Studies on Heck and Suzuki Reactions Catalyzed by Palladium(0) and Wacker-Type Oxidative Cyclization Catalyzed by Palladium(II)

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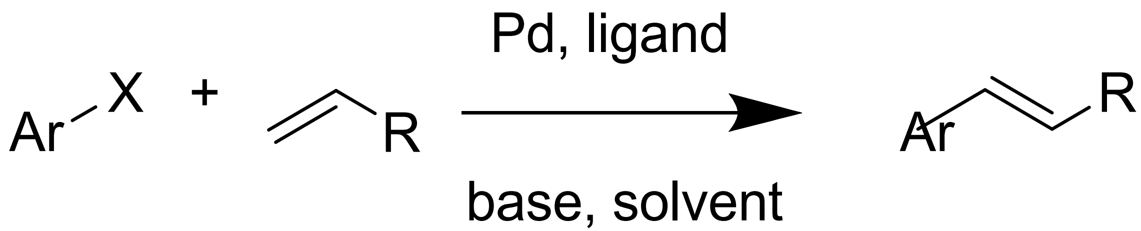
Denmark Group Meeting
10/21/2008

Part One: Palladium(0)-Catalyzed Heck Reaction and Suzuki Reaction

Part Two: Palladium(II)-Catalyzed Wacker Oxidative Cyclization to Construct Chromanone, Quinoline and Pyrrole

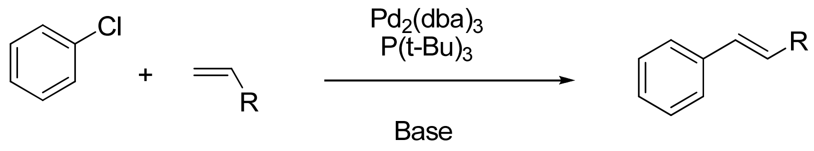
Section One: Heck reaction in aqueous mediums and its selectivity

Scheme 1. Heck reaction

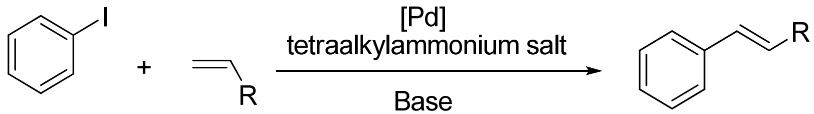


Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
Heck, R. F.; Nolley, Jr., J. P. *J. Org. Chem.* **1972**, *37*, 2320.

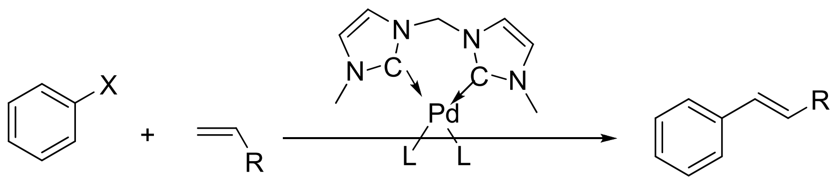
Previous Achievements:



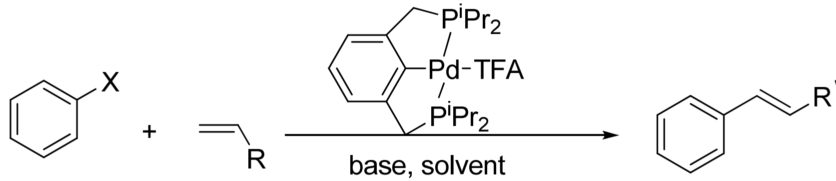
G. C. Fu, J. H. Hartwig etc.



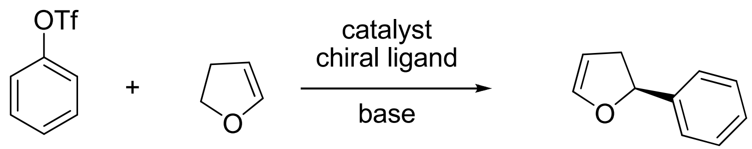
T. Jeffery, M. T. Reetz etc.



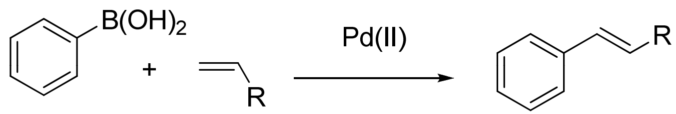
W. A. Herrmann, Merritt B. Andrus etc.



W. A. Herrmann, D. Milstein, J. Dupont, D. E. Bergbreiter, Q. W. Yao, D. G. Blackmond etc.



T. Hayashi, A. Pfaltz, L. F. Tietze, S. Uemura, X.-l. Hou,
M. Oestreich, D. P. Curran etc.



S. Uemura, A. Mori, M. C. White, K. W. Jung, J. L. Xiao etc.

Our Approach:

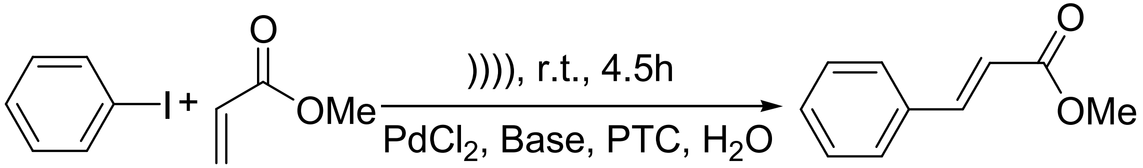
1) Choose water as solvent;

2) Room temperature;

3) Ultrasonic irradiation, in suit formed nano-palladium

4) Regioselectivity

Table 1. Opitimization of base and PTC for Heck reaction of Iodobenzene and Methyl Acrylate[a]

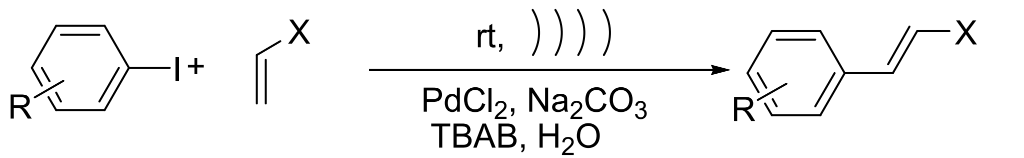


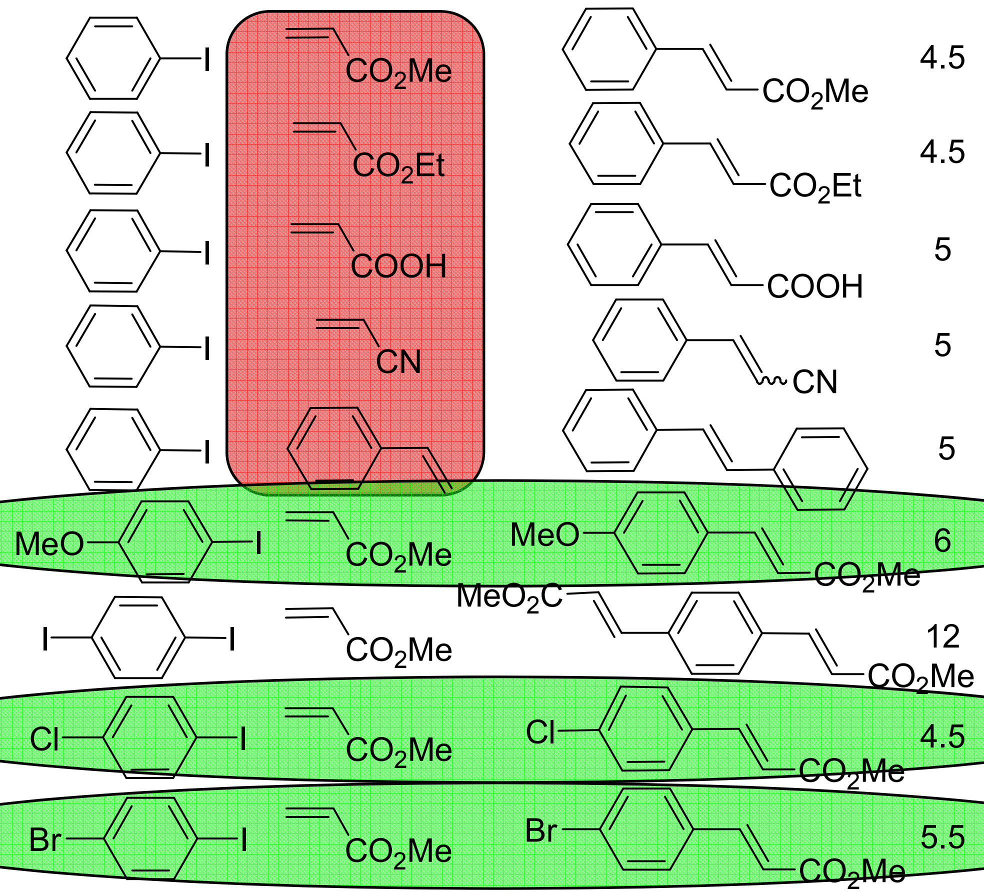
entry	base	PTC	yield(%)[b]
1	Na_2CO_3	TBAB	86
2	Na_2CO_3	TEAB[c]	trace
3	Na_2CO_3	TMAI[d]	trace
4	Na_2CO_3	TEAI[e]	trace
5	NaOH	TBAB	53
6	Et_3N	TBAB	67
7	NaOAc	TBAB	40

