Current Literature

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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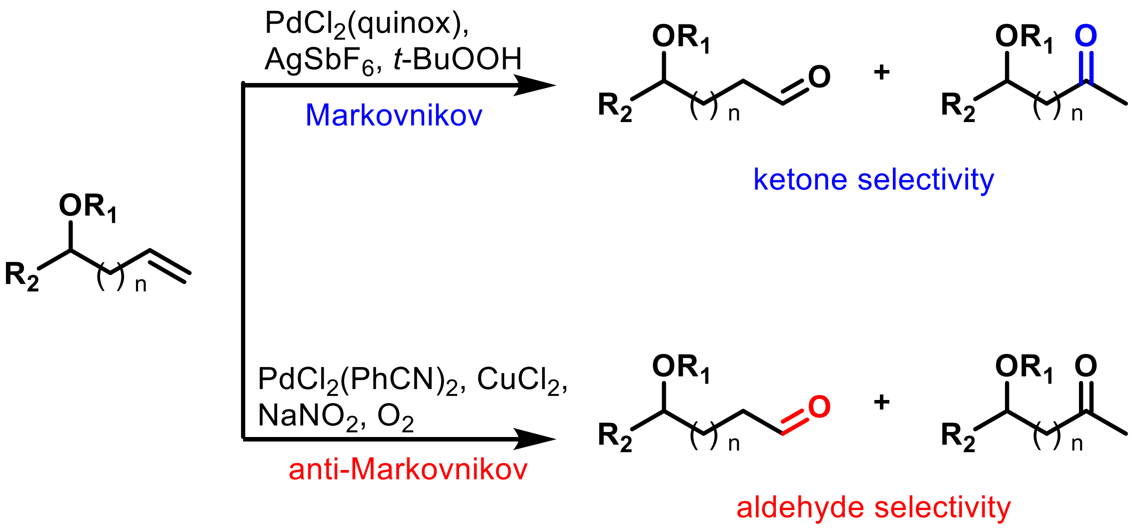
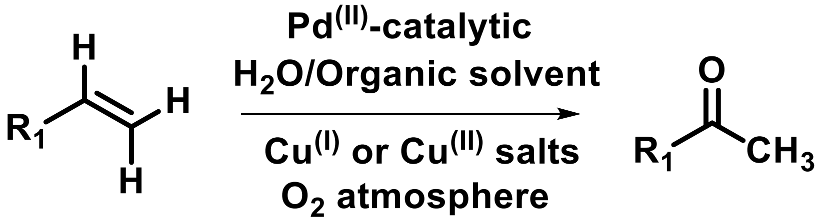
Catalyst-Controlled Wacker-Type Oxidation: Facile Access to Functionalized Aldehydes



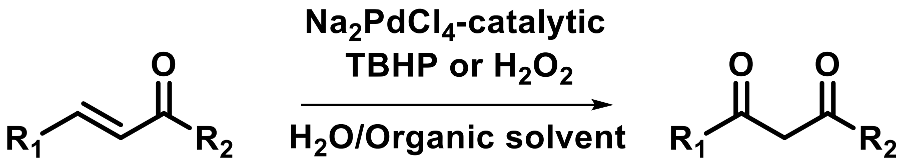
Gilmar A. Brito Jr.

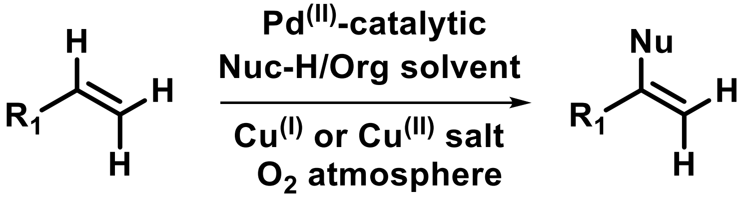
1/18/2014 – Wipf group

Wacker oxidation: Introduction



Oxidation of olefins to the corresponding ketones with catalytic amounts of $Pd^{(II)}$ salts



