Phosphine Catalyzed γ Addition to Activated Alkynes and Allenes

Lindsey Cullen

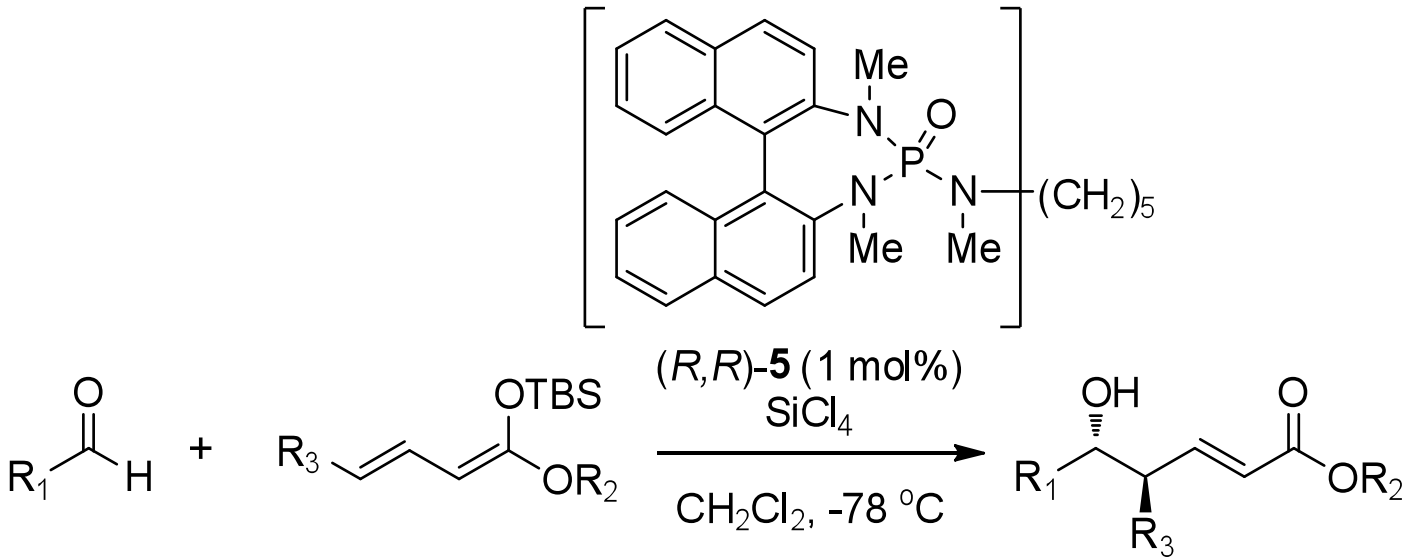
SED Group Meeting

3-23-2010

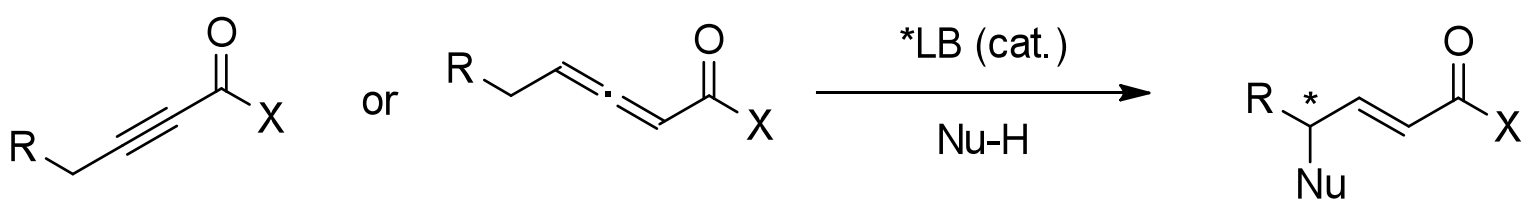
Enantioselective γ Functionalization

Few catalytic enantioselective methods exist to functionalize the γ position of a carbonyl compound

Vinylogous aldol reactions can stereoselectively add electrophiles to the γ position



A compliment to this strategy would be to addition of nucleophiles

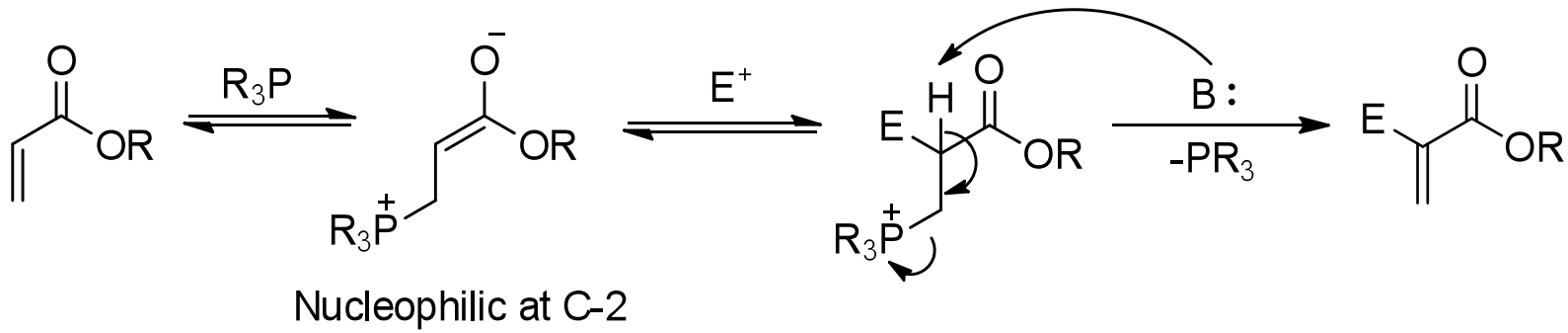


Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 1560.

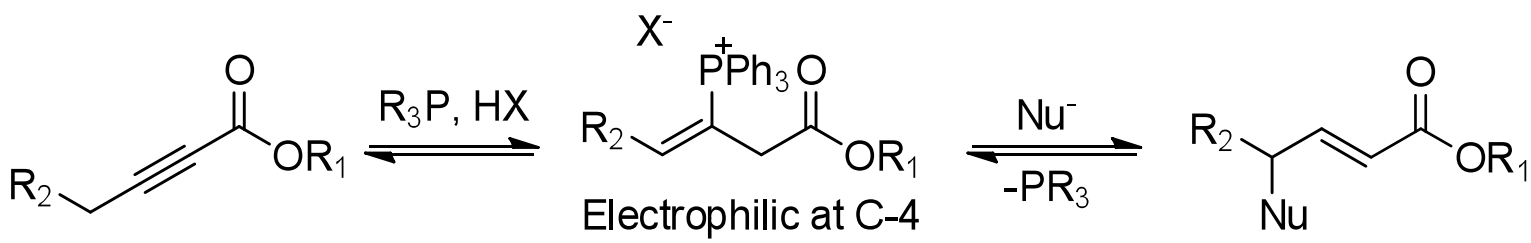
Phosphine as a Lewis Base Catalyst

Phosphines are strong Lewis bases that can interact with unsaturated substrates through a n - π* donation

A well known example is the Morita-Baylis-Hillman reaction:



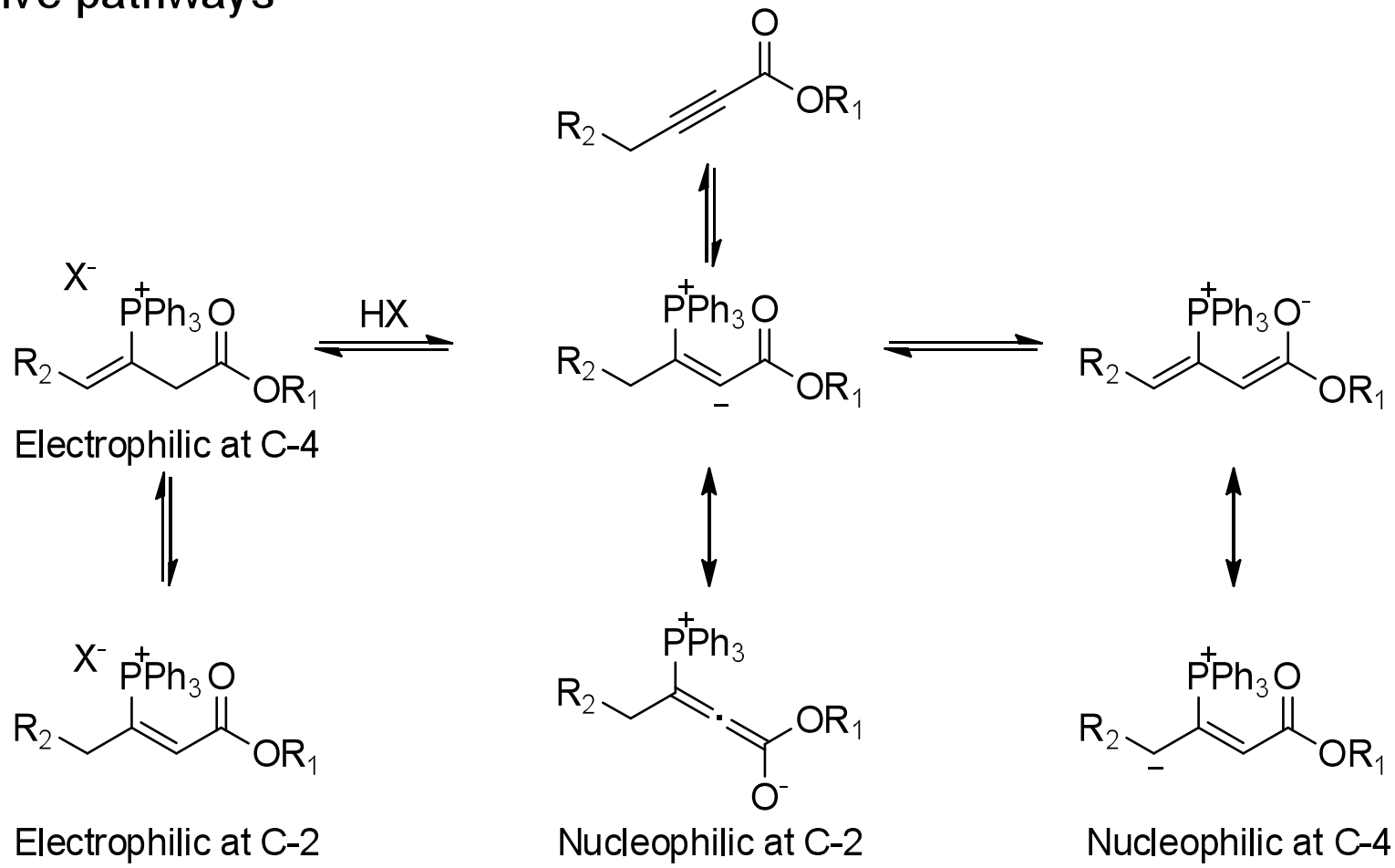
A zwitterionic intermediate in γ addition enhances the electrophilicity of C-4:



Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

A Variety of Reactive Intermediates

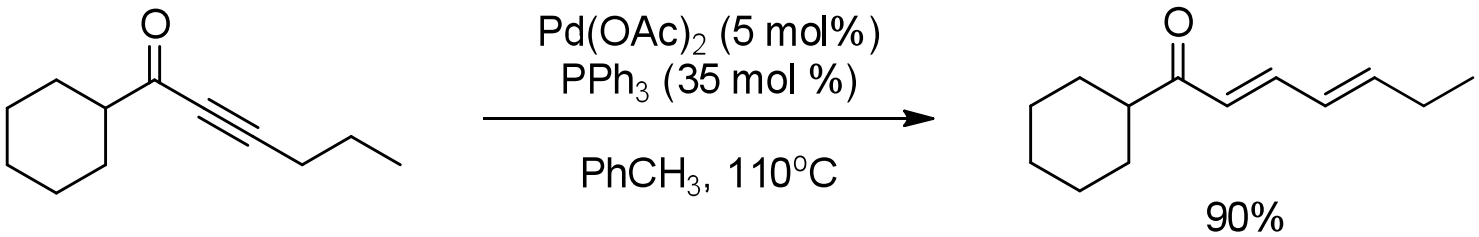
Phosphine n - π* interaction with alkynoates can lead to different reactive pathways

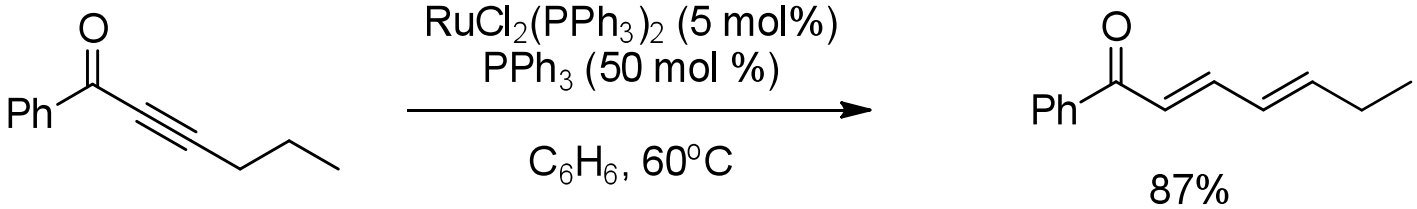


Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

Catalytic Isomerization of Alkynes

In the late 1980s a number of transition metal catalyzed isomerizations of electron deficient alkynes to 1,3-dienes were reported:

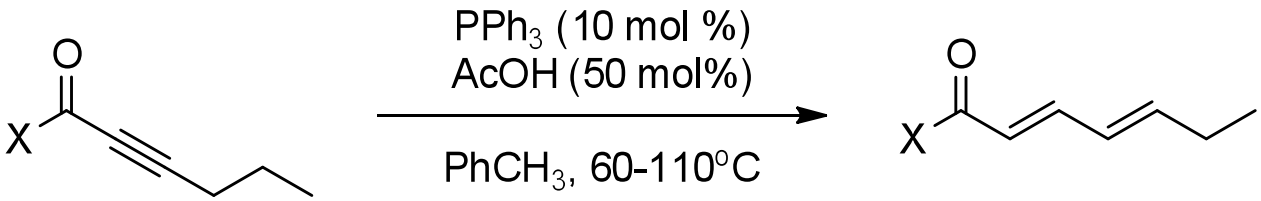




Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1998**, *110*, 2301.
Ma, D.; Yu, Y.; Lu, X. *J. Org. Chem.* **1989**, *54*, 1105.