[a] Reaction conditions: iodobenzene (1 mmol), methyl aceylate (2 mmol), phase transfer catalyst (PTC) (1 mmol), base (3 mmol)
and $PdCl_2$ (0.02 mmol) in 3 ml of water, the mixtures was sonicated at ambient temperature (25 °C) in running water bath for 4.5h.
[b] Isolated yield. [c] TEAB is tetraethylammonium bromide. [d] TMAI is tetramethylammonium iodide. [e] TEAI is tetraethylamminium iodide.

J. Org. Chem. **2006**, *71*, 4339-4342.

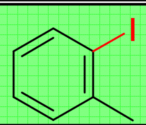
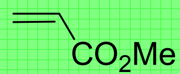
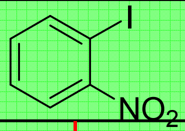
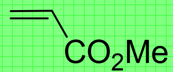
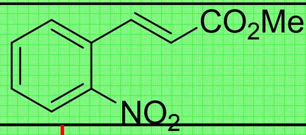
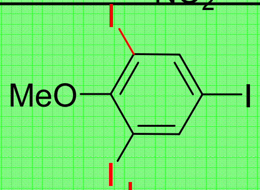
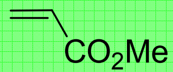
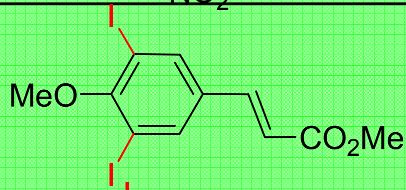
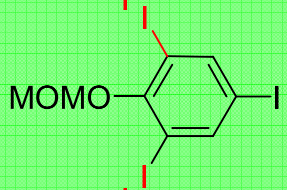
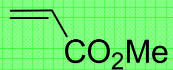
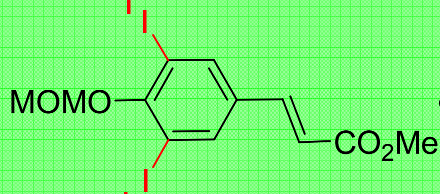
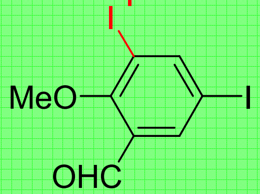
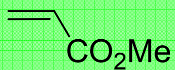
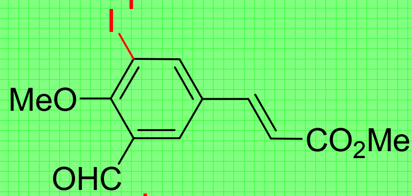
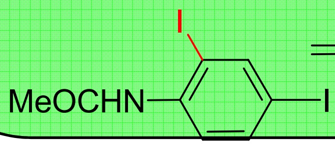
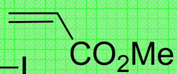
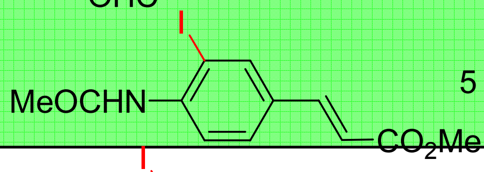
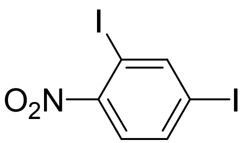
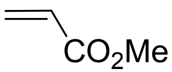
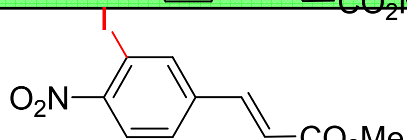
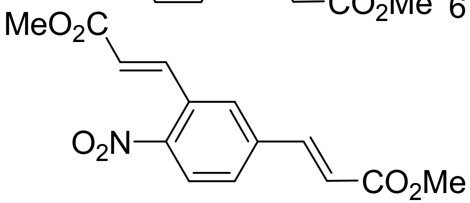
Table 2. Heck reaction promoted by ultrasonic aqueous media





entry	time(h)	yield(%)
1	4.5	86
2	4.5	82
3	5	83
4	5	78
5	5	75
6	6	76
7	12	43
8	4.5	93
9	5.5	90

J. Org. Chem. **2006**, *71*, 4339-4342.

entry	ArX	alkene	product	time(h)	yield(%)
10			—	4	—
11				4	55
12				8	68
13				8	76
14				8	70
15				5	75
16			 	6	43 20

Study the catalyst for the reaction

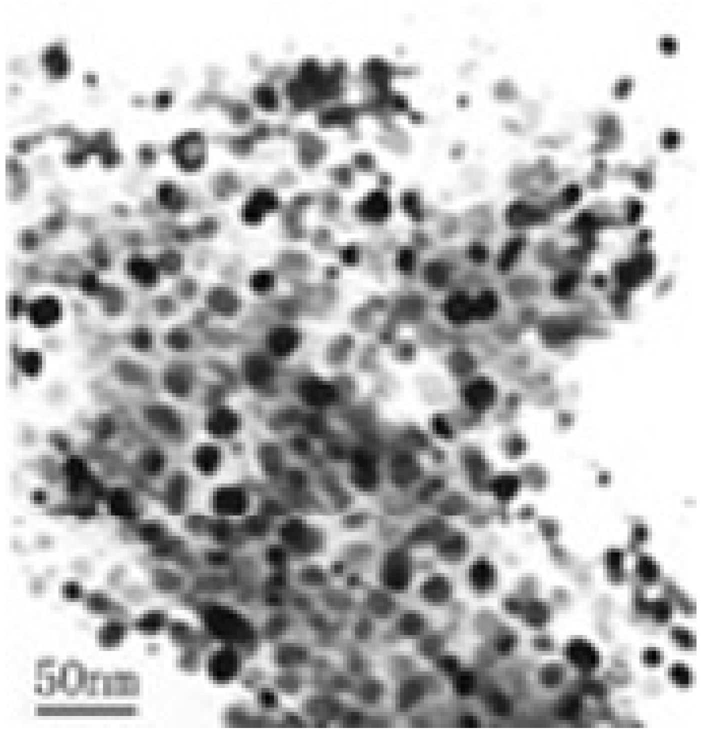
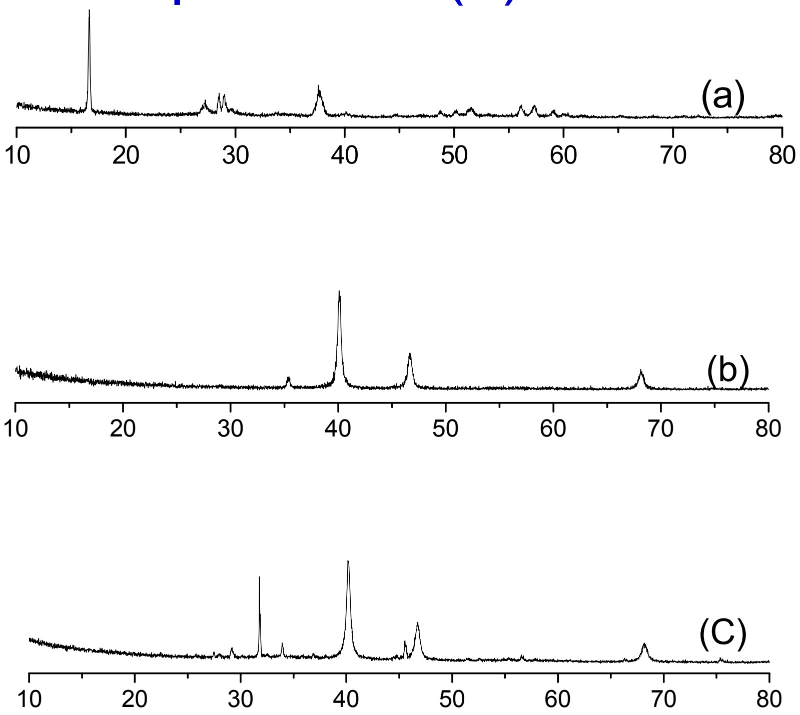


