Phosphine Catalysis:

Generation of Phosphonium Enolates

Justin Roberts

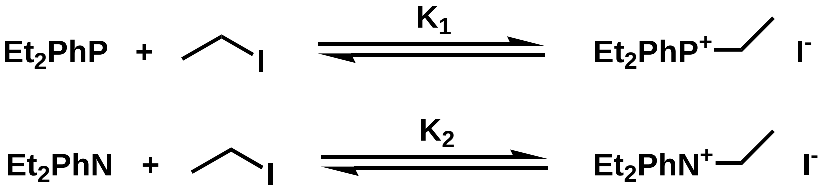
Organic Supergroup

January 25, 2006

- Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535-544.
- Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035-1050.

Why Phosphine?

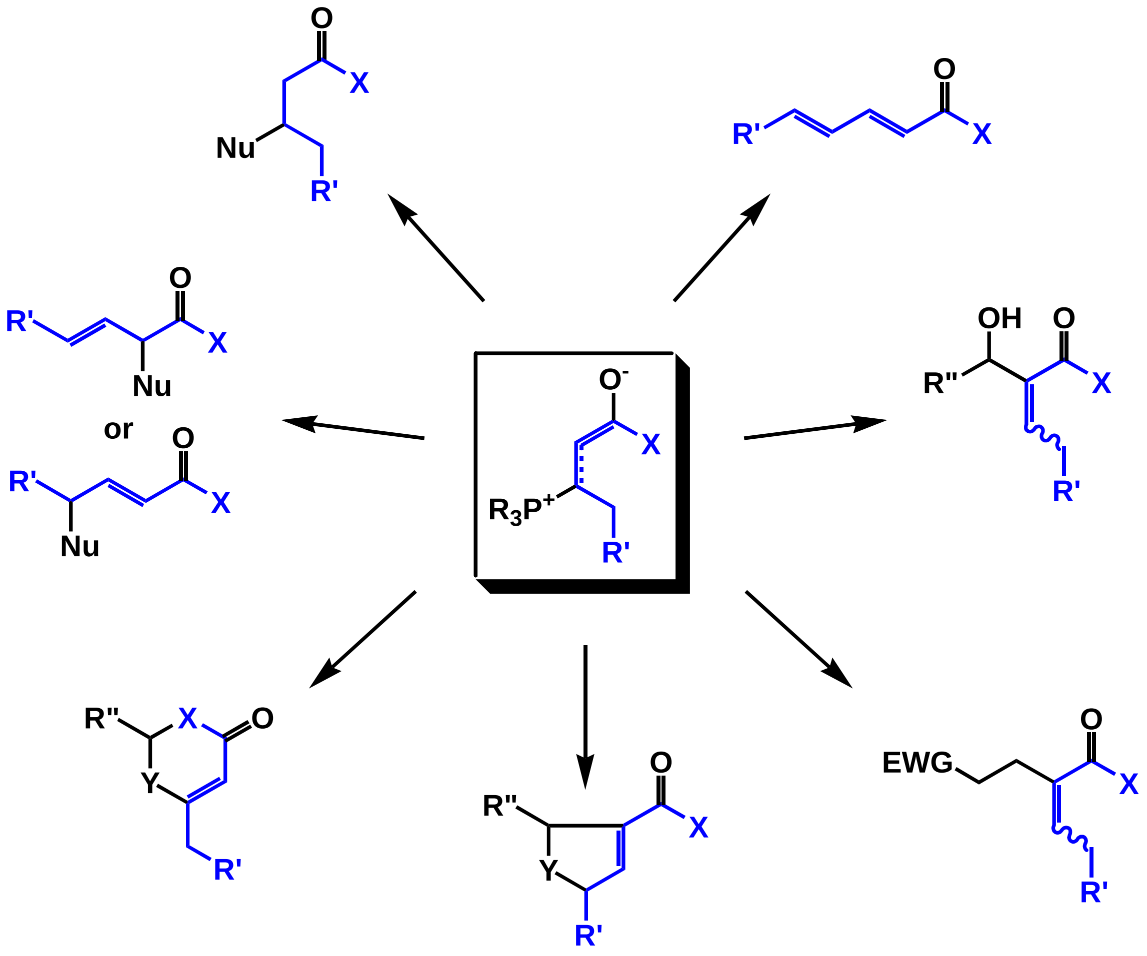
- Leaving group potential
  - pK_a $Et_3PH^+ = 8.7$ → better LG
    $Et_3NH^+ = 10.7$
- Nucleophilicity



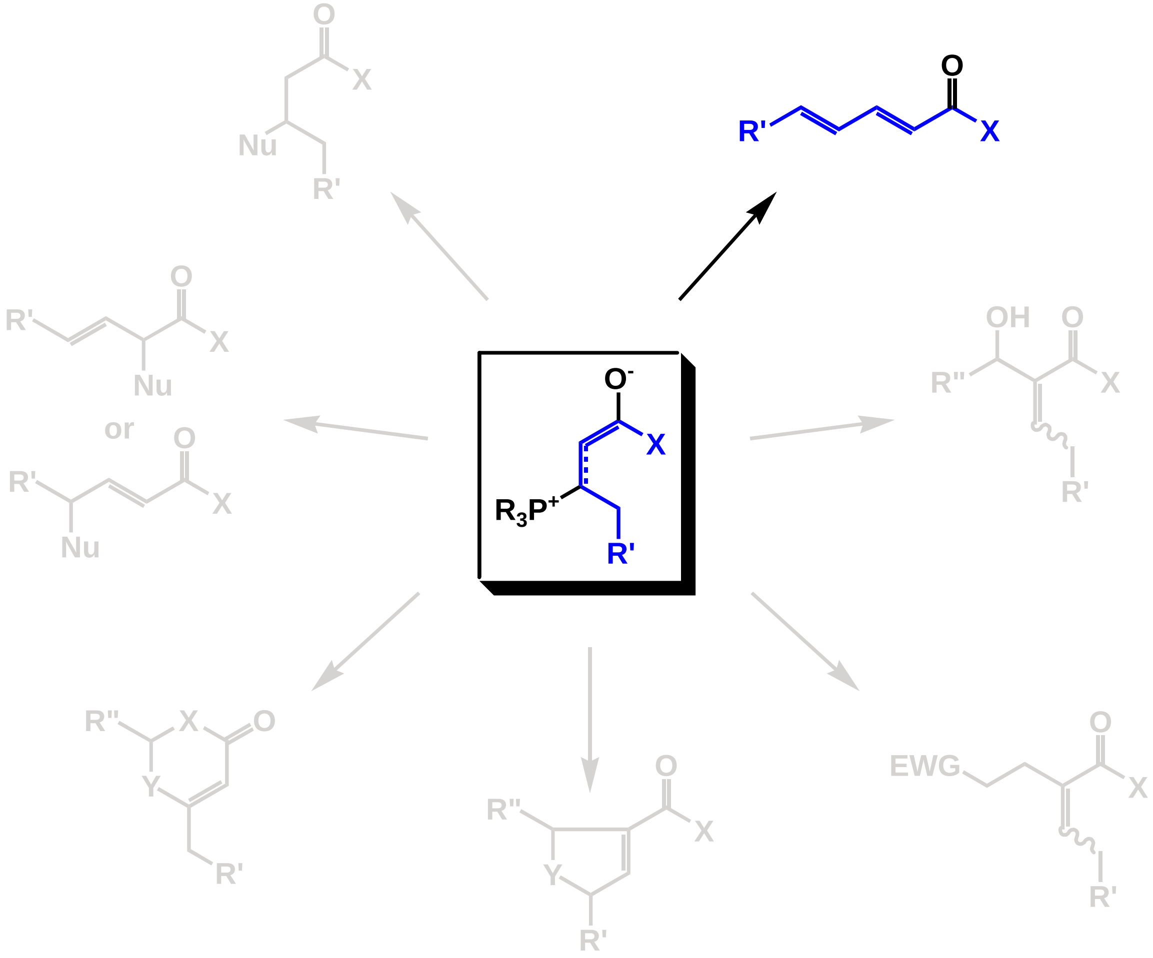
  - $K_1/K_2 > 500$
  - ↑ with e^- donating alkyl groups on phosphine
- Phosphonium stabilizes adjacent carbanion

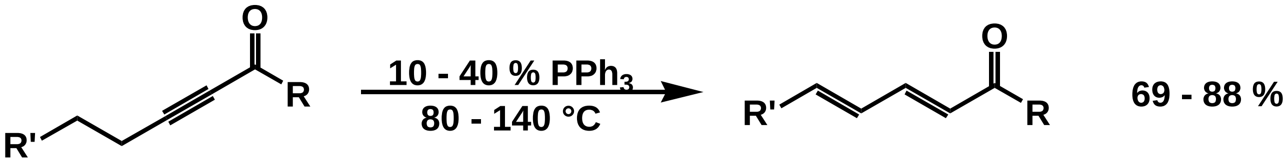
•Davies, W. C.; Lewis, W. P. G. *J. Chem. Soc.* **1934**, 1599.

Outline

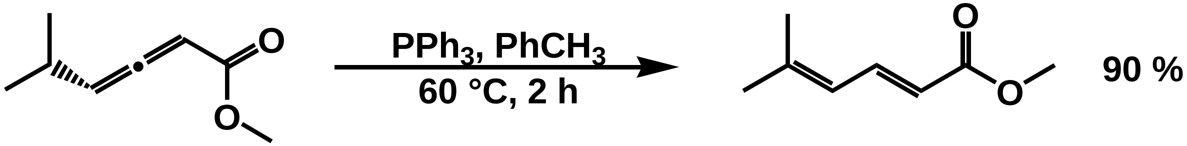


Internal Redox

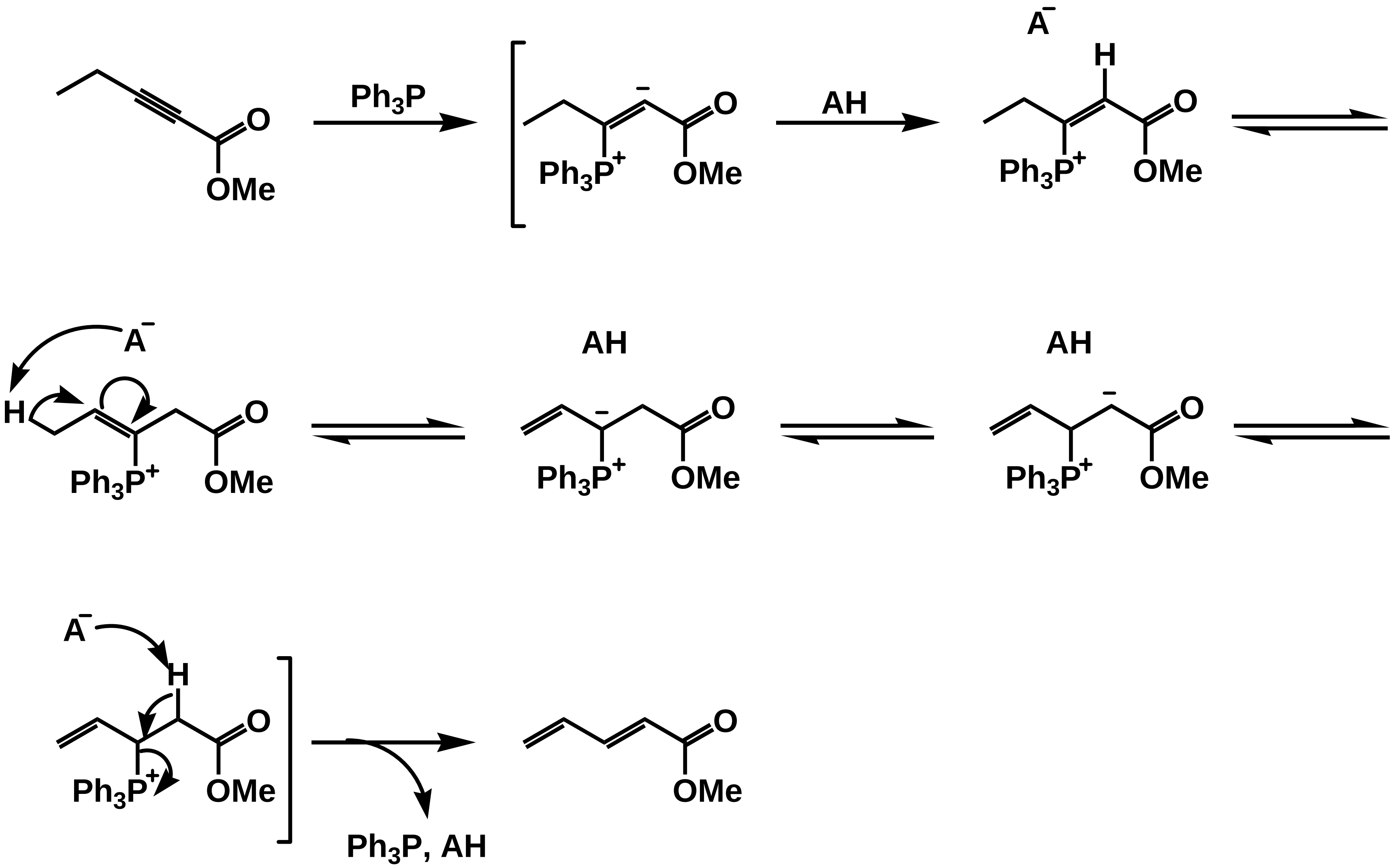




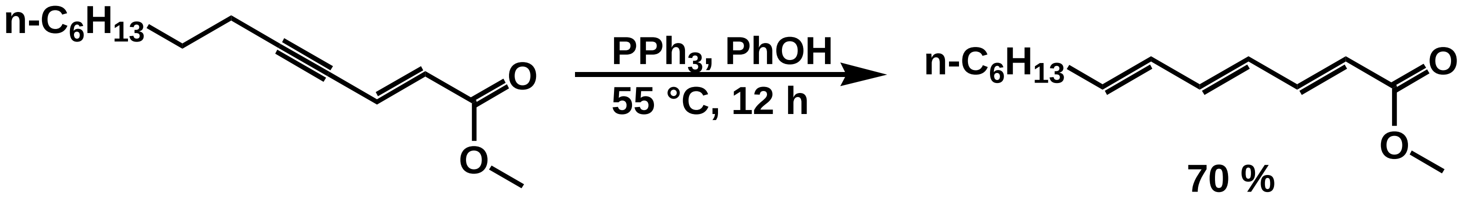
- Ketones, esters, amides
- AcOH promotes reaction
- More nucleophilic phosphines produced considerable amounts of oligamers.
- R_3N or $(RO)_3P$ = NR
- E,E-diene selective



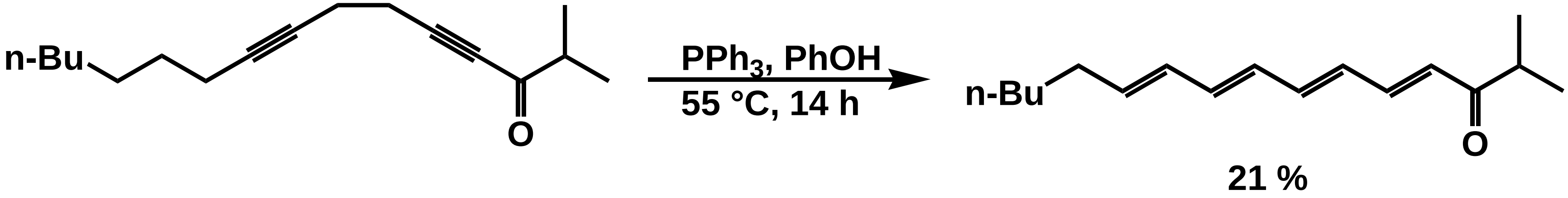
- Trost, B. M.; Kazmaier, V. *J. Am. Chem. Soc.* **1992**, *114*, 7933-7935.
- Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 1921-1923.

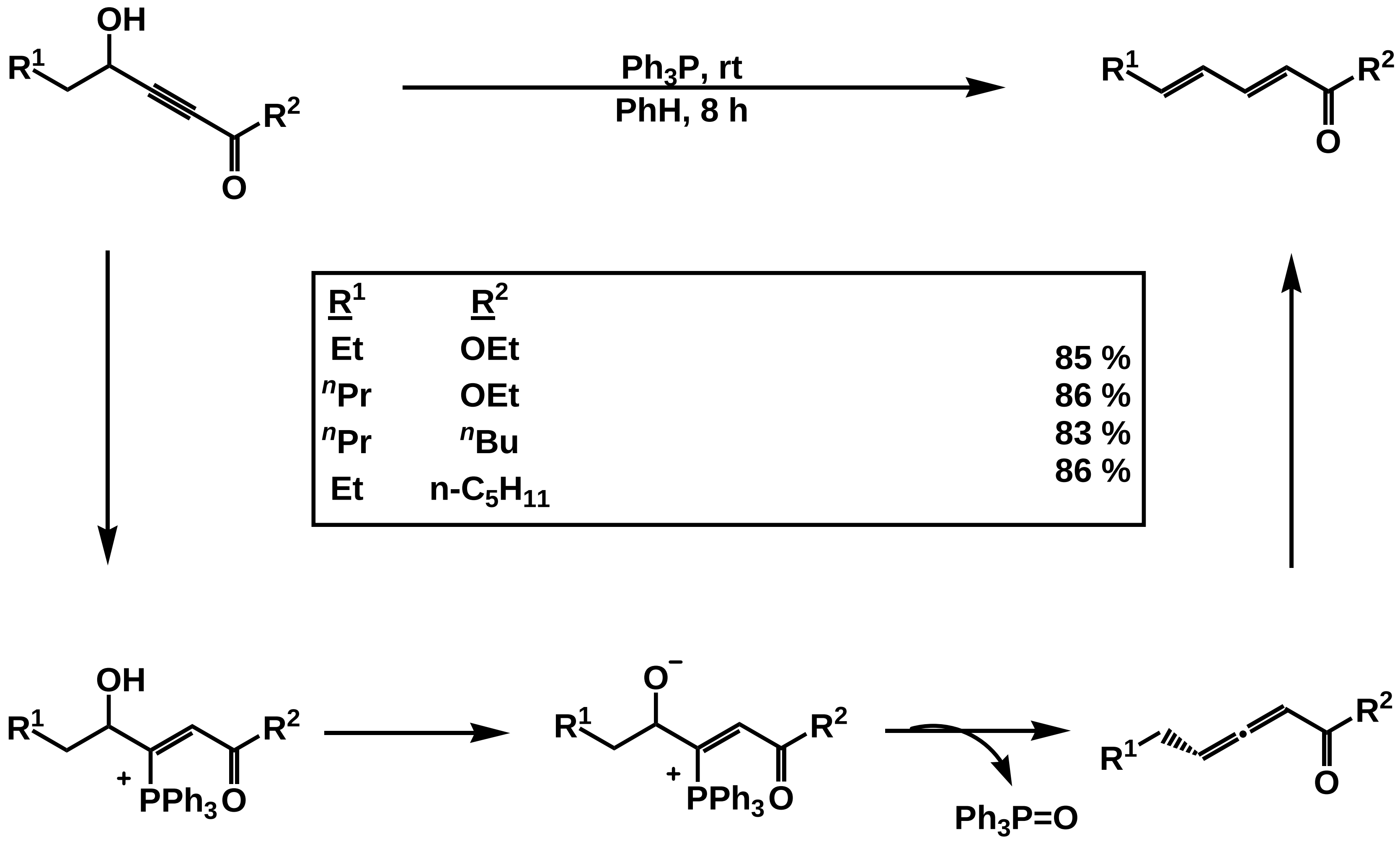


•Rychnovsky, S. P.; Kin, J. *J. Org. Chem.* **1994**, *59*, 2659-2660.



