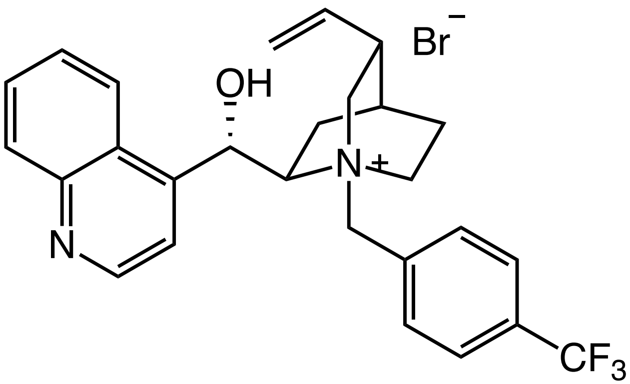
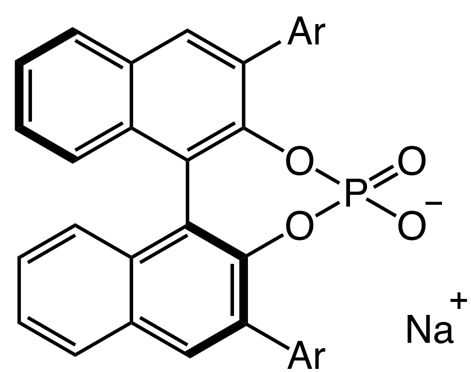
Long Literature Talk:

Recent Advances in Enantioselective Phase-Transfer Catalysis: Merging Two Catalytic Cycles



Chiral Cation Phase-Transfer



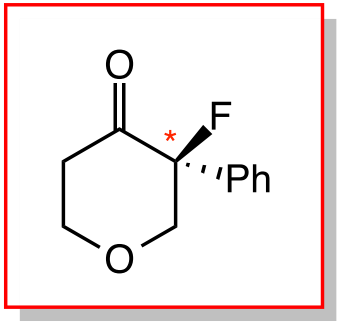
Chiral Anion Phase-Transfer

Jose M. Medina
Engle Laboratory

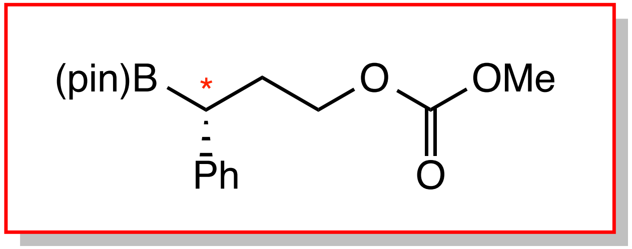
02/28/2018 Group Meeting

Presentation Overview

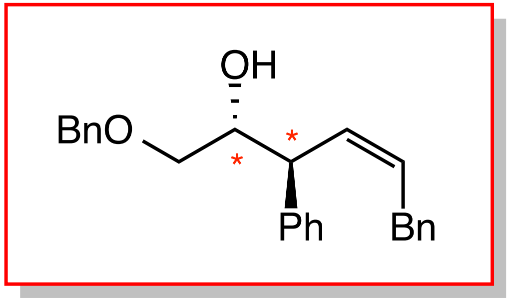
- Intro to phase-transfer catalysis
  - – Chiral cation phase-transfer catalysis (CCPT)
  - – Chiral anion phase-transfer catalysis (CAPT)



- The merging of CAPT and enamine catalysis
  - – α-Fluorinated ketones



- The merging of CAPT and palladium catalysis
  - – Benzylic boronic esters



- The merging of CAPT and palladium catalysis
  - – Homoallylic alcohols

What is a Phase-Transfer Catalyst

Phase-transfer catalysts facilitate the migration of a reactant from one phase into another where the reaction occurs.

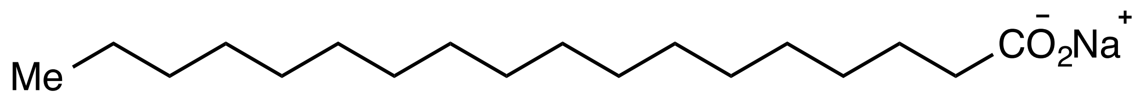
Aqueous phase	→	*Organic phase*
Solid phase	→	*Organic phase*

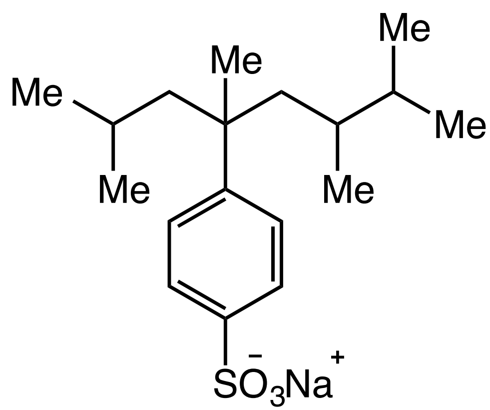
Hughes, D. L.; Dolling, U.-H; Ryan, K. M.; Schoenwaldt, E. F.; Grabowski, E. J. J.
J. Org. Chem. **1987**, *52*, 4745.

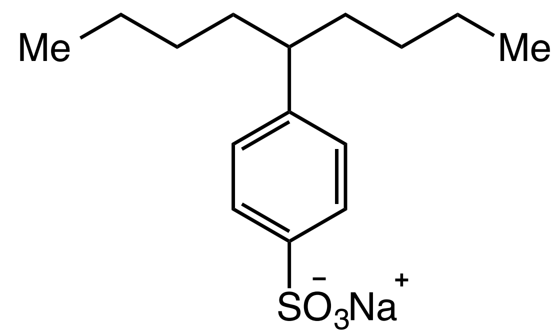
What is a Phase-Transfer Catalyst

Phase-transfer catalysts facilitate the migration of a reactant from one phase into another where the reaction occurs.

Aqueous phase	→	*Organic phase*
Solid phase	→	*Organic phase*

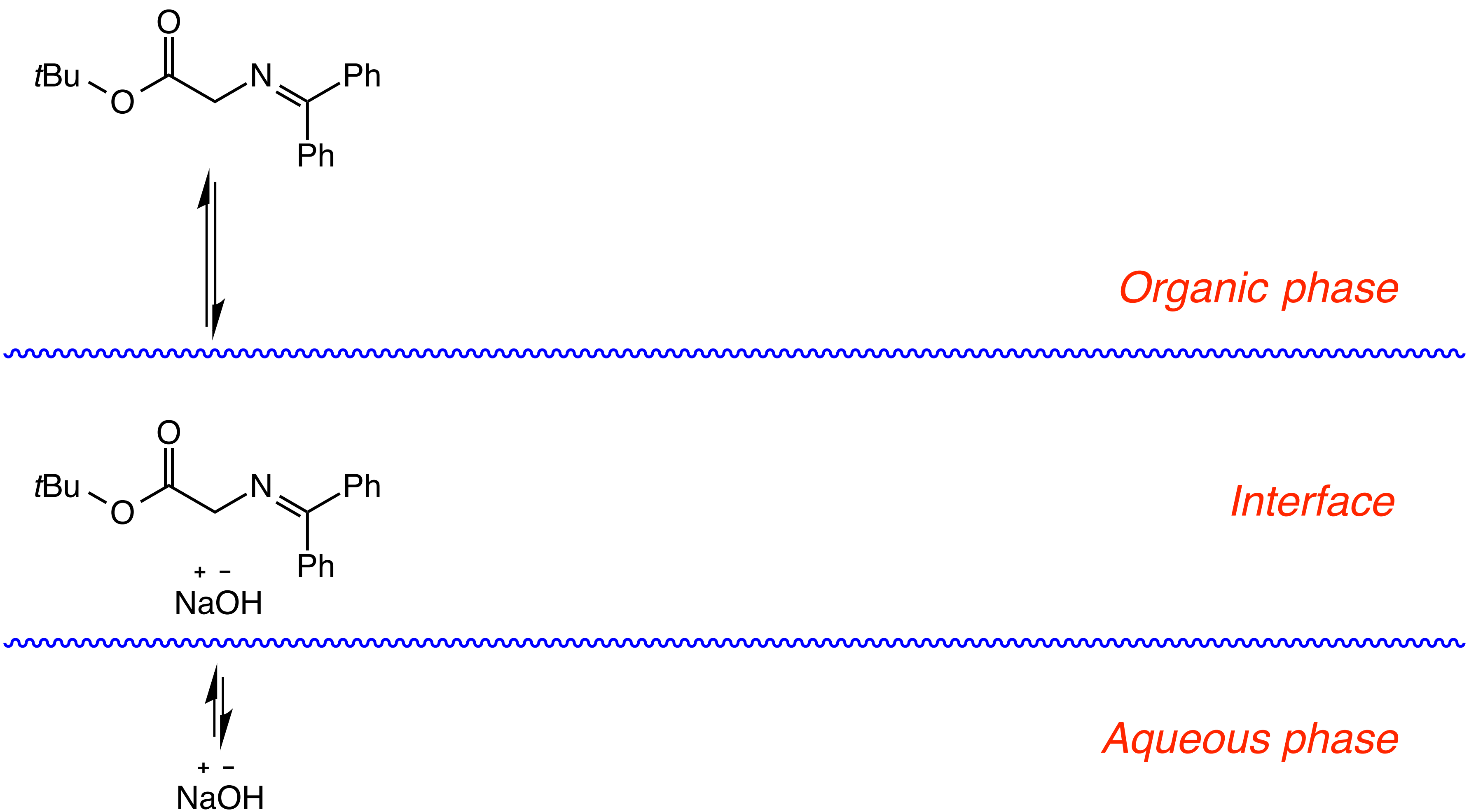






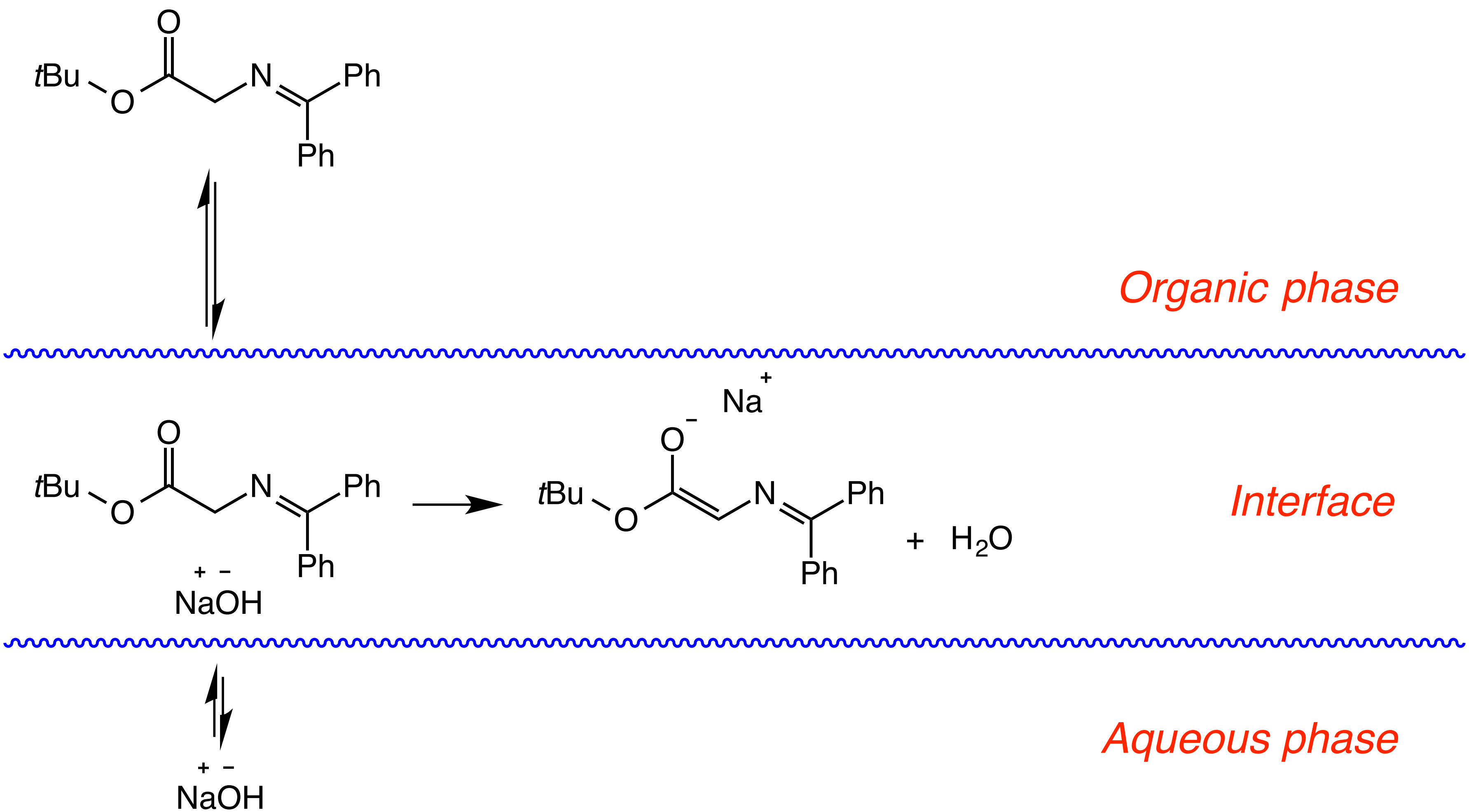
Hughes, D. L.; Dolling, U.-H; Ryan, K. M.; Schoenwaldt, E. F.; Grabowski, E. J. J.
J. Org. Chem. **1987**, *52*, 4745.

Mechanism of Phase-Transfer



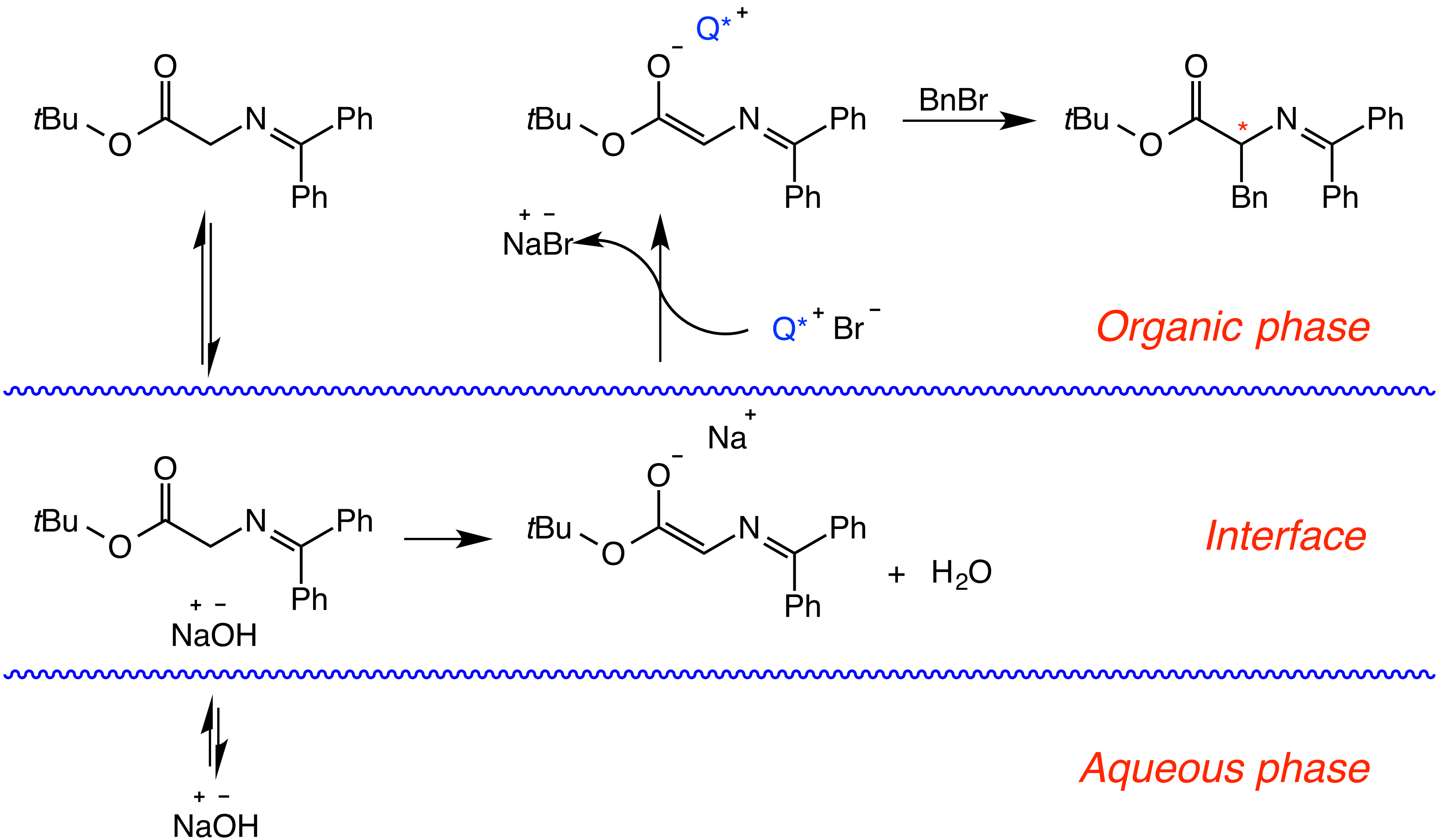
Hughes, D. L.; Dolling, U.-H; Ryan, K. M.; Schoenwaldt, E. F.; Grabowski, E. J. J.
J. Org. Chem. **1987**, *52*, 4745.

Mechanism of Phase-Transfer



Hughes, D. L.; Dolling, U.-H; Ryan, K. M.; Schoenwaldt, E. F.; Grabowski, E. J. J.
J. Org. Chem. **1987**, *52*, 4745.

Mechanism of Phase-Transfer



Hughes, D. L.; Dolling, U.-H; Ryan, K. M.; Schoenwaldt, E. F.; Grabowski, E. J. J.
J. Org. Chem. **1987**, *52*, 4745.

Key Benefits of Phase-Transfer Catalysis

Reduction of organic solvents (cost benefit for large process / Green chemistry)

Use of simple and inexpensive reagents (ie. NaOH vs. KHMDS)

High yields and purity of products

Processes are highly scalable

Maurin, L. J. U.S. Patent 4418232, Nov. 29, 1983.

Key Benefits of Phase-Transfer Catalysis

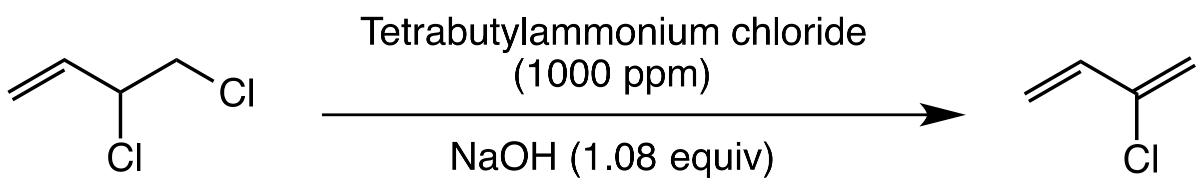
Reduction of organic solvents (cost benefit for large process / Green chemistry)

Use of simple and inexpensive reagents (ie. NaOH vs. KHMDS)

High yields and purity of products

Processes are highly scalable

Dehydrohalogenation Application of PTC



(99.2% yield)

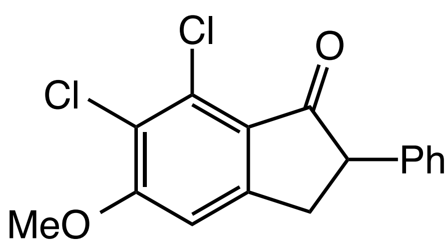
Productivity: 16 tons / hr

Cost effective *Efficient* *Green*	→	*Solution to synthetic problems?*

Maurin, L. J. U.S. Patent 4418232, Nov. 29, 1983.

Enantioselective Alkylation of Indanones

3-step sequence *Complex procedure* *Stoichiometric chiral auxiliaries*



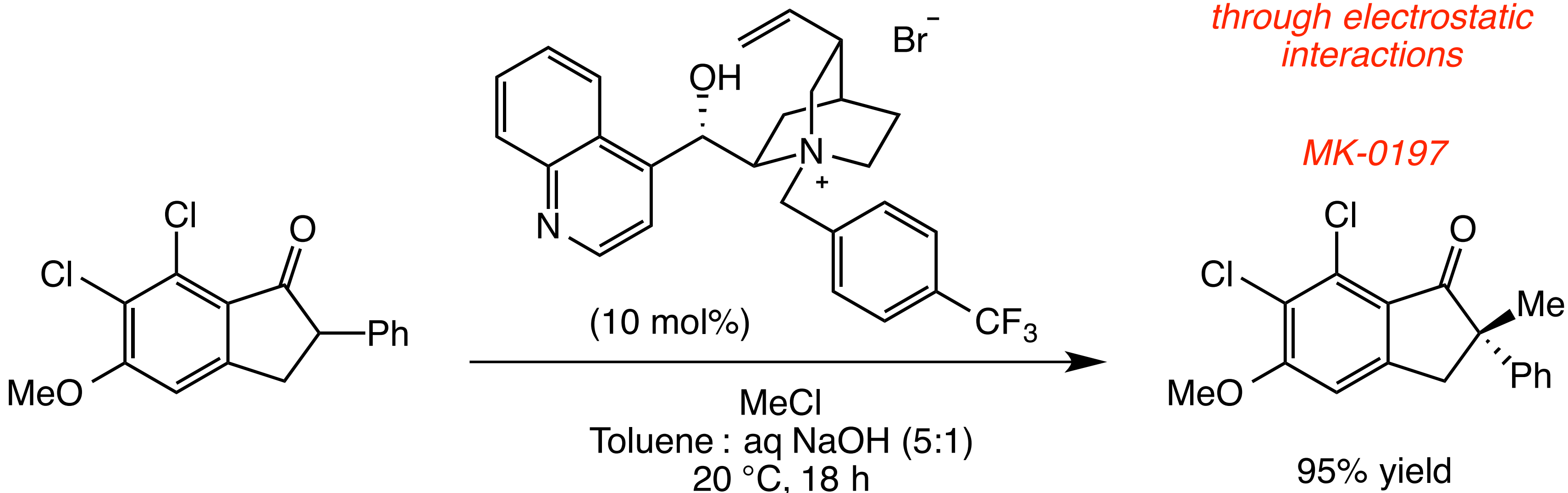
Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1984**, *106*, 446.

Enantioselective Alkylation of Indanones

3-step sequence *Complex procedure* *Stoichiometric chiral auxiliaries*

High enantioinduction through electrostatic interactions

MK-0197



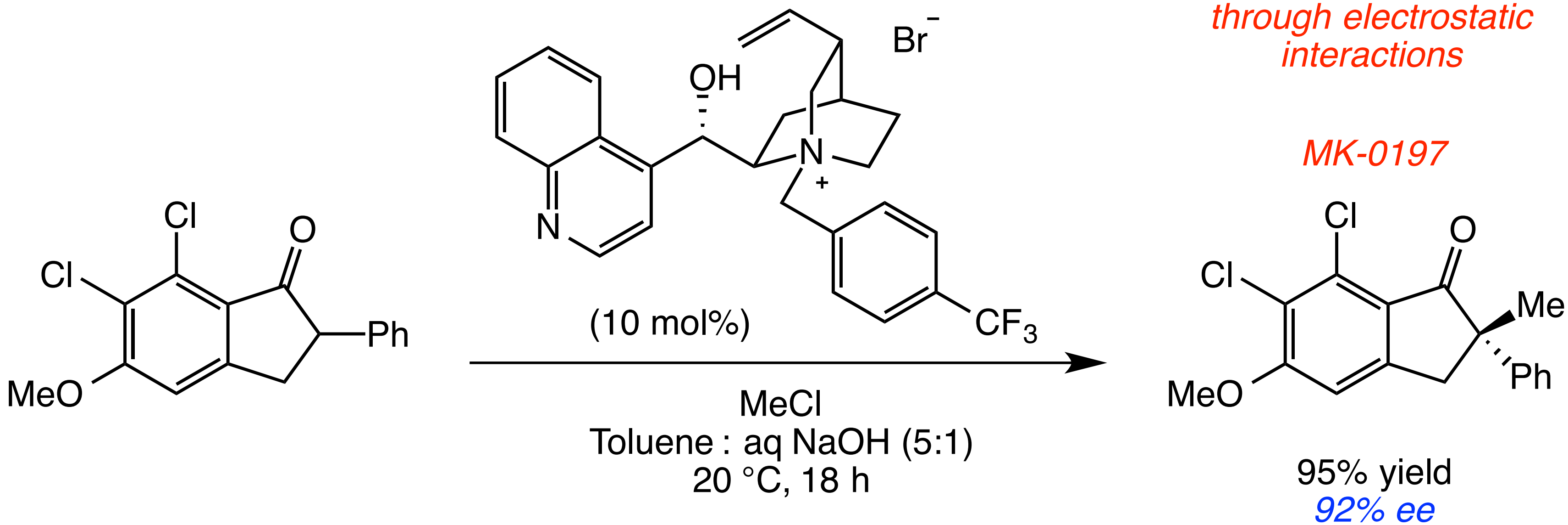
95% yield
92% ee

Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

Enantioselective Alkylation of Indanones

3-step sequence *Complex procedure* *Stoichiometric chiral auxiliaries*

High enantioinduction through electrostatic interactions



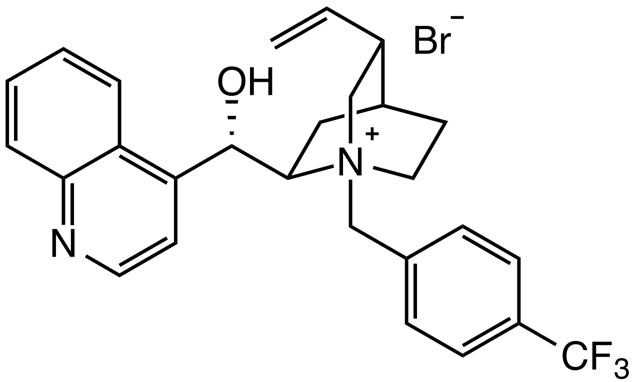
Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

Contemporary Asymmetric Phase-Transfer Catalysis: Large-Scale Industrial Applications

Alkylations *Conjugate additions* *Epoxidations* *Phosphorylations* *Desymmetrizations*

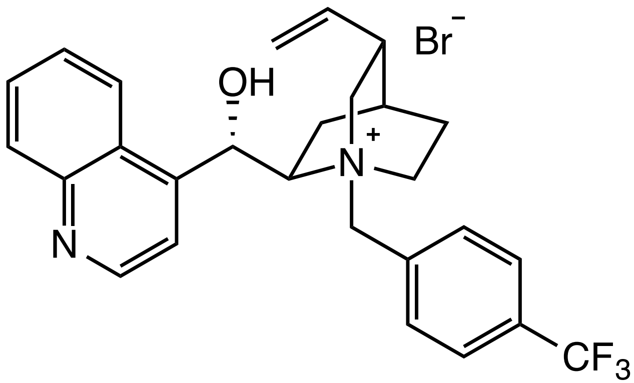
Tan, J.; Yasuda, N. *Org. Process Res. Dev.* **2015**, *19*, 1731.

Selected Examples of Phase-Transfer Catalysts

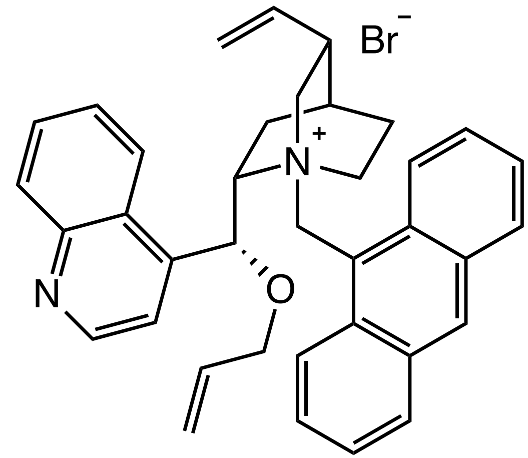


Merck
JACS **1984**
106, 446.

