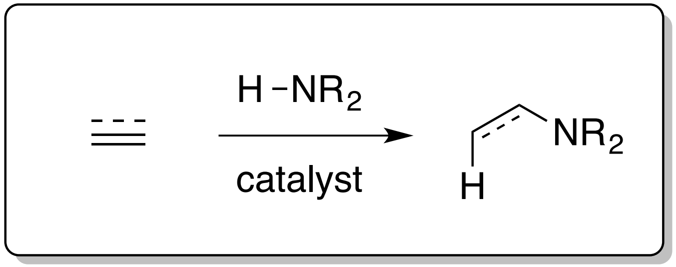
Catalytic asymmetric hydroamination of unactivated internal olefins

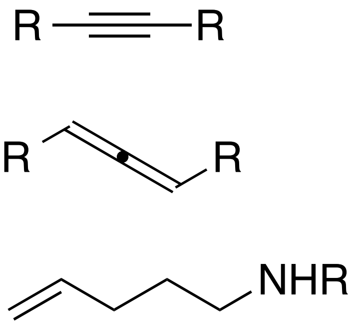
Yang, Y.; Shi, S-L.; Niu, D.; Liu, P.; Buchwald, S. L.
Science **2015**, *349 (6243)*, 62-66.

John Milligan
Current Literature
Wipf Group Meeting: July 25, 2015

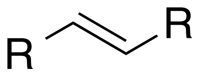
Hydroamination



Common substrates:



Much more rare:

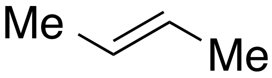


where R = alkyl

Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**,*108*, 3795-3892

Internal unactivated alkenes

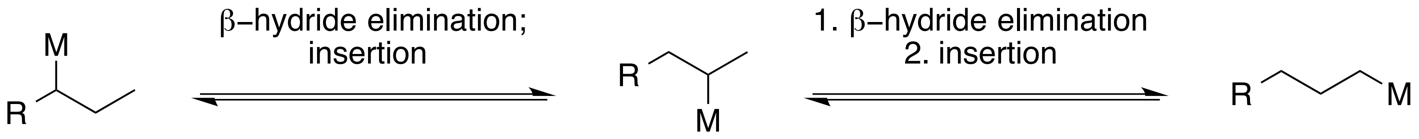
- Ubiquitous In nature
- Readily available from elthylene cracking
  - Example: 2-butene



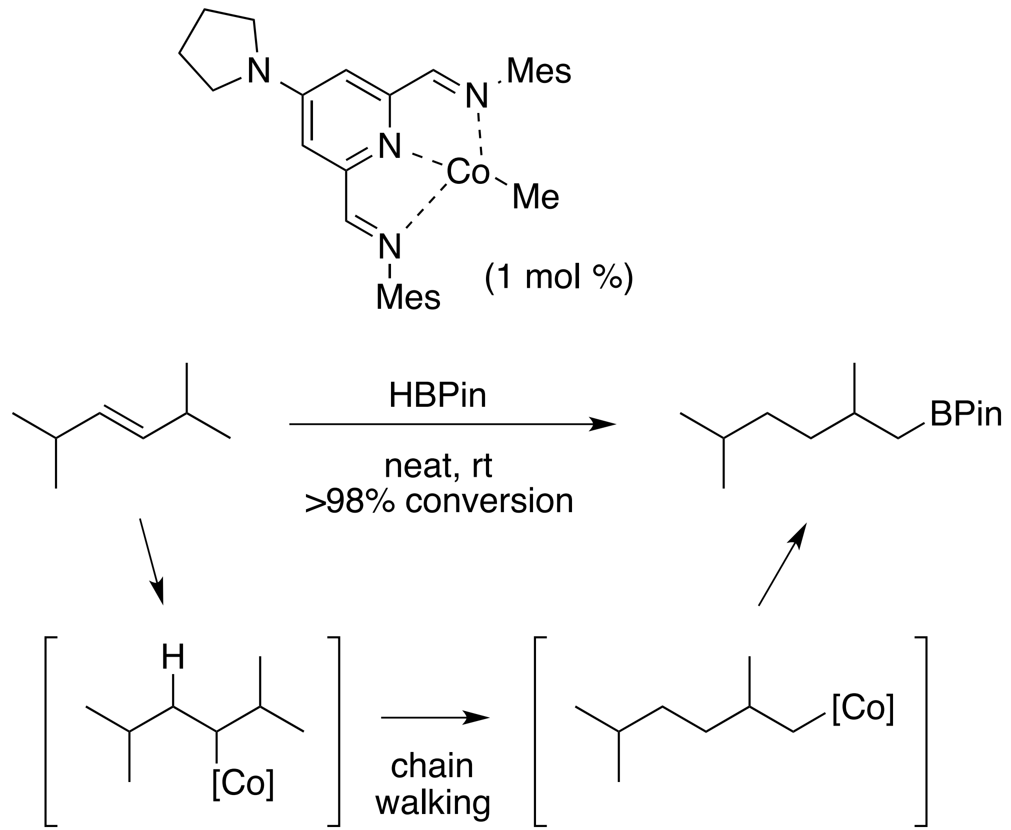
  - 20000 metric tons produced annually
- Orthogonal to carbonyl chemistry

