

Literature Report III

Regioselective Hydroarylation of Alkynes

Reporter: Zheng Gu

Checker: Cong Liu

Date: 2017-08-28

Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 10641-10644.
Ding, D.; Mou, T.; Feng, M.; Jiang, X. *J. Am. Chem. Soc.* **2016**, *138*, 5218-5221.

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- ◆ **Rh-Catalyzed asymmetric hydroheteroarylation of alkynes**
- ◆ **Au-Catalyzed regiodivergent hydroarylation of alkynes**
- ◆ **Summary**

CV of Vy M. Dong

Full Professor: University of California at Irvine

Education and Professional Appointments:

1998 B. S.	University of California at Irvine
2000 M. S.	University of California at Berkeley
2004 Ph. D.	California Institute of Technology
2006 Assistant Professor	University of Toronto
2010 Associate Professor	University of Toronto
2012 Full Professor	University of California at Irvine

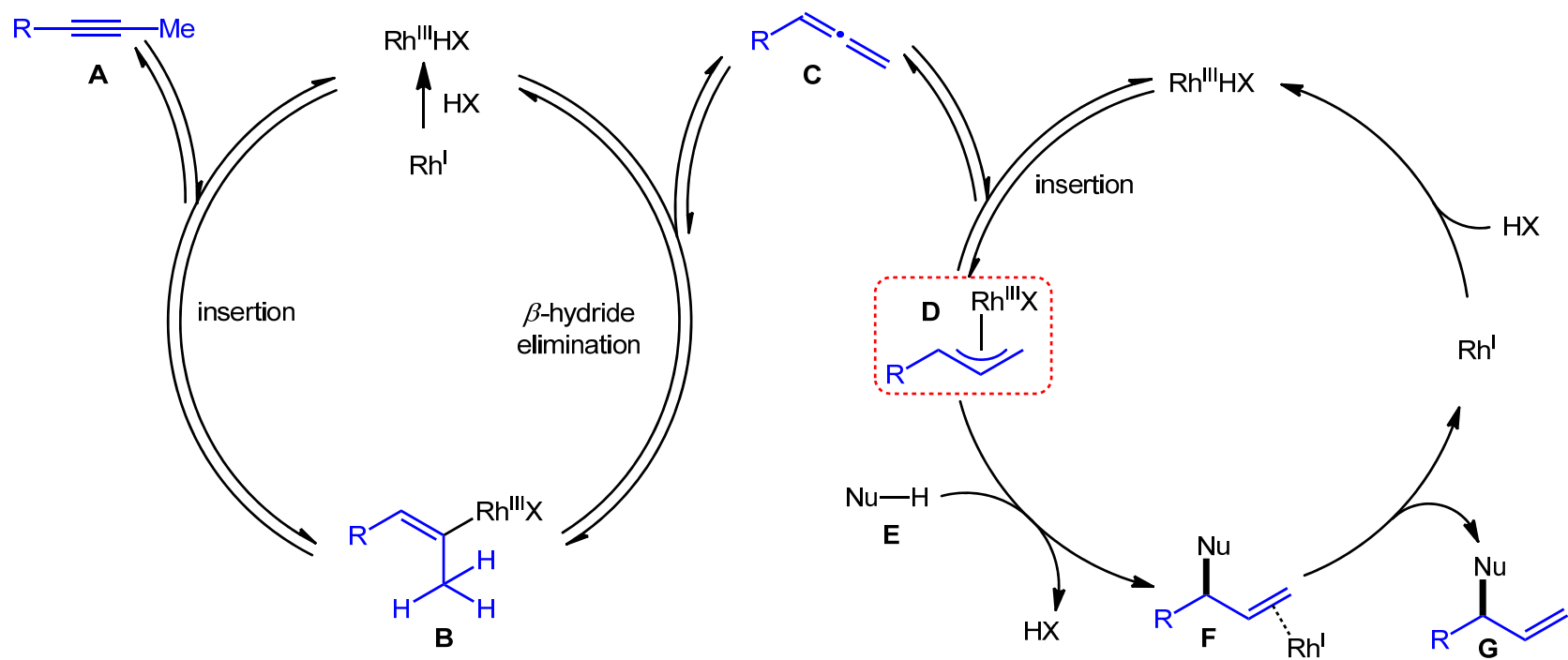
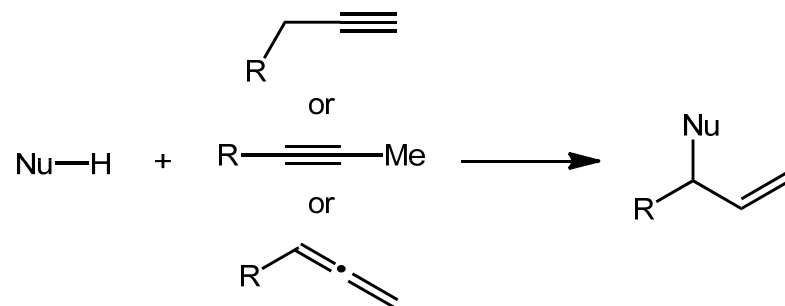


