DUDOGNON Yohan

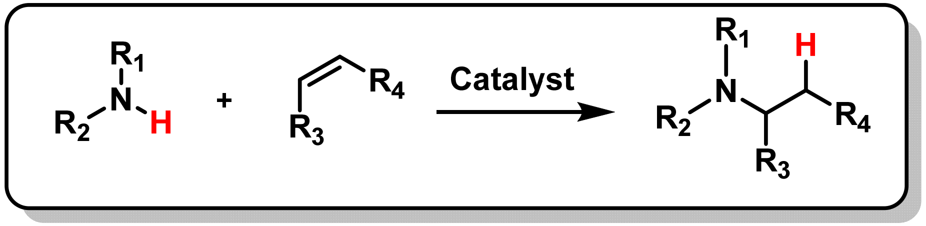
November 24, 2015

Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins

J. S. Bandar, M. T. Pirnor, S. L. Buchwald, *J. Am. Chem. Soc.*, ASAP 18th of November 2015

DOI: 10.1021/jacs.5b10219

State of art



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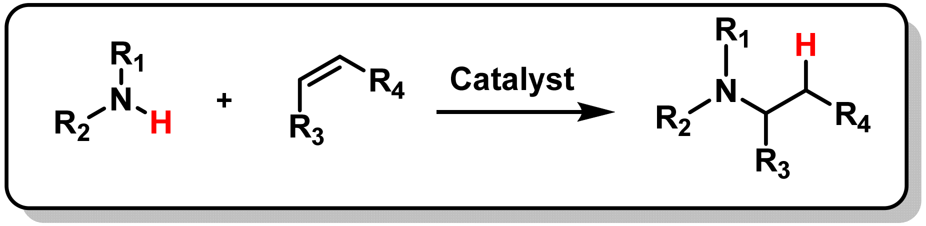
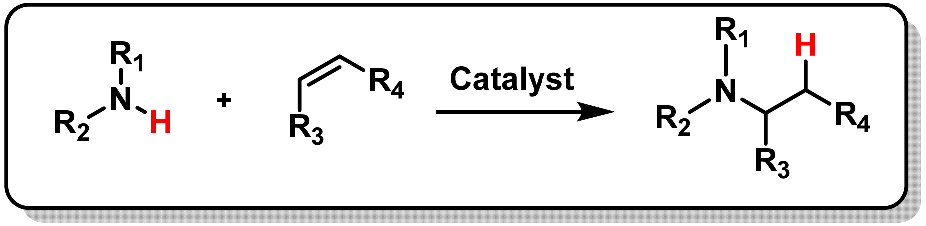


- **Late transition metal catalysis:**

Drawbacks: - Moderate stereoselectivities
- Limited to activated alkenes (vinyl arenes and acrylate derivatives)

Goossen and al., *Chem. Rev.* **2015**, *115*, 2596.

State of art



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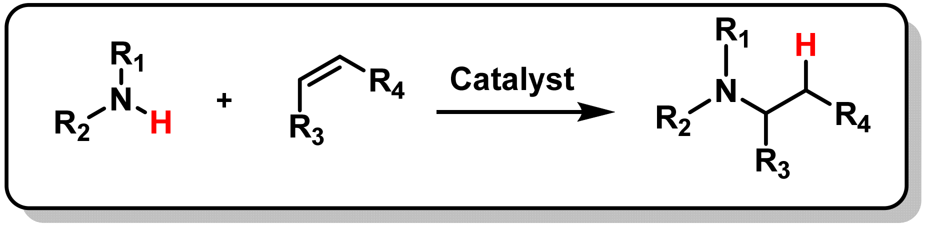
- **Lanthanide and early transition metal catalysis:**

  Drawback: Limited substrate scope

Parvulescu and al., *Org. Process. Res. Dev.* **2015**, *19*, 1327.

State of art



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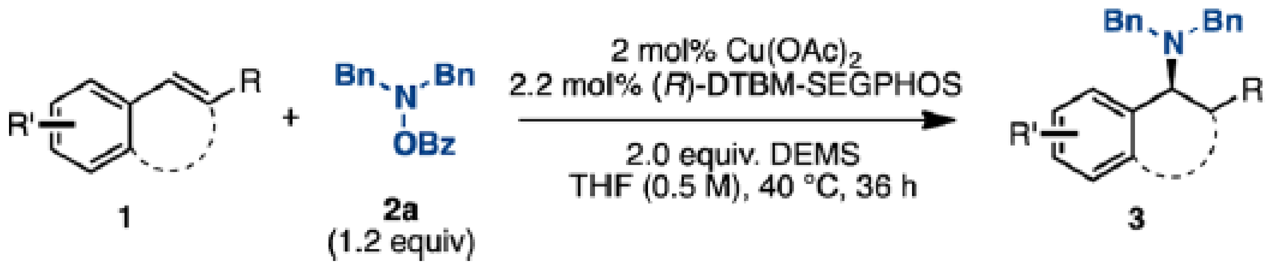
- **Challenges:** Develop a general approach for regio- and enantioselective hydroamination of a broad range of alkene

Previous work

- **Regio- and Enantio-selective CuH-Catalyzed Hydroamination of Alkenes**



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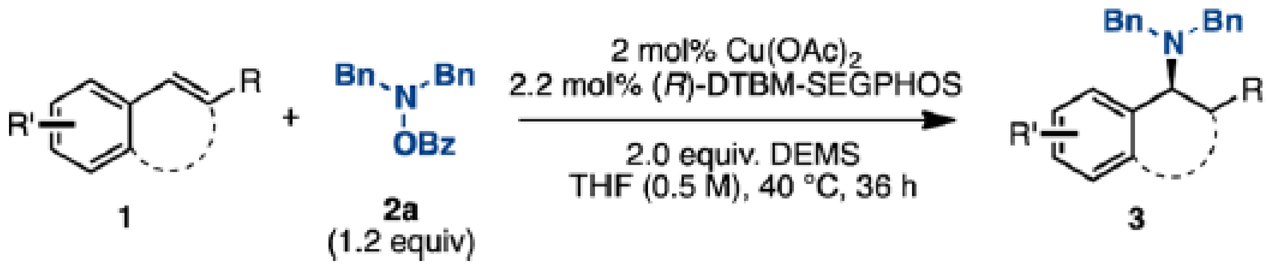


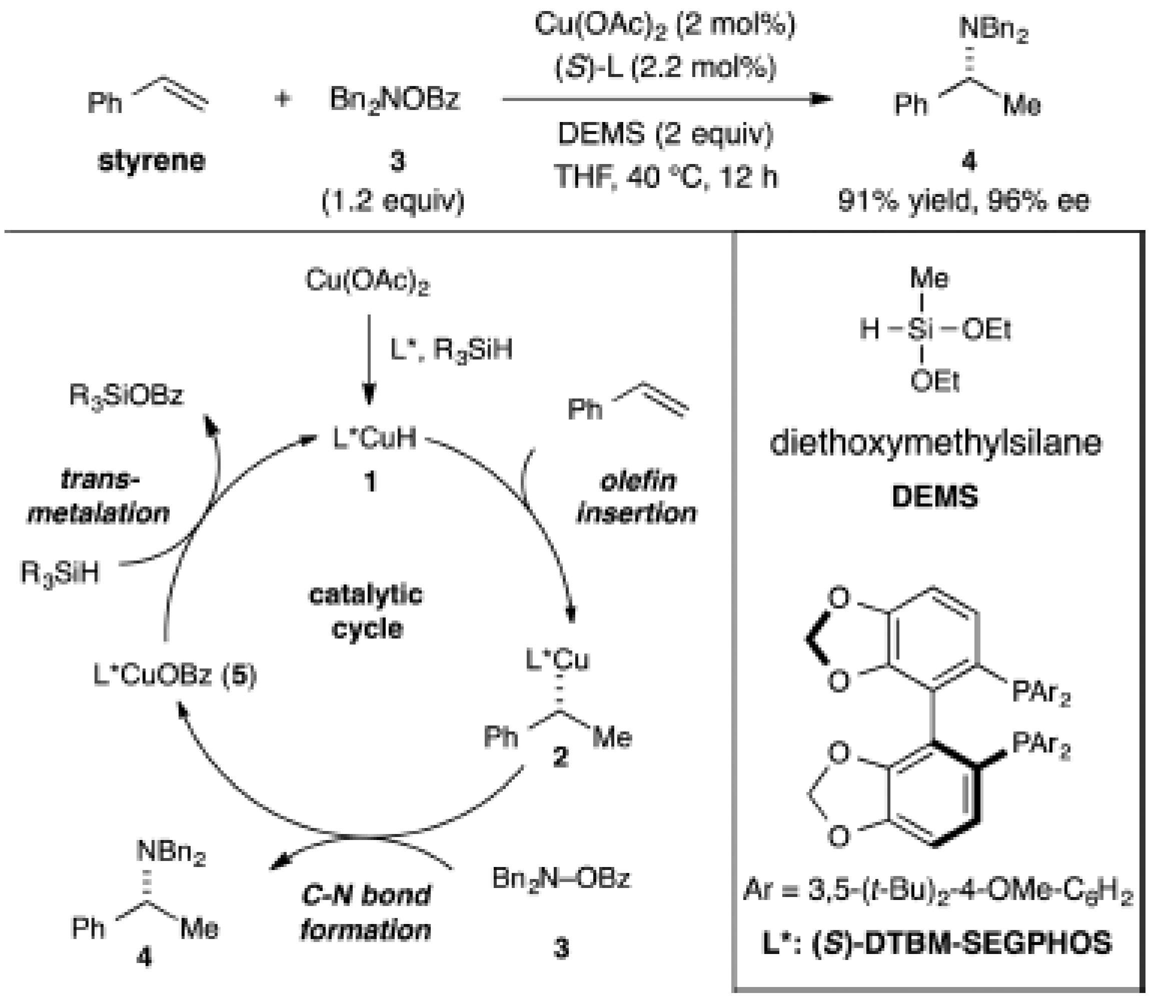
Buchwald and al., *J. Am. Chem. Soc.* **2013**, *135*, 15746.

- **Extented to a wide scope including vinyl silane, terminal alkenes, internal unactivated alkenes, alkynes and strained cyclic alkenes**

Buchwald and al.:
J. Am. Chem. Soc. **2014,** *136*, 15913.
Angew. Chem., Int. Ed. **2015**, *54*, 1638.
Nat. Chem. **2015**, *7*, 38.
Science **2015**, 349, 62.
J. Am. Chem. Soc. **2015**, 137, 9716.

