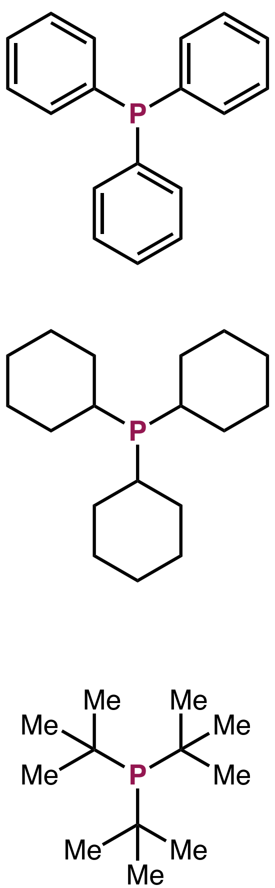
Novel Applications of Phosphorus in Catalysis for Organic Synthesis

15	30.97
[Ne]$3s^2 3p^3$	
+5, +3, –3	
P	
44	1.82
280	2.1

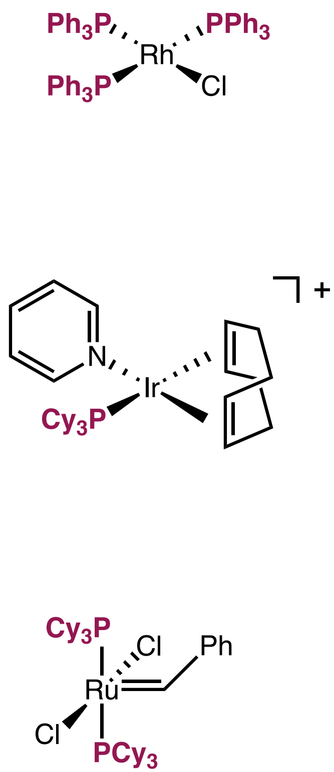
Eric Nacsa
MacMillan Group Meeting

June 22, 2017

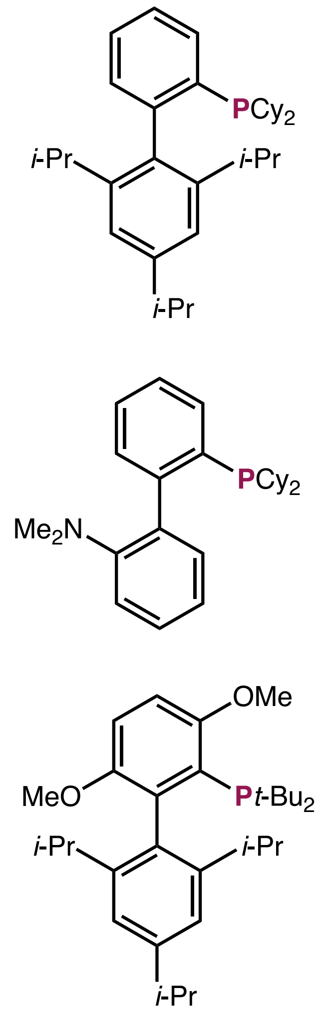
Phosphorus Catalysts in Organic Synthesis: Ligands



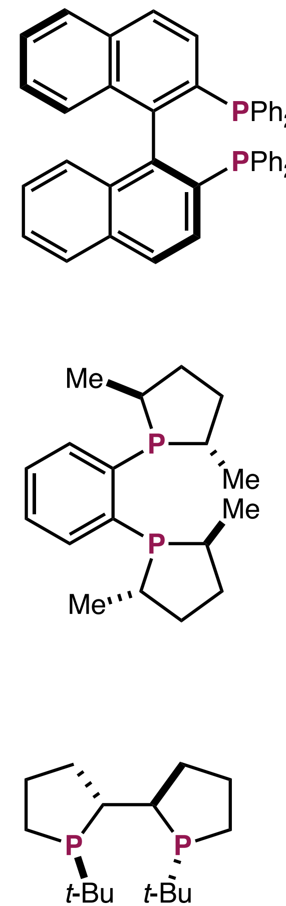
Simple phoshines



Phosphines in important metal complexes

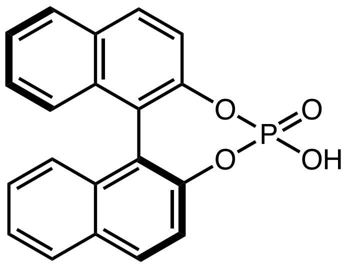


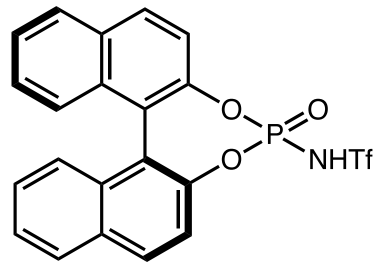
Biaryl phoshines (Buchwald ligands)

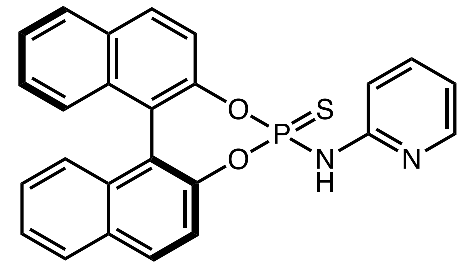


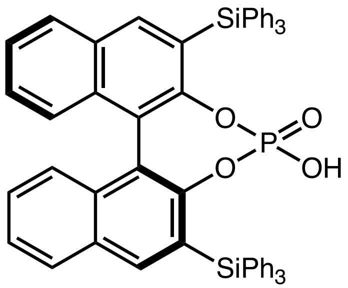
Chiral phoshines

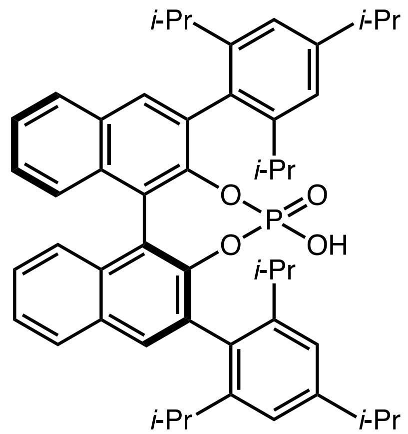
Phosphorus Catalysts in Organic Synthesis: Chiral Phosphoric Acids

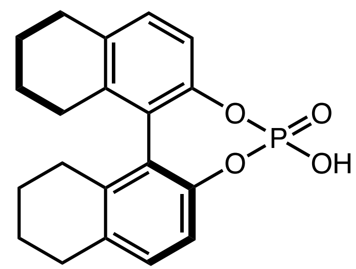










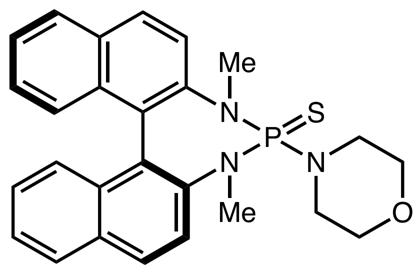


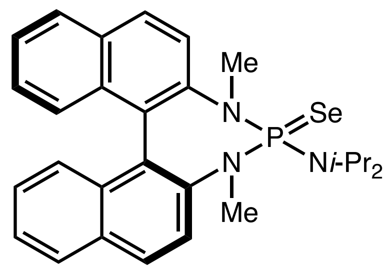
Chiral Brønsted acid catalysis

Chiral counterion catalysis

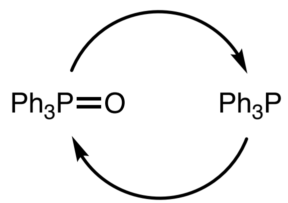
Outline

Part I: Enantioselective Nucleophilic Catalysis with Phosphine Chalcogenides

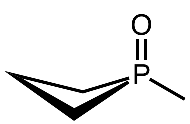


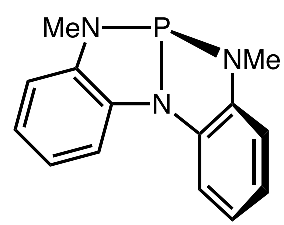


Part II: Recycling Phosphorus in Classical Reactions

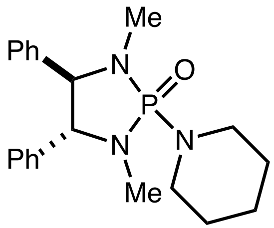


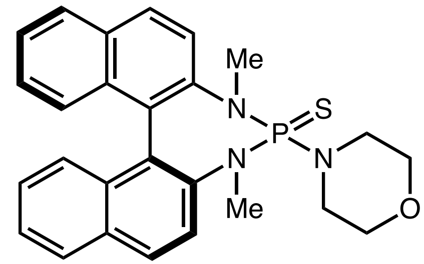
Part III: Strained Phosphines

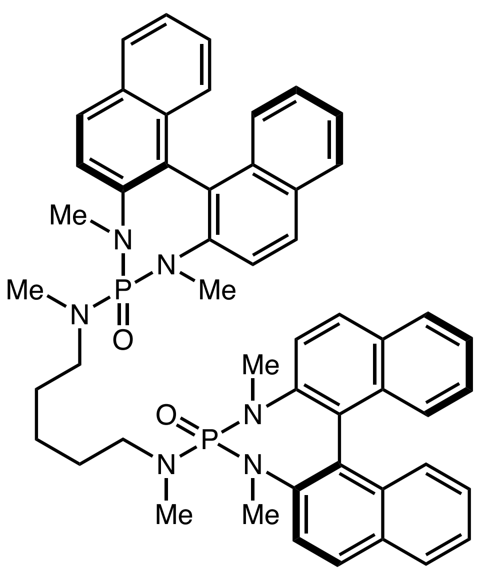


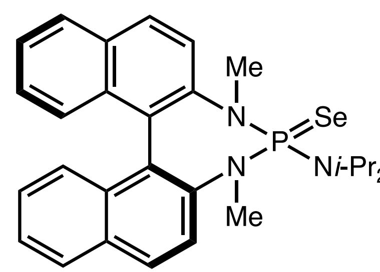


Denmark's Chiral Phosphoramide Catalysts and Chalcogenide Analogues

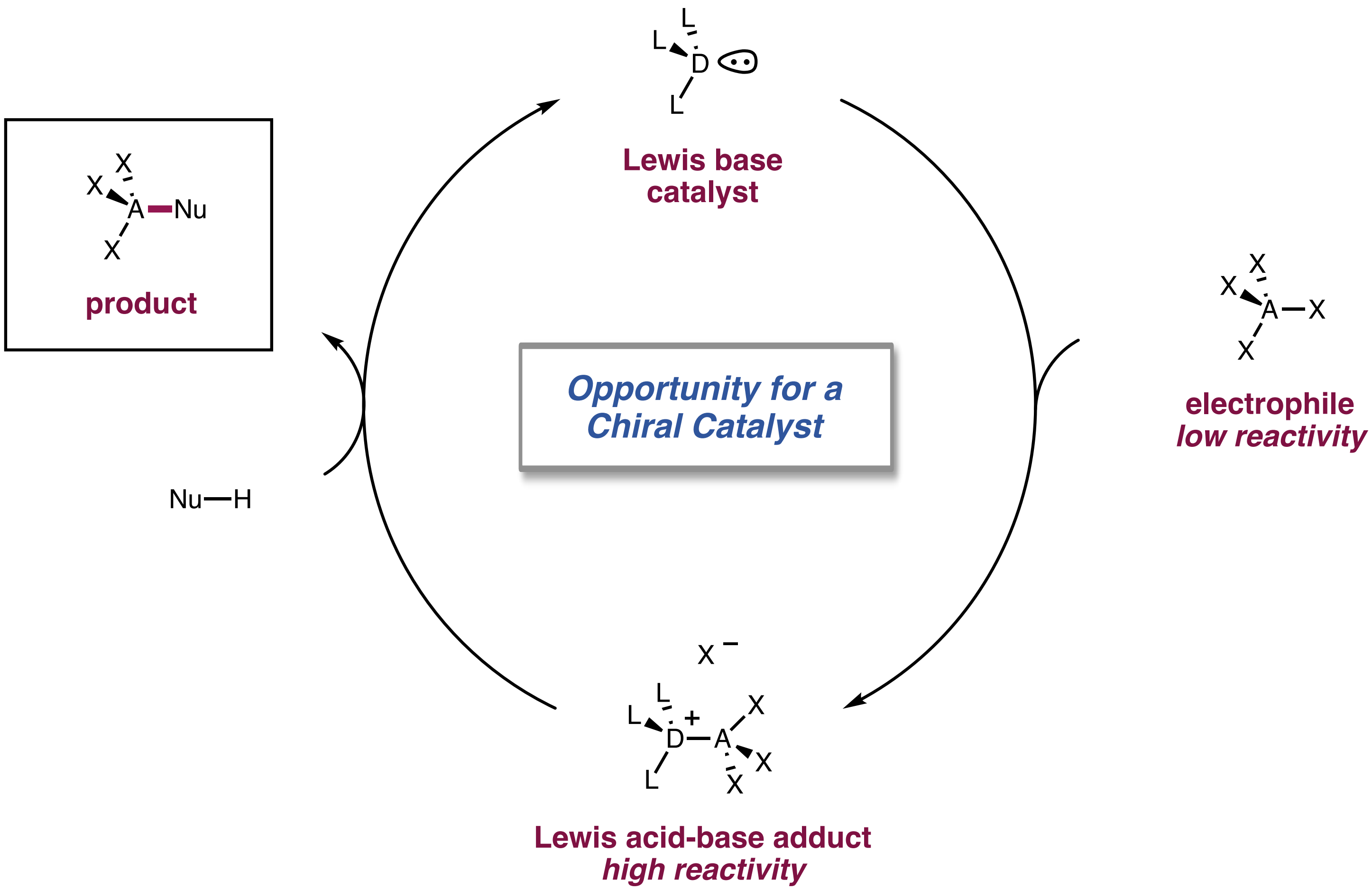






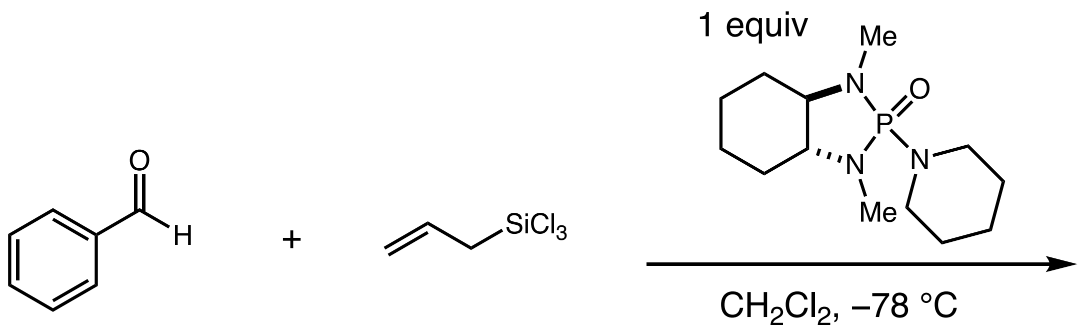


Lewis Base Catalysis



Discovery of Enantioselective Phosphoramide Catalyst

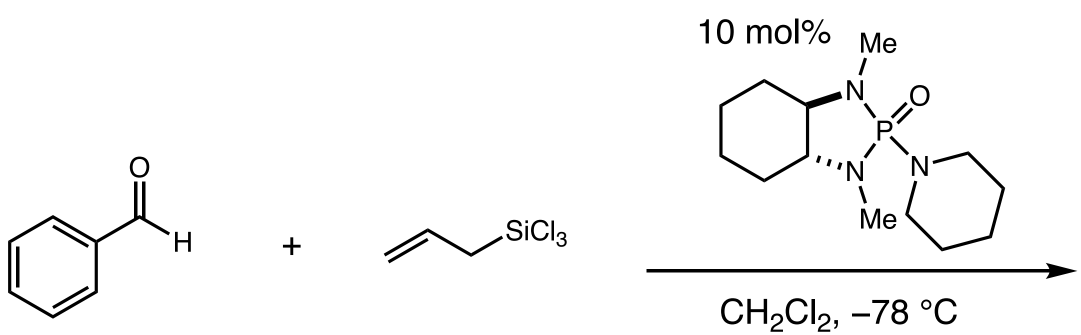
■ Stoichiometric enantioselective allylation of aldehydes



81% yield, 60% ee

- 6 aldehydes (aryl, styrenyl)
- 67–81% yield, 21–65% ee
- stereospecific for crotylsilanes

■ Demonstration of *catalytic* activity



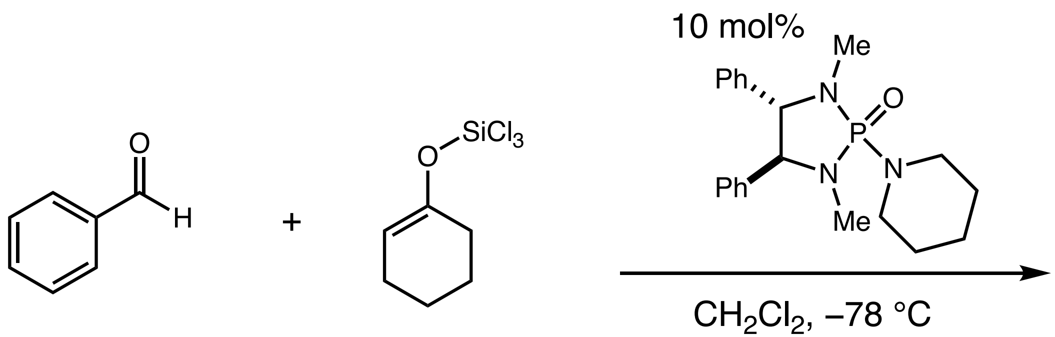
40% yield, 53% ee

single example

Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.

Enantioselective Phosphoramide-Catalyzed Aldol Reactions

■ Highly enantioselective activation of trichlorosilyl enol ethers

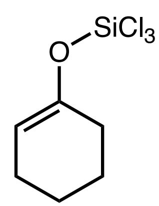


95% yield
65:1 dr, 93% ee

■ cinnamaldehyde as only other example with high selectivity

■ Later extended to other aldehydes and silyl enol ethers

…some drawbacks…



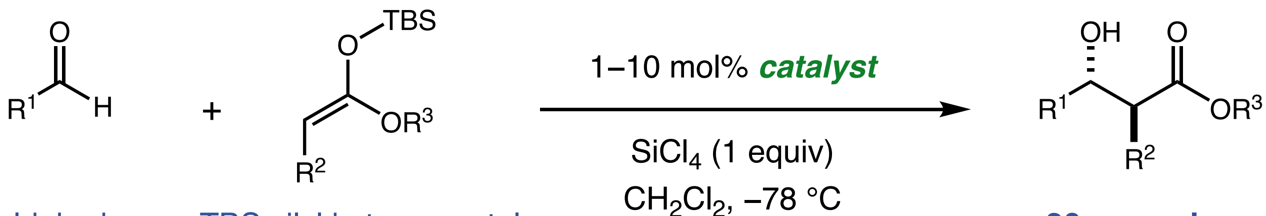
trichlorosilyl enol ether

■ unstable to chromatography
■ prepared from corresponding tributyltin reagent

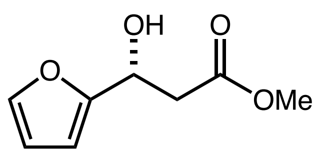
Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404.
Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.

Enantioselective Phosphoramide-Catalyzed Aldol Reactions

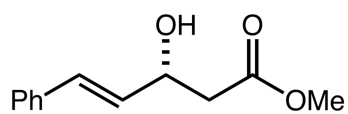
■ Crucial application to more stable silyl nucleophiles



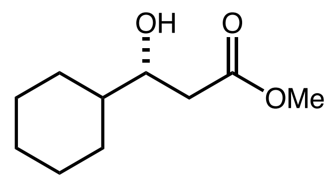
aldehyde — TBS silyl ketene acetal — **26 examples**



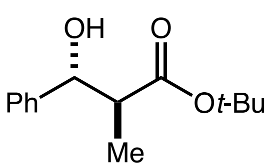
94% yield, 87% ee



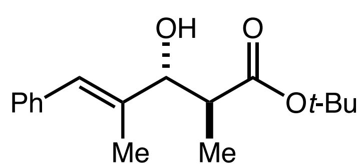
95% yield, 94% ee



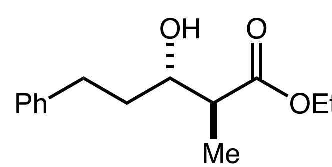
86% yield, 88% ee



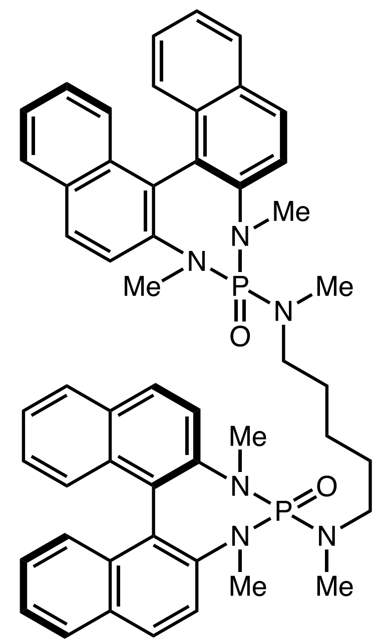
93% yield
99:1 dr, > 98% ee



90% yield
99:1 dr, 92% ee



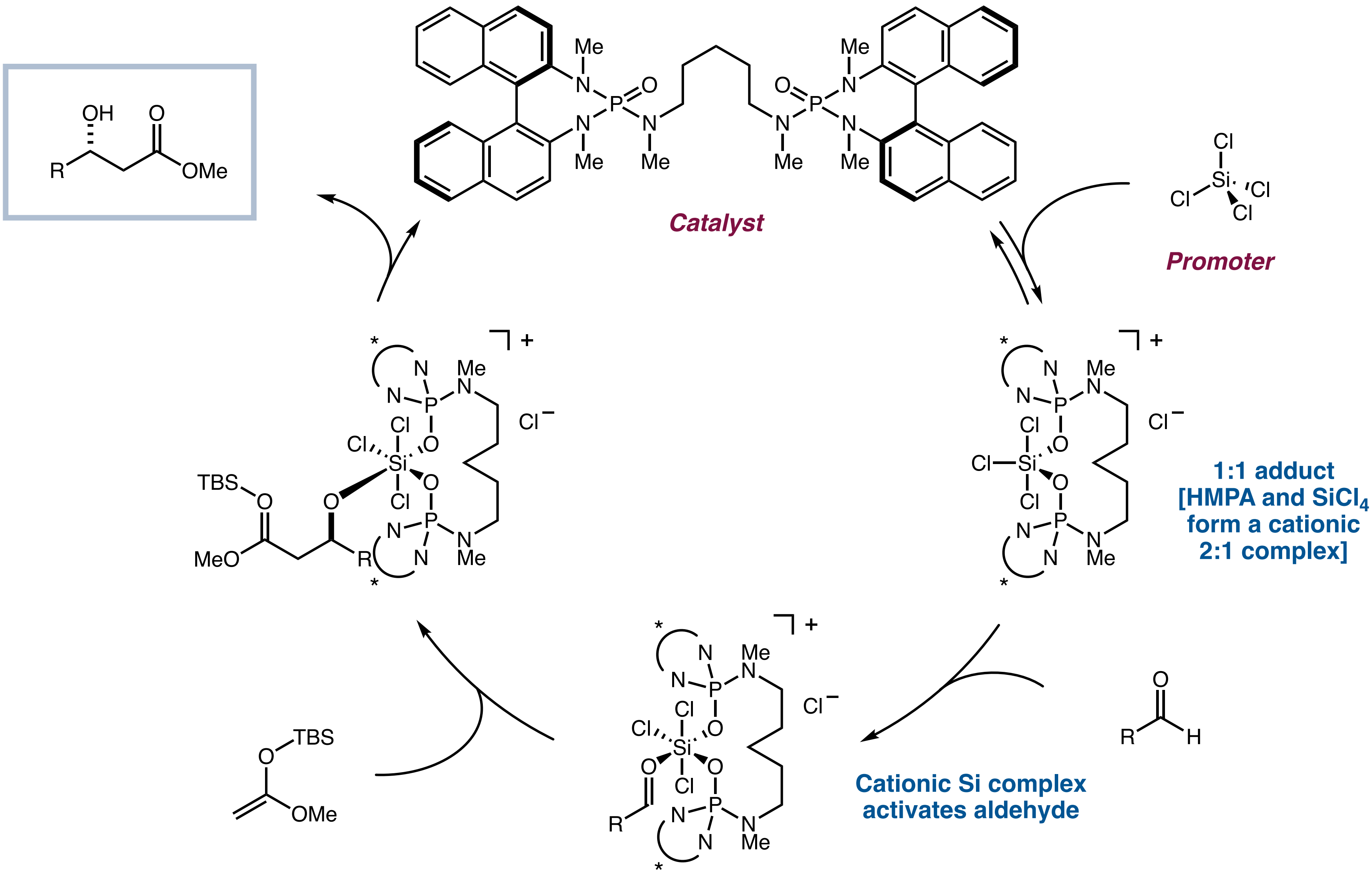
71% yield
91:9 dr, 88% ee



catalyst

Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.

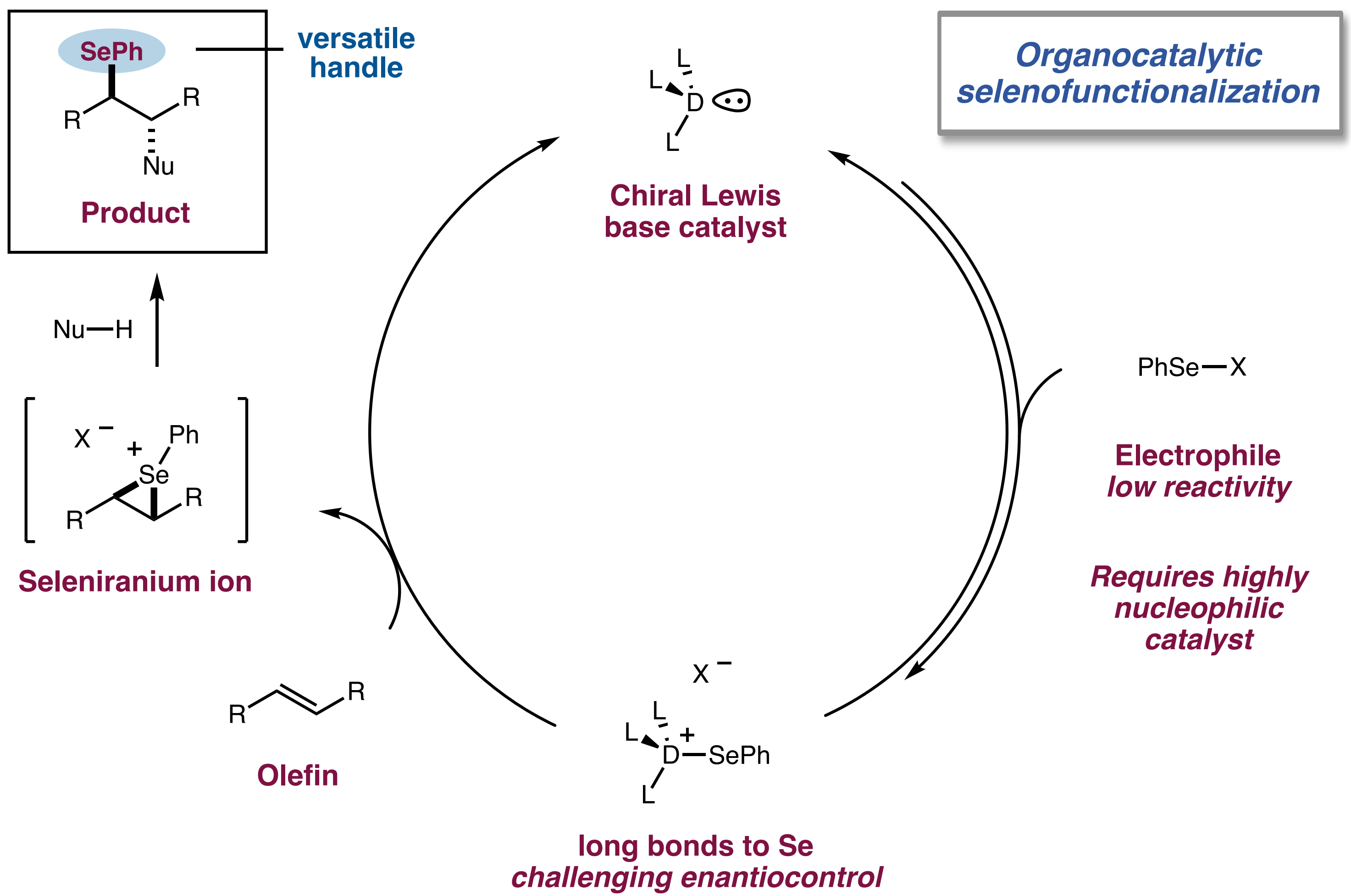
Mechanism of Phosphoramide-Catalyzed Aldol Reaction



Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.

