Metal-Catalyzed Regioselective Hydroamination of Alkynes

2020.9.26.

Kyohei Takaoka

Contents

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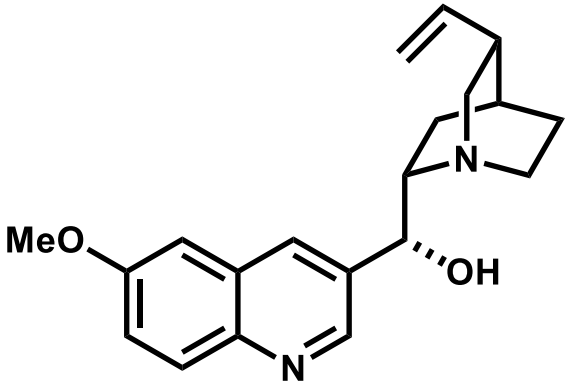
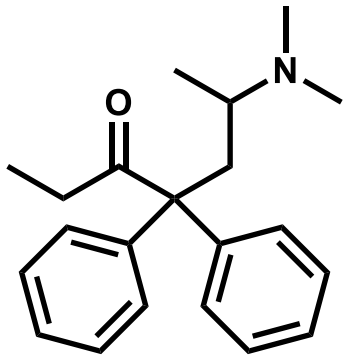
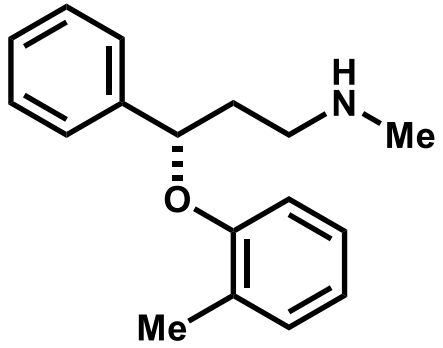
Aliphatic amines in medicines



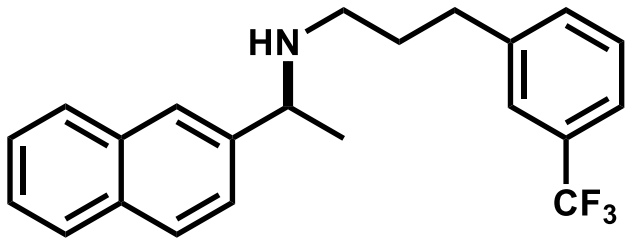
Quinine
(malaria)



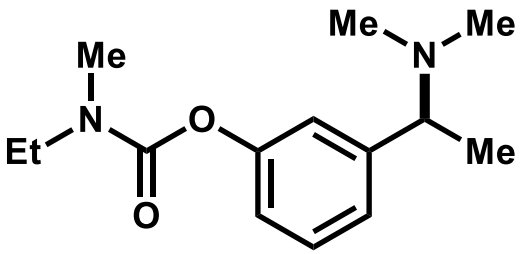
Methadone
(pain)



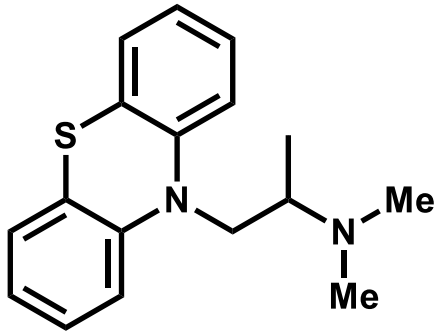
Atomoxetine
(ADHD drug)



Cinacalcet
(hyperparathyroidism)



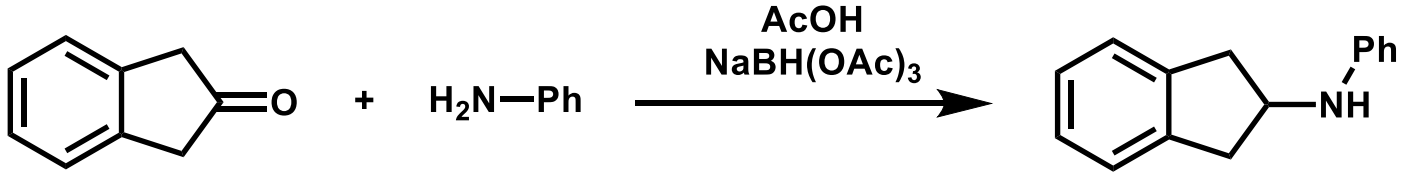
Rivastigmine
(dementia)



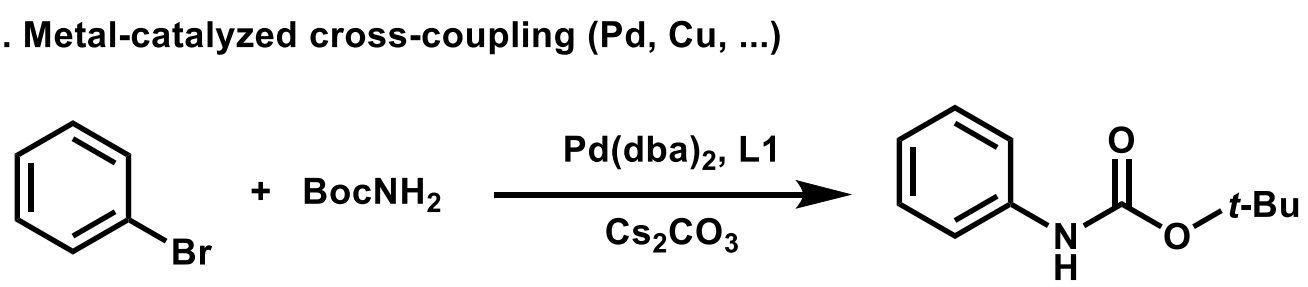
Promethazine
(allergies)

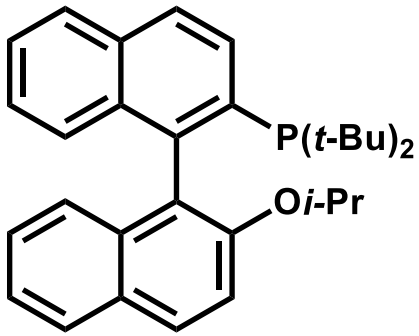
Synthesis of amines

1. Reductive amination



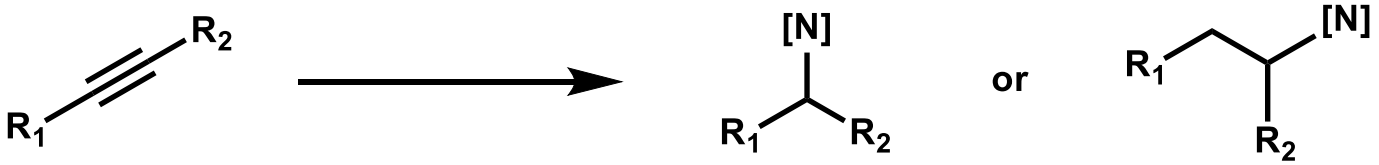
2. Metal-catalyzed cross-coupling (Pd, Cu, ...)





L1

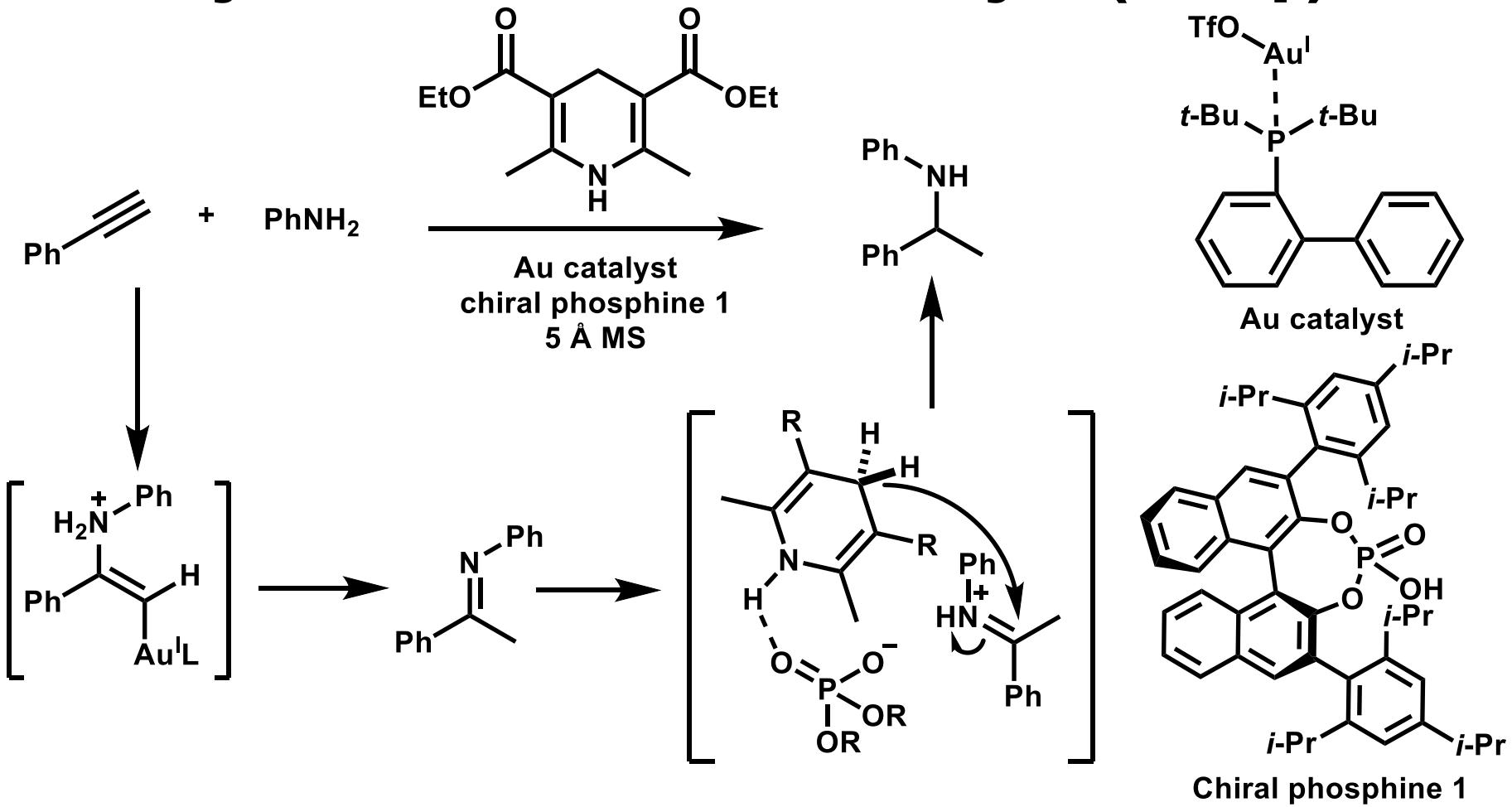
3. Synthesis from alkyne



1) Abdel-Magid, A. F.; Carson, K.G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996,** *61,* 3849-3862

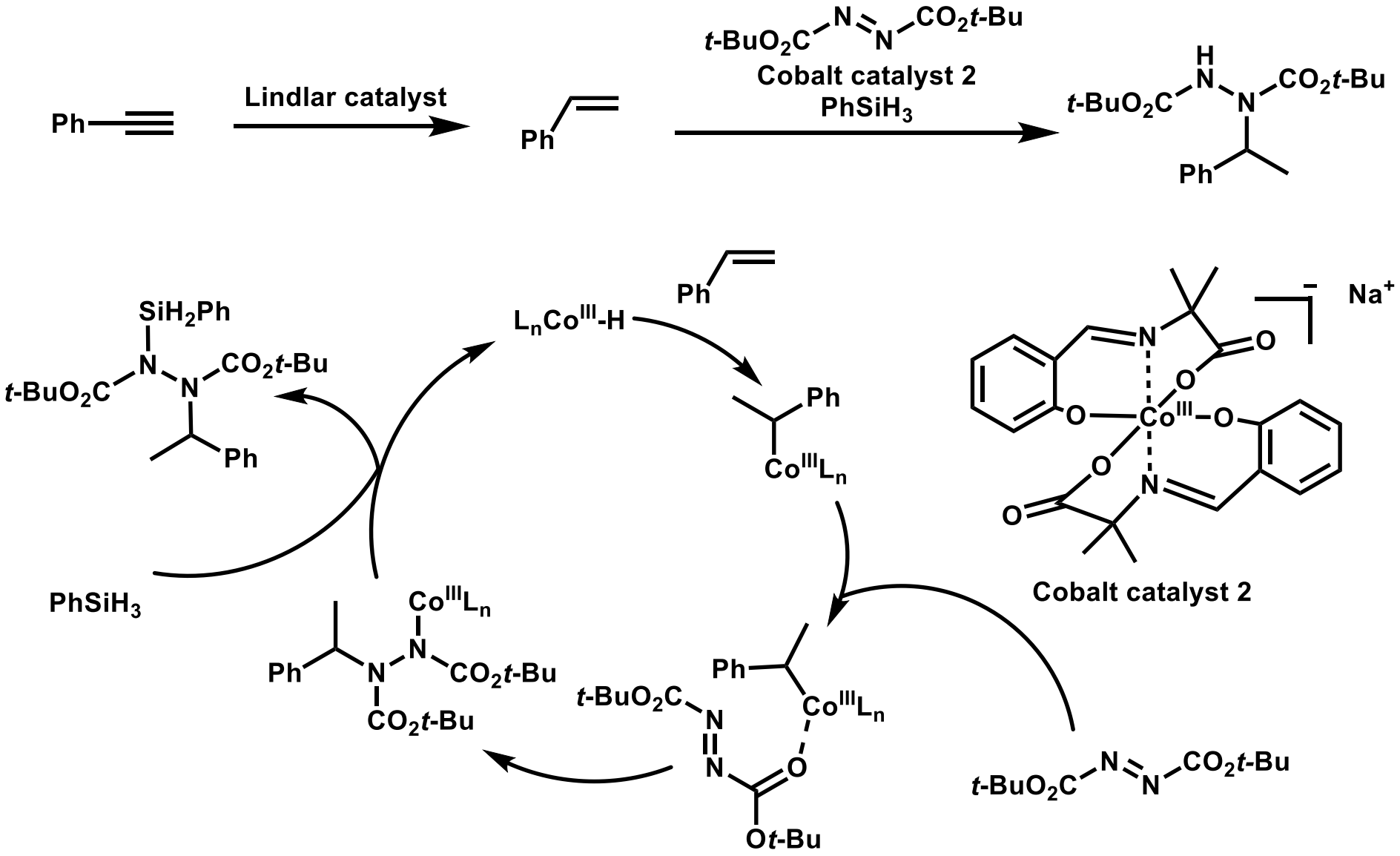
2) Ma, F.; Xie, X.; Zhang, L.; Peng, Z.; Ding, L.; Fu, L.; Zhang, Z. *J. Org. Chem.* **2012,** *77, 12,* 5279-5285

Synthesis of amine from alkyne (1 step)



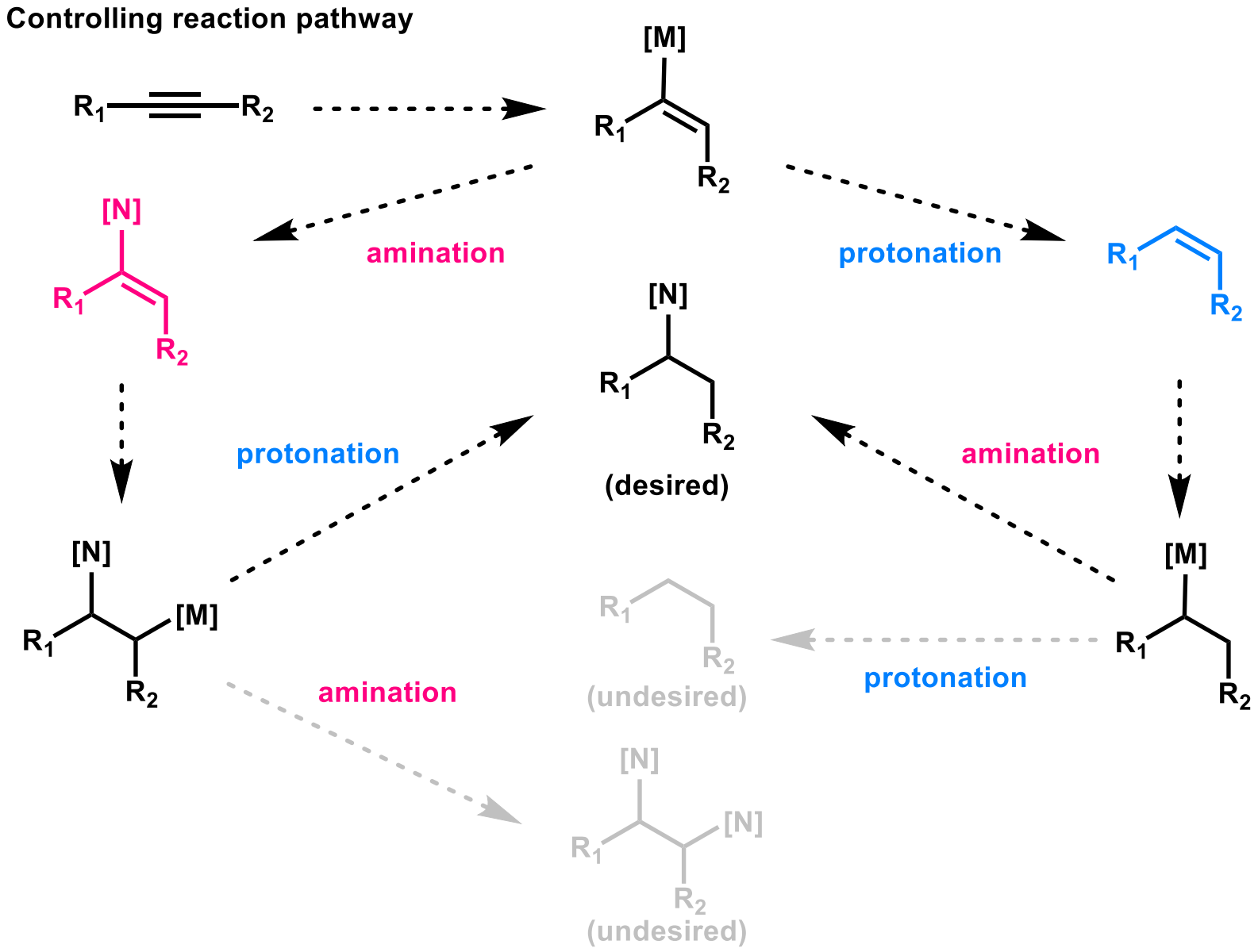
1) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009,** *11,* 4204-4207.

