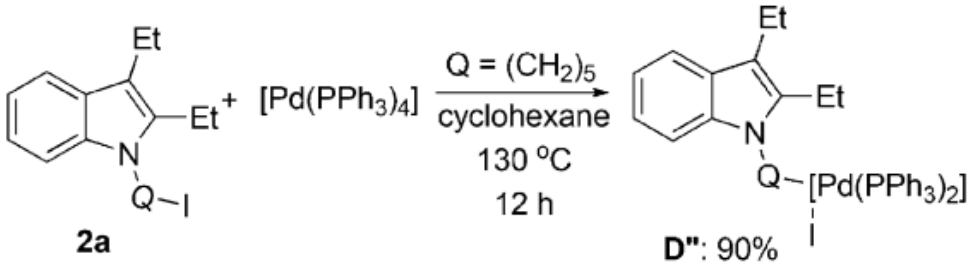
- *Controlled Experiments:*

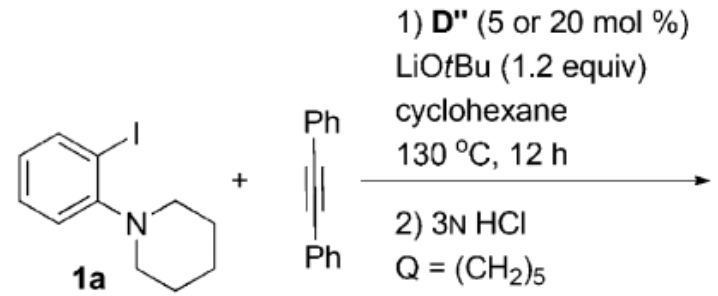


Compounds **6** —LiO*t*Bu (1.2 equiv), in cyclohexane, 130 °C, 12 h→ No reaction

New Strategy

- *Isolation and Catalytic Application of the Alkylpalladium Intermediate*





with 5 mol% of **D"**

2f: 88% **8**: 3% **2a**: 3%

with 20 mol% of **D"**

2f: 75% **8**: 15% **2a**: 17%

Summary and Outlook

- It provides an overview of the recent advances related to the R. E. of C-Pd-X specie. Many powerful strategies have been developed.

- The further attention should be paid to the following points
  - To develop the asymmetric version;
  - To uncover the mechanisms;
  - To develop strategies for more challenging alkyl-Br, alkyl-Cl and alkyl-F reductive elimination.

Thanks For Your attention