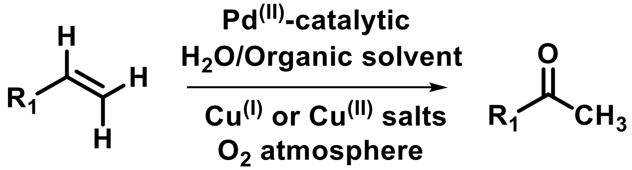


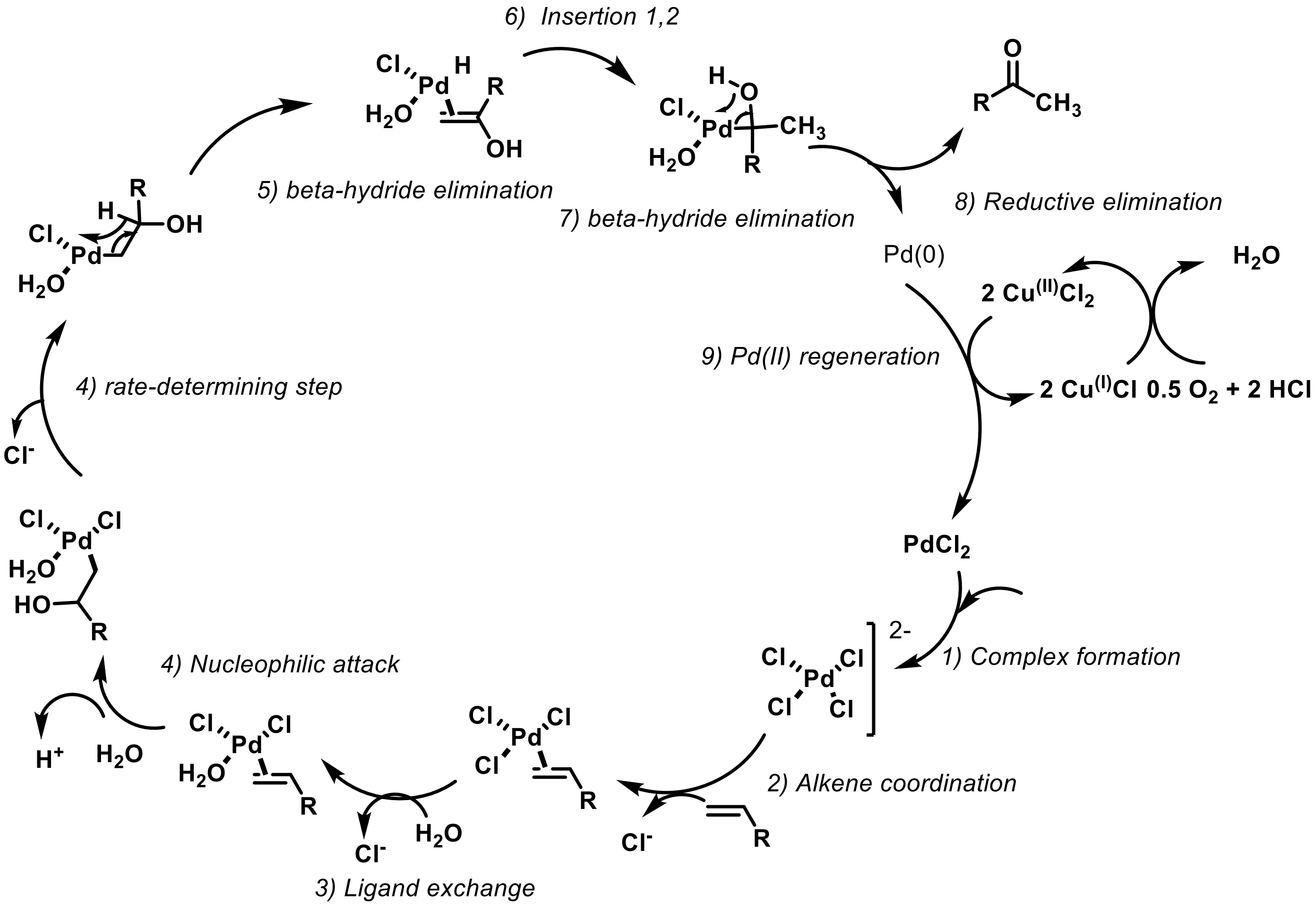
α,β-unsaturated carbonyl compounds are oxidized to 1,3-dicarbonyls