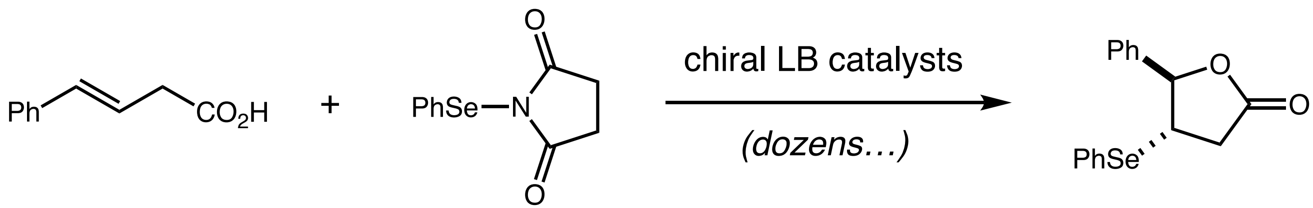
Generalizing Chiral Lewis Base Catalysis

- **Chiral phosphoramides activate silicon electrophiles in a variety of reactions**
- **Phosphoramides are modestly nucleophilic and match well with oxophilic Si electrophiles**
- **Can Lewis base catalysis realize a more challenging goal – alkene difunctionalization?**



Enantioselective Alkene Selenofunctionalization

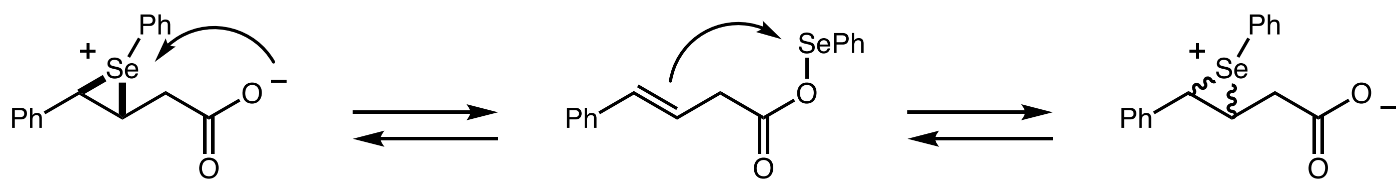
■ Extensive development of a selenolactonization was undertaken but ultimately unsuccessful



high yields
always 0% ee!

■ Intermediate seleniranium ions are configurationally labile via two potential mechanisms

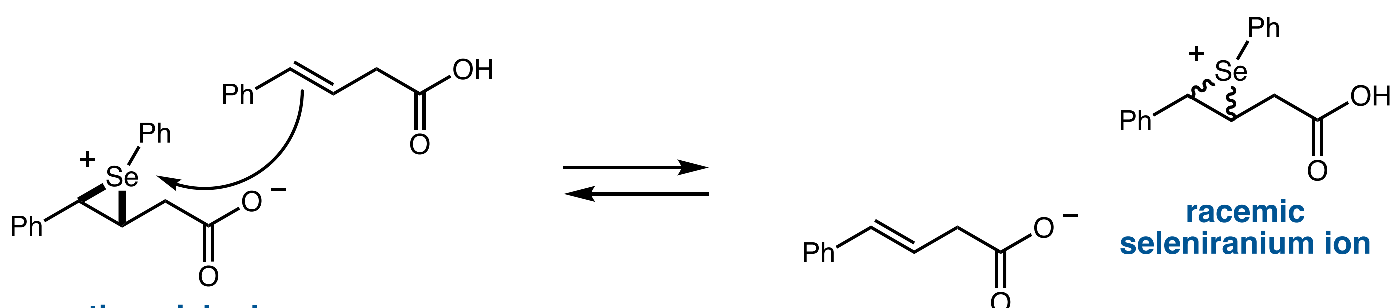
Unimolecular C/O Se exchange



enantioenriched seleniranium ion

racemic seleniranium ion

Bimolecular C=C/C=C Se exchange



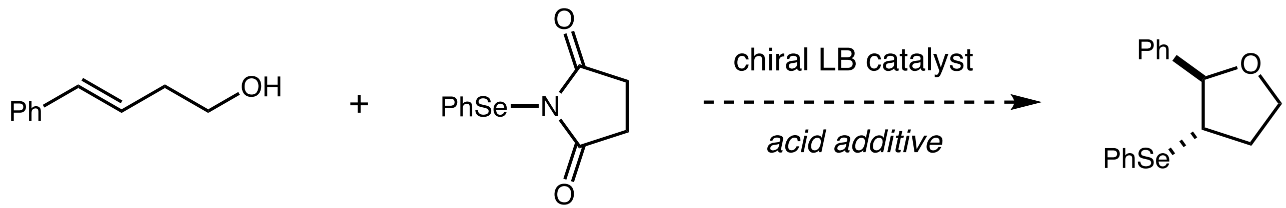
enantioenriched seleniranium ion

racemic seleniranium ion

Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

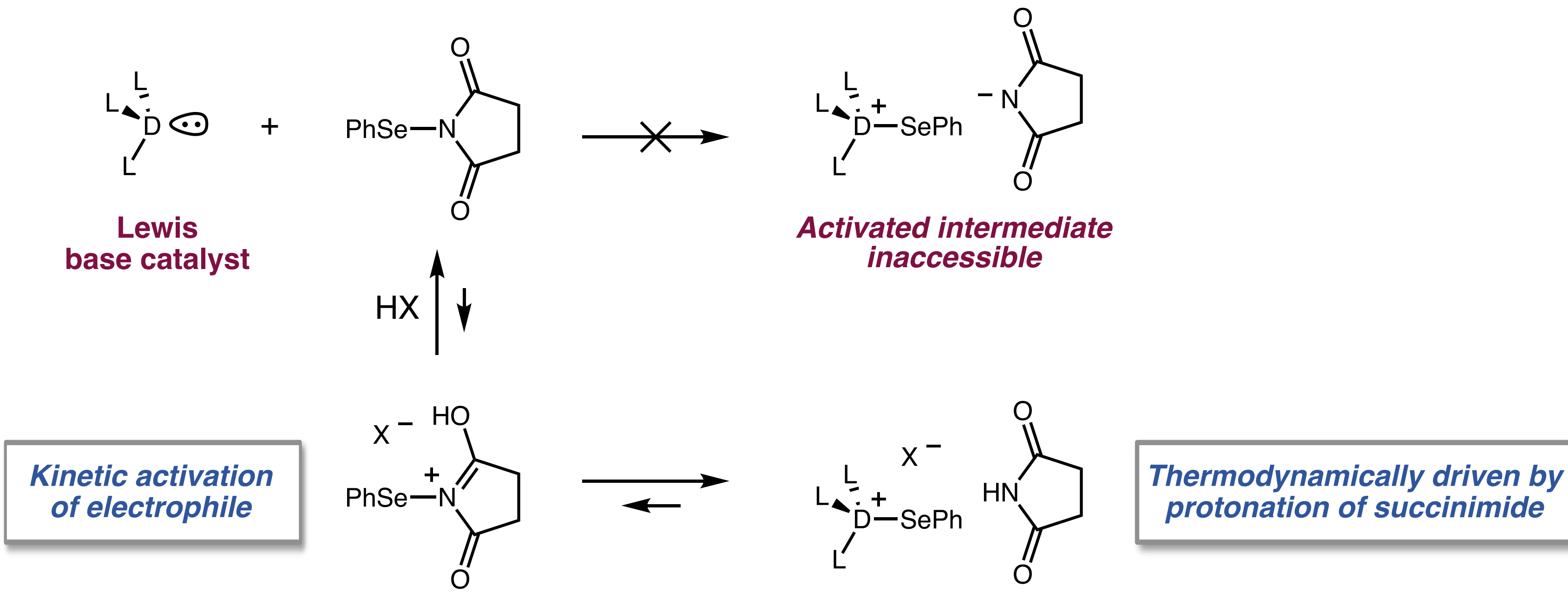
Enantioselective Alkene Selenofunctionalization

Modification 1: focus on selenoetherification (avoids intramolecular C/O Se exchange)



Further optimization of conditions to minimize racemization

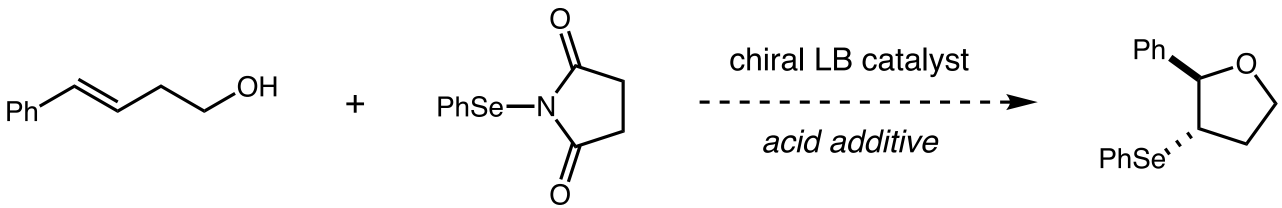
Acid is now essential to reactivity



Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

Enantioselective Alkene Selenofunctionalization

Modification 1: focus on selenoetherification (avoids intramolecular C/O Se exchange)



Modification 2: acid selection

Acid is now essential to reactivity

…but can also racemize the product

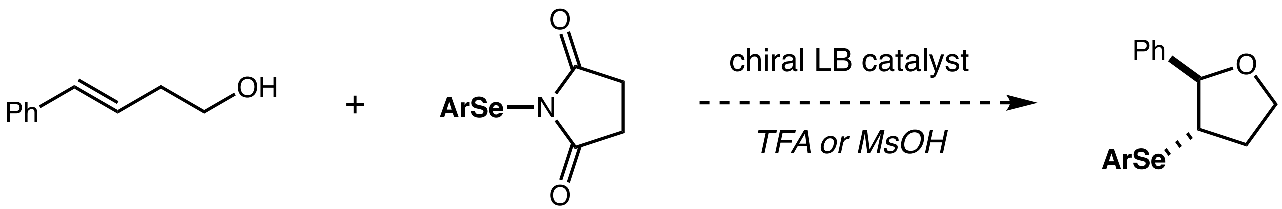
Qualitative summary of acid optimization

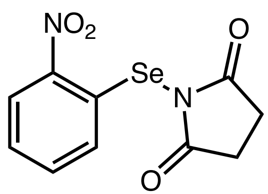
Acid	Reactivity	Racemization
AcOH	none	none
TFA	**high**	**none**
MsOH	**high**	**low**
TfOH	high	high

Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

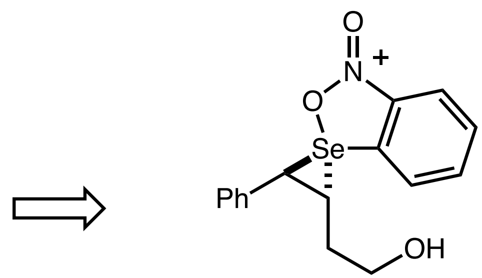
Enantioselective Alkene Selenofunctionalization

■ Modification 3: the Se–aryl substituent





limits racemization
synthetically practical

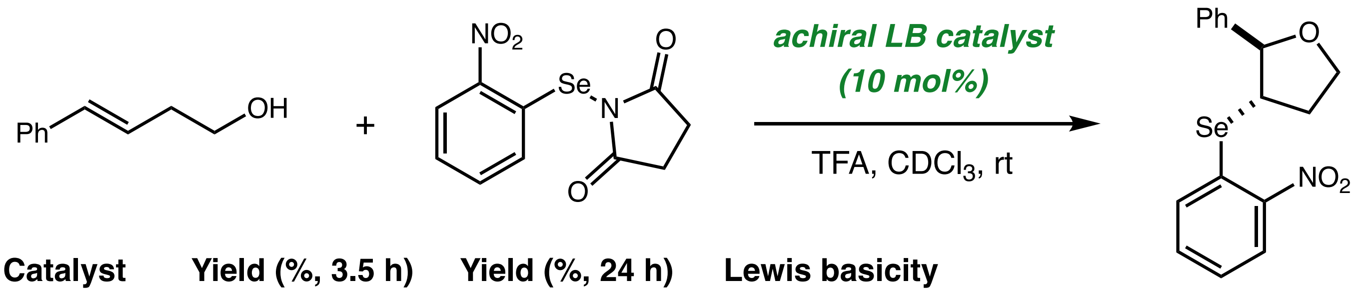


stabilized seleniranium ion

Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

Enantioselective Alkene Selenofunctionalization

Achiral catalyst evaluation



Catalyst	Yield (%, 3.5 h)	Yield (%, 24 h)
none	trace	trace
$(Me_2N)_3P{=}O$	trace	trace
$Ph_3P{=}S$	100	100
$Cy_3P{=}S$	100	100
$(Me_2N)_3P{=}S$	73	100
$(Me_2N)_3P{=}Se$	21	72

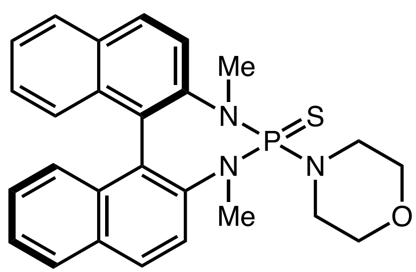
Lewis basicity

activated cation inaccessible

rate-limiting seleniranium formation

Chiral catalyst evaluation

Optimized chiral catalyst

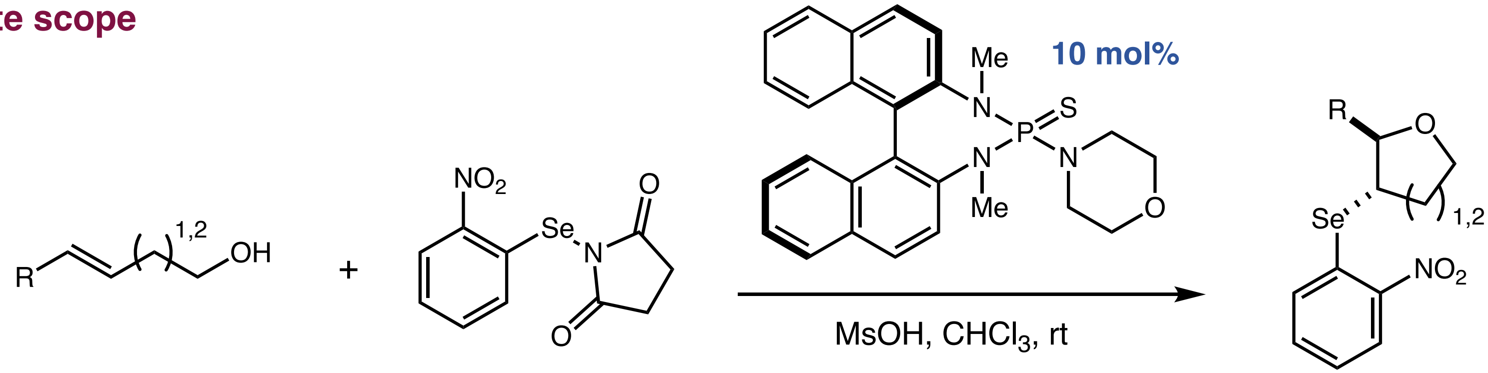


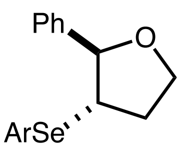
with TFA:
19 h, 67% conversion, 32% ee

Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

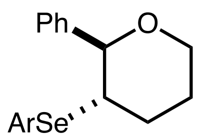
Enantioselective Alkene Selenofunctionalization

Substrate scope

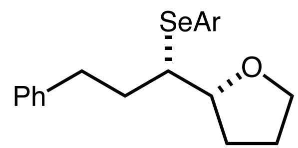




97% yield, 38% ee

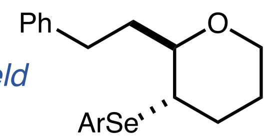


86% yield, 50% ee

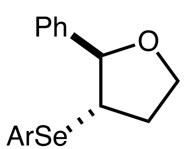


57% ee

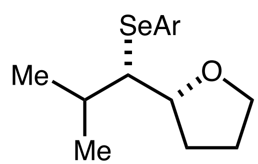
94% yield
1.4:1



70% ee

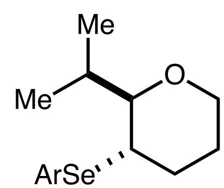


80% yield, 2% ee
(from Z-alkene)



65% ee

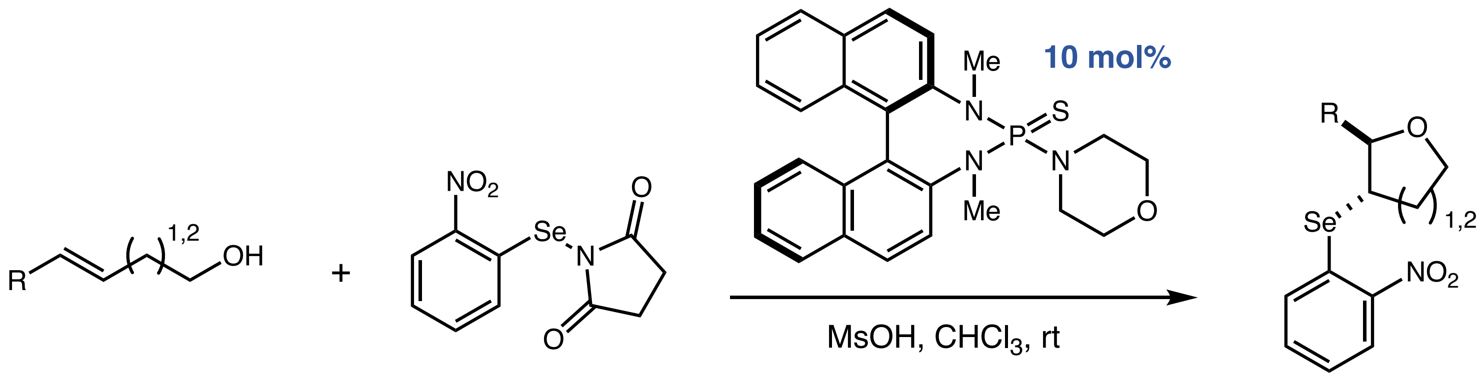
86% yield
4.5:1



68% ee

Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

Enantioselective Alkene Selenofunctionalization Outlook

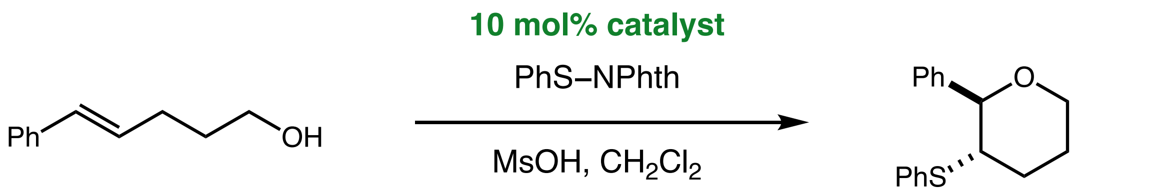


- Modest scope and selectivity
- Completely new enantioselective transformation
- Several challenges overcome, lessons learned
- Has led to several further alkene difunctionalization reactions

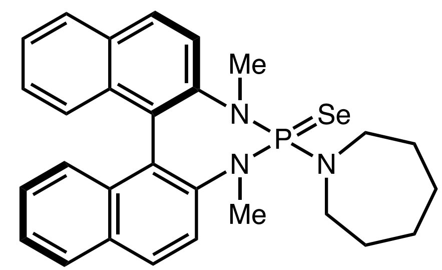
Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

Enantioselective Alkene Difunctionalization Program

■ Thioetherification

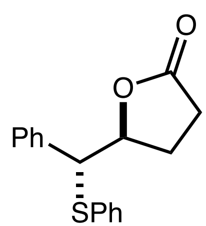


12 examples
up to 94% yield, 92% ee

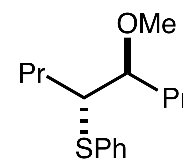


catalyst

additional motifs accessed

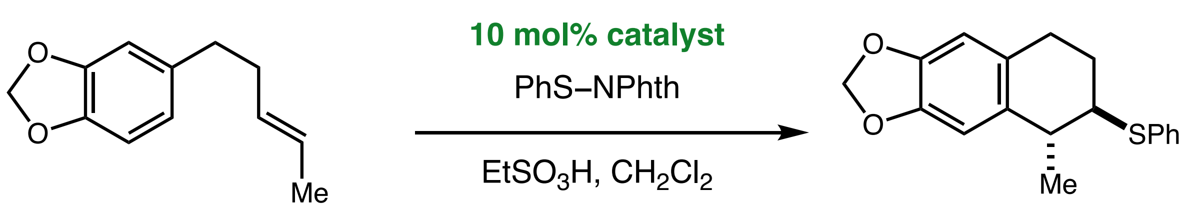


thiolactonization
83% yield, 82% ee

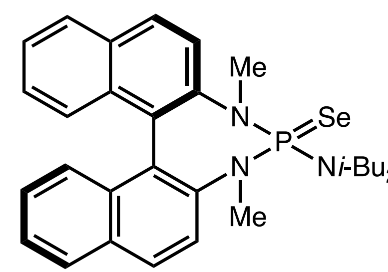


intermolecular etherification
93% yield, 84% ee

■ Carbosulfenylation



19 examples
up to 92% yield, 94% ee

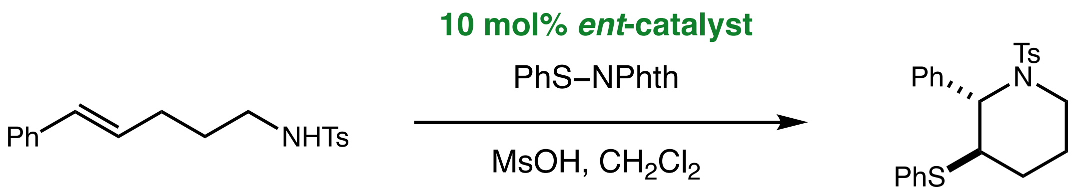


catalyst

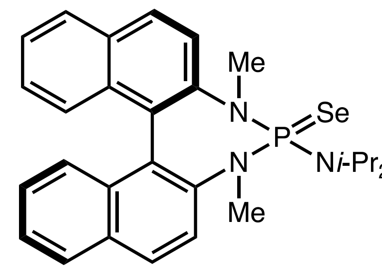
Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308.
Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419.

Enantioselective Alkene Difunctionalization Program

Sulfenoamination

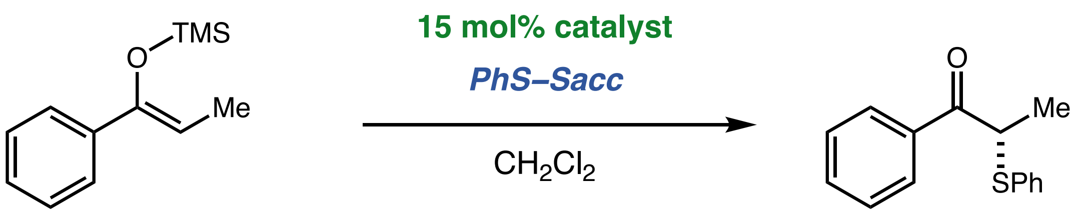


14 examples
up to 93% yield, 95% ee

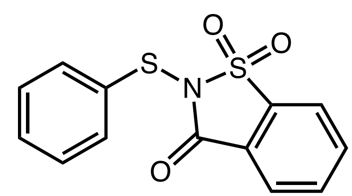


catalyst

Carbonyl α-sulfenylation



16 examples
up to 80% yield, 94% ee



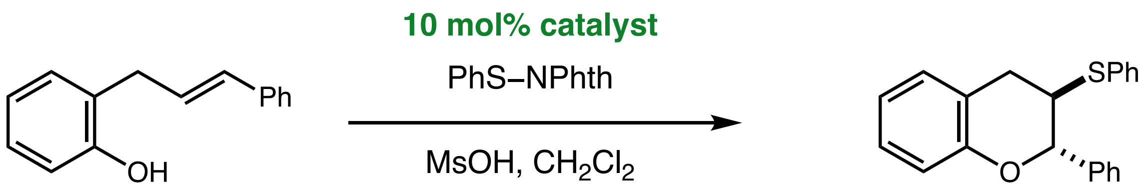
PhS–Sacc

activated without acid
avoids silyl enol ether hydrolysis

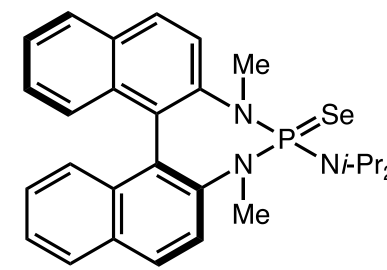
Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915.
Denmark, S. E.; Rossi, S.; Webster, M. P.; Wang, H. *J. Am. Chem. Soc.* **2014**, *136*, 13016.

Enantioselective Alkene Difunctionalization Program

Sulfenoetherification with phenols

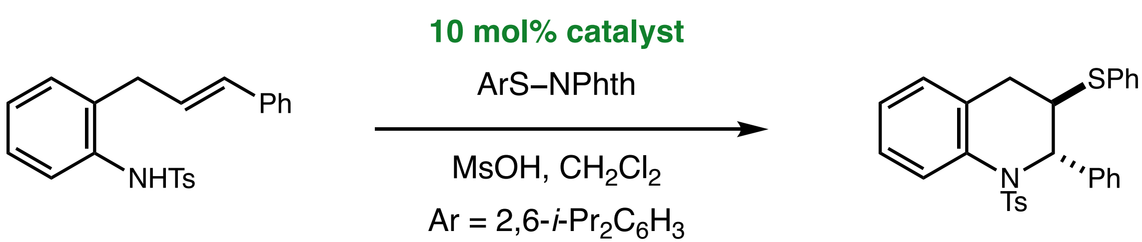


> 20 examples
up to 93% yield, 96% ee



catalyst

Sulfenoamination with anilines



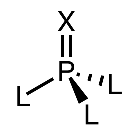
> 15 examples
up to 93% yield, 96% ee

Denmark, S. E.; Kornfilt, D. J. P. *J. Org. Chem.* **2017**, *82*, 3192.
Denmark, S. E.; Chi, H. M. *J. Org. Chem.* **2017**, *82*, 3826.

