The Chemistry of Jin-Quan YU

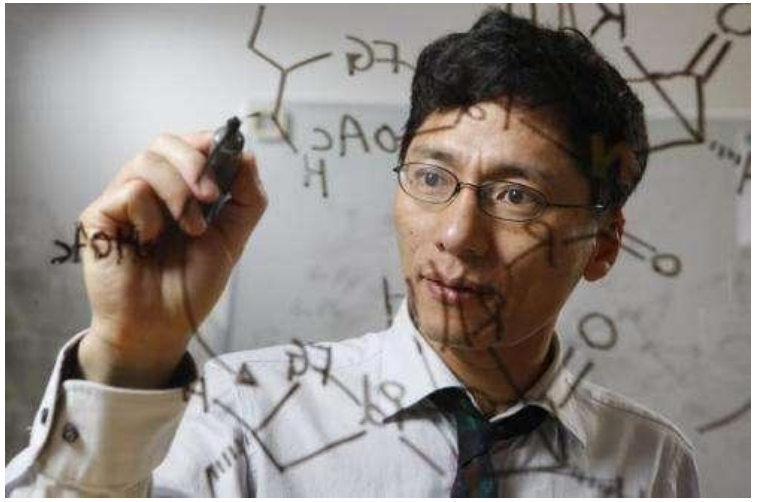
Ophélie Quinonero
Literature Seminar - Group Meeting
11 / 02 / 2016

Jin-Quan YU

- **B.S.** *(1982-87),* East China Normal University, China *(Pr. L.X. Dai, Pr. B.Q. Wu)*
- **M.S.** *(1988-90),* Guangzhou Institute of Chemistry, China *(Pr. S.D. Xiao)*
- **Ph.D.** *(1994-99),* University of Cambridge, UK *(Pr. J.B. Spencer)*
- **Postdoc**. *(2001-02),* Harvard University, USA *(Pr. E.J. Corey)*
- Currently, Frank and Bertha Hupp **Professor of Chemistry** at TSRI, USA

164 papers

4 papers published in *Nature*
4 papers in Science
68 papers in *J. Am. Chem. Soc*.
12 papers in *Angew. Chem. Int. Ed*.
…



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II - 3. Pd (II)/Pd(0)

III - Reactivity and scope: weak coordination as a powerful tool

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V - 2. Meta regioselectivity
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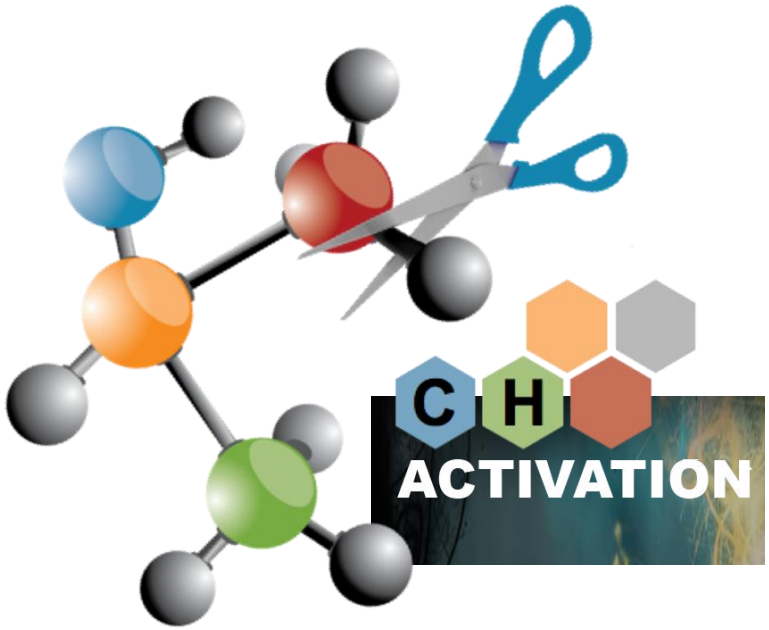
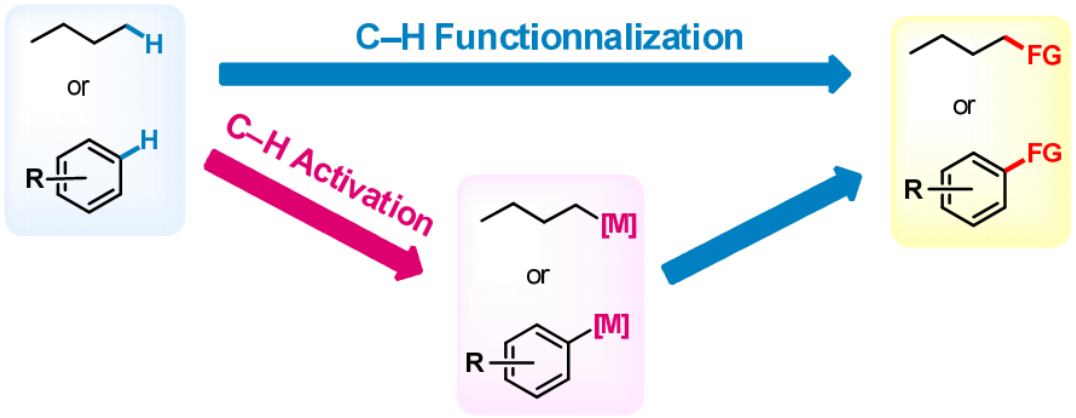


I - Introduction

I - 1. Definitions, Principle and Challenges

• **Definitions**



***C-H activation*:** formation of a C-M bond with rupture of a C-H bond

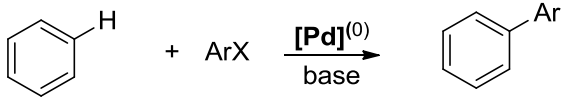
***C-H functionalization*:** overall process (H replaced with a functional group)

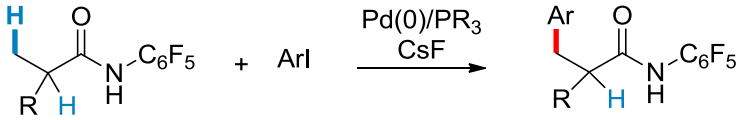
• **Principle:** Functionalization of unactivated C-H bonds

• **Challenges:** Find suitable catalysts and selectively functionalize one single C-H bond in a complex structure

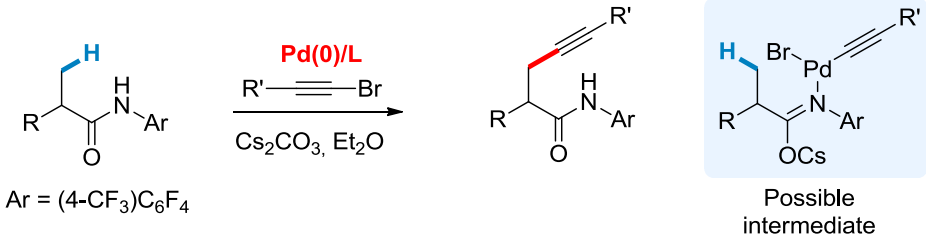
II - Catalytic Platforms: three types of Palladium-Catalyzed C-H activation

II - 1. Pd(0)/Pd(II): Ohno, Baudouin, Gevorgyan, Buchwald, Fagnou, Echavarren, Itami, Cramer…





M. Wasa,K.M. Engle,J.-Q. Yu, J. Am. Chem. Soc. **2009**, *131*, 9886



Ar = (4-CF_3)C_6F_4

Possible intermediate

J. He, M. Wasa, Kelvin S. L. Chan, and J.-Q. Yu, *J. Am. Chem. Soc*. **2013**, *135*, 3387

II – Catalytic Platforms: three types of Palladium-Catalyzed C-H activation

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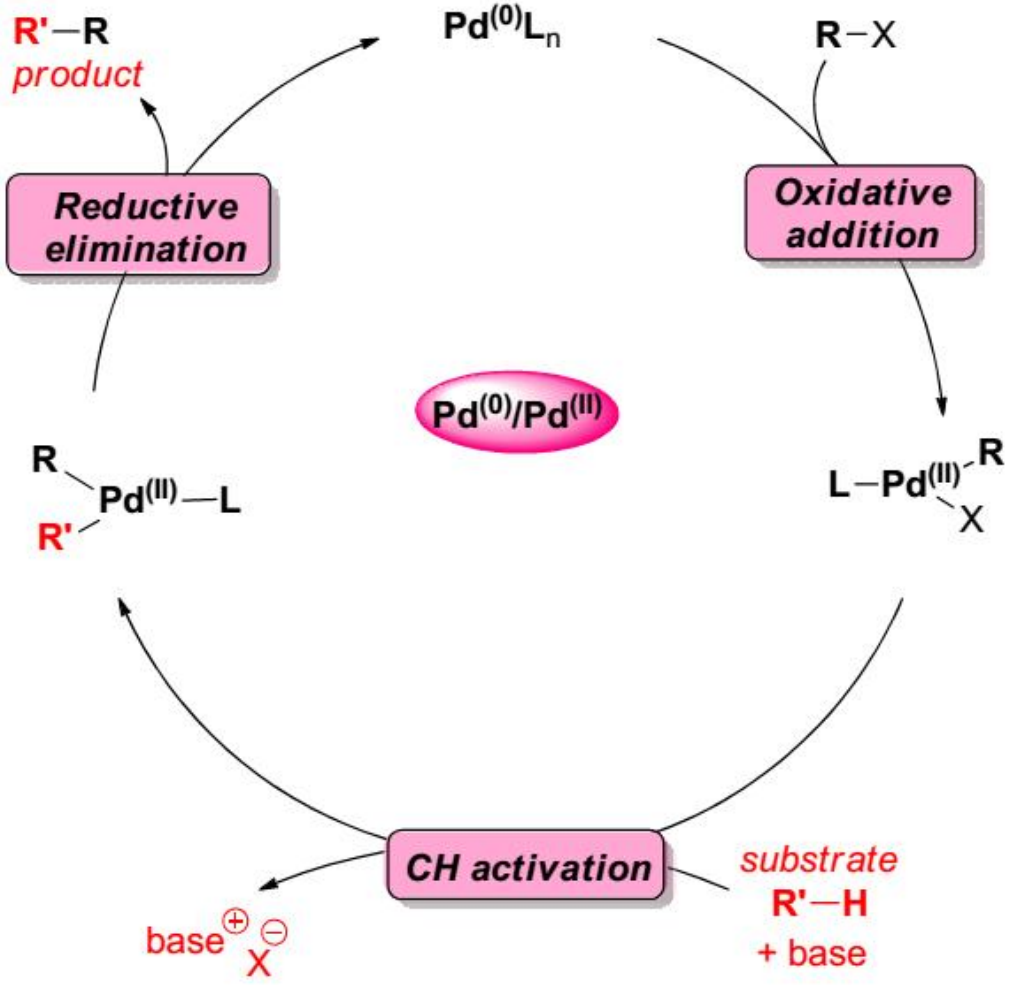

II - Catalytic Platforms: three types of Palladium-Catalyzed C-H activation

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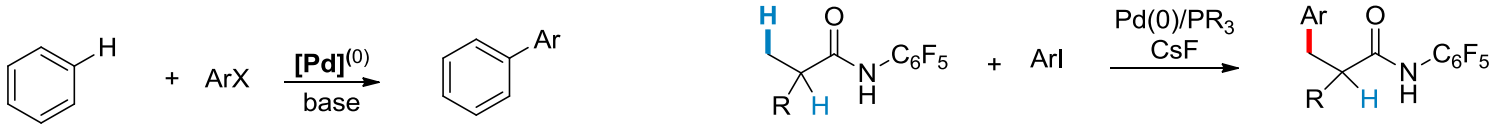
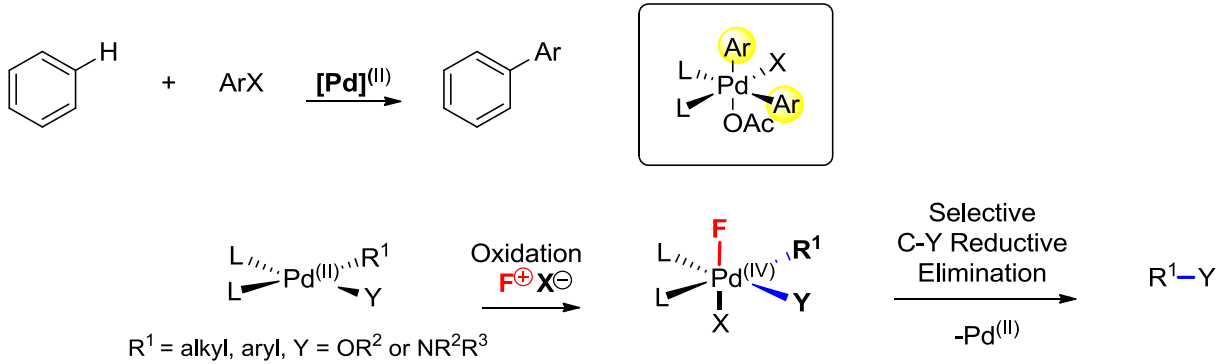


M. Wasa,K.M. Engle,J.-Q. Yu, J. Am. Chem. Soc. **2009**, *131*, 9886

II - 2. Pd(II)/Pd(IV): Canty, Tremont, Crabtree, Stock, Dyker, Carretero, Sanford, Daugulis…



R^1 = alkyl, aryl, Y = OR^2 or NR^2R^3

K.M. Engle,T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 1478

II - Catalytic Platforms: three types of Palladium-Catalyzed C-H activation

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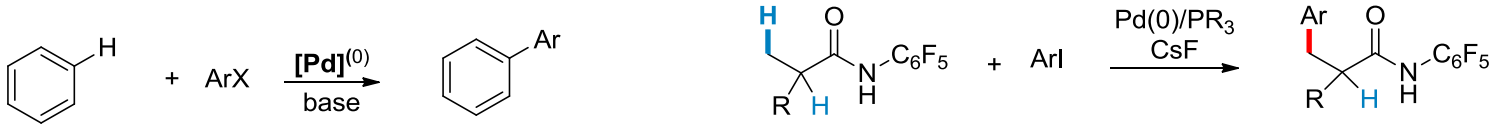

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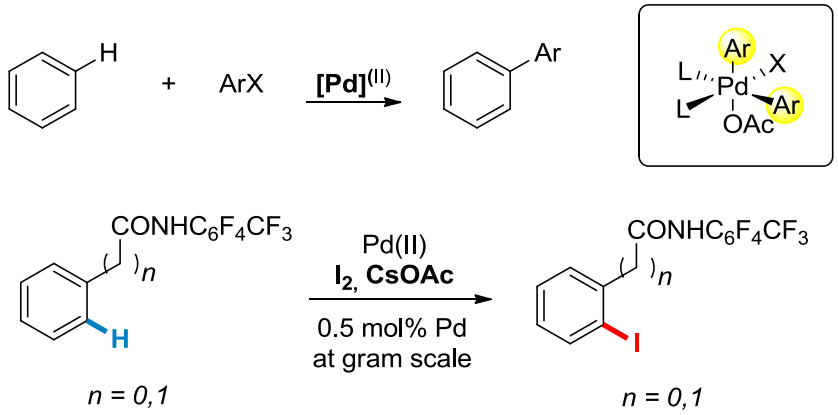

Compatible heterocyclic arenes
imidazole, pyrazole, oxazole, isoxazole, thiazole, pyridine

X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 10326.