Other nucleophillic species can be used in place of water (halides)

Kurti, L.; Czakó, B. *Strategic applications of named reactions in organic synthesis,* 474

Wacker oxidation: Mechanism

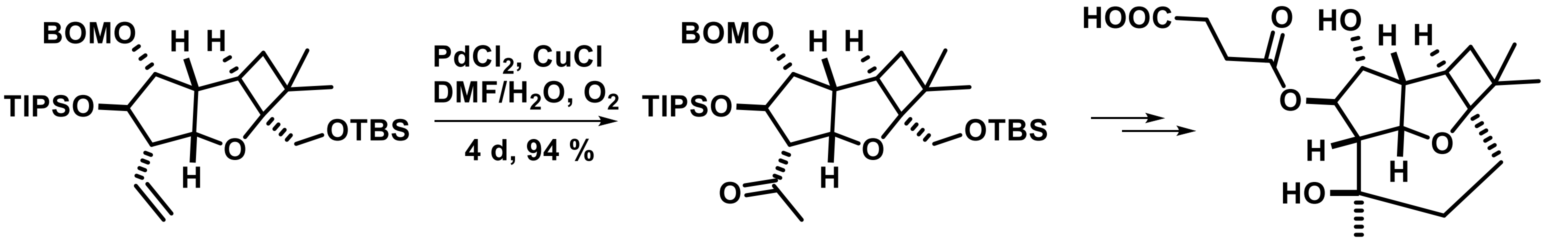




Kurti, L.; Czakó, B. *Strategic applications of named reactions in organic synthesis*, 474

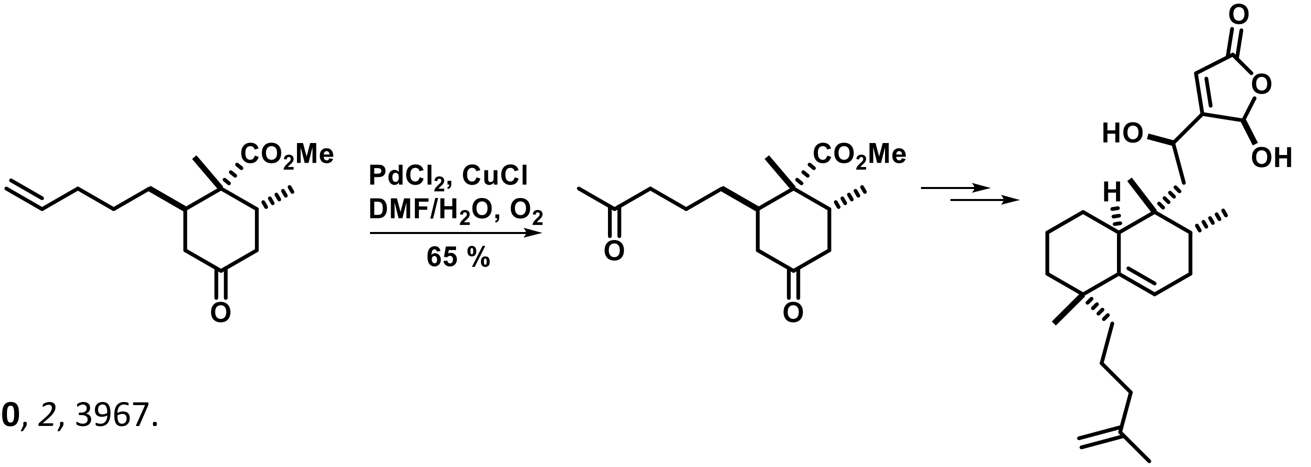
Wacker oxidation: Tool for total synthesis

Synthetically, the Wacker reaction is useful for conversion of terminal alkenes to ketones with generally predictable regioselectivy.



(+/-)-Punctaporonin C

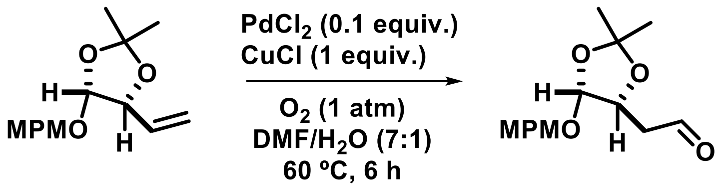
Angew. Chem. Ind. Ed. **2008**, *47*, 6189.



