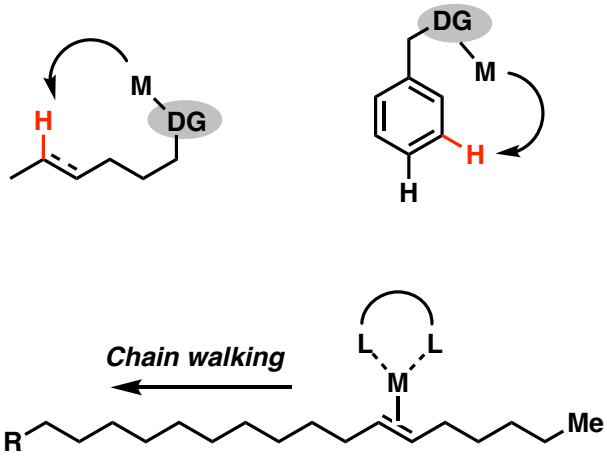
Distal Functionalization



2024/ 11/ 7 (Thu.)
Kotaro ASADA

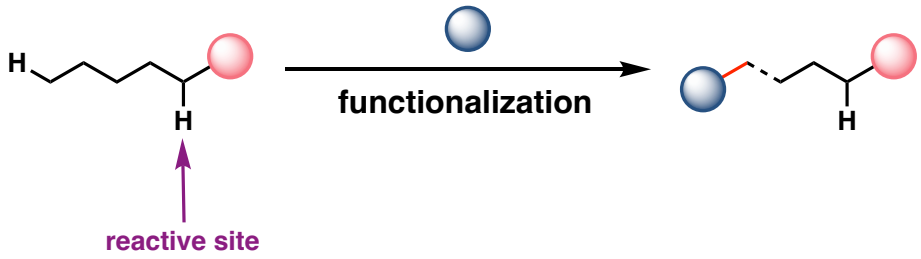
Contents

1. Introduction

1-1. Definition of distal functionalization

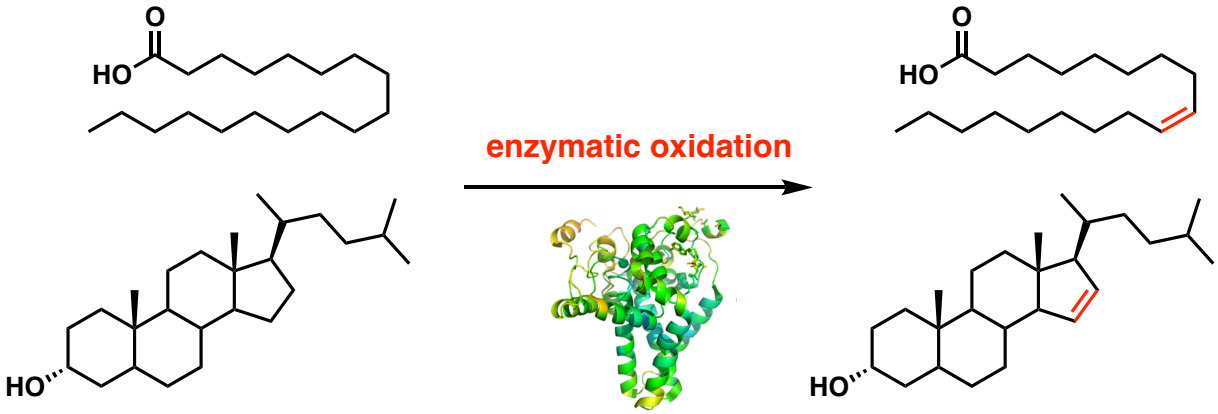
"**indirect** and **selective** activation of a site distant(2-3 atoms) from the initial functional group"

Advantage : Steric and/or electronic influences can be manipulated through the design of suitable catalysts, ligands, or reagents that alter the traditional patterns of regioselectivity.

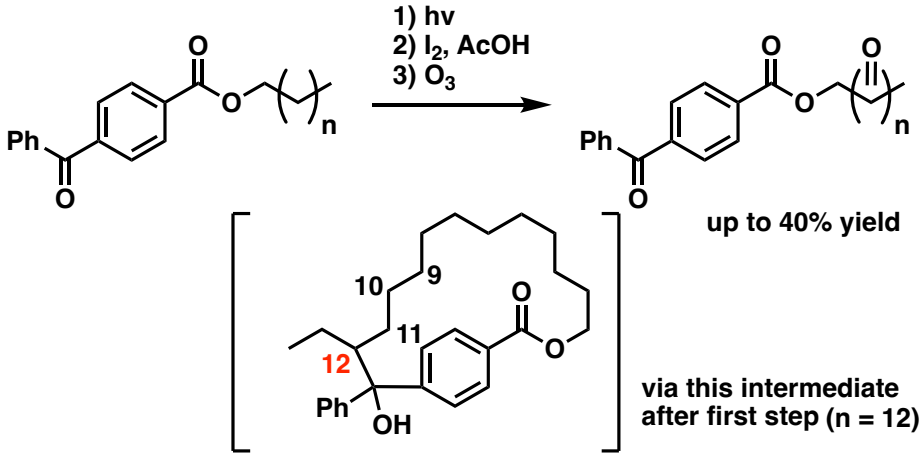


1-2. Early research in distal functionalization

- **Enzymatic distal functionalization**



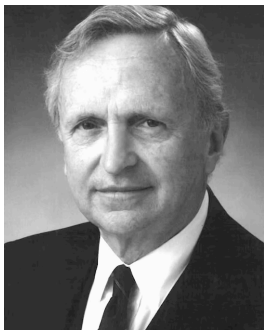
- **First distal C-H oxidation (Breslow 1969)**



up to 40% yield

via this intermediate after first step (n = 12)

n = 12, C12 selective
n = 14, C14 selective



Ronald Breslow

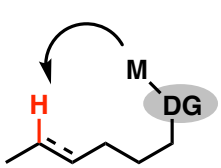
Refference

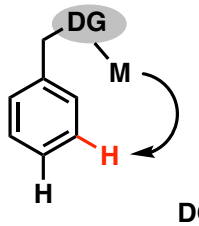
1) Yu, J-Q., *J. Am. Chem. Soc.* **2020**, 142, 10571
2) Marek, I. *Nat. Chem.* **2016**, 8, 209.
3) Breslow, *R. Acc. Chem. Res.* **1980**, 13, 170.

1. Introduction

1-3. Strategies for distal functionalization

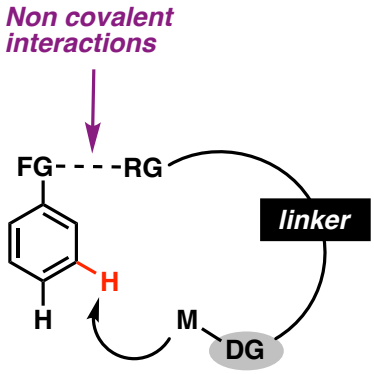
i) Template and Transition metal-mediated