Isomerization of Alkynes Catalyzed by Phosphine

Trost was the first to show that PPh_3 can catalyze the isomerization of alkynes

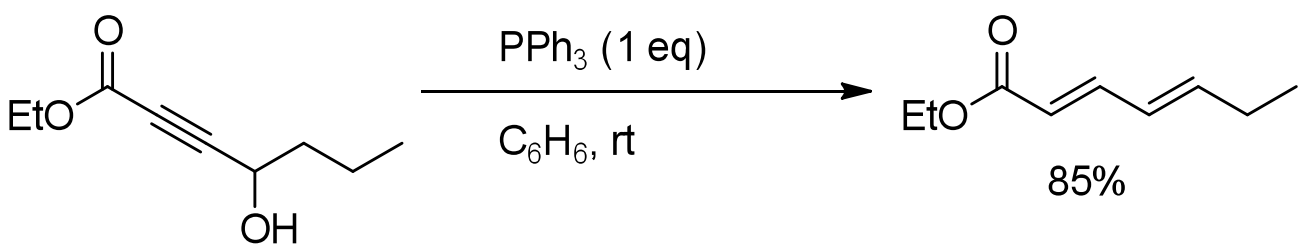


X = R, OR, or NHR

Yields 69-88%

Rate of reaction was dependent on the electron-withdrawing group:
ketone > ester > amide

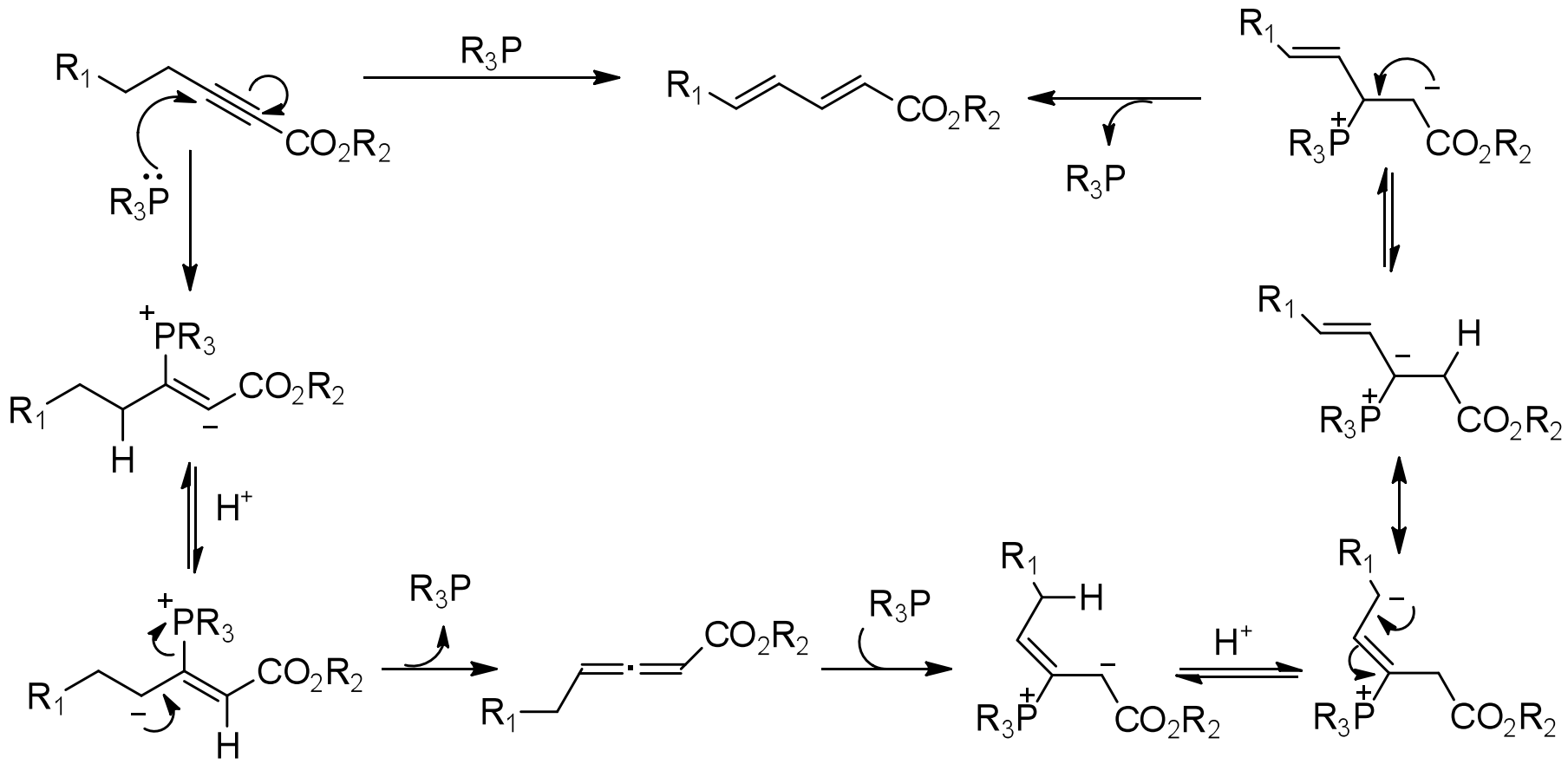
Lu published a similar finding with 4-hydroxy-2-yonic esters



85%

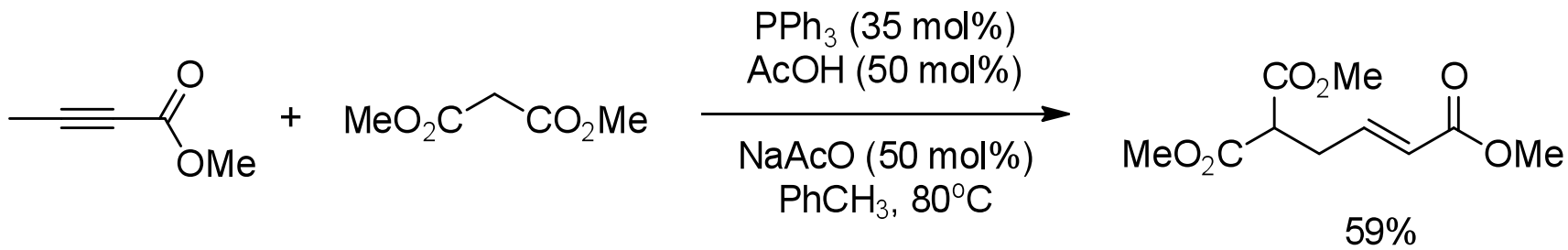
Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.
Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 394.

Mechanism of Isomerization

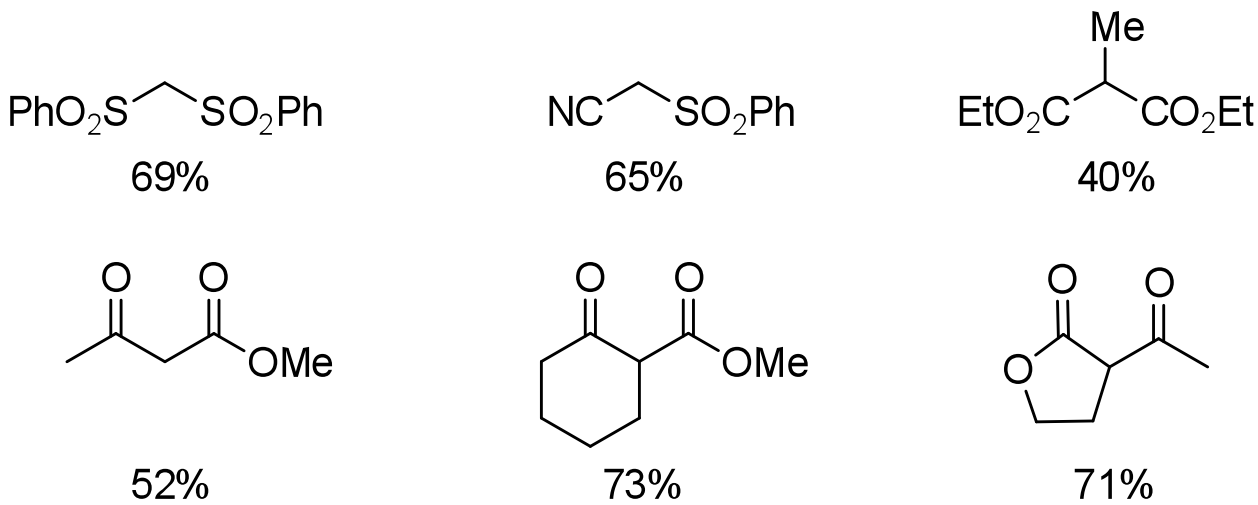


Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.
Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

Initial Report of Catalytic γ Addition to Alkynoates



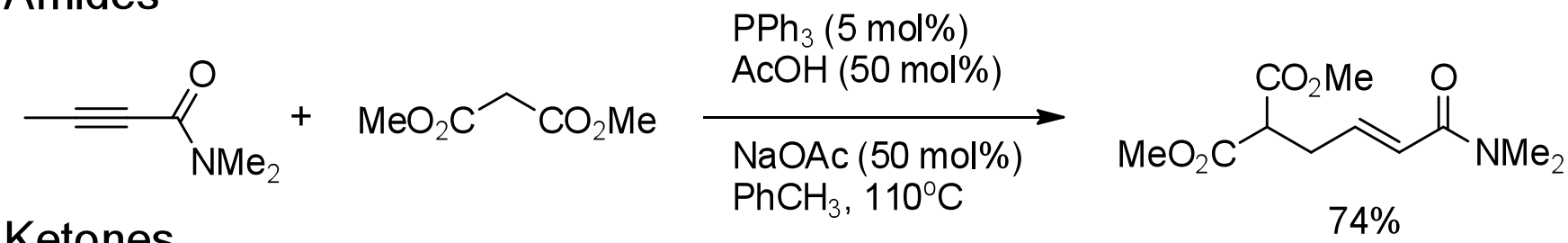
Applied to a variety of carbon nucleophiles with pK_a's under 16:



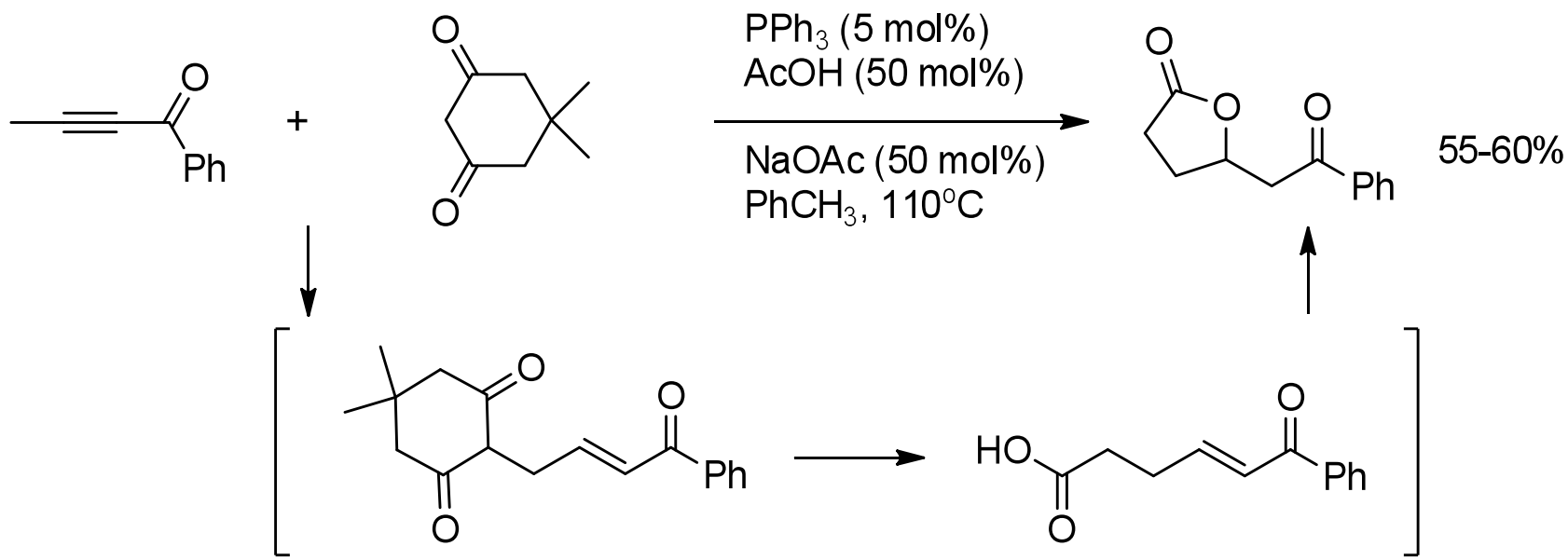
Trost, B. M.; Li, C. *J. Am. Chem. Soc.* **1994**, *116*, 3167.

