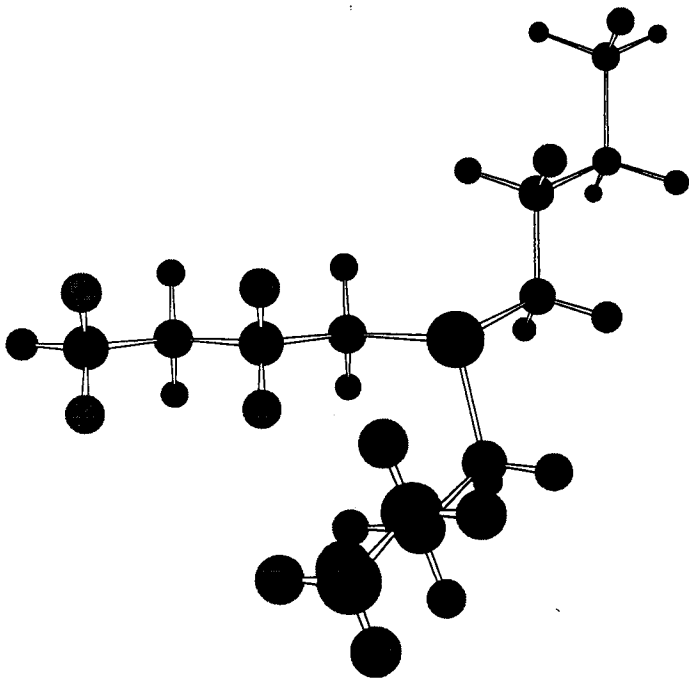
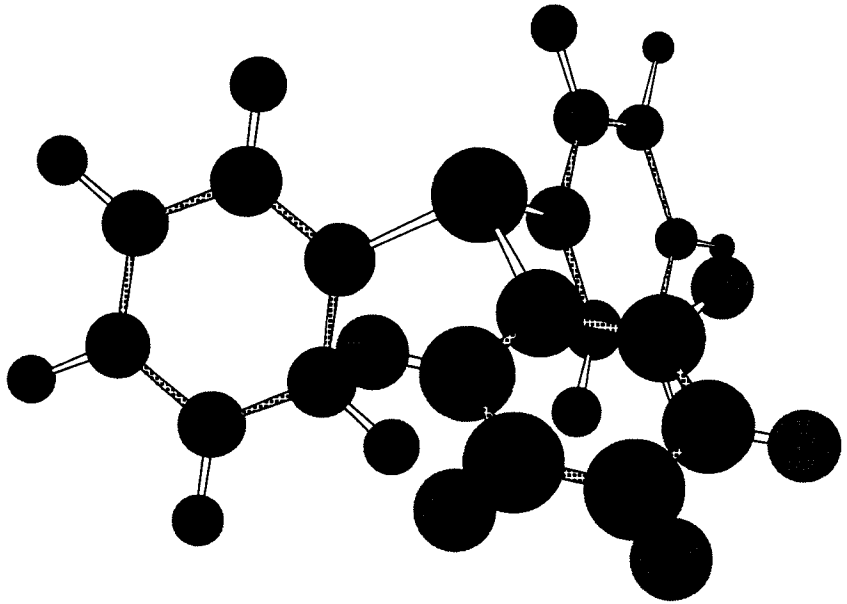
Phosphine Catalyzed Reactions



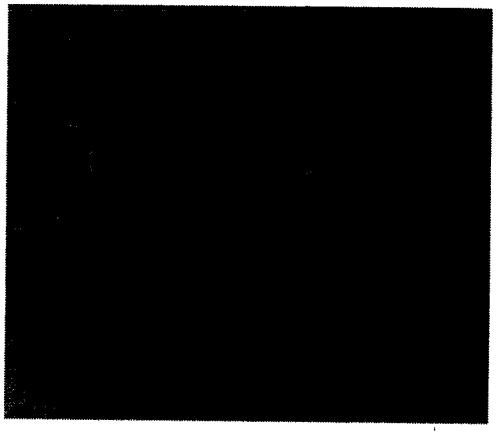


Justin I. Montgomery

June 24, 2003

Phosphorus

- Group VB, non-metal, AN 15, MW 30.97, $[Ne]3s^2p^3$
- First prepared by Hennig Brand (1669) while trying to convert silver to gold – distilled large volumes of urine and obtained a white liquid that emitted a strange light (white phosphorus which oxidized in air)
- Industrial uses (fertilizer 70%, detergents 15%, animal food 8%, corrosion control 5%, pharmaceutical, insecticidal and plastics 2%) – #'s are total phosphorus used, not commercial value



PR_3

Phosphine
Phosphane (IUPAC)

$(RO)_3P$

Phosphite

$(HO)_3P$

Phosphorous Acid

$O{=}PR_3$

Phosphine Oxide

PR_5

$R_3P{=}R$

Phosphorane
(ylide)

$(RO)_2P(=O)R$

Phosphonate

$(HO)_3P{=}O$

Phosphoric Acid

The Chemistry of Organophosphorus Compunds: Volume 1, Ed. by F.R. Hartley, John Wiley & Sons, © 1990.

Phosphines

Why are organophosphorus reagents useful in organic synthesis?

- Ease of progression from lowest to highest coordination number [P(III)→ P(IV)→P(V)→P(VI)]
- High nucleophilicity of phosphines towards many electrophiles
- Strong bonds phosphorus forms with oxygen, sulfur, nitrogen, halogens, and carbon
- Capability of phosphorus to stabilize adjacent anions (Wittig ylide)

Phosphines

- Weaker bases, but stronger nucleophiles than nitrogen analogs
- React with saturated and unsaturated carbon, oxygen, sulfur, halogens, and nitrogen
- Practically all useful transformations involve R_3P + Electrophile → $[R_3P]^+[\text{Electrophile}]^-$
- Can be a leaving group (catalysis)

Activation Parameters for Quaternisation with EtI

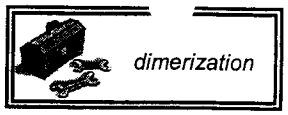
	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e.u.)
n-Bu_3P	12.5	-31
Ph_3P	14.2	-33
Et_3N	12.2	-39

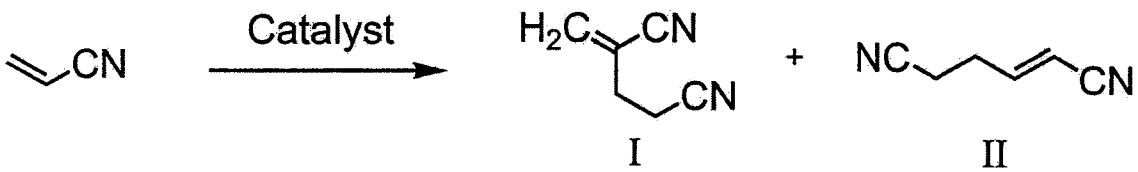
Basicity and Structure

	pK_a	*Bond angles*	*Bond length*
Me_3P	8.67	99°	1.84 Å
Me_3N	9.76	108°	1.47 Å

Organophosphorus Reagents in Organic Synthesis, Ed. by J.I.G. Cadogan, Academic Press, © 1979.
The Organic Chemistry of Phosphorus, A.J. Kirby, S.G. Warren, Elsevier Publishing Company, © 1967.

PR_3 Catalyzed Dimerization of Acrylonitrile

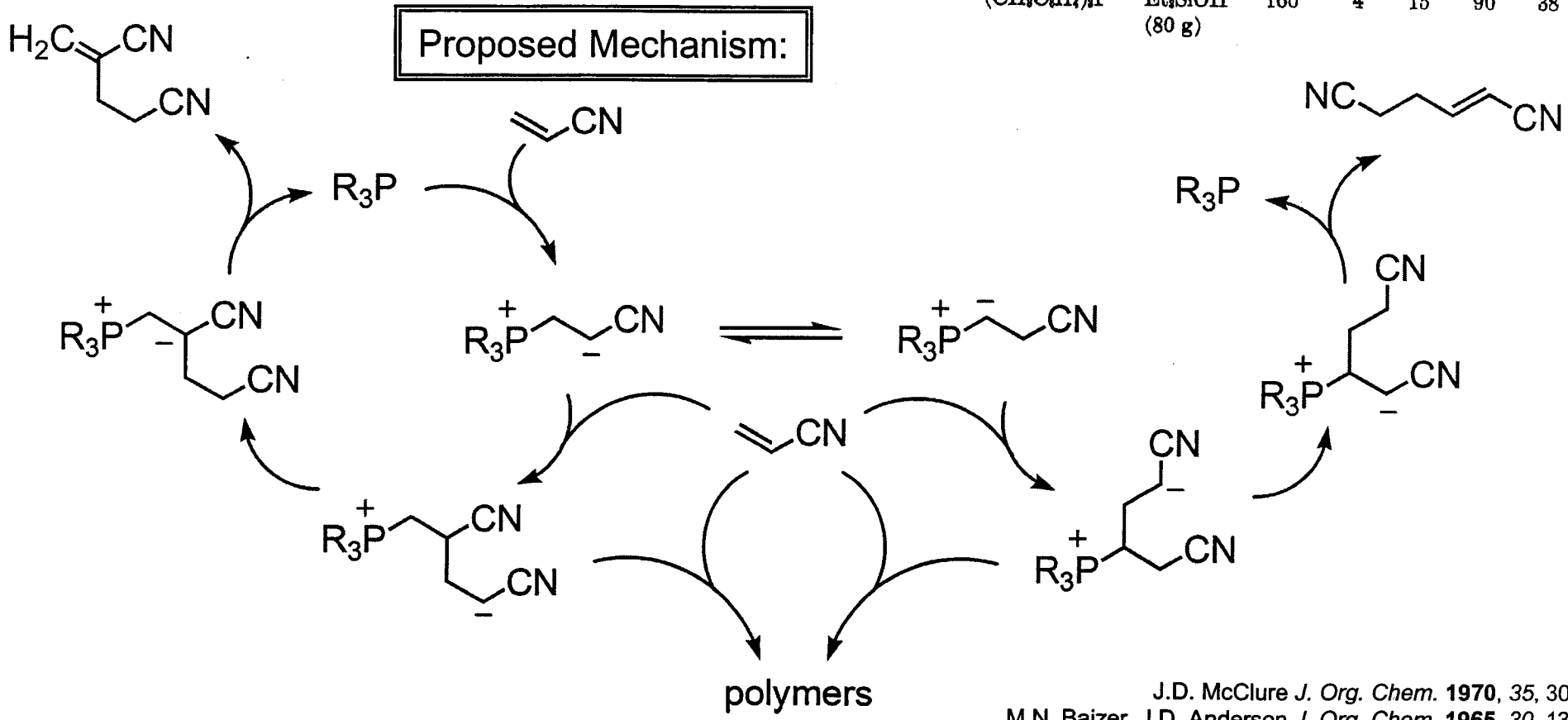




40 g AN scale

Catalyst (1 g)	Solvent	Temp, °C	Time, hr	% convn of acrylonitrile	% yield of dimer (I + II)	% II in dimer
$(C_6H_5)_3P$	Me_3COH (40 g)	175	8	15	45	39
$(CH_3C_6H_4)_3P$	Me_3COH (80 g)	160	8	30	65	30
$(C_6H_5)_3P$	Et_3SiOH (40 g)	175	8	16	75	40
$(CH_3C_6H_4)_3P$	Et_3SiOH (80 g)	160	11	36	85	32
$(CH_3C_6H_4)_3P$	Et_3SiOH (80 g)	160	4	15	90	38

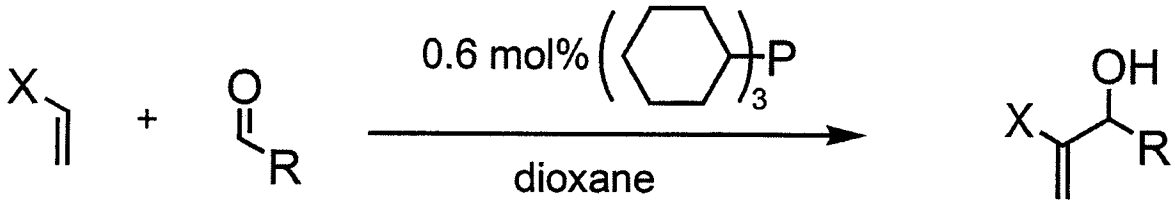
Proposed Mechanism:



J.D. McClure *J. Org. Chem.* **1970**, *35*, 3045.
M.N. Baizer, J.D. Anderson *J. Org. Chem.* **1965**, *30*, 1357.

PCy_3 Catalyzed Addition to Aldehydes

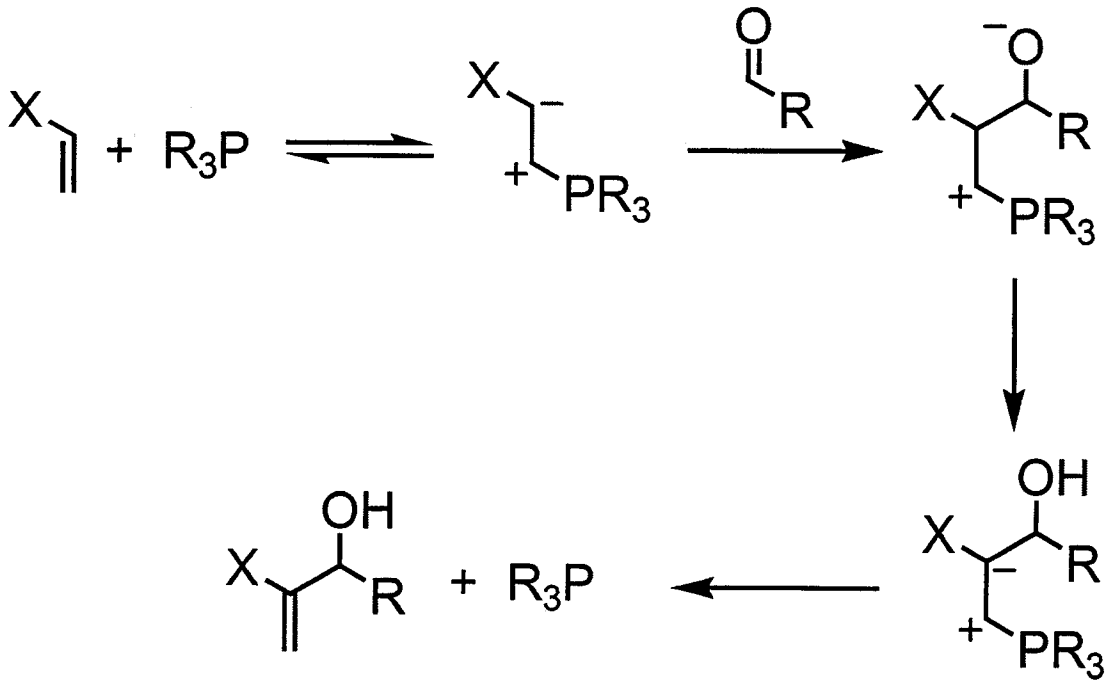
Morita-Baylis-Hillman



X = CN, CO_2CH_3

R = Me, Et, *n*-Pr, *i*-Pr, Ph, 4-Cl-Ph

70-90% based on conversion
(23% conv. for the example they gave)

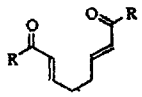
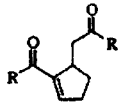
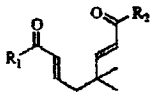
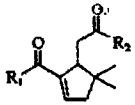
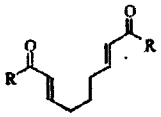
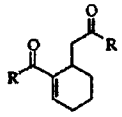
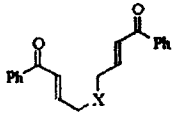
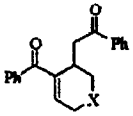
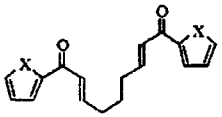
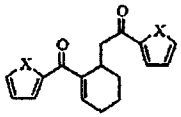
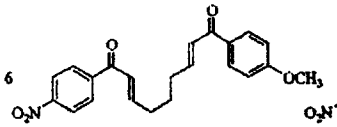
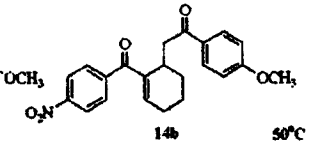
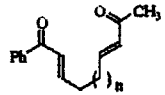
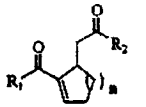
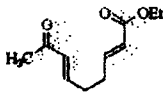
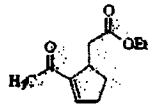
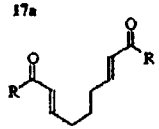
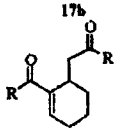
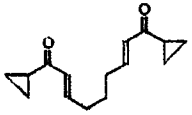
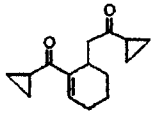
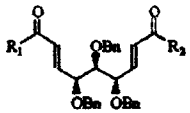
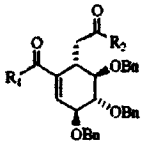


Reported 4 years BEFORE Baylis-Hillman patent! (Now Morita-Baylis-Hillman)

K. Morita, Z. Suzuki, H. Hirose *Bull. Chem. Soc. Jpn.* **1968**, 2815.

PR_3 Catalyzed Cycloisomerization Reactions

Table 1. Phosphine-Catalyzed Cycloisomerization of Bis(enones)[a]

Entry	Substrate	Product	T (°C)	Solvent	Isolated Yield (%)
1					
	1a, R = Ph	1b	50°C	EtOAc	86
	2a, R = 2-Furyl	2b	40°C	EtOAc	95
2					
	3a, $R_1 = R_2 = Ph$	3b	50°C	EtOAc	85
	4a, $R_1 = CH_3$, $R_2 = Ph$	4b	76°C	EtOAc	81
3					
	5a, R = phenyl	5b	25°C	Acetone	82
	6a, R = 4-methoxyphenyl	6b	50°C	Acetone	78
	7a, R = 4-trifluoromethylphenyl	7b	25°C	EtOAc	79
	8a, R = 3-naphthyl	8b	50°C	EtOAc	88
4					
	9a, X = O	9b	25°C	Acetone	95
	10a, X = NTs	10b	25°C	EtOAc:Acetone (1:1)	90
5					
	11a, X = O	11b	50°C	EtOAc	98
	12a, X = S	12b	25°C	EtOAc	82
	13a, X = NCH_3	13b	56°C	Acetone	88[b]
6					
	14a	14b	50°C	EtOAc	75
7					
	15a, n = 1 16a, n = 2	15b/16b, $R_1 = Ph$, $R_2 = CH_3$ 15c/16c, $R_1 = CH_3$, $R_2 = Ph$ 15b:15c (1:1) 16b:16c (7:1)	76°C 76°C	EtOAc EtOAc	79 77
8					
	17a	17b	25°C	^{t}BuOH	87
9					
	18a, R = CH_3 19a, R = $CH_2CH(CH_3)_2$	18b 19b	84°C 84°C	^{t}BuOH ^{t}BuOH	61 70
10					
	20a	20b	84°C	^{t}BuOH	82
11					
	21a, $R_1 = R_2 = CH_3$ 22a, $R_1 = CH_3$, $R_2 = OEt$	21b 22b	84°C 102°C	^{t}BuOH ^{t}AmylOH	81[c] 71[c]

[a] Procedure: Tributylphosphine was added to a 0.1 M solution of substrate in the indicated solvent and the reaction was allowed to stir at the indicated temperature until complete. [b] Yield based on recovered starting material. [c] 20 mol % PBu_3 used.