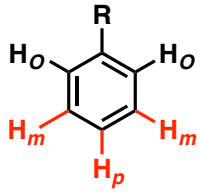
DG : Directing Group

ii) Noncovalent interaction–enabled distal C–H functionalization

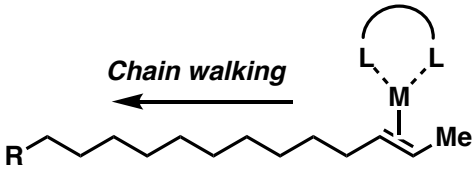


FG : Functional Group
RG : Receptor Group

iii) Non-directed distal C–H functionalization

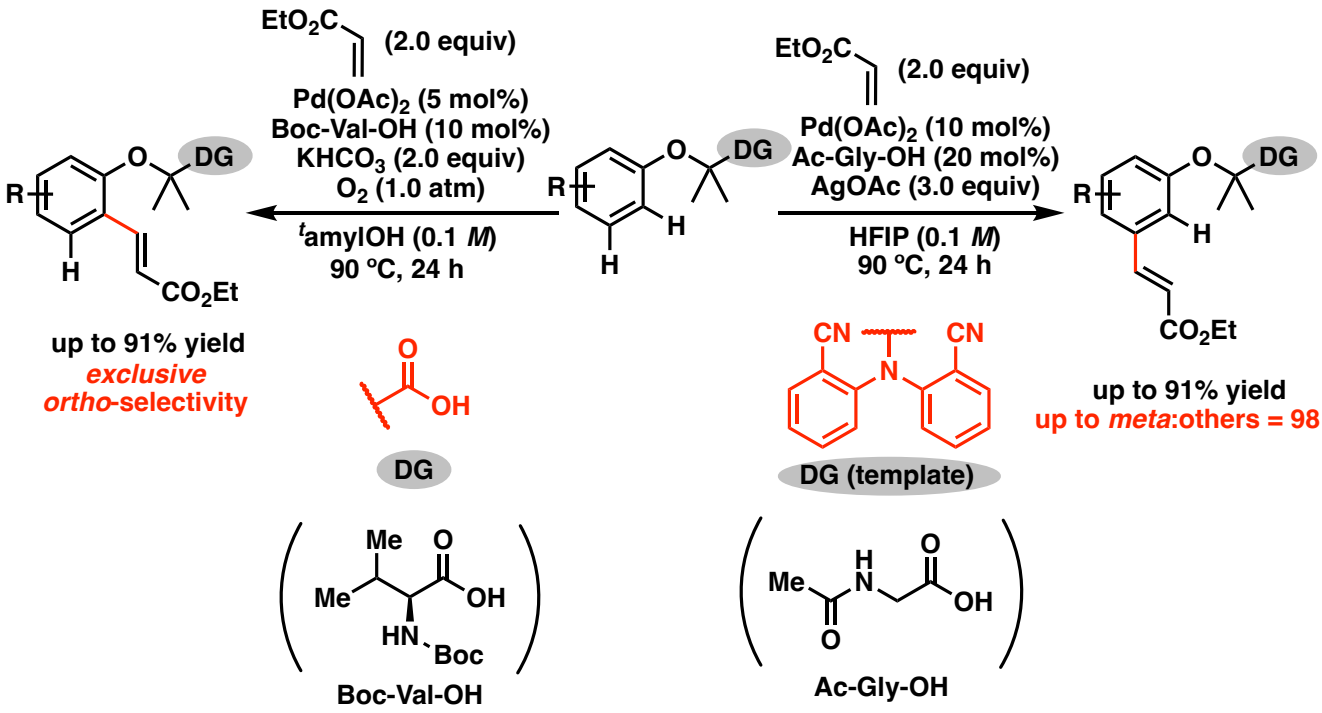


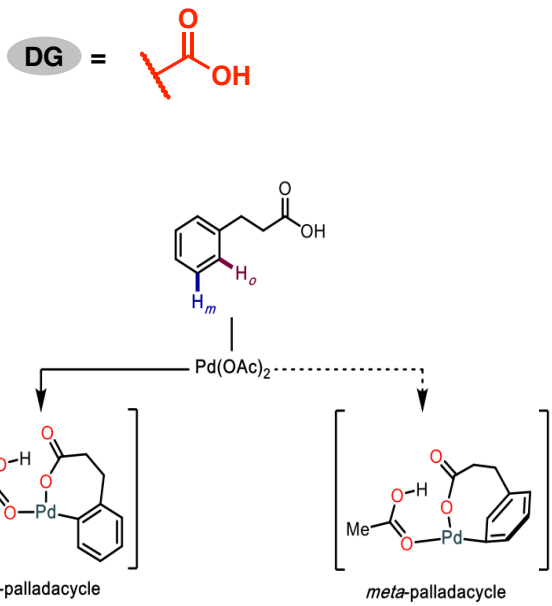
Reagent/ligand controlled activation

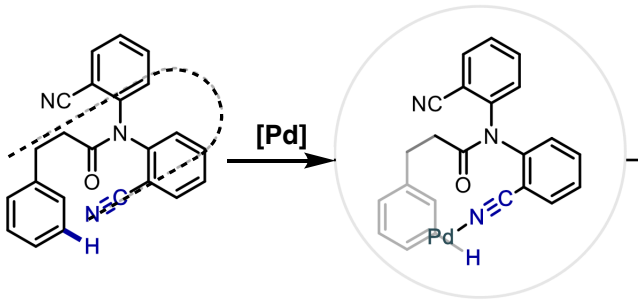


2. Template and Transition metal-mediated

2-1. Pd(II)-Catalyzed *ortho*- or *meta*-C–H Olefination of Phenol Derivatives (w/ U shaped template) (Yu, 2013)

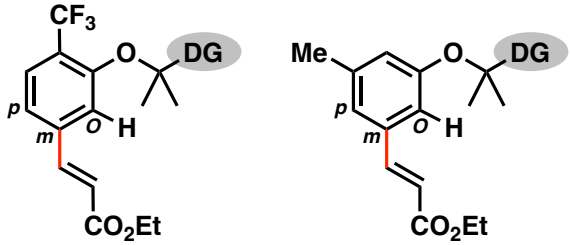






Consideration of template distance and geometry to the target C-H bond allows for the precise positioning of Pd to enable C-H activation.

Representative examples (electron baiases overridden)

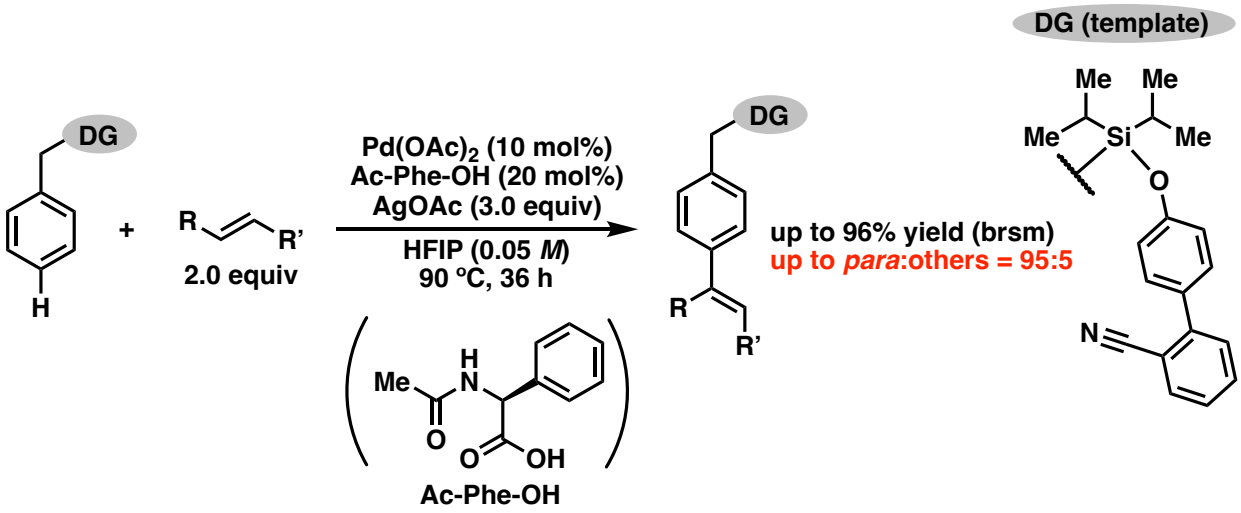


Refference

1) Yu, J.-Q., *J. Am. Chem. Soc.* **2013**, *135*, 7567

2. Template and Transition metal-mediated

2-2. Distal para-C–H Functionalization of Arenes (w/ D shaped template)

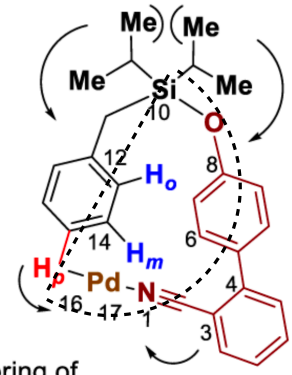


Thorpe-Ingold Effect

H_o : highly strained assembly; disfavored

H_m : rigidity of biphenyl and linearity of coordinating group; less favored

H_p : longer chain length, greater proximity of donor to target C–H; more favored

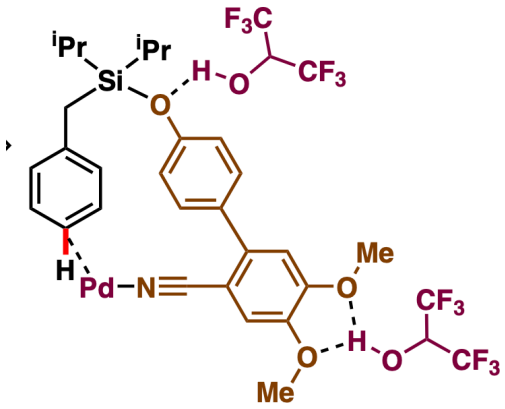


Strained T.S.

Flexible cyclophane like T.S.