γ Addition to Other Electron Deficient Alkynes

Amides

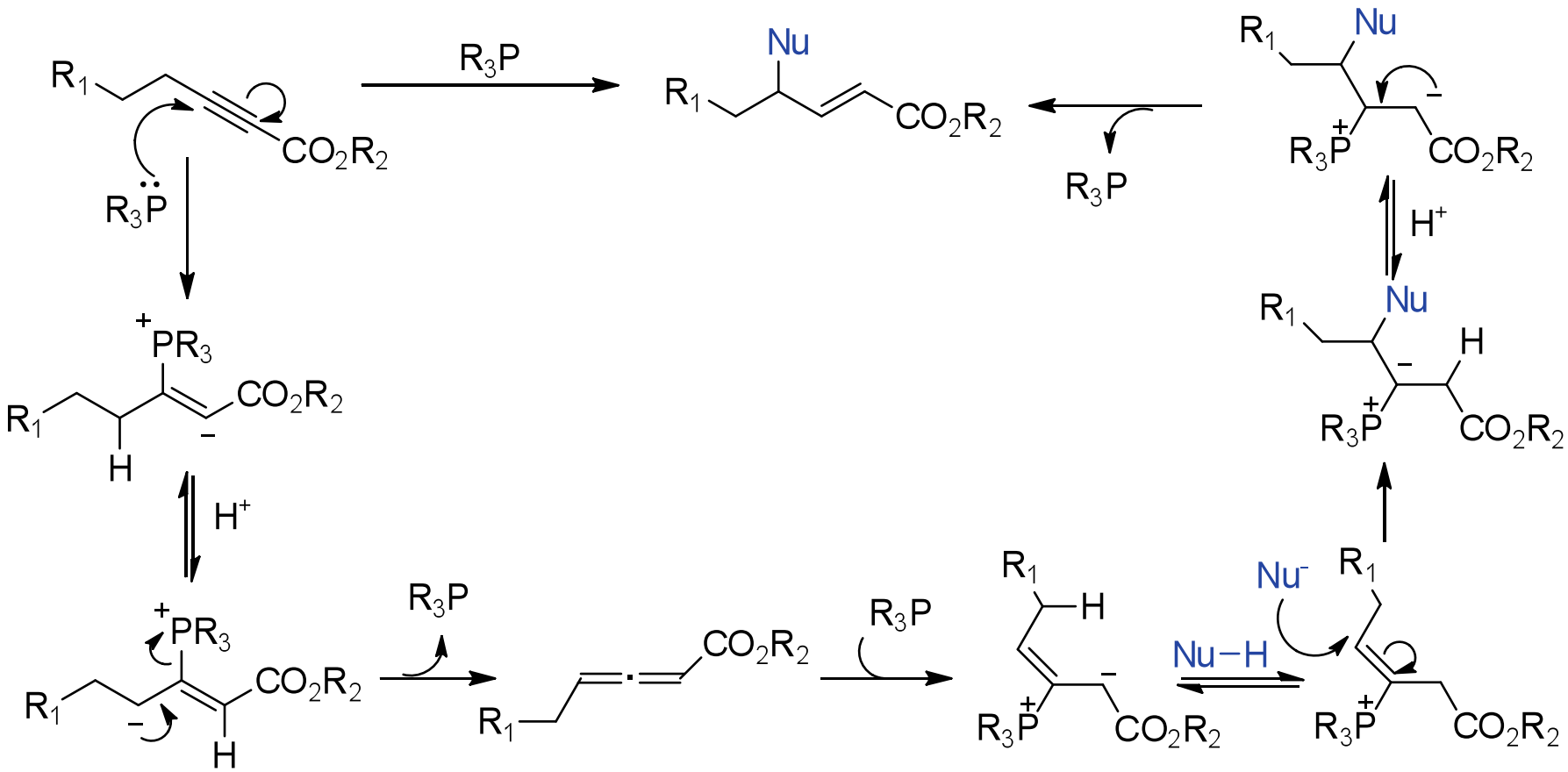


Ketones



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

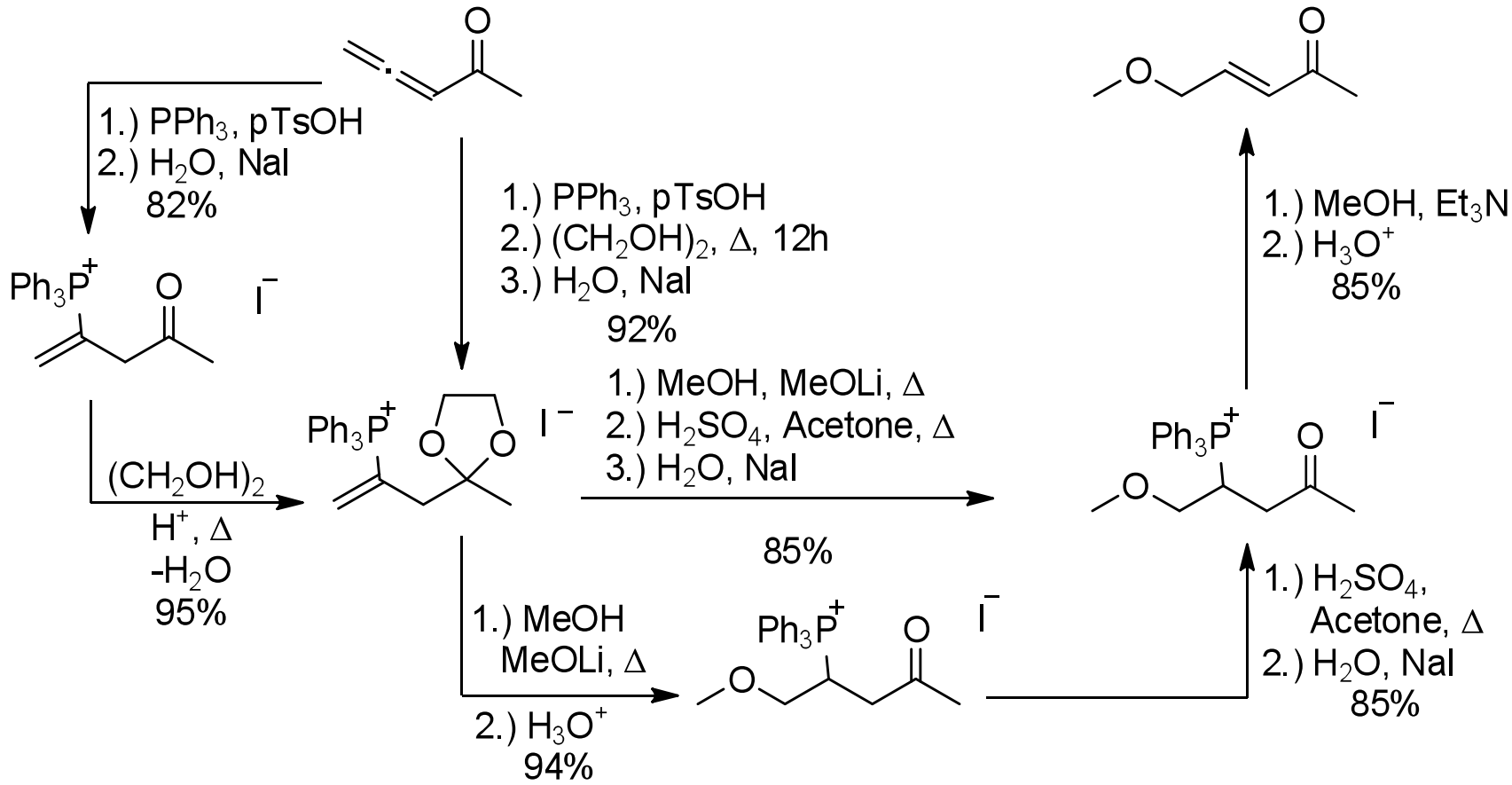
Proposed Mechanism of γ Addition



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

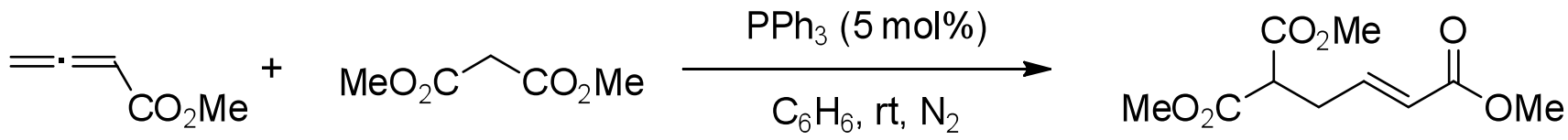
Sequential γ Addition to Alkynoates

Earlier in 1982, umpolung γ addition was reported as a sequential process

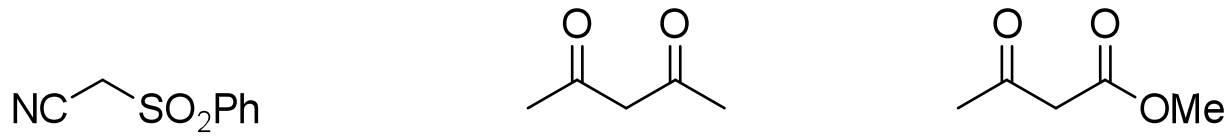


Cristau, H.; Viala, J.; Christol, H. *Tet. Lett*. **1982**, *23*, 1569.

γ Addition of Carbon Nucleophiles to Allenoates

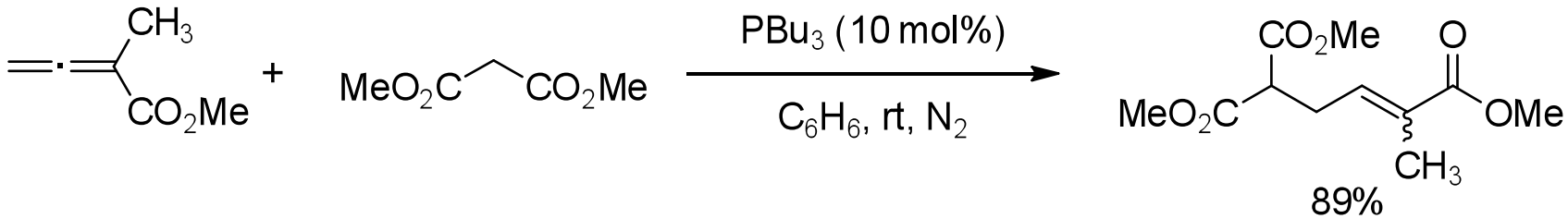


65%
E:Z >97:3



65% 87% 65%

α-substituted allenes require a more nucleophilic catalyst



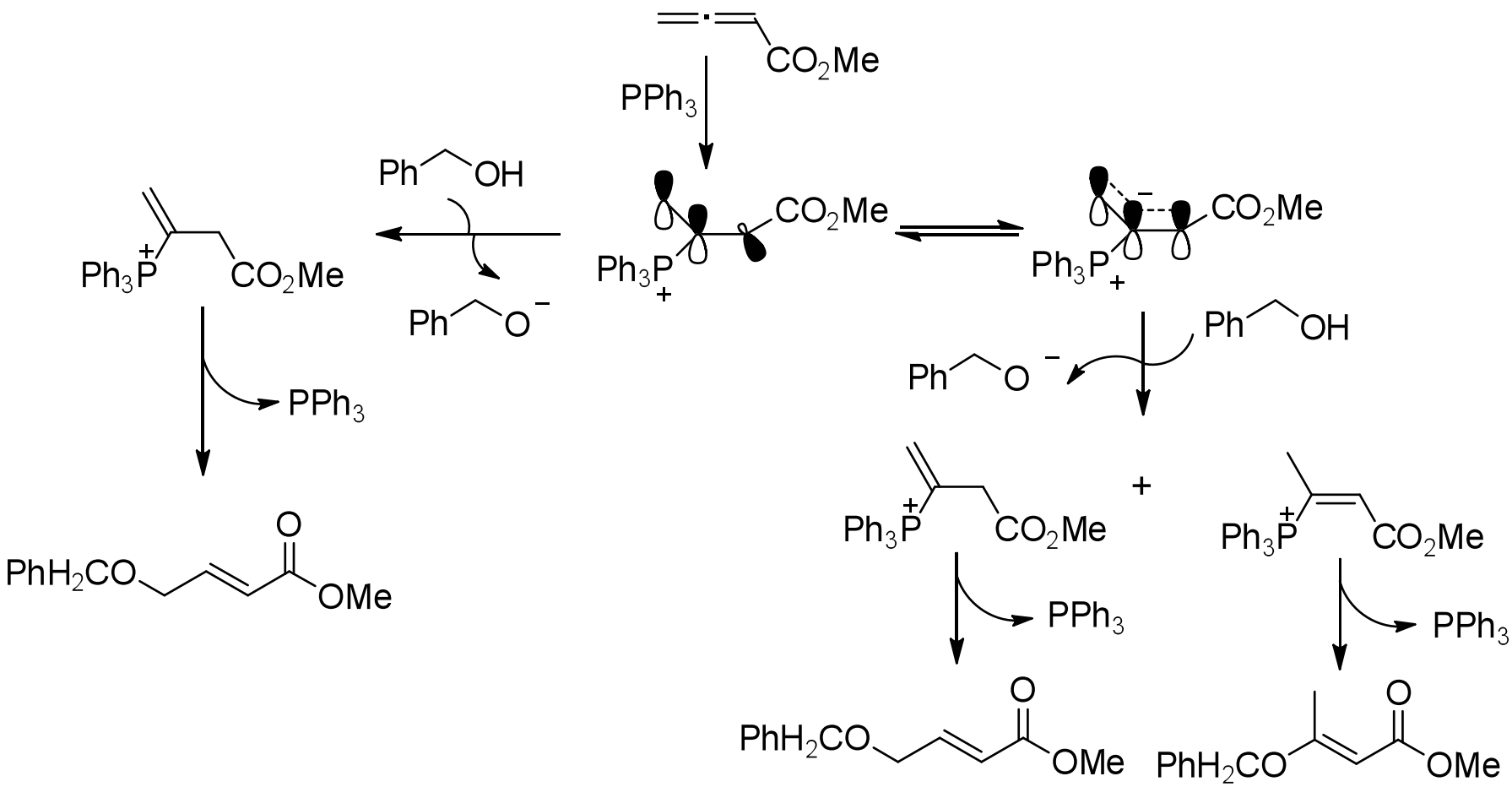
89%
E:Z = 56:44

γ-substituted allenes give only isomerization

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

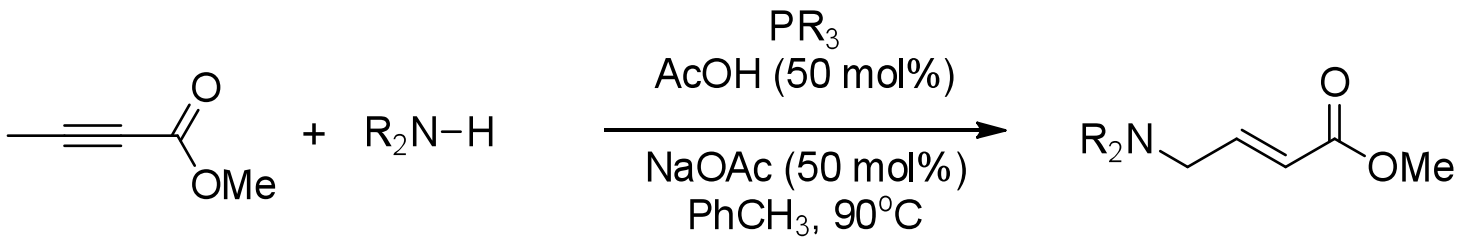
γ Addition of Oxygen Nucleophiles to Allenoates

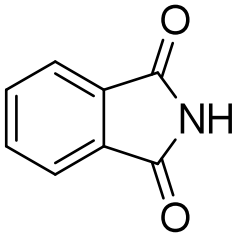
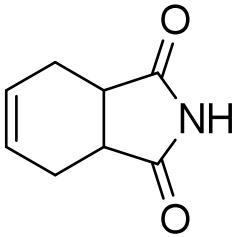
Higher pK_a nucleophiles allow for redistribution of negative charge:



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

γ Addition of Nitrogen Nucleophiles

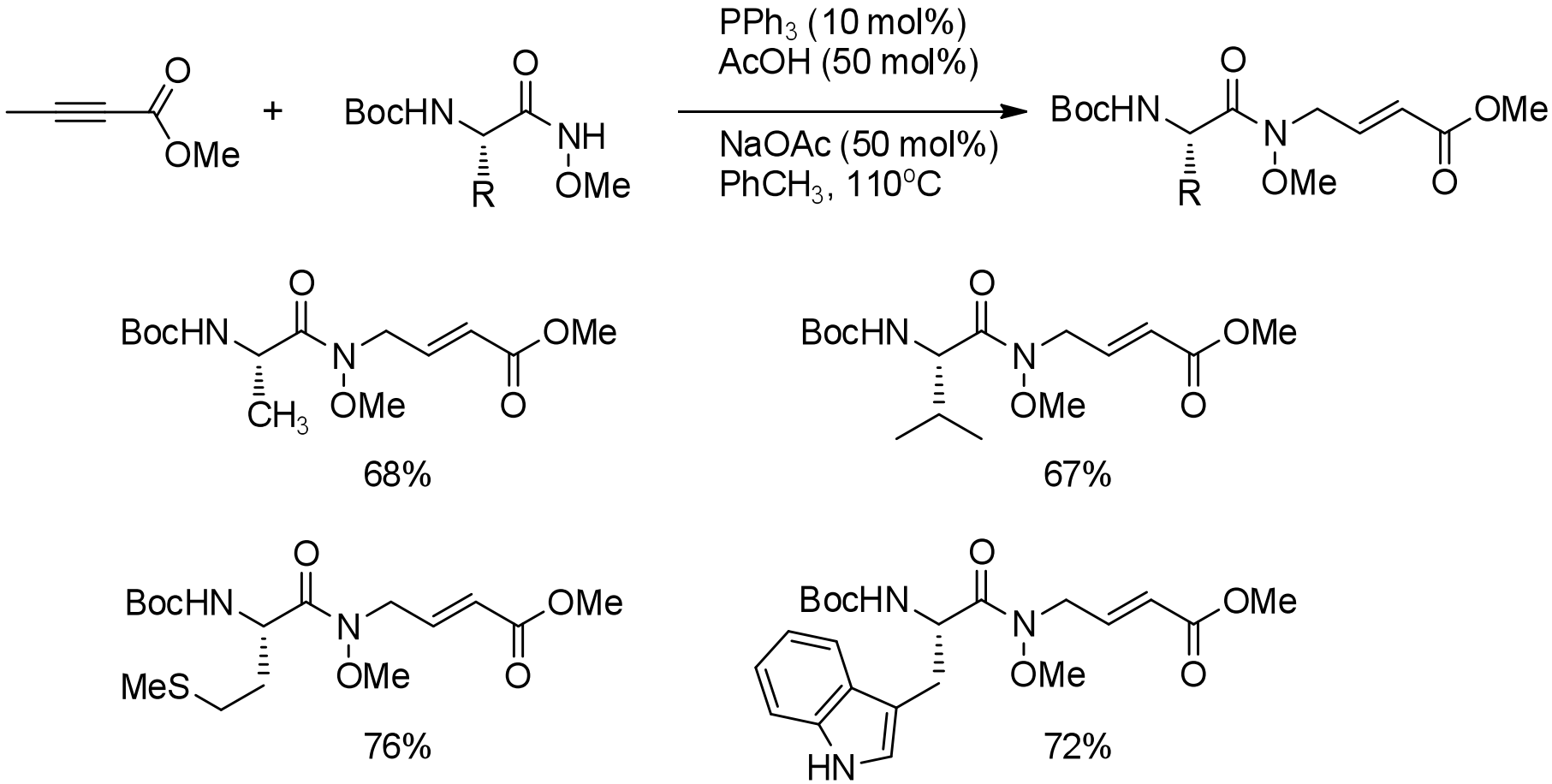


R_2NH	PR_3	Catalyst Loading	Yield
$TsNH_2$	PPh_3	10 mol %	72%
$TsNH_2$	dppm	5 mol%	28%
$TsNH_2$	dppe	5 mol%	39%
	dppp	15 mol%	88%
	dppp	15 mol%	57% (81% brsm)