Internal alkenes: challenges

- Low affinity to a transition metal
- Chain walking

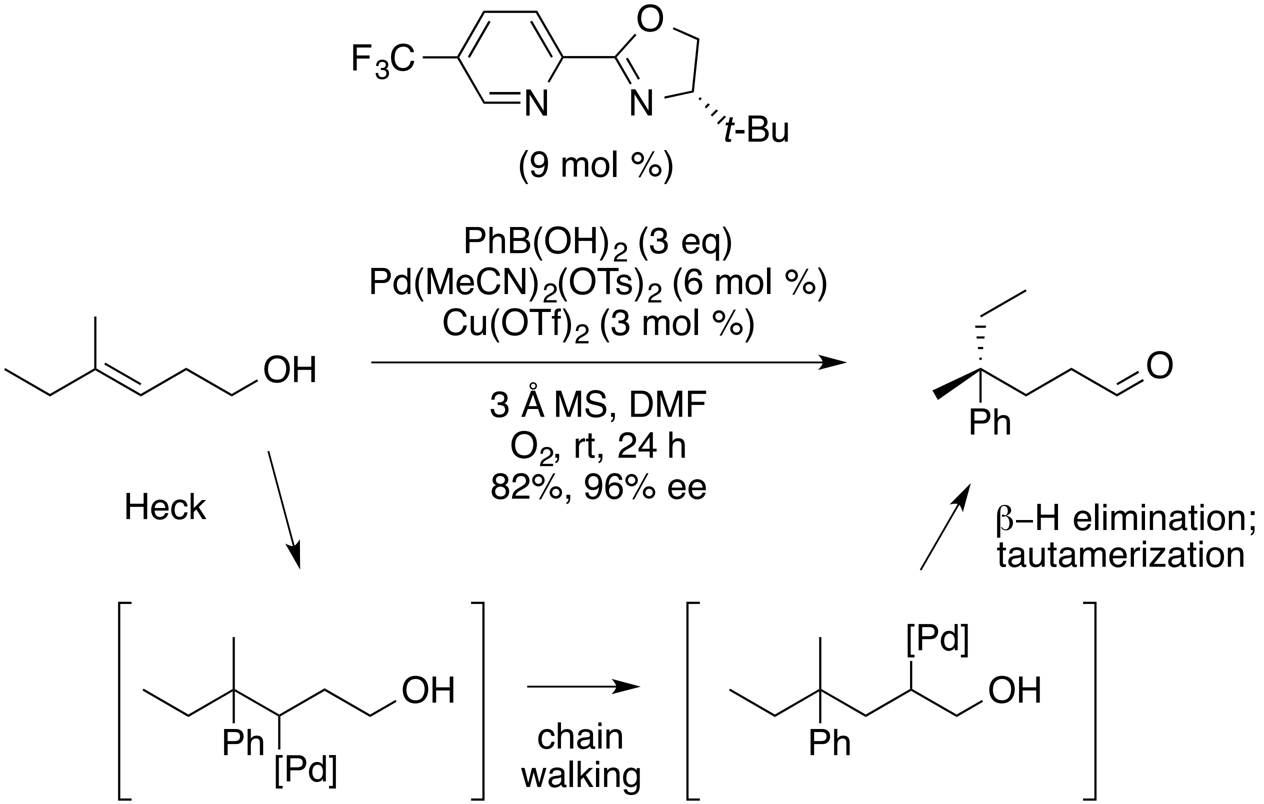


Internal alkenes: chain walking



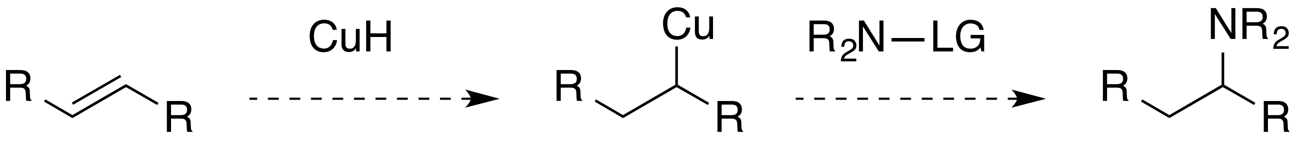
Obligacion, J. V.; Chirik, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 19107-19110

