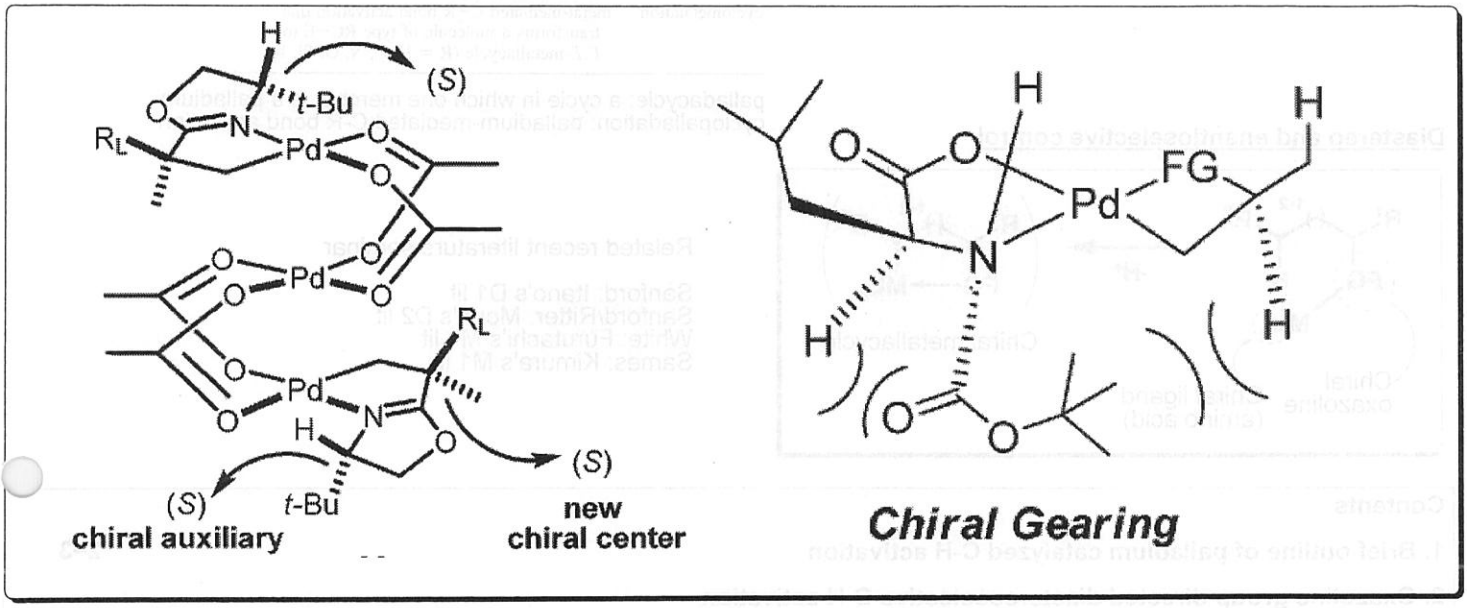
H.Mitsunuma(B4)

Palladium catalyzed C-H functionalizations : regioslectivity, stereoselectivity and enantioselectivity ~Chemistry of Jin-Quan Yu ~



Jin-Quan Yu

Jin-Quan Yu received his BSc in Chemistry from East China Normal University and his MSc from the Guangzhou Institute of Chemistry.

In 2000, he obtained his PhD at the University of Cambridge with Prof. J. B. Spencer.

Following time as a junior research fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow.

He then began his independent career at Cambridge (2003~2004), before moving to Brandeis University (2004~2007), and finally to The Scripps Research Institute, where he is currently Associate Professor of Chemistry.

His group studies transition metal-catalyzed C-H activation.

0.Introduction

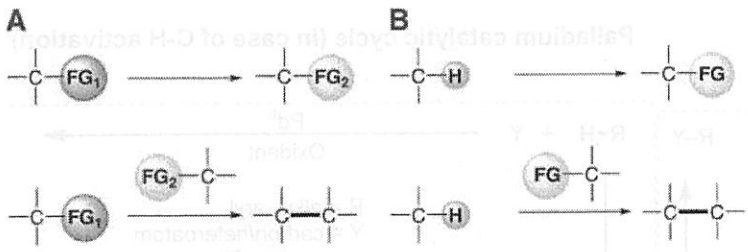


Fig. 2. (A) Traditional approach to organic synthesis by means of functional group (FG) transformation. (B) Synthesis by means of C–H bond functionalization.

Ubiquitousness of C-H bond

Atom economically good

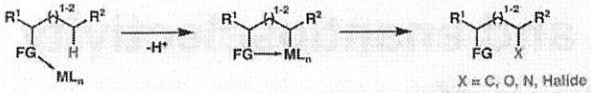
⇓

New synthetic target in organic chemistry

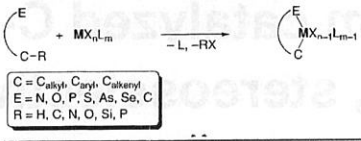
Transition metal complexes that cleave C-H bonds are necessarily high in energy.

⟶ One of the principle challenge in the field of C-H activation that limits its synthetic relevance is rooted in **selectivity**.

In many C-H activation chemistry, functional groups are used as directing group in order to arrange transition metal to appropriate position.



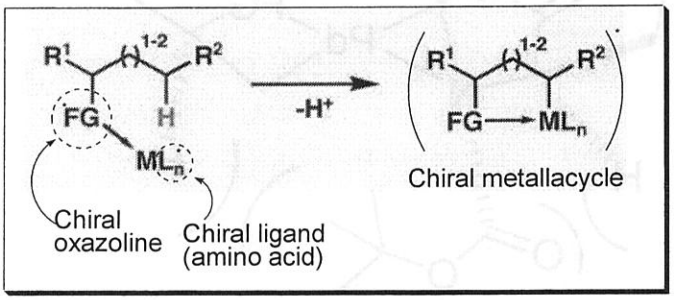
Difinitions applied in this seminar



metallacycle	a cycle in which one member is a metal
C,E-metallacycle	a metallacycle in which the metal is σ-bonded to the atoms C and E
cyclometalation	metal-mediated C−R bond activation that transforms a molecule of type RC−E to a *C,E*-metallacycle (R = H, C, N, O, Si, P)

palladacycle: a cycle in which one member is a palladium
cyclopalladation: palladium-mediated C-R bond activation

Diastereo and enantioselective control



Related recent literature seminar

Sanford: Itano's D1 lit
Sanford/Ritter: Mouri's D2 lit
White: Furutachi's M1 lit
Sames: Kimura's M1 lit

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1. Brief outline of palladium catalyzed C-H activation	**2~3**
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3. Pyridine group directed enantioselective C-H selective activation using chiral ligand	**6~9**
4. Carboxylic acid group directed enantioselective and regioselective C-H activation using chiral ligand	**10~13**
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1. Brief outline of palladium catalyzed C-H activation

Merit of C-H functionalization reactions catalyzed by palladium

1. C-H functionalization at Pd centers can be used to install many different types of bonds, including C-O, C-halogen, C-N, C-S, and C-C linkages.

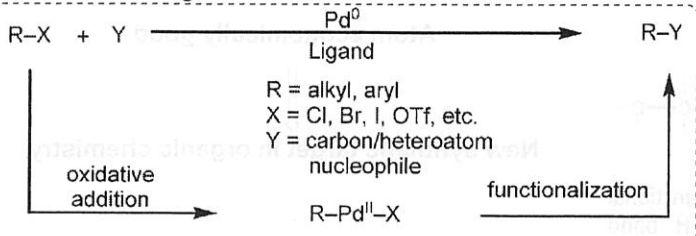
   i) Compatibility of many Pd(II) catalysts with oxidants
   ii) Ability to selectively functionalize cyclopalladated intermediates

2. Palladium participates in cyclometalation in wide a varity of directing groups.

3. Vast majority of Pd-catalyzed directed C-H functionalization reactions can be performed in the presence of ambient air and moisture, making them exceptionally practical for applications in organic synthesis.

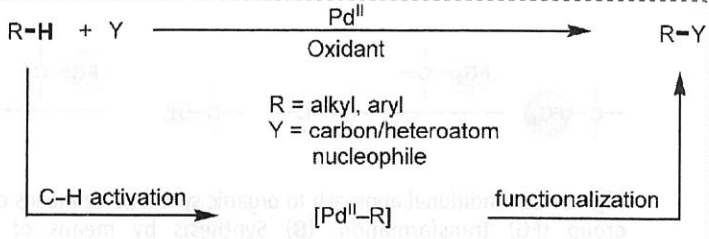
Common palladium catalytic cycle

Heck rxn, cross coupling, Tuji-Trost allylation, and Buchwald-Hartwig amination etc



Scheme 1. Palladium(0)-catalyzed reactions of aryl(alkyl) halides. Tf = trifluoromethanesulfonyl.