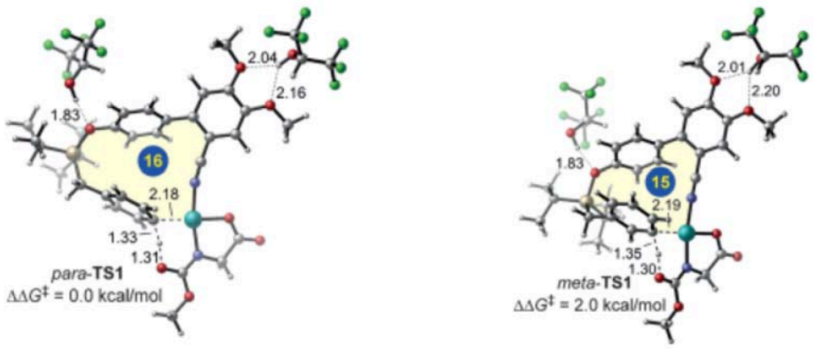
preferred anchoring of metal to *para*-C–H bond

17-membered metallacycle in pre-transition state



2nd Generation template

- **less conformational flexibility**
- **more electron density on N-atom**



DFT optimized transition state
(para-C–H activation preferred over meta-C–H activation)

Refference

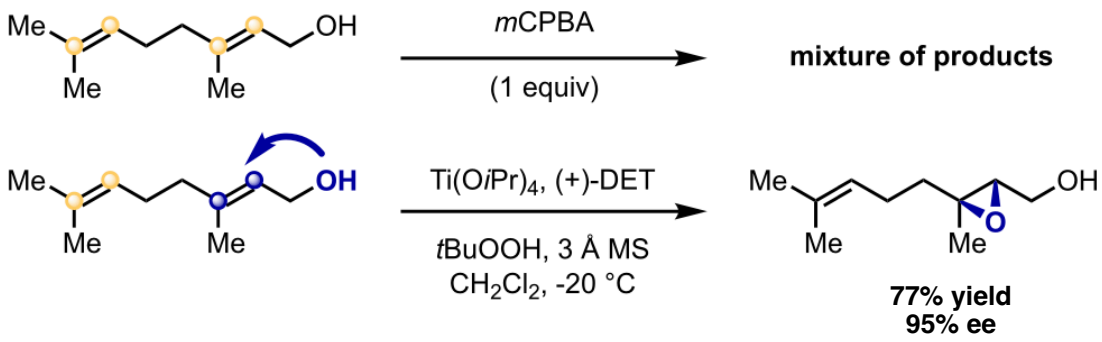
1) Maiti, D.*et al. J. Am. Chem. Soc.* **2015**, *137*, 11888

2) Bag, S. *et al. J. Am. Chem. Soc.* **2015,** *137,* 11888.

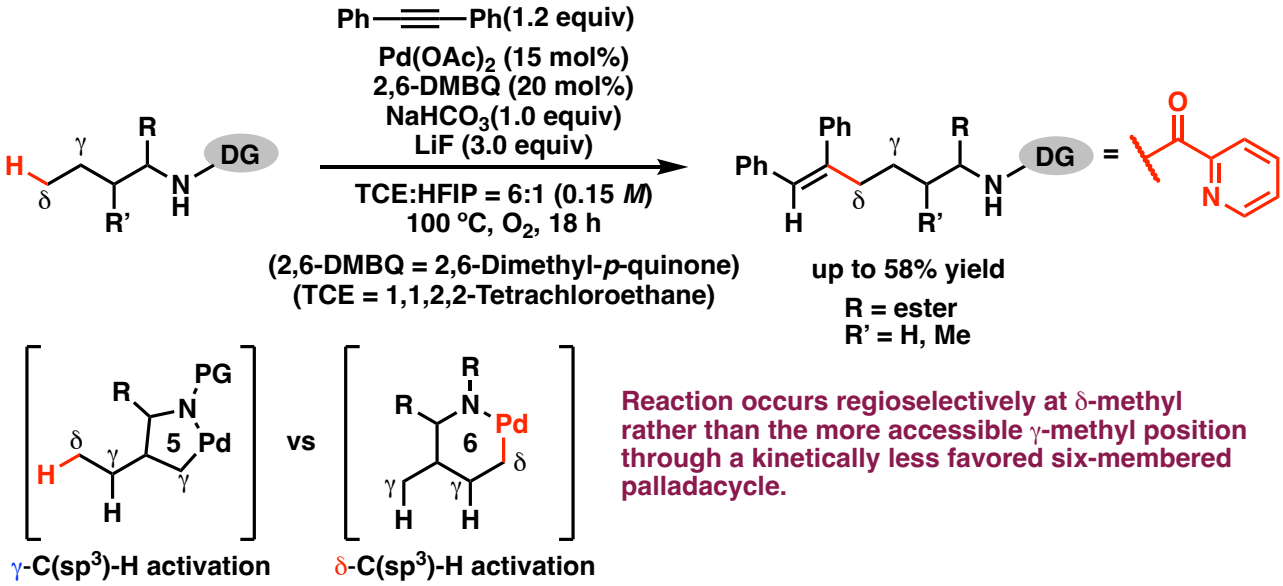
3) Patra, T. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 7751.

2. Template and Transition metal-mediated

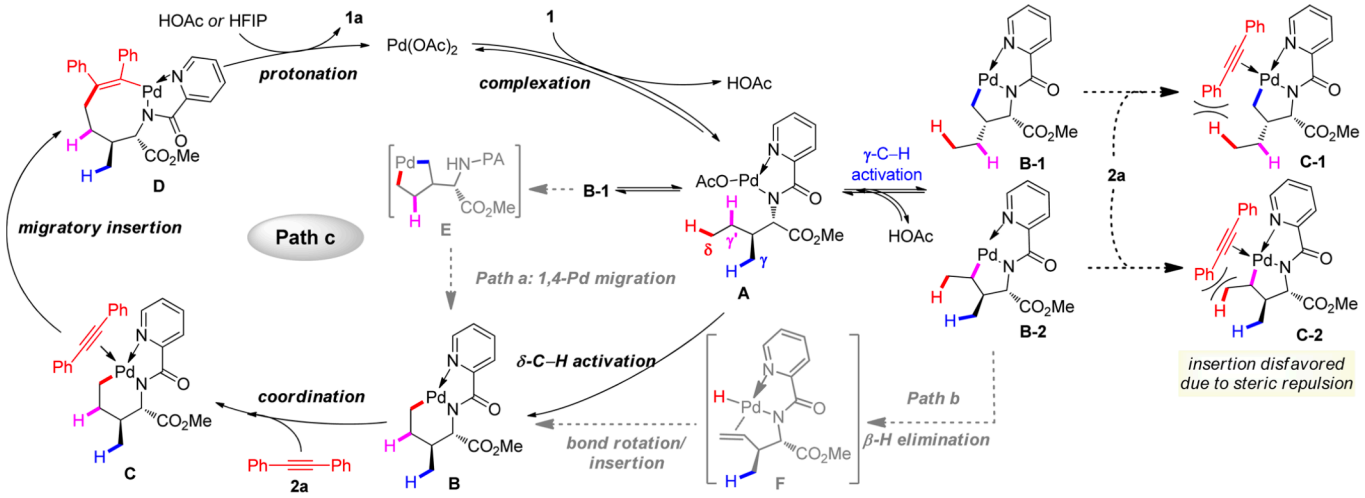
2-3. Directing group-enabled regioselectivity (alkyl substrate)
2-3.1. Sharpless asymmetric epoxidation



2-3.2 Pd catalyzed δ-C(sp3)–H alkenylation of aliphatic amines



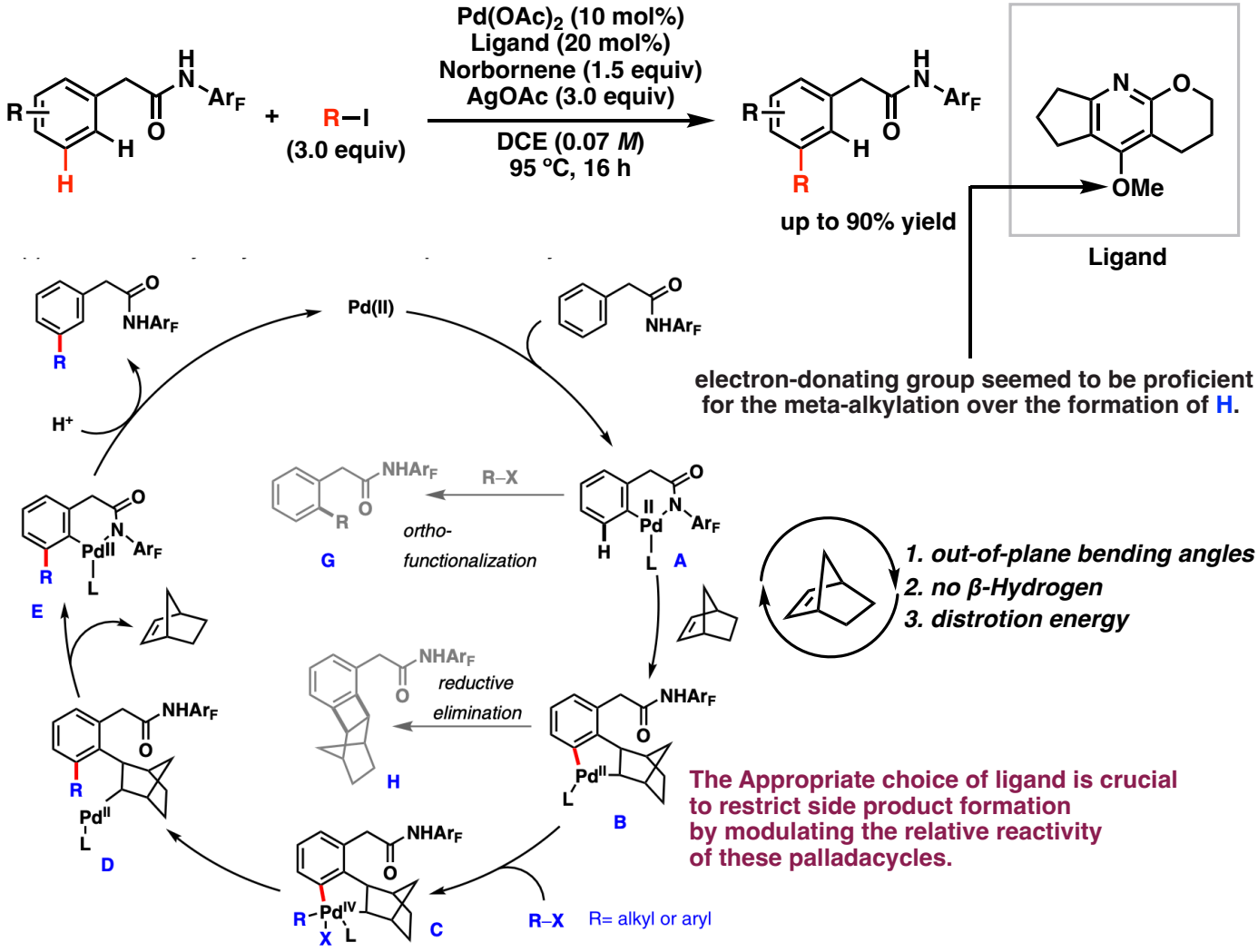
Reaction occurs regioselectively at δ-methyl rather than the more accessible γ-methyl position through a kinetically less favored six-membered palladacycle.