Miura and al.:
Angew. Chem., Int. Ed. **2013**, *52*, 10830.
Org. Lett. **2014**, *16*, 1498.
J. Am. Chem. Soc. **2013**, *135*, 4934.
J. Am. Chem. Soc. **2015**, *137*, 6460.

Proposed mechanism



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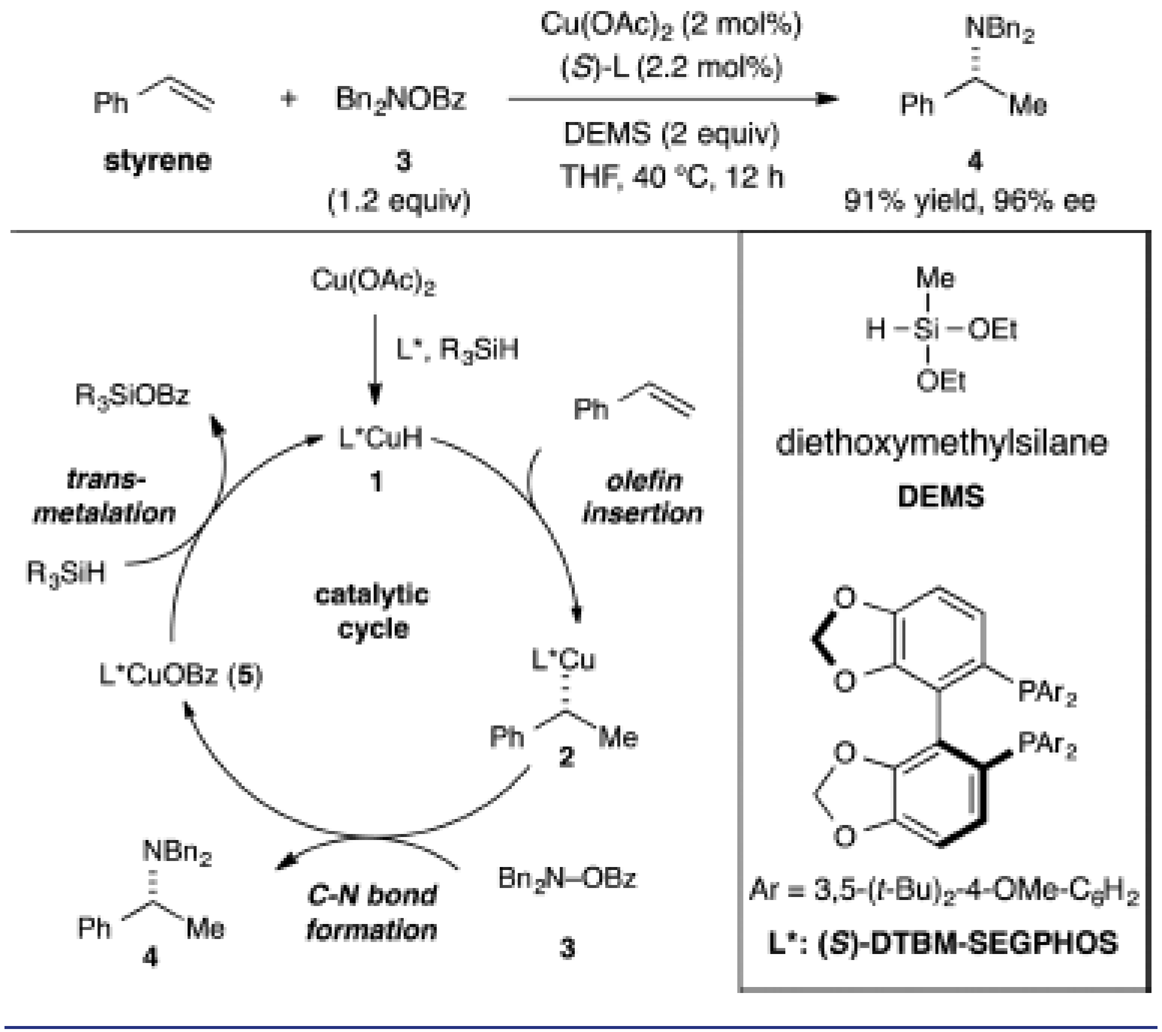
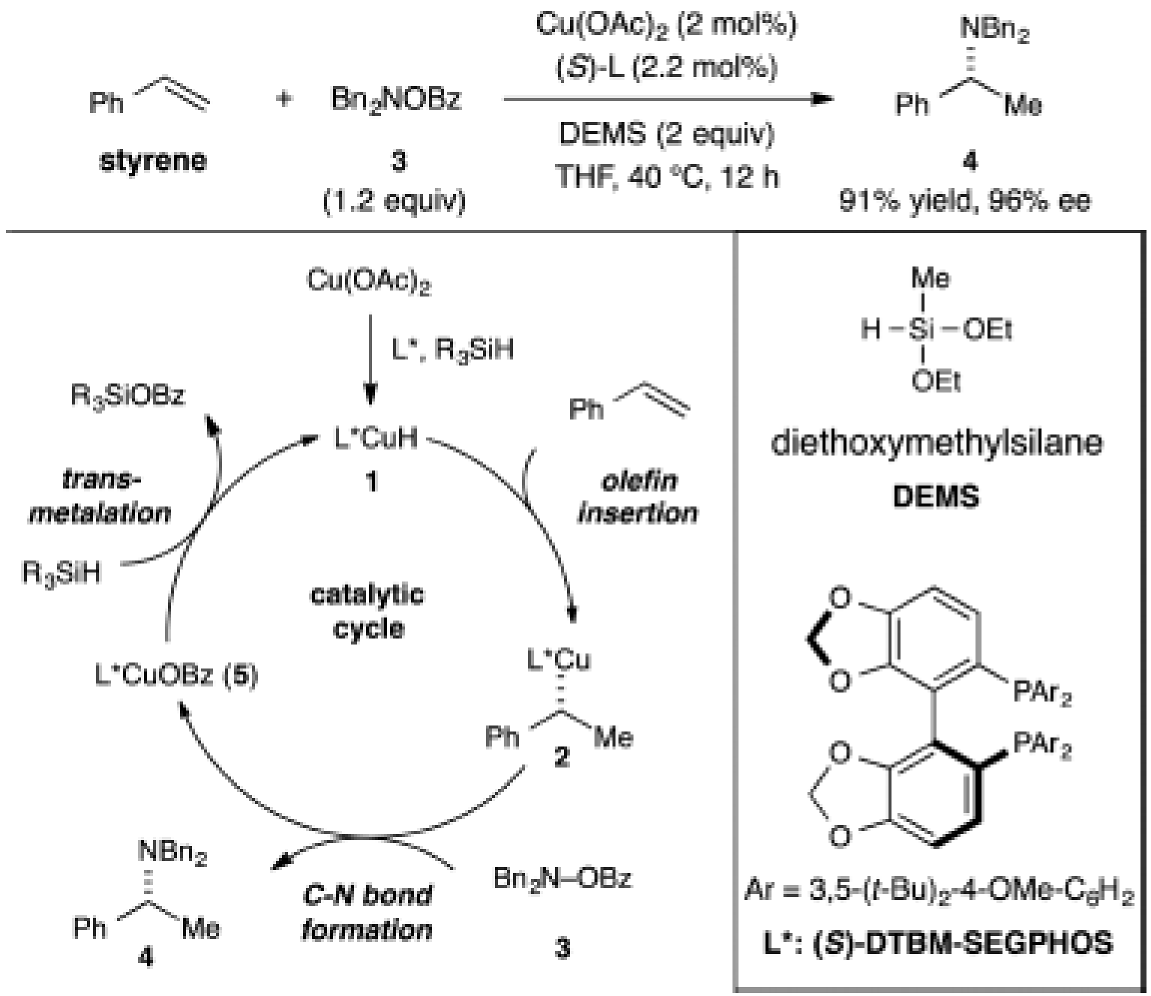


Aim of the work:
Have a better general understanding of the mechanism

Proposed mechanism



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In particular, **identify** the:

Turnover-Limiting and Enantio-Determining steps

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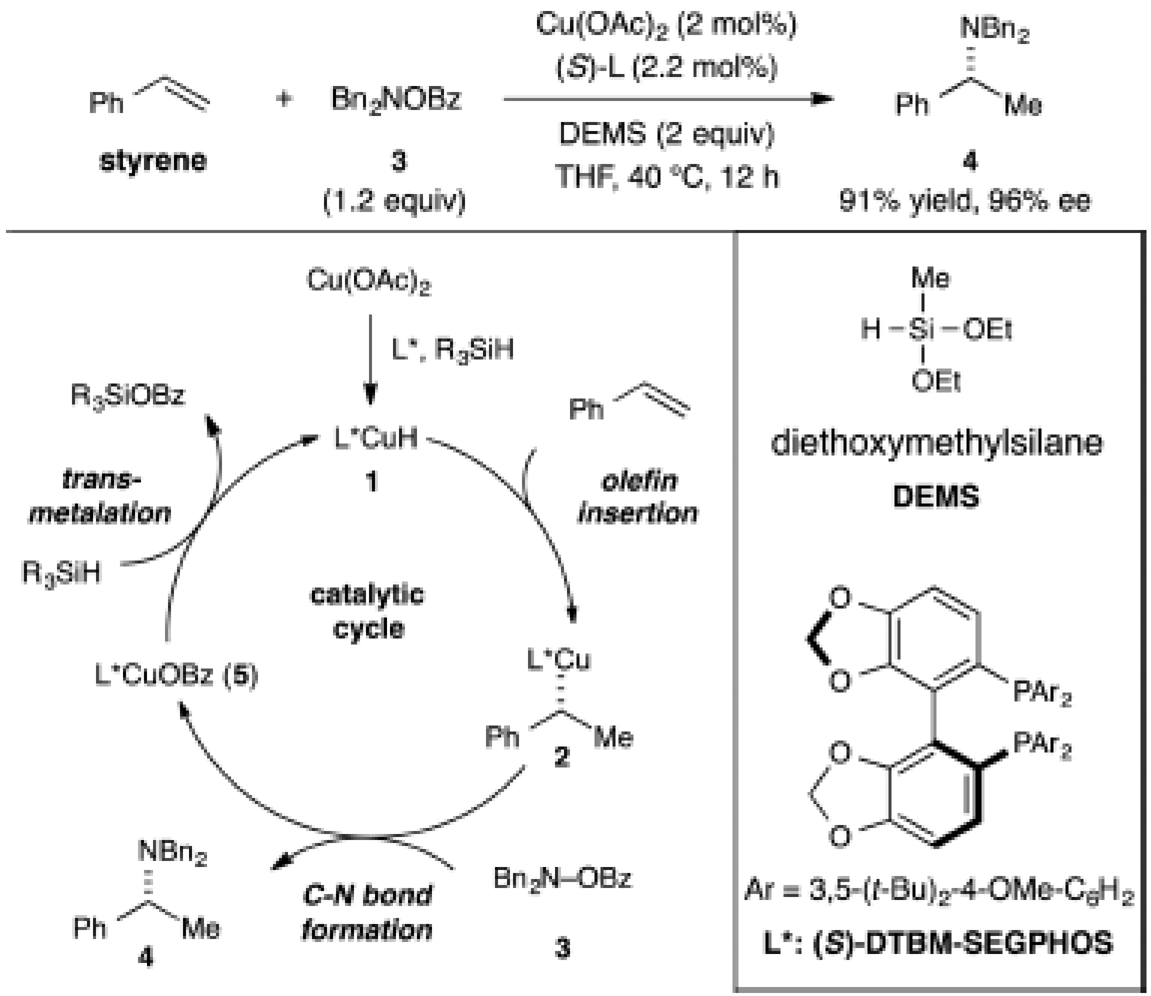

