Anti-Markovnikov Olefin Functionalization
~Prof. Robert H. Grubbs' Work~

4th Literature Seminar

July 5, 2014

Soichi Ito (D1)

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Hydration

+ Reduction

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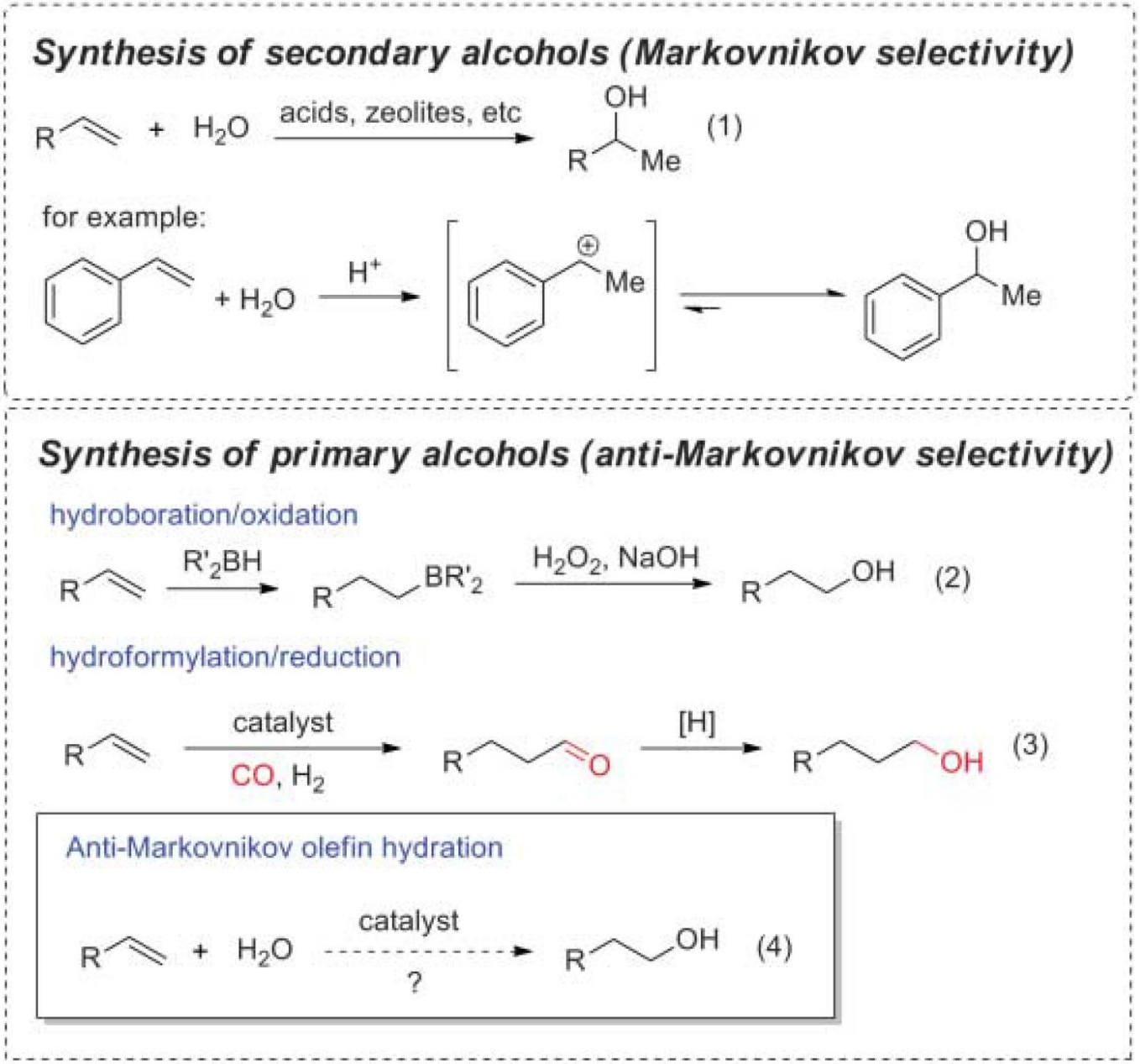
Introduction ~Markovnikov's Rule~



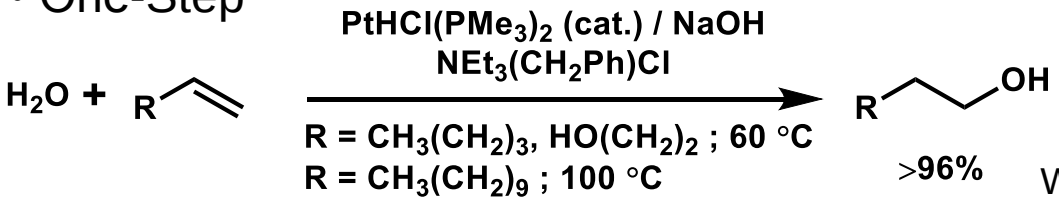
Two-Step

Two-Step (+1C)

Robert H. Grubbs *et al. Science*, **2011**, *333*, 1609.

Anti-Markovnikov Hydration of Olefins

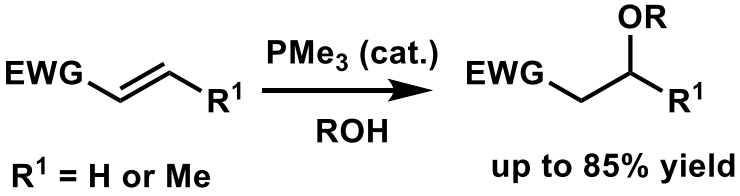
- One-Step



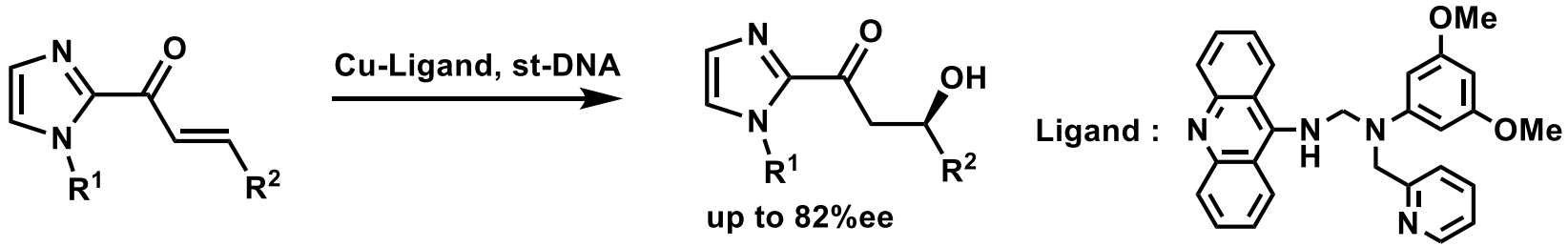
William C. Trogler *et al. Science* **1986**, *233,* 1069.

☹ This work was difficult to reproduce. *Inorg. Chem.* **1988**, *27,* 3151.

- One-Step with Activated Olefins

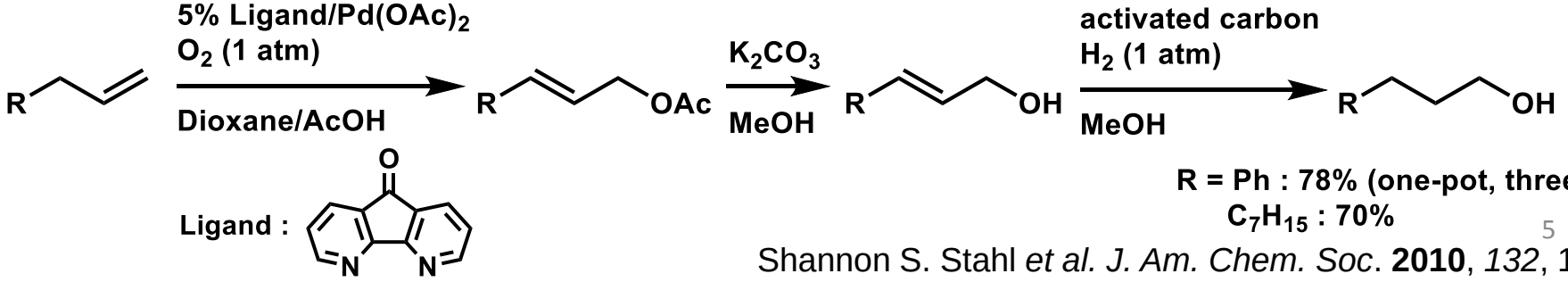


Robert G. Bergman and F. Dean Toste *et al.*
J. Am. Chem. Soc. **2003**, *125*, 8696.



Ben L. Feringa and Gerard Roelfes *et al. Nat. Chem.* **2010**, *2*, 991.

- Three-Step



Shannon S. Stahl *et al. J. Am. Chem. Soc*. **2010**, *132*, 15116.

Anti-Markovnikov Wacker Oxidation / Reduction Strategy

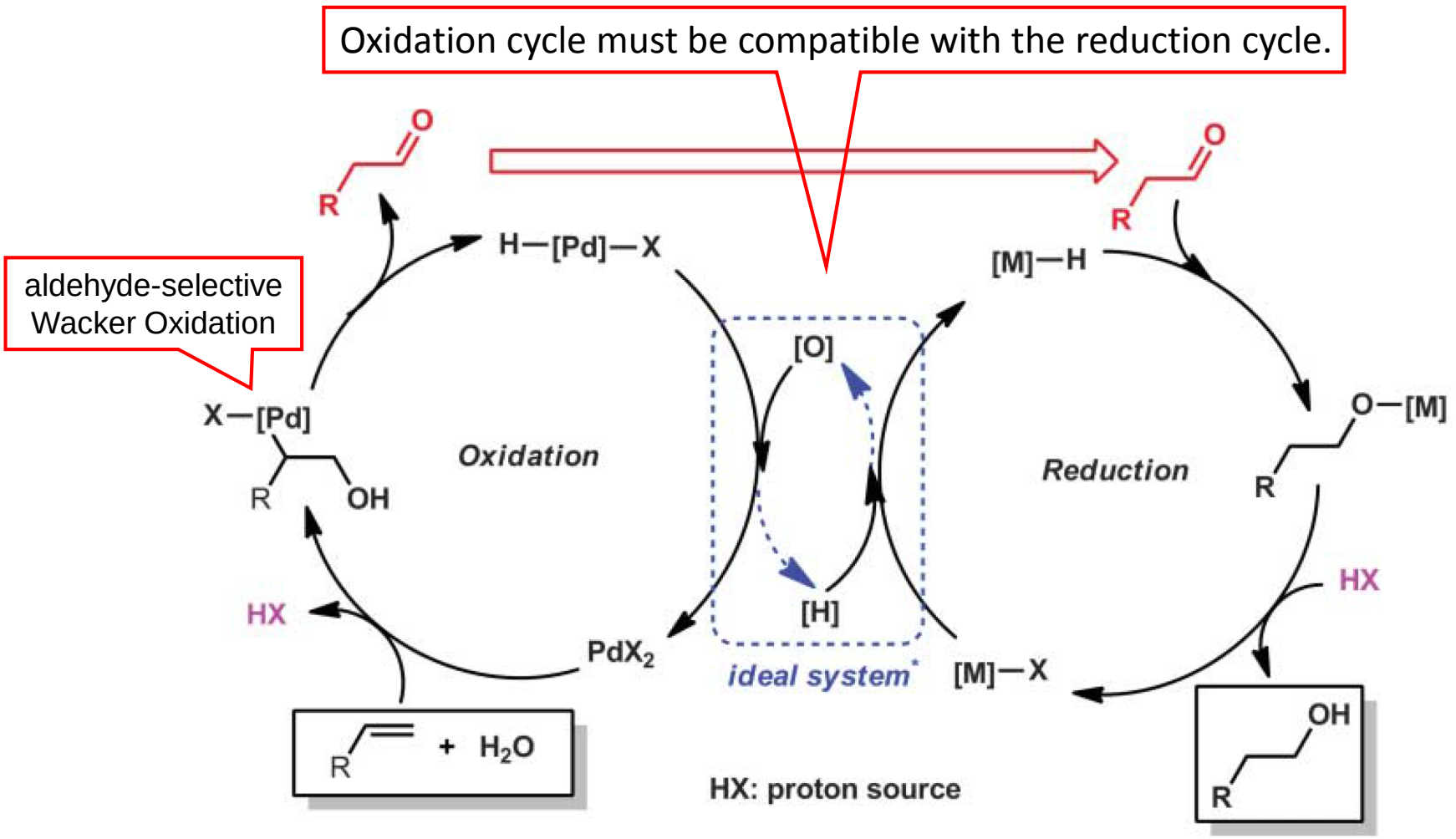


Fig. 2. Proposed cooperative catalytic system for alcohol synthesis from olefins and water. Asterisk: In the ideal system, either the hydride would be directly transferred from Pd to M or the oxidant [O] and the reductant [H] would be coupled with each other. X, anionic ligands, such as chlorides and acetates.

Robert H. Grubbs *et al. Science*, **2011**, *333*, 1609.

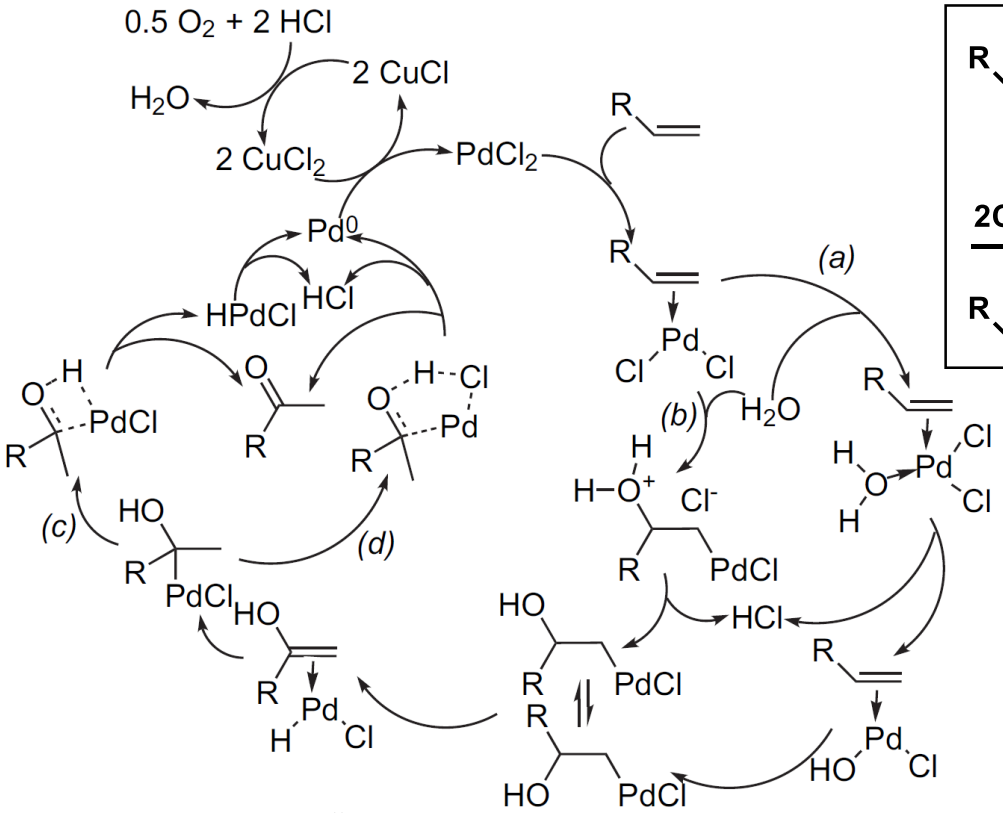
Introduction ~Wacker-Tsuji Oxidation~

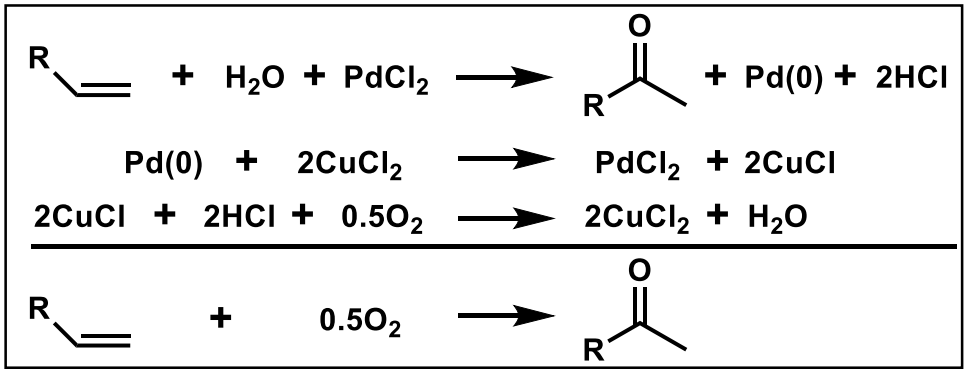
- 1894 F. C. Phillips reported stoichiometric reaction.
- 1959 J. Smidt *et al*. reported the Wacker process.

  (oxidation of ethylene to acetaldehyde)

Investigations for convenient laboratory methods

- 1976 J. Tsuji *et al.* reported $PdCl_2$, CuCl / DMF, H_2O method.





"*Terminal alkenes may be viewed as masked ketones*."

Jacques Muzart *Tetrahedron* **2007**, *63*, 7505.

DMF / H_2O System

TABLE I

CONVERSION OF 1-DODECENE TO 2-DODECANONE[a]

Run	Solvent: DMF, ml.	Solvent: water, ml.	1-Dodecene content of olefin, %	Yield,[b] %
1[c]		25	84	0
2	50	4	96	78
3	50	7	96	78
4	50	7	94	81
5	50	7	84	85
6	50	7	96	87
7	50	10	84	85
8	40	15	96	51
9	25	25	84	20

[a] Each experiment was carried out at 60–70° using 0.020 mole of $PdCl_2$, 0.020 mole of $CuCl_2 \cdot 2H_2O$, 0.20 mole of olefin, and an O_2 flow of 3.3 l./hr. In run 6 the olefin was added over a 3.5-hr. period; in all other cases the time of introduction was 2.5 hr. [b] Determined by v.p.c. [c] This experiment was stopped after 1.5 hr. as no reaction occurred.

DMSO, acetone, AcOH, THF, dioxane, MeCN were not good.

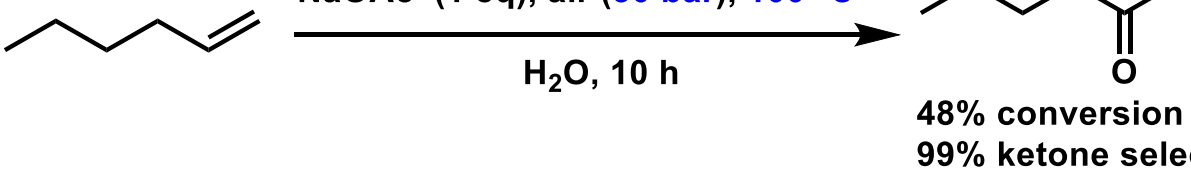
Charles M. Selwitz *et al. J. Org. Chem.* **1964**, *29*, 241.

$PdCl_2$ (10 mol%)
CuCl (1 eq)
→
DMF / H_2O = 8 / 1
O_2 (1 atm), rt

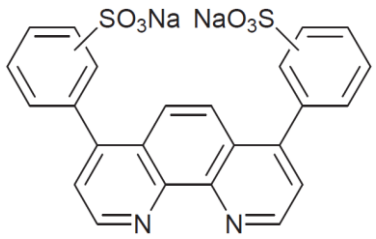
"$CuCl_2$ tends to chlorinate ketones."

Jiro Tsuji *et al.*
Tetrahedron Lett. **1976**, 2975.