Palladium catalytic cycle (in case of C-H activation)

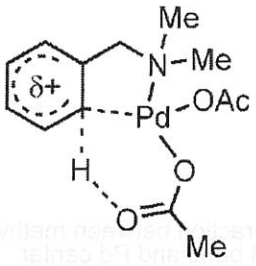


Scheme 2. Palladium(II)-catalyzed functionalization of C–H bonds.

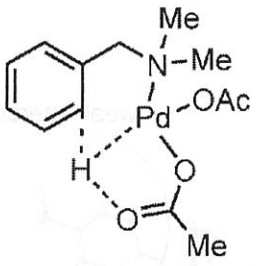
Pd(II)-Pd(0) catalysis
Pd(II)-Pd(IV) catalysis (involvement of Pd(III) spices: Mouri's D2 lit)
Pd(II) catalysis
Pd(0)-Pd(II)-Pd(IV) catalysis

Cyclopalladation (for more detail: see Dr.Itano's D1 lit)

Cyclopalladation is thought to be through electrophilic pathway.



electrophilic aromatic substitution



agostic C-H interaction

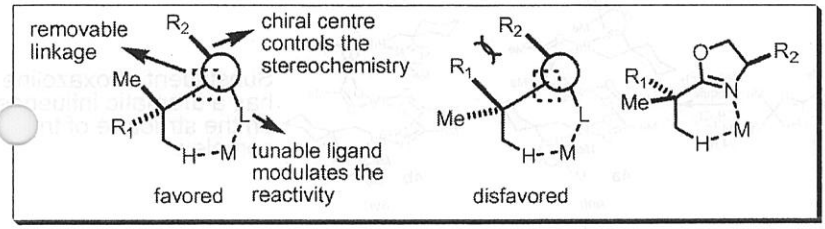
Recent computational study supports 6-membered TS via agostic interaction.

Acetate has a flexible metal cordination mode and works as a base.

Nitrogen-containing directing group is fovorable over oxygen-containing directing group due to strong coordination nature.

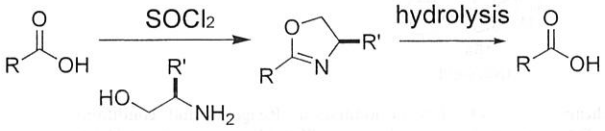
2. Oxazoline group directed diastereoselective C-H activation

Concept



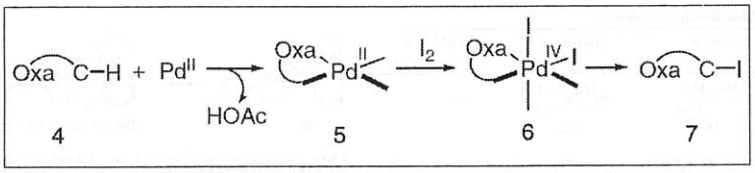
Oxazoline group

Chiral oxazoline auxiliary is easily introduced and removed to afford carboxylic acid. Carboxylic acid is one of the most popular functional group in the organic synthesis.



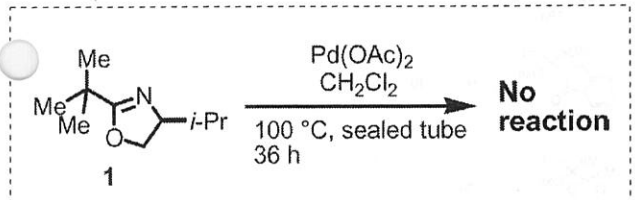
2-1. Diastereoselective iodination

Jin-Quan Yu. et al. *Angew. Chem. Int. Ed.* **2005**, 44, 2112
Tetrahedron: Asymmetry. **2005**, 16, 3502



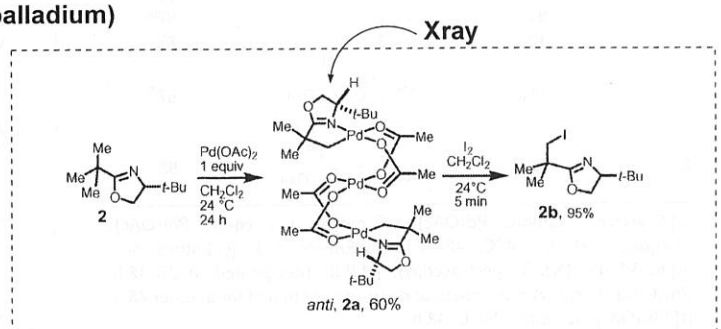
Scheme 2. Proposed reaction pathway for iodination of unactivated C–H bonds.

Initial try (cyclopalladation using stoichiometric amount of palladium)

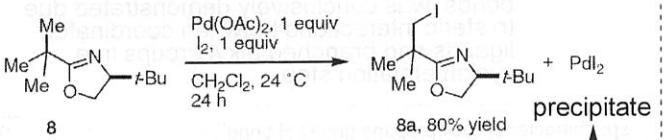


Scheme 6 Unreactive oxazoline.

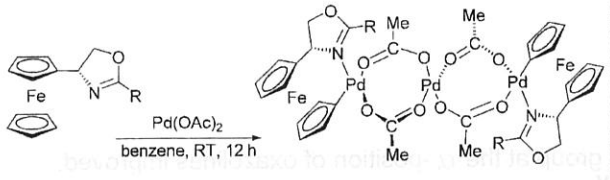
Xray



Scheme 7 Room temperature sp^3 C–H cleavage directed by oxazolines.



First example of trimer palladium complex (Xray)



Angew. Chem. Int. Ed. **2005**, 44, 1865

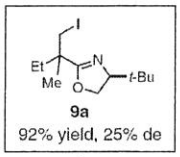
Palladium turnover

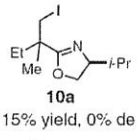
$$PdI_2 + 2IOAC \rightarrow Pd(OAc)_2 + 2I_2 \quad (1)$$

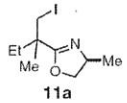
$$AgOAc + I_2 \rightarrow AgI + IOAc \quad (2)$$

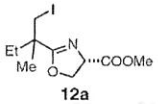
$$PhI(OAc) + I_2 \rightarrow PhI + 2\,IOAc \quad (3)$$

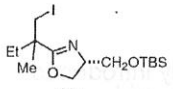
Chiral oxazoline effect

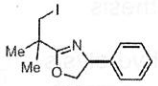




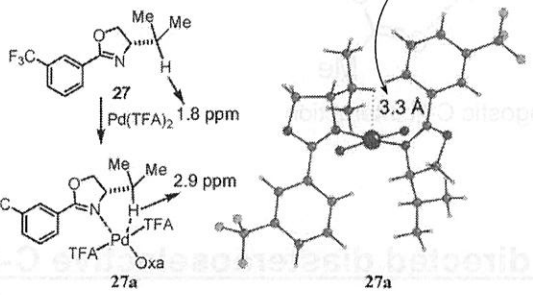








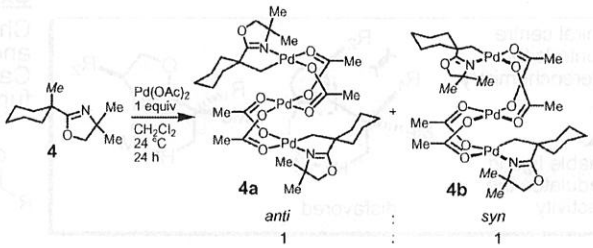
Scheme 5. Ligand effect in iodination. Reagents and conditions: $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 64 h (**9a–11a**, **14a** and **15a**); 50 °C, 48 h (**12a–13a**).



Interaction between methyne C-H bond and Pd center

↓

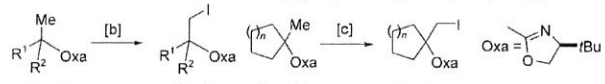
Inhibition of cyclopalladation?

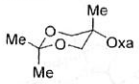
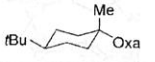


Substituent of oxazoline has a dramatic influence on the structure of tri… complex.