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

γ Addition of Nitrogen Nucleophiles

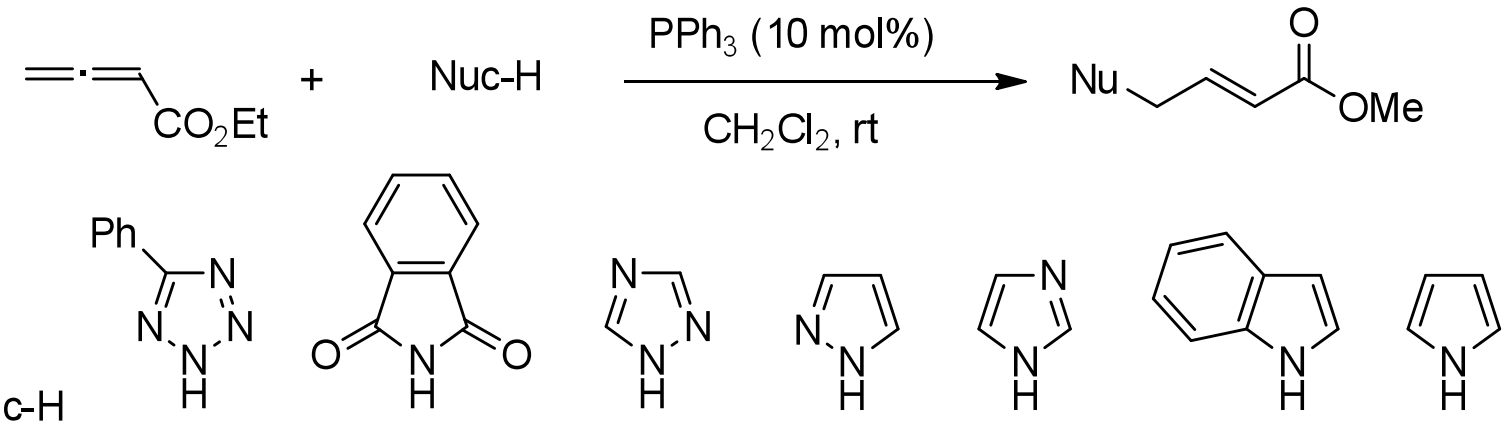
Hydroxamic acids as more versatile nitrogen nucleophiles:



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

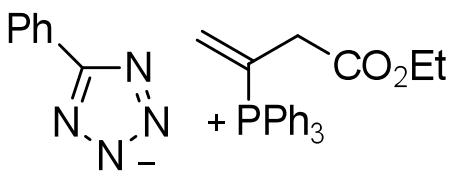
pK_a Requirement of Nitrogen Nucleophiles

Virieux et. al. found that only azoles within a pKa range of *ca*. 8.5 to 14.5 were effective

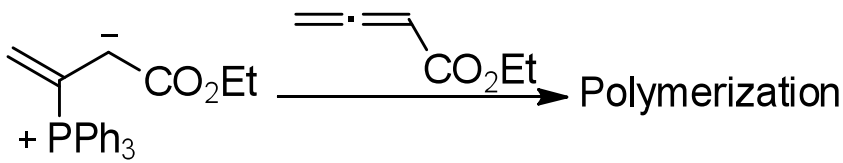


pK_a	4.5	8.5	9.5	14.2	14.5	16.2	17.5
Yield	0%	94%	79%	80%	72%	16%	0%
E/Z	-	89:11	84:16	64:36	82:18	65:35	-

At low pK_a the anion is not nucleophilic enough:



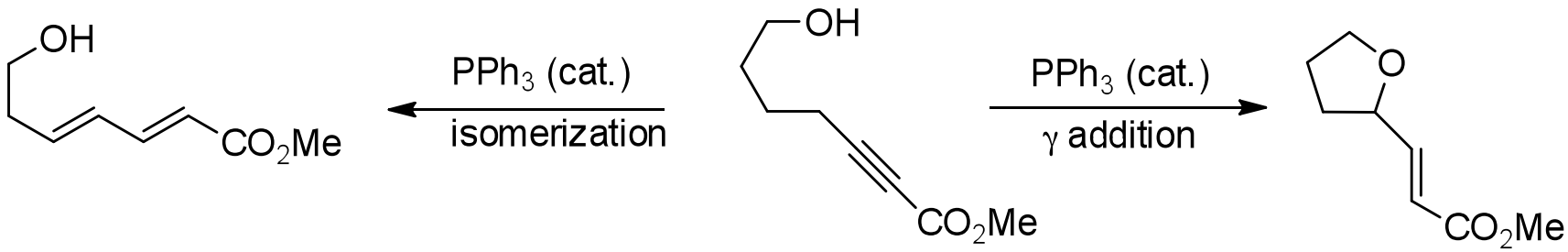
At high pK_a the nucleophile isn't deprotonated:



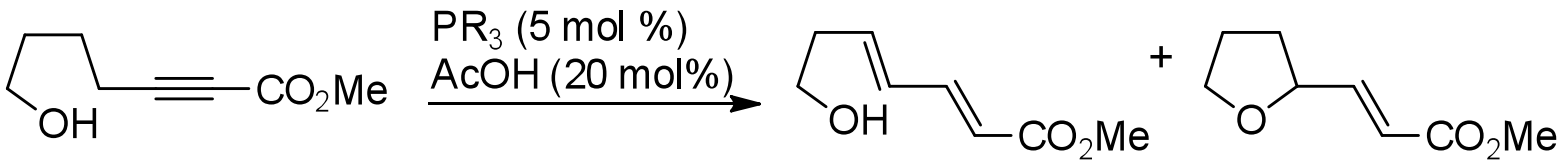
Virieux, D.; Guillouzic, A.; Cristau, H. *Tetrahedron* **2006**, *62*, 3710.

Intramolecular γ Addition of Oxygen Nucleophiles

Must preference γ additon over isomerization to the 1,3-diene:



Control is highly dependent on solvent and catalyst:

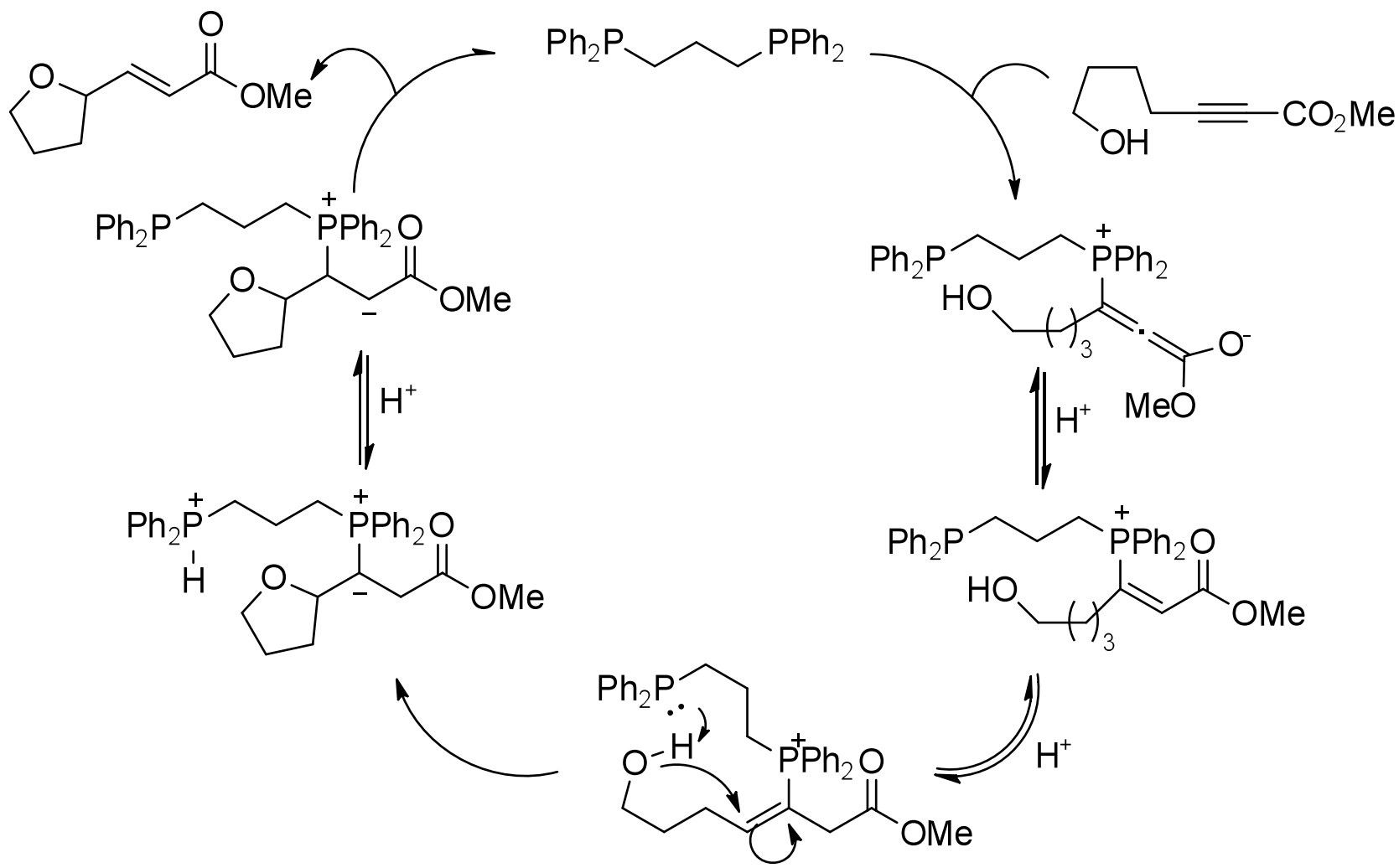


PR_3	Solvent	T (°C)	Yield	
PPh_3	Toluene	110	47%	53%
PPh_3	DMSO	110	91%	9%
dppp	Toluene	85	3%	97%

