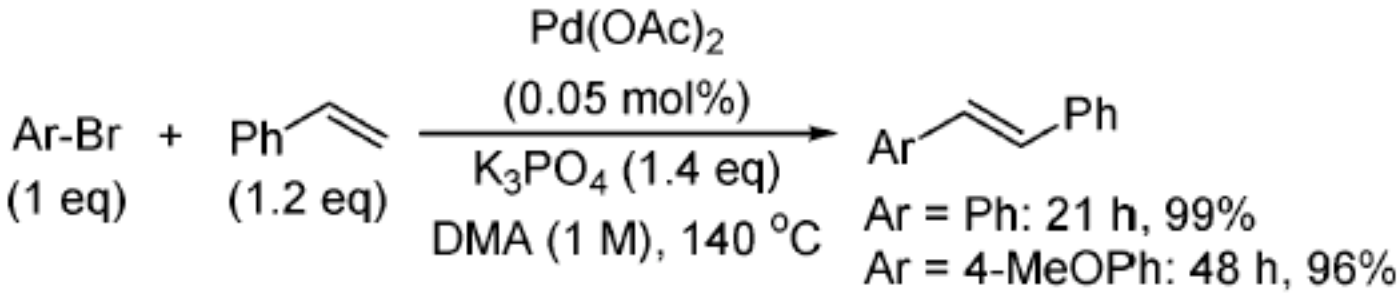
Ligand-Free Heck Reaction: $Pd(OAc)_2$ as an Active Catalyst Revisited

Qingwei Yao,* Elizabeth P. Kinney, and Zhi Yang†



J. Org. Chem., *Vol. 68, No. 19, 2003*

Pd

- A versatile catalyst for carbon-carbon bond formation.
- Tolerant to many functional groups such as carbonyl and hydroxyl groups.
- NOT “VERY” sensitive to oxygen.
- Not toxic

BUT

- Expensive (less expensive than Rd, Pt and Os)

Palladium reagents and catalysts, Jiro Tsuji, Wiley

Two kinds of Pd compounds useful for organic synthesis:

Pd(II): such as $PdCl_2$ $Pd(acac)_2$ and $Pd(OAc)_2$

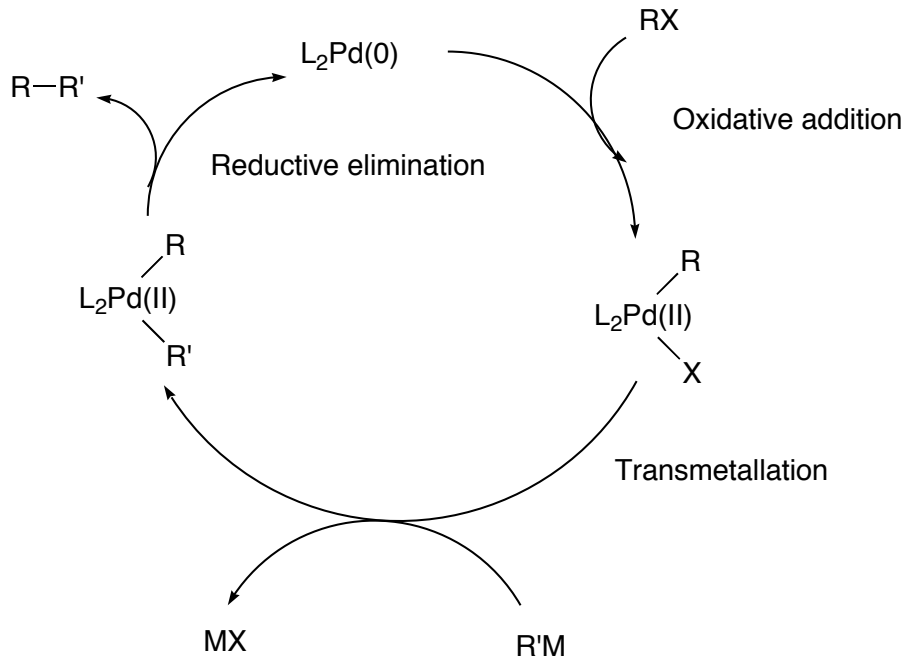
- Used either stoichiometric rgts or catalysts
- Stable
- Used as unique stoichiometric oxidizing agents and s precursors of Pd(0) compelxes

Pd(0): reduced from Pd(II)

- Used as catalysts
- Usually prepared from $Pd(OAc)_2$ with phosphine ligands.