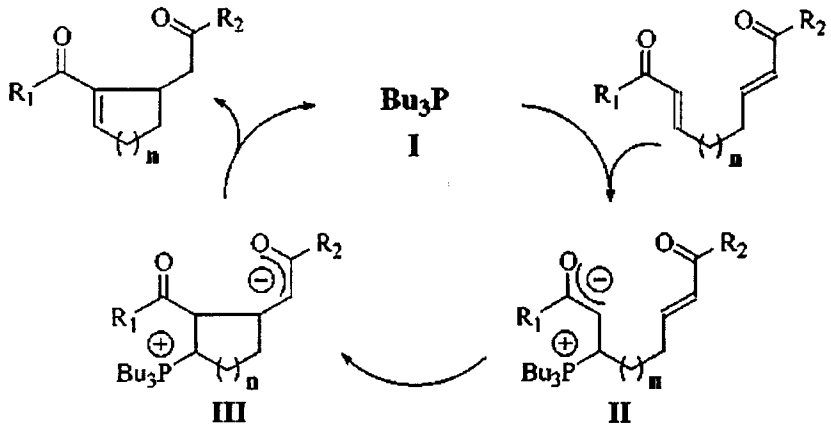
Same reactions reported in:
Frank, Mergott, Roush* *J. Am. Chem. Soc.* **2002**, *124*, 2404.

Optimized Conditions: 10 mol% Me_3P, *t*-amyl alcohol, RT

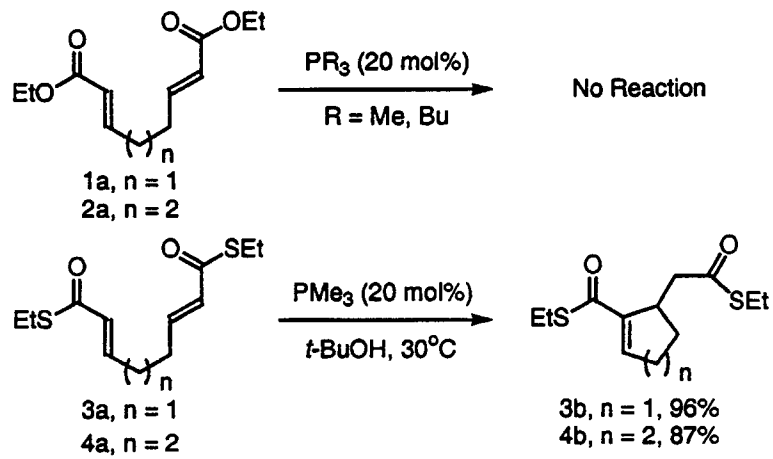
L-C Wang, A.L. Luis, K. Agapiou, H-Y Jang, M.J. Krische* *J. Am. Chem. Soc.* **2002**, *124*, 2402.

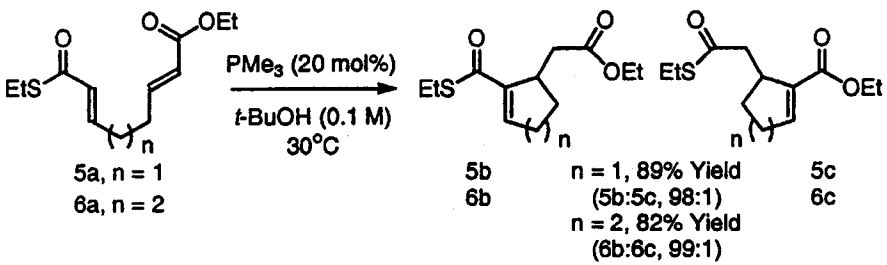
Mechanism and Applications

Proposed Mechanism



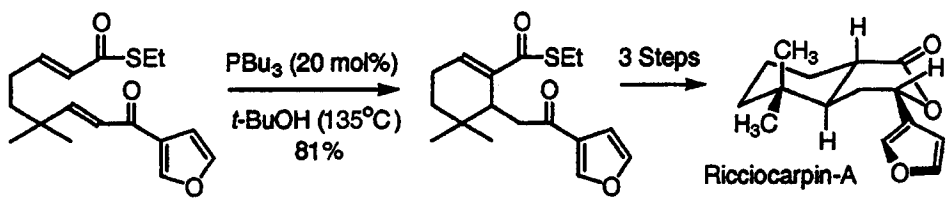
Bis(enoates)





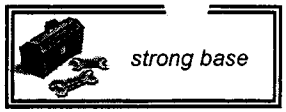
Mixed enoate/thioenoate system cyclizes selectively

Total synthesis of Ricciocarpin-A



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

PR_3 Catalyzed Conjugate Additions



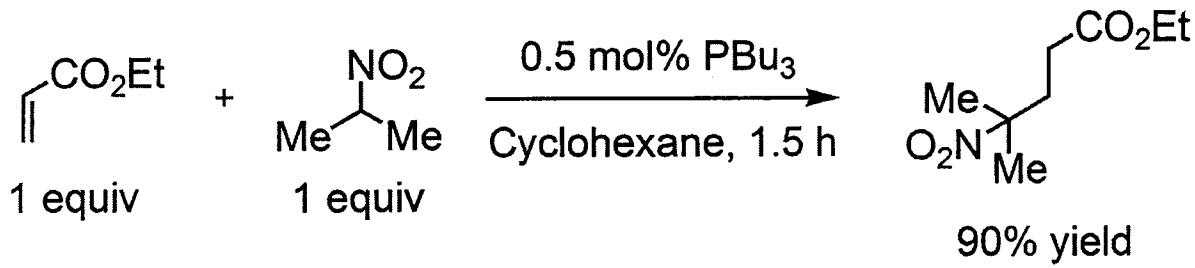
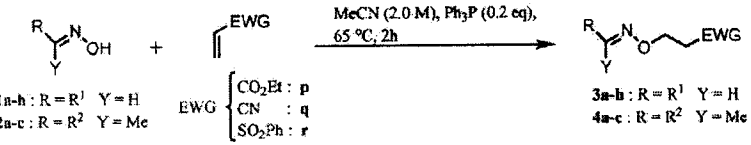
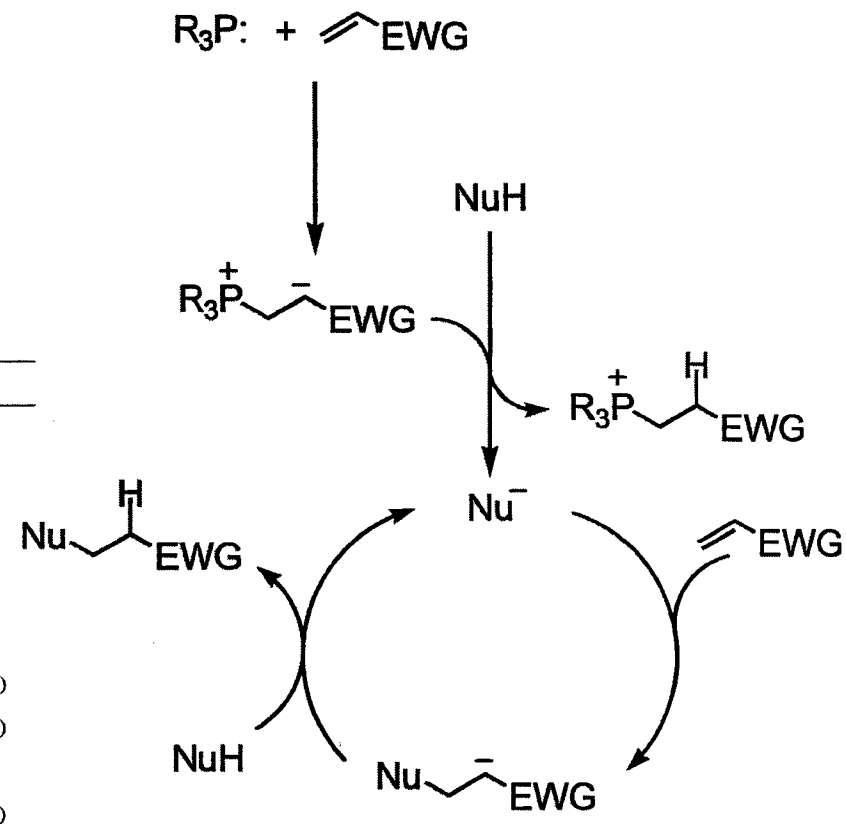


Table 1 Triphenylphosphine Catalyzed Michael Addition of Oximes onto Activated Olefins



Entry	Oxime	EWG	Michael adduct	Yield[a]	Entry	Oxime	EWG	Michael adduct	Yield[a]
1	**1a**	CO_2Et	**3ap**	85	16	**1f**	CN		[b]
2	**1a**	CN	**3aq**	80	17	**1f**	SO_2Ph	**3fr**	89
3	**1a**	SO_2Ph	**3ar**	90	18	**1g**[c]	SO_2Ph	**3gr**	88[c]
4	**1b**	CO_2Et	**3bp**	80	19	**1h**	CO_2Et	**3hp**	71
5	**1b**	CN	**3bq**	80	20	**1h**	CN	**3hq**	62
6	**1b**	SO_2Ph	**3br**	95	21	**1h**	SO_2Ph	**3hr**	90
7	**1c**	CO_2Et	**3cp**	70	22	**2a**	CO_2Et	**4ap**	30 (65)
8	**1c**	CN	**3cq**	65	23	**2a**	CN	**4aq**	40 (78)
9	**1c**	SO_2Ph	**3cr**	88	24	**2a**	SO_2Ph	**4ar**	84
10	**1d**	CO_2Et	**3dp**	66	25	**2b**	CO_2Et	**4bp**	50 (75)
11	**1d**	CN	**3dq**	76	26	**2b**	CN	**4bq**	62 (85)
12	**1d**	SO_2Ph	**3dr**	92	27	**2b**	SO_2Ph	**4br**	87
13	**1e**	CN	**3eq**	85	28	**2c**	CO_2Et		[d]
14	**1e**	SO_2Ph	**3er**	96	29	**2c**	CN		[d]
15	**1f**	CO_2Et		[b]	30	**2c**	SO_2Ph	**4cr**	84

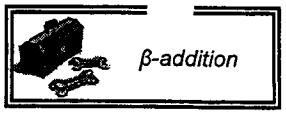
[a] Yields of isolated products after column chromatography, which were characterized by routine spectroscopy (^1H, ^{13}C NMR, mass, IR). Unless otherwise mentioned, all the reactions were carried out following the typical procedure described in the experimental section for **3ar**. Yields in parentheses were realized when the reactions were carried out for 16 h using 3 equiv of Michael acceptors with respect to oximes.
[b] Starting material remained mainly unreacted, even after 24 h of reaction.
[c] Oxime was a mixture of *cis* and *trans* isomers in 1:4 ratio. The same ratio was reflected in isolated product.
[d] Undesired reaction occurred in each case.

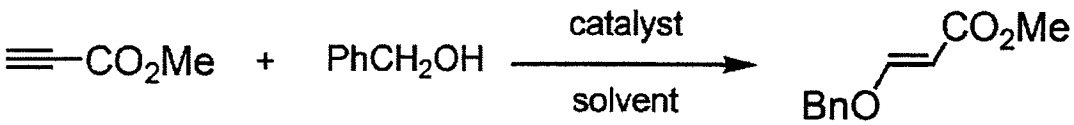


Phosphine generates strong base *in situ*

D.A. White, M.M. Baizer *Tetrahedron Lett.* **1973**, *37*, 3597.
D. Bhuniya,* S. Mohan, S. Narayanan *Synthesis* **2003**, 1018.

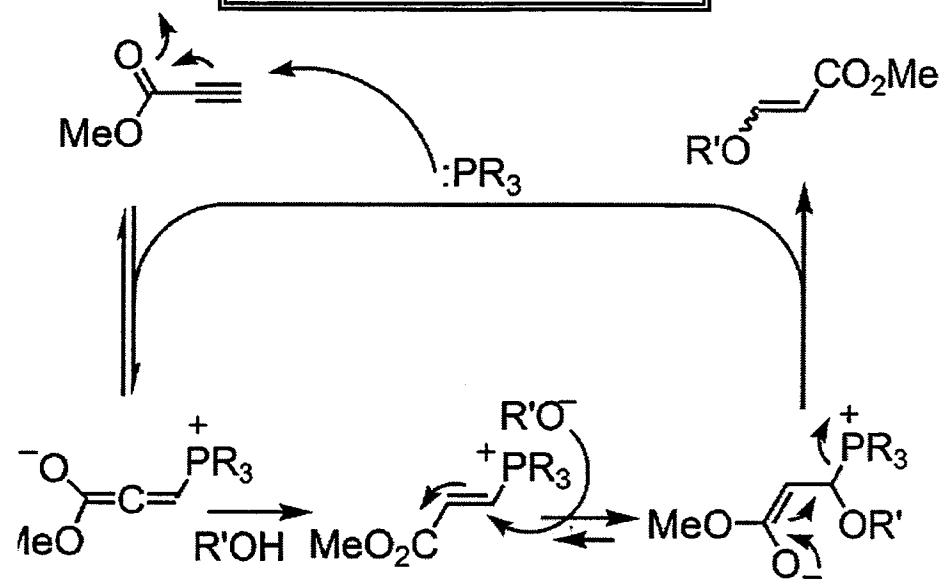
PR_3 Catalyzed Conjugate Additions to Alkynes





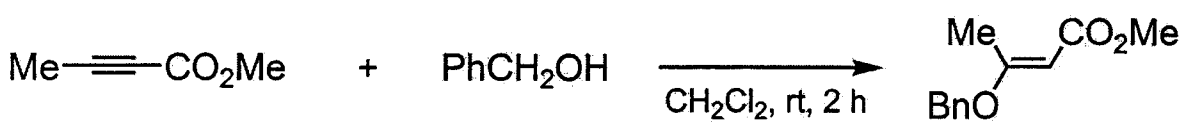
Entry	Catalyst (0.1 equiv)	Solvent	Time	Yield (NMR)	*E/Z*
1	PPh_3	PhH	8 h	86	3/1
2	PPh_3	CH_2Cl_2	8 h	85	5/1
3	PPh_3	THF	8 h	62	3/1
4	PPh_3	CH_3CN	8 h	>98	5/1
5	PBu_3	PhH	10 min	83	*E*
6	PBu_3	CH_2Cl_2	10 min	>98	*E*
7	PBu_3	THF	10 min	>98	*E*
8	PBu_3	CH_3CN	10 min	>98	99/1
9	P(*c*-Hex)$_3$	CH_3CN	2 h	66	7/1
10	$P(OMe)_3$	CH_3CN	8 h	N.R.	

Proposed Mechanism



- 6 primary alcohol examples (90 - >98% isolated yields)
- 4 secondary alcohol examples (lower yields)
- 1 primary thiol example (95%)

See: Yavari and Ramazani
Syn. Comm. **1997**, 1449.
for synthesis of *O*-vinyl oximes
using PPh_3 cat. 1,4 addition

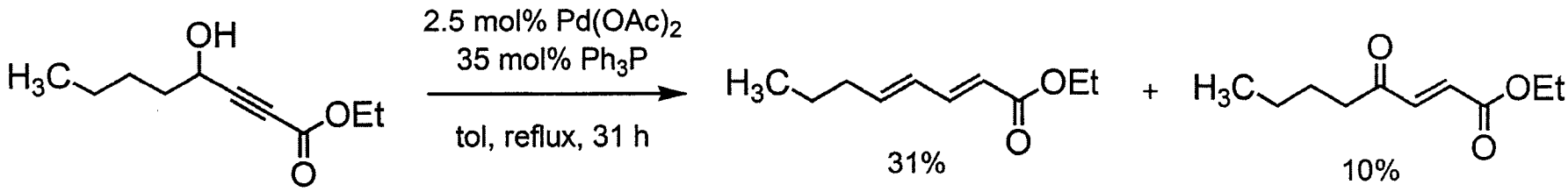


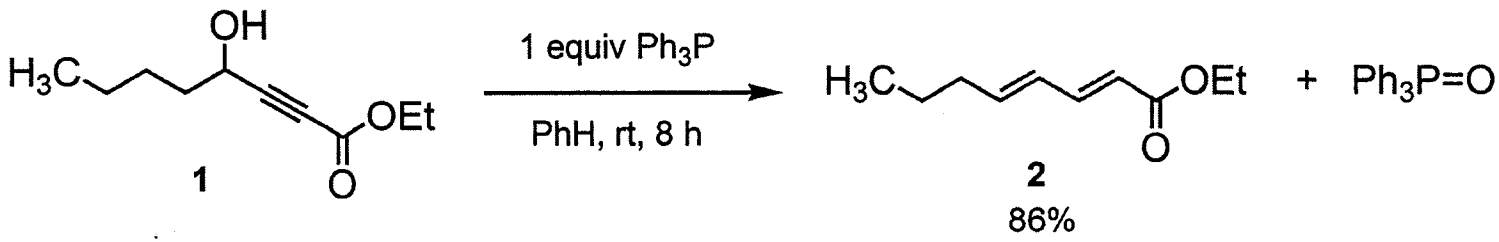
PBu_3 (0.2 equiv) - 67%
PMe_3 (0.2 equiv) - 76%

See: Kuroda, Tomita, Endo
Macromolecules **1995**, *28*, 433.
for polymer synthesis (bis acetylenes/diols)
Macromolecules **1995**, *28*, 6020.
for polymer synthesis (di-thiols)

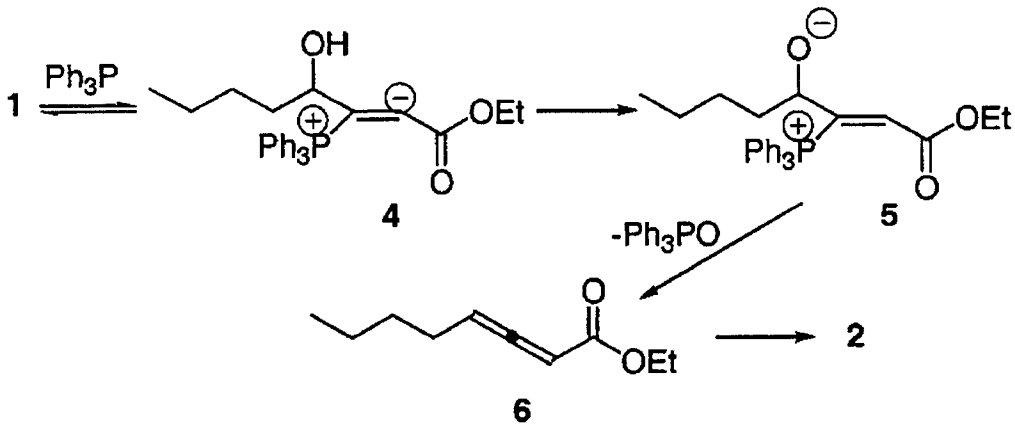
J. Inanaga,* Y. Baba, T. Hanamoto *Chem. Lett.* **1993**, 241.