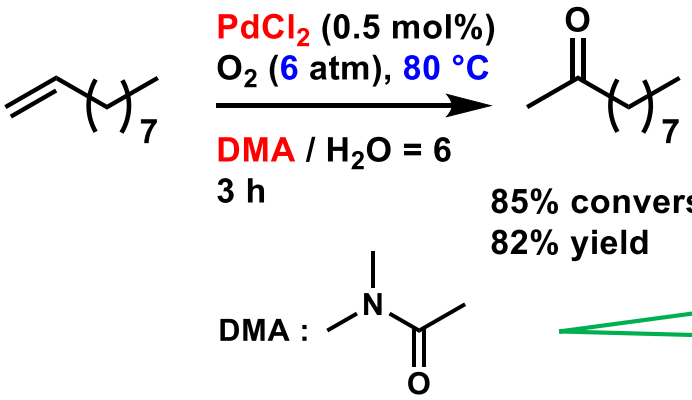
Development: Direct O_2-Coupled Wacker Oxidation



Ligand :



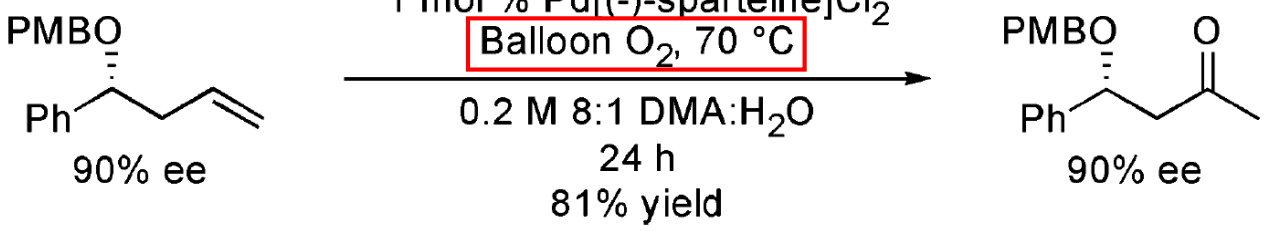
Roger A. Sheldon *et al. Chem. Commun*. **1998**, 2359.

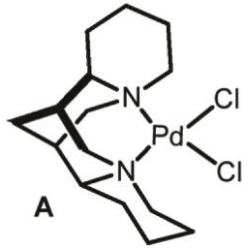


Pd cat. (1 mol%), O_2 (1 atm), 80 °C

Entry	Catalyst	Solvent	Yield [%][b]
1	$PdCl_2$	DMA	84
2	$PdCl_2$	NMP	74
3	$PdCl_2$	DMPA	33
4	$PdCl_2$	DMF	trace
5	$PdCl_2$	EtOH	trace
6	$PdCl_2$	MeCN	trace
7	$Pd(OAc)_2$	DMA	trace
8	$[PdCl_2(NH_3)_4]$	DMA	trace

Kiyotomi Kaneda *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 481.



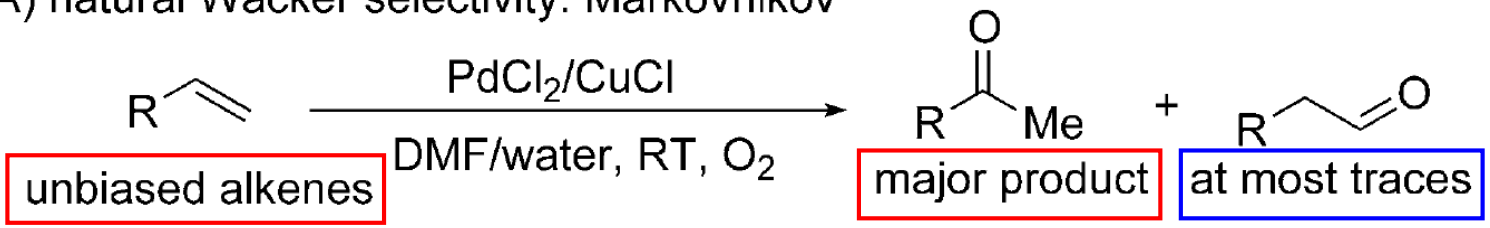


Pd[(-)-sparteine]Cl_2

Matthew S. Sigman *et al. Org. Lett*. **2006**, *8*, 4117.

Selectivity of Wacker Oxidation

A) natural Wacker selectivity: Markovnikov

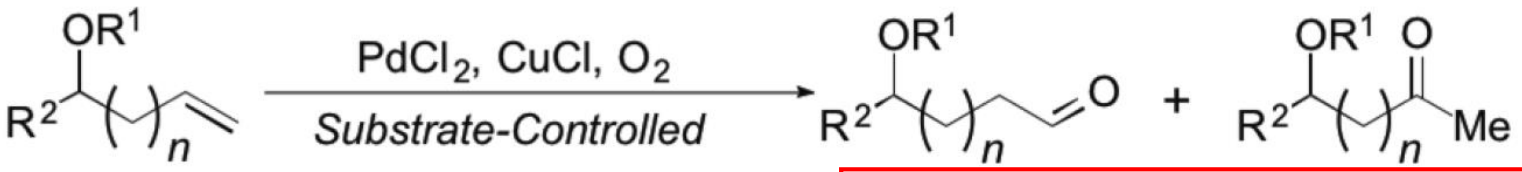


unbiased alkenes

major product

at most traces

A. Traditional Tsuji–Wacker Oxidation



With directing group

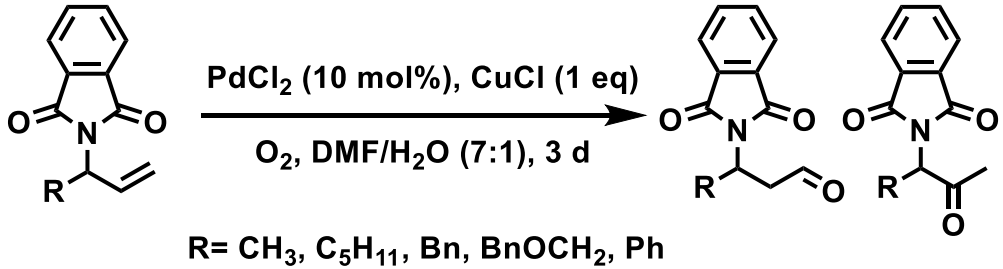
selectivity difficult to predict *a priori*

Catalyst-controlled selectivity is required.

Robert H. Grubbs *et al. J. Am. Chem. Soc.* **2014**, *136*, 890.

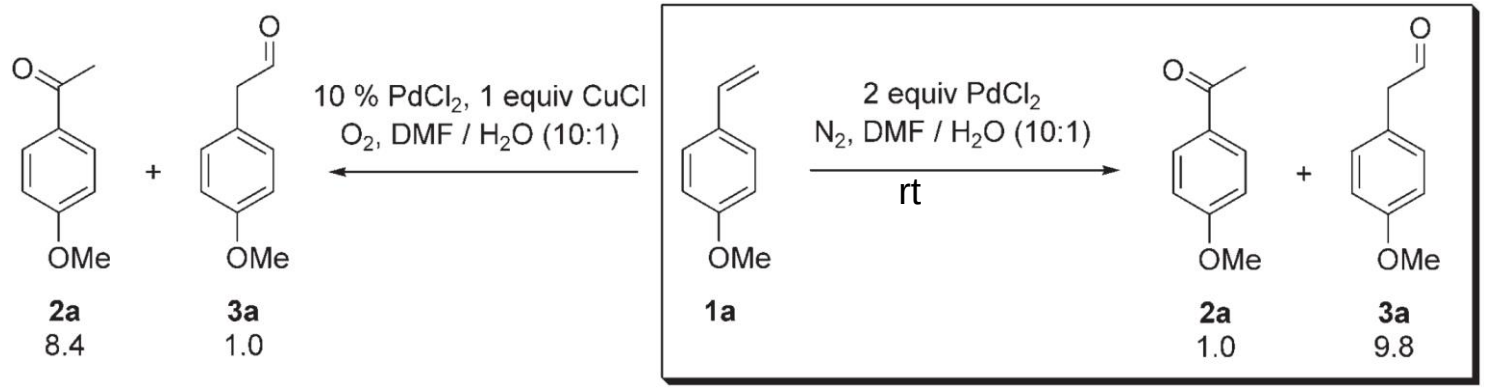
Anti-Markovnikov Wacker Oxidation Strategies

- with Directing Groups

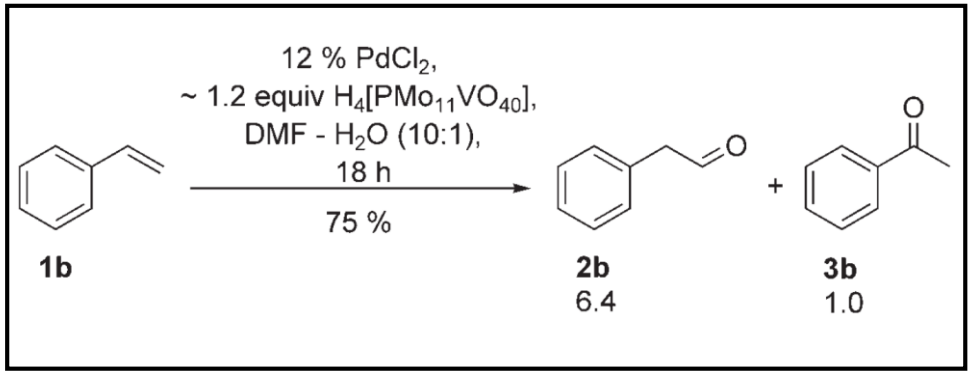


Ben L. Feringa *et al*. *J. Am. Chem. Soc.* **2009**, *131*, 9473.

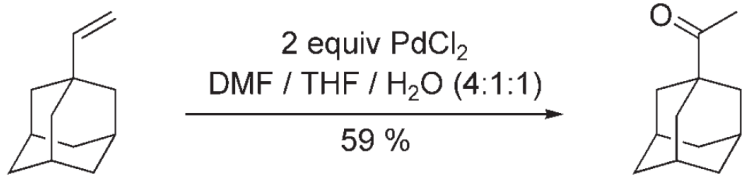
- with Stoichiometric Palladium or Excess Heteropolyacid



Other Pd(II) such as $Pd(OAc)_2$ and $Pd(NO_3)_2$ gave exclusively the methyl ketone.



Aromatic group was crucial.

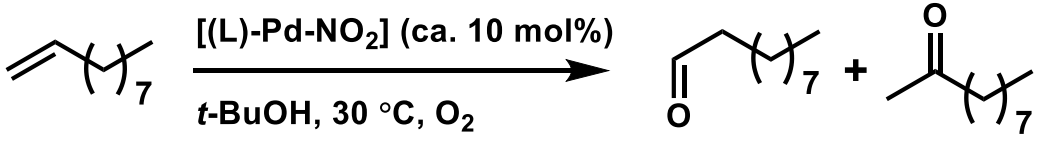


Jonathan B. Spencer *et al. Chem. Eur. J*. **2006**, *12*, 949.

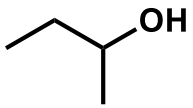
• Catalyst-Controlled (or Solvent-Controlled?)

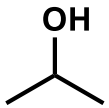
$Pd(CH_3CN)_2ClNO_2$ + $CuCl_2$ —(*t*-BuOH, 55 °C)→ [(L)-Pd-NO_2] brown solid

1 : 4~4.5



y. 27% 60 / 40

solvent:  y. 20% 38 / 62

 y. 73% 0 / 100

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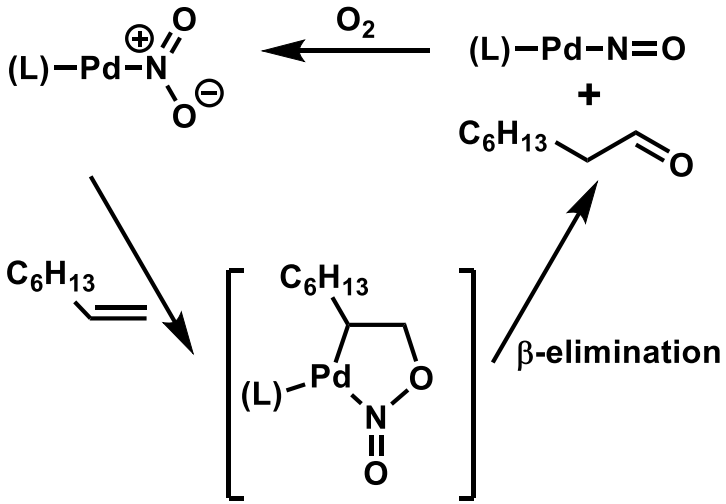
additive: KNO_2 (45 mol%) → y. 10% 70 / 30

$Pd cat. : CuCl_2 = 1 : 1$ → y. 68% 18 / 82

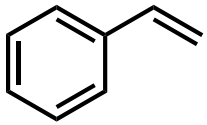
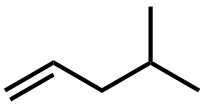
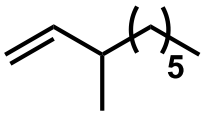
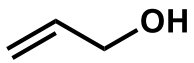
without $CuCl_2$ → y. 3% 0 / 100

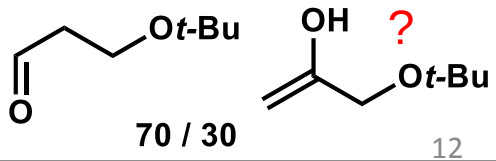
$Pd(CH_3CN)_2Cl_2$ instead of $Pd(CH_3CN)_2ClNO_2$ → No Oxidation

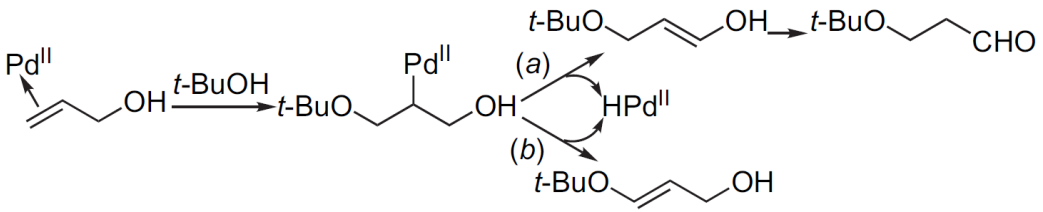
Proposed Mechanism



Substrate Scope

	aldehyde / ketone
	y. 9% 100 / 0
	y. 13% 60 / 40
	y. 18% 18 / 82
	y. 73%



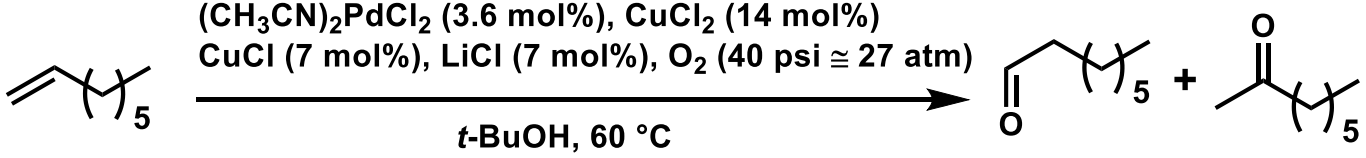


Jacques Muzart *Tetrahedron* **2007**, *63*, 7505.

Ben L. Feringa *J. Chem. Soc., Chem. Commun.* **1986**, 909.

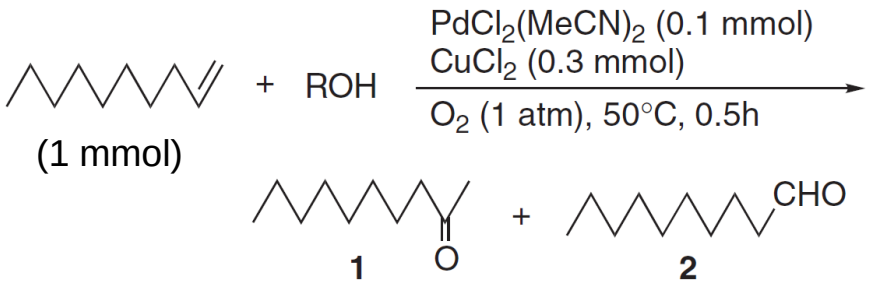
$Pd(CH_3CN)_2ClNO_2 + CuCl_2 \xrightarrow[t\text{-BuOH}]{} t\text{-BuONO}$

Tert-butyl nitrite tends to lower the aldehyde selectibity.

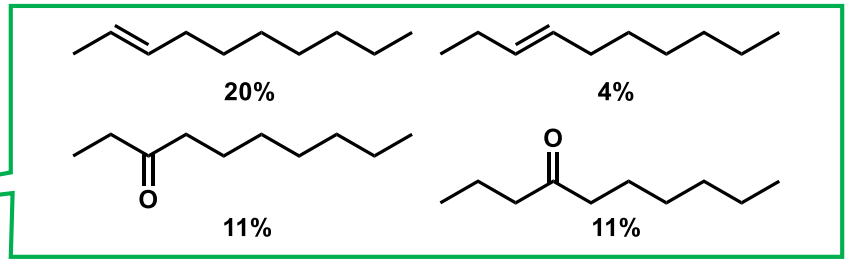


	t (h)	conversion (%)	yield ald + ket (%)	ald / ket
	0.5	12	8	30 / 70
	3	49	38	31 / 69
no CuCl	0.5	4	1	57 / 43
no CuCl	3	56	39	28 / 72

Timothy T. Wenzel *J. Chem. Soc., Chem. Commun.* **1993**, 862.



R	Yield / %	1 : 2
Me	26	97 : 3
Et	22	84 : 16
i-Pr	11	58 : 42
t-Bu	7	16 : 84



Similar Trends

No Isomerization

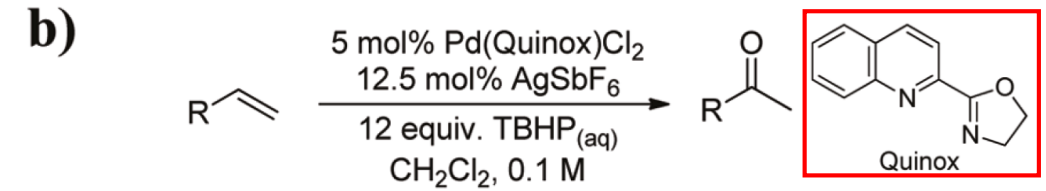
High Selectivity
Low Yield

Scheme 1.

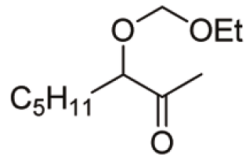
The use of LiCl and/or CuCl reduced the regioselectivity.

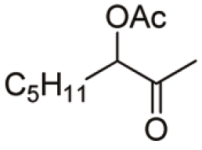
Takahiro Hosokawa *et al*. *Bull. Chem. Soc. Jpn.* **2005**, 78, 1555.

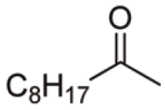
Ketone-Selective Wacker-Type Oxidation

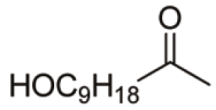


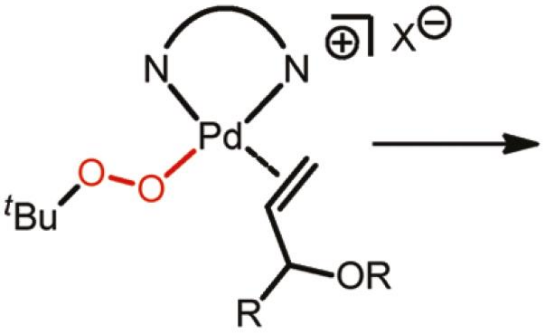
bidentate ligand to discourage substrate chelation

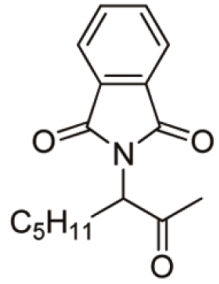

81% yield
4 h

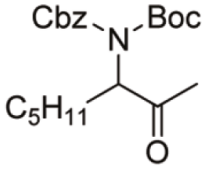

89% yield
20 h

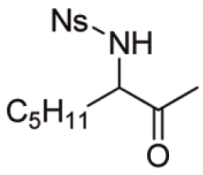

86% yield
20 min
2 mol% catalyst

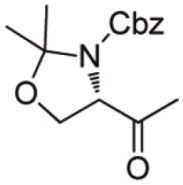

91% yield
40 min
1 mol% catalyst

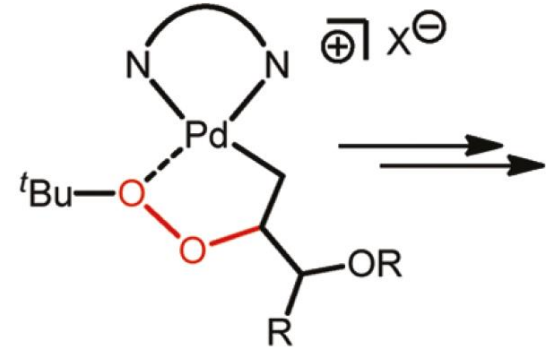



91% yield
19 h


76% yield
14 h


88% yield
4 h


69% yield
16 h



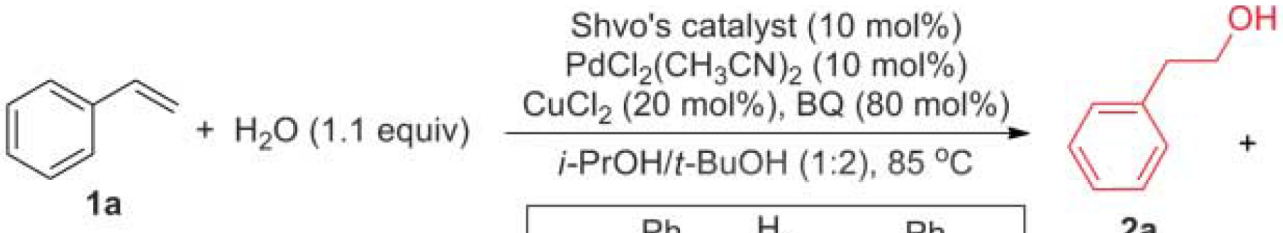
Catalyst-Controlled!!

syn addition of TBHP to encourage Markovnikov addition

Matthew S. Sigman *et al. J. Am. Chem. Soc.* **2009**, *131*, 6076.
Matthew S. Sigman *et al. J. Am. Chem. Soc.* **2011**, *133*, 8317.
Matthew S. Sigman *et al. Acc. Chem. Res.* **2012**, *45*, 874.