Selected Examples of Phase-Transfer Catalysts

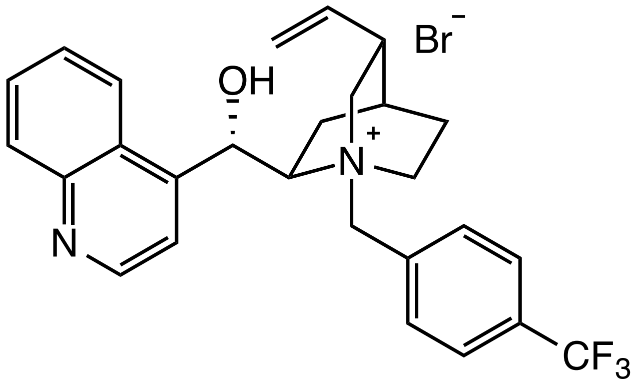


Merck
JACS **1984**
106, 446.

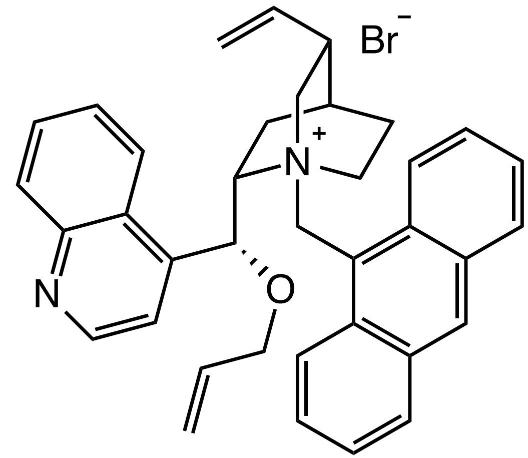


Corey
JACS **1997**
119, 12414.

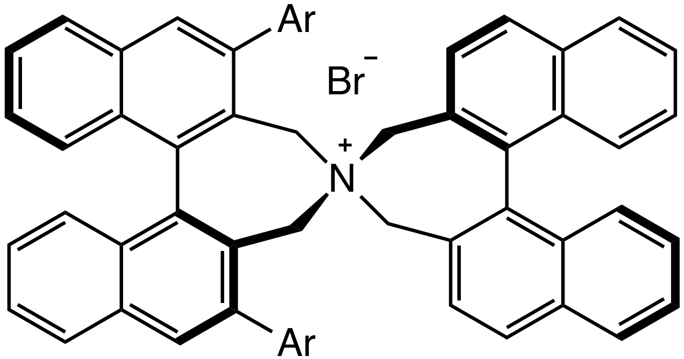
Selected Examples of Phase-Transfer Catalysts



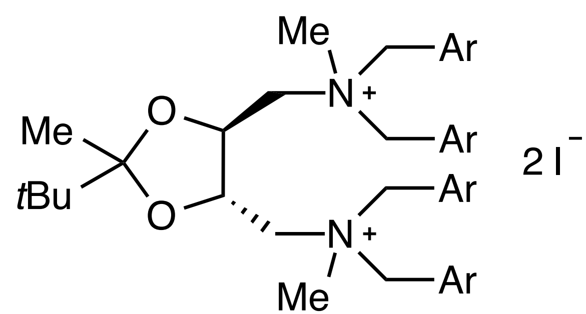
Merck
JACS **1984**
106, 446.



Corey
JACS **1997**
119, 12414.

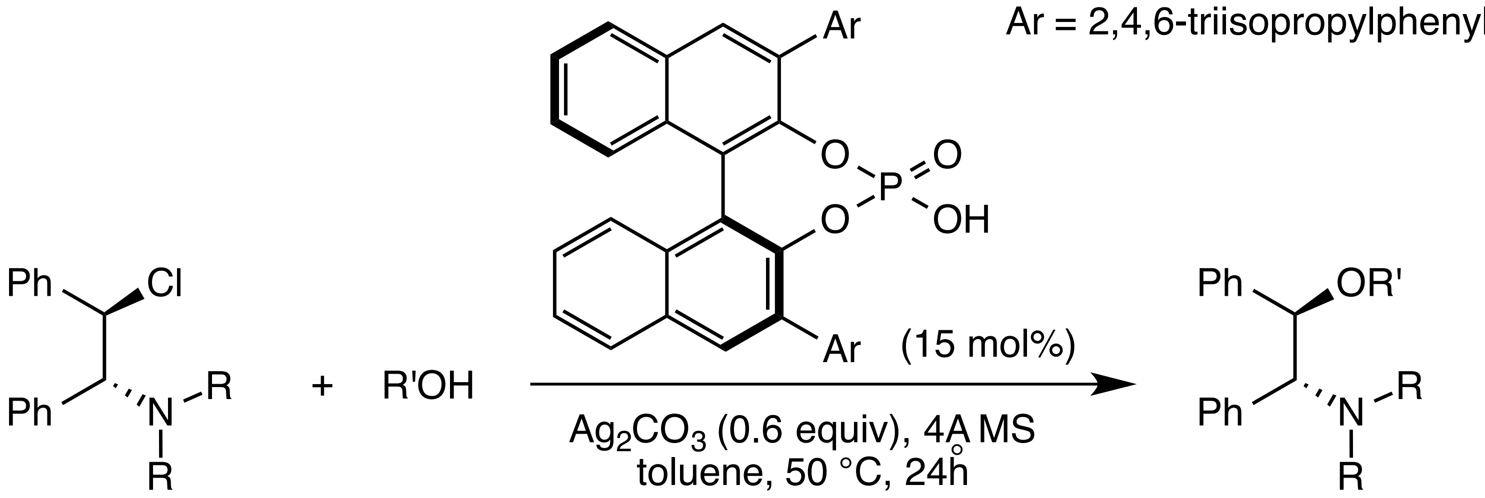


Maruoka
Chem. Commun.
2007, 1487.



Shibasaki
ACIE **2005**
44, 4564.

First Example of Enantioselective Chiral Anion Phase-Transfer Catalysis



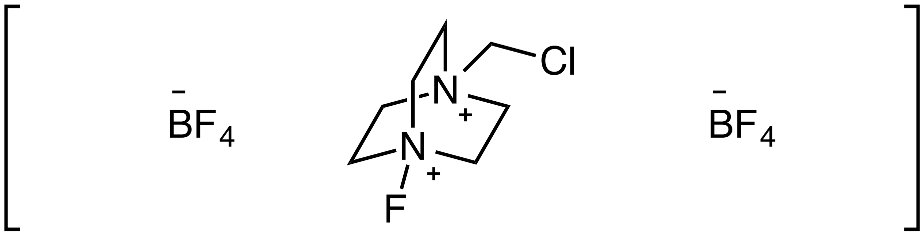
50–95% yield
90–99% ee

- *Reaction served as proof of concept*
- *Solution to reactions involving cationic intermediates with no basic site*

Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984.

CAPT Catalysis in Enantioselective Fluorinations

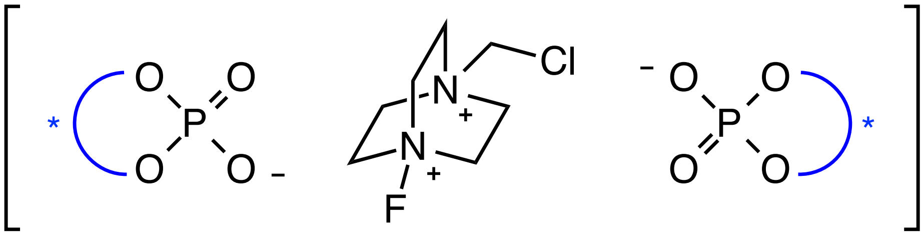
Selectfluor (Insoluble)



Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.

CAPT Catalysis in Enantioselective Fluorinations

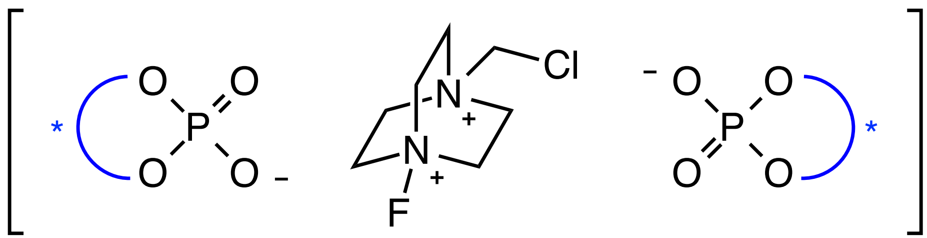
Soluble chiral fluorinating agent



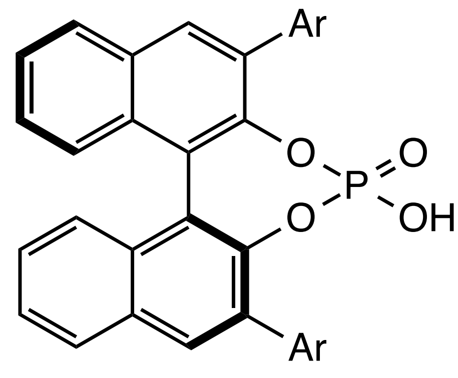
Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.

CAPT Catalysis in Enantioselective Fluorinations

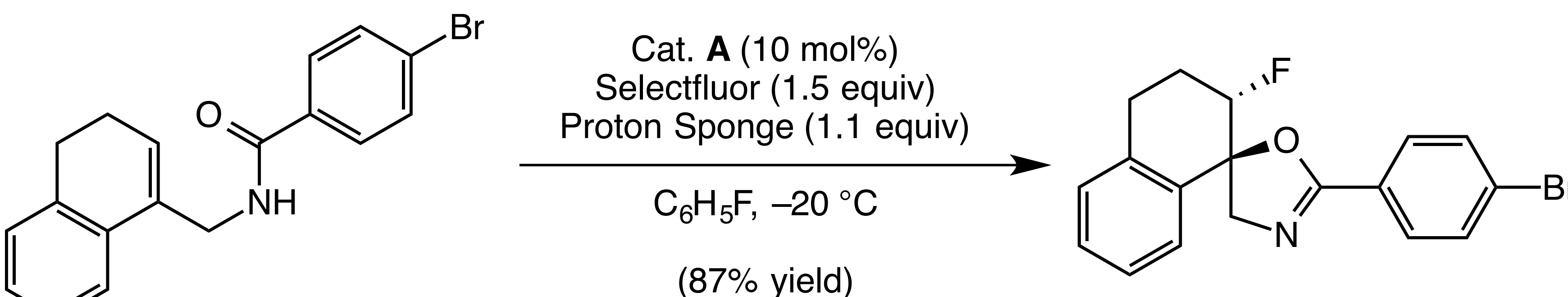
Soluble chiral fluorinating agent



Cat. **A**



Ar = 4-NO_2-C_6H_4



>20:1 d.r, *93% ee*

Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.

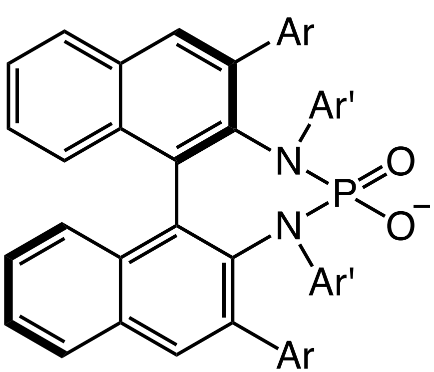
CAPT Catalysis in Enantioselective Fluorinations

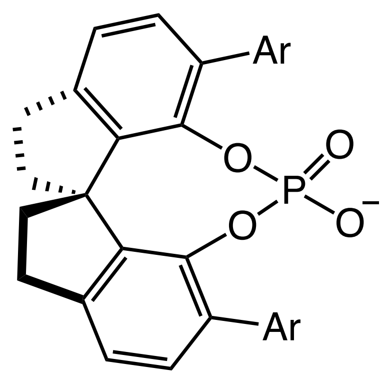
Soluble chiral fluorinating agent

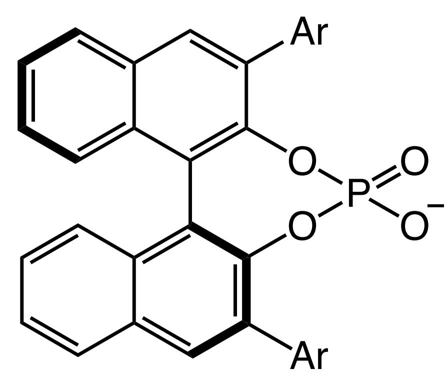
Cat. **A**

Ar = 4-NO_2-C_6H_4

Commonly Employed CAPT Catalysts

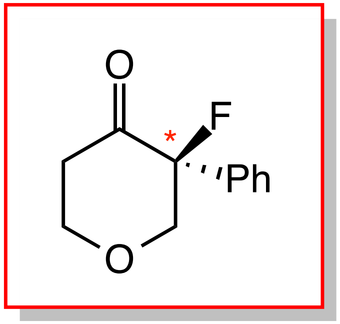




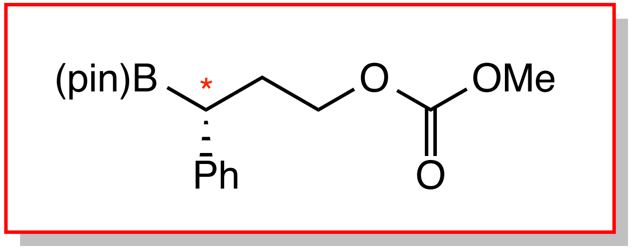


Presentation Overview

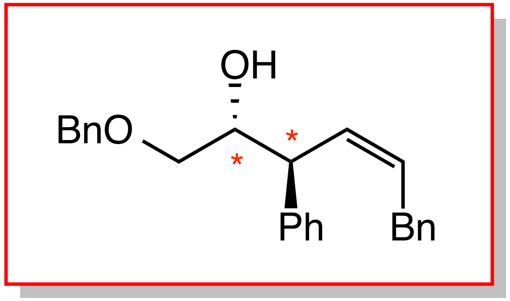
- Intro to phase-transfer catalysis
  - – Chiral cation phase-transfer catalysis (CCPT)
  - – Chiral anion phase-transfer catalysis (CAPT)



- The merging of CAPT and enamine catalysis
  - – α-Fluorinated ketones



- The merging of CAPT and palladium catalysis
  - – Benzylic boronic esters



- The merging of CAPT and palladium catalysis
  - – Homoallylic alcohols

Asymmetric Fluorination of α-Branched Cyclohexanones

Expand the scope of chiral anion phase-transfer catalysis

Achieve the fluorination of alpha-branched cyclic ketones

Chiral enamine catalysis successful for alpha-fluorination of aldehydes

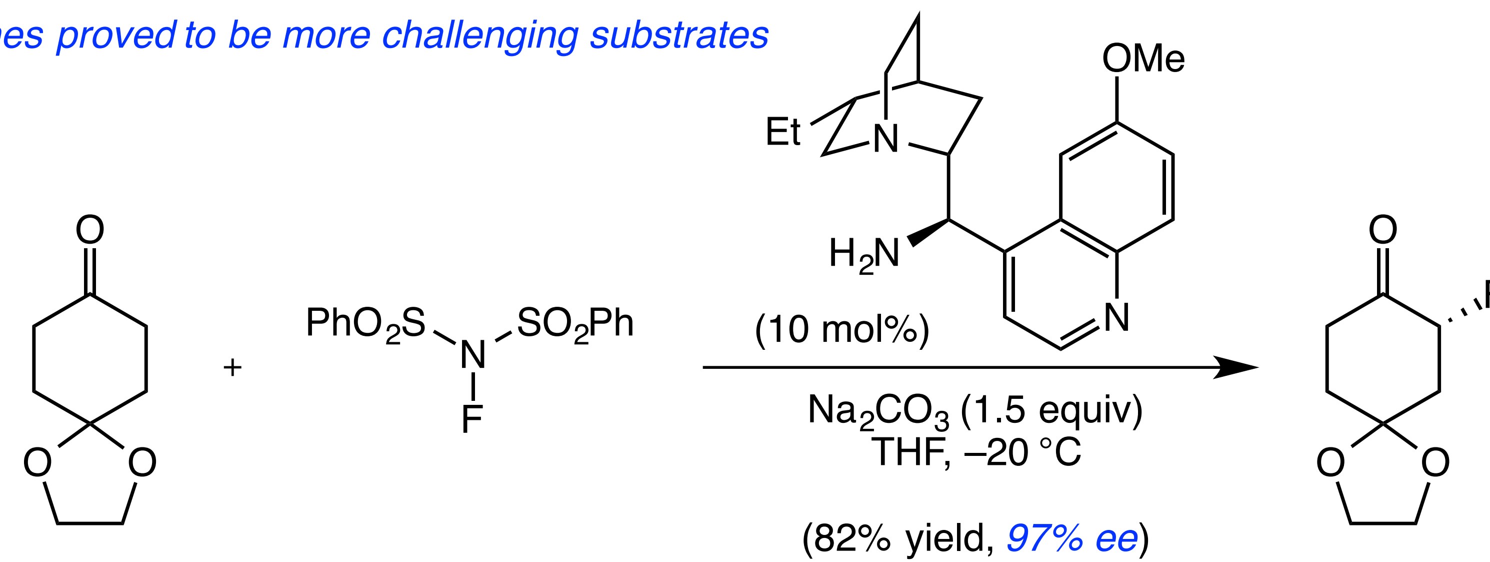
Asymmetric Fluorination of α-Branched Cyclohexanones

Expand the scope of chiral anion phase-transfer catalysis

Achieve the fluorination of alpha-branched cyclic ketones

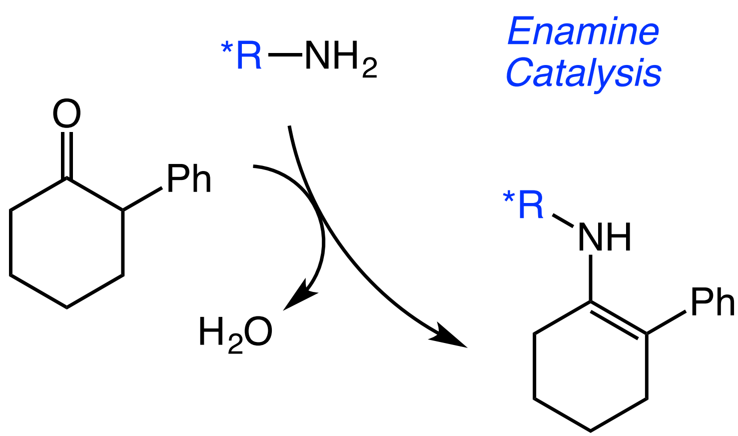
Chiral enamine catalysis successful for alpha-fluorination of aldehydes

Ketones proved to be more challenging substrates



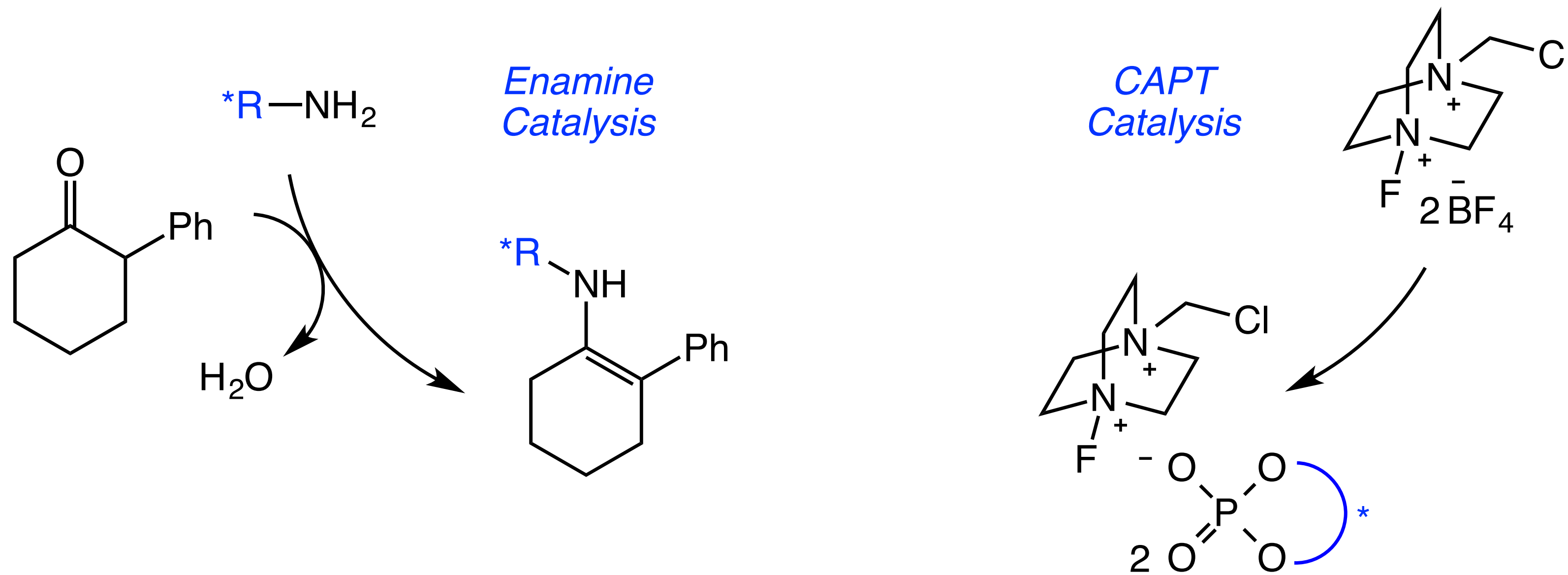
Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738.

Proposed Dual Catalytic Cycle for the Enantioselective Fluorination of Ketones



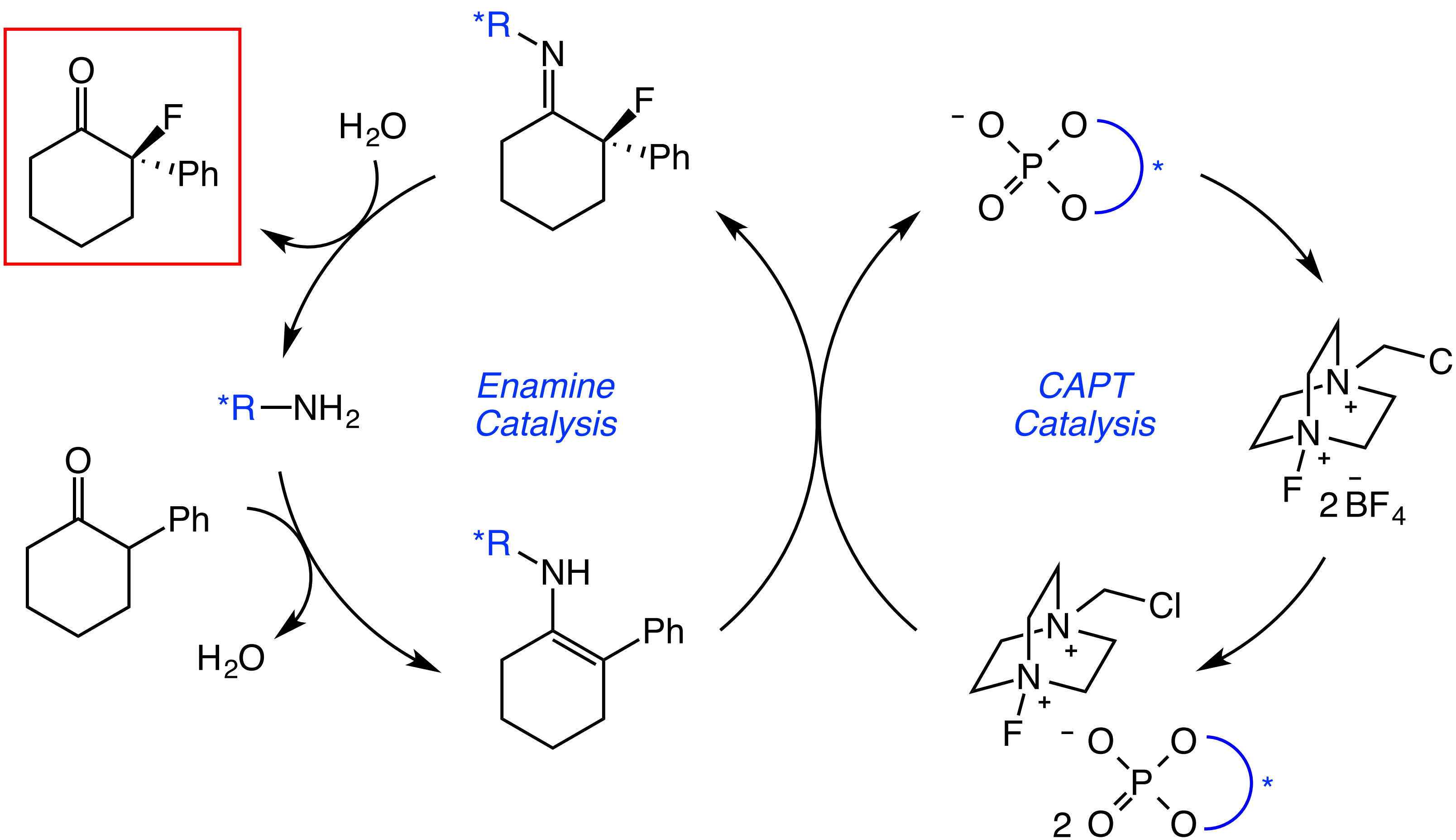
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Proposed Dual Catalytic Cycle for the Enantioselective Fluorination of Ketones



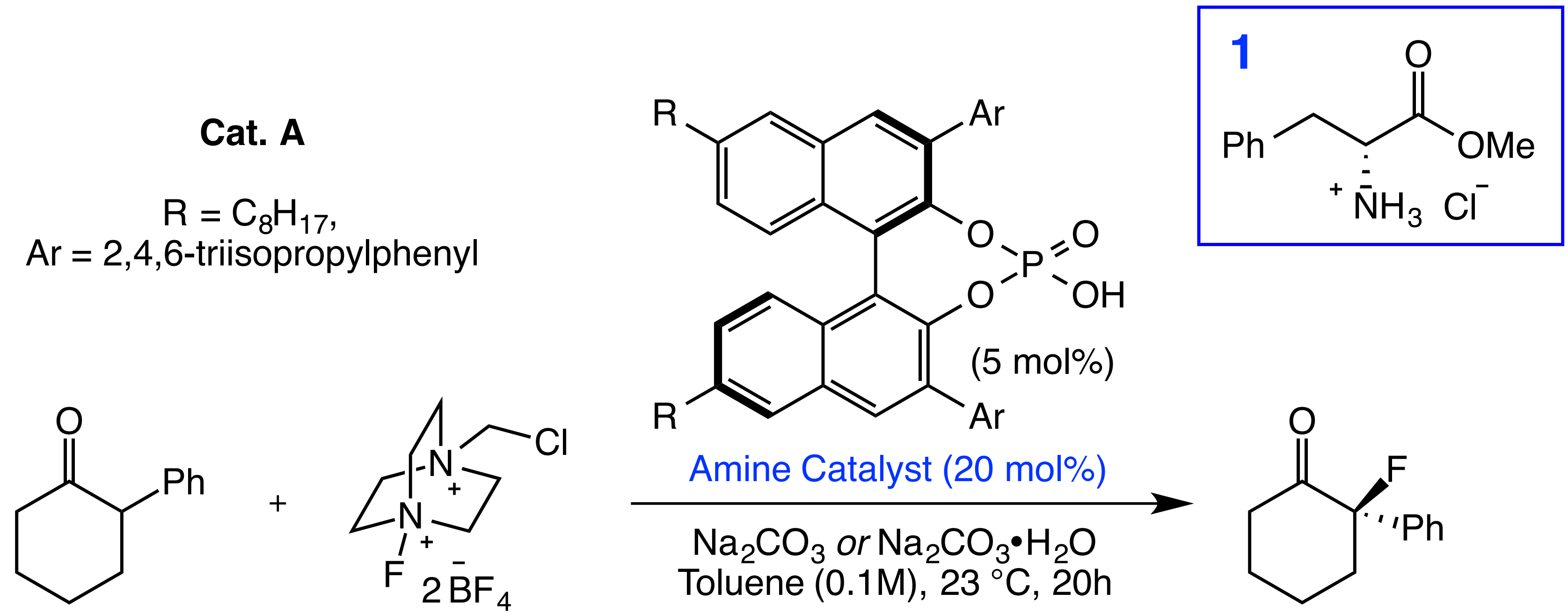
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Proposed Dual Catalytic Cycle for the Enantioselective Fluorination of Ketones



Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

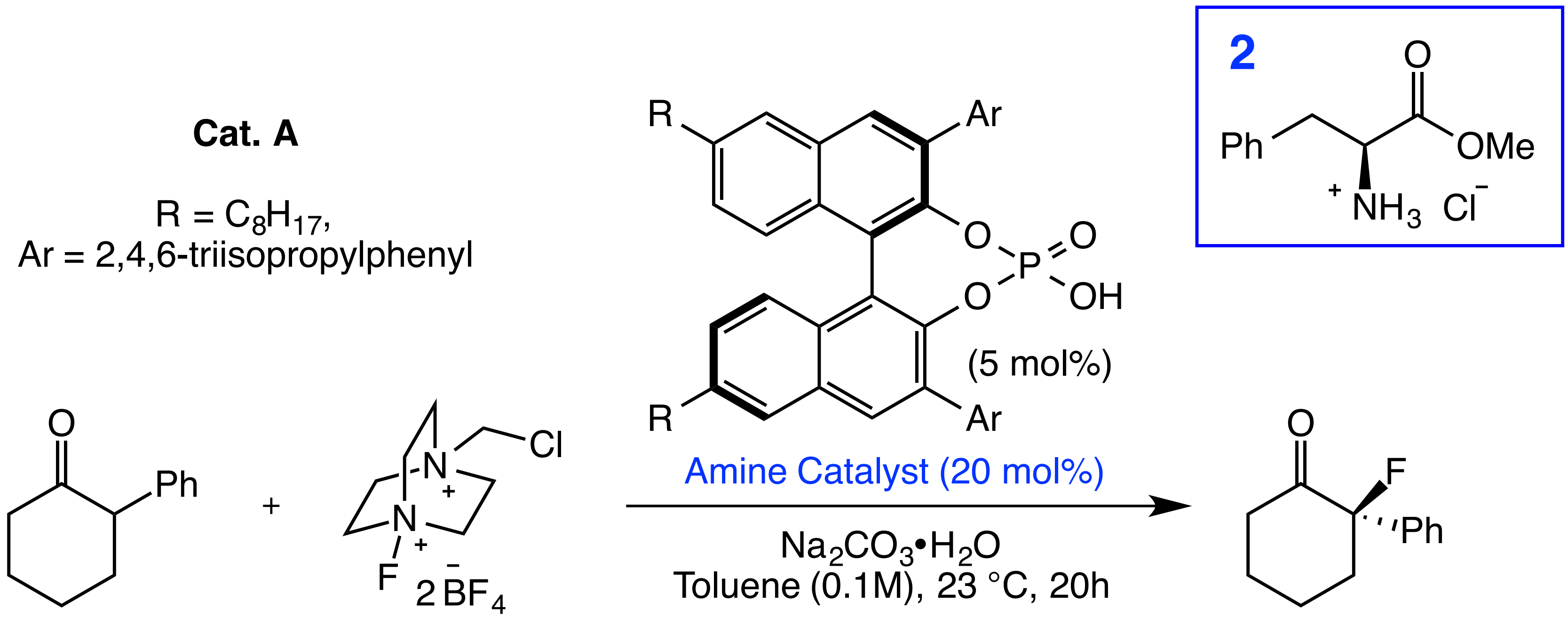
Reaction Optimization Studies



entry	*phosphoric acid*	*amine*	*yield*	*ee*
1	**Cat. A**	none	5%	–2
2	**Cat. A**	$BnNH_2$	29%	–3
3	**Cat. A**	**1**	63–73%	+63–78
4	**Cat. A**	**1** (dry Na_2CO_3)	50%	+32
5	**Cat. A**	**1** ($Na_2CO_3•H_2O$)	74%	+88

Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Reaction Optimization Studies

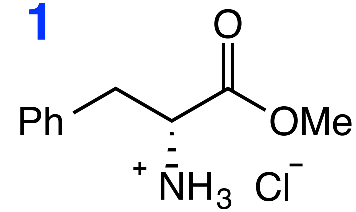


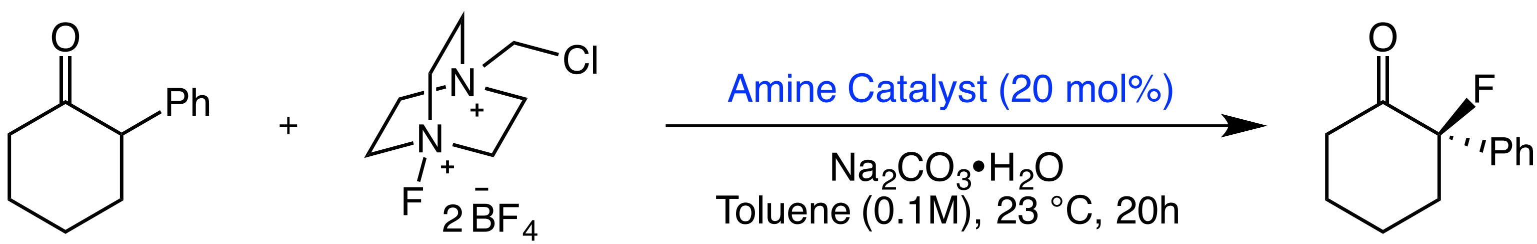
entry	*phosphoric acid*	*amine*	*yield*	*ee*
6	**Cat. A**	**2**	70%	–40

Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Reaction Optimization Studies

1

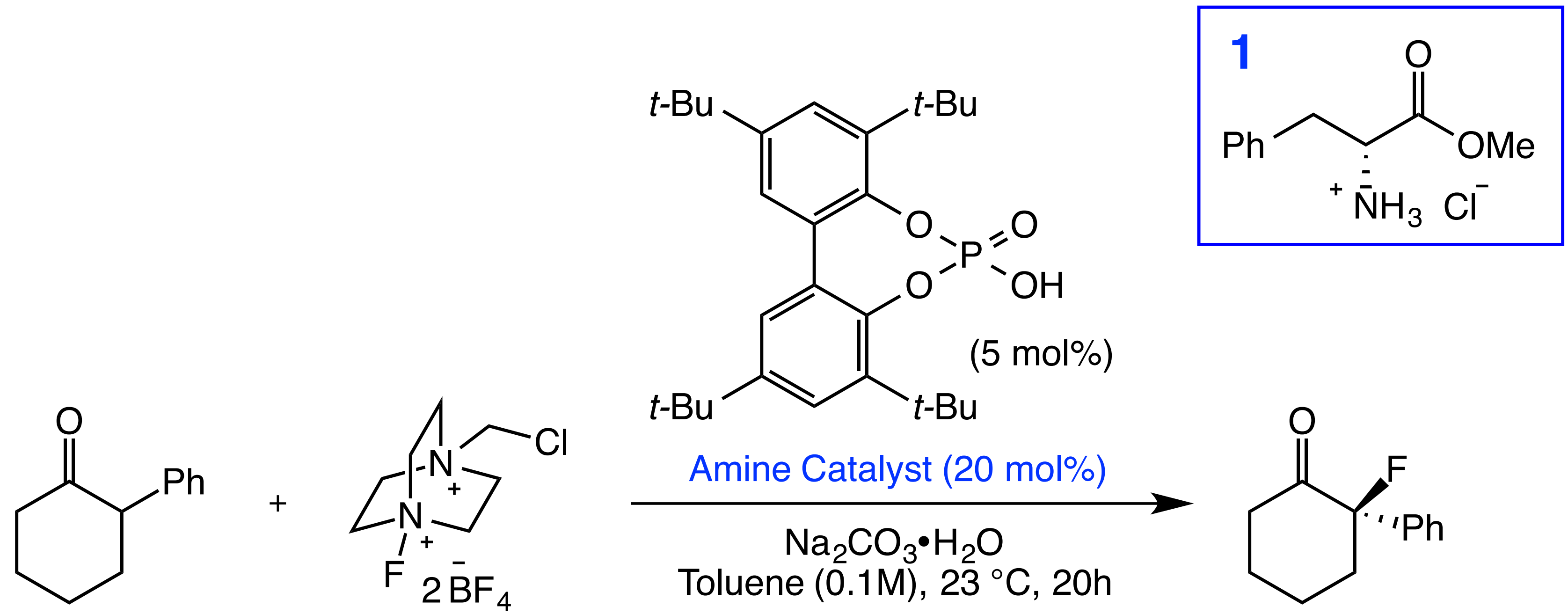




entry	*phosphoric acid*	*amine*	*yield*	*ee*
6	**Cat. A**	**2**	70%	–40
7	none	**1**	10%	+10

Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

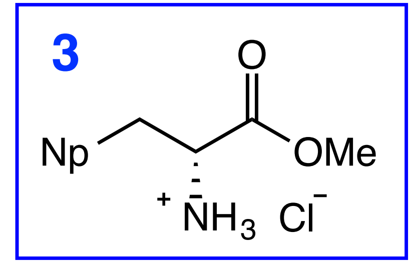
Reaction Optimization Studies

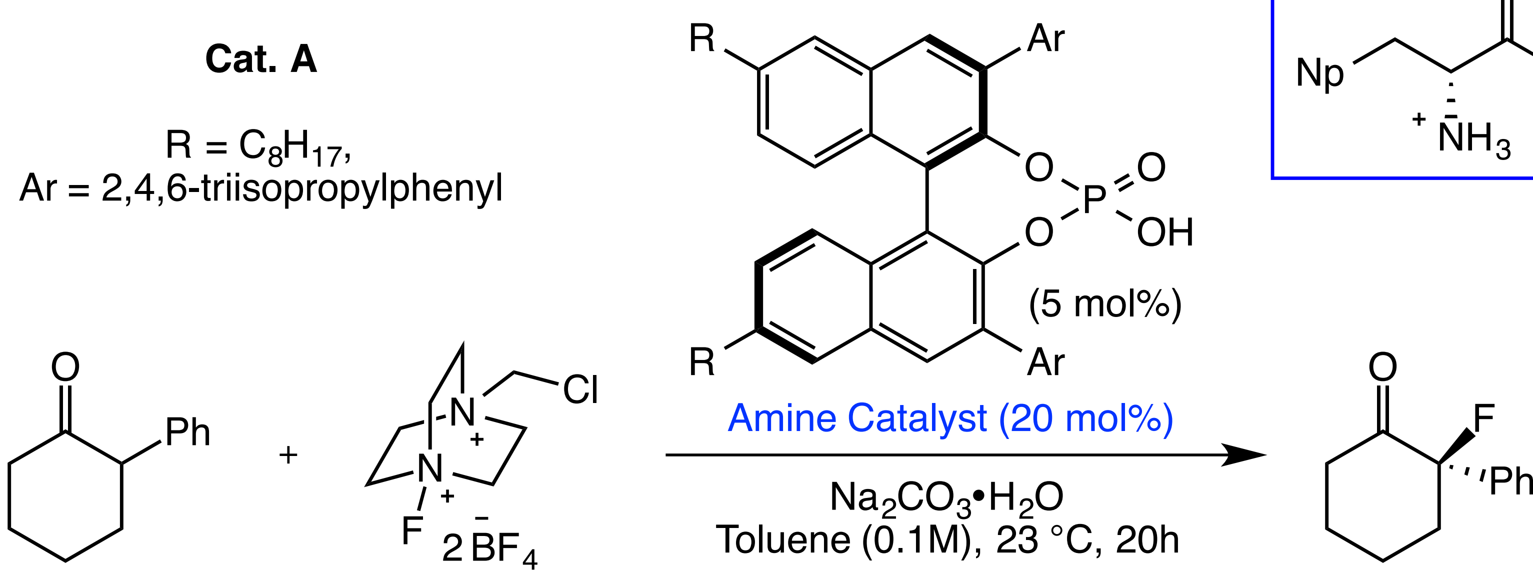


entry	*phosphoric acid*	*amine*	*yield*	*ee*
6	**Cat. A**	**2**	70%	–40
7	none	**1**	10%	+10
8	**AP**	**1**	57%	+20

Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Reaction Optimization Studies





entry	*phosphoric acid*	*amine*	*yield*	*ee*
6	**Cat. A**	**2**	70%	–40
7	none	**1**	10%	+10
8	**AP**	**1**	57%	+20
9	**Cat. A**	**3**	62%	+94

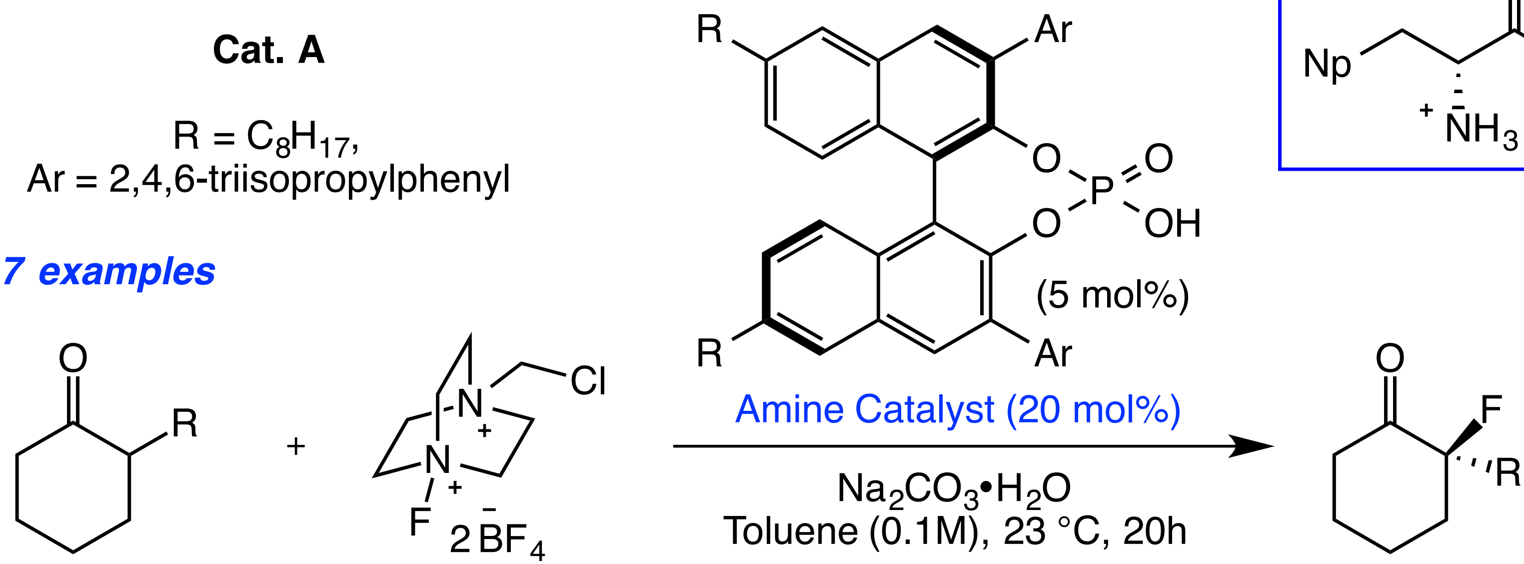
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Substrate Scope

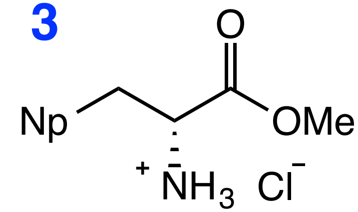
Cat. A

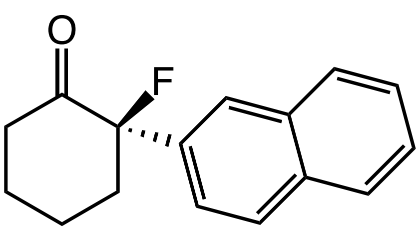
R = C_8H_{17},
Ar = 2,4,6-triisopropylphenyl

17 examples

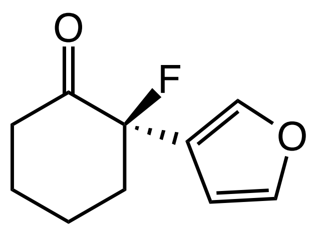


3

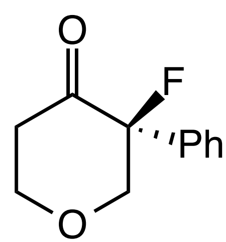




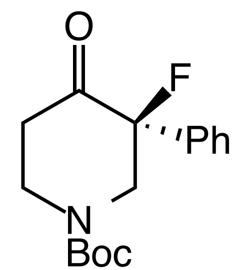
57% yield
91% ee



62% yield
89% ee



55% yield
86% ee



48% yield
86% ee

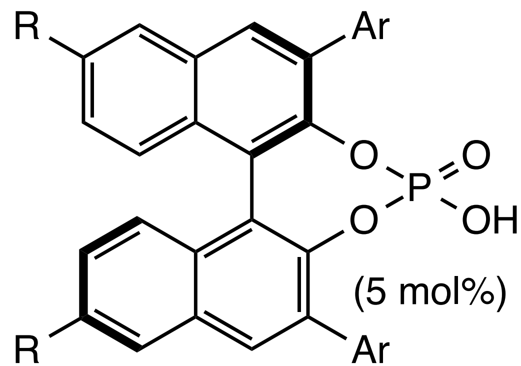
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

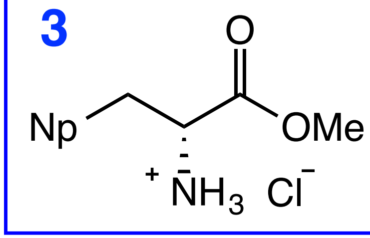
Substrate Scope

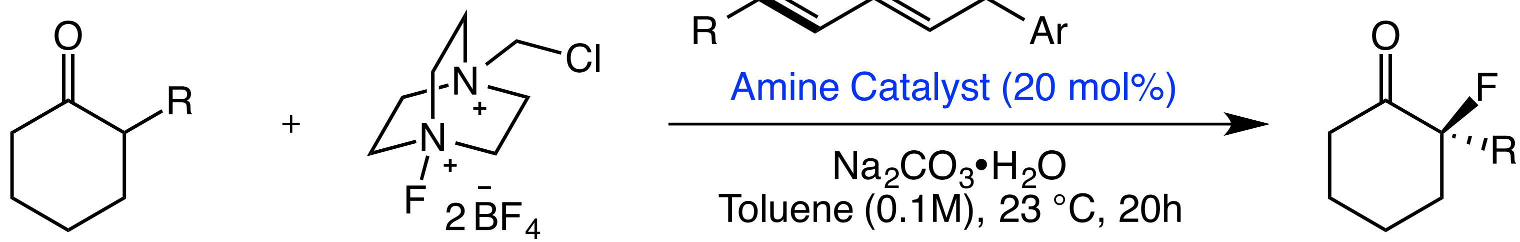
Cat. A

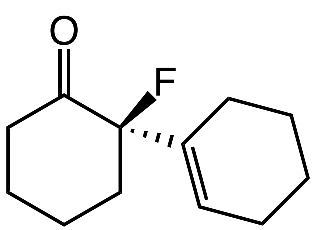
R = C_8H_{17},
Ar = 2,4,6-triisopropylphenyl

17 examples

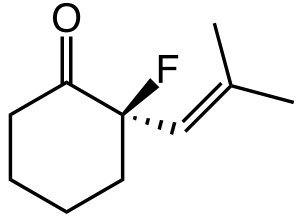




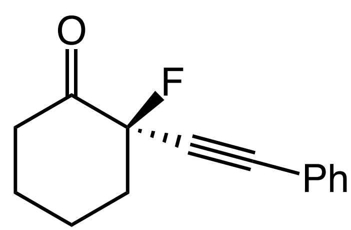




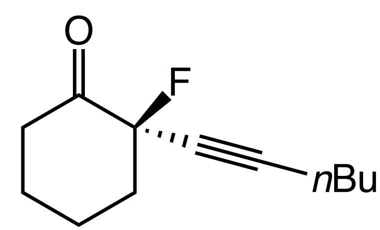
52% yield
86% ee



70% yield
85% ee



86% yield
78% ee



77% yield
77% ee

Big step toward controlled fluorinations of simple substrates

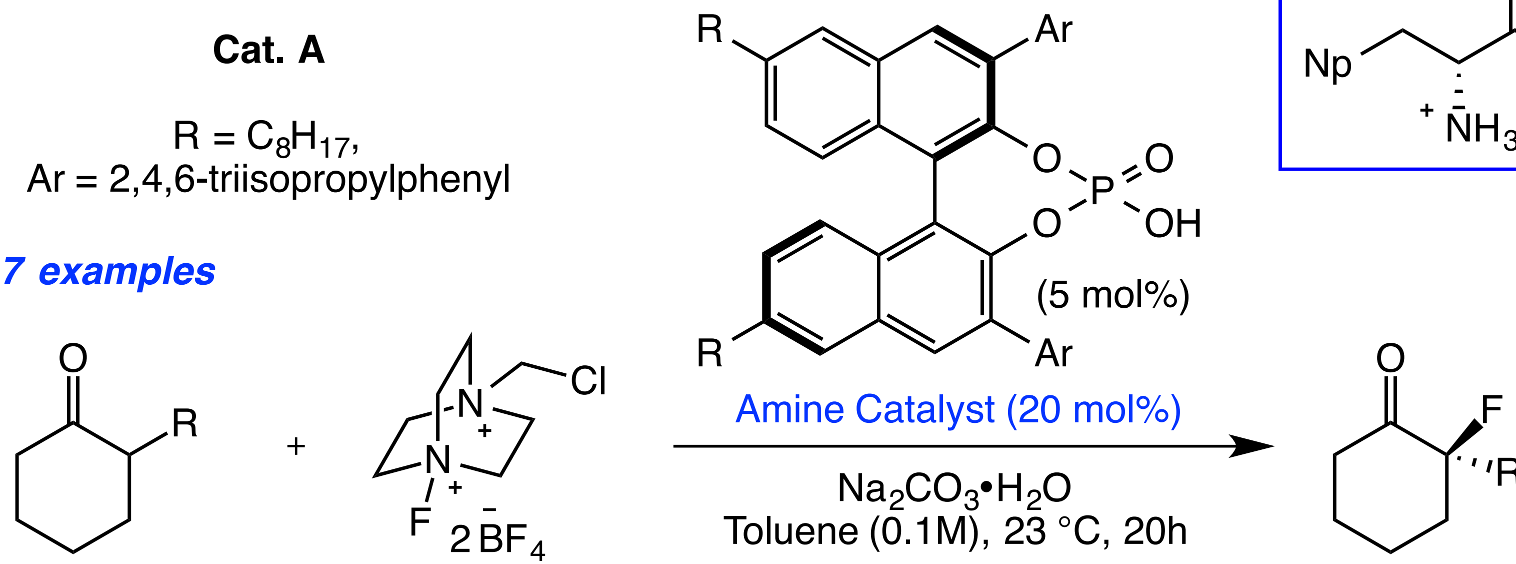
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Substrate Scope

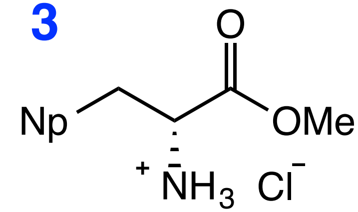
Cat. A

R = C_8H_{17},
Ar = 2,4,6-triisopropylphenyl

17 examples



3



Limitations

Fluorination limited to branched cyclohexanones

Methodology not amenable to 2-alkyl cyclohexanones

No fluorination of acyclic or non-branched ketones

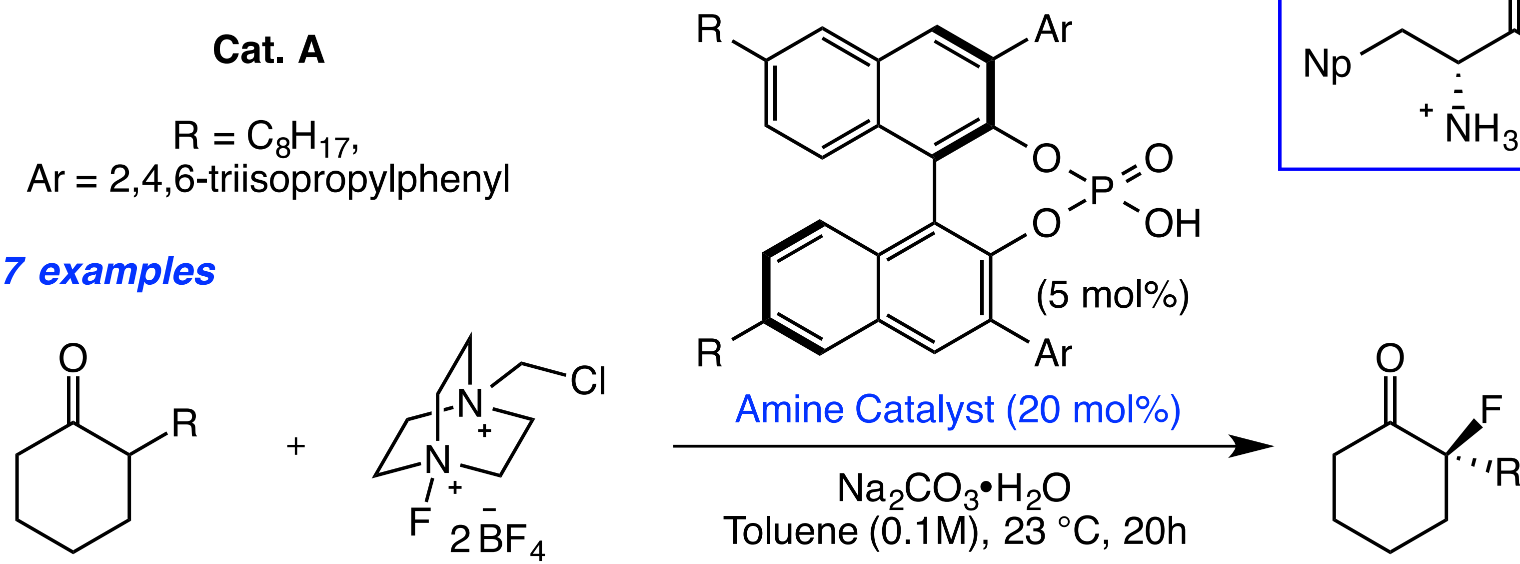
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Substrate Scope

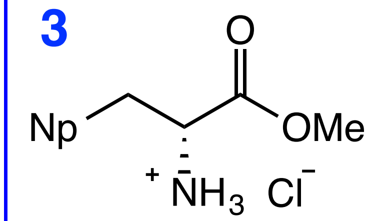
Cat. A

R = C_8H_{17},
Ar = 2,4,6-triisopropylphenyl

17 examples



3



Accomplishments

Developed the fluorination of branched cyclohexanones

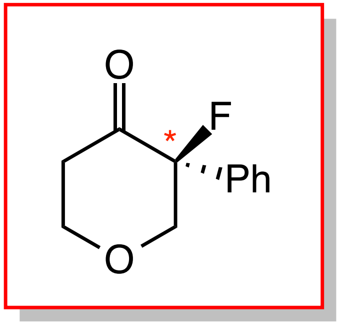
Established the compatibility of CAPT and enamine catalysis

Among the first reports to combine two chiral organocatalytic cycles

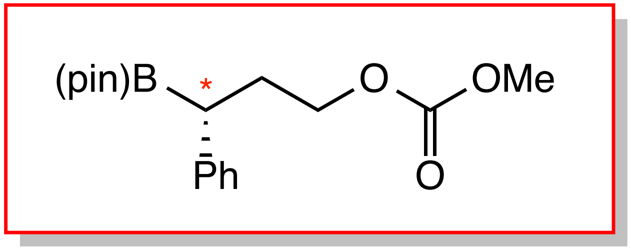
Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.