- E & Z enynes transfer selectively to E,E,E-trienes
- Ynoates transfer to dienes @ rt with PhOH

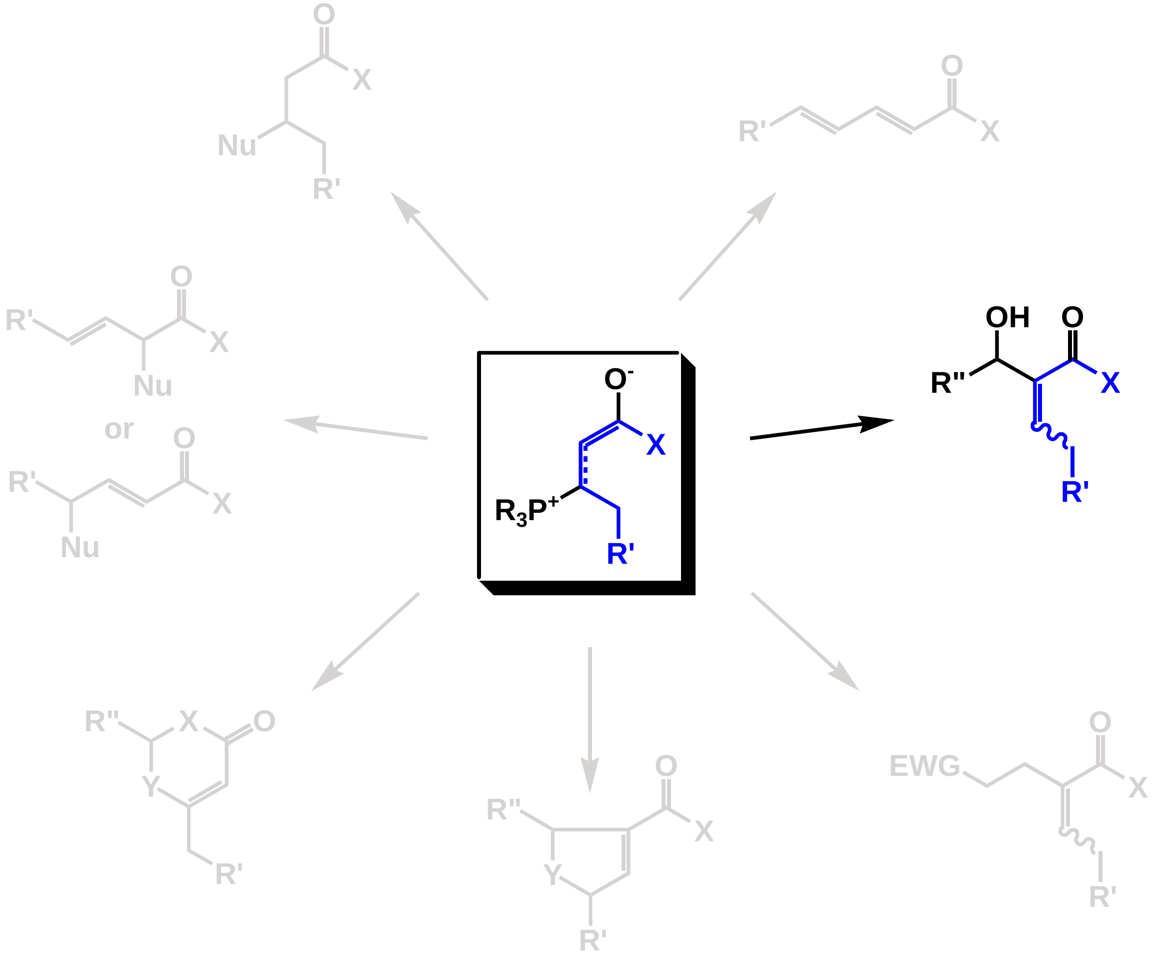


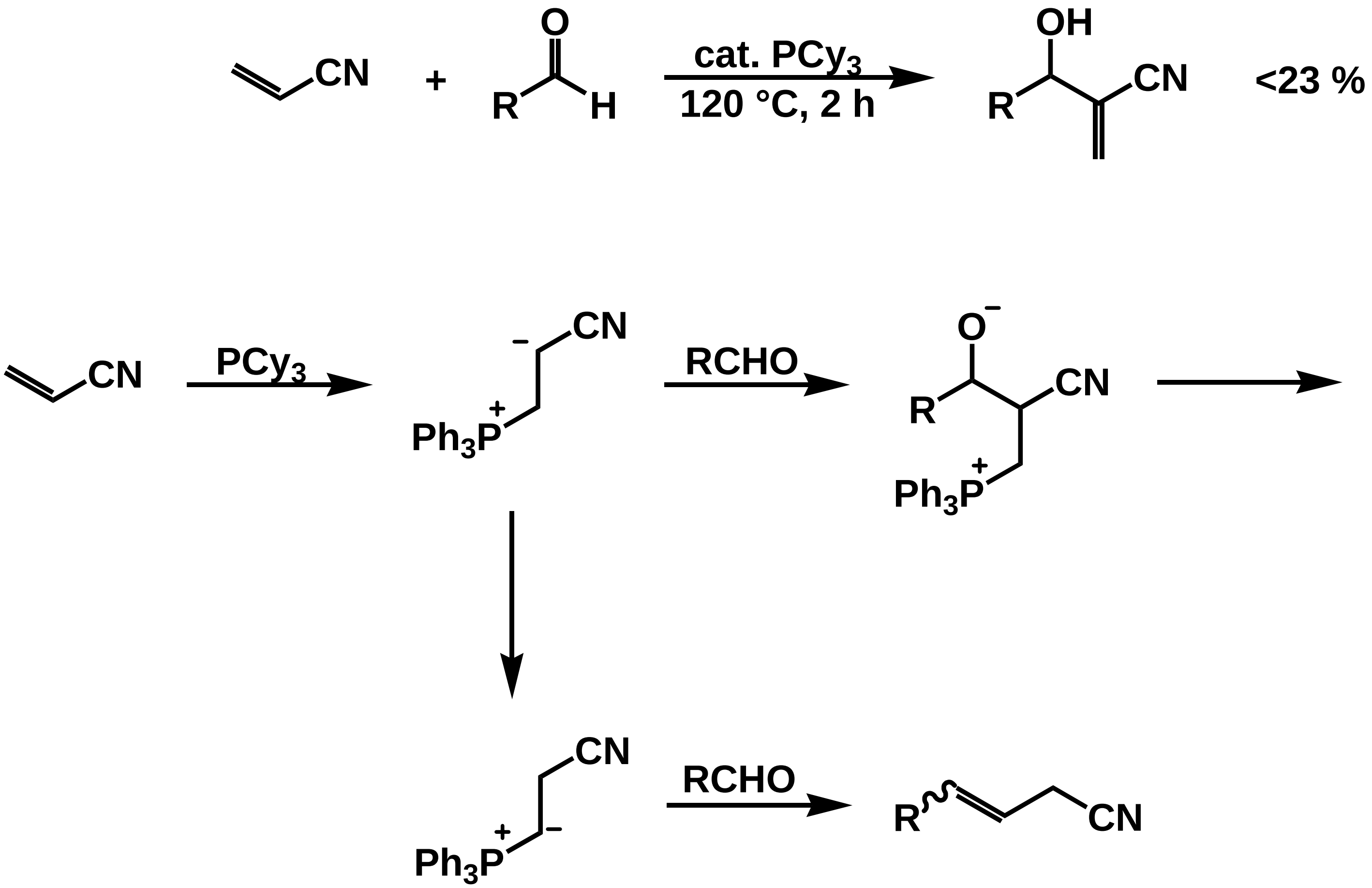


R^1	R^2	
Et	OEt	85 %
^{n}Pr	OEt	86 %
^{n}Pr	^{n}Bu	83 %
Et	n-C_5H_{11}	86 %

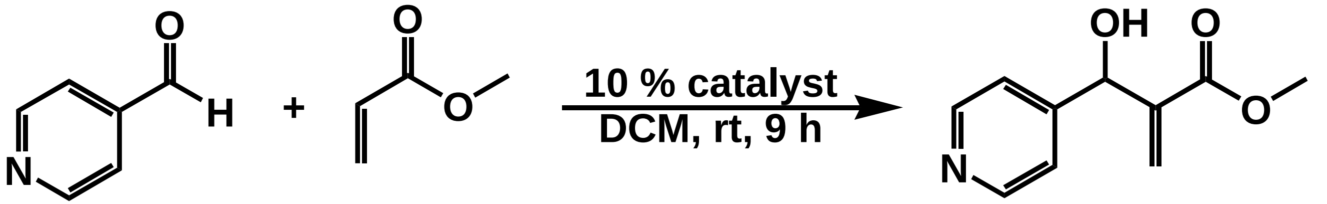
•Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 394-395.

Morita-Baylis-Hillman Reaction



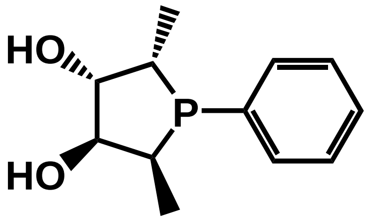


- •Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
- •Basavaiah, D.; Rao, A. J.; Batyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891.
- •Stephen Goble “The Morita-Baylis-Hillman Reaction” Organic Supergroup Meeting, November 19, 2003.

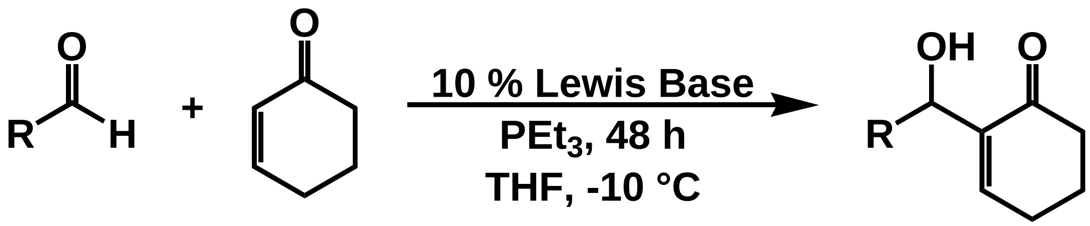


83 %, 17 % ee (+)

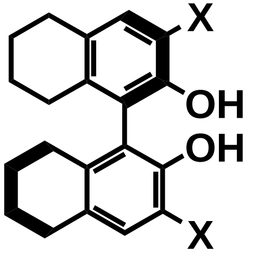
catalyst =



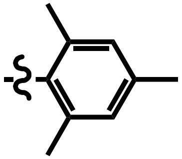
- Li, W.; Zhang, Z.; Ziao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489-3496.



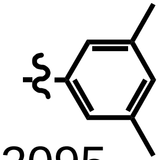
Entry	R	Lewis Base	% yield	% ee
1	PhCH$_2$CH$_2$	A	88	90
2	Cy	B	71	96
3	^{i}Pr	B	82	95
4	Ph	A	40	67
5	PhCHCH	B	39	81



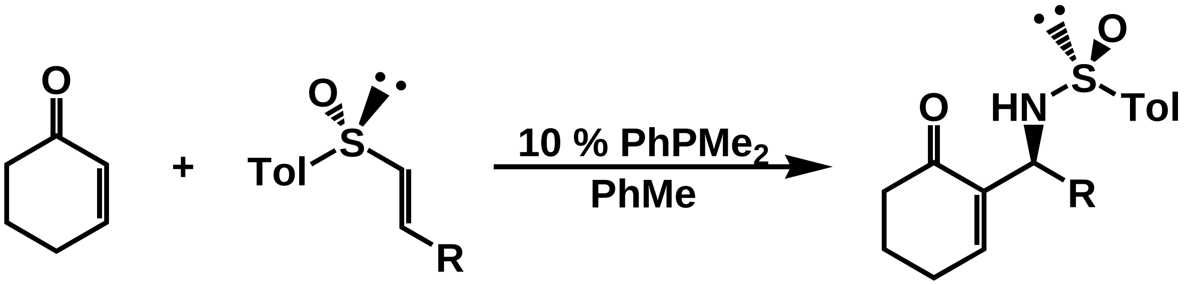
A: X =



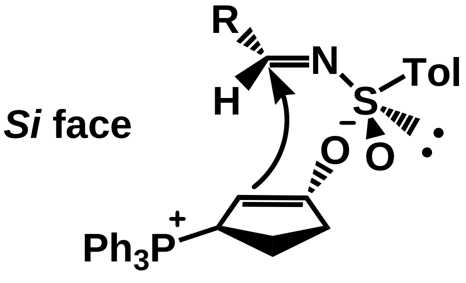
B: X =



- McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *123*, 12094-12095.

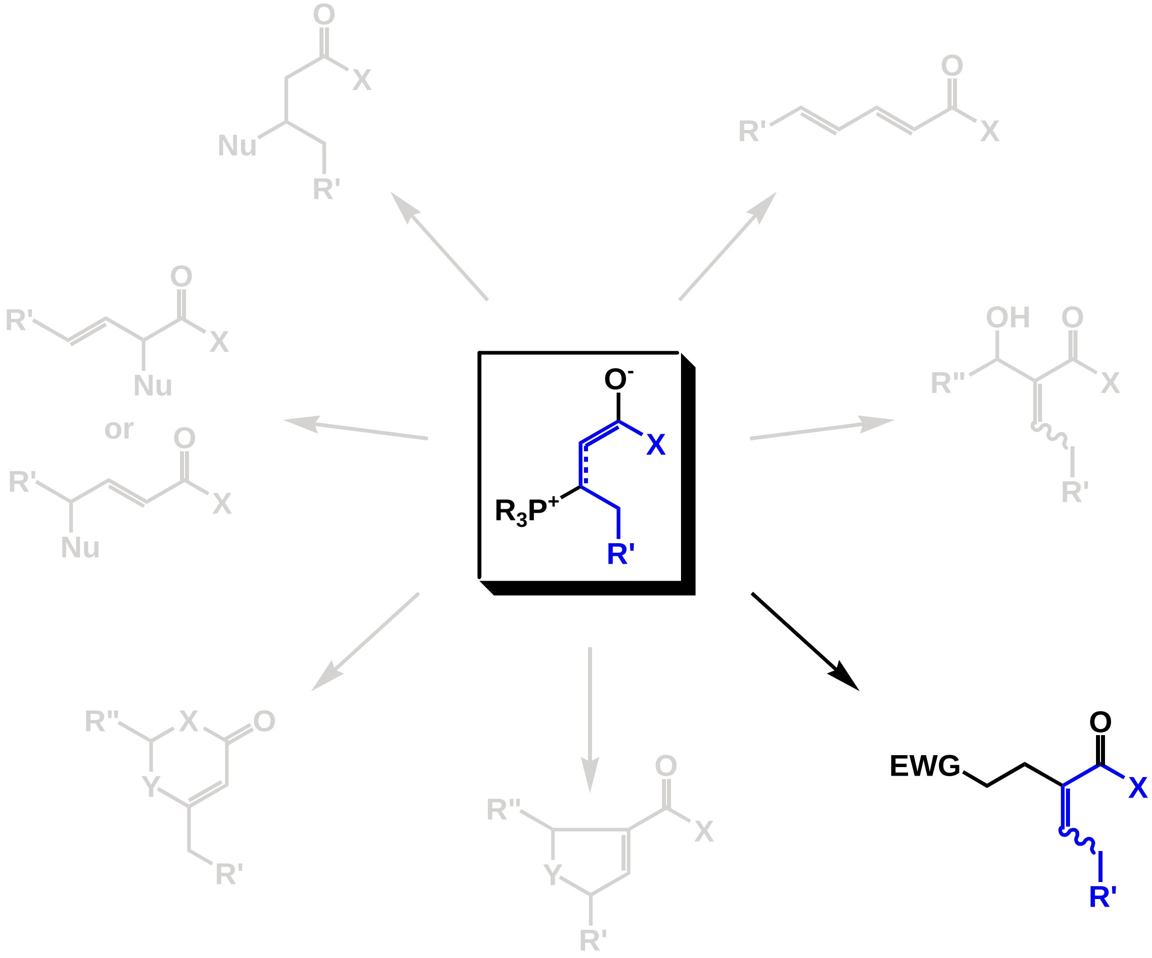


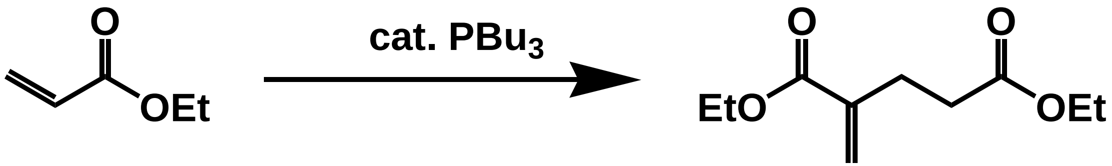
R		
$PhCH_2CH_2$	71 %	84 % de
Bu	52 %	82 % de
m-FC_6H_4	76 %	76 % de
p-BrC_6H_4	83 %	86 % de
m,p-$Cl_2C_6H_3$	80 %	80 % de



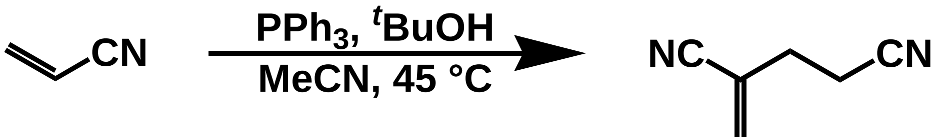
- Shi, M.; Xu, Y. *Tetrahedron Asym.* **2002**, *13*, 1195-1200.