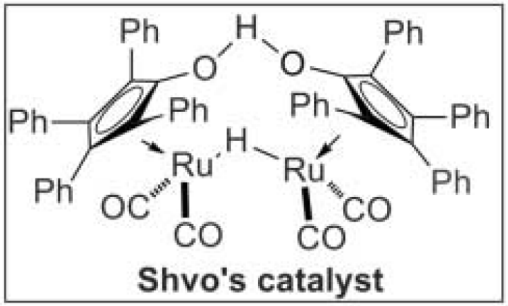
Contents

General Reaction Scheme



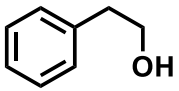
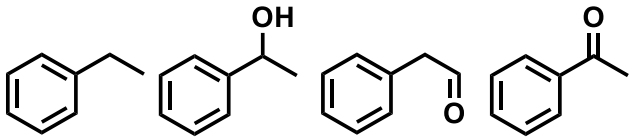
(5)

about Shvo's catalyst, see:
Chem. Rev. **2010,** *110,* 2294.

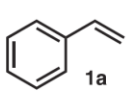
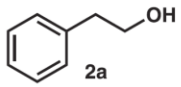
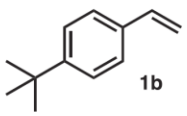
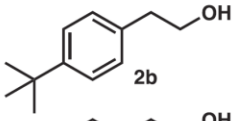
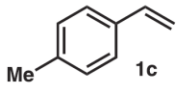
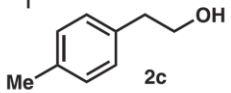
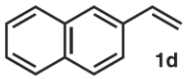
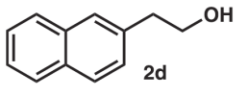
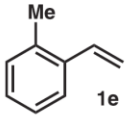
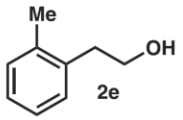
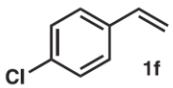
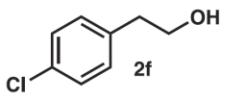
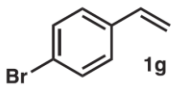
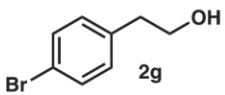


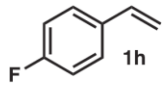
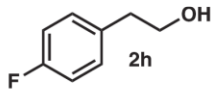
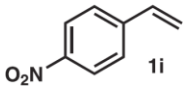
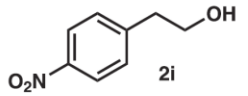
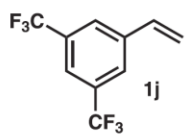
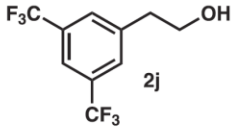
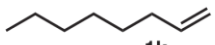
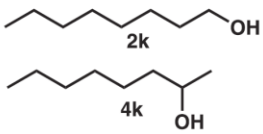
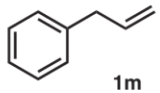
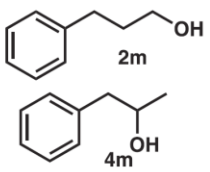
$$\text{Anti-Markovnikov selectivity} = \frac{[\,1^{o}\text{ alcohol}] + [\text{aldehyde}]}{[\,2^{o}\text{ alcohol}] + [\text{ketone}]} = 38 \quad (6)$$

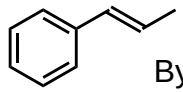
- Control Experiments

Change	Conversion (%)	Yield (%) ()	Yield of byproduct (%) ()			
None	89	77	1.3	0.7	1.5	1.4
No $PdCl_2(CH_3CN)_2$	34	0	26	0	0	0
No Shvo's catalyst	80	0	0.2	0	42	0
No $CuCl_2$	>99	48	32	5.9	0.5	1.4
No BQ	58	0	0.9	0	0	0
No *i*-PrOH	88	0	0.5	0	57	0
No *t*-BuOH	48	18	2.0	trace	trace	trace
No *t*-BuOH, but 28 equiv H_2O	75	64	2.0	4.9	0.96	9.9
Replace H_2O with 4A MS	>99	0	57	0	0	0

Substrate Scope

Entry	Substrate	Product	Yield	Selectivity (1°OH : 2° OH)#
1	 1a	 2a	61% (GC yield 65%)* 84% (GC yield 83%)‡	≥ 20:1
2	 1b	 2b	42%†	≥ 20:1
3	 1c	 2c	61%†	≥ 20:1
4	 1d	 2d	60%‡	≥ 20:1
5	 1e	 2e	72%†	≥ 20:1
6	 1f	 2f	75%‡	≥ 20:1
7	 1g	 2g	72%†	≥ 20:1

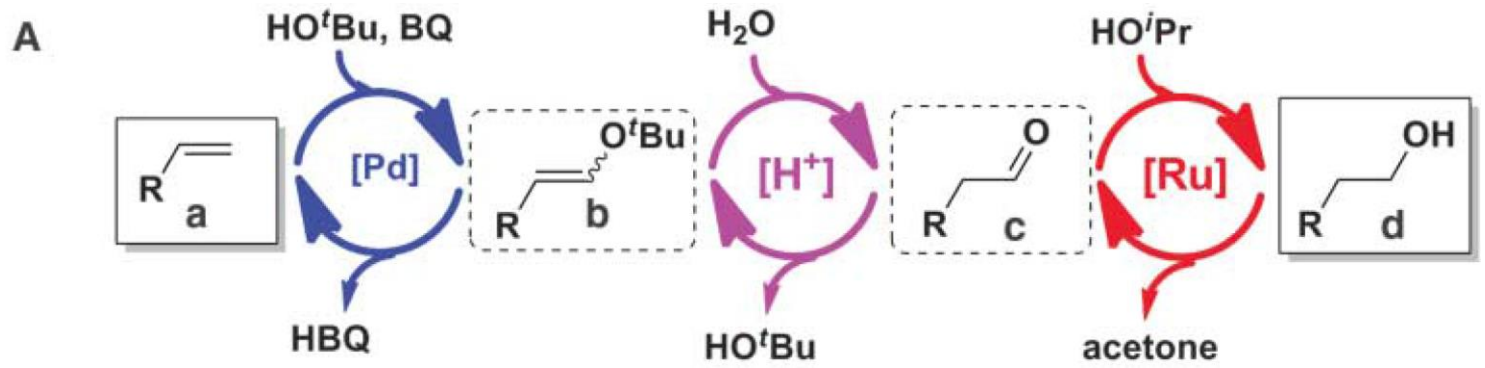
Entry	Substrate	Product	Yield	Selectivity (1°OH : 2° OH)#
8	 1h	 2h	63%* 84%‡	≥ 20:1
9	 1i	 2i	83%‡	≥ 20:1
10	 1j	 2j	74%†	≥ 20:1
11	 1k	 2k 4k	56%‖,§ (**2k**:**4k** = 1:1.4) 54%¶,§ (**2k**:**4k** =1:1.9)	
12	 1m	 2m 4m	12%‡ (**2m**) (**2m**:**4m** =1:2.1)#	

 Major Byproduct

*Isolated yield and [C] (initial substrate concentration) = 0.25 M. †Isolated yield and [C] = 0.125 M. ‡Isolated yield, [C] = 0.067 M, and 1 equiv of BQ was employed. §Attempted purification through column chromatography; yield was determined via ^{1}H-NMR using mesitylene as the internal standard. ‖*i*-PrOH:*t*-BuOH = 1:1, [C] = 0.067 M, and 1 equiv of BQ. ¶*i*-PrOH:*t*-BuOH = 1:2, [C] = 0.067 M, and 1 equiv of BQ. #The ratio was determined via ^{1}H-NMR analysis of the crude reaction mixture.

Triple Relay Catalysis System

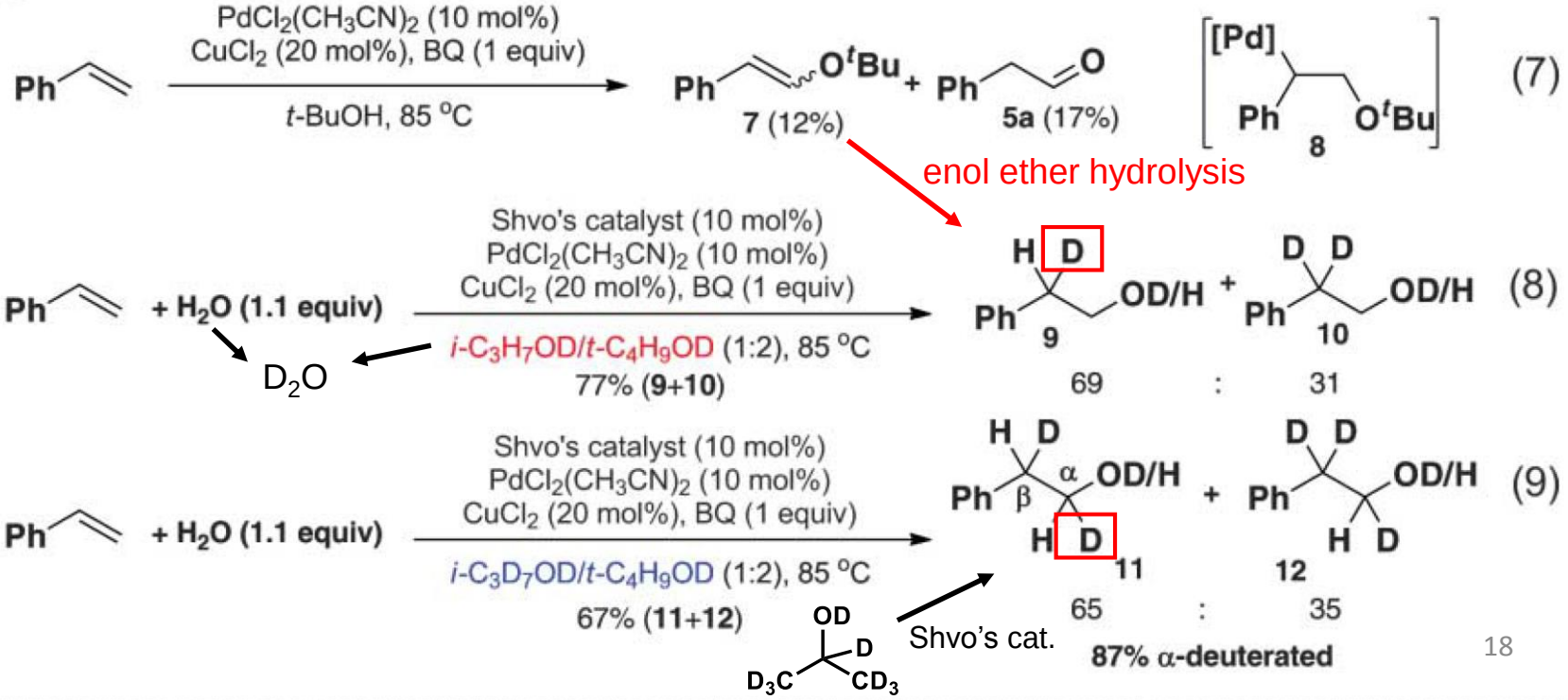
- Proposed Mechanism



- Initial Mechanistic Study

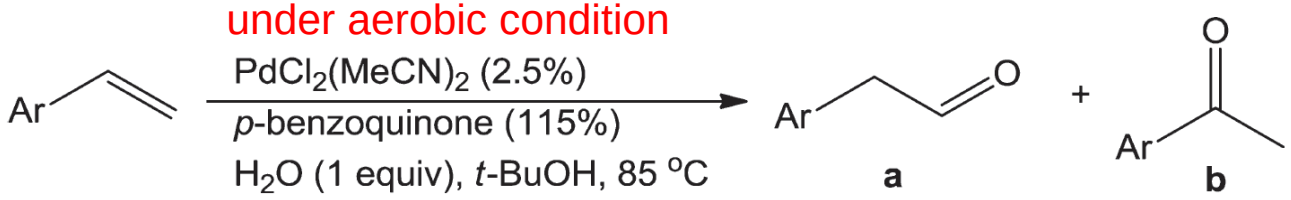
B

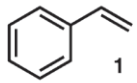
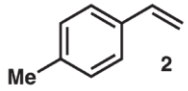
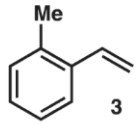
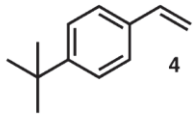
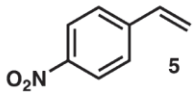
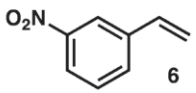
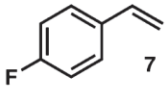
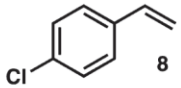
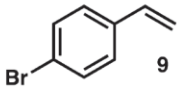
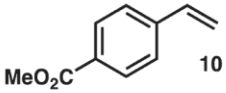
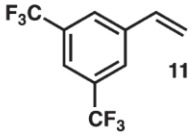
without H_2O, IPA, Shvo's cat.



Aldehyde Selective Wacker Oxidation

under aerobic condition



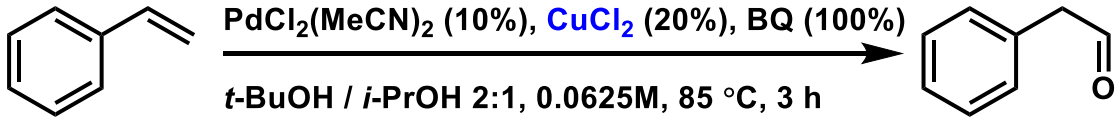
entry	substrate	aldehyde (a) yield[b]	selectivity[c]
1		83 (90[d])	98 (97[d])
2		81	97
3		90	96
4		42	98
5		96	99
6		96	> 99
7		74	99
8		92	99
9		90	99
10		59	96
11		72	99

[a] Reactions carried out with 2.5 mol % catalyst loading in 0.125 M solution for 60 min at 85 °C. [b] Isolated aldehyde (**a**) yield (%) (as 2,4-dinitrophenylhydrazone derivative (**c**)). [c] (**c**)/(**c** + **d**) (%). [d] GC yield and selectivity of aldehyde (**a**).

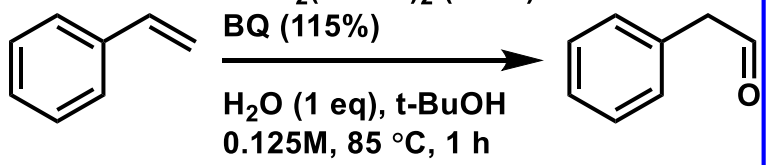
Robert H. Grubbs *et al. Org. Lett.* **2012**, *14*, 3237.

Aldehyde Selective Wacker Oxidation

Previous condition without reductants



36% yield, 100% selectivity
(cf. 85% anti-Malkovnikov products in hydration)



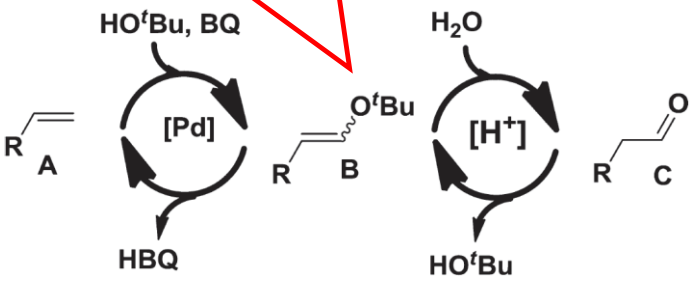
2.5 mol% $CuCl_2$ → 10% lower yield
because of the increase in acidity?

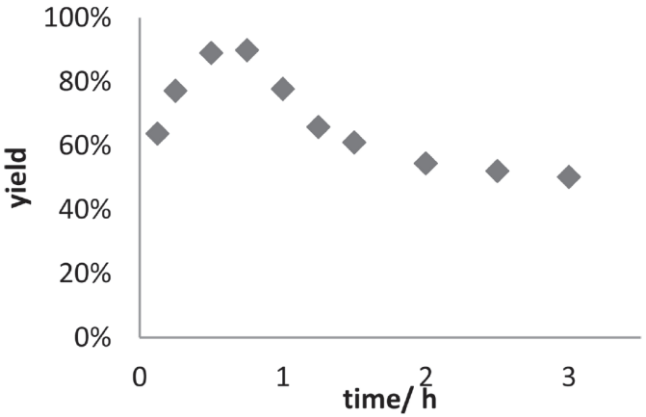
Table 1. Styrene Oxidation Control Experiments[a]

BQ/%	solvent	H_2O/%	yield/%	selectivity/%[b]
115	*t*-BuOH	110	83	98
115	*i*-PrOH	110	40	74
0	*t*-BuOH	110	5	100
115	*t*-BuOH	0	38	95

[a] Reactions carried out in 0.125 M solution (0.1 mmol) with 2.5 mol % catalyst loading at 85 °C. [b] Selectivity and yield determined by GC with tridecane as internal standard.

The bulkiness of *t*-BuOH is important for aldehyde-selectivity.

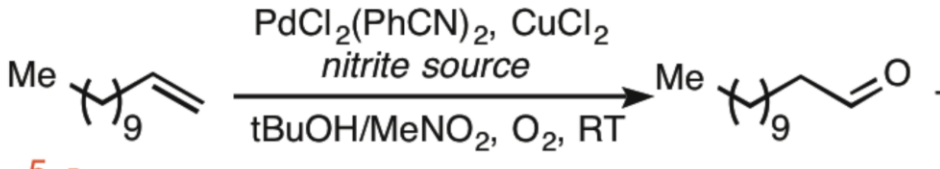




Product yield starts decreasing likely due to self-condensation.

Figure 1. Aldehyde yield (%) as a function of reaction time (h) for styrene Wacker on 0.1 mmol scale.

Catalyst-Controlled Wacker-Type Oxidation



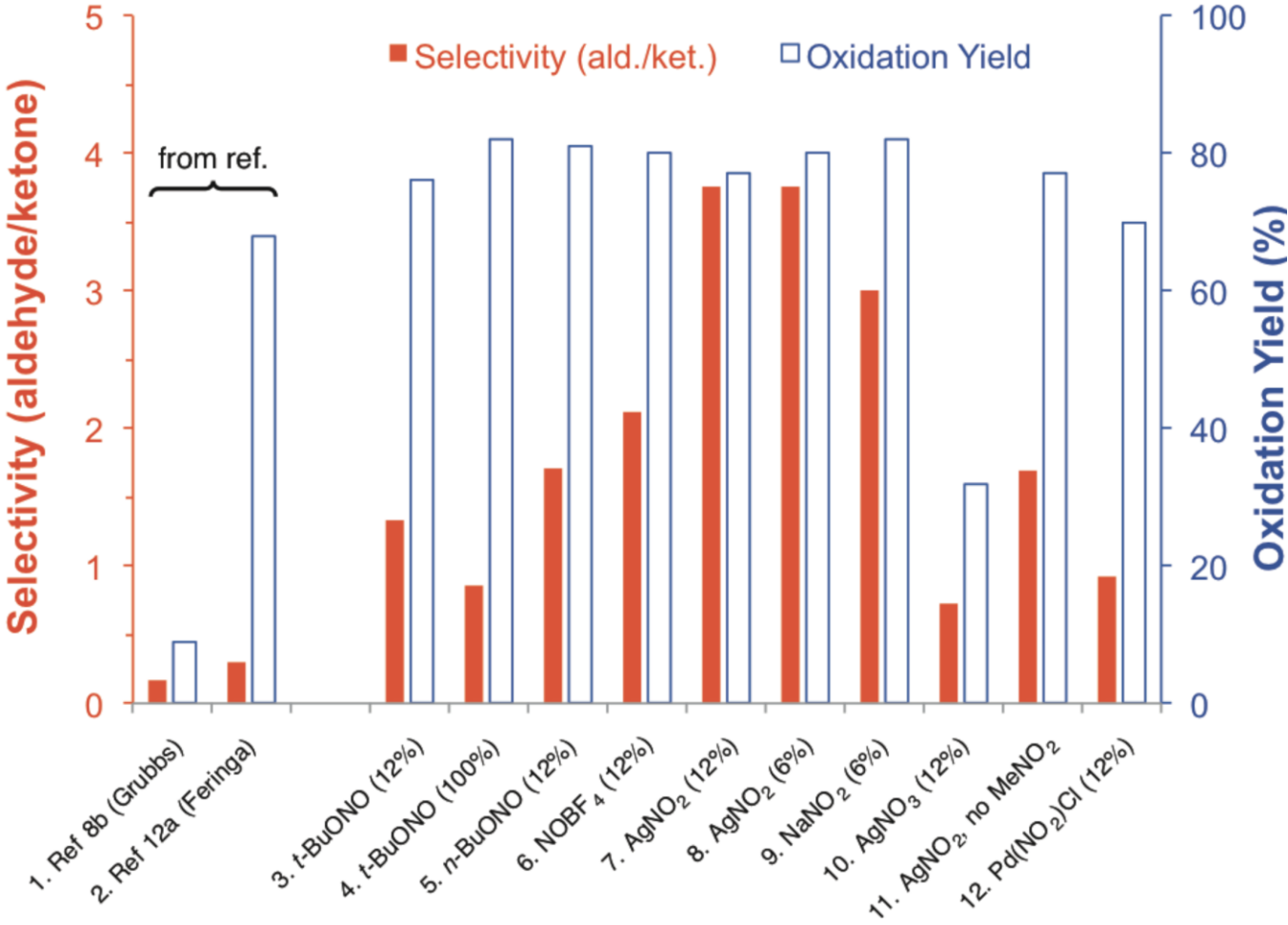


Figure 1. Catalyst optimization. Entries 3–12: 1-dodecene (0.2 mmol), $[PdCl_2(PhCN)_2]$ (12 mol%), and $CuCl_2 \cdot 2H_2O$ (12 mol%) were used. Entry 12: $[PdCl_2(PhCN)_2]$ was replaced by $[PdNO_2Cl(MeCN)_2]$.