Synthesis of amine from alkyne (2 steps)



1) Lindlar, H.; Dubuis, R. *Org. Synth.* **1996,** *46,* 89-92
2) Waser, J.; Carreira, E. C. *J. Am. Chem. Soc.* **2004,** *126,* 5676-5677.

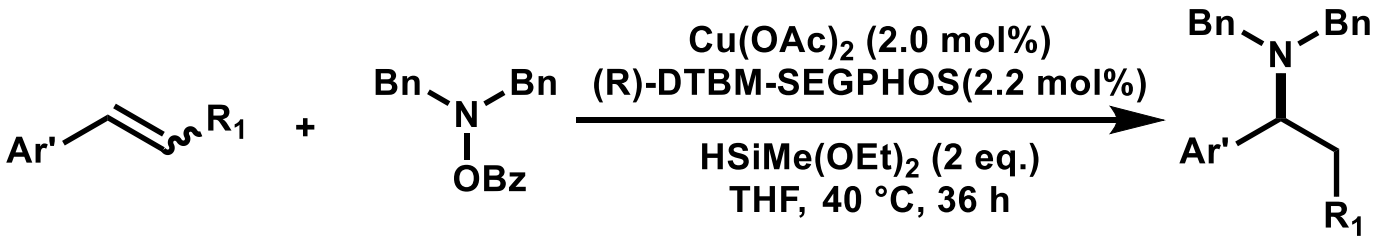
Difficulty in one pot reaction

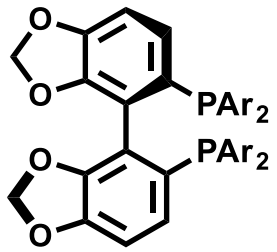


1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

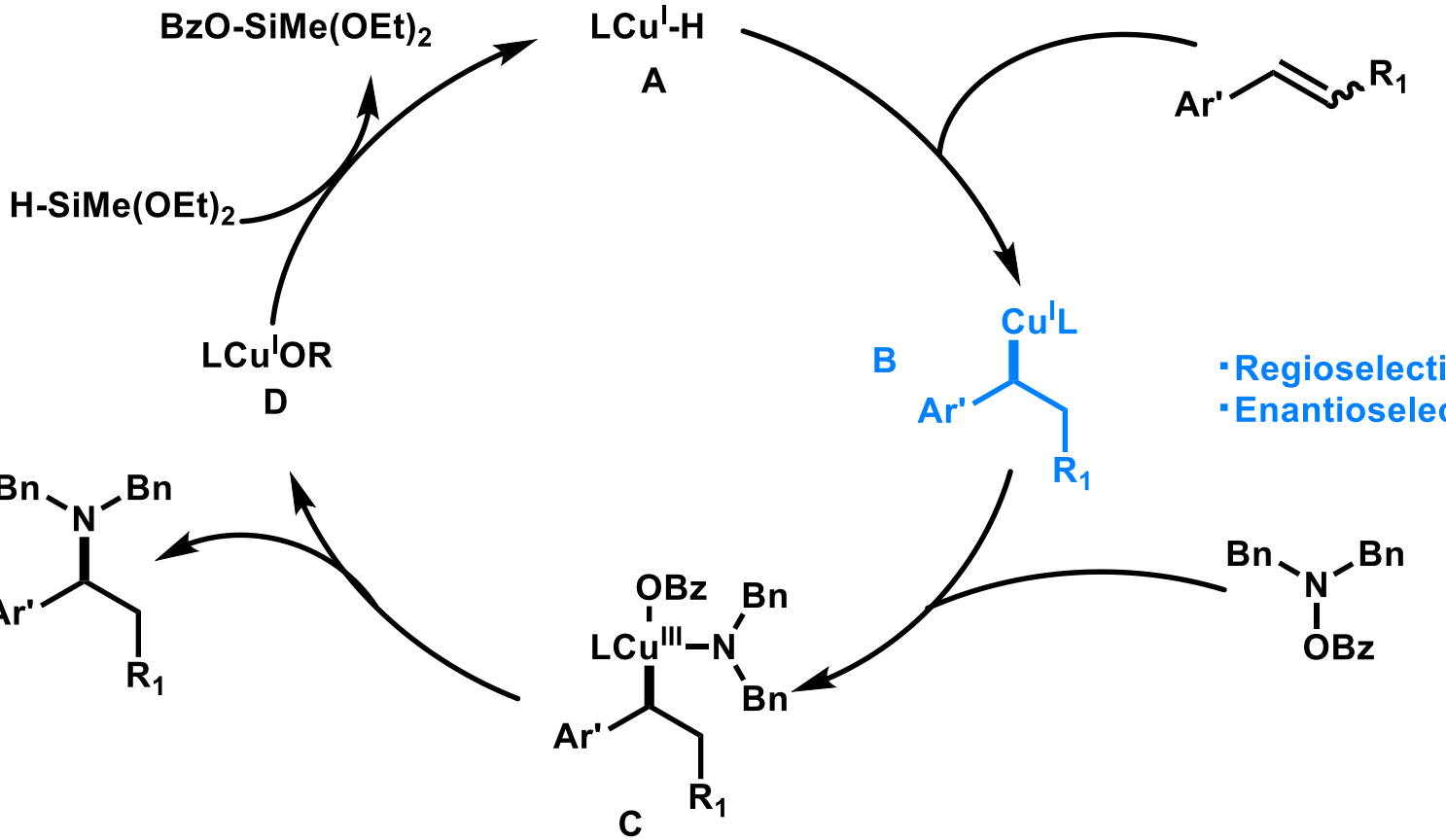
Contents

Hydroamination of alkene



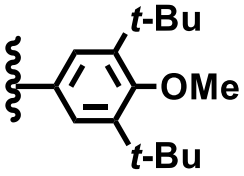


(R)-DTBM-SEGPHOS



- Regioselective
- Enantioselective

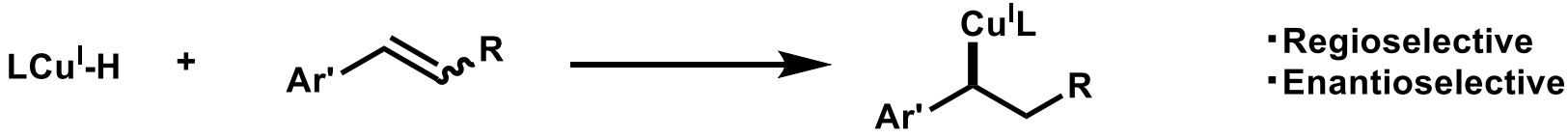
Ar =



1) Zhu, S.; Niljianskul, N. Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135,* 15746-15749

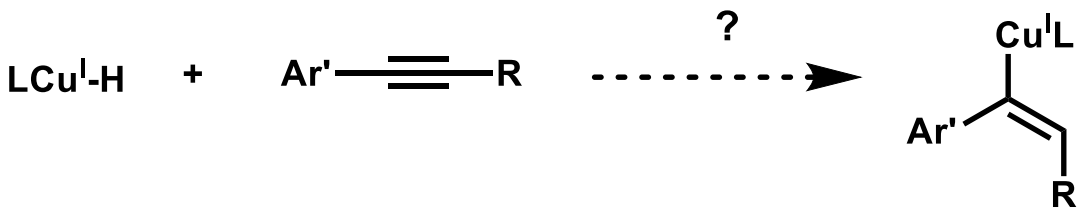
Alkyne Hydroamination strategy

Previous work:

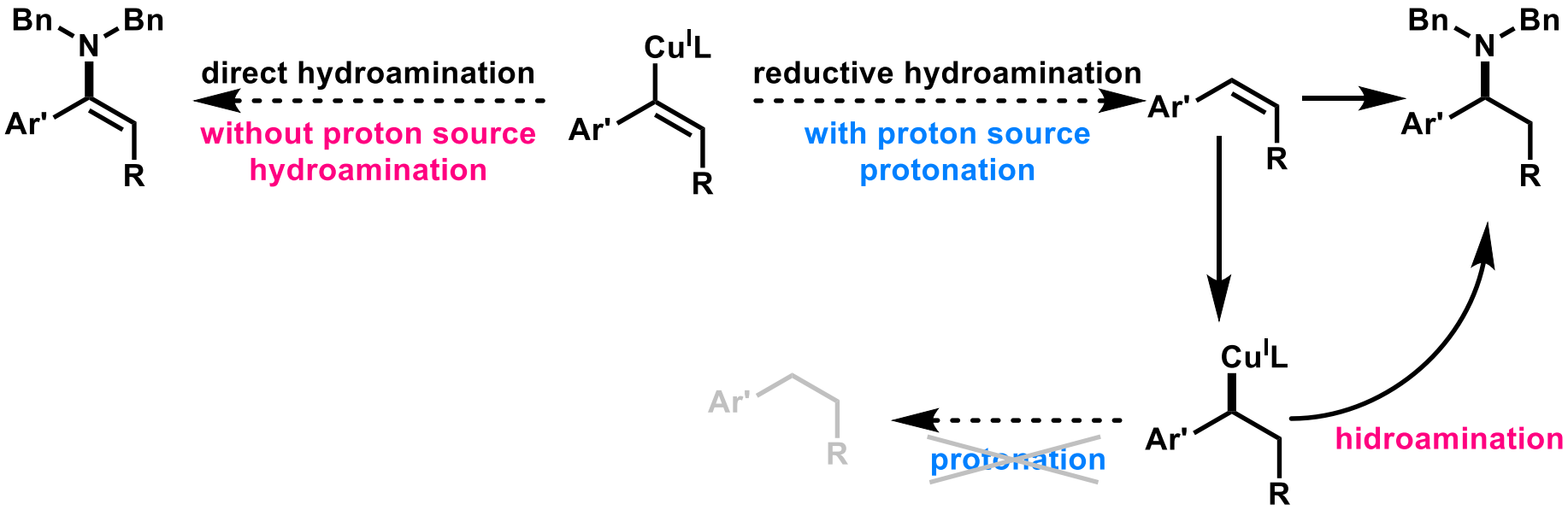


- Regioselective
- Enantioselective

This work:

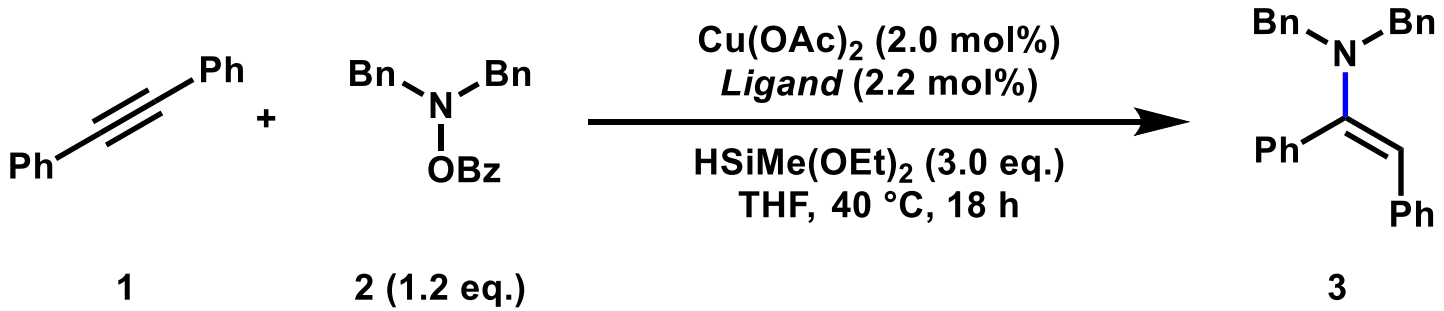


- Regioselective?



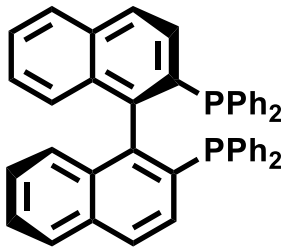
1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44
2) Zhu, S.; Niljianskul, N. Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135,* 15746-1574

Optimization (directive hydroamination)

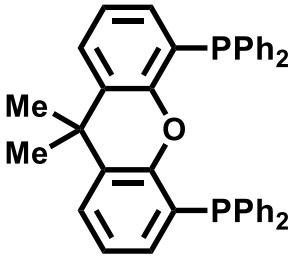


1 2 (1.2 eq.) 3

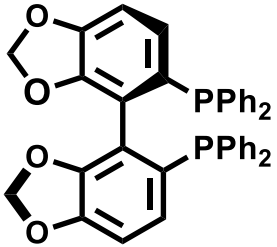
Entry	Ligand	Yield
1	*rac*-L1	90%
2	L2	95%
3	*rac*-L3	87%
4	*rac*-L4	99%



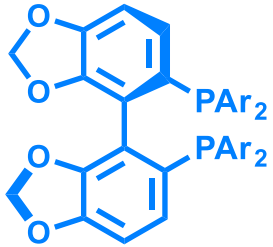
(R)-L1
(R)-BINAP



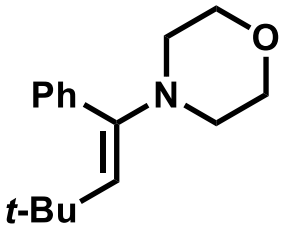
L2
Xantphos



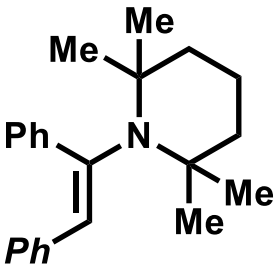
(R)-L3
(R)-SEGPHOS



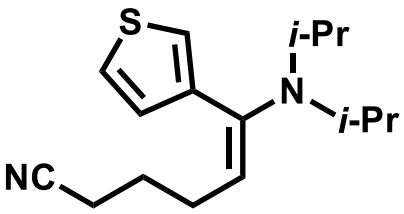
(R)-L4
(R)-DTBM-SEGPHOS



with *rac*-L4, 97%

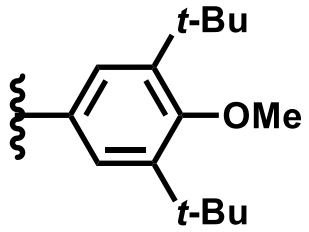


with *rac*-L4, 99%



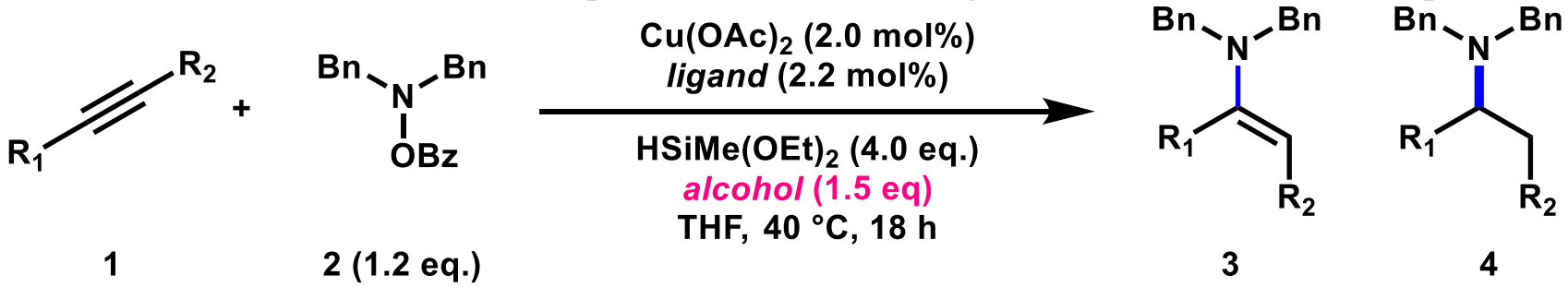
with *rac*-L4, 80%

Ar =



1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

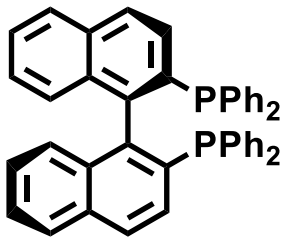
Optimization (reductive hydroamination)



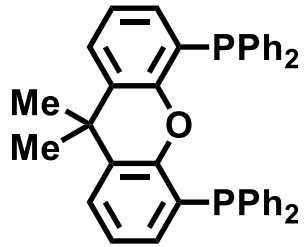
1 2 (1.2 eq.) 3 4

a: $R_1 = R_2 = Ph$
b: R_1 = 4-(*t*-Bu)C_4H_6, $R_2 = H$

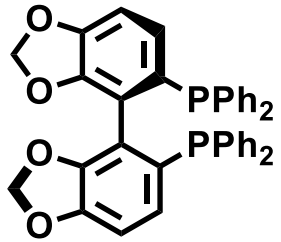
Entry	Substrate	Ligand	Alcohol	Yield 3	Yield 4
1	1a	(R)-L4	MeOH	18%	60% (89% e.e.)
2	1a	(R)-L4	EtOH	2%	92% (89% e.e.)
3	1a	(R)-L4	*i*-PrOH	2%	82% (89% e.e.)
4	1a	(R)-L1	EtOH	83%	0
5	1a	L2	EtOH	95%	0
6	1a	(R)-L3	EtOH	80%	0
7	1b	(R)-L4	EtOH	-	78% (99% e.e.)
8	1b	(R)-L4	*i*-PrOH	-	83% (99% e.e.)