Presentation Overview

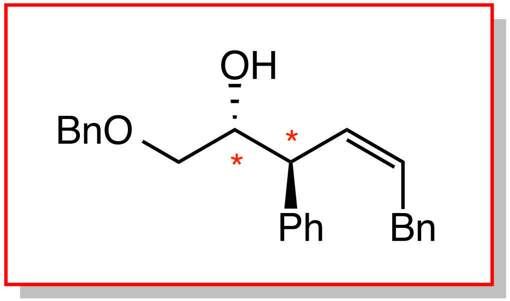
- *Intro to phase-transfer catalysis*
  - *– Chiral cation phase-transfer catalysis (CCPT)*
  - *– Chiral anion phase-transfer catalysis (CAPT)*



- *The merging of CAPT and enamine catalysis*
  - *– α-Fluorinated ketones*



- *The merging of CAPT and palladium catalysis*
  - *– Benzylic boronic esters*



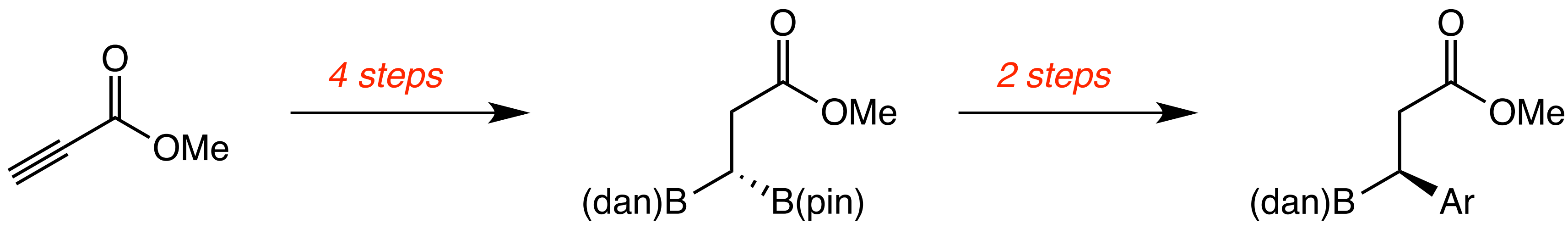
- *The merging of CAPT and palladium catalysis*
  - *– Homoallylic alcohols*

Recent Approaches to Enantioenriched Benzylic Boronic Esters

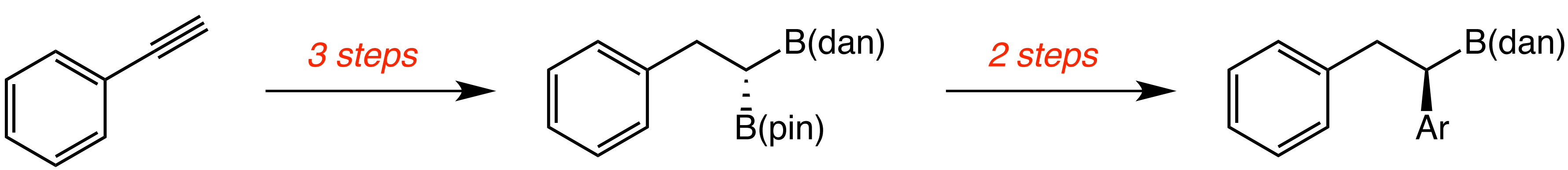
Benzylic boronic esters as building blocks for the formation of C–C, C–O, and C–N

Recent Approaches to Enantioenriched Benzylic Boronic Esters

Benzylic boronic esters as building blocks for the formation of C–C, C–O, and C–N



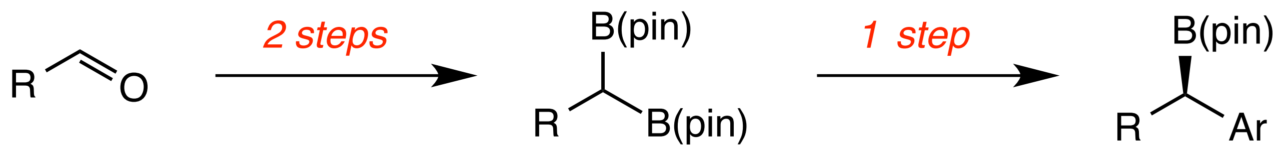
Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem*. **2011**, *3*, 894.



Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed*. **2013**, *52*, 3989.

Recent Approaches to Enantioenriched Benzylic Boronic Esters

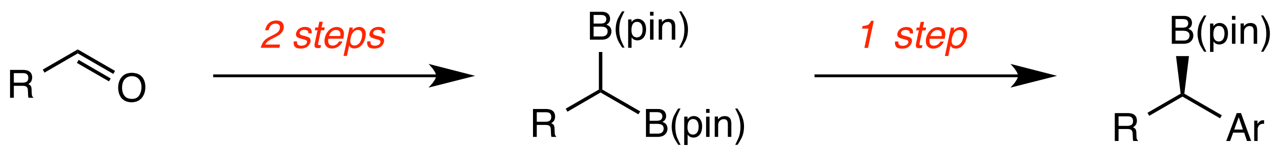
Benzylic boronic esters as building blocks for the formation of C–C, C–O, and C–N



Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

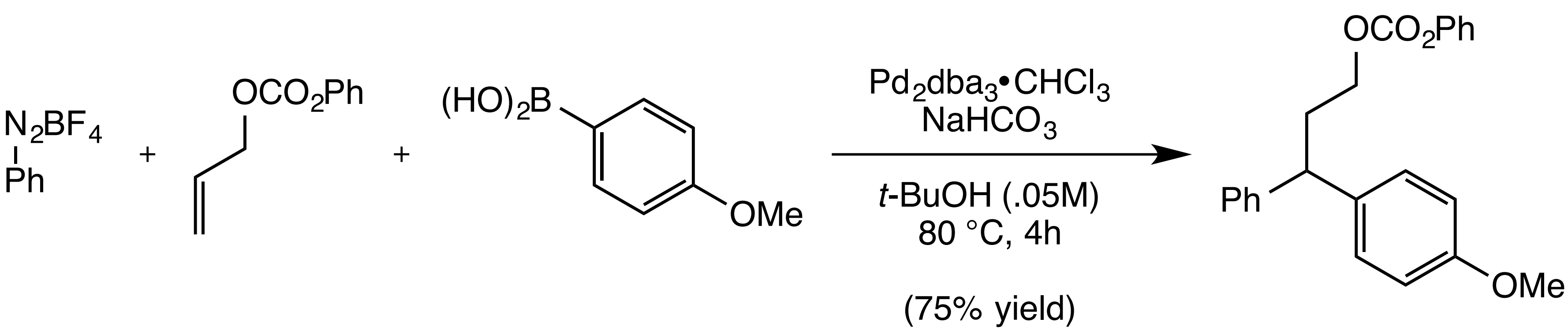
Recent Approaches to Enantioenriched Benzylic Boronic Esters

Benzylic boronic esters as building blocks for the formation of C–C, C–O, and C–N



Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

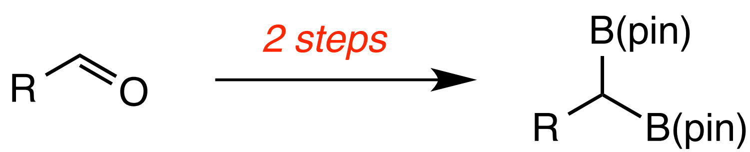
1,1-diarylation of simple alkenes



Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008.

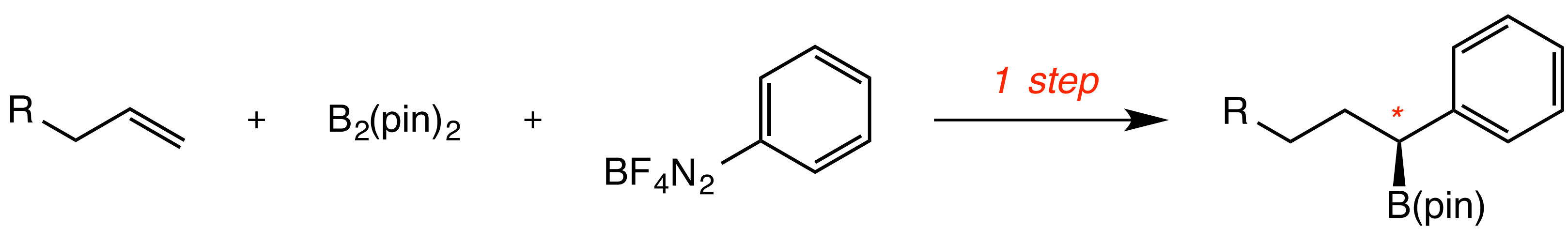
Recent Approaches to Enantioenriched Benzylic Boronic Esters

Benzylic boronic esters as building blocks for the formation of C–C, C–O, and C–N



Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

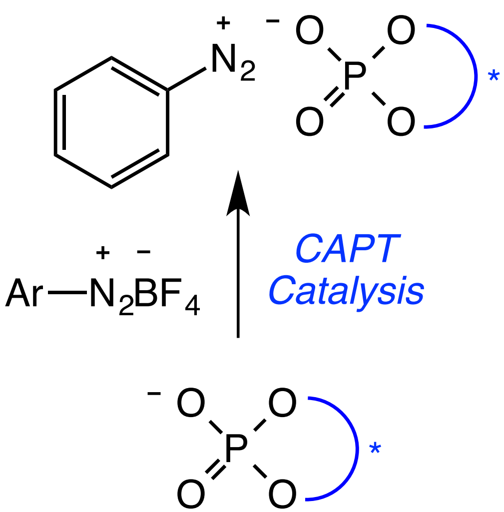
Single step 1,1-arylboration of simple alkenes



Enantioselectivity via CAPT

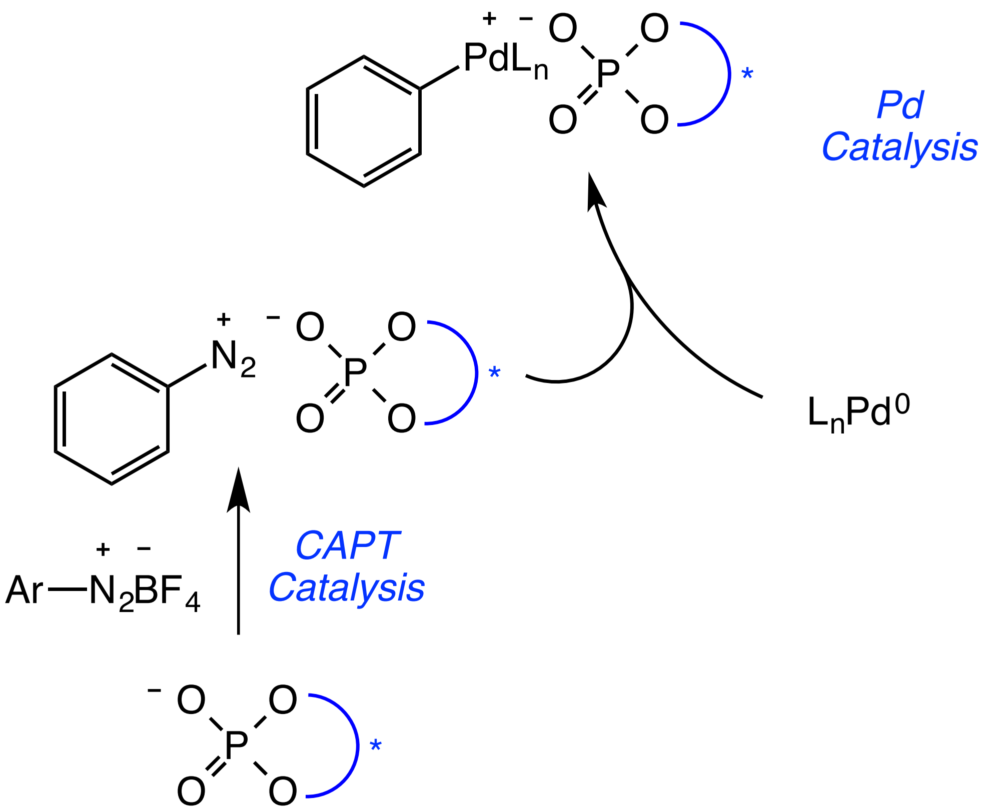
Nelson, H. M.; Williams, B. D.; Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Proposed Dual Catalytic Cycle for 1,1-Arylborylation



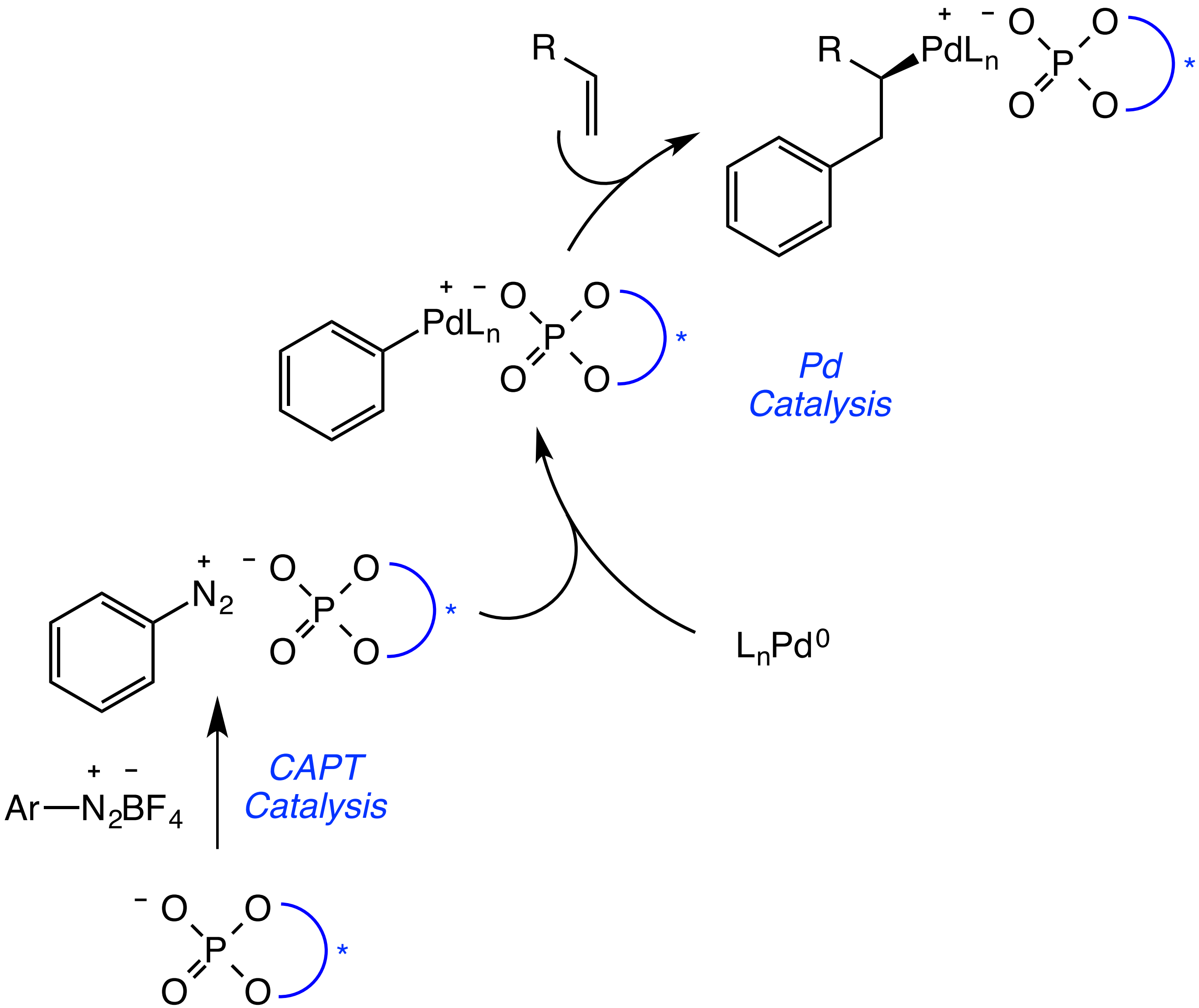
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc*. **2015**, *137*, 3213.

Proposed Dual Catalytic Cycle for 1,1-Arylborylation



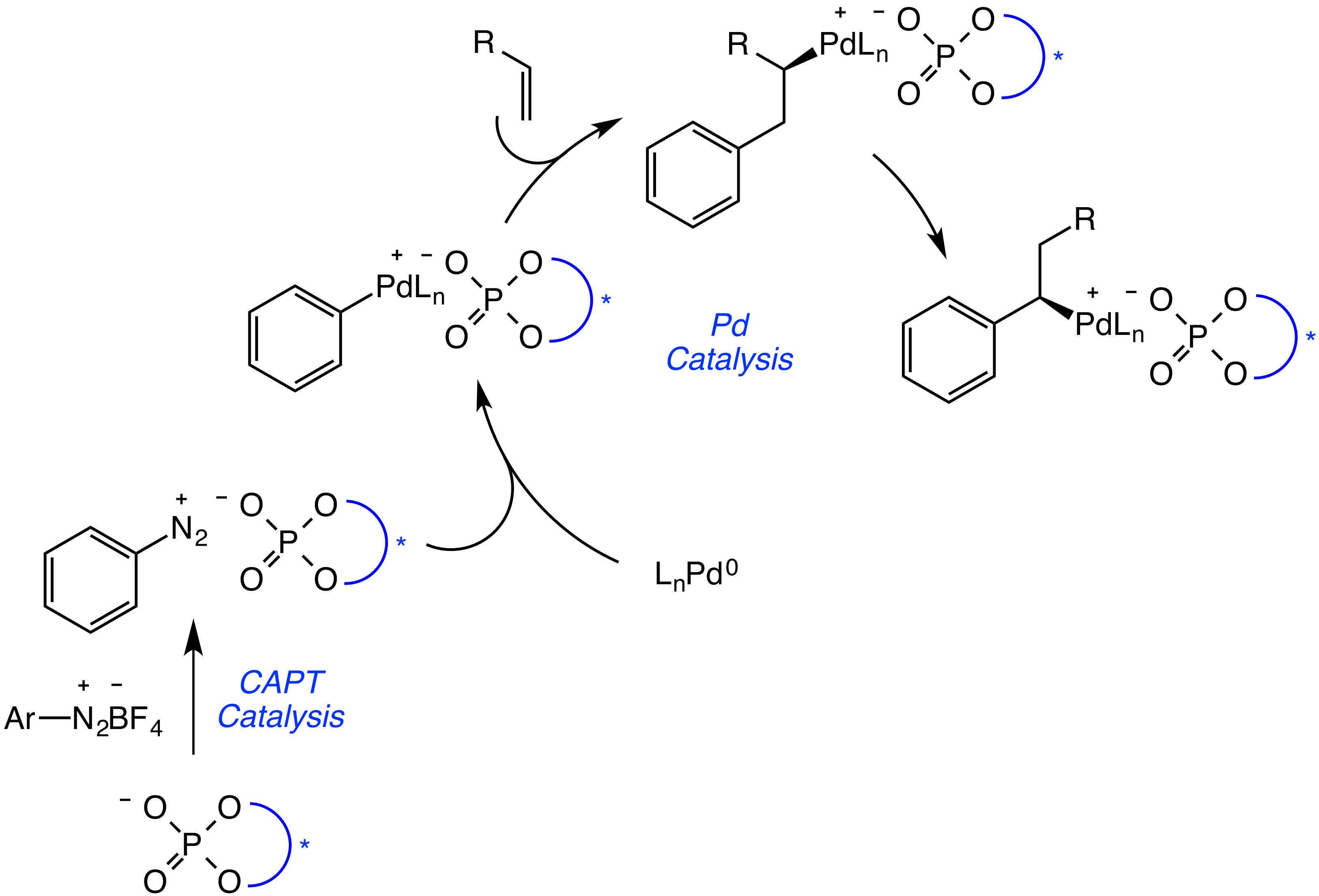
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc*. **2015**, *137*, 3213.

Proposed Dual Catalytic Cycle for 1,1-Arylborylation



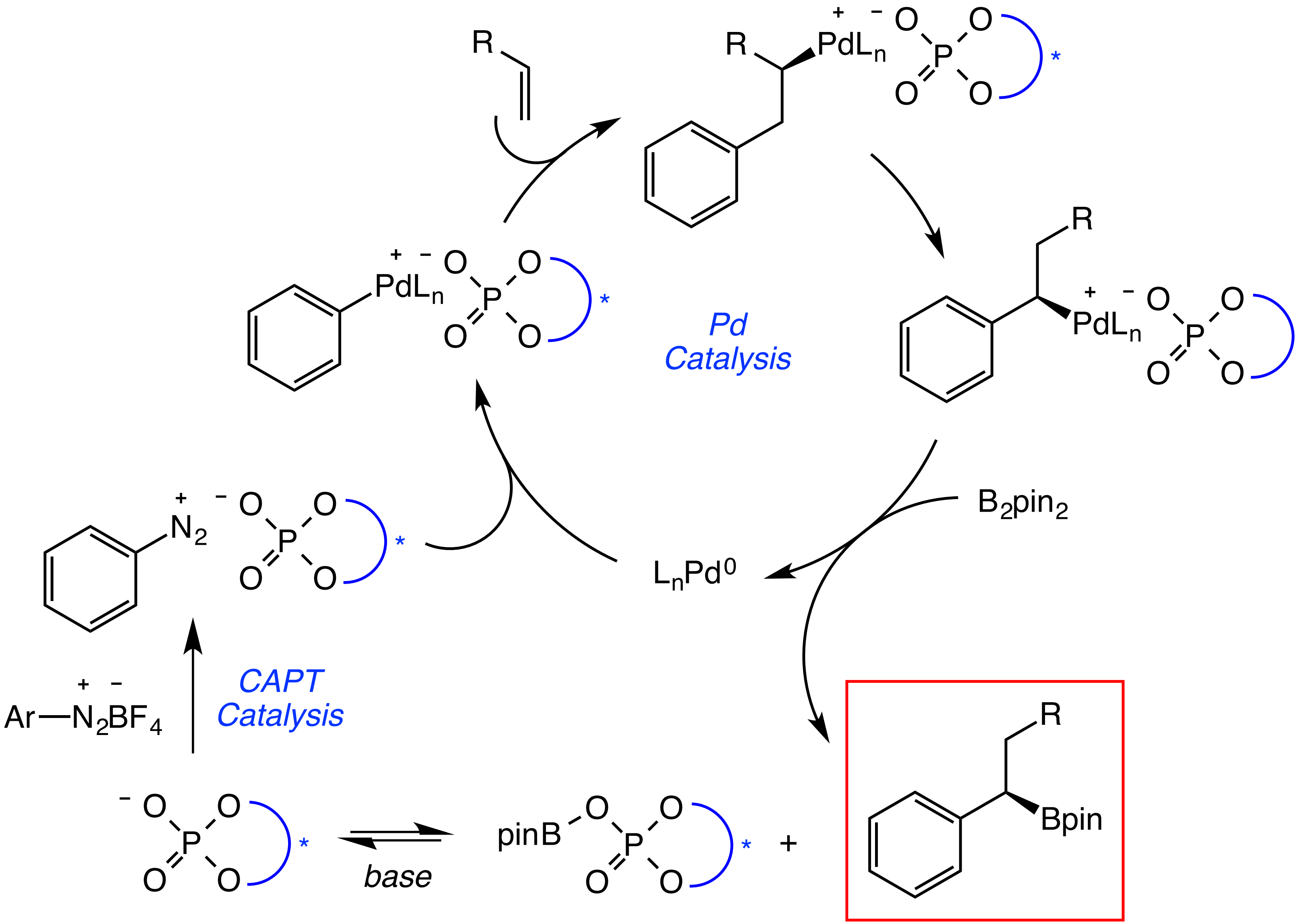
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Proposed Dual Catalytic Cycle for 1,1-Arylborylation



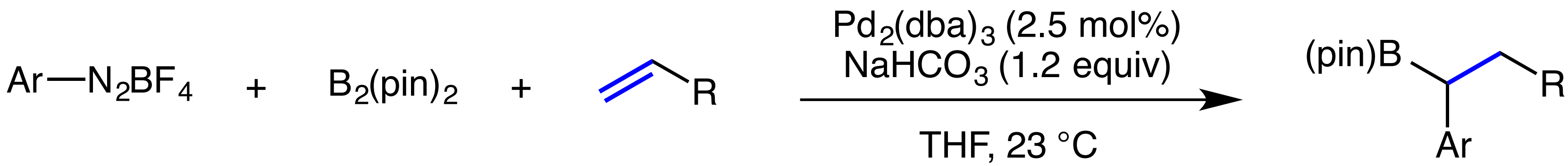
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Proposed Dual Catalytic Cycle for 1,1-Arylborylation



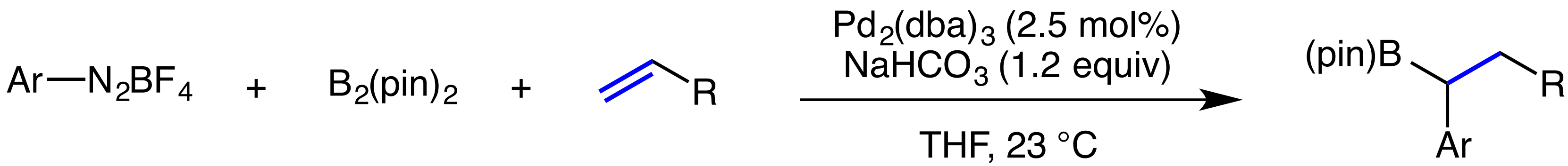
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

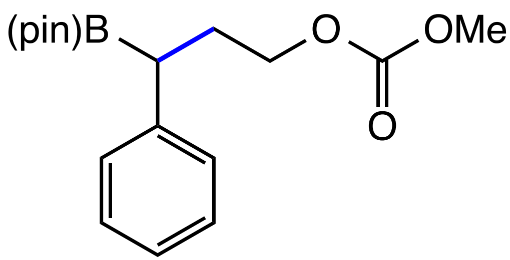
Non-enantioselective Reaction Scope
Aryldiazonium Partner

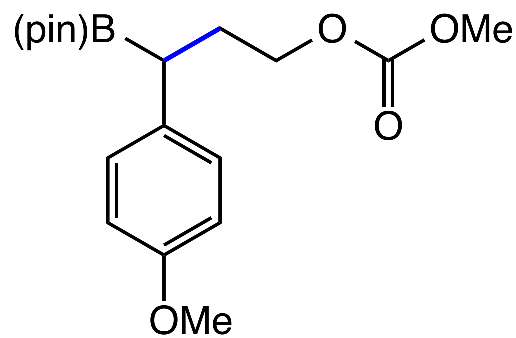


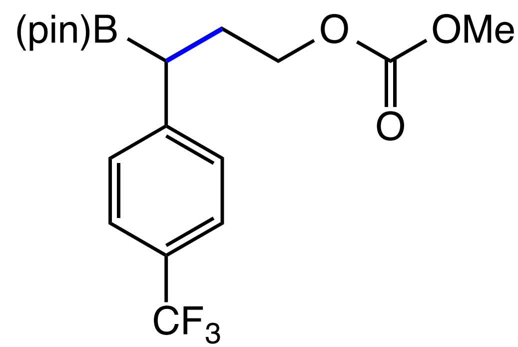
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc*. **2015**, *137*, 3213.