Result

Table 1: Monoiodination of methyl groups catalyzed by $Pd(OAc)_2$.[a]

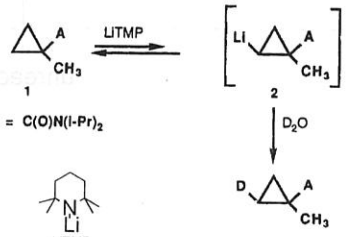


Entry		Substrate	Yield [%]
1	**5a**	$R^1 = R^2 = Me$	92
2	**6a**	$R^1 = Me$; $R^2 = Et$	91[d]
3	**7a**	$R^1 = R^2 = Et$	88[e]
4	**8a**	$n = 1$	90[e]
5	**9a**	$n = 2$	97[e]
6	**10a**	$n = 3$	81
7	**11a**		67[f]
8	**12a**		98

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 48–72 h. [b] Entries 1–3. [c] Entries 4–6. [d] 63:37 d.r. (NMR spectroscopy). [e] PdI_2 precipitated at 36–48 h, $PhI(OAc)_2$ (1 equiv) was added, and stirring continued for another 48 h. [f] $PhI(OAc)_2$ (2 equiv), 50 °C, 48 h.

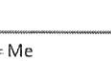
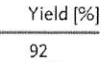
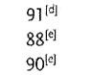
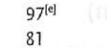
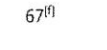
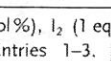
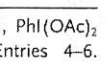
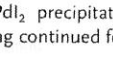
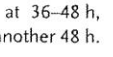
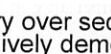
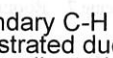
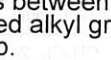
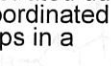
Entry **1 ~3** : Iodination of primary over secondary C-H bonds was conclusively demonstrated due to steric interactions between coordinated ligands and branched alkyl groups in a cyclometalation step.

sp2 character of cyclopropane ring C-H bond

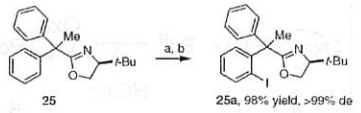


J. Org. Chem., **1987**, 52, 2100

Table 1. Diastereoselective iodination[a]

Entry	Substrate	Product	Yield (%)	de (%)
1	**16**	**16a**	60[b]	35
2	 **17**	 **17a**	41[c]	55
3	 **18**	 **18a**	45[d]	55
4	**19**	 **19a**	50[b]	25
5	**20**	 **20a**	60[b]	10
6	 **21**	 **21a**	70[e]	0
7	 **22**	 **22a**	83[f]	82
8	 **23**	 **23a**	62[g]	87
9	 **24**	 **24a**	65[h]	99

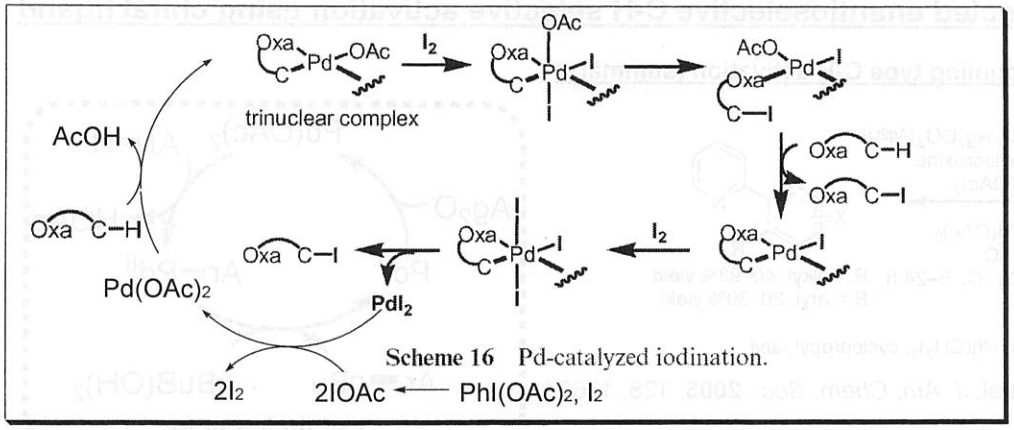
[a] Oxa = (*S*)-4-*tert*-Butyloxazoline-2-. Reaction conditions: $Pd(OAc)_2$ (10 mol %) I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2.
[b] 65 °C. $PhI(OAc)_2$ (1 equiv) was added after 12 h, and stirring continued for another 24 h.
[c] 50 °C, 41 h.
[d] 24 °C, 42 h.
[e] 24 °C, 24 h.
[f] 24 °C, 30 h.
[g] 50 °C, 48 h.
[h] 24 °C, 96 h.



Scheme 6. Diastereoselective iodination of aryl C–H bonds. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C; (b) 13 h; (c) 48 h

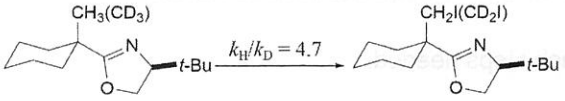
Presence of bulky group at the α -position of oxazolines improved diastereoselectivity.

Proposed catalytic cycle



Scheme 16 Pd-catalyzed iodination.

kinetic isotope effect

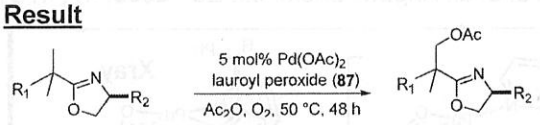


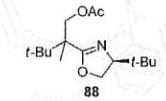
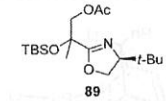
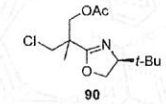
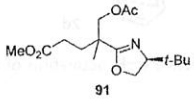
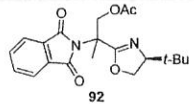
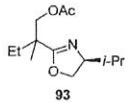
⟹ **Rate determining step is cyclopalladation.**

2-2. Diastereoselective acetoxylation

Jin-Quan Yu. et al. *Angew. Chem. Int. Ed.* **2005**, 44, 7420

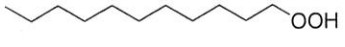
Result



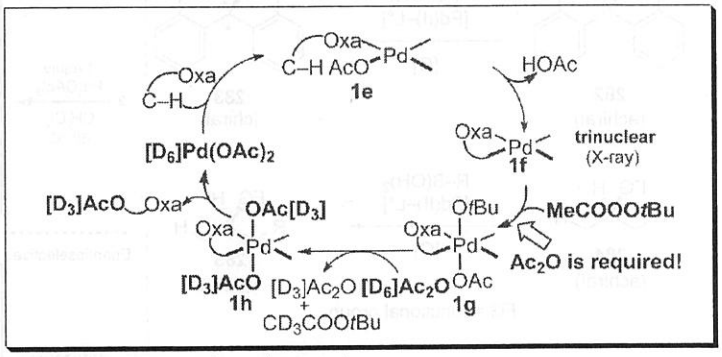
Entry	Product	Yield (%)	de (%)
1	 88	49	82
2	 89	43	62
3	 90	66	38
4	 91	73	24
5	 92	38	12
6	 93	67	18

* In optimized condition, MeCOOtBu was used as oxidant.

lauroyl peroxide



Proposed catalytic cycle



Scheme 4. Proposed catalytic cycle.

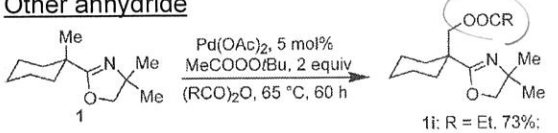
Mechanistic study

In cyclopalladation step (**1e~1f**), the rate was not affected by the amount of Ac_2O.