Rauhut-Currier Reaction



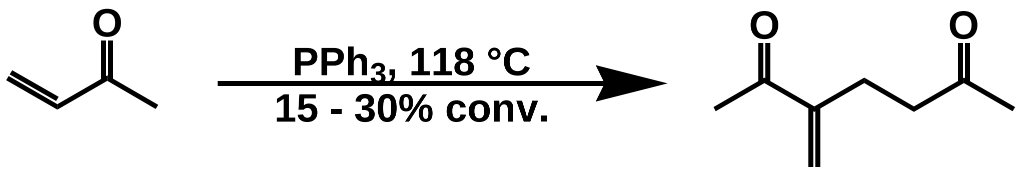


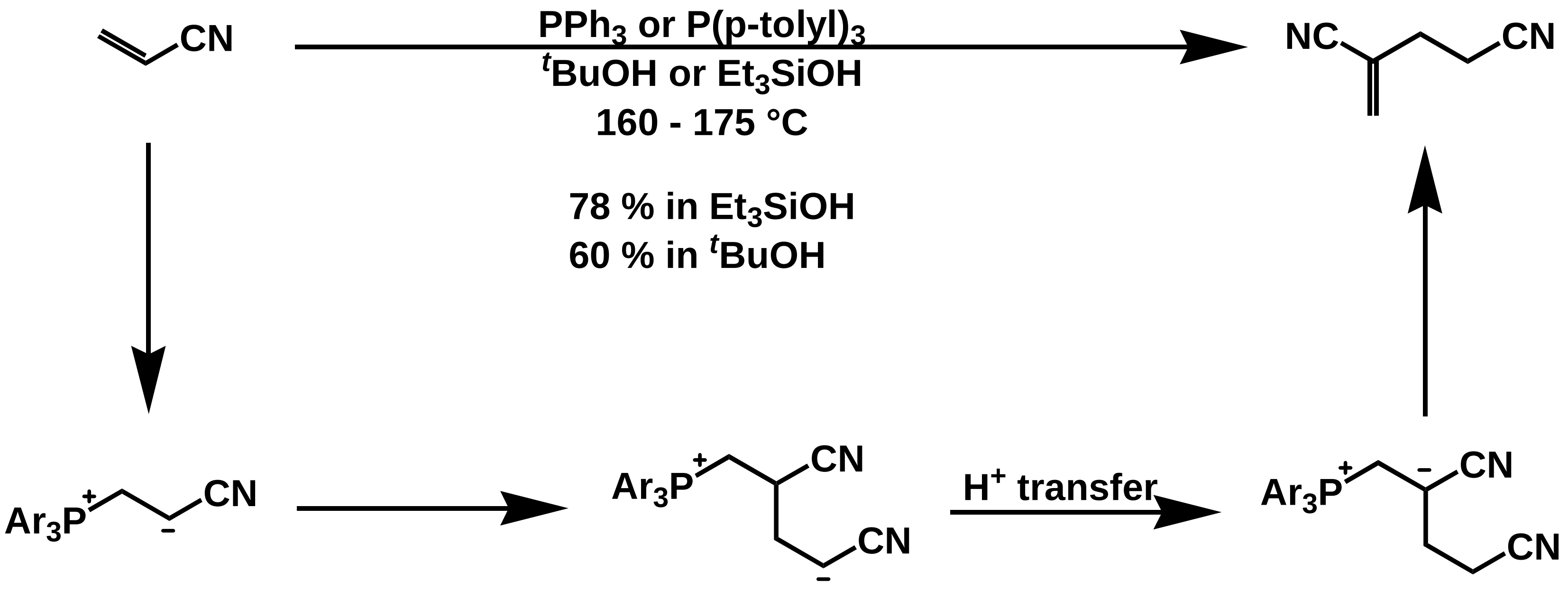
- Rauhut, M.; Currier, H. U. S. Patent 3074999 **1963**



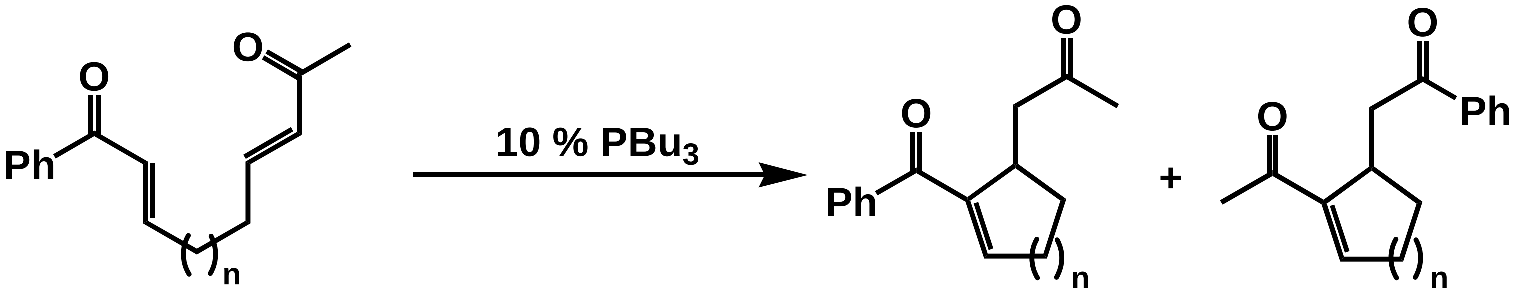
- Reaction let to polymerization without proton donor to terminate process

- Baizer, M. M.; Anderson, J. D. *J. Org. Chem.* **1965**, *30*, 1357-1360.





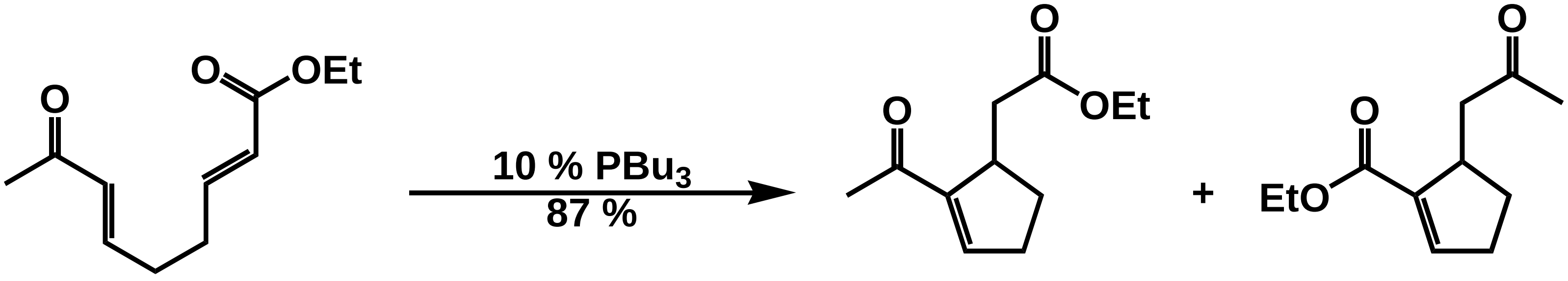
- •McClure, J. D. U. S. Patent 3,225,083 **1965**.
- •McClure, J. D. *J. Org. Chem.* **1970**, *35*, 3045-3048.



n = 1 1 : 1 79 %

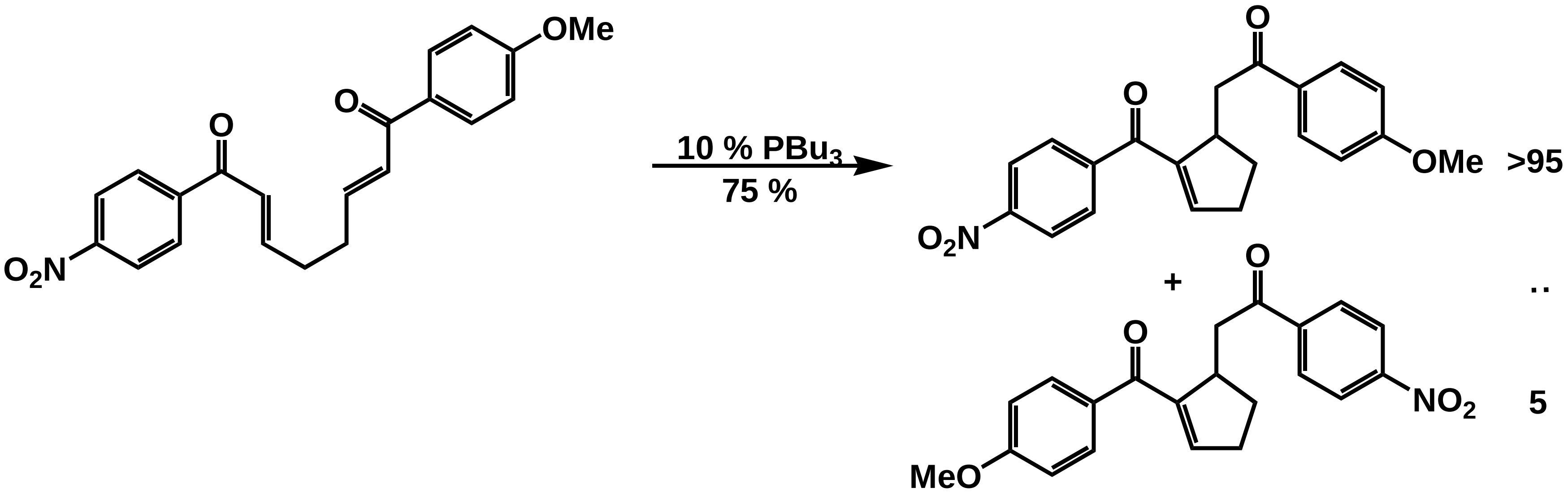
n = 2 7 : 1 77 %

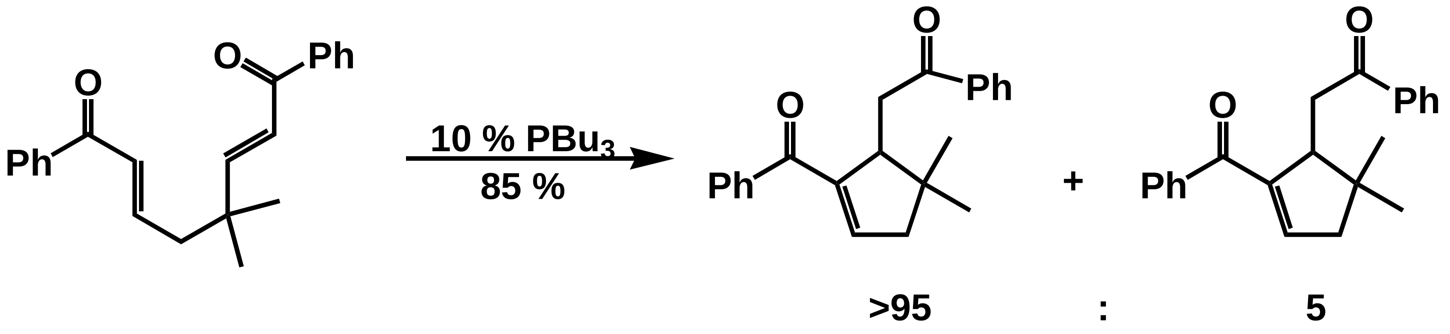
- Increased rate with polar solvent
- PBu$_3$addition is indiscriminate: 5-member ring is trapped by cyclization
  6-member ring → cyclization becomes rate determining

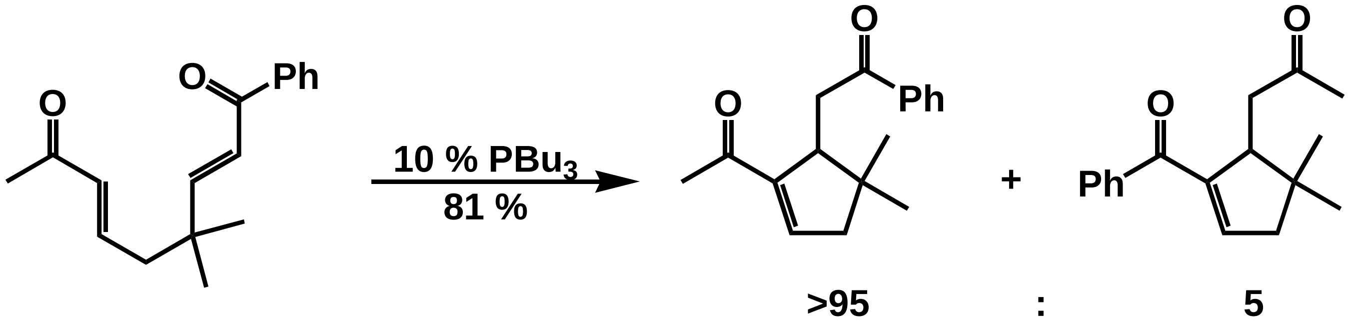


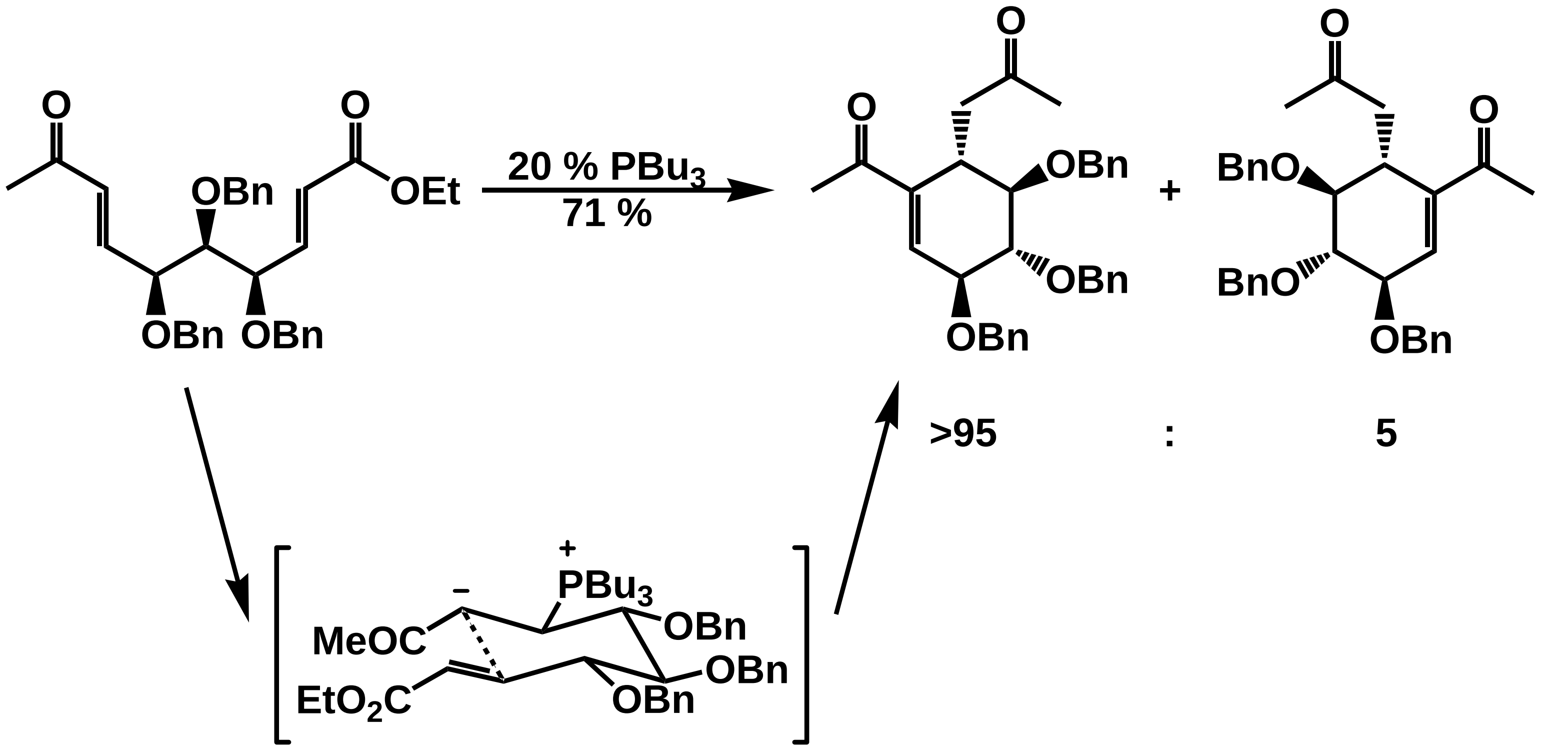
>95 : 5

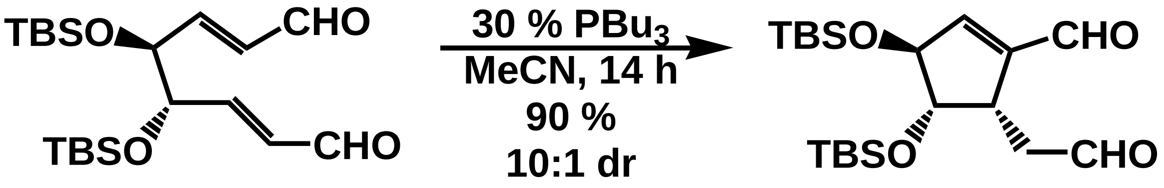
- Wang, L.; Luis, A. L.; Agapiou, K.; Jang, H.; Krische, M. *J. Am. Chem. Soc.* **2002**, *124*, 2402-2403.