Figure 1. TEM image of Pd nano-particles formed under ultrasound

Study the formation of palladium(0)



Olefin as a reducer for the formation of Pd(0)

Figure 2. (a) XRD pattern of $PdCl_2$ (0.1mmol), TBAB (1mmol) and H_2O (3ml) under ultrasonic irradiation for 30 min;

(b) XRD pattern of $PdCl_2$ (0.1mmol), TBAB (1mmol), methyl acrylate (2mmol) and H_2O (3ml) under ultrasonic irradiation for 30 min;

(c) XRD pattern of the reaction system (1mmol iodobenzene, 2 mmol methyl acrylate, 0.02 mmol $PdCl_2$, 3 mmol Na_2CO_3 and 1 mmol TBAB in 3 ml of water) under ultrasonic irradiation for 30 min.

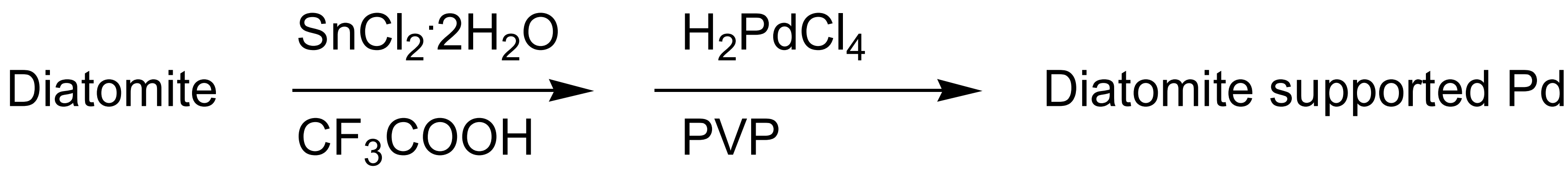
Section Two: Diatomite-supported palladium nanoparticles catalyzed Heck and Suzuki reactions

Homogeneous palladium catalysis
Advantages: high reaction rate, high turnover numbers (TON), high yields and the Pd catalysts can be tuned by ligands.

Disadvantages: the lack of reuse of the catalyst, a loss of expensive metal and ligands and to impurities in the products and the need to remove residual metals

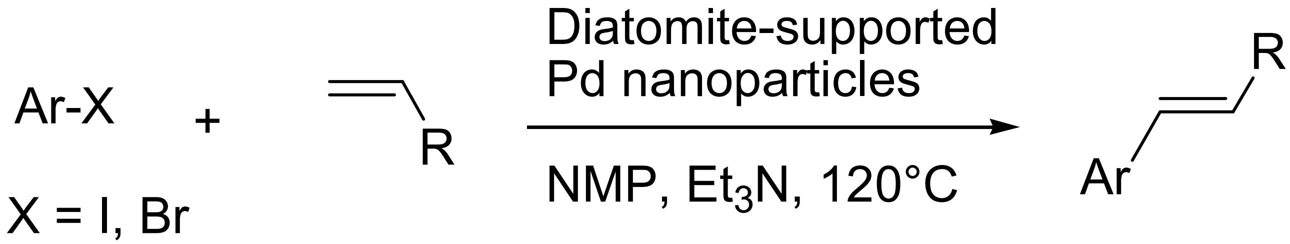
Diatomite, a type of widespread natural porous material, was first reported by us as a suitable template to supported palladium nanoparticles

Scheme 2. Preparation of diatomite-supported palladium nanoparticles



J. Org. Chem. **2006**, *71*, 7485-7487.

Scheme 3. Heck reaction of aryl halides with olefins with heterogeneous palladium



Scheme 4. Suzuki reaction of aryl halides with olefins with heterogeneous palladium

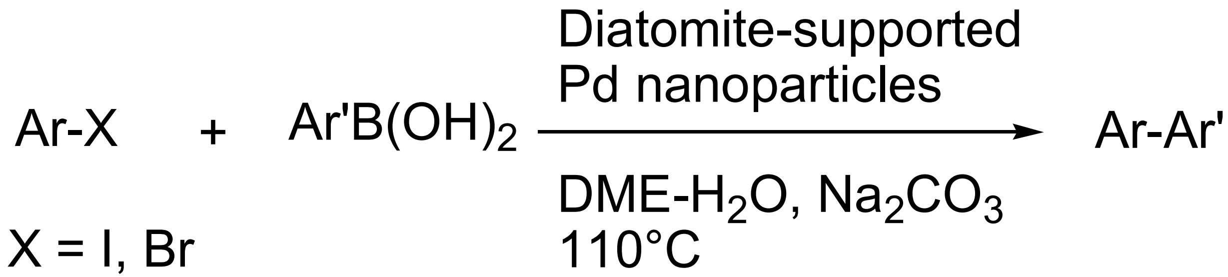
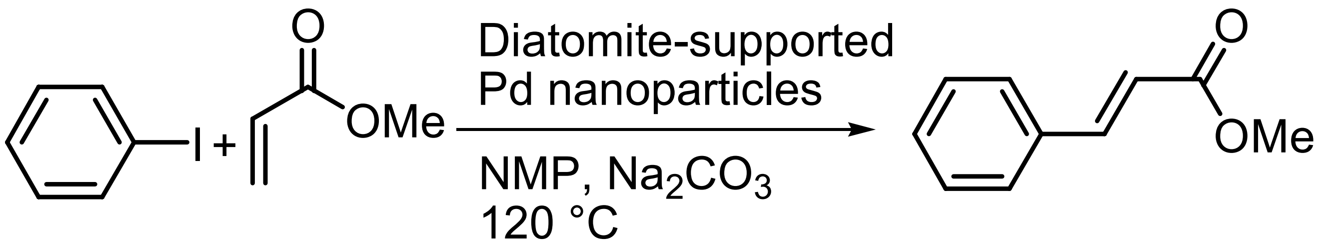


Table 2. Recycling of diatomite-supported Pd for the Heck reaction of iodobezene with methyl acrylate



entry	catalyst	time	isolated yield (%)
1	first cycle	20 min	96
2	second cycle	20 min	95
3	third cycle	20 min	97
4	fourth cycle	20 min	95
5	fifth cycle	40 min	96
6	sixth cycle	70 min	95

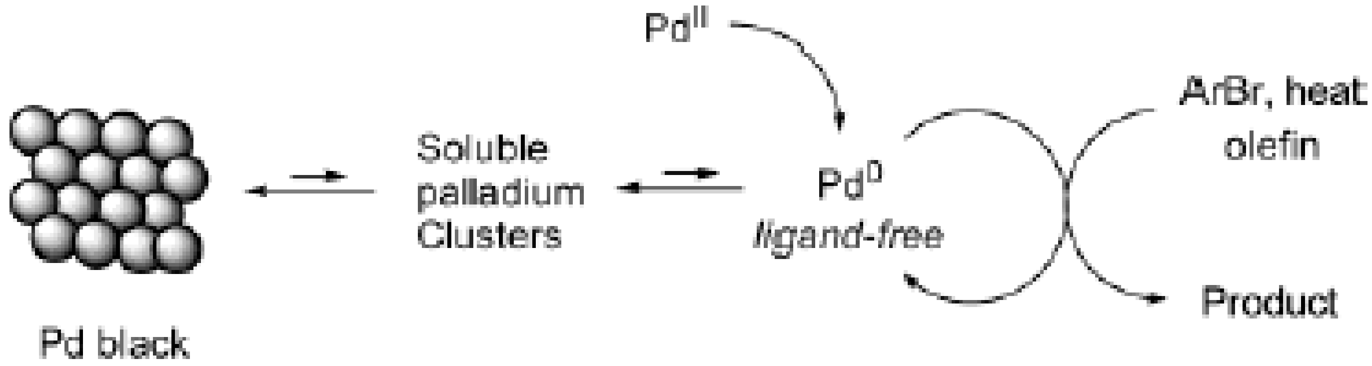
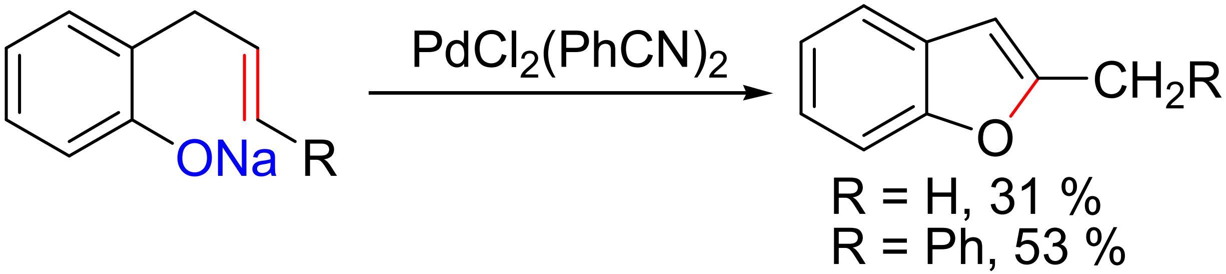