In oxidative addition step (**1f~1h**), the rate was affected by the amount of Ac_2O.

solvent 的味

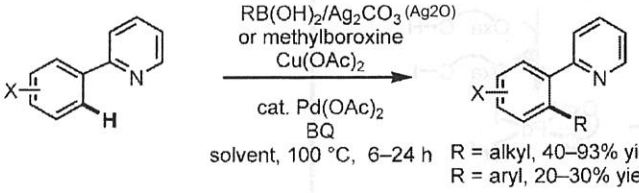
Other anhydride



1i: R = Et, 73%;
1j: R = *i*Pr, 49%

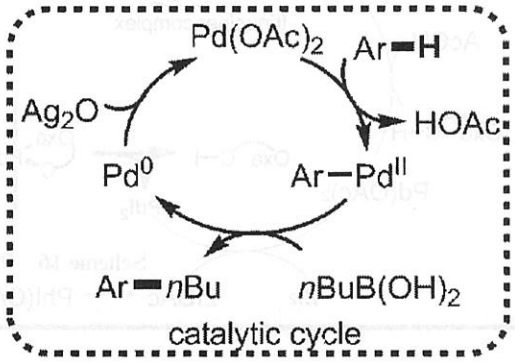
3. Pyridine group directed enantioselective C-H selective activation using chiral ligand

Pridine directed Suzuki coupling type C-H activation (summary)



R = Me, Et, *n*Bu, *n*Hex, $Ph(CH_2)_2$, cyclopropyl, aryl

Jin-Quan Yu. et al. *J. Am. Chem. Soc.*, **2006**, 128, 12634



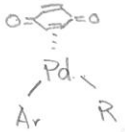
Pd(II)/Pd(0) cycle: broad functionalization, undesired homocoupling, undesired β -hydride elimination

↓

Promotion for speed of each steps needed.

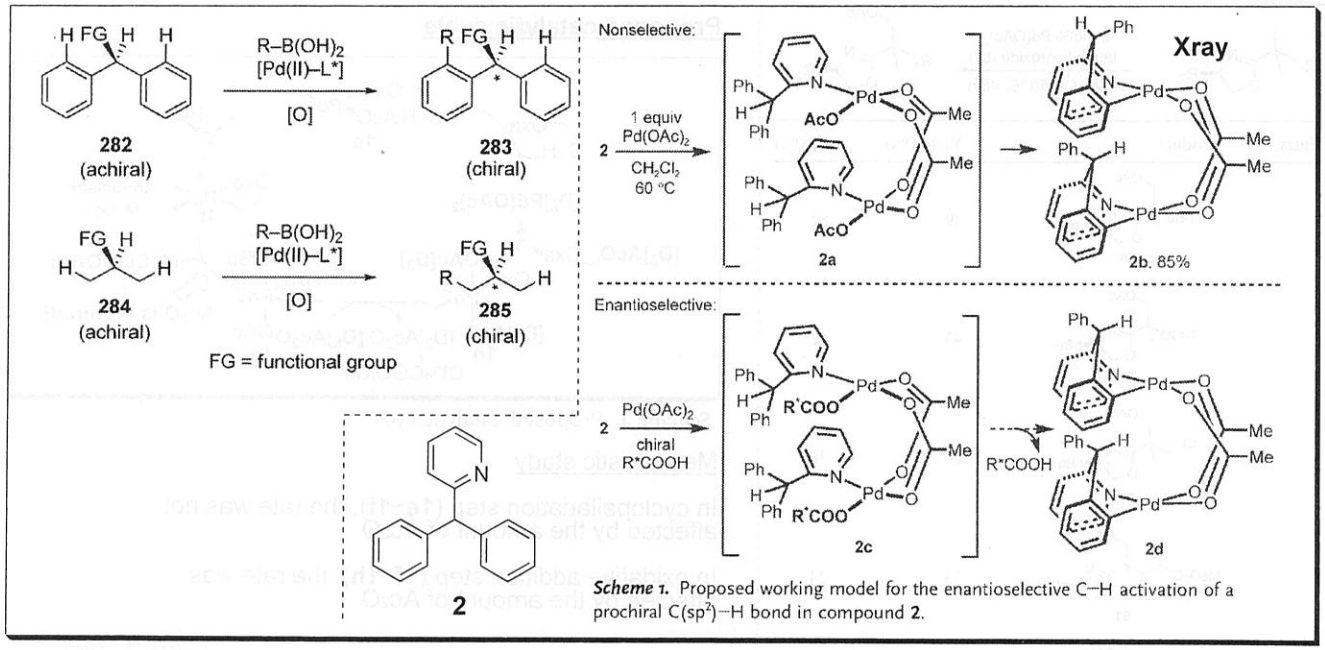
Ag_2O: efficient promoter(base) for the transmetalation and co-oxidant

benzoquinone: promoter for reductive elimination



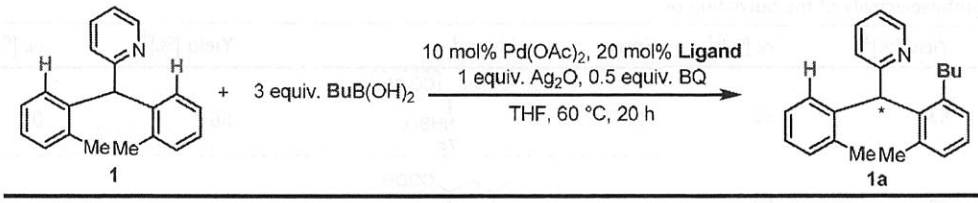
Concept

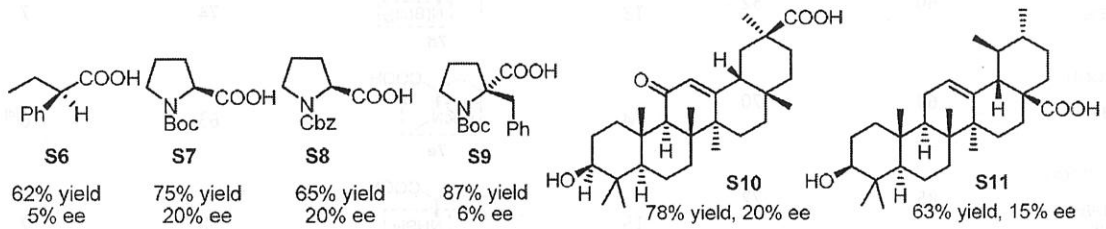
Jin-Quan Yu. et al. *Angew. Chem. Int. Ed.*, **2008**, 47, 4761.



Scheme 1. Proposed working model for the enantioselective C–H activation of a prochiral $C(sp^2)$–H bond in compound **2**.

Preliminary result with commercially available carboxylic acid



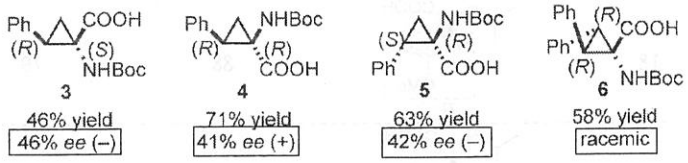


Enantioselectivity was poor...

R group of carboxylic acid is free to rotate ⟶ Low chiral induction?

More restricted conformational backbone

Cyclopropane amino acid



Unexpectedly, similar ee was obtained from **3** and **5**.

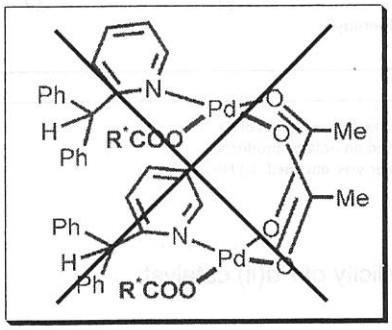
3 and **4** suggests that the chirality of the α -carbon center plays a dominant role.

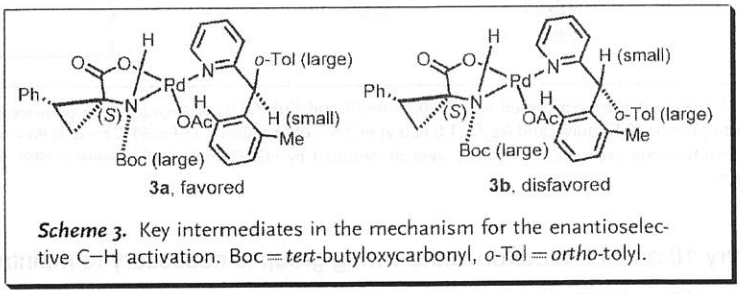
Scheme 2. Cyclopropane amino acid ligands used for the enantioselective butylation of compound **1**.

Previous mechanistic model was wrong?

Based on these experimental deta, new model is needed.

New model



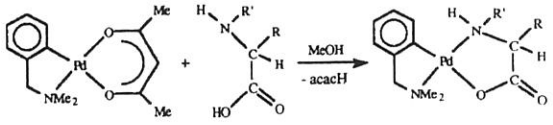


Scheme 3. Key intermediates in the mechanism for the enantioselective C–H activation. Boc = *tert*-butyloxycarbonyl, *o*-Tol = *ortho*-tolyl.

NH moiety and carboxylate with Pd(ii) center in bidentate manner.

In case of ligand **6**, the steric difference of the α -carbon is minimized.