Implications for Catalyst Design

■ Why are triamino(chalcogeno)phosphoranes uniquely effective?

Lewis basicity is highly tunable



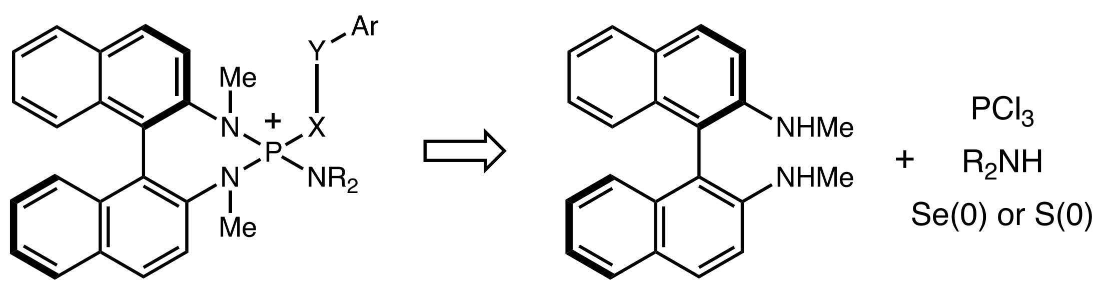
P efficiently transmits electron density from L to X

Appropriate L and X enable reactivity without restricting the chiral framework

Good Lewis bases but poor Brønsted bases (critical when using acid additives)

Ability of P to form 4 covalent bonds maximizes structural diversity

key activated electrophile



Many derivatives are rapidly and modularly prepared (especially when 3,3′-substitution is unnecessary)

BINAM backbone provides a chiral pocket that bites back around the long X–Y bond

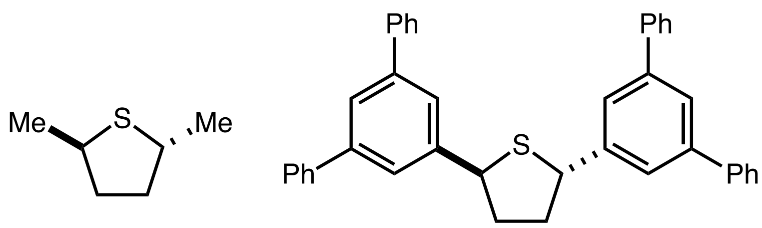
Third amino substituent provides a further electronic and/or steric handle

Denmark, S. E.; Rossi, S.; Webster, M. P.; Wang, H. *J. Am. Chem. Soc.* **2014**, *136*, 13016.

Implications for Catalyst Design

■ **Why are triamino(chalcogeno)phosphoranes uniquely effective?**

Compare to dialkyl sulfides (only 2 covalent bonds available)

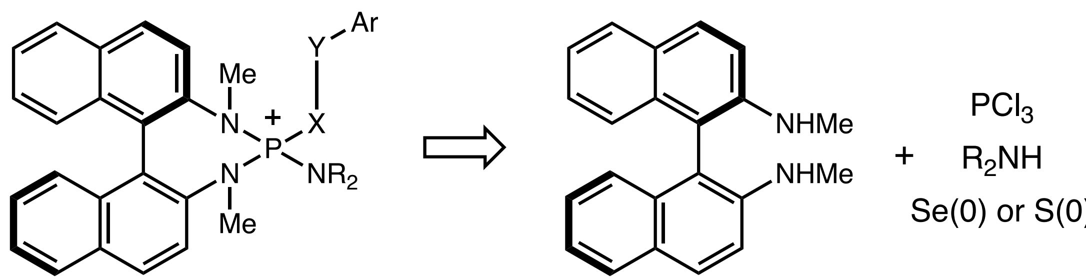


≤ 10% ee

Can be highly reactive but the few synthetically accessible chiral variants are poorly enantioselective

Ability of P to form 4 covalent bonds maximizes structural diversity

key activated electrophile

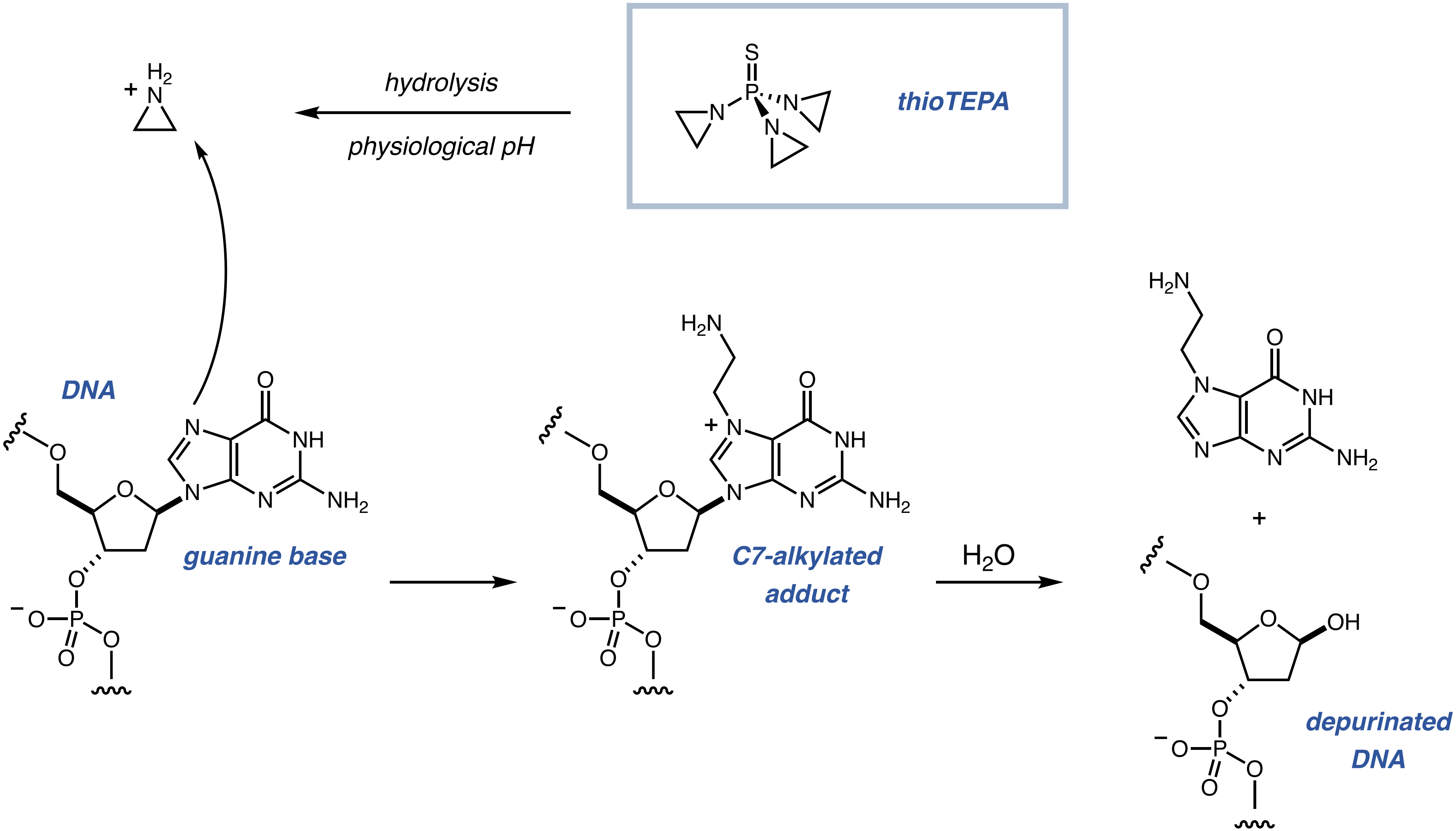


Many derivatives are rapidly and modularly prepared (especially when 3,3′-substitution is unnecessary)
BINAM backbone provides a chiral pocket that bites back around the long X–Y bond
Third amino substituent provides a further electronic and/or steric handle

Denmark, S. E.; Rossi, S.; Webster, M. P.; Wang, H. *J. Am. Chem. Soc.* **2014**, *136*, 13016.

Triamino(chalcogeno)phosphoranes in Medicine

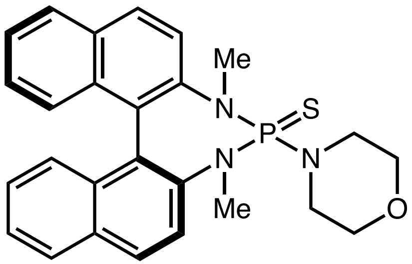
■ **Also, this is a cancer drug…**

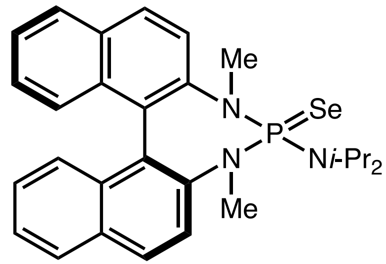


Musser, S. M.; Pan, S.-S.; Egorin, M. J.; Kyle, D. J.; Callery, P. S. *Chem. Res. Toxicol.* **1992**, *5*, 95.

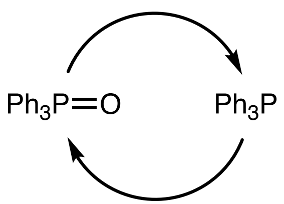
Outline

Part I: Enantioselective Nucleophilic Catalysis with Phosphine Chalcogenides

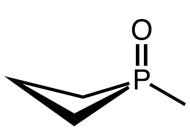


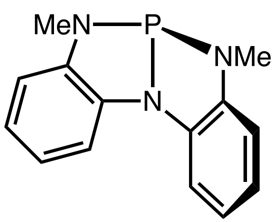


Part II: Recycling Phosphorus in Classical Reactions



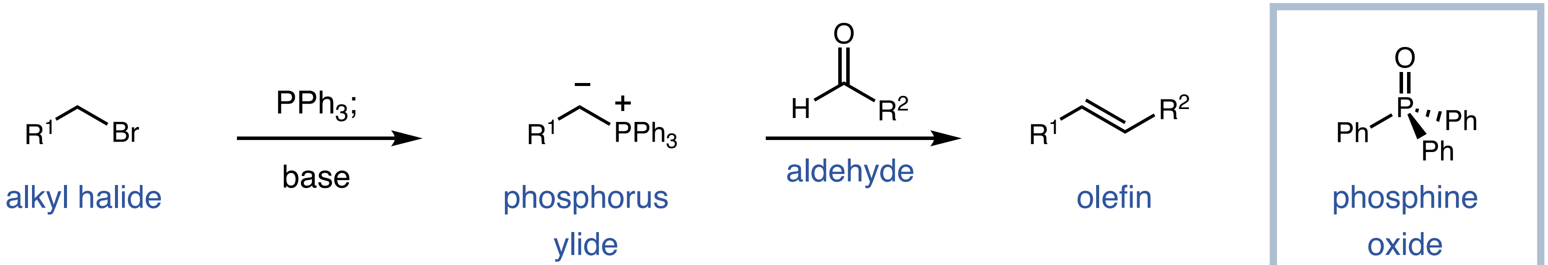
Part III: Strained Phosphines



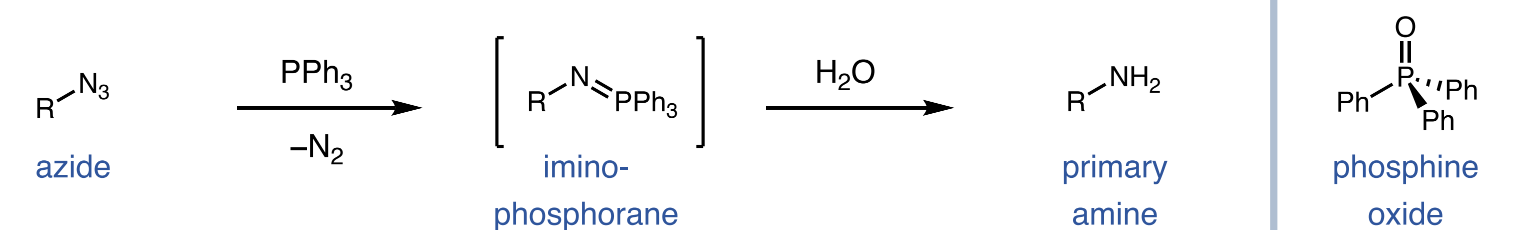


Classical Phosphine-Mediated Transformations

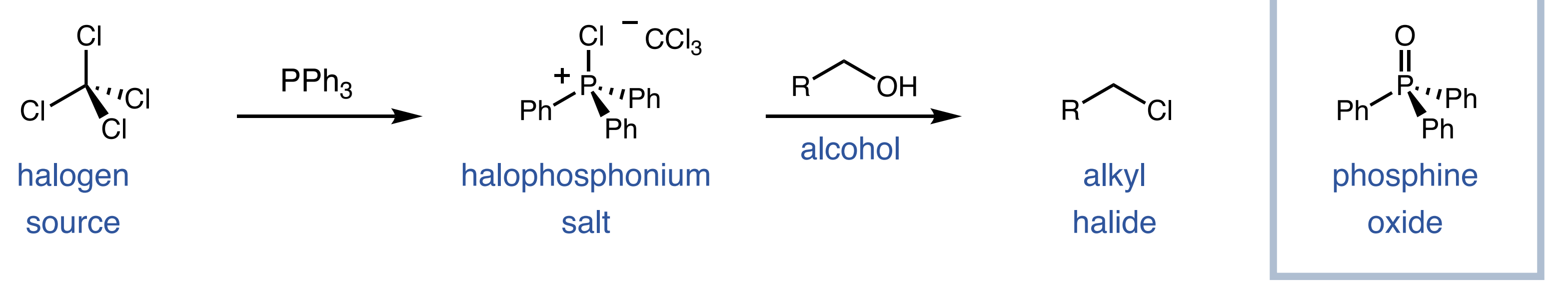
■ Wittig reaction



■ Staudinger reduction

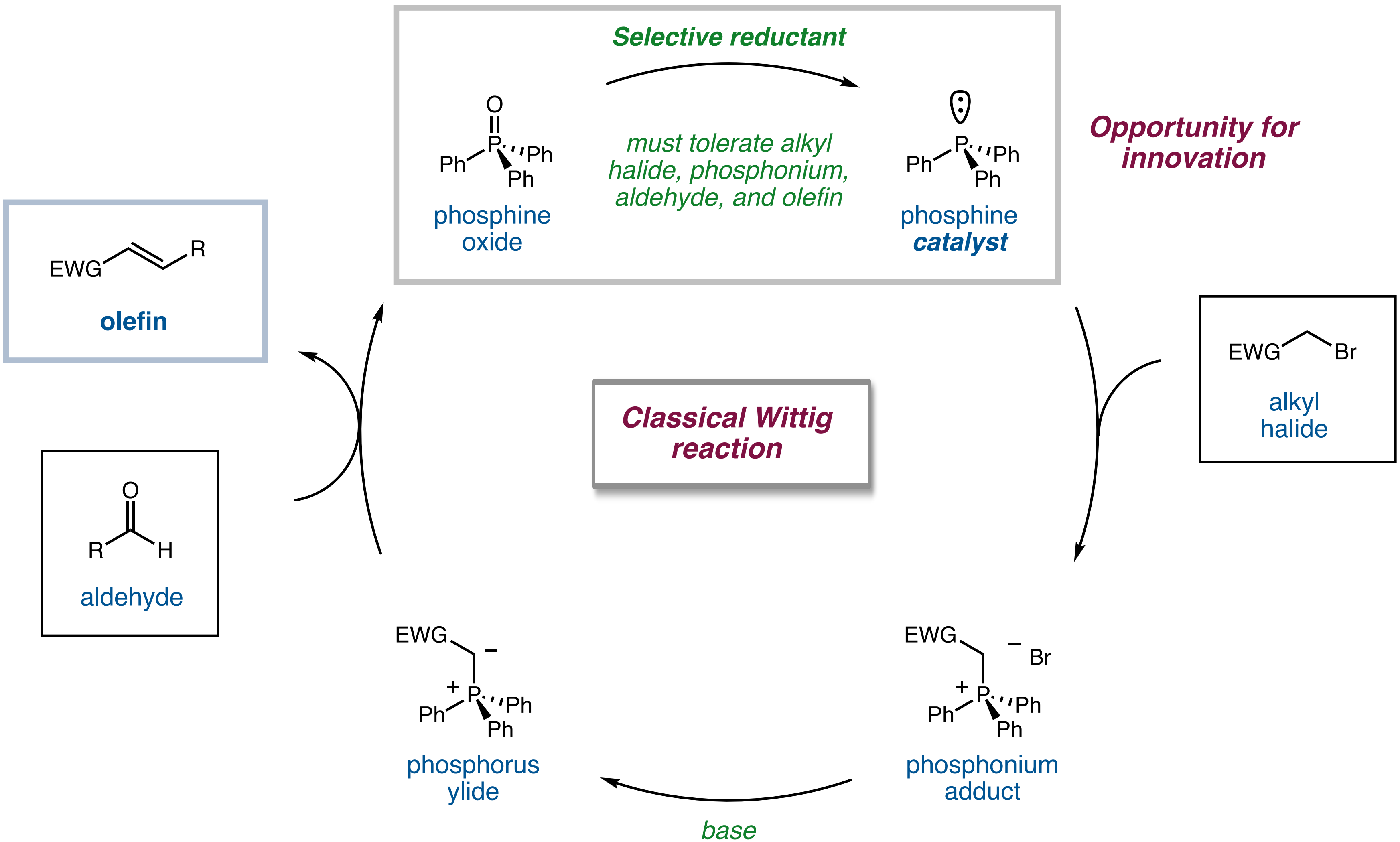


■ Appel reaction

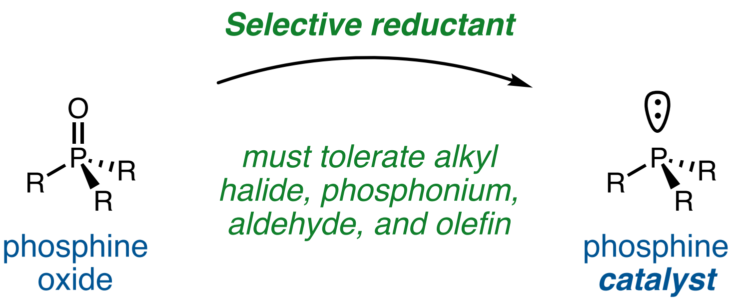


can this stoichiometric byproduct be avoided?

Imagining a Catalytic (in Phosphine) Wittig Reaction

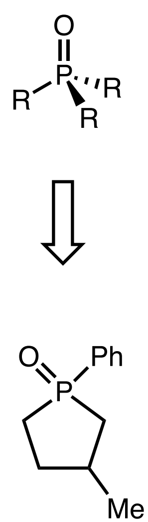


Imagining a Catalytic (in Phosphine) Wittig Reaction



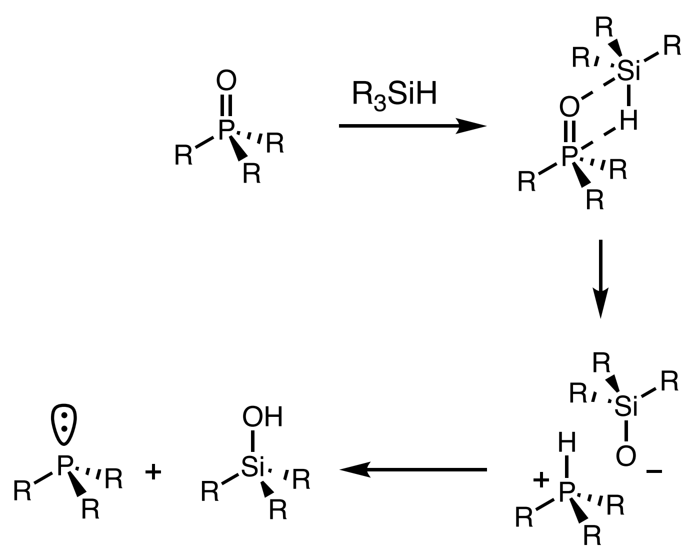
2 key insights

Use a more reducible phosphine



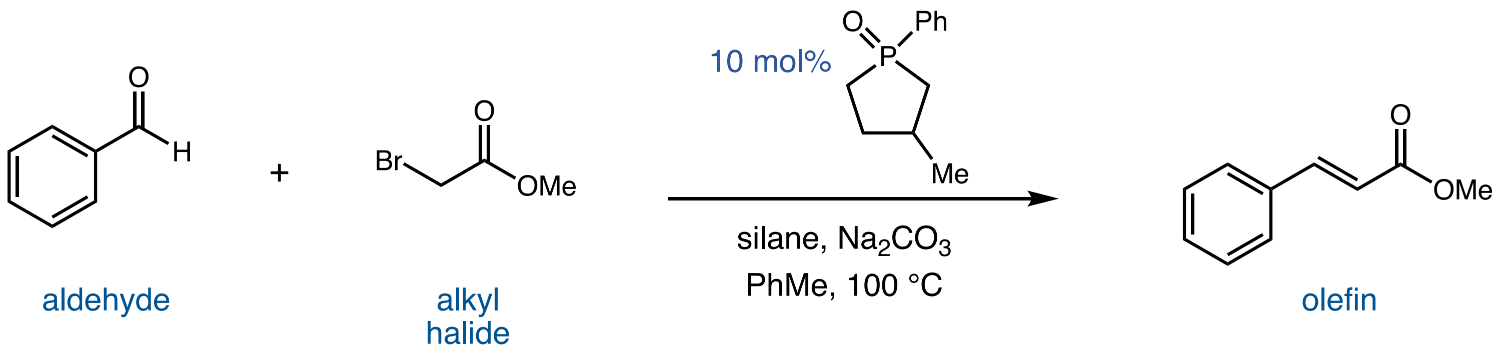
more reducible due to ring strain

Evaluate silanes as reductants *known as P=O-selective*



O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836.

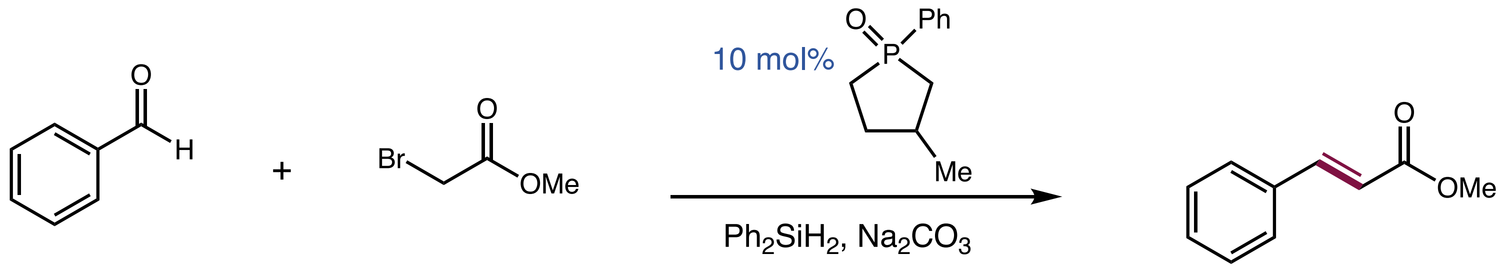
Silane Optimization for Catalytic Wittig Reaction



Silane	Yield (%)	*E*/*Z*
Ph_3SiH	trace	nd
Ph_2SiH_2	**75**	**> 95:5**
$PhSiH_3$	46	> 95:5
$(MeO)_3SiH$	61	70:30

O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836.

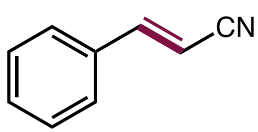
Substrate Scope for Catalytic Wittig Reaction



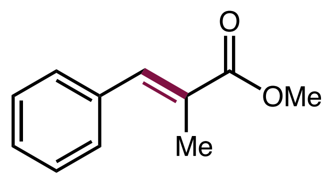
aldehyde

alkyl bromide
(or choride)

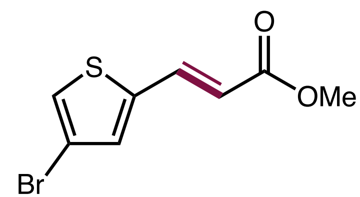
19 examples
61–81% yield, 60:40 – > 95:5 E/Z



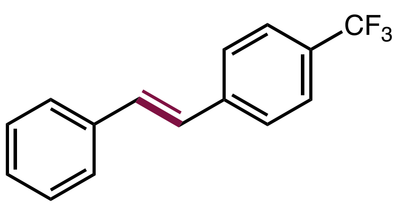
80% yield, 75:25



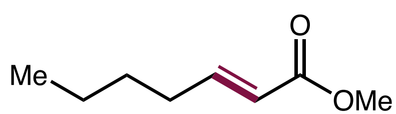
77% yield, 83:17



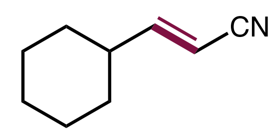
70% yield, > 95:5



70% yield, 60:40



68% yield, > 95:5



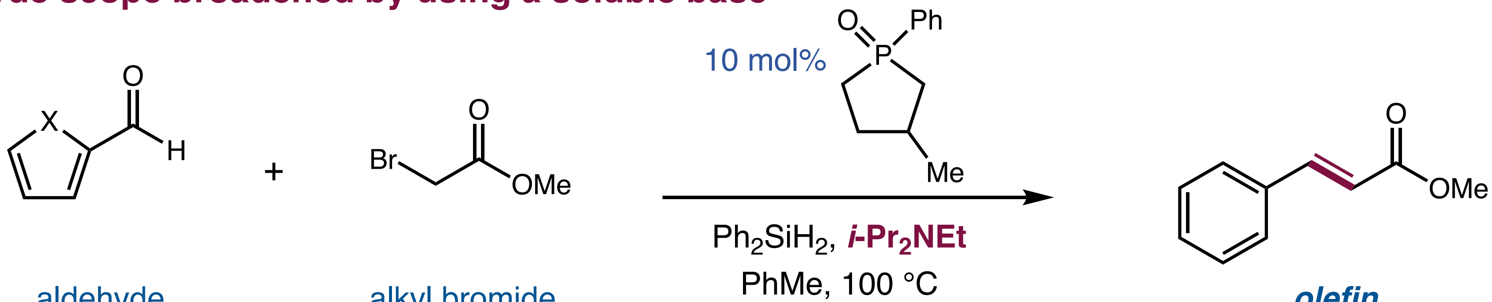
63% yield, 67:33

- **Good aldehyde scope: alkyl, (hetero)aryl**
- **Needs high temperature**
- **Only stabilized ylides**

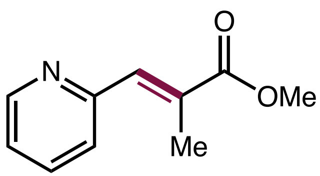
O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836.