- Without t-BuOH (only $MeNO_2$), no conversion was observed.

- Entry 1

$PdCl_2(MeCN)_2$ (2.5%)
p-benzoquinone (115%)
H_2O (1 equiv), *t*-BuOH, 85 °C

- Entry 2

$(MeCN)_2PdClNO_2$ - $CuCl_2$
(10 mol% : 40 mol%)

***t*-BuOH, 30 °C, 2.06 h**

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Detailed Yield & Selectivity

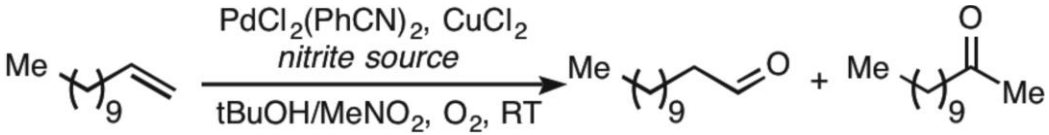


Table S1. Nitrite sources

entry	Nitrite source	Overall yield (aldehyde yield)	aldehyde/ketone (% selectivity)
1	Ref 8b (Grubbs)	9 (<1)	.16 (14)
2	Ref 12a (Feringa)	68 (12)	.22 (18)
3	*tert*-BuONO	76 (43)	1.3 (57)
4	*tert*-BuONO[a]	82 (38)	.85 (46)
5	*n*-BuONO	81 (51)	1.7 (63)
6	$NOBF_4$	80 (54)	2.1 (68)
7	$AgNO_2$	77 (61)	3.8 (79)
8	$AgNO_2$[b]	80 (63)	3.8 (79)
9	$NaNO_2$[b]	82 (62)	3 (75)
10	$AgNO_3$	32(13)	.72 (42)
11	$AgNO_2$[c]	77 (49)	1.7 (63)
12	$PdNO_2Cl(MeCN)_2$[d]	70 (34)	.9 (48)

[a]1 equiv *tert*-BuONO used instead of 12%. [b]6% nitrite used [c]$MeNO_2$ was omitted and reaction run at 30 ºC. [d]No $PdCl_2(PhCN)_2$

- Entry 1

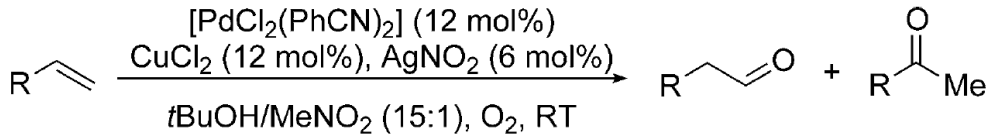
$PdCl_2(MeCN)_2$ (2.5%)
p-benzoquinone (115%)
H_2O (1 equiv), *t*-BuOH, 85 °C

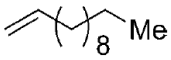
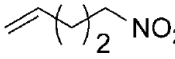
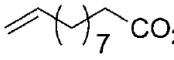
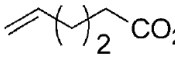
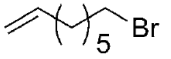
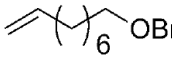
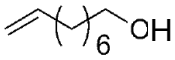
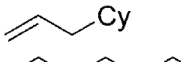
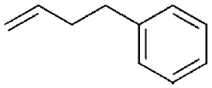
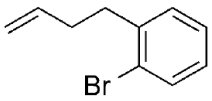
- Entry 2

$(MeCN)_2PdClNO_2$ - $CuCl_2$
(10 mol% : 40 mol%)

***t*-BuOH, 30 °C, 2.06 h**

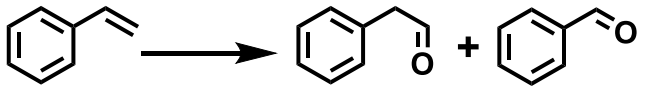
- Substrate Scope



Entry	Substrate	Yield of oxidation (aldehyde)[b] [%]	Sel.[c] [%]
1		80 (63)[d]	79
2		74 (61)	79
3		78 (70)	89
4		72 (59)	79
5		68 (51)[e]	67
6		77 (65)	82
7		70 (59)	81
8		80 (45)	57
9		75 (60)[e]	80
10		77 (69)	89
11		71 (64)[e]	90

[a] Alkene (0.5 mmol) treated with $[PdCl_2(PhCN)_2]$ (12 mol%), $CuCl_2 \cdot 2H_2O$ (12 mol%), and $AgNO_2$ (6 mol%) in *t*BuOH/$MeNO_2$ (15:1, 8 mL) under O_2 atmosphere (1 atm) at 20–25 °C. [b] Yield of isolated aldehyde. Overall yield (of oxidation) calculated using selectivity. [c] Selectivity determined by ^1H NMR analysis. [d] Yield and selectivity both determined by GC analysis. [e] Yield determined by ^1H NMR analysis.

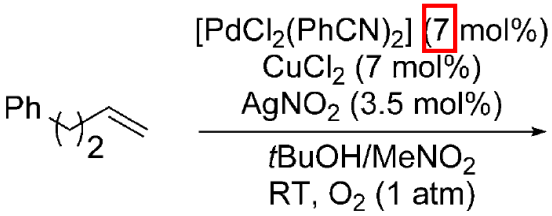
With styrene…

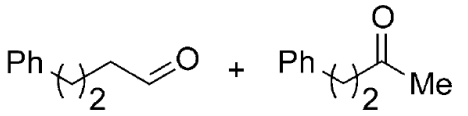


47% yield **12% yield**
(≥20:1 selectivity)

Intermolecular Markovnikov Attack
+
Hydrolysis

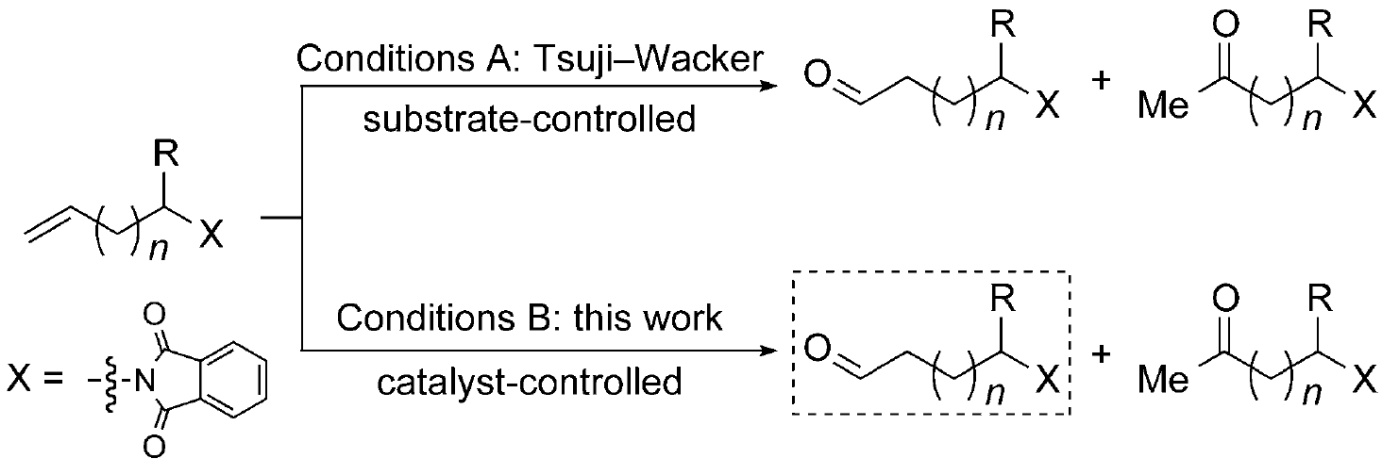
- Aldehyde-Selective Wacker Oxidation on a 10 mmol Scale with Reduced Catalyst Loading





71% overall yield
85% aldehyde selectivity
gram scale (10 mmol)

Comparison of Innate Selectivity

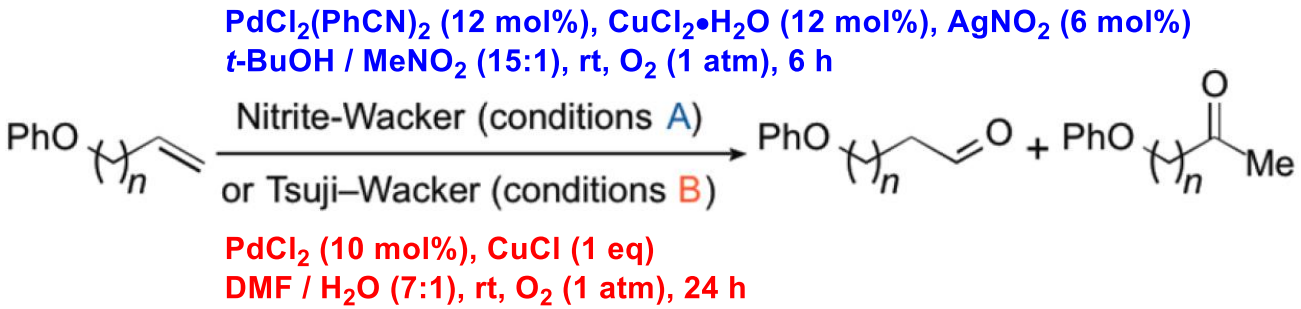


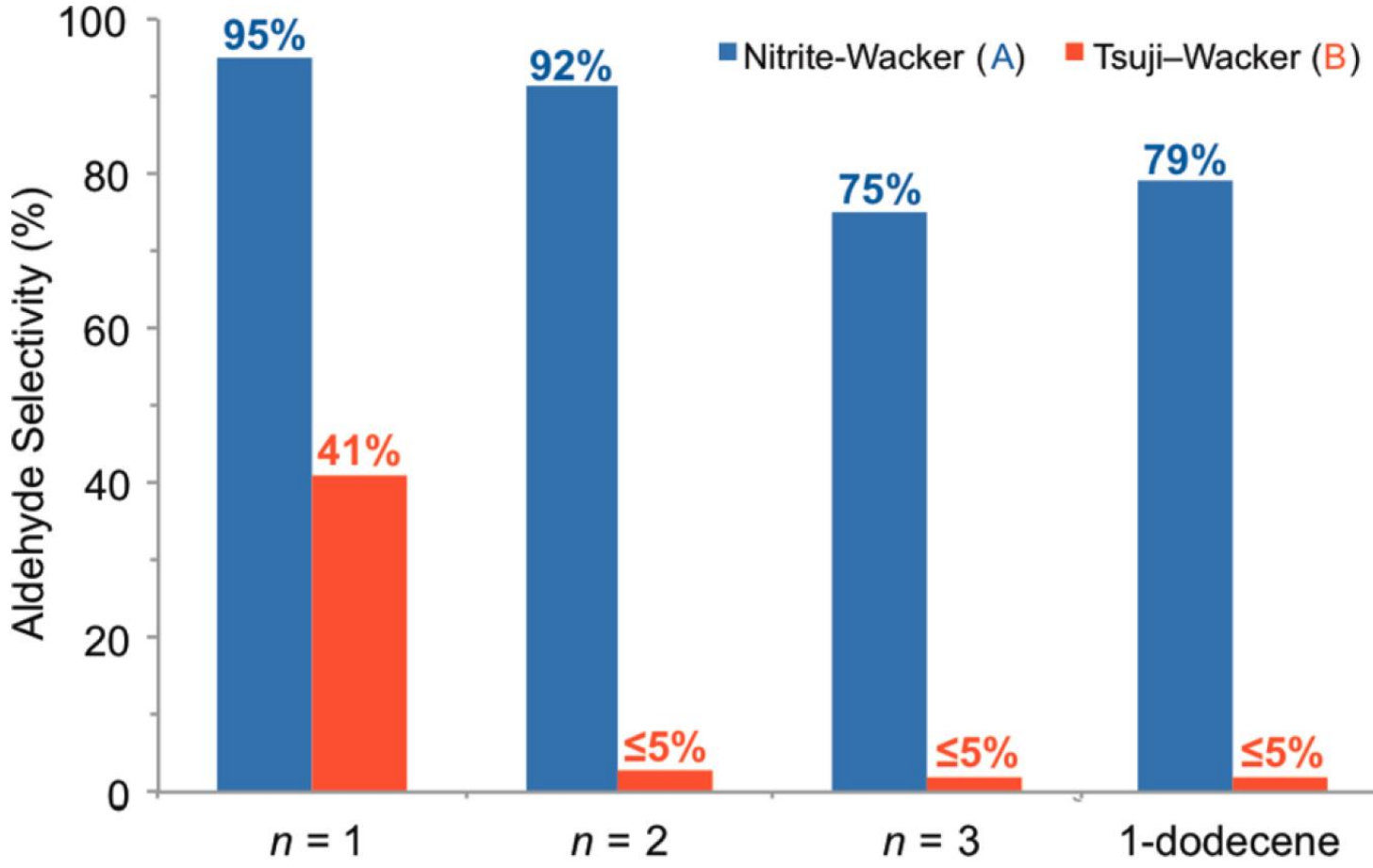
Substrate	Conditions A selectivity	Conditions B selectivity (yield)
n = 0, R = Me	**99**:1	**99**:1 (79)
n = 0, R = H	**60**:**40**	**98**:2 (75)
n = 1, R = H	15:**85**	**90**:10 (77)

without assistance from a Thorpe-Ingold effect

Scheme 3. Comparison of innate selectivity (conditions A) to catalyst-controlled selectivity (conditions B). Conditions A: (Ref. [4b]) $PdCl_2$ (10–30 mol%), CuCl (1 equiv), DMF/H_2O (7:1), RT, O_2 (1 atm). Conditions B: alkene (0.5 mmol), [$PdCl_2(PhCN)_2$] (12 mol%), $CuCl_2$ (12 mol%), $AgNO_2$ (6 mol%), *t*BuOH/$MeNO_2$ (15:1), RT, O_2 (1 atm). Aldehyde yield determined after purification. Selectivity determined by ^{1}H NMR analysis prior to purification.

Influence of PhO-Proximity





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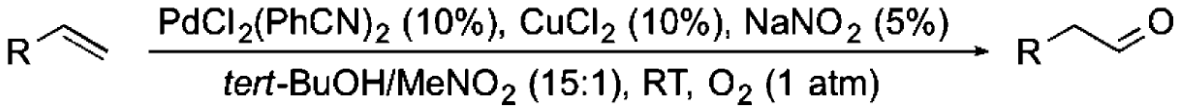
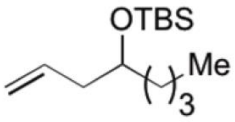
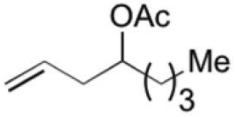
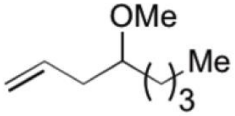
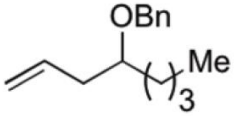
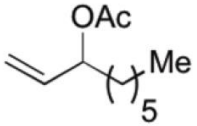
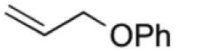
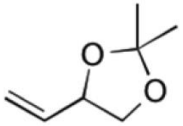
Influence of Oxygen Functionality

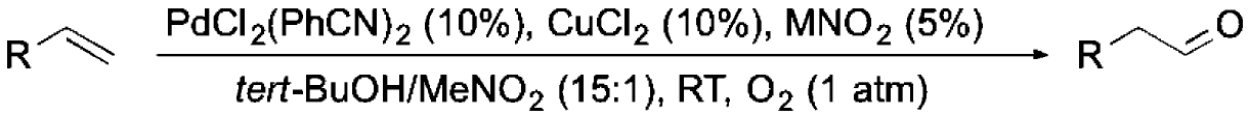


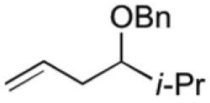
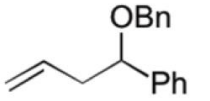
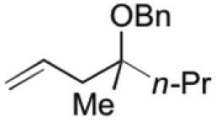
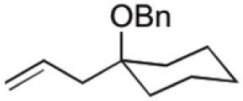
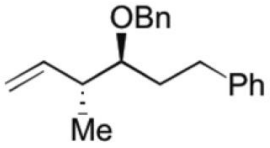
Entry	Substrate	Oxidation Yield (Aldehyde Yield)[b]	Selectivity[c]	Innate Selectivity (Tsuji-Wacker)[d]
			aldehyde / ketone	
1		76%	90:10	4:96
2		76%	90:10	20:80
3		71%[e]	92:8	9:91
4		88%	91:9	3:97
5		85%	94:6	7:93
6[f]		75%[e]	94:6	64:46
7		82%	96:4	41:59
8		64%[e]	92:8	86:14

[a]0.5 mmol of alkene (0.0625 M), 5 h. [b]Yield of isolated aldehyde product. [c]Selectivity (aldehyde/ketone) obtained by ^{1}H NMR analysis of the unpurified reaction mixture. [d]Reaction conditions:[1b] 0.1 mmol of alkene, $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF/H_2O (7:1, 0.125M), rt (20−25 °C), run to ≥95% conversion. [e]Yield determined by ^{1}H NMR analysis of the unpurified reaction mixture. [f]$AgNO_2$ used in place of $NaNO_2$.