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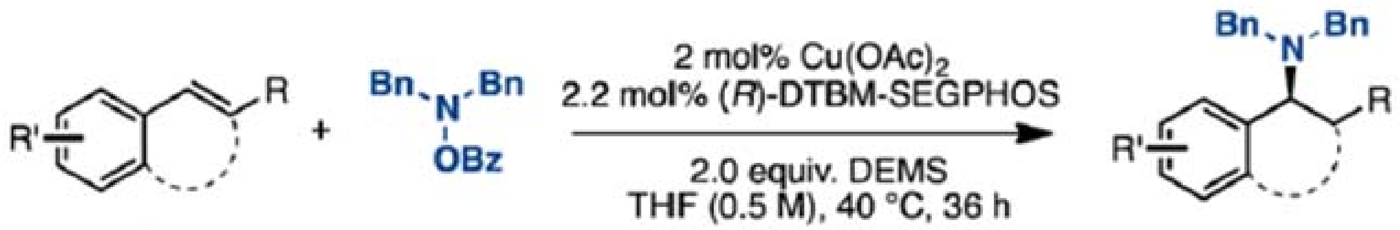
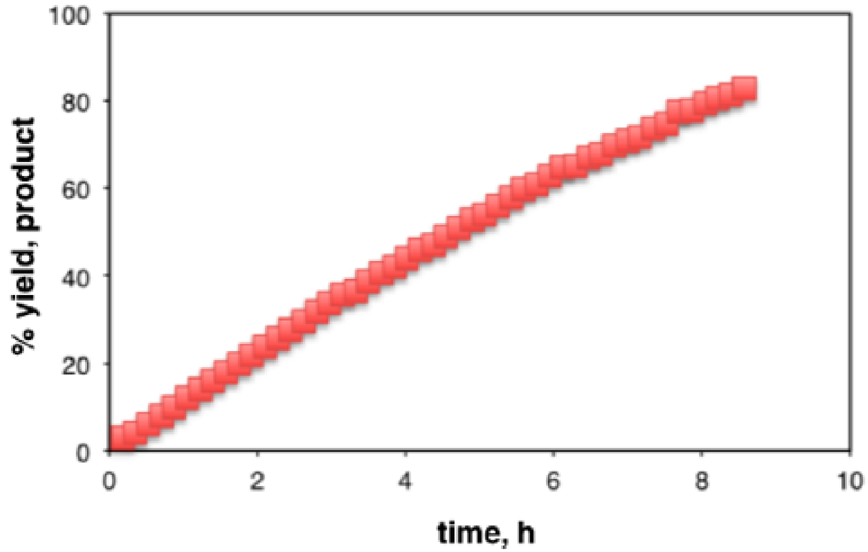
Resting state of the copper catalyst

Kinetic studies



Yields monitored in situ by ^{19}F NMR



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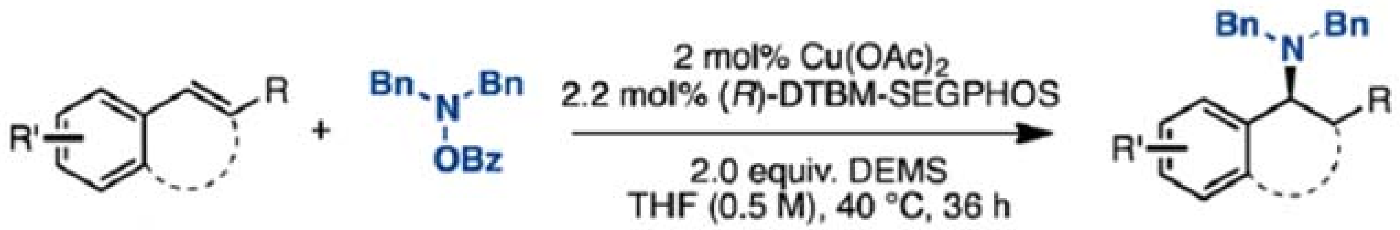

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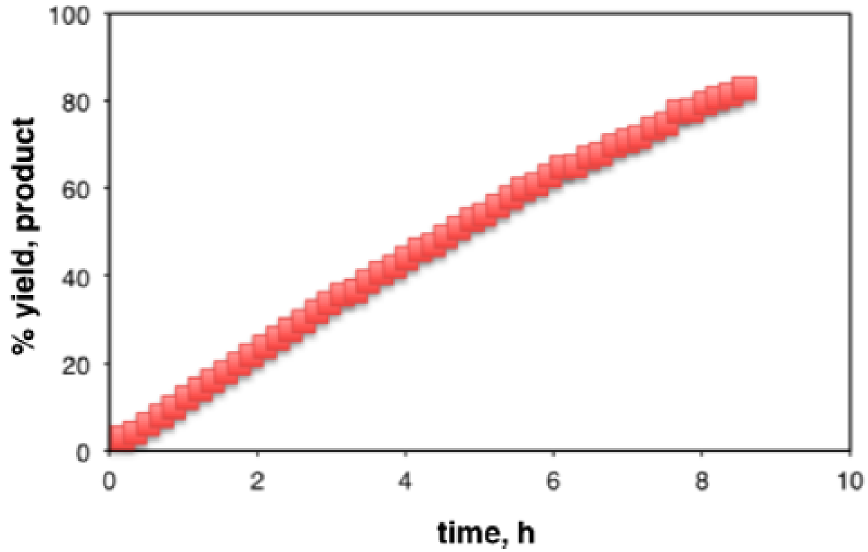
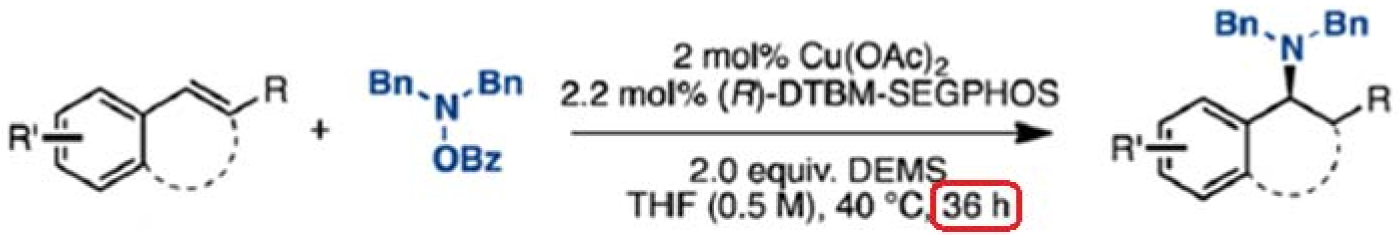


Reaction approximately completed after 9 h.

Kinetic studies



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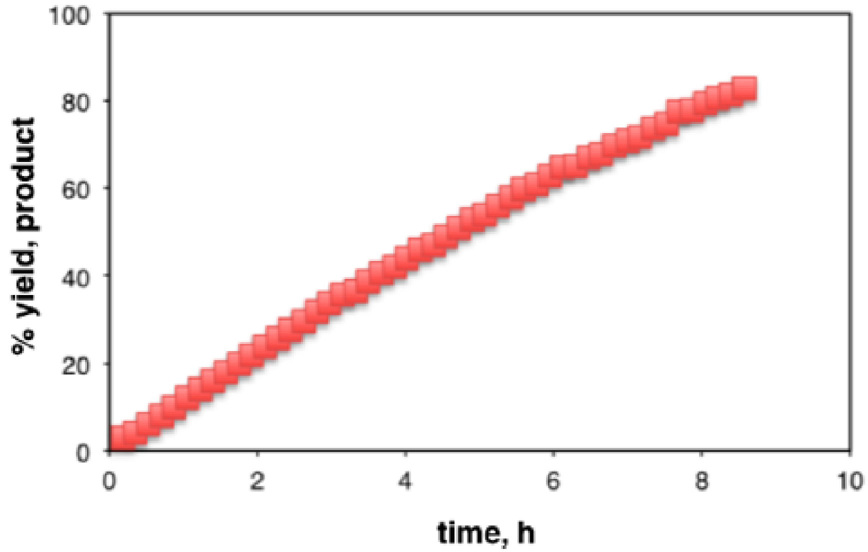

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Criticism: Why is there so much difference ?