Non-enantioselective Reaction Scope
Aryldiazonium Partner





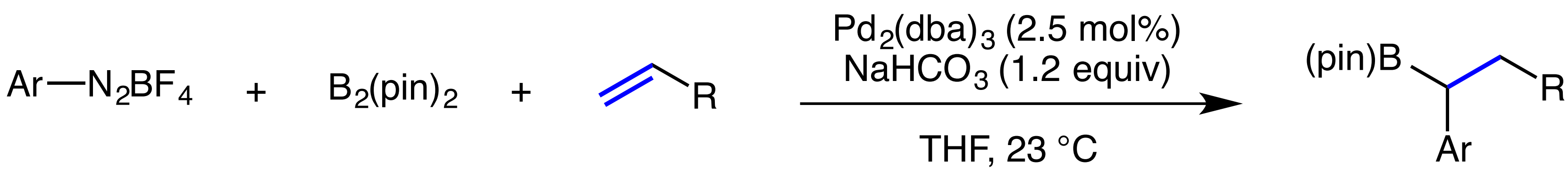


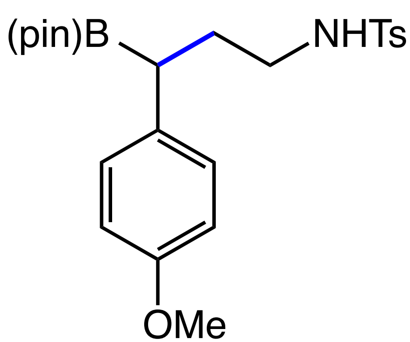


72% yield | 90% yield | 71% yield

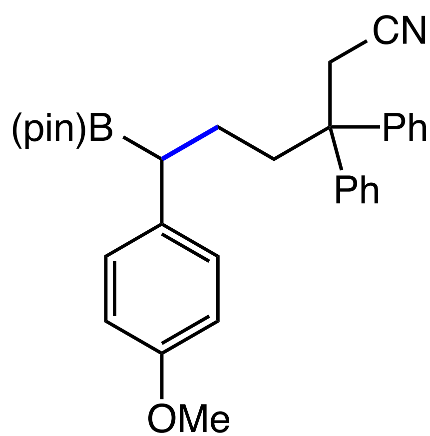
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Non-enantioselective Reaction Scope
Alkene Partner

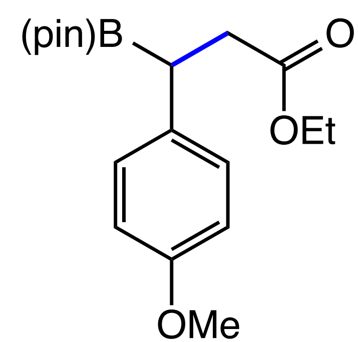




91% yield



99% yield



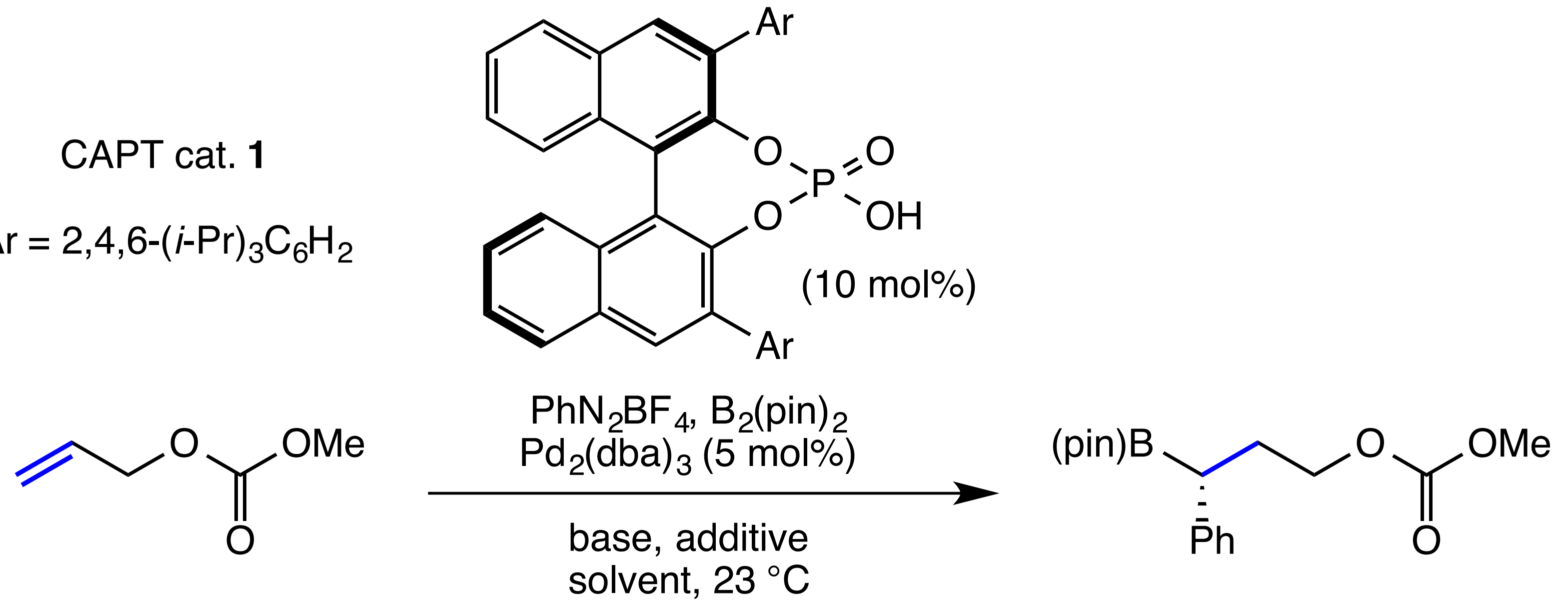
46% yield

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Enantioselective Reaction Optimization Studies

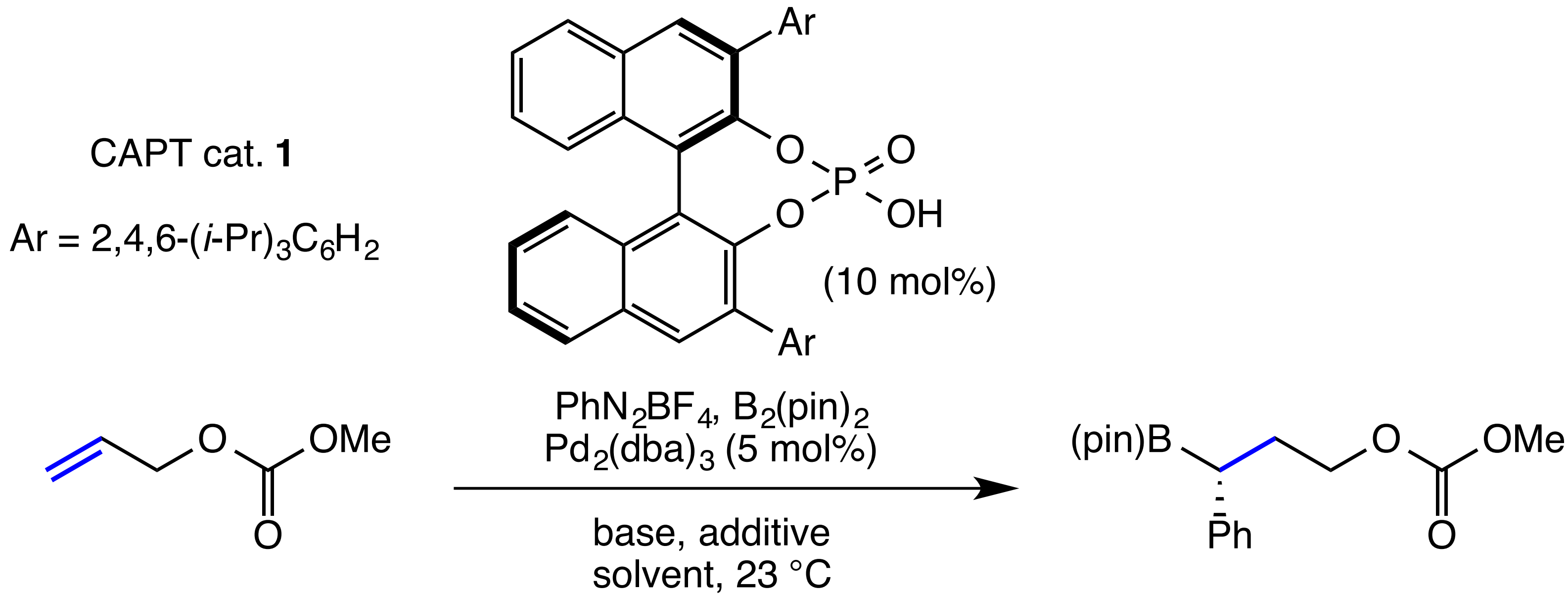
CAPT cat. **1**

Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$



Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

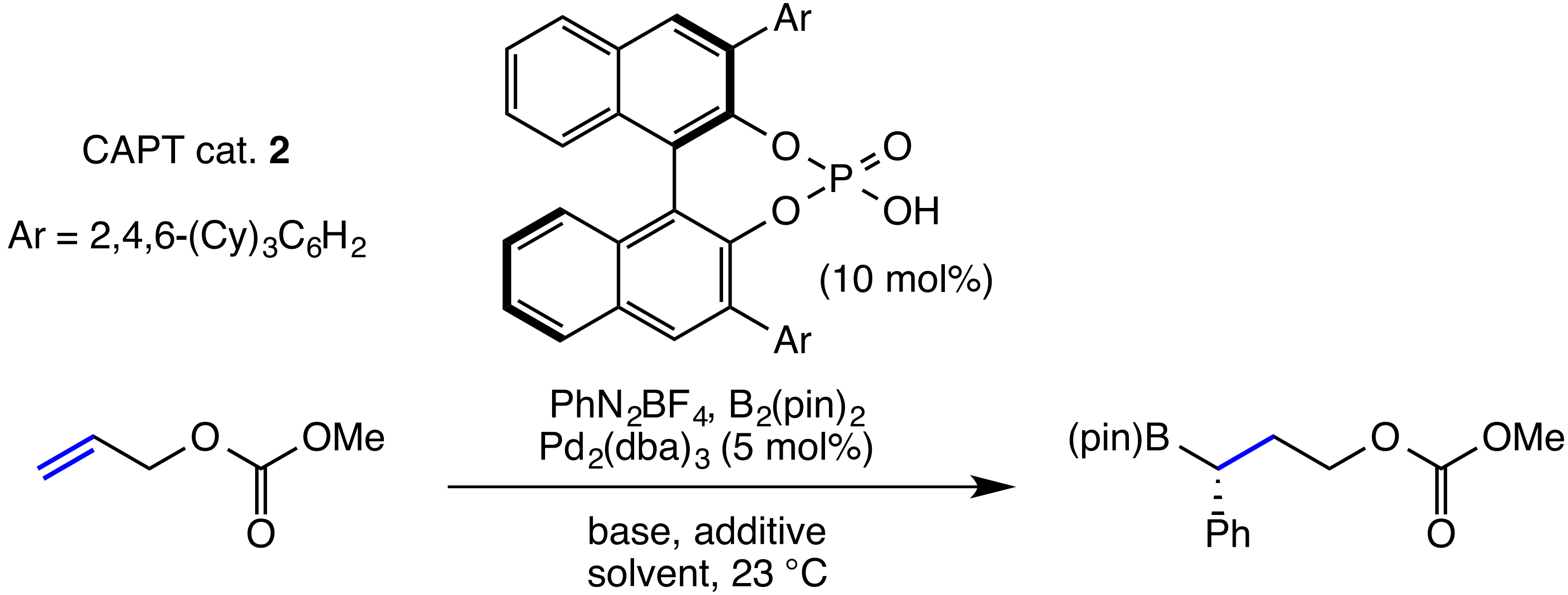
Enantioselective Reaction Optimization Studies



entry	*CAPT cat.*	*solvent*	*base*	*additive*	*yield*	*ee*
1	**1**	hexanes	$NaHCO_3$	–	5%	–
2	**1**	THF	$NaHCO_3$	–	72%	< 5
3	**1**	Et_2O	$NaHCO_3$	–	45%	33

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

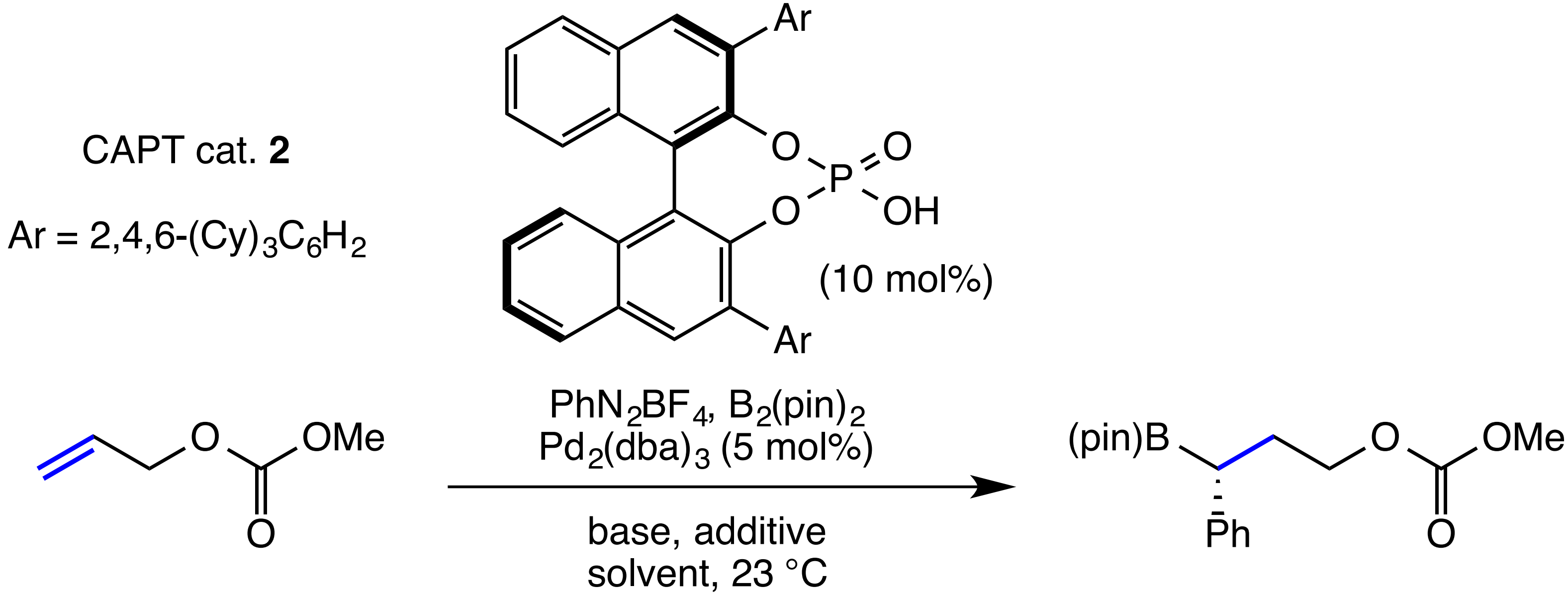
Enantioselective Reaction Optimization Studies



entry	*CAPT cat.*	*solvent*	*base*	*additive*	*yield*	*ee*
1	**1**	hexanes	$NaHCO_3$	–	5%	–
2	**1**	THF	$NaHCO_3$	–	72%	< 5
3	**1**	Et_2O	$NaHCO_3$	–	45%	33
4	**2**	Et_2O	$NaHCO_3$	–	25%	88

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

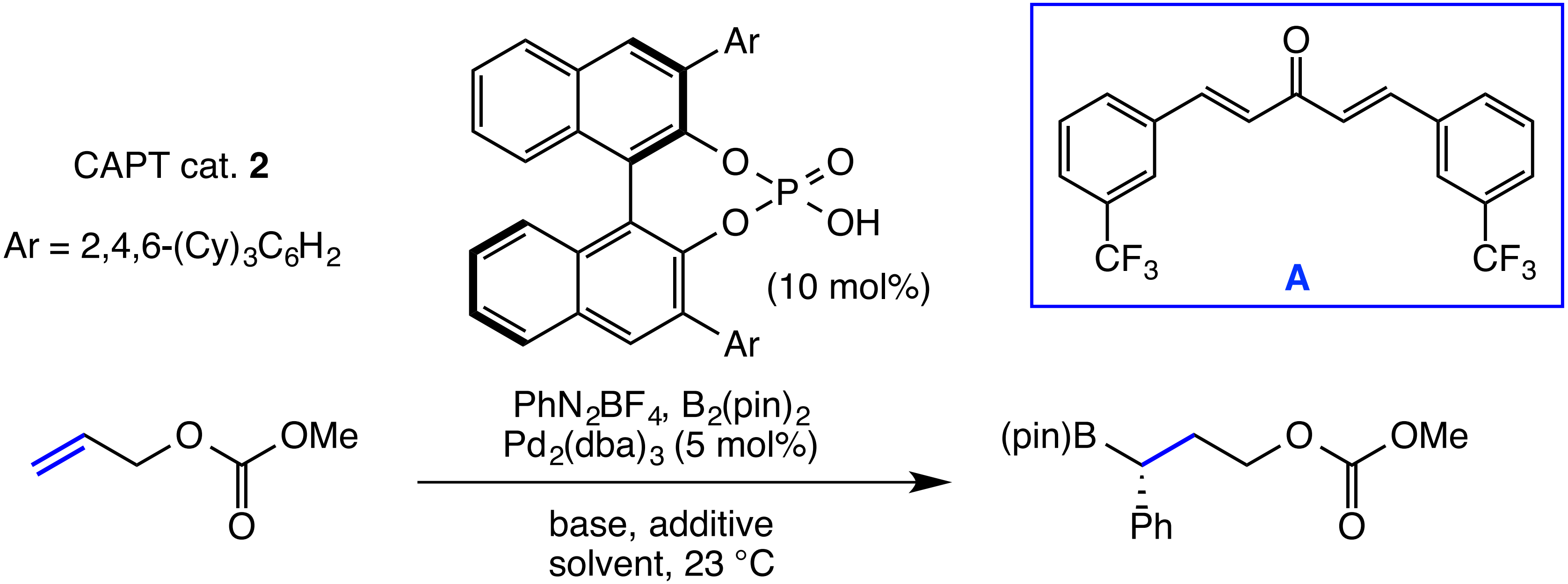
Enantioselective Reaction Optimization Studies



entry	*CAPT cat.*	*solvent*	*base*	*additive*	*yield*	*ee*
1	**1**	hexanes	$NaHCO_3$	–	5%	–
2	**1**	THF	$NaHCO_3$	–	72%	< 5
3	**1**	Et_2O	$NaHCO_3$	–	45%	33
4	**2**	Et_2O	$NaHCO_3$	–	25%	88
5	**2**	Et_2O	Na_3PO_4	–	26%	93

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Enantioselective Reaction Optimization Studies



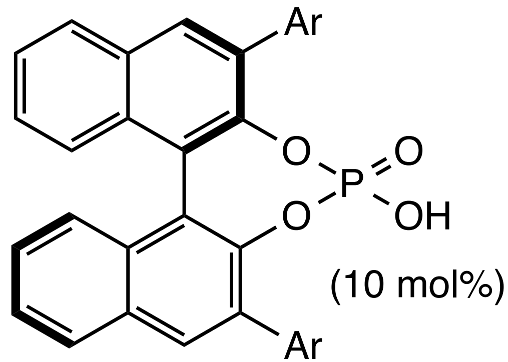
entry	*CAPT cat.*	*solvent*	*base*	*additive*	*yield*	*ee*
1	**1**	hexanes	$NaHCO_3$	–	5%	–
2	**1**	THF	$NaHCO_3$	–	72%	< 5
3	**1**	Et_2O	$NaHCO_3$	–	45%	33
4	**2**	Et_2O	$NaHCO_3$	–	25%	88
5	**2**	Et_2O	Na_3PO_4	–	26%	93
6	**2**	Et_2O	Na_3PO_4	**A**	39%	90

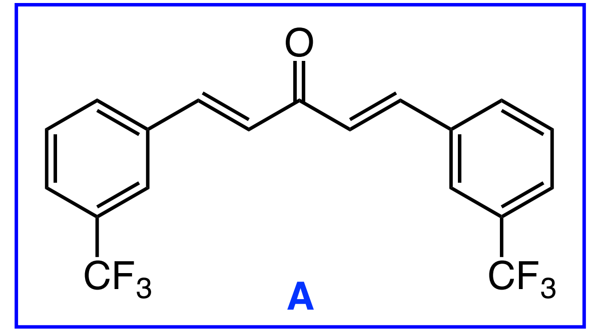
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

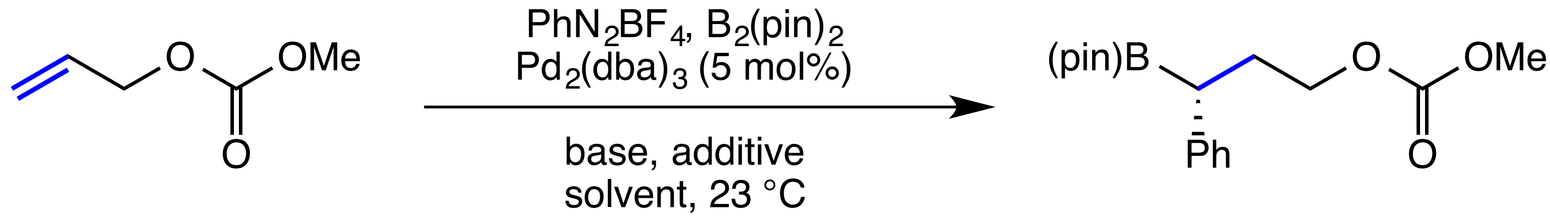
Reaction Scope - Aryldiazonium Partner

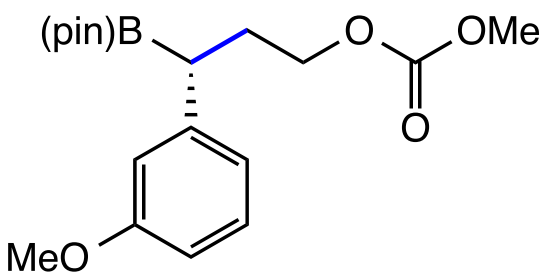
CAPT cat. **2**

Ar = 2,4,6-$(Cy)_3C_6H_2$

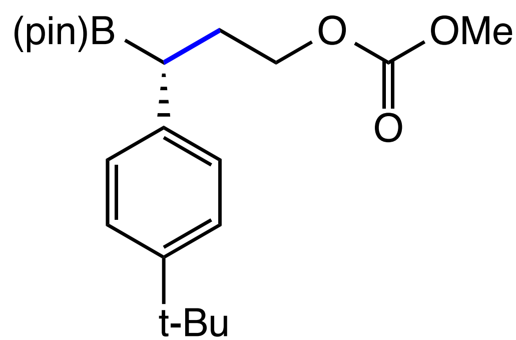




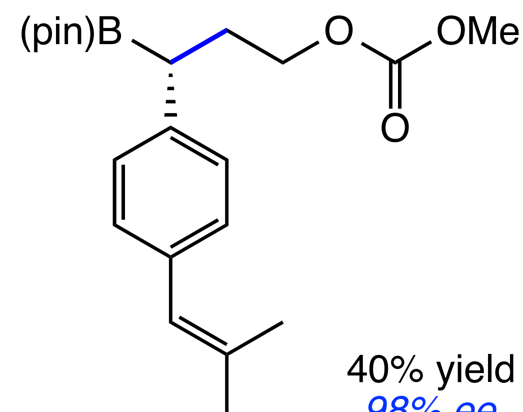




58% yield
87% ee



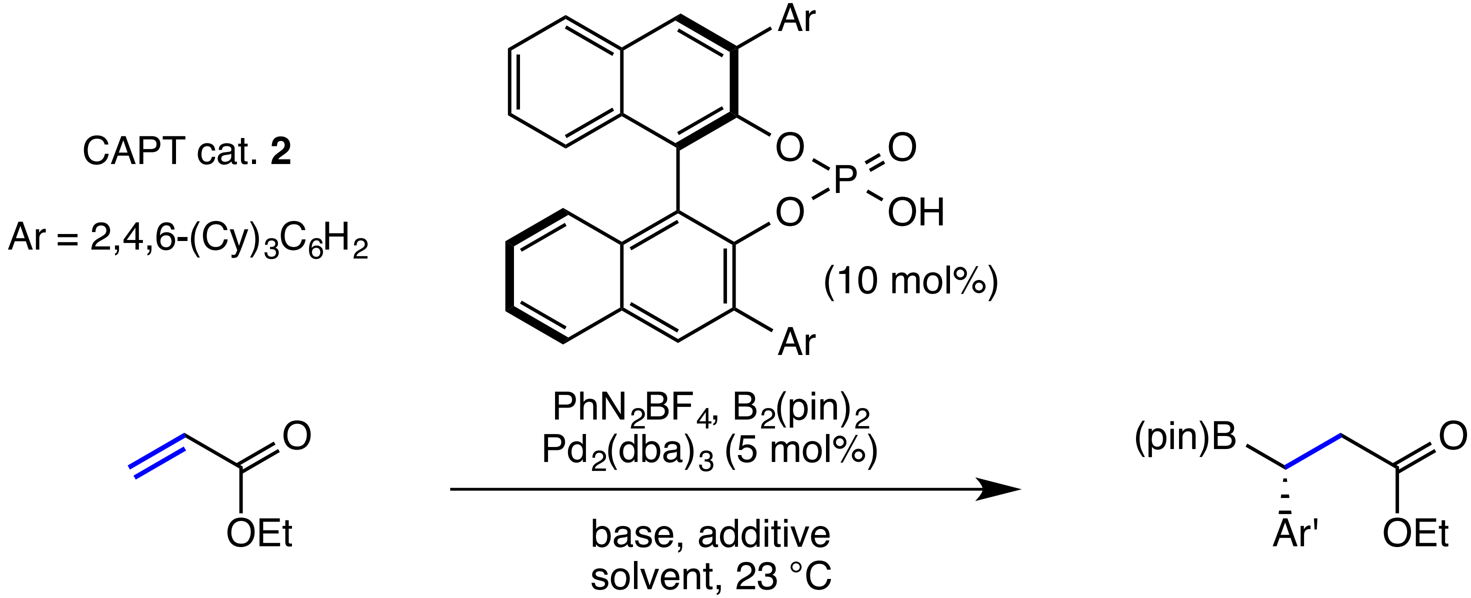
32% yield
96% ee

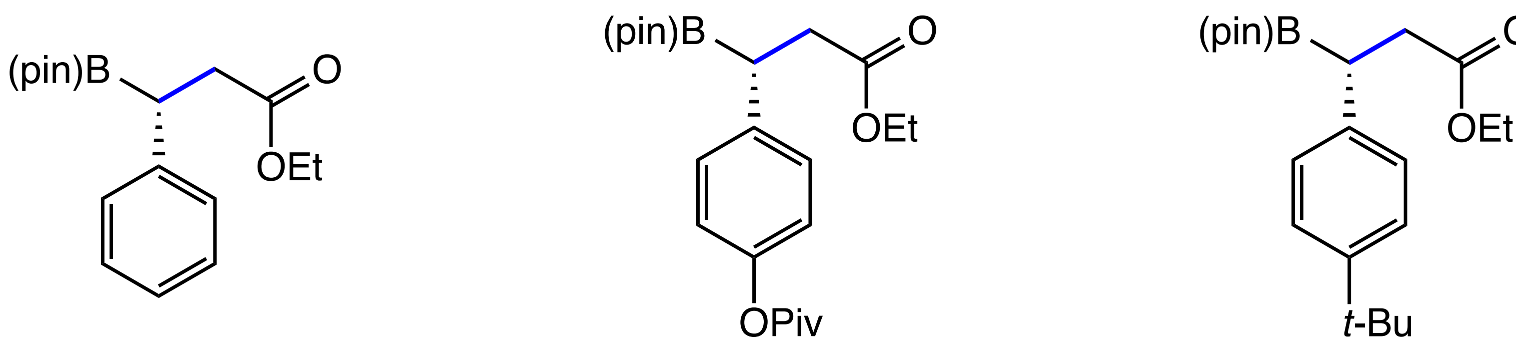


40% yield
98% ee

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Reaction Scope - Alkene Partner

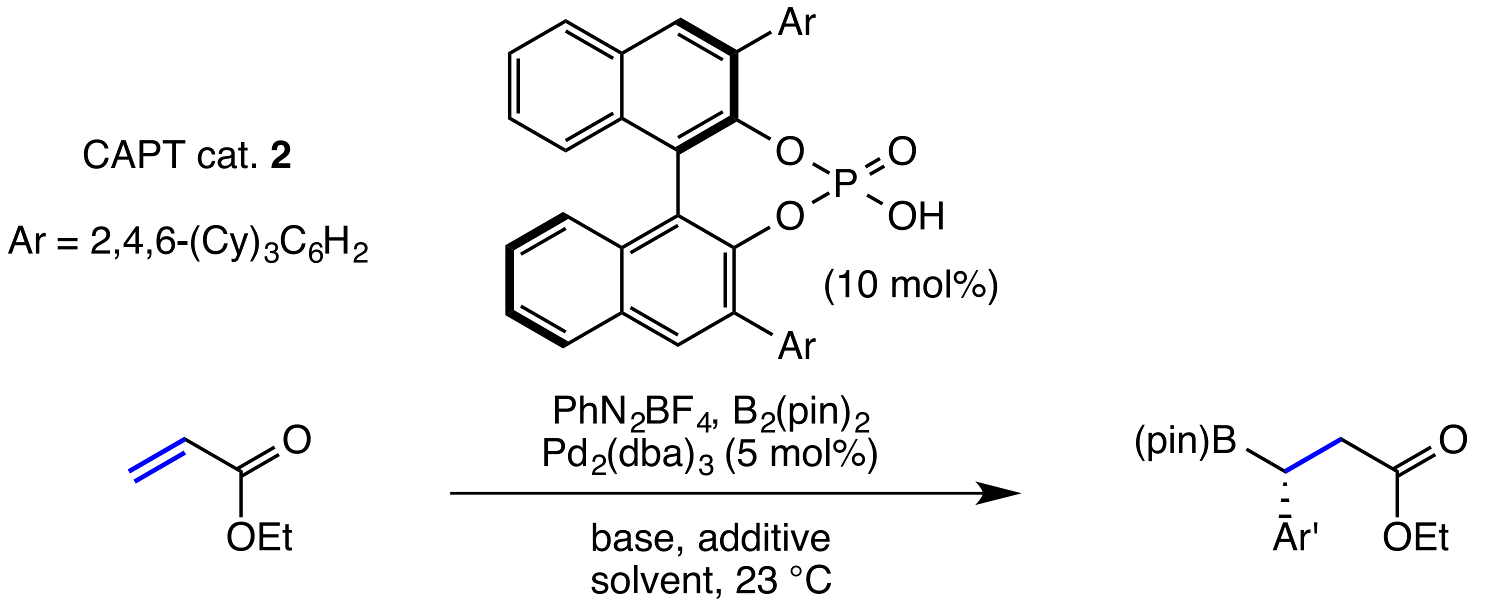




47% yield	40% yield	33% yield
89% ee	*97% ee*	*98% ee*

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Reaction Scope - Alkene Partner