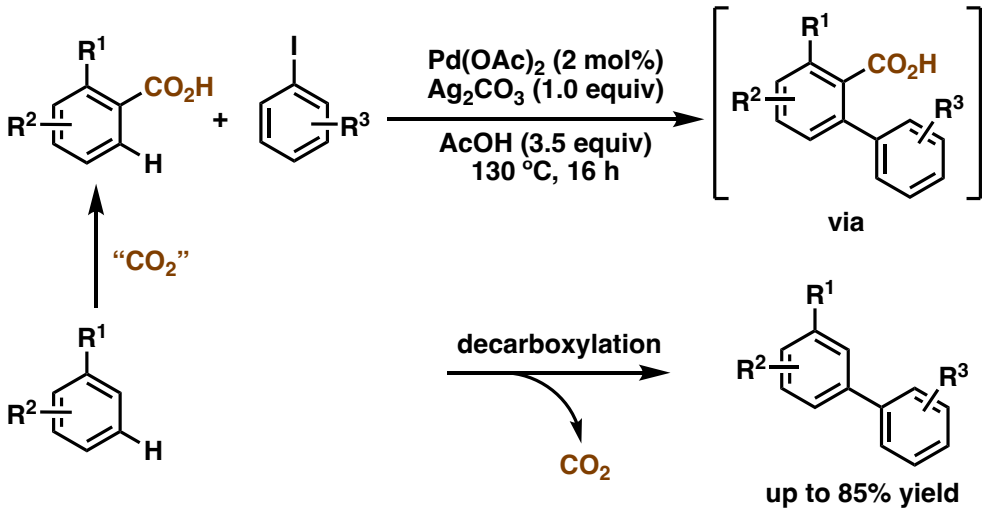
Refference
1) Sharpless, K. B.*et al. J. Am. Chem. Soc.* **1980**, *102*, 5974
2) Shi, B.-F.et *al. J. Am. Chem. Soc.* **2016**, *138*, 10750

2. Template and Transition metal-mediated

2-2.1 Transient mediator assisted Pd catalyzed distal C–H activation (mediator : Norbornene) (Yu, 2015)



2-2.2 Transient mediator assisted Pd catalyzed distal C–H activation (mediator : CO_2) (Larroas, 2011)



Refference

1) Yu, J.-Q. *et al. Nauter* **2015**, *519*, 338

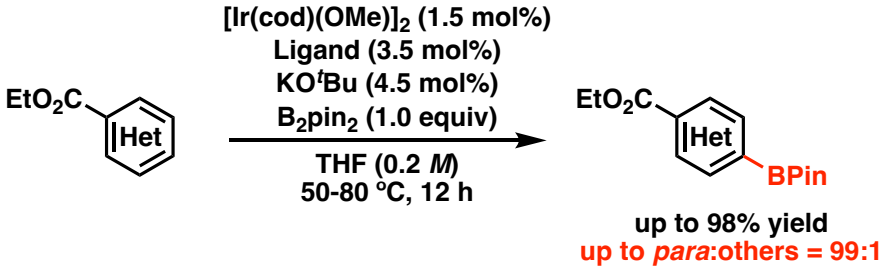
2) Larroas, I. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 9429.

3) Dong, G. *et al. Chem. Rev.* **2019**, *119*, 7478

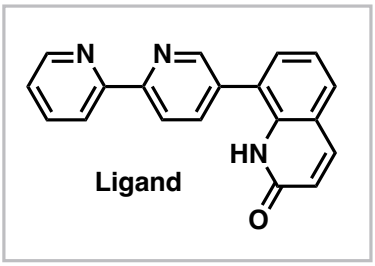
3. Noncovalent interaction-enabled distal functionalization

3-1. Remote C–H Borylation Mediated by a Bifunctional Template Anchored through Potassium Coordination

3-1.1 O–K noncovalent interaction (*para*-selective C-H borylation)

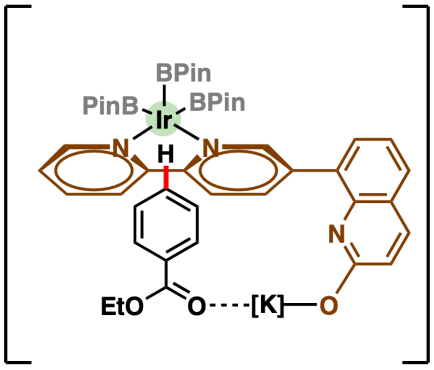


up to 98% yield
up to *para*:others = 99:1



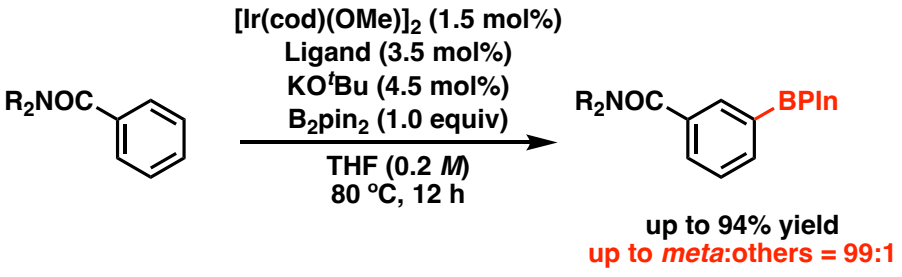
Effect of alkali metal on selectivity.

MO^tBu	additive	conv. (%)	*para*/*meta*
LiO^tBu	none	–	–
NaO^tBu	none	75	3.8/1.0
KO^tBu	none	>99	32.3/1.0
KO^tBu	18-Crown-6	90	5.6/1.0

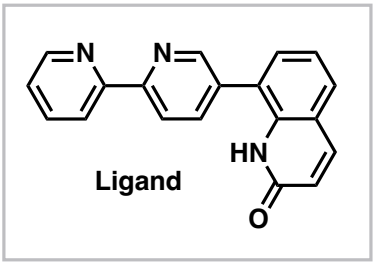


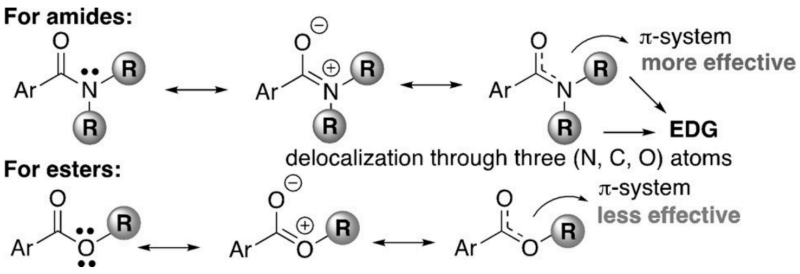
via

3-1.2 Cation-pi interaction (*meta*-selective C-H borylation) (Chattopadhyay, 2018)

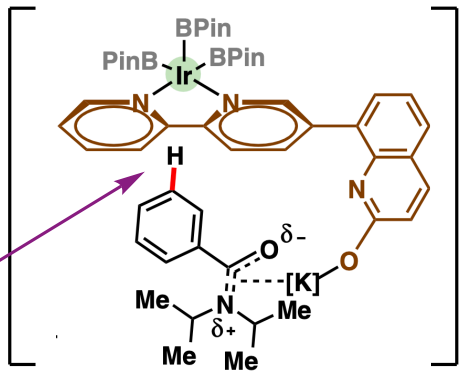


up to 94% yield
up to *meta*:others = 99:1





Ir positioned proximal to meta-C–H bond.