Improvements to Catalytic Wittig Reaction

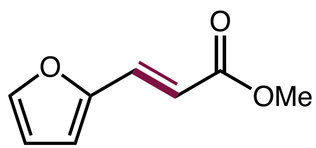
■ Aldehyde scope broadened by using a soluble base



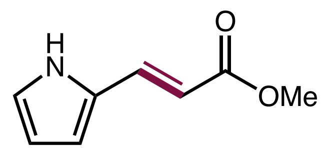
aldehyde — alkyl bromide (or choride) — ***olefin***



70% yield, 70:30

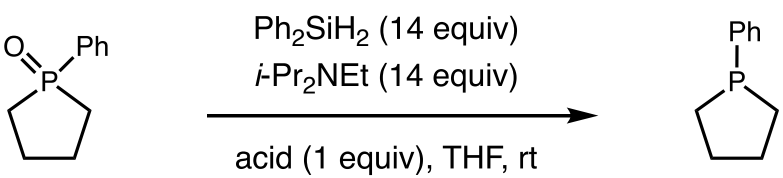


75% yield, > 95:5



61% yield, 92:8

■ Acid additive dramatically accelerates P=O reduction

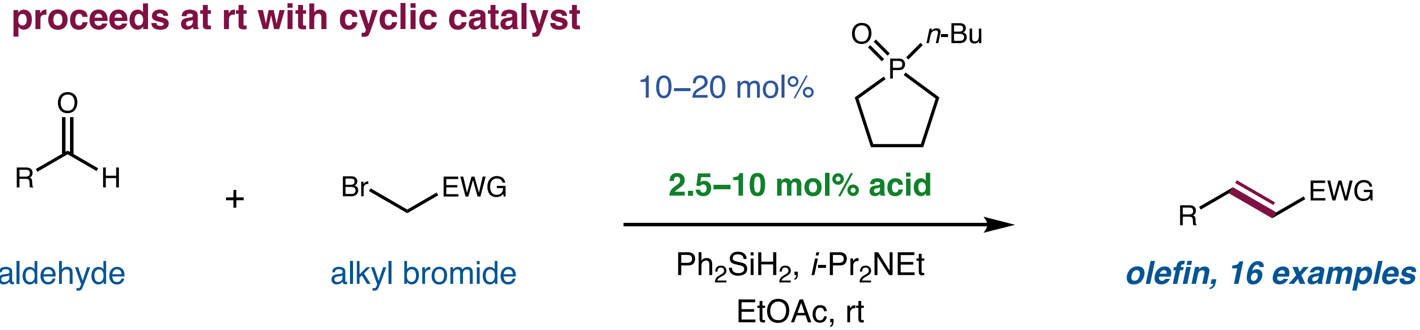


Acid	Time (min)	Conversion (%)
none	60	6
4-$NO_2C_6H_4CO_2H$	60	61
4-$NO_2C_6H_4CO_2H$ (with $PhSiH_3$)	**2**	**74**

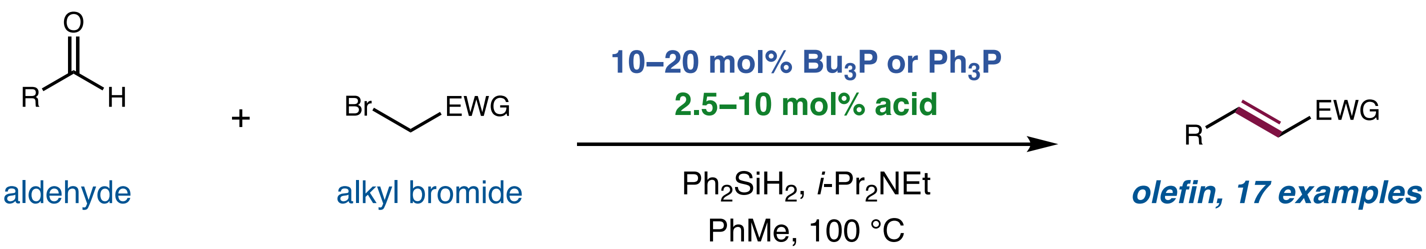
O'Brien, C. J.; *et al. Chem. Eur. J.* **2013**, *19*, 15281.
O'Brien, C. J.; Lavigne, F.; Coyle, E. E.; Holohan, A. J.; Doonan, B. J. *Chem. Eur. J.* **2013**, *19*, 5854.

Improvements to Catalytic Wittig Reaction

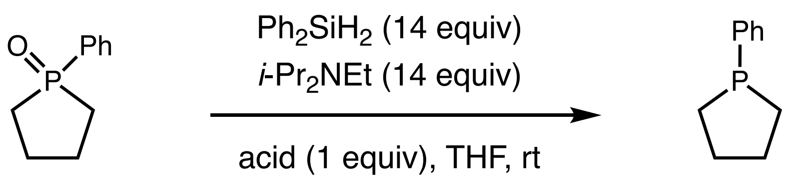
Reaction proceeds at rt with cyclic catalyst



Commercial n-Bu_3P or Ph_3P may be used at 100 °C



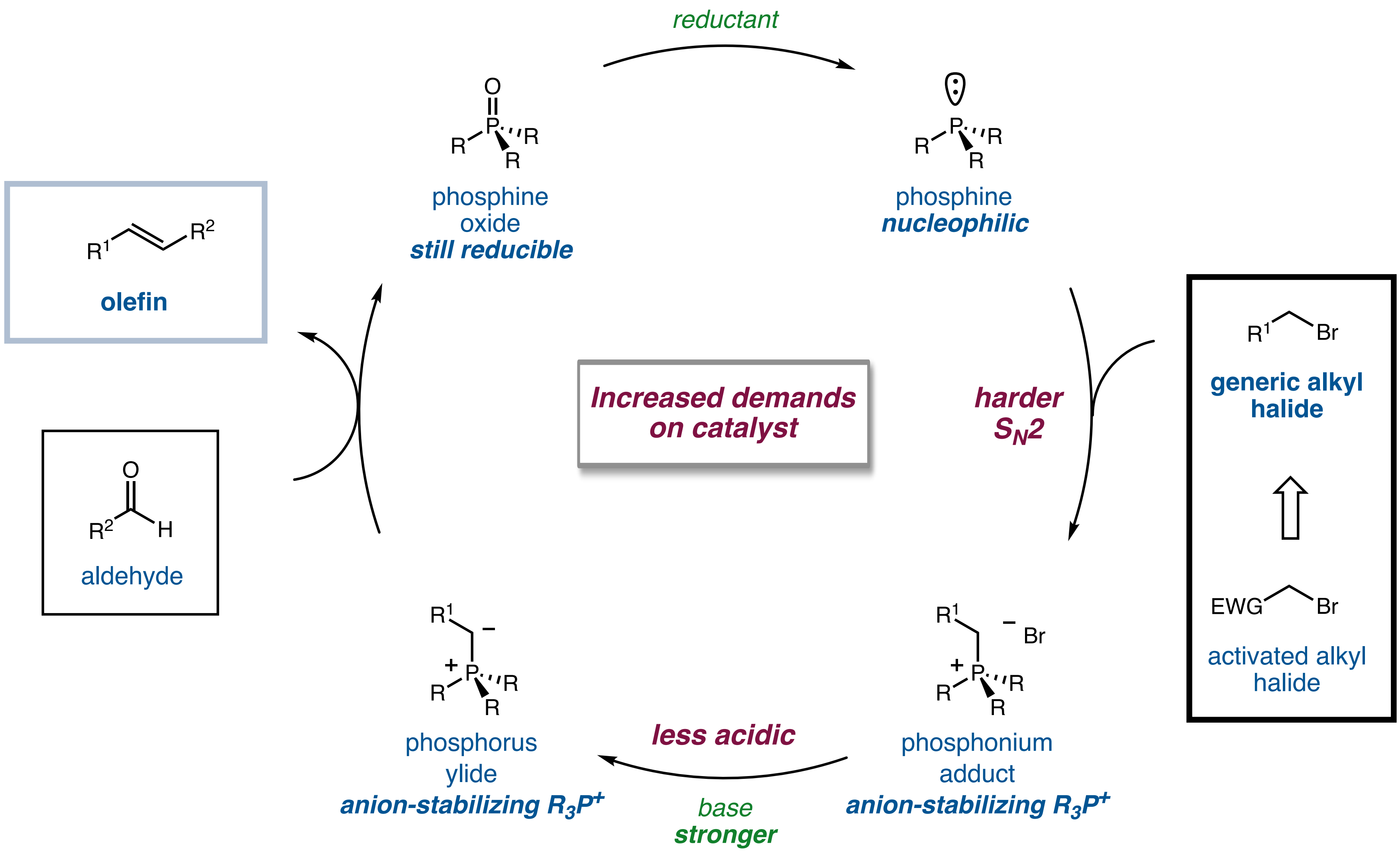
Acid additive dramatically accelerates P=O reduction



Acid	Time (min)	Conversion (%)
none	60	6
4-$NO_2C_6H_4CO_2H$	60	61
4-$NO_2C_6H_4CO_2H$ (with $PhSiH_3$)	**2**	**74**

O'Brien, C. J.; Lavigne, F.; Coyle, E. E.; Holohan, A. J.; Doonan, B. J. *Chem. Eur. J.* **2013**, *19*, 5854.

Catalytic Wittig Reaction with Unstabilized Ylides



Catalytic Wittig Reaction with Unstabilized Ylides

■ Fine-tuning the base

stabilized ylides — *too weak*: *i*-Pr_2NEt, Na_2CO_3

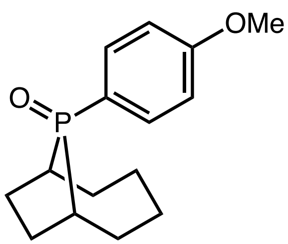
$NaOCO_2$*t*-Bu → *slow release* ($-CO_2$) → NaO*t*-Bu

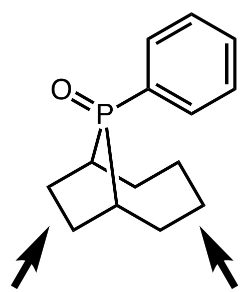
unstabilized ylides — *…but reacts with silane*: NaO*t*-Bu, NaHMDS, *n*-BuLi

lower pK_a → *higher pK_a*

■ Optimizing the phosphine: [4.2.1]-bicylcic structure performs best

phosphonium not acidic enough

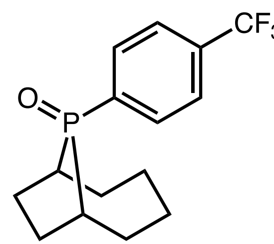




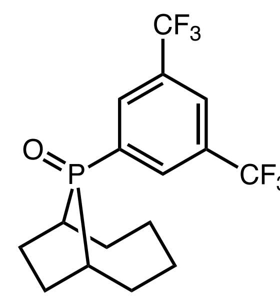
5-membered ring:
P=O reducible
(electronics)

7-membered ring:
E-selectivity
(sterics)

optimal catalyst



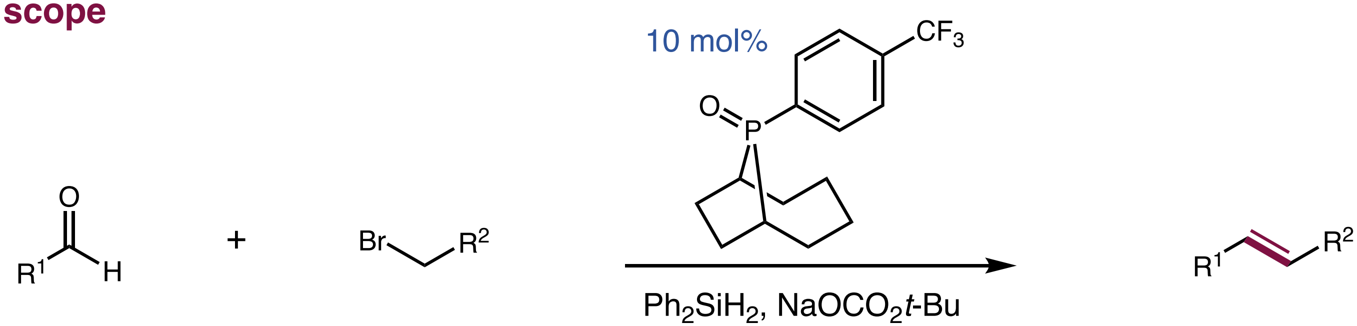
phosphine not
nucleophilic enough



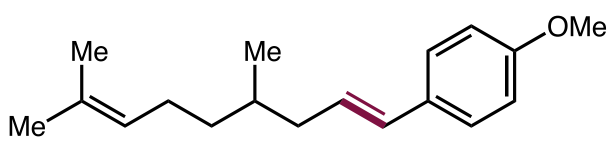
Coyle, E. E.; Doonan, B. J.; Holohan, A. J.; Walsh, K. A.; Lavigne, F.; Krenske, E. H.; O'Brien, C. J. Angew. *Chem. Int. Ed.* **2014**, *53*, 12907.

Catalytic Wittig Reaction with Unstabilized Ylides

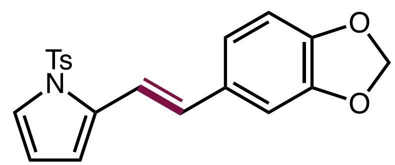
Substrate scope



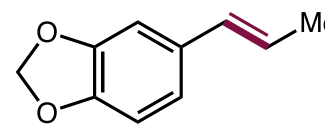
aldehyde — alkyl bromide (or iodide) — ***olefin, 28 examples***



61% yield, 85:15 *E*/*Z*

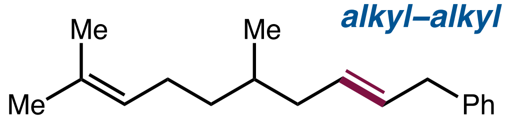


69% yield, 83:17 *E*/*Z*

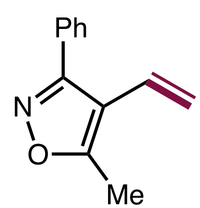


74% yield, 75:25 *E*/*Z*

alkyl–alkyl

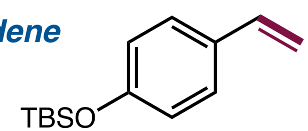


68% yield, 80:20 *E*/*Z*



60% yield

methylidene



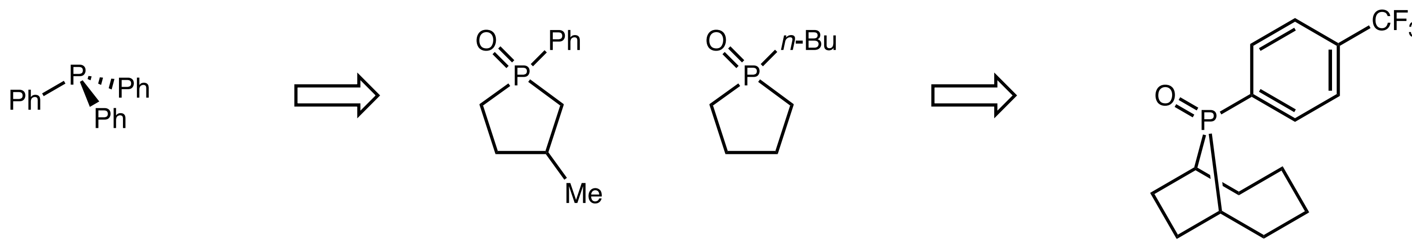
68% yield

benzylic halides typically require only one of the improved base or phosphine

Coyle, E. E.; Doonan, B. J.; Holohan, A. J.; Walsh, K. A.; Lavigne, F.; Krenske, E. H.; O'Brien, C. J. Angew. *Chem. Int. Ed.* **2014**, *53*, 12907.

Catalyst Evolution in the Catalytic Wittig Reaction

Typical Wittig reagent | ***1st-generation catalysts*** | ***2nd-generation catalyst***



Typical Wittig reagent

- **Stoichiometric phospine oxide byproduct**

1st-generation catalysts

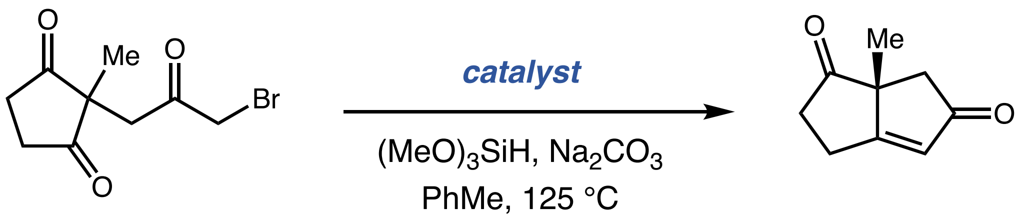
- **Cyclic structure enables P=O reduction by silane**
- **Still nucleophilic enough to effect S_N2**
- **Active at rt with an acid cocatalyst**
- ***Cannot form unstabilized ylides***

2nd-generation catalyst

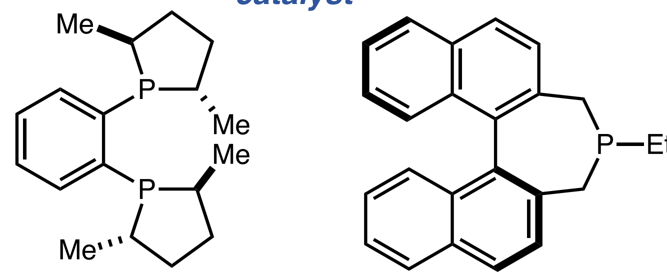
- **Maintains advantages of 1st-generation catalysts**
- **Electron-deficient aromatic gives access to unstabilized ylides**
- **Additional ring improves *E*-selectivity**

Some Extensions of Phosphine-Catalyzed Wittig Reactions

"First Enantioselective Catalytic Wittig Reaction"

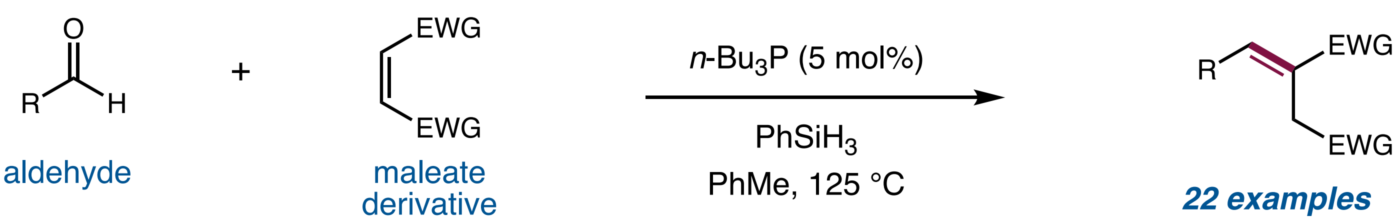


catalyst



5 mol%	10 mol%
< 10% conv, 90% ee	62% conv, 34% ee

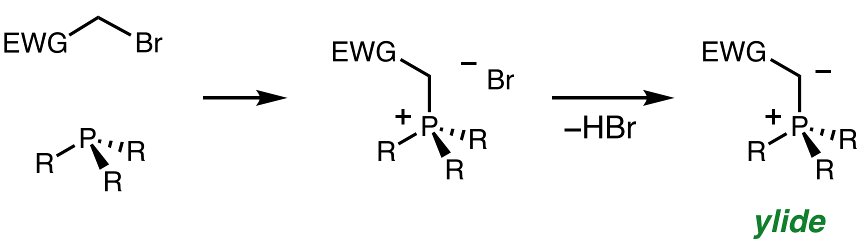
"First Base-Free Catalytic Wittig Reaction"



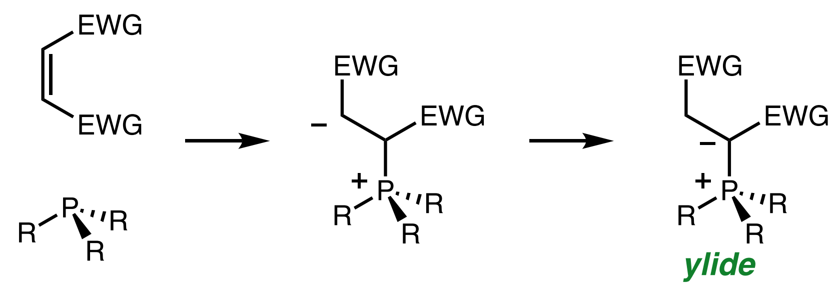
22 examples
62–95% yield, ≥ 5:1 E/Z

alkylidene succinate-type products (EWG = ester, CN)

Typical ylide formation: S_N2 and deprotonation

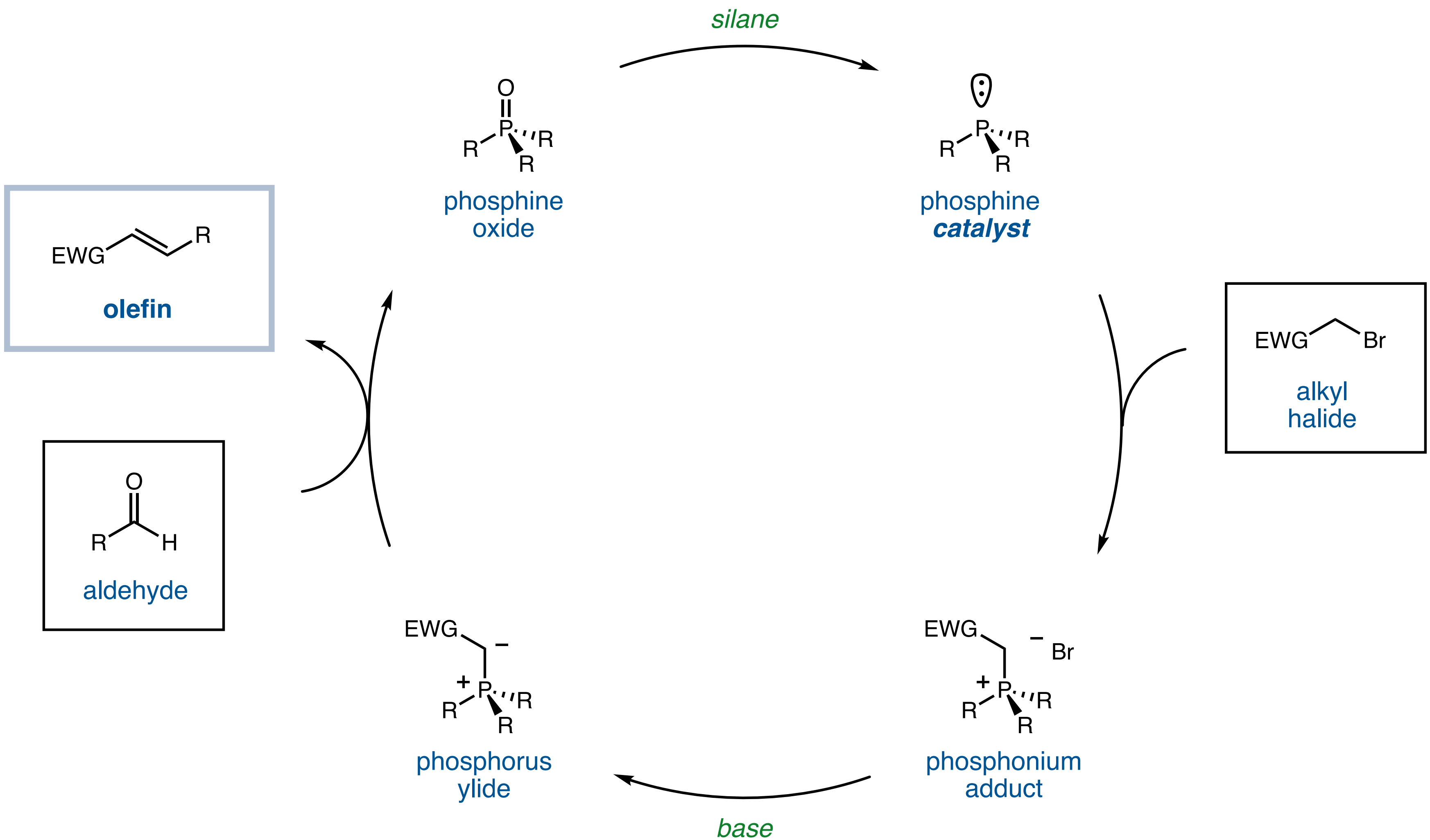


Base-free manifold: conjugate addition and proton transfer

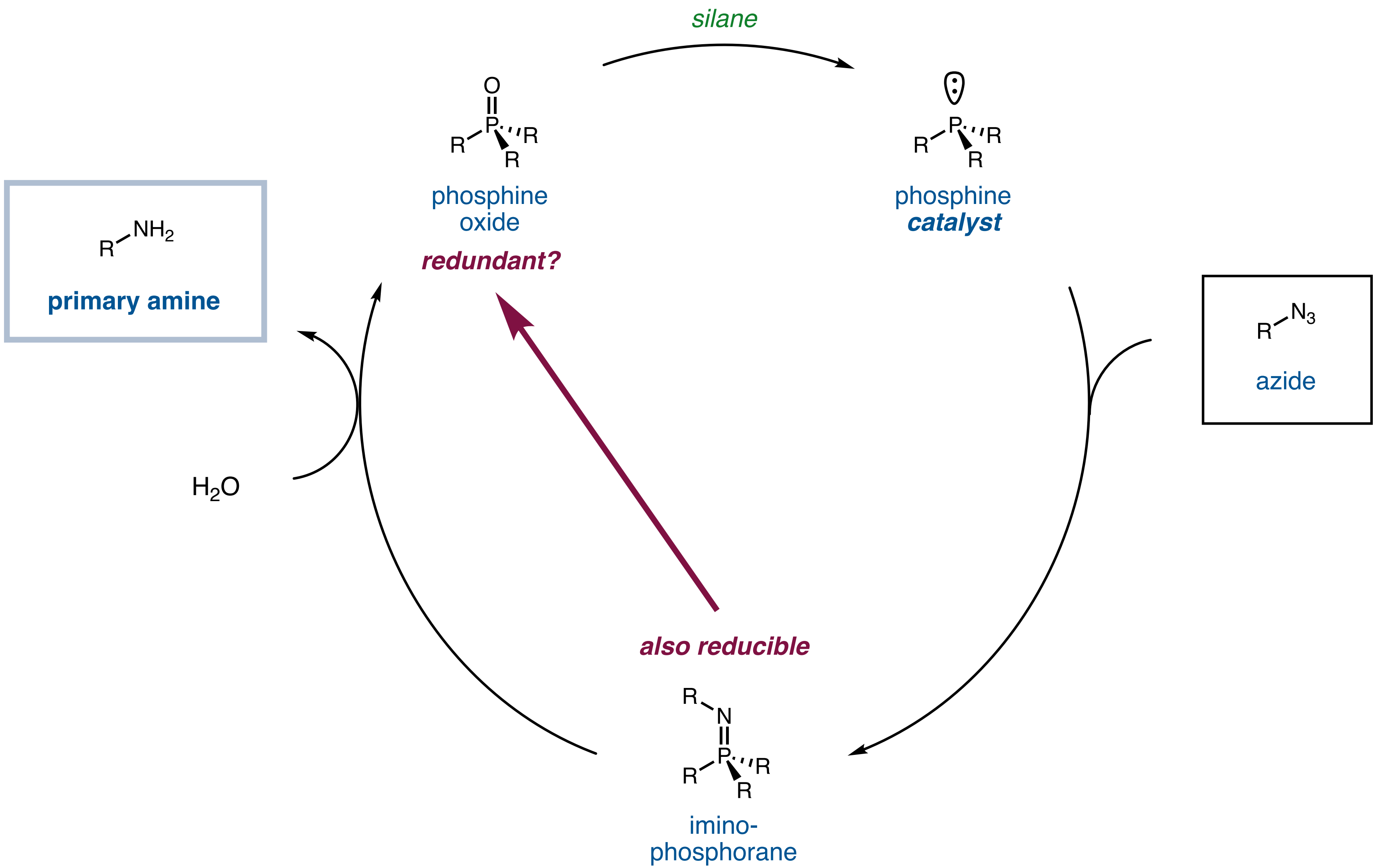


Werner, T.; Hoffman, M.; Deshmukh, S. *Eur. J. Org. Chem.* **2014**, 6630.
Schirmer, M.-L.; Adomeit, S.; Werner, T. *Org. Lett.* **2015**, *17*, 3078.