O₂N
O
O
OMe
10 % PBu₃
75 %
O
O
O₂N
OMe
>95
+
:
O
O
MeO
NO₂
5

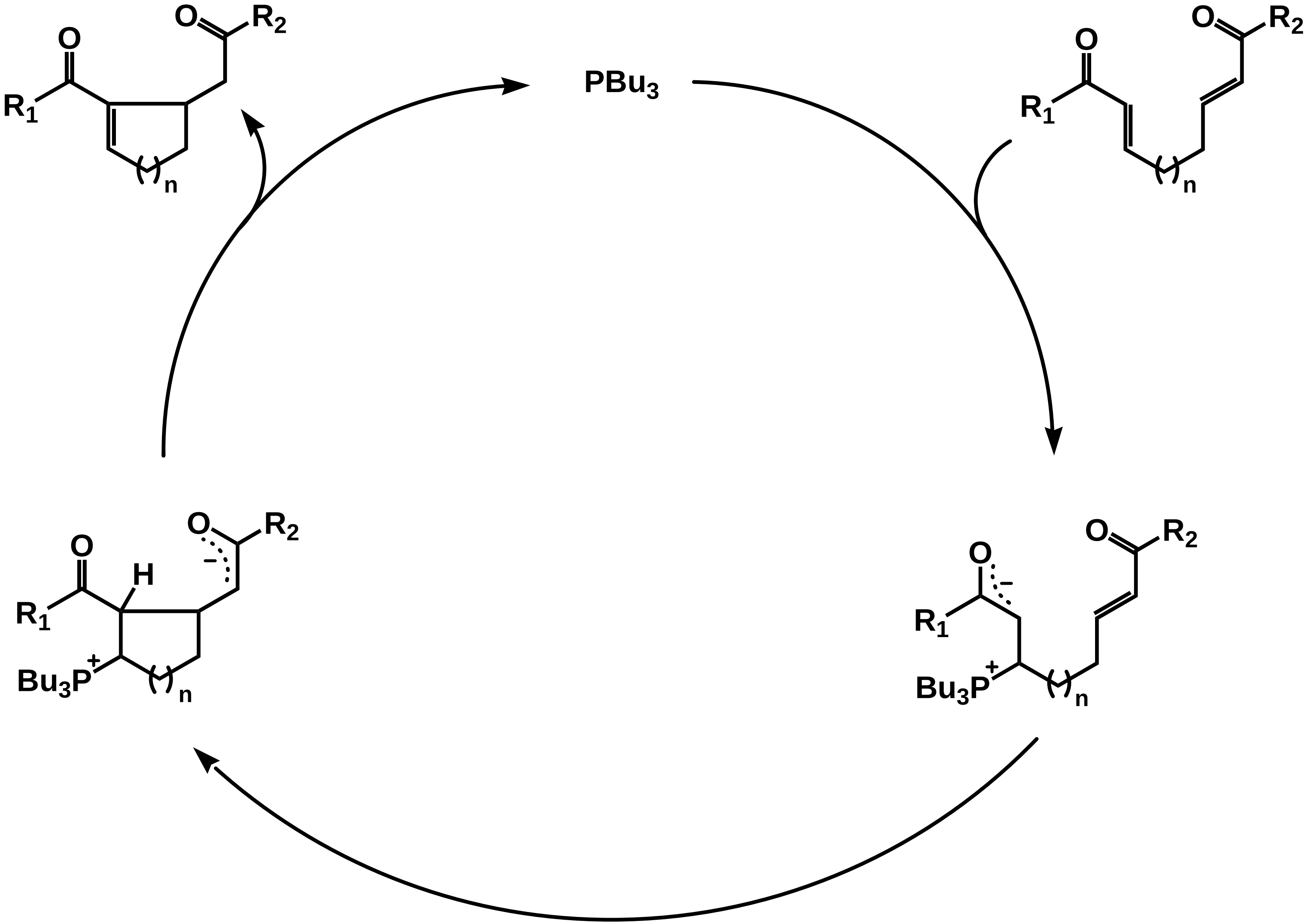

Ph
O
O
Ph
10 % PBu₃
85 %
O
O
Ph
Ph
+
O
O
Ph
Ph
>95
:
5


O
O
Ph
10 % PBu₃
81 %
O
O
Ph
+
O
O
Ph
>95
:
5

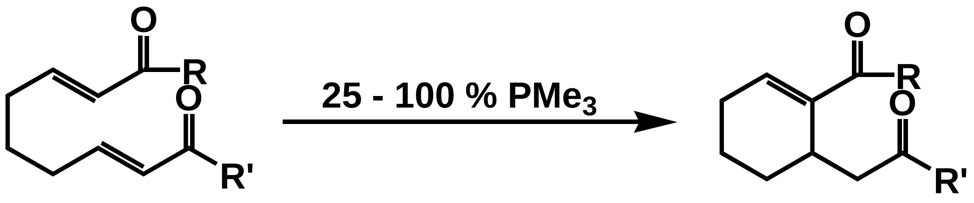




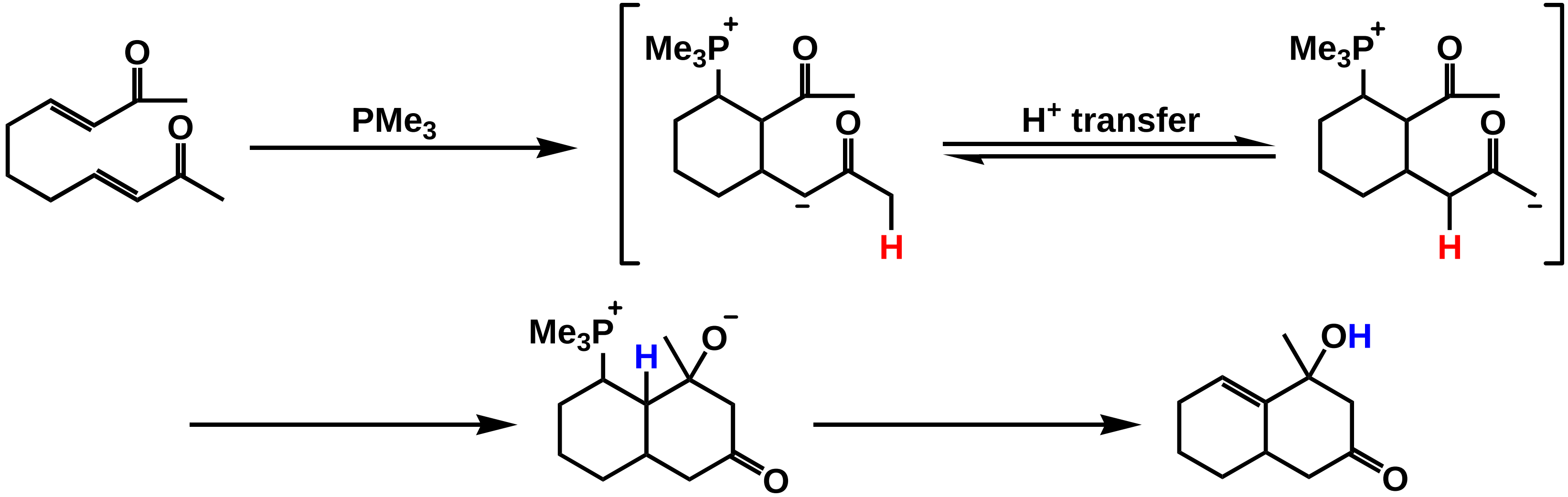
- Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404-2405.



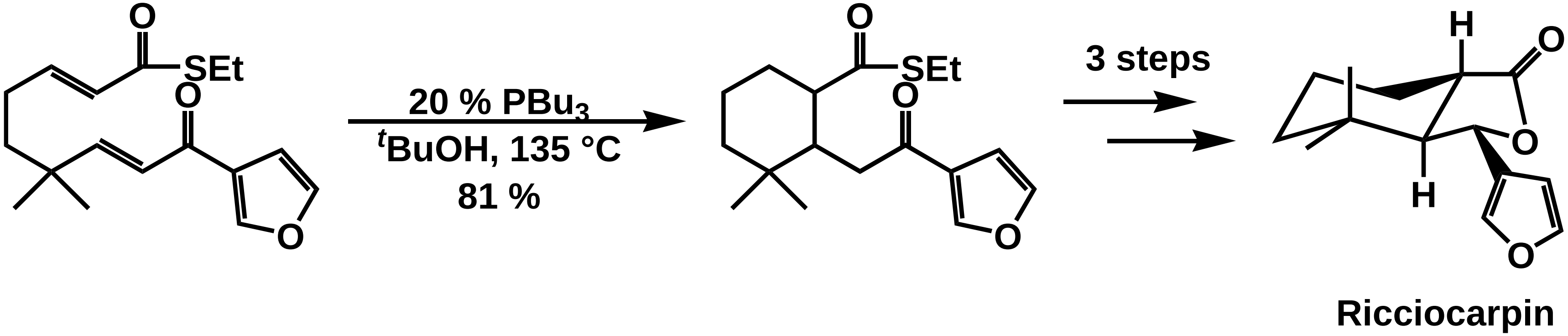
- With acetone-d6, not deuterium incorporation was observed



R	R'	
Me	OMe	83 %
Me	Me	46 % → 23 % aldol
H	Me	45 % → 20 % aldol
H	OMe	47 % (67 % in MeCN)



- Presumably PMe_3 is slow to eliminate allowing for proton transfer

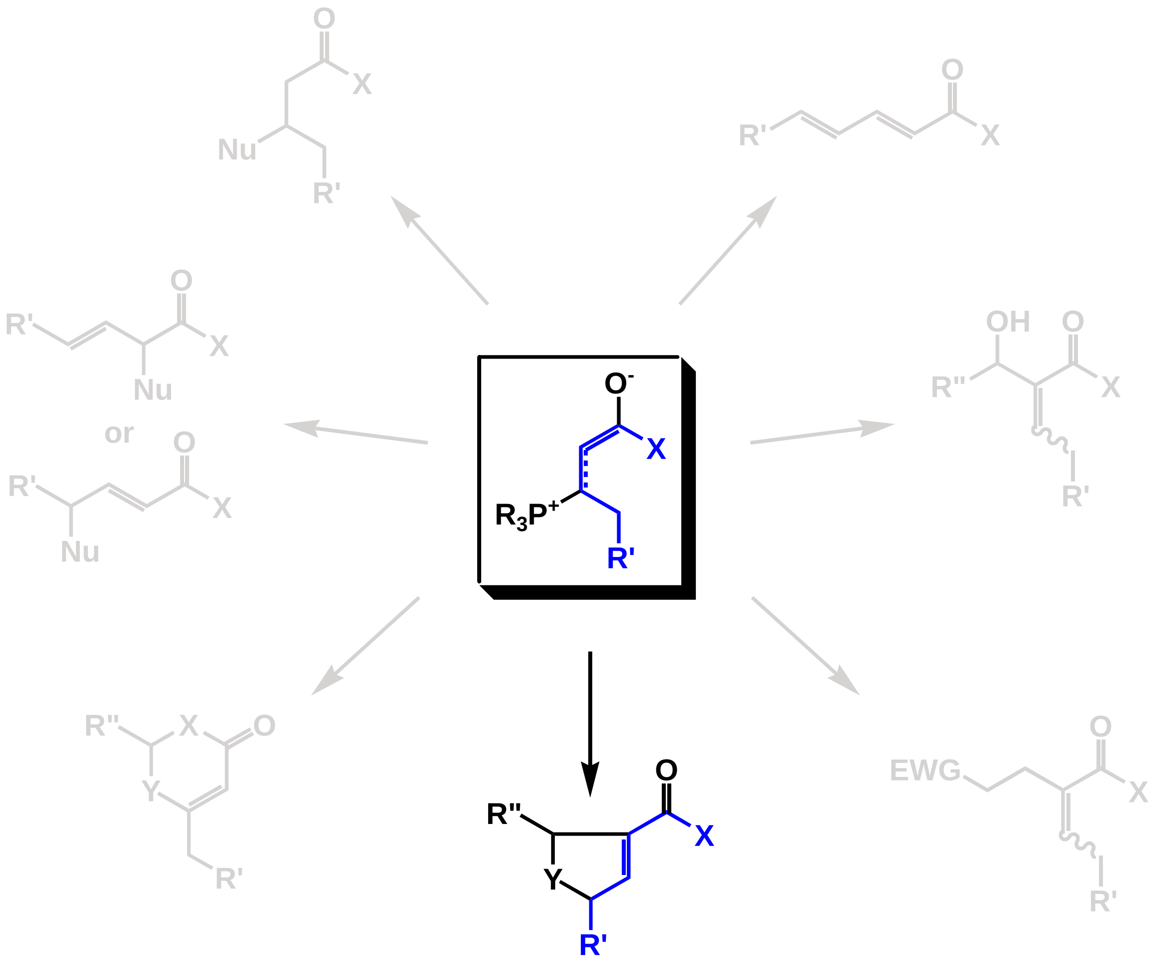


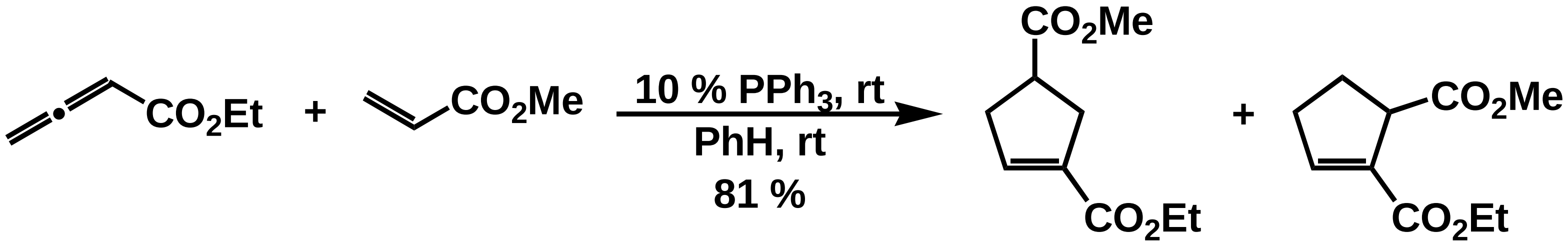
- Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737-1740.

- Thioenolates work well with MBH reactions

- Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3667-3690.

[3+2]

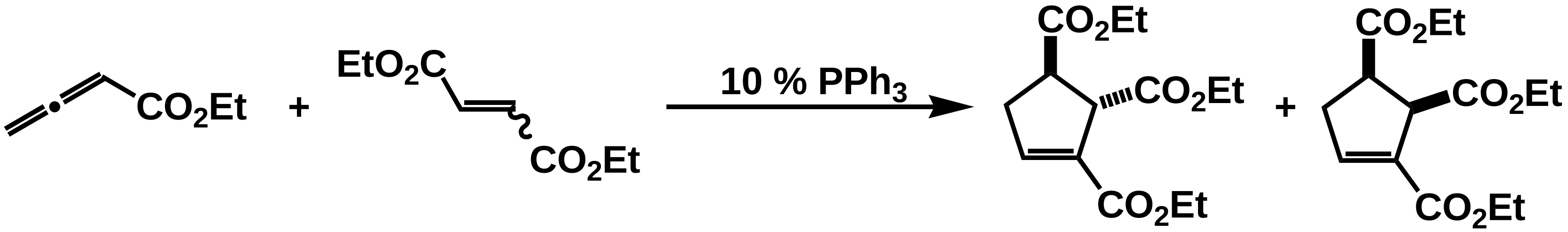




10 % PPh_3, rt
PhH, rt
81 %

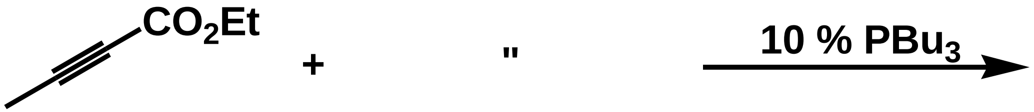
80 : 20

•Ketones & nitriles



10 % PPh_3

trans	67 %	1	:	0
cis	46 %	0	:	1

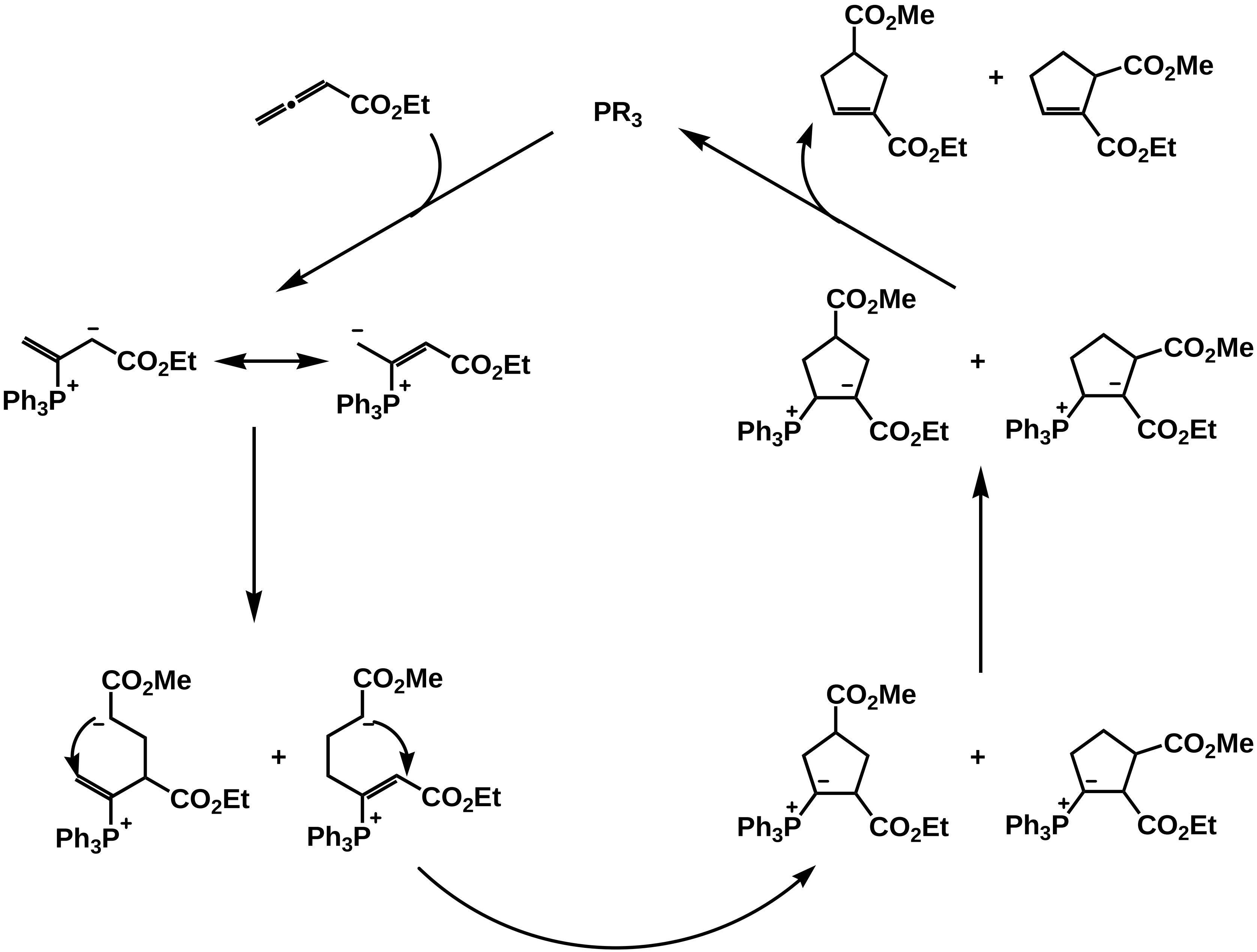


10 % PBu_3

" "

trans	88 %	1	:	0
cis	91 %	1	:	0

•Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906-2908.



CO2Et
PR3
CO2Me
CO2Et
+
CO2Me
CO2Et
Ph3P+
CO2Et
Ph3P+
CO2Et
CO2Me
CO2Et
Ph3P+
+
CO2Me
CO2Et
Ph3P+
CO2Me
CO2Et
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CO2Et
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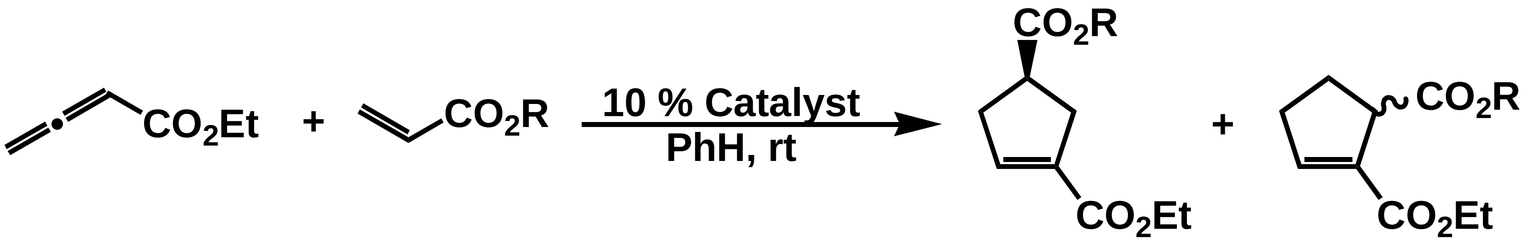
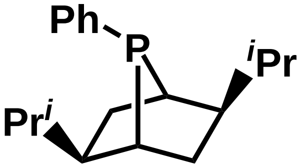
Ph3P+
+
CO2Me
CO2Et
Ph3P+



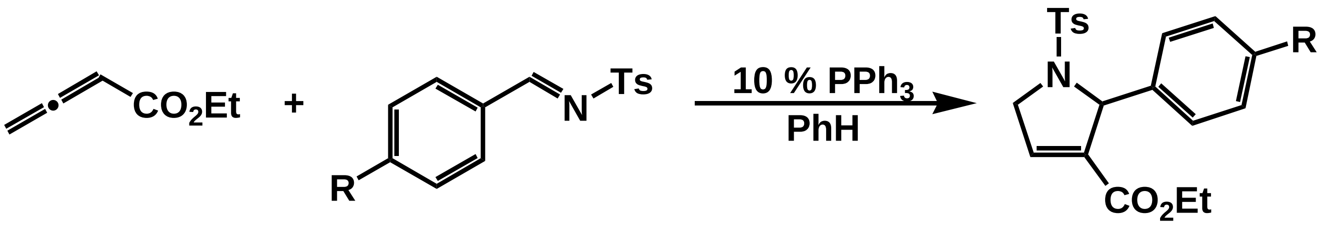
A **B**

	R	%yield	%ee	A:B
	Et	87	79 (R)	96:4
	^{i}Bu	92	88 (R)	100:0
0 °C →	^{i}Bu	88	93 (R)	100:0
	^{t}Bu	75	88 (R)	95:5

Catalyst =

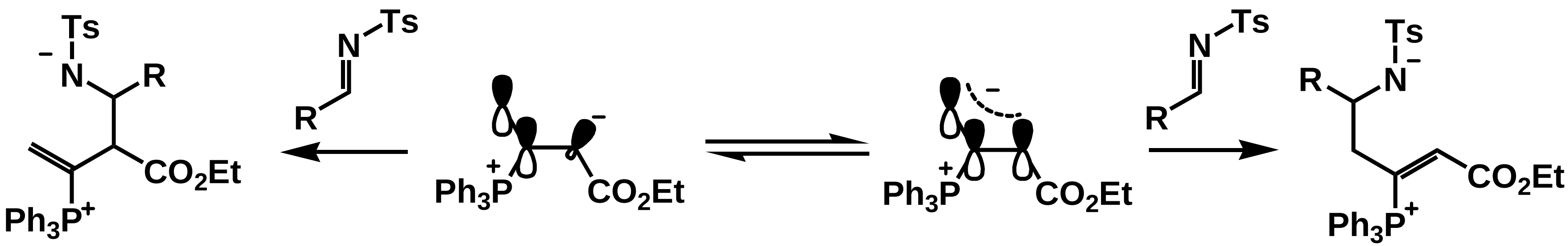


- Zhu, G.; Chem, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**,*119*, 3836-3837.