Known analogous structure

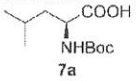
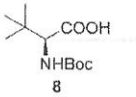
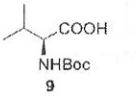
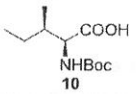
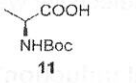
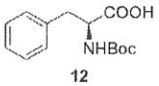
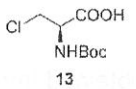
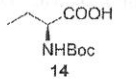
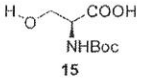
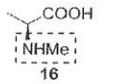
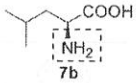


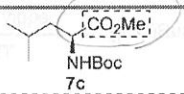
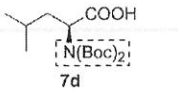
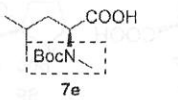
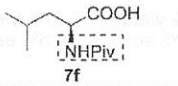
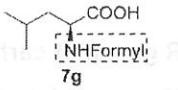
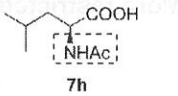
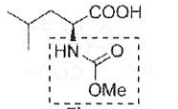
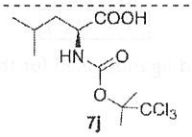
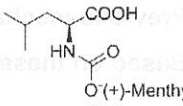
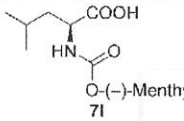
NMR analysis showed trans N-N geometry.
In addition, NH moiety is not deprotonated.

J. Organomet. Chem. **1995**, 490, 35.

Ligand screening

Table 1: Influence of the ligand on enantioselectivity of the butylation of

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	 **7a**	63	90
2	 **8**	60	52
3	 **9**	69	70
4	 **10**	85	72
5	 **11**	60	80
6	 **12**	66	81
7	 **13**	83	83
8	 **14**	47	85
9	 **15**	65	88
10	 **16**	n.r.[e]	–
11	 **7b**	n.r.[e]	–

Entry	Ligand	Yield [%][b]	*ee* [%][c]
12	 **7c**	86	0
13	 **7d**	74	7
14	 **7e**	63	6[d]
15	 **7f**	58	7
16	 **7g**	53	6
17	 **7h**	74	80
18	 **7i**	88	79
19	 **7j**	89	85
20	 **7k**	87	85
21	 **7l**	91	87

[a] All reactions were performed with **1** (0.2 mmol) and $BuB(OH)_2$ (0.6 mmol) in the presence of $Pd(OAc)_2$ (10 mol%), chiral ligand (20 mol%), benzoquinone (0.5 equiv), and Ag_2O (1.0 equiv) in 2 mL of anhydrous THF at 60°C for 20 h. Piv = pivaloyl. [b] Yields were based on isolated products. [c] Enantiomeric excesses (*ee* values) were determined by HPLC on a chiral stationary phase. [d] The opposite enantiomer was obtained. [e] No reaction.

Entry **10** and **11**: electron-withdrawing group is necessary to maintain the electrophilicity of Pd(ii) catalyst.

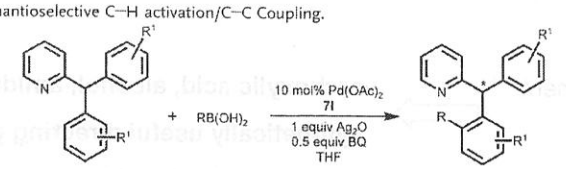
Entry **12**: esterification leads to a complete loss of ee.

Entry **13~15**: diprotected amino group and a poor coordination NHPiv group afford low ee.

Entry **16~18**: reduction in the size of protecting group from Boc results in steady decrease of selectivity.

Result

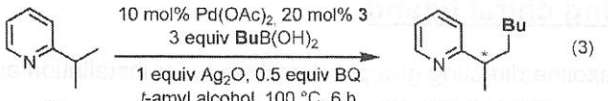
Table 2: Enantioselective C–H activation/C–C Coupling.



Entry	Substr.	R^1	R	T [°C]	**7l** [mol%]	t [h]	Yield [%][a]	*ee* [%][b]
1	1	*o*-Me	*n*Bu	60	20	20	91	87
2	1	*o*-Me	*n*Bu	50	20	20	50	95
3	1	*o*-Me	*n*Bu	60	10	20	96	88
4	2	H	*n*Bu	80	20	20	47	79
5	2	H	*n*Bu	80	10	20	56	74
6	1	*o*-Me	Et	60	10	20	81	84
7	1	*o*-Me	Cy[c]	60	10	20	61	89
8[d]	17	*m*-Me	*n*Bu	60	10	40	58	84
9[d]	18	*m*-OMe	*n*Bu	80	10	20	55	54
10[d]	19	*m*-OAc	*n*Bu	80	10	20	43	72
11	20	*p*-Me	*n*Bu	80	10	20	61	78

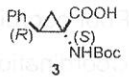
[a] Yield of isolated product. [b] *ee* values were determined by HPLC on a chiral stationary phase. [c] Cy = cyclopropyl. [d] Alkylation occured only at the less hindered position.

sp_3 C-H bond



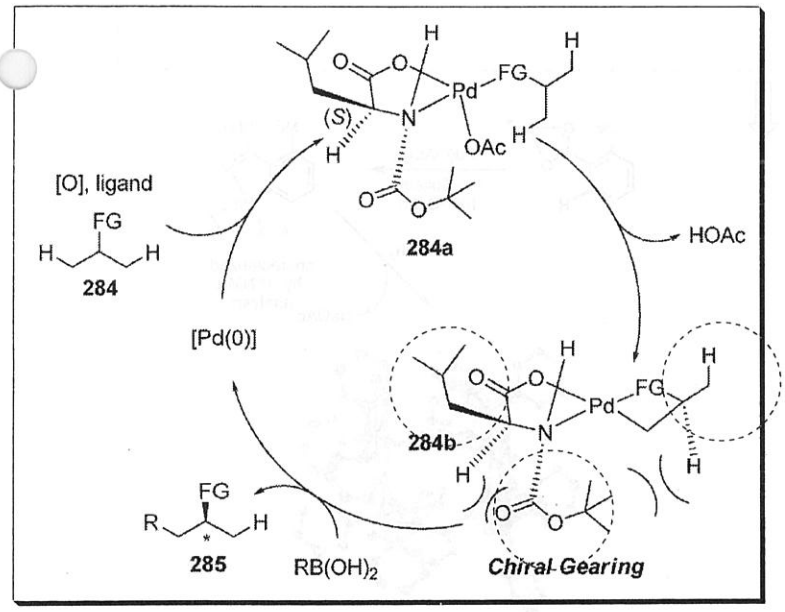
21 **21a**, 38% yield, 37% *ee*

Poor enantioselectivity(10~15% ee) was obtained with ligands **7k**, **7l**, and **8**.



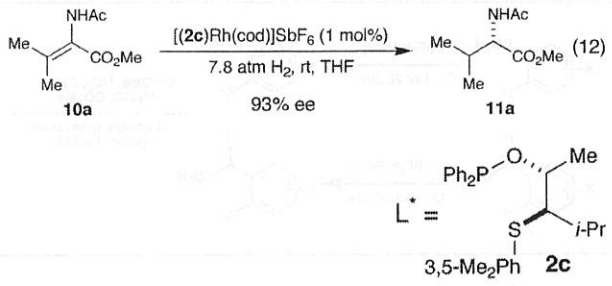
3

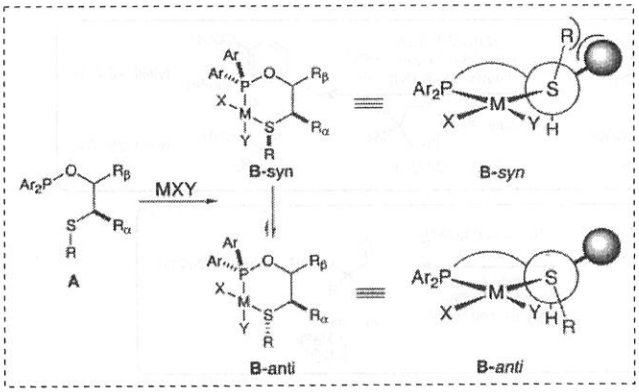
Proposed catalytic cycle



Steric hinderance is minimized

Other gearing system





David A. Evans. et al. *J. Am. Chem. Soc.*, **2003**, 125, 3534

4. Carboxylic acid group directed enantioselective and regioselective C-H activation using chiral ligand

Oxazoline directing group: several steps for installation and detachment

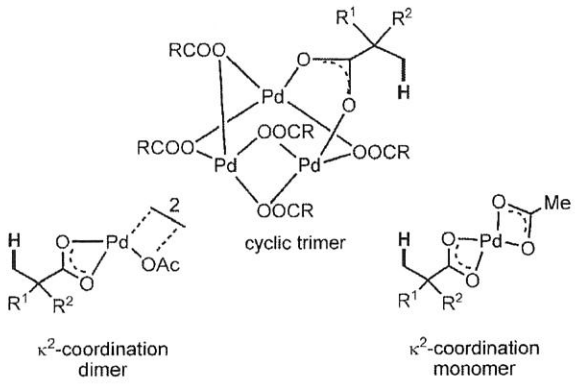
Pyridine directing group: irremovabale and poor synthetic utility