Deoxygenation – Isomerization Reaction



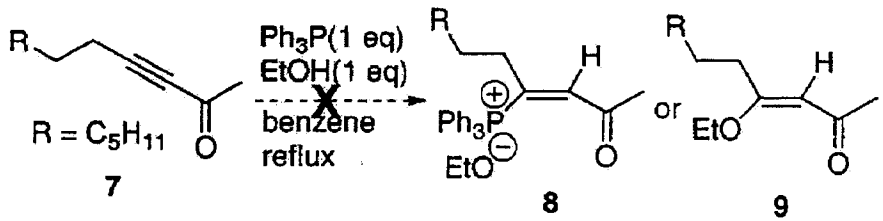


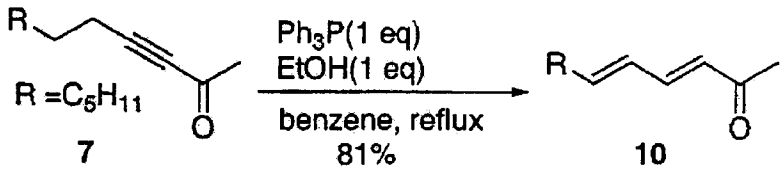
Proposed Mechanism:



- IR 1965 cm^{-1} – allene
- Near quantitative recovery of $PPh_3=O$

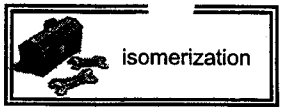
Alcohol Additive:

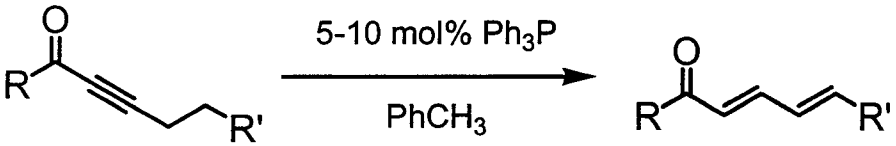




C. Guo, X. Lu* *J. Chem. Soc., Chem. Commun.* **1993,** 394.

Catalytic Isomerization of Triple Bonds



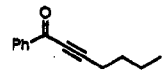
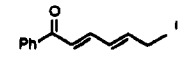
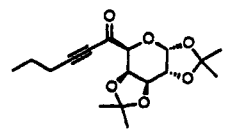
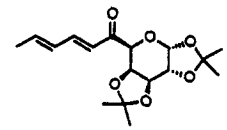
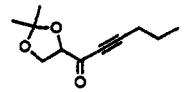
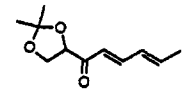
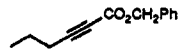
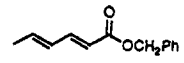
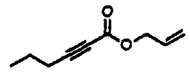
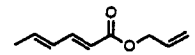
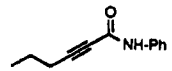
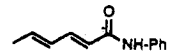
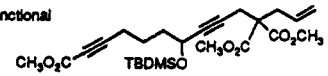
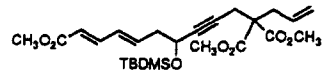
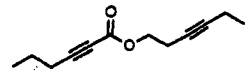
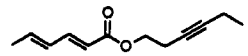
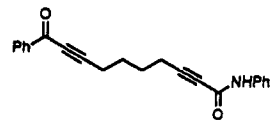
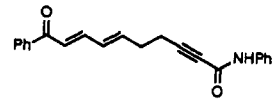
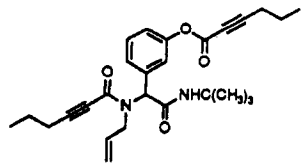
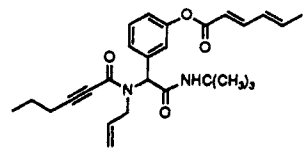


- Esters require AcOH
- Tolerates other unsaturated groups (unlike T-metal catalyzed version)
- Amides require forcing conditions
- No reaction with 3° amines

Lu's contribution:

- Ynoates can be converted with Bu_3P
- ynamides w/ Bu_3P and high temp
- ynols still require T-metal catalysis

Table I. Isomerization of Yne–Carbonyl to Diene–Carbonyl[a]

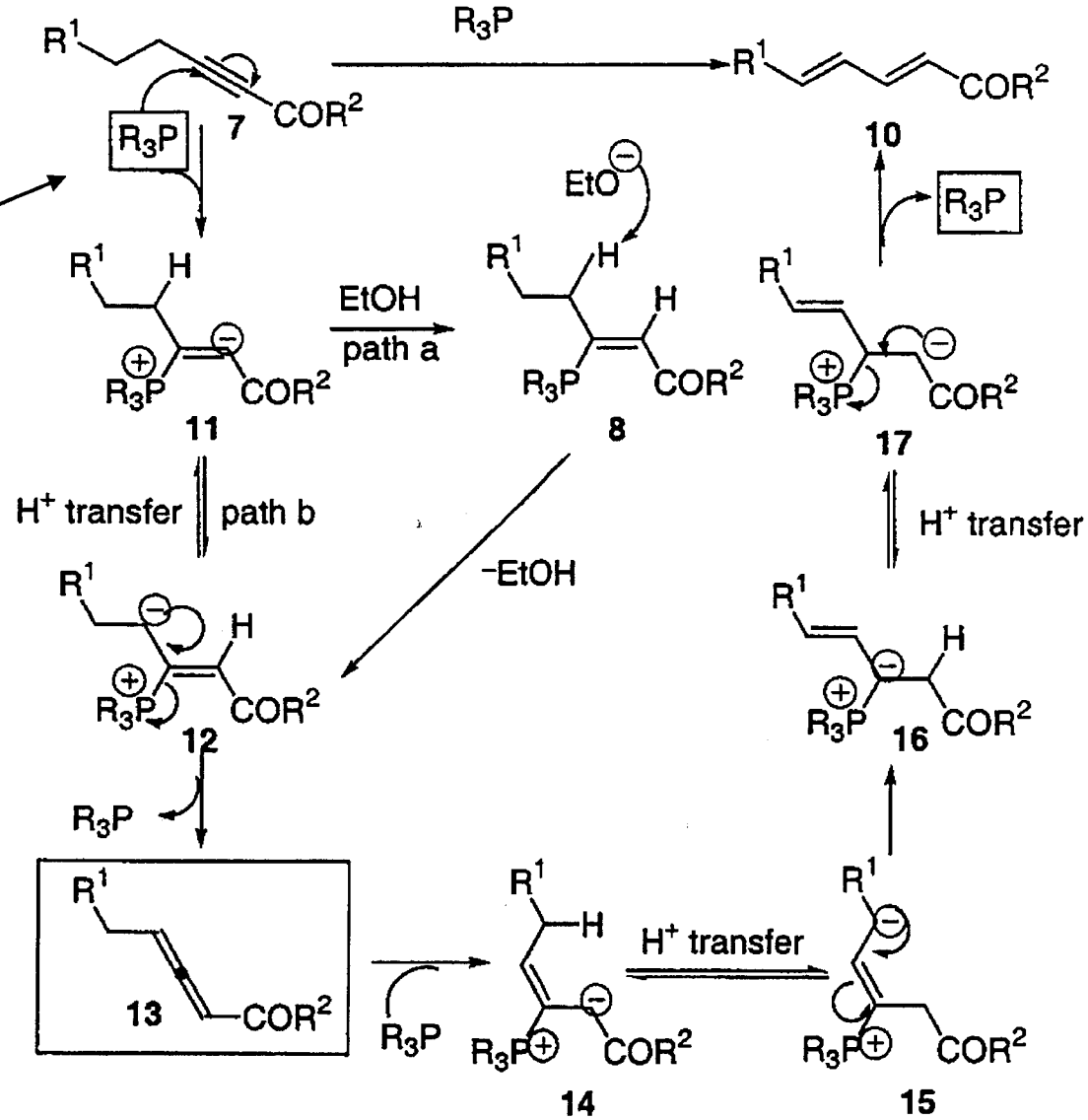
Entry	Substrate	Temp/Time(h)	Product[a]	Isolated Yield
A. Ketones				
1		80°/4		83%
2		110°/16		83%
3		110°/2		88%
B. Ester				
4[b]		110°/6		75%
5[b]		110°/14		83%
C. Amide				
6[b,c]		140°/14		84%
D. Polyfunctional				
7[b]		110°/14		69%
8[b,c]		60°/5		79%
9		110°/14		82%
10[d]		100°		71%

[a] All reactions were performed at 0.5–1 M in toluene with 10–40 mol % Ph_3P. [b] 50 mol % of acetic acid added. [c] Reaction performed in xylene. [d] Reaction performed in C_6D_6 at 100 °C. [e] All new compounds have been satisfactorily characterized. [f] See ref 5.

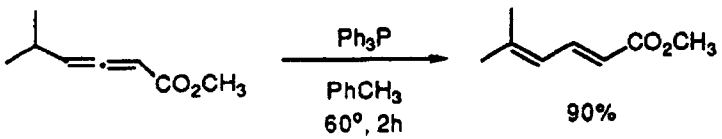
B.M. Trost*, U. Kazmaier *J. Am. Chem. Soc.* **1992**, *114*, 7933.
C. Guo, X. Lu* *J. Chem. Soc. Perkin Trans. 1* **1993**, 1921.

Proposed Isomerization Mechanism

Electron deficient alkyne required for PR_3 addition

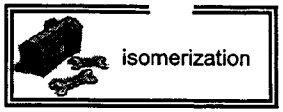


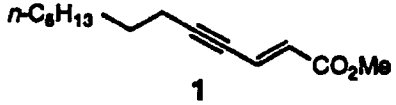
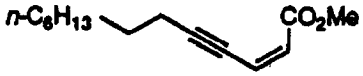
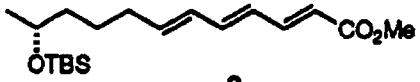
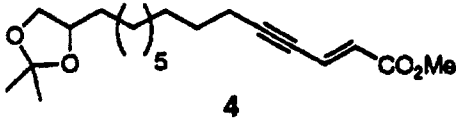
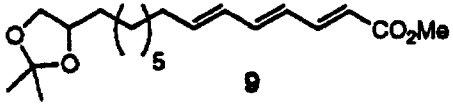
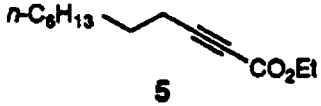
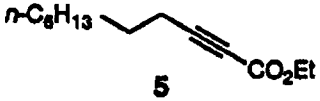
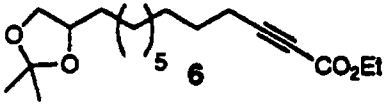
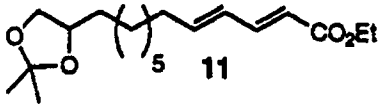
Allenes undergo PR_3 catalyzed isomerization



X. Lu,* C. Zhang, Z. Xu *Acc. Chem. Res.* **2001**, *34*, 535.
B.M. Trost,* U. Kazmaier *J. Am. Chem. Soc.* **1992**, *114*, 7933.

Isomerization of Enyne Esters

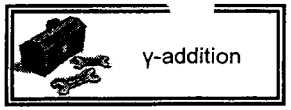


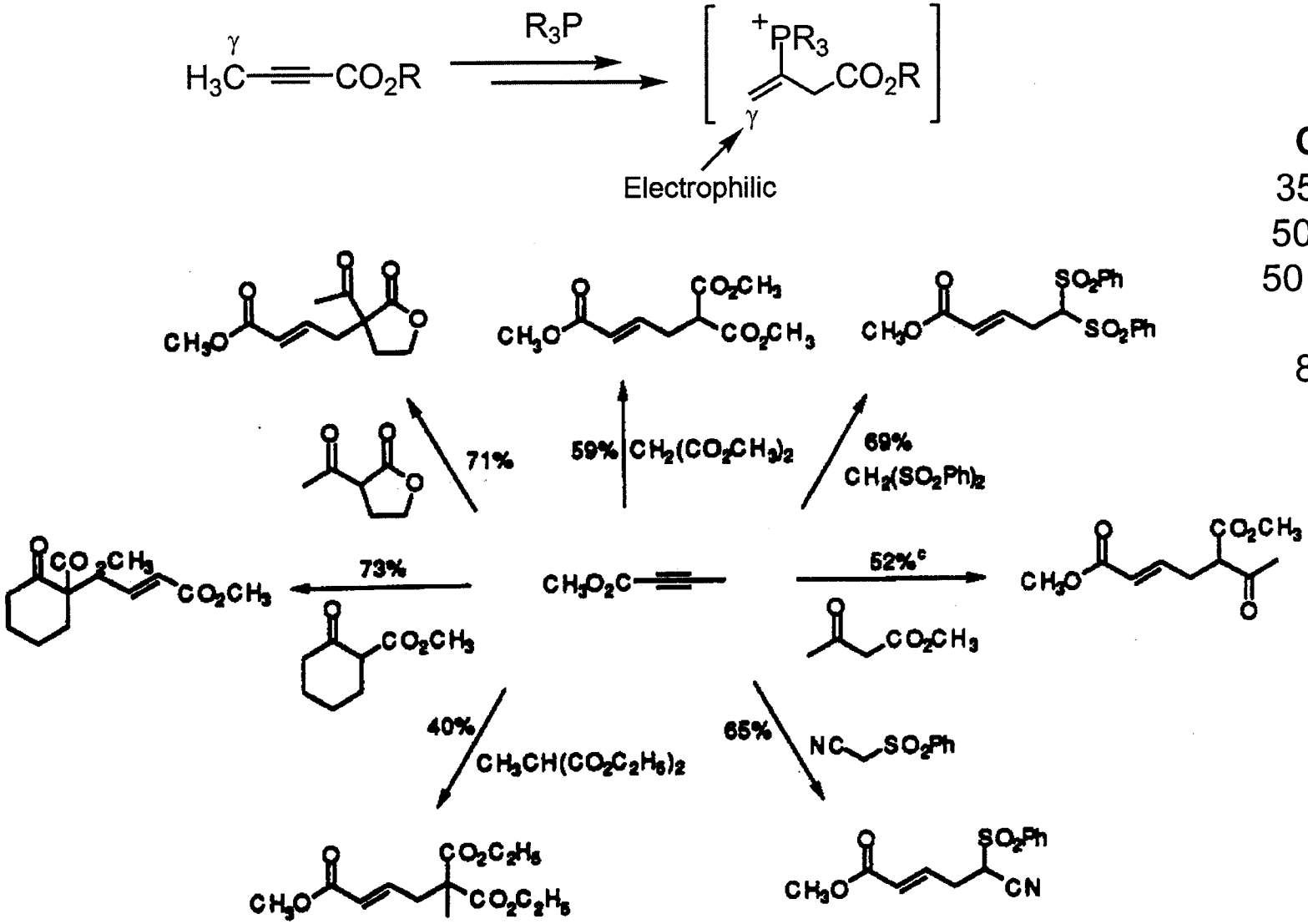
entry	starting material	reagents	T (°C)/time (h)	product	yield (%)
1	 1	PPh_3/PhOH	55/12	 7	70
2	 2	PPh_3/PhOH	55/12	 7	74
3	 3	PPh_3/PhOH	55/14	 8	75
4	 4	PPh_3/PhOH	55/14	 9	88
5	 5	PPh_3/PhOH	25/14	 10	85
6	 5	PPh_3/AcOH	25/14	 10	17 + SM
7	 6	PPh_3/PhOH	25/14	 11	80

- Paper title: "Triphenylphosphine-Catalyzed Isomerizations of Enynes to (*E,E,E*)-Trienes: Phenol as Cocatalyst" – Use 1 equiv of PPh_3 and PhOH
- Lower rxn temps than previous work using AcOH as co-catalyst

S.D. Rychnovsky,* J. Kim *J. Org. Chem.* **1994**, *59*, 2659.