Figure 2. Catalytic model of heterogeneous palladium catalyst

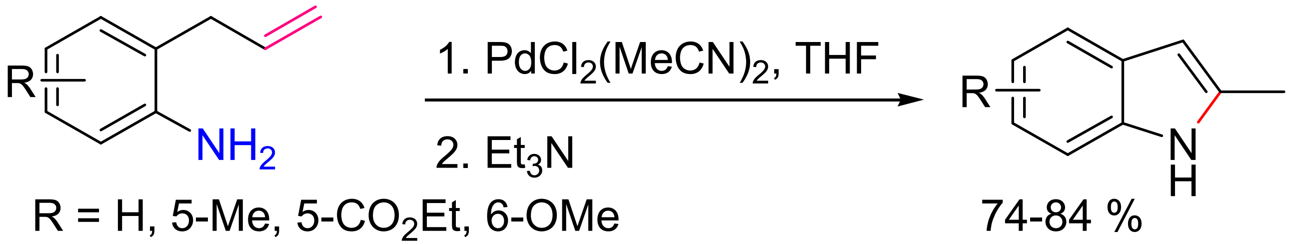
De Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; De Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.

Part Two: Palladium(II)-Catalyzed Wacker Oxidative Cyclization to Construct Chromanone, Quinoline and Pyrrole

Original reports about Wacker cyclization



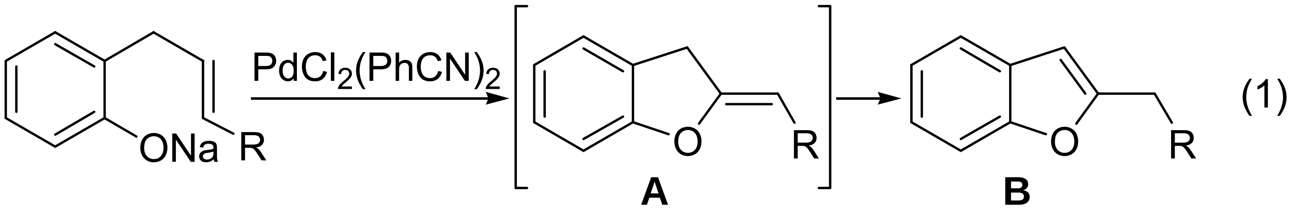
Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett*. **1973**, *14*, 739.



Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc*. **1976**, *98*, 2674.

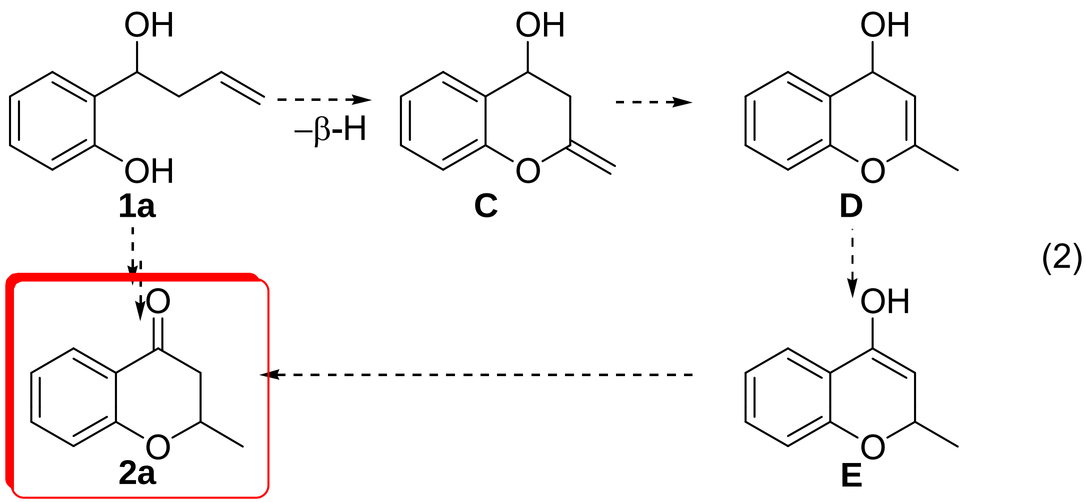
Section One: Palladium catalyzed Wacker-type reaction for the synthesis of chromanone and involving 1,5-hydride alkyl to palladium migration

Scheme 5. Original report on Wacker-type oxidative cyclization

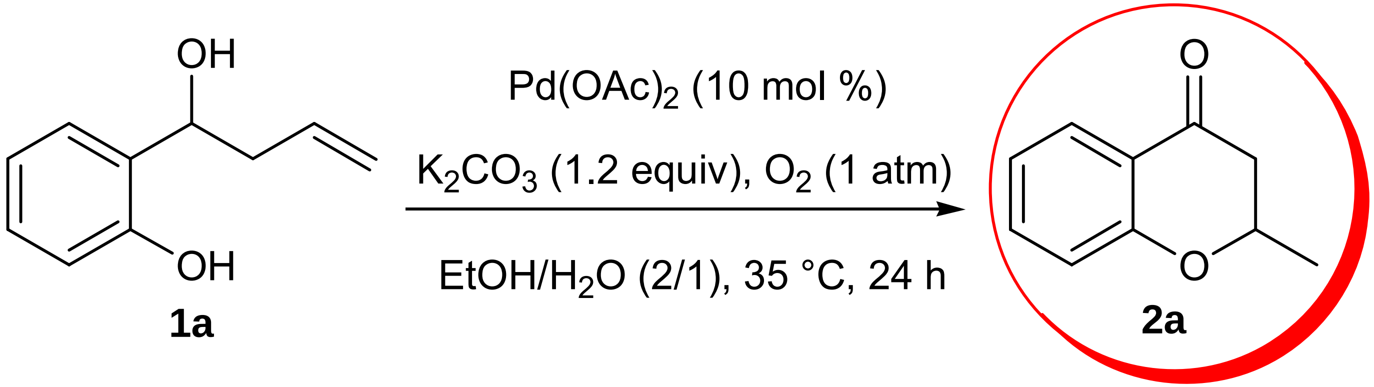


Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett*. **1973**, *14*, 739-740.

Scheme 6. Our initial proposal



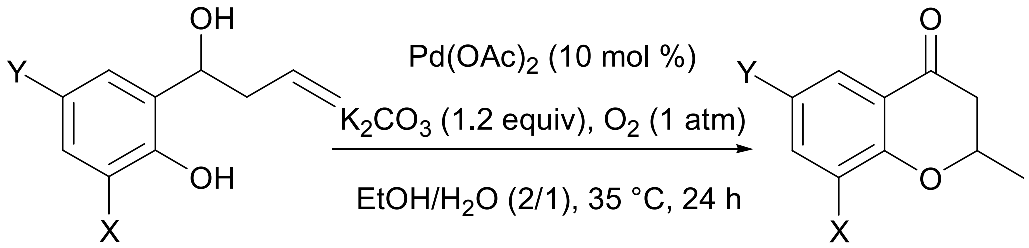
Scheme 7. Wacker-type oxidative cyclization of **1a**.

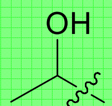
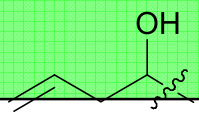


1a **2a**

Chem. Commun. **2007**, 4686-4689.