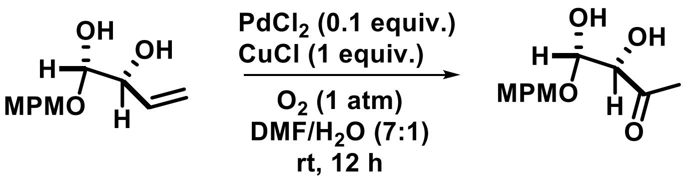
(+/-)-dysidiolide
(formal synthesis)

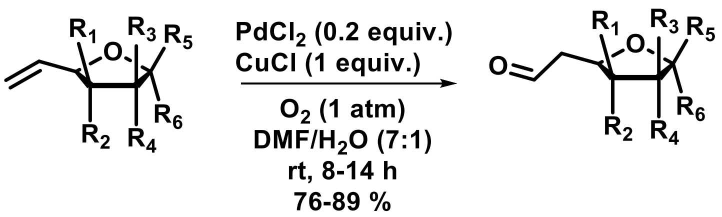
Org. Lett. **2000**, *2*, 3967.

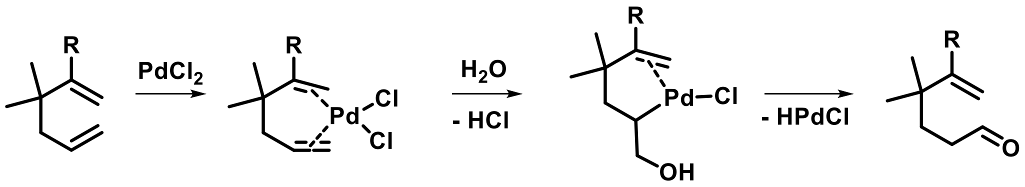
Wacker oxidation: Scope/Limitations



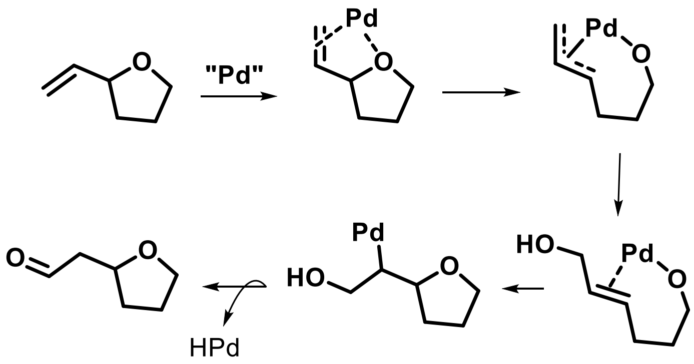
The regioselectivity of alkenes bearing hetereoatoms can’t be easily predicted





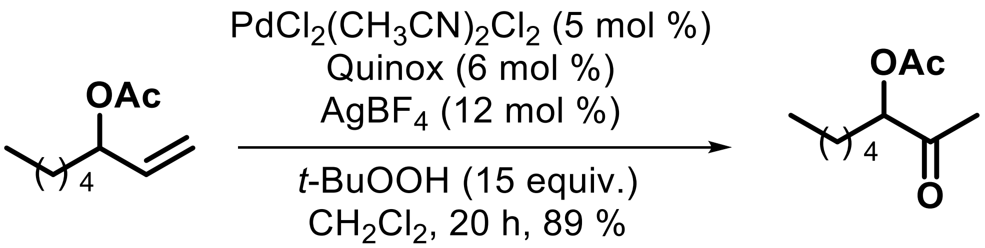


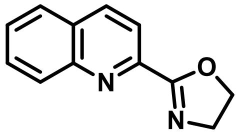
Substrate-controlled anti-Markovnikov selectivity



Tetrahedron **2007**, *63*, 7505.