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

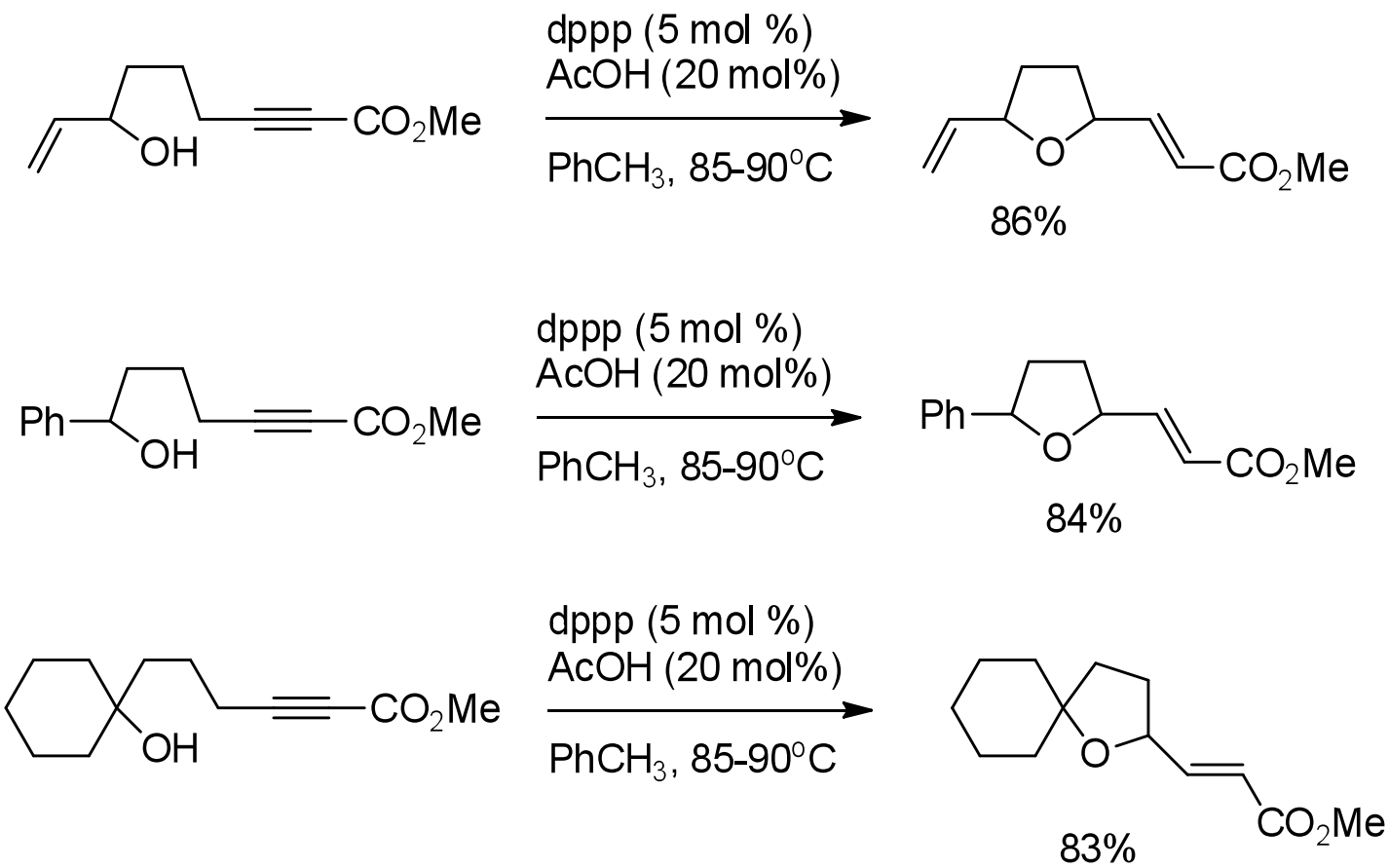
Dependence Upon Bidentate Phosphine

Bidentate phosphines favor γ addition by acting as a general base catalyst



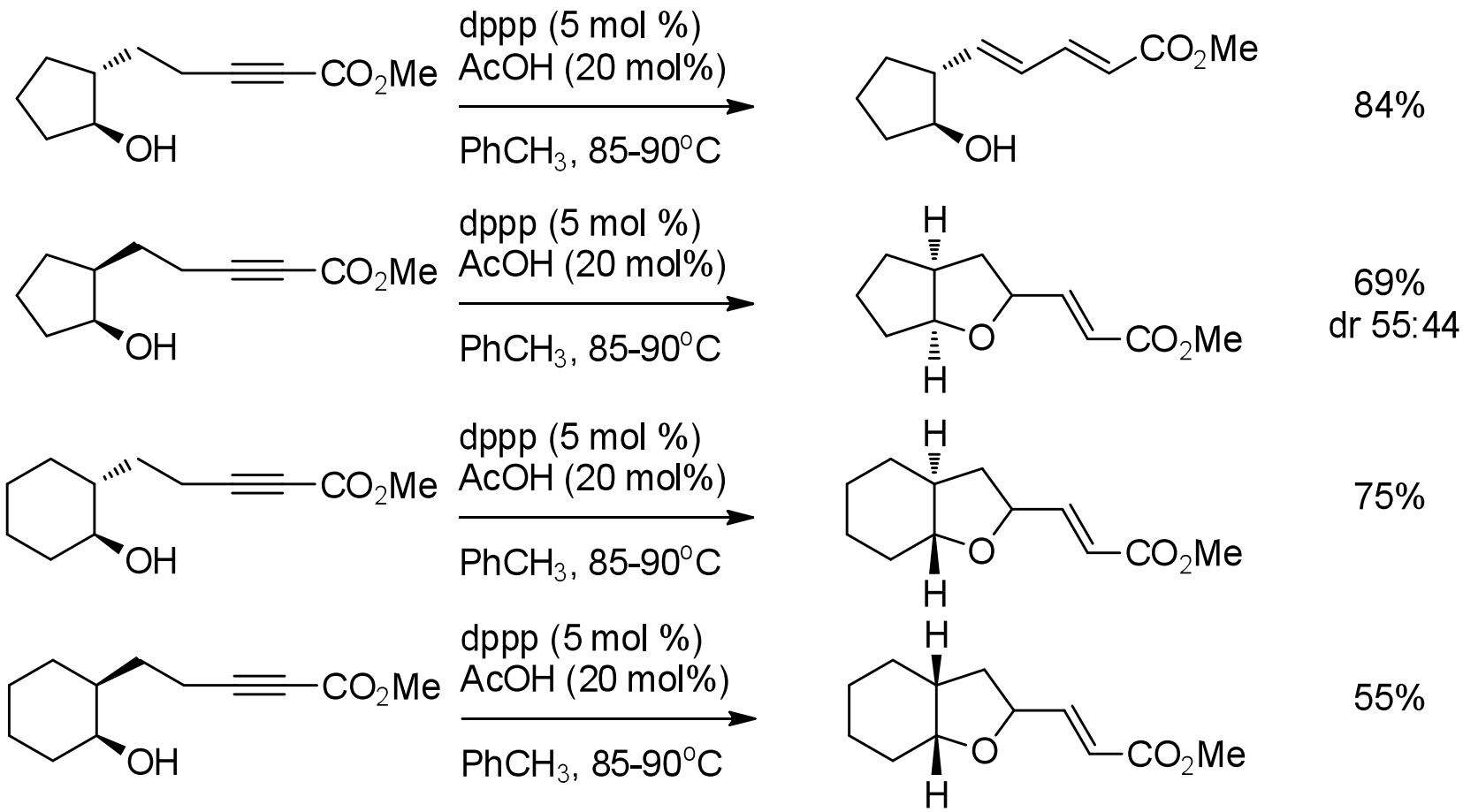
Trost, B. M.; Li, C. *J. Am. Chem. Soc.* **1994**, *116*, 10819.

Intramolecular γ Addition of Oxygen Nucleophiles



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

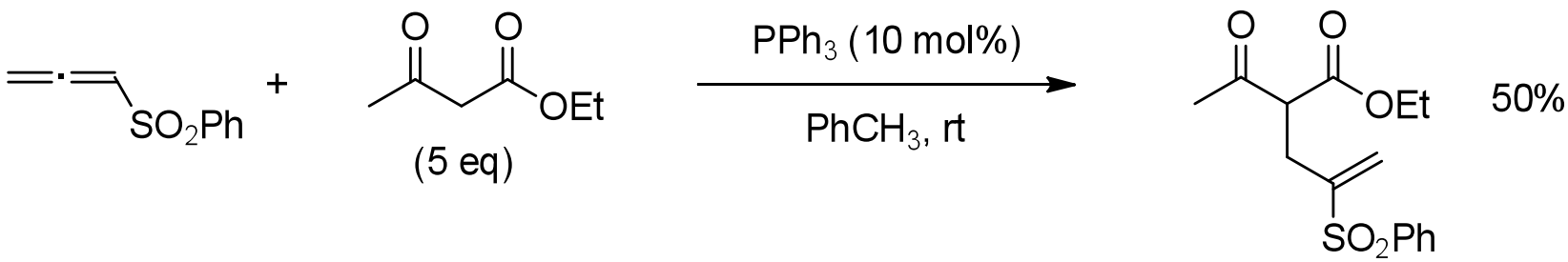
γ Addition is Sensitive to Substrate Stereochemistry



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

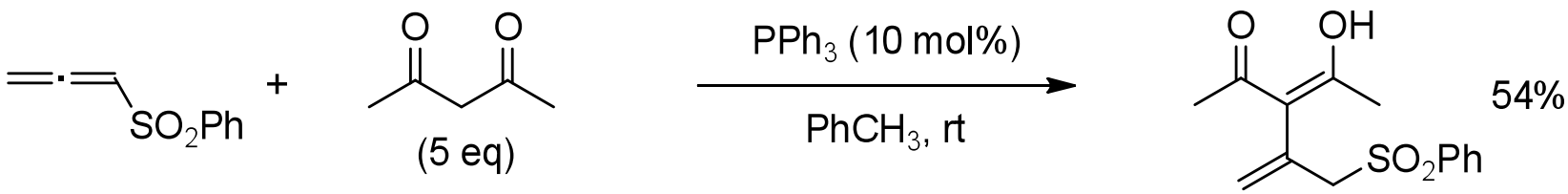
Group Problem: Allenic Sulfones?

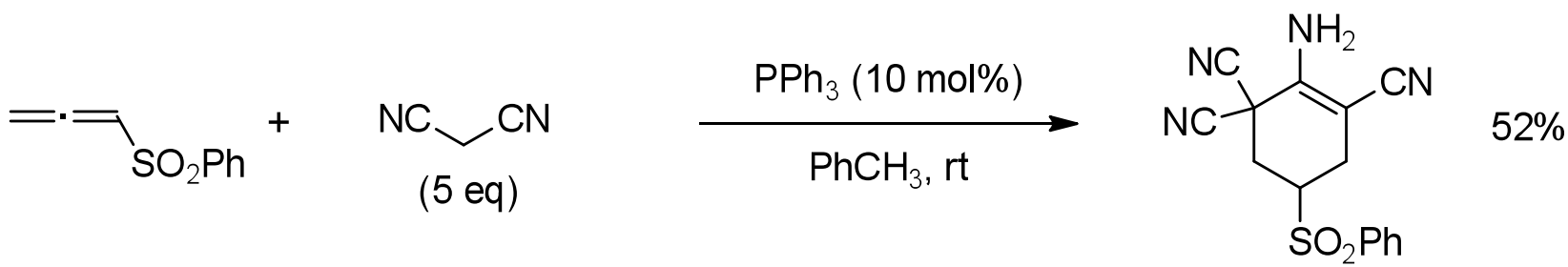
In testing other electron deficient allene substrates, Lu found that phenylsulfonyl-1,2-propadiene did not give the expected γ addition product



1.) Provide a mechanism that is consistent with the observation that $PhSO_2Na$ (10 mol %) will also catalyze the reaction at 90°C in the absence of PPh_3 with a lower yield of 23%.

2.) Provide a rationale of why a different result was obtained with the substrates below:

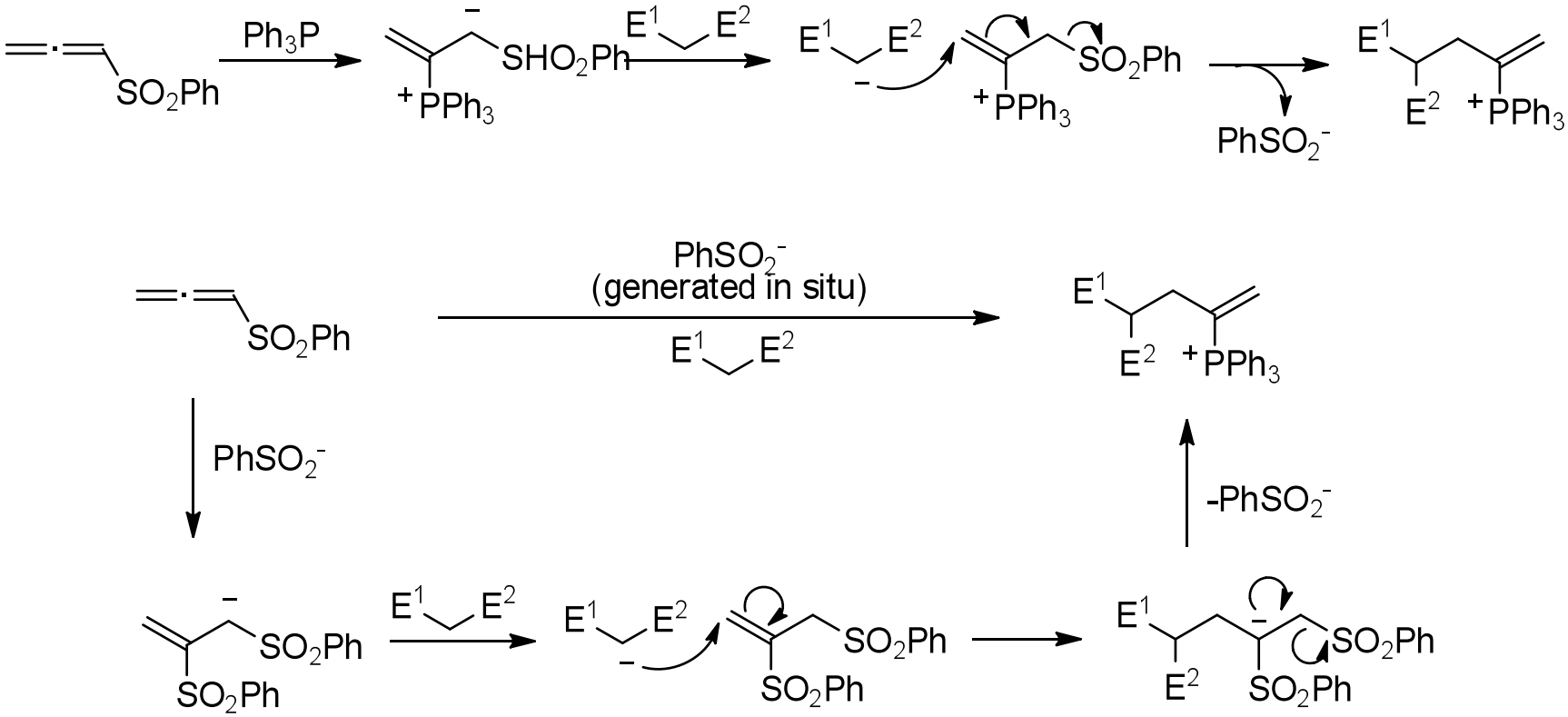




Lu, C.; Lu, X. *Tetrahedron* **2004**, *60*, 6575.

Group Problem: Allenic Sulfones?

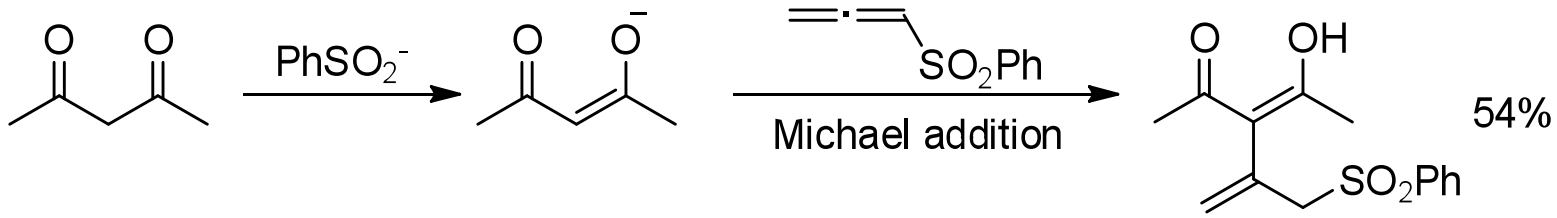
1.) Lu proposes that sulfinate anion is generated in situ which can act as a nucleophilic catalyst similarily to PPh_3



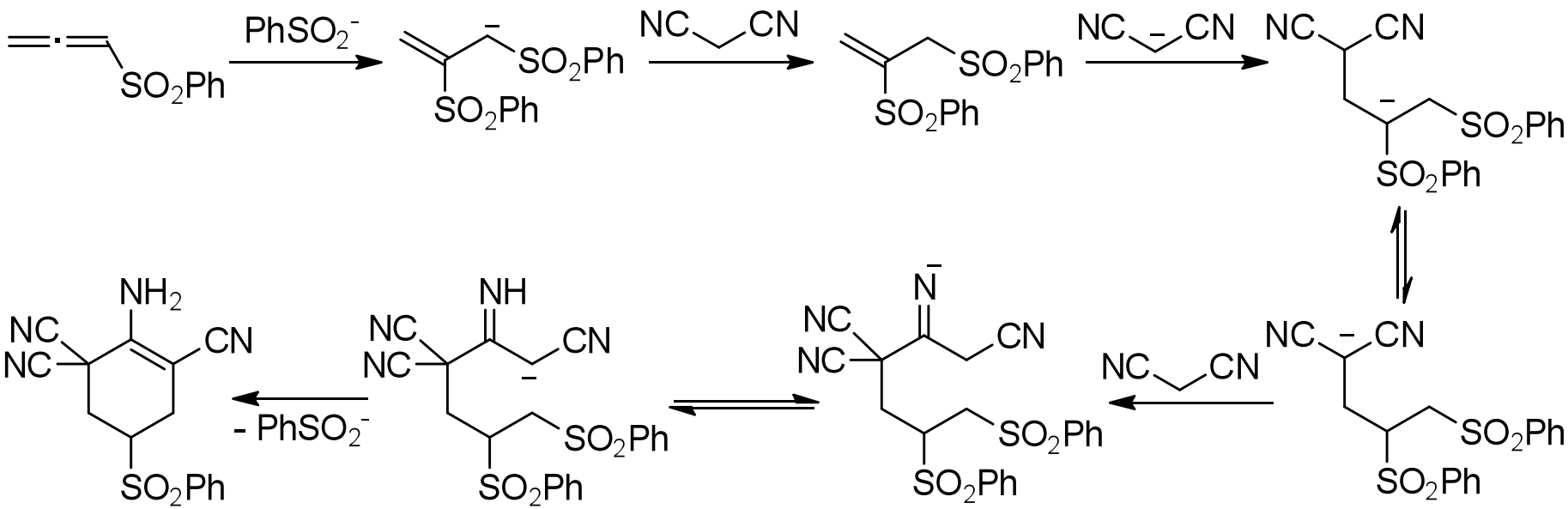
Lu, C.; Lu, X. *Tetrahedron* **2004**, *60*, 6575.