Internal alkenes: chain walking



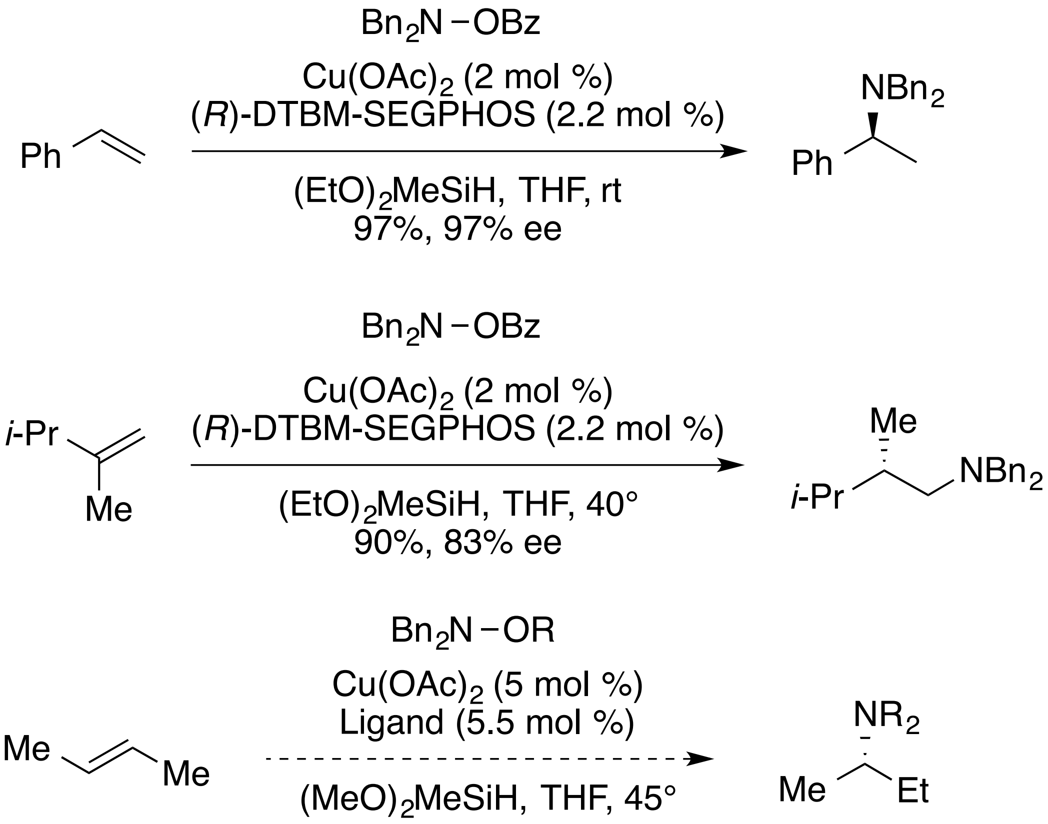
Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340-344

Central question



Can a secondary alkyl copper capture an electrophillic amine without chain walking?

Previous work by Buchwald

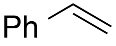
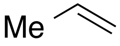
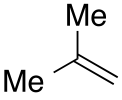
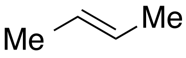


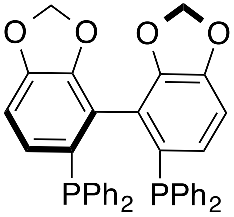
Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746-15749.

Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913-15916.

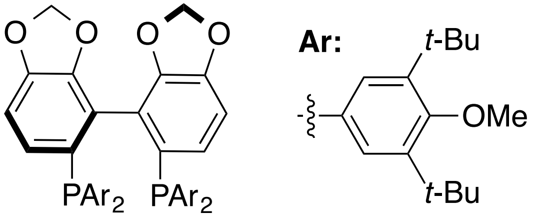
Computational predictions

Copper-hydride hydrocuparation transition state
Relative computed (DFT) energies (kcal/mol):

				
(*S*)-SEGPHOS	18.1	23.2	23.7	26.0
(*S*)-DTBM-SEGPHOS	–	–	–	23.3

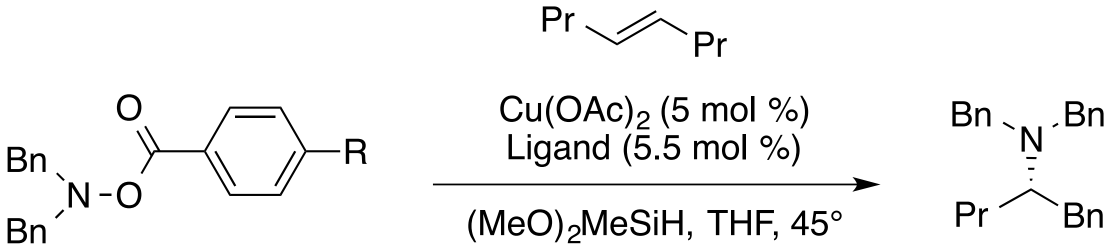


(*S*)-SEGPHOS

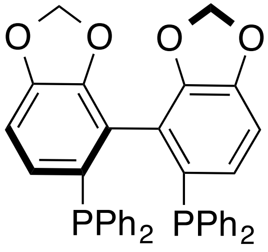


(*S*)-DTBM-SEGPHOS

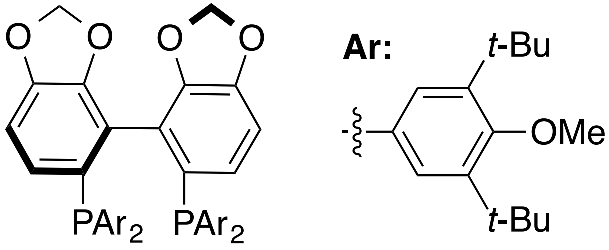
Initial results



R	Ligand	yield (%)	ee
H	(*S*)-SEGPHOS	<1	—
H	(*S*)-DTBM-SEGPHOS	34	98%
OMe	(*S*)-DTBM-SEGPHOS	47	98%
NMe_2	(*S*)-DTBM-SEGPHOS	65	98%
NEt_2	(*S*)-DTBM-SEGPHOS	75	98%