Table 7. Palladium (II) -Catalyzed Wacker-Type Cyclization



Entry	X	Y	Yield (%)
1	H	H	67
2	H	MeO	80
3	H	Me_3C	72
4	H	Me	70
5	MeO	H	76
6	Me	H	83
7	Me_3C	Me_3C	71
8	Cl	H	70
9	H	Cl	64
10	H	MeCO	42
11	H	Br	43
12	H		65
13	H		61

Electron-donating group facilitate the reaction

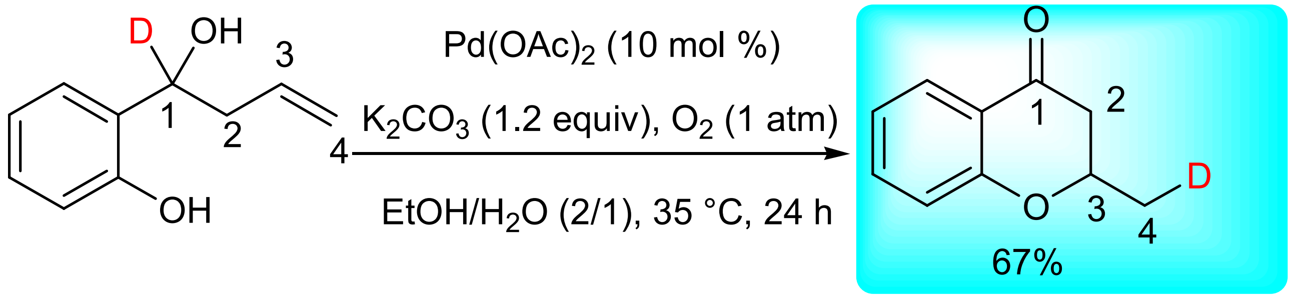
steric effort is unclear

stong electon-withdrawing group retards the reacton

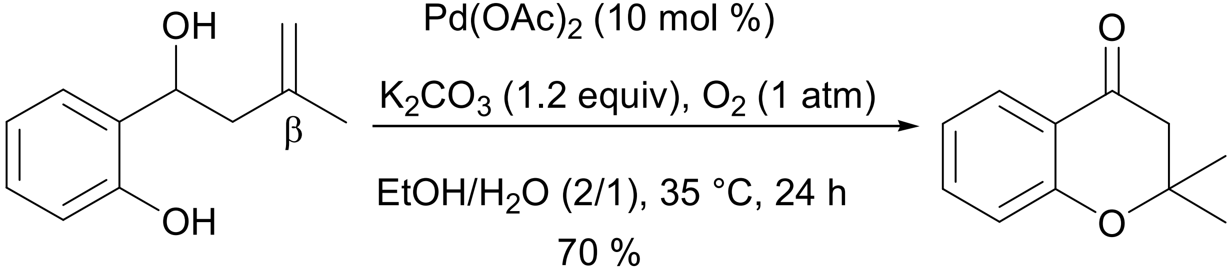
Groups sensitive to palladium survived

Mechanism insight: β-H elimination was excluded.

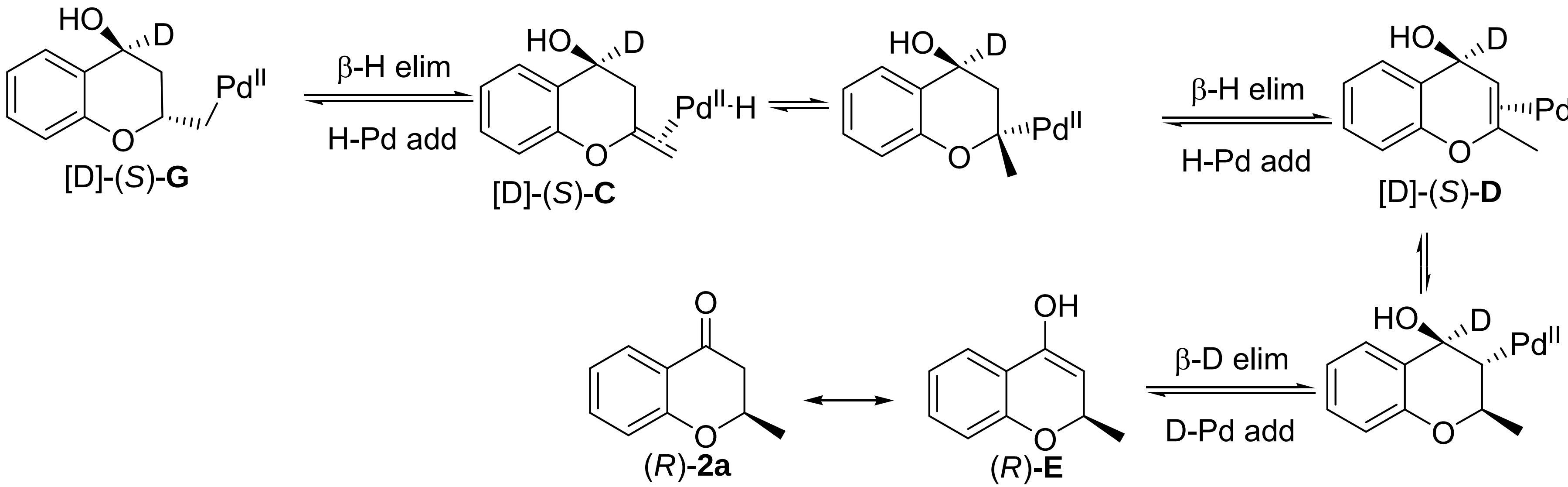
Scheme 9. Deuterium labelling experiment of Wacker-type cyclization