Examples of organic reactions using Pd(0)

Coupling reaction



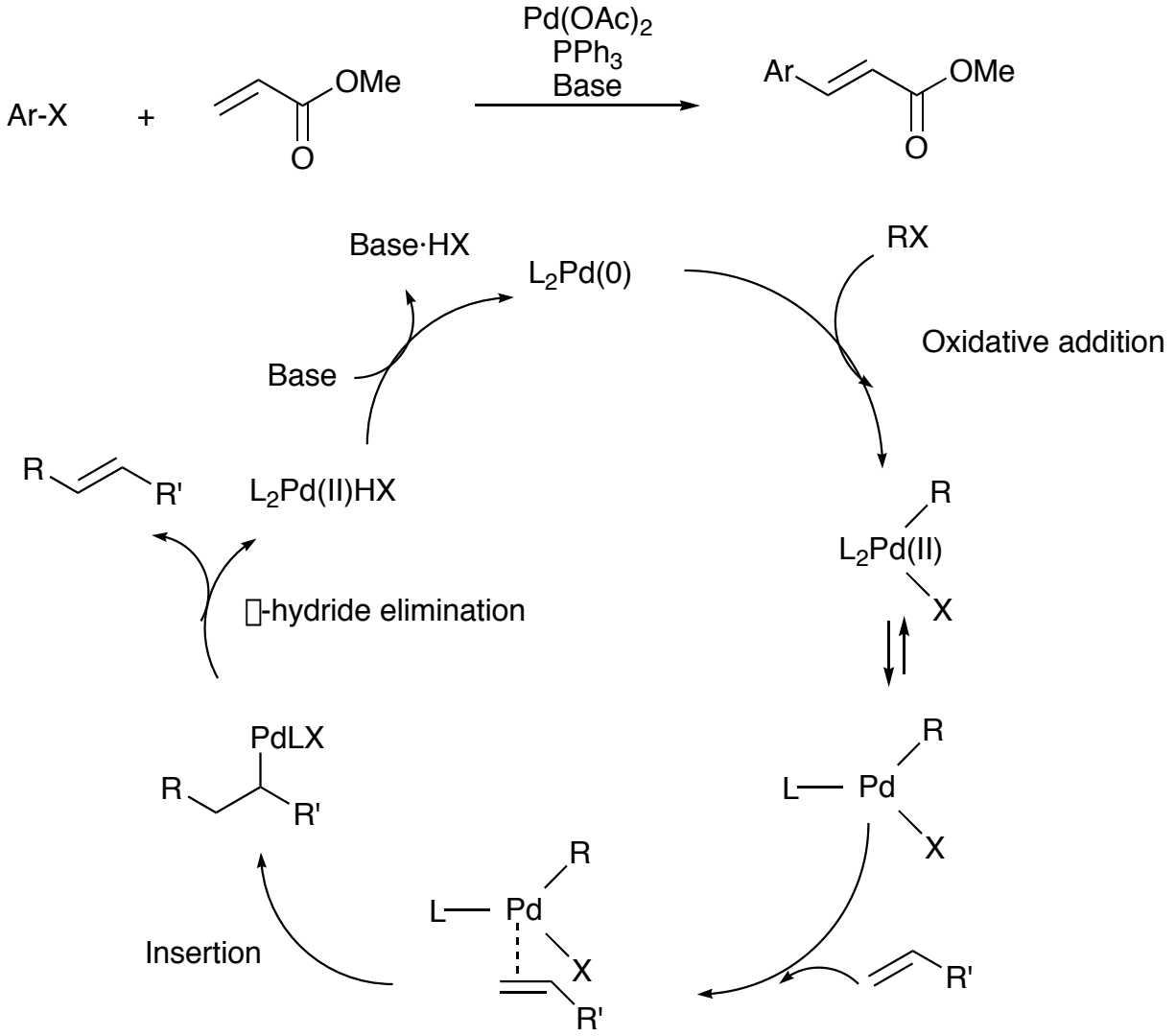
When M is

Sn : Stille reaction
B : Suzuki reaction
Cu : Sonogashira reaction
Zn : Negishi reaction