Catalyst-Controlled Regioselectivity

Influence of Steric Profile

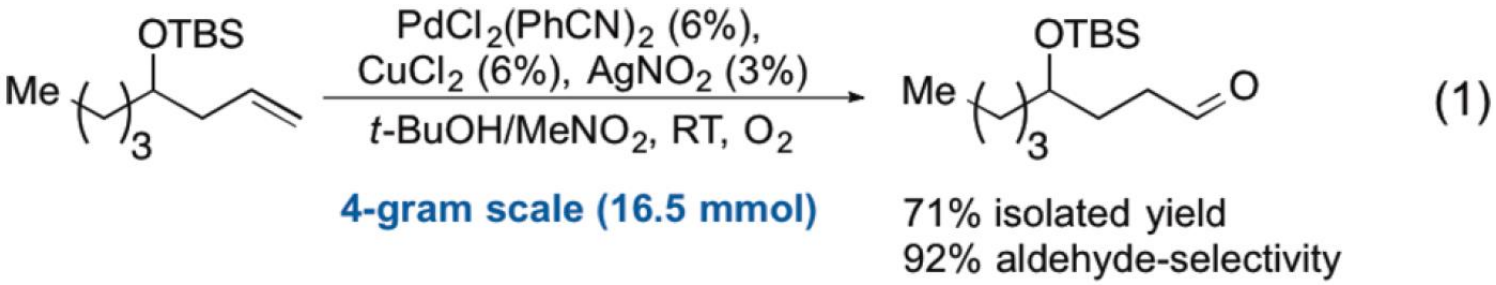


Entry	Substrate	Nitrite Source	Aldehyde Yield[b]		Selectivity[c]	Innate Selectivity (Tsuji–Wacker)[d]
1		$NaNO_2$	80%		**93**:7	7:**93**
2		$NaNO_2$	74%		**94**:6	20:**80**
3		$NaNO_2$	51%[e]		**93**:7	9:**91**
4		$AgNO_2$	77%[f]		**90**:10	–
5		$NaNO_2$	37%[e]	5 h	**95**:5	8:**92**
6[g]		$NaNO_2$	75%[e]	24 h	**88**:12	–
7[g]		$AgNO_2$	77%	24 h	**95**:5	–
8		$NaNO_2$	38%[e]	5 h	**66**:34	10:**90**
9[g]		$AgNO_2$	65%	24 h	**75**:25	–

[a]0.5 mmol of alkene (0.0625 M), 5 h. [b]Yield of isolated aldehyde product. [c]Selectivity (aldehyde/ketone) obtained by ^{1}H NMR analysis of the unpurified reaction mixture. [d]0.1 mmol of alkene, $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF/H_2O (7:1, 0.125 M), rt (20–25 °C), run to ≥95% conversion (24 h). Selectivity determined by ^{1}H NMR analysis. [e]Yield determined by ^{1}H NMR analysis. [f]Isolated as an inseparable mixture of aldehyde and ketone. [g]24 h reaction time

Applicability of Nitrate-Modified Wacker Oxidation

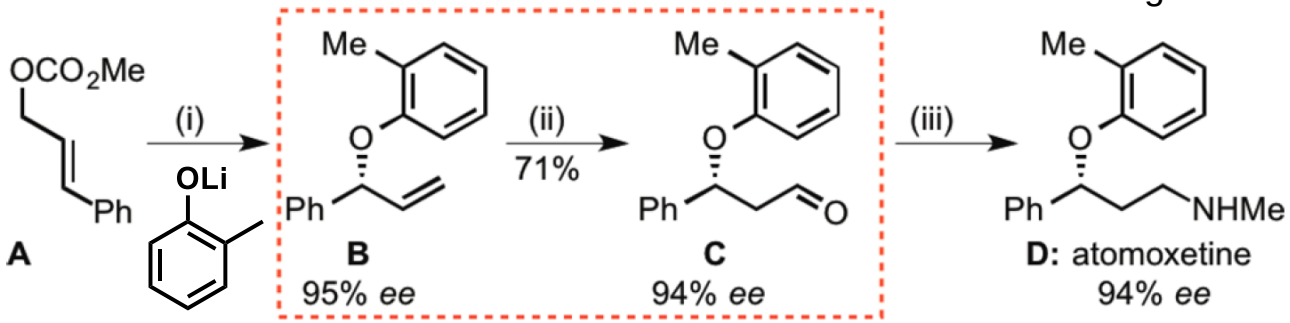
- On a Larger Scale



- Synthesis of Atomoxetine

Retention of Stereochemical Information

Drug for the treatment of ADHD

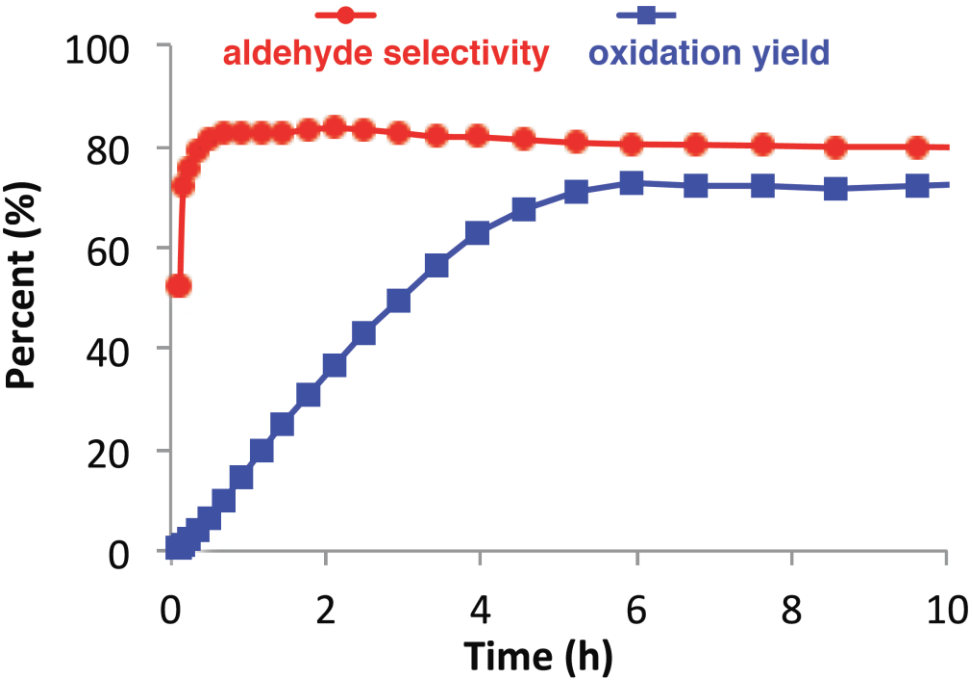


[a](i) $[Ir(COD)Cl]_2$ (1 mol %), (*R*,*R*,*R*)-(3,5-dioxa-4-phospha-cyclo-hepta[2,1-a;3,4-a′]dinaphthalen-4-yl)bis(1-phenylethyl)amine (2 mol %), THF, 50 °C, 16 h; (ii) $PdCl_2(PhCN)_2$ (10%), $CuCl_2 \cdot 2H_2O$ (10%), $AgNO_2$ (5%), *t*-BuOH/$MeNO_2$ (15:1), O_2 (1 atm), rt, 5 h; (iii) $NaBH_3CN$ (2 equiv), $MeNH_3Cl$ (excess), rt, 24 h.

about Ir catalyst, see John F. Hartwig *et al*. *J. Am. Chem. Soc.* **2003**, *125*, 3426.

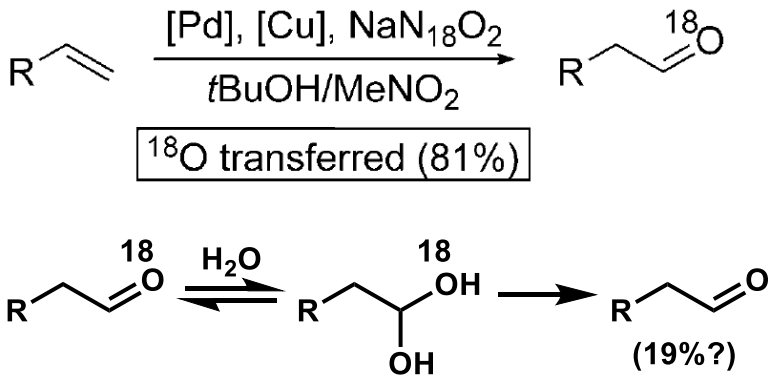
Preliminary Mechanistic Insight

Figure 2. Reaction profile of nitrite-modified Wacker oxidation to assess stability of aldehyde-selective catalytically active species.

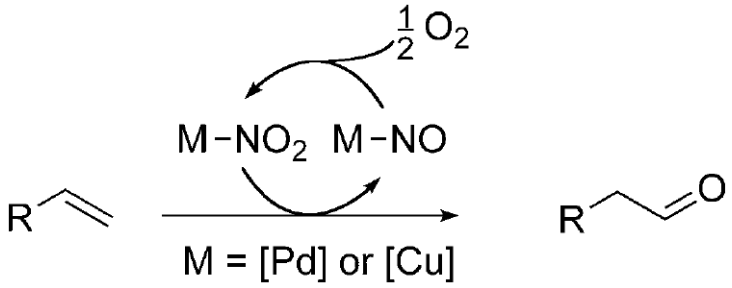


- ✓ Brief induction period
- ✓ The same catalytic species remains active.

· Stoichiometric ^{18}O-Labeling Experiment



· Plausible Mode of Oxygen Transfer



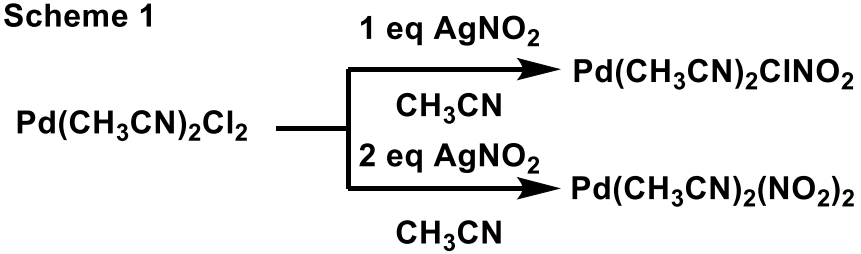
Robert H. Grubbs *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 11257.

Oxidation of Olefins with Nitro-Nitrosyl Redox Couple

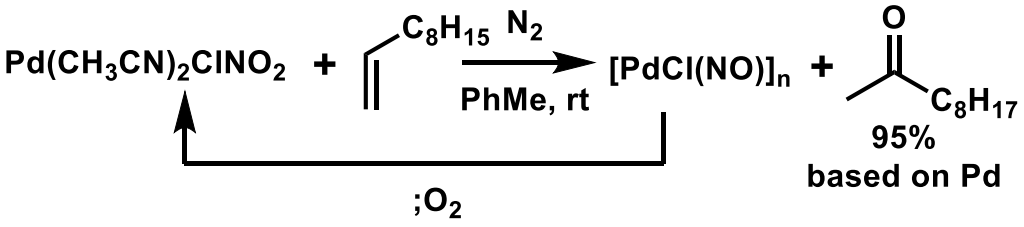
- Transition-Metal Nitro-Nitrosyl Redox Coupling

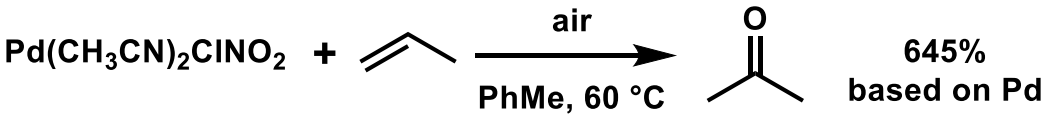
$$M\text{–}NO_2 + L \rightarrow M\text{–}NO + L\text{–}O$$
$$M\text{–}NO + {}^1/_2O_2 \rightarrow M\text{–}NO_2$$
$$L + {}^1/_2O_2 \rightarrow L\text{–}O$$

Scheme 1

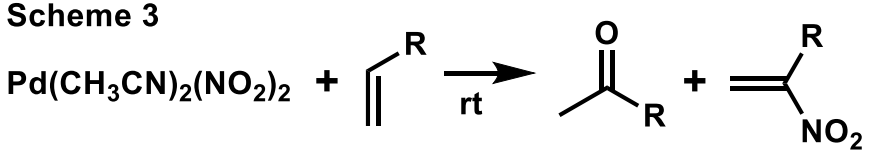


Scheme 2





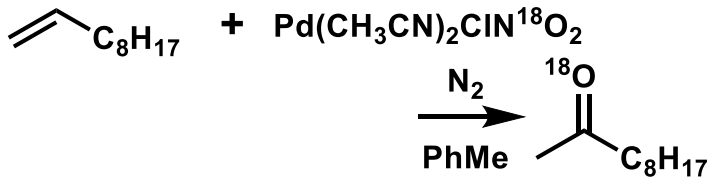
Scheme 3



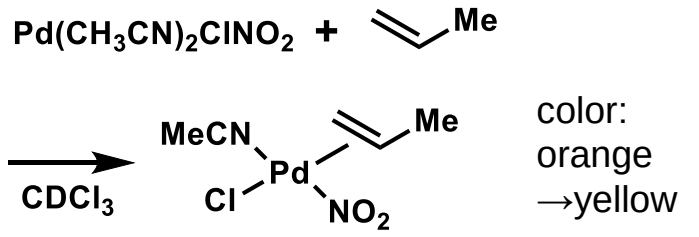
PhMe	1	:	11 (total 110%)
Me_2CO	7	:	1 (total 108%)

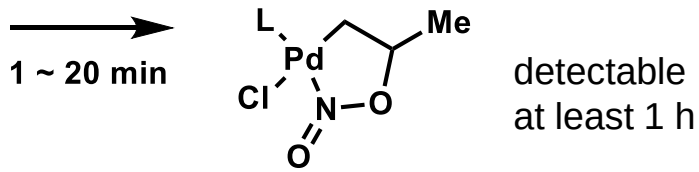
based on Pd

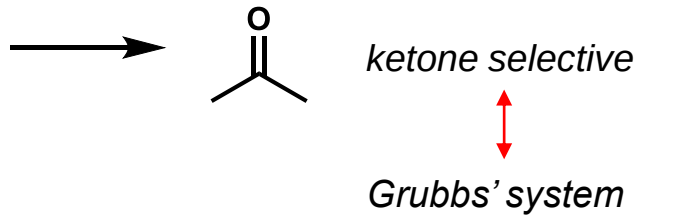
^{18}O-Labeling Experiment



IR & NMR showed...

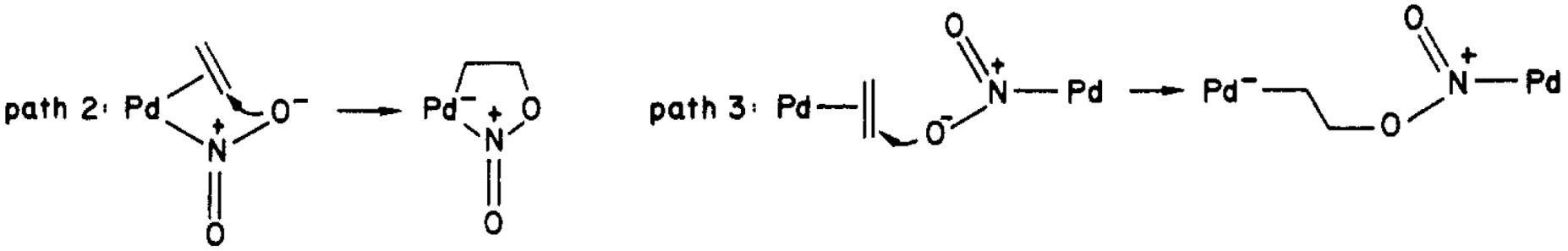




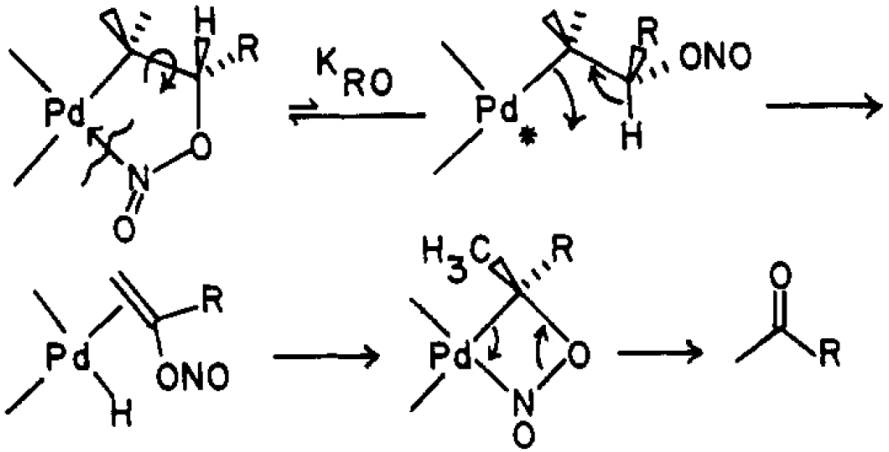


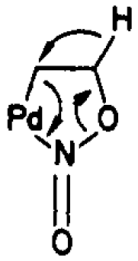
Mark A. Andrews *et al. J. Am. Chem. Soc.* **1981**, *103*, 2894.

Metal Nitro Complexes as Catalysts



Scheme II. Proposed Mechanism for Ketone Formation

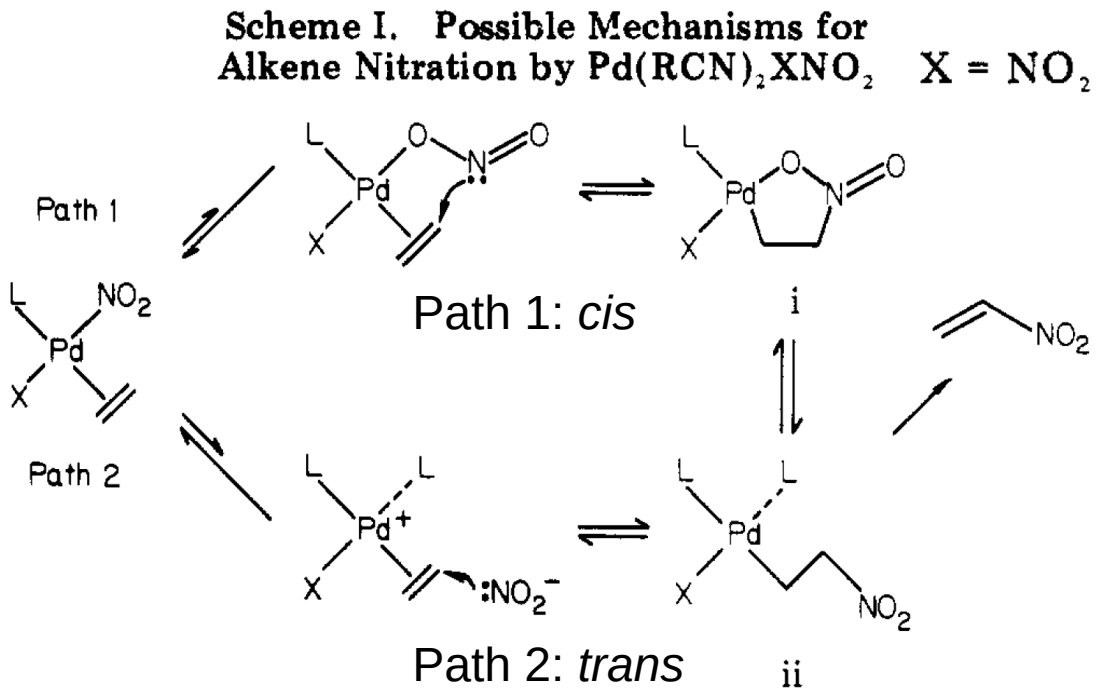




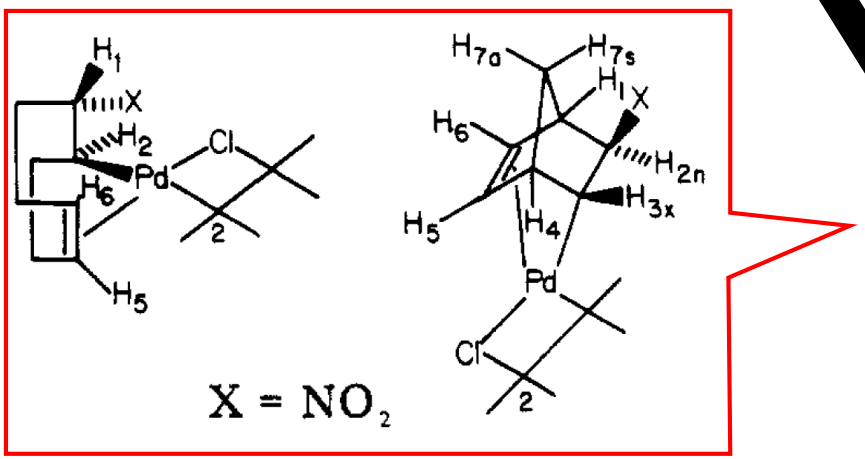
"*we believe far less likely*"

Mark A. Andrews *et al. Organometallics* **1984**, *12*, 1777.

Nitration of Alkenes by Palladium Nitro Complexes



support

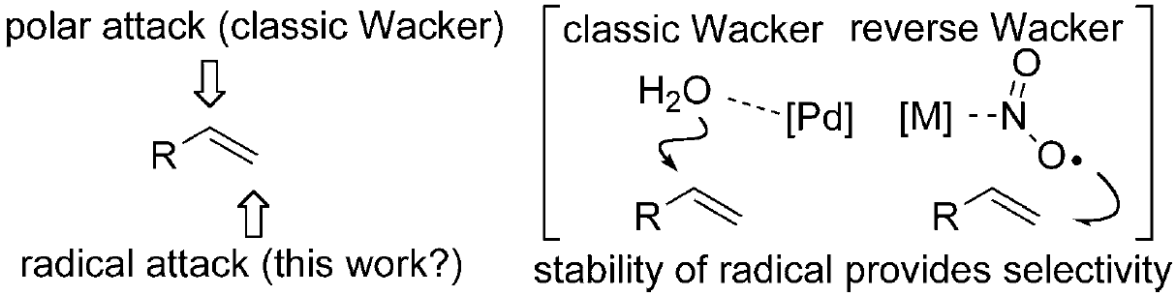


trans

Mark A. Andrews *et al. Organometallics* **1984**, *3*, 1479.