Vy M. Dong

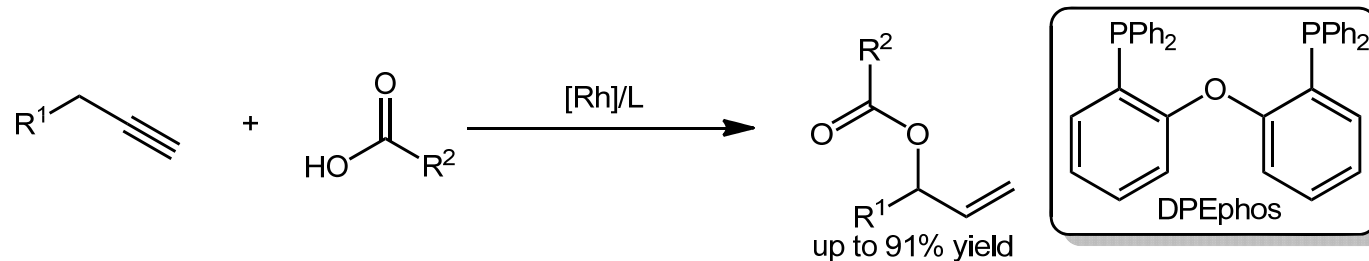
Research:

➤ New reaction methods, enantioselective catalysis, and natural product synthesis.

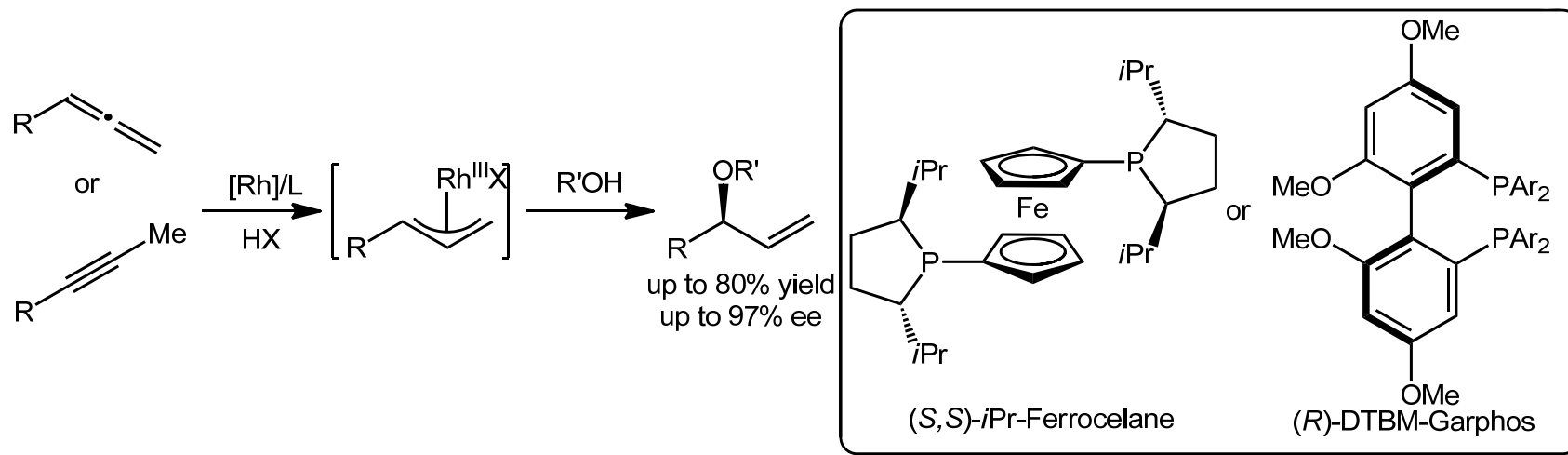
Alkyne Hydrofunctionalization—Proposed Mechanism