Organic Synthesis using Transition metals, Rod Bates, Sheffield academic press

Alkene insertion reaction

Heck reaction



Heck reaction

- Typically needs 1-5 mol % Pd catalyst along with Phosphine ligand and base
- Maximum turnover numbers (TON): only 20-100
- Not practical for large-scale industrial application

Challenge

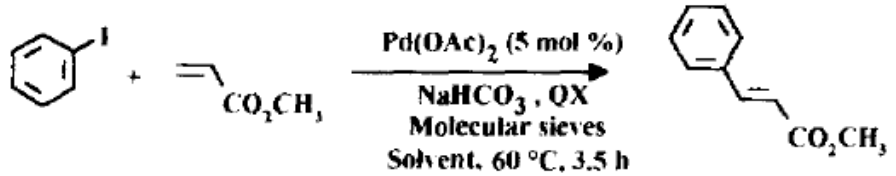
New Heck reaction catalyst

- with higher TON
- and enhanced reactivity with deactivated aryl bromides or aryl chloride

Precedents of Ligand-free Heck reaction

In Phase-transfer condition

Table 2: Effect of Tetraalkylammonium Salts on Palladium-catalysed Arylation of Methyl Acrylate in the Presence of Alkali Metal Hydrogencarbonate as the Base and *in the Absence of Phosphine Ligand.* [a]

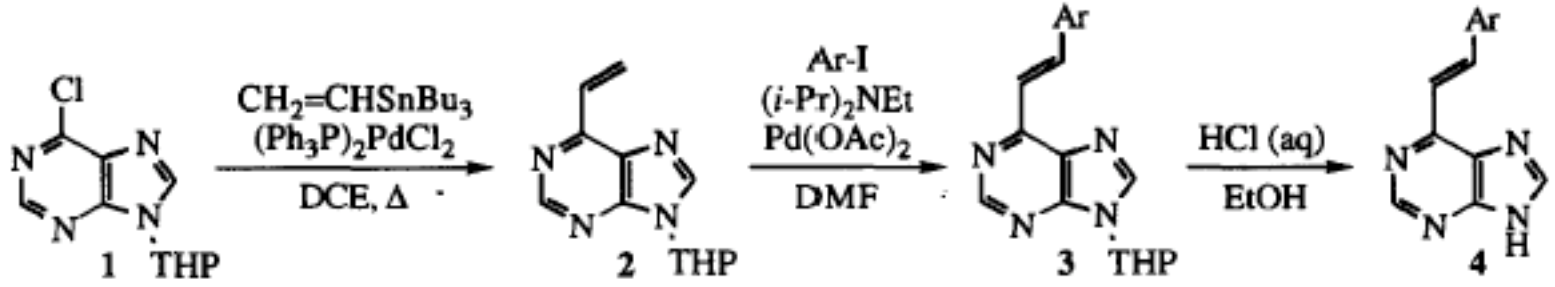


Entry	Solvent	QX	Yield (%) [b]
1	CH_3CN	-	3
2	CH_3CN	n-Bu_4NCl [c]	90
3	CH_3CN	n-Bu_4NHSO_4	45
4	CH_3CN	n-Bu_4NBr	20
5	DMF	-	5
6	DMF	n-Bu_4NCl [c]	99
7	DMF	n-Bu_4NHSO_4	99
8	DMF	n-Bu_4NBr	62

Tetrahedron, Vol. 52, No. 30, pp. 10113-10130, 1996

Precedents of Ligand-free Heck reaction

alkenylpurines **3** in good yields, calculated from the chloropurine **1**. We obtained better results when $Pd(OAc)_2$ alone was employed as catalyst compared with catalysts containing phosphine ligands like triphenylphosphine. Reduced yields in Heck reactions in the presence of phosphine ligands have also been noted by others.[22]



Scheme 1

They did not explain why.