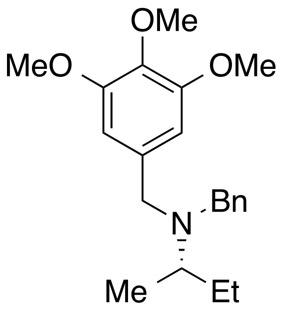


(*S*)-SEGPHOS

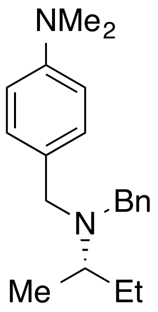


(*S*)-DTBM-SEGPHOS

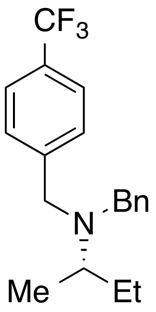
Substrate scope



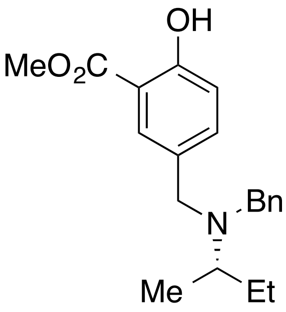
79%, 97% ee



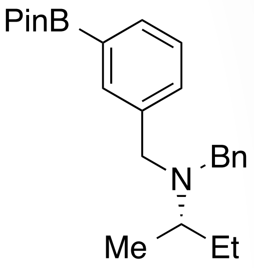
63%, 97% ee



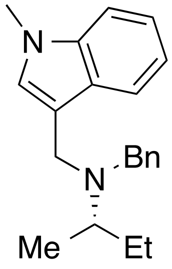
78%, 97% ee



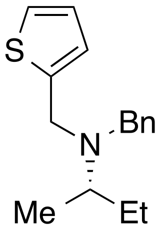
81%, 96% ee



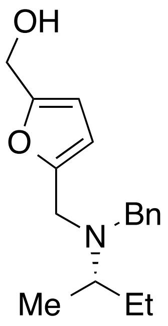
52%, 96% ee



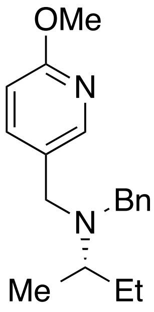
76%, 97% ee



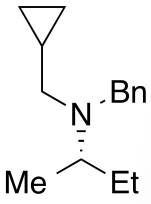
78%, 97% ee



70%, 97% ee

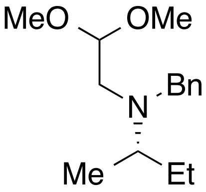


74%, 97% ee

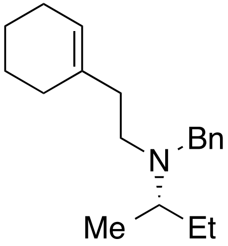


65%, 98% ee

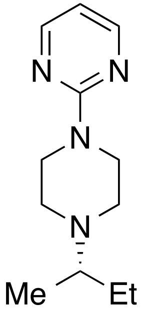
Substrate scope



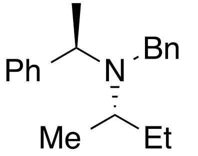
85%, 98% ee



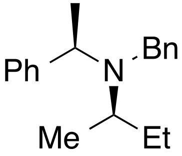
64%, 97% ee



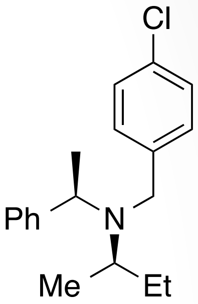
58%, 97% ee



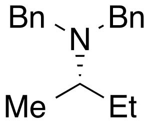
70%, >95:5 dr



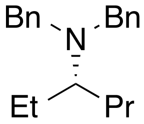
70%, >95:5 dr
(*R*-catalyst used)



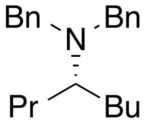
59%, >95:5 dr
(*R*-catalyst
used)