II – Catalytic Platforms: three types of Palladium-Catalyzed C-H activation

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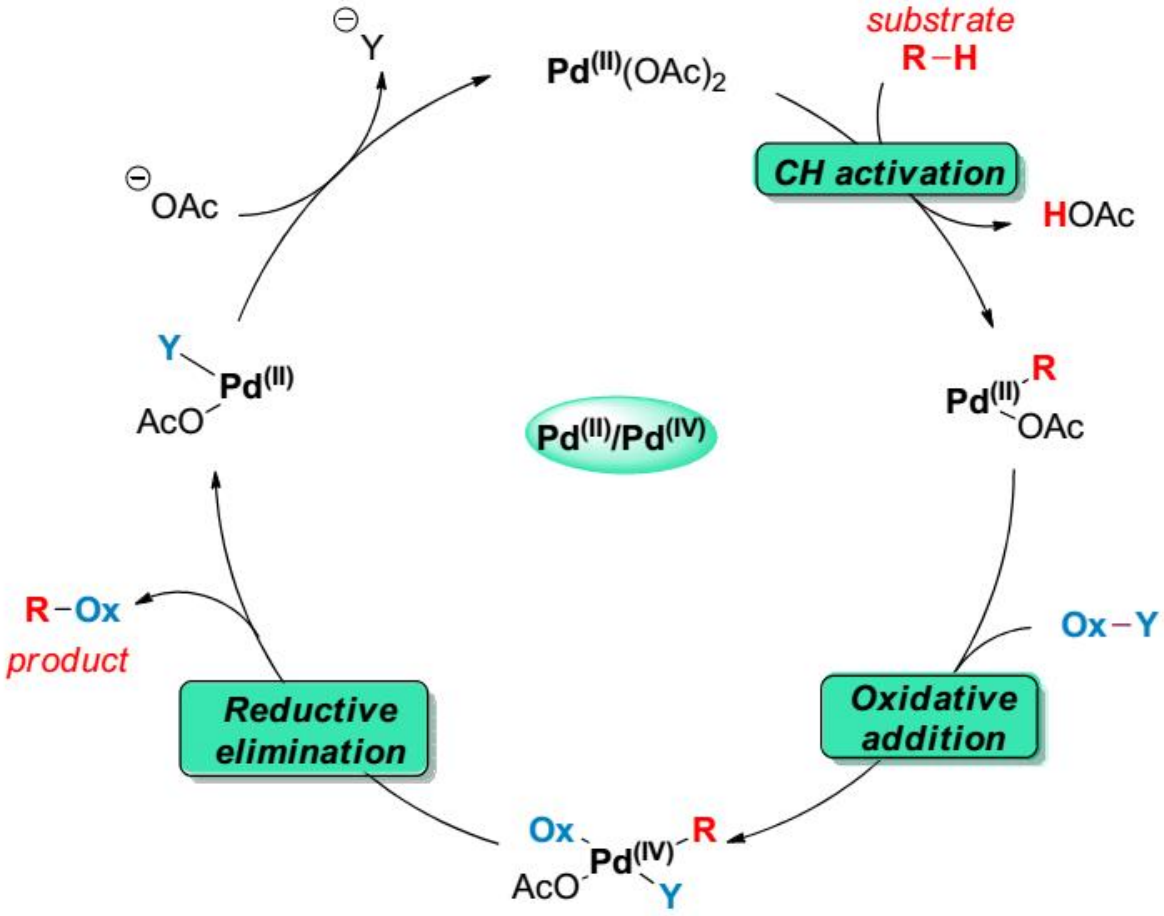

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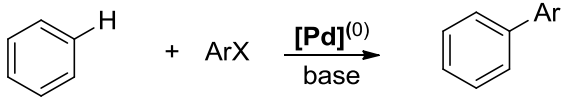

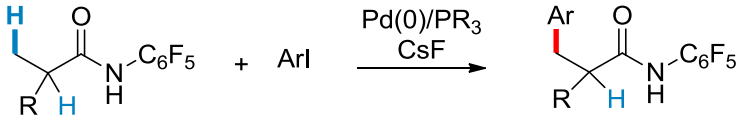

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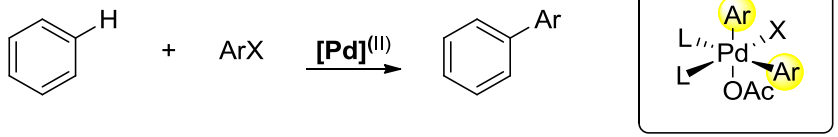
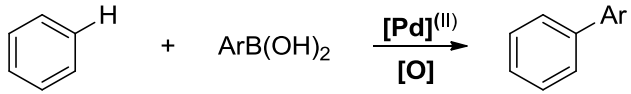


II - 3. Pd(II)/Pd(0):



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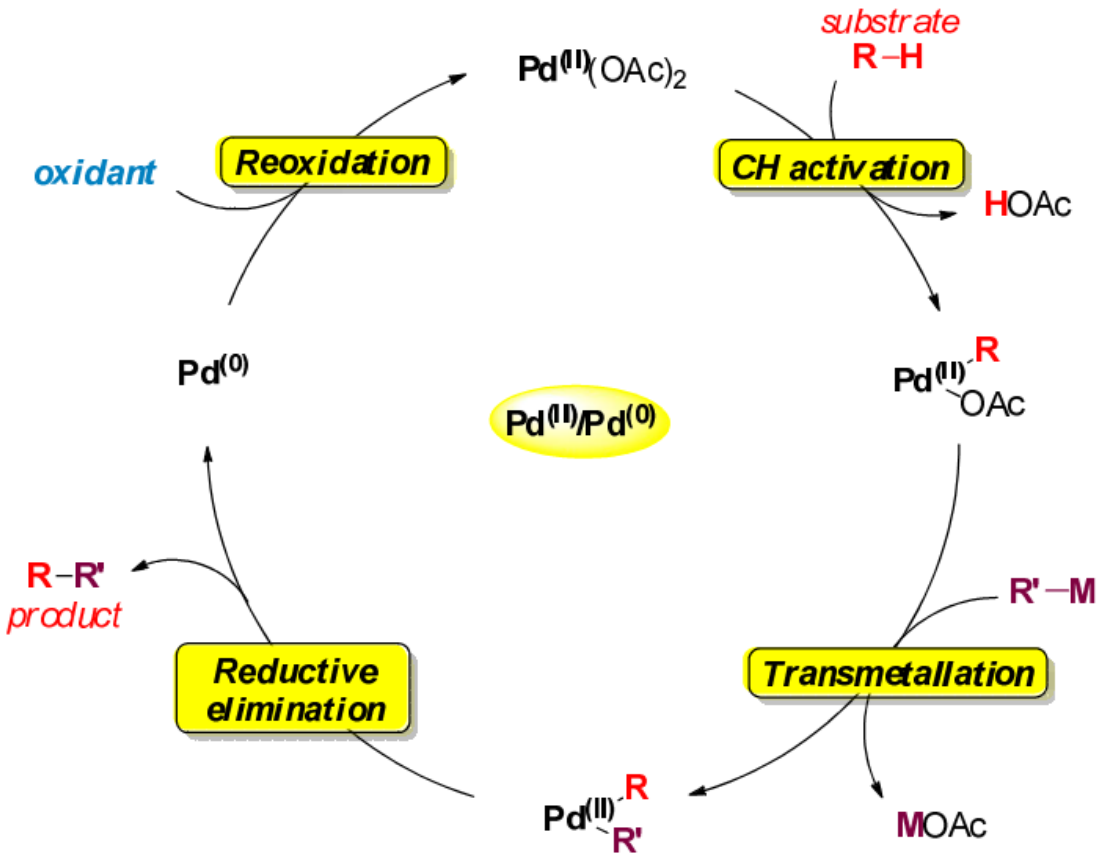

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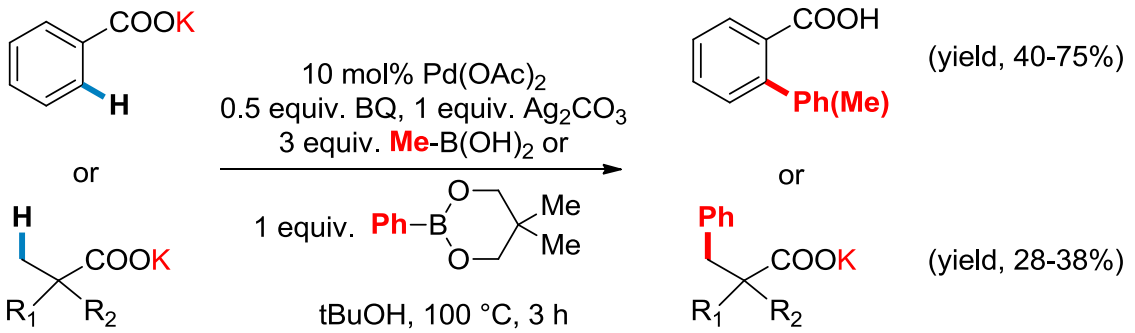
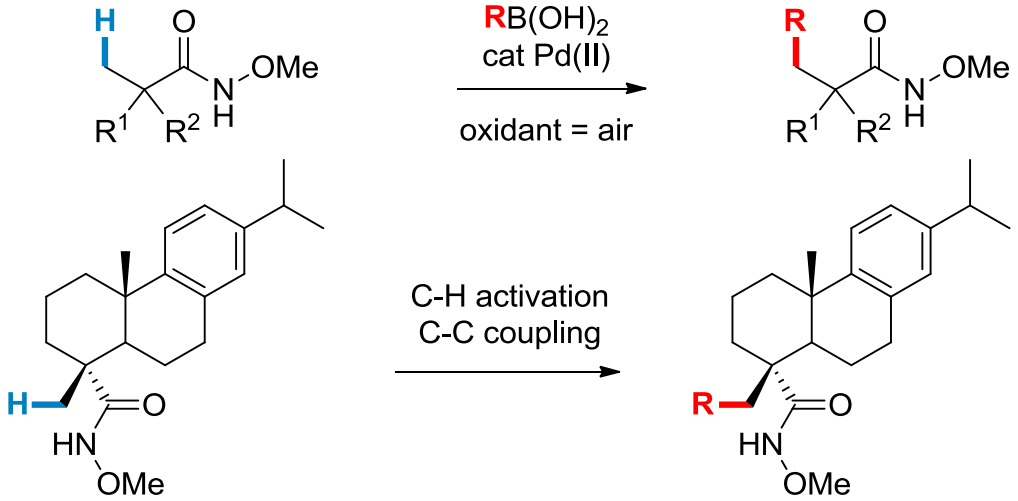


R. Giri, N. L. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L.B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc* **2007**, *129*, 3510

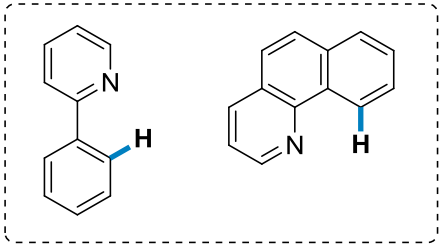


D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc*. **2008,** *130*, 7190

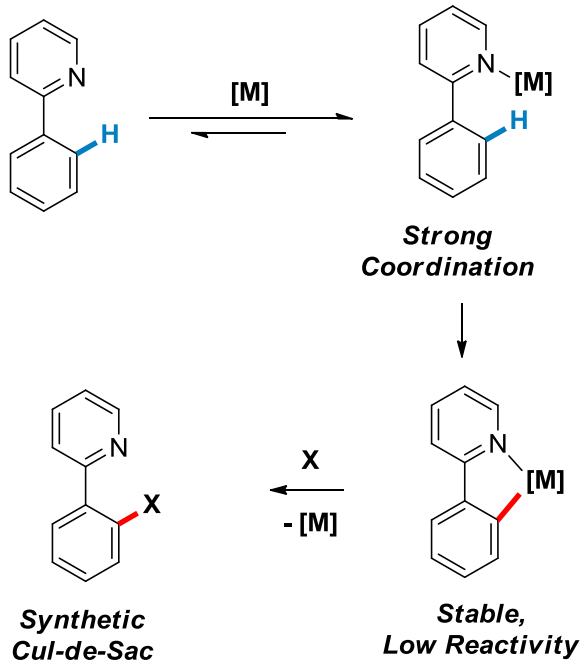
III - Reactivity and Scope: weak coordination as a powerful tool

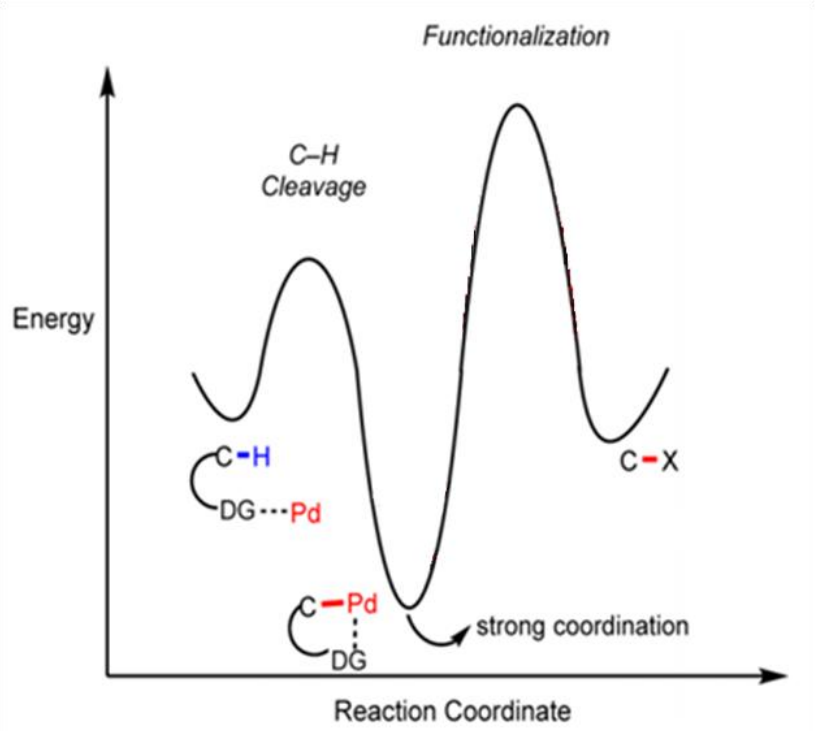
III - 1. Coordinating directing groups:

- **Strongly coordinating directing groups**



C-H Functionalization via Classical Cyclometalation





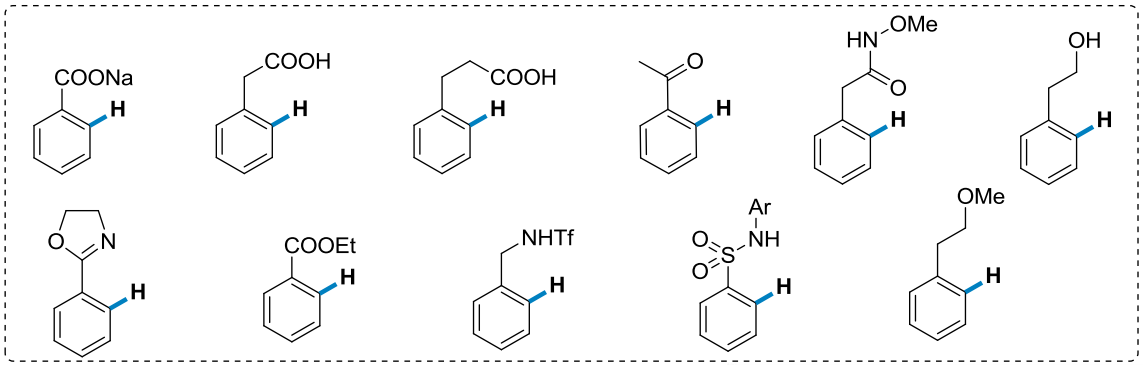
K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res,* **2011**, *45,* 788

G. Li, L. Wan, G.Zhang, D. Leow, J. Spangler, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4391

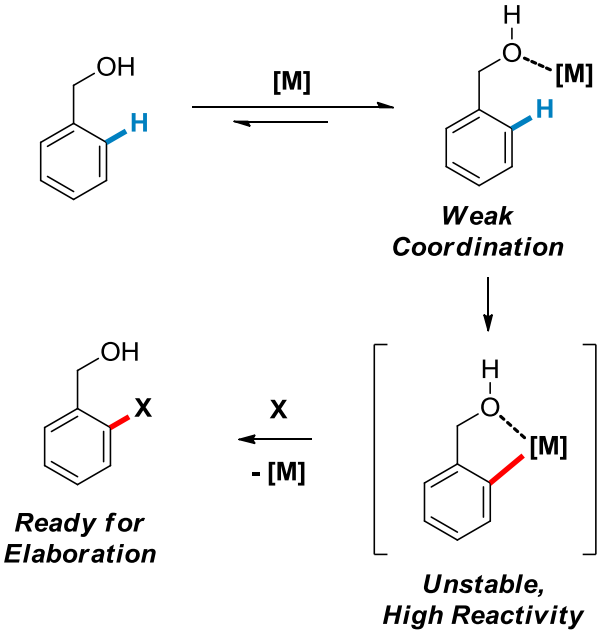
III - Reactivity and Scope: weak coordination as a powerful tool

III - 1. Coordinating directing groups:

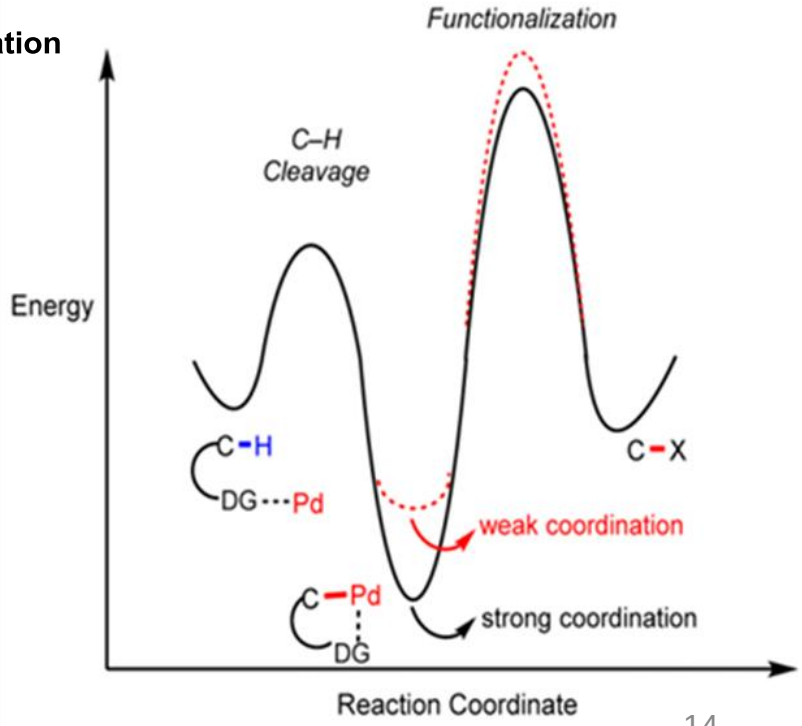
- **Weakly coordinating directing groups**



C-H Functionalization via Weak Coordination-Driven Metalation



K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res,* **2011**, *45,* 788

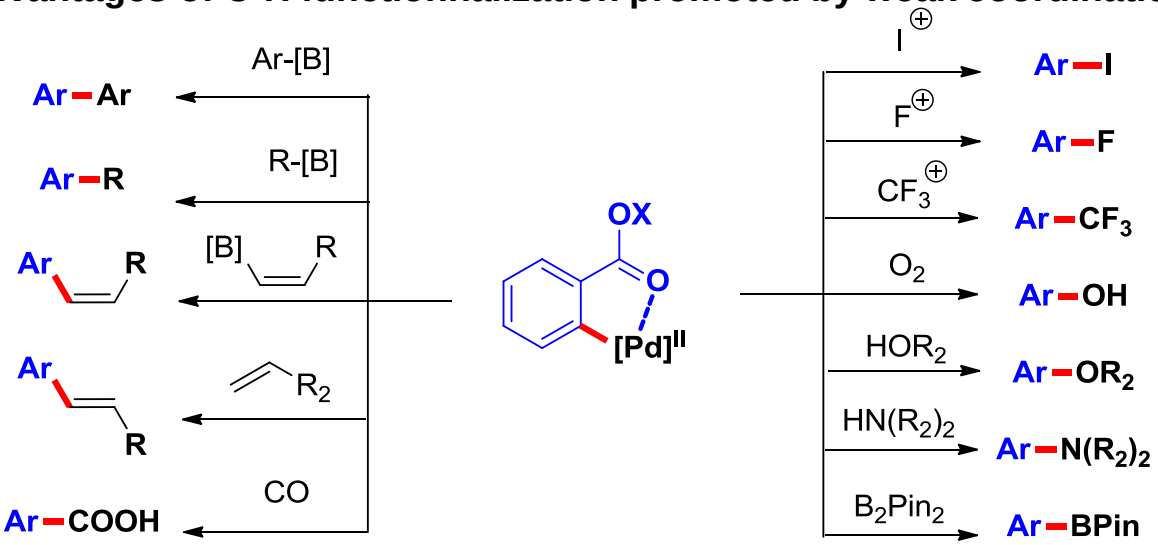


G. Li, L. Wan, G.Zhang, D. Leow, J. Spangler, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4391

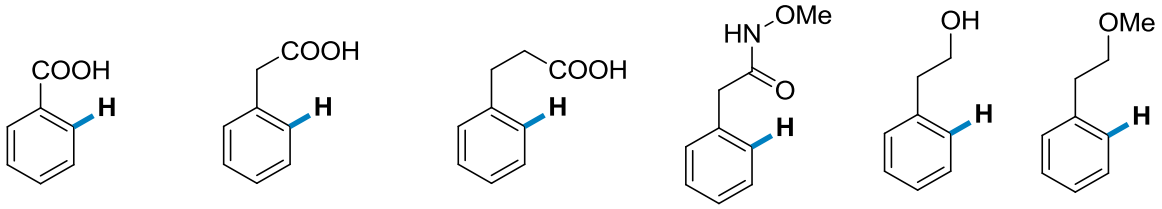
III - Reactivity and Scope: weak coordination as a powerful tool

III - 1. Coordinating directing groups:

- **Advantages of C-H functionnalization promoted by weak coordination**



For a review: K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res,* **2011**, *45,* 788



Hydroxyl-directing group: Y. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* ***2010***, *132,* 5916
X. Wang, Y. Lu, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc*. **2010**, *132*, 12203
Y. Lu, D. Leow, X. Wang, K.M. Engle, J.-Q. Yu, *Chem.Sci.* **2011**, 2, 967

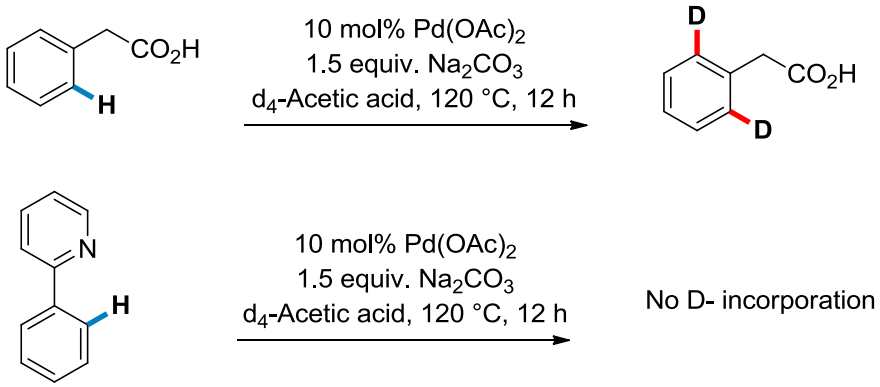
Ether-directing group *:* G. Li, D. Leow, L. Wan, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2013**, *52*, 1245

C-H Functionnalisation directed by Distal Weakly Coordinating Functional Groups: G. Li, L. Wan, G. Zhang, D. Leow, J. Spangler, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137,* 4391

III - Reactivity and Scope: weak coordination as a powerful tool

III - 1. Coordinating directing groups:

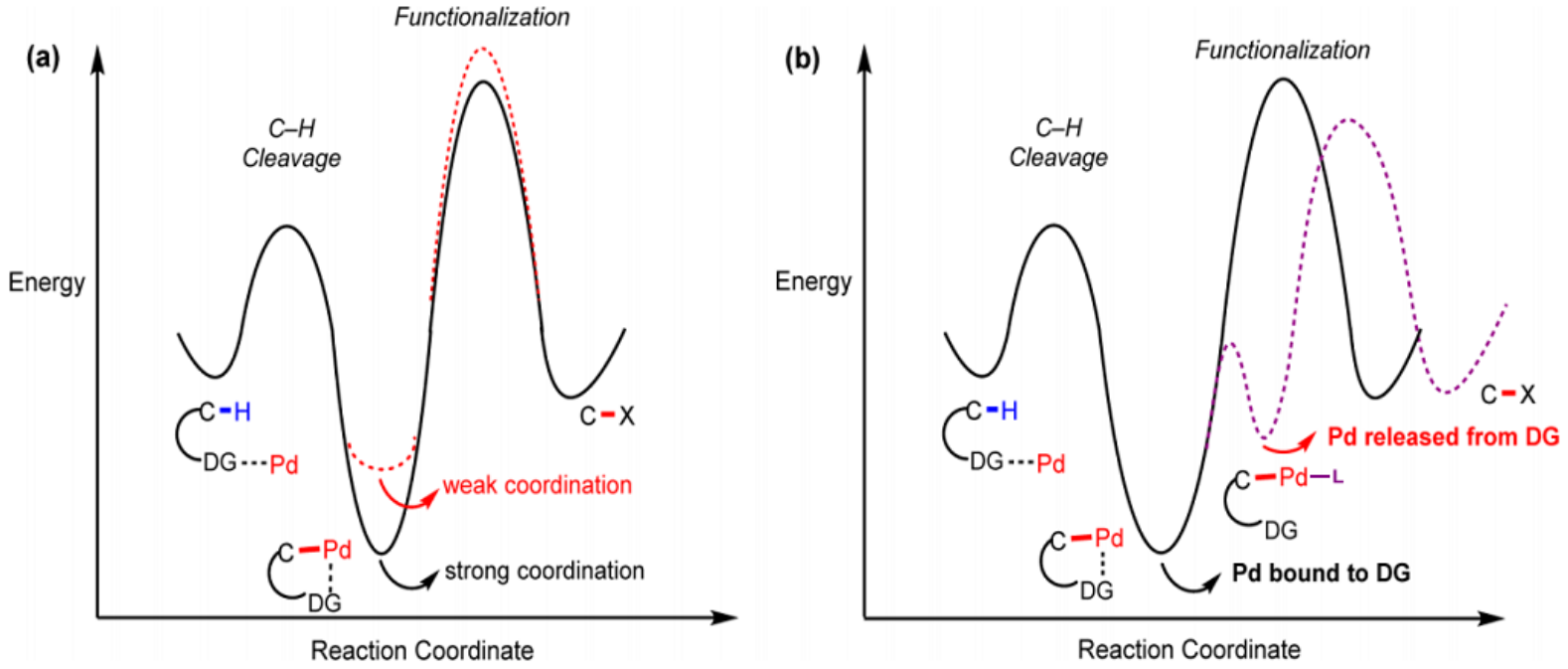
- **Weaker is better**



S. Ma, G. Villa, P.S. Thuy-Boun, A. Homs, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2014**, *53*, 734

III - Reactivity and Scope: weak coordination as a powerful tool

III - 2. Ligand acceleration



G. Li, L. Wan, G.Zhang, D. Leow, J. Spangler, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4391

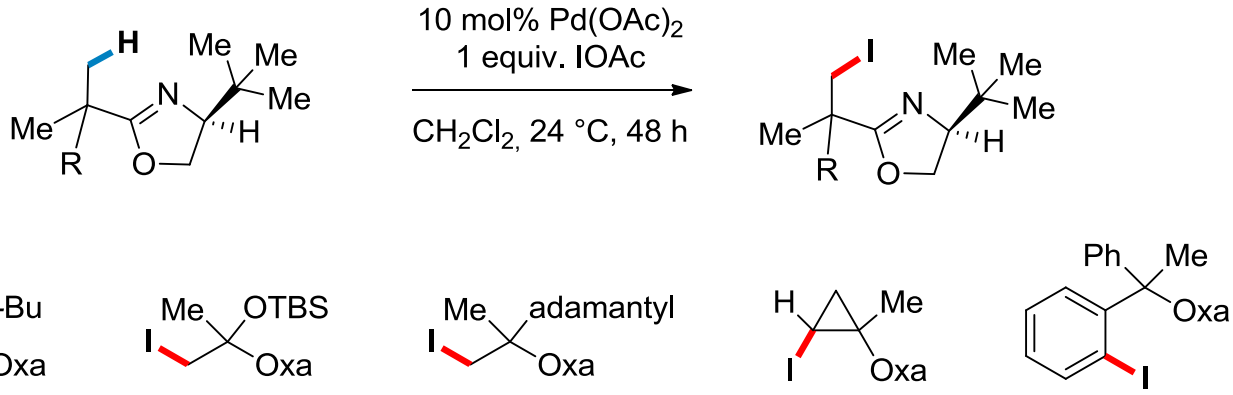
Weak coordinating substrate allows:

the use of an **external ligand as competitive coordination** (influence TS)

- regioselectivity, enantioselectivity, site selectivity (cf part IV and V)
- accelerate the reaction (scheme b)

IV – Enantioselective methodologies

IV - 1. Early stages: diastereoselectivity using chiral DG

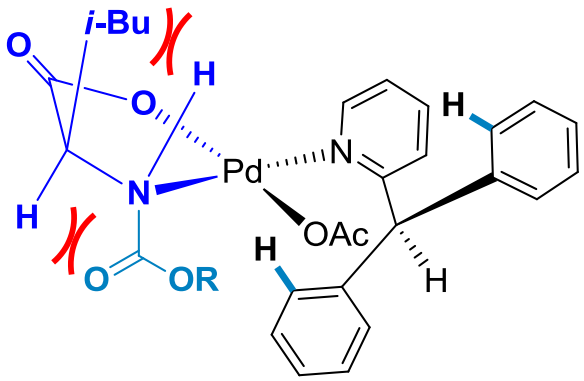


R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112

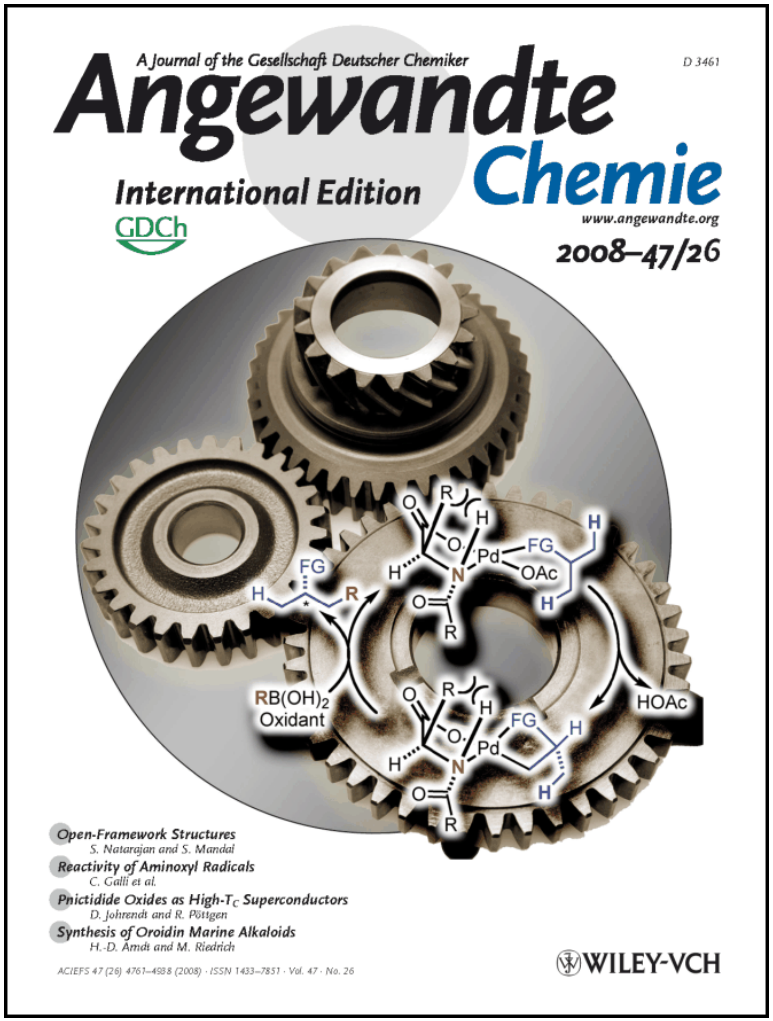
IV – Enantioselective methodologies

IV - 2. Chiral Ligand

- **Structure-based stereomodel**

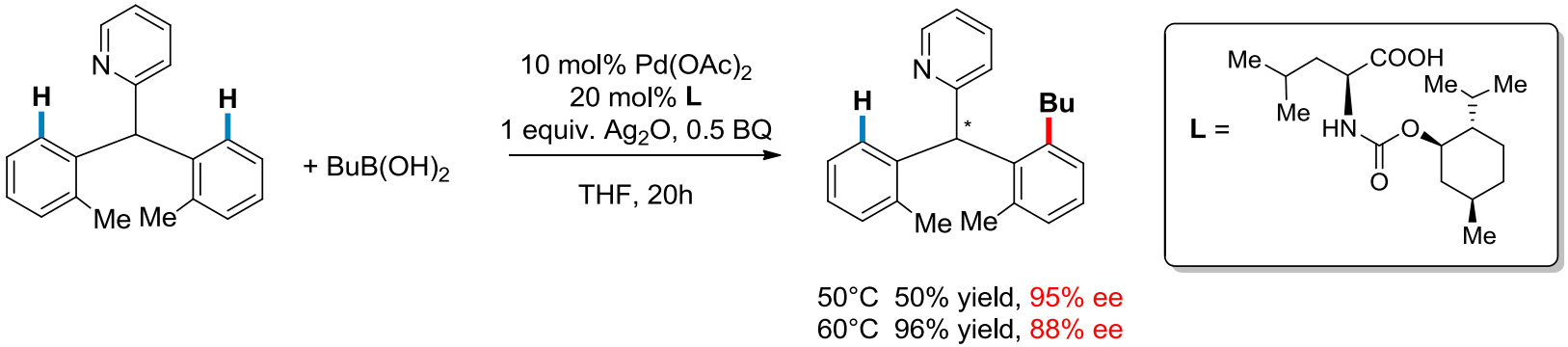


B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2008**, *47*, 4882



IV – Enantioselective methodologies

IV - 2. Chiral Ligand



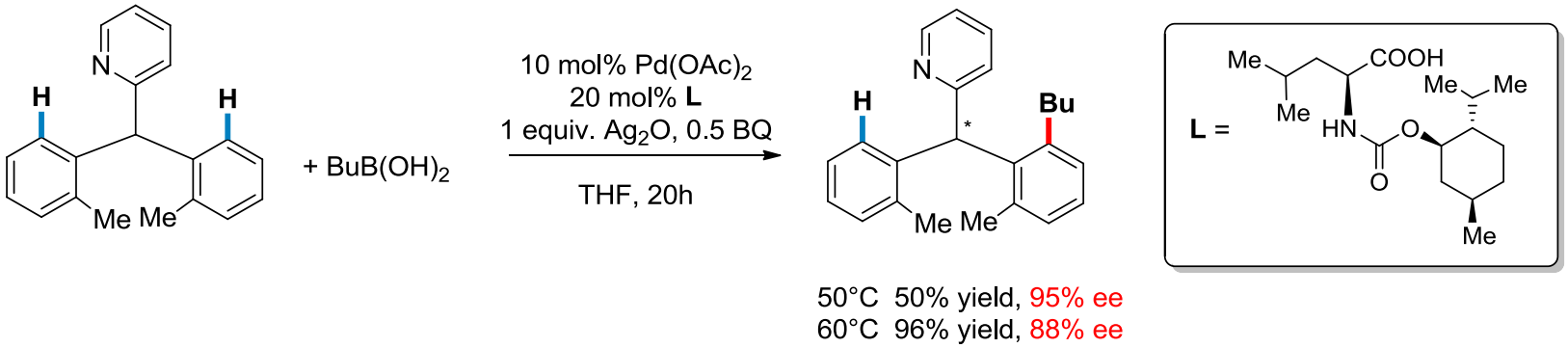
50°C 50% yield, 95% ee
60°C 96% yield, 88% ee