Group Problem: Allenic Sulfones?

2.)For nucleophiles with higher kinetic acidity the sulfinate anion is simply acting as a base to promote Michael addition:



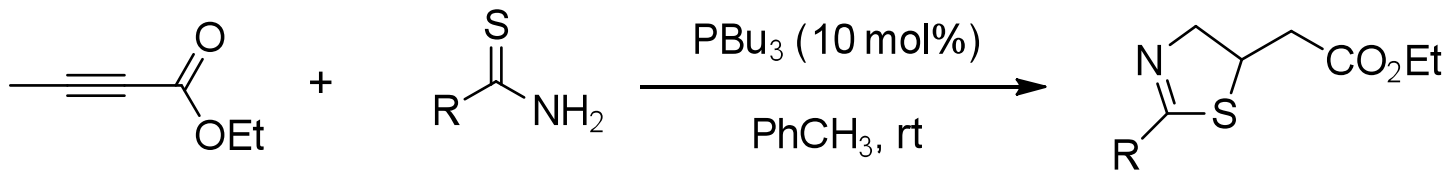
In the case of malonitrile, a reaction intermediate is caputred:

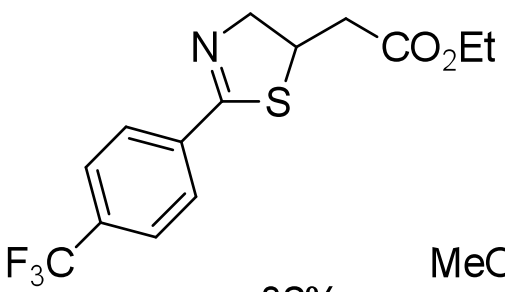


Lu, C.; Lu, X. *Tetrahedron* **2004**, *60*, 6575.

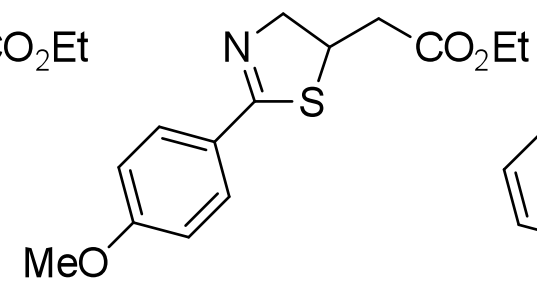
Tandem Reactions to Construct Heterocycles

Liu and coworkers envisioned using phosphine catalyzed γ addition to construct thioamides:

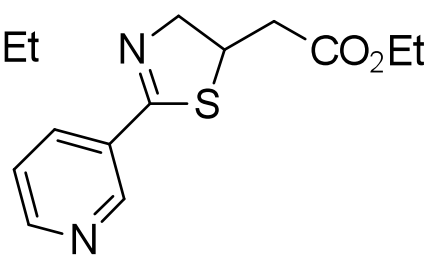




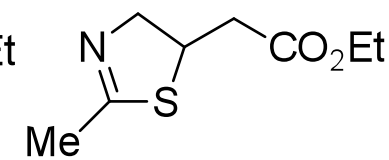
82%



67%



86%

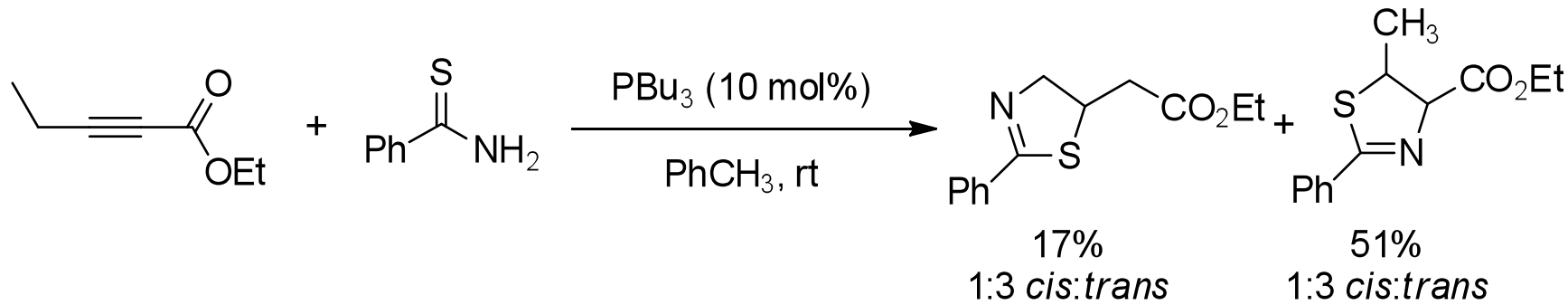


21%

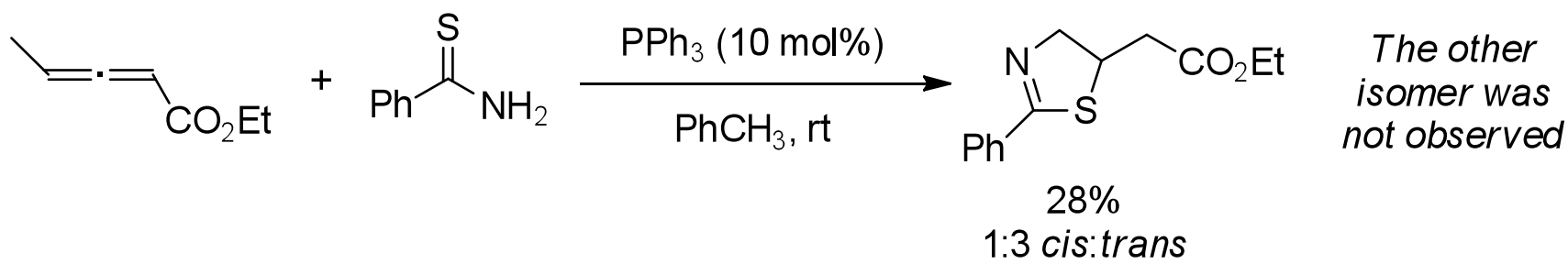
Liu, B.; Davis, R.; Jochi, B.; Reynolds, D. *J. Org. Chem.* **2002**, *67*, 4595.

Tandem Reactions to Construct Heterocycles

γ-substituted alkynes gave a mixture of products:



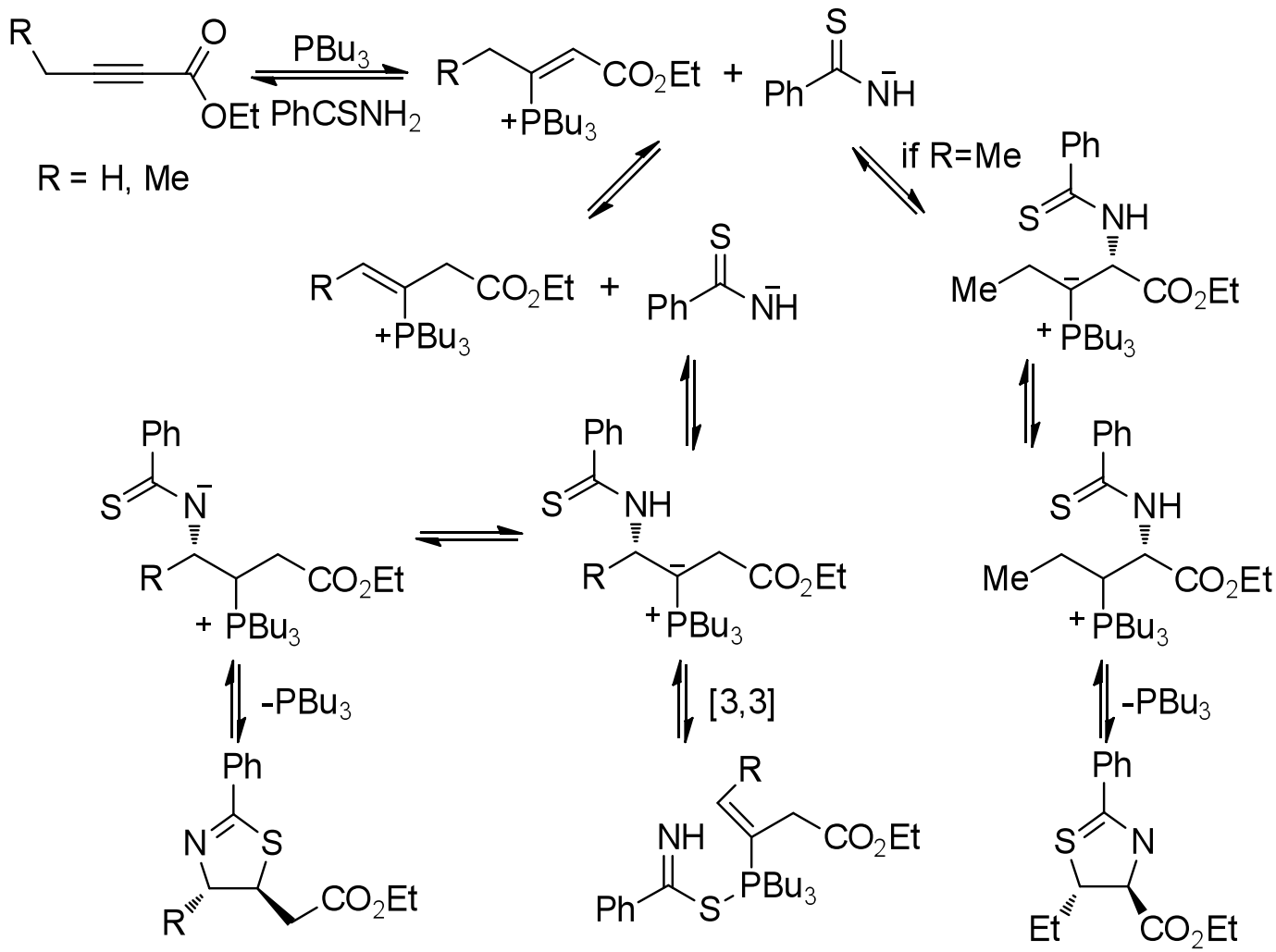
γ-substituted allenes did not give the same result:



Results imply that the allene is not an intermediate in the reaction.

Liu, B.; Davis, R.; Jochi, B.; Reynolds, D. *J. Org. Chem.* **2002**, *67*, 4595.

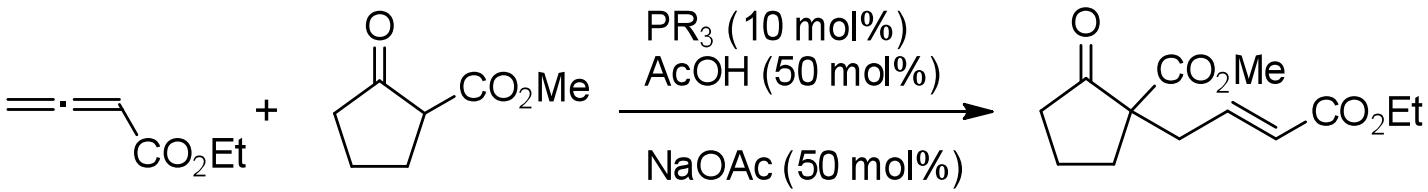
Proposed Mechanism

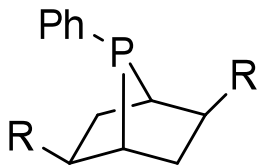


Liu, B.; Davis, R.; Jochi, B.; Reynolds, D. *J. Org. Chem.* **2002**, *67*, 4595.

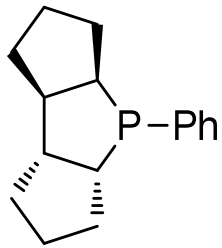
First Asymmetric γ Addition

Zhang was the first to develop an asymmetric γ addition using chiral phosphine catalysts:

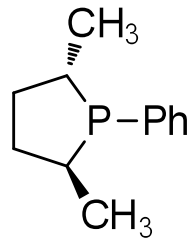




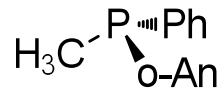
R=Me 76%, 74%ee
R=^{i}Pr 80%, 69%ee



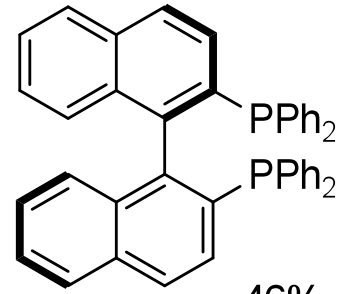
71%
35%ee



58%
8% ee



66%
20% ee



46%
20% ee

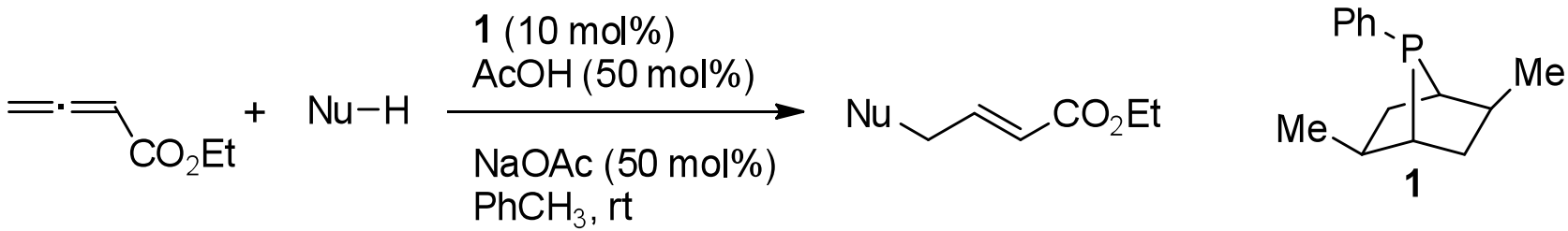
Observations during optimization:

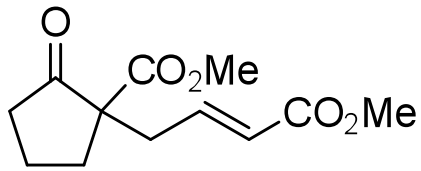
(1) Increased catalyst loading decreased reaction time but decreased %ee
(2) Decreased temperature increase %ee
(3) Without buffer or with only NaOAc the %ee drops dramatically
(4) Counterion of buffer does not effect %ee, however Na^+, K^+, and Cs^+ are more reactive than Li^+ and NH_4^+

Chen, Z.; Zhu, G.; Jiang, D.; Cao, P.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 5631.