Tetrahedron 55 (1999) 211–228

Precedents of Ligand-free Heck reaction

In ionic liquid

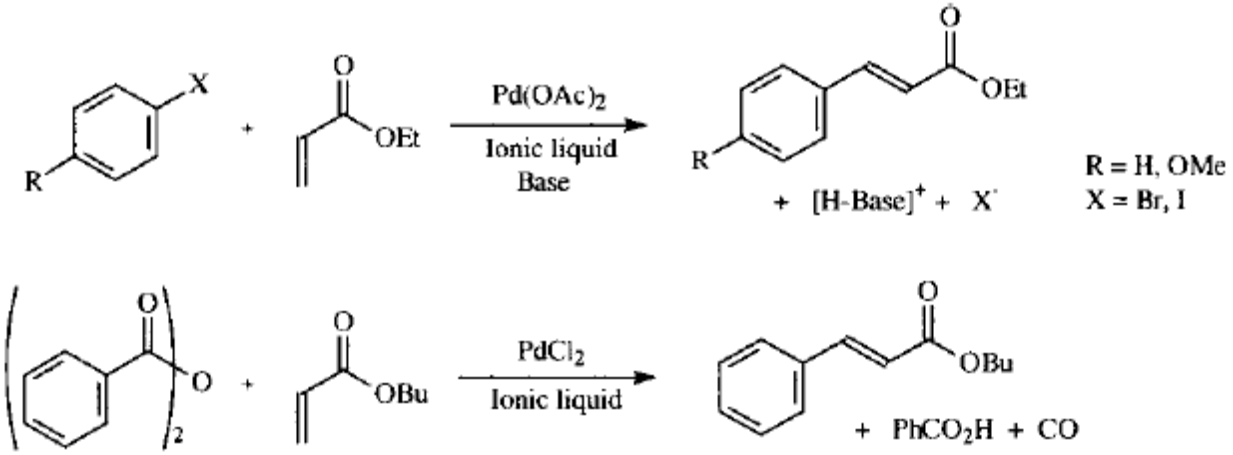


Table 1. Heck Reaction of Iodobenzene and Ethyl Acrylate To Give *trans*-Ethyl Cinnamate in Ionic Liquids with 2 mol % of $Pd(OAc)_2$

entry	ionic liquid	additive	base	temp, °C	time, h	yield, %
1	$[C_6py]Cl$	none	Et_3N	40	24	99
2	$[C_6py]Cl$	none	$NaHCO_3$	40	24	98
3	$[C_6py][PF_6]$	none	$NaHCO_3$	80	72	42
4	$[C_6py][BF_4]$	none	$NaHCO_3$	80	72	99
5	$[bmim][PF_6]$	Ph_3P	Et_3N	100	1	95−99[19]

Majorly, to recycle palladium catalyst

Of course, phosphine ligand accelerated the reaction significantly.