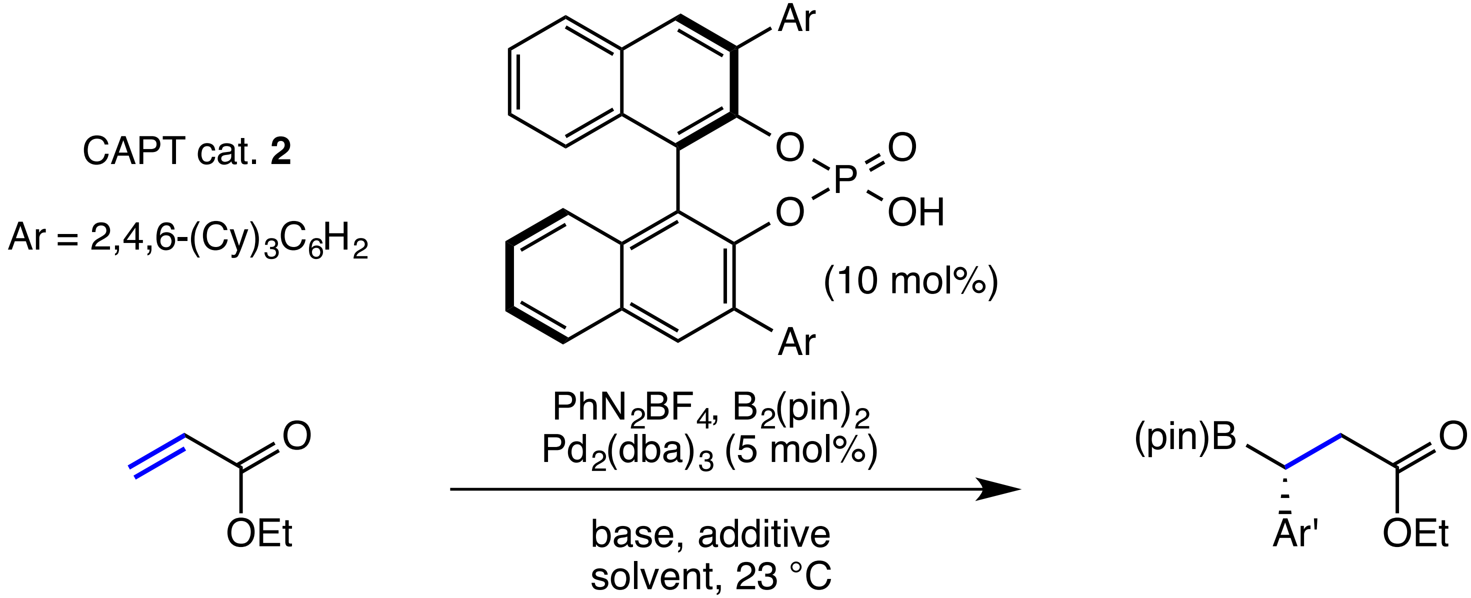
Limitations

Yields range from low to synthetically useful

Limited scope in terms of functional group tolerance and alkene partners

Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Reaction Scope - Alkene Partner



Accomplishments

Modular and step-economical method for access to chiral benzylic boronates

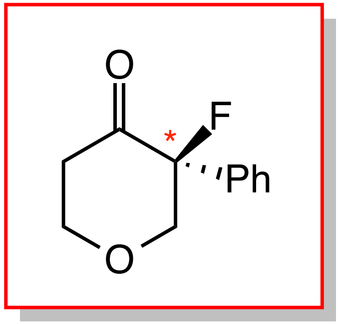
Process rendered enantioselective via chiral anion phase-transfer

Alternative strategy for achieving enantioinduction

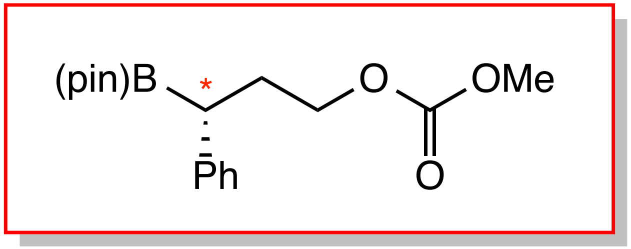
Nelson, H. M.; Williams, B. D., Miro, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.

Presentation Overview

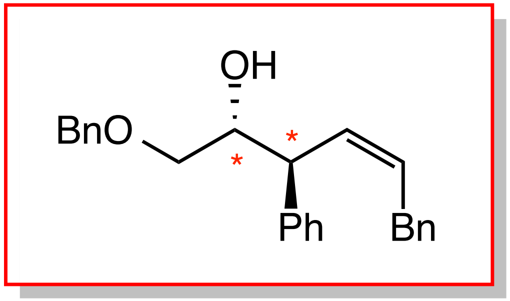
- Intro to phase-transfer catalysis
  - Chiral cation phase-transfer catalysis (CCPT)
  - Chiral anion phase-transfer catalysis (CAPT)



- The merging of CAPT and enamine catalysis
  - α-Fluorinated ketones



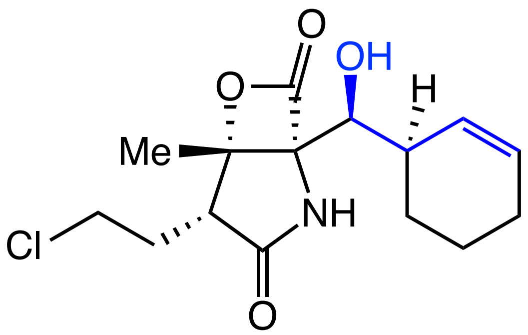
- The merging of CAPT and palladium catalysis
  - Benzylic boronic esters



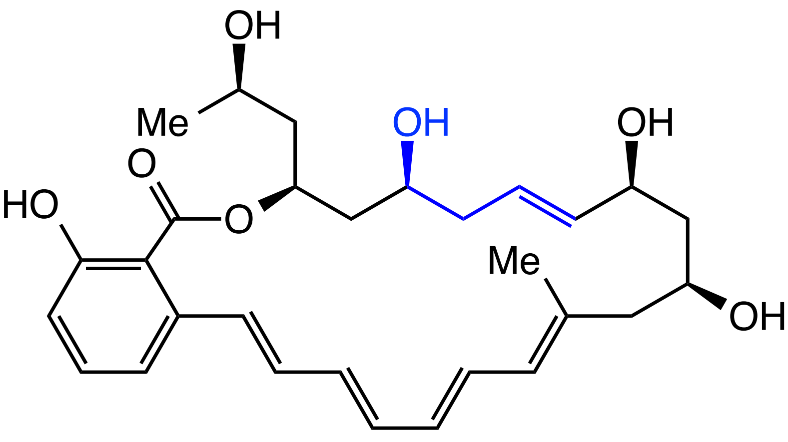
- The merging of CAPT and palladium catalysis
  - Homoallylic alcohols

Prevalence of Homoallylic Alcohols

Homoallylic alcohols are present in many pharmaceuticals and natural products



salinosporamide A

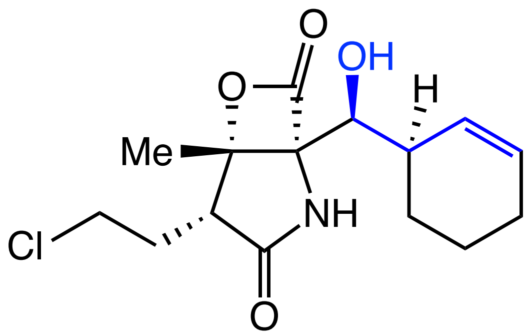


monomarinomycin A

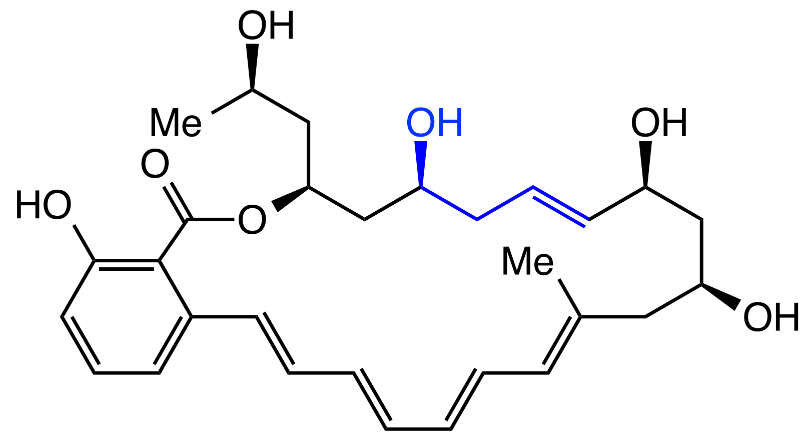
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Prevalence of Homoallylic Alcohols

Homoallylic alcohols are present in many pharmaceuticals and natural products

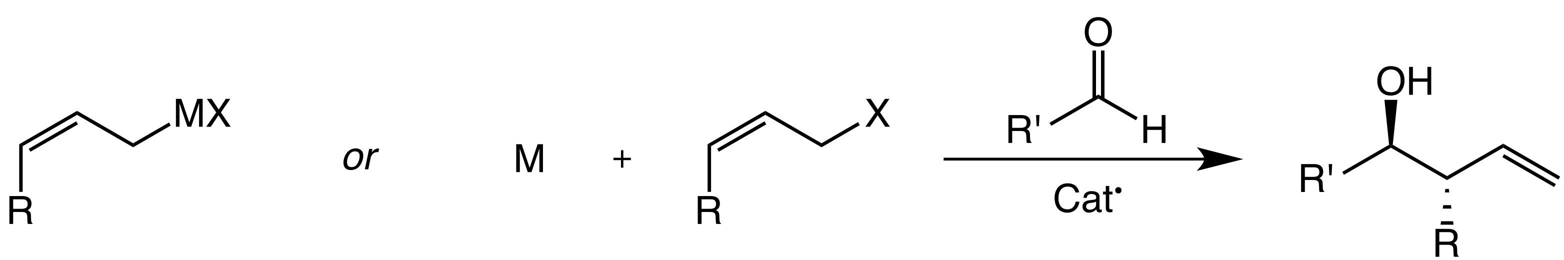


salinosporamide A



monomarinomycin A

Asymmetric allylation of carbonyls

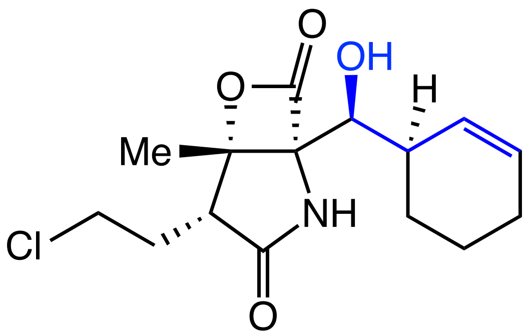


pre-formed *in-situ generated*

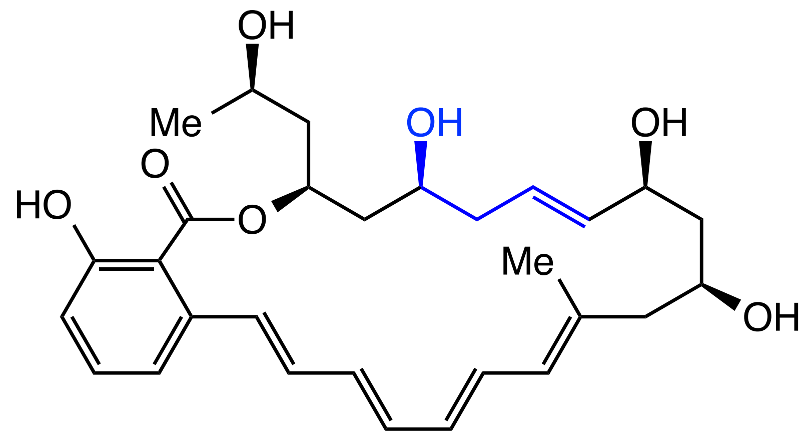
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Prevalence of Homoallylic Alcohols

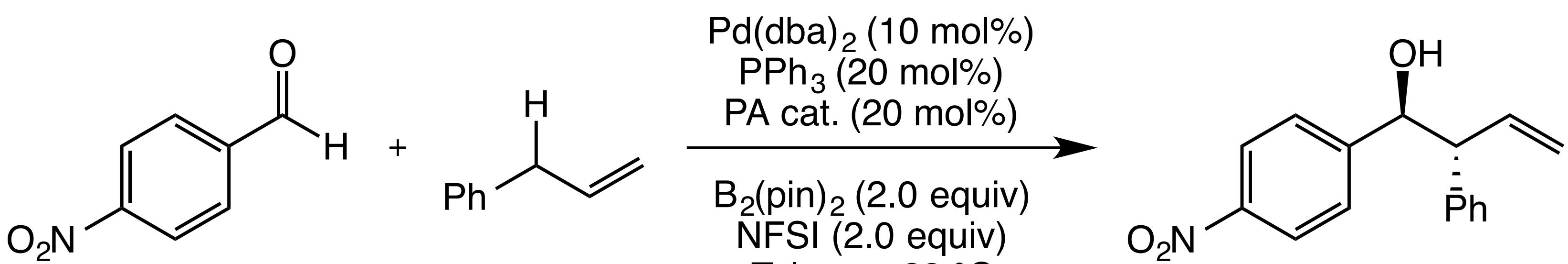
Homoallylic alcohols are present in many pharmaceuticals and natural products



salinosporamide A



monomarinomycin A

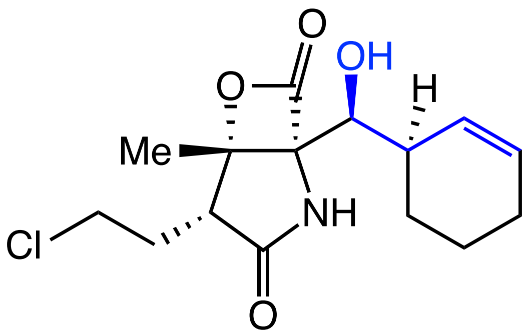


65% yield, >20:1 dr
67% ee

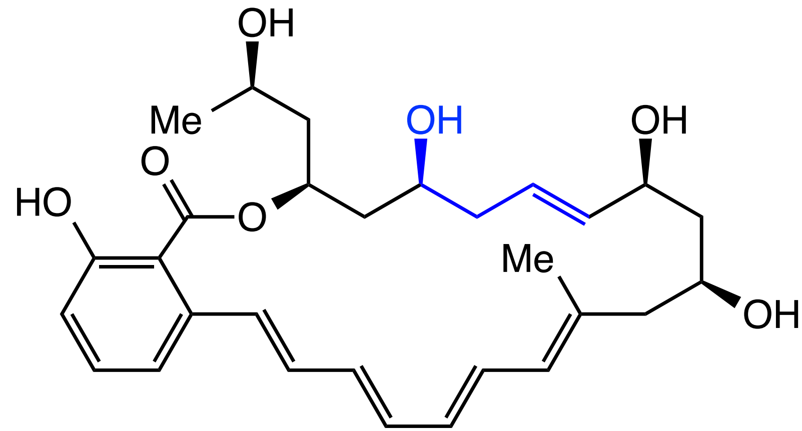
Tao, Z.-L.; Li, X.-H.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 4054.

Prevalence of Homoallylic Alcohols

Homoallylic alcohols are present in many pharmaceuticals and natural products

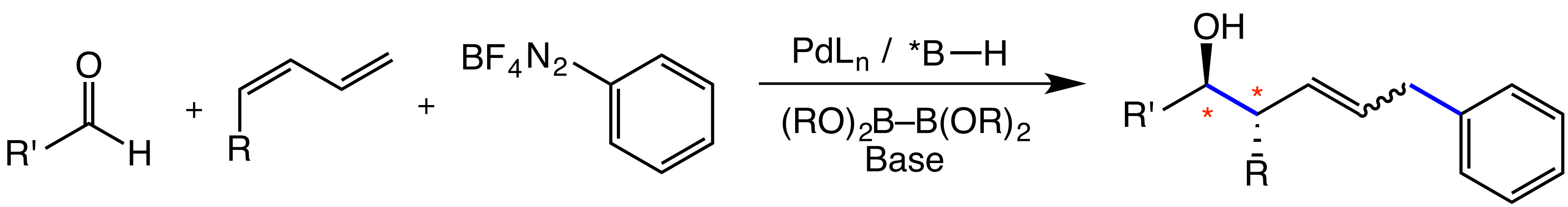


salinosporamide A



monomarinomycin A

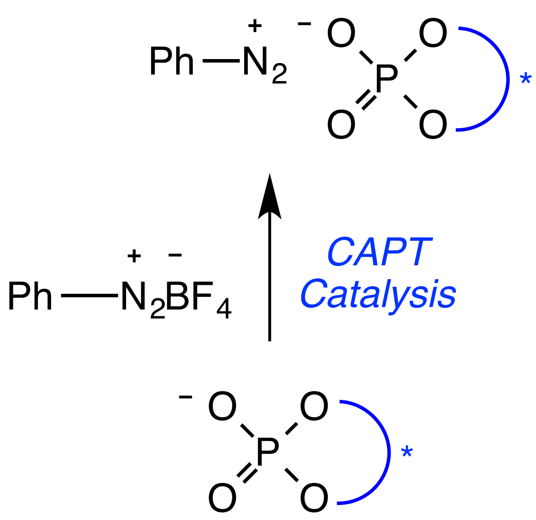
Multicomponent asymmetric allylation of carbonyls



Two new C–C bonds
Two new vicinal stereocenters

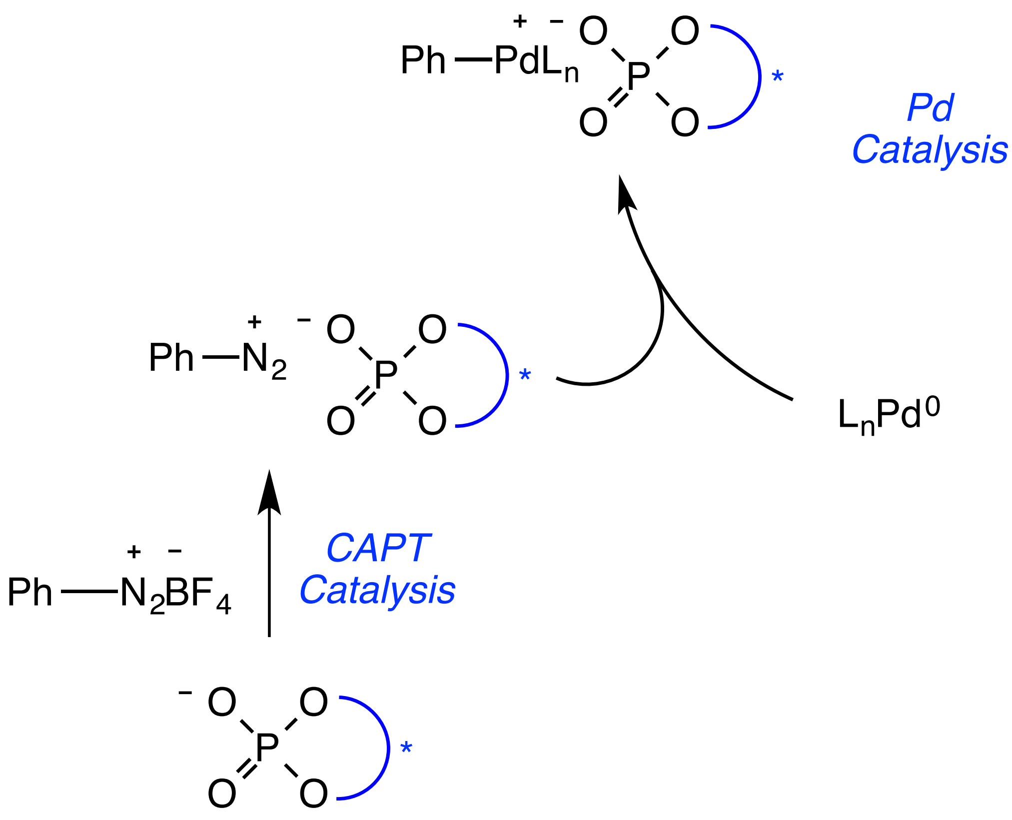
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Proposed Dual Catalytic Cycle - Carbonyl Allylation



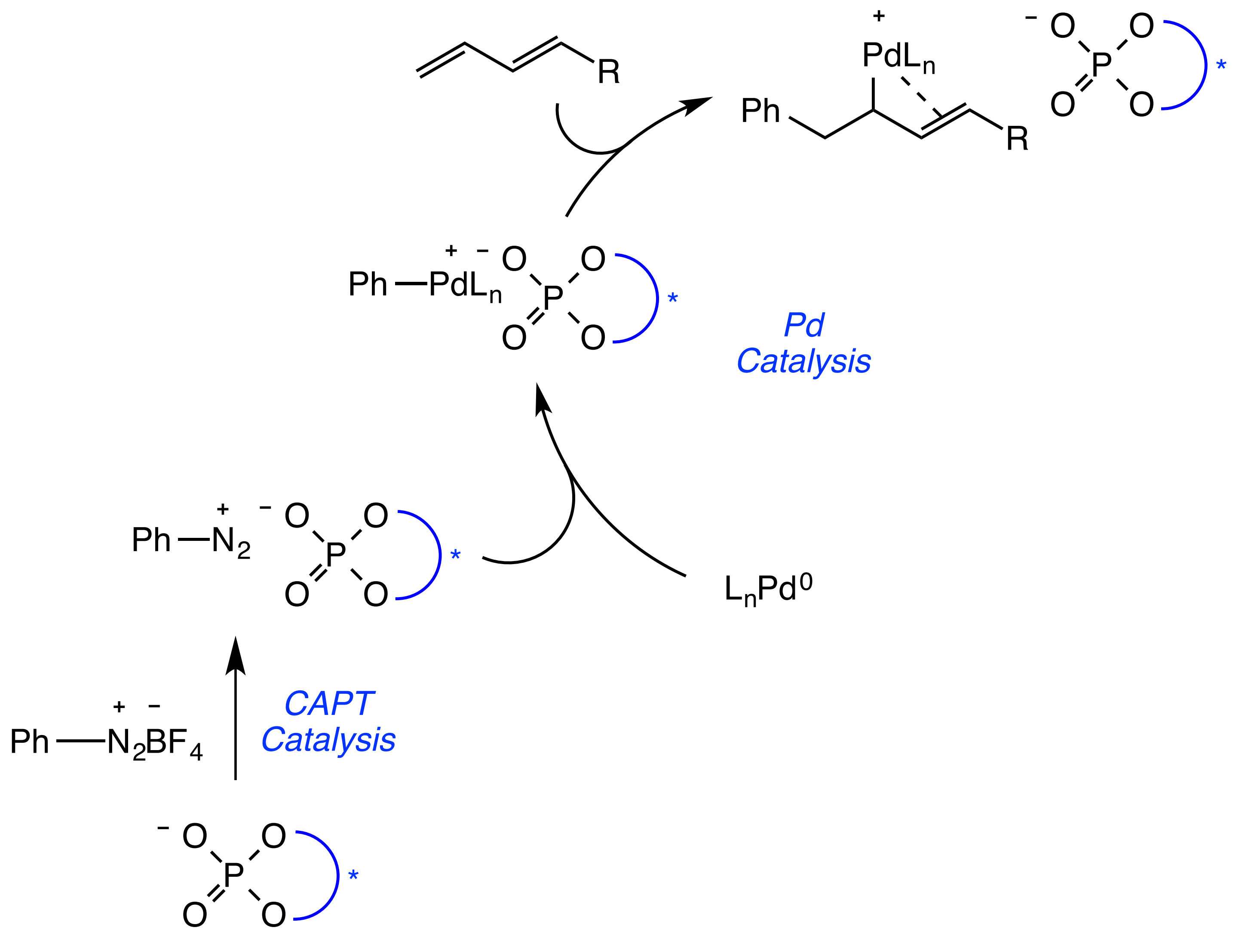
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Proposed Dual Catalytic Cycle - Carbonyl Allylation



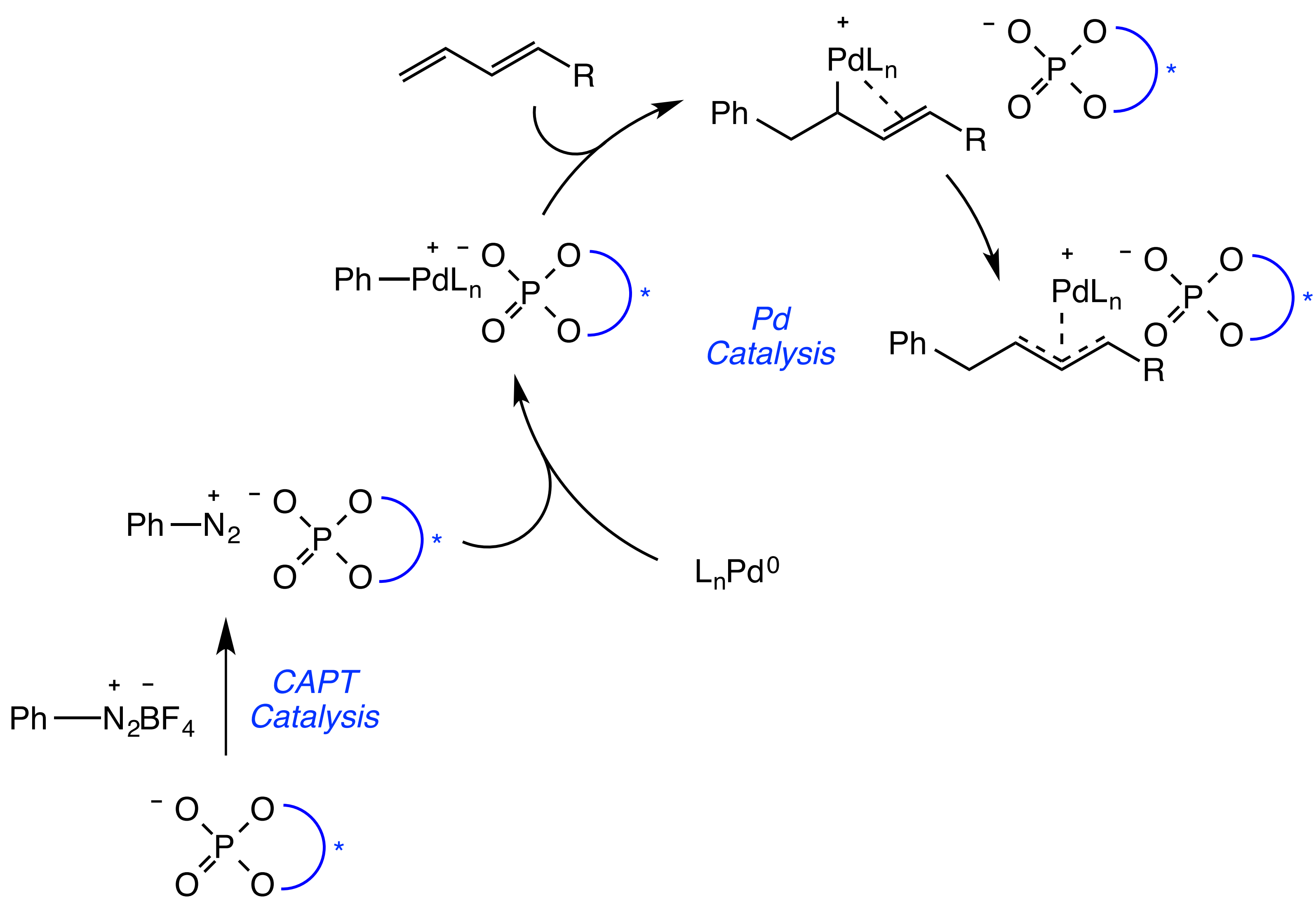
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed*. **2016**, *55*, 4322.