Scheme 10. Cyclization of starting material without β-H

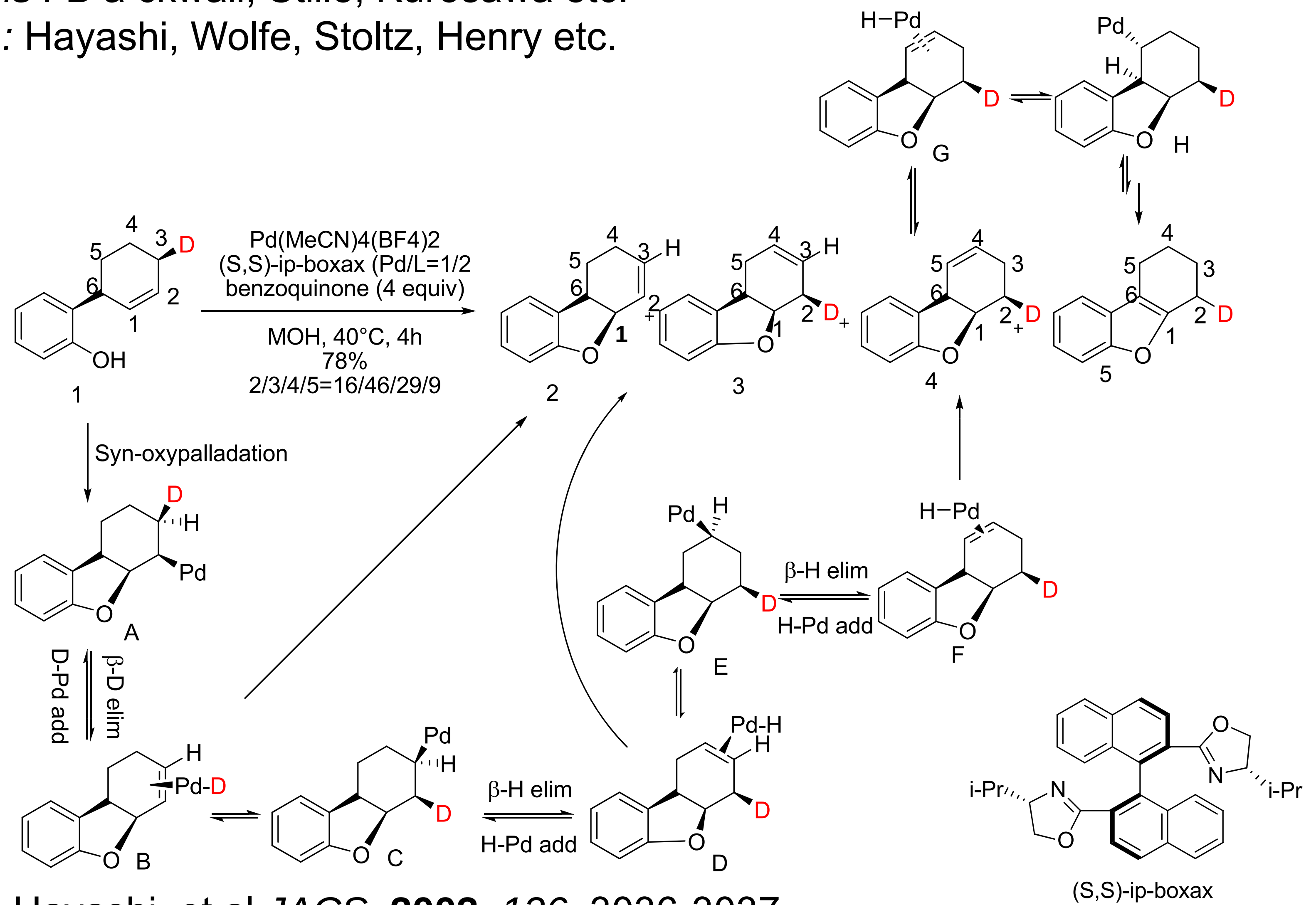


Scheme 11. β-Hydride Elimination/Hydropalladation Sequences



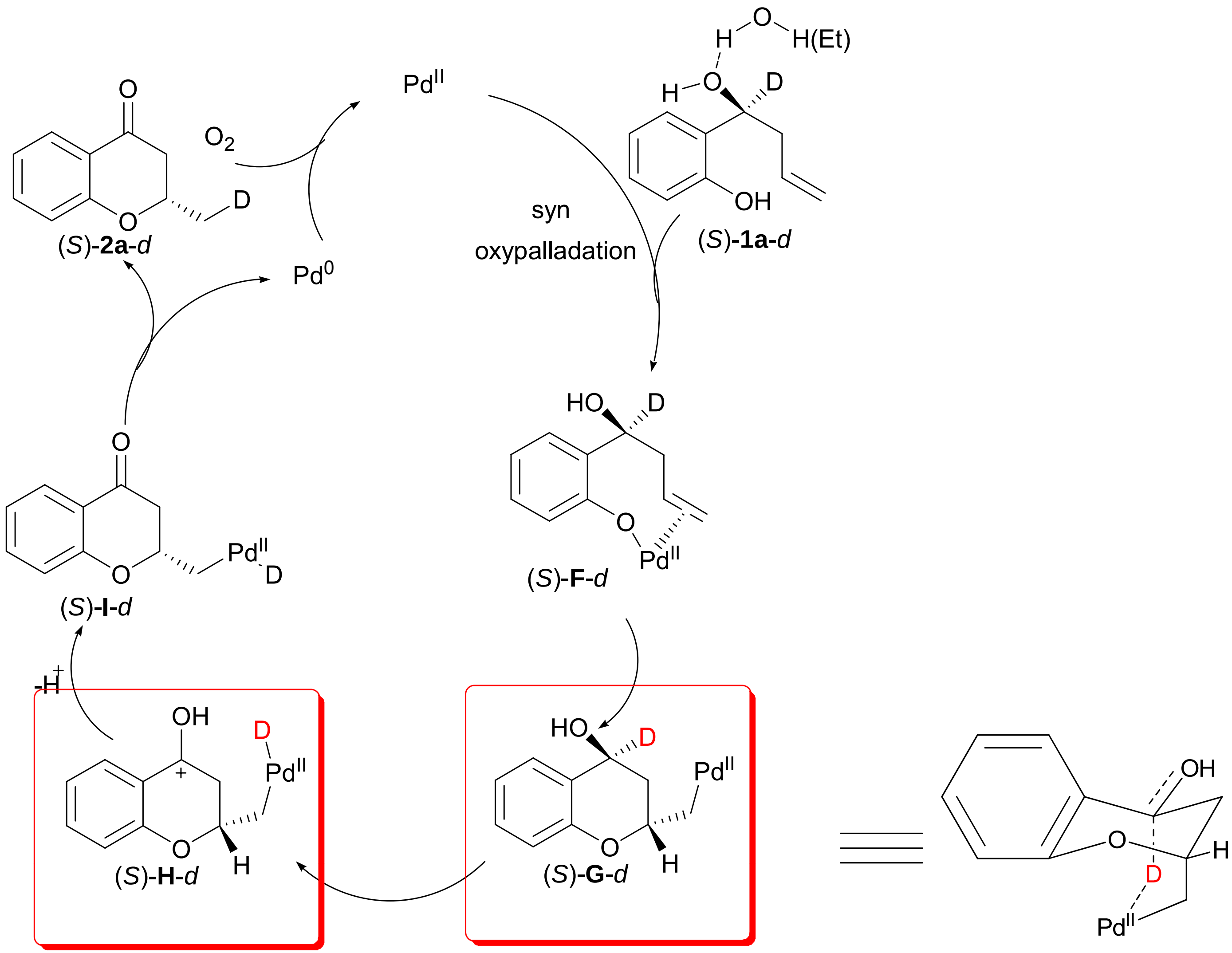
Stereochemistry of oxypalladation: *cis* or *trans* ?

Trans : B ǎ ckwall, Stille, Kurosawa etc.
Cis : Hayashi, Wolfe, Stoltz, Henry etc.



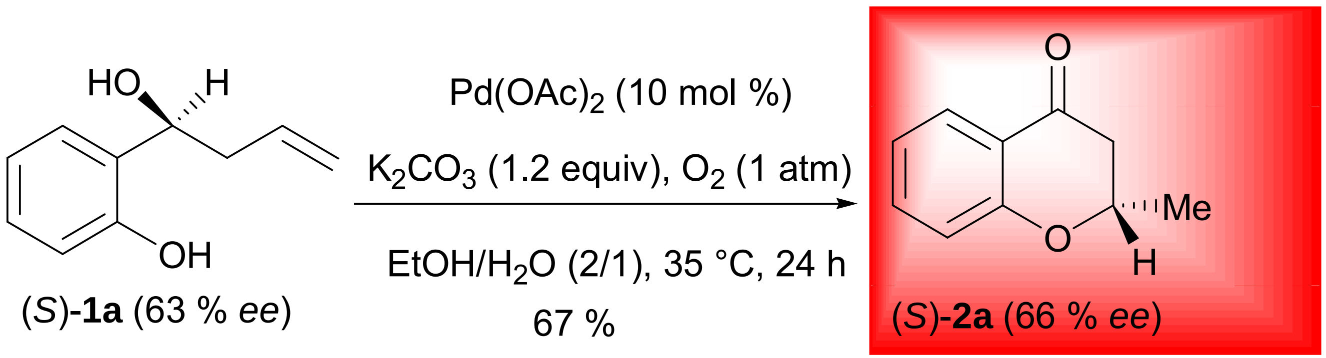
T. Hayashi, et al *JACS*, **2003**, *126*, 3036-3037

Scheme 9. Proposed mechanism for the Wacker-type cyclization of (*S*) -**1a**-*d* involving 1,5-palladium migration.



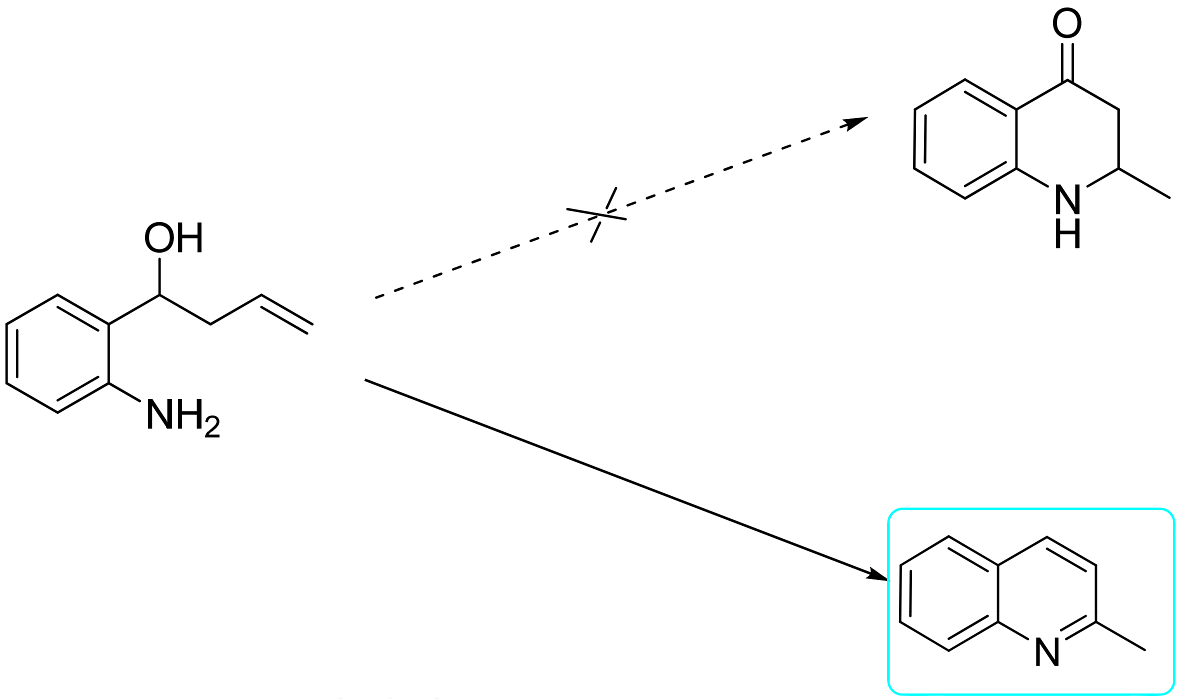
Further experiment to support 1,5-hydride alkyl to palladium migration