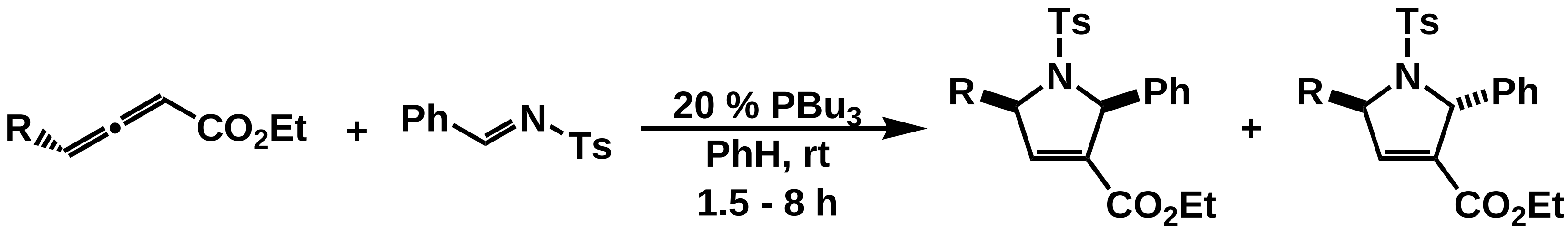


R	
H	98 %
OMe	98 %
NO$_2$	88 %

- Ts protection is necessary
- One regioisomer



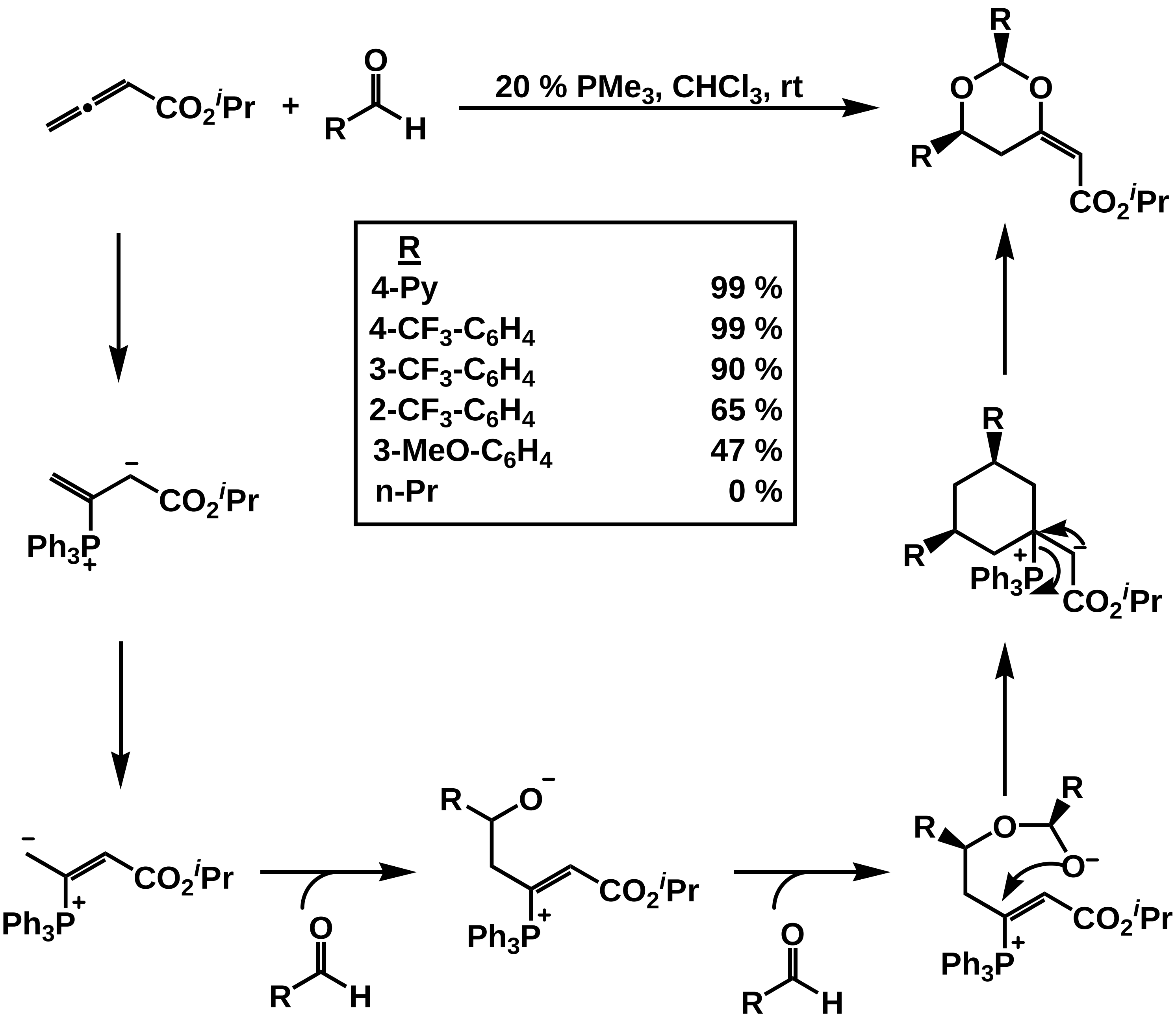
- Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461-3464.
- Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031-5041.



R				
Me	89 %	91	:	9
Et	99 %	95	:	5
^{i}Pr	99 %	100	:	0
^{t}Bu	99 %	100	:	0
Ph	99 %	100	:	0

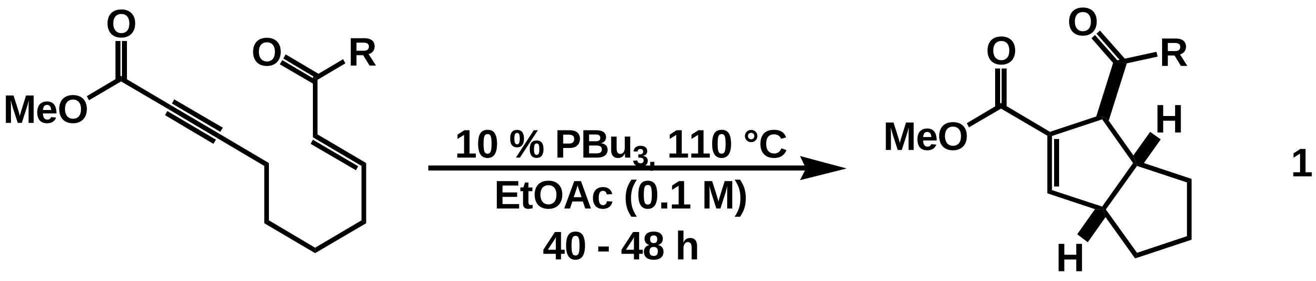
- Aryl aldimines only
- PBu_3 necessary for initial 1,4-addition

- Zhu, X.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276-6282.



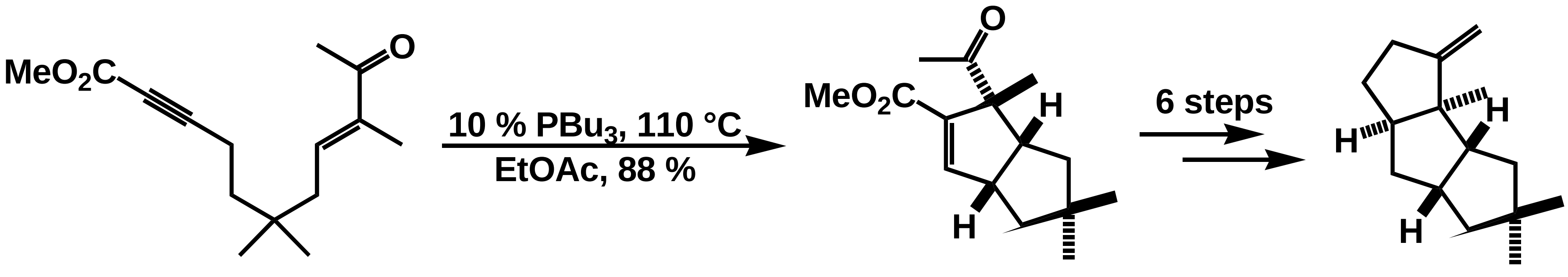
R	
4-Py	99 %
4-CF$_3$-C$_6$H$_4$	99 %
3-CF$_3$-C$_6$H$_4$	90 %
2-CF$_3$-C$_6$H$_4$	65 %
3-MeO-C$_6$H$_4$	47 %
n-Pr	0 %

- Zhu, S.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387-1390.



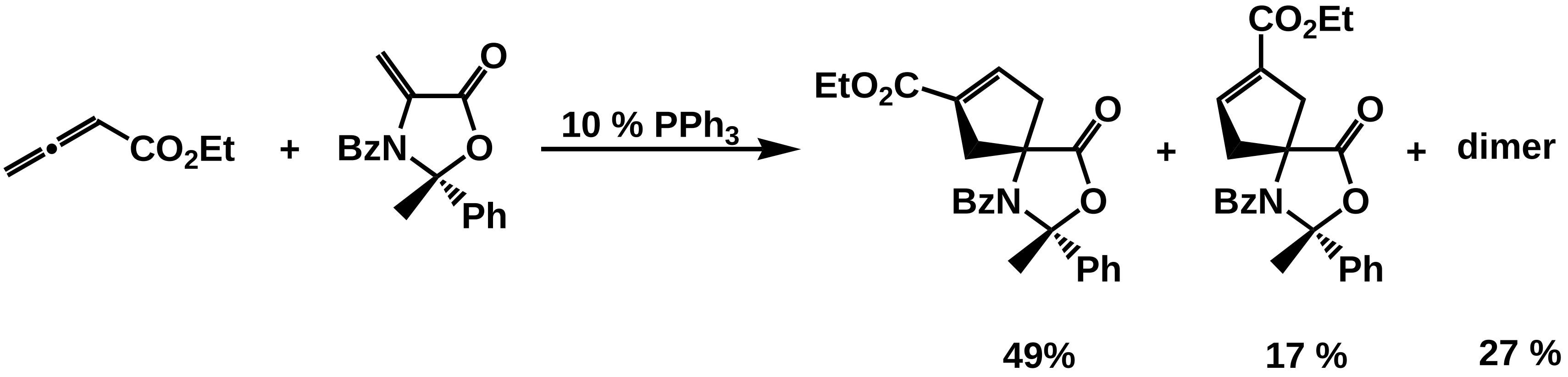
1 isomer

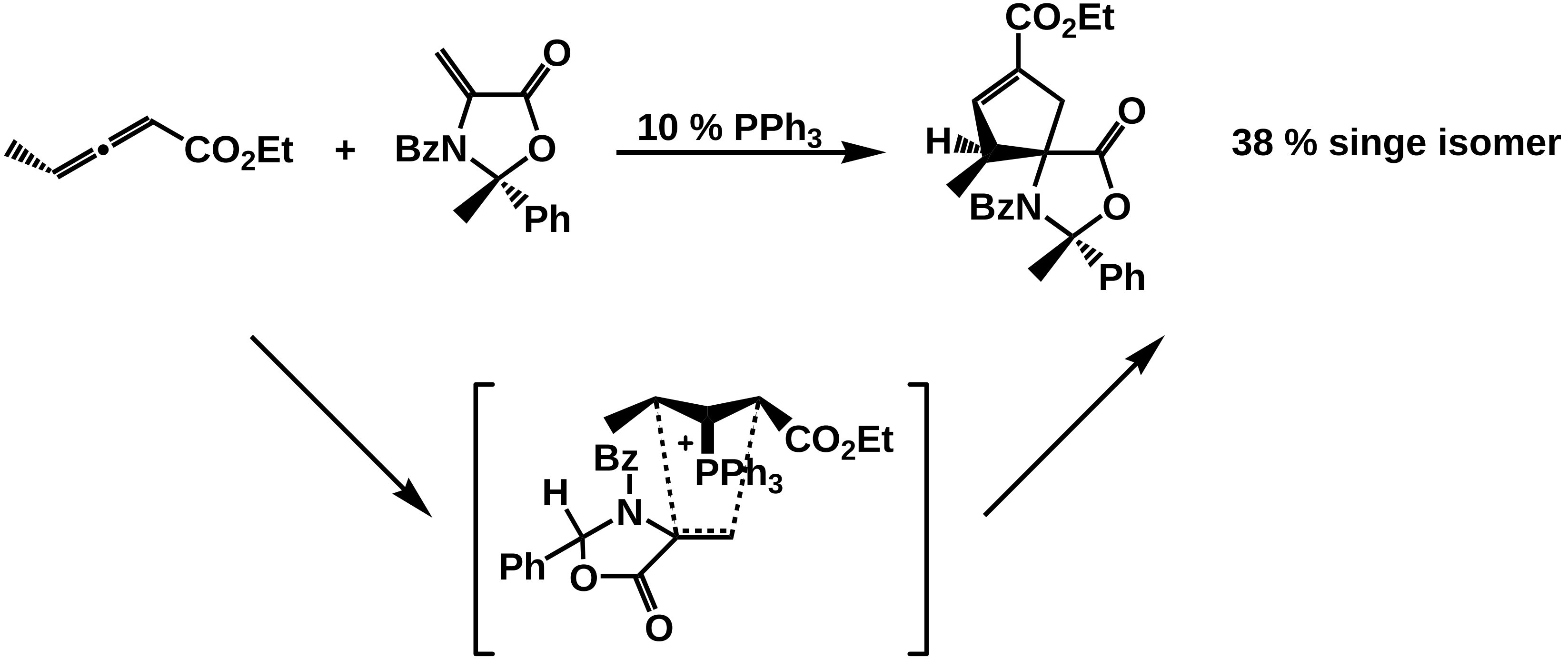
R	
Ph	76 %
SEt	78 %
2-furyl	74 %
c-Pr	86 %



Hirsutene

- Wang, J.; Ng, s.; Krishe, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682-3683.
- Wang, J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855-5857.





- Pyne, S. G.; Schafer, K.; Skelton, B. W.; White, A. H. *Chem. Commun.* **1997**, 2267-2268.

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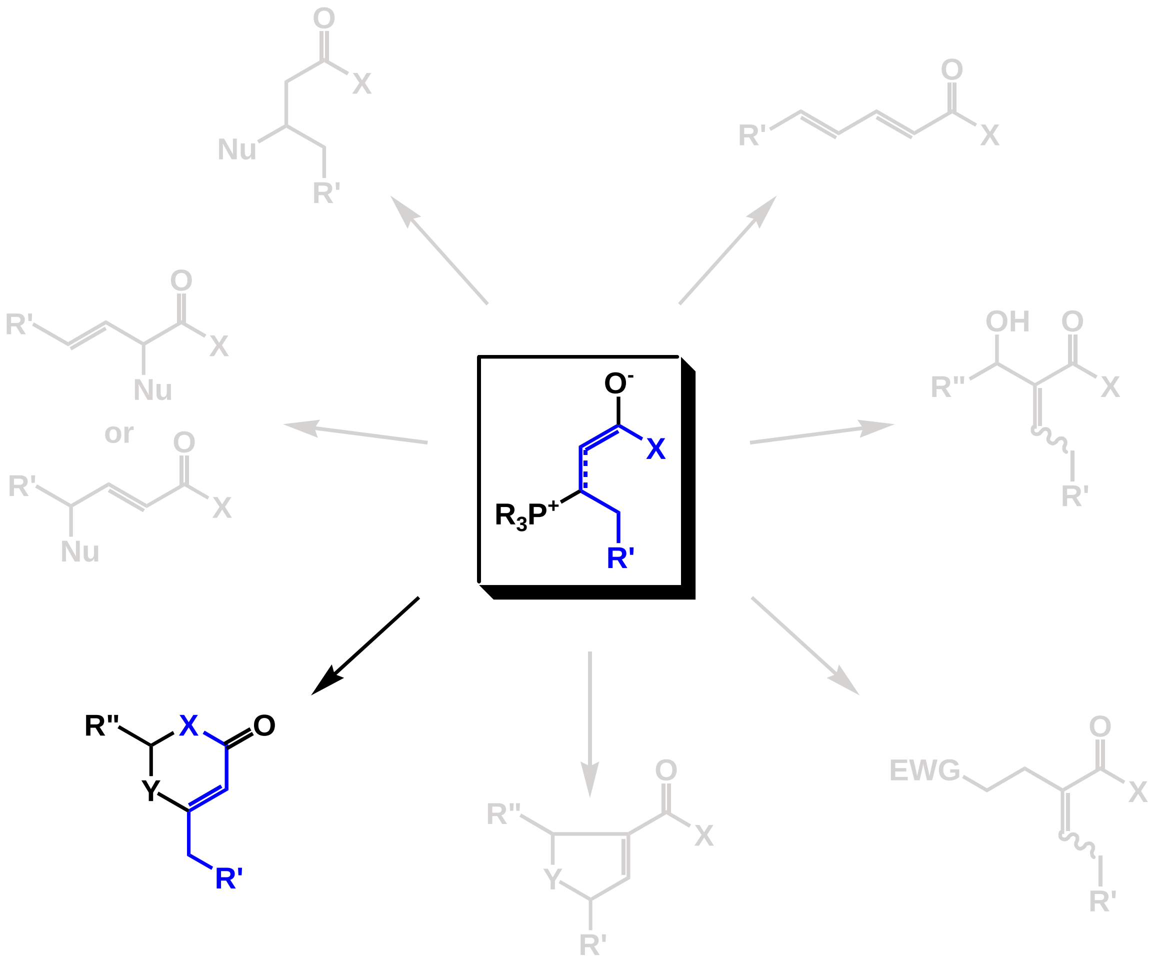
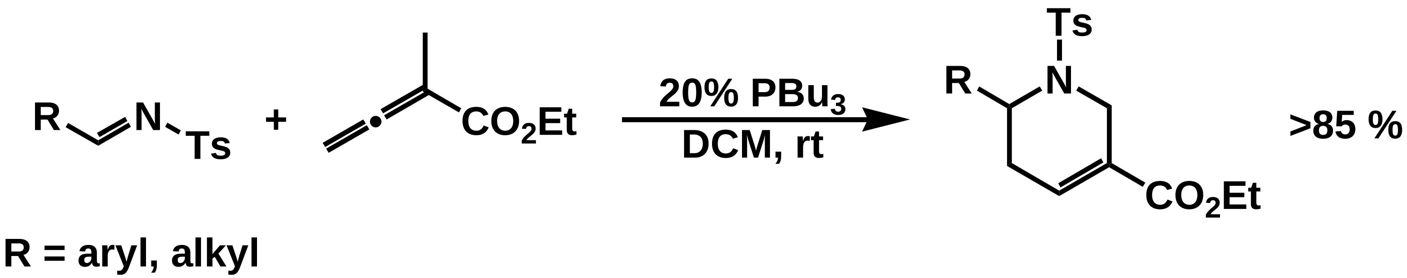
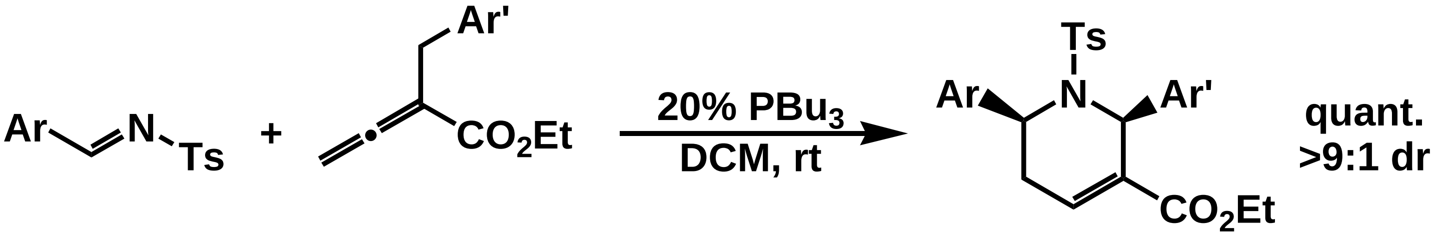