Proposed Dual Catalytic Cycle - Carbonyl Allylation



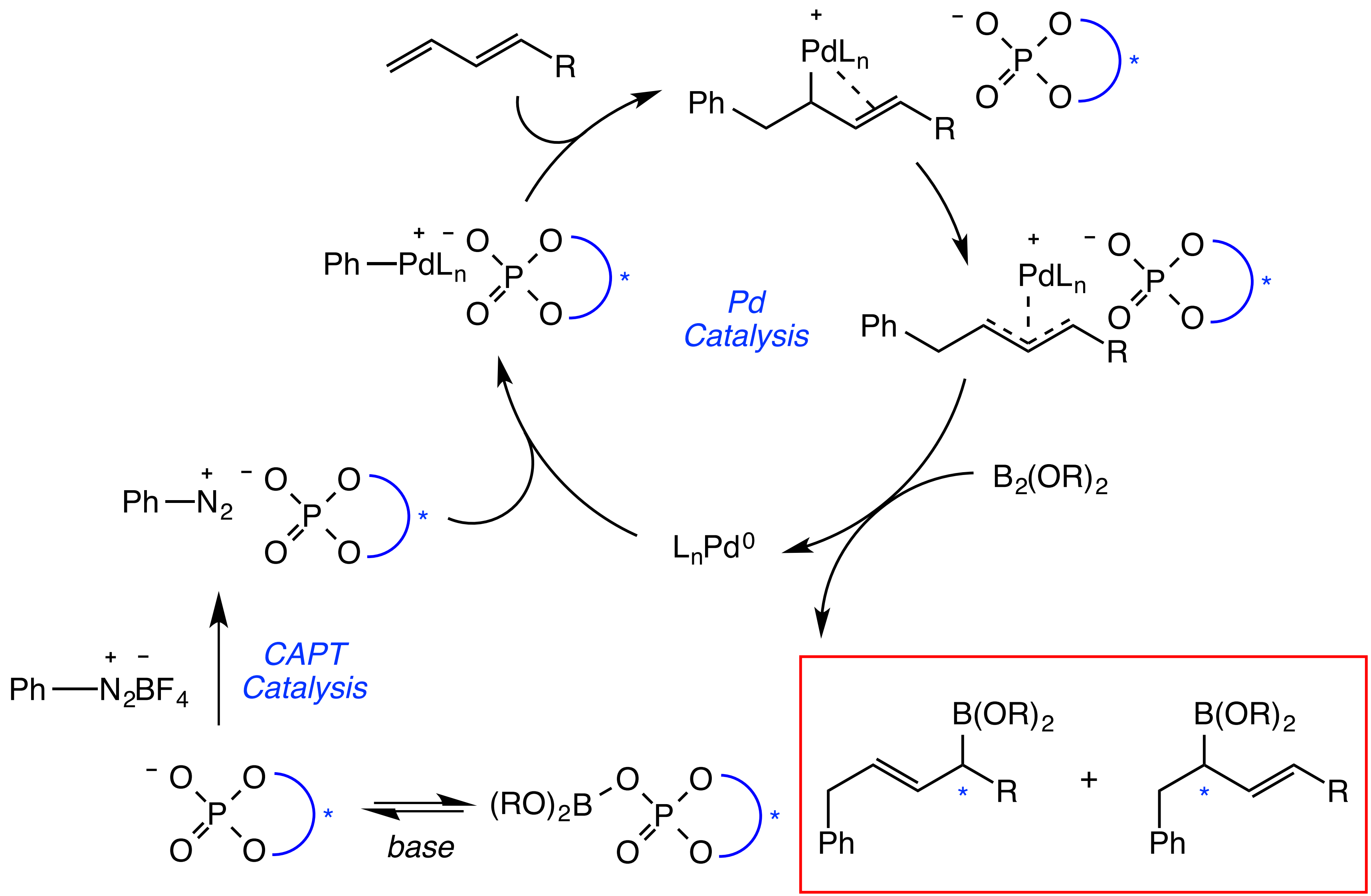
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Proposed Dual Catalytic Cycle - Carbonyl Allylation



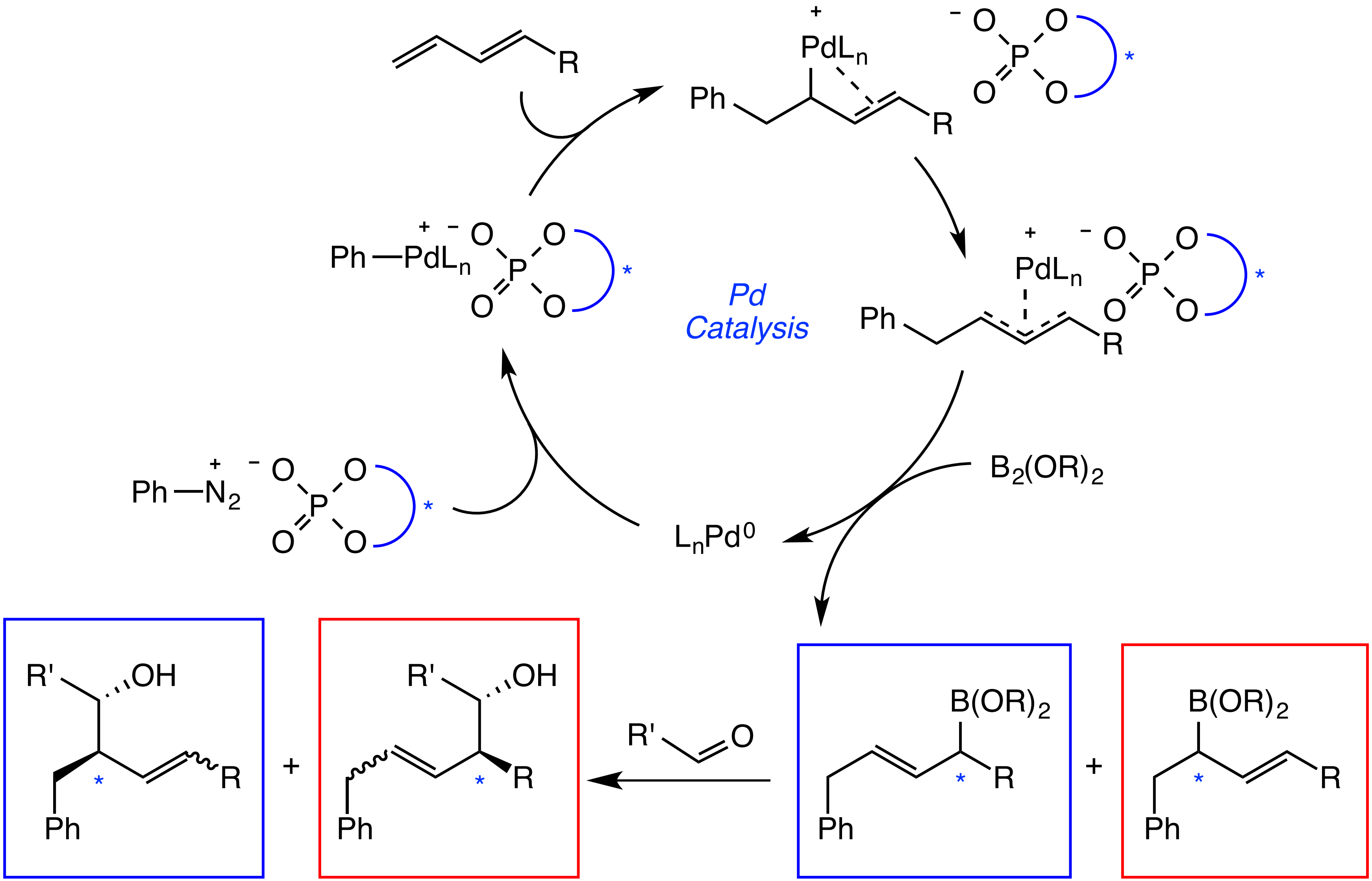
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Proposed Dual Catalytic Cycle - Carbonyl Allylation



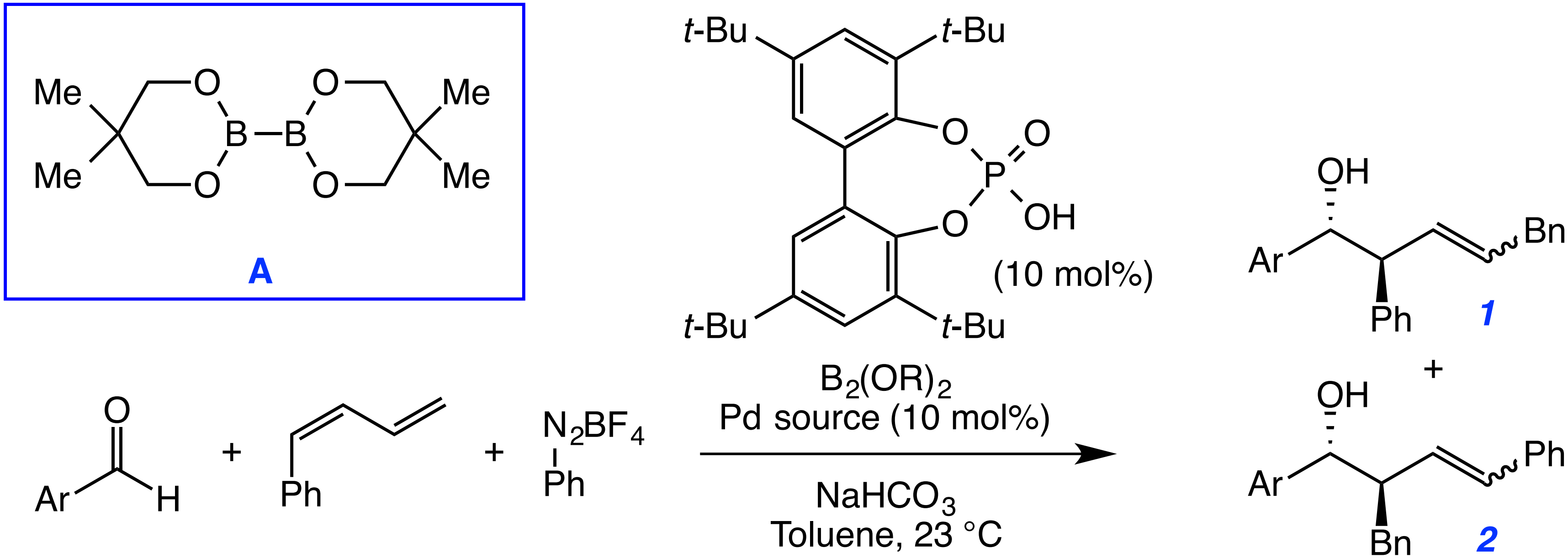
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Proposed Dual Catalytic Cycle - Carbonyl Allylation



Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

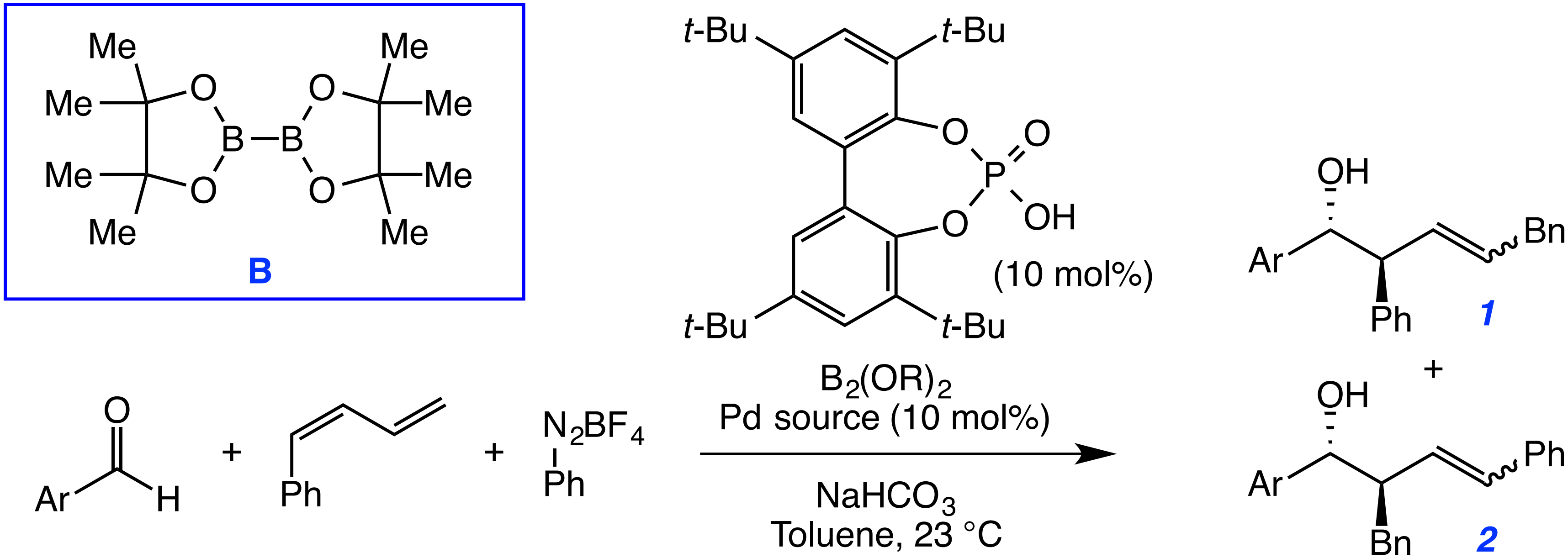
Reaction Optimization Studies



entry	*diborate*	*phosphoric acid*	*Pd*	*yield*	***1* / *2***	*Z / E*	*ee*
1	**A**	PA 1	$Pd(dba)_2$	70%	1.3:1	1:2	–

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

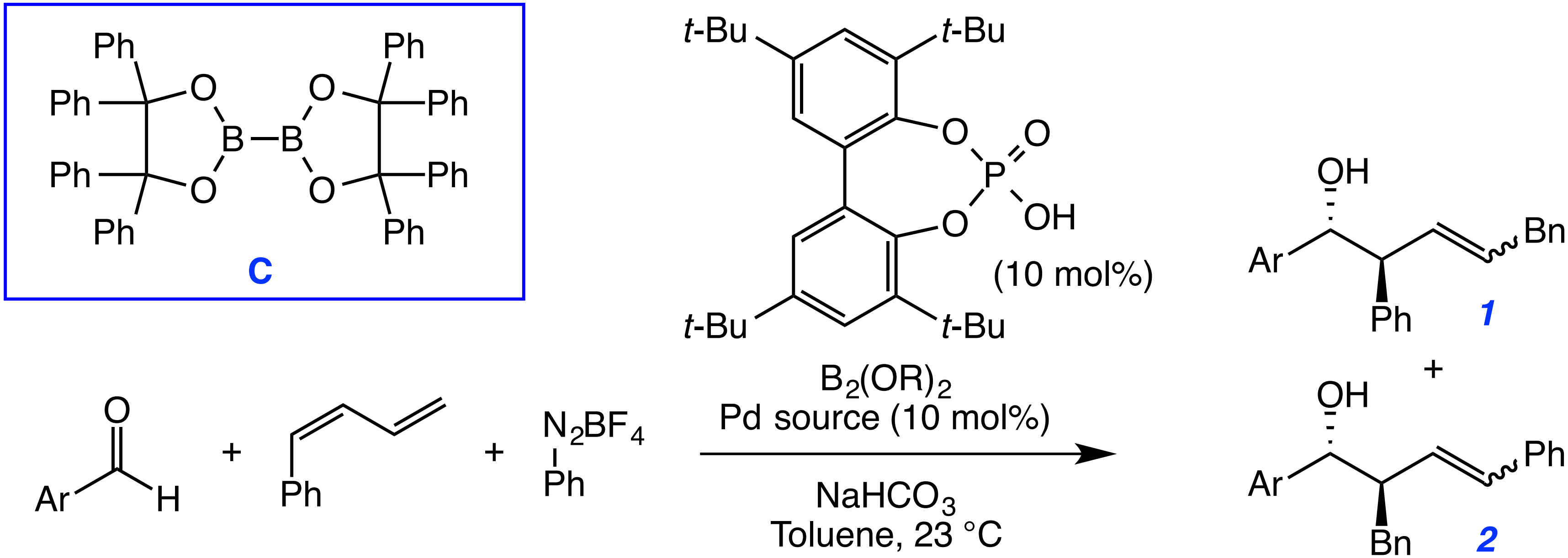
Reaction Optimization Studies



entry	*diborate*	*phosphoric acid*	*Pd*	*yield*	***1* / *2***	*Z / E*	*ee*
1	**A**	PA 1	$Pd(dba)_2$	70%	1.3:1	1:2	–
2	**B**	PA 1	$Pd(dba)_2$	90%	2.7:1	1.7:1	–

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

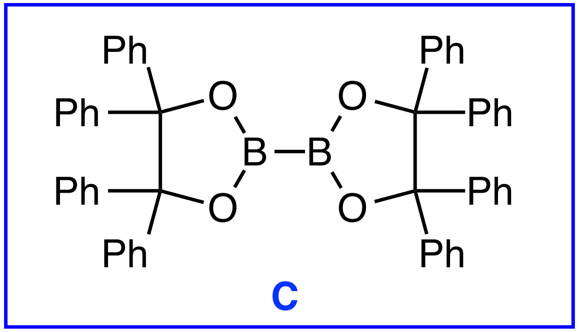
Reaction Optimization Studies

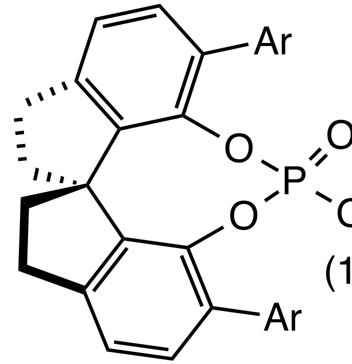


entry	*diborate*	*phosphoric acid*	*Pd*	*yield*	***1* / *2***	*Z* / *E*	*ee*
1	**A**	PA 1	$Pd(dba)_2$	70%	1.3:1	1:2	–
2	**B**	PA 1	$Pd(dba)_2$	90%	2.7:1	1.7:1	–
3	**C**	PA 1	$Pd(dba)_2$	99%	>20:1	>20:1	–

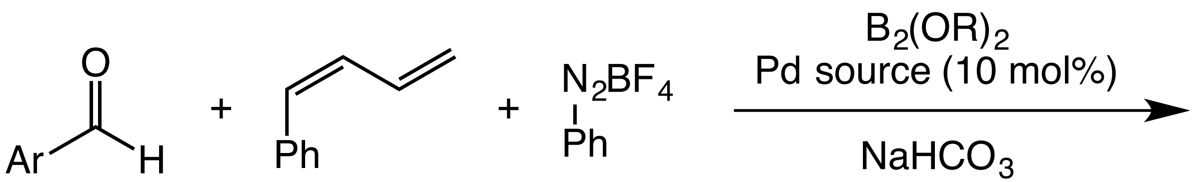
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

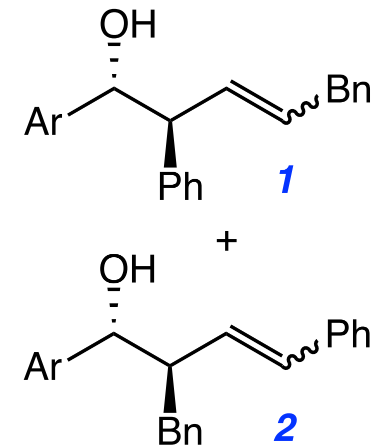
Reaction Optimization Studies





PA 2
Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$
(10 mol%)

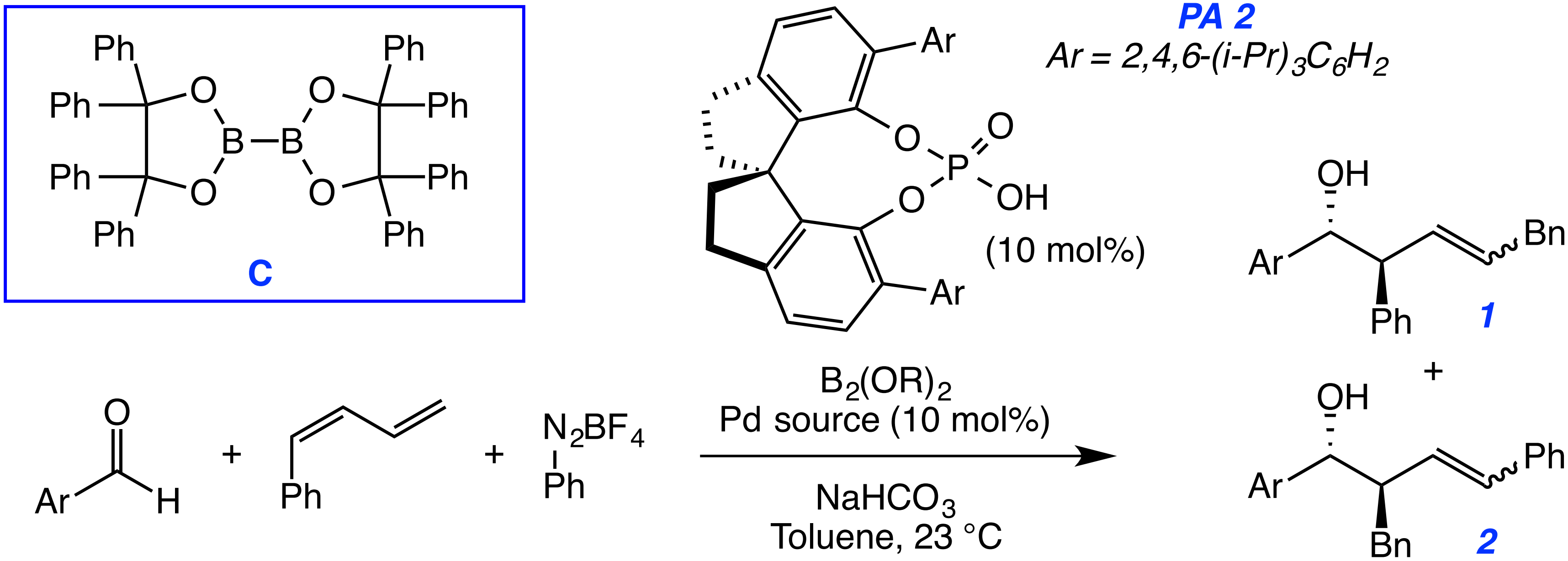




entry	*diborate*	*phosphoric acid*	*Pd*	*yield*	***1 / 2***	*Z / E*	*ee*
1	**A**	PA 1	$Pd(dba)_2$	70%	1.3:1	1:2	–
2	**B**	PA 1	$Pd(dba)_2$	90%	2.7:1	1.7:1	–
3	**C**	PA 1	$Pd(dba)_2$	99%	>20:1	>20:1	–
4	**C**	PA 2	$Pd(dba)_2$	99%	>20:1	>20:1	82%

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

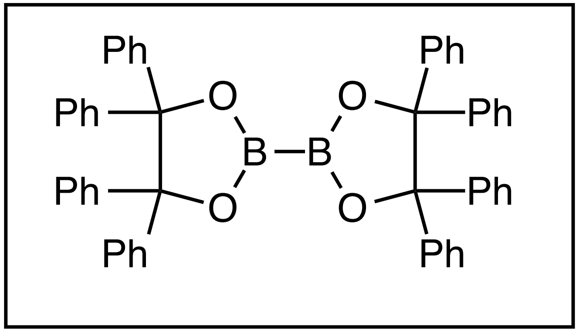
Reaction Optimization Studies

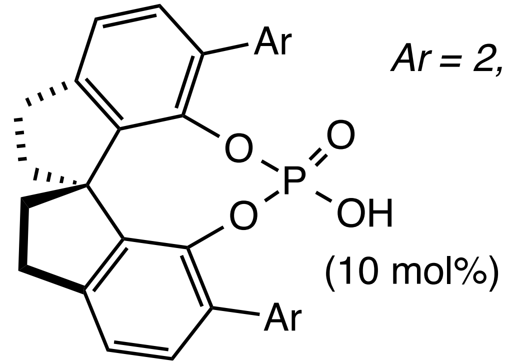


entry	*diborate*	*phosphoric acid*	*Pd*	*yield*	***1* / *2***	*Z / E*	*ee*
1	**A**	PA 1	$Pd(dba)_2$	70%	1.3:1	1:2	–
2	**B**	PA 1	$Pd(dba)_2$	90%	2.7:1	1.7:1	–
3	**C**	PA 1	$Pd(dba)_2$	99%	>20:1	>20:1	–
4	**C**	PA 2	$Pd(dba)_2$	99%	>20:1	>20:1	82%
5	**C**	PA 2	$Pd(OAc)_2$	99%	>20:1	>20:1	93%

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

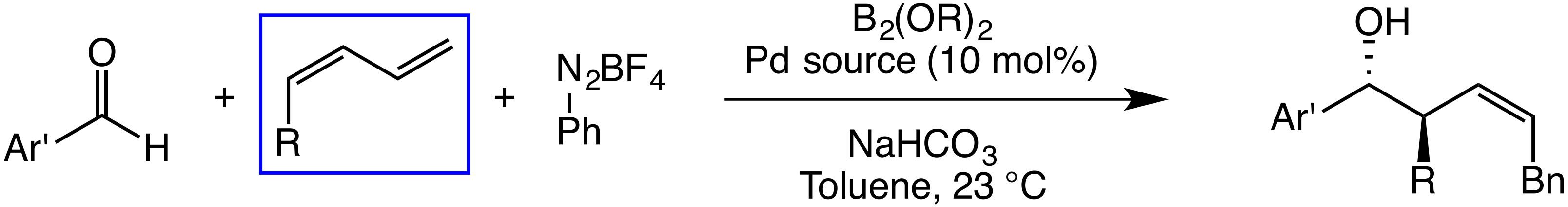
Reaction Scope - 1,3-Butadienes





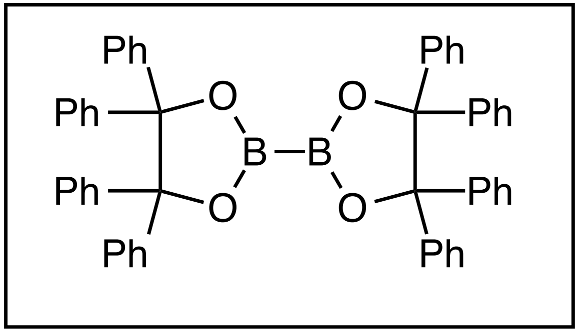
Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$