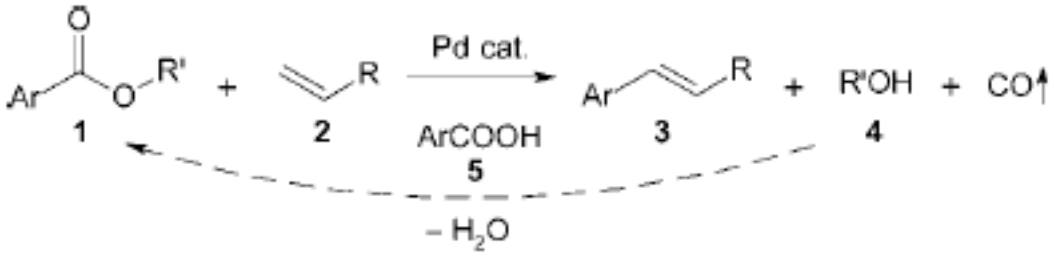
ORGANIC LETTERS

1999
Vol. 1, No. 7
997−1000

Precedents of Ligand-free Heck reaction

Waste-free Heck reactions

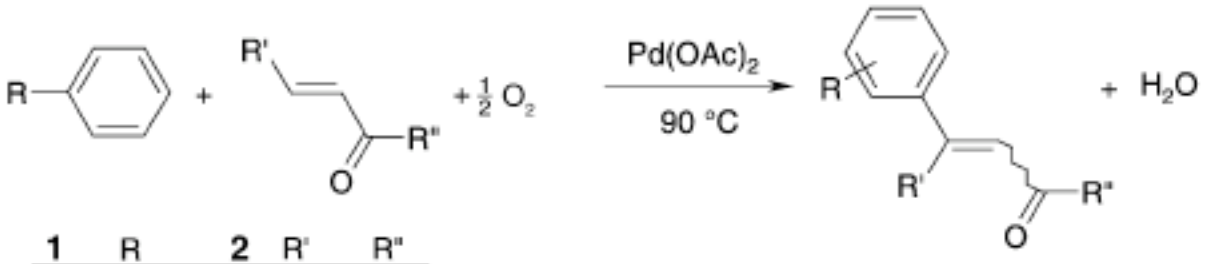
Angew. Chem. Int. Ed. **2002**, *41*, No. 7 1237



Scheme 1. Decarbonylative Heck olefination of esters.

Various additives were tested

Angew. Chem. Int. Ed. **2003**, *42*, 3512 –3515



1	R	2	R'	R"
a	H	a	H	OBu
b	Me	b	Ph	OEt
c	OMe	c	Ph	Me

Halogen free condition

Oxygen oxidized Pd(0) to active Pd(II)

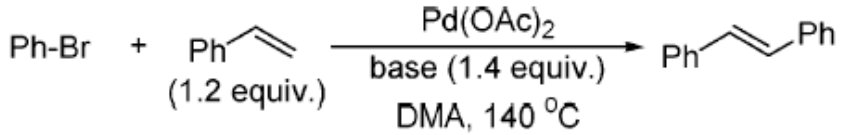
Water is the only by-product

Ligand-free Heck reaction

Possbility of $Pd(OAc)_2$ as an active catalyst without Phosphine ligands

Base Selection : K_3PO_4 showed the best result

TABLE 1. Effect of the Base on the $Pd(OAc)_2$-Catalyzed Reaction of Bromobenzene and Styrene[a]



entry	base	mol % of $Pd(OAc)_2$	time (h)	yield[b] (%)	TON
1	Et_3N	0.1	21		
2	Na_2CO_3	0.1	21	56	560
3	NaOAc	0.1	21	72	720
4	K_3PO_4	0.1	19	93	930
5	K_3PO_4	0.01	19	82	8200
6[c]	K_3PO_4	0.00247	44	95	38500

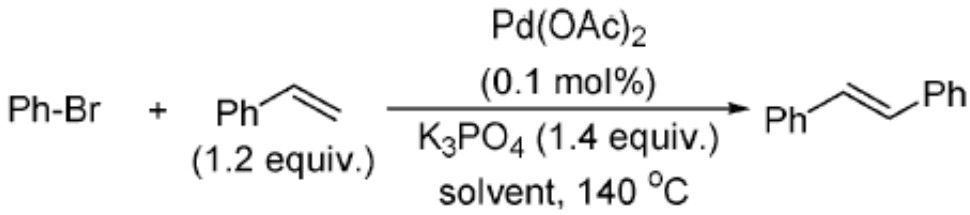
[a] Unless otherwise noted, all reactions were performed with 1.0 mmol of PhBr in DMA (1−2 mL) at 140 °C. [b] Isolated yield after chromatography on silica gel. [c] 2.0 mmol of PhBr was used.