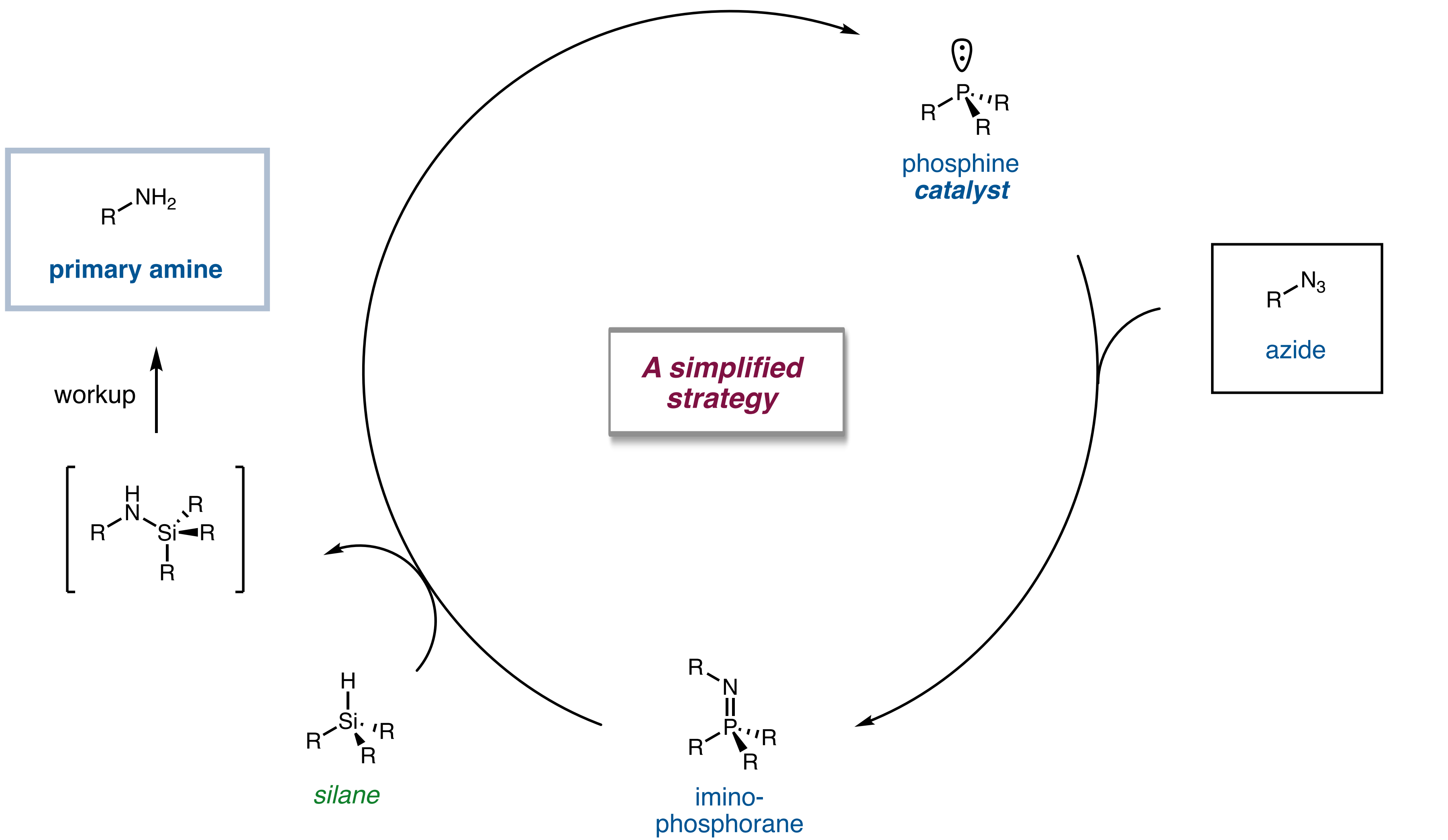
Catalytic Wittig Reaction



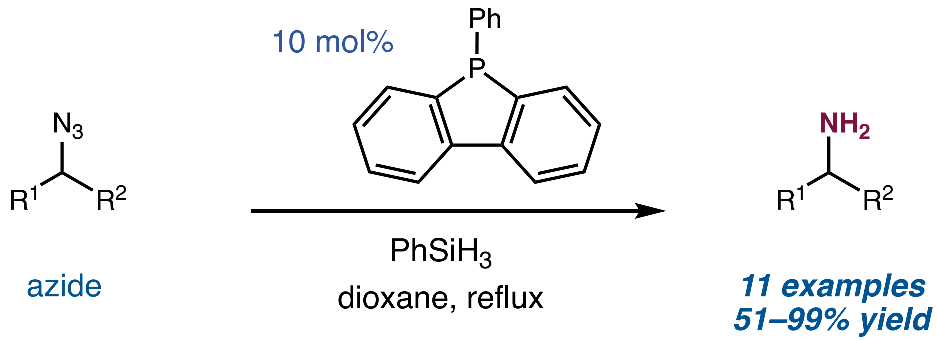
A Potential Catalytic Staudinger Reduction

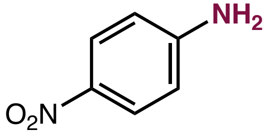


An Alternate Potential Catalytic Staudinger Reduction

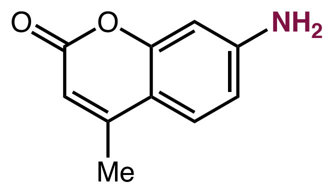


Substrate Scope for Catalytic Staudinger Reduction

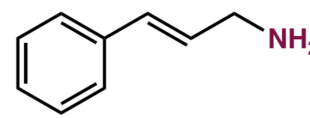




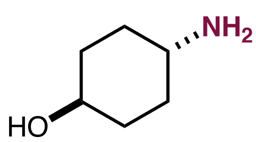
80% yield



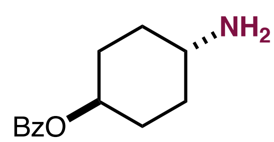
93% yield



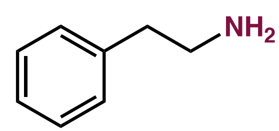
74% yield



99% yield



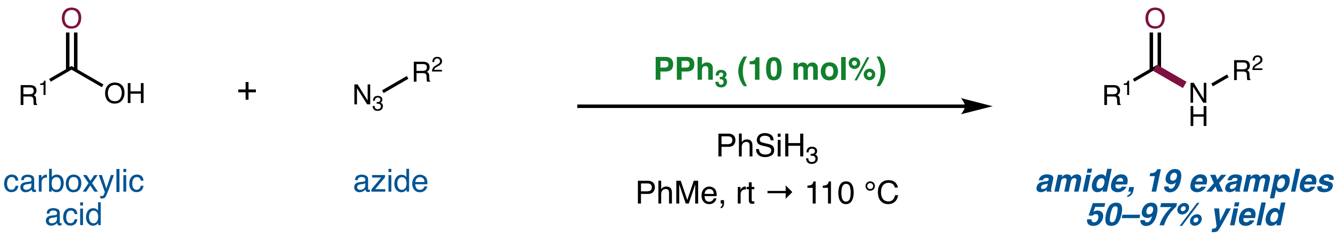
85% yield

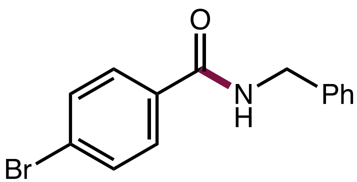


71% yield

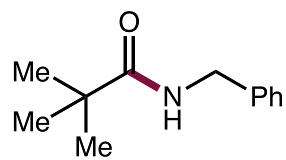
van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. *Adv. Synth. Catal.* **2012**, *354*, 1417.

Catalytic Staudinger Ligation

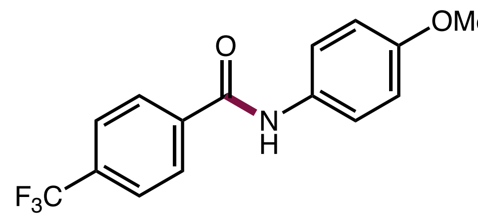




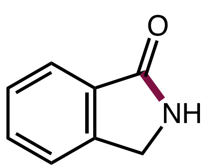
95% yield



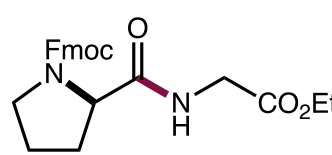
61% yield



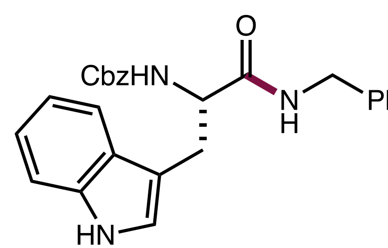
80% yield



77% yield



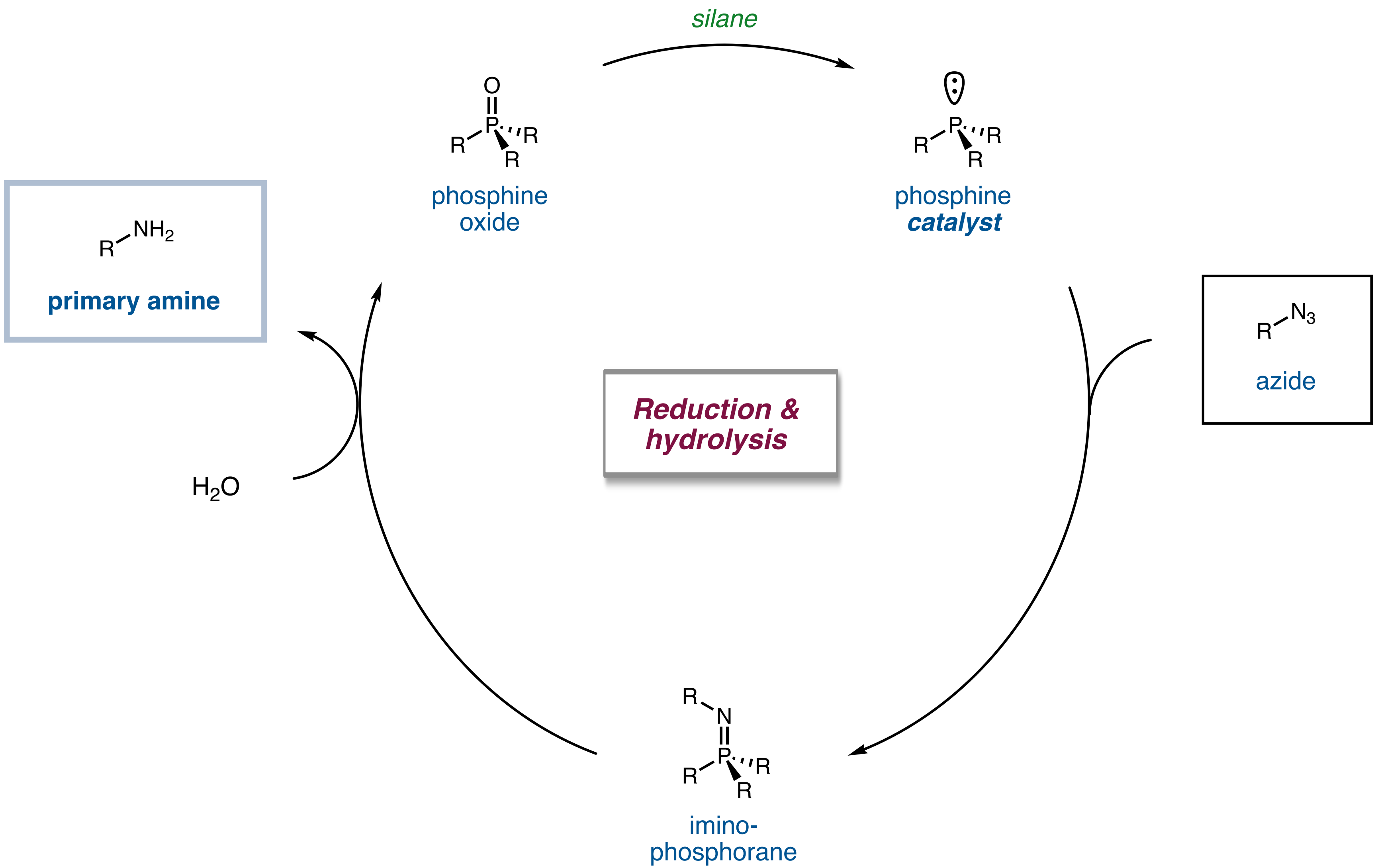
60% yield



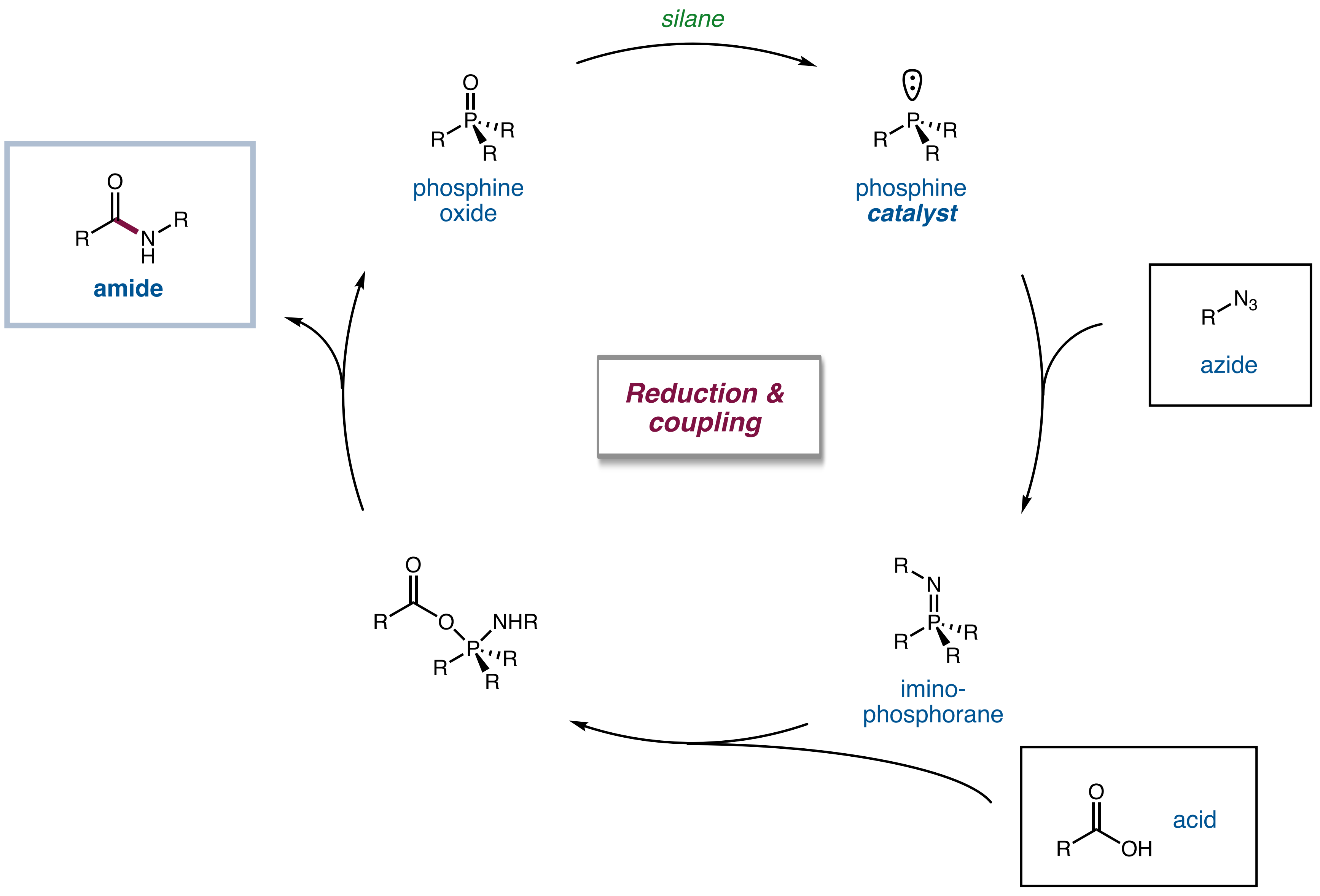
50% yield

Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12036.

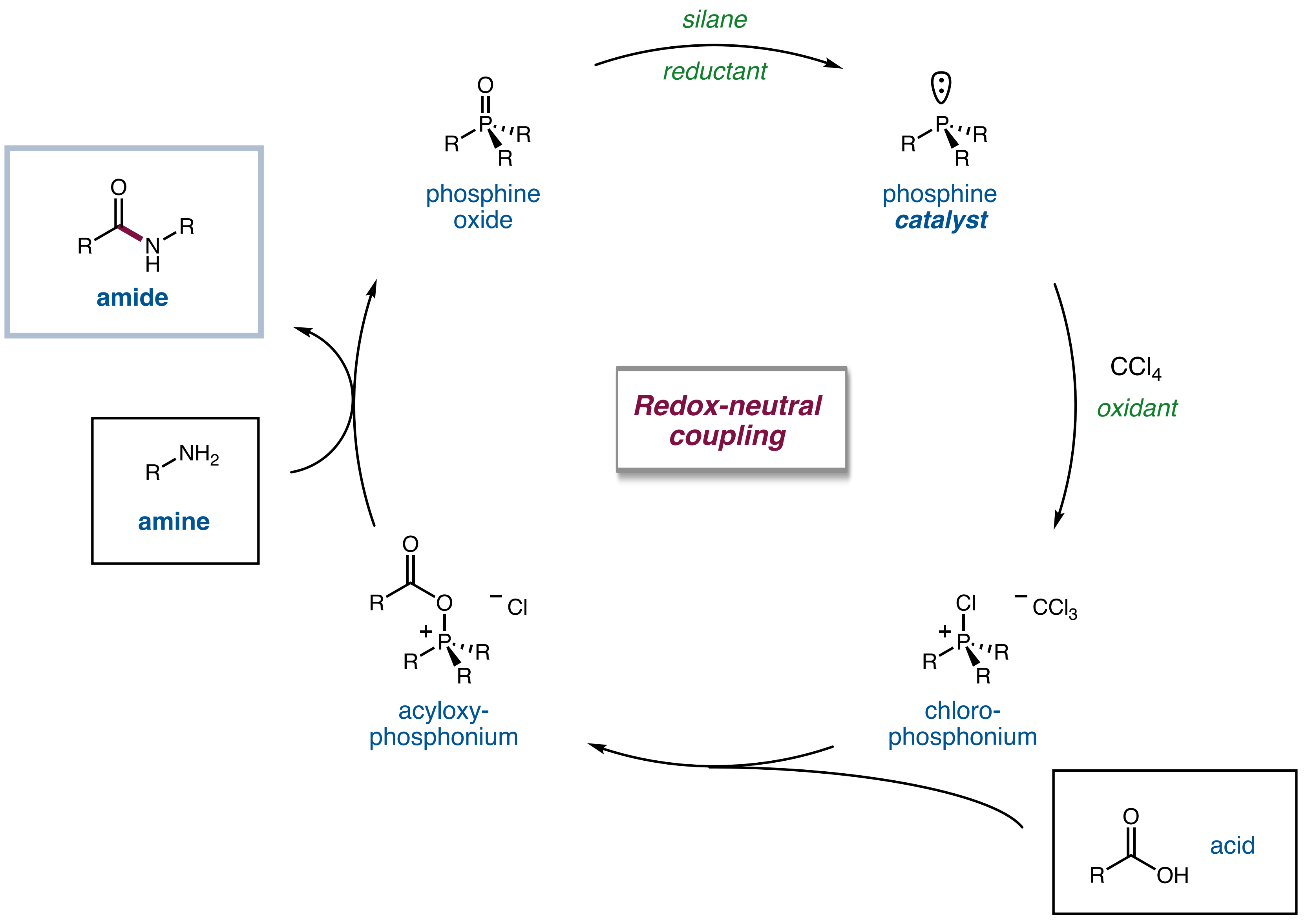
A Potential Catalytic Staudinger Reduction



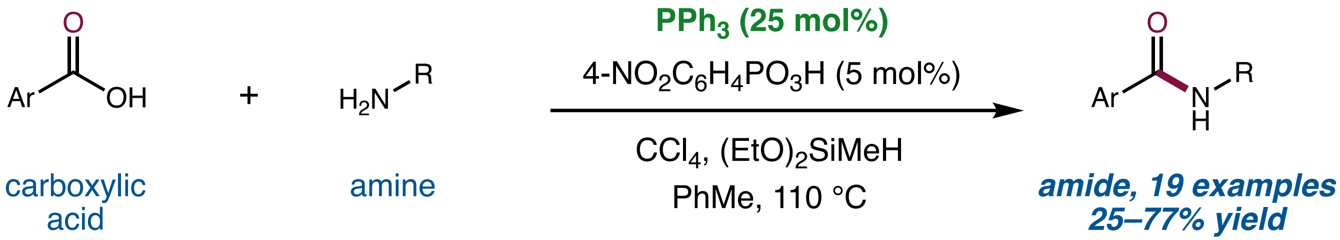
Catalytic Staudinger Ligation

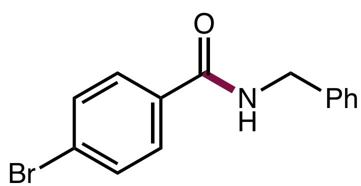


Phosphine-Catalyzed Amide Coupling

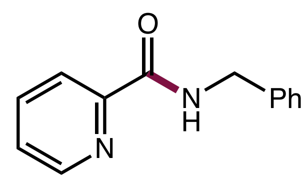


Catalytic Amidation

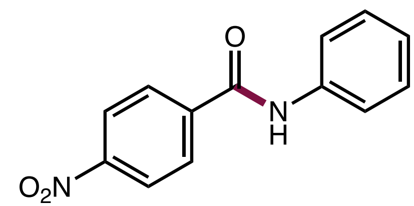




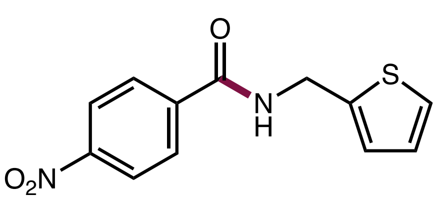
68% yield



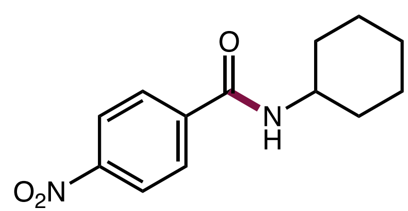
76% yield



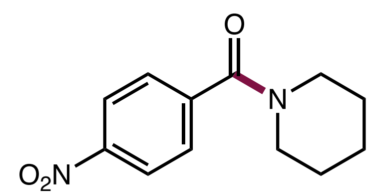
25% yield



58% yield



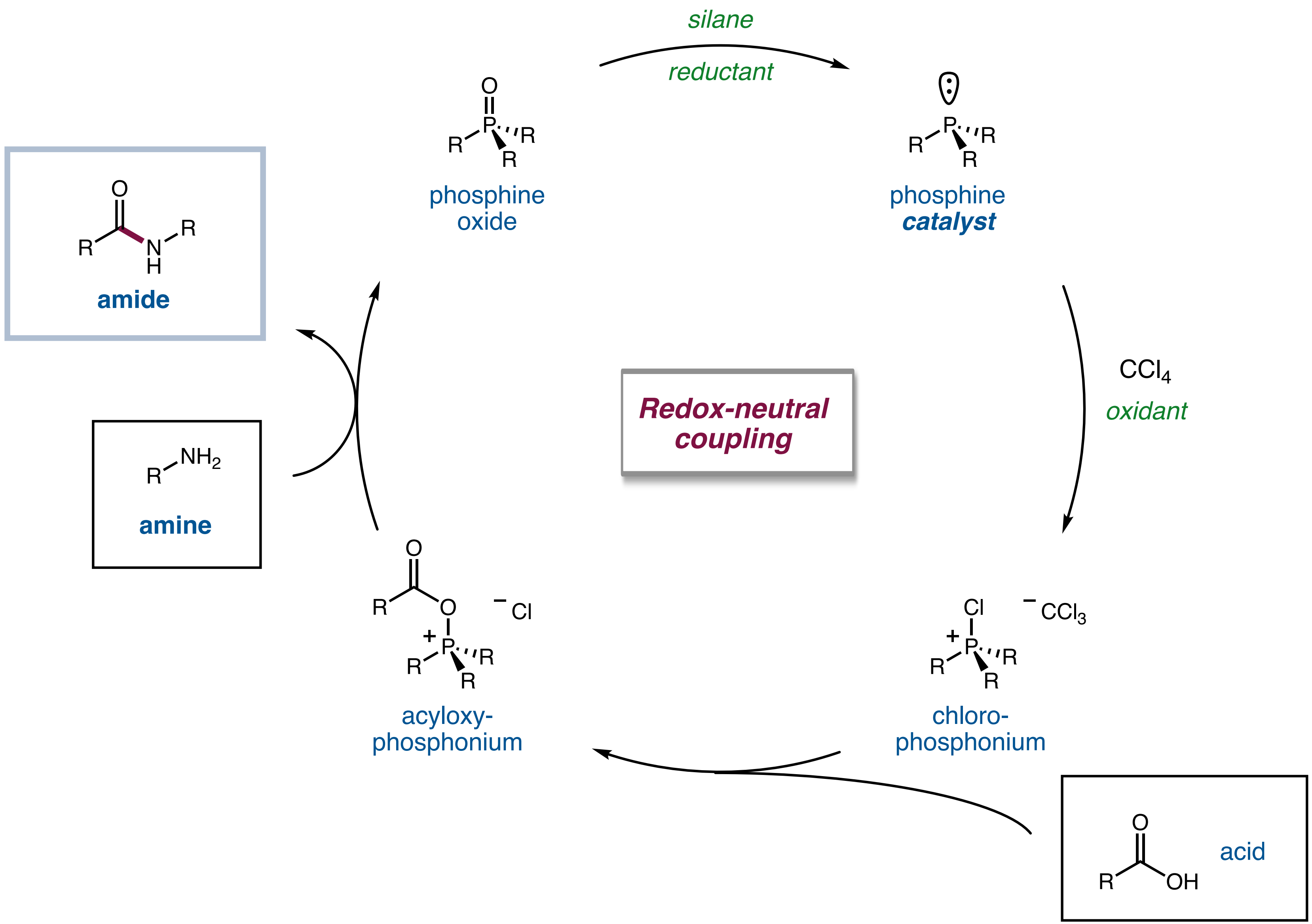
48% yield



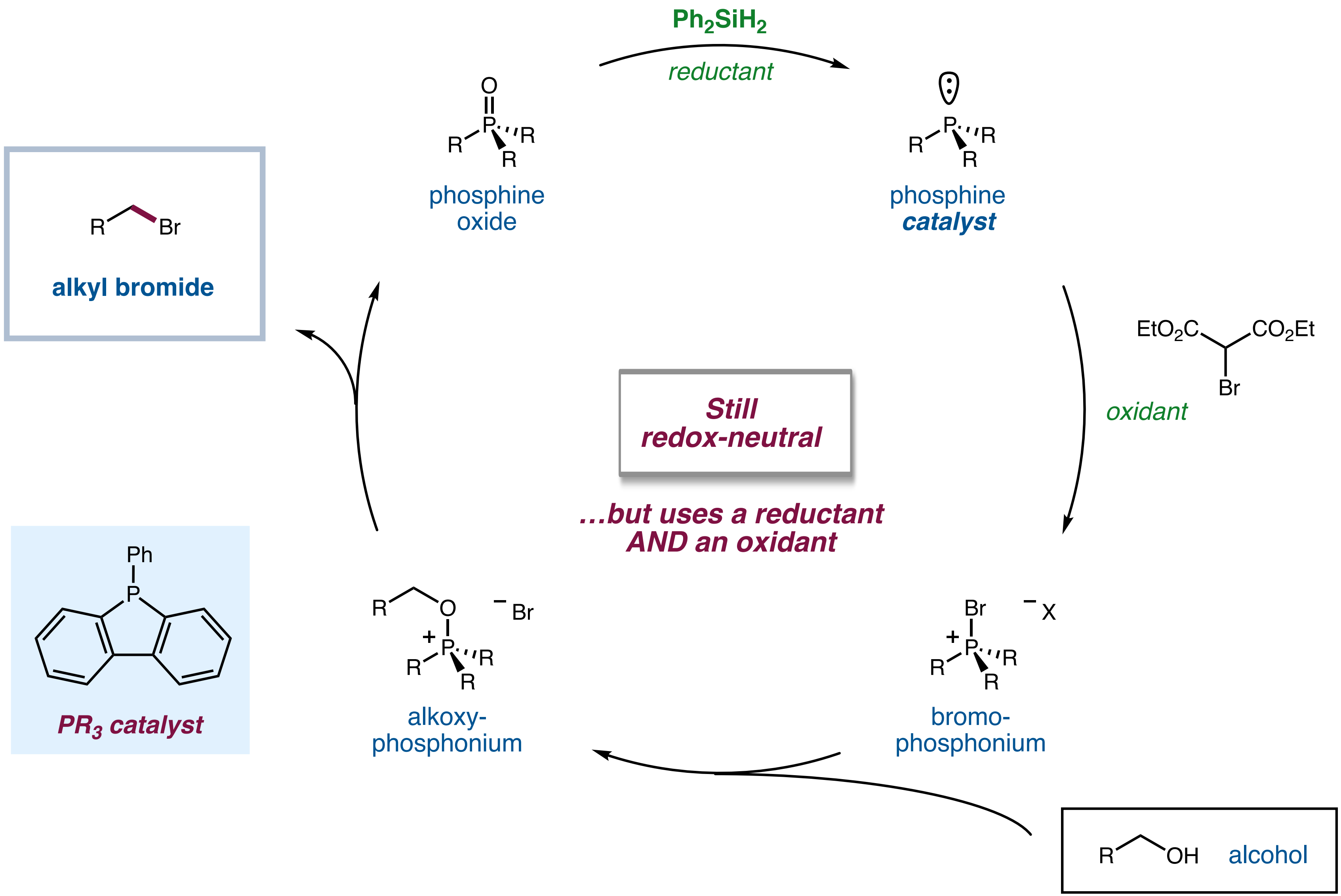
77% yield

Lenstra, D. C.; Rutjes, F. P. J. T.; Mecinović, J. *Chem. Commun.* **2014**, *50*, 5763.