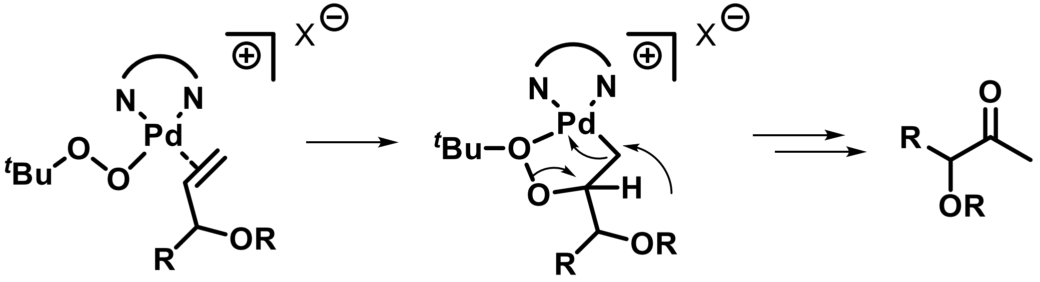
Wacker oxidation: Sigman work





Quinox

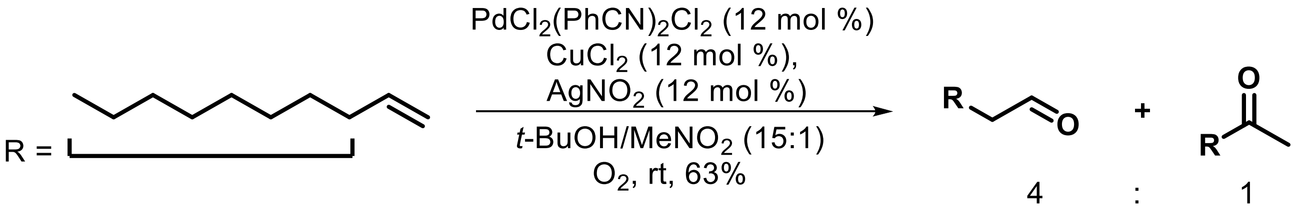
Catalyst-controlled Markovnikov selectivity. Even with substrates that often give a mixture of products.



5-membered palladacycle controls the regioselectivity of this reaction

J. Am. Chem. Soc. **2009**, *131*, 6076.

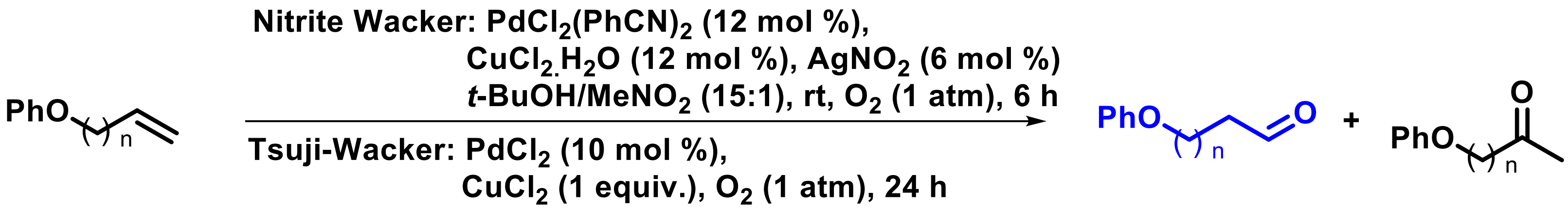
Wacker oxidation: Nitrite version



Grubbs and co-workers reported the **first catalyst-controlled anti-Markovnikov Wacker oxidation**, for terminal alkenes

Angew. Chem. Ind. Ed. **2013**, *52*, 11257.

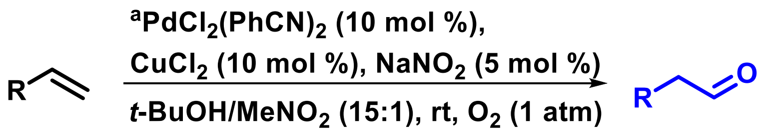
Aldehyde selectivity



n =	Nitrite Wacker	Tsuji-Wacker
1	95 %	41 %
2	92 %	< 5 %
3	75 %	< 5 %
4	75 %	< 5 %