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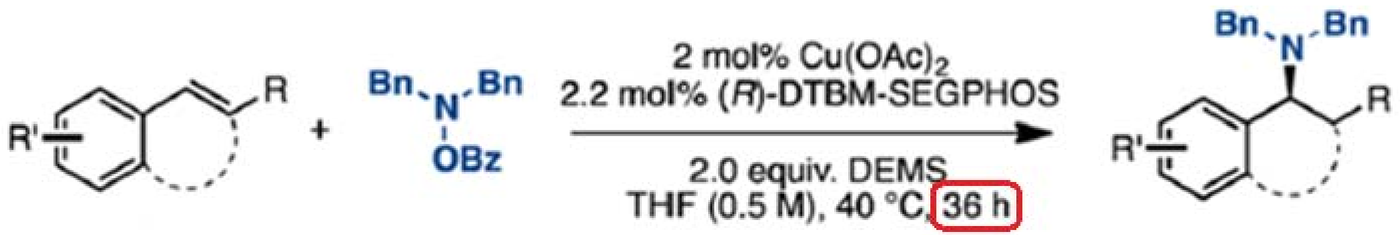

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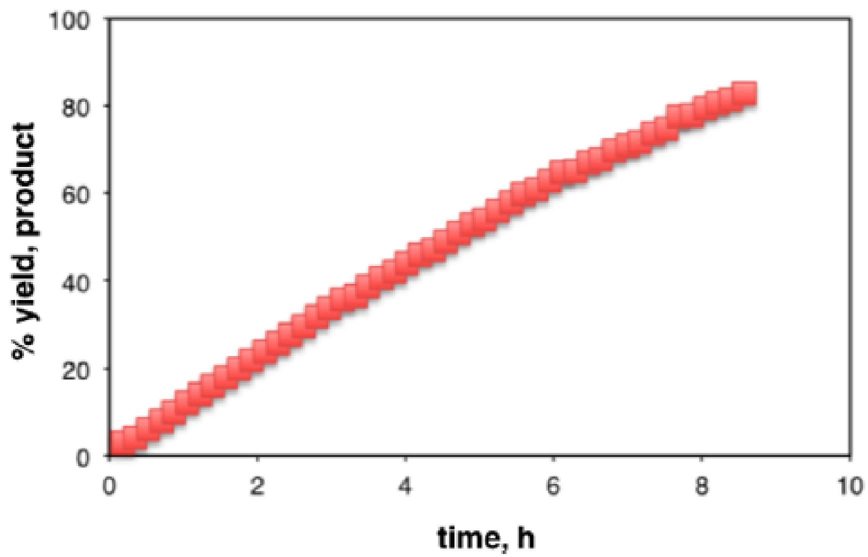

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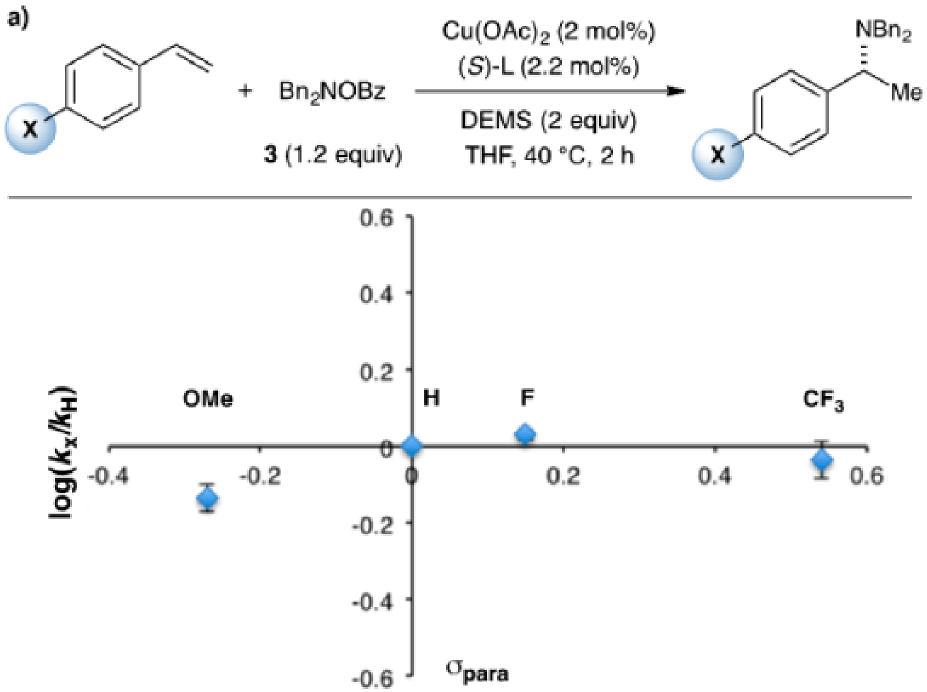
Rate order study

component	rate order
styrene	zero
Bn_2NOBz	zero
DEMS	first
$Cu(OAc)_2$ + L	fractional

Criticism: Why is there so much difference ?

Hammet studies

Influence of *p*-substituted styrene on the rate of hydroamination



Similar rates
Alkene **not involved** in the
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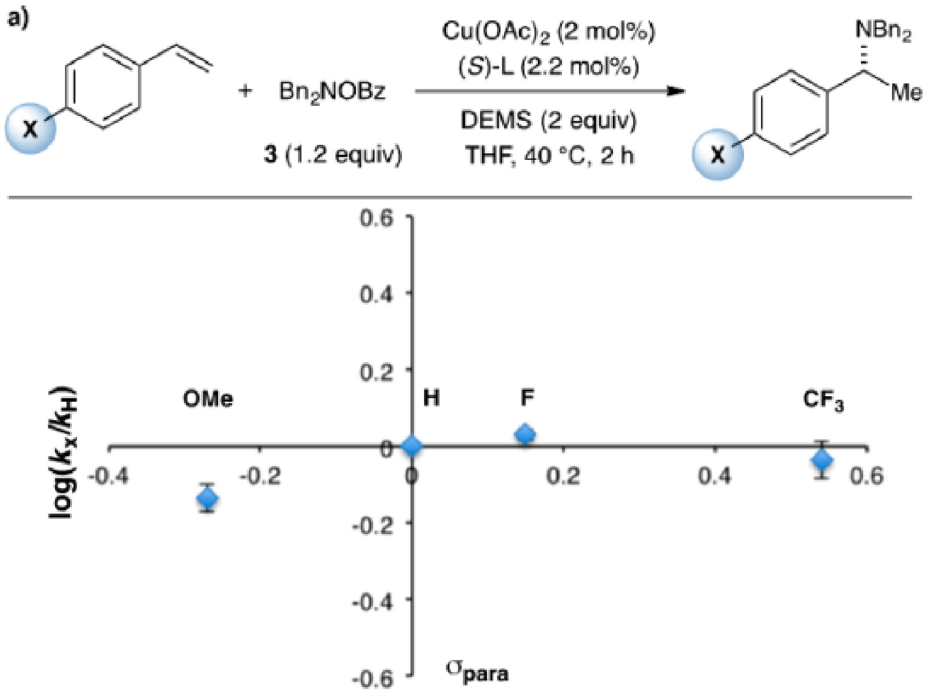

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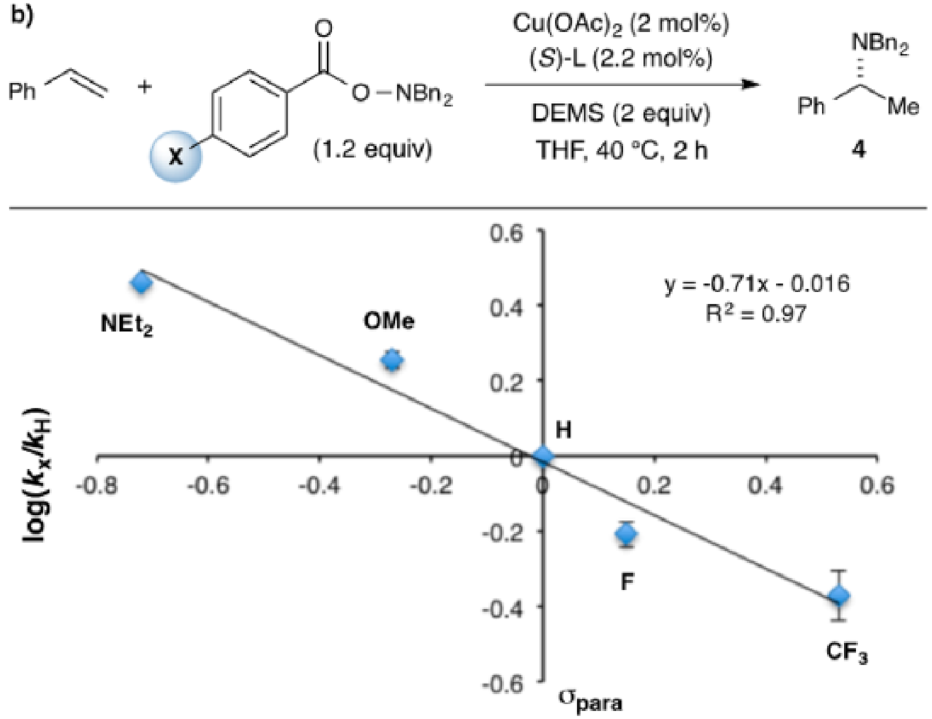
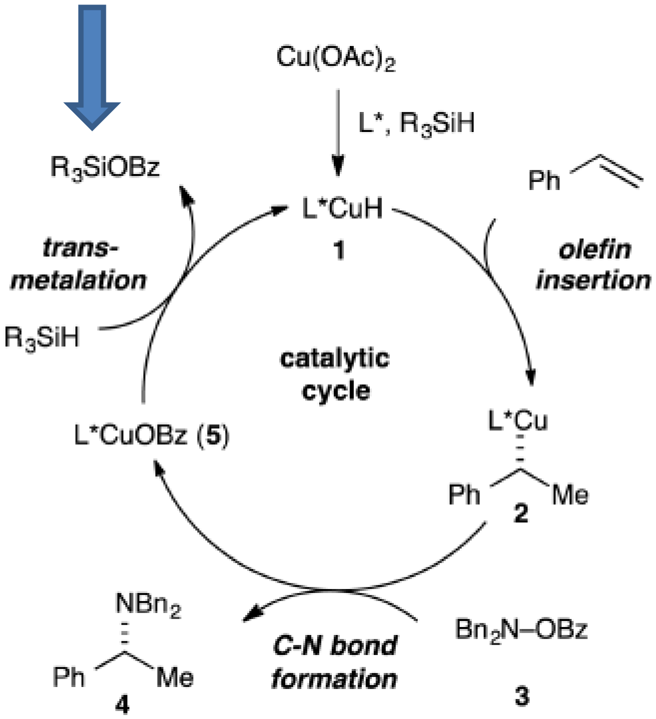
Influence of amine on the rate of hydroamination



Significant differences of rates
Amine (or Bz) are most likely **involved** in the **Turnover-limiting step**

First conclusion

Turnover-limiting step



Regeneration of the CuH catalyst 1 is most likely the **Turnover-limiting step**:

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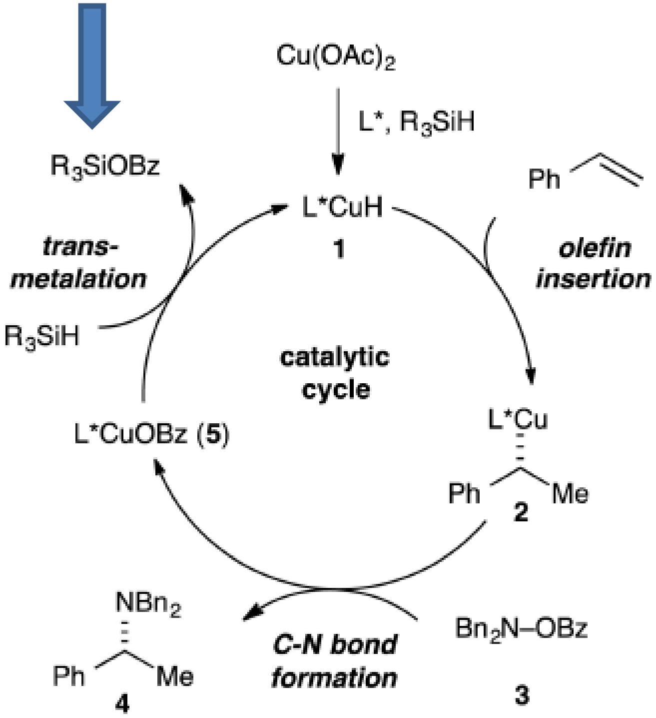

Regeneration of the CuH catalyst 1 is most likely the **Turnover-limiting step**:

- Zero-order dependance on styrene and amine
- First-order on the silane
- Linear correlation between Hammet parameters and reaction rate for the amine (or OBz)

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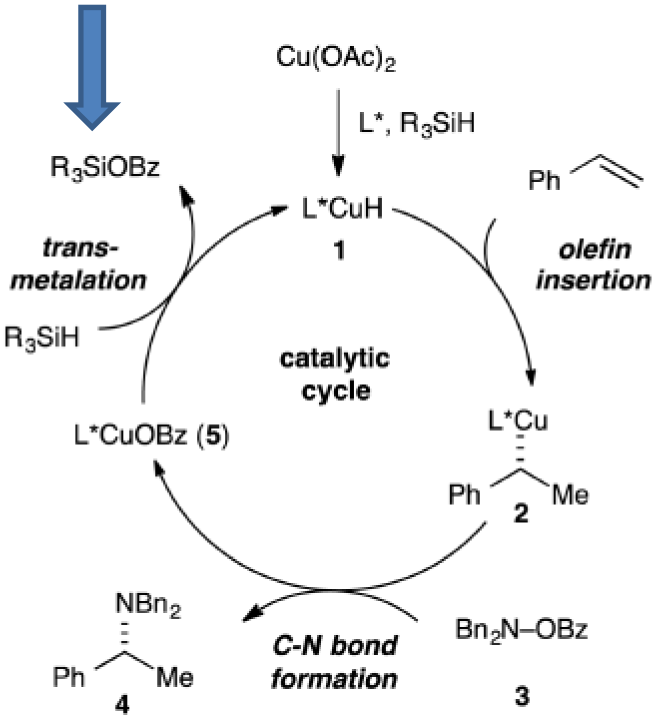
Turnover-limiting step



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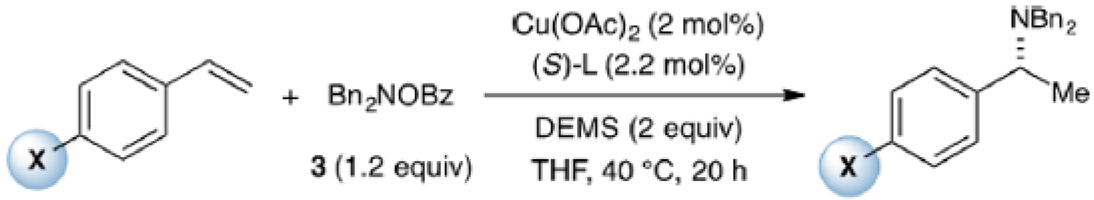
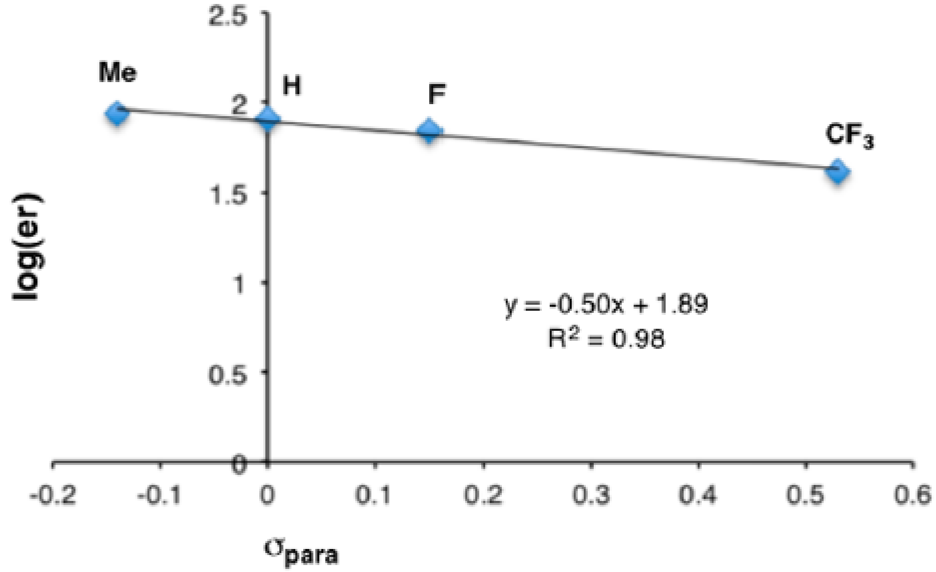
Higher reaction rates with more electron-enriched amine is consistent with a faster transmetalation

Hammet studies – Enantio-determining step ?





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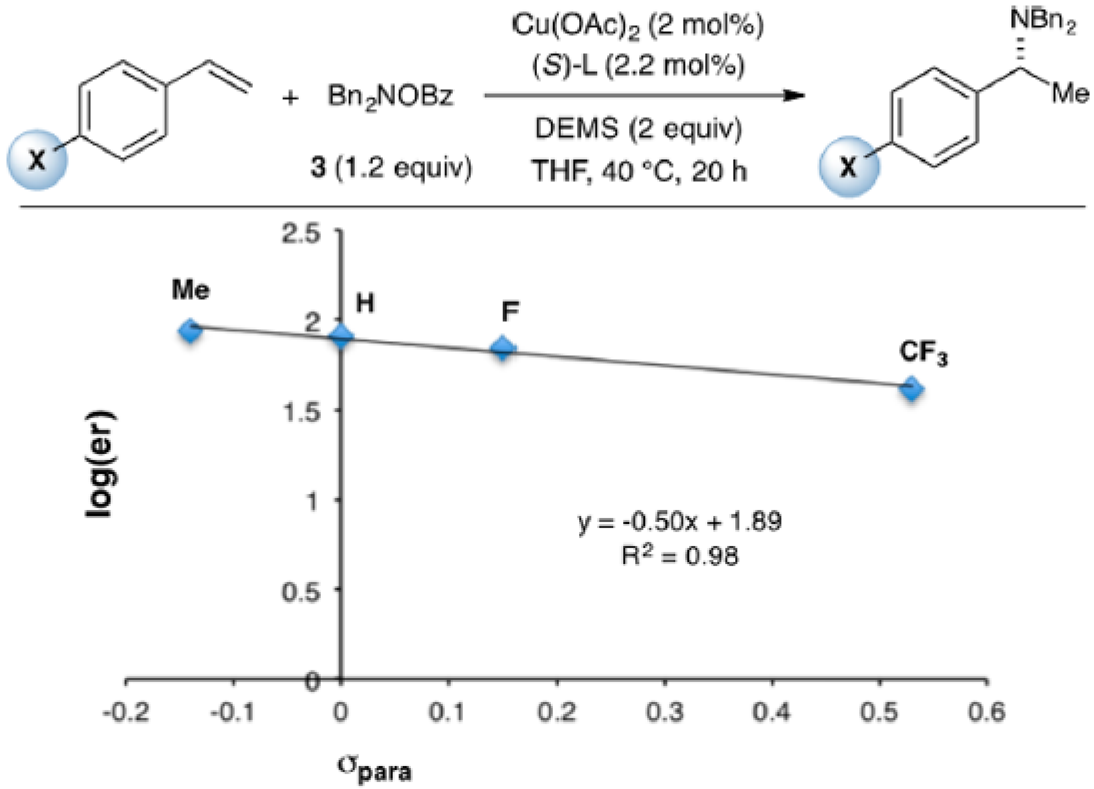

Linear relationship observed for the styrene

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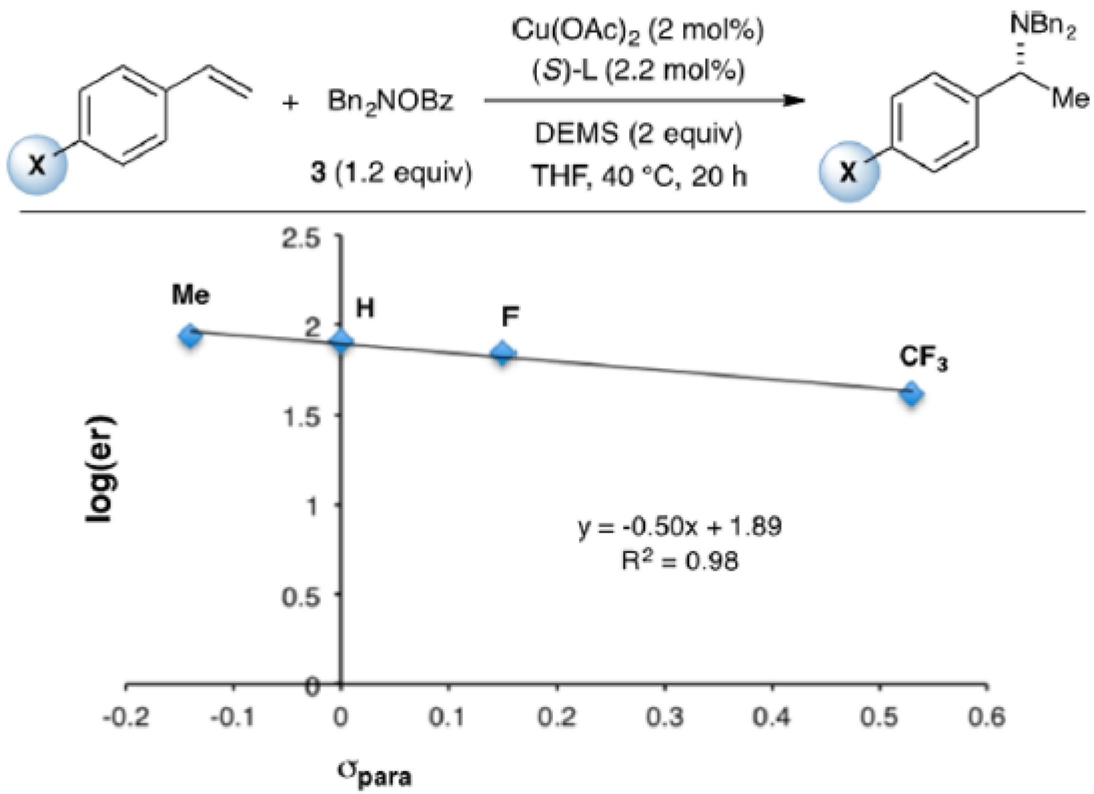