via

Refference

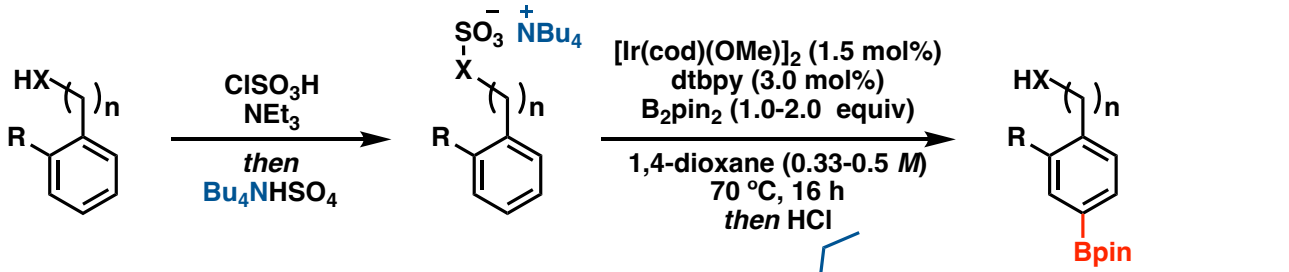
1) Chattopadhyay, B. *et al. J. Am. Chem. Soc.* **2017**, *139*, 7745–7748

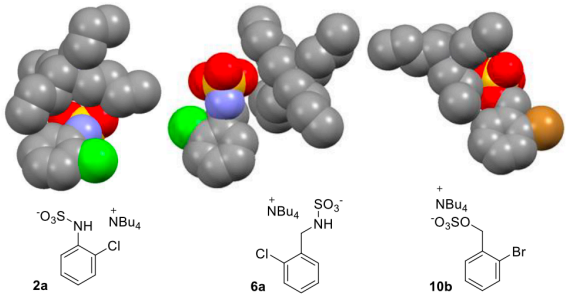
2) Chattopadhyay, B. *et al. et al. Angew. Chem. Int. Ed.* **2018**, 57, 15762 –15766

3. Noncovalent interaction-enabled distal functionalization

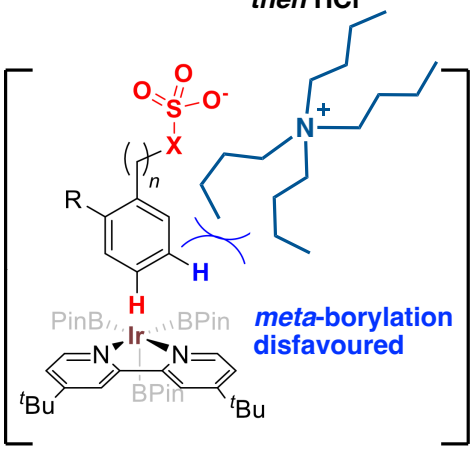
3-2 Ion-pair interaction wtih ammonium cation

3-2.1 Ion-pairing with a Bulky countercation (Phipps, 2019)





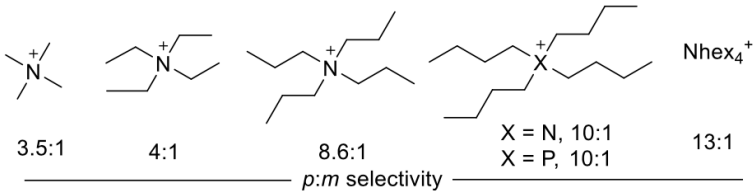
Cation act as a noncovalent "shield" to block the arene *meta*-position.



up to 92% yield
up to *para*:others = >20:1

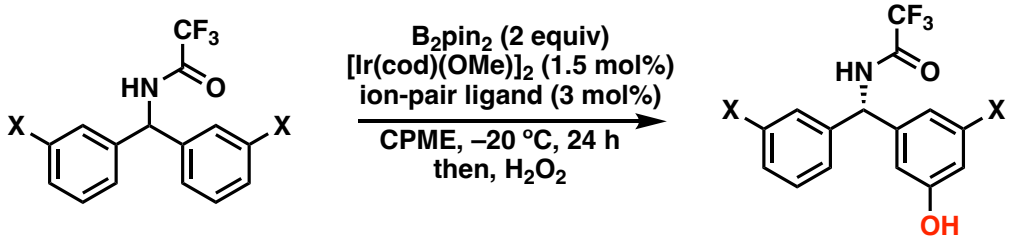
n= 0,1; X=O, NH
R= halogen, NO_2, OMe, Me, CF_3, ester….

Para-selectivity: Steric repulsion of bulky ammonium cation

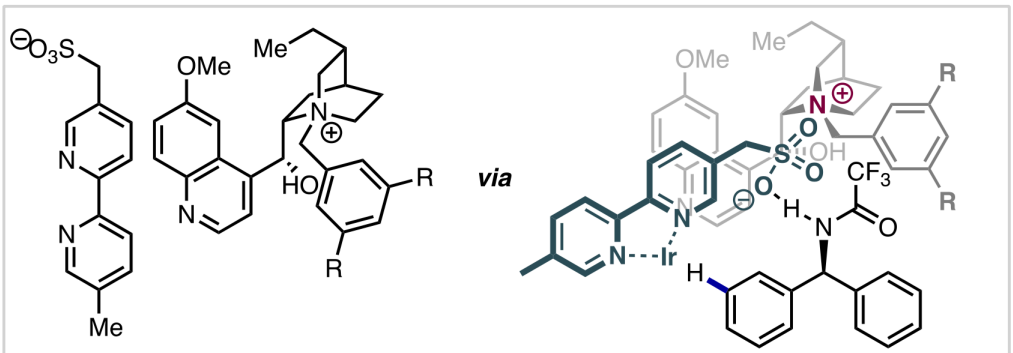


Consistent trend to higher para-selectivity as the cation grows larger

3-2.2 Combination of hydrogen-bonding and ion-pair interaction(Phipps, 2020)



5 examples
(w/ regioselectivity)
up to 72% yield
up to 85% ee
up to >20 : 1 rr
(*meta* : *para*)



Refference

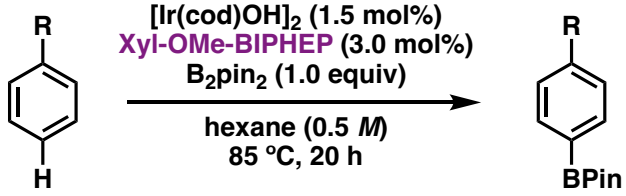
1) Phipps, R. J. *et al. J. Am. Chem. Soc.* **2019**, *141*, 15477

2) Phipps, R. J. *et al. Science* **2020**, *367*, 1246.

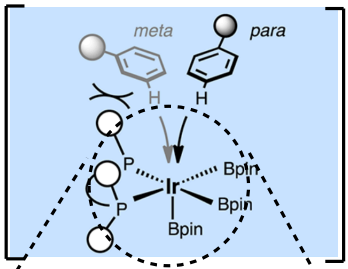
4. Non-directed distal C–H functionalization

4-1. Non-directed ligand controled distal C-H functionalizaion

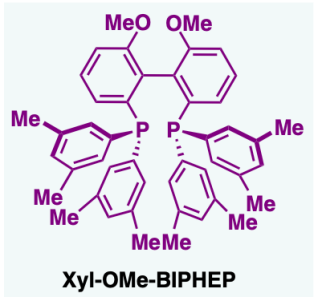
4-1.1Bulky ligand controlled *para*-C–H borylation (Itami, 2015)



up to 84% yield
up to *para*:others = 91:9

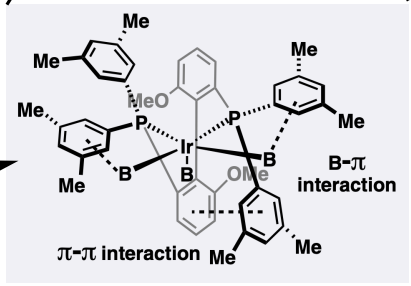


via

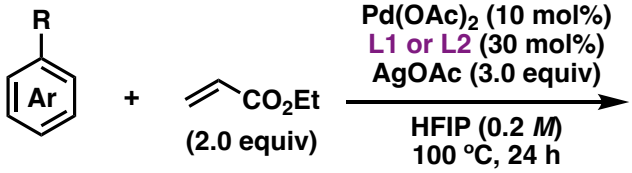


Xyl-OMe-BIPHEP

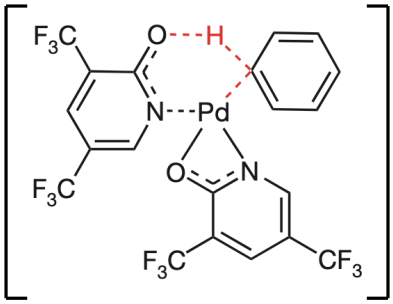
Active catalyst, tris-boryl-Ir(III), was coordinated by Xyl-MeO-BIPHEP, which is spatially oriented through π–π interactions to surround the Ir(III) center.