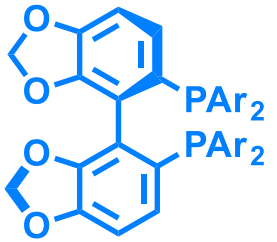
(R)-L1
(R)-BINAP



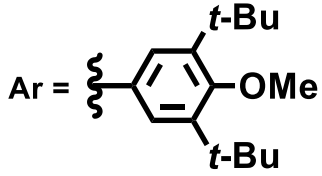
L2
Xantphos



(R)-L3
(R)-SEGPHOS

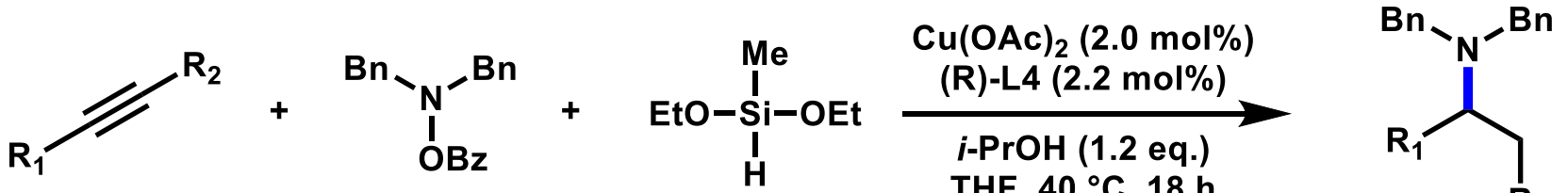


(R)-L4
(R)-DTBM-SEGPHOS

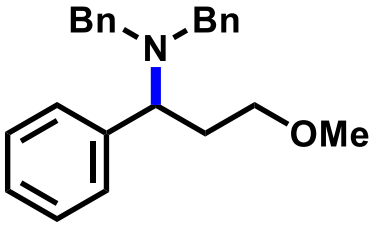


1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

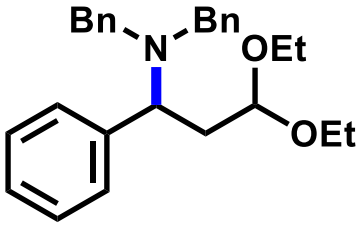
Substrate scope (aryl acetylenes)



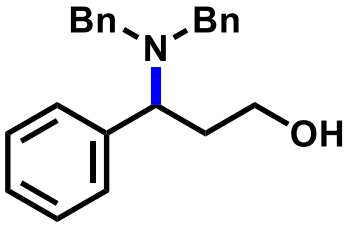
1 (1.1 eq.) 2 (1.0 eq.) 3 (4.0 eq.) 5



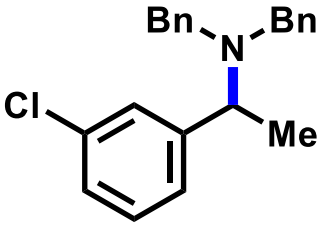
83%, 98% e.e.[a)]



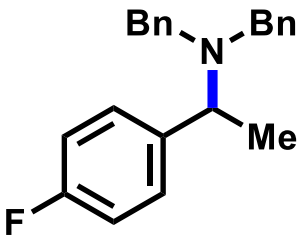
85%, 99% e.e.[a)]



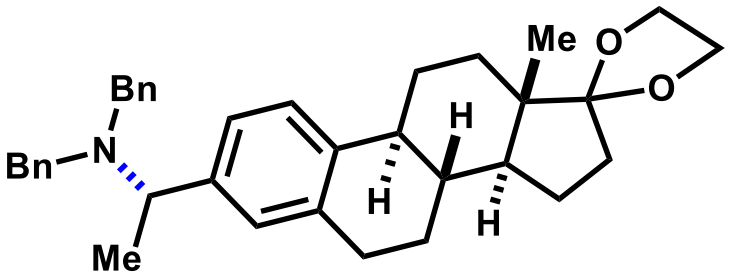
70%, 98% e.e.[a)]



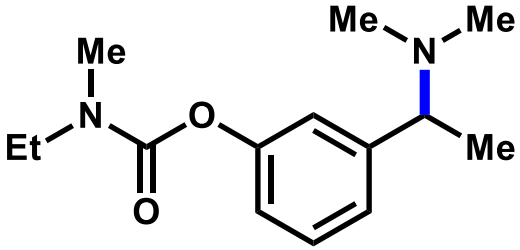
71%, 97% e.e.



75%, 97% e.e.



62%, 99:1 d.r.

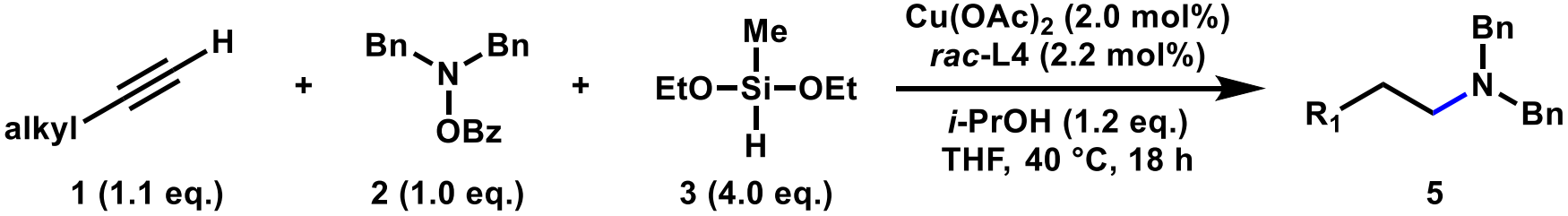


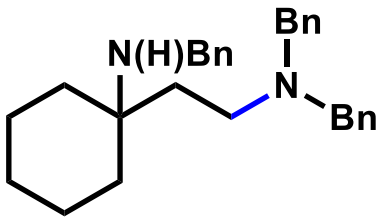
Rivastigmine
(antidementia drug)
69%, >99% e.e.

a) using EtOH instead of *i*-PrOH

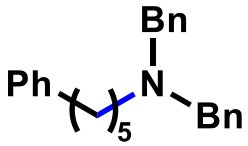
1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

Substrate scope (alkylacetylenes)

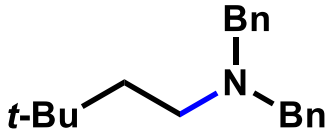




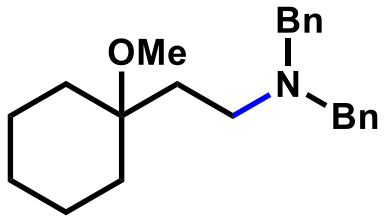
86%



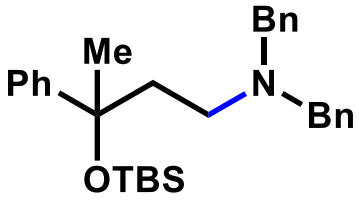
76%



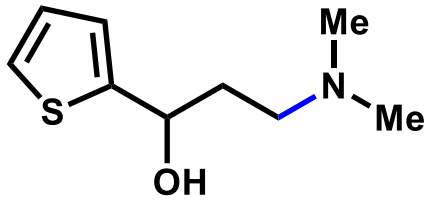
71%



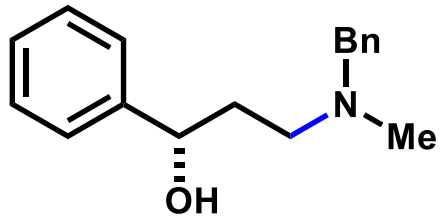
88%



73%



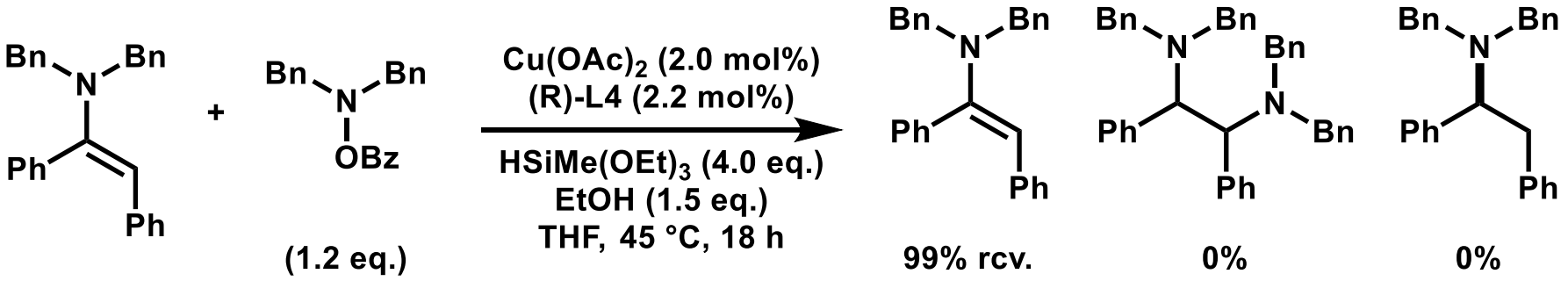
72%
(from silyl ether)

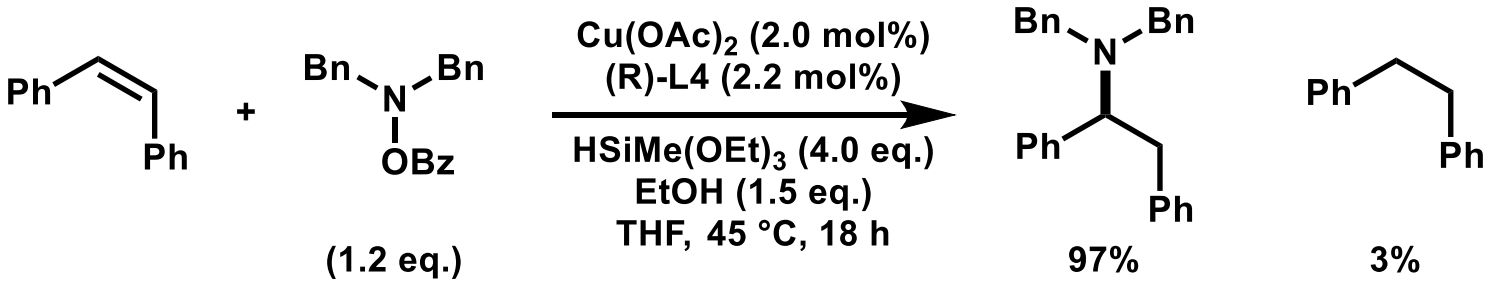


72%
(from silyl ether)

1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

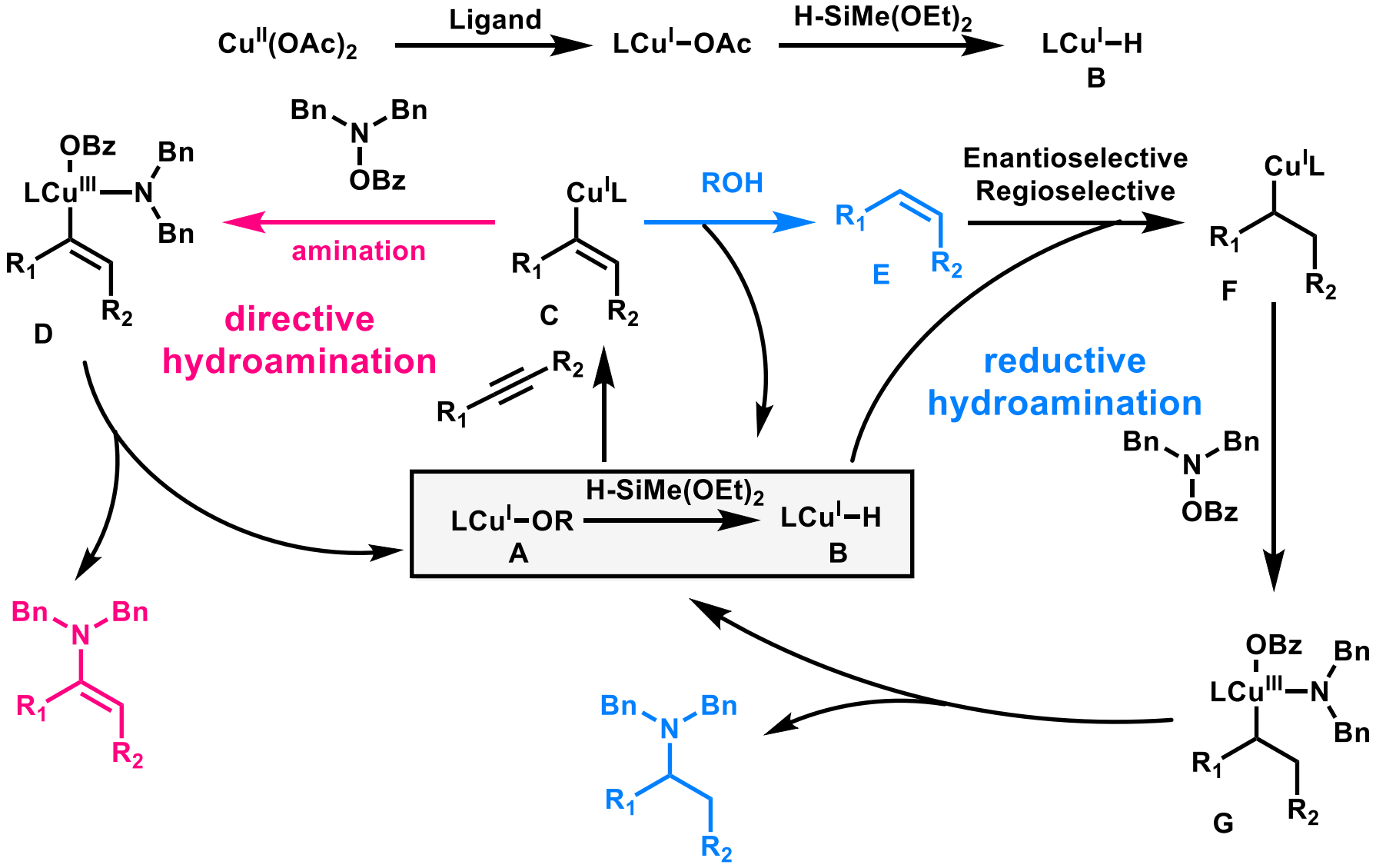
Control experiments





1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

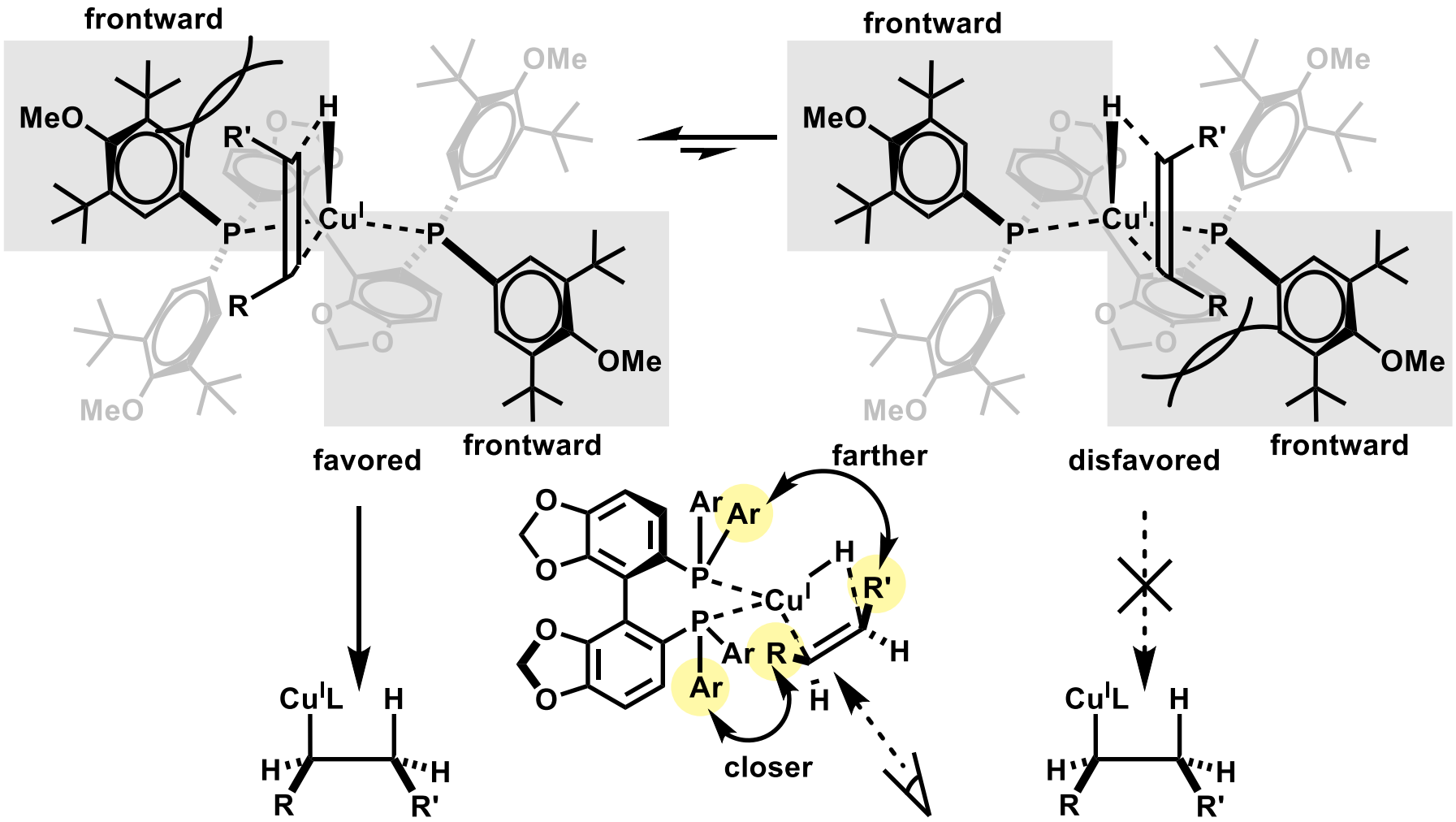
Reaction mechanism



1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44
2) Zhu, S.; Niljianskul, N. Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135,* 15746-15749