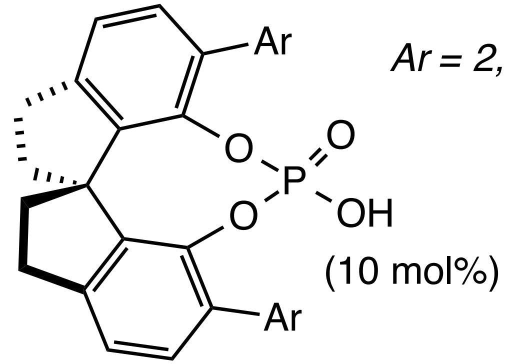
14 examples



Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

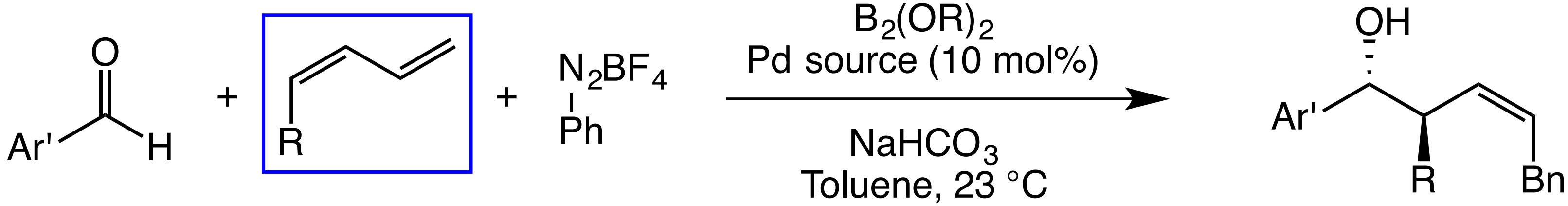
Reaction Scope - 1,3-Butadienes



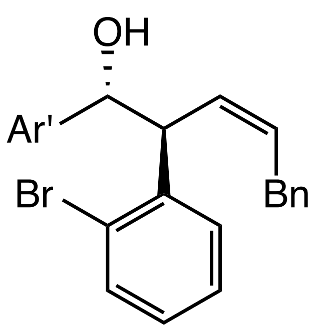


Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$

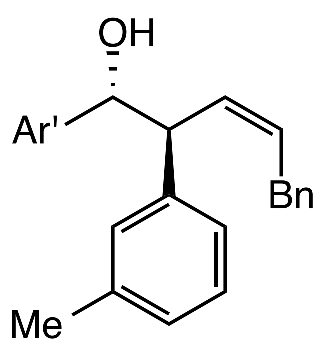
14 examples



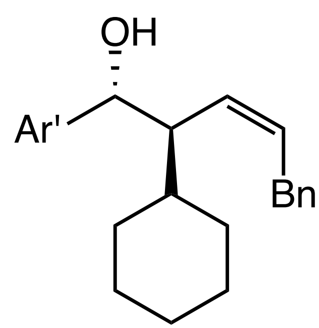
Ar' = 4-NO$_2$-C$_6$H$_4$



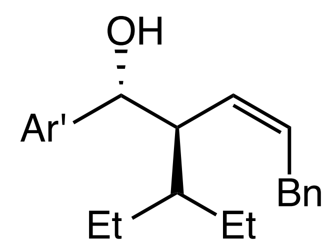
99% yield
90% ee



99% yield
89% ee



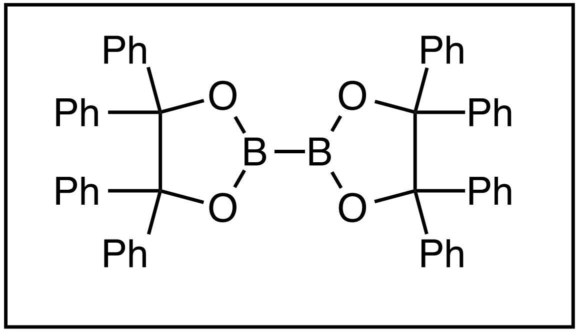
96% yield
88% ee

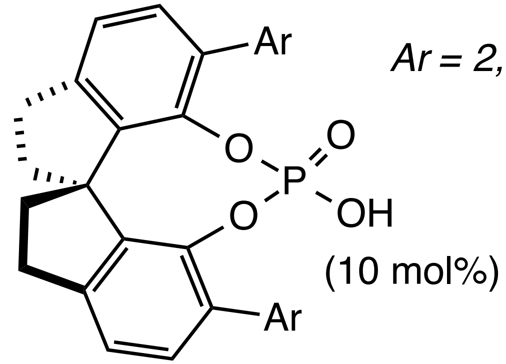


74% yield
88% ee

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

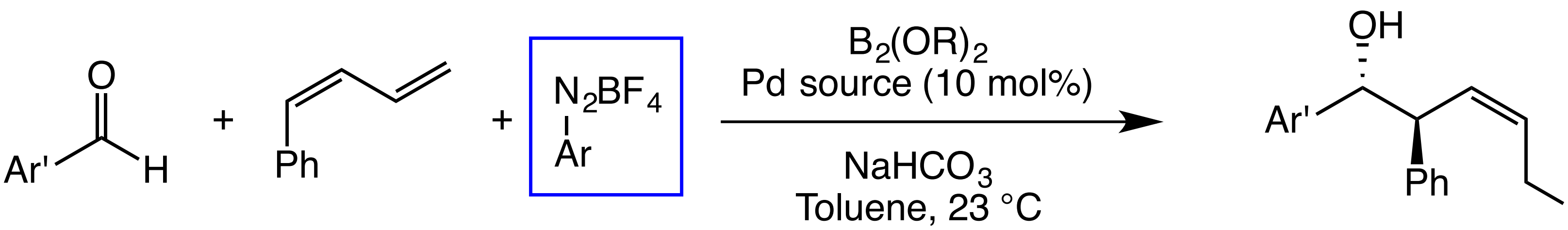
Reaction Scope - Aryldiazonium Tetrafluoroborate



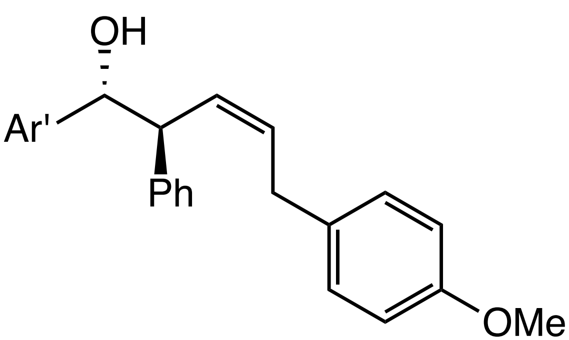


Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$

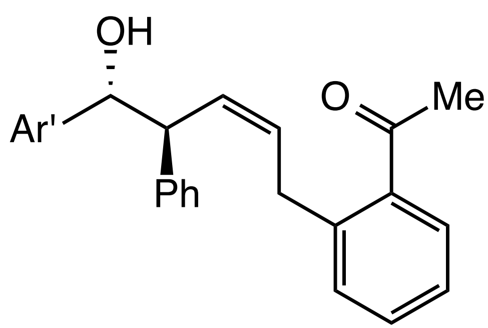
14 examples



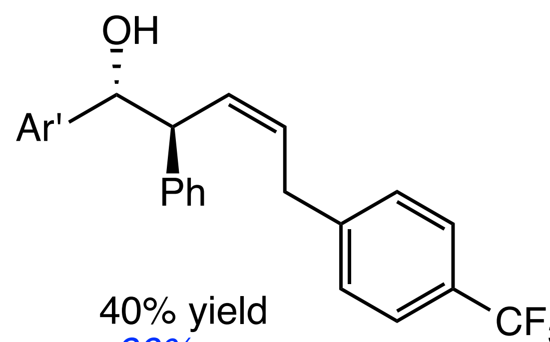
Ar' = 4-NO$_2$-C$_6$H$_4$



99% yield
87% ee



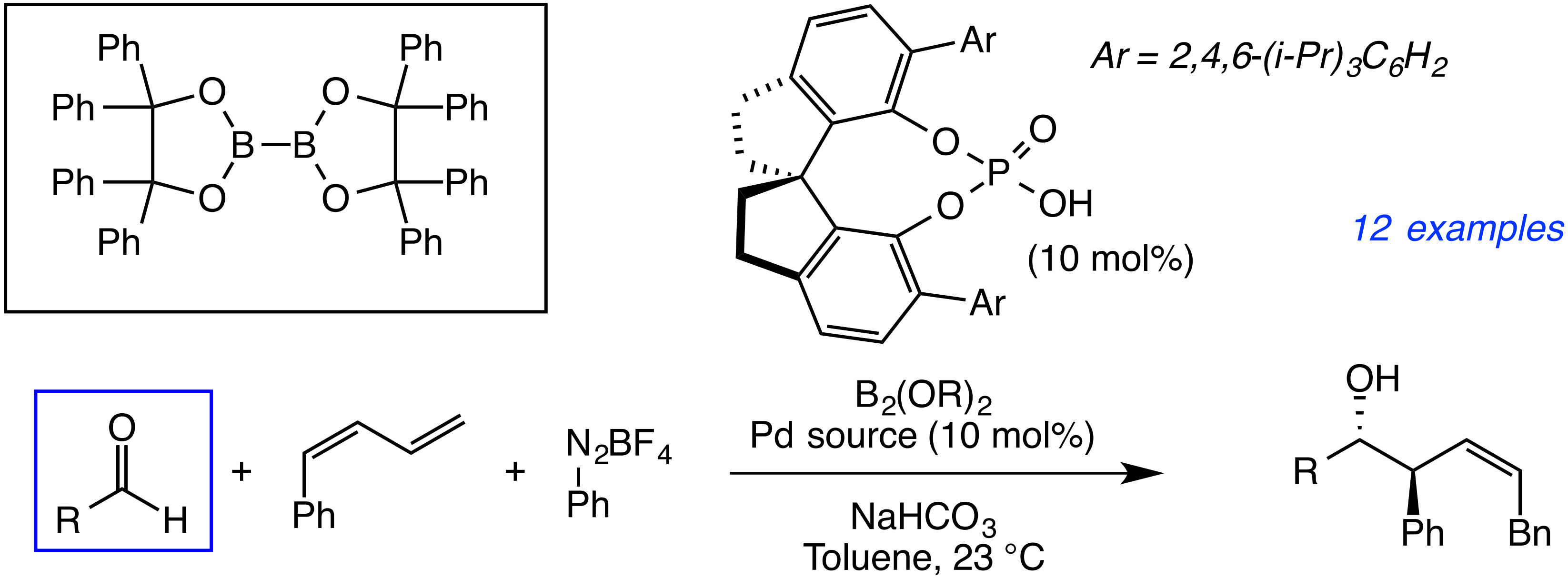
90% yield
94% ee

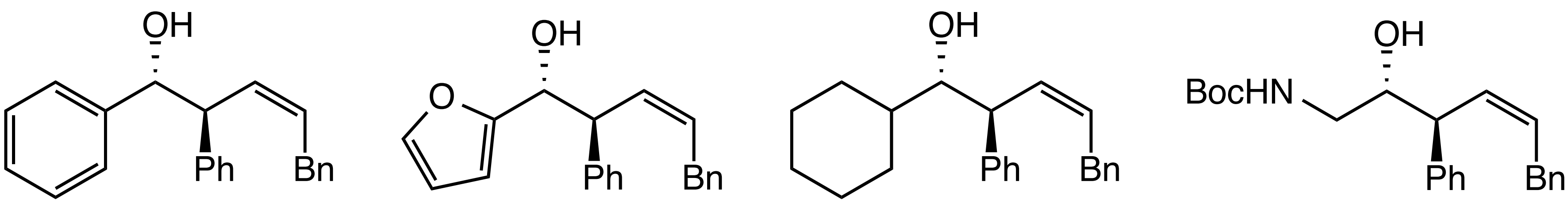


40% yield
90% ee

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Reaction Scope - Aldehydes

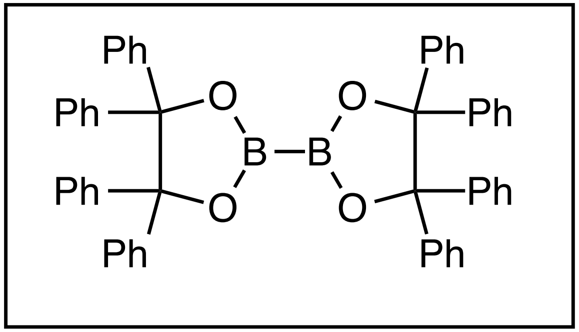


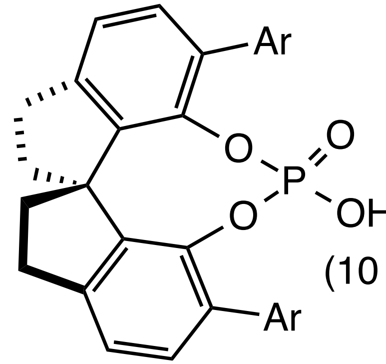


99% yield	99% yield	99% yield	99% yield
90% ee	*92% ee*	*92% ee*	*94% ee*

Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Reaction Scope - Aldehydes

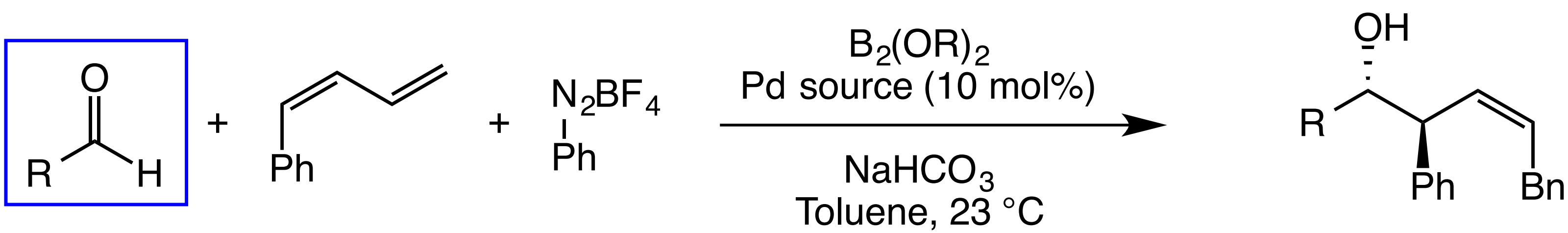




(10 mol%)

Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$

12 examples



Accomplishments

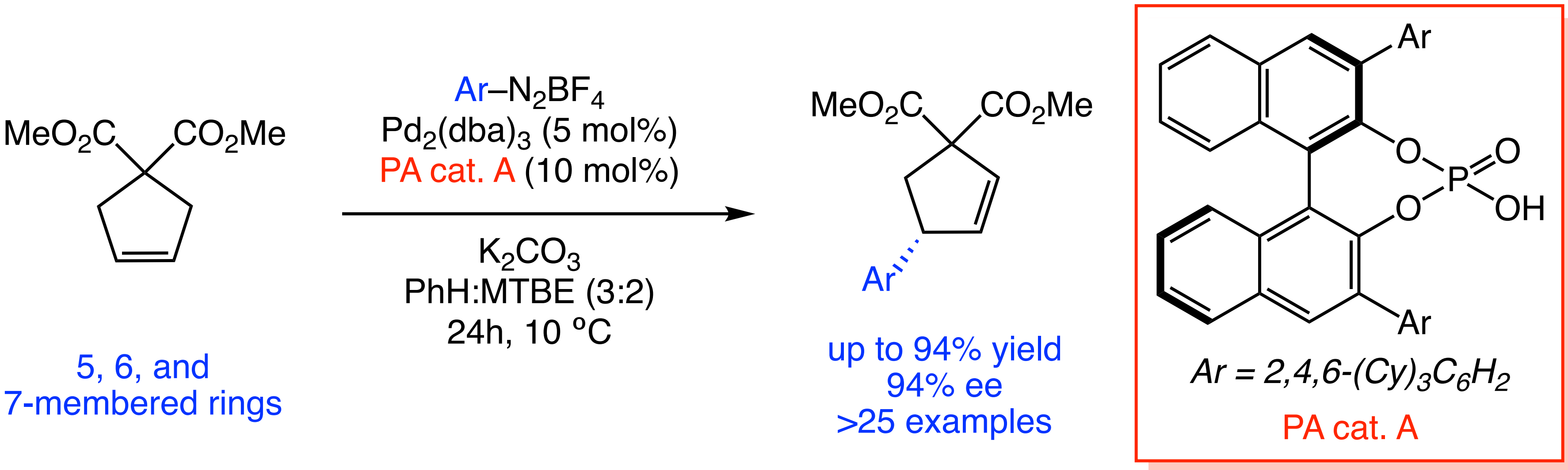
New strategy for the asymmetric functionalization of 1,3-dienes

Over 40 different enantioenriched homoallylic alcohols synthesized

Most complex application of CAPT in cooperative catalysis

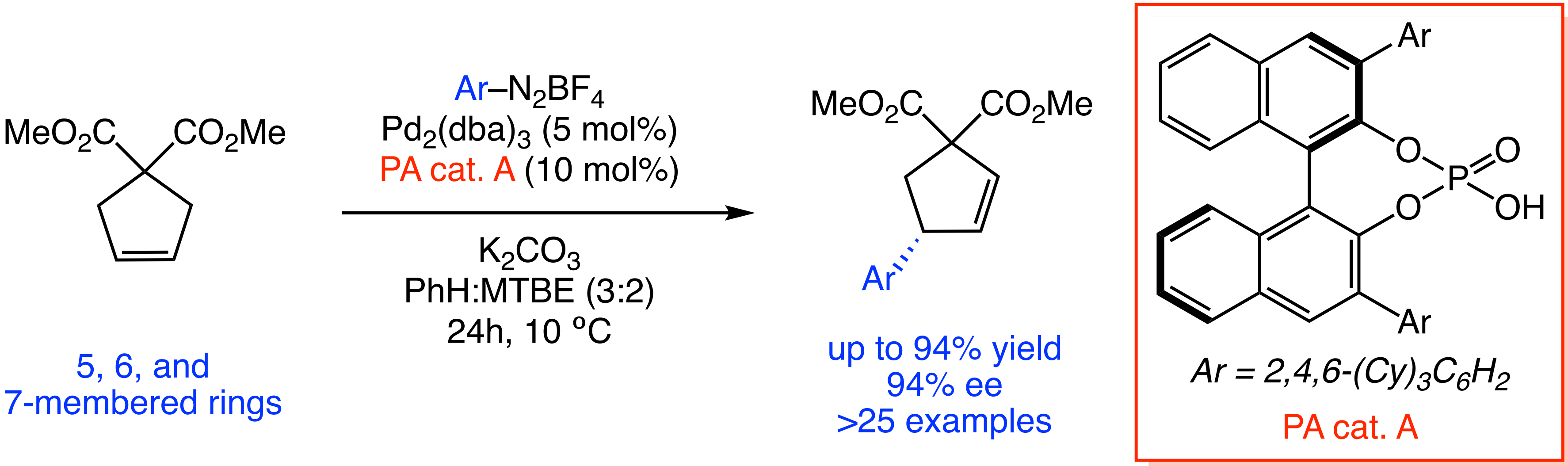
Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 4322.

Enantioselective Heck–Matsuda Arylations



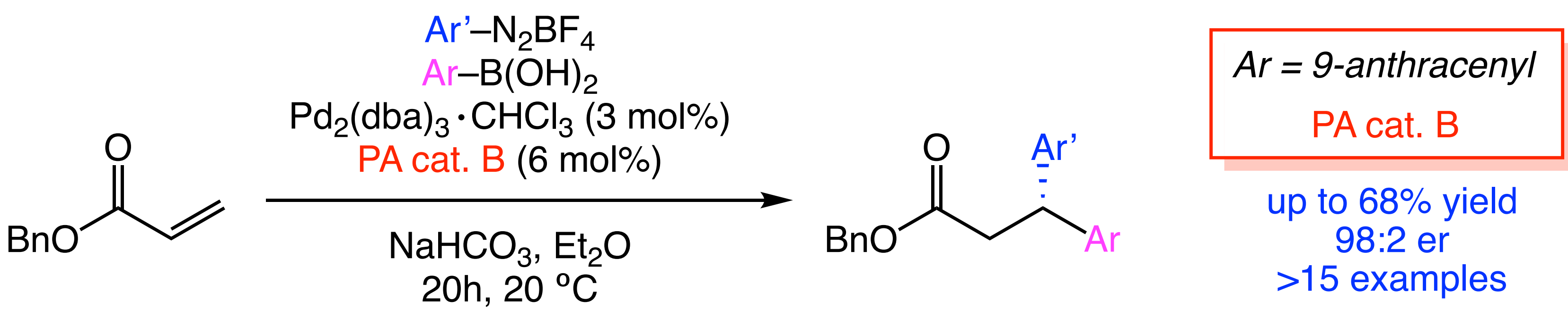
Avila, C. M.; Patel, J. S.; Reddi, Y.; Saito, M.; Nelson, H. M.; Shunatona, H. P.; Sigman, M. S.; Sunoj, R. B.; Toste, F. D. *Angew. Chem., Int. Ed.* **2017**, *56*, 5806.

Enantioselective Heck–Matsuda Arylations



Avila, C. M.; Patel, J. S.; Reddi, Y.; Saito, M.; Nelson, H. M.; Shunatona, H. P.; Sigman, M. S.; Sunoj, R. B.; Toste, F. D. *Angew. Chem., Int. Ed.* **2017**, *56*, 5806.

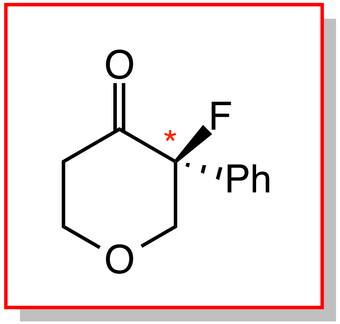
Enantioselective 1,1-Diarylation of Acrylates



Yamamoto, E.; Hilton, M. J.; Orlandi, M.; Saini, V.; Toste, F. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 15877.

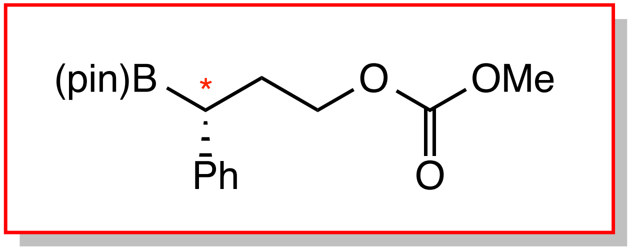
Summary

- *Intro to phase-transfer catalysis*
  - *How the catalysts work*
  - *Industrial applications*



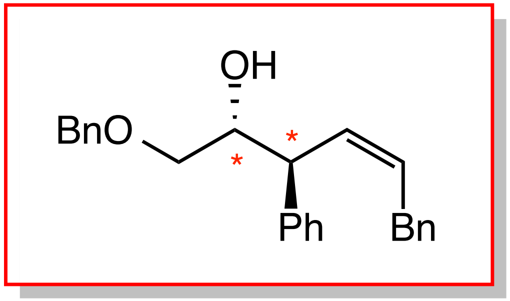
- *The merging of CAPT and enamine catalysis*
  - *α-Fluorinated ketones*

    J. Am. Chem. Soc. **2014**, *136*, 5225.



- *The merging of CAPT and palladium catalysis*
  - *Benzylic boronic esters*

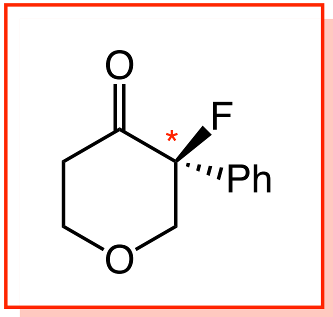
    J. Am. Chem. Soc. **2015**, *137*, 3213.

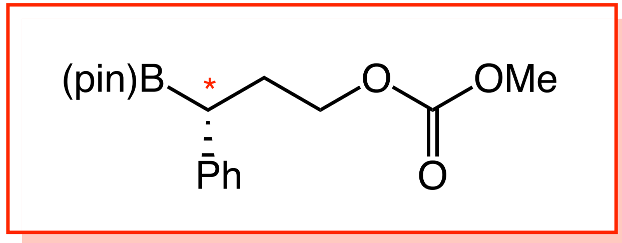


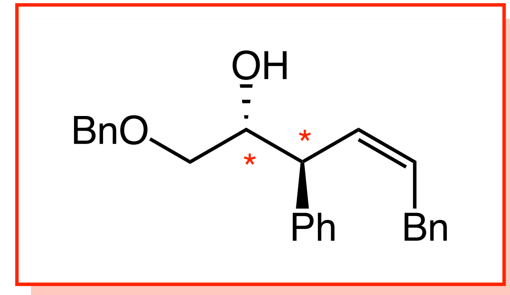
- *The merging of CAPT and palladium catalysis*
  - *Homoallylic alcohols*

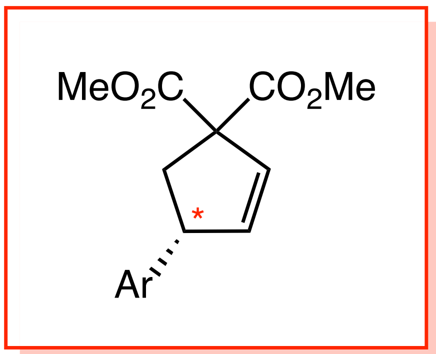
    Angew. Chem., Int. Ed. **2016**, *55*, 4322.

Conclusions





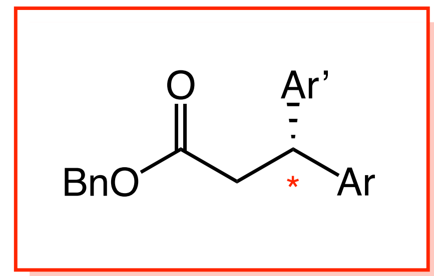




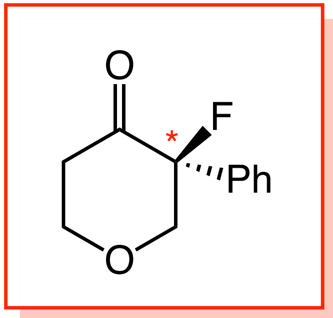
PTC is a widely used process in industry and academia

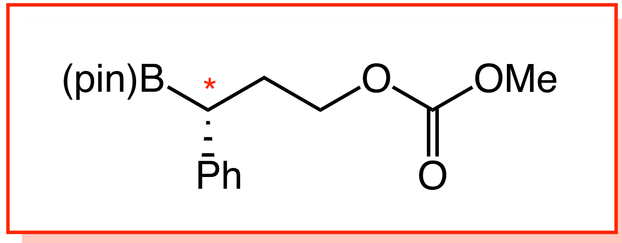
Cost effective and green process

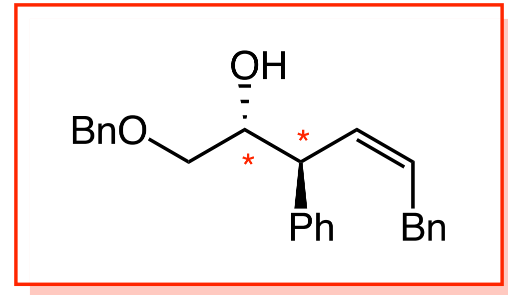
Recent cooperative catalysis approach enabled complex molecule synthesis

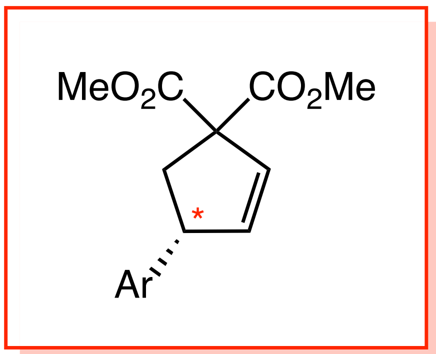


Conclusions





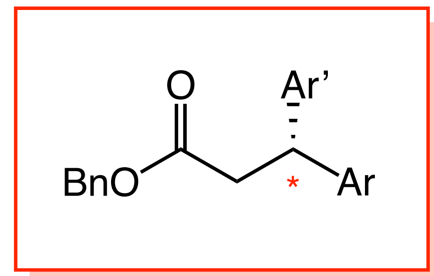




PTC is a widely used process in industry and academia

Cost effective and green process

Recent cooperative catalysis approach enabled complex molecule synthesis



Future Directions

Expansion of cooperative catalysis work to include other types of catalysis

Development of new reagents and catalysts tailored for PTC

Application of CCPT in enantioselective cooperative catalysis

Acknowledgments

Institution:

TSRI

Advisor:

Prof. Keary M. Engle

Group Members:

Dr. De-Wei Gao
Dr. Miriam O'Duill
Dr. Sri Krishna Nimmagadda
Dr. Malkanthi K. Karunananda
Joseph Derosa
Zhen Liu
John A. Gurak
Rei Matsuura
Tanner Jankins
Andrew Romine
Mingyu Liu
Van Tran
Denise Kahler
Yiyang (Elaine) Xiao
Huiqi Ni
Pusu Yang
Vincent van der Puyl
Tian (May) Zeng
Hermione