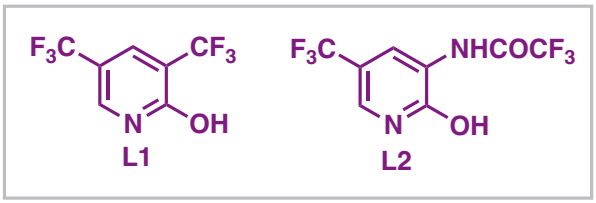
4-1.2 Ligand enabled remote C–H functionalization (Yu, 2017)



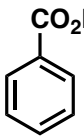
up to 71% yield
up to *meta*:others = 76:24

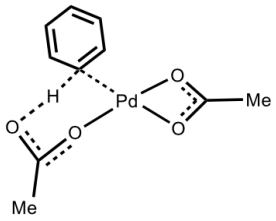


via

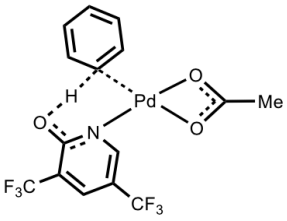


Ligand effects on reactivity and site selectivity

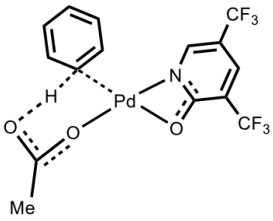
SM	Ligand	yield (%)	*m*/*p*
	none	9	1.4/1.0
	L1	72	4.4/1.0



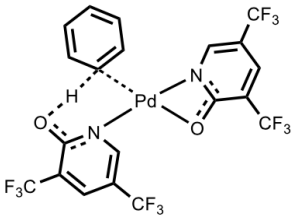
TS-acetate-acetate
$\Delta\Delta G_{TS}$ = 9.6 kcal/mol



TS-pyridone-acetate
$\Delta\Delta G_{TS}$ = 4.4 kcal/mol



TS-acetate-pyridone
$\Delta\Delta G_{TS}$ = 4.5 kcal/mol



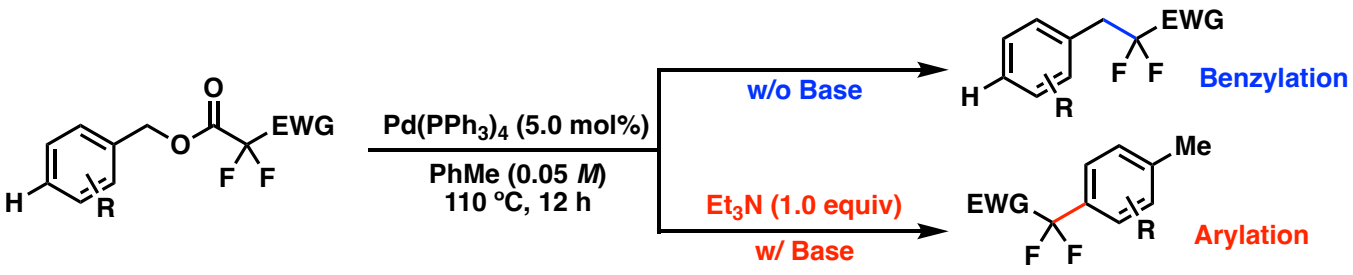
TS-pyridone-pyridone
$\Delta\Delta G_{TS}$ = 0.0 kcal/mol

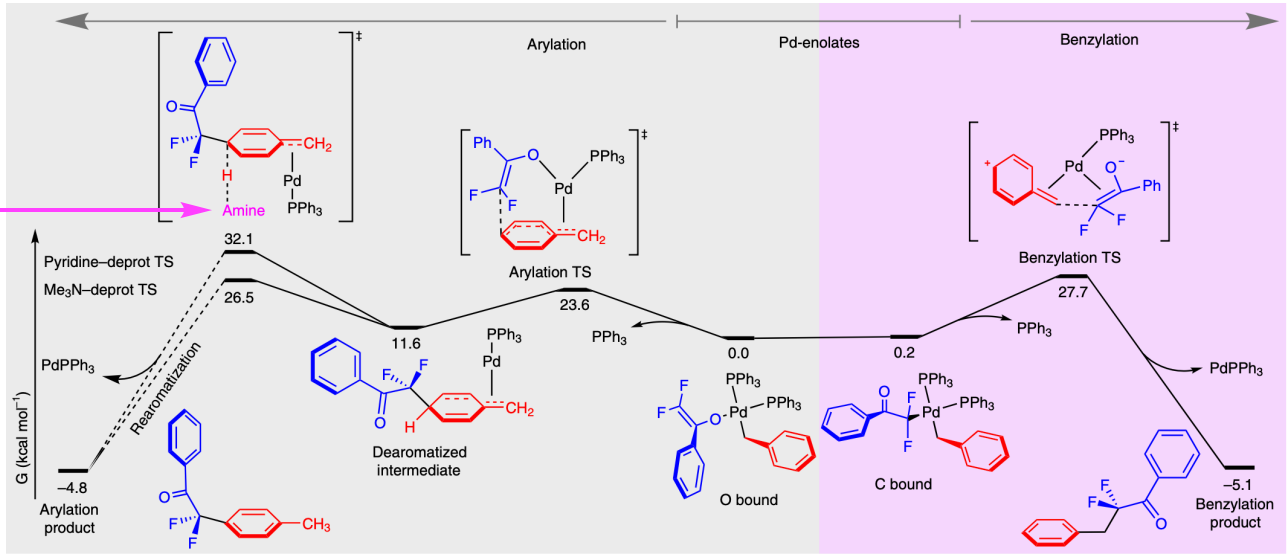
Refference
1) Itami, K, *et. al. J. Am. Chem. Soc.* **2015**, *137*, 5193.
2) Yu, J.-Q. *et. al. Nature* **2017**, *551*, 489.

4. Non-directed distal C–H functionalization

4-2. Non-directed reagent controled distal C-H functionalizaion

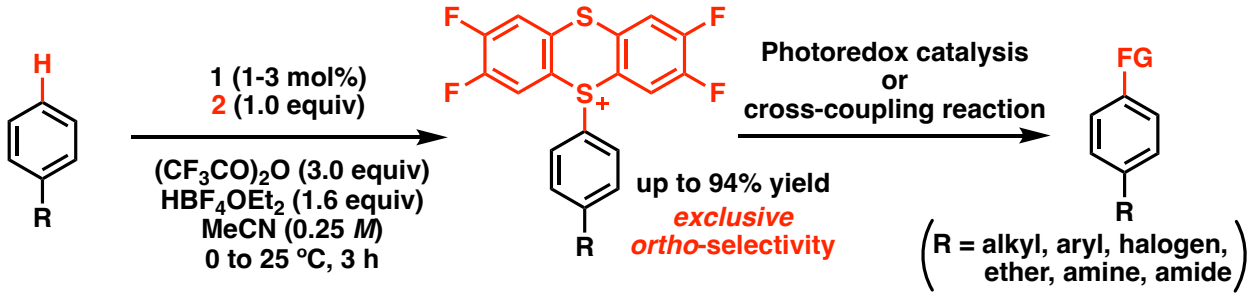
4-2.1. Base enabled *para*-C–H fluoromethylation *via* 1,5-hydrogen shift (Altman, 2020)

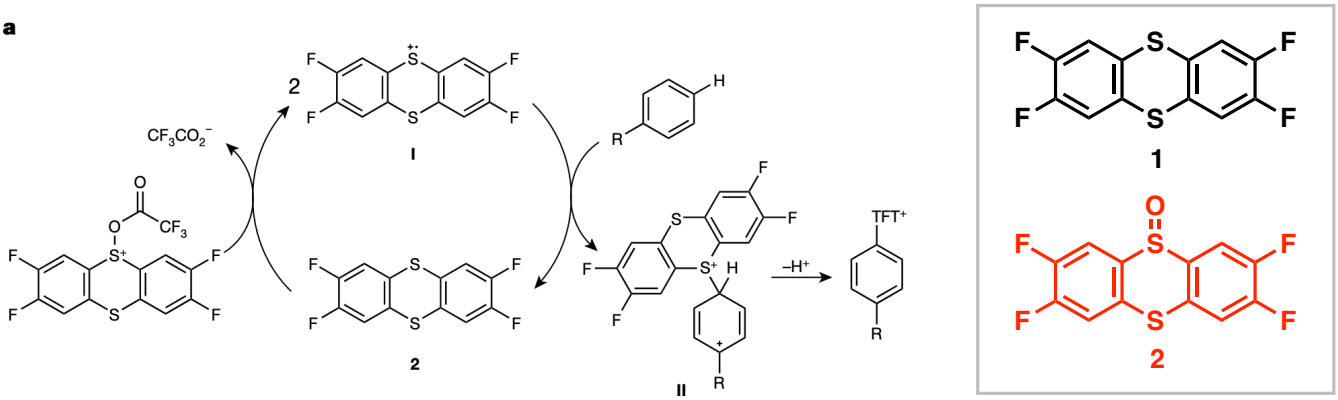




The use of weak bases(p*K*a : 4.0 to 8.0) and too bulky trialkyl amine bases favoured the benzylation product. Arylation products only formed w/ trialkyl amine bases with p*K*a 8.0–10.5.