Stereoselectivity

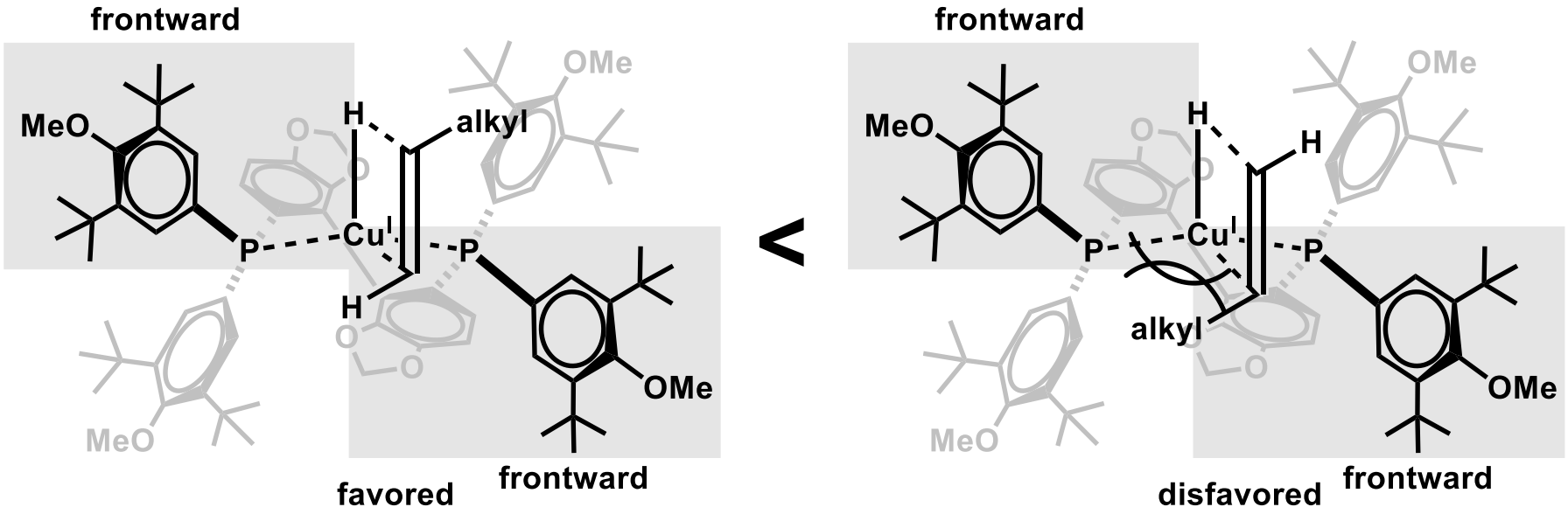
Enantioselectivity (using (R)-DTBM-SEGPHOS)



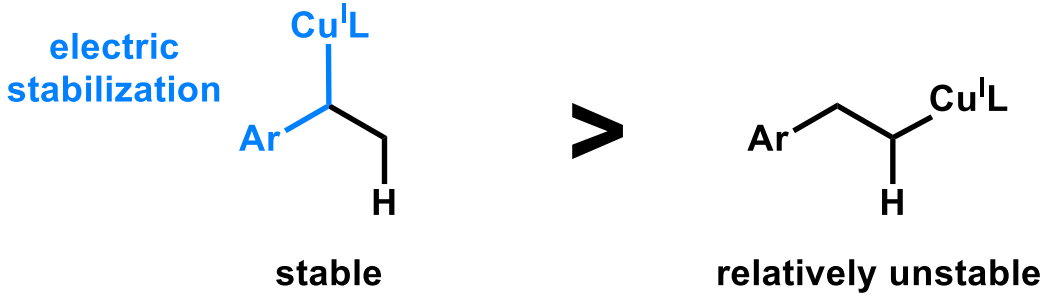
1) Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62.
2) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc.* **2017,** *139,* 16548-16555

Regioselectivity

Aliphatic alkynes (anti-Markovnikov selectivity)



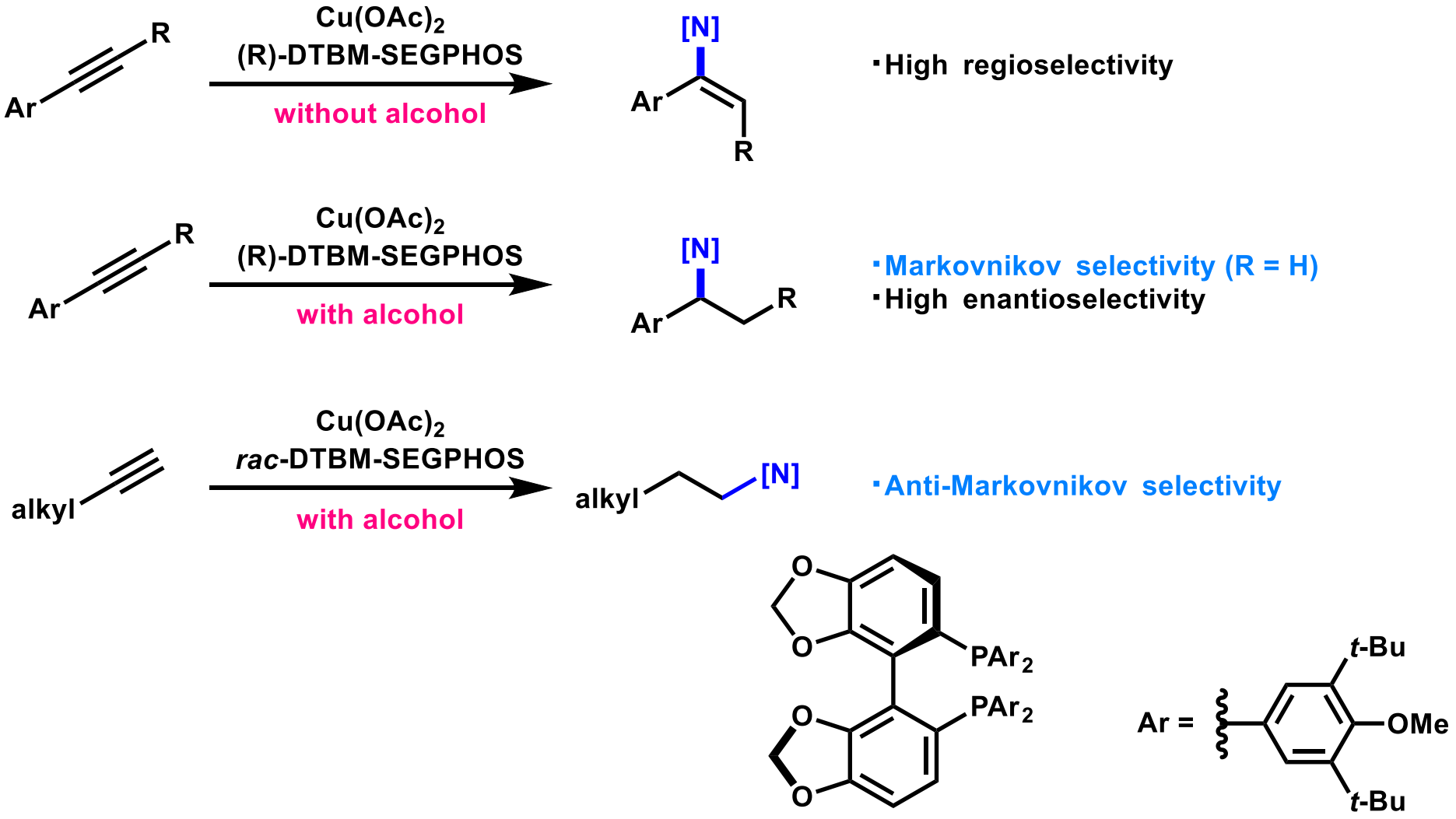
Aryl alkynes (Markovnikov selectivity)



1) Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62.
2) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

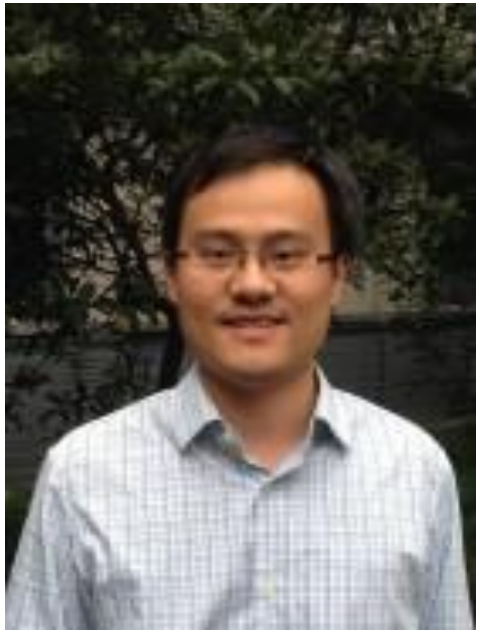
Short summary

1. Buchwald's group (2015)



Contents

Prof. Zhan Lu



Research Carrer:

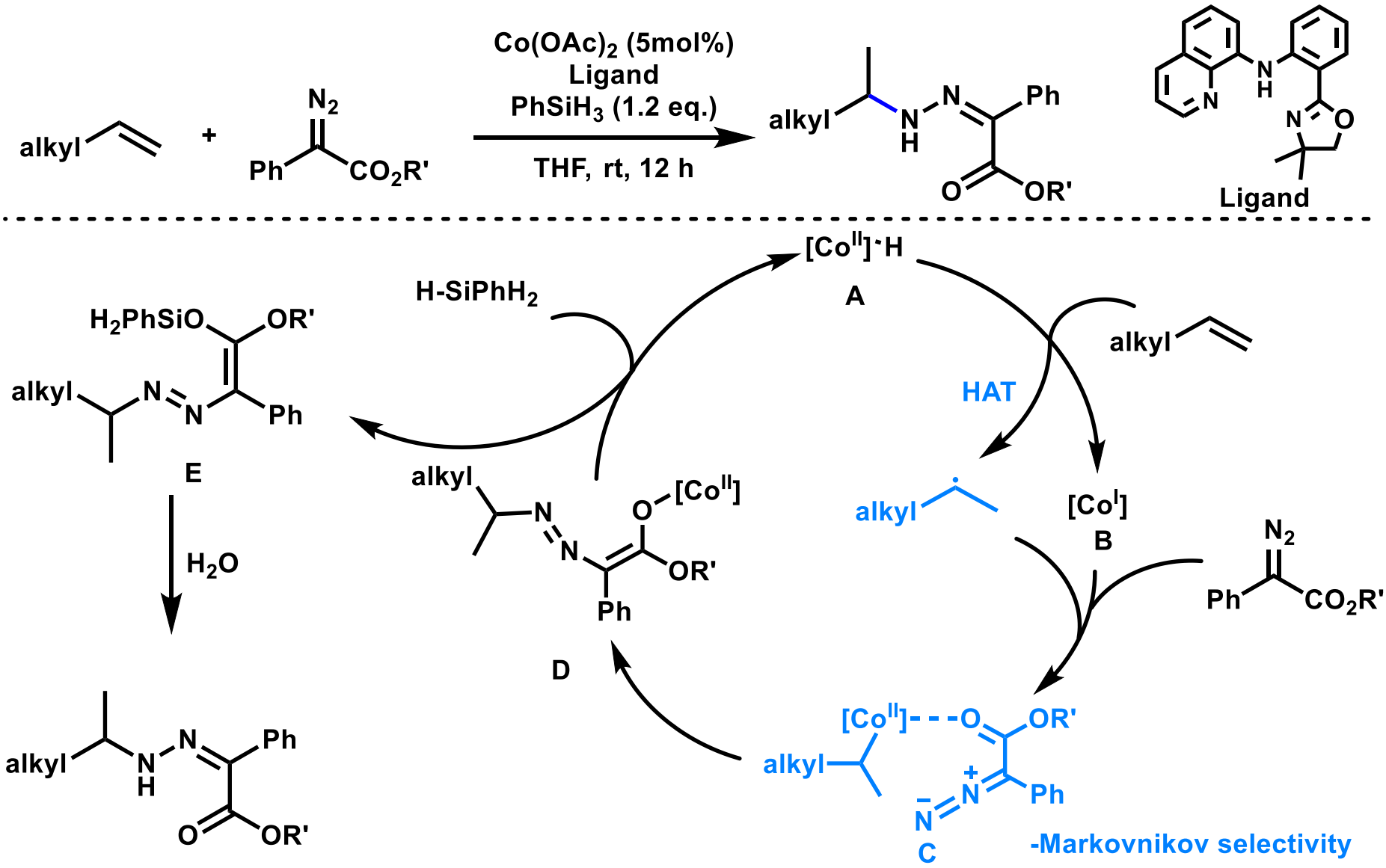
2003 B. S. @ Zhejiang University
2008 Ph.D. @ Zhejiang University (Prof. Shengming Ma)
Research: Asymmetric catalysis
2008- Postdoctoral Fellow @ University of Wisconsin-Madison
(Prof. Shannon S. Stahl and Tehshik P. Yoon)
Research: Photocatalysis
2013- Principle Investigator @ Zhejang University
2019- Professor @ Zhejiang University

Research Interests

- Asymmetric catalysis
- Photocatalysis
- Total synthesis

https://person.zju.edu.cn/en/lu

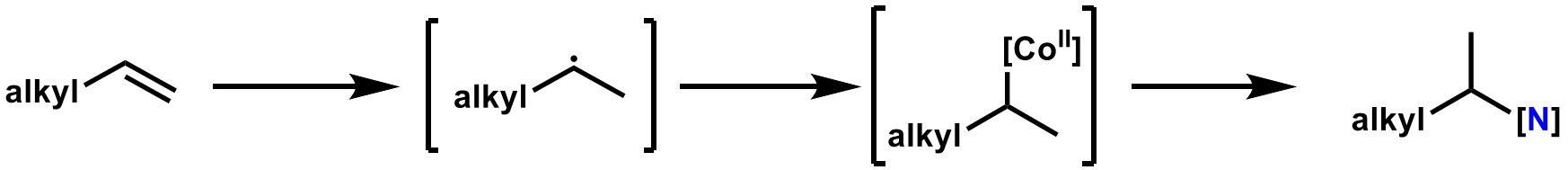
Hydroamination by Cobalt catalyst



1) Chen, J.; Shen, X.; Lu, Z. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460
2) Shen, X.; Chen, X.; Chen J.; Sun, Y.; Cheng, Z.; Lu, Z. *Nat. Commun.* **2020,** *11,* 783