Phosphine-Catalyzed Amide Coupling

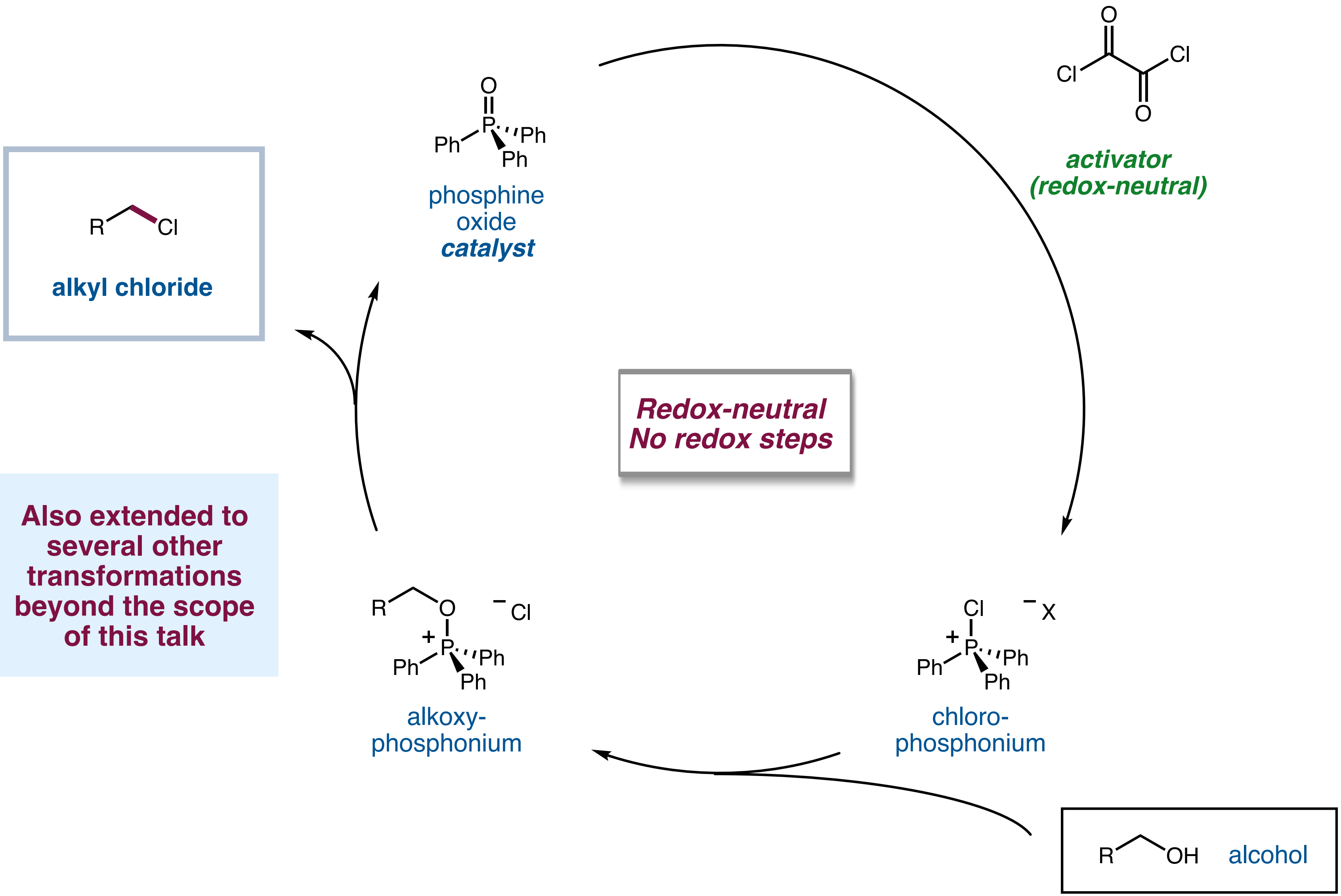


Phosphine-Catalyzed Appel Reaction



van Kalkeren, H. A.; Leenders, S. H. A. M.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Eur. J.* **2011**, *17*, 11290.

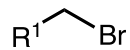
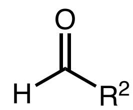
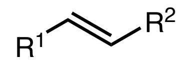
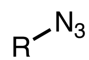
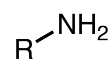
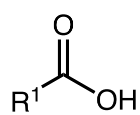
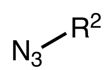
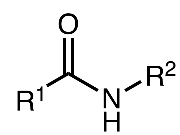
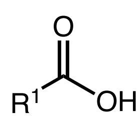
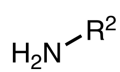
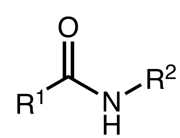
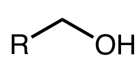
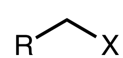
Phosphine Oxide-Catalyzed Appel Reaction



Also extended to several other transformations beyond the scope of this talk

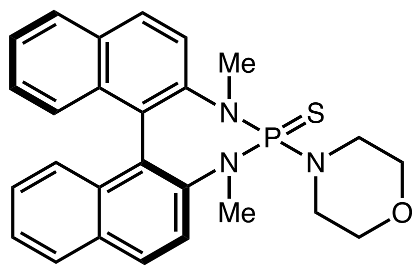
Denton, R. M.; An, J.; Adeniran, B. *Chem. Commun.* **2010**, *46*, 3025.

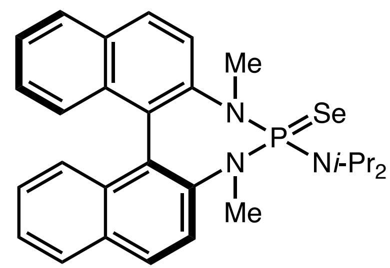
New Phosphine-Catalyzed Transformations

Reaction type	Reactant(s)	Product	Reagent(s)
Wittig reaction	 alkyl halide;  aldehyde	 olefin	silane (reductant) base
Staudinger reduction	 azide	 amine	silane (reductant)
Staudinger ligation	 acid;  azide	 amide	silane (reductant)
Amide coupling	 acid;  amine	 amide	silane (reductant) CCl_4 (oxidant)
Appel reaction	 alkyl halide	 alkyl halide	silane (reductant) bromomalonate (oxidant) OR oxalyl chloride

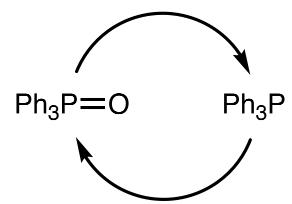
Outline

Part I: Enantioselective Nucleophilic Catalysis with Phosphine Chalcogenides

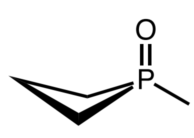


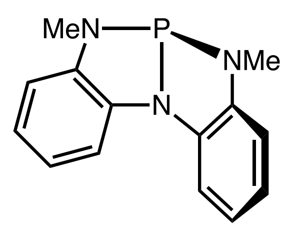


Part II: Recycling Phosphorus in Classical Reactions



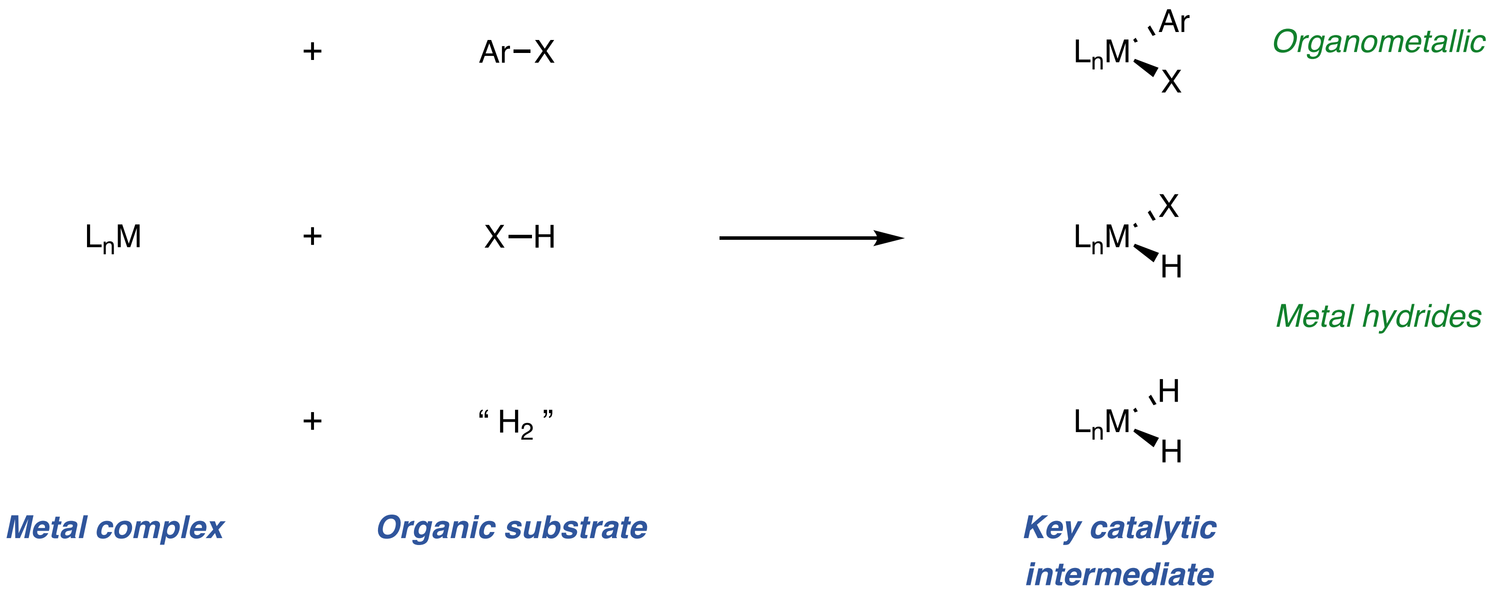
Part III: Strained Phosphines





Catalytic Substrate Activation with Transition Metal Complexes

Oxidative addition



Further reactions of these intermediates enable a broad range of important transformations

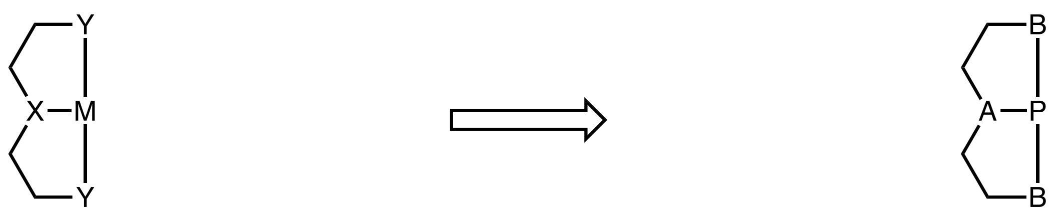
> ***This activation mode is almost completely beyond the capacity of main group catalysts***

Main Group Catalysis in the Radosevich Group

Alex Radosevich

Joined faculty in 2010

■ **Phosphorus compounds inspired by metal pincer complexes**



Metal pincer complex
M = Rh, Ir, Pd, Pt, etc.

Important catalyst template

Phosphorus "pincer complex"

- ***Sustainable alternative to precious metals?***
- ***Basis for discovering new reactivity?***

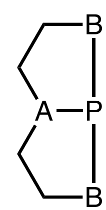
Main Group Catalysis in the Radosevich Group

Alex Radosevich

Joined faculty in 2010

- **Phosphorus compounds inspired by metal pincer complexes**

> **"Guided by the precept that molecular geometry dictates electronic structure, we attempt to enforce nontrigonal geometries on tricoordinate P(III) compounds in order to [colocalize] both electron-donor and -acceptor behavior at a single catalytic site."**
>
> ***-Group website***



Phosphorus "pincer complex"

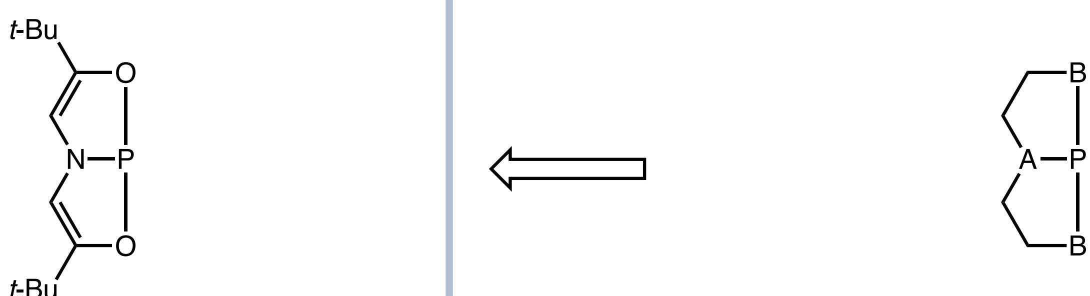
- ***Sustainable alternative to precious metals?***
    - ***Basis for discovering new reactivity?***

Main Group Catalysis in the Radosevich Group

Alex Radosevich

Joined faculty in 2010

- **Phosphorus compounds inspired by metal pincer complexes**



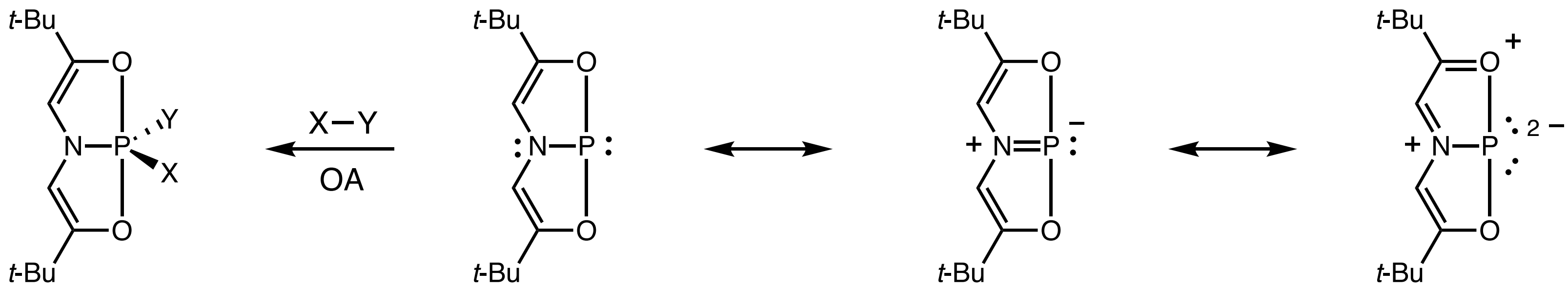
"Tricoordinate hypervalent P compound"
First prepared and studied by Arduengo

Phosphorus "pincer complex"

- ***Sustainable alternative to precious metals?***
- ***Basis for discovering new reactivity?***

Novel P^{III}/P^{V} Redox Cycling

■ A structure well-poised for oxidative addition?



Excess e⁻s in new bonds

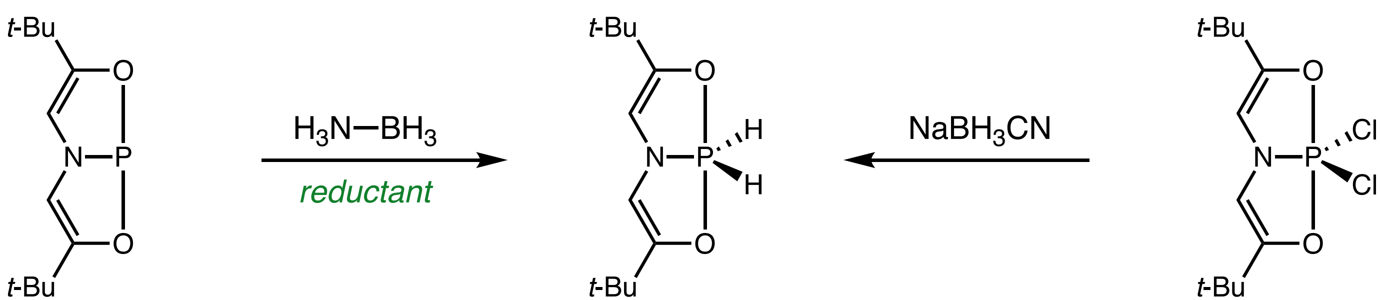
Strain release

Electron-rich P atom

Strained P atom

Important contributors

■ Novel access to a dihydridophosphorane



P^{III} compound

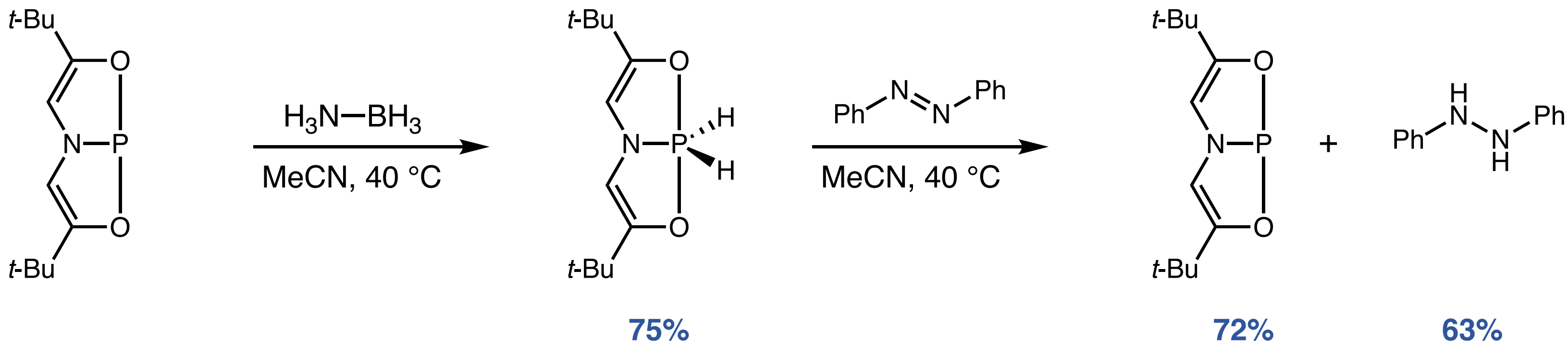
P^{V} compound (oxidized)

- ***X-ray***
- ***Independent synthesis***

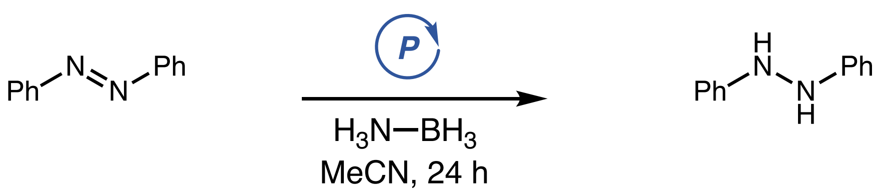
Dunn, N. L.; Ha, M.; Radosevich, A. T. *J. Am. Chem. Soc.* **2012**, *134*, 11330.

Novel P^{III}/P^{V} Redox Cycling

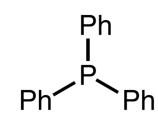
Stepwise transfer hydrogenation



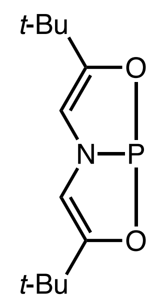
Catalytic transfer hydrogenation



no catalyst, 80 °C
< 5% yield



100 mol%, 80 °C
< 5% yield

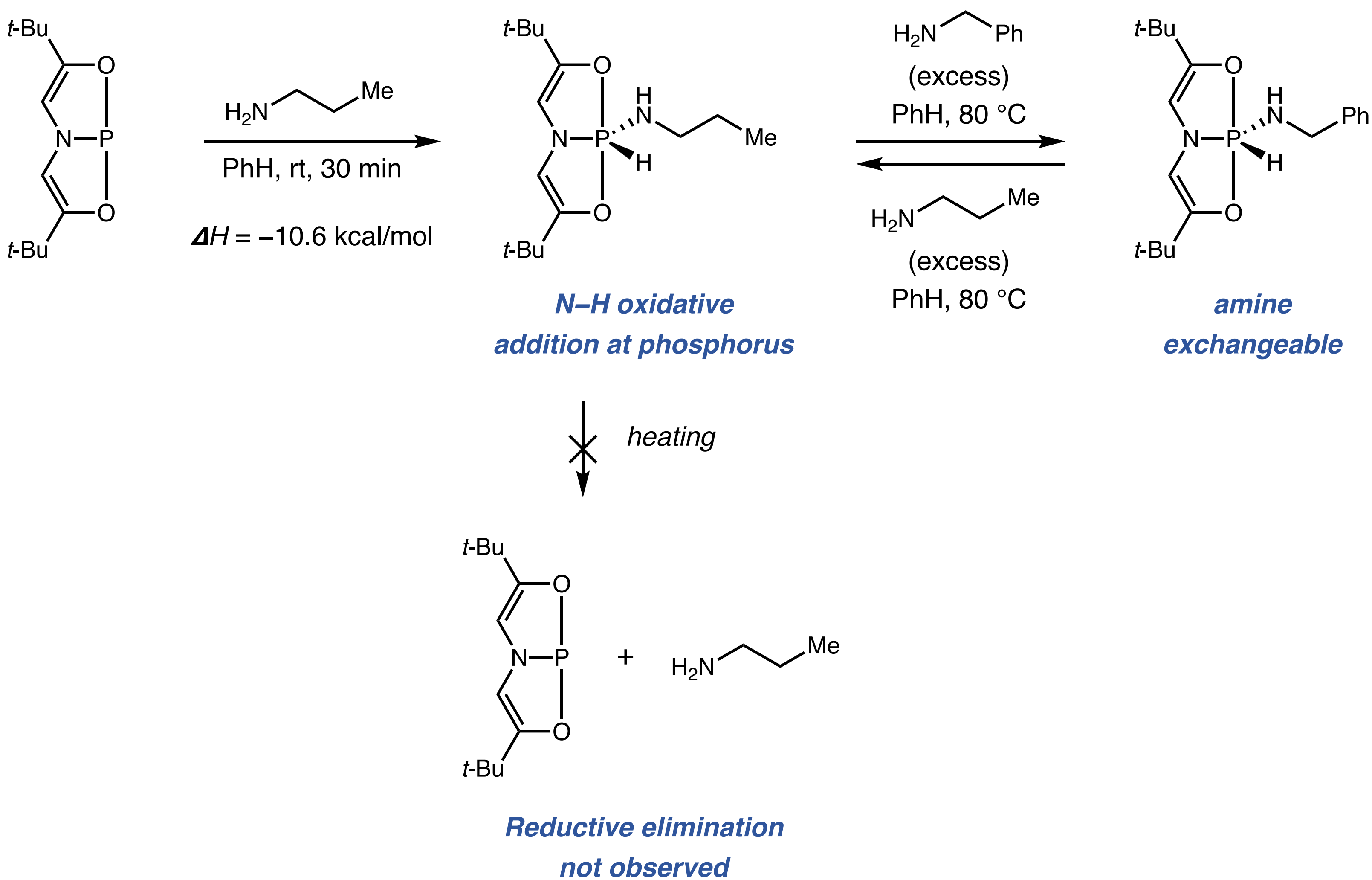


10 mol%, 40 °C
80% yield

Dunn, N. L.; Ha, M.; Radosevich, A. T. *J. Am. Chem. Soc.* **2012**, *134*, 11330.