4-2.2. Distal C–H functionalization by thianthrenation (Ritter, 2019)





Refference

1) Altman, R. A. *et al.Nat. Chem.* **2020**, *12*, 489.

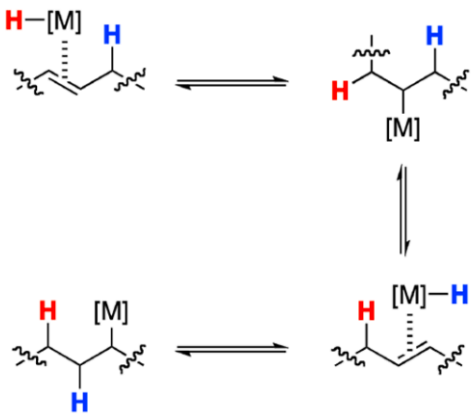
2) Ritter, T. *et al. Nature.* **2019**, *567*, 223.

4. Non-directed distal C–H functionalization

4-3. Chain walking

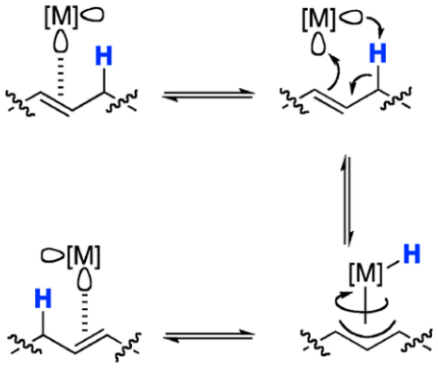
4-3.1. General mechanism of olefin isomerization

a) 1,2-hydride shift



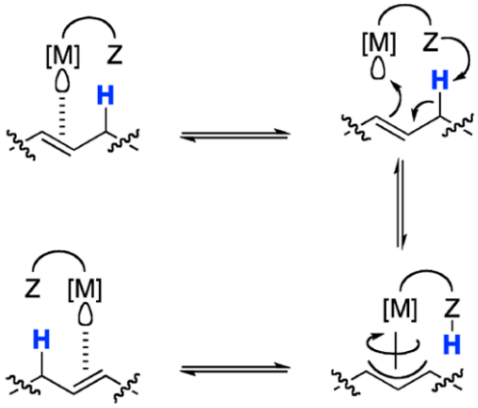
Reaction starts with a metal-hydride (M–H)

b) 1,3-hydride shift (agostic interaction)



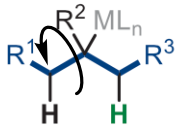
It requires two vacant orbitals:
1. olefine coordination
2. C–H allylic activation to occur

c) 1,3-hydride shift (with ligand)

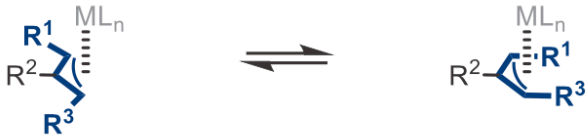


Stereocontrol

a) 1,2-hydride shift



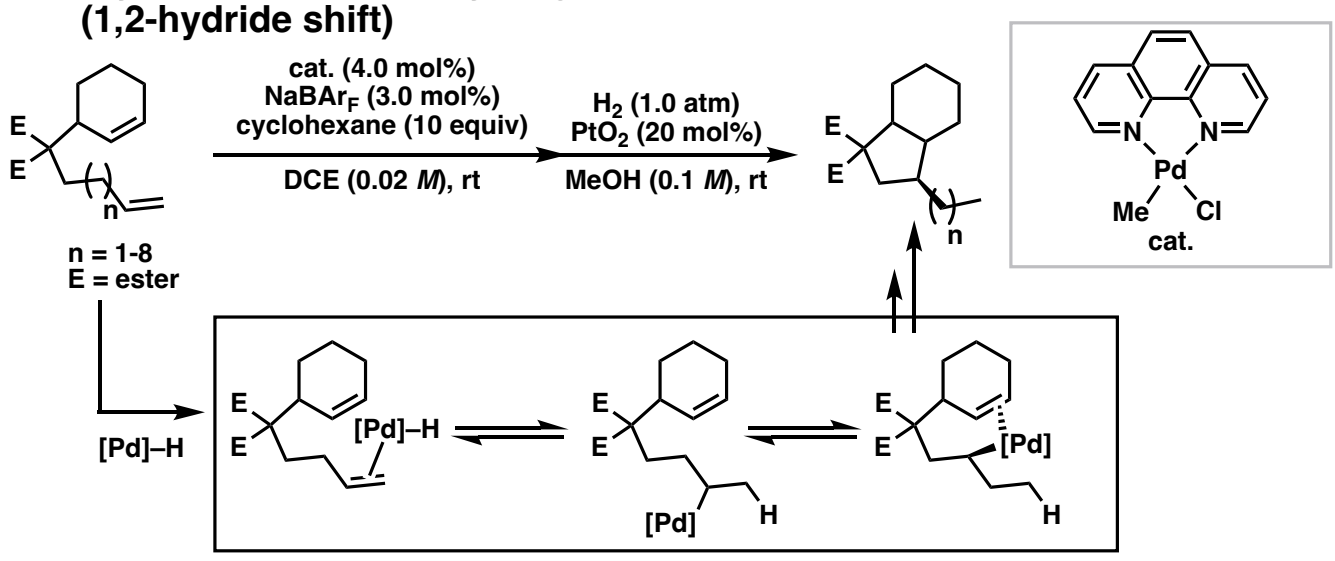
b) 1,3-hydride shift



1,2-allylic strain

steric interactions with ML_n
1,3-allylic strain

4-3.2. Cycloisomerization/Hydrogenation of 1,n-dienes (Kakiuchi, 2012) (1,2-hydride shift)



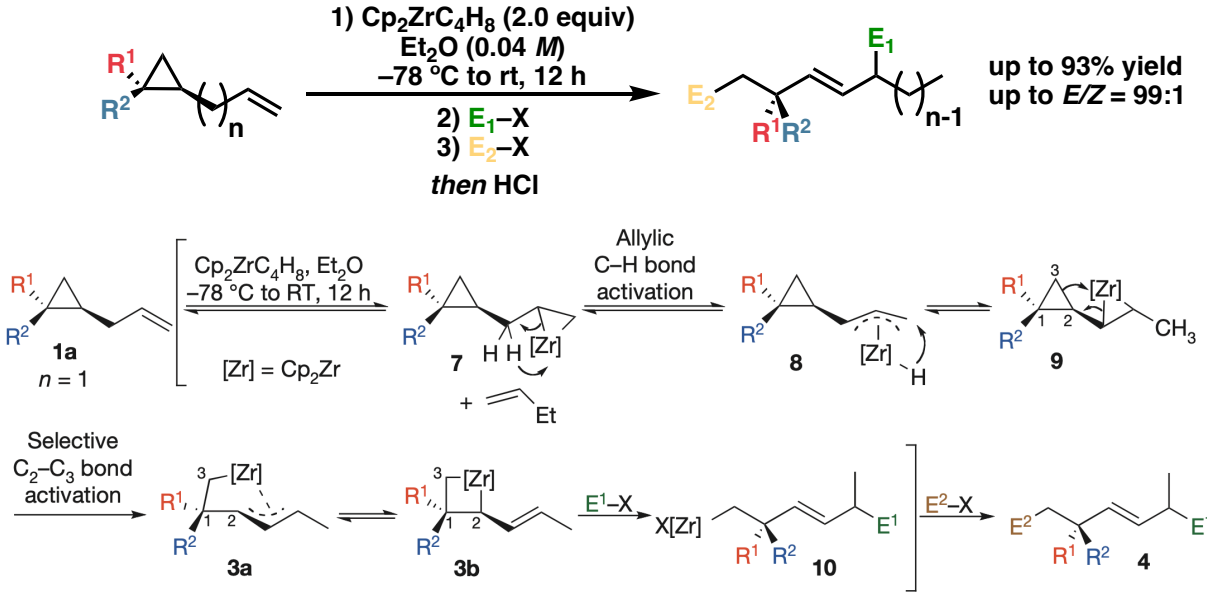
Refference

1) Marek, I. *et al. ACS Cent Sci.* **2018**, *4*,153.
2) Marek, I. *et al. ACS Catal.* **2020**, *10*, 5793.
3) Kakiuchi, F. *et al. Jacs,* **2012**, *134,* 16544