B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2008**, *47*, 48825

For Pd(0)/Phosphine catalysis and other approaches see works from: Kundig, Kagan, Cramer…

IV – Enantioselective methodologies

IV - 2. Chiral Ligand



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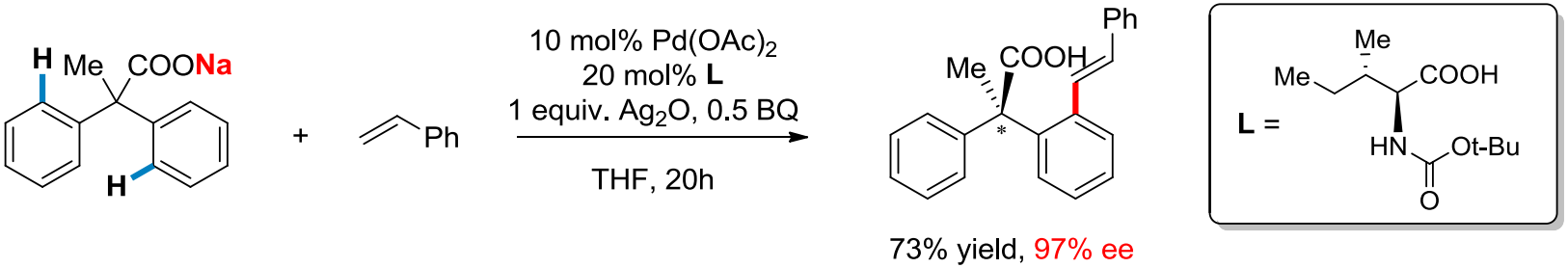


73% yield, 97% ee

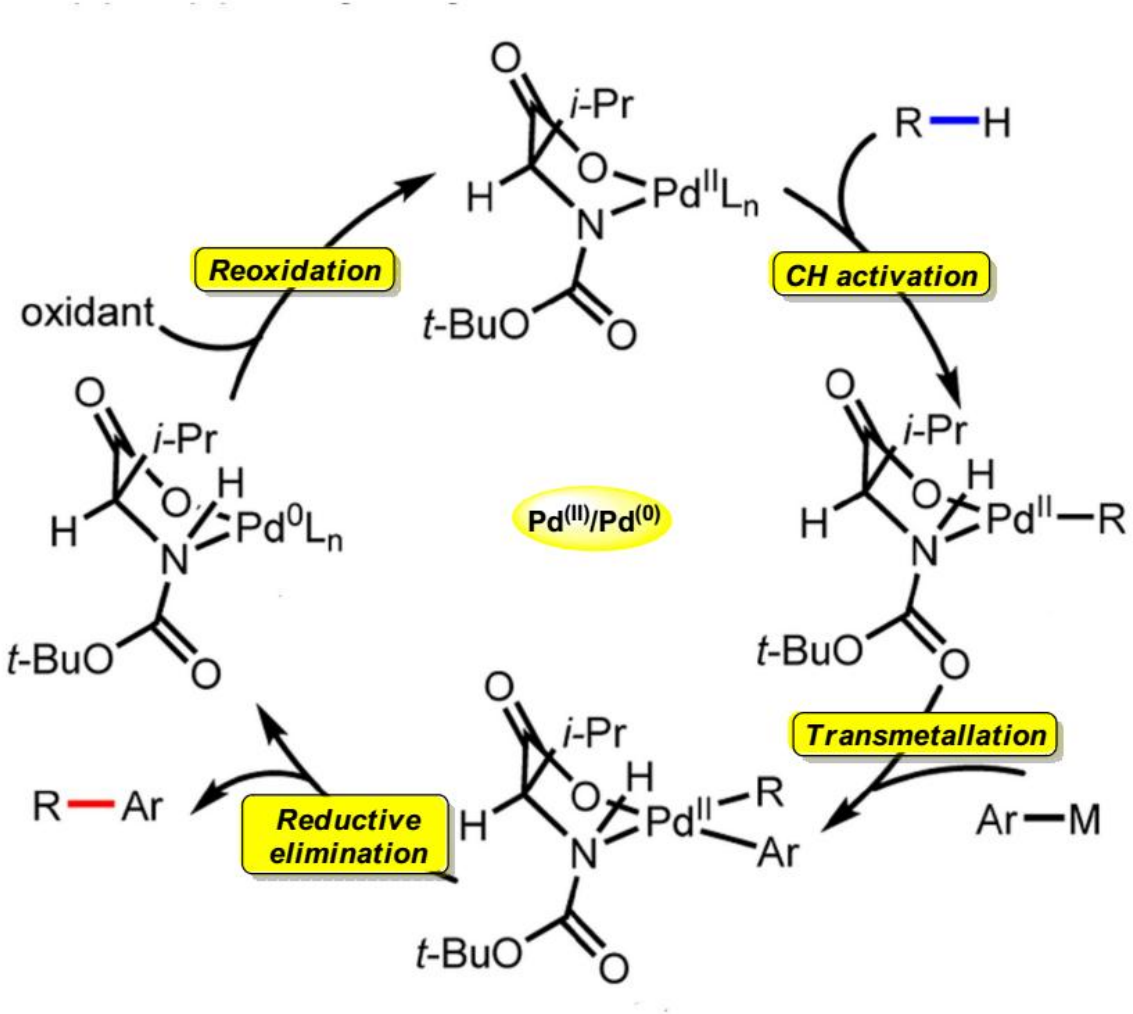
B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010,** *132*, 460

For Pd(0)/Phosphine catalysis and other approaches see works from: Kündig, Kagan, Cramer…

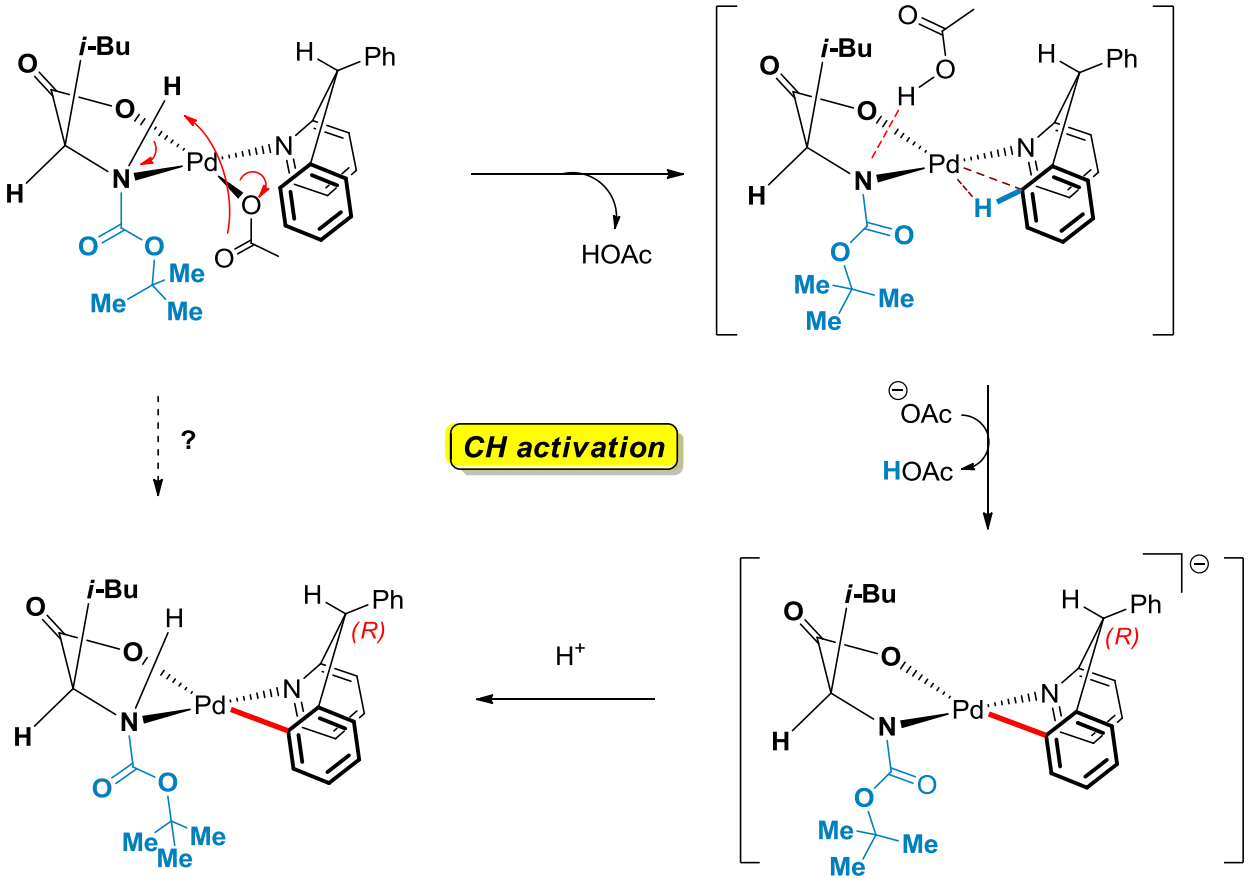
IV – Enantioselective methodologies

IV - 2. Chiral Ligand

- **Mechanism**



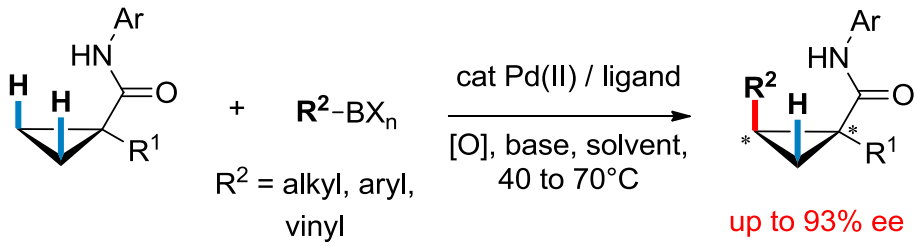
- **Key Mechanistic Features: C-H activation step**



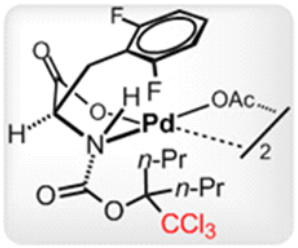
D. G. Musaev, A. Kaledin,B.-F. Shi, J.-Q. Yu, *J. Am. Chem.Soc*. **2012**, *134*, 1690

IV – Enantioselective methodologies

IV - 2. Chiral Ligand



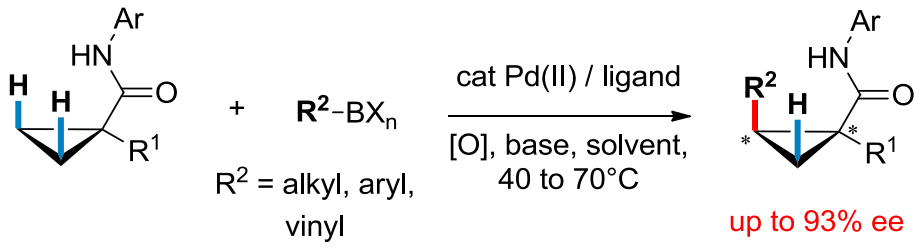
Precatalyst:



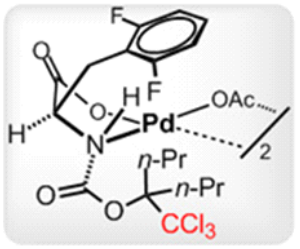
M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 19598

IV – Enantioselective methodologies

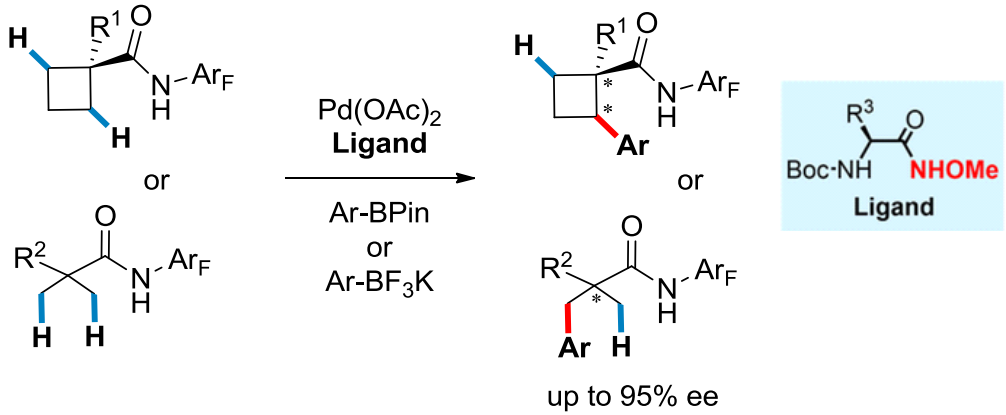
IV - 2. Chiral Ligand



Precatalyst:



M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 19598



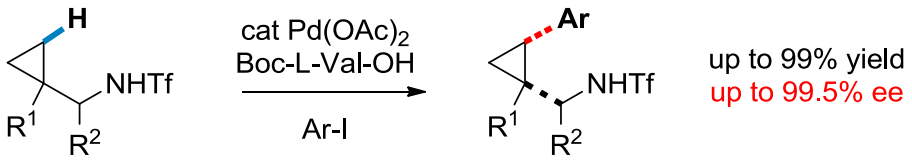
K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 8138.