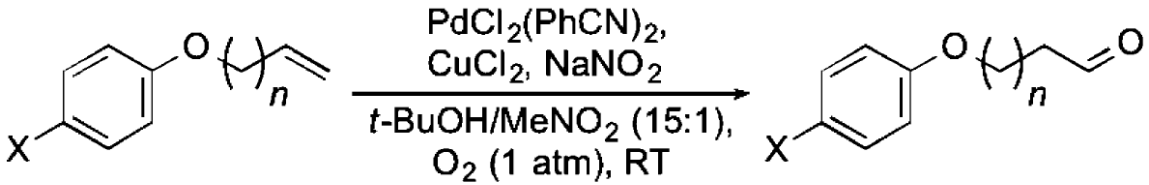
Preliminary Mechanistic Insight

- Radical Model to Explain Anti-Markovnikov Selectivity



Robert H. Grubbs *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 11257.

- Influence of Electronic Properties



		X = NO_2	X = H	X = OMe
n = 1 (allylic)	Selectivity	97:3	97:3	96:4
	Relative rate	1.2	1.0	1.2
n = 2 (homoallylic)	Selectivity	90:10	91:9	90:10
	Relative rate	1.3	1.0	1.1

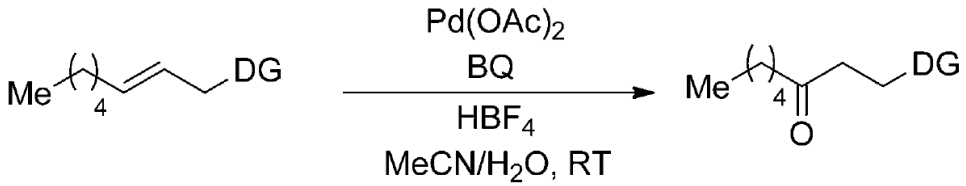
electron-deficient

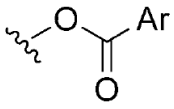
Robert H. Grubbs *et al. J. Am. Chem. Soc.* **2014**, *136*, 890.

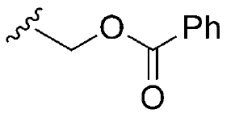
Compared with Cationic Transition State

• Intermolecular Competition Experiments

a)





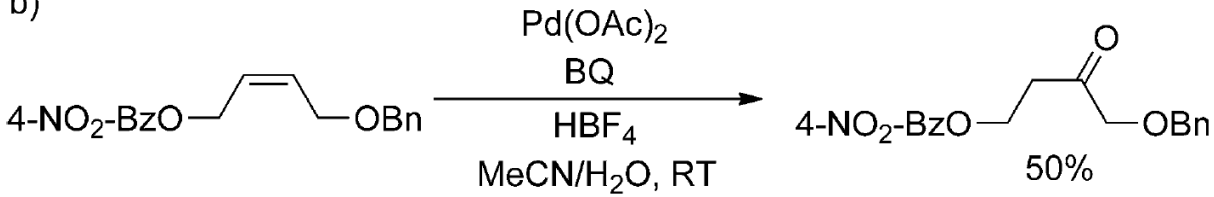


DG	4-$NO_2C_6H_4$	Ph	4-$MeOC_6H_4$	OBn	
Relative rate:	0.5 <	1 <	1.2 <	3.5	7.7
Selectivity:	28:1 >	20:1 >	16:1 >	9:1	10:1
Yield:	76%	80%	74%	71%	83%

electron-deficient

• Intramolecular Competition Experiments

b)



Robert H. Grubbs *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 9751

Preliminary Mechanistic Insight

✓ *Is NO_2 generated?*

in a sealed vessel (air)

NO_2 (gas) flies away?

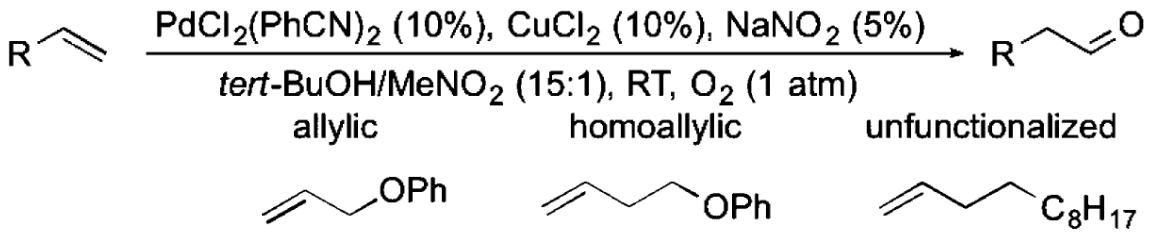
When the reaction is run in an unsealed vessel, significantly lower yield and selectivity is observed.

✓ *What mediates NO_2 delivery?*

Stoichiometric reaction of $CuCl_2$ and $AgNO_2$ with an alkene (without Pd) gave no conversion of alkene.

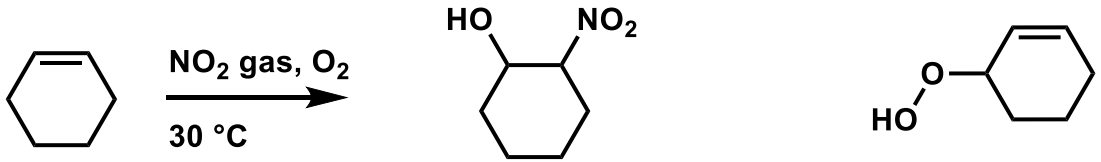
➡ Pd may mediate NO_2 delivery.

• One-pot Intermolecular Competition Experiments



Robert H. Grubbs *et al. J. Am. Chem. Soc.* **2014**, *136*, 890.

✓ *Without metal…*

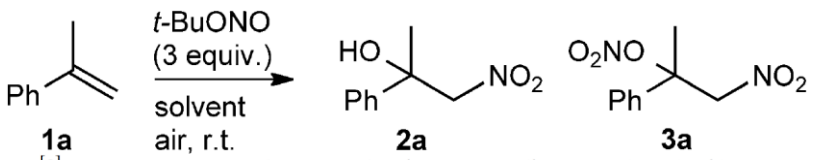


(NO_2 49wt% in carrier gas)
64 mol% of the SM consumed

(NO_2 0.0076 wt% in carrier gas)
76 mol% of the SM consumed

William A. Pryor *et al. J. Am. Chem. Soc.* **1982**, *104*, 6685.

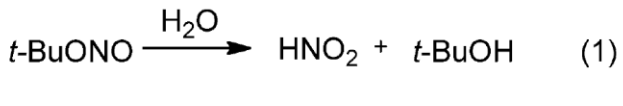
cf. Plausible Mechanism of Radical Nitration



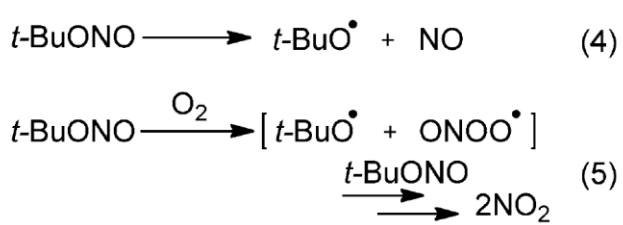
[a] *Reaction conditions:* **1a** (0.4 mmol), *t*-BuONO (1.2 mmol) and in solvent (2.5 mL) under air (1 atm).
[b] Isolated yield.
[c] Conversion was determined by GC analysis with dodecane as an internal standard.
[d] 2-Methoxy-1-nitro-2-phenylpropane was obtained instead of **3a**.
[e] 3 equivalents of water (21.6 μL) were added.
[f] A solution of *t*-BuONO (1.2 mmol) in hexane (2.5 mL) was added to a solution of **1a** (0.4 mmol) in hexane (2.5 mL)-H_2O (5 mL) over 1 h and the mixture was further stirred for 2 h.
[g] *i*-AmONO was employed instead of *t*-BuONO.
[h] Under O_2 atmosphere (1 atm).

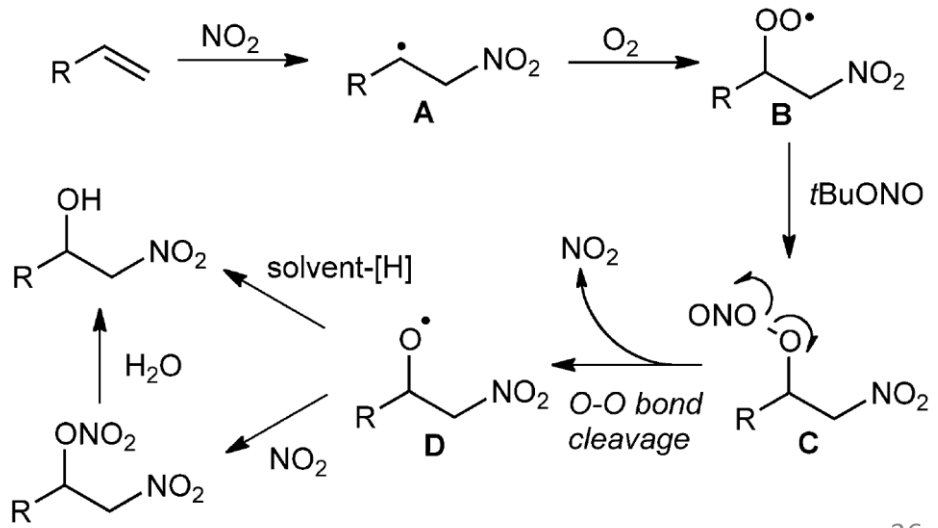
Entry	Solvent	Time [h]	Yield [%][b] 2a	Yield [%][b] 3a	Conversion [%][c]
1	toluene	120	32	20	93
2	MeOH	48	51	9[d]	>99
3	H_2O	2.5	45	–	>99
4	toluene-H_2O (1:1)	3	48	28	94
5	THF-H_2O (1:1)	3	60	–	95
6	CH_2Cl_2-H_2O (1:1)	2	40	31	95
7	EtOAc-H_2O (1:1)	2	41	19	93
8	hexane-H_2O (1:1)	3	74	–	>99
9[e]	hexane	6	26	32	96
10[f]	hexane-H_2O (1:1)	3	71	–	>99
11[g]	hexane-H_2O (1:1)	17	56	–	>99
12[h]	hexane-H_2O (1:1)	1.5	54	–	97

In the presence of water (major path)



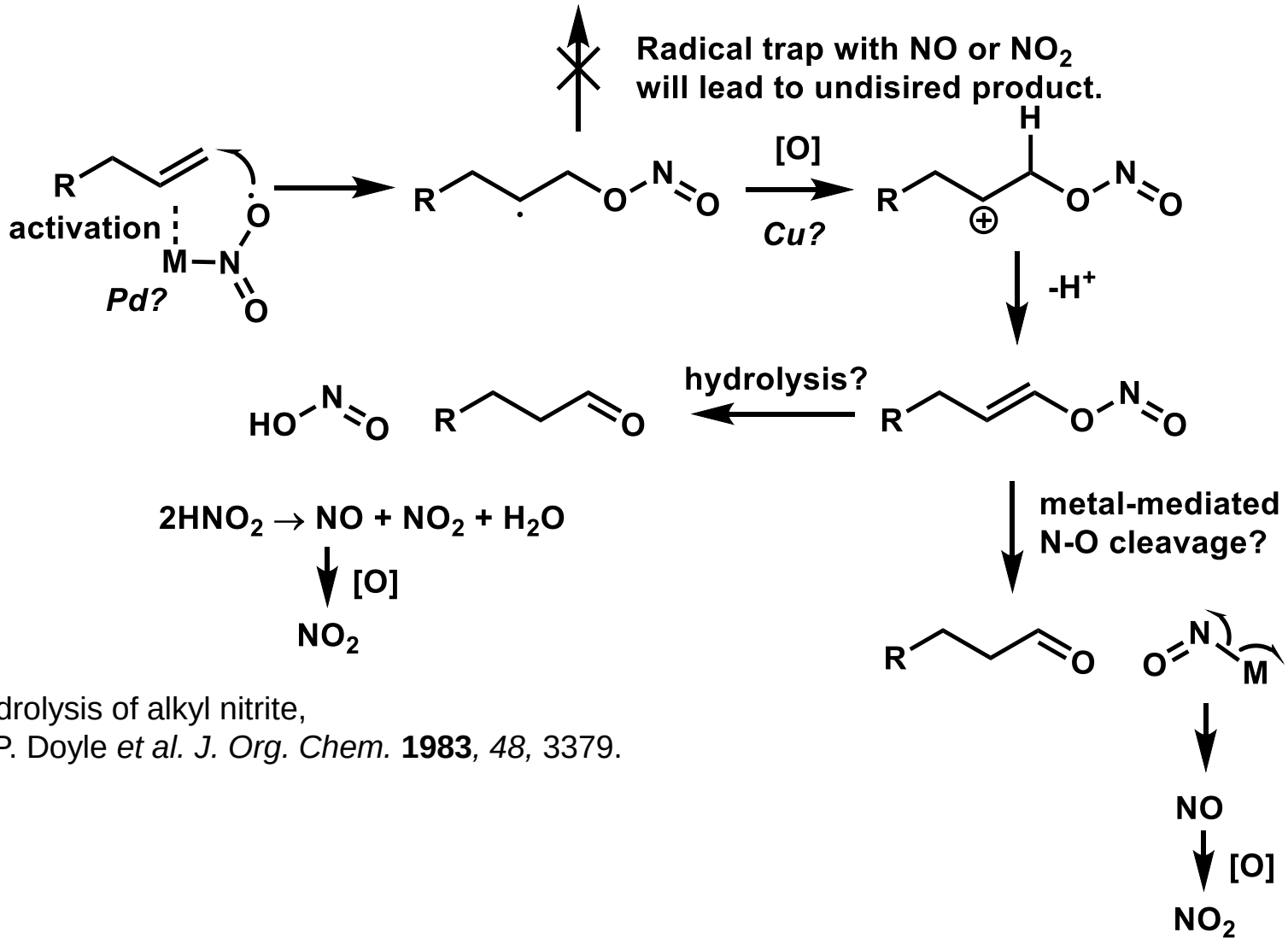
In the absence of water (minor path)





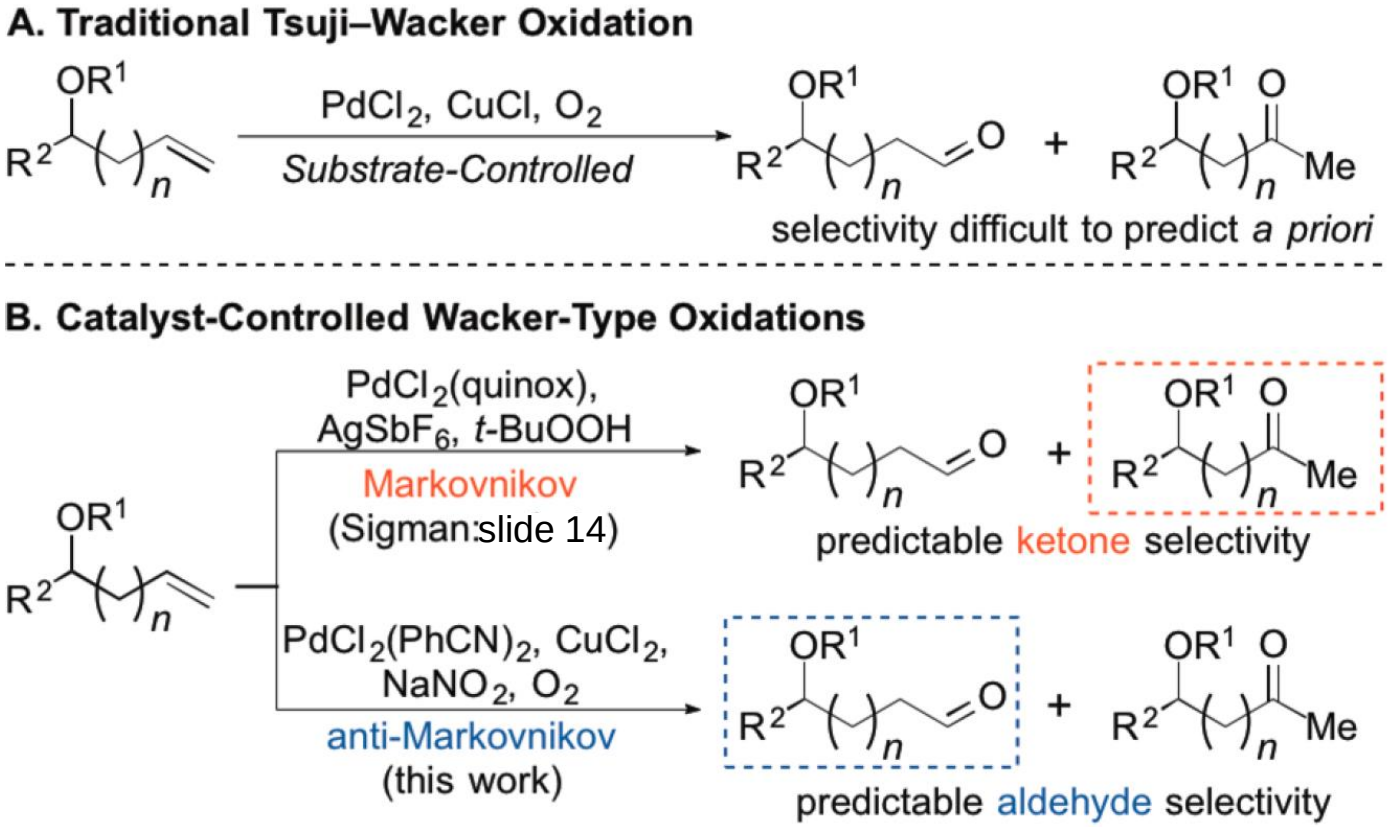
Hiroyuki Ishibashi *et al. Adv. Synth. Catal.* **2011**, *353*, 2643.

Mechanism?



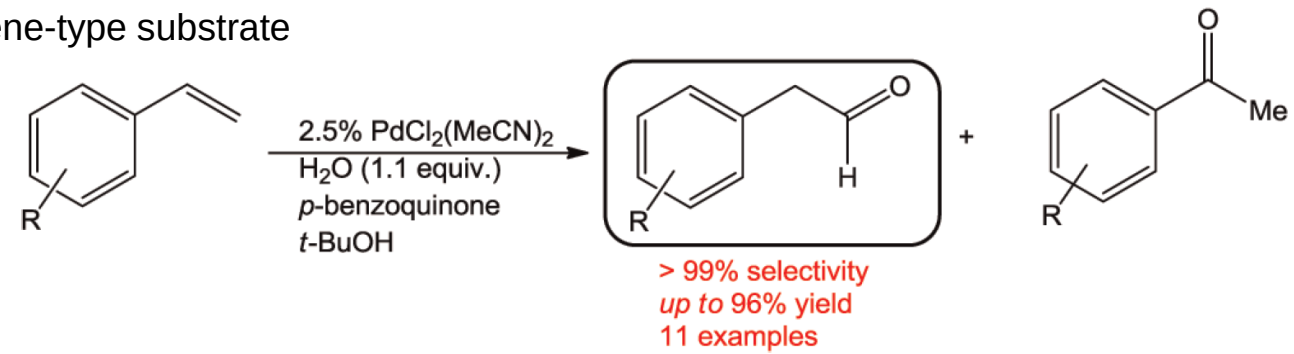
about hydrolysis of alkyl nitrite,
Michael P. Doyle *et al. J. Org. Chem.* **1983**, *48*, 3379.

Summary



Robert H. Grubbs *et al. J. Am. Chem. Soc.* **2014**, *136*, 890.