PPh_3 Catalyzed "Umpolung" Additions



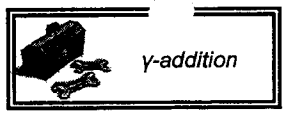


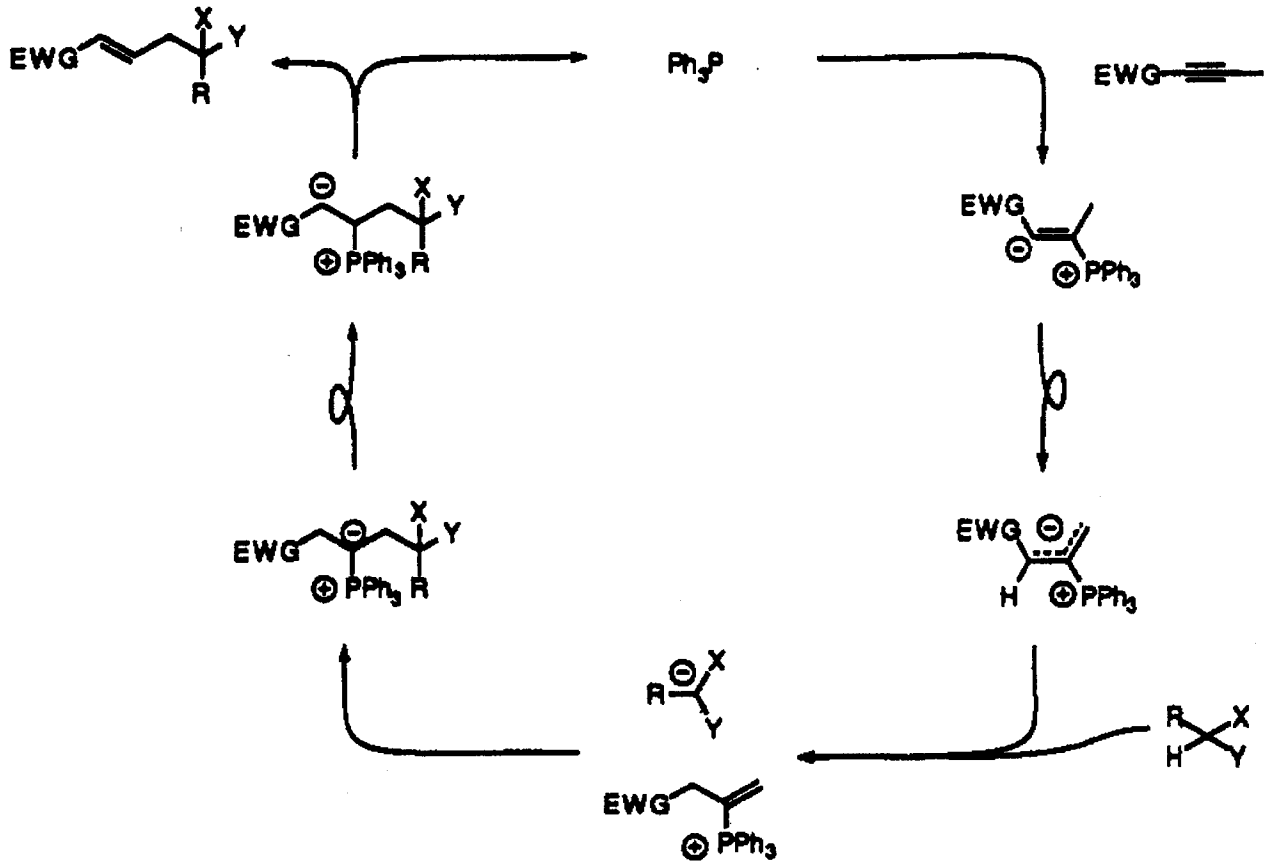
Conditions:
35 mol% PPh3
50 mol% AcOH
50 mol% NaOAc
toluene
80 or 100 °C

PPh_3 can impart electrophilic character to the γ-carbon of activated acetylenes

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

γ-Addition Mechanism

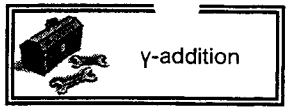


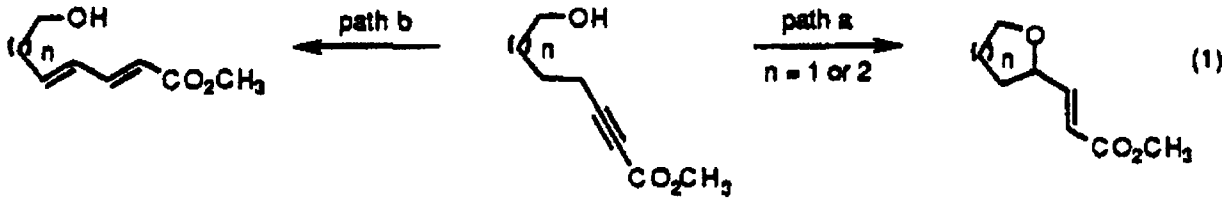


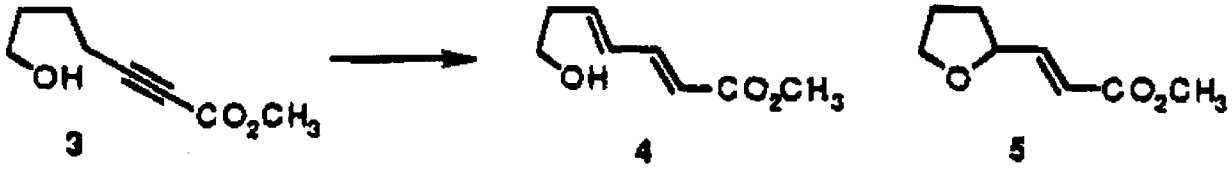
- pronucleophiles for which pKa < 16 work well with AcOH/KOAc buffer
- Bu_3P only leads to oligomers
- Isomerization products formed if further substitution on γ-carbon

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

γ-Addition of Oxygen Nucleophiles

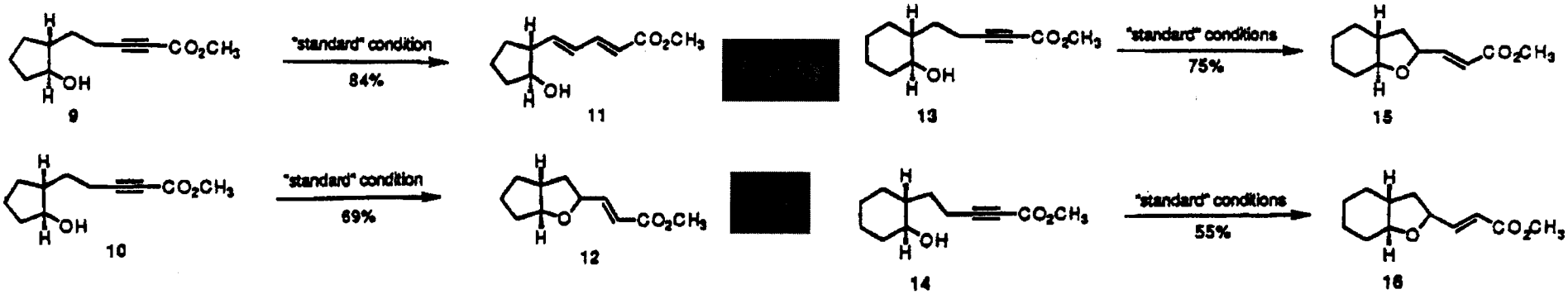






	4	5
Ph_3P, HOAc, $PhCH_3$, 110°	47%	53%
Ph_3P, HOAc, DMSO, 110°	91%	9%
dppp, HOAc, $PhCH_3$, 85°	3%	97%

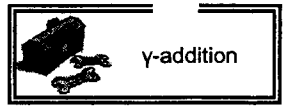
"standard conditions"
5 mol% dppp
20 mol% AcOH
tol, 85-90 °C

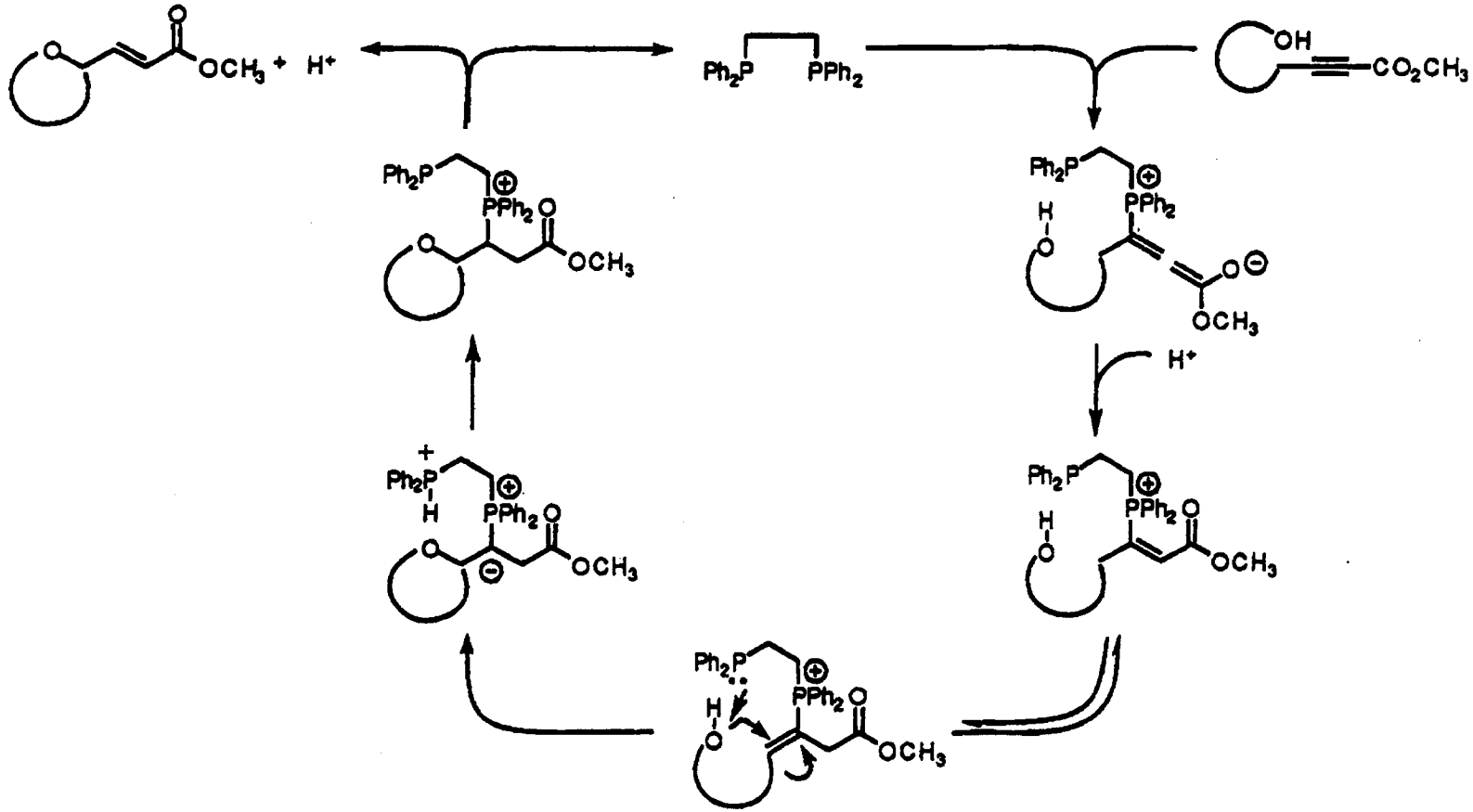


Bidentate phosphine allows for path a

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

Proposed Mechanism





- Second phosphine functions as a general base catalyst
- Hydroxyl oxygen adds in preference to carboxylic acid (cocatalyst) – shows importance of electron density over polarizability for donor group
- Overall, an "atom economical" cycloisomerization

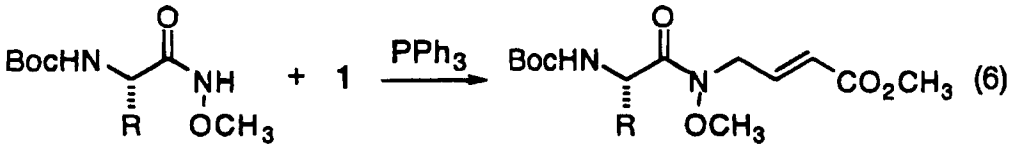
B.M. Trost,* C-J. Li *J. Am. Chem. Soc.* **1994**, *116*, 10819.

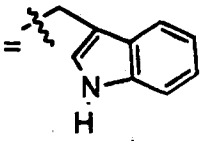
γ-Addition of Other Nucleophiles

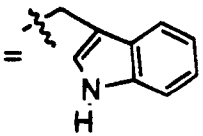
γ-addition

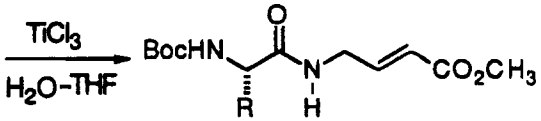
Nitrogen nucleophiles:

$H_3C{-}{\equiv}{-}CO_2CH_3$ = **1**



6c) R = CH_3
8a) R = $CH(CH_3)_2$
8b) R = 
8c) R = $CH_2CH_2SCH_3$

7c) R = CH_3, 68%
9a) R = $CH(CH_3)_2$, 67%
9b) R =  , 76%
9c) R = $CH_2CH_2SCH_3$, 72%



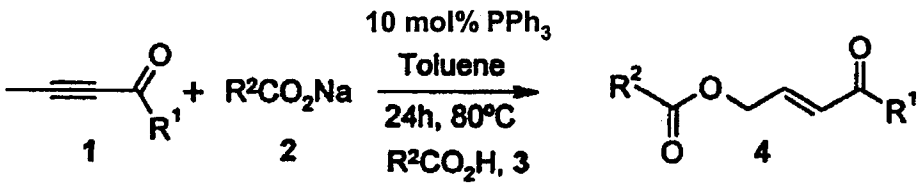
10

a) R = $CH(CH_3)_2$, 80% **c)** R = $CH_2CH_2SCH_3$, 88%

Vinylogous glycine derivatives
"tripeptide mimics"

B.M. Trost,* G.R. Dake *J. Org. Chem.* **1997**, *62*, 5670.

Carboxylate nucleophiles:



1a, $R^1 = OCH_3$
1b, $R^1 = {}^tBu$

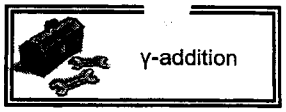
2a, 3a, $R^2 = CH_3$
2b, 3b, $R^2 = Ph$
2c, 3c, $R^2 = Et$
2d, 3d, $R^2 = PhCH_2$

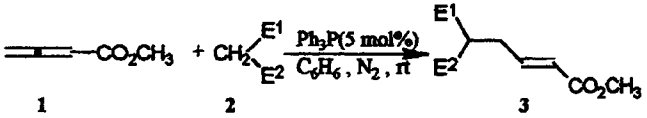
4a, $R^1 = OCH_3$, $R^2 = CH_3$
4b, $R^1 = OCH_3$, $R^2 = Ph$
4c, $R^1 = OCH_3$, $R^2 = Et$
4d, $R^1 = OCH_3$, $R^2 = PhCH_2$
4e, $R^1 = {}^tBu$, $R^2 = CH_3$
4f, $R^1 = {}^tBu$, $R^2 = Ph$
4g, $R^1 = {}^tBu$, $R^2 = Et$
4h, $R^1 = {}^tBu$, $R^2 = PhCH_2$

Entry	1	2, 3	Molar ratio 1 : 2 : 3	4 (%)[a]
1	1a	2a, 3a	1.0 : 1.0 : 1.0	4a (60)
2	1a	2a, 3a	2.0 : 1.0 : 1.0	4a (90)
3	1a	2b, 3b	2.0 : 1.0 : 1.0	4b (75)
4	1a	2c, 3c	2.0 : 1.0 : 1.0	4c (75)
5	1a	2d, 3d	2.0 : 1.0 : 1.0	4d (70)
6	1b	2a, 3a	2.0 : 1.0 : 1.0	4e (80)
7	1b	2b, 3b	2.0 : 1.0 : 1.0	4f (70)
8	1b	2c, 3c	2.0 : 1.0 : 1.0	4g (70)
9	1b	2d, 3d	2.0 : 1.0 : 1.0	4h (70)

C. Alvarez-Ibarra,* A.G. Csákÿ, C. Gómez de la Oliva *Tetrahedron Lett.* **1999**, *40*, 8465.

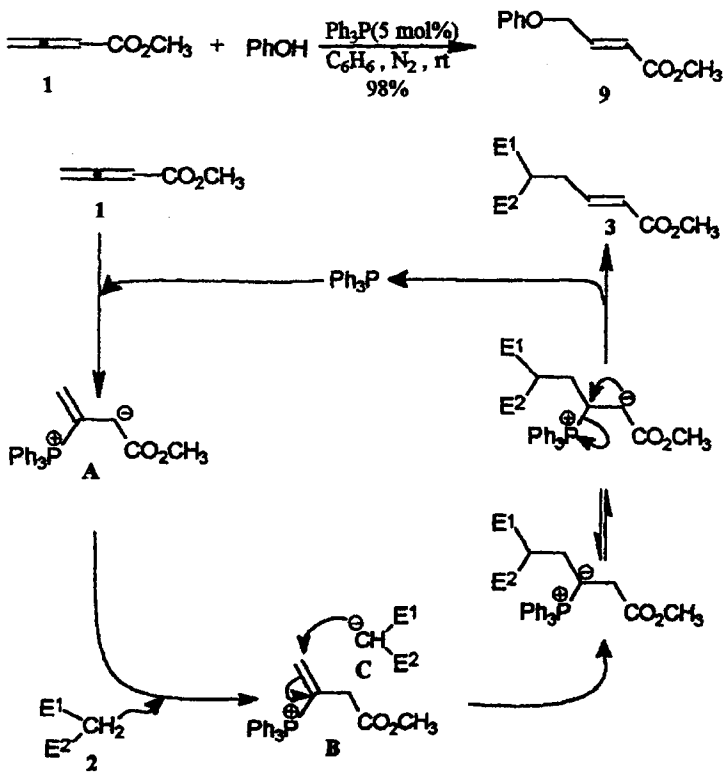
Umpolung Addition to 2,3-Butadienoates

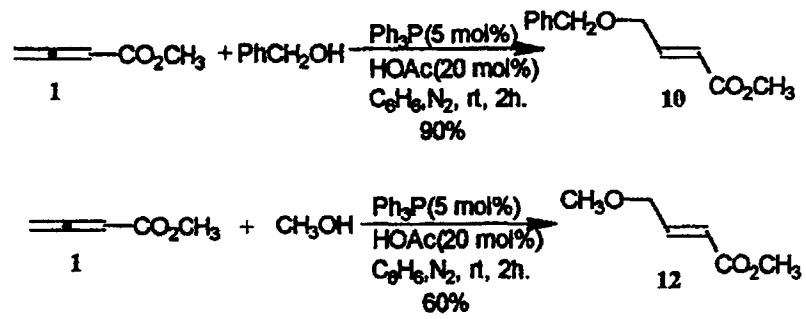


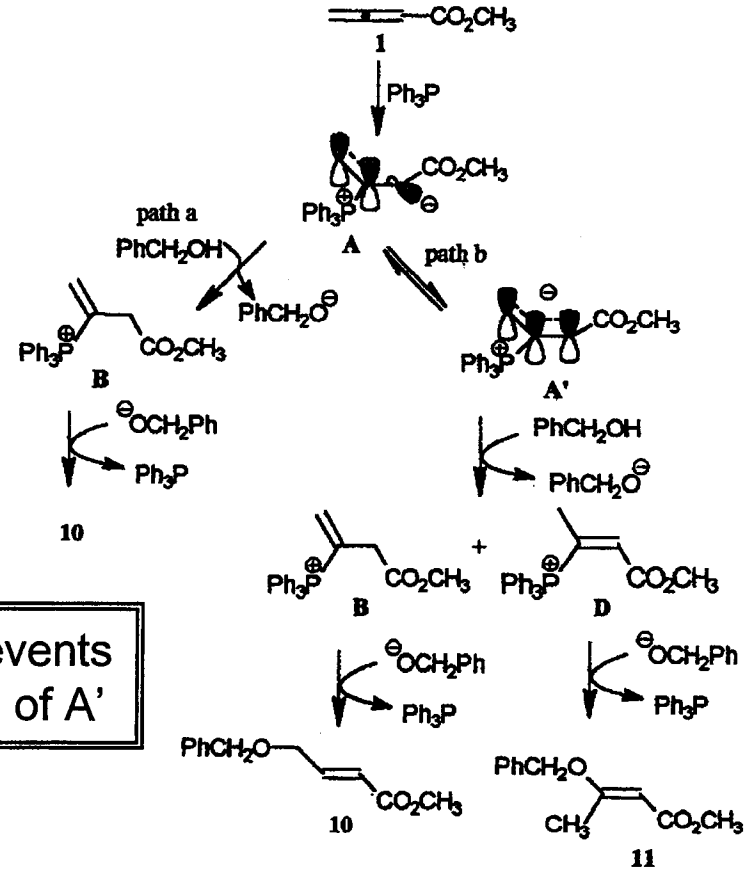


Entry	2	Time (h)	Product 3	Yield (%)[b]	E/Z[c]
1	**2a**: $E^1=E^2=CO_2CH_3$	5	**3a**	65	>97/3
2	**2b**: $E^1=E^2=COCH_3$	5	**3b**	65	>97/3
3	**2c**: $E^1=CN$, $E^2=SO_2Ph$	5	**3c**	87	>97/3
4	**2d**: $E^1=COCH_3$, $E^2=CO_2CH_3$	5	**3d**	65	44:56
5[d]	**2d**	1	**3d**	56	>97/3