Other examples: B. N. Laforteza, K. S. L. Chan, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54, 11143*

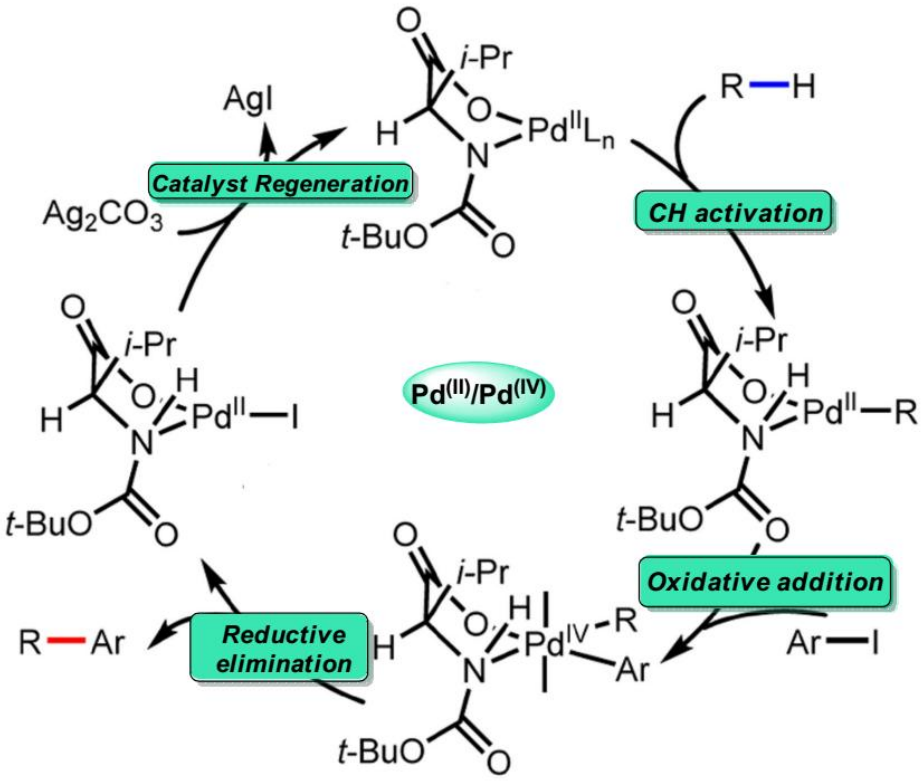
IV – Enantioselective methodologies

IV - 2. Chiral Ligand

- **Pd(II)/Pd(IV) catalysis**



First example of enantioselective C-H arylation via Pd(II)/Pd(IV) catalysis

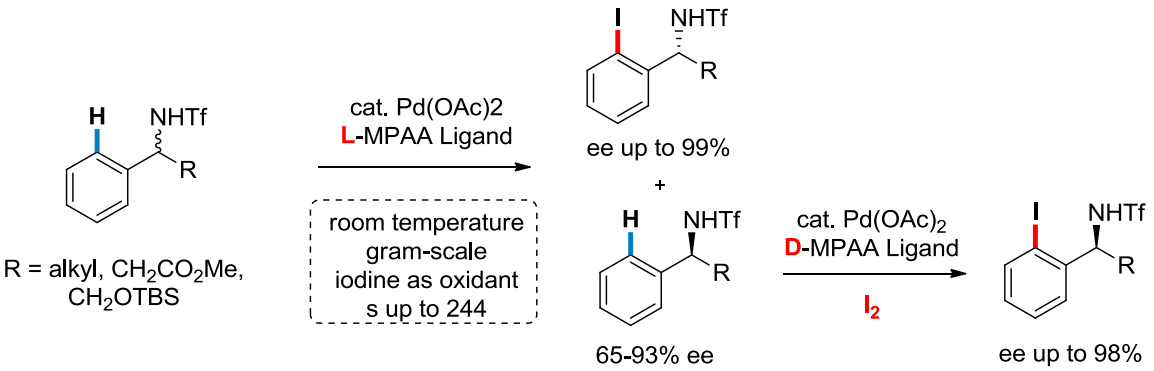


K. S. L. Chan, H.-Y. Fu, J.-Q. Yu, *J. Am. Chem. Soc*. **2015**, *137*, 2042.

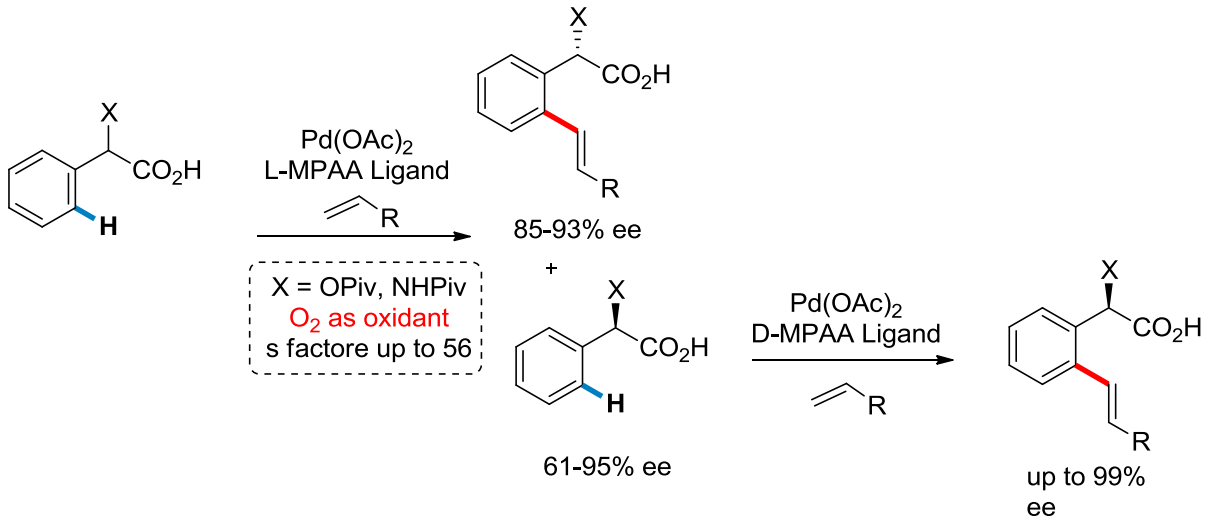
IV – Enantioselective methodologies

IV - 2. Chiral Ligand

- **Kinetic Resolution**



L. Chu, K.-J. Xiao, J.-Q. Yu, *Science* **2014**, *346*, 451.

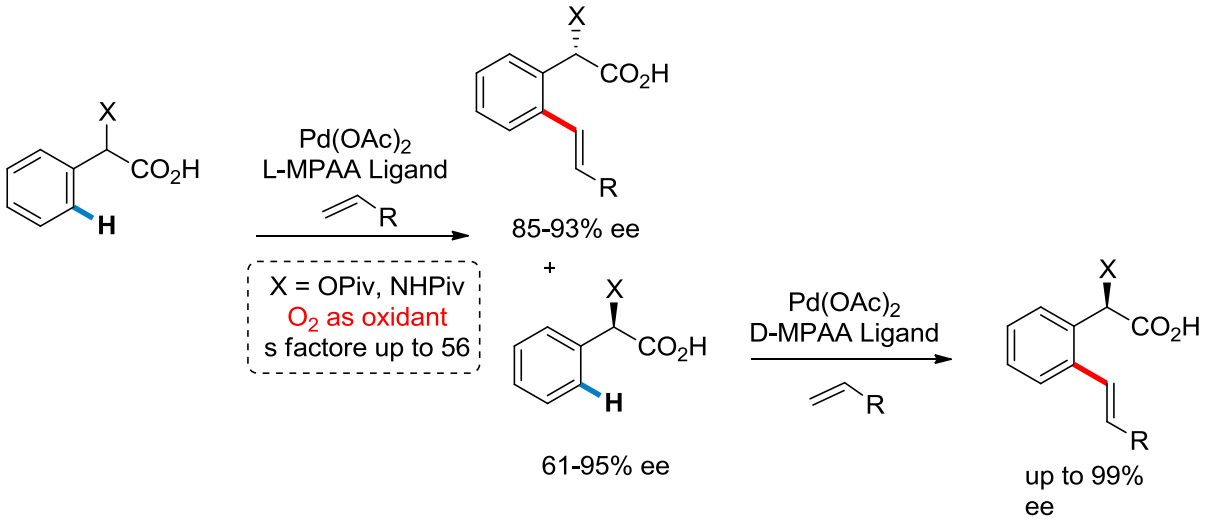


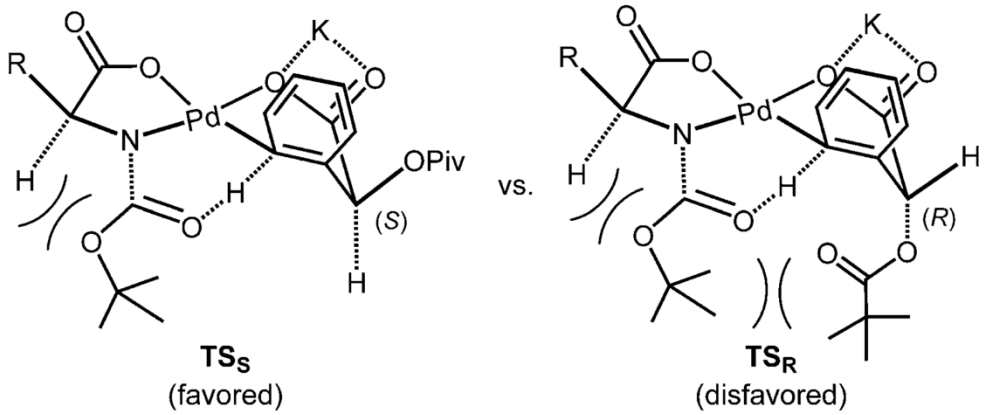
K.-J. Xiao, L. Chu, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2016**, Early view.

IV – Enantioselective methodologies

IV - 2. Chiral Ligand

- **Kinetic Resolution**

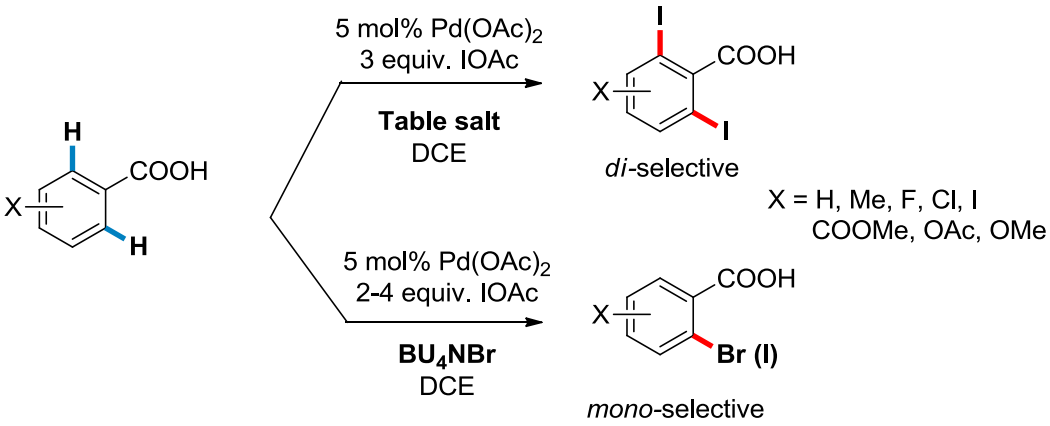




K.-J. Xiao, L. Chu, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2016**, Early view.

V – Site selective methodologies

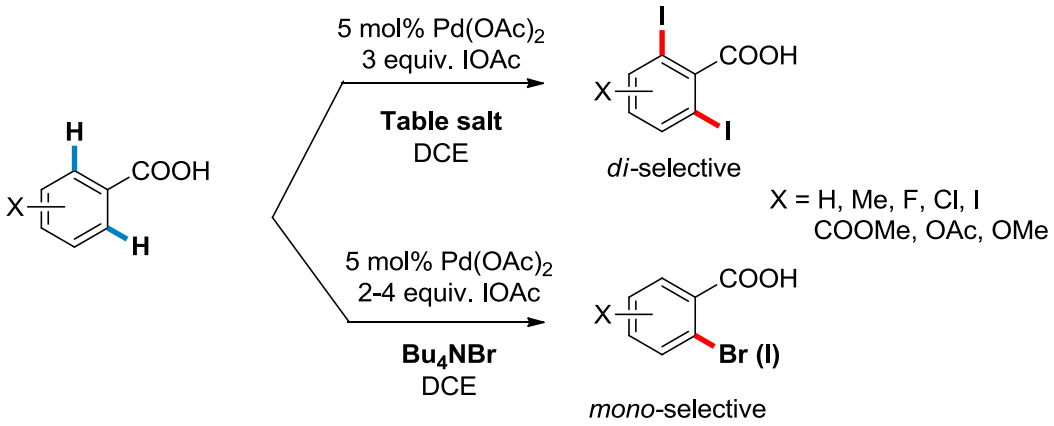
V - 1. Ortho regioselectivity



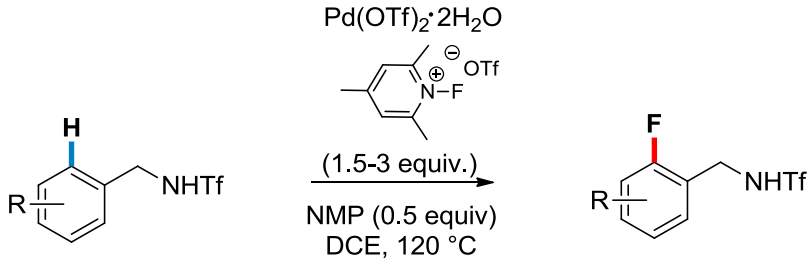
T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5215

V – Site selective methodologies

V - 1. Ortho regioselectivity



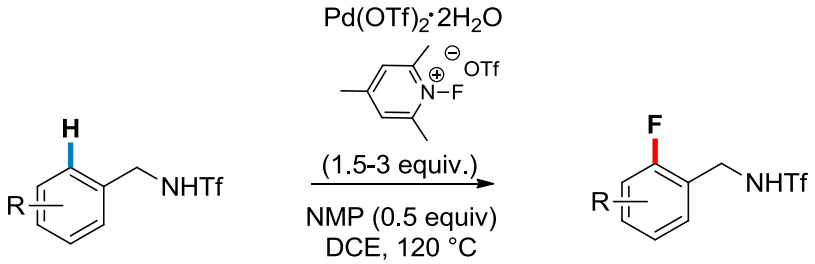
T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5215



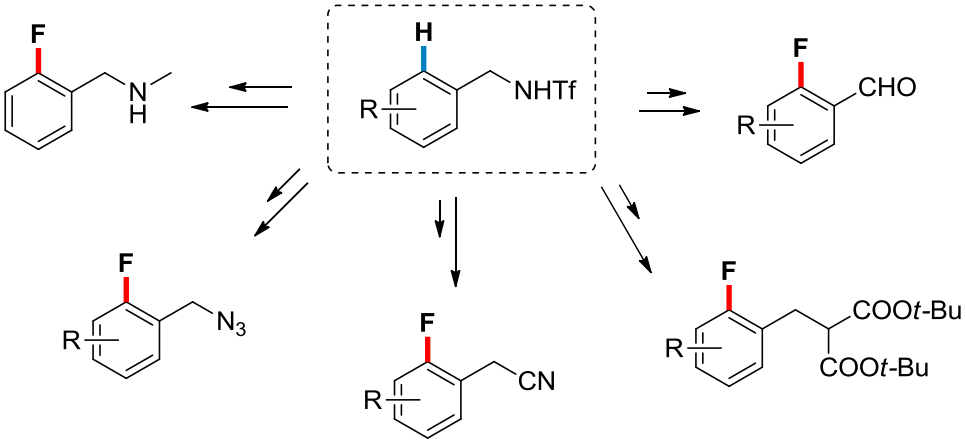
X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520

V – Site selective methodologies

V - 1. Ortho regioselectivity

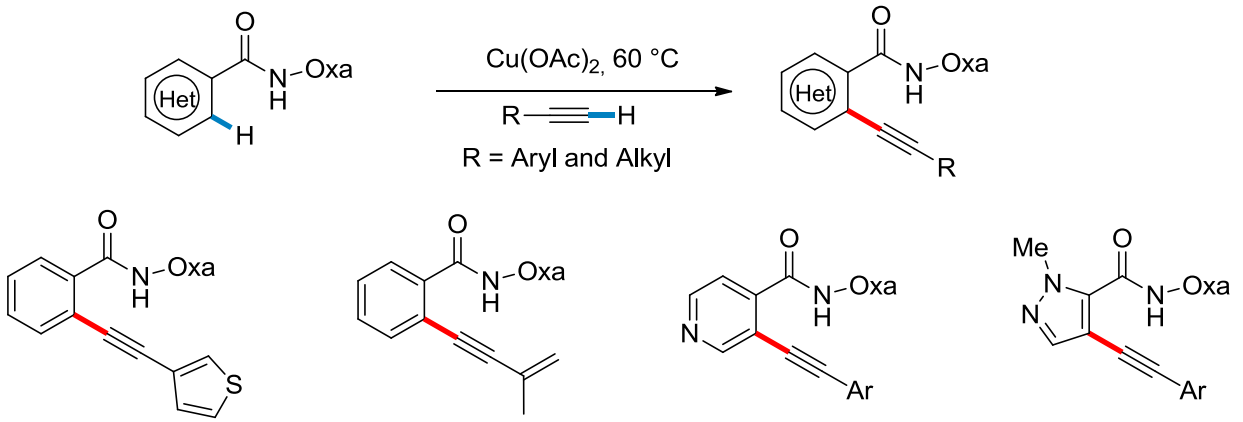


X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc*. **2009**, *131*, 7520

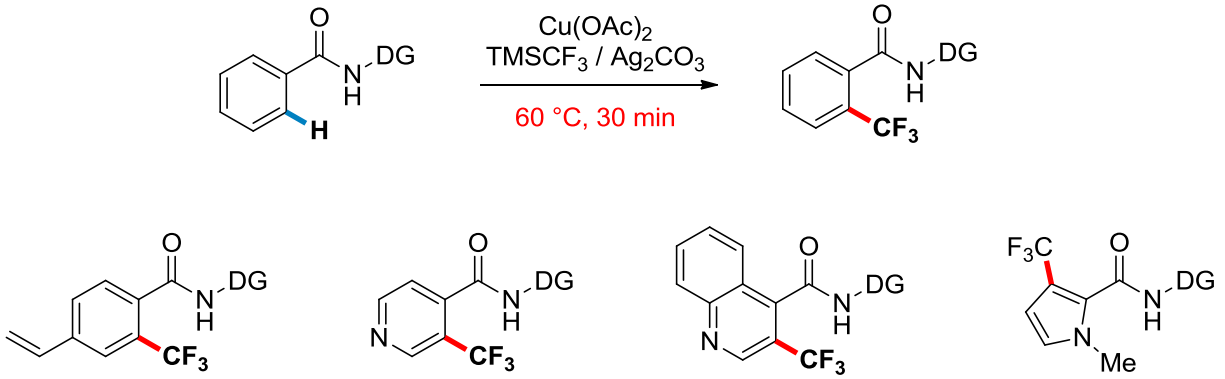


V – Site selective methodologies

V - 1. Ortho regioselectivity



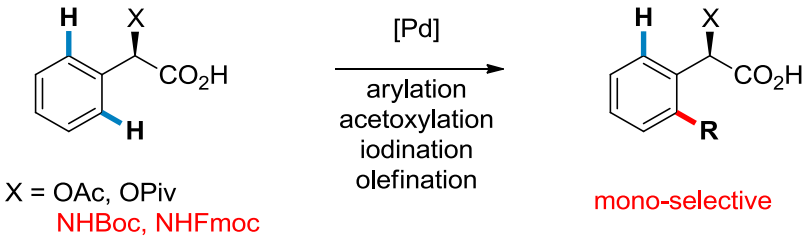
M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc*. **2014**, *136*, 11590.