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From Supporting Information:

No linear relationship for the amine

Identity of the **Silane does not affect the Enantioselectivity**

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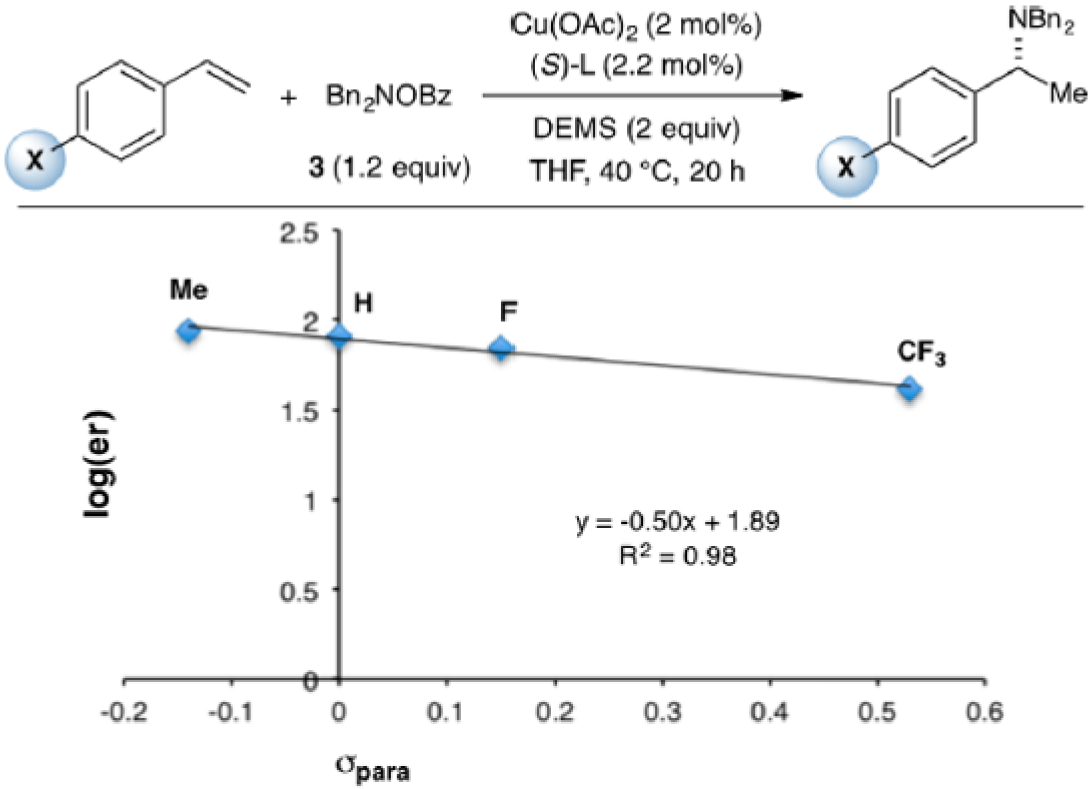

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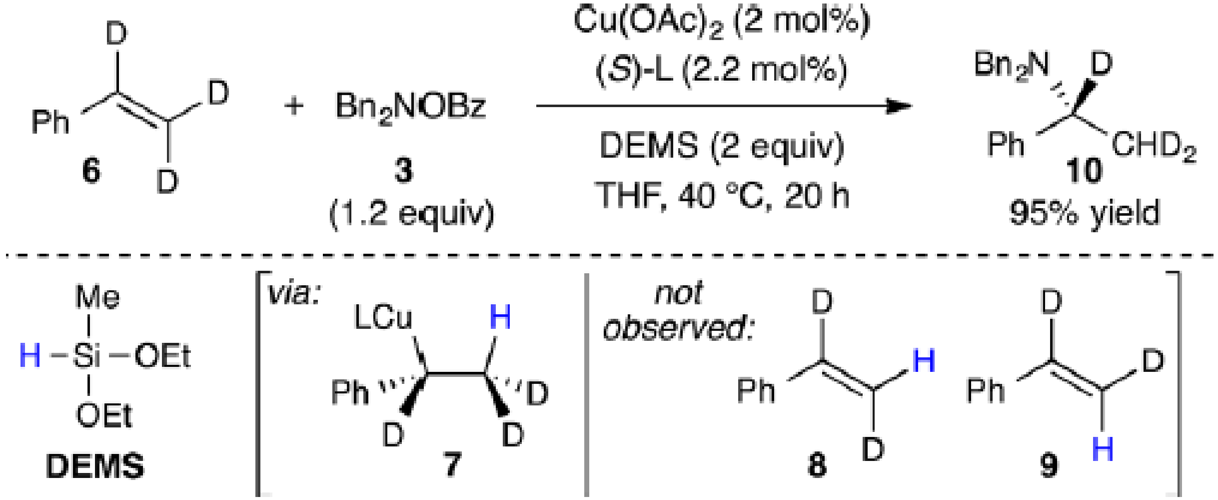
Conclusion:
Hydrocupration is most likely the **Enantio-Determining step**

Isotopic study – Is hydrocupration reversible ?



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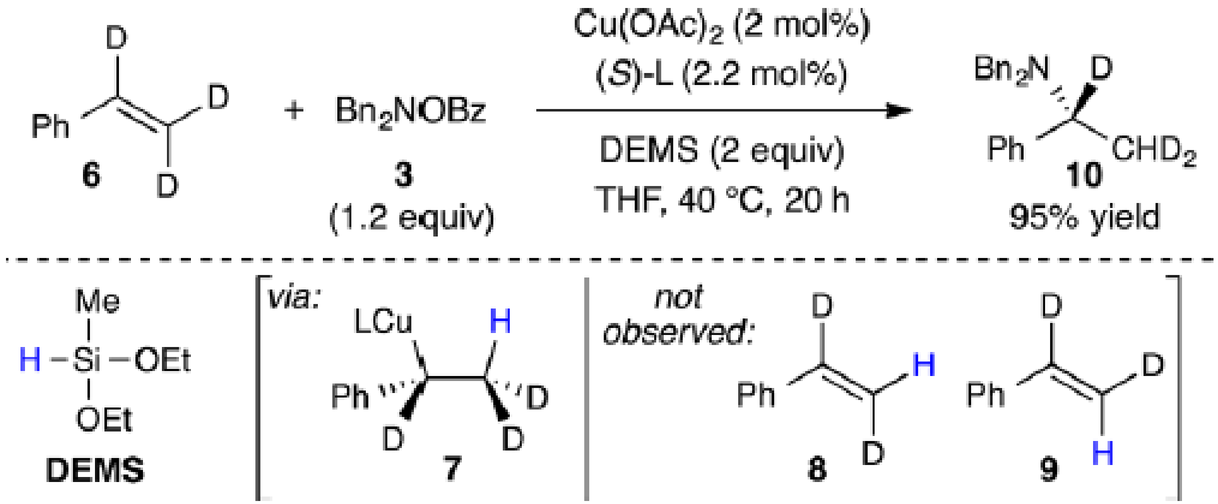

Postulate: Hydrocupration is irreversible since it is the enantio determining step and occurs before the rate-determining step

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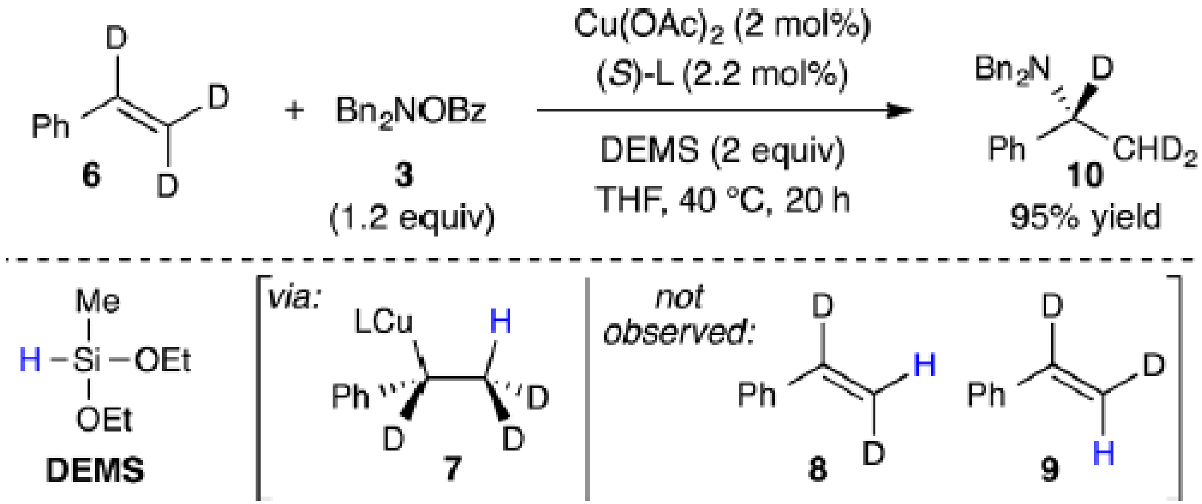