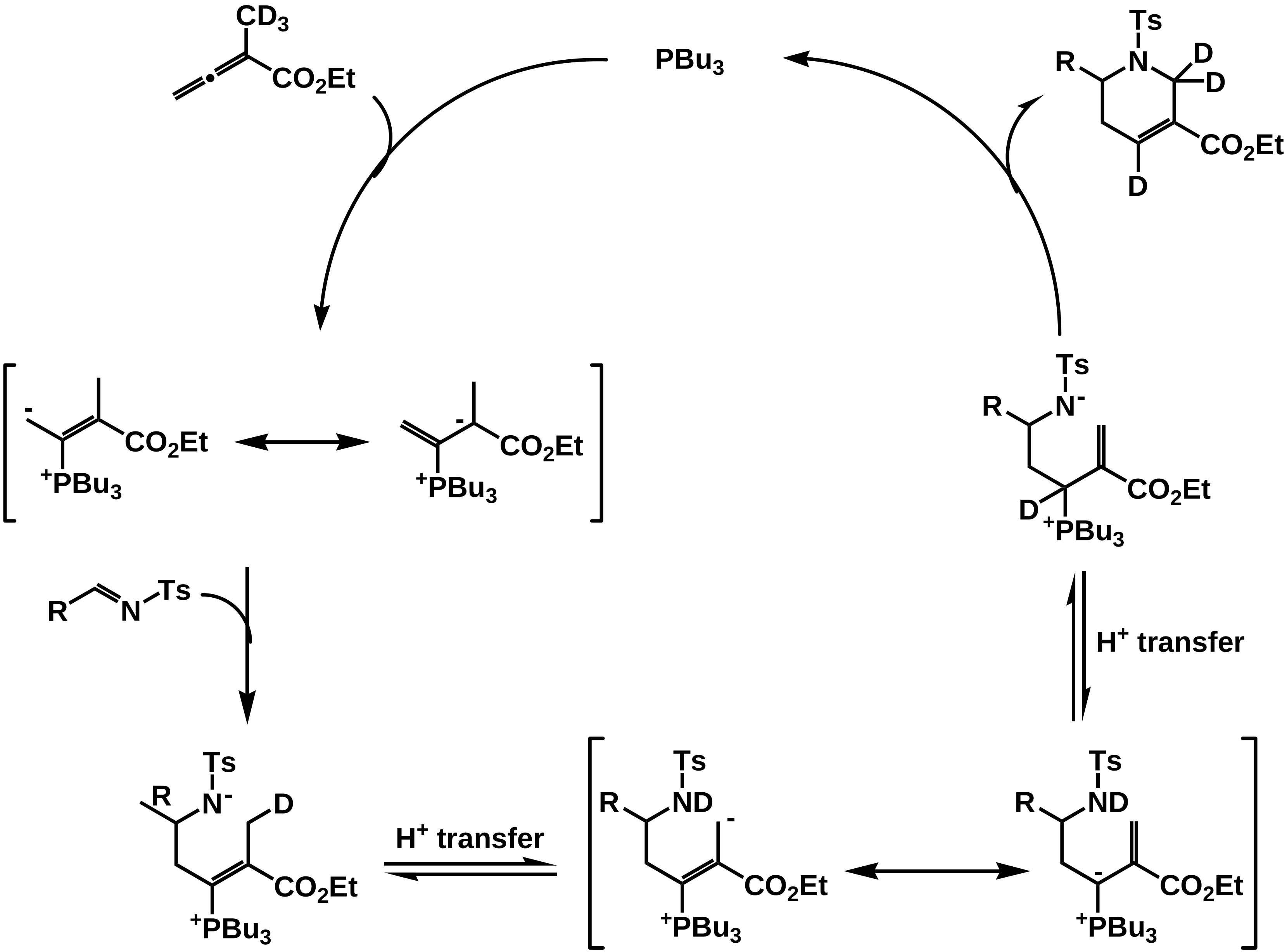


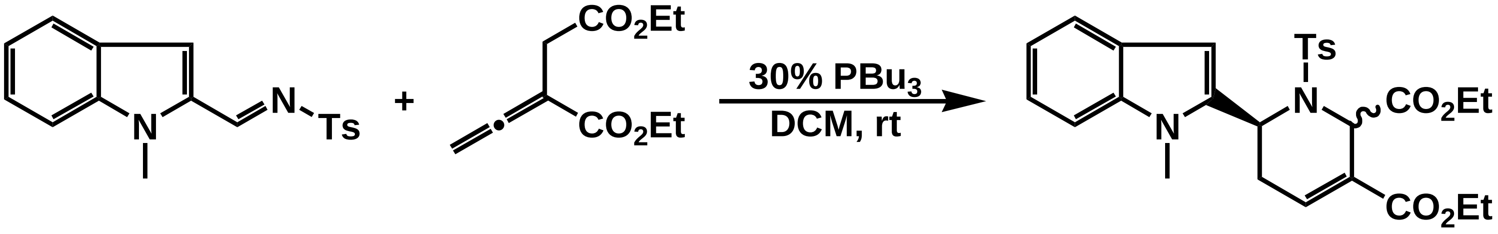
→ Free hydroxyl or pyrrolyl groups were disastrous

→ Aliphatic imines, if stable to reaction conditions, gave 85 % with $NaCO_3$



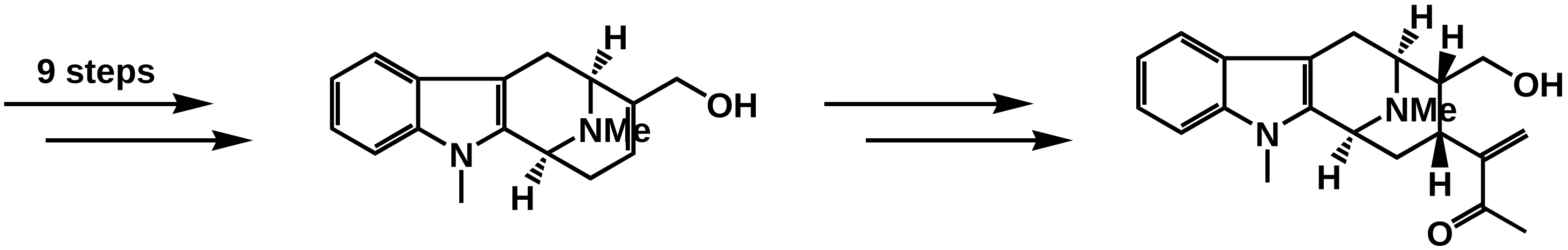
•Zhu, X. F.; Lan, P.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716-4717.


CD3
CO2Et
PBu3
Ts
R
N
D
D
CO2Et
D
-
CO2Et
+PBu3
-
CO2Et
+PBu3
Ts
R
N-
CO2Et
D
+PBu3
R
N
Ts
H+ transfer
Ts
R
N-
D
CO2Et
+PBu3
H+ transfer
Ts
R
ND
-
CO2Et
+PBu3
Ts
R
ND
-
CO2Et
+PBu3



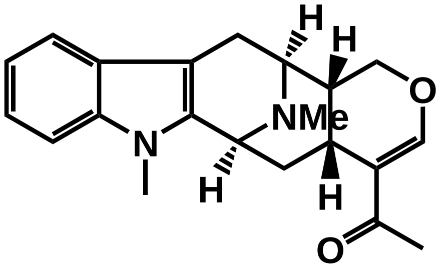
73 %
3:1 dr

- When BOC protected indole was used, 84 %, 1.1:1 dr



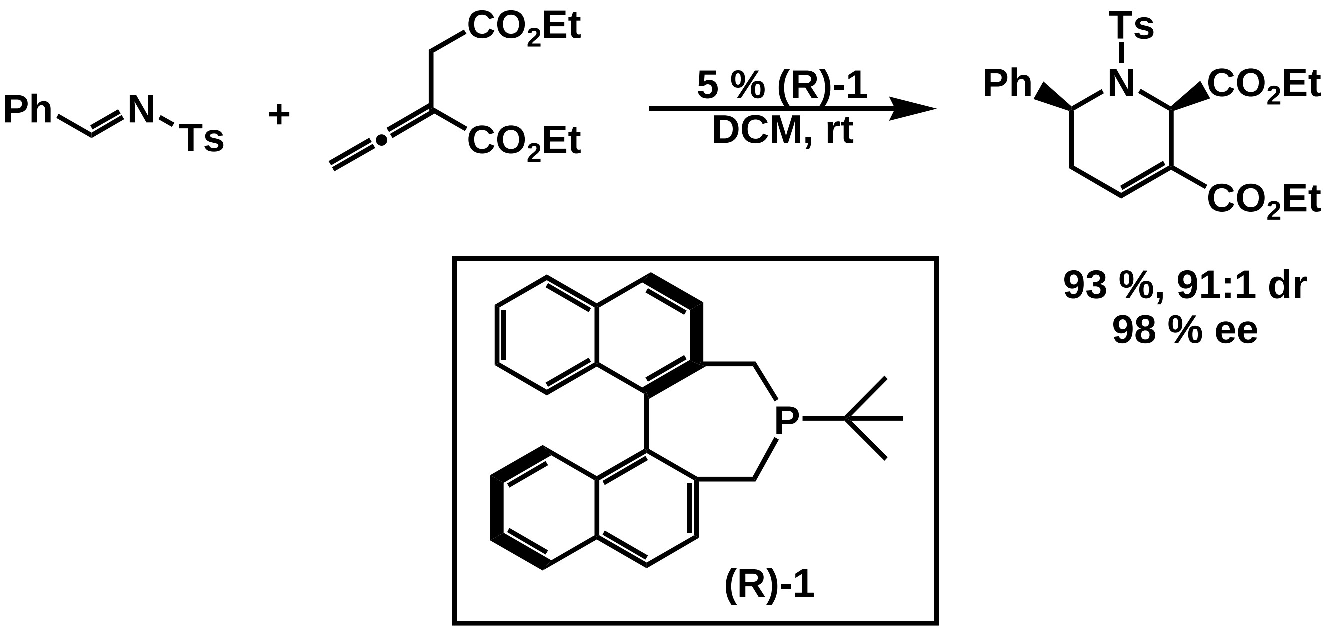
31 %
(26 %, 12 steps)

(+)-Macroline



(-)-Alstonerine

- Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289-4291.

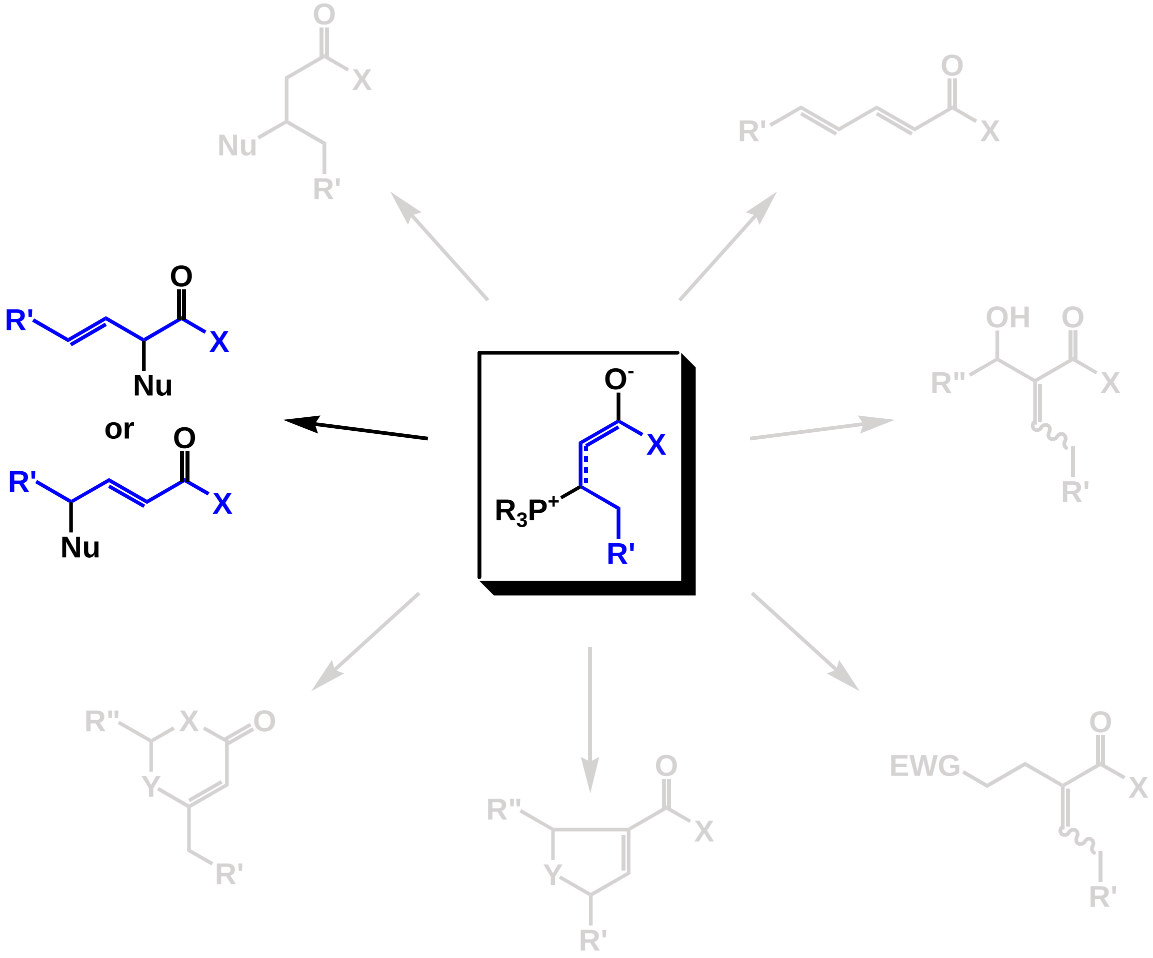


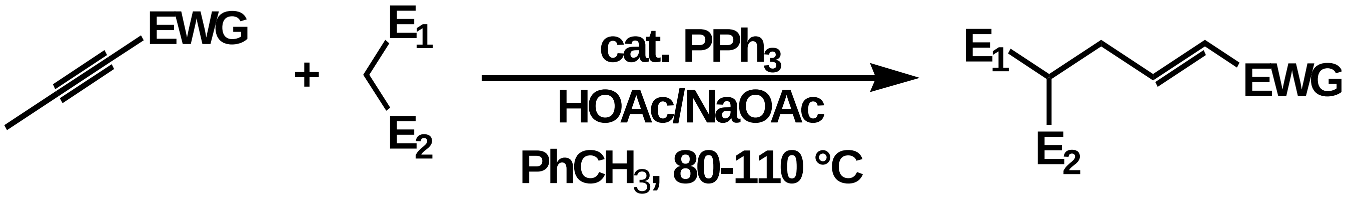
93 %, 91:1 dr
98 % ee

- >5 % catalyst needed without 2nd ester group
- Various aromatic aldimines tolerated
- Yields 75-99 %, >96 % ee, >9:1 cis:trans

- Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234-12235.

Umpolung





EWG = ester, ketone, amide

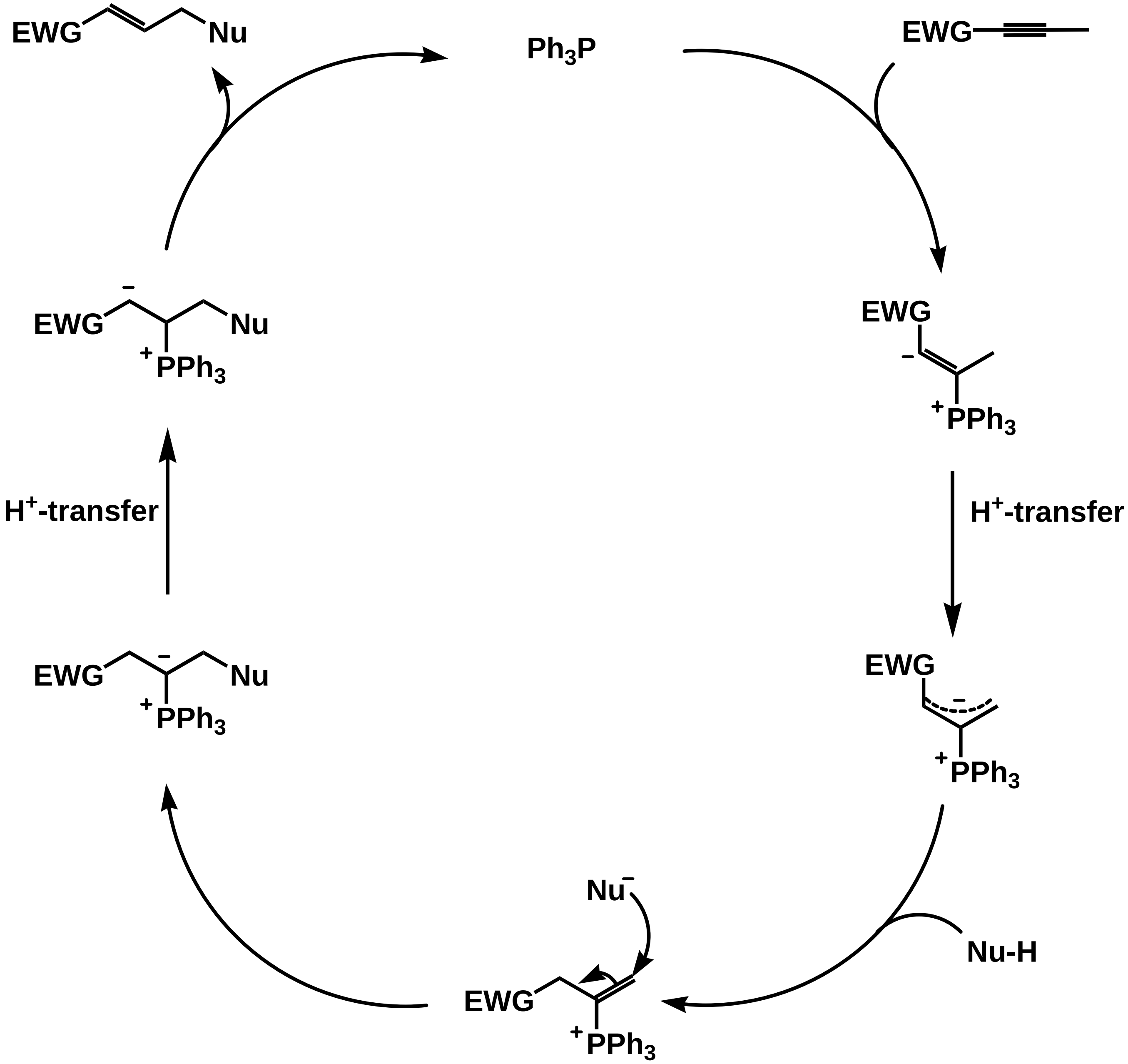
E_1, E_2 = ketone, ester, nitrile, SO_2R

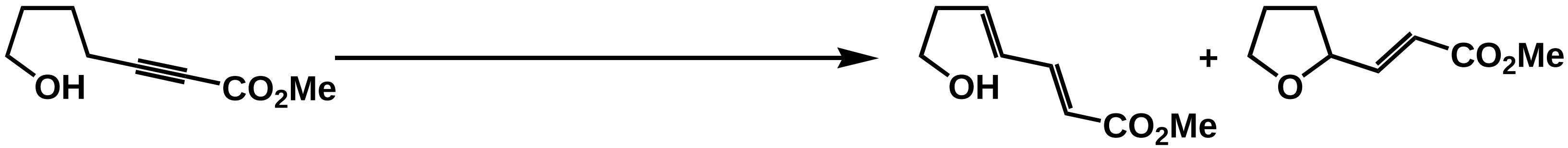
→Phosphine acts as a nucleophilic trigger

→Suitable pronucleophiles: $pK_a < 16$

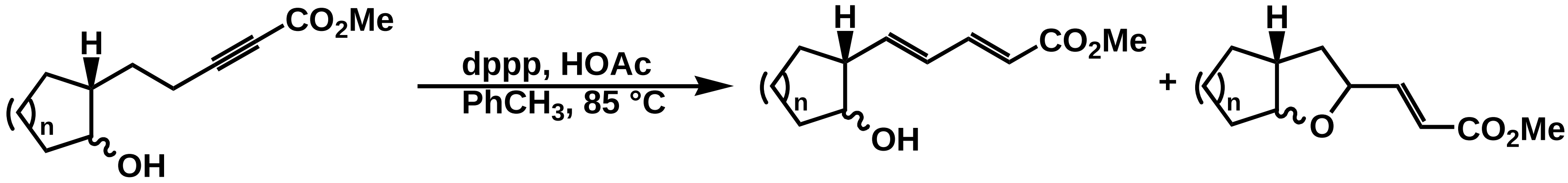
  →Less EWG reacts better with less acidic nucleophile

•Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167-3168.