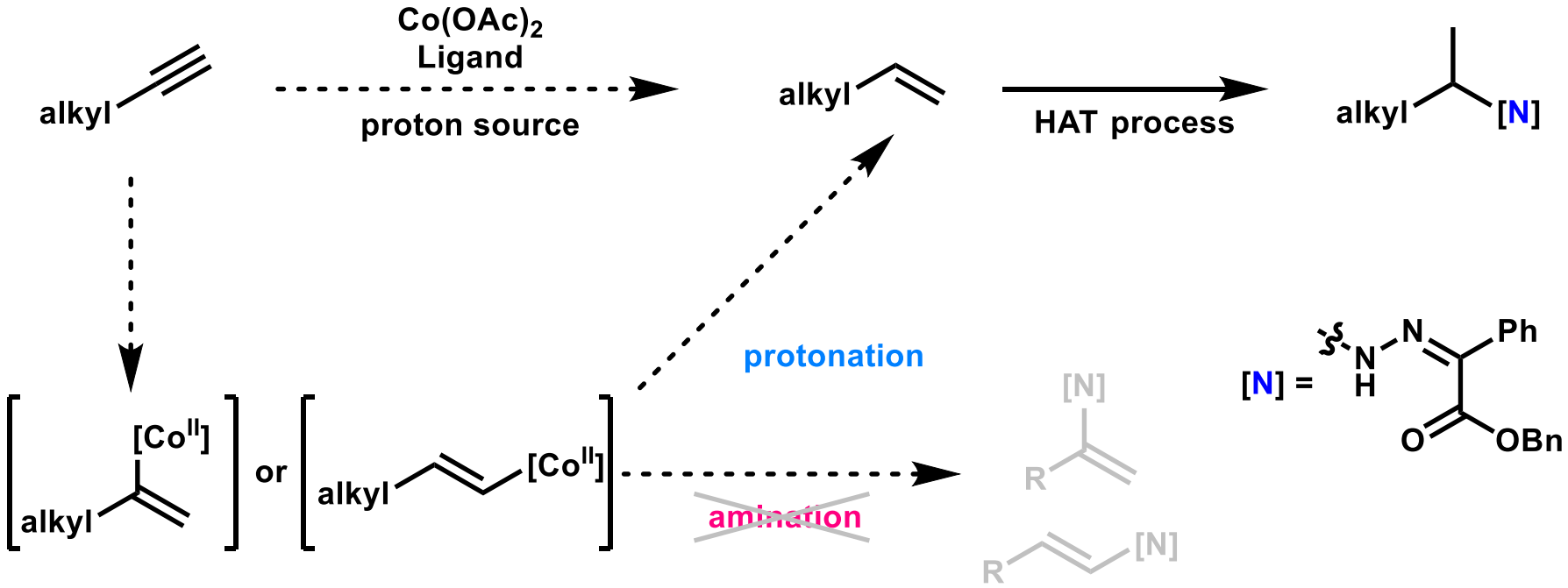
Reductive hydroamination strategy

Previous work:



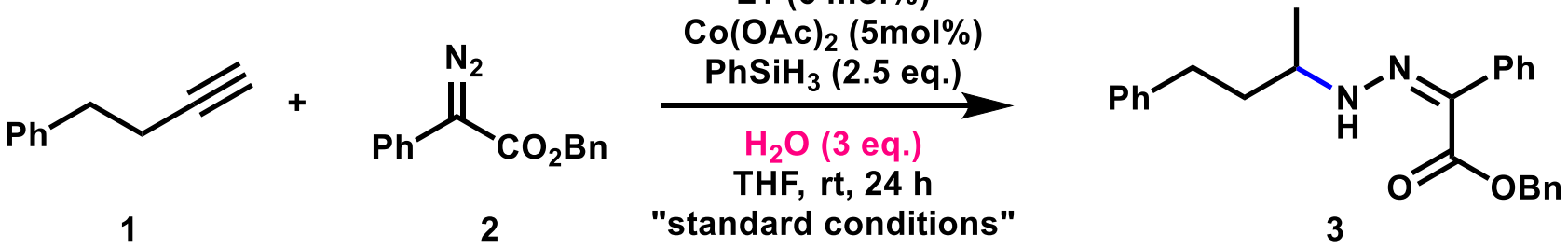
-Markovnikov selectivity

This work: one pot reaction



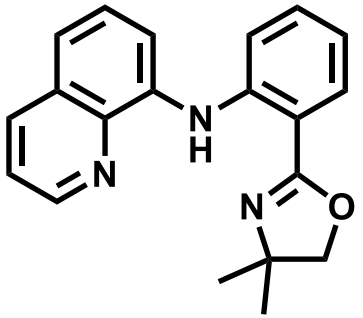
1) Chen, J.; Shen, X.; Lu, Z. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460
2) Shen, X.; Chen, X.; Chen J.; Sun, Y.; Cheng, Z.; Lu, Z. *Nat. Commun.* **2020,** *11,* 783

Optimization (1)



1 2 3

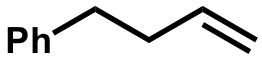
entry	variation from "standard conditions"	yield
1	-	83%
2	no $PhSiH_3$	-
3	no L1	-
4	no $Co(OAc)_2$	-
5	$CoCl_2$ insted of $Co(OAc)_2$	-
6	under air, rather than under N_2	-*



L1

* Alkene 4 was detected (13%)

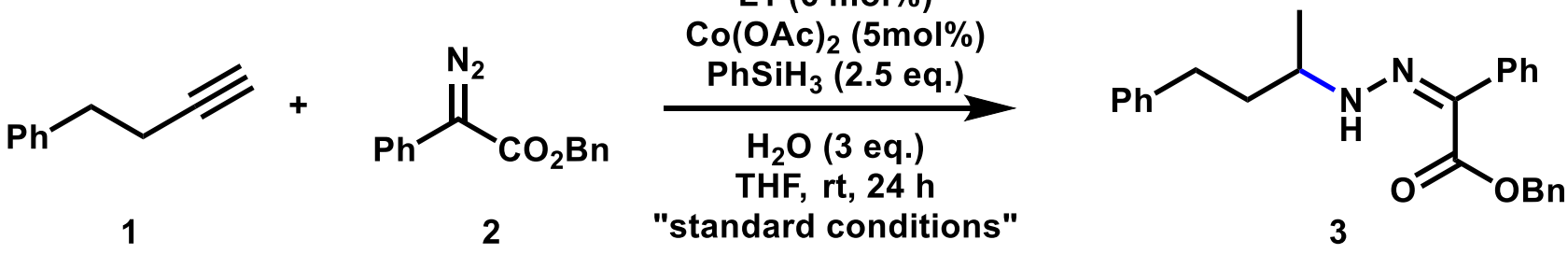
Yields were determined by ^1H NMR



4

1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

Optimization (2)

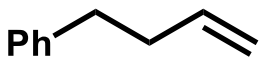


1 2 3

entry	variation from "standard conditions"	yield
1	-	83%
7	L2 instead of L1	-
8	L3 instead of L1	9%**
9	L4 instead of L1	63%
10	L5 instead of L1	-
11	L6 instead of L1	-

** Alkene 4 was detected (45%)

Yields were determined by ^{1}H NMR



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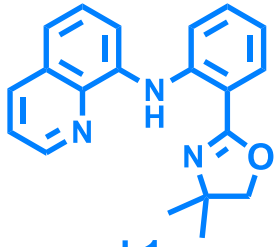
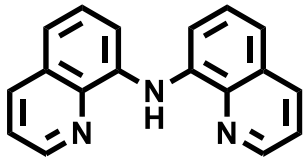
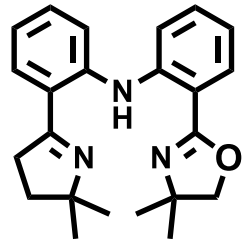


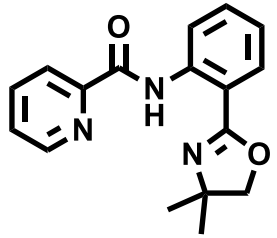
L1



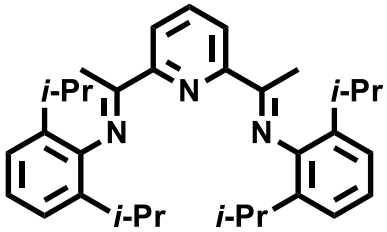
L2



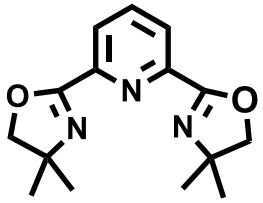
L3



L4



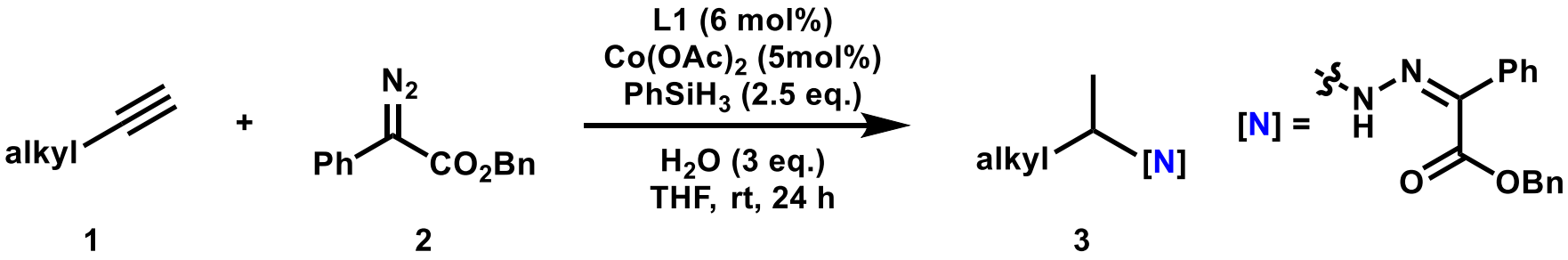
L5



L6

1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

Substrate scope



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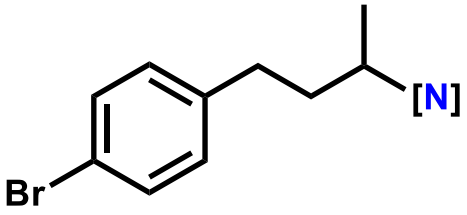
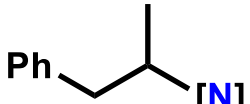
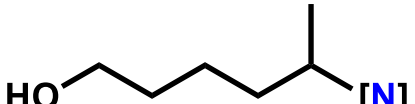


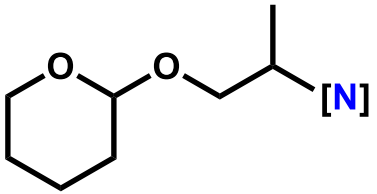
80%



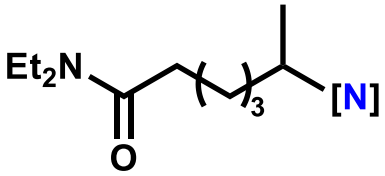
84%



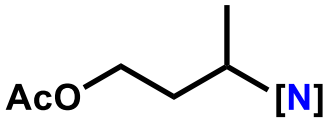
36 h, 69%



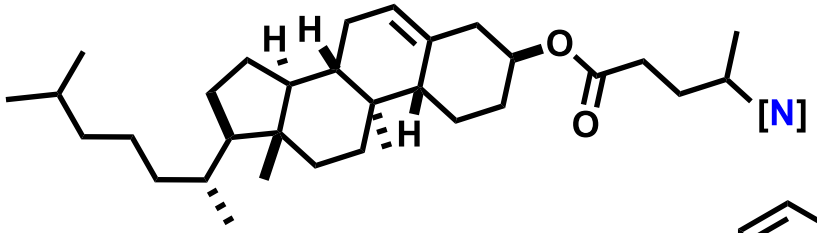
70%



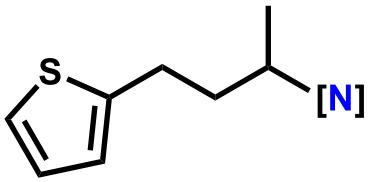
36 h, 66%



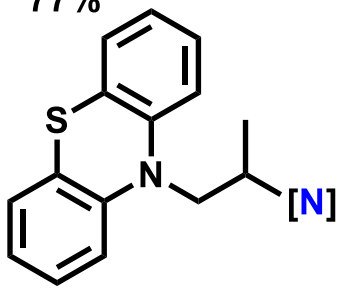
77%



74%

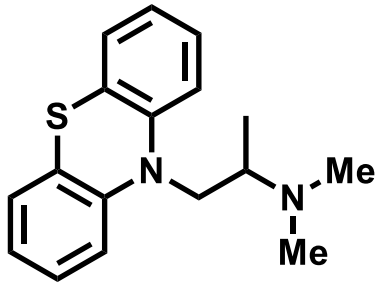


74%



1) Zn dust, AcOH, 60 °C

2) HCOOH, HCHO, rt

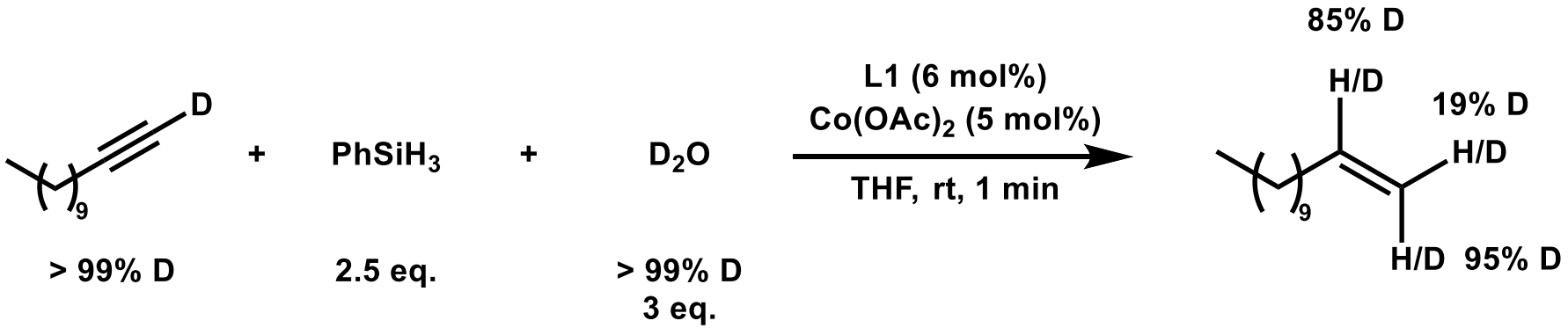


Promethazine
60%

1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

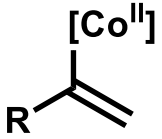
Control experiments (1)

1. Isotopic labeling experiments

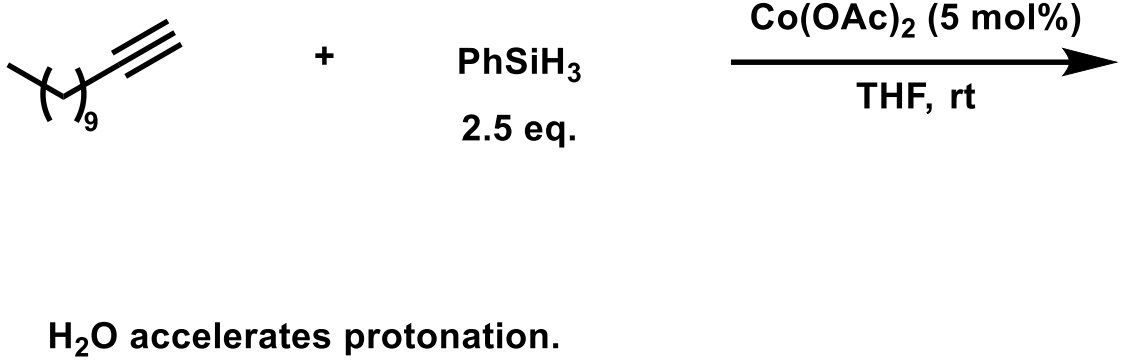


> 99% D | 2.5 eq. | > 99% D, 3 eq.

Syn-Markovnikov selectivity.



2. Role of H_2O



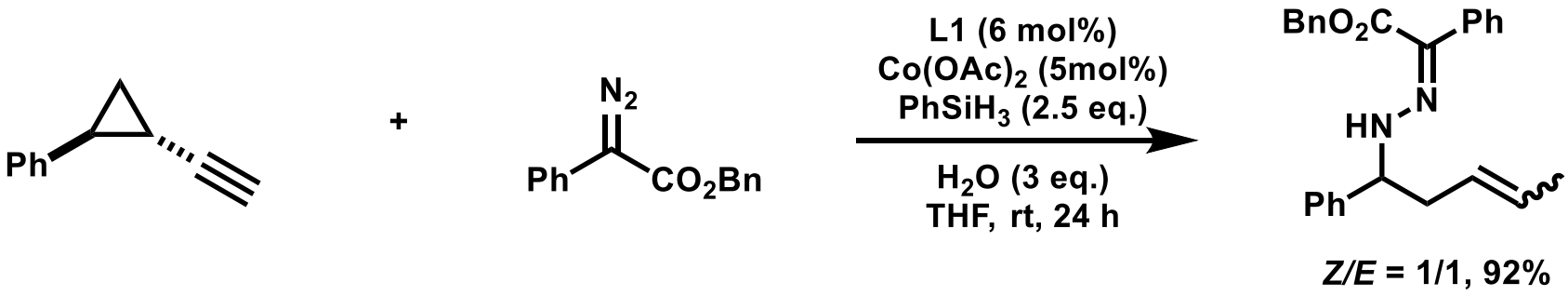
11% (without H_2O, 30 min)
55% (without H_2O, 60 min)
68% (without H_2O, 120 min)
68% (with 3 eq. H_2O, 2 min)

H_2O accelerates protonation.