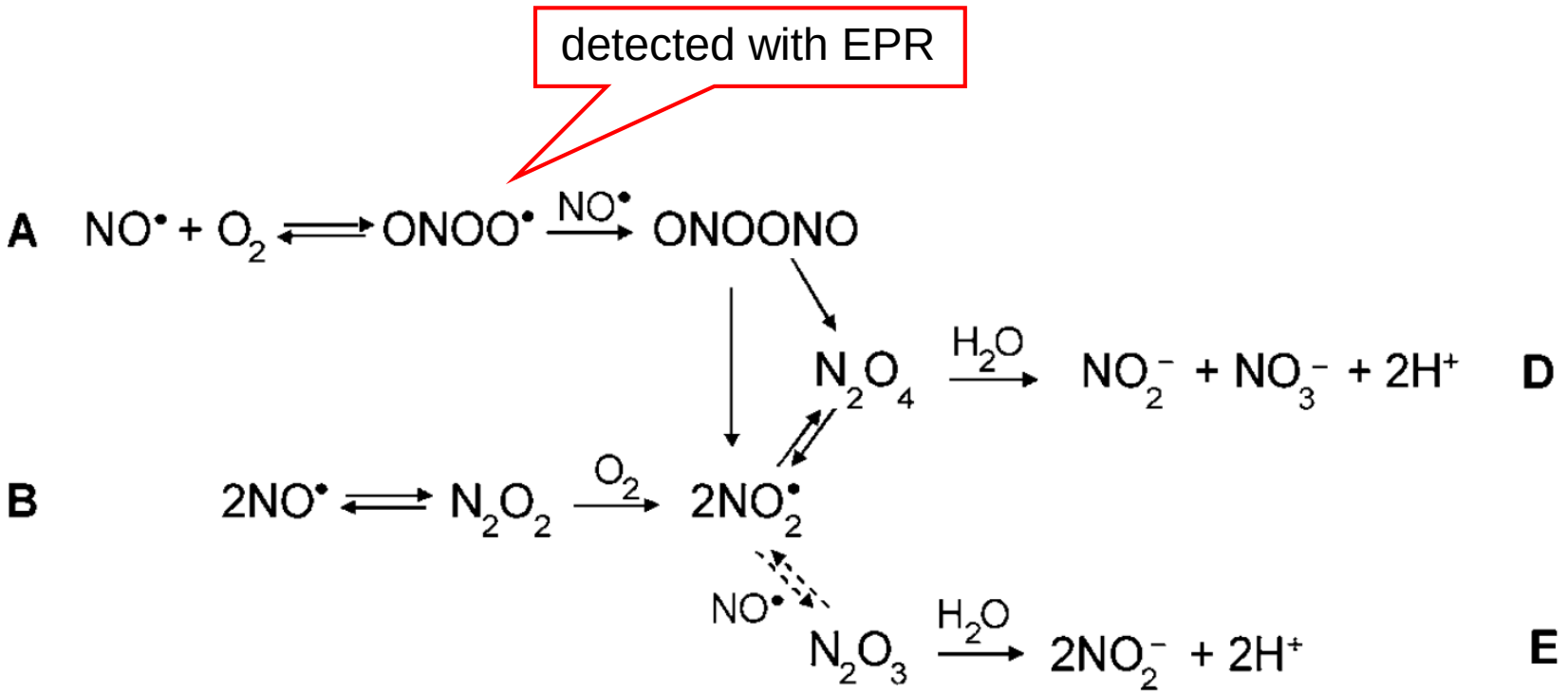
Styrene-type substrate



Robert H. Grubbs *et al. Org. Lett.* **2012**, *14*, 3237.

Appendix

Intermediates in the Autoxidation of Nitrogen Monoxide



Williem H. Koppenol *et al. Chem. Eur. J.* **2009**, *15*, 6161.

cf. Nitration of Olefins with $AgNO_2$ and TEMPO

Scheme 8. Proposed Mechanism for Nitration of Olefins

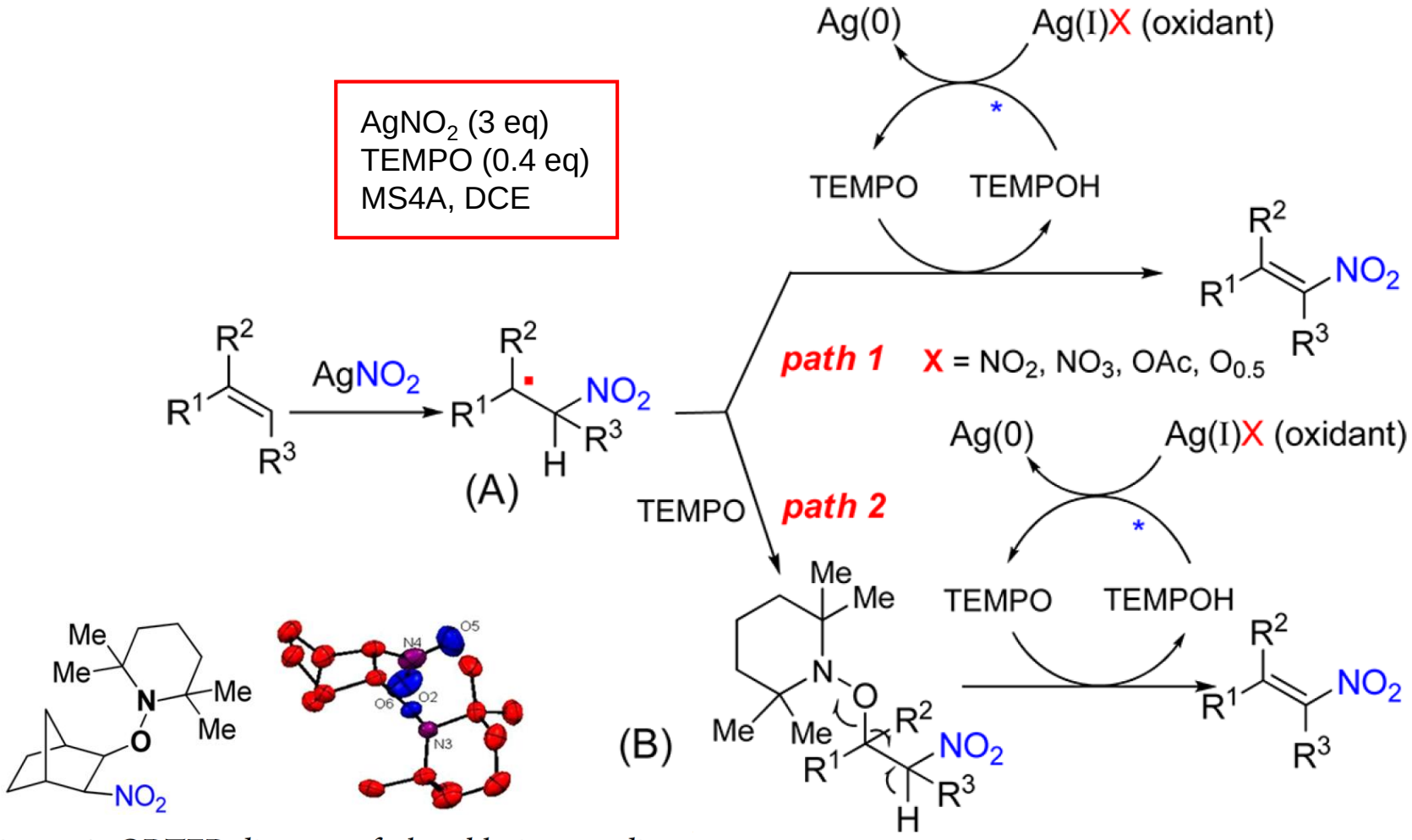
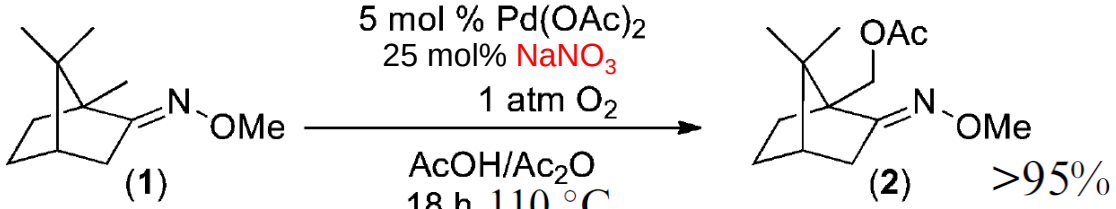
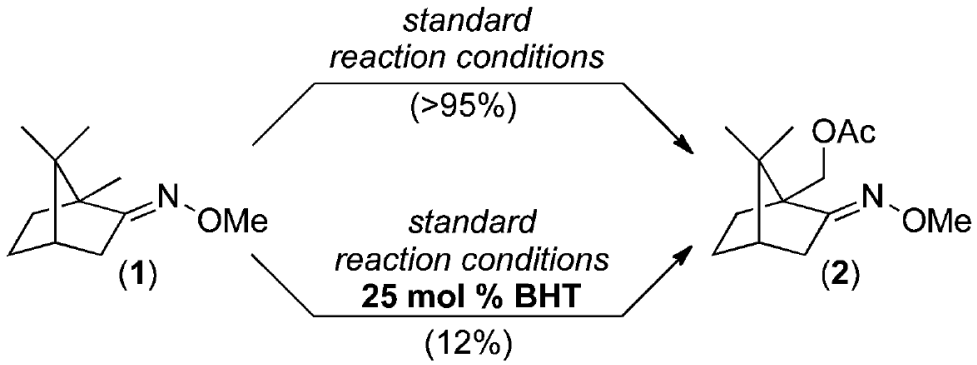


Figure 1. ORTEP diagram of plausible intermediate.

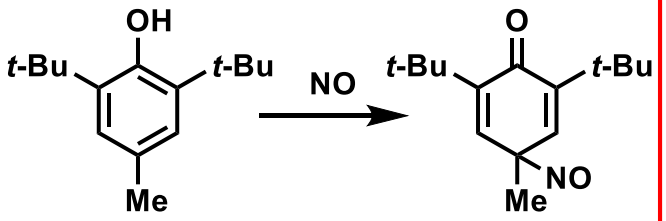
Debabrata Maiti *et al. J. Am. Chem. Soc.* **2013**, *135*, 3355.

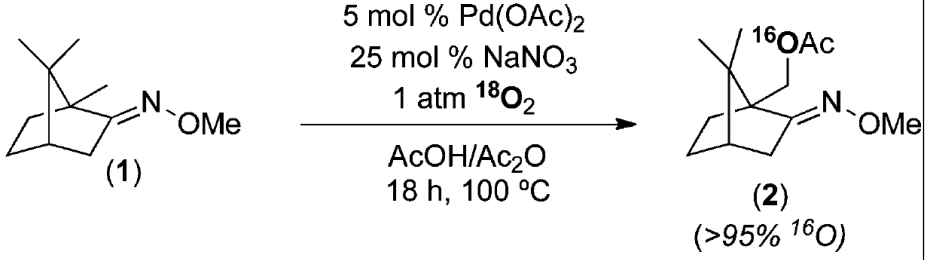
cf. Nitrate as a Redox Co-Catalyst

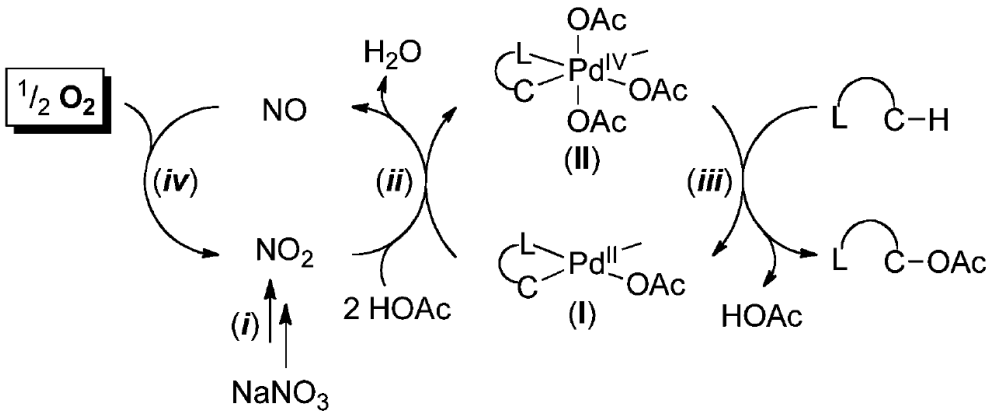




Known Reaction







Proposed catalytic cycle

Melanie S. Sanford *et al. Chem. Sci.* **2012**, *3*, 3192.

Other Olefin Functionalizations

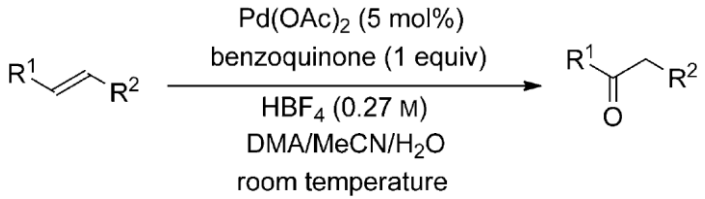
- Hydroamination

Wacker Oxidation / Transfer Hydrogenative Reductive Amination

Two-Step, One-Pot Hydroamination Protocol

see: Robert H. Grubbs *et al. Chem. Sci.* **2014**, *5,* 101.

- Wacker Oxidation of Internal Olefins



see: Robert. H. Grubbs *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 2944.

Robert H. Grubbs *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 9751.

- Hydrophosphonation

see: slide 44,45

Robert H. Grubbs *et al. Org. Lett.* **2011***, 13,* 6429.

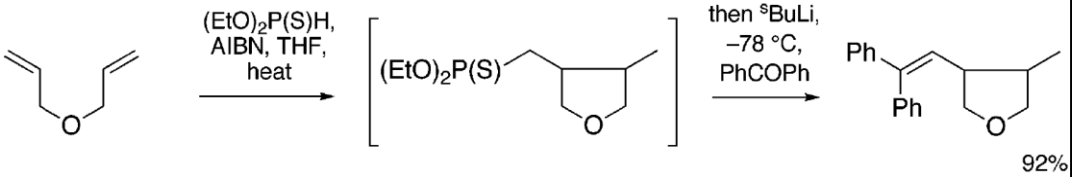
- Pd-Catalyzed Decarbonylative Dehydration of Fatty Acids

see: slide 46~49

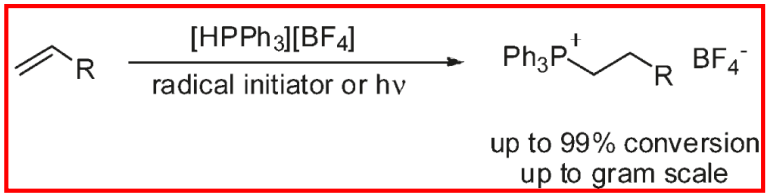
Robert H. Grubbs, Brian M. Stoltz *et al. Adv. Synth. Catal.* **2014***, 356,* 130.

Hydrophosphonation

Precedent : Radical Cyclization – HWE Reactions

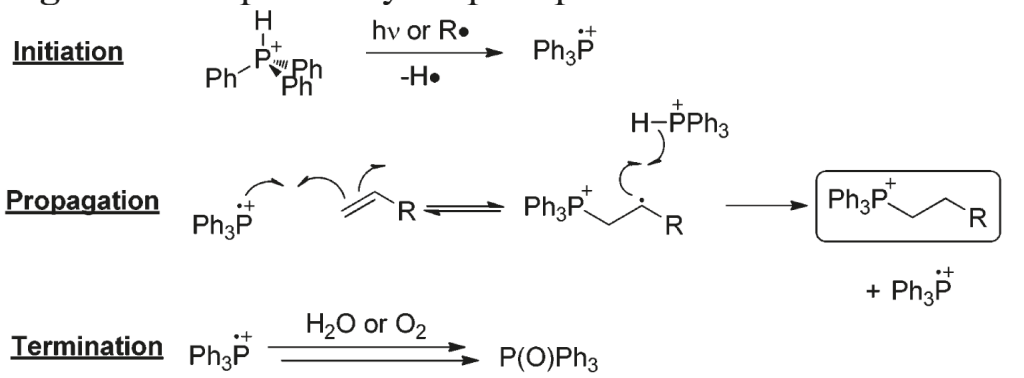


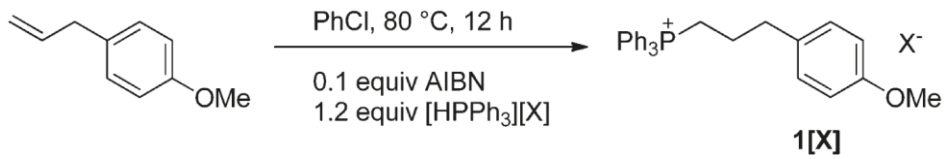
James G. T. Rawlinson *et al. Org. Lett.* **2005**, *7*, 1597.



Robert H. Grubbs *et al. Org. Lett.* **2011**, *13*, 6429.

Figure 1. Proposed hydrophosphonation mechanism.





Scheme 1. Anion Effect

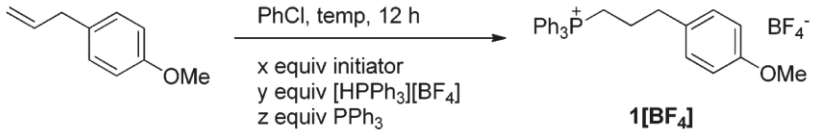
conversion

1[BF4] = 50%

1[PF6] = 13%

1[Br] = 0%

Table 1. Hydrophosphonation Optimization

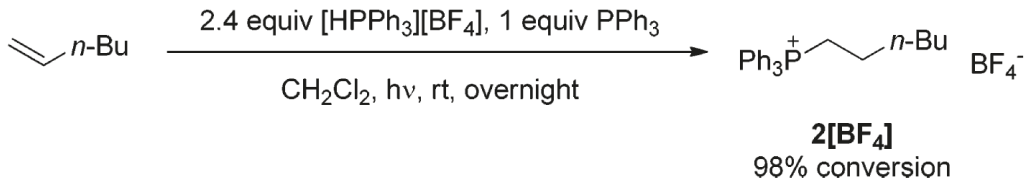


entry	initiator[a]	x[b]	y	z[b]	conv (%)[c]
1	ACN	0.01	2.4	0	78
2	ACN	0.02	2.4	0	72
3	ACN	0.02	2.4	0	81
4	ACN	0.02	2.4	0.1	86
5	ACN	0.02	2.4	0.5	76
6	ACN	0.02	2.4	1	65
7	ACN	0.1	1.2	0	50
8	ACN	0.2	1.5	0	57
9	ACN	0.2	1.5	0.1	67
10	ACN	2×(0.1)	1.5	0.1	72
11	ACN	2×(0.1)	2	0	81
12	ACN	2×(0.1)	2.4	2×(0.1)	94
13	AIBN	0.02	2.4	0	34
14	AIBN	0.2	1.2	0	36
15	AIBN	0.5	2	0	52
16	DBP	0.2	2.4	0	35
17	DBP	2×(0.1)	2.4	0	17

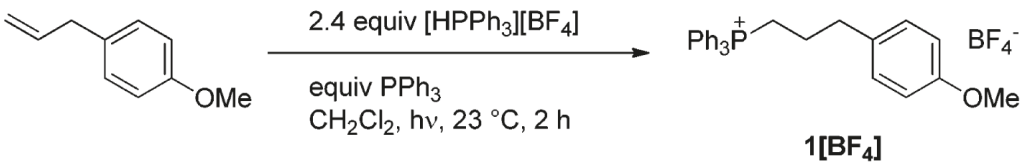
[a] ACN and DBP were activated at 110 °C. AIBN was activated at 80 °C. [b] 2×(0.1) indicates that 0.1 equiv of initiator was added at the beginning and halfway through the reaction. [c] Conversion measured by ^{1}H NMR and based on recovered starting material.