⇒ **carboxylic acid, alcohol, amide**

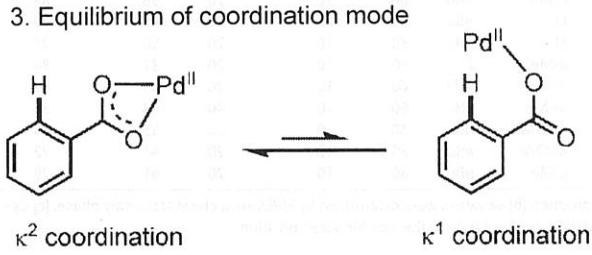
synthetically useful directing group

In carboxylic acid directed C-H activation, problem is

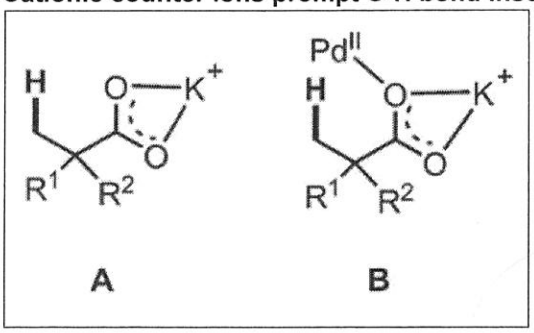
1. Poor coordination ability of oxygen atom comared to nitrogen atom
2. Coordination mode of Pd(ii) with carboxylic acid

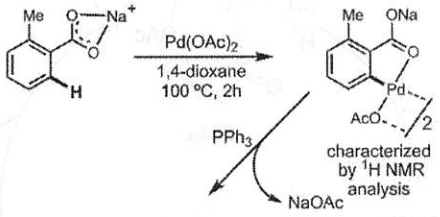


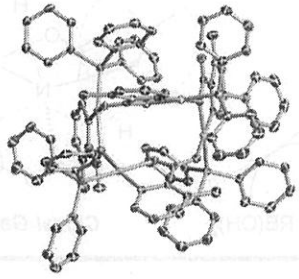
3. Equilibrium of coordination mode



Cationic counter ions prompt C-H bond insertion



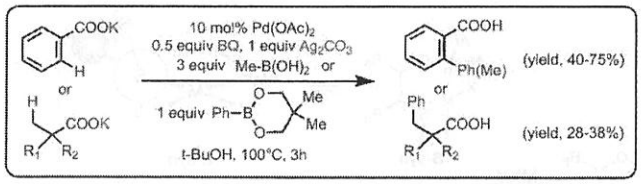


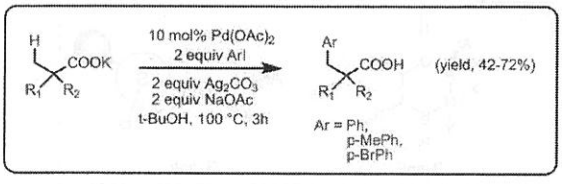


Jin-Quan Yu. et al. *J. Am. Chem. Soc.* **2008**,130, 14082.

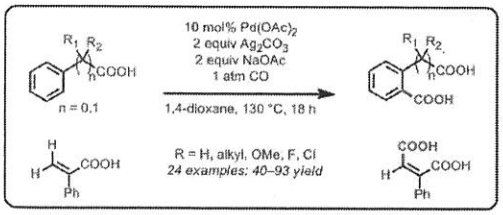
Various applications

Suzuki coupling type *J. Am. Chem. Soc.* **2007**, 129, 3510.

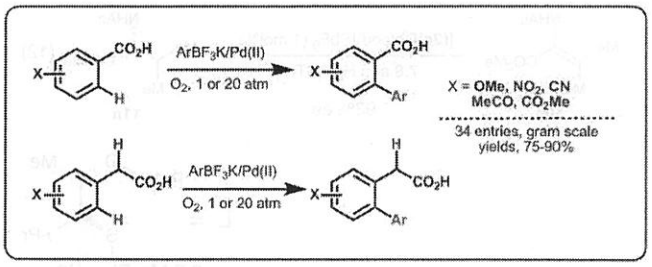




Carboxylation *J. Am. Chem. Soc.* **2008**,130, 14082.

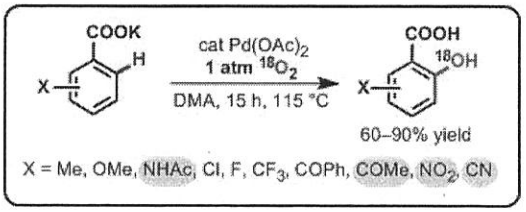


Aryl-Aryl coupling *J. Am. Chem. Soc.* **2008**, 130, 17676.

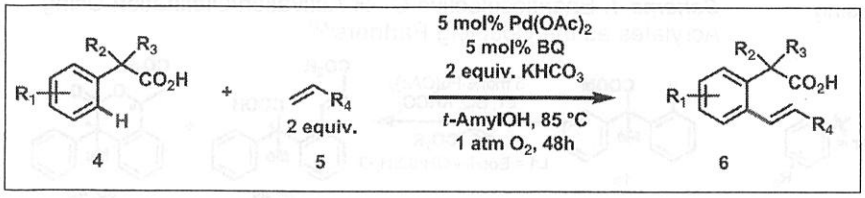


Hydroxylation using oxigen

J. Am. Chem. Soc. **2009**, 131, 14654.



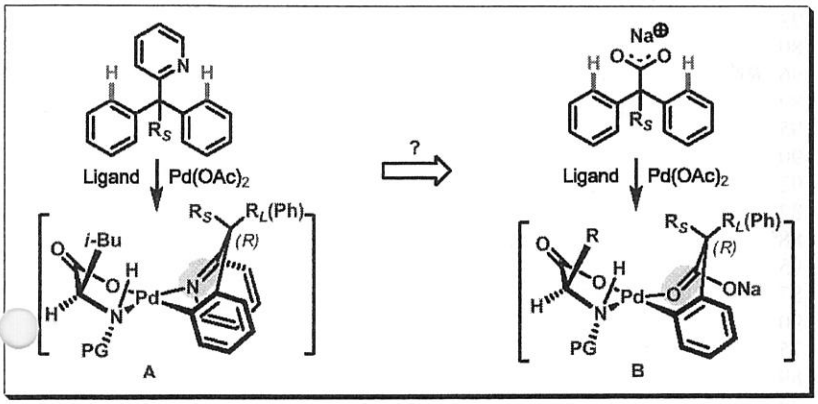
Mizoroki-Heck reaction



Jin-Quan Yu. et al. *Science* **2010**, 327, 315.

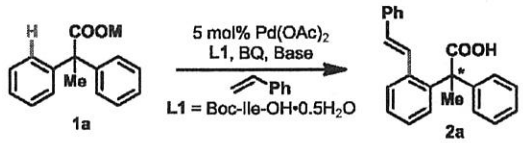
Asymmetric Mizoroki-Heck reaction

Concept



Jin-Quan Yu. et al. *J. Am. Chem. Soc.* **2010**, 132, 460.