Novel P^{III}/P^{V} Redox Activation

A novel oxidative addition reaction

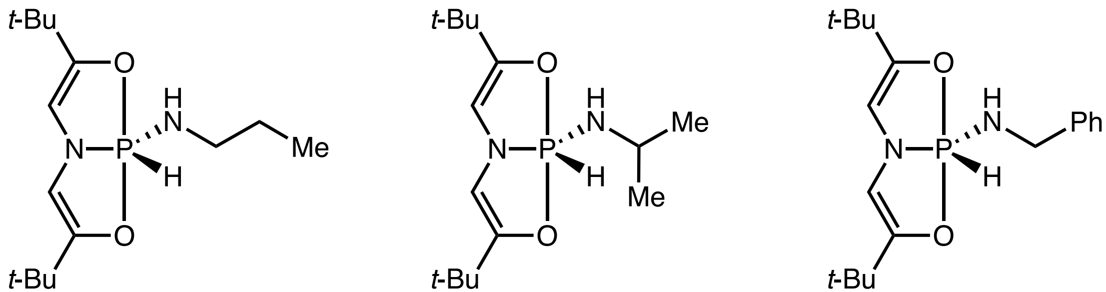


McCarthy, S. M.; Lin, Y.-C.; Devarajan, D.; Chang, J. W.; Yennawar, H. P.; Rioux, R. M.; Ess, D. H.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.

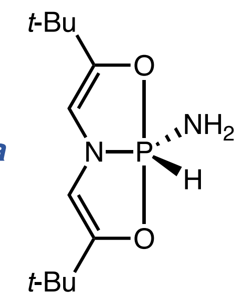
Novel P^{III}/P^{V} Redox Activation

■ General for a broad range of N–H substrates

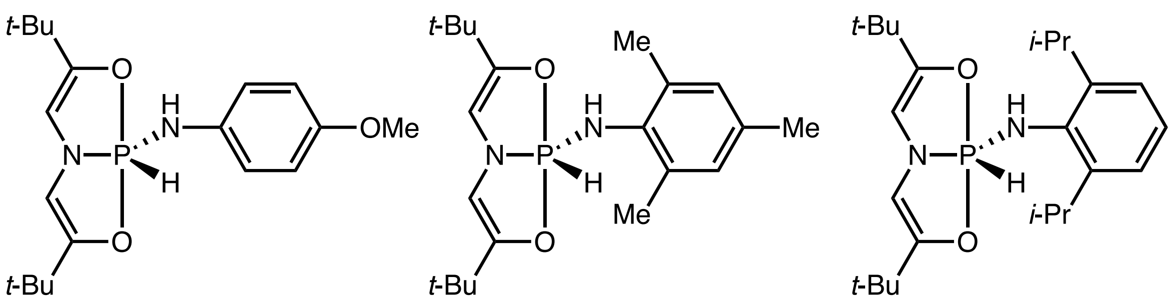
alkyl amines



ammonia



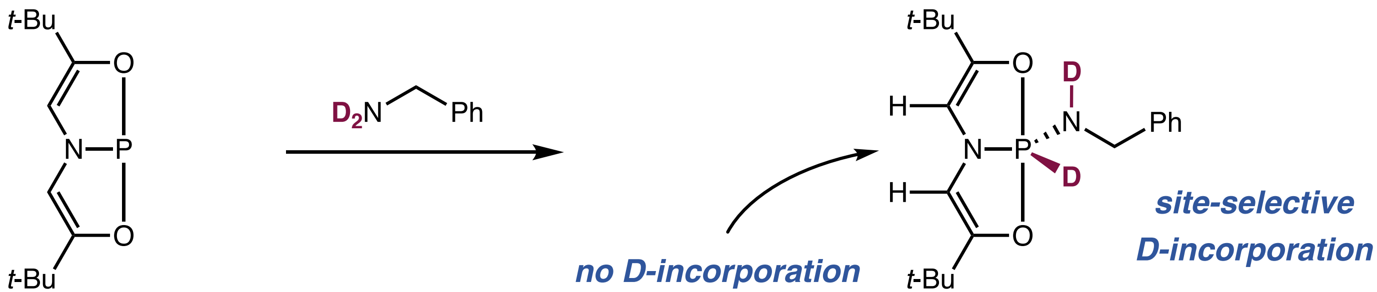
anilines



McCarthy, S. M.; Lin, Y.-C.; Devarajan, D.; Chang, J. W.; Yennawar, H. P.; Rioux, R. M.; Ess, D. H.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.

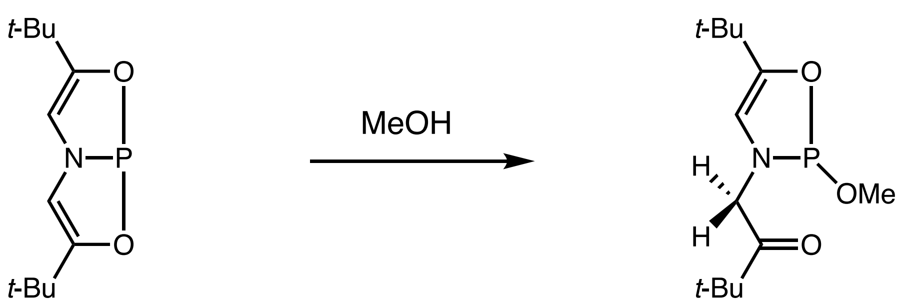
Novel P^{III}/P^{V} Redox Activation

■ Mechanistic experiments: D-incorporation



Ligand probably not involved in N–H bond breaking

■ In contrast to reactivity with O–H substrates

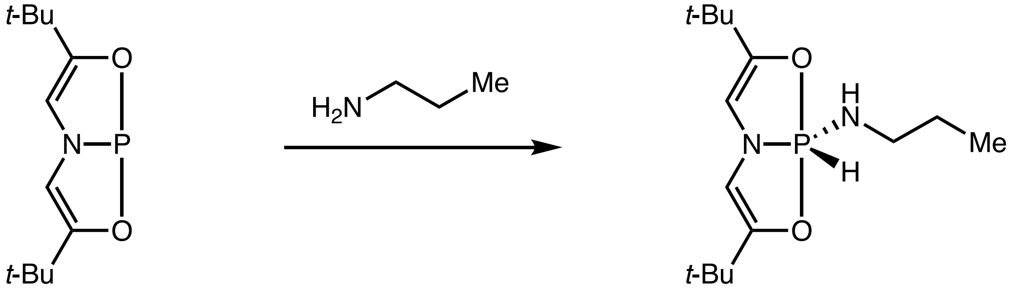


■ ***Also observed with other alcohols, phenols, and TfOH***

McCarthy, S. M.; Lin, Y.-C.; Devarajan, D.; Chang, J. W.; Yennawar, H. P.; Rioux, R. M.; Ess, D. H.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.
Arduengo, A. J. III; Stewart, C. A.; Davidson, F.; Dixon, D. A.; Becker, J. Y.; Cul;ley, S. A.; Mizen, M. B. *J. Am. Chem. Soc.* **1987**, *109*, 627.

Novel P^{III}/P^{V} Redox Activation

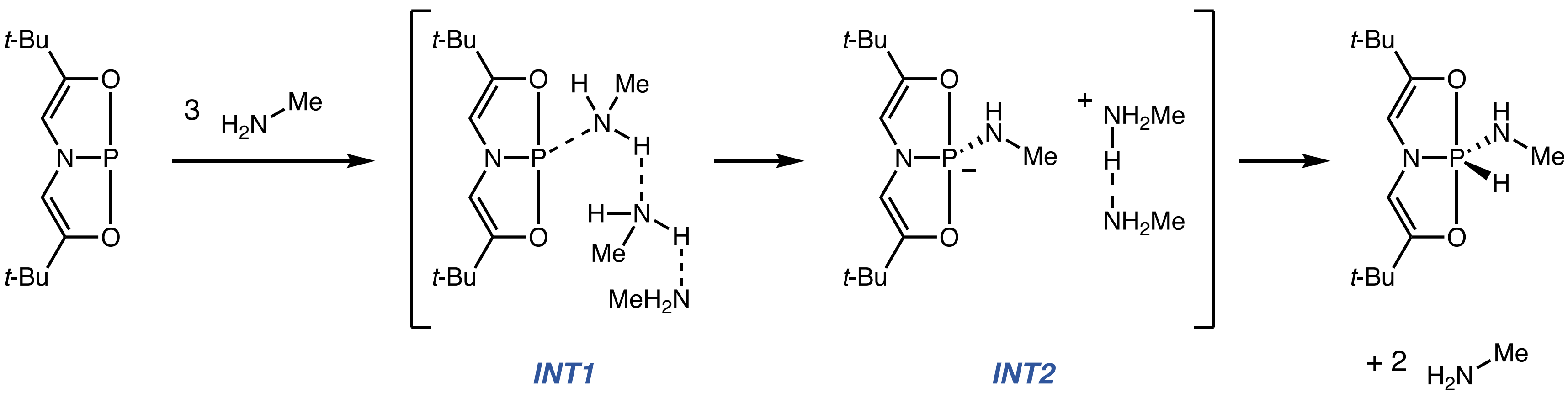
Mechanistic experiments: kinetics



Rate = k[P^{III}]^1[H_2NPr]^3

3rd-order in amine!

Calculations suggest additional amines are needed for proton transfer



INT1
N→P adduct

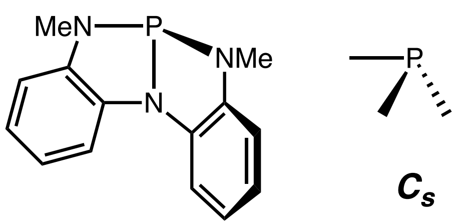
INT2
amidophosphoranide anion

- ***Energies are prohibitively high without additional amines***
- ***Mechanism reflects the electrophilicity of the P^{III} center***

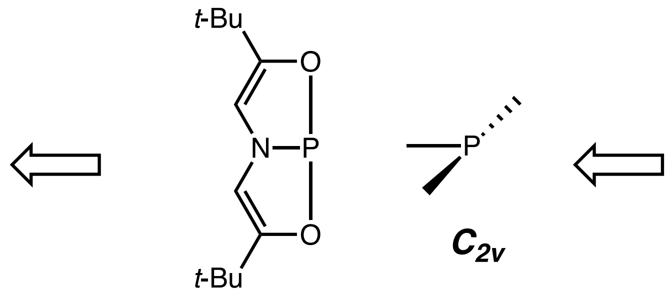
McCarthy, S. M.; Lin, Y.-C.; Devarajan, D.; Chang, J. W.; Yennawar, H. P.; Rioux, R. M.; Ess, D. H.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 4640.

Novel P^{III}/P^{V} Reactivity

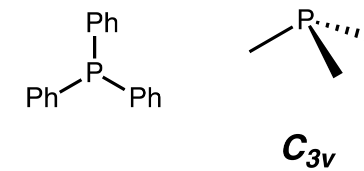
Next steps?



New P framework



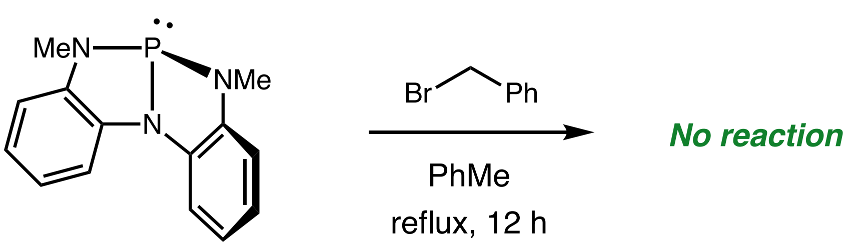
Arduengo 10-P-3



Conventional phosphine

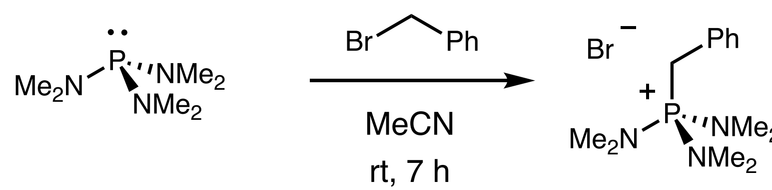
- ***Prepared on multigram scale***
- ***Study of key fundamental properties***

Poorly nucleophilic



Lone pair: 65% s-character (NBO)

Compare to

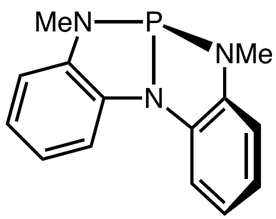


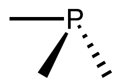
90% isolated yield

Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 17634.

Novel P^{III}/P^{V} Reactivity

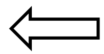
Next steps?

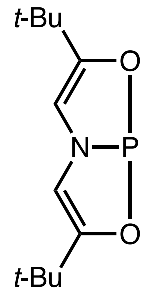


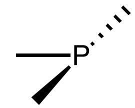


C_s

New P framework

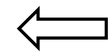


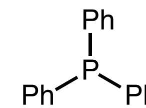


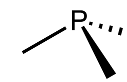


C_{2v}

Arduengo 10-P-3







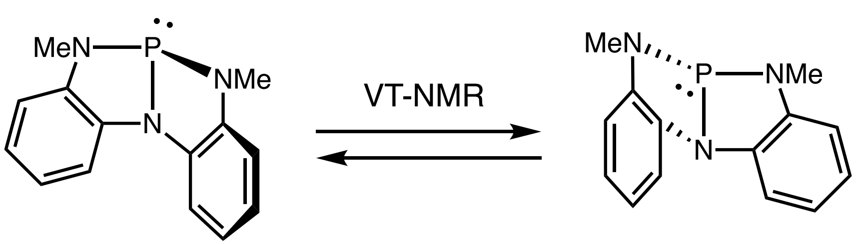
C_{3v}

Conventional phosphine

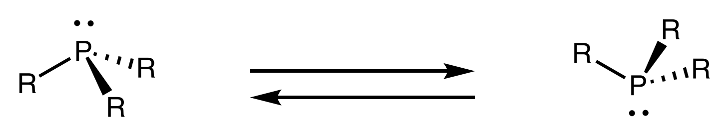
- ***Prepared on multigram scale***
- ***Study of key fundamental properties***

Low inversion barrier

Compare to typical phosphines



$\Delta G^{\ddagger 298}$ = +10.7 kcal/mol

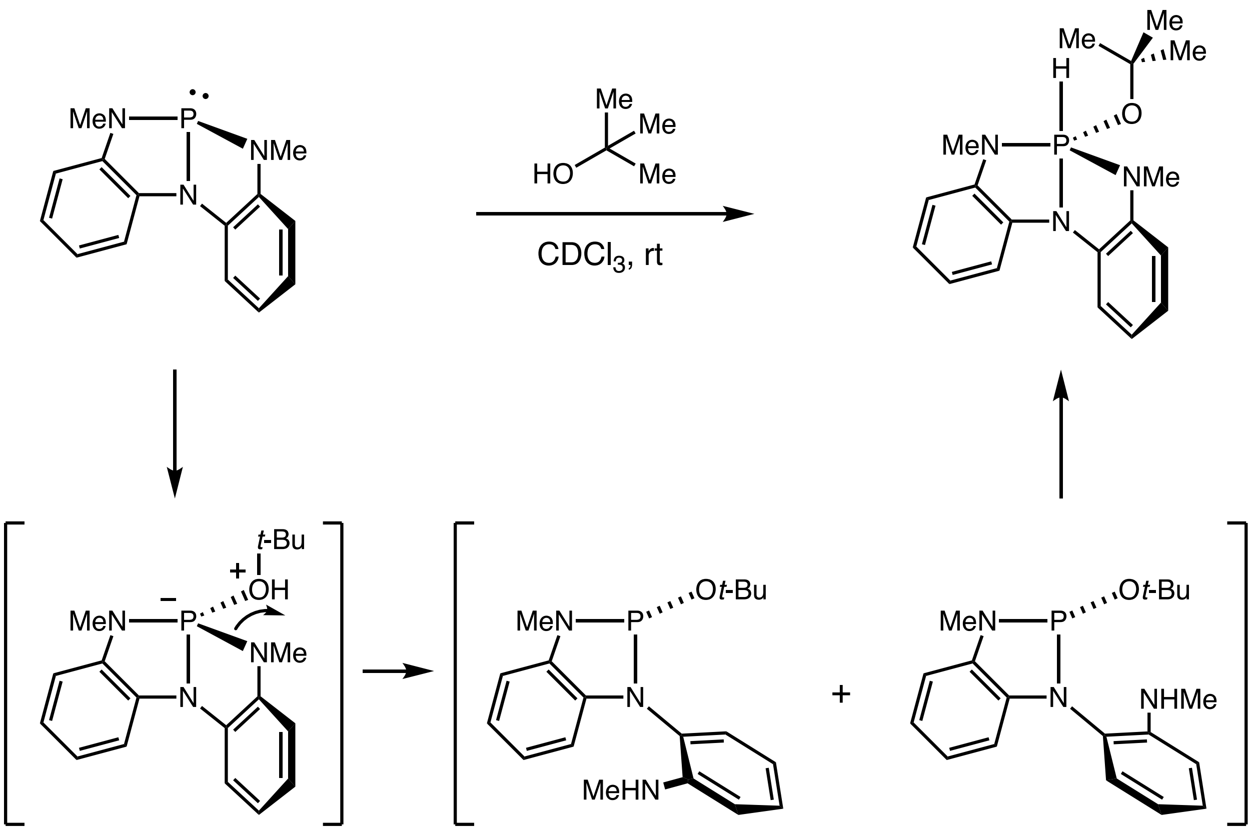


$\Delta G^{\ddagger 298}$ = +25–40 kcal/mol

Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 17634.

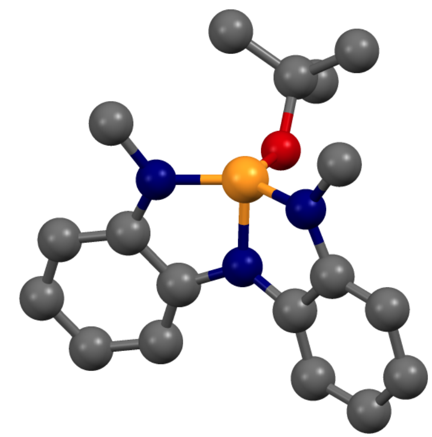
Broader P^{III}/P^{V} Oxidative Addition

■ The new phosphorus triamide also undergoes oxidative addition with X–H substrates



Presumed initial O→P adduct

Higher-energy diastereomeric intermediates observed by NMR



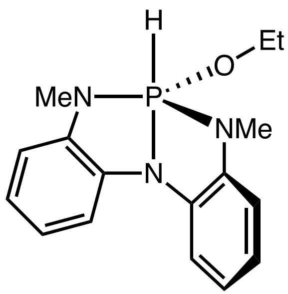
- ***X-ray structure***
- ***Reactivity not seen with Arduengo compound***

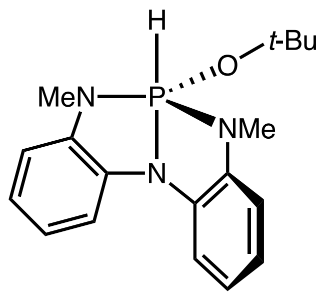
Ligand is now involved in O–H bond breaking

Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 17634.

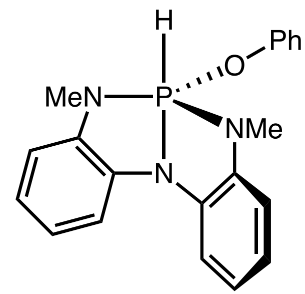
Broader P^{III}/P^{V} Oxidative Addition

■ A more diverse array of oxidative addition adducts can be obtained

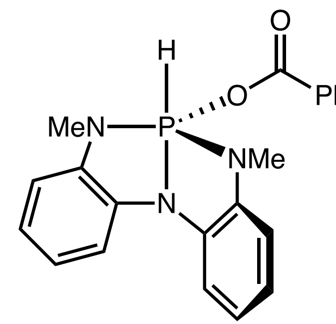




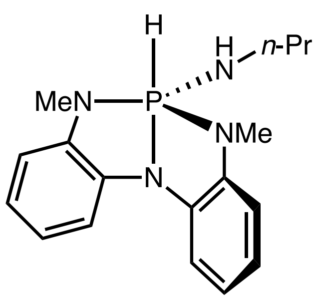
alcohols

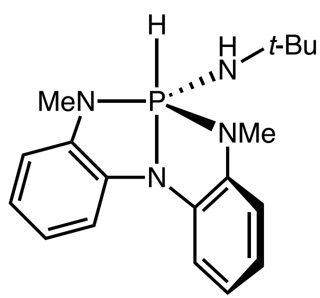


phenols

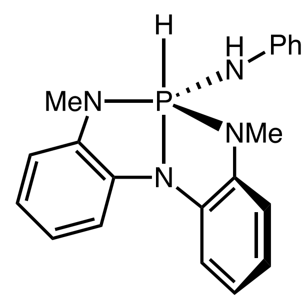


carboxylic acids

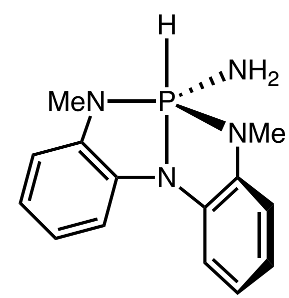




alkyl amines



anilines

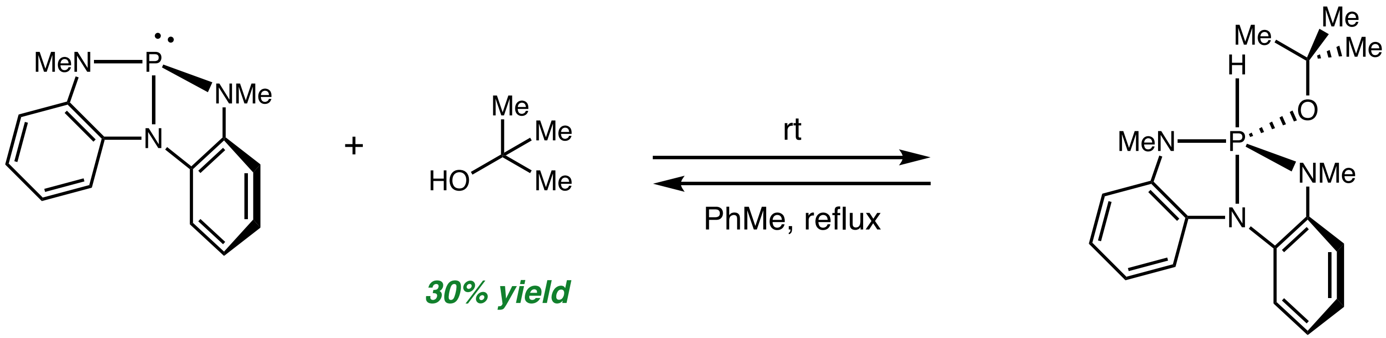


ammonia

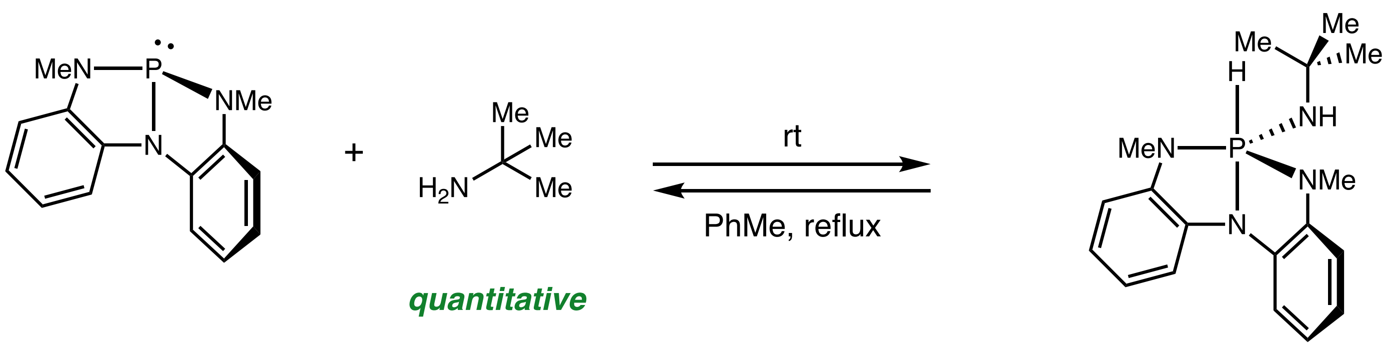
Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 17634.

Reversible P^{III}/P^{V} Oxidative Addition

■ **Starting materials can be reisolated after heating the products**



30% yield



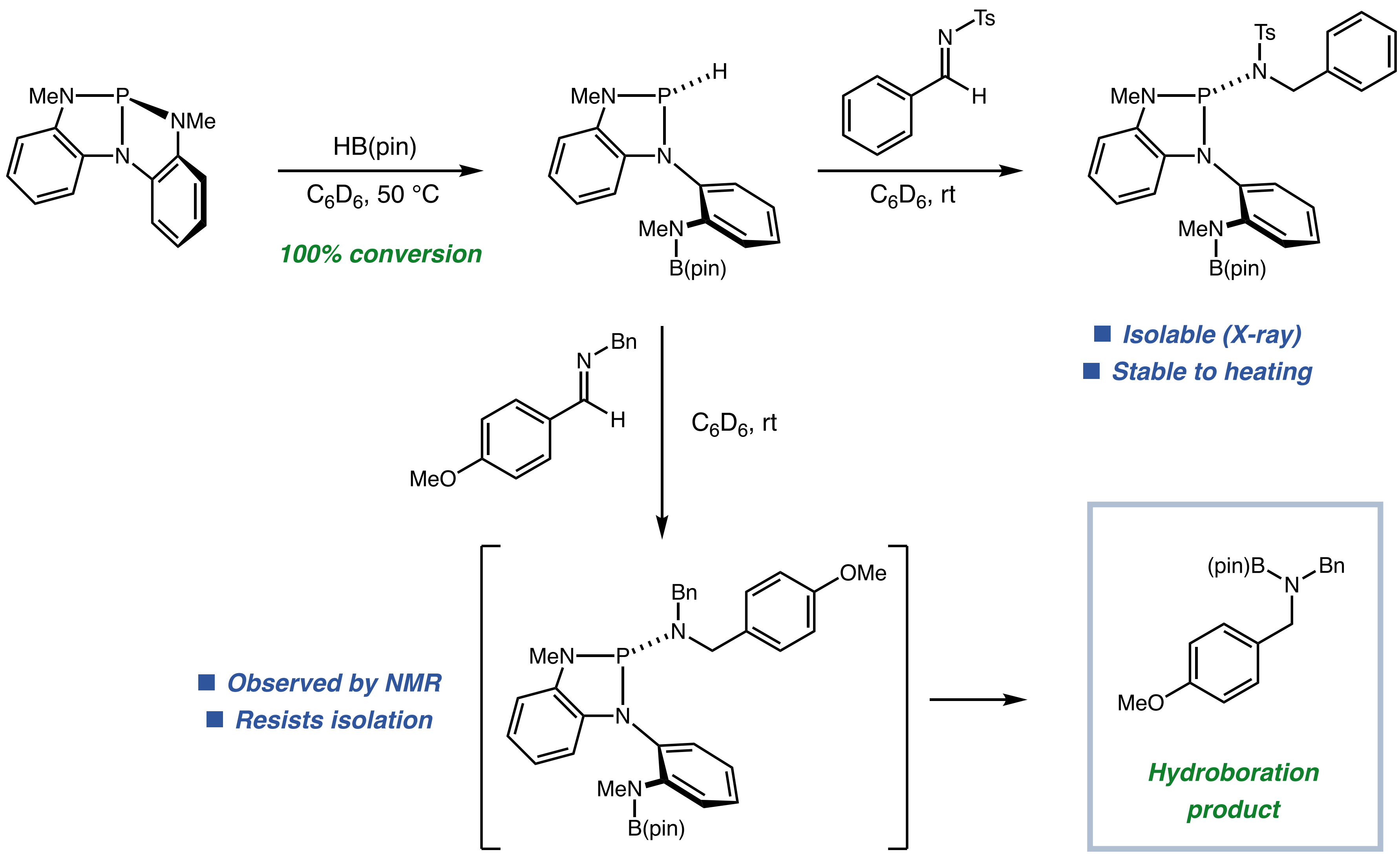
quantitative

Reductive elimination is also possible

Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 17634.