Hydrophosphonation

Scheme 2. Photochemical Hydrophosphonation of 1-Hexene



2[BF$_4$]
98% conversion

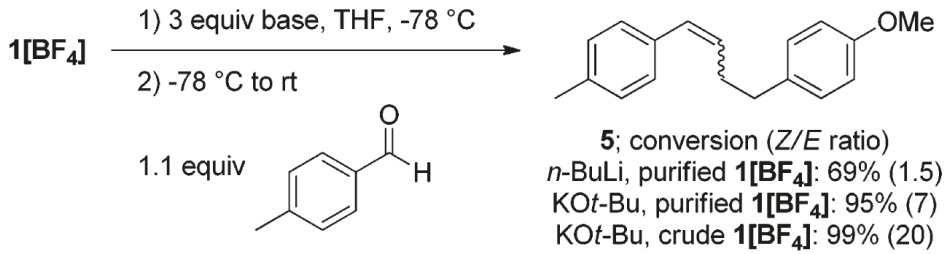


1[BF$_4$]

equiv PPh_3	conv (%)
0.00	0
0.10	31
0.25	65
0.50	61
1.00	72

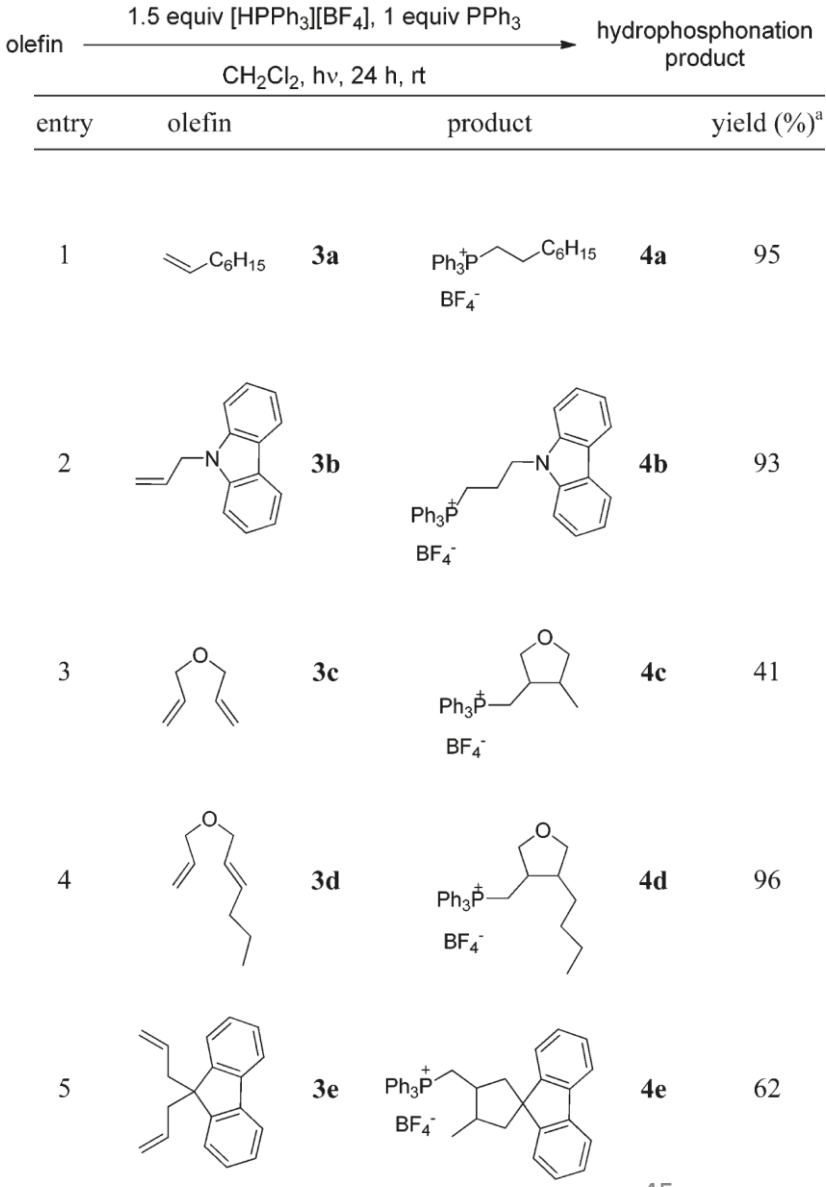
Figure 2. Effect of PPh_3 in photochemical hydrophosphonation.

Scheme 3. Wittig Reaction with Hydrophosphonation-Derived Phosphonium Salts



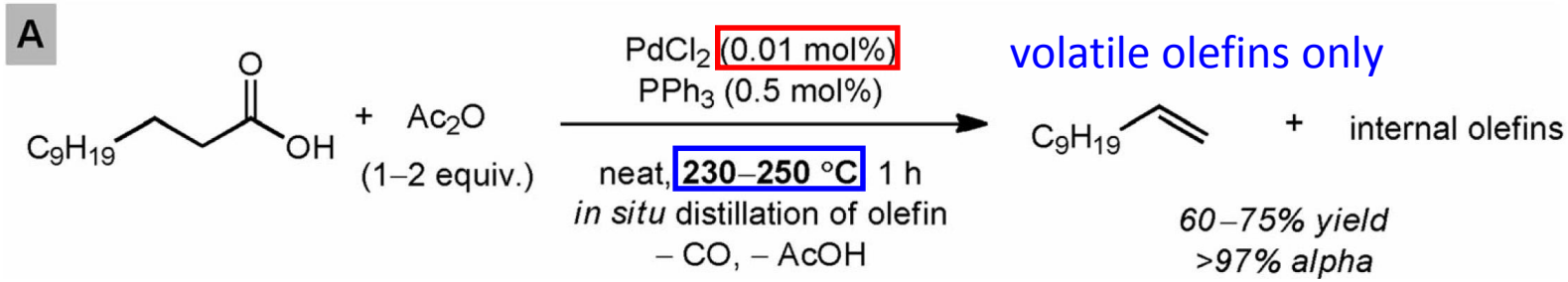
5; conversion (*Z*/*E* ratio)
n-BuLi, purified **1[BF$_4$]**: 69% (1.5)
KO*t*-Bu, purified **1[BF$_4$]**: 95% (7)
KO*t*-Bu, crude **1[BF$_4$]**: 99% (20)

Table 2. Substrate Scope

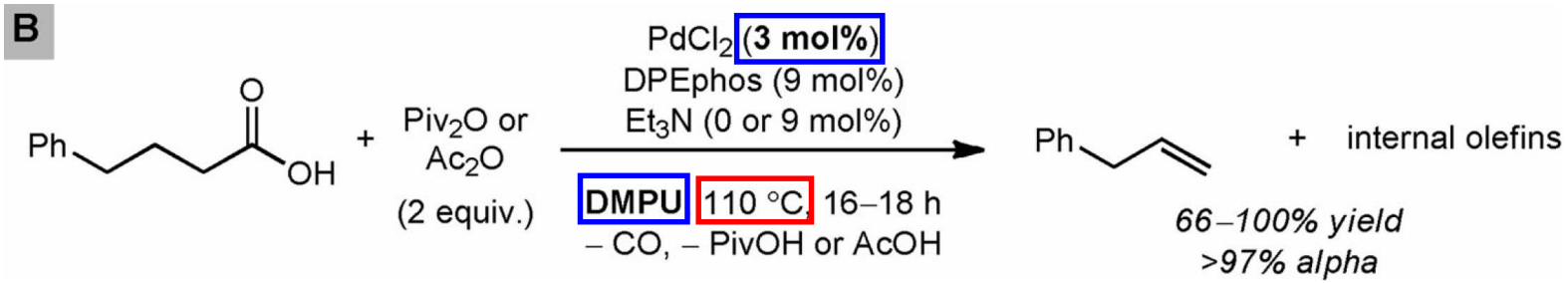


Pd-Catalyzed Decarbonylative Dehydration of Fatty Acids

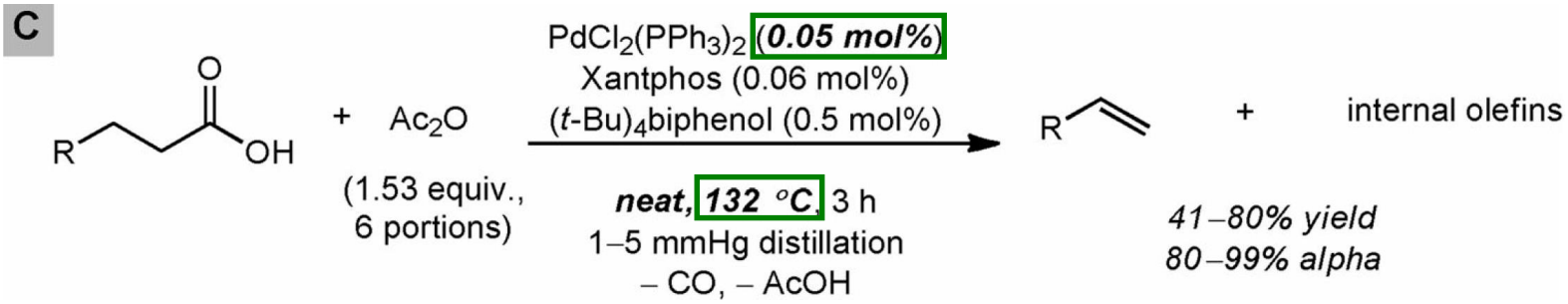
· High Temperature Process (Miller, Kraus)



· Low Temperature Process (Gooβen, Scott)



· Grubbs' Work



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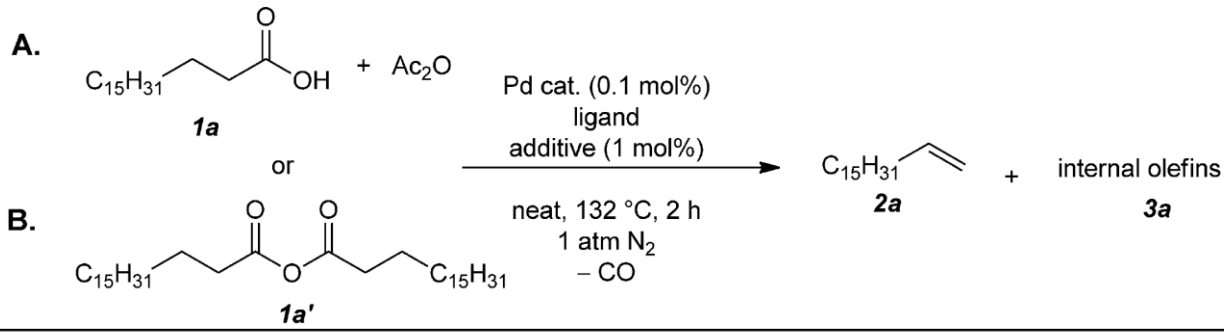
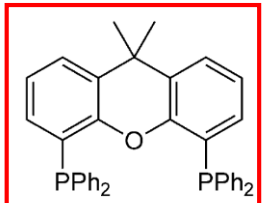
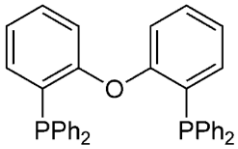
Effect of Catalyst, Ligand, and Additive



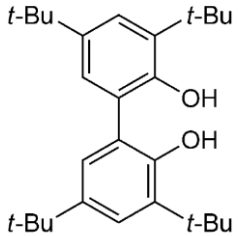
Entry	Rxn	Pd cat.	Ligand (mol%)	Additive	Yield [%][b]	Alpha [%][b]	Y x A [%][c]
1	A	$PdCl_2(nbd)$	PPh_3 (0.8)	--	0	--	0
2	A	$PdCl_2(nbd)$	dppp (0.4)	--	0	--	0
3	A	$PdCl_2(nbd)$	DPEphos (0.4)	--	43	59	25
4	A	$PdCl_2(nbd)$	Xantphos (0.4)	--	60	55	33
5	B	$PdCl_2(nbd)$	Xantphos (0.4)	--	12	100	12
6	B	$PdCl_2(nbd)$	Xantphos (0.4)	isophthalic acid	22	96	21
7	B	$PdCl_2(nbd)$	Xantphos (0.12)	isophthalic acid	92	31	29
8	B	$PdCl_2(PPh_3)_2$	Xantphos (0.12)	isophthalic acid	90	54	49
9	B	$PdCl_2(PPh_3)_2$	Xantphos (0.12)	*p*-TsOH·H_2O	86	5	4
10	B	$PdCl_2(PPh_3)_2$	Xantphos (0.12)	salicylamide	60	90	54
11	B	$PdCl_2(PPh_3)_2$	Xantphos (0.12)	2,2'-biphenol	59	91	54
12	**B**	**$PdCl_2(PPh_3)_2$**	**Xantphos (0.12)**	**(*t*-Bu)$_4$biphenol**	**84**	**70**	**59**



Xantphos



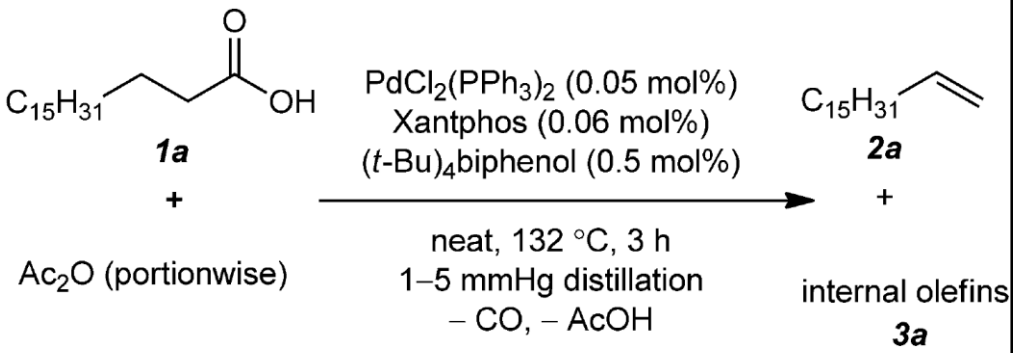
DPEphos



(*t*-Bu)$_4$biphenol

[a] *Conditions*: **A**) 1 equiv. **1a** (5 mmol), 2 equiv. Ac_2O; **B**) 1 equiv **1a'** (5 mmol).
[b] Determined by ^1H NMR with methyl benzoate as internal standard. Alpha = **2a**/(**2a**+**3a**).
[c] Y × A = Yield × Alpha.

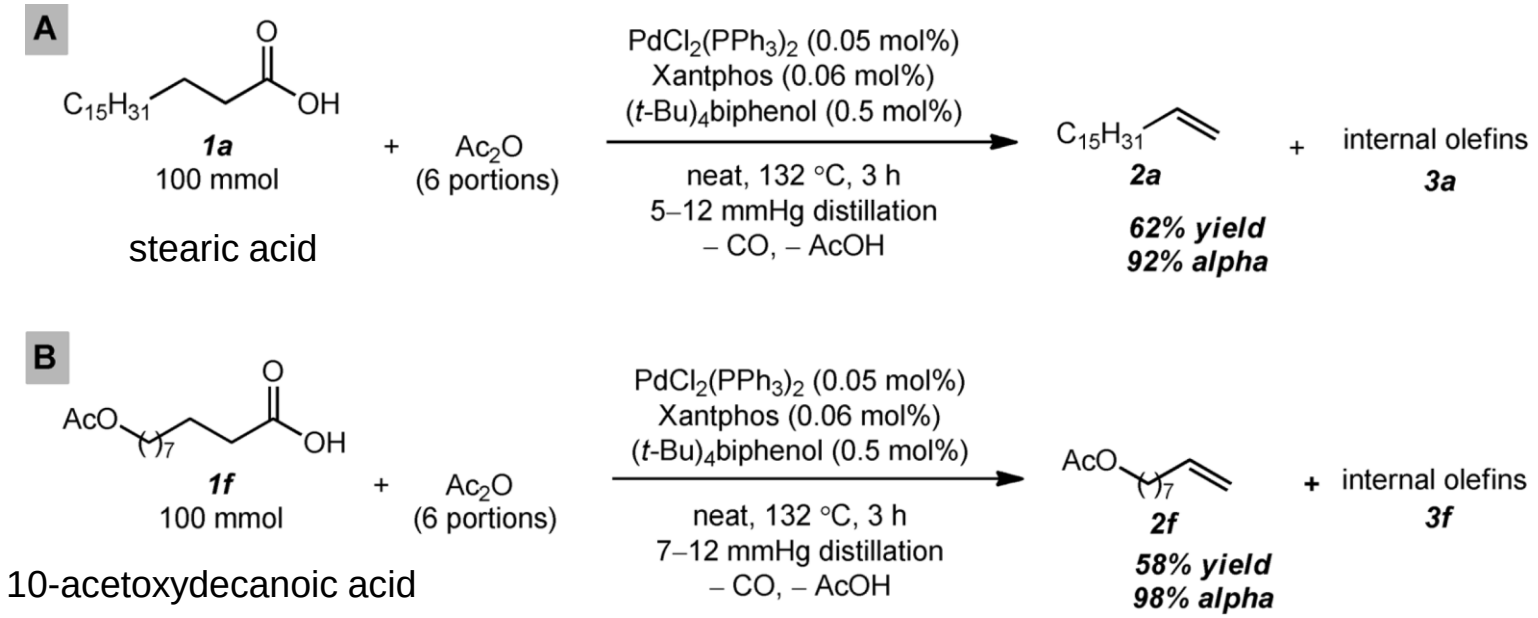
· Portionwise Addition of Acetic Anhydride



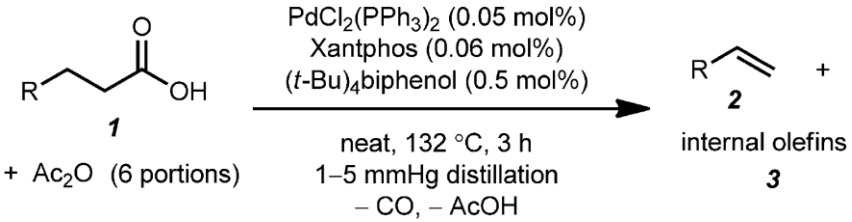
Entry	Equiv. of Ac_2O	Yield [%][b]	Alpha [%][b]
1	1+0.5 (once every 1.5 hours)	69	62
2	1+0.5+0.25 (once every hour)	67	86
3	**1+0.14+0.12+0.1+0.09+0.08 (once every half hour)**	**68 (67)**	**89**

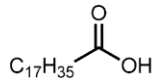
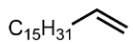
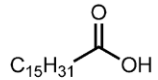
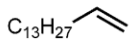
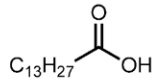
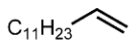
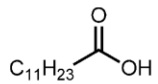
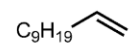
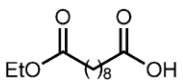
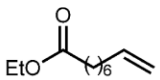
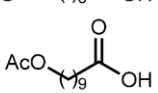
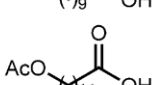
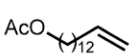
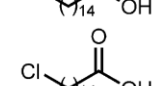
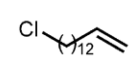
[a] 20 mmol **1a**.
[b] Determined by ^{1}H NMR (isolated yield in parentheses).

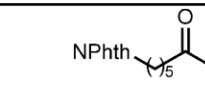
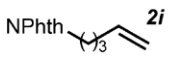
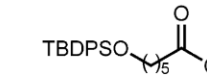
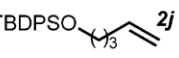
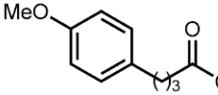
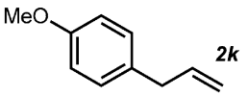
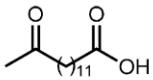
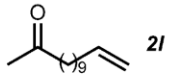
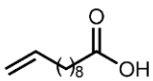
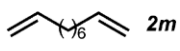
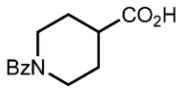
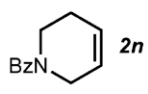
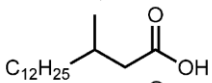
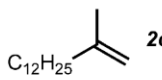
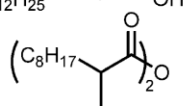
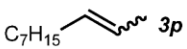
· Large-Scale Decarbonylative Dehydration



Substrate Scope



Entry	Substrate	Product	Yield [%][b]	TON	Alpha [%][c]
1	 **1a**	 **2a**	67	1340	89
2	 **1b**	 **2b**	41	820	97
3	 **1c**	 **2c**	65	1300	99
4	 **1d**	 **2d**	73	1460	99
5[d,e]	 **1e**	 **2e**	63	1260	98
6[d]	 **1f**	 **2f**	67	1340	96
7[d]	 **1g**	 **2g**	60	1200	89
8	 **1h**	 **2h**	75	1500	86

Entry	Substrate	Product	Yield [%][b]	TON	Alpha [%][c]
9	 **1i**	 **2i**	76	1520	83
10	 **1j**	 **2j**	64	1280	80
11	 **1k**	 **2k**	80	1600	91
12	 **1l**	 **2l**	49	980	88
13	 **1m**	 **2m**	59	1180	87
14[f]	 **1n**	 **2n**	20 80[h]	400 320[h]	--[g] --[h]
15	 **1o**	 **2o**	19	380	--[g]
16[i]	 **1p'**	 **3p**	71	71	--[i]

[a] *Conditions*: 20 mmol **1**, 6 portions of Ac_2O, 1 + 0.14 + 0.12 + 0.10 + 0.09 + 0.08 equiv., added every 30 min.
[b] Isolated yield (column chromatography).
[c] Determined by ^1H NMR.
[d] Purified by distillation.
[e] 18.5 mmol **1e**.
[f] $PdCl_2$(nbd) (0.05 mol%), PPh_3 (0.05 mol%), Xantphos (0.06 mol%), 1.5 h, 3 portions of Ac_2O (1 + 0.15 + 0.10 equiv.).
[g] Single isomer observed.
[h] $PdCl_2(PPh_3)_2$ (0.25 mol%), Xantphos (0.30 mol%), (*t*-Bu)$_4$biphenol (1 mol%), **2n**:**3n** = 49:51.
[i] 2-Methyldecanoic anhydride (10 mmol), no Ac_2O, $PdCl_2$(nbd) (1 mol%), Xantphos (1.1 mol%), salicylamide (2 mol%), 160 °C, 10 mmHg distillation, 10 h, **3p**:**2p** = 73:27.