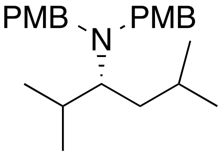
76%, 98% ee



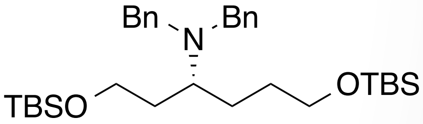
83%, 98% ee



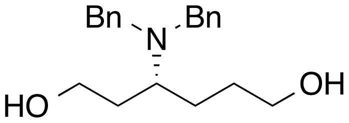
82%, 98% ee



65%, 99% ee

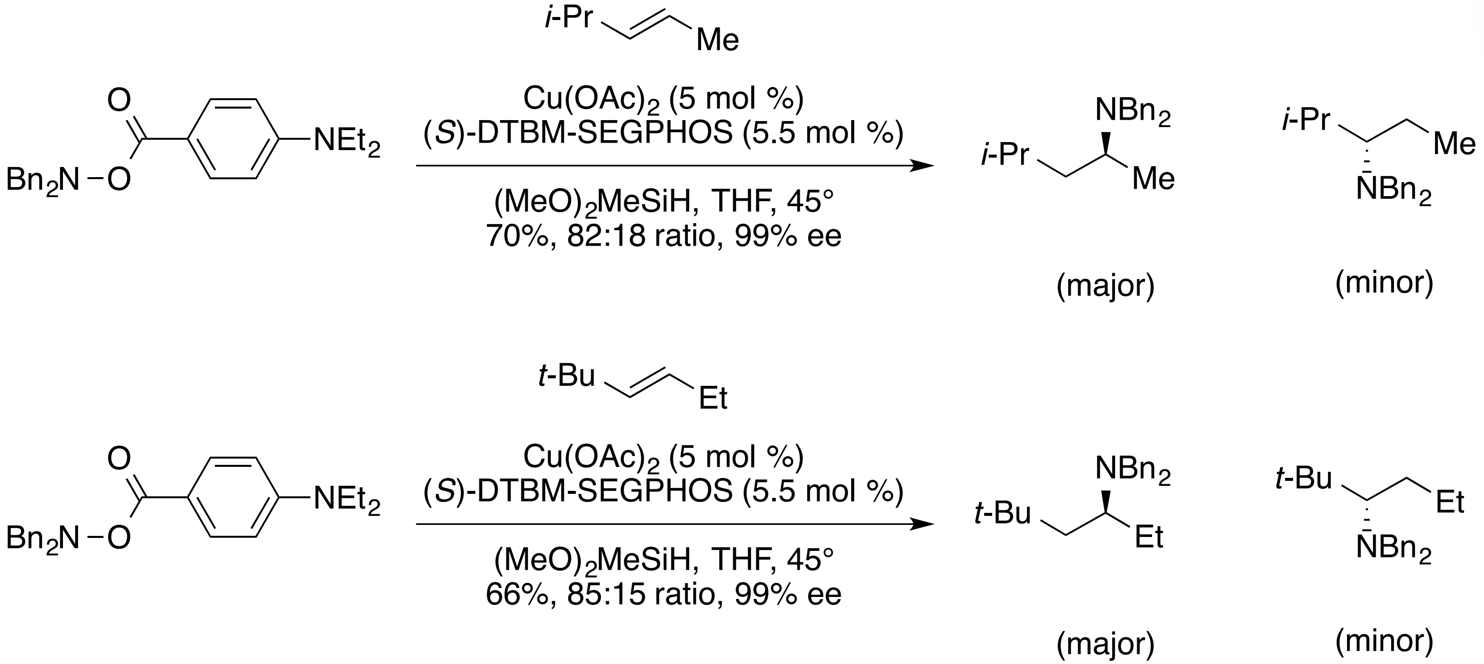


94%, 97% ee

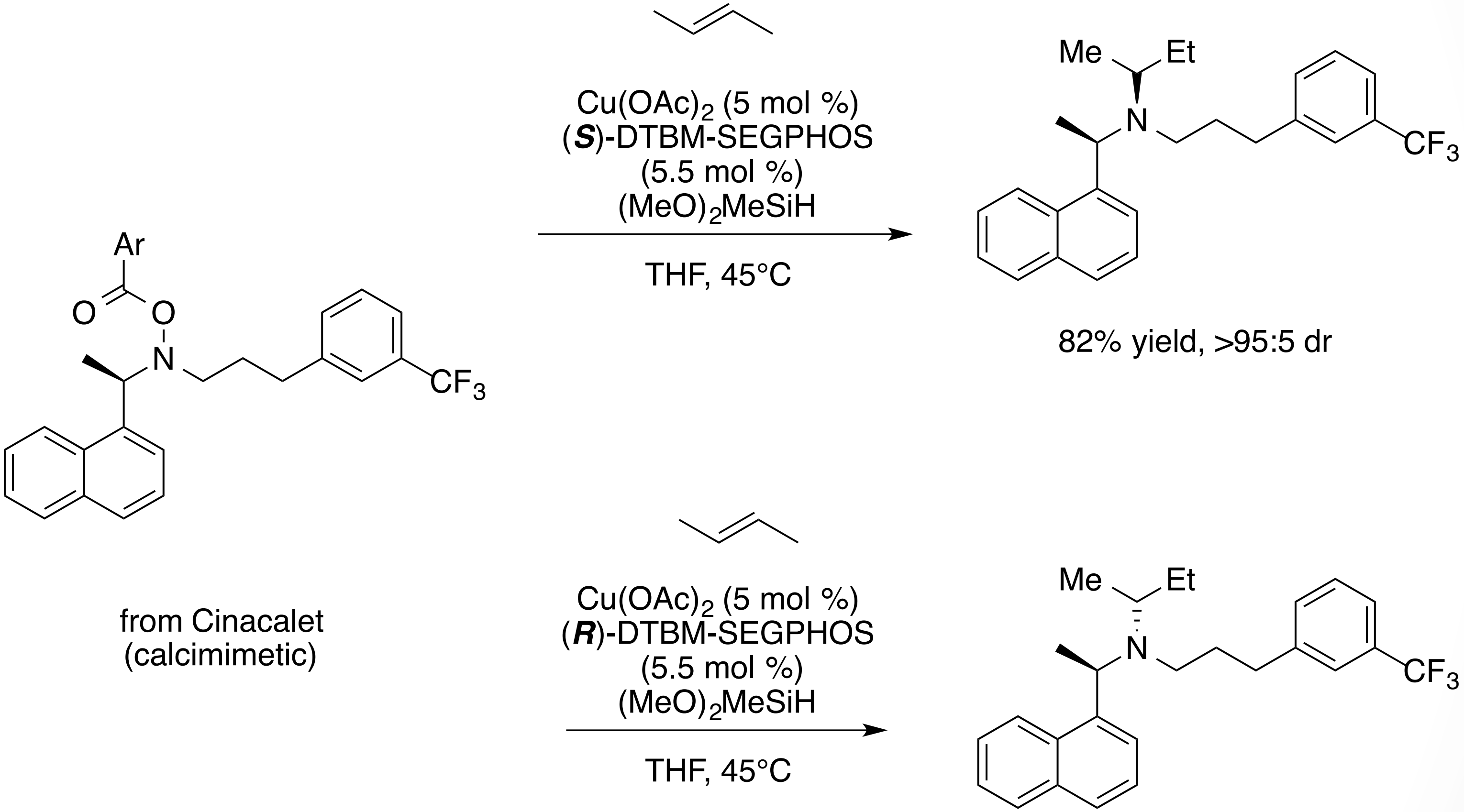