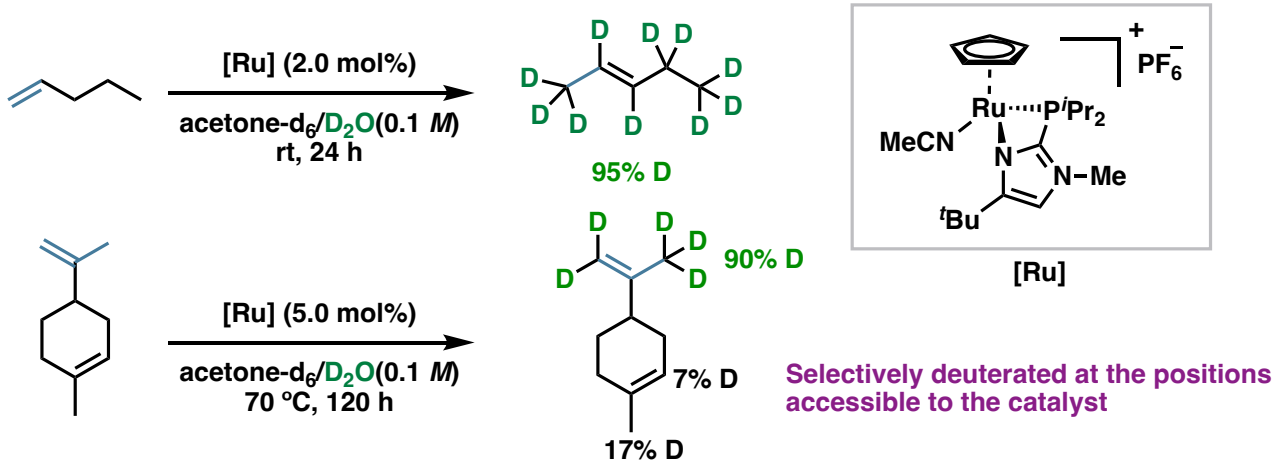
4. Non-directed distal C–H functionalization

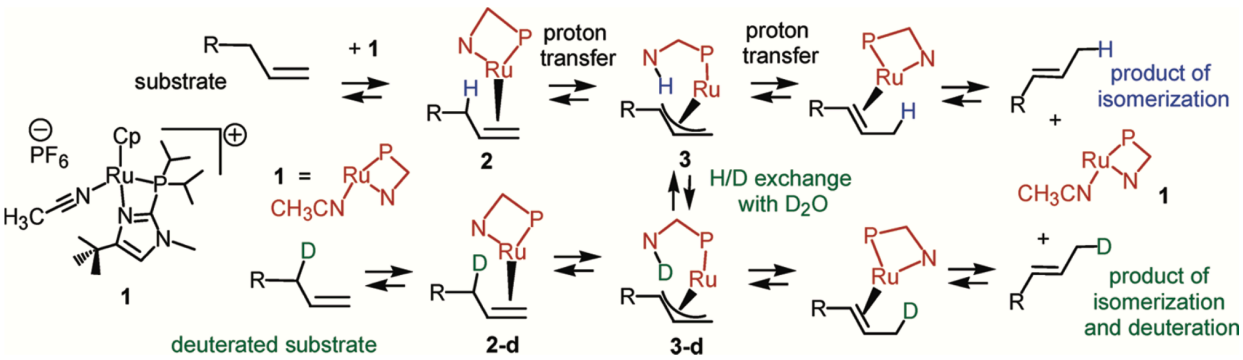
4-3. Chain walking

4-3.3. Merging allylic carbon–hydrogen and selective carbon–carbon bond activation (Marek, 2014)(1,3-hydride shift/agostic interaction)



4-3.4. Isomerization–deuteration using D_2O. (Grotjahn, 2009) (1,3-hydride shift/with ligand)





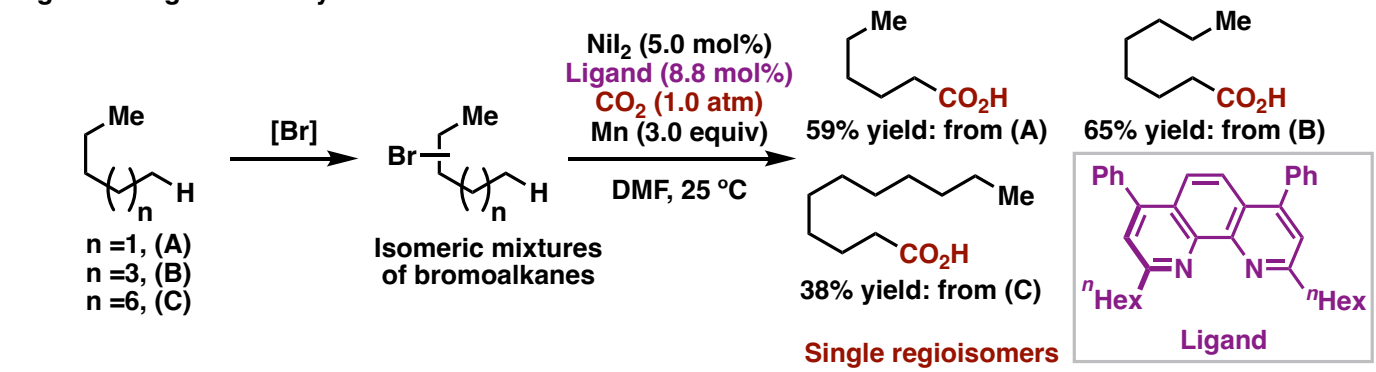
Refference

1) Marek, I. *et al. Nature.* **2014**, *505*, 199.
2) Grotjahn, B. *et al. Jacs.* **2009**, *131*, 10354.

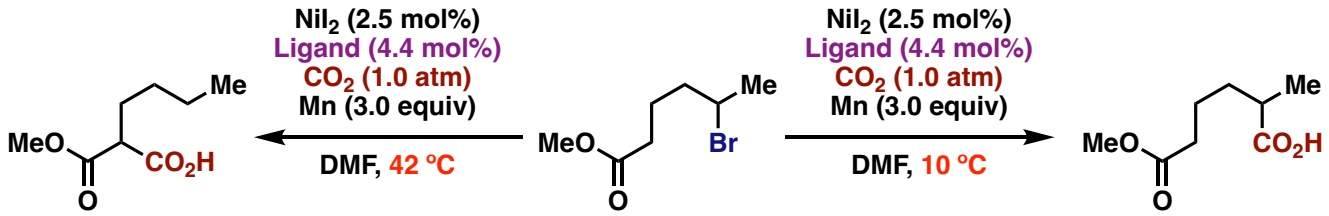
4. Non-directed distal C–H functionalization

4-3. Chain walking
4-3.5. Remote carboxylation (Martin, 2017)

Regioconvergent carboxylation of alkanes

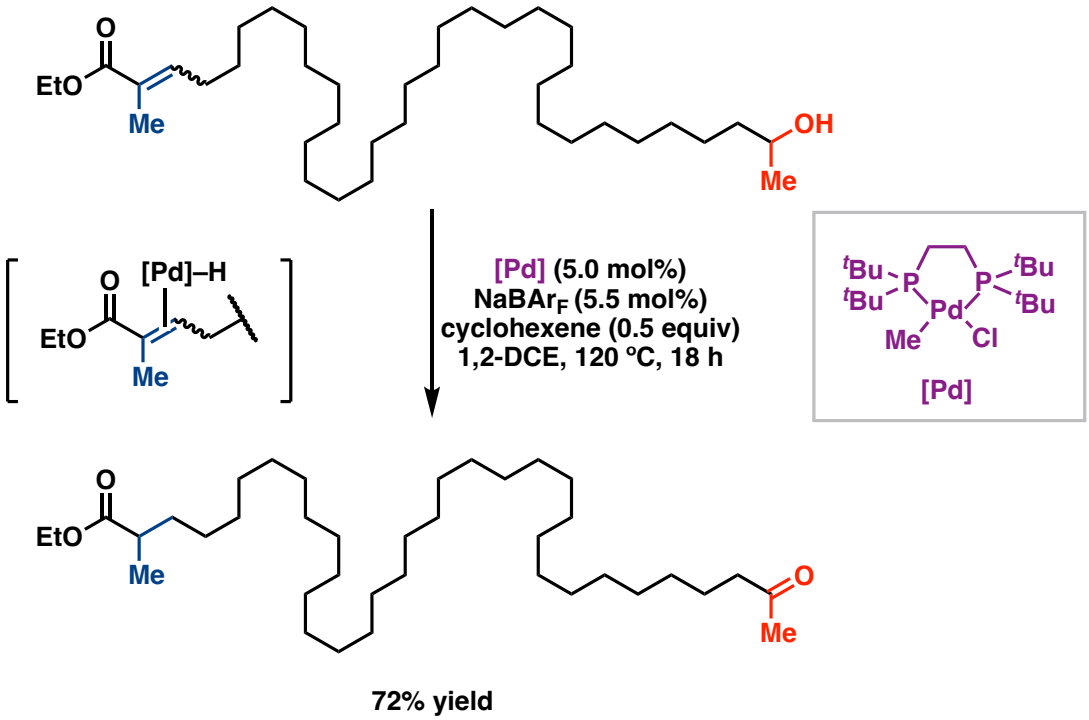


Switchable site-selective carboxylation of unactivated alkyl bromides



Thermodynamically controlled intermediates
(Ni on α-position of carbonyls) at higher temperatures

4-3.6. Long-Range Isomerizaion (Mazet, 2016)



72% yield

Refference
1) Martin, R. *et al. Nature.* **2017**, *545*, 84.
2) Mazet, C. *et al. Jacs.* **2016**, *138*, 10344.