EWG
Nu
Ph3P
EWG
EWG
PPh3
H+-transfer
EWG
PPh3
Nu-H
Nu
EWG
PPh3
EWG
Nu
PPh3
H+-transfer
EWG
Nu
PPh3

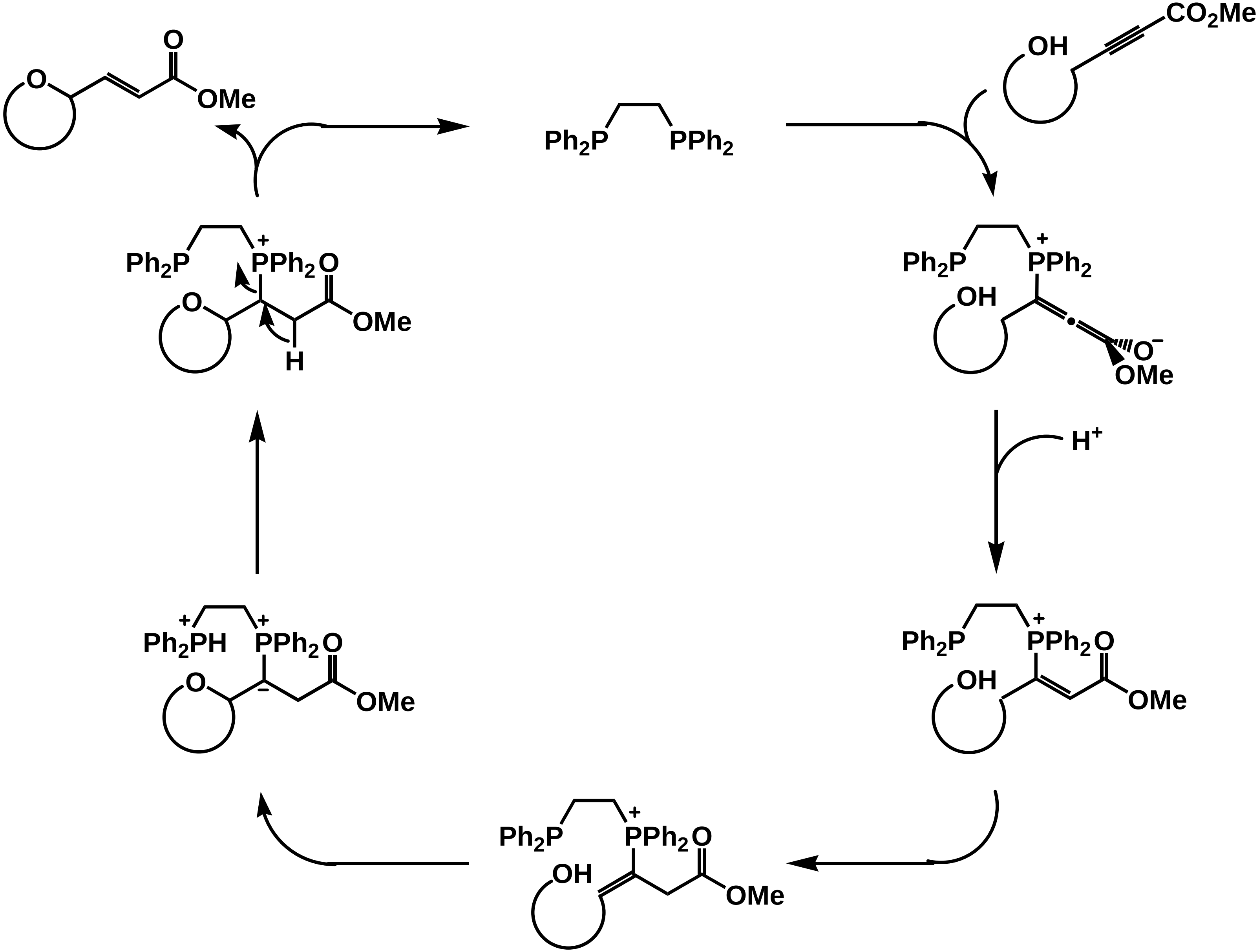


PPh$_3$, HOAc, PhCH$_3$, 110 °C	47 %	53 %
PPh$_3$, HOAc, DMSO, 110 °C	91 %	9 %
dppp, HOAc, PhCH$_3$, 85 °C	3 %	97 %

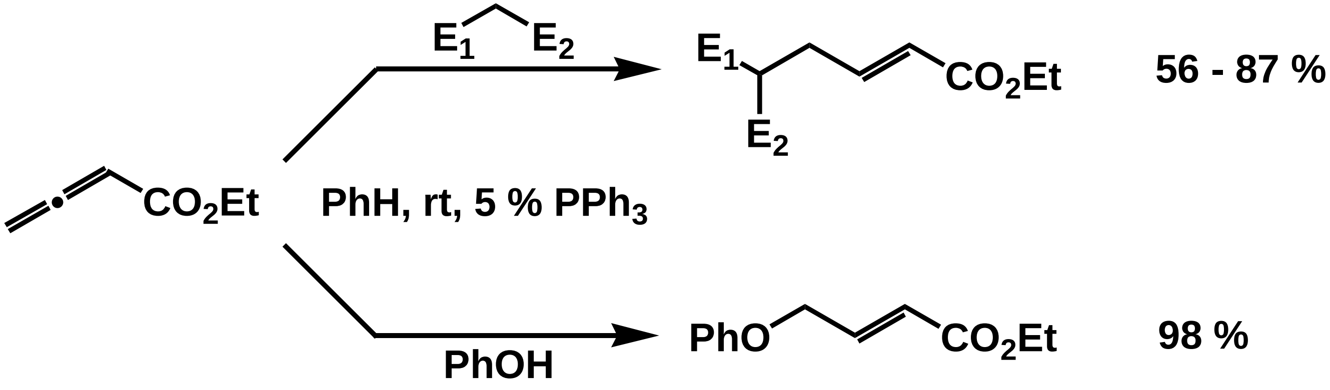


n = 1	trans	84 %	-
	cis	-	69 %
n = 2	trans	-	75 %
	cis	-	55 %

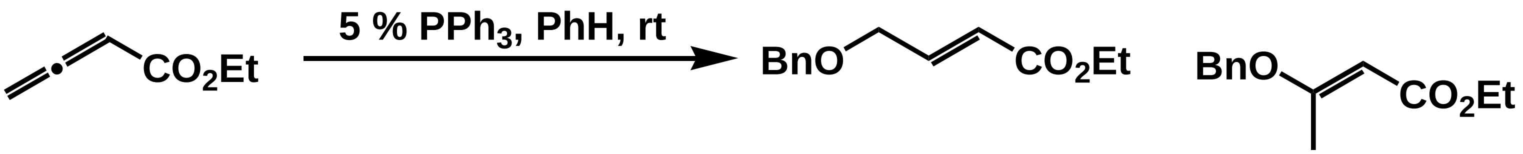
- Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819-10820.



Ph2P
PPh2
OH
CO2Me
O
OMe
+
PPh2
O−
H+
Ph2PH
H
−



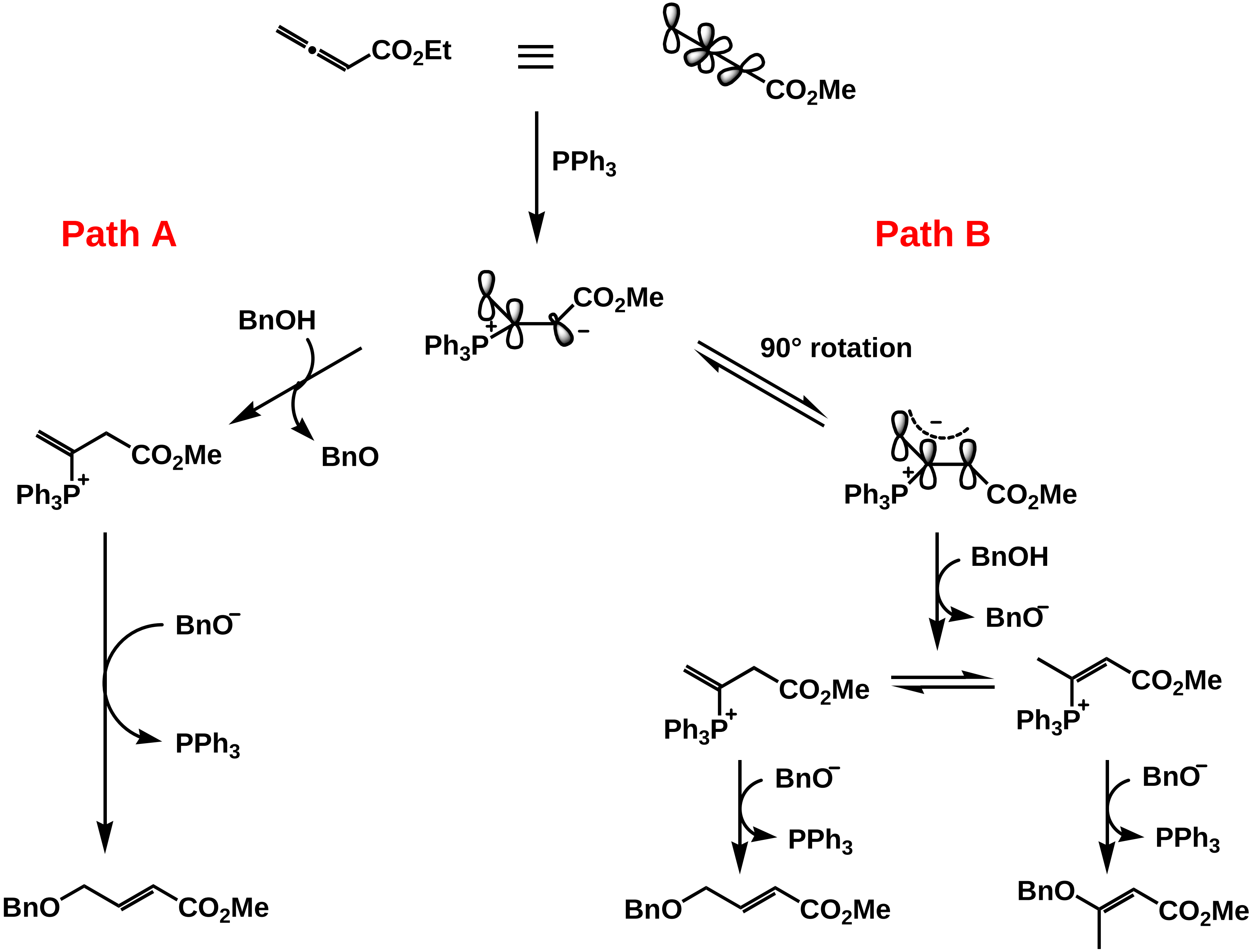
- α-substituents require more nucleophilic phosphine and longer reaction times
- γ-substituents give redox products

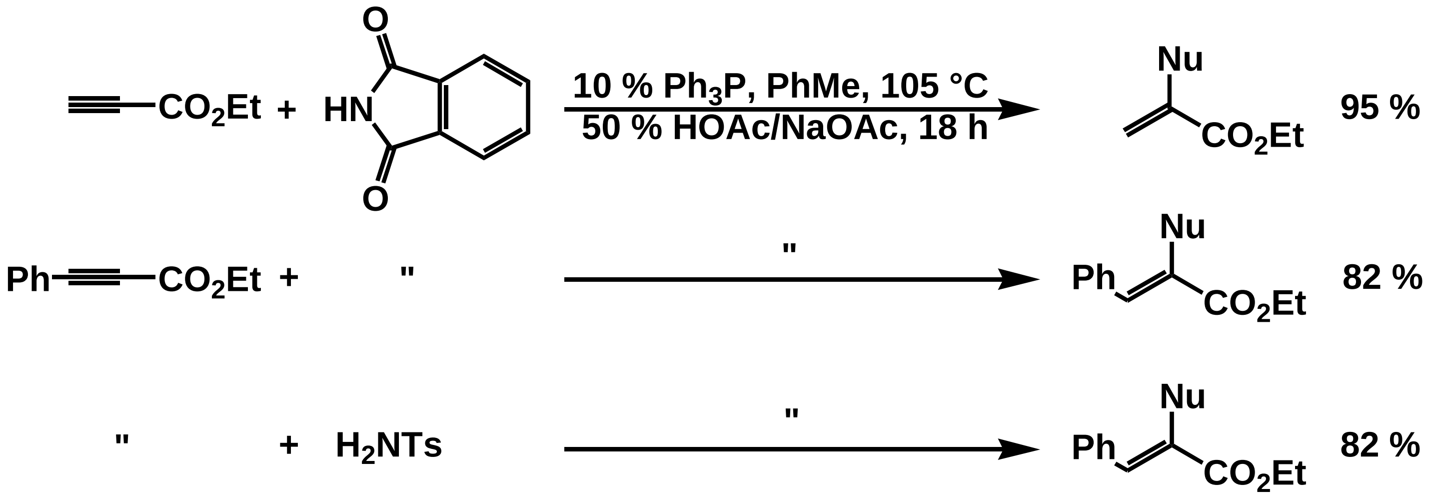


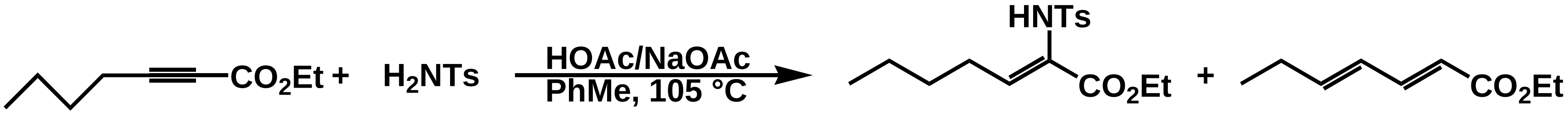
BnOH	**20 %**	**35 %**
BnOH, 20 % AcOH	**90 %**	**-**

- Protonation of initial enolate requires higher acidity

•Zhang, C.; Lu, X. *Synlett* **1995**, 645-646.


CO$_2$Et
≡
CO$_2$Me
PPh$_3$
Path A
Path B
Ph$_3$P
+
CO$_2$Me
−
BnOH
BnO
90° rotation
CO$_2$Me
Ph$_3$P
+
−
Ph$_3$P
+
CO$_2$Me
BnOH
BnO$^-$
BnO$^-$
PPh$_3$
CO$_2$Me
Ph$_3$P
+
CO$_2$Me
Ph$_3$P
+
BnO$^-$
PPh$_3$
BnO$^-$
PPh$_3$
BnO
CO$_2$Me
BnO
CO$_2$Me
BnO
CO$_2$Me

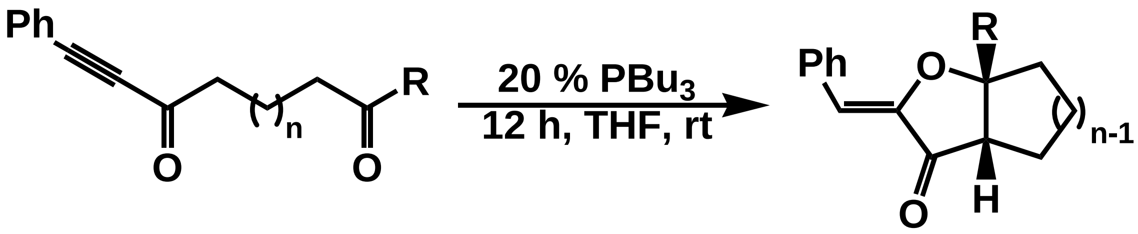




PPh_3 (92 %)	1	:	7.3
dppp (45 %)	1	:	0

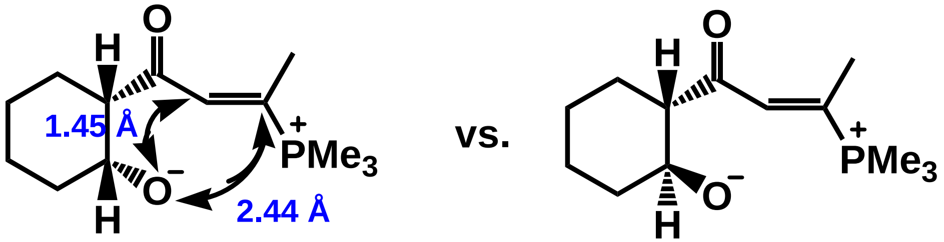
- Phthalimide requires phenol as cocatalyst

- Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595-7596.