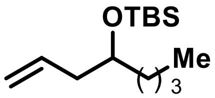
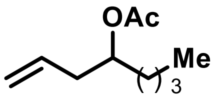
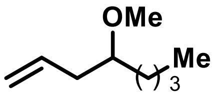
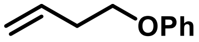
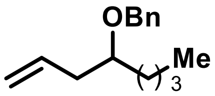
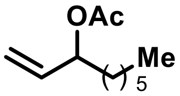
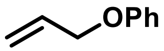
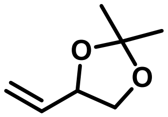
J. Am. Chem. Soc. **2013** (current lit)

Wacker oxidation: Nitrite version



[a] $PdCl_2(PhCN)_2$ (10 mol %), $CuCl_2$ (10 mol %), $NaNO_2$ (5 mol %)

t-BuOH/$MeNO_2$ (15:1), rt, O_2 (1 atm)

Entry	Substrate	Aldehyde yield[b]	Selectivity[c]	Tsuji-Wacker conditions[d]
1		**76 %**	**90:10**	**4:96**
2		**76 %**	**90:10**	**20:80**
3		**71 %**	**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.

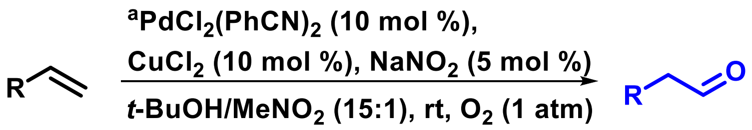
[c] Selectivity (aldehyde/ketone) obtained by ^1H NMR analysis of the unpurified reaction mixture.

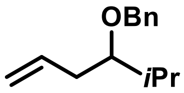
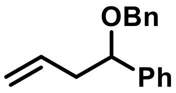
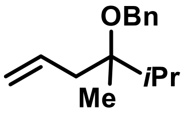
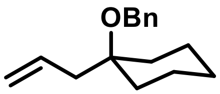
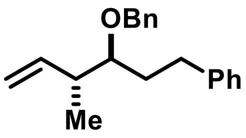
[d] Reaction conditions: [1b] 0.1 mmol of alkene, $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF/H_2O (7:1, 0.125 M), rt (20-25 ºC), run to > 95 % converstion.

[e] Yield determined by ^1H NMR analysis of the unpurified reaction mixture.

[f] $AgNO_2$ used in place of $NaNO_2$.

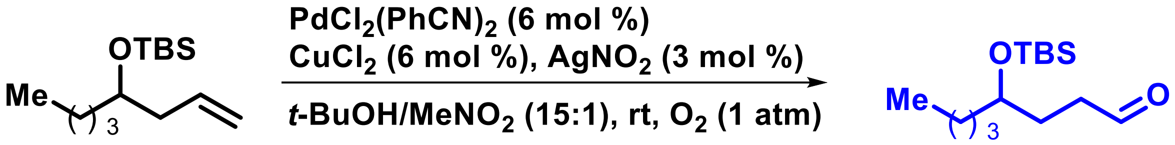
Wacker oxidation: Nitrite version



Entry	Substrate	Nitrite source	Aldehyde yield[b]	Selectivity[c]	Tsuji-Wacker conditions[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 %	95:5	8:92
6[g]		$AgNO_2$	77 %	95:5	-
7		$NaNO_2$	38 %	66:34	10:90
8		$AgNO_2$	65 %[e]	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 ^1H NMR analysis of the unpurified reaction mixture. [d] Reaction conditions: 0.1 mmol of alkene, $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF/H_2O (7:1, 0.125 M), rt (20-25 ºC), run to > 95 % converstion. [e] Yield determined by ^1H NMR analysis of the unpurified reaction mixture. [f] Isolated as an inseparable mixture of aldehyde and ketone. [g] 24 h reaction time

Nitrite Wacker reaction: Asymmetric synthesis

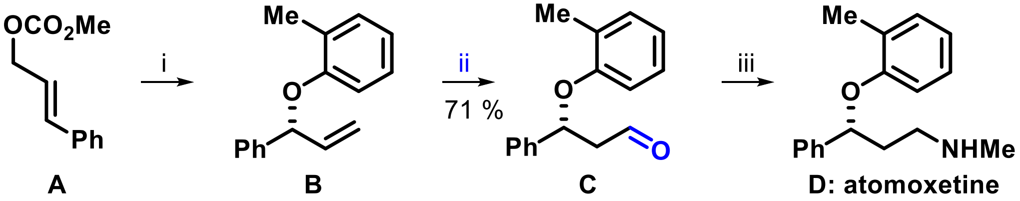


4 g scale (16.5 mmol)