J. Org. Chem. **2003**, *68*, 7528−7531

Solvent optimization

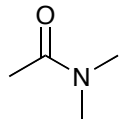
DMA showed the best result.

TABLE 2. Effect of the Solvent on the $Pd(OAc)_2$-Catalyzed Reaction of Bromobenzene and Styrene[a]



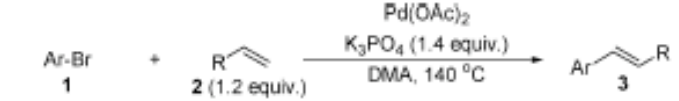
entry	solvent	yield[b] (%)
1	DMA	95
2	DMF	74
3	NMP	54
4[c]	dioxane	<2

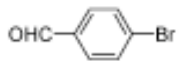
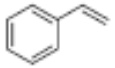
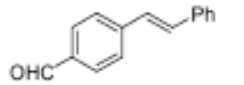
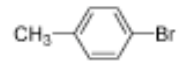
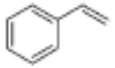
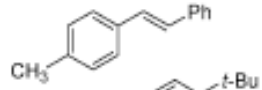
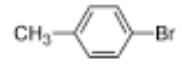
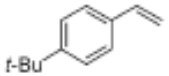
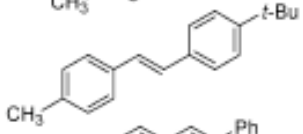
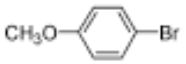
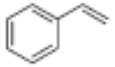
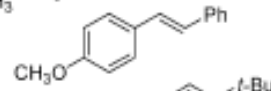
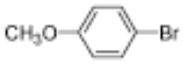
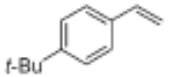
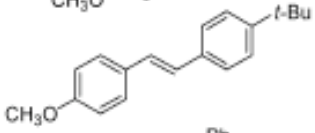
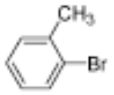
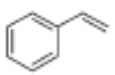
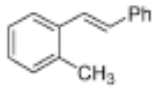
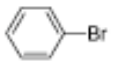
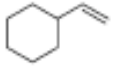
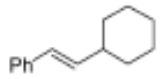
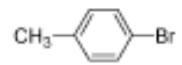
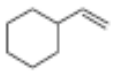
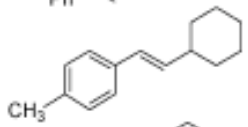
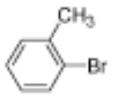
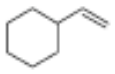
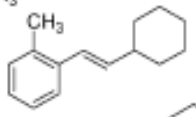
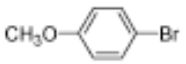
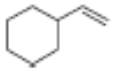
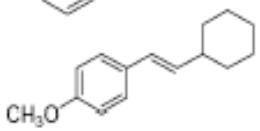
[a] Unless otherwise noted, all reactions were performed with 1.0 mmol of PhBr in 1.6 mL of the solvent at 140 °C for 19 h. [b] Isolated yield after chromatography on silica gel. [c] This reaction was performed at 100 °C.

DMA=*N*,*N*-dimethylacetamide 

Generality of this reaction

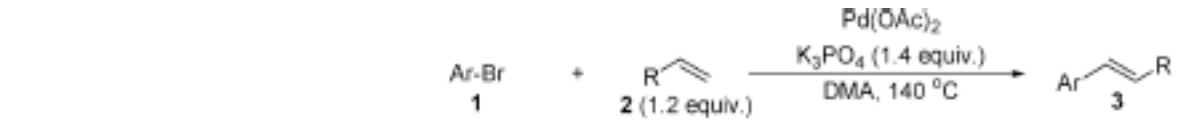
TABLE 3. $Pd(OAc)_2$-Catalyzed Heck Reactions of Aryl Bromides with Terminal Olefins, Using K_3PO_4 as the Base[a]