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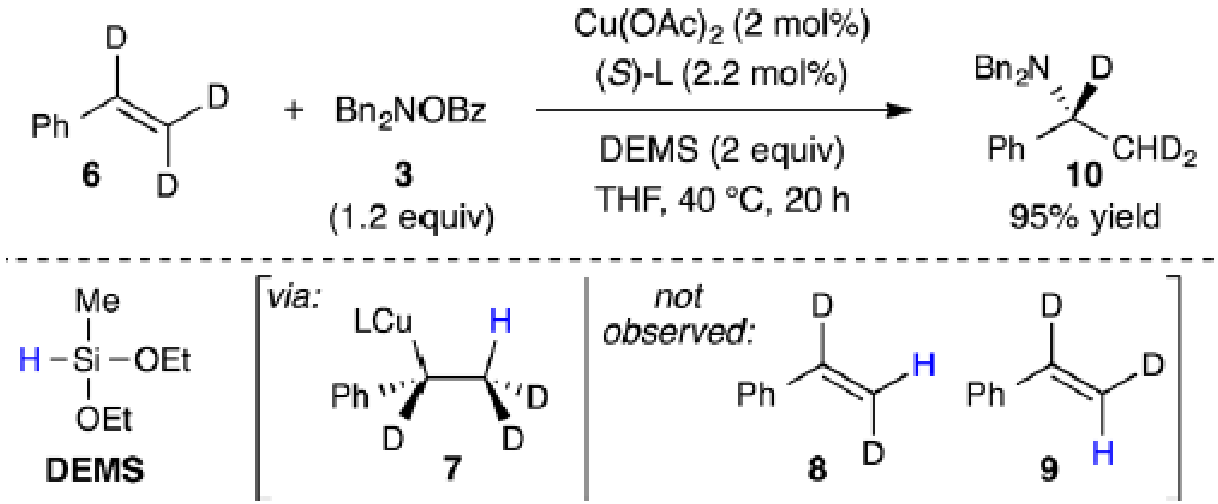

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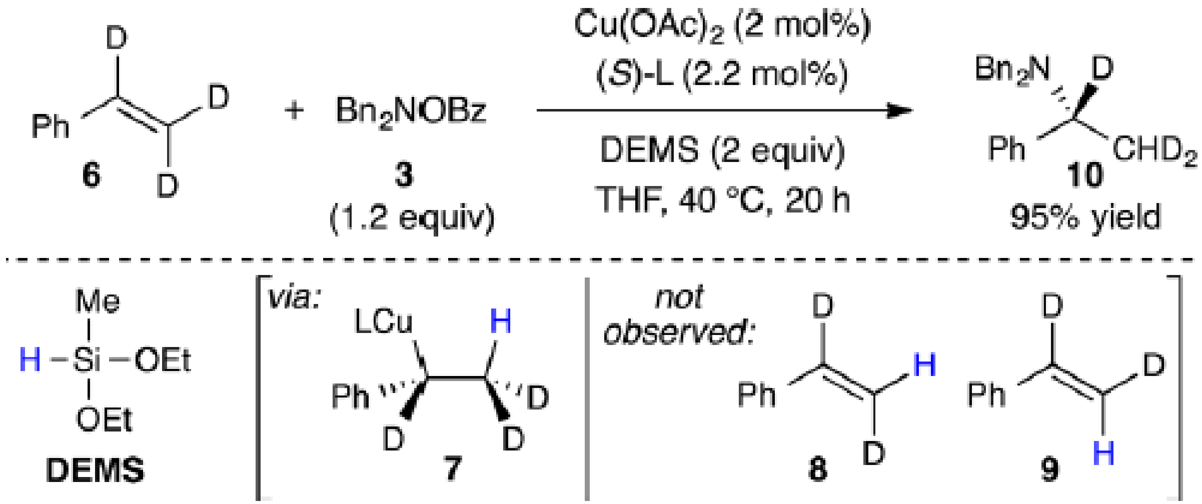

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- **10** bearing only two deuteria was never found.

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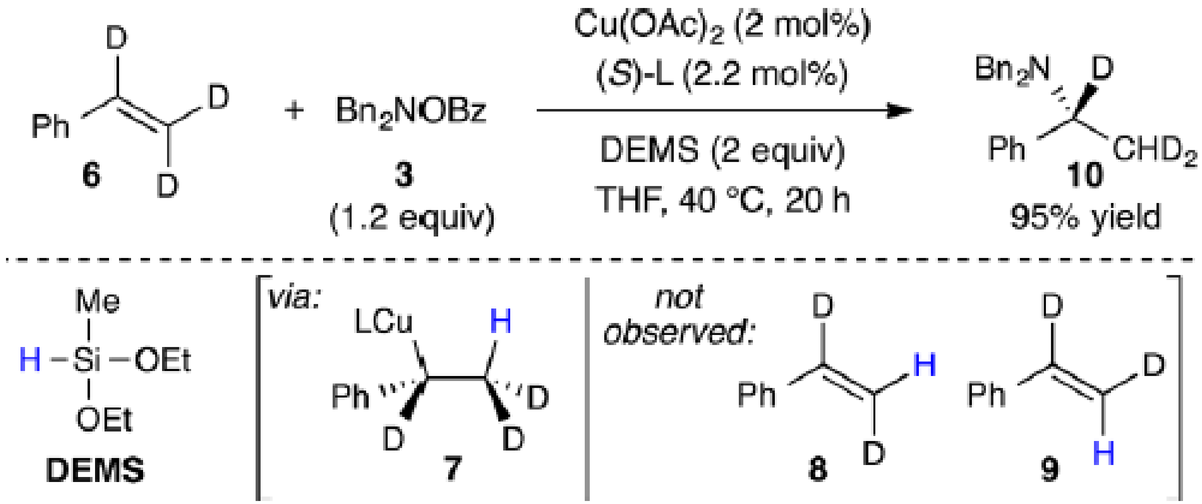

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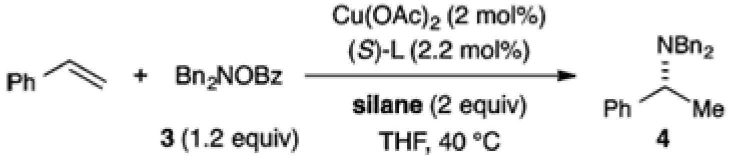
Conclusion: Hydrocupration is indeed most likely **irreversible**

Optimization

Effect of Silane on Initial-Rate:



entry	silane	rate (M/min)	rel rate
1	$HSiMe(OEt)_2$	$5.6(3) \times 10^{-4}$	1
2	$HSiMe(OMe)_2$	$1.8(1) \times 10^{-3}$	3.1
3	$(HMe_2Si)_2O$	$3.1(4) \times 10^{-4}$	0.6
4	PMHS	$1.9(1) \times 10^{-4}$	0.3
5	Ph_2SiH_2	$1.3(4) \times 10^{-3}$	2.3
6	Et_3SiH	nr[b]	–

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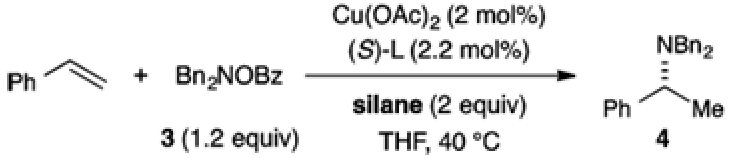

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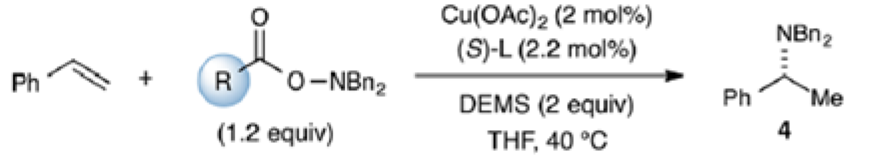
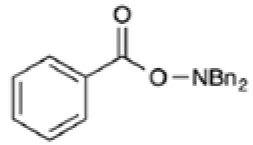
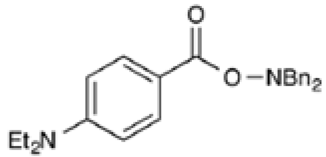
Effect of Amine Electrophile on Initial-Rate:

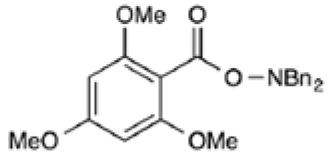




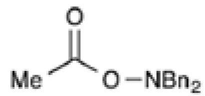
3
$5.6(7) \times 10^{-4}$ M/min
rel rate: 1



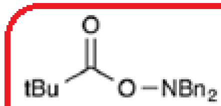
11
$1.6(2) \times 10^{-3}$ M/min
2.9



12
$2.5(1) \times 10^{-3}$ M/min
4.5

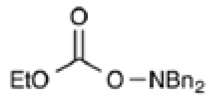


13
$2.8(2) \times 10^{-3}$ M/min
rel rate: 5.0



14
$2.5(2) \times 10^{-3}$ M/min
4.5

More accessible and more stable



15
$7.2(2) \times 10^{-4}$ M/min
1.3

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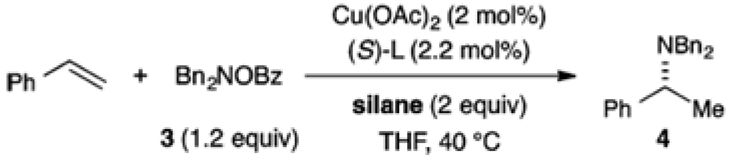

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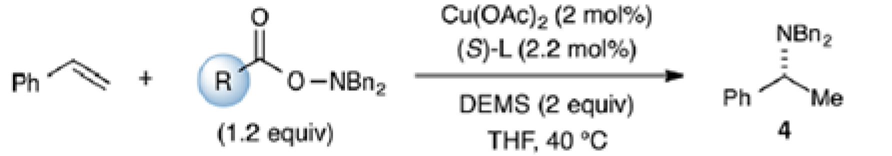

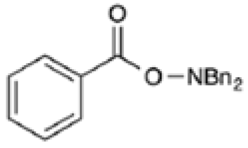

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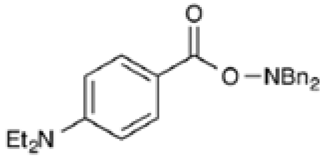

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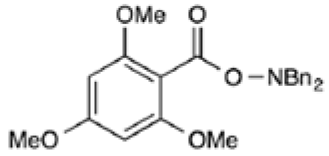

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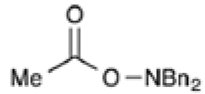

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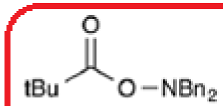
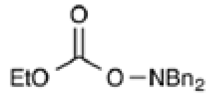
2.8(2) x 10^{-3} M/min
rel rate: 5.0



14
2.5(2) x 10^{-3} M/min
4.5



15
7.2(2) x 10^{-4} M/min
1.3

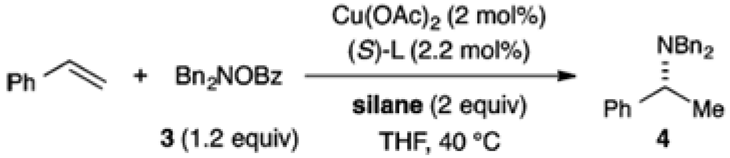
More accessible and
more stable

Effect of phosphine ligands:
With 2.2 mol % PPh_3:
1.2-fold rate enhancement

Lipshutz and al., *J. Am. Chem. Soc.* **2003**, *125*, 8779.