a. Reactions are normally carried out with **1** (1.0 mmol), **2** (1.0 mmol) and Ph_3P (0.05 mmol) in benzene (5 mL) at rt under N_2. b. Isolated yield. c. Determined by 300 MHz ^1H NMR. d. The reaction is carried out with Ph_3P (0.05 mmol), HOAc (0.5 mmol) and NaOAc (1.0 mmol) in benzene at 80°C.



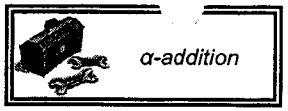


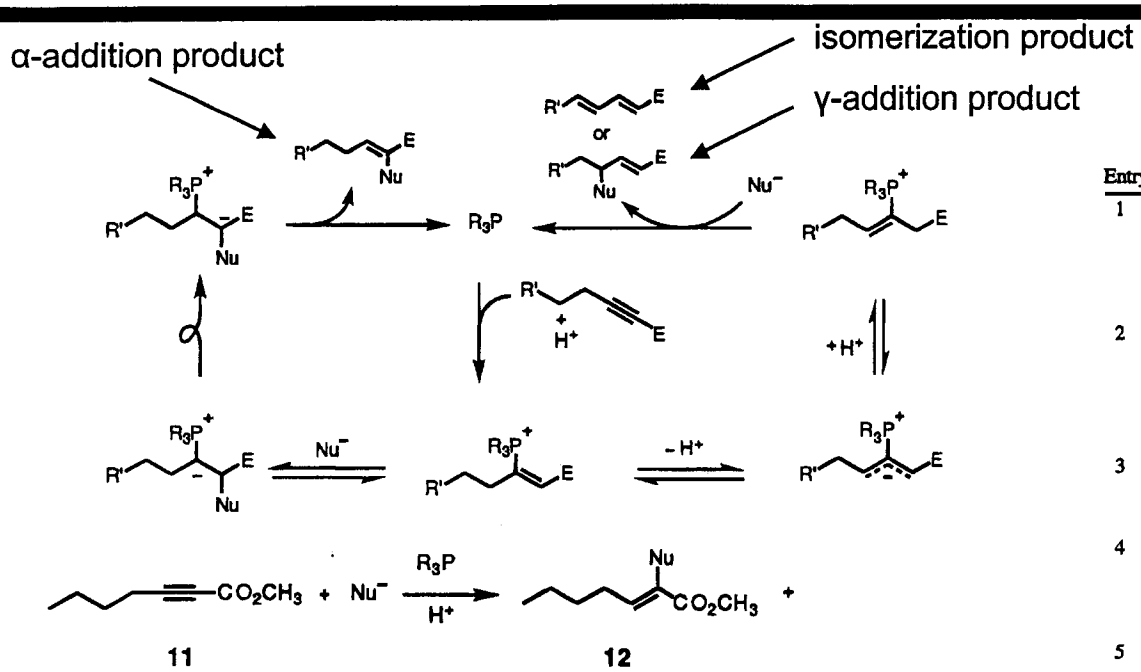


AcOH prevents formation of A'

C. Zhang, X. Lu* *Synlett* **1995**, 645.

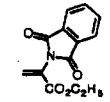
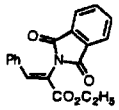
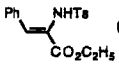
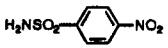
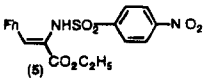
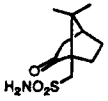
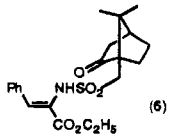
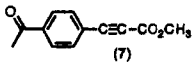
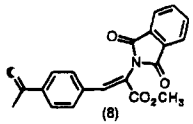
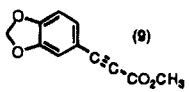
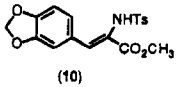
PR_3 Catalyzed α-Addition Reactions





Entry	Nucleophile	Phosphine	Co-Catalyst	% 12	% 13	% 14	Yield
1	$TsNH_2$	Ph_3P	HOAc/ NaOAc	12%	—	88%	92%
2	$TsNH_2$	DPPBA	—	—	—	—	0%
3	$TsNH_2$	$(i\text{-}C_3H_7O)_3P$	HOAc/ NaOAc	—	—	—	0%
4	$TsNH_2$	dppp	HOAc	100%	—	—	45%
5	$TsNH_2$	dppp	HOAc/ NaOAc	76%	—	24%	82%
6		dppp	HOAc/ NaOAc	—	—	100%	70%
7		dppp	PhOH	45%	—	55%	73%
8		dppp	PhOH	87%	13%	—	67%

Alkynoates with no γ H's

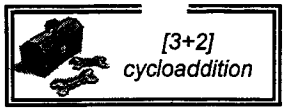
Entry	Alkynoate	Nucleophile	Time (h)	Product	Isolated Yield
1	$HC{\equiv}CCO_2C_2H_5$		18	 (1)	95%
2	$PhC{\equiv}CCO_2C_2H_5$		18	 (3)	82%
3	$PhC{\equiv}CCO_2C_2H_5$	H_2NTs	18	 (4)	82%
4	$PhC{\equiv}CCO_2C_2H_5$		5	 (5)	57%
5	$PhC{\equiv}CCO_2C_2H_5$		18	 (6)	66%
6	 (7)		18	 (8)	66%
7	 (9)	H_2NTs	18	 (10)	56%

[a] All reactions were run in $PhCH_3$ at 105 °C with 10 mol % Ph_3P, 50 mol % HOAc, and 50 mol % NaOAc.

Changing reactants and conditions can lead to α-, β-, γ-additions, or isomerization

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

PR_3 Catalyzed [3+2] Cycloadditions



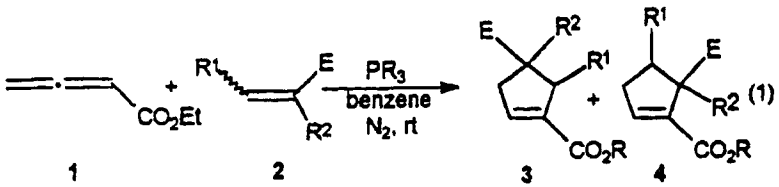
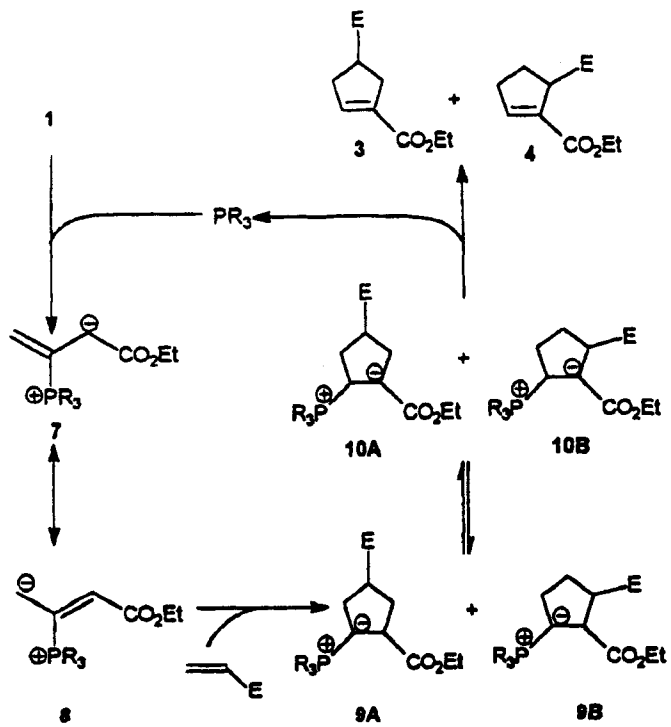
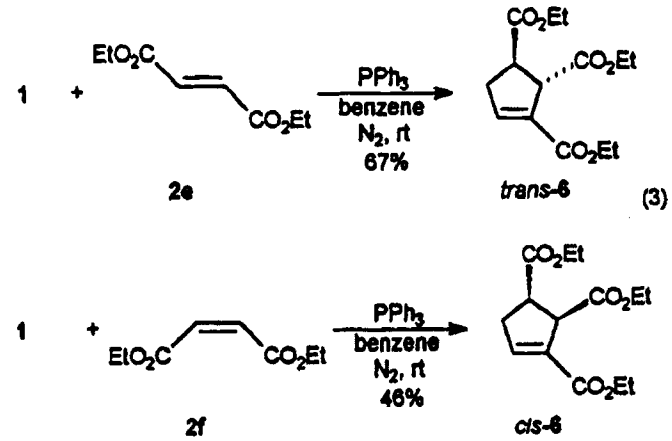


Table 1. Phosphine-Catalyzed Cycloaddition of 2,3-Butadienoates with Electron-Deficient Olefins

entry	olefin 2	olefin E	PR_3	products yield (%)	products 3:4[a]
1	2a[b]	COOEt	PPh_3	76	75:25
2	2a	COOEt[c]	PBu_3	66	75:25
3	2b[b]	COOMe	PPh_3	81	80:20
4	2b	COOMe[c]	PBu_3	66	85:15
5	2c[b]	COMe	PPh_3	55	63:37
6	2d[b]	CN	PPh_3	79	83:17[d]

[a] Ratios were determined by isolation. [b] $R^1 = R^2 = H$. [c] 2 equiv of olefin was used. [d] Ratio was determined by ^1H NMR spectra.





Cycloadditions with Butynoates

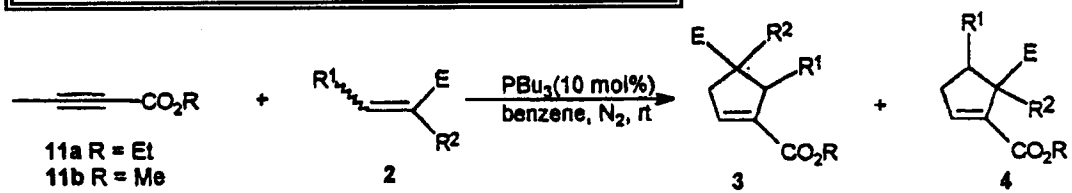


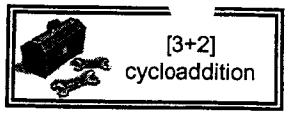
Table 2. Cycloaddition of 2-Butynoates with Electron-Deficient Olefins under the Catalysis of Tributylphosphine

entry	11	2	products yield (%)	products 3:4[a]
1	11a	2a[b]	85	89:11 (3a:4a)
2	11a	2b[b]	78	84:16 (3b:4b)
3	11a	2d[b]	80	93:7 (3d:4d)[c]
4	11a	2e	88	*trans*-6
5	11a	2f	91	*trans*-6
6	11b	2b	62	87:13 (3b′:4b′)
7	11b	2g[d]	46	72:28 (3g:4g)

[a] Ratios were determined by isolation. [b] See Table 1. [c] Ratio was determined by ^1H NMR spectra. [d] 2g: $R^1 = H$, $R^2 = Me$, $E = CO_2Me$.

C. Zhang, X. Lu* *J. Org. Chem.* **1995**, *60*, 2906.

Asymmetric [3+2] Cycloadditions



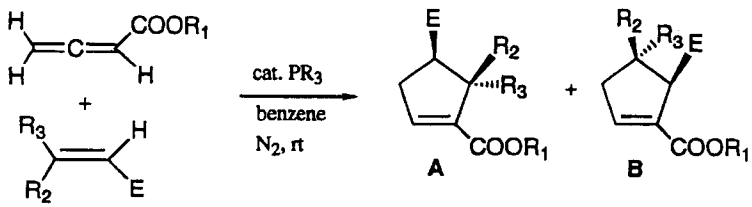


Figure 1.

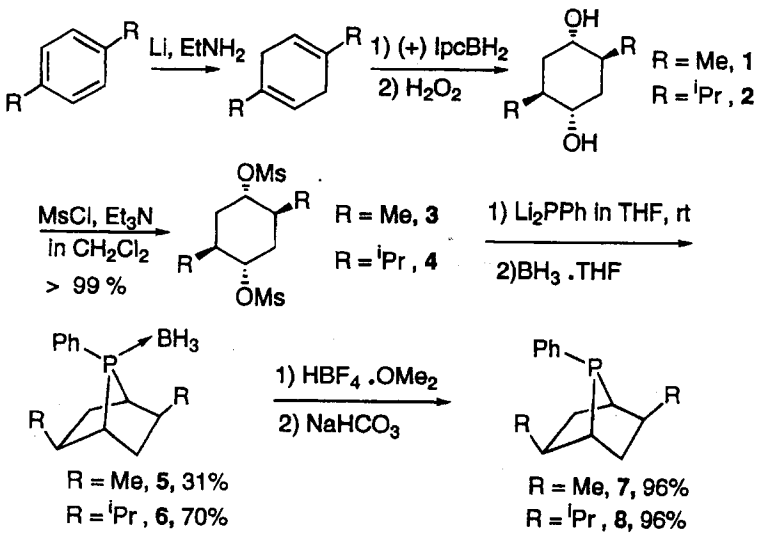


Figure 2. Synthesis of chiral monophosphines.

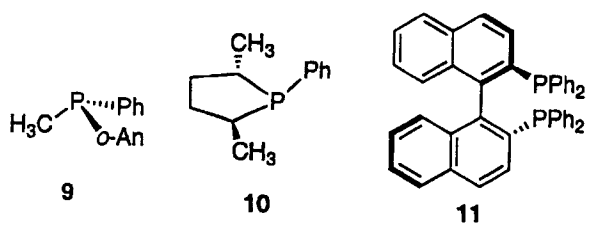
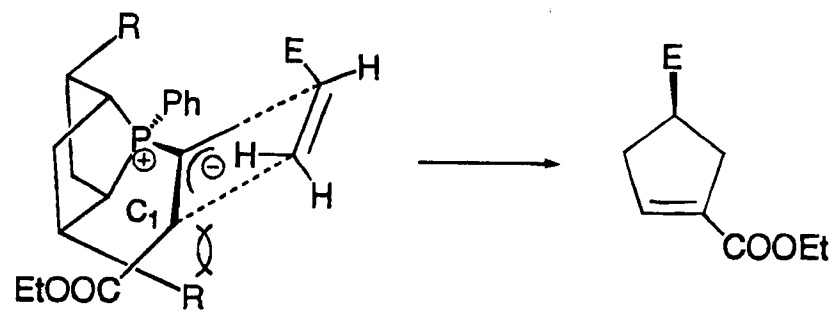


Table 1. Phosphine-Catalyzed Asymmetric [3 + 2] Cycloaddition[a]

entry	phosphine	E	R_1	R_2	R_3	solvent	T (°C)[e]	yield (%)	A:B[b]	% ee of A[b]	config[c]
1	7	COOEt	Et	H	H	benzene	rt	66	95:5	81	(−) *R*
2	8	COOEt	Et	H	H	benzene	rt	76	97:3	81	(−) *R*
3	9	COOEt	Et	H	H	benzene	rt	80	80:20	56	(+) *S*
4	10	COOEt	Et	H	H	benzene	rt	83	72:29	6	(+) *S*
5	11	COOEt	Et	H	H	benzene	rt	33	73:27	12	(−) *R*
6	7	COO^{i}Bu	Et	H	H	benzene	rt	46	100:0	86	(−) *R*
7	7	COO^{t}Bu	Et	H	H	benzene	rt	69	95:5	89	(−) *R*
8	7	COO^{t}Bu	Et	H	H	toluene	0	42	97:3	93	(−) *R*
9	8	COOMe	Et	H	H	benzene	rt	87	96:4	79	(−) *R*
10	8	COO^{i}Bu	Et	H	H	benzene	rt	92	100:0	88	(−) *R*
11	8	COO^{t}Bu	Et	H	H	toluene	0	88	100:0	93	(−) *R*
12	8	COO^{t}Bu	Et	H	H	benzene	rt	75	95:5	88	(−) *R*
13	7	COOEt	^{t}Bu	H	H	benzene	rt	13	97:3	89	(−) *R*
14	8	COOEt	^{t}Bu	H	H	benzene	rt	84	94:6	69	(−) *R*
15[d]	8	COOEt	Et	COOEt	H	toluene	0	49		79	(+)
16[d]	8	COOMe	Et	H	COOMe	benzene	rt	84		36	(−)

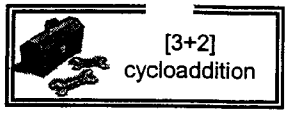
[a] The reaction was carried out under N_2 with a chiral phosphine (10 mol %), 2,3-butadienoate (100 mol %), and electron deficient olefins (1000 mol %). [b] A:B and % ee were measured by GC with β and γ-DEX columns. [c] The absolute configuration was determined by comparing the optical rotation with the literature value.[16] [d] Olefins (200 mol %) were used. [e] rt = room temperature.