Scheme 10 Chirality transfer experiment of cyclization



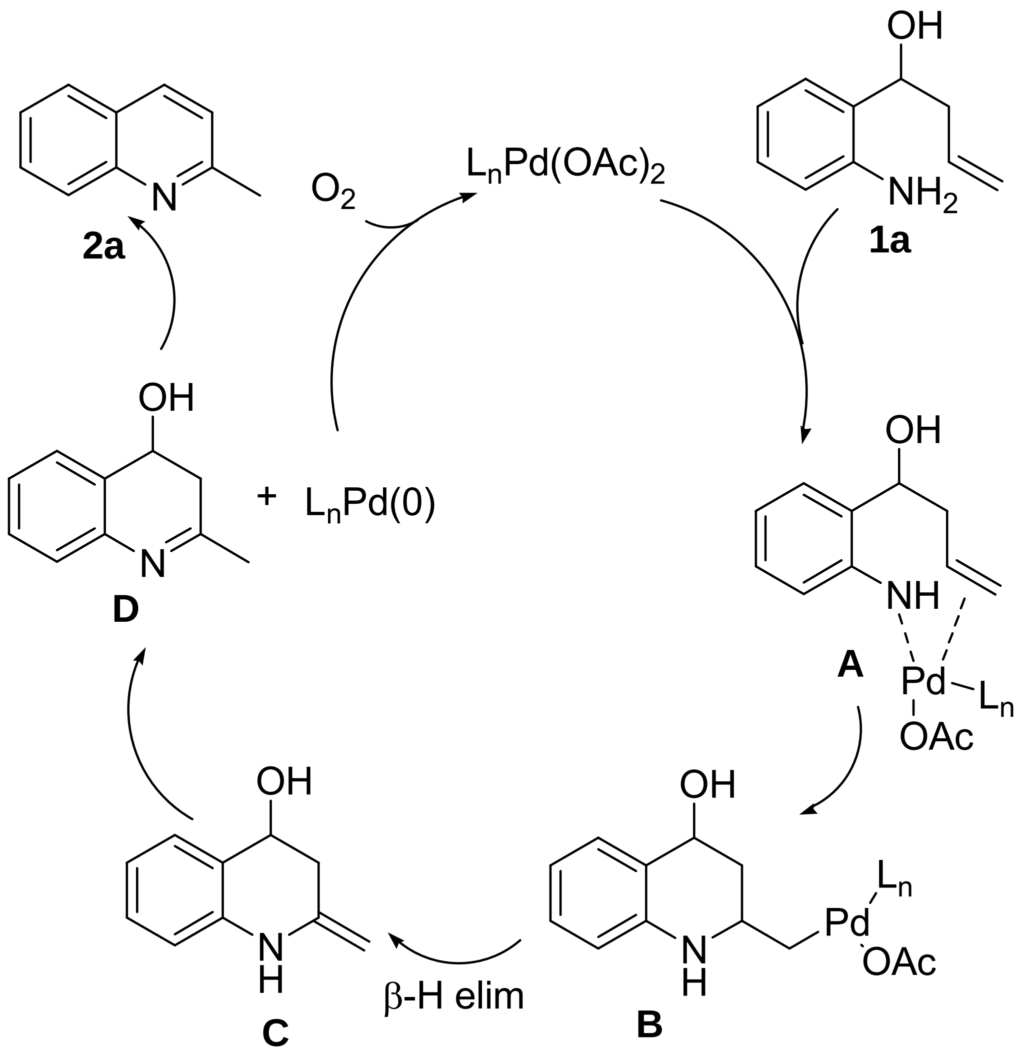
Section Two: Facile synthesis of 2-methyl quinolines by aza-Wacker oxidative cyclization catalyzed by palladium(II)

Scheme 11. Aza-Wacker oxidative amination



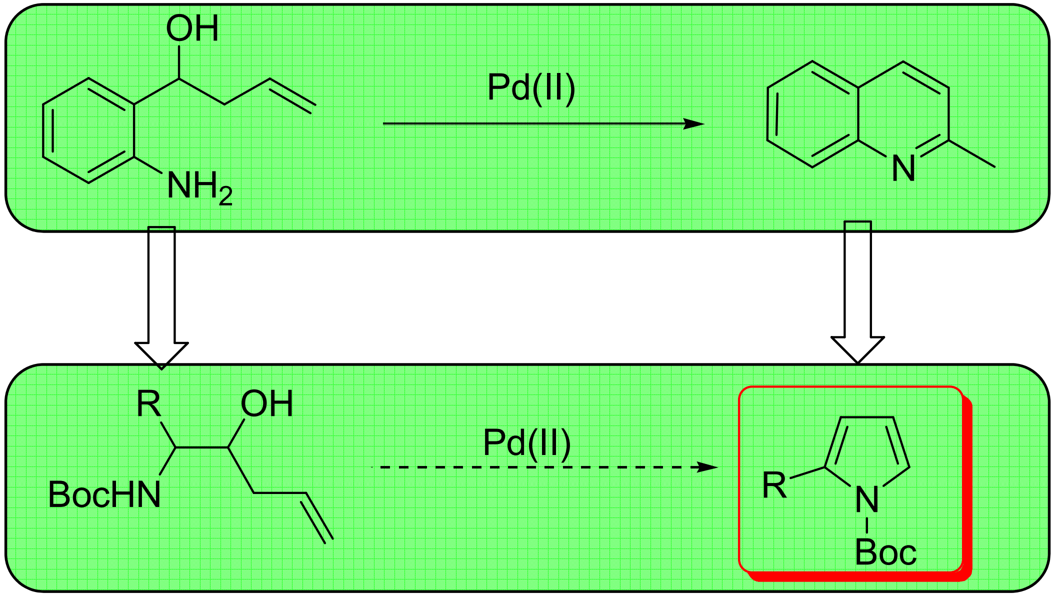
Org. Lett. **2008**, *10*, 173-175.

Scheme 12. Proposed mechanism for the Pd-Catalyzed Aza-Wacker reaction to form 2-methyl-quinoline



Section Three: Facile synthesis of 2-methyl pyrroles by aza-Wacker oxidative cyclization catalyzed by palladium(II)