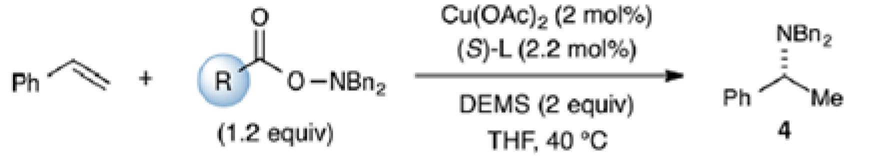
Optimization

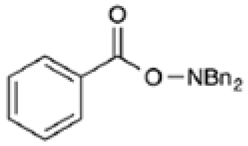
Effect of Silane on Initial-Rate:



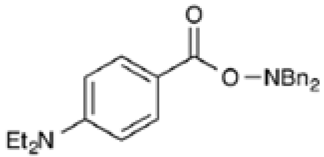
entry	silane	rate (M/min)	rel rate
1	$HSiMe(OEt)_2$	$5.6(3) \times 10^{-4}$	1
2	$HSiMe(OMe)_2$	$1.8(1) \times 10^{-3}$	3.1
3	$(HMe_2Si)_2O$	$3.1(4) \times 10^{-4}$	0.6
4	PMHS	$1.9(1) \times 10^{-4}$	0.3
5	Ph_2SiH_2	$1.3(4) \times 10^{-3}$	2.3
6	Et_3SiH	nr[b]	–

Effect of Amine Electrophile on Initial-Rate:

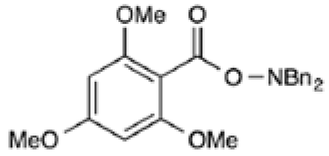




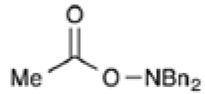
3
5.6(7) x 10^{-4} M/min
rel rate: 1



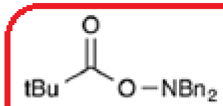
11
1.6(2) x 10^{-3} M/min
2.9



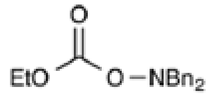
12
2.5(1) x 10^{-3} M/min
4.5



13
2.8(2) x 10^{-3} M/min
rel rate: 5.0



14
2.5(2) x 10^{-3} M/min
4.5



15
7.2(2) x 10^{-4} M/min
1.3

More accessible and more stable

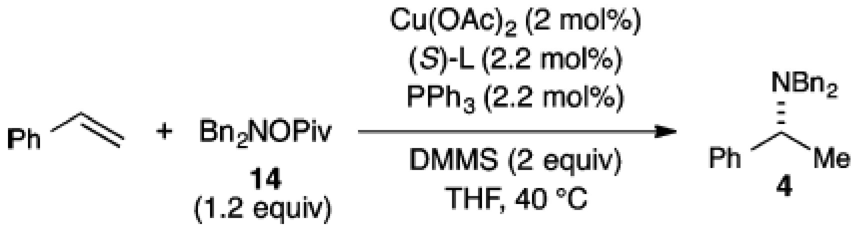
Effect of phosphine ligands:

With 2.2 mol % PPh_3:

1.2-fold rate enhancement

Lipshutz and al., *J. Am. Chem. Soc.* **2003**, *125*, 8779.

Optimized Conditions:

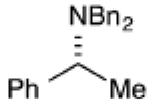
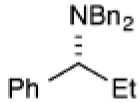
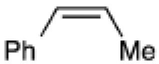
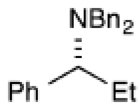
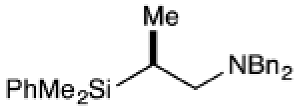
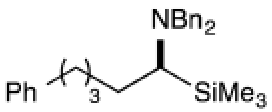
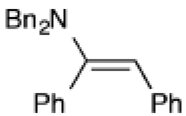


1 h
99% yield
96% ee

Optimized Protocol – Air stable catalyst

Conditions:

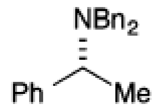
Bn_2NOPiv (1.2 equiv), CuCatMix (2 mol%), DMMS (2 equiv), THF, 60 °C, air

Entry	***Substrate***	***Product***	
1			10 min 91% yield 95% ee
2			20 min 89% yield 98% ee
3[b]			2 h 83% yield 96% ee
4			20 min 91% yield
5[b]			3 h 95% yield 95% ee
6			15 min 88% yield 99% ee
7			15 min 91% yield[c]

Air stable Cu-cat. mixture

Optimized Protocol – Low Loadings

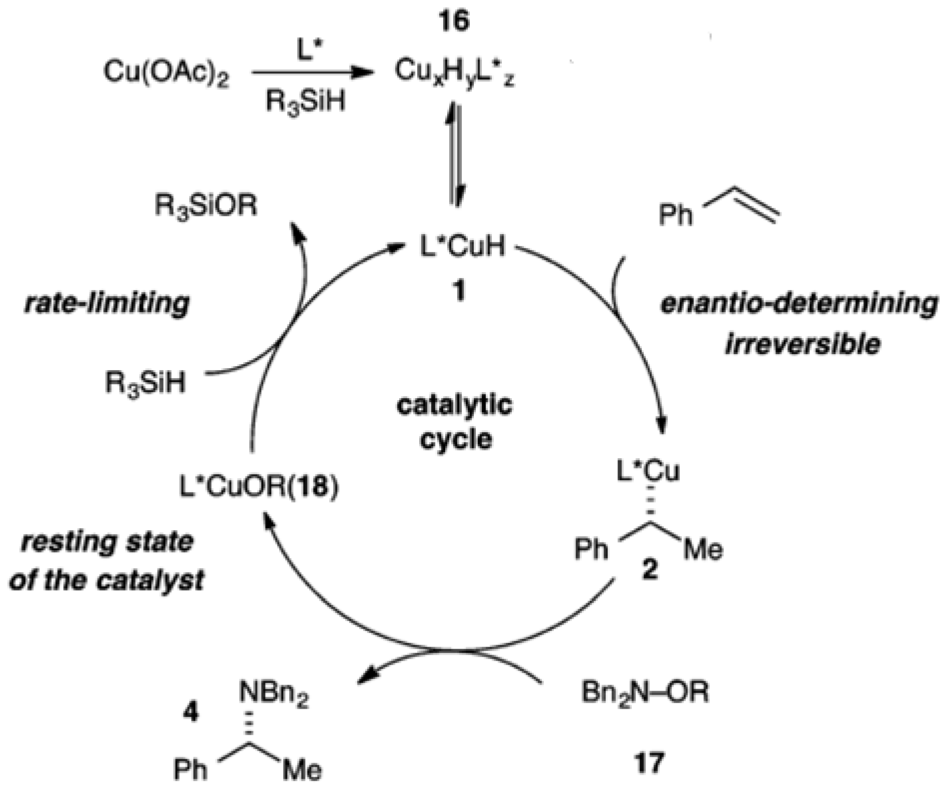
Conditions: Bn_2NOPiv (1.2 equiv), $Cu(OAc)_2$ (2 mol%), PPh_3 (2 mol%), DMMS (2 equiv), THF, 60 °C, N_2, 24 h

Entry	*(S)-DTBM-SEGPHOS*	*Substrate*	*Product*	
1	0.1 mol%			88% yield 92% ee
2	0.2 mol%			85% yield

Lower ligand loading
Decrease of the price of the reaction

More air sensitive
Required longer time

Conclusion

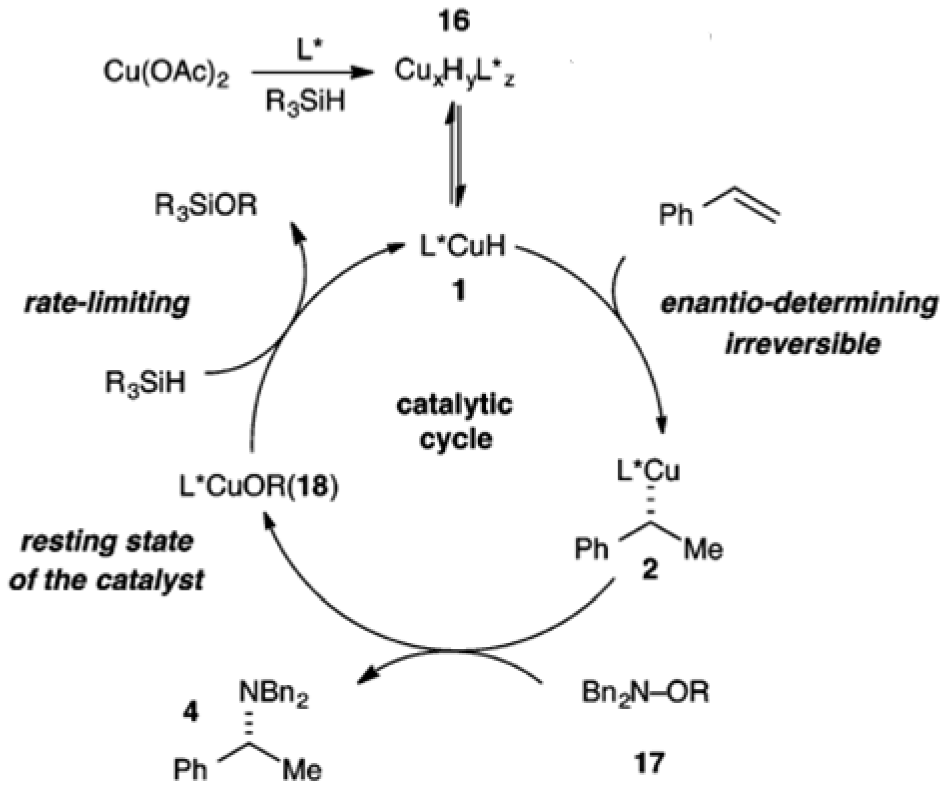


Great example on how **Mechanistical Study** could:

- Give a **Better Understanding** on the mechanism

- Improve Reaction Conditions

Conclusion



Great example on how
Mechanistical Study could:

- Give a **Better Understanding** on the mechanism

- Improve Reaction Conditions

Prospects: - Stoechiometric studies
- Computational investigations for the mechanism of the C-N bond formation
- New avenues for asymmetric olefin functionalization