n = 2	63 %
3	73 %
4	0 %

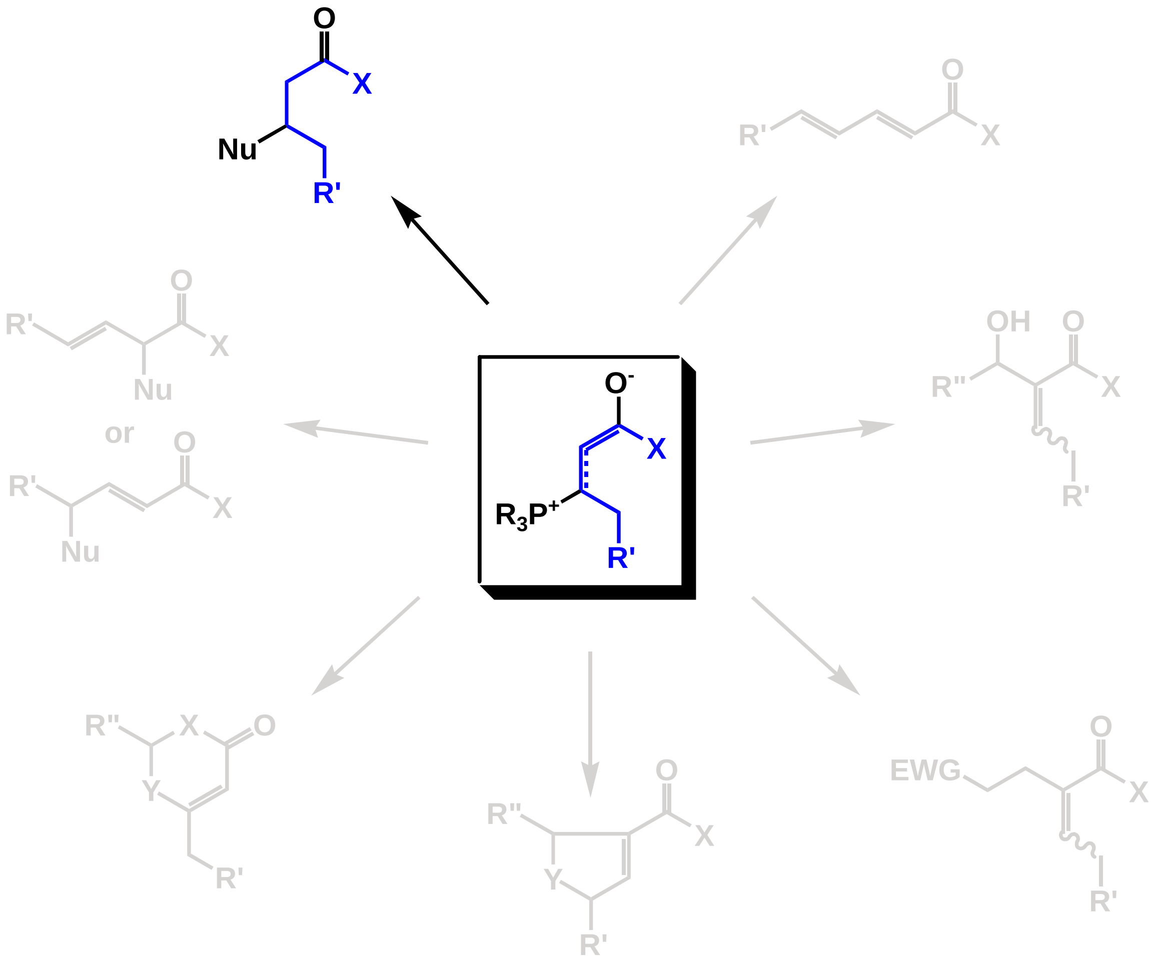
- Highly stereoselective
- PM3 calculations:

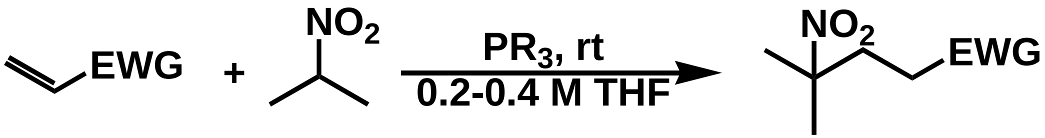


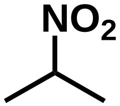
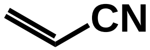
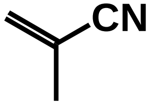
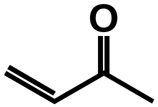
-93.44 kcal/mol **-54.05 kcal/mol**

- Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129-131.

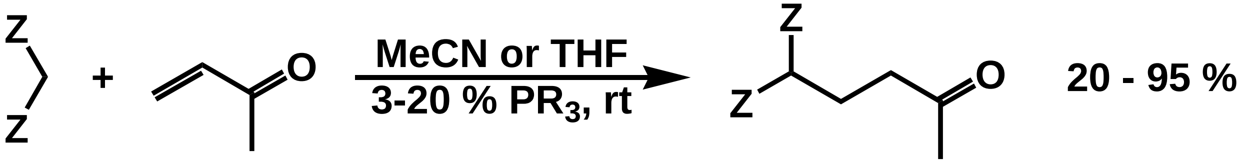
Michael Reaction





Entry	Olefin	Cat. (mol %)	Time (h)	% yield	
1		PBu$_3$ (0.5)	1.5	82	
2	“	PMePh$_2$ (1)	1.5	79	
3	“	PMe$_2$Ph (5)	20	80	
4	“	PPh$_3$ (0.5)	160	36	
5	“	“	24	78	→ in 
6		PBu$_3$ (1)	1	70	
7		PBu$_3$ (0.5)	1	21	
8		PBu$_3$ (1)	16	75	
9		PBu$_3$ (10)	20	33	

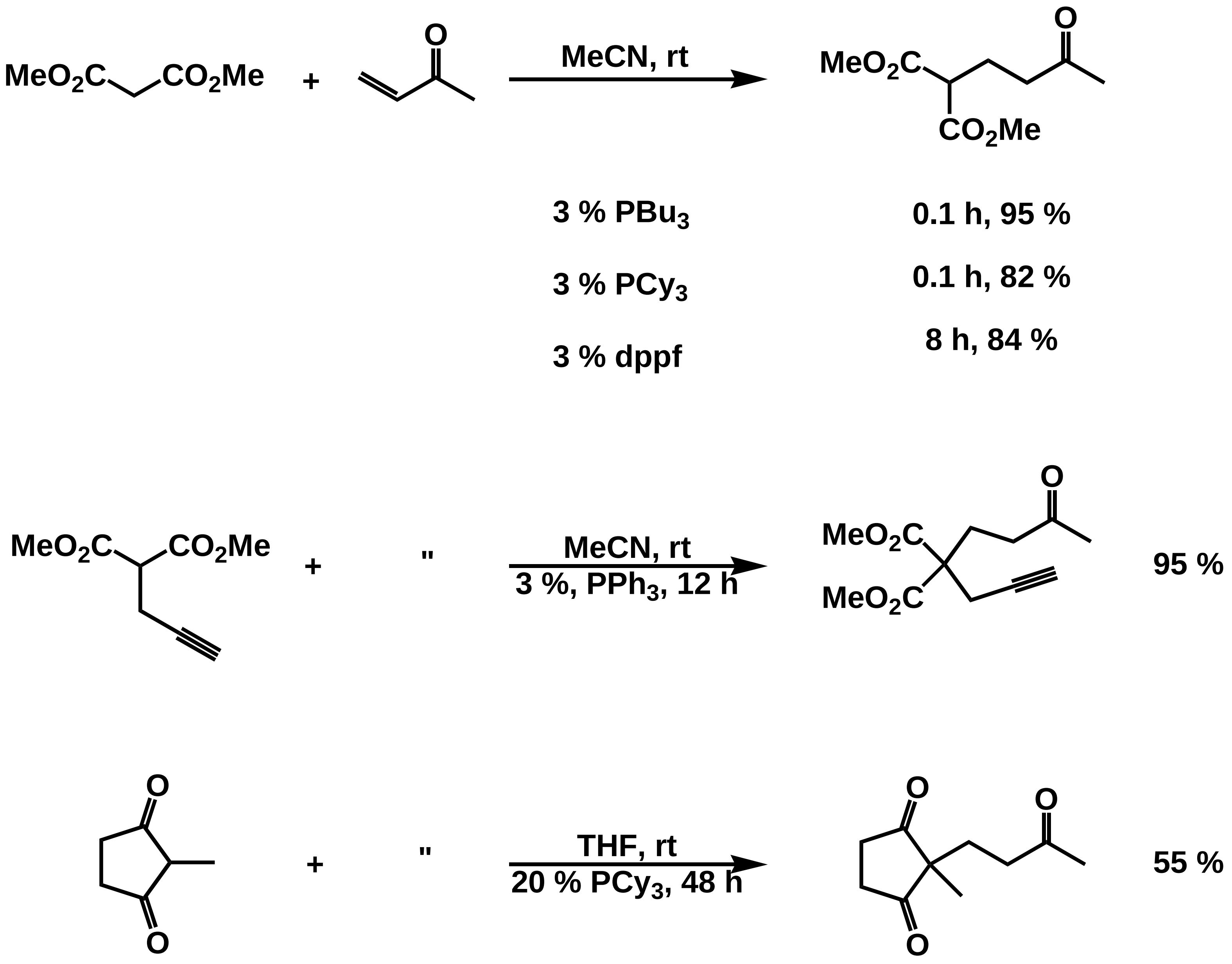
- White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, *14*, 3597-3600.

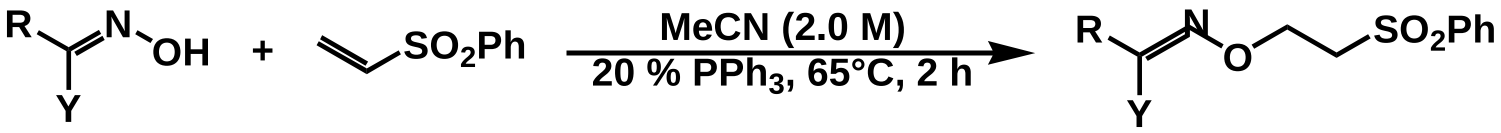


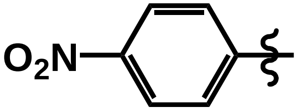
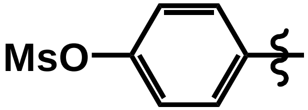
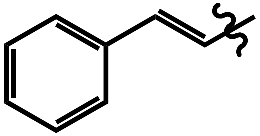
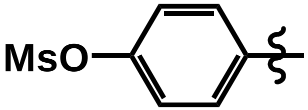
Z = ester, ketone

- PPh_3, PBu_3, PCy_3, dppf
- Discovered while studying Ru catalyzed Michael reaction
  - phosphine ligand thought to dissociate

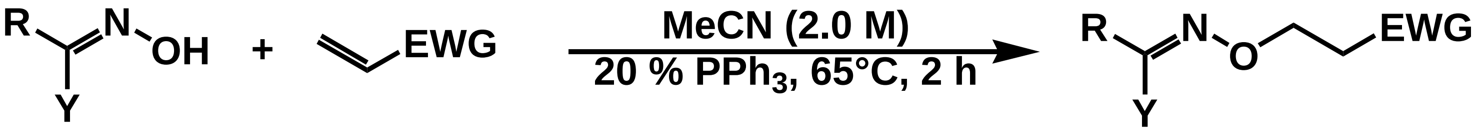
- Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, N. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553-8565.


MeO$_2$C
CO$_2$Me
+
O
MeCN, rt
MeO$_2$C
O
CO$_2$Me
3 % PBu$_3$
0.1 h, 95 %
3 % PCy$_3$
0.1 h, 82 %
3 % dppf
8 h, 84 %
MeO$_2$C
CO$_2$Me
+
"
MeCN, rt
3 %, PPh$_3$, 12 h
O
MeO$_2$C
MeO$_2$C
95 %
O
O
+
"
THF, rt
20 % PCy$_3$, 48 h
O
O
O
55 %



Entry	R	Y	% yield
1		H	90
2		H	96
3	**py**	H	88
4	**^{i}Bu**	H	89
5	**Cy**	H	88
6		H	90
7		Me	84
8	**Et**	Me	84

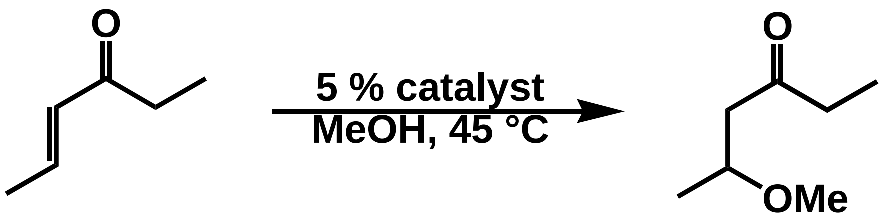
- Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis*, **2003**, *7*, 1018-1024.



A: R = m-$NO_2C_6H_4$, Y = H
B: R = Ph, Y = Me

Entry	Oxime	EWG	% yield
1	A	CO_2Et	80
2	B	“	50 (75)[a]
3	A	CN	80
4	B	“	62 (75)[a]
5	A	SO_2Ph	95
6	B	“	87
7	A	COMe	87
8	B	“	85

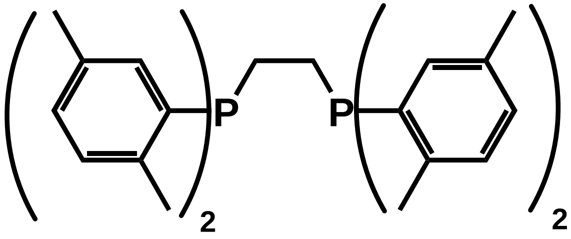
[a] Reaction in parenthesis run with 3 eq. acceptor for 16 h @ rt.



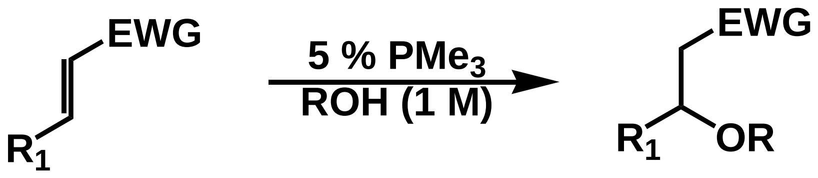
Entry	Catalyst	Time (h)	% conv.
1	PMe_3	6	95
2	PBu_3	6	95
3	Me-BPE	4	93
4	Quinuclidene	48	54[a]
5	DABCO	16	0[a]
6	$O{=}PMe_3$	20	0[a]

[a] 10 % catalyst.

M-BPE =

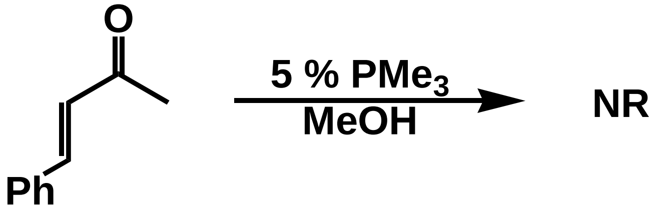


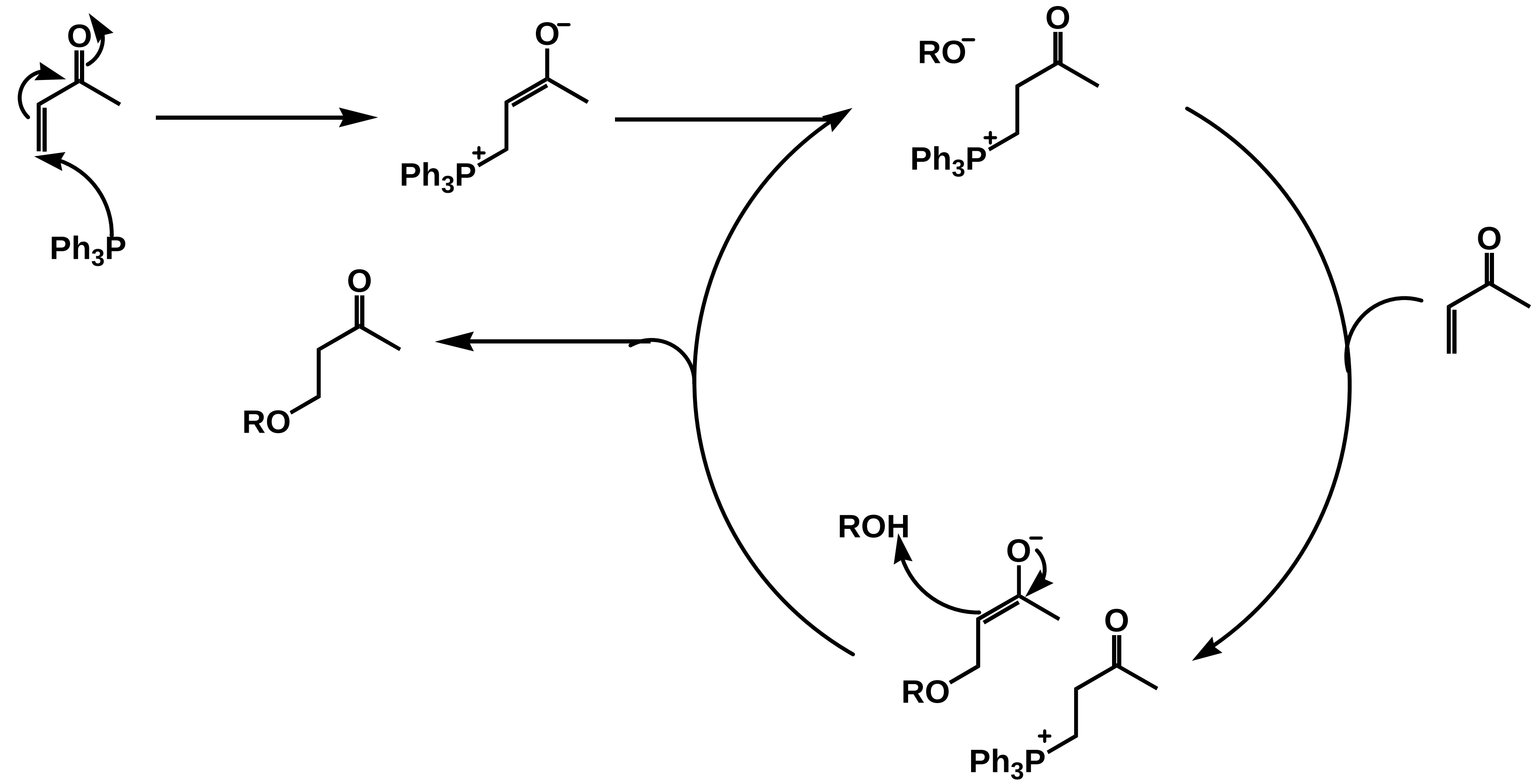
- Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696 -8697.

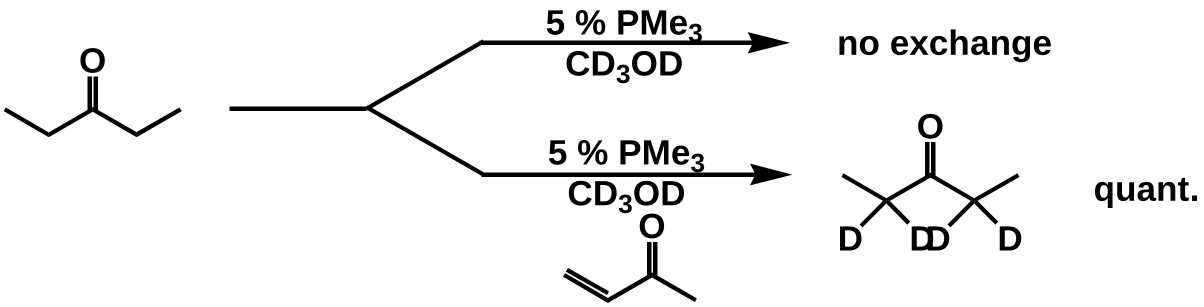


Entry	EWG	R_1	ROH	Time (h)	% yield
1	COEt	Me	H_2O	20	77
2	“	“	MeOH	24	85
3	COMe	H	MeOH	1	56
4	“	“	Me_2CHOH	1	83[a]
5	“	“	PhOH	16	59[a]
6	CO_2Me	Me	MeOH	36	71
7	CN	H	MeOH	4	79

[a] MeCN as solvent.




O
Ph3P
O−
Ph3P+
RO−
O
Ph3P+
O
RO
ROH
O−
RO
O
Ph3P+


O
5 % PMe3
CD3OD
no exchange
5 % PMe3
CD3OD
O
O
D
DD
D
quant.

Conclusions

- Simple & readily available
- Various reactions stemming from phosphonium enolate
- Efficient reactivity
- Lesson: Always run the control experiment