Table 1. Effect of Inorganic Cations and Bases[a]

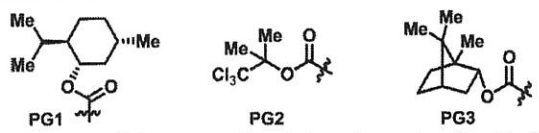


entry	M	base	% yield[b]	% ee[c]	entry	M	base	% yield[b]	% ee[c]
1	H	$KHCO_3$[d]	46	95	8	Na	$NaHCO_3$	56	89
2	Na	—	51	86	9	Na	Na_2CO_3	61	91
3	Na	$KHCO_3$	73[e]	97	10	Na	Cs_2CO_3	—	—
4	NH_4	$KHCO_3$	—	—	11	Na	K_2HPO_4	37	83
5	K	$KHCO_3$	49	84	12	Na	Li_2CO_3	44	85
6	Cs	$KHCO_3$	—	—	13	Na	NaOTs[f]	57	79
7	Na	K_2CO_3	25	87	14	K	$NaHCO_3$	53	91

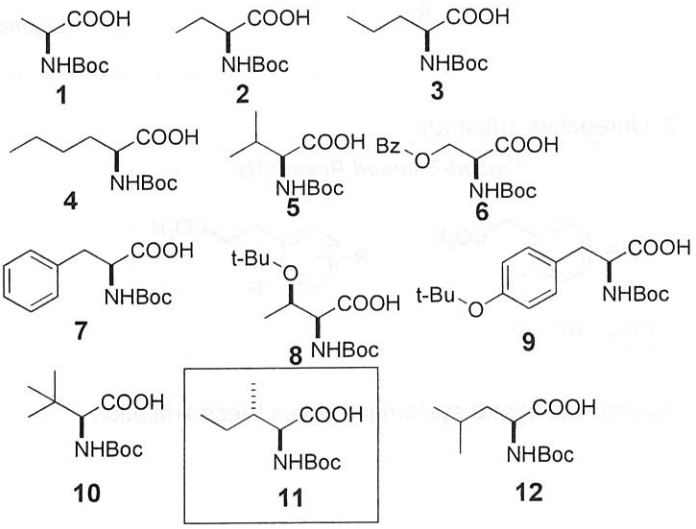
[a] Conditions: 0.5 mmol of **1a**, 5 mol % $Pd(OAc)_2$, 10 mol % **L1**, 5 mol % BQ, 0.5 equiv of base, and 1 atm O_2 in 3 mL of *tert*-amyl alcohol at 90 °C for 48 h. [b] Determined by ^1H NMR analysis using CH_2Br_2 as a calibrated internal standard. [c] Determined by chiral HPLC analysis. [d] Using 2 equiv of $KHCO_3$. [e] Isolated yield. [f] Using 1 equiv of NaOTs.

Table 2. Evaluation of Amino Acids[a]

entry	ligand	% yield	% ee	entry	ligand	% yield	% ee
1	Boc-Ala-OH	46	54	9	Boc-Tyr(*t*-Bu)-OH	45	96
2	Boc-Abu-OH	51	67	10	Boc-Tle-OH	43	94
3	Boc-Nva-OH	63	61	11	Boc-Ile-OH·0.5H_2O	73	97
4	Boc-Nle-OH	59	81	12	Boc-Leu-OH	60	86
5	Boc-Val-OH	39	93	13	Formyl-Leu-OH	44	79
6	Boc-Ser(Bzl)-OH	61	91	14	**PG1**-Leu-OH	57	84
7	Boc-Phe-OH	25	93	15	**PG2**-Leu-OH	44	69
8	Boc-Thr(*t*-Bu)-OH	50	86	16	**PG3**-Leu-OH	37	65

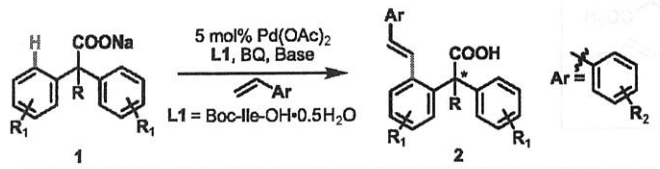


[a] The reaction conditions were identical to those described in Table 1.



Result

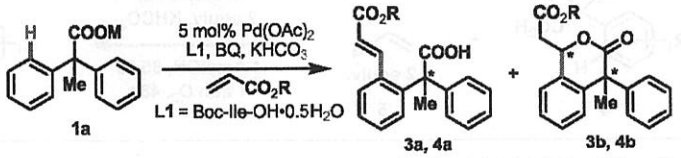
Table 3. Enantioselective C–H Activation/Olefination Using Substituted Styrenes as the Coupling Partners[a]



entry	2	R	R_1	R_2	% yield[b]	% ee[c] (config)
1	**2a**	Me	H	H	73	97
2	**2b**	Me	H	*p*-Me	71	97
3	**2c**	Me	H	*m*-Me	63	92
4	**2d**	Me	H	*o*-Me	51	80
5	**2e**	Me	H	*p*-Cl	74	96 (*R*)[d]
6	**2f**	Me	H	*p*-F	51	89
7	**2g**	Me	H	*p*-*t*-Bu	51	95
8	**2h**	Me	*p*-Me	H	63	90[e]
9	**2i**	Me	*m*-Me	H	58	92
10	**2j**	Me	3,4-dimethyl	H	63	82[e]
11	**2k**	Me	*p*-*t*-Bu	H	45	88[e]
12	**2l**	Me	*p*-OPiv	H	51	95
13	**2m**	Me	*p*-Cl	H	35	87
14	**2n**	Me	3-chloro-4-methoxy	H	47	90
15	**2o**	Me	3-methyl-4-methoxy	H	40	75
16	**2p**	Me	4-methoxy-3-trifluoromethyl	H	39	89
17	**2q**	Et	H	H	61	72
18	**2r**	Pr	H	H	52	76[e]
19	**2s**	H	H	H	69	58[f]

[a] The reaction conditions were identical to those described in Table 1. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined by analysis of the X-ray crystal structure. [e] Boc-Tyr(*t*-Bu)-OH was used as the ligand. [f] Racemization occurred during the reaction.

Scheme 1. Enantioselective C–H Activation/Olefination Using Acrylates as the Coupling Partners[a,b]



M = H, R = Et, 44% yield, 3a:3b = 4.4:1, 3.2:1 dr, >99% ee (3a)
M = Na, R = Et, 57% yield, 3a:3b = 1.3:1, 3.2:1 dr, 99% ee (3a)
M = Na, R = *t*-Bu, 46% yield, 4a:4b = 1:1, 2.8:1 dr, >99% ee (4a) (97% ee based on 4b)

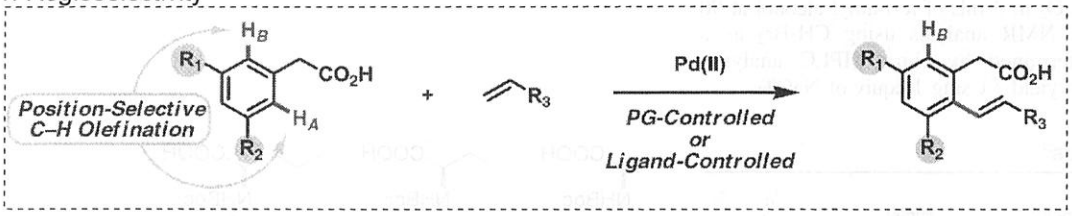
[a] The reaction conditions were identical to those described in Table 1. [b] The product ratio and dr were determined by ^{1}H NMR analysis.

Improvement of regioselectivity and reactivity using amino acid ligand

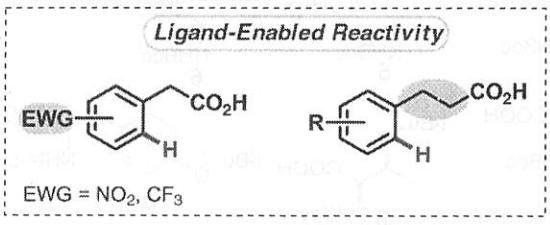
Jin-Quan Yu. et al. *Science* **2010**, 327, 315.

Mizoroki-Heck type C-H activation can be applied to various substrates, but...

1. Regioselectivity



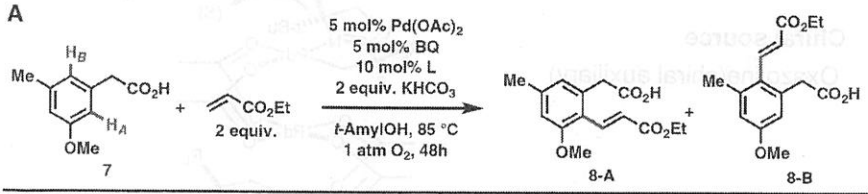
2. Unreactive substrate



Amino acid ligand system improves these limitation.