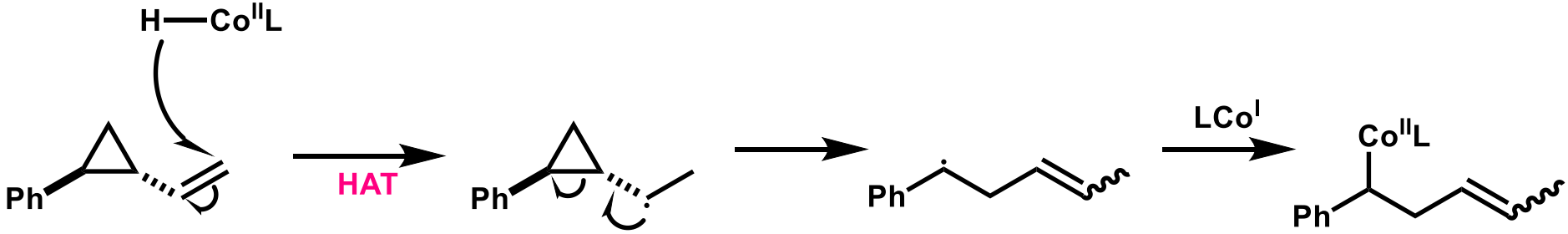
1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

Control experiments (2)

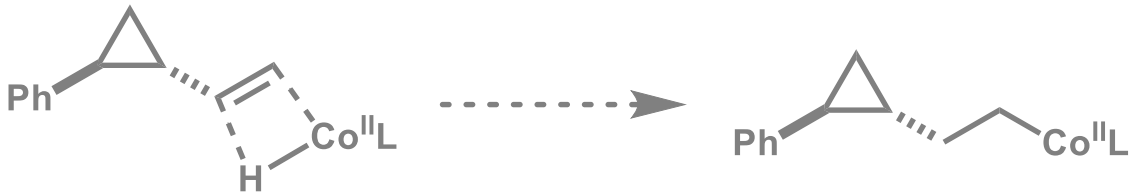
3. Radical clock experiment



Z/E = 1/1, 92%

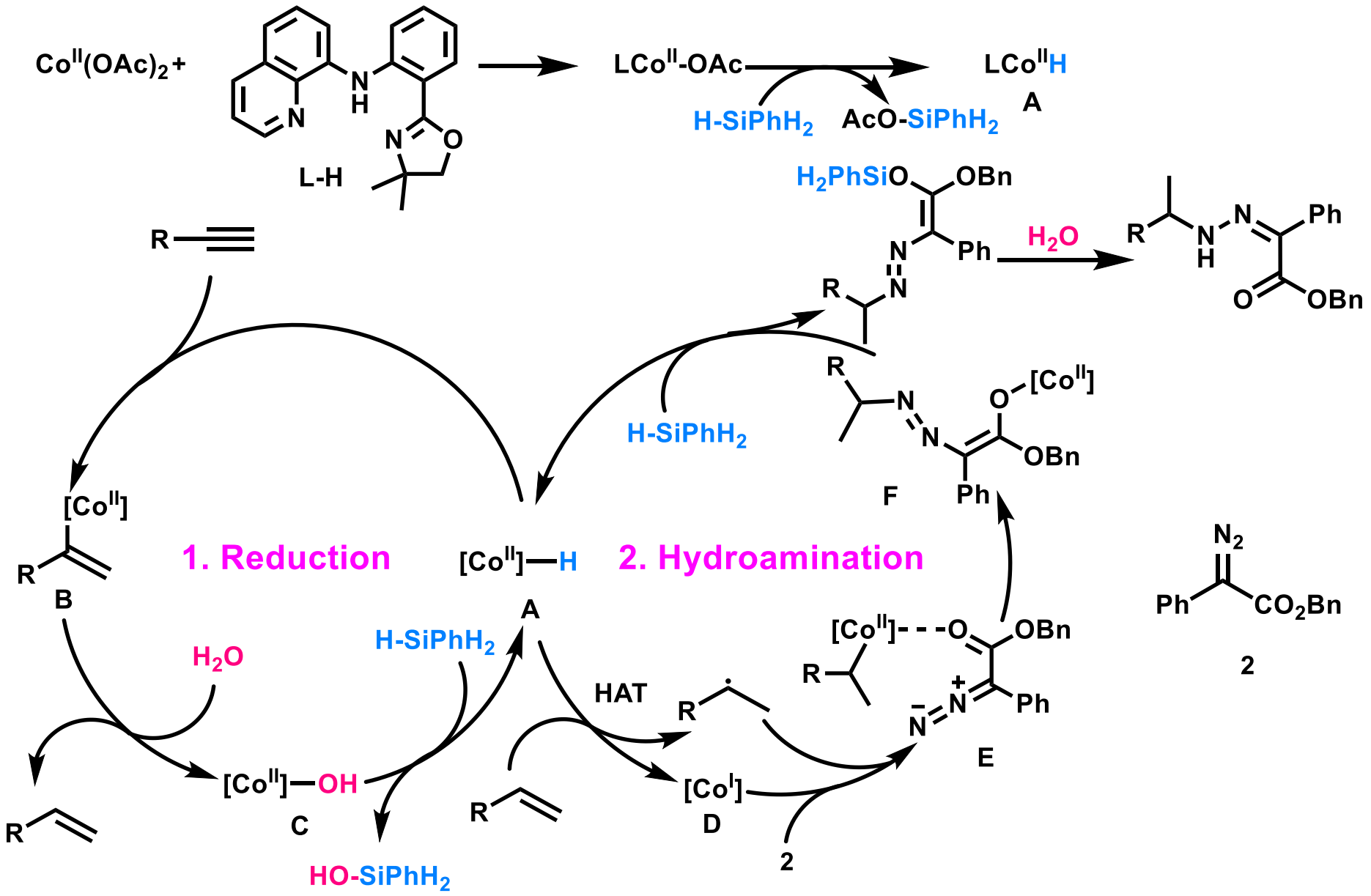


HAT process occured.



1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

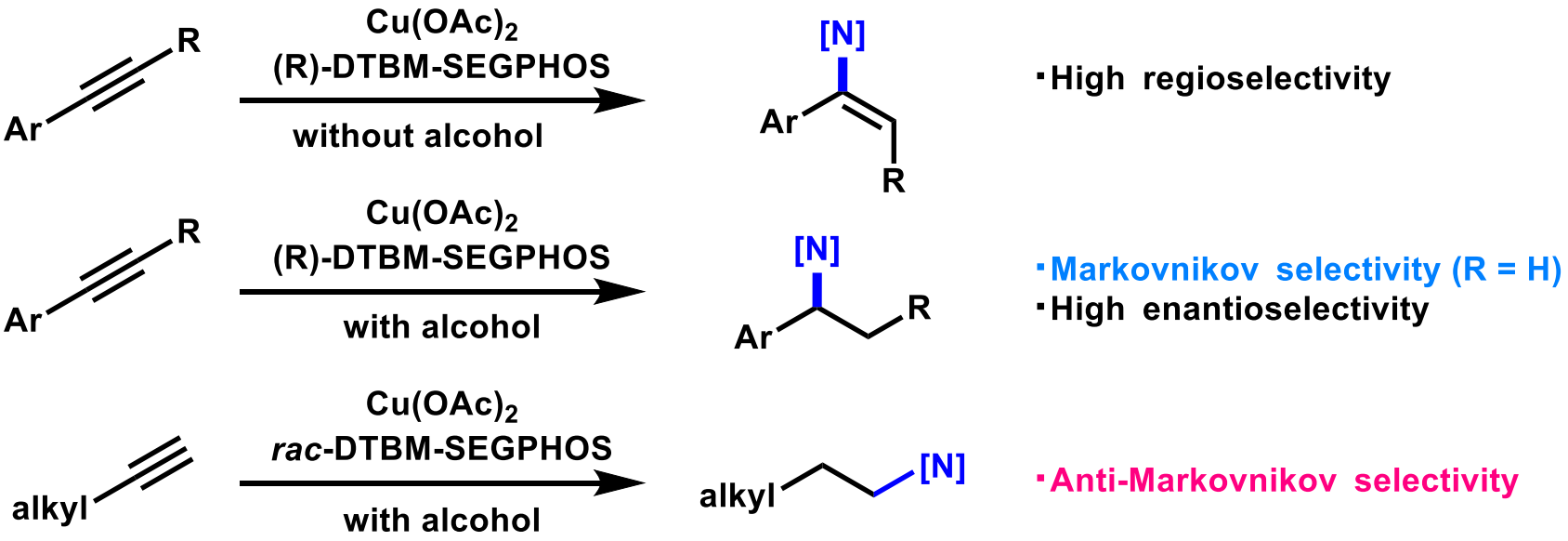
Reaction mechanism



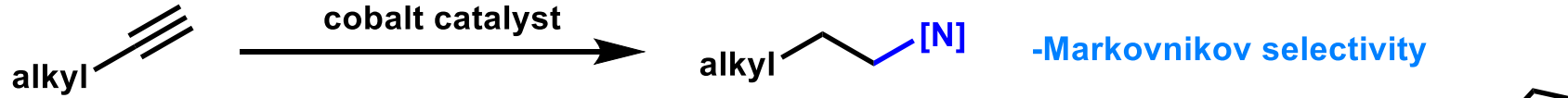
1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

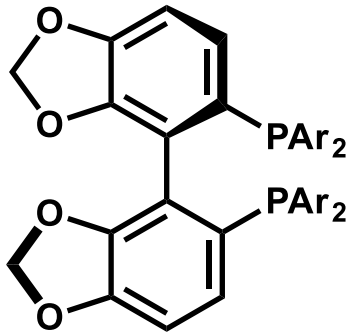
Summary

1. Buchwald's group (2015)

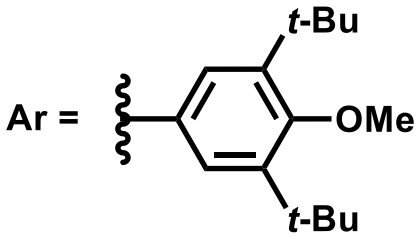


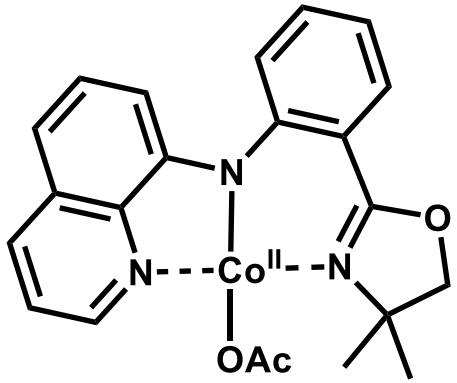
2. Lu's group (2020)





(R)-DTBM-SEGPHOS

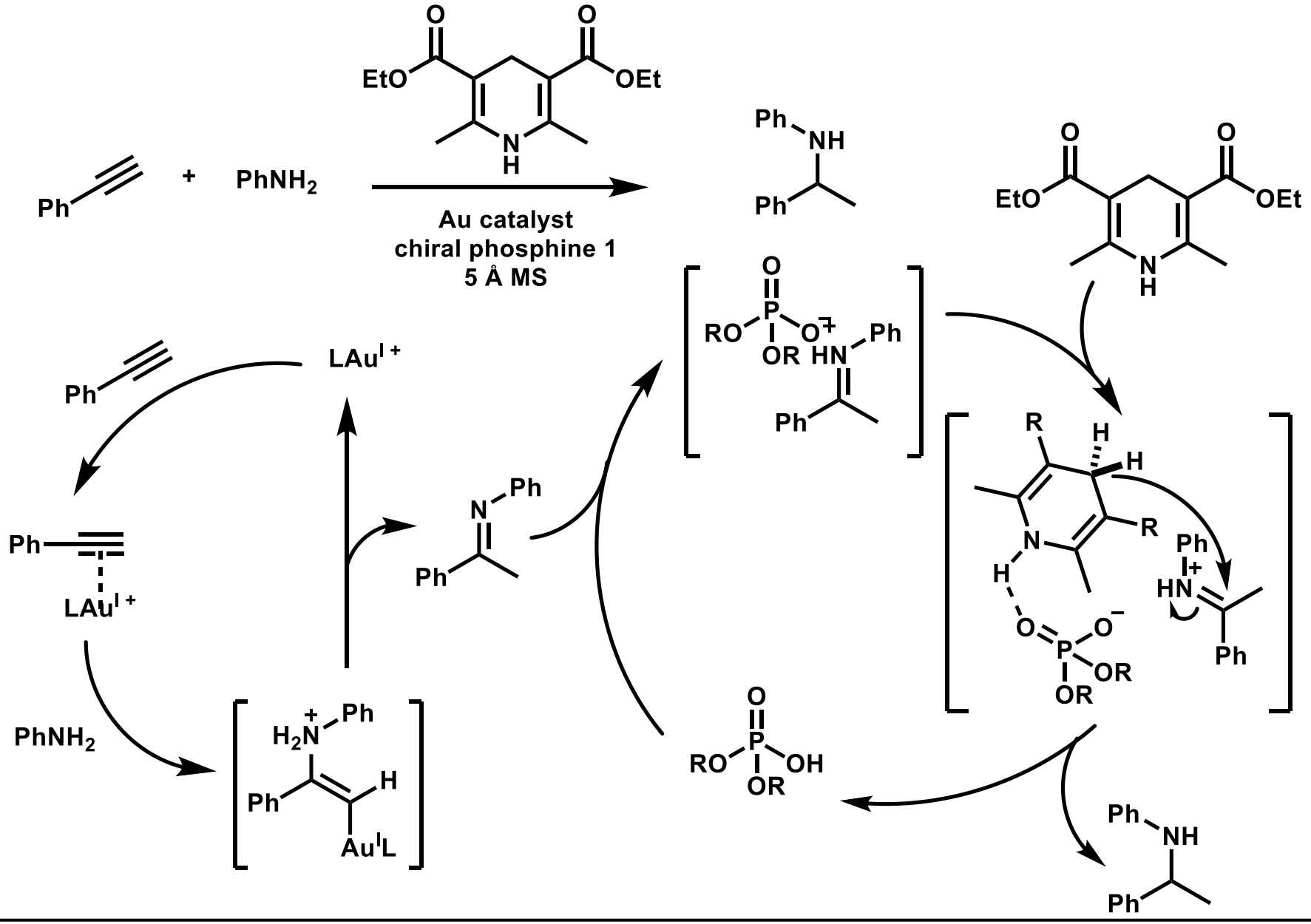




cobalt catalyst

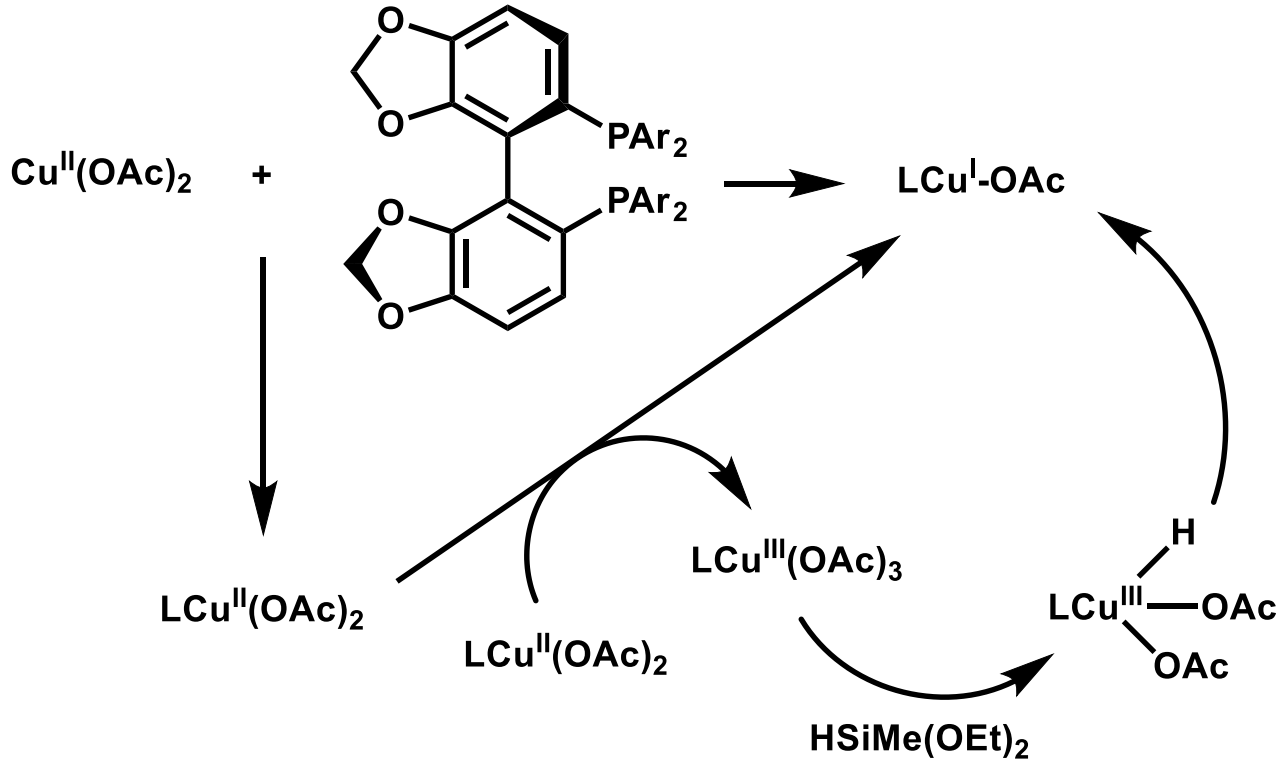
Appendix

Reaction mechanism (page 5)



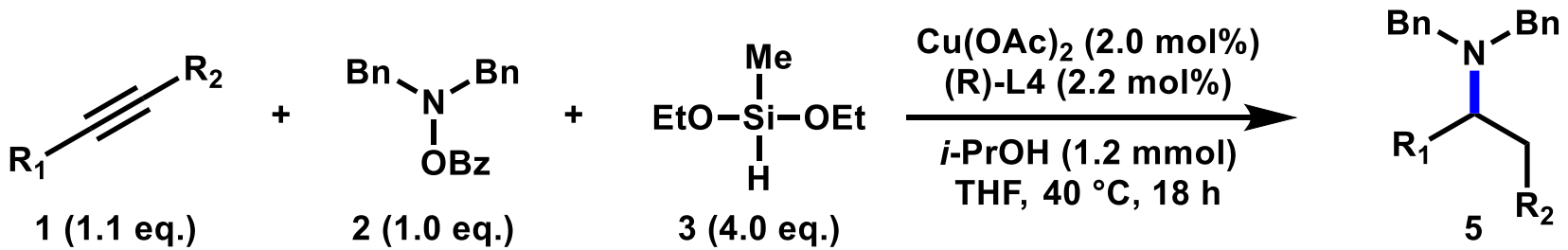
1) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009,** *11,* 4204-4207.