Scheme 13. Synthesis of pyrroles by aza-Wacker oxidative cyclization



J. Org. Chem. 2008, 73, 5180-5182

Scheme 14. General process to substrates from amino acids

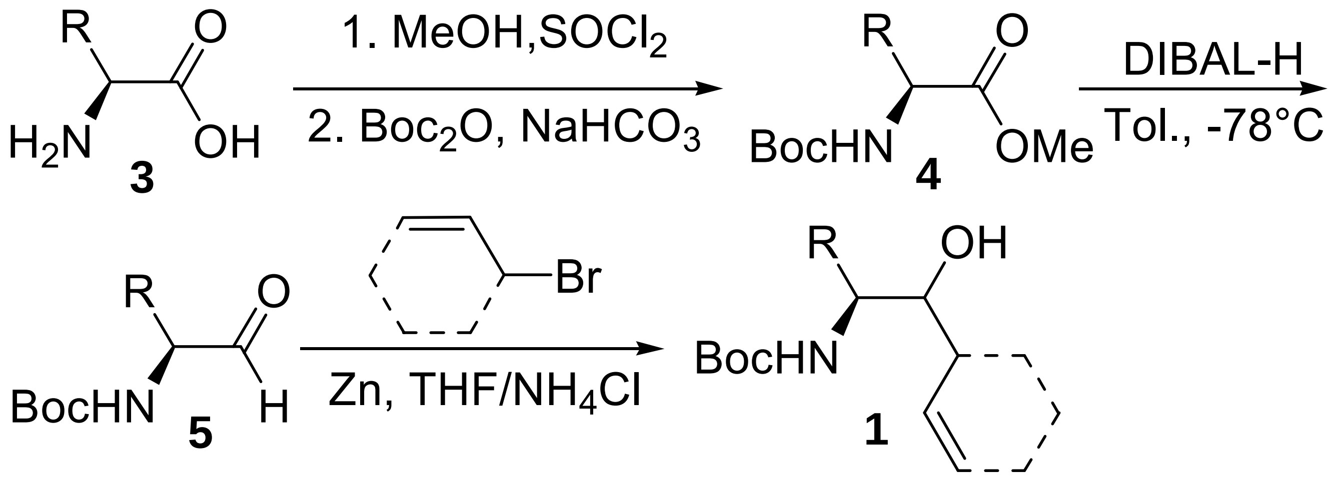
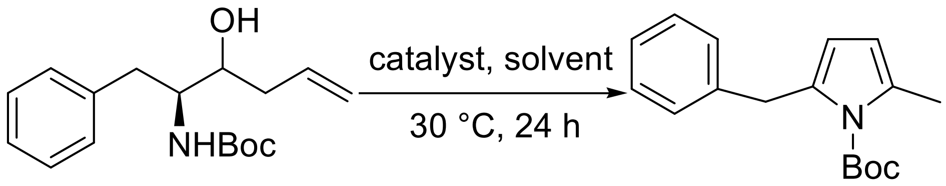


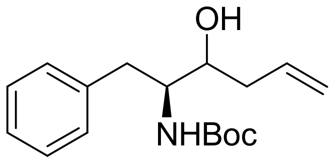
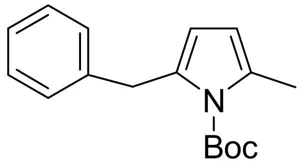
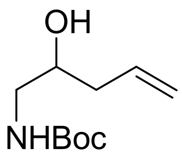
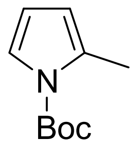
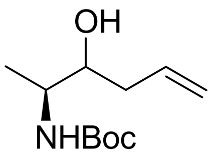
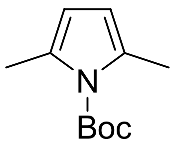
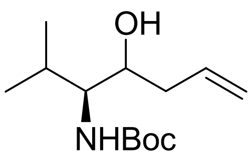
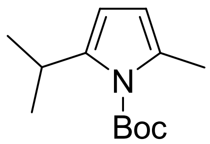
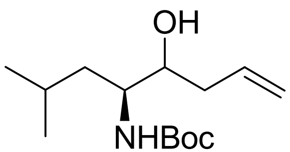
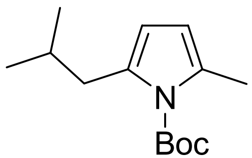
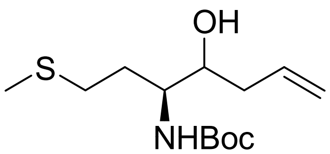
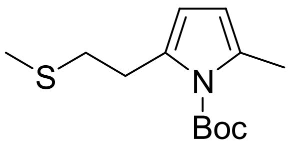
Table 11. Optimazation of Aza-Wacker cyclization[a]

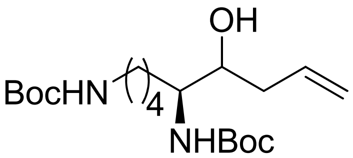
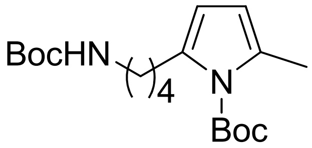
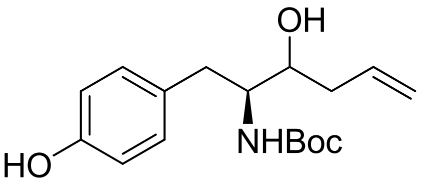
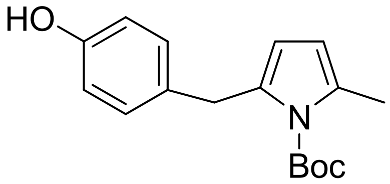
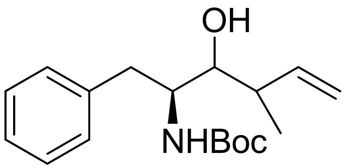
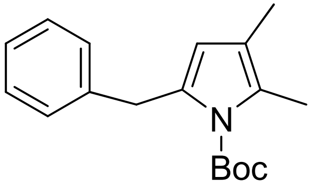
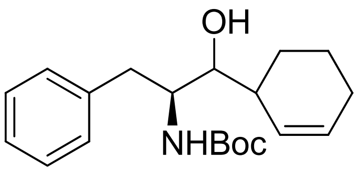
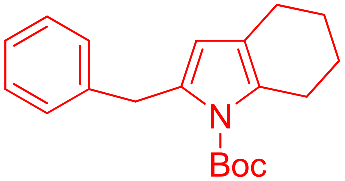
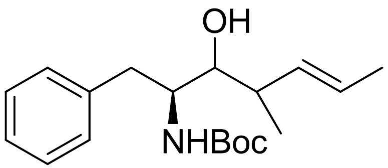
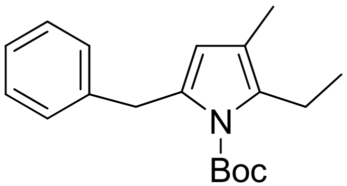


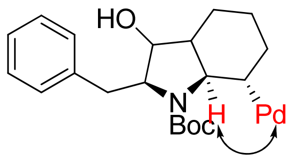
entry	solvent	catalyst (10 mol %)	oxidant	yield[b] (%)
1	MeOH	$Pd(OAc)_2$	air	23
2	EtOH	$Pd(OAc)_2$	air	25
3	*i*-PrOH	$Pd(OAc)_2$	air	trace
4	THF	$Pd(OAc)_2$	air	trace
5	Tol	$Pd(OAc)_2$	air	trace
6	DMF	$Pd(OAc)_2$	air	trace
7	DMSO	$Pd(OAc)_2$	air	trace
8	$CHCl_3$	$Pd(OAc)_2$	air	trace
9	EtOH	$PdCl_2$	air	41
10	EtOH	$PdCl_2(MeCN)_2$	air	44
11	EtOH	$PdCl_2(PhCN)_2$	air	45
12	EtOH	$PdCl_2(PhCN)_2$	O_2	50
13	EtOH	$PdCl_2(PhCN)_2$	$CuCl_2$ (10 mol %)	52
14	EtOH	$PdCl_2(PhCN)_2$	$Cu(OTf)_2$ (10 mol %)	69
15	EtOH	$PdCl_2(PhCN)_2$	$Cu(OTf)_2$ (50 mol %)	80
16	EtOH	$PdCl_2(PhCN)_2$	$Cu(OTf)_2$ (100 mol %)	88

[a] Reaction conditions: 0.2 M of substrate in solvent. [b] Isolated yield.

Table 12. Synthesis of Pyrrole by Aza-Wacker Cyclization[a]

entry	substrate	product	yield[b] (%)
1			88
2			86
3			89
4			87
5			92
6			85

entry	substrate	product	yield[b] (%)
7			62
8			79
9			76
10			70
11			26



[a] Reaction conditions: substrate (1 mmol), $PdCl_2(PhCN)_2$ (0.1 mmol) and $Cu(OTf)_2$ (1 mmol) in 5mL of ethanol at 30°C for 24 h. [b] Isolated yield.

Conclusion:

1) Regioselective Heck reaction at different C-I bonds was first reported;

2) Diatomite as a suitable template to support palladium was first developed and used to catalyze Heck and Suzuki reactions;

3) *1,5-hydride alkyl to palladium migration* was first proposed in Wacker-type reaction and a series of chromanones were synthesized by this method;

4) Quinolines and pyrroles were obtained by aza-Wacker cyclization.

Acknowledgement

Prof. Zhiyong Wang
Wang’s Group