M. Shang,S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2014,** *53*, 10439

V – Site selective methodologies

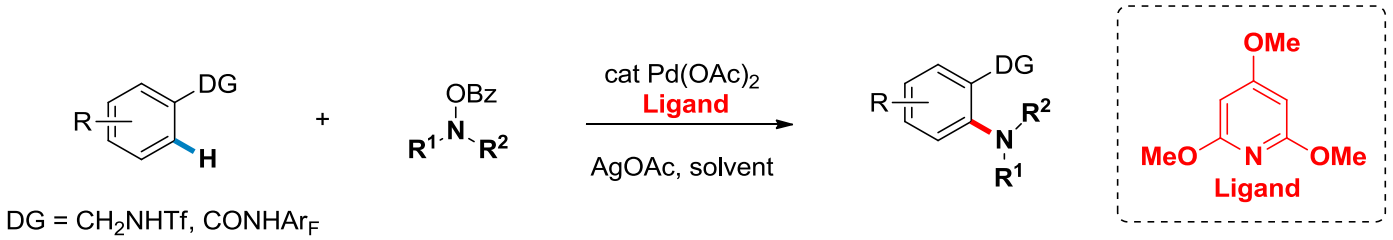
V - 1. Ortho regioselectivity



X = OAc, OPiv
NHBoc, NHFmoc

mono-selective

N. Dastbaravardeh, T. Toba, M. Farmer, J.-Q. Yu, *J. Am. Chem. Soc*. **2015**, *137*, 9877.



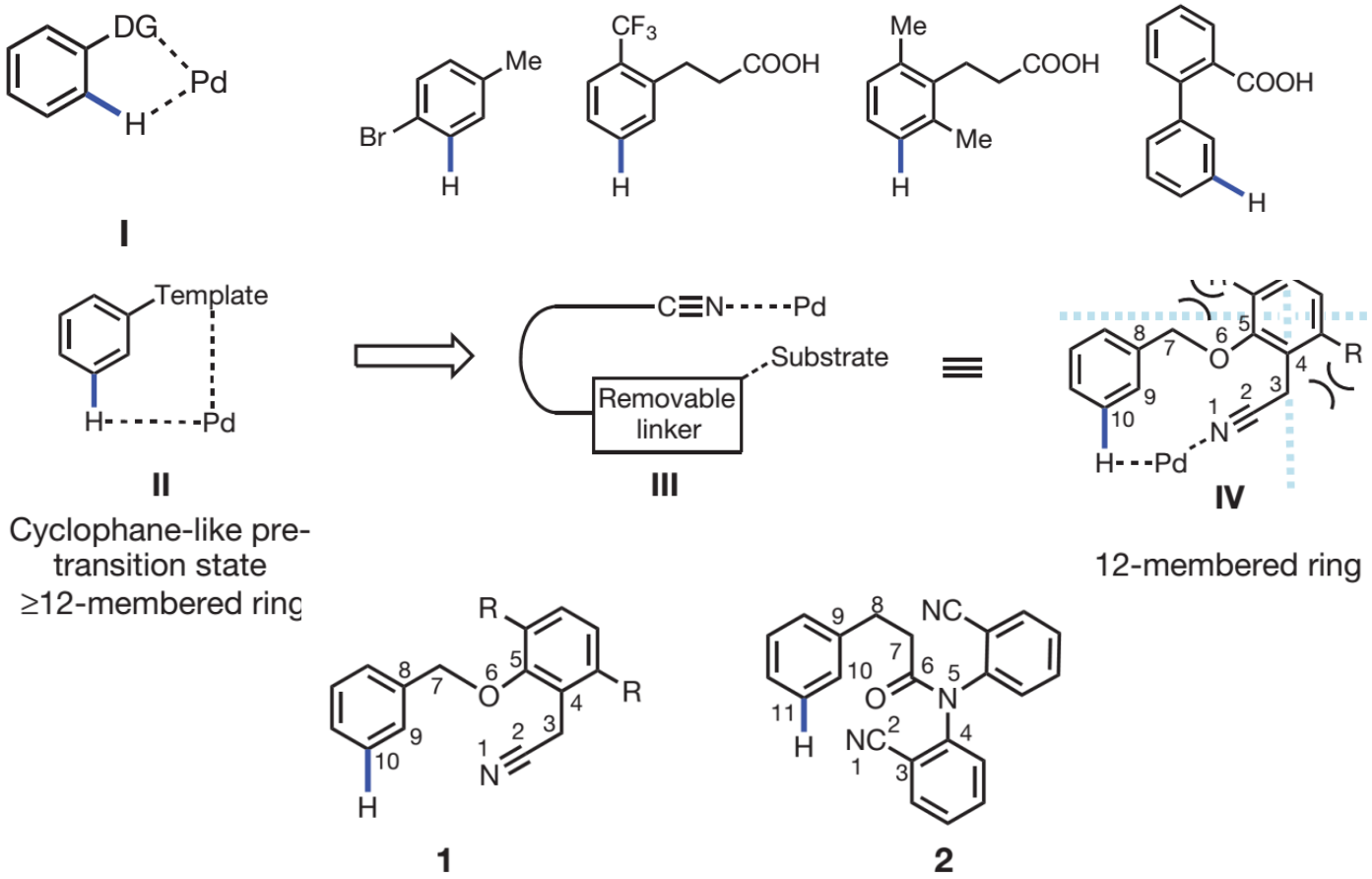
DG = CH_2NHTf, $CONHAr_F$

D. Zhu, G. Yang, J. He, L. Chu, G. Chen, W. Gong, K. Chen, M. D. Eastgate, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2015**, *54*, 2497

V - Site selective methodologies

V - 2. Meta regioselectivity

- **Substrate control: U-shaped Template**

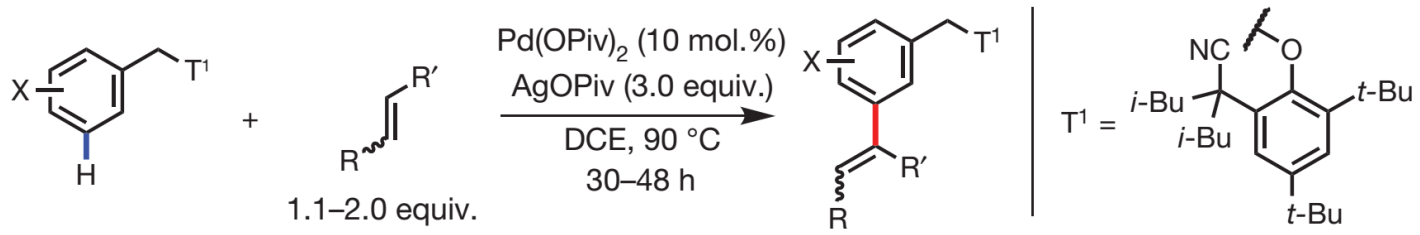


D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486,* 518.
Y. Deng, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 888

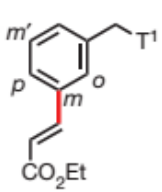
V - Site selective methodologies

V - 2. Meta regioselectivity

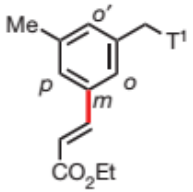
- **Substrate control: U-shaped Template**



8a–p **11a–n** **17a–p**

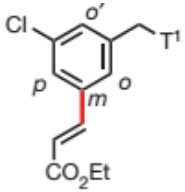


17a$_{mono}$, 55%
m:*p*:*o* = 93:5:2
17a$_{di}$, 31%
m,m′):others= 88:12

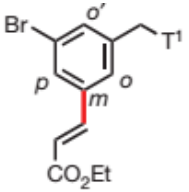


17b$_1$, 86%
m:(*p*+*o*+*o*′)= 94:6

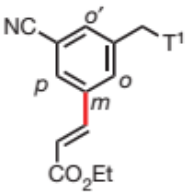
17c, 52%
m:*p*:(*o*+*o*′)= 75:18:7



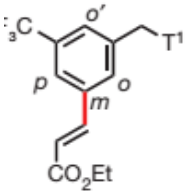
17d, 75%
m:(*p*+*o*+*o*′) = 97:3



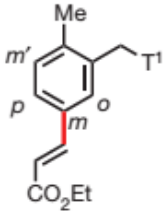
17e, 63%
m:(*p*+*o*+*o*′) = 93:7



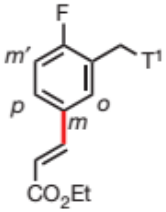
17f, 54%
m:(*p*+*o*+*o*′) = 98:2



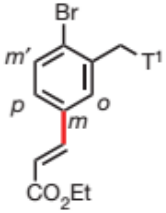
17g, 54%
n:(*p*+*o*+*o*′) = 98:2



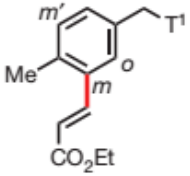
17h, 89%
m:(*p*+*o*+*m*′) = 91:9



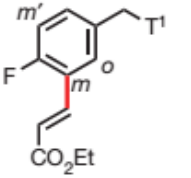
17i$_{mono}$, 70%
m:(*p*+*o*+*m*′) =98:2
17i$_{di}$, 18%
(*m*,*m*′):others = 89:11



17j, 77%
m:(*p*+*o*+*m*′) =90:10



17k$_{mono}$, 54%
m:*o* = 96:4
17k$_{di}$, 26%
(*m*,*m*′):others = 88:12



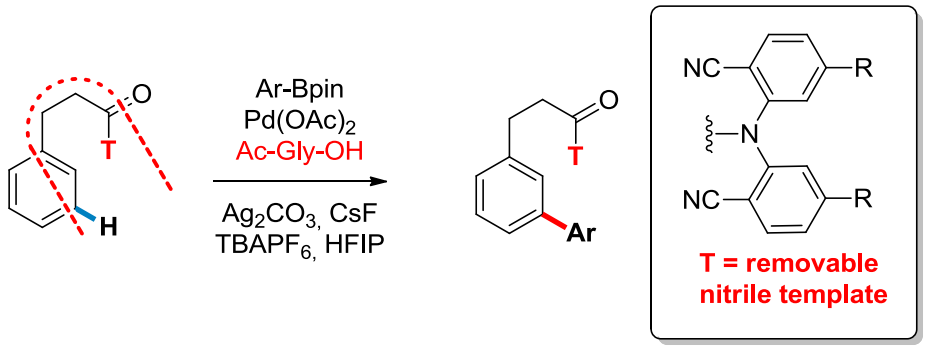
17l$_{mono}$, 45%
m:*o* = 95:5
17l$_{di}$, 44%
(*m*,*m*′):others = 90:10

D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486,* 518.

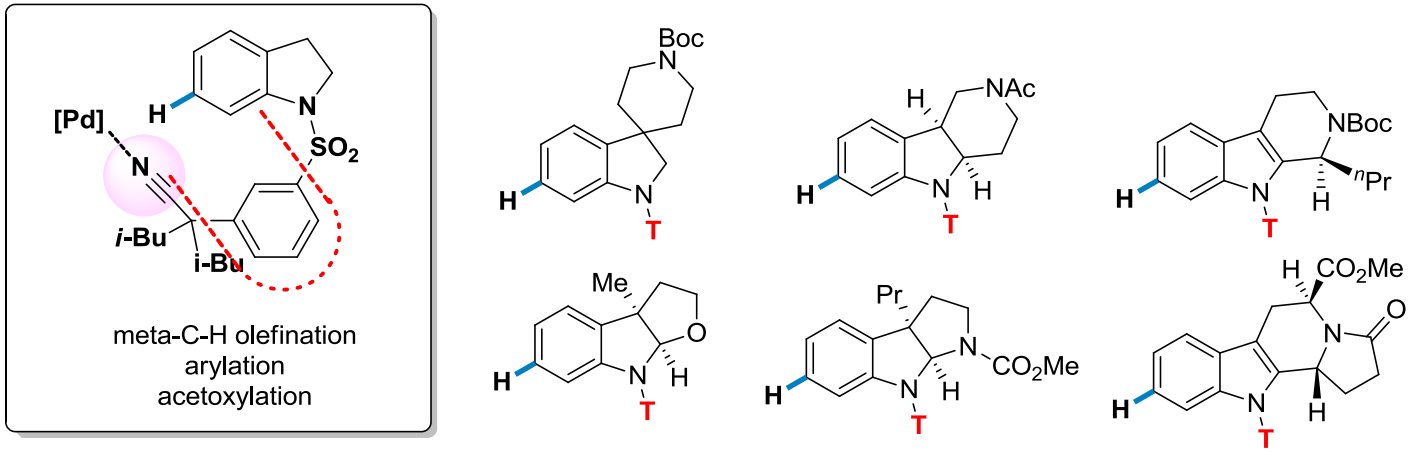
V - Site selective methodologies

V - 2. Meta regioselectivity

- **Substrate control: U-shaped Template**



L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056

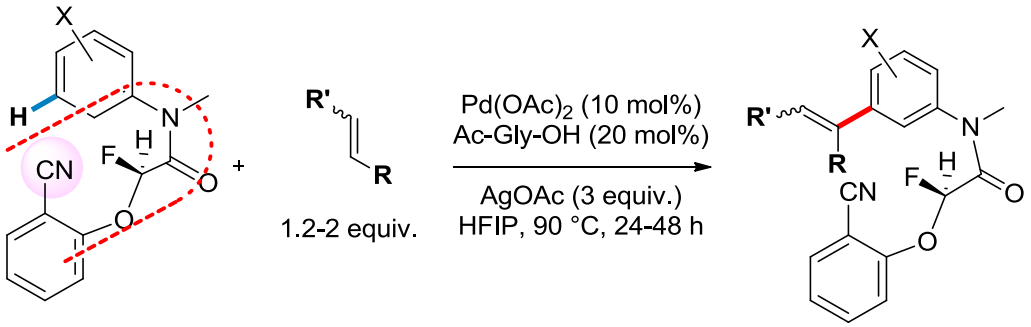


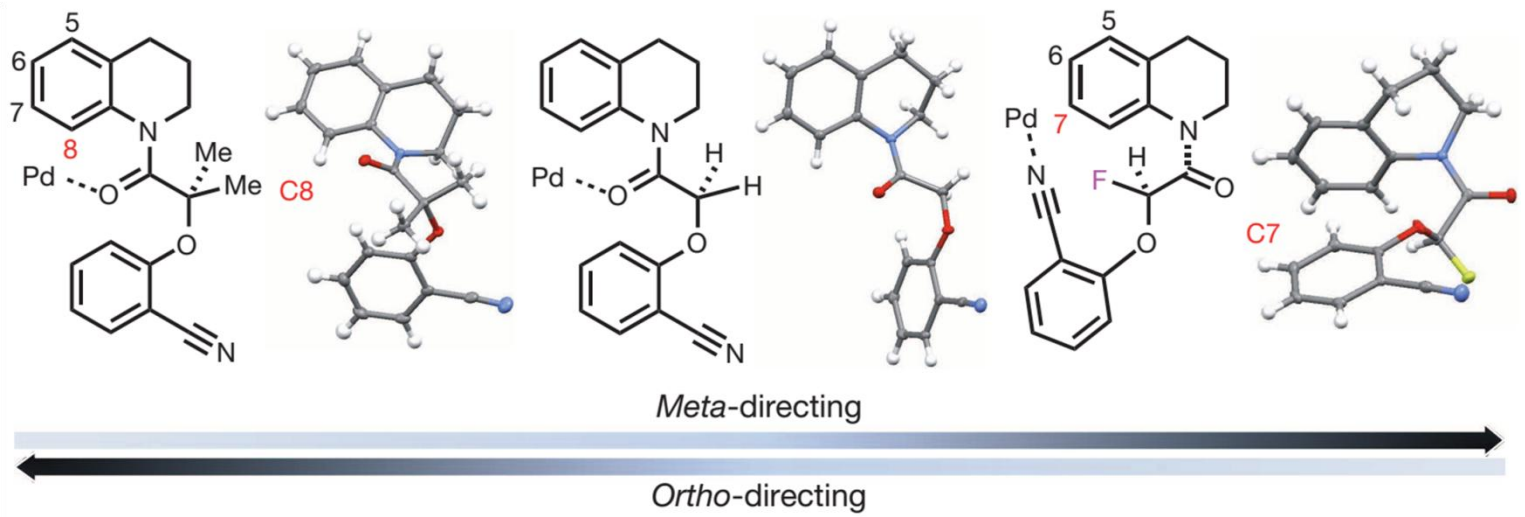
G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc*. **2014**, *136*, 10807.