61%, 97% ee

Unsymmetrical alkenes



Applications in medicinal chemistry



$Cu(OAc)_2$ (5 mol %)
(***S***)-DTBM-SEGPHOS
(5.5 mol %)
$(MeO)_2MeSiH$

THF, 45°C

82% yield, >95:5 dr

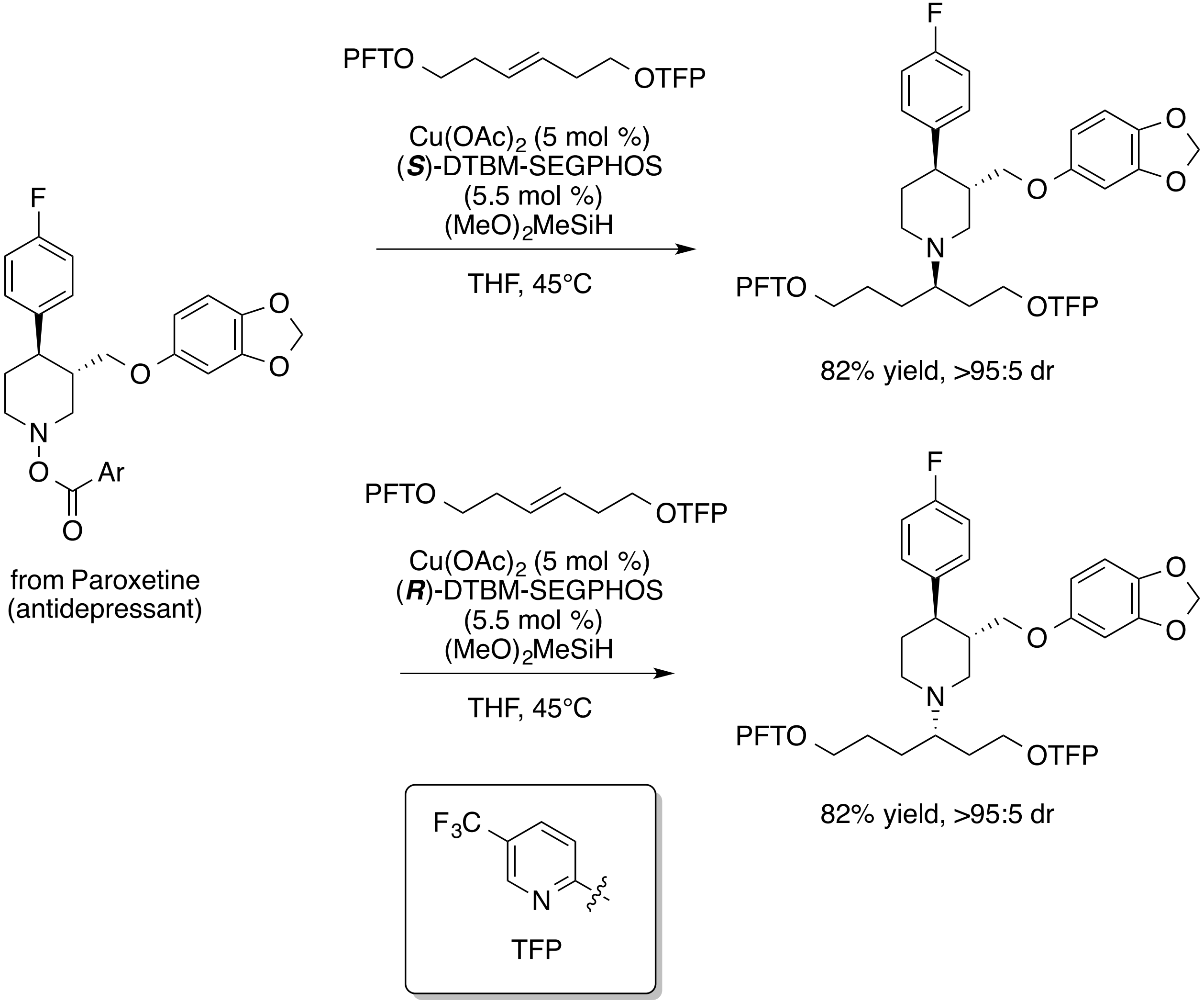
from Cinacalet
(calcimimetic)