- For **7/8** – ee increases with size of ester in olefin
- For **7** ee up with dipole ester size (entry 1 vs 13)
- For **8** ee down with dipole ester size (entry 2 vs 14)
- Generally better yields with **8**



G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cau, X. Zhang* *J. Amer. Chem. Soc.* **1997**, *119*, 3836.

[3+2] Cycloaddition with Imines



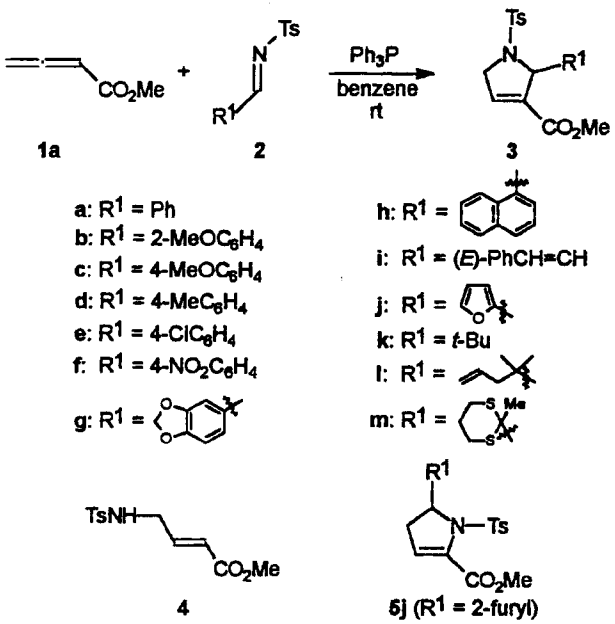


Table 1. Triphenylphosphine-Catalyzed Cycloaddition of Methyl 2,3-Butadienoate with *N*-Tosylimines[a]

entry	2	product 3	yield[b] (%)
1	**2a**	**3a**	98
2	**2b**	**3b**	96
3	**2c**	**3c**	98
4	**2d**	**3d**	98
5	**2e**	**3e**	97
6	**2f**	**3f**	88[c]
7	**2g**	**3g**	98
8	**2h**	**3h**	98
9	**2i**	**3i**	53[d]
10	**2j**	**3j**	83[e]
11	**2k**	**3k**	trace
12	**2l**	**3l**	trace

[a] Reaction conditions: A mixture of **1a** (1.1 mmol), **2** (1.0 mmol), and Ph_3P (0.1 mmol) in dry benzene at room temperature. [b] Isolated yield. [c] A small amount of methyl 4-(*p*-toluenesulfonamido)-2-butenoate (**4**)[14] was isolated. [d] 34% of **2i** was recovered. [e] Another adduct, methyl 4,5-dihydro-5-furyl-1-tosyl-pyrrole-2-carboxylate (**5j**), was isolated in 15% yield.

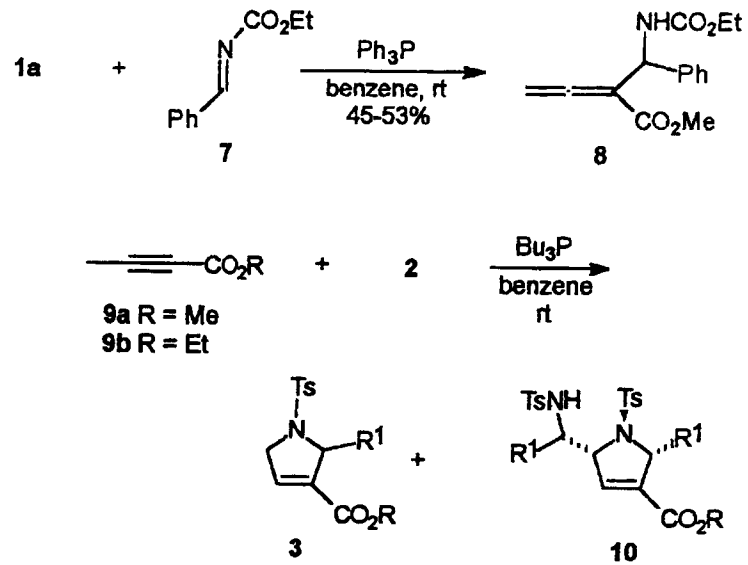


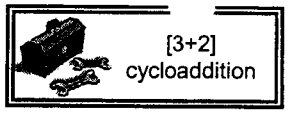
Table 4. Tributylphosphine-Catalyzed Cycloaddition of Methyl 2,3-Butadienoate or 2-Butynoates with *N*-Tosylimines[a]

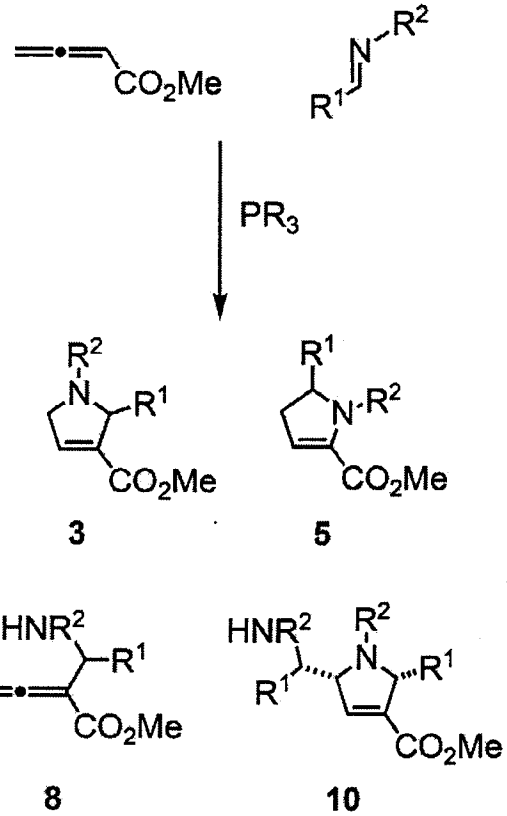
entry	1/9	2	products yield[b] (%)	products 3:10[c]
1	**1a**	**2a**	98	87:13 (**3a:10a**)
2	**9b**	**2a**	96	85:15 (**3a′:10a′**)
3	**9a**	**2b**	95	81:19 (**3b:10b**)
4	**9b**	**2c**	86	90:10 (**3c′:10c′**)
5	**9b**	**2d**	93	82:18 (**3d′:10d′**)
6	**9a**	**2e**	87	85:15 (**3e:10e**)
7	**9a**	**2k**	57	100:0 (**3k:10k**)
8	**9a**	**2l**	14	100:0 (**31:101**)
9	**9a**	**2m**	47	100:0 (**3m:10m**)

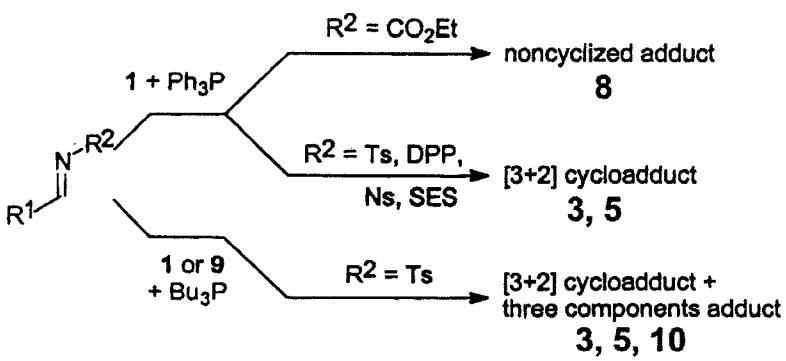
[a] Reaction conditions: A mixture of **1** or **9** (1.1 mmol), **2** (1.0 mmol), and Bu_3P (0.1 mmol) in dry benzene at room temperature. [b] Isolated yield. [c] Ratios were determined by isolation.

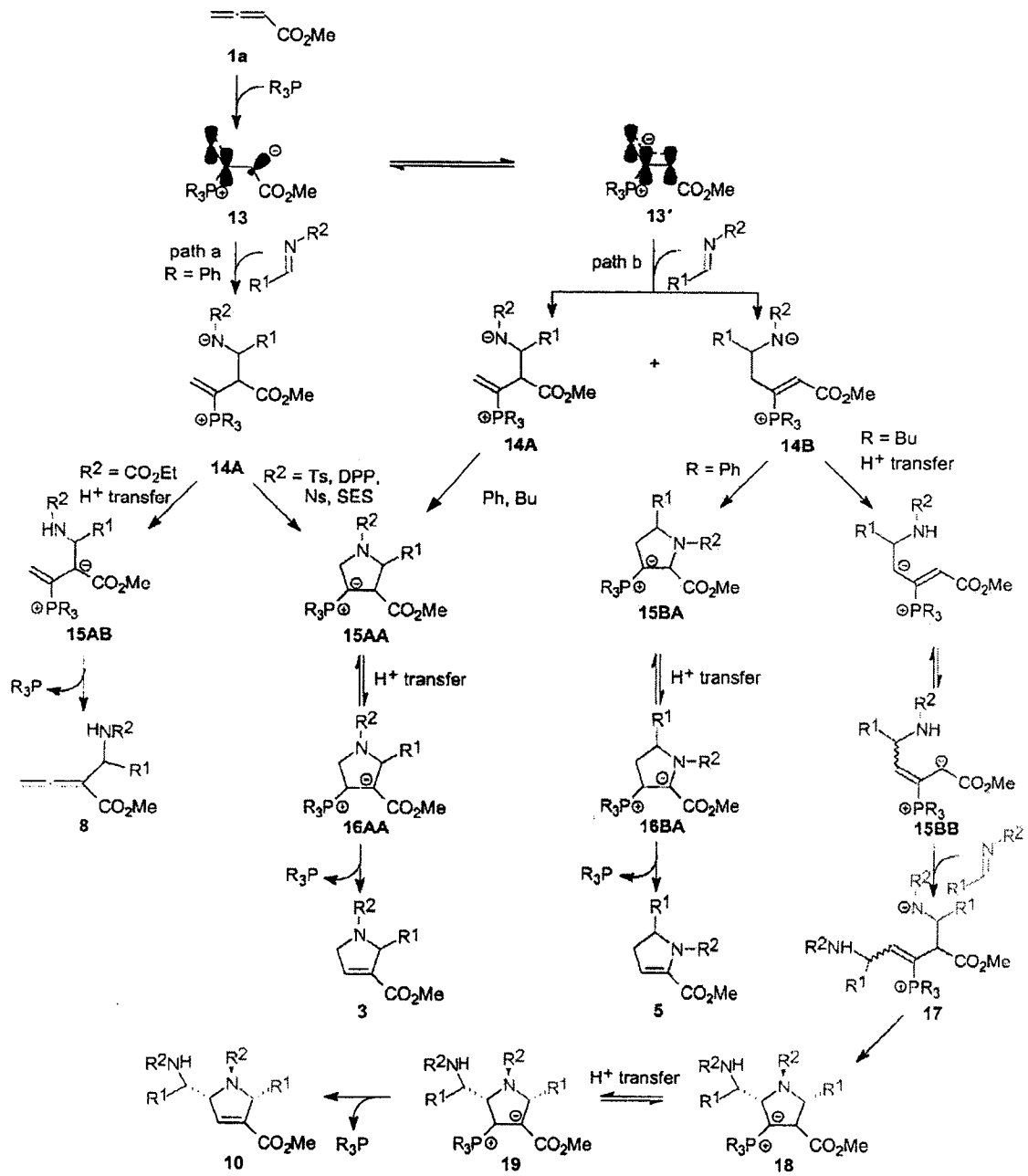
Z. Xu, X. Lu* *Tetrahedron Lett.* **1997**, *38*, 3461.
Z. Xu, X. Lu* *J. Org. Chem.* **1998**, *63*, 5031.

Proposed Mechanism









Z. Xu, X. Lu* *J. Org. Chem.* **1998**, *63*, 5031.

PR_3 Catalyzed [4+2] Annulation

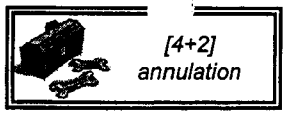
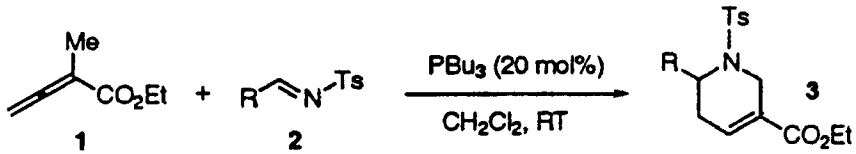


Table 1. Synthesis of Tetrahydropyridines **3** from Ethyl 2-Methyl-2,3-butadienoate and *N*-Tosylaldimines[a]



entry	R	product	yield (%)[b]
1	Ph (**2a**)	**3a**[c]	98
2	4-$OMeC_6H_4$ (**2b**)	**3b**	99
3	4-MeC_6H_4 (**2c**)	**3c**	95
4	3-ClC_6H_4 (**2d**)	**3d**	96
5	2-ClC_6H_4 (**2e**)	**3e**	93
6	4-FC_6H_4 (**2f**)	**3f**	95
7	4-CNC_6H_4 (**2g**)	**3g**	98
8	2-$CF_3C_6H_4$ (**2h**)	**3h**	98
9	1-naphthyl (**2i**)	**3i**	96
10	2-furyl (**2j**)	**3j**	97
11	4-pyridyl (**2k**)	**3k**	92[d]
12	4-$NO_2C_6H_4$ (**2l**)	**3l**	86
13	2-OHC_6H_4 (**2m**)	**3m**	0
14	2-$OTBSC_6H_4$ (**2n**)	**3n**	93
15	2-pyrrolyl (**2o**)	**3o**	0
16	*N*-Boc-2-pyrroyl (**2p**)	**3p**	99
17	*trans*-styrenyl (**2q**)	**3q**	trace[e]
18	*t*-butyl (**2r**)	**3r**	86[f]
19	*n*-propyl (**2s**)	**3s**	0[g]

[a] See Supporting Information for a detailed experimental procedure. [b] Isolated yields. [c] The structure was confirmed by X-ray crystallographic analysis. [d] 30 mol % PBu_3 was used. [e] The product was inseparable from the starting imine. [f] 3 equiv of Na_2CO_3 was added. [g] The imine was decomposed to aldehyde and *p*-toulenesulfonamide.

Scheme 1. Mechanistic Rationale for the Formation of **3**

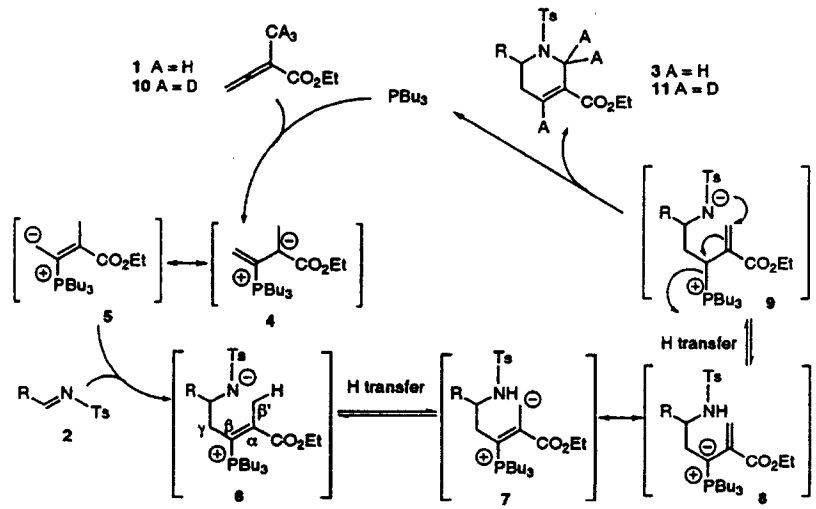
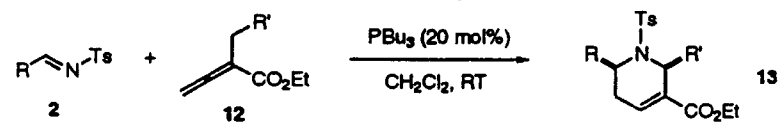


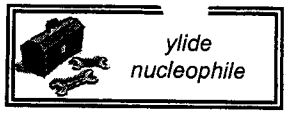
Table 2. Synthesis of Tetrahydropyridines **13** from Ethyl 2-Benzyl-2,3-butadienoates and *N*-Tosylaldimines[a]



entry	R	R′	product	yield (%)[b]	dr[c]
1	Ph (**2a**)	4-CNC_6H_4 (**12a**)	**13a**	99	98:2
2	Ph (**2a**)	2-FC_6H_4 (**12b**)	**13b**	99	97:3
3	Ph (**2a**)	3-$OMeC_6H_4$ (**12c**)	**13c**	99	98:2
4	Ph (**2a**)	2-MeC_6H_4 (**12d**)	**13d**	82	88:12
5	Ph (**2a**)	Ph (**12e**)	**13e**[d]	99	98:2
6	4-$OMeC_6H_4$ (**2b**)	Ph (**12e**)	**13f**	99	97:3
7	4-$NO_2C_6H_4$ (**2l**)	Ph (**12e**)	**13g**	90	95:5
8	3-ClC_6H_4 (**2d**)	4-CNC_6H_4 (**12a**)	**13h**	99	98:2
9	2-$CF_3C_6H_4$ (**2h**)	4-CNC_6H_4 (**12a**)	**13i**	80	90:10
10	2-ClC_6H_4 (**2e**)	3-$OMeC_6H_4$ (**12c**)	**13j**	96	83:17
11	4-MeC_6H_4 (**2c**)	3-$OMeC_6H_4$ (**12c**)	**13k**	99	98:2