Improvement of regioselectivity

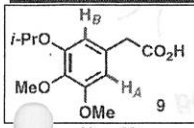
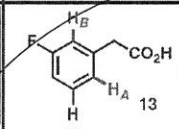
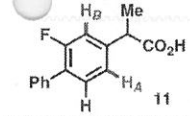
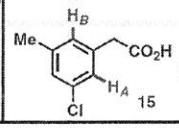
A



Entry	Ligand	Conv. (%)*	A : B	Entry	Ligand	Conv. (%)*	A : B
1	---	68	1.4 : 1	7	Boc_2-Leu-OH	50	3 : 1
2	Boc-Tyr(Bzl)-OH	17	2.5 : 1	8	H-Leu-OH	16	6 : 1
3	Boc-Abu-OH	17	5 : 1	9	Formyl-Leu-OH	24	13 : 1
4	Boc-Val-OH	23	6 : 1	10	Fmoc-Ile-OH	16	5 : 1
5	Boc-Leu-OH	24	7 : 1	11	Ac-Ile-OH	23	10 : 1
6	Boc-Ile-OH	27†	8 : 1	12	Formyl-Ile-OH	43 (75)‡	20 : 1

*Based on ^{1}H NMR. The di-olefinated product was formed in less than 5% conversion. †24 h. ‡7 mol% $Pd(OAc)_2$, 7 mol% BQ, 14 mol% L.

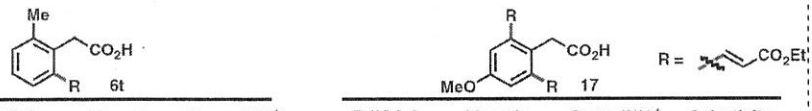
B

Substrate	Ligand	Conv. (%)*	A : B	Substrate	Ligand	Conv. (%)*	A : B
 9	---	65†	1.5 : 1	 13	---	63	1.6 : 1
	Boc-Ile-OH	86†	23 : 1		Formyl-Ile-OH	77	3.5 : 1
 11	---	82	2.8 : 1	 15	---	8	1.2 : 1
	Formyl-Ile-OH	78	5.7 : 1		Formyl-Ile-OH	50‡	4.7 : 1

*Based on ^{1}H NMR. Products derived from substrates **9**, **11**, **13**, and **15** are labeled **10-A/B**, **12-A/B**,**14-A/B**, and **16-A/B** respectively. Only the major products were isolated and characterized. †*t*-Butyl acrylate was used as the coupling partner. ‡15 mol% $Pd(OAc)_2$, 15 mol% BQ, 30 mol% Formyl-Ile-OH.

Improvement of reactivity

C

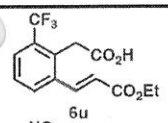
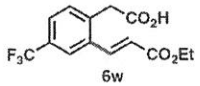
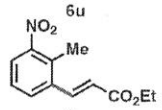
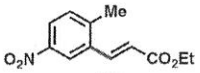
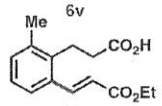
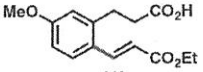


$Pd(OAc)_2$	Ligand	Conv. (%)*,†
2 mol%	---	31
2 mol%	Boc-Ile-OH	>99

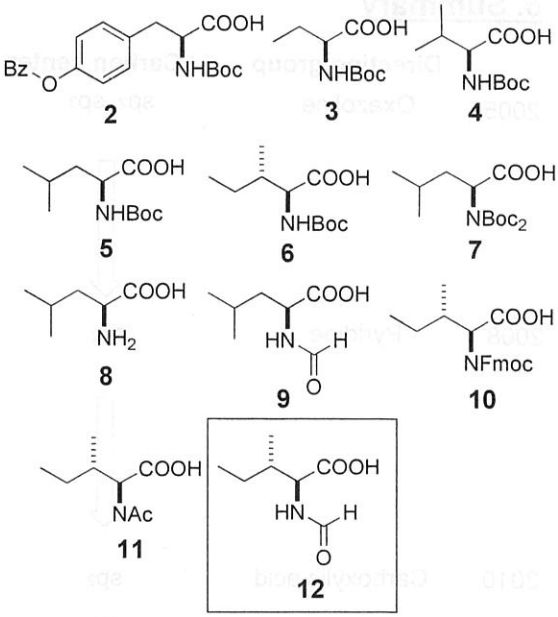
$Pd(OAc)_2$	Ligand	Conv. (%)*,†	Selectivity
2 mol%	---	10	mono
2 mol%	Boc-Ile-OH	>99	di

*Based on ^{1}H NMR. †2 mol% $Pd(OAc)_2$, 2 mol% BQ, 4 mol% Ligand.

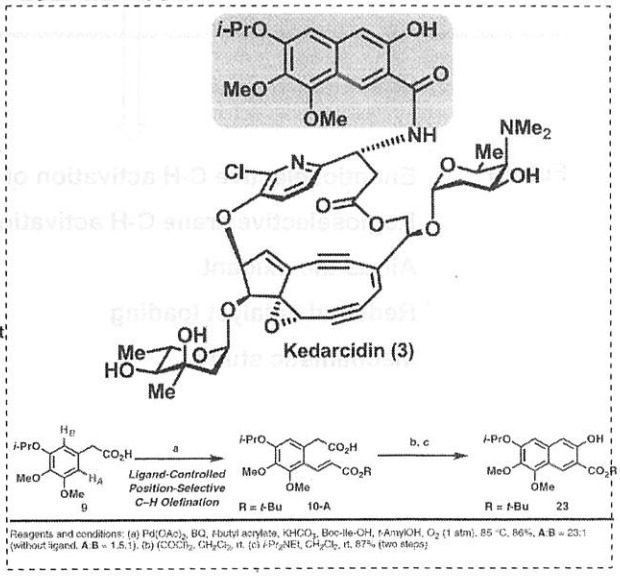
D

Product	Ligand	Yield (%)*	Product	Ligand	Yield (%)*
 6u	---	12	 6w	---	13
	Boc-Val-OH	90		Boc-Ile-OH	85‡
 6v	---	0	 6x	---	0
	Boc-Val-OH	50†		Boc-Val-OH	57§
 18a	---	8	 18b	---	22
	Boc-Val-OH	60		PG_1-Leu-OH‖	75¶

*Isolated Yield. †2-Nitrophenylacetic acid was used as substrate; the product was completely decarboxylated under the reaction conditions: 10 mol% $Pd(OAc)_2$, 10 mol% BQ, 20 mol% Boc-Val-OH. ‡Mono:Di = 2:1. §4-Nitrophenylacetic acid was used as substrate; decarboxylated:non-decarboxylated = 2:1. ‖PG_1 = (−)-Menthyl(O_2C). ¶Mono:Di = 3:1.



Synthetic application

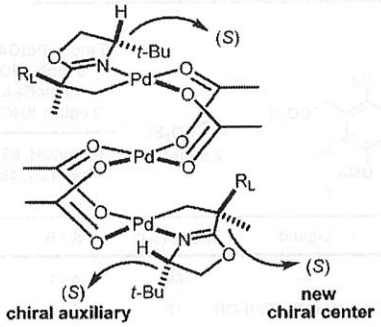


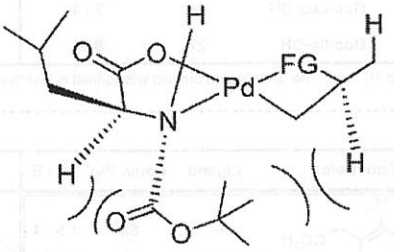
Reagents and conditions: (a) $Pd(OAc)_2$, BQ, *t*-butyl acrylate, $KHCO_3$, Boc-Ile-OH, *t*-AmylOH, O_2 (1 atm), 85 °C, 86%, A:B = 23:1 (without ligand, A:B = 1.5:1). (b) $(COCl)_2$, CH_2Cl_2, rt. (c) *i*-Pr_2NEt, CH_2Cl_2, rt, 87% (two steps).

Although the mechanistic details remain to be elucidated, the steric and electronic properties around the metal center are changed by using ligands.

5. Summary

	Directing group	Carbon center	Chiral source
2005	Oxazoline	sp_2, sp_3	Oxazoline(chiral auxiliary)
2008	Pyridine	sp_2	Ligand(amino acid)
2010	Carboxylic acid	sp_2	Ligand(amino acid)





Chiral Gearing

Future

Enantioselective C-H activation of sp_3 carbon center

Regioselective arene C-H activation(meta- or para-positions)

Air as the oxidant

Reduced catalyst loading

Mechanistic study