$Cu(OAc)_2$ (5 mol %)
(***R***)-DTBM-SEGPHOS
(5.5 mol %)
$(MeO)_2MeSiH$

THF, 45°C

82% yield, >95:5 dr

Applications in medicinal chemistry

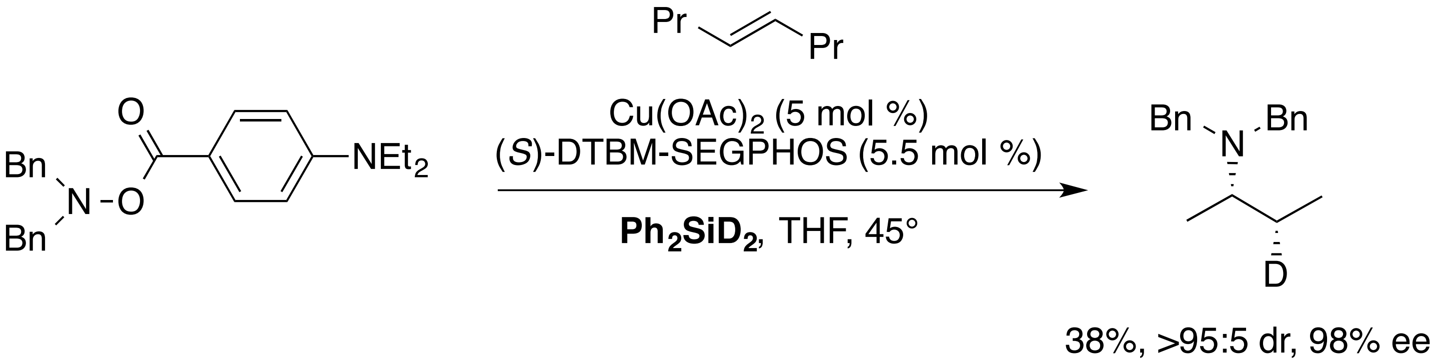


from Paroxetine
(antidepressant)