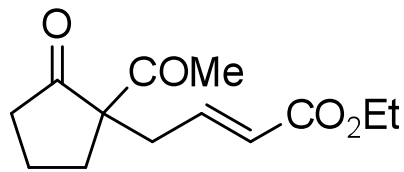
First Asymmetric γ Addition

Zhang achieved moderate enantioselectivities with a variety of nucleophiles:

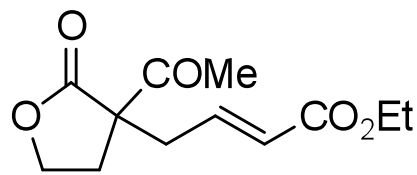




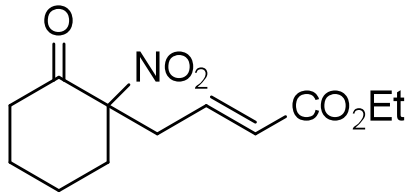
80%
73% ee



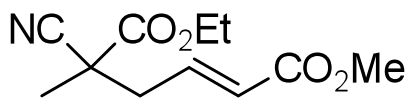
67%
56% ee



83%
48% ee



31%
41% ee

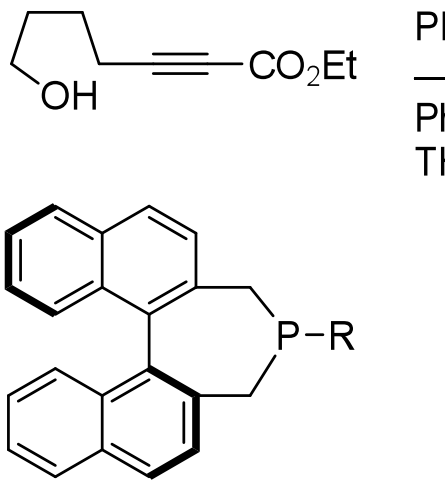


47%
45% ee

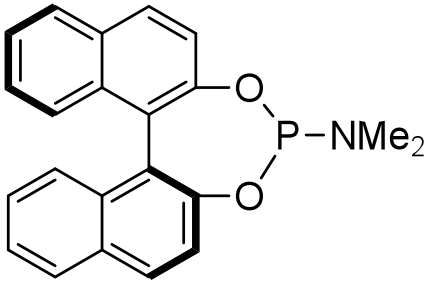
Chen, Z.; Zhu, G.; Jiang, D.; Cao, P.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 5631.

Enantioselective Intramolecular γ Addition

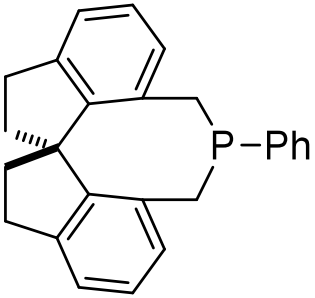
Fu reported an enantioselective intramolecular γ addition to synthesize oxygen heterocycles:



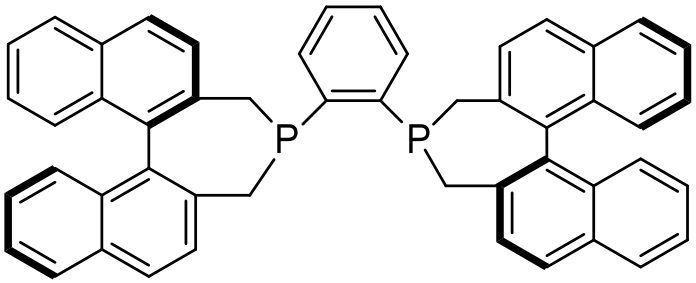
R=*t*-Bu 72%, -66% ee
R=Ph 65%, -45% ee



<2% Yield



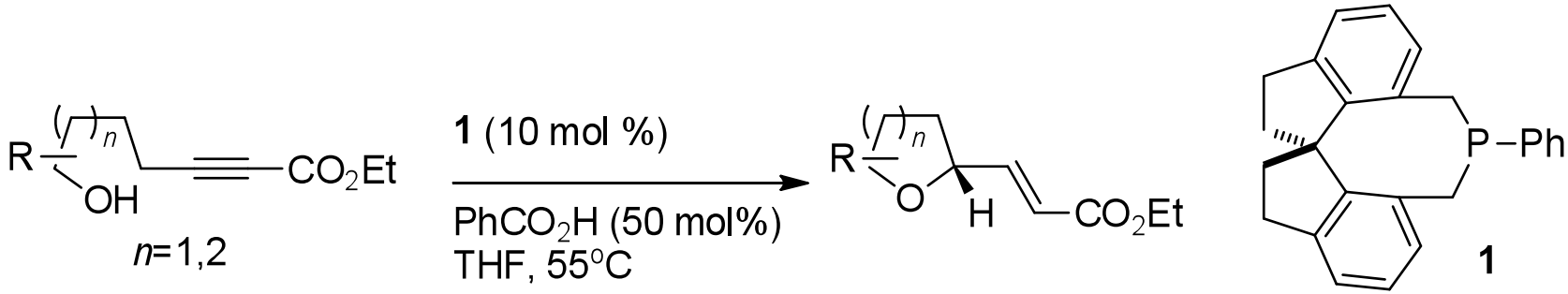
80%
87% ee

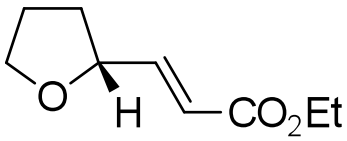


9%
17% ee

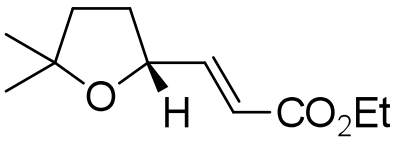
Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225.

Enantioenriched Tetrahydropyrans and Tetrahydrofurans

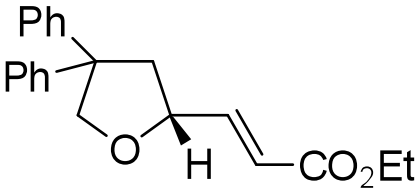




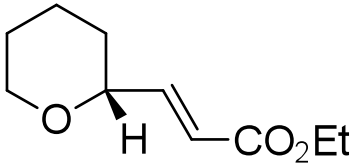
78%, 87%ee



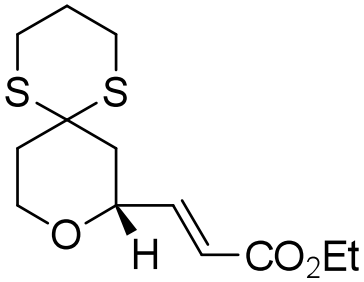
90%, 94%ee



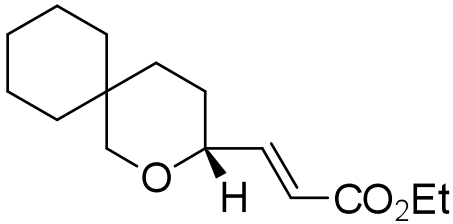
63%, 87%ee



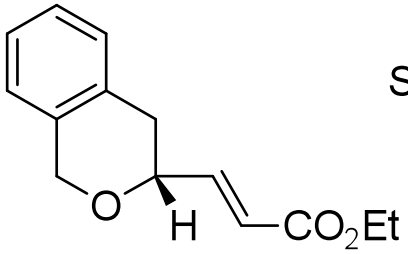
90%, 92%ee



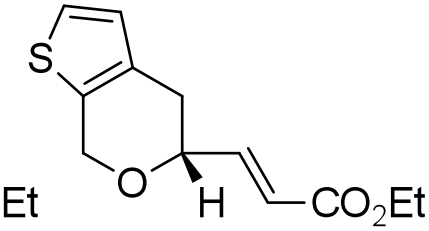
72%, 92%ee



85%, 84%ee



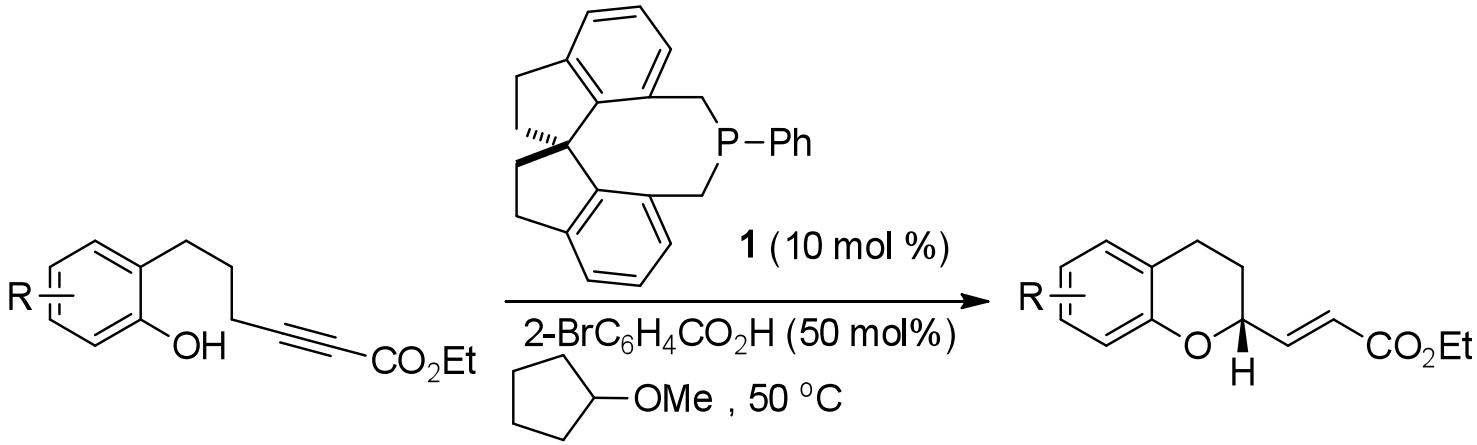
82%, 94%ee

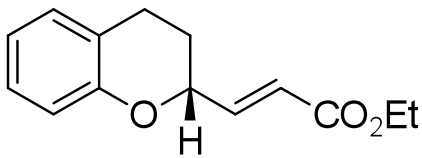


80%, 91%ee

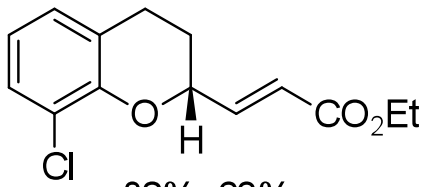
Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225.

Enantioenriched Dihydrobenzopyrans

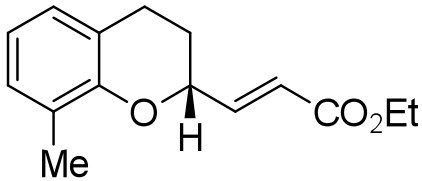




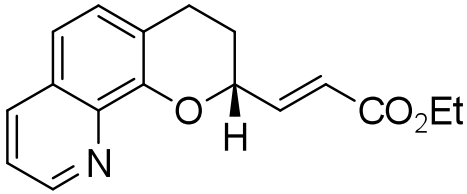
86%, 88%ee



82%, 63%ee



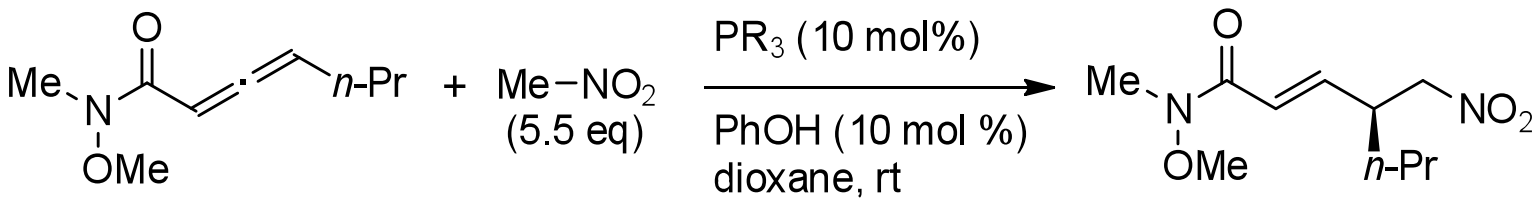
89%, 84%ee

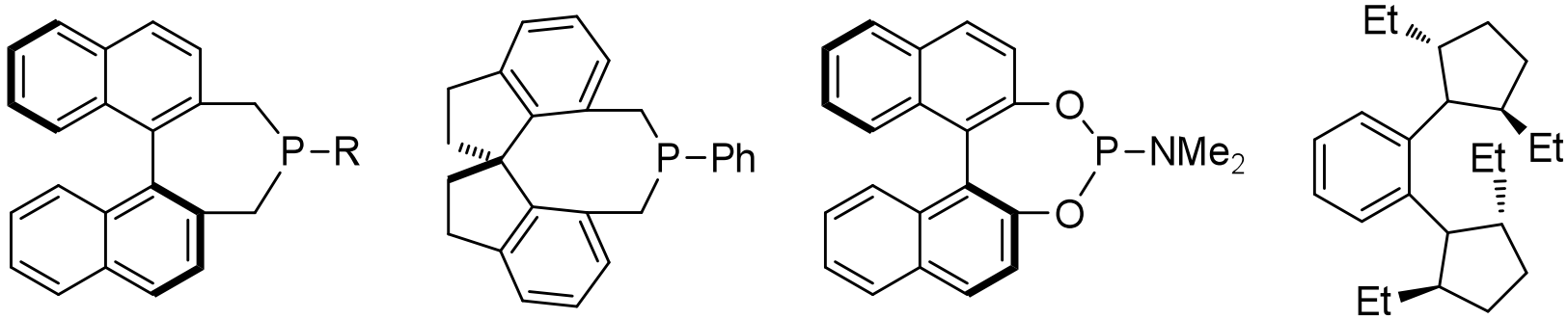


79%, 84%ee

Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225.

Enantioselective γ Addition of Nitromethane





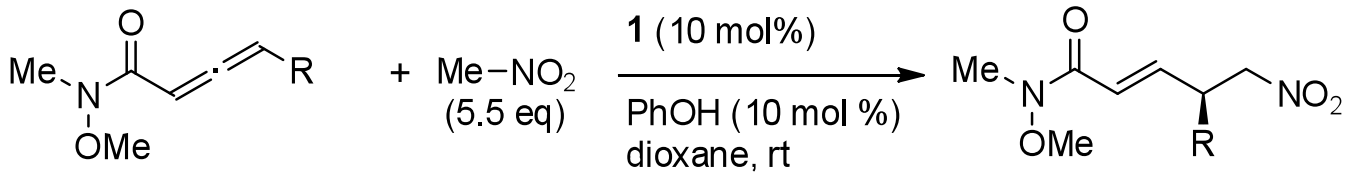
R=NEt_2	83%	93% ee	47%	<2%	<2%
R=*t*-Bu	<2%%	-	-83% ee	-	-
R=*i*-Pr	51%	67% ee			
R=Ph	51%	68% ee			

- PhOH additive is necessary
- Solvent changes to toluene and CH_2Cl_2 significantly decreased the enantioselectivity
- ^{31}P NMR studies show that free phosphine is the catalyst resting state
- No evidence of a kinetic resolution of the racemic allene is seen

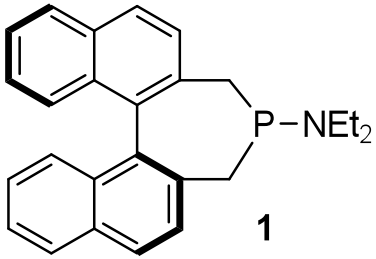
Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231.