71 % isolated yield

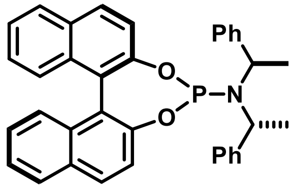
92 % aldehyde-selectivity

Methodology suitable for large scale process



95 % ee | 94 % ee | 94 % ee

i. $[Ir(COD)Cl]_2$ (1 mol %), (R, R, R)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a'] dinaphtalen-4-yl)bis(1-phenyethyl)amine (2 mol %), THF, 50 ºC, 16 h; ii. $PdCl_2(PhCN)_2$ (10 mol %) $CuCl_{2.}2H_2O$ (10 mol %), $AgNO_2$ (5 mol %), *t*-BuOH/$MeNO_2$ (15:1), rt, O_2 (1 atm), 5 h; iii. $NaBH_3CN_2$ equiv., $MeNH_3Cl$ (excess), rt, 24.

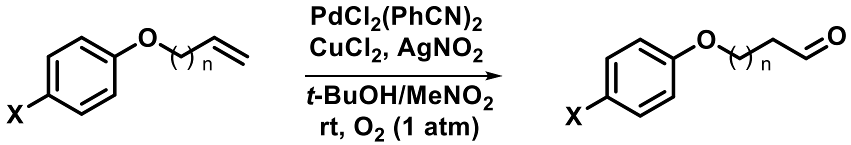


(R, R, R)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a'] dinaphtalen-4-yl)bis(1-phenyethyl)amine

No racemization observed on nitrite-Wacker reaction

J. Am. Chem. Soc. **2003**, *125*, 3436; *J. Am. Chem. Soc.* **2010**, *132*, 8918 (Ir allylic etherification)

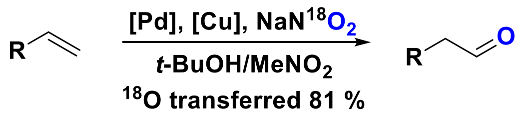
Nitrite Wacker reaction: Mechanism



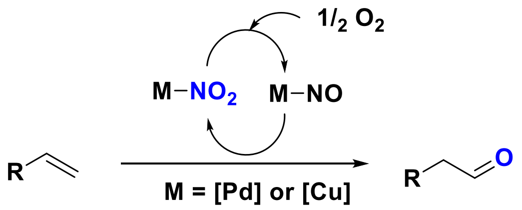
		X = NO_2	X = H	X = OMe
n = 1 (allylic)	Selectivity	97:3	97:3	96:4
	Relative rate	1.2	1.0	1.2
n = 2 (homoallylic)	Selectivity	90:10	91:9	90:10
	Relative rate	1.3	1.0	1.1

Minimal inductive influence which is consistent to an apolar, radical-type addition

A)

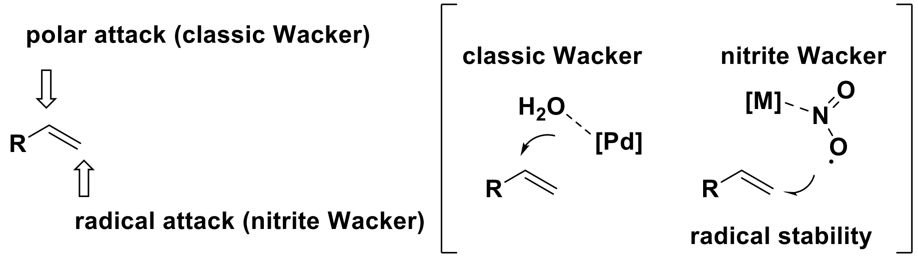


B)



NO_2 radical generated *in situ*

C)



Conclusions

- Grubbs and co-workers had develeped a methodology to prepare **aldehydes from terminal alkenes** with generally selectivity.

- Preliminary evidence of **radical-type addition**.

- Mechanism under investigation.