82% yield, >95:5 dr

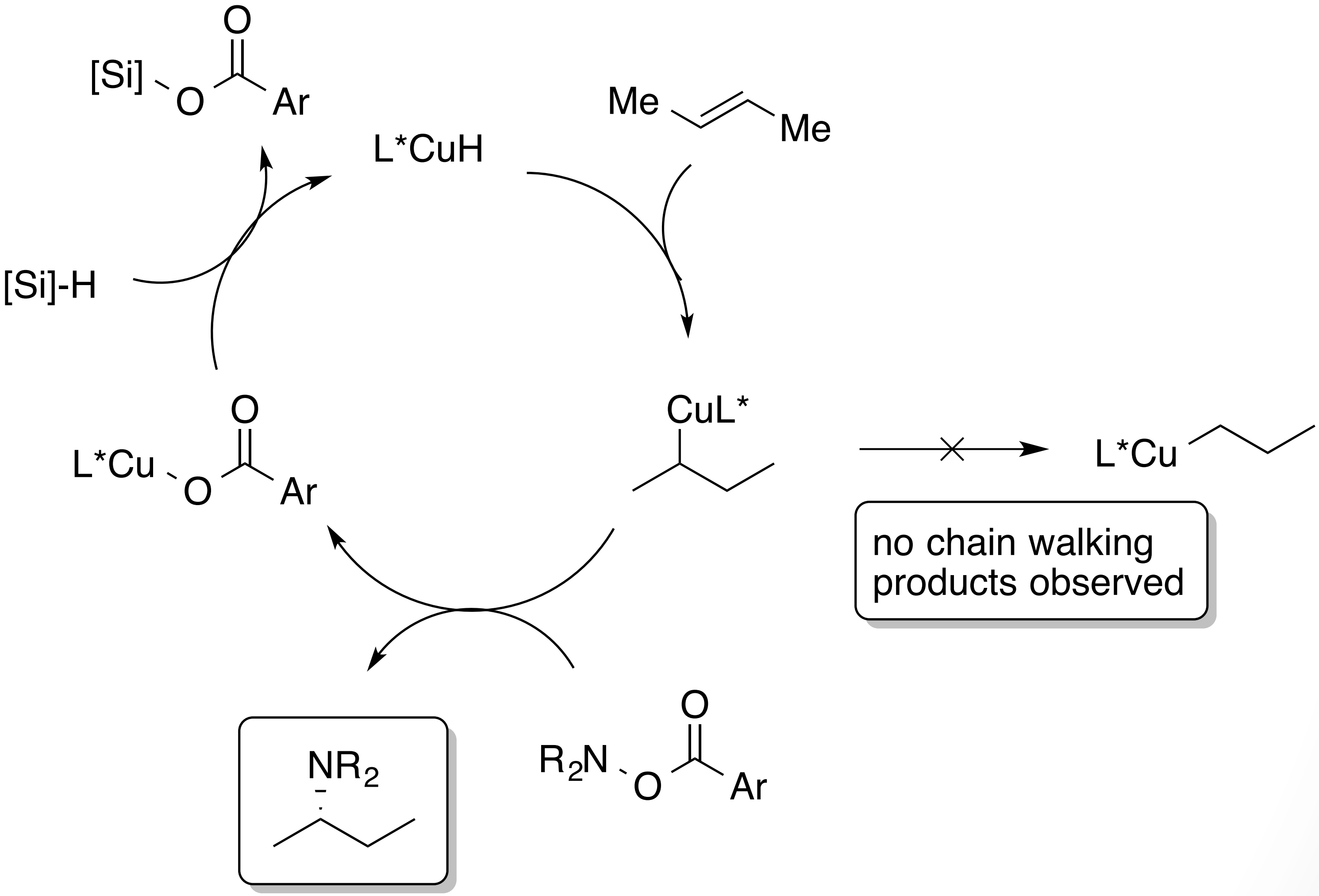
82% yield, >95:5 dr

Duterium incoportation



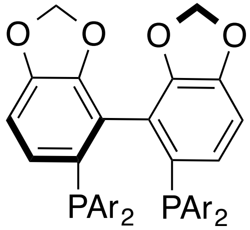
- Cu-D addition is synfacial

Proposed mechanism

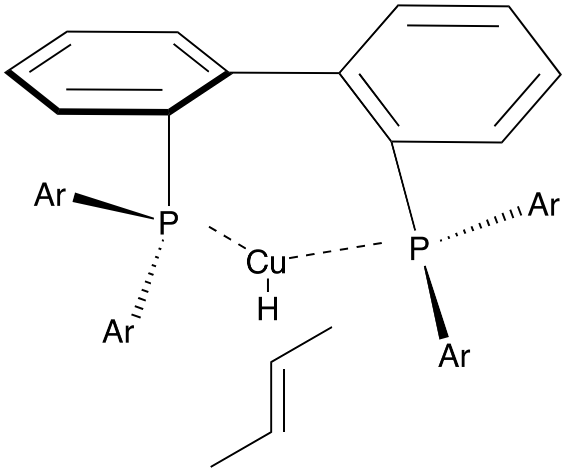


no chain walking products observed

Computational rationalization

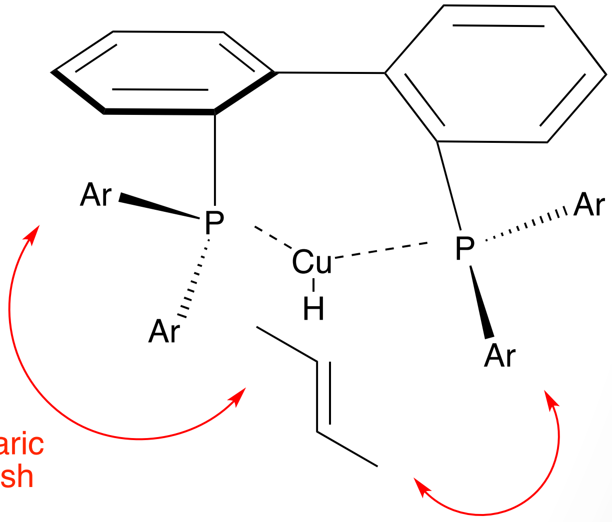


(*S*)-DTBM-SEGPHOS



(*Re*)-face attack

favored by 3.3 kcal/mol



stearic clash

(*Si*)-face attack

stearic clash

Conclusion

- This method constitutes a powerful hydroamination of internal, unactivated alkenes
- An inexpensive metal catalyst is used
- The products (alkyl α–branched chiral amines) are not easily accessed by other methods.
- This work illustrates an effective use of computation to predict and rationalize organometallic reactivity