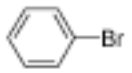
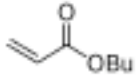
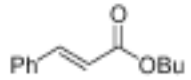
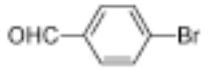
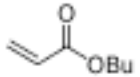
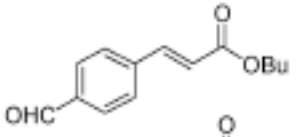
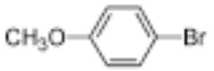
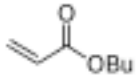
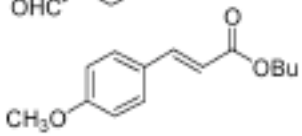


entry	Ar-Br (**1**)	R (**2**)	product (**3**)		mol % $Pd(OAc)_2$	time (h)	yield[b]	TON
1				**3a**[6a]	0.05	25.5	98%	1960
2				**3b**[6b]	0.05	24.5	92%	1840
3				**3c**[13]	0.05	24.5	97%	1940
4				**3d**[3a]	0.05	17	71%[c]	1420
5				**3e**	0.05	17	93%	1860
6[d]				**3f**[3a]	0.10	20	63%	630
7				**3g**[14]	0.05	21	89%	1780
8[d]				**3h**[15]	0.10	22.5	86%	860
9[d]				**3i**	0.10	22.5	77%	770
10[d]				**3j**[16]	0.10	21	82%	820

Showed very high yield and TON in various combinations.

Interesting point:



entry	Ar-Br (1)	R (2)	product (3)		mol % $Pd(OAc)_2$	time (h)	yield[b]	TON
11[a]				**3k**[5a]	0.05	22	36%	720
12				**3l**[8]	0.10	22	91%	910
13				**3m**[8]	0.10	22	9%	90

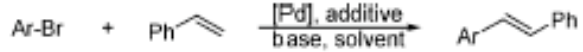
•Activated terminal olefin such as n-butyl arylate gove low yields except for the coupling with the more active 4-bromobenzaldehyde. -> New mechanism?!

•Cyclic olefins such as norbornene and 2,4-dihydropyran did not react.

•Triflate and chloride were completely ineffective in this system.

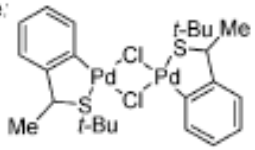
Comparison with other catalyst systems

TABLE 4. $Pd(OAc)_2/K_3PO_4$ in DMA as an Active Catalyst System for the Heck Reaction: Comparison with Other Catalyst Systems[18]

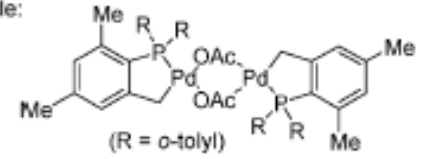


entry	Ar-Br	[Pd] (mol %)	base	solvent	Additive (amount)	conditions	yield	TON	Ref
1	PhBr	$Pd(OAc)_2$ (0.01)	K_3PO_4	DMA	none	140 °C, 19 h	82%	8,200	This work
2	PhBr	$Pd(OAc)_2$ (0.00247)	K_3PO_4	DMA	none	140 °C, 44 h	95%	38,500	This work
3	4-MePhBr	$Pd(OAc)_2$ (0.05)	K_3PO_4	DMA	none	140 °C, 24.5 h	92%	1,840	This work
4	4-MeOPhBr	$Pd(OAc)_2$ (0.05)	K_3PO_4	DMA	none	140 °C, 17 h	71%	1,420	This work
5	PhBr	$Pd(OAc)_2$ (1.5)	NaOAc	NMP	Bu_4NBr (20 mol %)	150 °C, 30 h	70%	47	9g
6	PhBr	$PdCl_2(SEt_2)_2$ (0.1)	NaOAc	DMA	Bu_4NBr (20 mol %)	150 °C, 24 h	76%	760	18
7	4-MeOPhBr	$PdCl_2(SEt_2)_2$ (0.1)	NaOAc	DMA	Bu_4NBr (20 mol %)	140 °C, 24 h	38%	380	18
8[a]	PhBr	Dupont's Pd-cycle (0.002)	NaOAc	DMA	Bu_4NBr (100 mol %)	140 °C, 28 h	56%	28,000	6a
9[a]	4-MeOPhBr	Dupont's Pd-cycle (0.002)	Et_3N	DMA	Bu_4NBr (20 mol %)	140 °C, 90 h	10%	5,000	6a
10[b]	PhBr	Herrmann's Pd-cycle (0.1)	NaOAc	DMA	none	140 °C, 26 h	77%	770	4b
11[b]	4-MeOPhBr	Herrmann's Pd-cycle (0.1)	NaOAc	DMA	none	140 °C, 30 h	69%	690	4b