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

Catalytic Carbon-Phosphorus Ylide Reaction



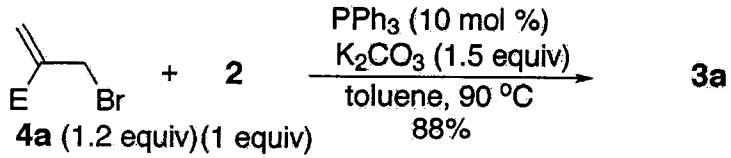
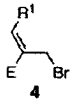
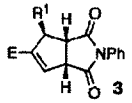
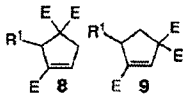
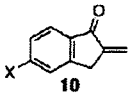
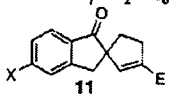
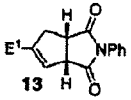
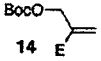
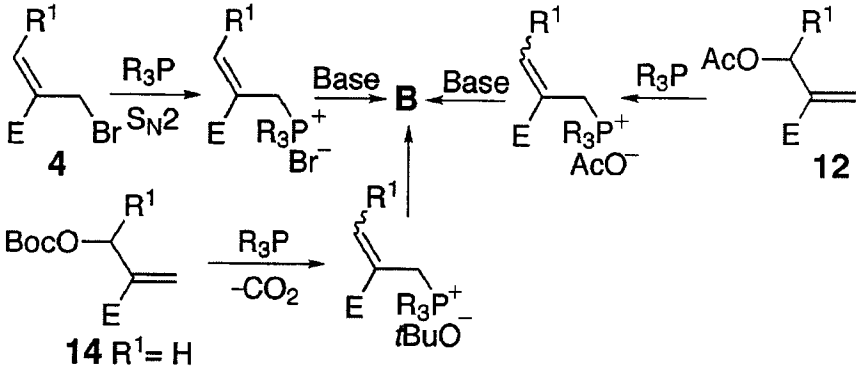
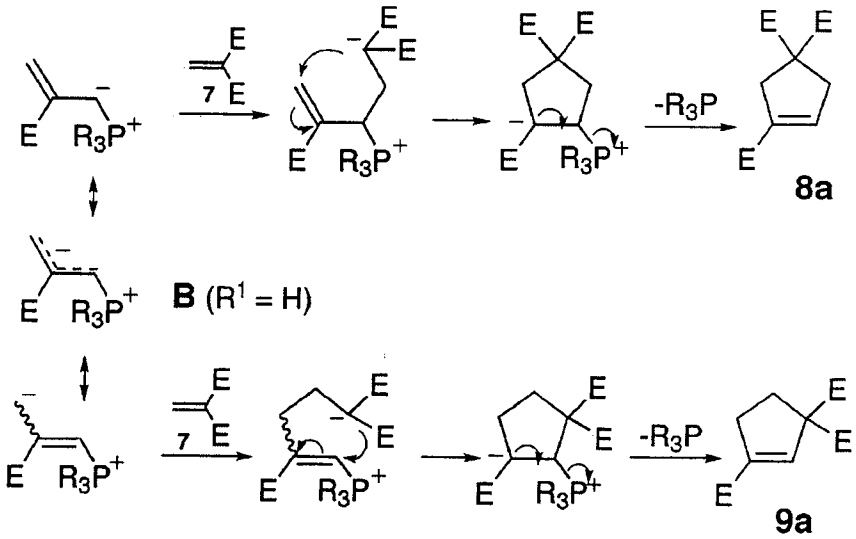


Table 1: Phosphane-catalyzed annulation reaction of ylides.[a]

Entry	C_3 component	C_2 component	T [°C]	t [h]	Product	Yield [%][b]
	 4	 2			 3	
1[c]	**4a**: $R^1=H$	**2**	90	12	**3a**: $R^1=H$	88
2[c]	**4b**: $R^1=Ph$	**2**	110	4	**3b**: $R^1=Ph$	50[d]
3	**4b**	**2**	110	4	**3b**	68[d]
4	**4c**: $R^1=p\text{-}MeC_6H_4$	**2**	110	4	**3c**: $R^1=p\text{-}MeC_6H_4$	66[d]
5	**4d**: $R^1=p\text{-}O_2NC_6H_4$	**2**	110	4	**3d**: $R^1=p\text{-}O_2NC_6H_4$	71[d]
6	**4e**: $R^1=p\text{-}MeOC_6H_4$	**2**	110	4	**4e**: $R^1=p\text{-}MeOC_6H_4$	74[d]
7	**4f**: $R^1=n$Pr	**2**	110	4	**4f**: $R^1=n$Pr	60[d]
8	**4a**	 5	110	20	 6	70[e]
		 7			 8 9	
9	**4a**	**7**	110	20	**8a**: $R^1=H$; **9a**: $R^1=H$	61[f]
10	**4d**	**7**	110	6	**8d**: $R^1=p\text{-}O_2NC_6H_4$	66
		 10			 11	
11	**4a**	**10a**: X=H	110	20	**11a**: X=H	72[g]
12	**4a**	**10b**: X=MeO	110	20	**11b**: X=MeO	65
	 12					
13	**12a**: $R^1=H$	**2**	70	4	**3a**	76
14	**12b**: $R^1=Ph$	**2**	110	4	**3b**	62[d]
15	 12c	**2**	30	2	 13	64
16[h]	 14	**2**	110	2	**3a**	74

Proposed Mechanism

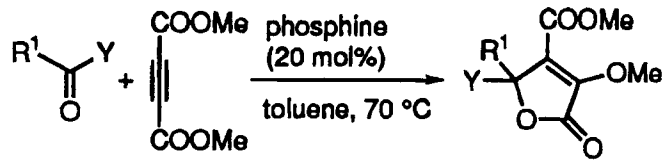


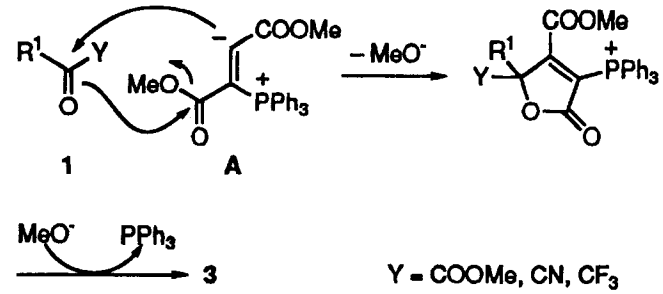


Lu is now using the descriptor "phosphane" instead of "phosphine" for PR_3

Y. Du, X. Lu,* C. Zhang *Angew. Chem. Int. Ed.* **2003**, *42*, 1035.

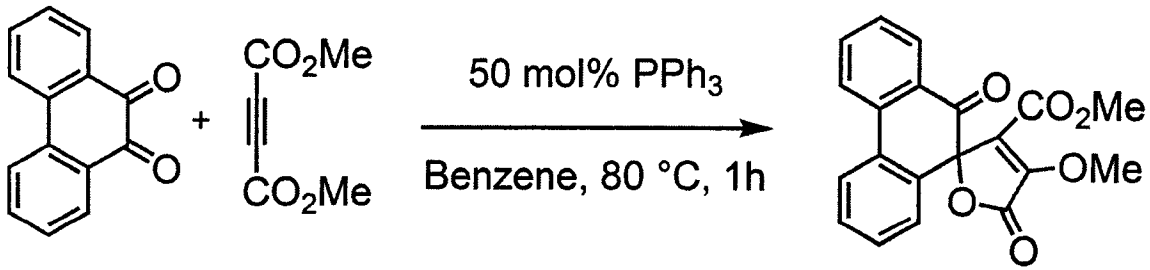
γ-Butyrolactones through PR_3 Catalysis





run	substrate **1**	R^1	R^2(Y)	phosphines	time (h)	yield of **3** (%)[a,b]
1	**1a**	4-$NO_2C_6H_4$	COOMe	PPh_3	22	94
2	**1b**	Ph	COOMe	PPh_3	8	11[c–e]
3	**1c**	4-ClC_6H_4	COOMe	PPh_3	22	*c*
4	**1d**	Ph	CN	PPh_3	8	58
5	**1e**	4-MeC_6H_4	CN	PPh_3	19	58
6	**1f**	4-$MeOC_6H_4$	CN	PPh_3	19	67
7	**1g**	4-ClC_6H_4	CN	PPh_3	22	30[d]
8	**1h**	4-$NO_2C_6H_4$	CN	PPh_3	22	<30[d,e]
9	**1i**	c-C_6H_{11}	CN	PPh_3	22	38
10	**1j**	Ph	CH_3	PPh_3	22	*c*
11	**1k**	Ph	CF_3	PPh_3	17	75
12	**1a**	4-$NO_2C_6H_4$	COOMe	(*S*)-BINAP[f]	49	6[c] (8)
13	**1a**	4-$NO_2C_6H_4$	COOMe	(*R*)-MeO-MOP[g]	47	41[c] (10)
14	**1a**	4-$NO_2C_6H_4$	COOMe	(+)-NMDPP[h]	48	5[c] (5)

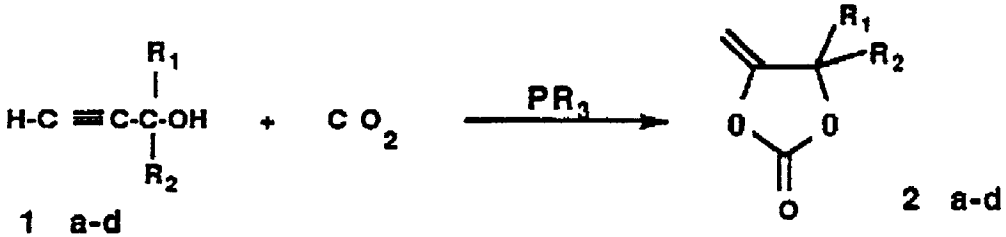
[a] Isolated yield. [b] %*ee* for **3** are shown in parentheses. The absolute configuration of the major isomer has not been determined. [c] The unreacted starting materials were recovered. [d] A complex mixture was obtained. [e] The product was not obtained in pure form. [f] (*S*)-BINAP = (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [g] (*R*)-MeO-MOP = (*R*)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl. [h] (+)-NMDPP = (1*S*,2*S*,5*R*)-neomenthyldiphenylphosphine.



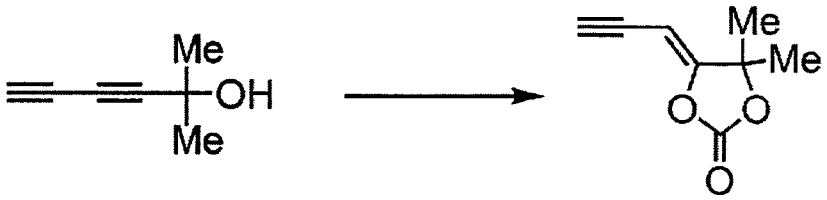
75% Yield

K. Nozaki,* N. Sato, K. Ikeda, H. Takaya* *J. Org. Chem.* **1996**, *61*, 4516.
V. Nair,* J.S. Nair, A.U. Vinod, N.P. Rath *J. Chem. Soc., Perkin Trans. 1* **1997**, 3129.

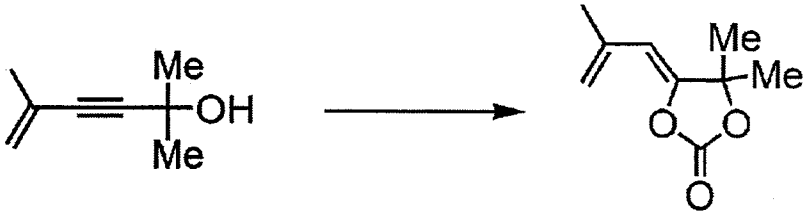
PR_3 Catalyzed Carbonate Formation



Doesn't work for aliphatic alkyne substitution but:



54%



47%

Table 2 : Reaction of CO_2 with 2-methyl-3-butyn-2-ol (1a) [a)]

Catalyst	Temperature (°C)	Time (h)	Yield (%)
PBu_3	140	20	86
-	100	8	98
-	50	20	97
PPh_3	140	20	78
-	100	8	7
PCy_3	140	20	97
-	100	8	8

a) alcohol 1a (50 mmol), phosphine (4 mmol), CO_2 (50 kg/cm^2)

Table 1 : Reaction of CO_2 with α-Ethynyl Alcohols [a)]

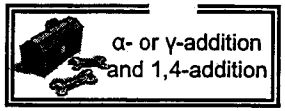
Alcohol		Product	Yield(%) [b)]
1a	$R_1 = R_2 = CH_3$	2a	98
1b	$R_1 = CH_3$, $R_2 = C_2H_5$	2b	92
1c	$R_1 = CH_3$, $R_2 = C_6H_5$	2c	32[c]
1d	$R_1 \cdot R_2 = (CH_2)_5$	2d	58

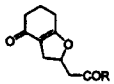
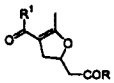
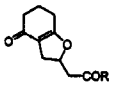
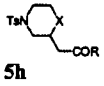
a) alcohol (50 mmol), PBu_3 (4 mmol), CO_2 (50 kg/cm^2), 100 °C, 8 h.
b) isolated yield based on alcohol, c) 20 h.

Et_3N/other amine bases
are not catalysts for this reaction

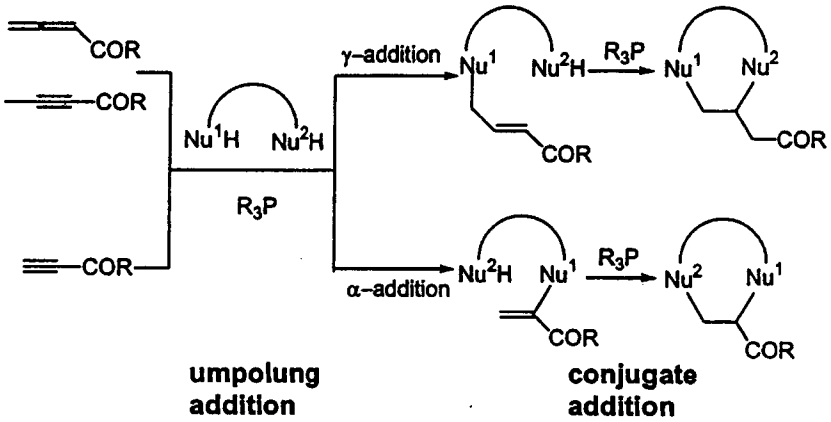
J. Fournier, C. Bruneau, P. Dixneuf *Tetrahedron Lett.* **1989**, *30*, 3981.
J.M. Joumier, J. Fournier, C. Bruneau, P.H. Dixneuf* *J. Chem. Soc. Perkin Trans 1* **1991**, 3271.

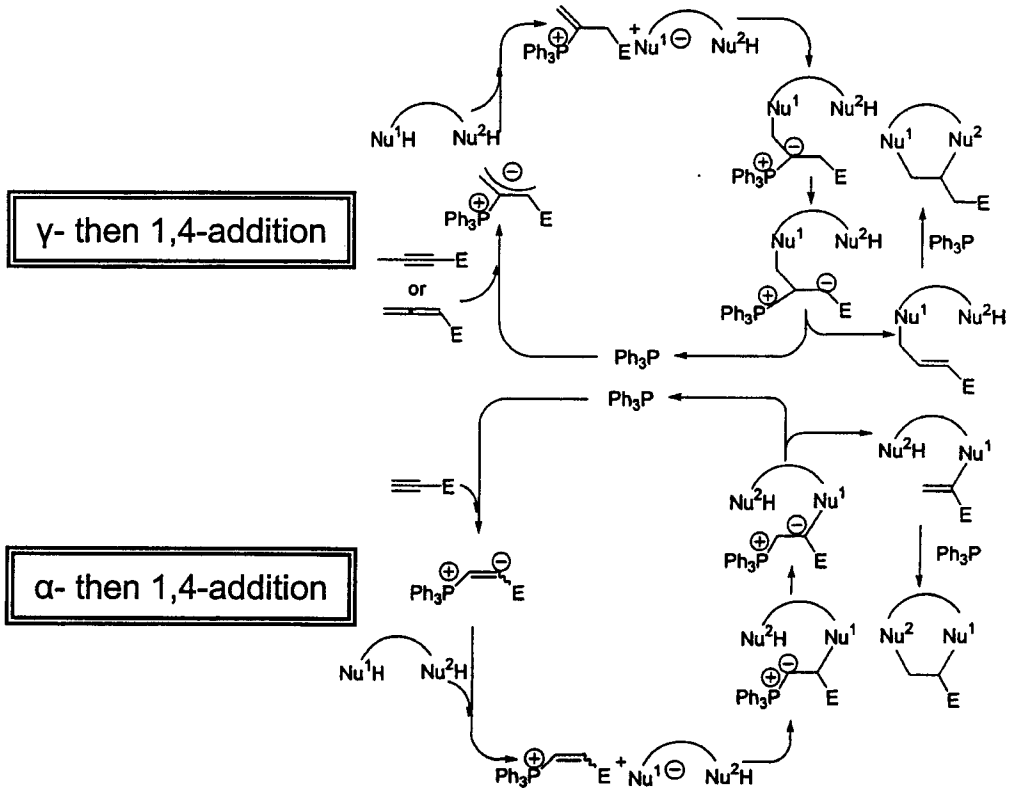
PR_3 Catalyzed Tandem RXNS



entry	NuH	allenes or alkynes	T(°C)/ T (h)	product	yield (%)[b]
1	 1a	 R=OEt 2a	110/24	 5a	68
2[c]	1a	2b R=Me	70/2	5b	84
3[c]	1a	2c R=Ph	70/5	5c	70
4[c]	 1b R^1=Me	2b	70/5	 5d	66[d]
5[c]	1c R^1=OEt	2b	70/5	5e	77[d]
6	1a	 R=OBn 3d	110/48	 5f	71
7	1a	3e R=Cy	110/48	5g	92
8[e]	 1d X=NTs	3b R=Me	80/24	 5h	93
9[e]	1d	3c R=Ph	80/24	5i	81[g]
10[e]	1d	3e R=Cy	80/24	5j	96
11[e]	1e X=O	3b	80/24	5k	66[g]
12[e]	1e	3e	80/24	5l	66[e]
13[f]	1d	 4a R=OEt	80/24	 5m	86
14[f]	1d	4f R=^{n}Pr	80/24	5n	83[g]
15[f]	 1f	4a	80/72	 5o	88

[a] Reaction conditions: a solution of bifunctional nucleophile (0.5 mmol), allene or alkyne (0.5 mmol), and Ph_3P (0.1 mmol) were heated at the indicated temperature. For details of the reaction conditions, see ref 8. [b] Isolated yield. [c] Used 0.025 mmol of Ph_3P. [d] Solution of 1 equiv of allenone in toluene was added dropwise to the solution of 5 equiv of 1,3-dicarbonyl compound in toluene, and the yields were based on the allenone. [e] CH_3CN was used as solvent. [f] Toluene−CH_3CN(v:v = 4:1) was used as a solvent. [g] Alkynone (1.1 equiv) in toluene or CH_3CN was added dropwise.