V - Site selective methodologies

V - 2. Meta regioselectivity

- **Substrate control: U-shaped Template**



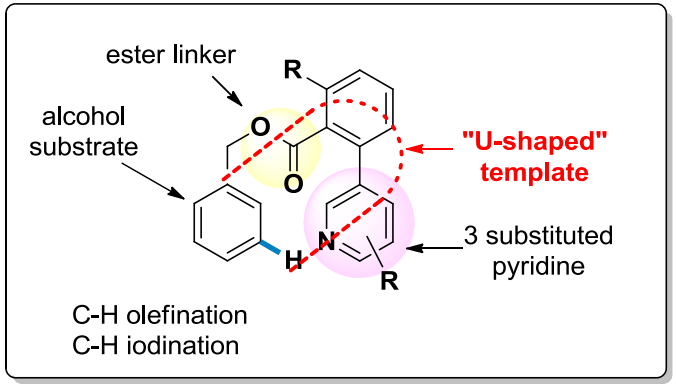


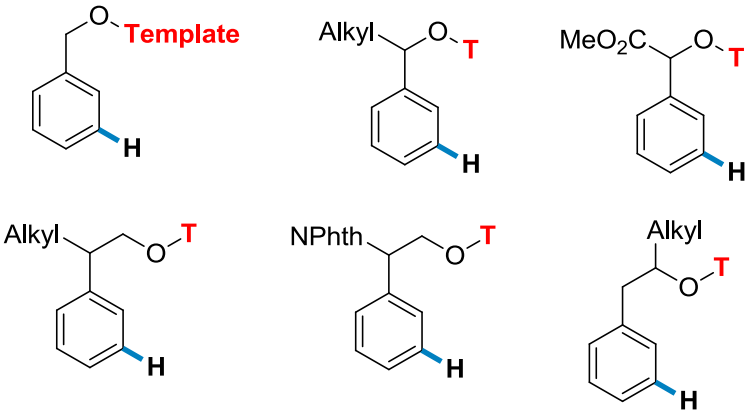
R. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507,* 215

V - Site selective methodologies

V - 2. Meta regioselectivity

- **Substrate control: U-shaped Template**



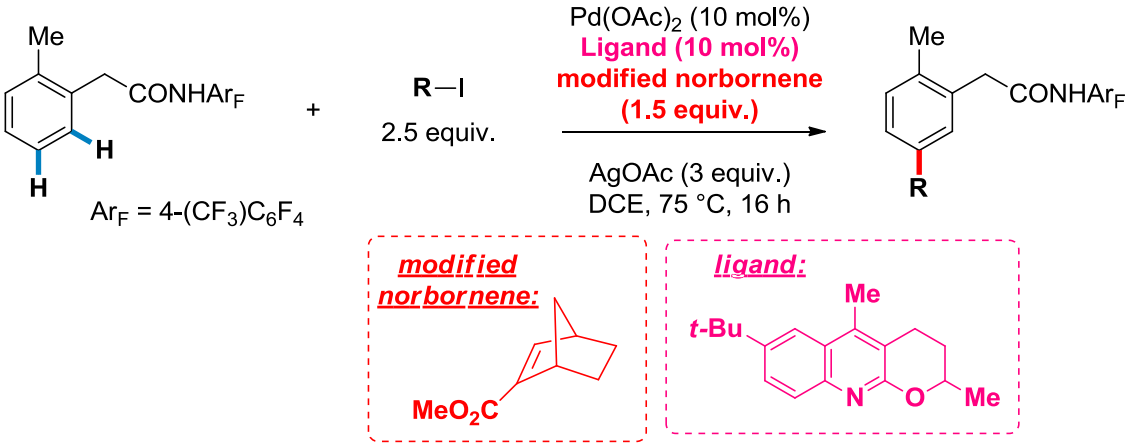


L. Chu, M. Shang, K. Tanaka, Q. Chen, N. Pissarnitski, E. Streckfuss, J.-Q. Yu, *ACS Cent. Sci*. **2015**, *1*, 394

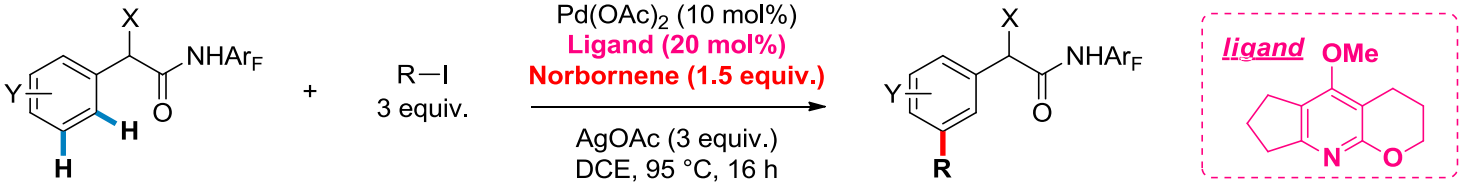
V - Site selective methodologies

V - 2. Meta regioselectivity

- **Ligand control**



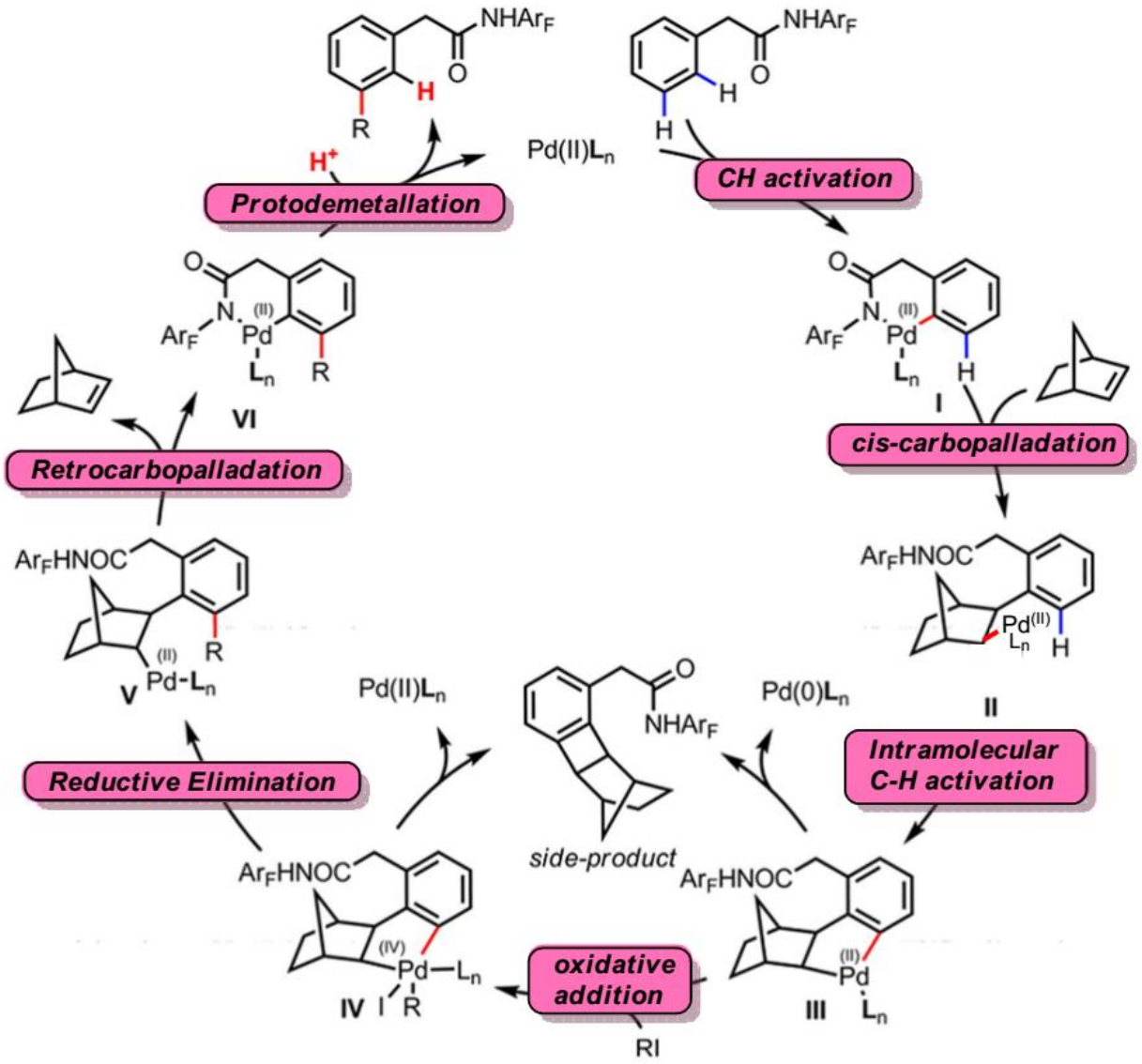
P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574



X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature,* **2015**, *519*, 334

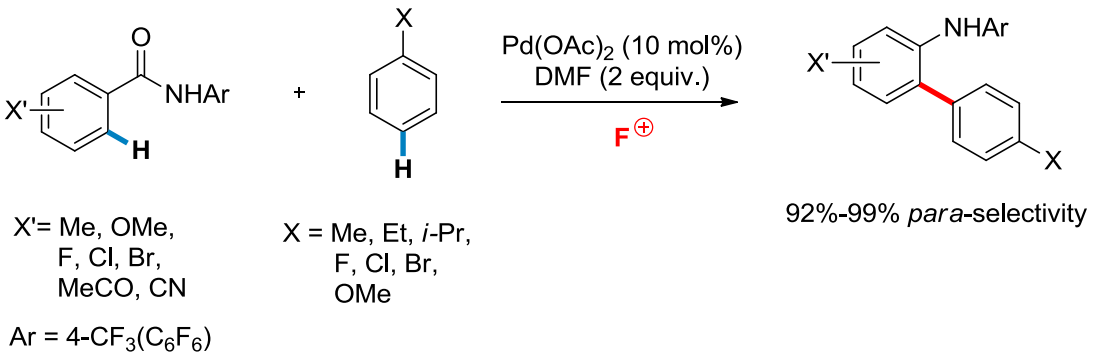
V - Site selective methodologies

V - 2. Meta regioselectivity

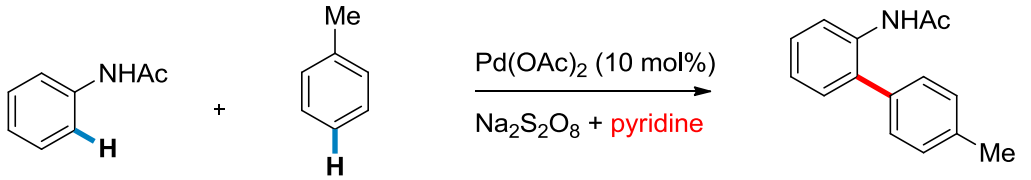


V - Site selective methodologies

V - 3. Para regioselectivity



X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 13864.



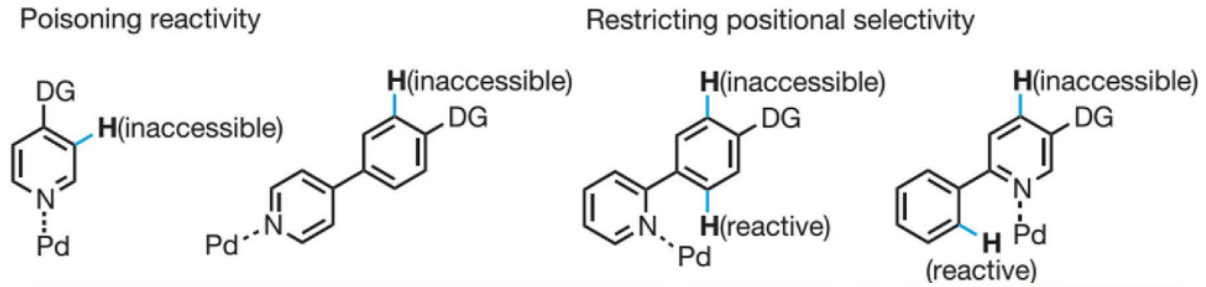
H. Xu, M. Shang, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2015**, *17*, 3830

V - Site selective methodologies

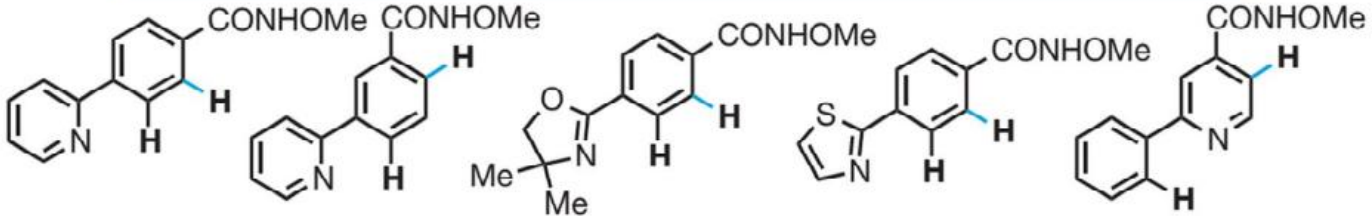
V - 4. Competitive site selectivity

- **Heterocycle**

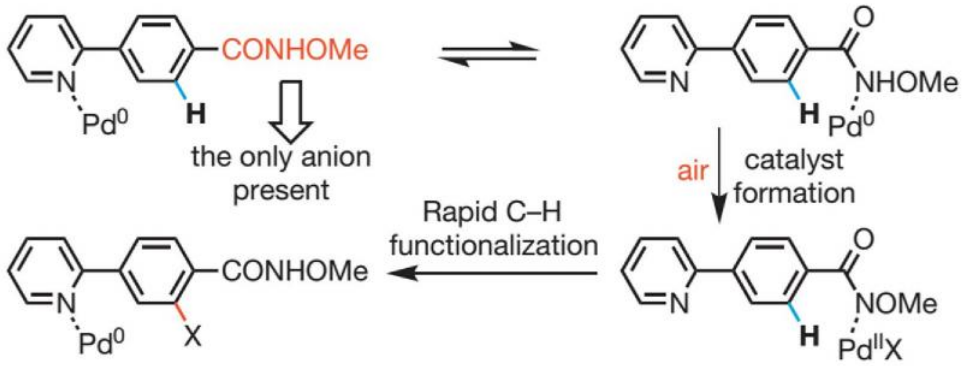
Fundamental limitations of directed C-H functionalization of heterocycles