[a] Dupont's Pd-cycle:



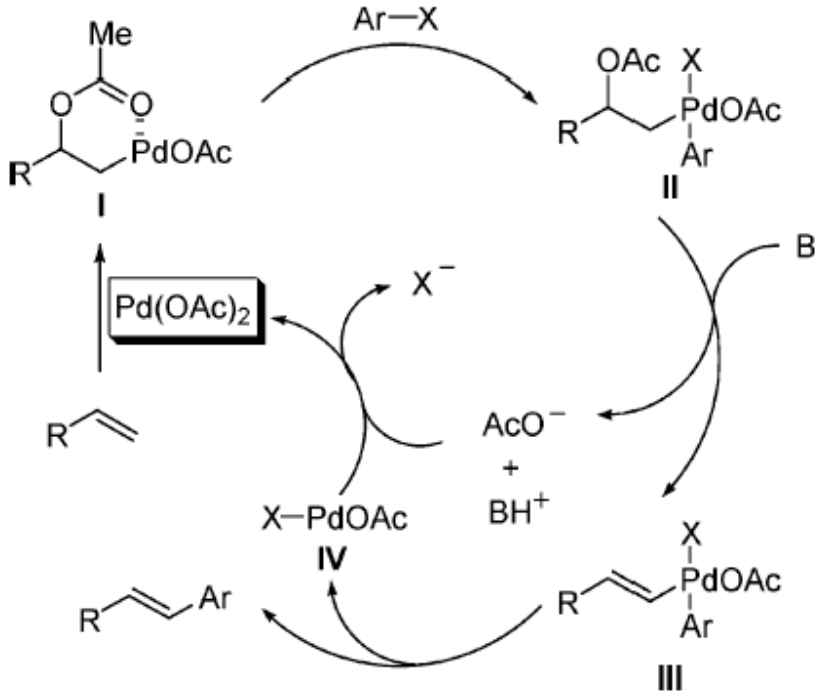
[b] Herrmann's Pd-cycle:



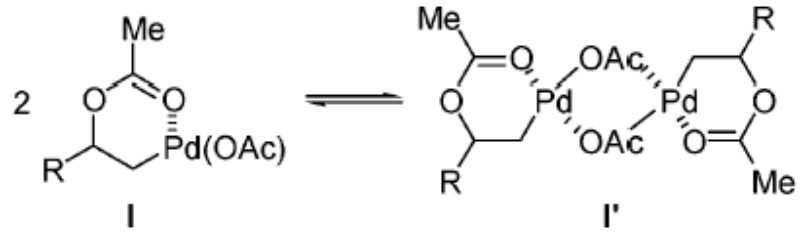
Similar or better than the other catalytic systems.

Proposed mechanism: without Pd(0) species

SCHEME 1. Proposed Mechanism for the Heck Reaction Catalyzed by $Pd(OAc)_2$



(20) By analogy to other palladacycles, **I** may exist in equilibration with its dimeric form:



Intermediate I was assumed because there's no predents of direct oxidative addtion of Ar-X to $Pd(OAc)_2$

Summary

$Pd(OAc)_2$, in combination with K3PO4 as the base and DMA as the solvent, can be used as a highly reactive catalyst for the Heck reaction.

Activated and deactivated aryl bromides can be used in the absence of any stabilizing ligands or special additives.

Cheap reaction! (cheap catalyst, cheap base and ligand-free)

Limitation

Beneficial to only aryl bromides and unactivated terminal olefins
Needs long reaction time
Needs high temperature