Proposed mechanism of copper reduction

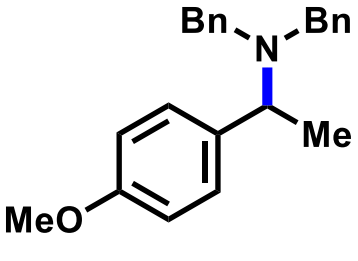


1) MacCann, S. D.; Stahl, S. S. *Acc. Chem. Res.* **2015,** *48,* 1756－1766

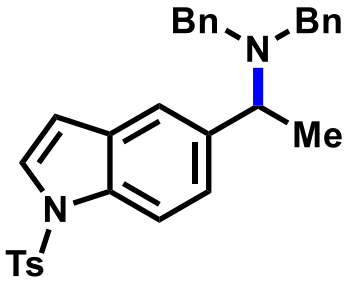
Substrate scope of copper catalyst



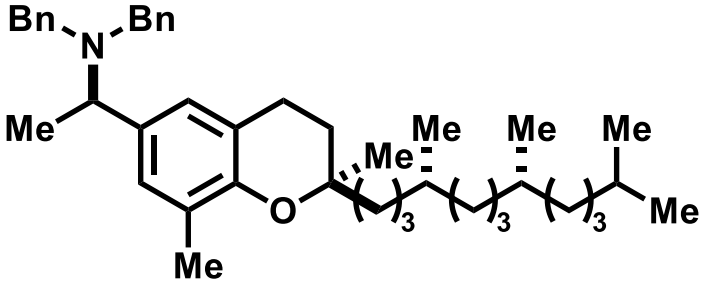
1 (1.1 eq.) 2 (1.0 eq.) 3 (4.0 eq.) 5



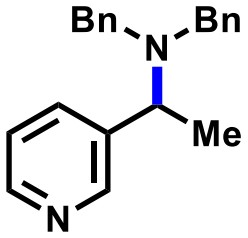
81%, > 99% e.e.



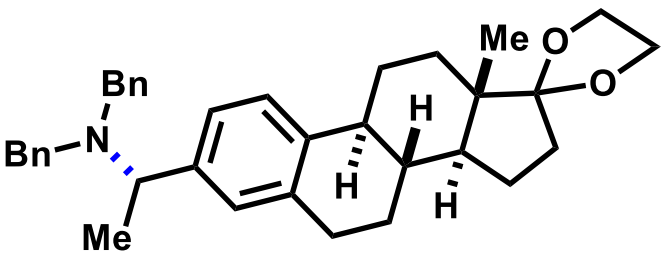
80%, 98% e.e.



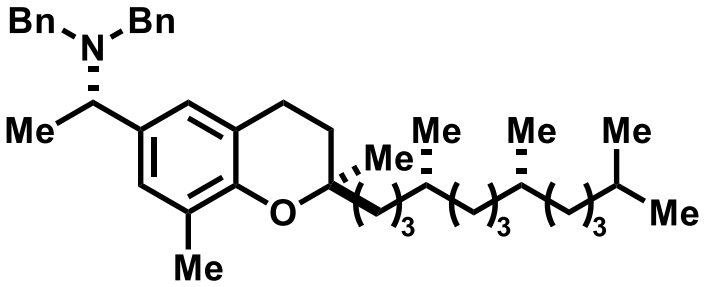
with (R)-4, 75% yield, >99:1 d.r.



63%, 98% e.e.



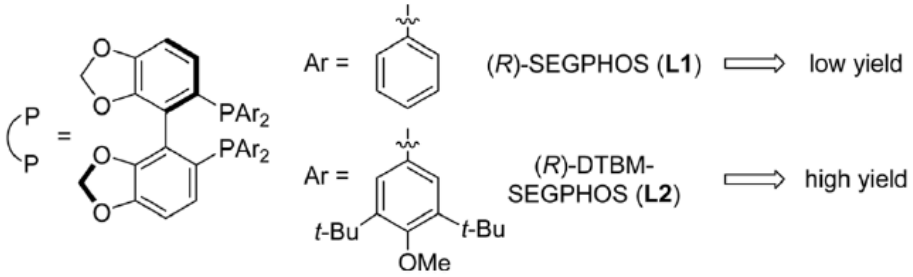
with (S)-L4, 76%, < 1:99 d.r.

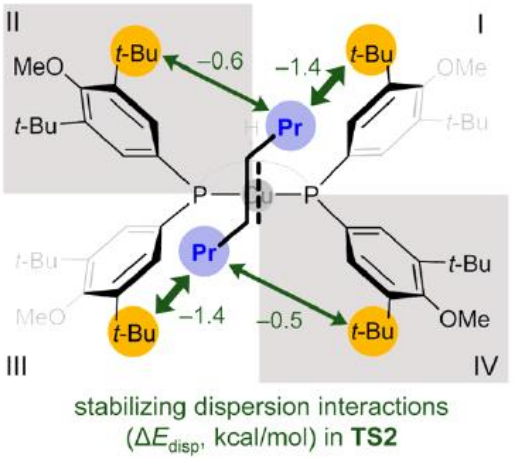


with (S)-4, 75% yield, >1:99 d.r.

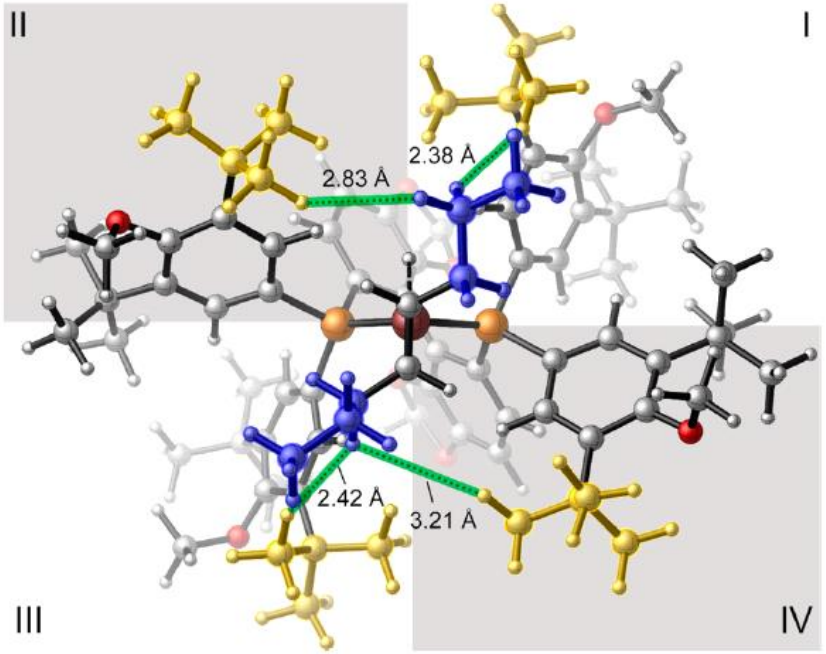
1) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015,** *7,* 38-44

Catalyst reactivity





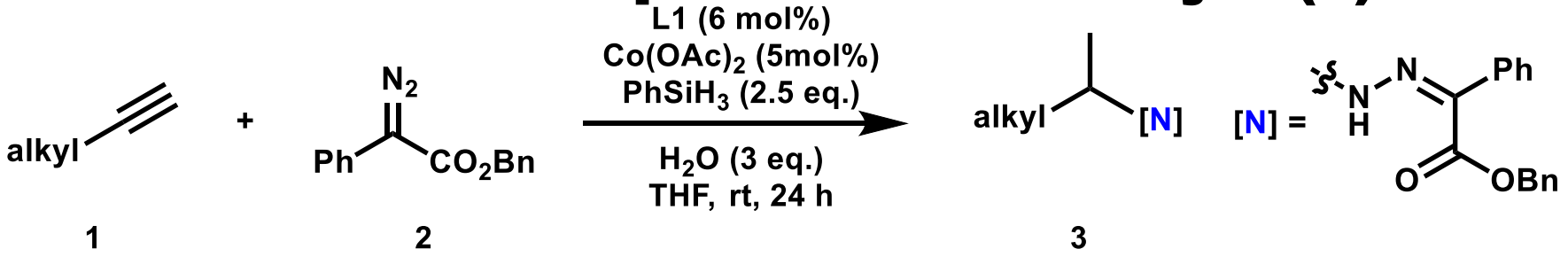
stabilizing dispersion interactions (ΔE_{disp}, kcal/mol) in **TS2**



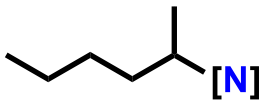
Dispersion interactions between *t*-Bu groups and substrate enhances reactivity.

1) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc.* **2017,** *139,* 16548-16555

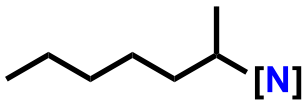
Substrate scope of cobalt catalyst (1)



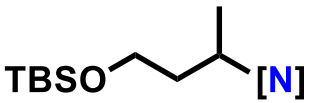
1 2 3



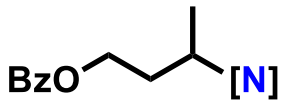
56%*



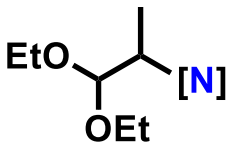
63%*



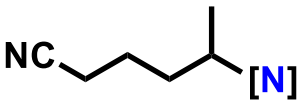
78%*



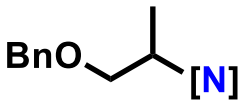
63%**



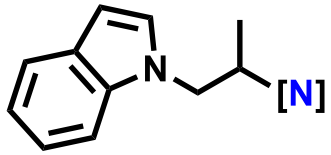
48%



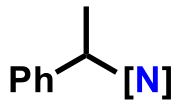
45%*



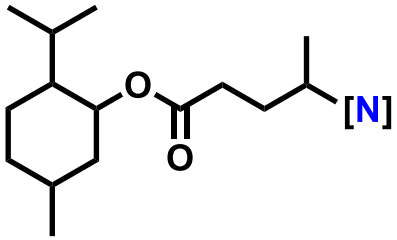
63%**



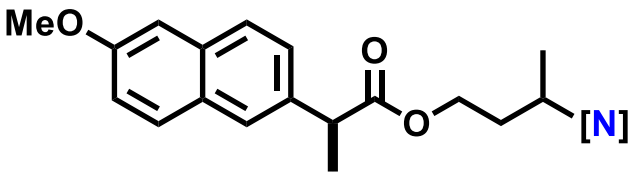
86%*



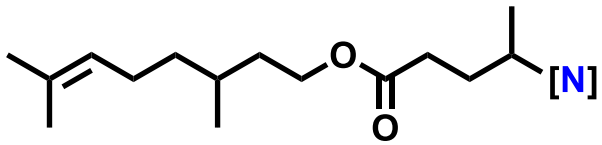
96%



61%



65%

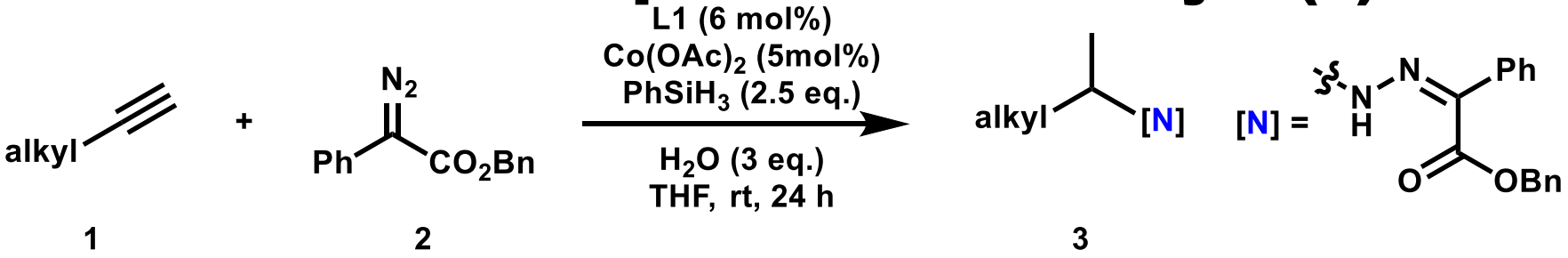


68%

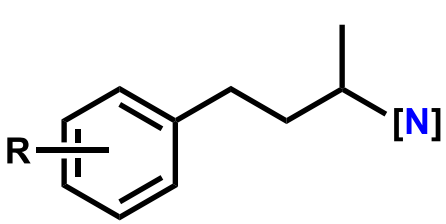
* stirred for 36 h
** stirred for 36h, without water

1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

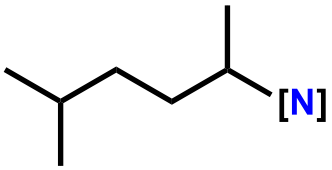
Substrate scope of cobalt catalyst (2)



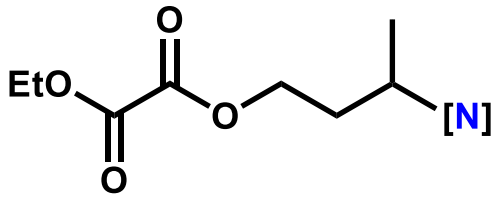
1 2 3



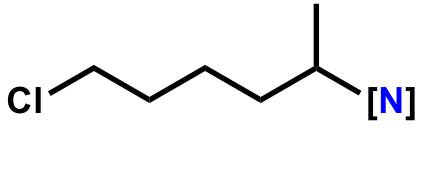
R = 2-Me, 67%
R = 3-Me, 68%*
R = 4-Me, 69%*
R = 3,5*di*Me, 70%*
R = 4-Ph, 65%*



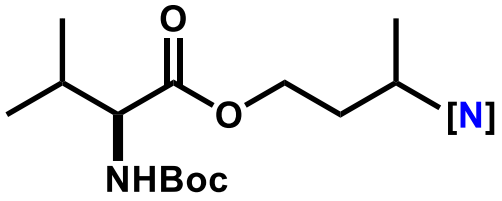
58%*



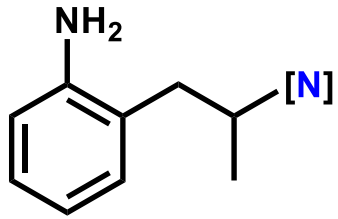
59%**



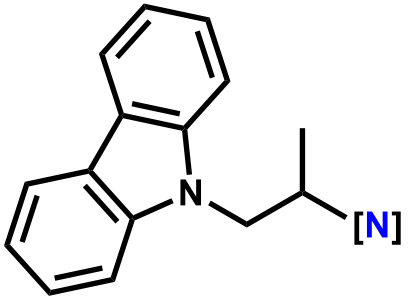
58%*



76%



54%*

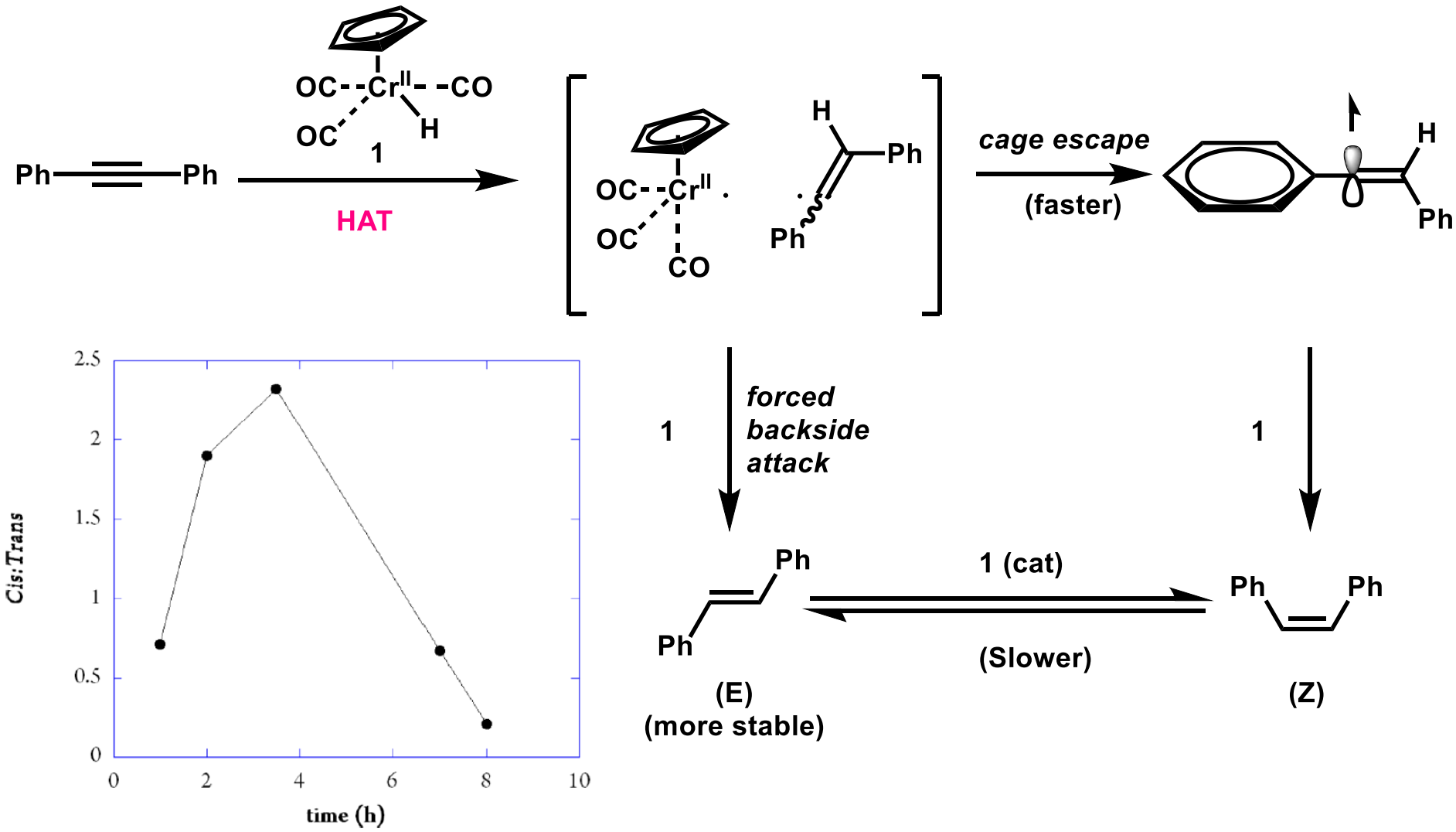


85%*

* stirred for 36 h
** stirred for 36h, without water

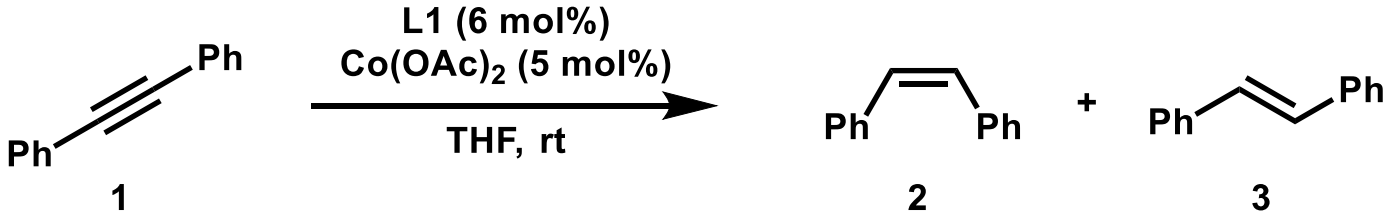
1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