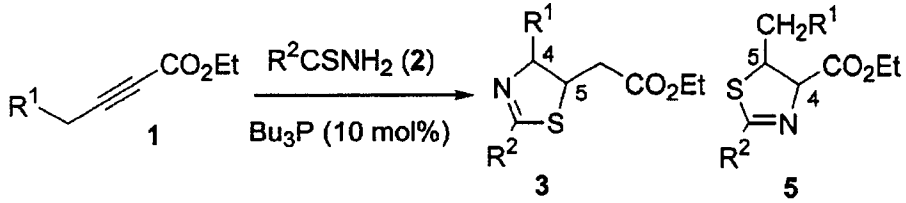




C. Lu, X. Lu* *Org. Lett.* **2002**, *4*, 4677.

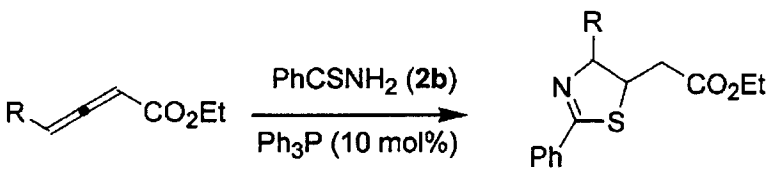
PR_3 Catalyzed Synthesis of Thiazolines

γ or α-addition and displacement



R^1	R^2	product (yield, %)
H (**1a**)	*p*-$CF_3C_6H_4$ (**2a**)	**3a** (82)
H (**1a**)	Ph (**2b**)	**3b** (64)
H (**1a**)	*p*-$MeOC_6H_4$ (**2c**)	**3c** (67)
H (**1a**)	3-pyridyl (**2d**)	**3d** (86)
H (**1a**)	2-thienyl (**2e**)	**3e** (70)
H (**1a**)	Me (**2f**)	**3f** (21)
H (**1a**)	CF_3 (**2g**)	**3 g** (54)
Me (**1b**)	Ph (**2b**)	**3h** (17, cis/trans 1:3) + **5a** (51, cis/trans 1:3)

[a] Reactions were run at 0.2 M with 1.2 equiv of alkynoate and 10 mol % of Bu_3P in toluene at room temperature for 24 h.

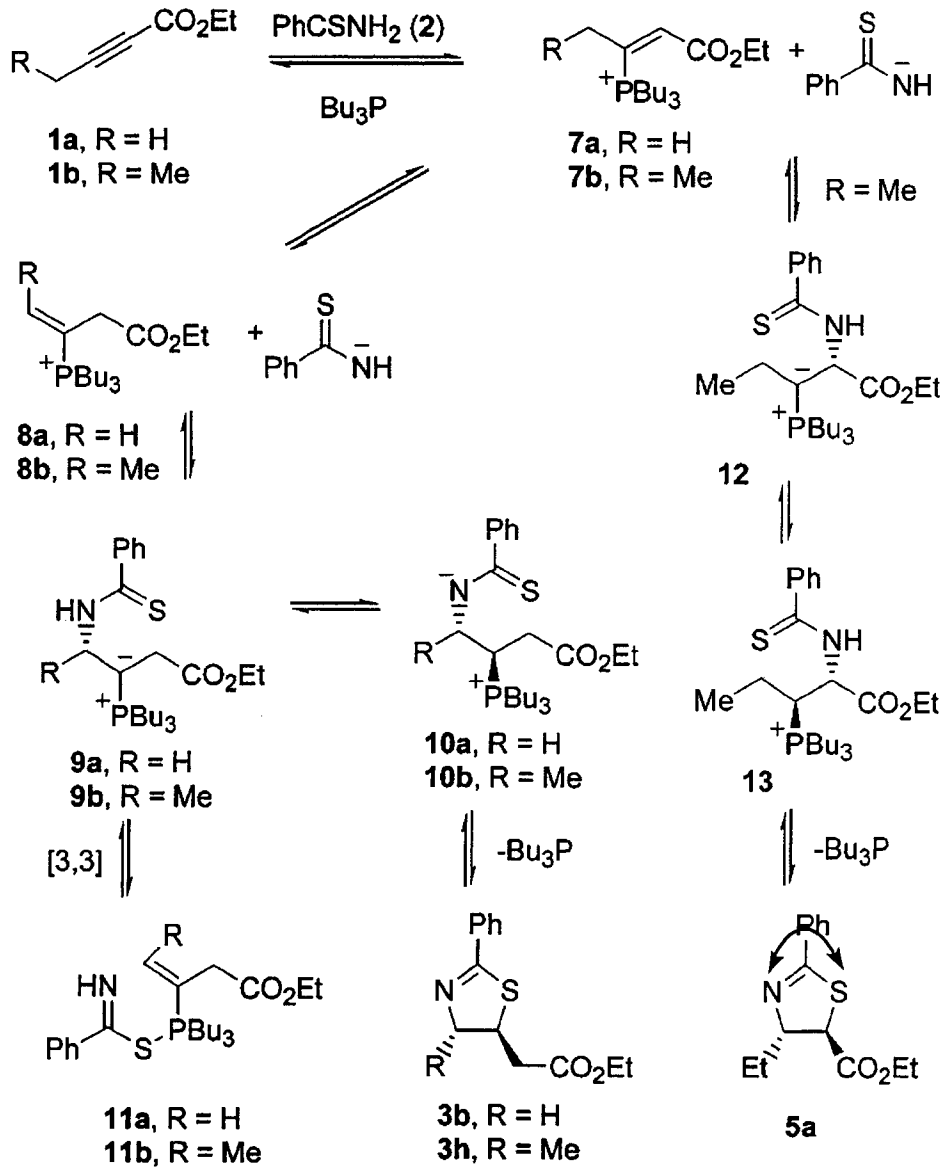


6a, R = H
6b, R = Me

3b, R = H, 54%
3h, R = Me, 28% (*cis/trans* 1:3)

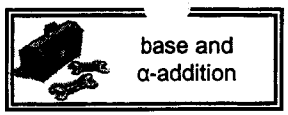
Enantioselective version is in development

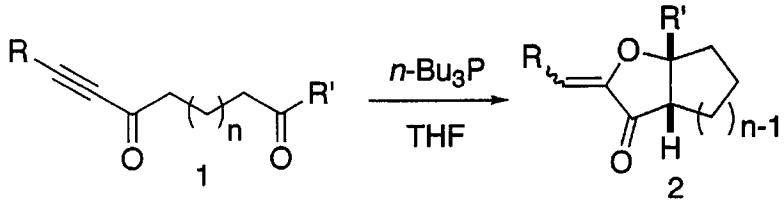
Proposed Mechanism:



(GlaxoSmithKline) B. Liu,* R. Davis, B. Joshi, D.W. Reynolds *J. Org. Chem.* **2002**, *67*, 4595.

PBu_3 Catalyzed Zipper Cyclization

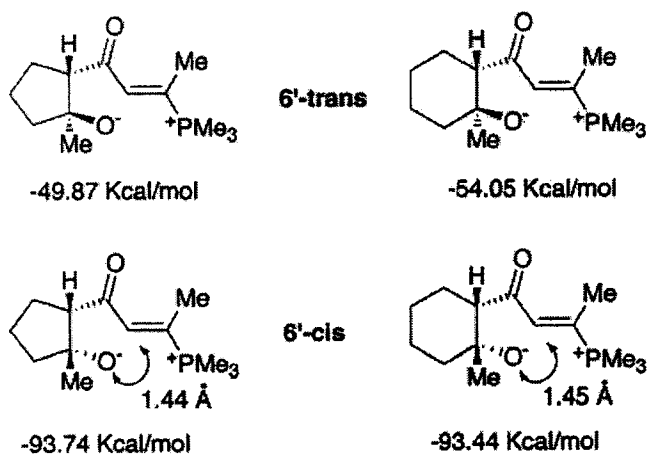




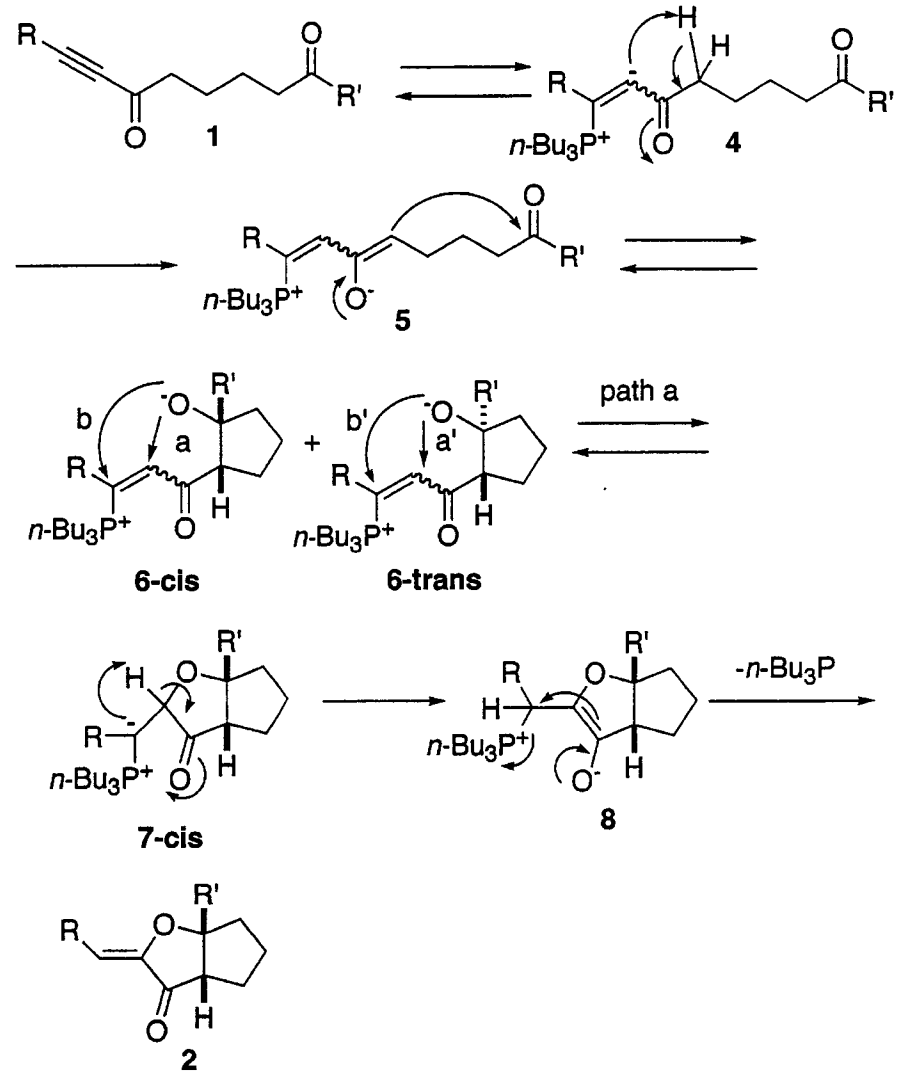
run	R	R′	n	1 and 2	1 → 2 yield (%)[b]
1	n-Bu	n-BuC≡C	2	**a**	59
2	Ph	PhC≡C	2	**b**	63
3	Ph	PhC≡C	3	**c**	73
4	Ph	PhC≡C	4	**d**	0
5	Ph	H	2	**e**	50
6	n-Bu	CH_3	3	**f**	41

[a] The reaction was carried out at room temperature in THF (0.5 M) in the presence of n-Bu_3P (20 mol %) as a catalyst. [b] Isolated yield by SiO_2 column.

Justification for stereochemical outcome:



Proposed Mechanism



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

Conclusion

- Many variations of phosphine catalysis have been reported
- Intermediates can act as nucleophiles, electrophiles, bases, ylides, dipoles, etc.
- Umpolung reactivity can be achieved (α- and γ-additions)
- Reaction pathway is controllable (for the most part) through reactant choice and reaction conditions
- Starting materials are mainly activated olefins, alkynes, or allenes
- PBu_3 and PPh_3 are the most studied catalyst (PBu_3 more reactive)
- Most processes lead to thermodynamic products
- Tandem processes have been developed leading to more complex molecules
- Not much use in total synthesis (PR_3 too reactive?), but seems useful – especially early in a synthesis

Other Papers of Interest

- Phoshine catalyzed [3+2] cycloadditions with [60]fullerene
  Wu et al. *Chem. Commun.* **1997**, 79.
  O'Donovan et al. *Chem. Commun.* **1997**, 81.

- [3+2] route to L-glutamate analogues
  Pyne et al. *Chem. Commun.* **1997**, 2267.

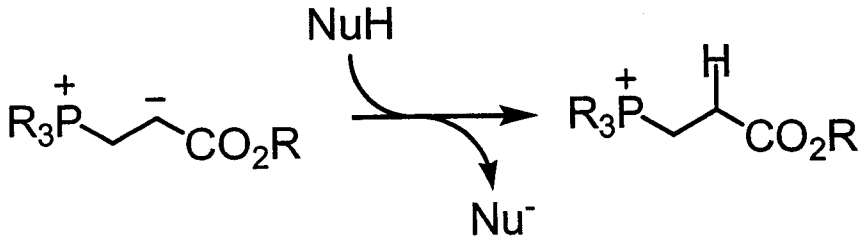
- Phosphine catalyzed [8+2] Annelation of Tropone
  Ishar et al. *Org. Lett.* **2000**, *2*, 787.

- Phosphine catalyzed [3+2] cycloadditions to give spirocycles
  Lu et al. *J. Org. Chem.* **2002**, *67*, 8901.

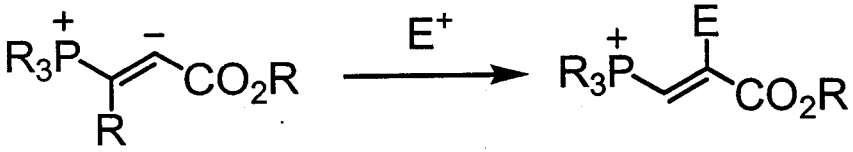
- Tandem Michael/Michael reactions mediated by phosphines
  Murphy et al. *Tetrahedron Lett.* **2002**, *43*, 8707.

Phosphine Catalysis Toolbox

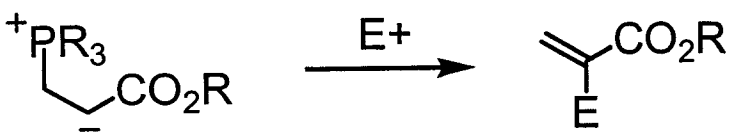
Strong Base



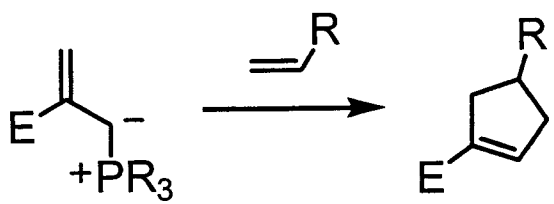
Nucleophile



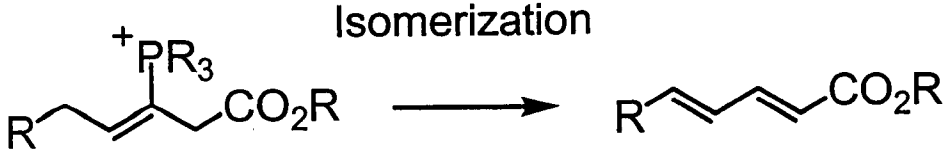
Morita-Baylis-Hilman
or Dimerization



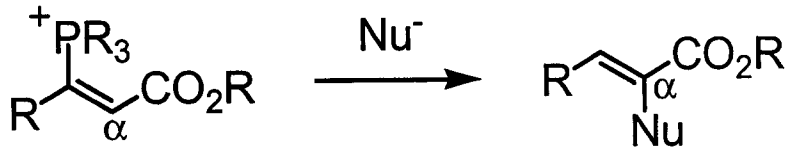
Ylide Nucleophile



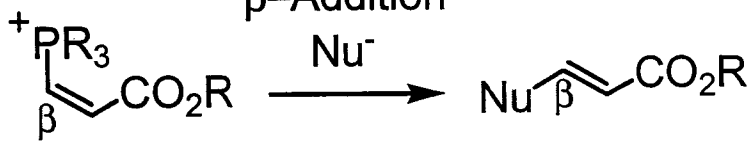
Isomerization



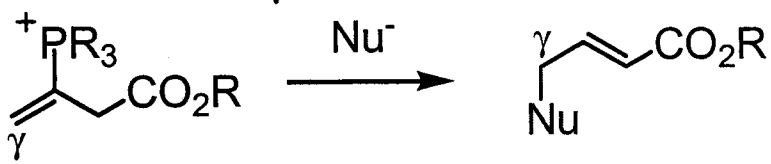
α-Addition



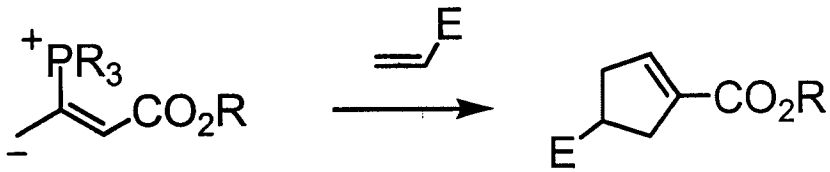
β–Addition



γ-Addition



[3+2] Cycloaddition



[4+2] Annulation