What About Catalysis?

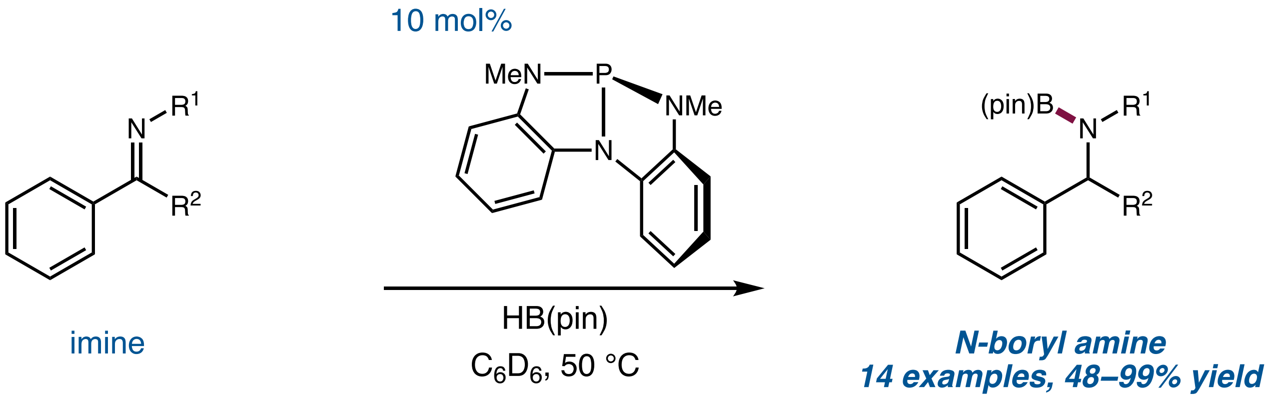
■ Boranes also add to the new phosphorus triamide giving reactive adducts

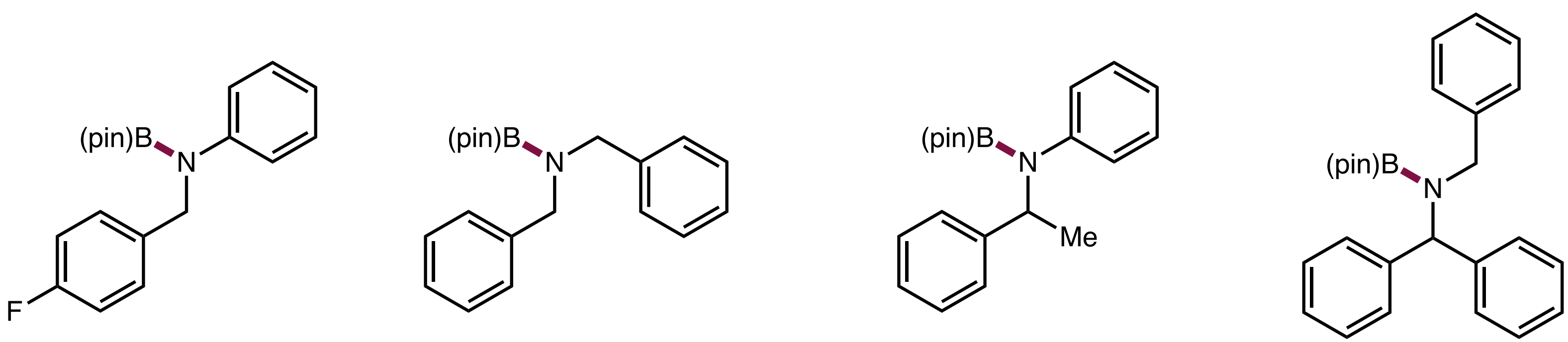


Lin, Y.-C.; Hatzakis, E.; McCarthy, S. M.; Reichl, K. D.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6008.

What About Catalysis?

Phosphorus triamide is an active transfer hydroboration catalyst



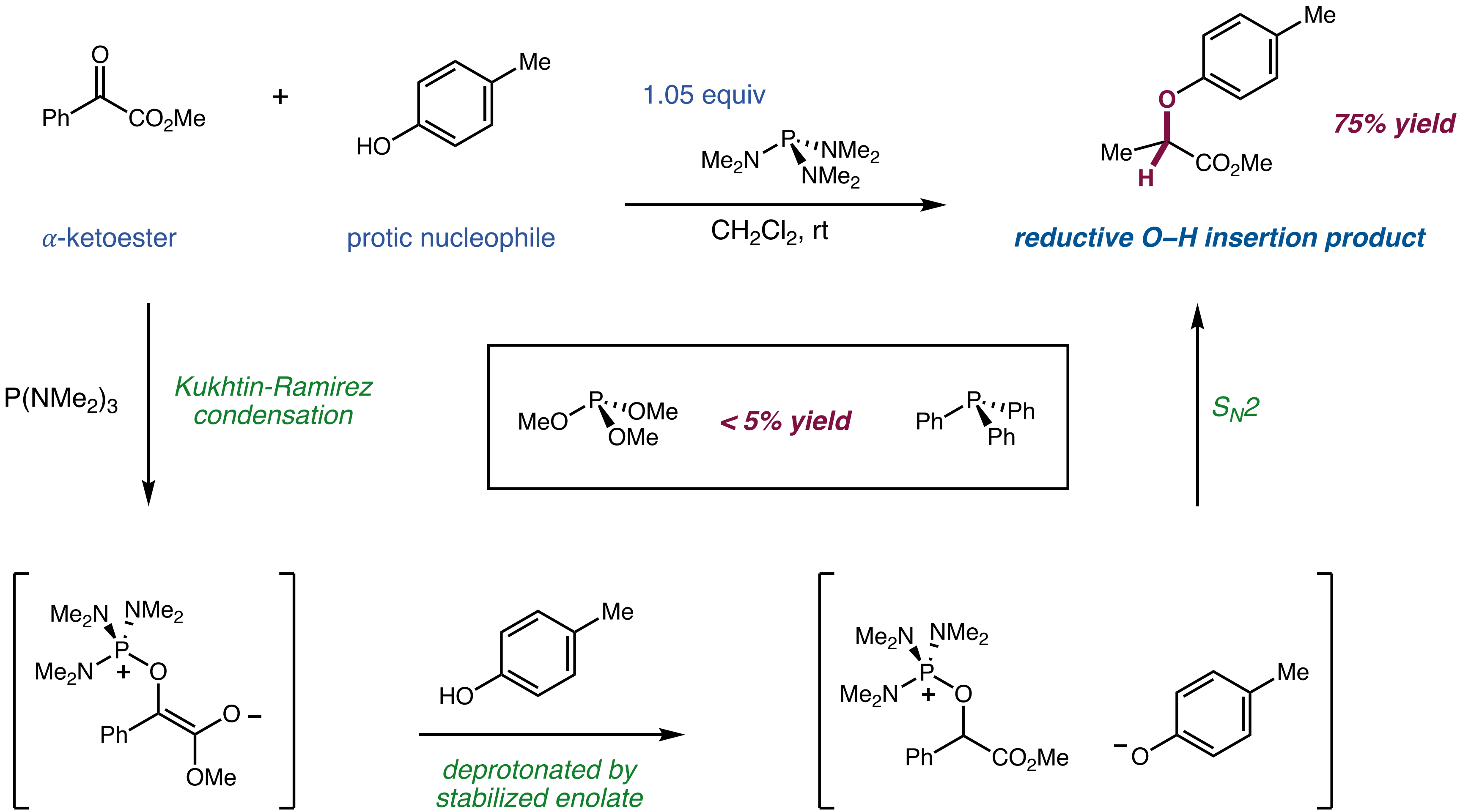


99% yield *99% yield* *99% yield* *99% yield*

Lin, Y.-C.; Hatzakis, E.; McCarthy, S. M.; Reichl, K. D.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6008.

Further Modes of P^{III}/P^{V} Catalysis

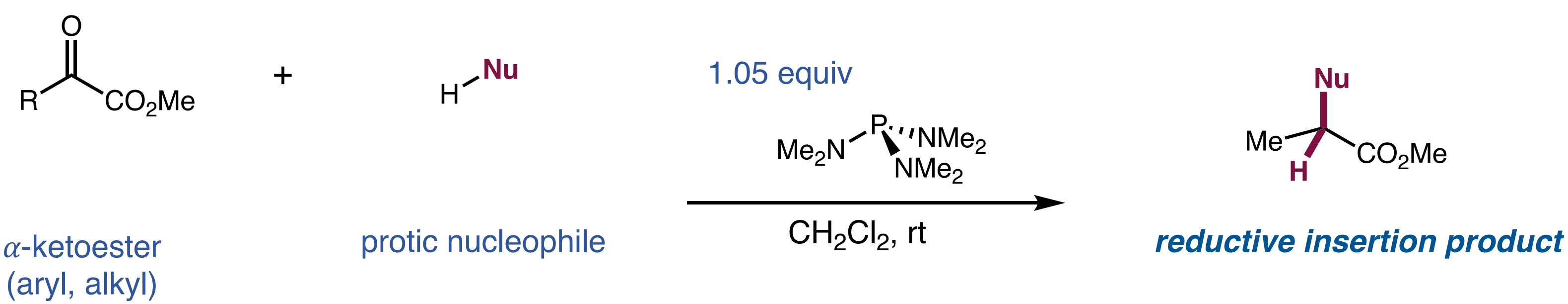
■ Reductive X–H insertion to α-ketoesters

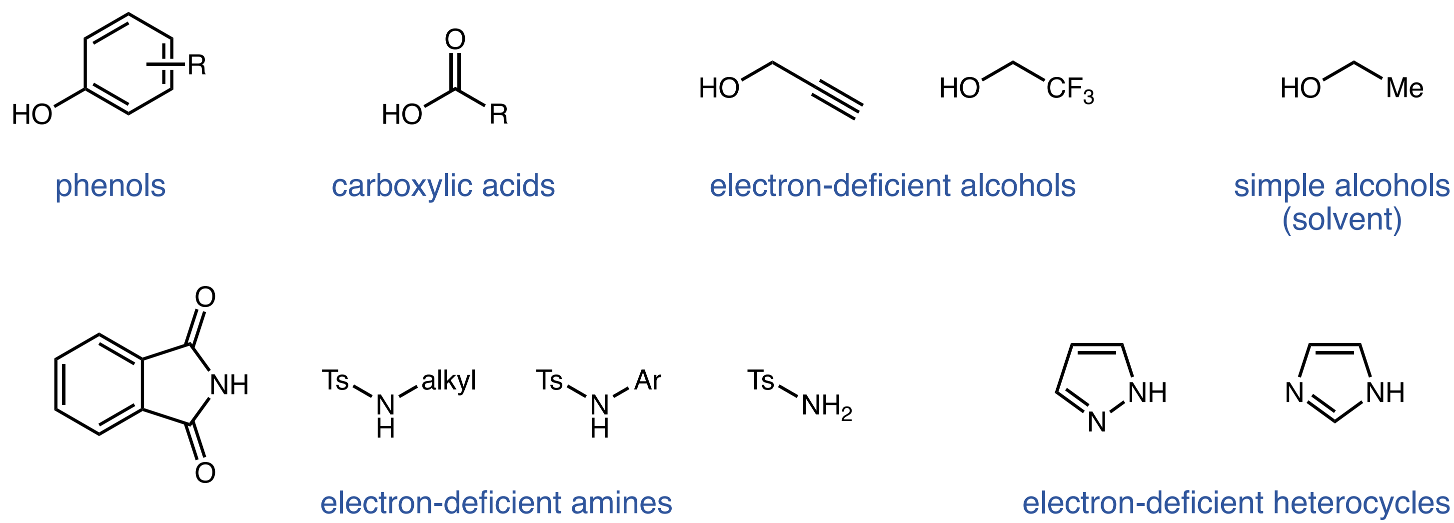


Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2013**, *51*, 10609.

Further Modes of P^{III}/P^{V} Catalysis

Nucleophile scope for reductive X–H insertion to α-ketoesters

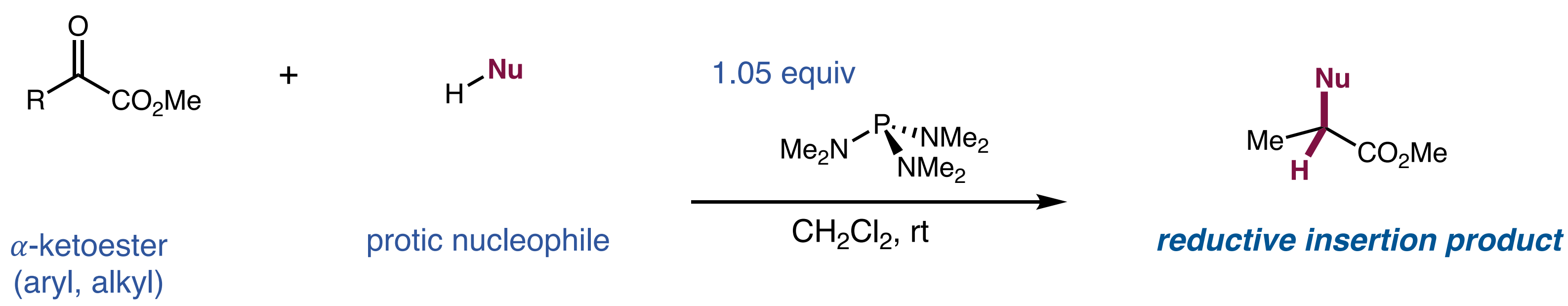


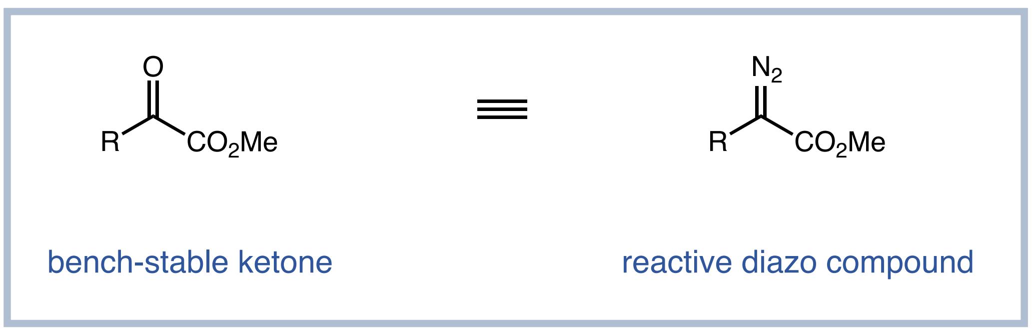


Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2013**, *51*, 10609.

Further Modes of P^{III}/P^{V} Catalysis

■ Expands the versatility of this ketone class

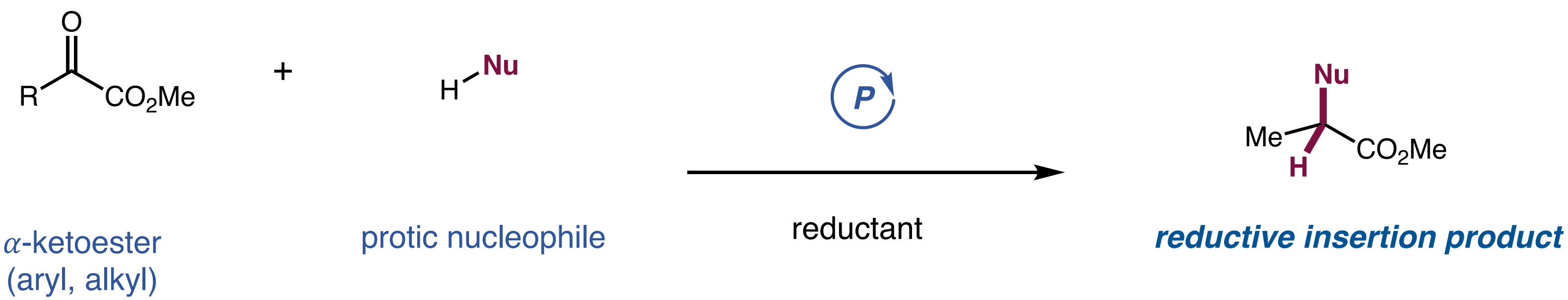




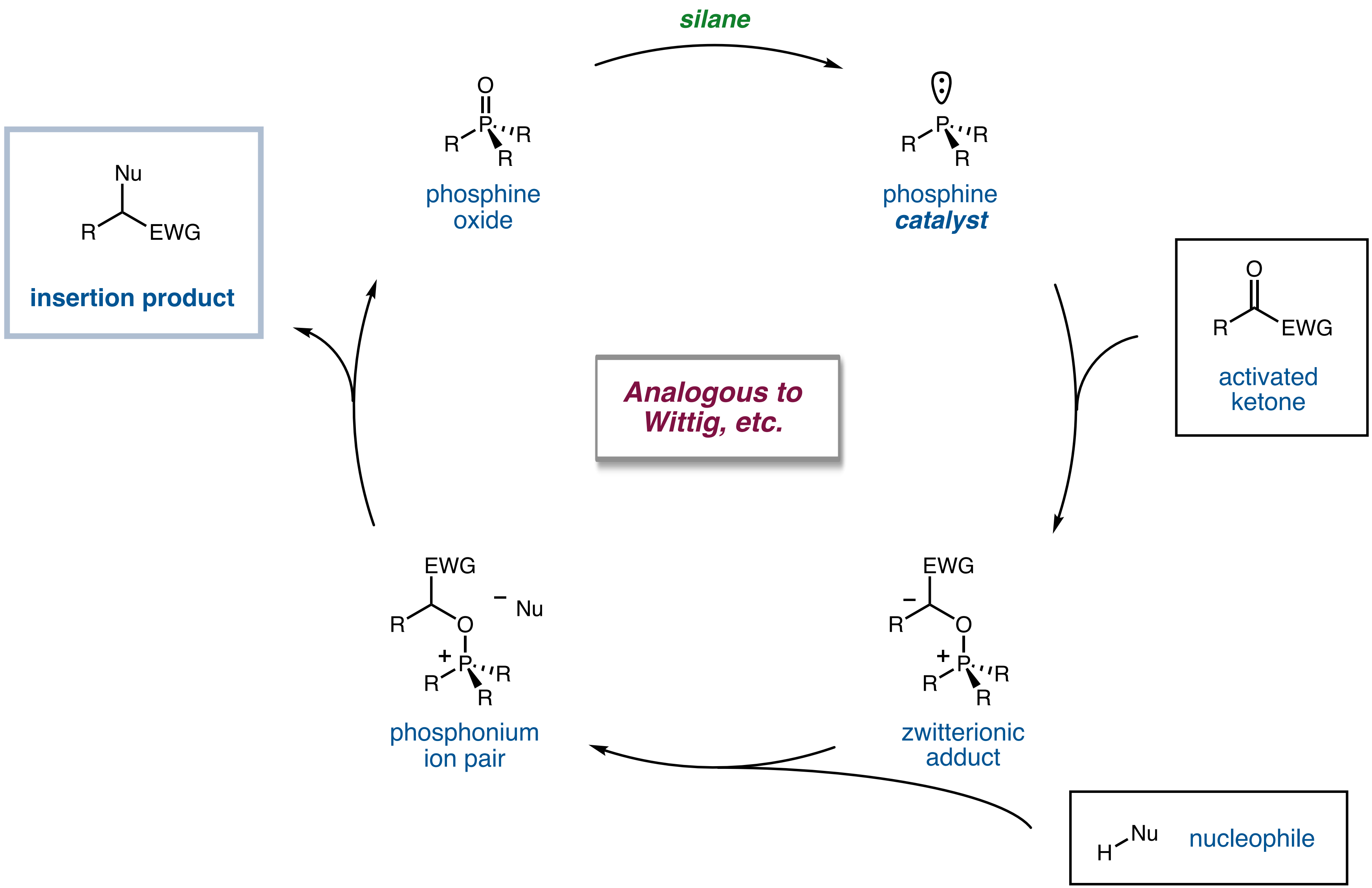
Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2013**, *51*, 10609.

Further Modes of P^{III}/P^{V} Catalysis

■ Can this transformation be catalytic in phosphine?

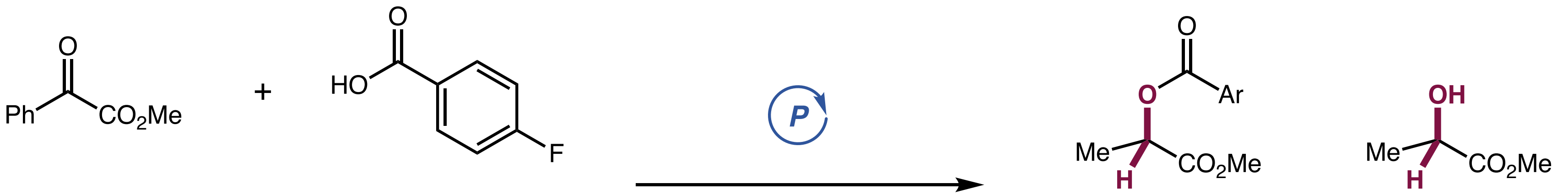


Further Modes of P^{III}/P^{V} Catalysis

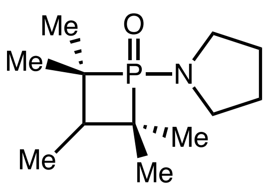


Further Modes of P^{III}/P^{V} Catalysis

Can this transformation be catalytic in phosphine?

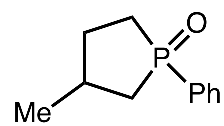
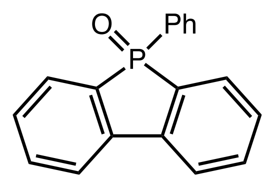
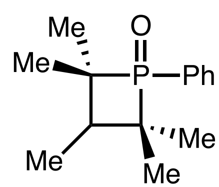
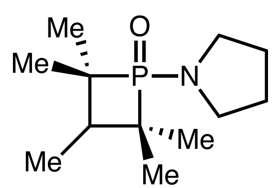


α-ketoester (aryl, alkyl) | carboxylic acid | $PhSiH_3$, PhMe, 100 °C | ***reductive insertion product*** | ***direct reductive byproduct***



- **Small ring accelerates P=O reduction**
- **Pyrrolidine substituent restores nucleophilicity**
- **Ketoester and carboxylic acid scope explored**

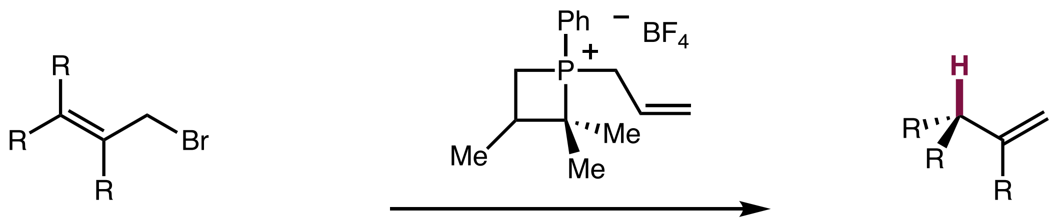
Catalyst optimization

Catalyst	reductive insertion product	direct reductive byproduct
	*0%*	*73%*
	*0%*	*83%*
	*41%*	*42%*
	***84%***	***7%***

Zhao, W.; Yan, P. K.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 616.

Further Modes of P^{III}/P^{V} Catalysis

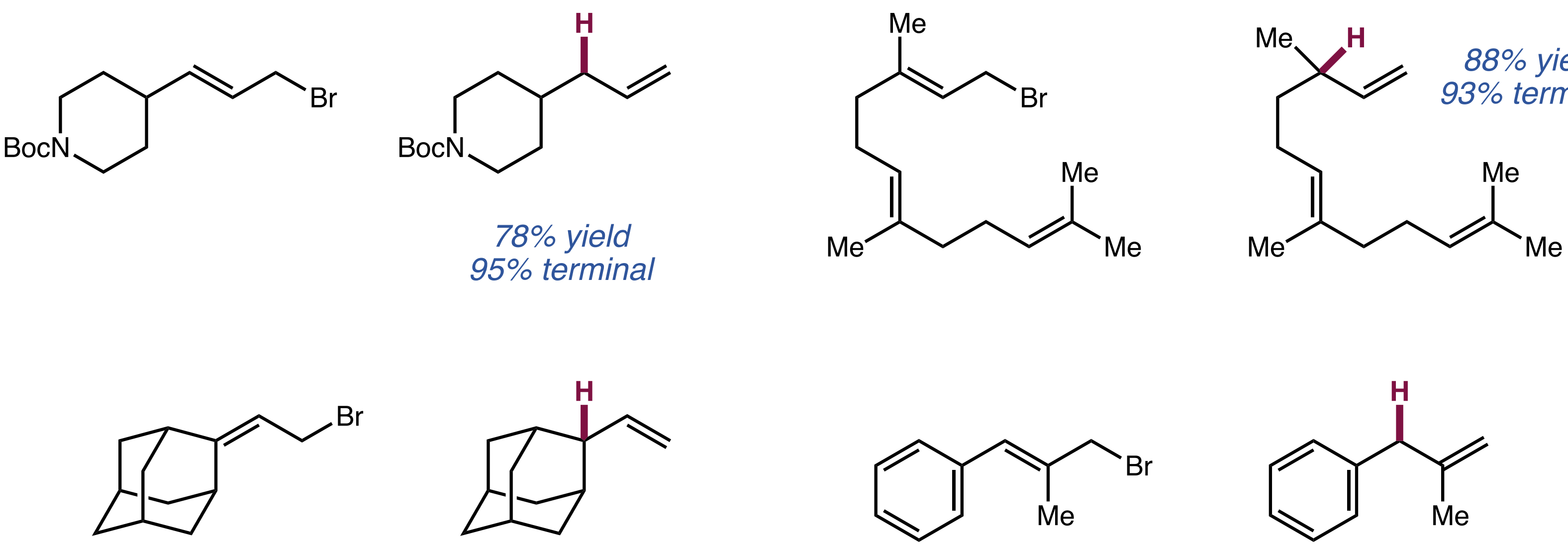
A final reaction with a novel mechanism



internal allylic bromide

LiAlH(O*t*-Bu)$_3$, 90 °C

terminal, reductive transposition product



78% yield
95% terminal

88% yield
93% terminal

hindered substrate

88% yield
94% terminal

conjugated substrate

91% yield
97% terminal

Reichl, K. D.; Dunn, N. L.; Fastuca, N. J.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 5292.

Mechanism of Reductive Transposition