Enantioselective γ Addition of Nitromethane

Compatible with a variety of Weinreb amides with γ substitution!



entry	R	ee(%)	yield (%)
1	Me	97	94
2	*n*-Pr	93	81
3	CH_2—	87	73
4	*i*-Pr	81	62
5	$(CH_2)_4OTBS$	92	57
6	$(CH_2)_3CO_2Me$	93	75
7	$(CH_2)_5CO_2Me$	92	82
8	$(CH_3)_7$—	92	83
9	$(CH_3)_6$— *n*-Oct	93	84

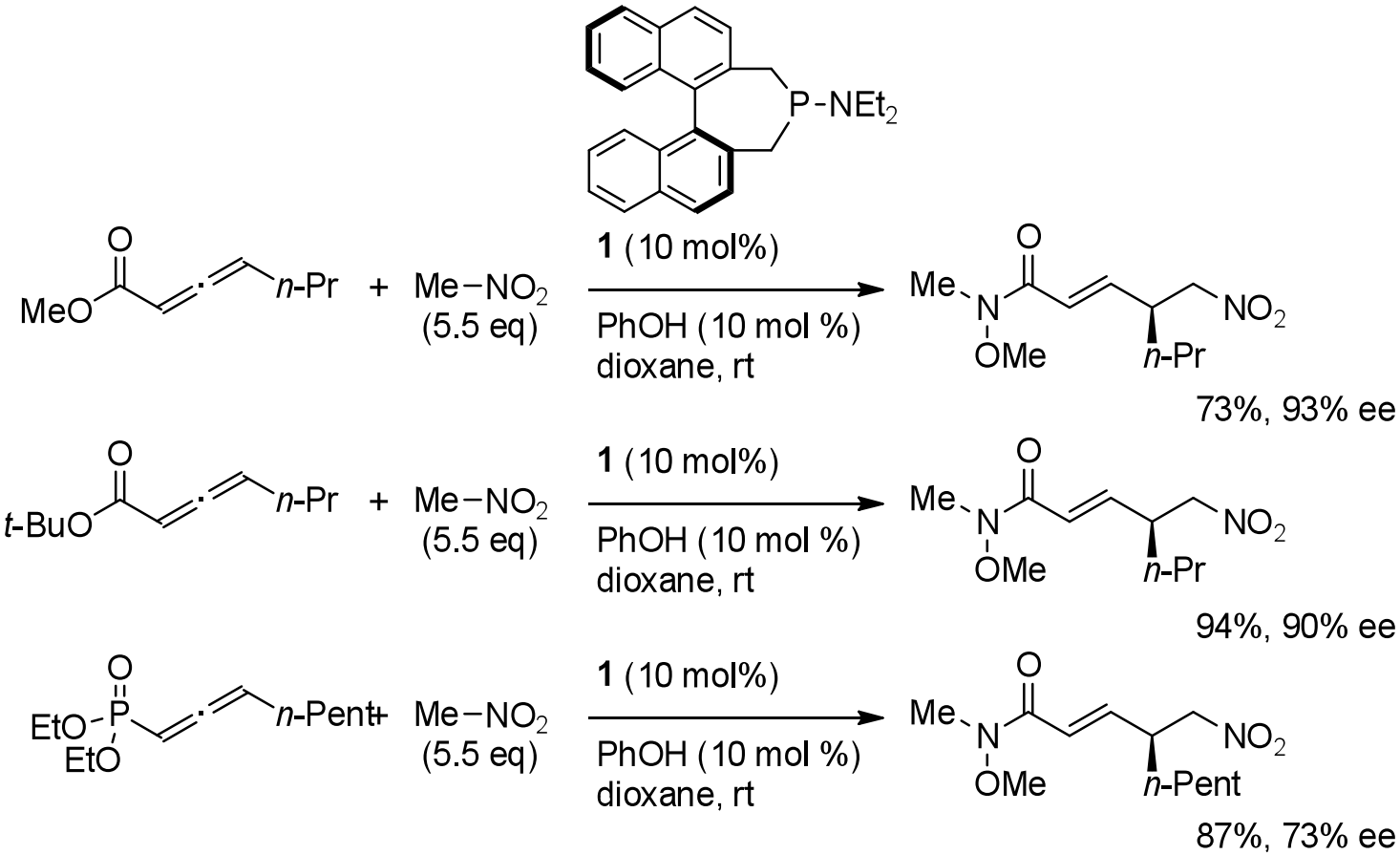


1

Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231.

Enantioselective γ Addition of Nitromethane

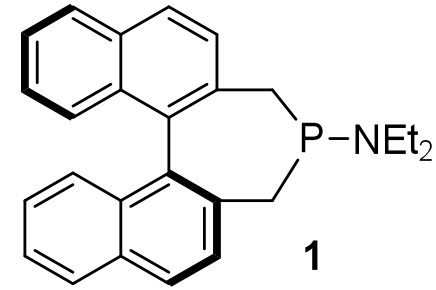
This method is also compatible with other electron deficient allenes:



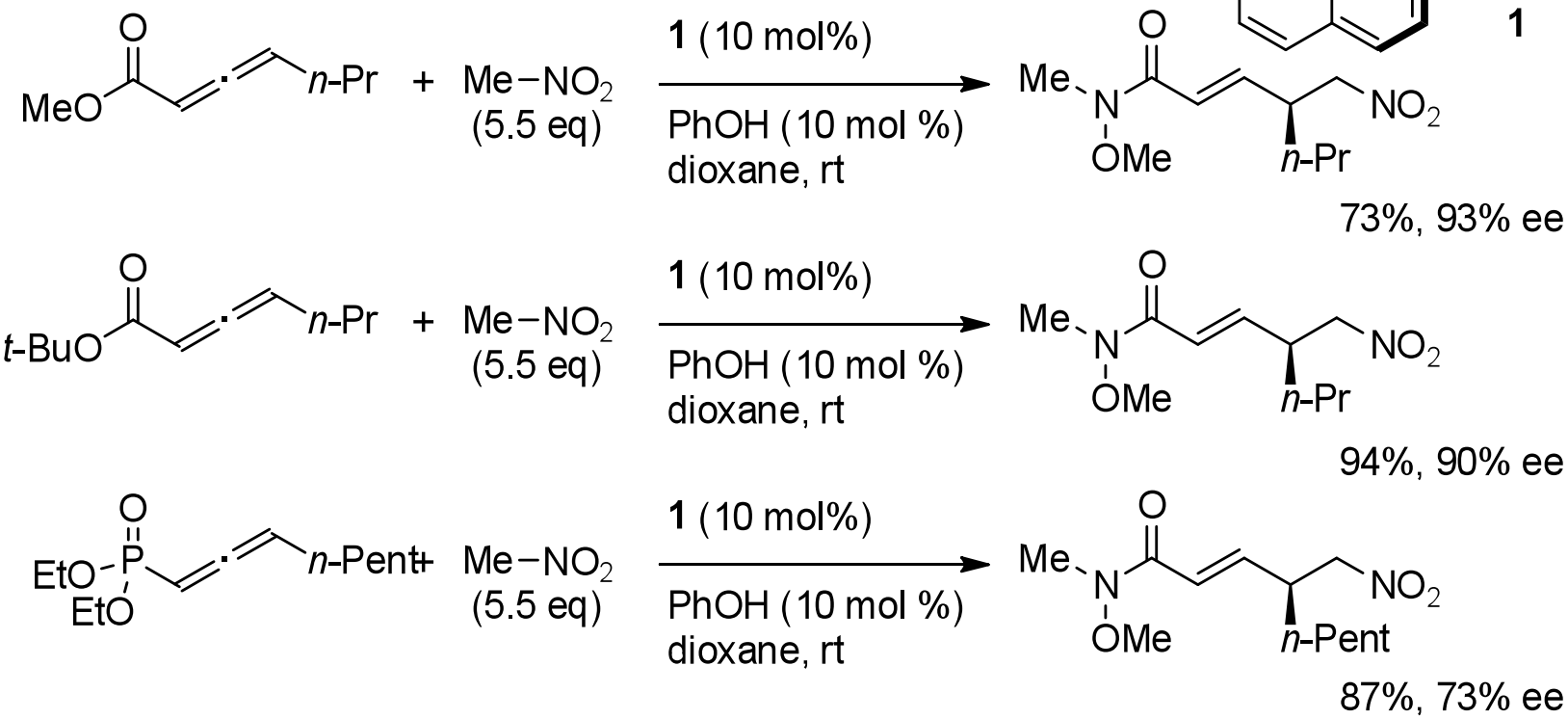
Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231.

Enantioselective γ Addition of Nitromethane

This method is also compatible with other electron deficient allenes:

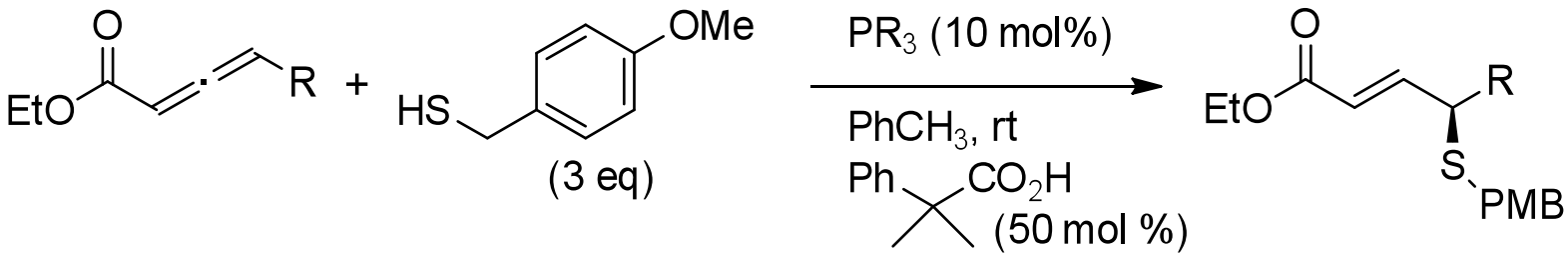


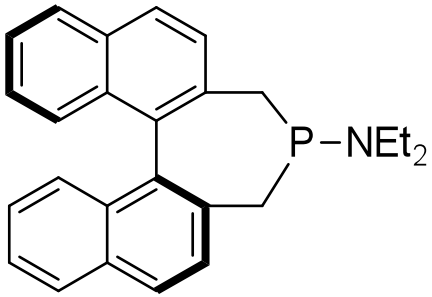
1



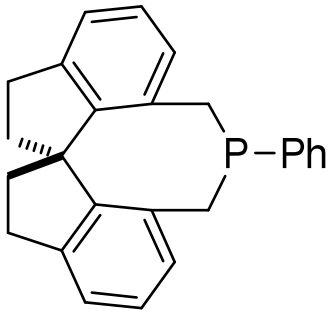
Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231.

Enantioselective γ Addition of Thiols

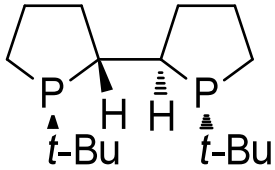




<5% Yield



81%, 80% ee

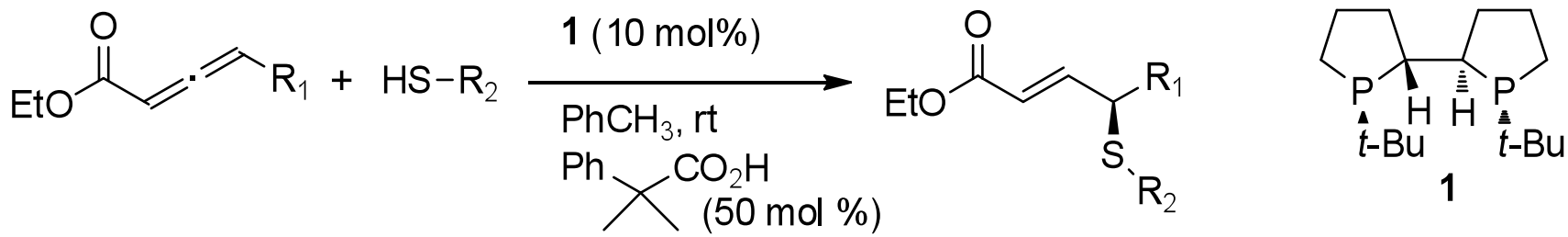


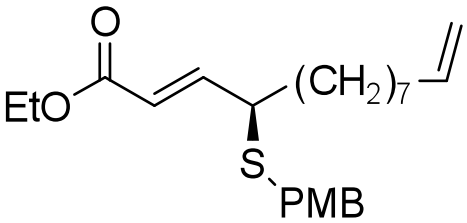
89%, 92% ee

- No γ addition is observed without carboxylic acid additive or with PhOH.
- Decreased yield with 1.1 eq thiol

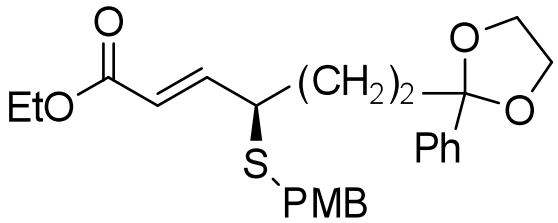
Sun. J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, ASAP.

Enantioselective γ Addition of Thiols

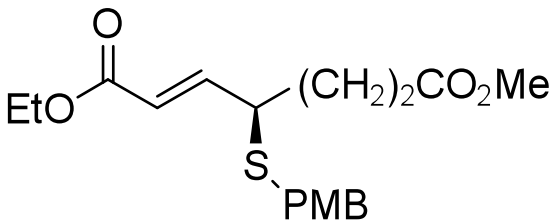




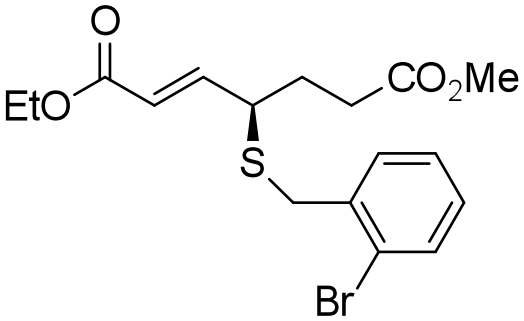
81%, 91% ee



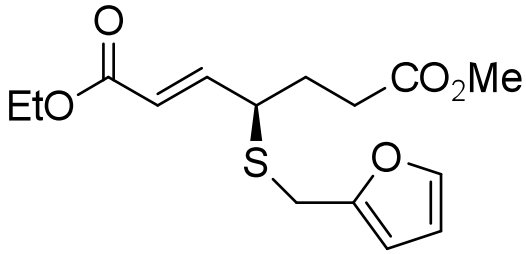
89%, 90% ee



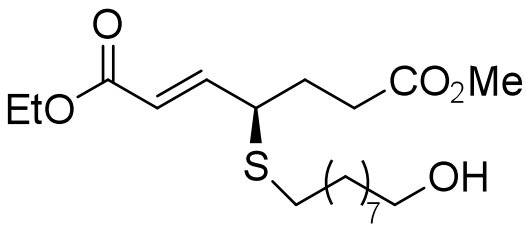
72%, 92% ee



76%, 92% ee



72%, 92% ee



79%, 88% ee

Sun. J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, ASAP.

Conclusions

* Phosphine catalysis can yield γ substituted products in good yields under mild reaction conditions.

* The high reactivity of the phosphonium intermediates can lead to a variety of side reactions, especially isomerization to the 1,3-diene.

* Advancement of this reaction is limited to a narrow pK_a range of nucleophiles in the range of 5 to 17.

* Recently γ additions to electron deficient alkynes and allenes have been performed enantioselectively using chiral phosphine catalysts. Products are obtained in high yield and high er.