HAT process semihydrogenation



1) 1) Estes, D. P.; Norton, J. R.; Jockusch, S.; Sattler, W. *J. Am. Chem. Soc.* **2012,** *134,* 15512-15518

HAT or insertion? (without water)

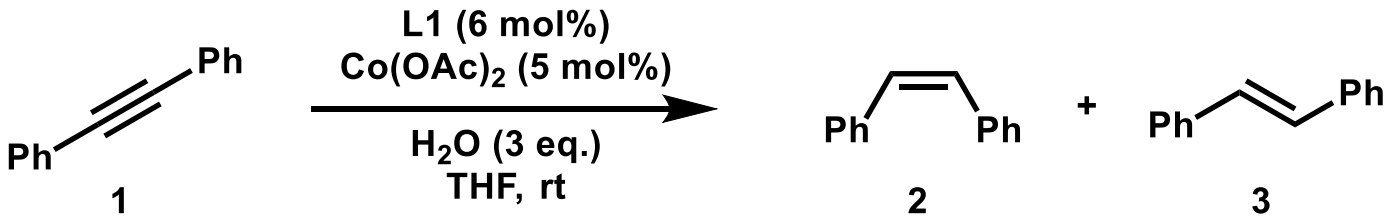


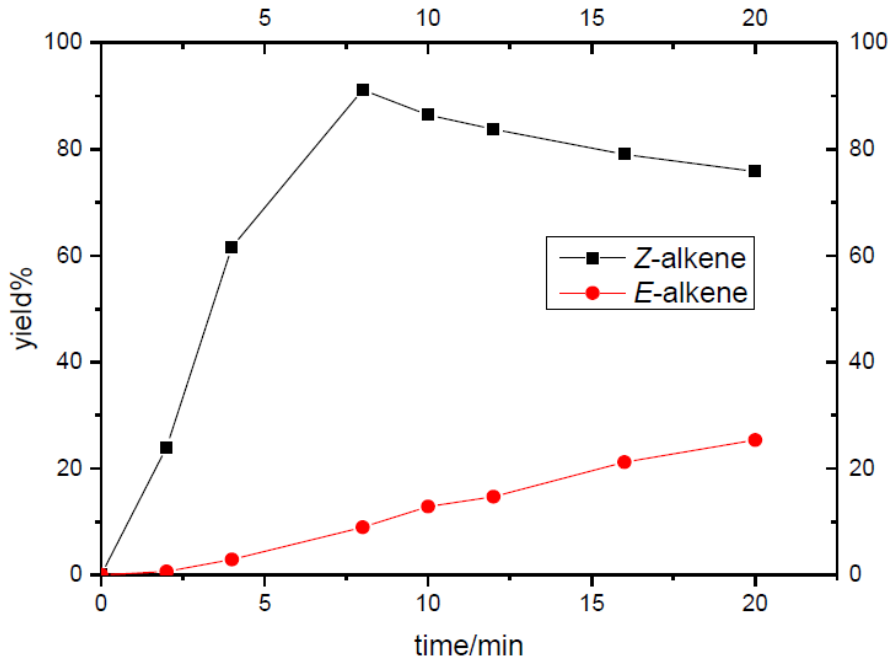
Entry	time (h)	2 (%)	3 (%)
1	0.5	3	-
2	8	77	2

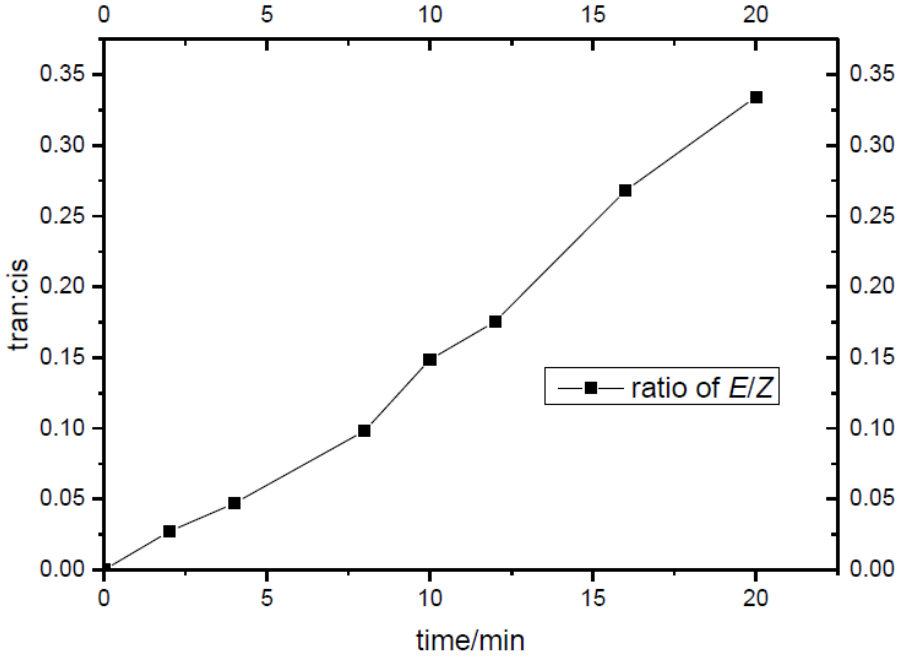
No alkene isomerization occured in this reaction.

1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

HAT or insertion? (with water)





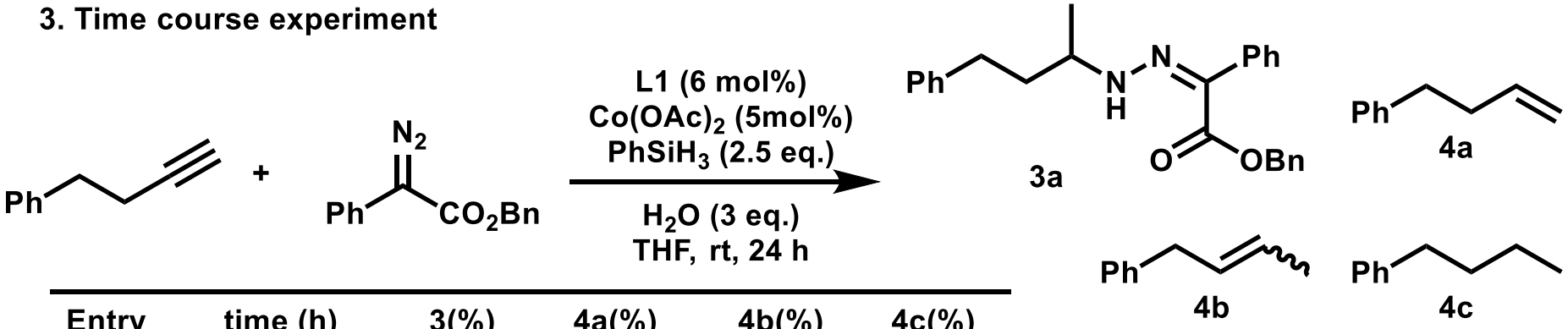


No HAT process

1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

Time course study

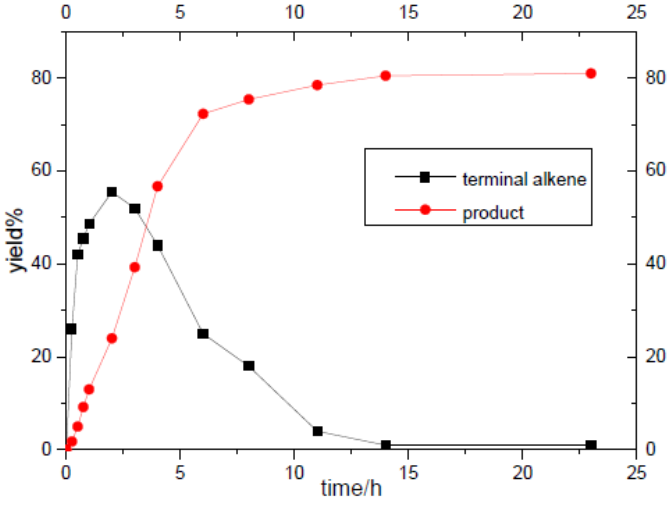
3. Time course experiment



Entry	time (h)	3(%)	4a(%)	4b(%)	4c(%)
1	0.25	2	26	-	-
2	0.5	5	42	-	-
3	0.75	9	45	-	-
4	1	13	49	-	-
5	2	26	57	-	3
6	3	39	51	-	5
7	4	57	44	-	9
8	6	72	25	9	13
9	8	75	14	16	14
10	23	81	1	20	17

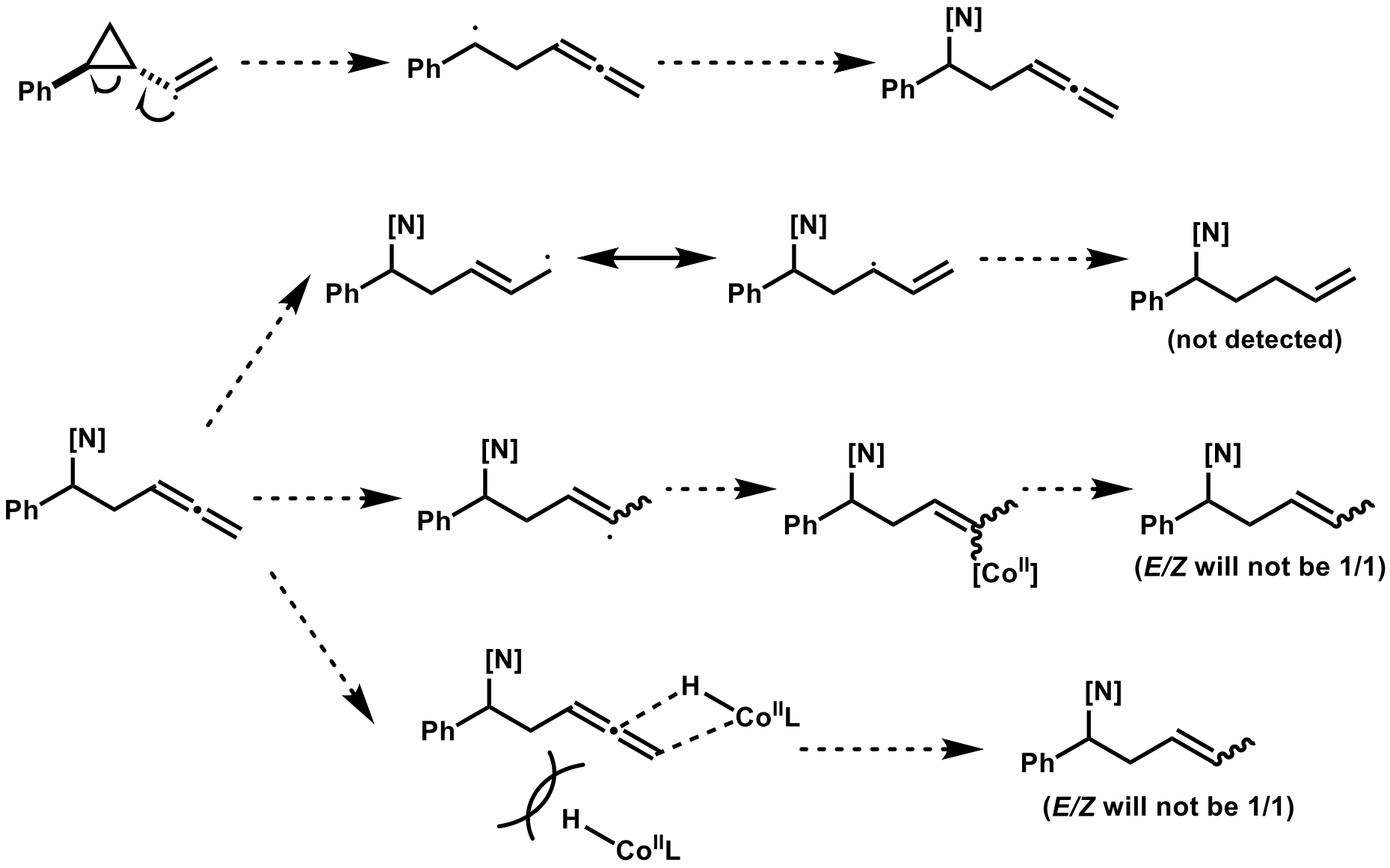
Yields were determined by ^{1}H NMR

Diazo compounds reduce the rate of alkyne semihydrogenation, which could make the reaction conduct smoothly.

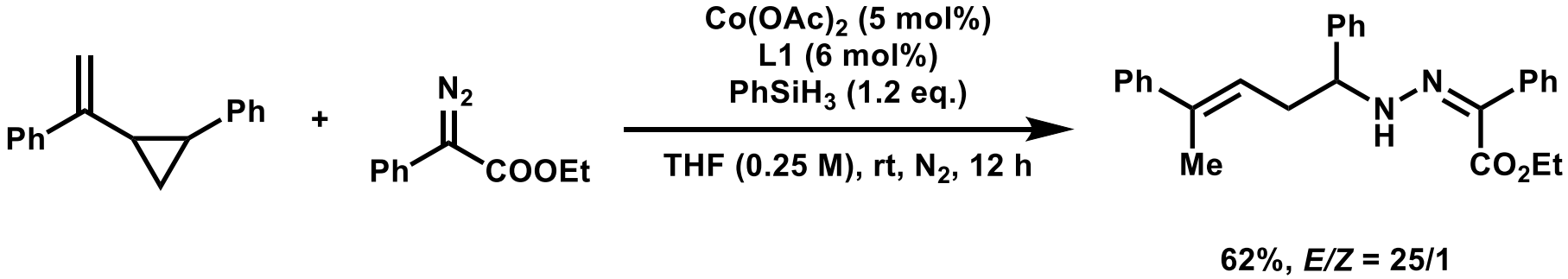


1) Chen, J.; Shen, X.; Lu, Zhan. *J. Am. Chem. Soc.* **2020,** *142, 34,* 14455-14460

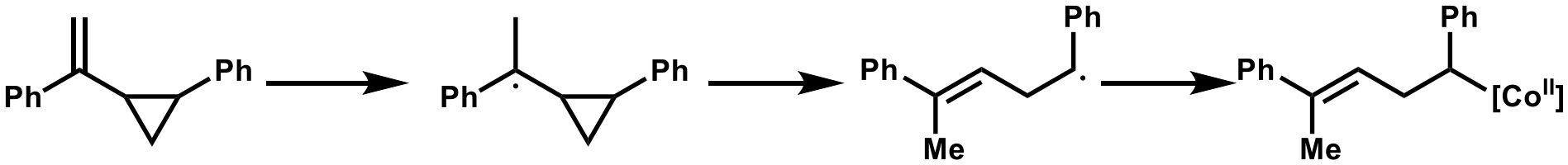
Wrong pathway (radical clock experiment)



Another radical clock experiment



62%, *E/Z* = 25/1



1) Shen, X.; Chen, X.; Chen J.; Sun, Y.; Cheng, Z.; Lu, Z. *Nat. Commun.* **2020,** *11,* 783