Overriding site-selectivity dictated by the strongly coordinating heterocycles



On-site generation of a Pd(II) catalyst assisted by the anionic directing group

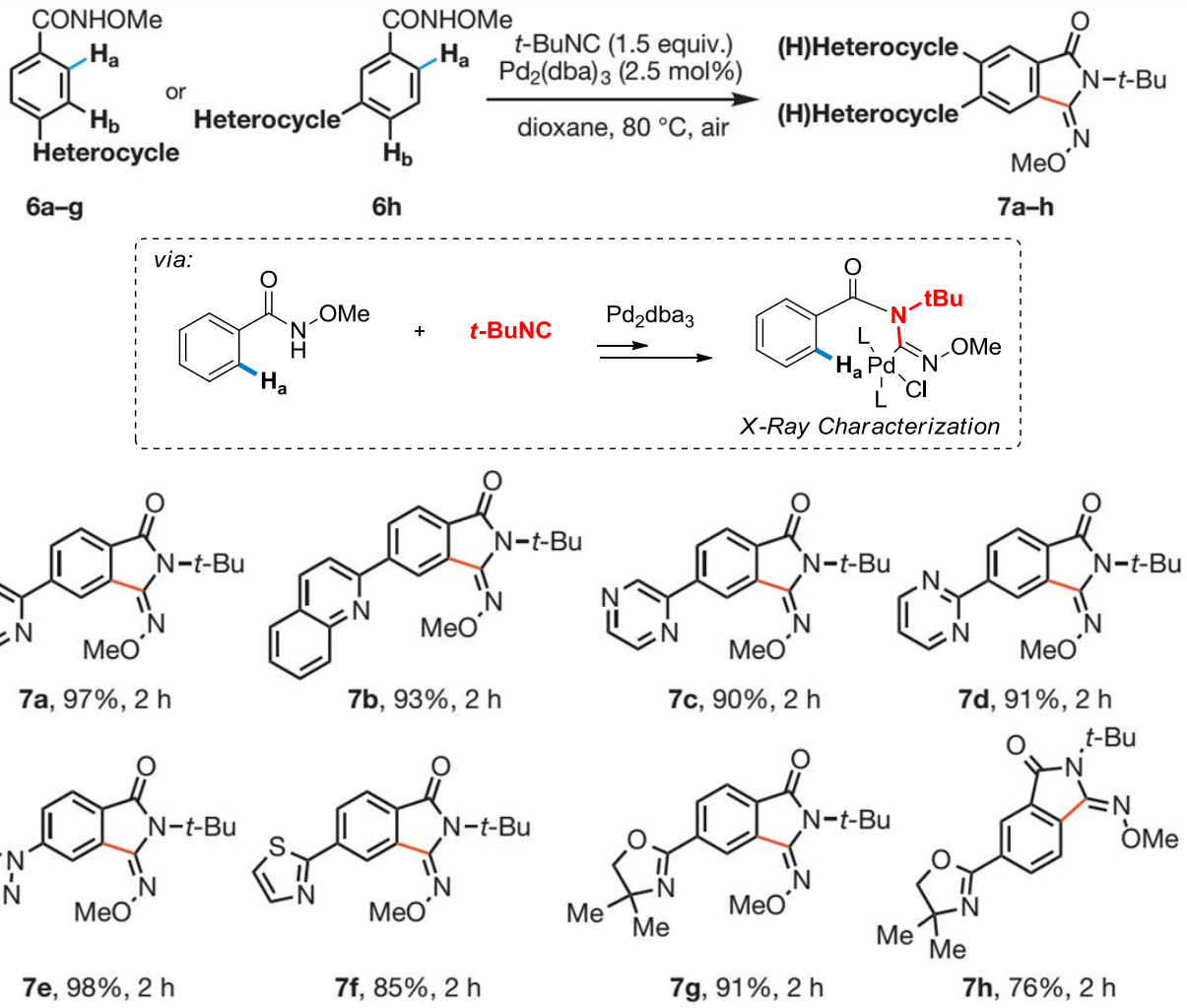


Y.-J. Liu, H. Xu, W.-J Kong, M. Shang, H.-X. Dai, J.-Q. Yu**,** *Nature,* **2014**, *515*, 389

V - Site selective methodologies

V - 4. Competitive site selectivity

- **Heterocycle**

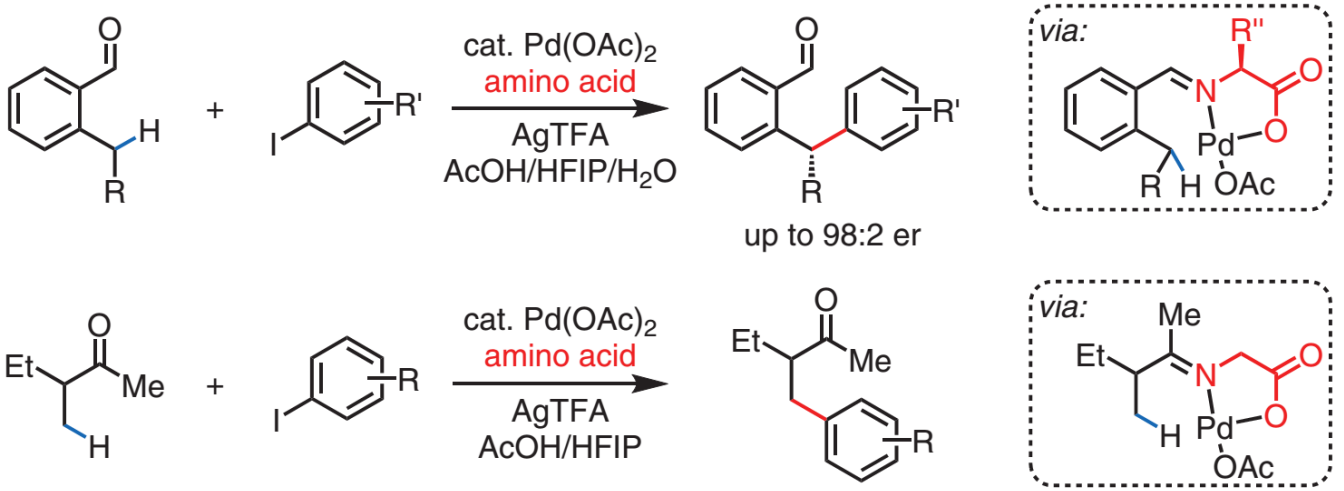


Y.-J. Liu, H. Xu, W.-J Kong, M. Shang, H.-X. Dai, J.-Q. Yu**,** *Nature,* **2014**, *515*, 389

V - Site selective methodologies

V - 4. Competitive site selectivity

- **C(Sp^3)**



F.-L. Zhang, K. Hong, T.-J. Li, H. Park , Jin-Quan Yu, *Science* **2016**, *351, 252*

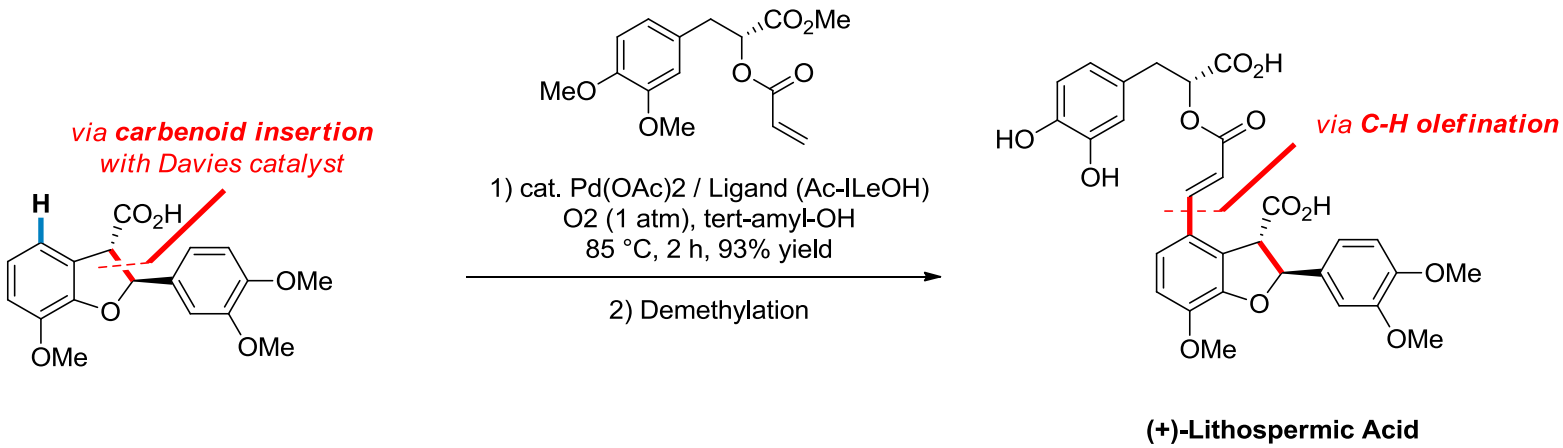
VI - Application

VI – 1. Total Synthesis

• Lithospermic acid

• 1st racemic synthesis by: Jacobson group, (J.Org. Chem, **1979**, 44, 4013)

• 1st total synthesis of (+) lithospemic acid: by the Ellman and Bergman group, (*J. Am. Chem. Soc*. **2005**, *127*, 3496) in **10 steps** with 5.9% overall yield

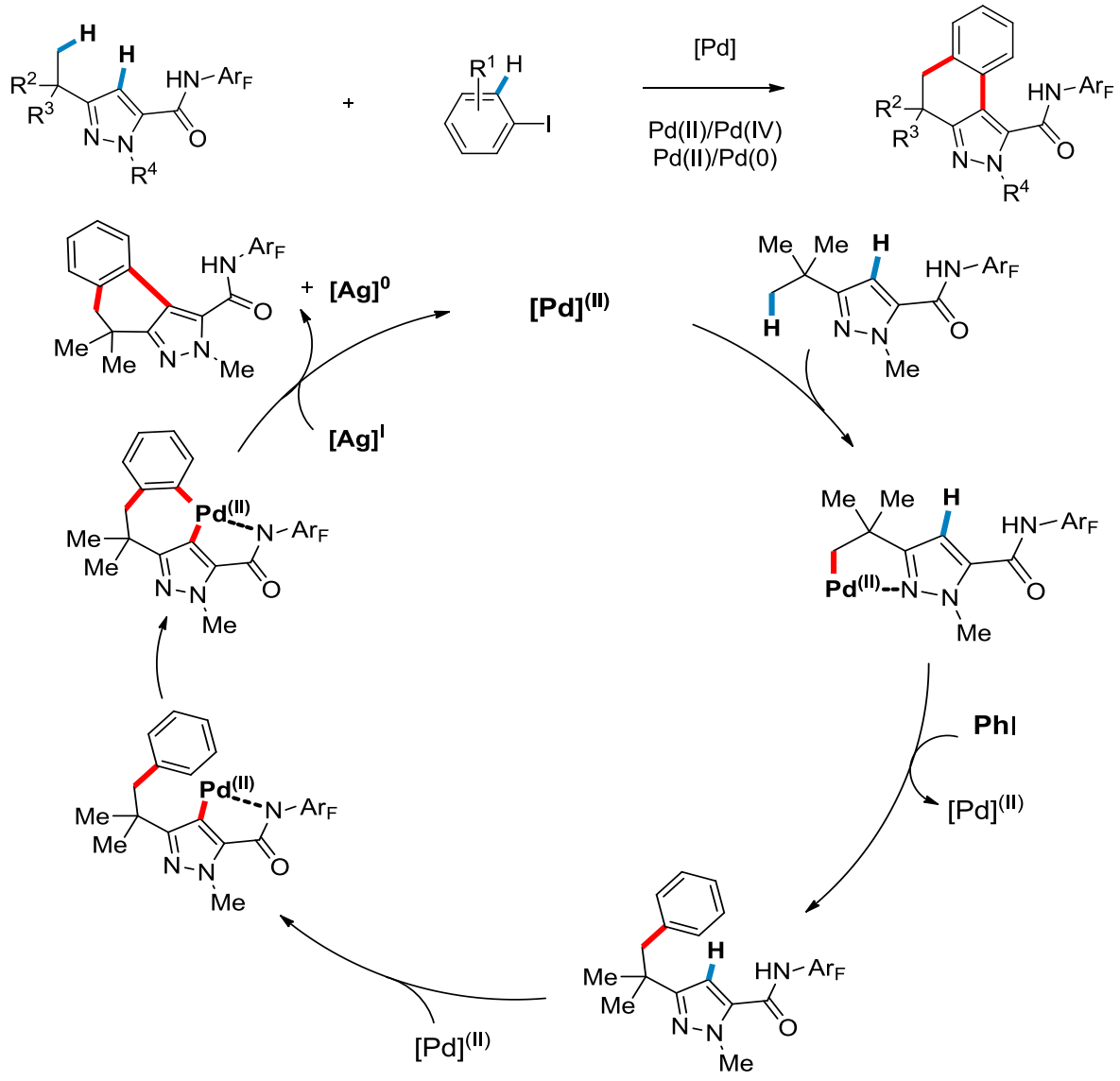


12 steps with 11% overall yield

D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *33, 5767*.

VI - Application

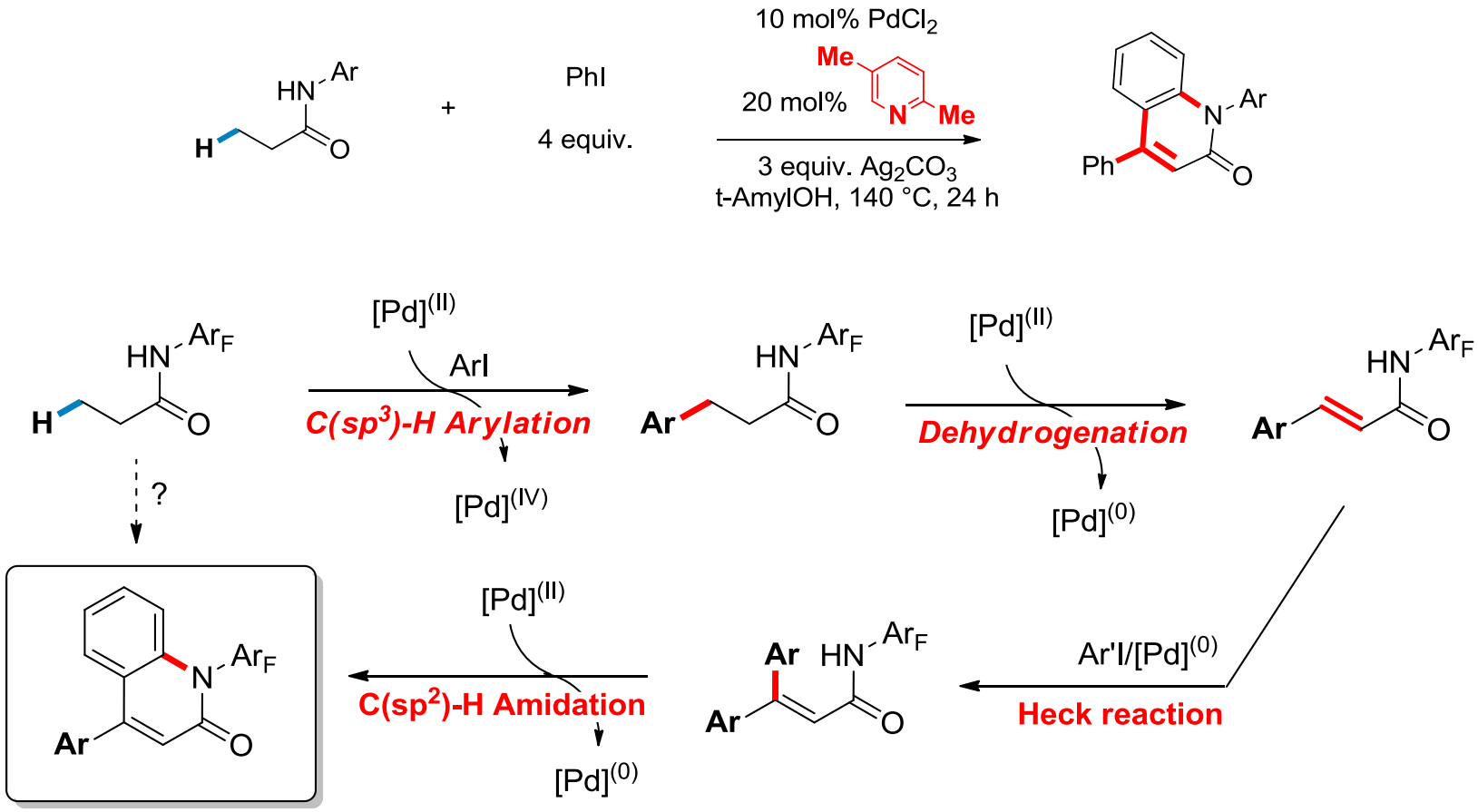
VI – Cascade C-H



W. Yang, S. Ye, D. Fanning, T. Coon, Y. Schmidt, P. Krenitsky, D. Stamos, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2015**, 54, 2501

VI - Application

VI – Cascade C-H



Y. Deng, W. Gong, J. He, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2014**, 53, 6692

Thank you for your kind attention