Formation of C-O Bond *via* Rh- π -allyl Species

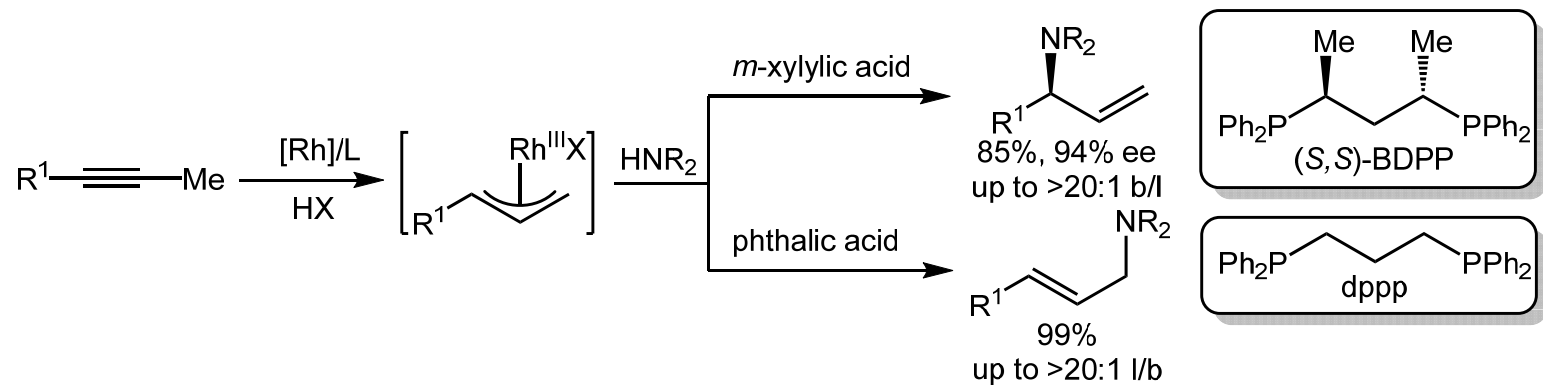


Breit, B. et al. *J. Am. Chem. Soc.* **2011**, 133, 2386.

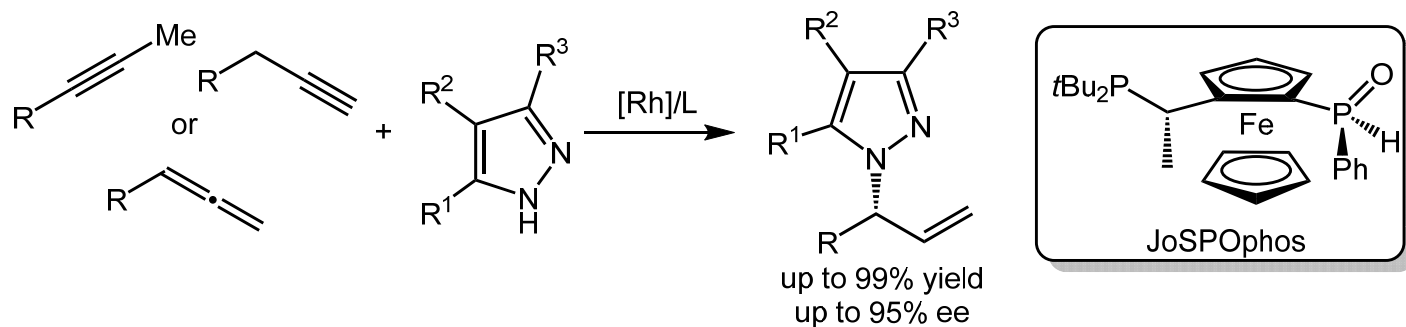


Breit, B. et al. *Angew. Chem. Int. Ed.* **2016**, 55, 8440.

Formation of C-N Bond via Rh- π -allyl Species

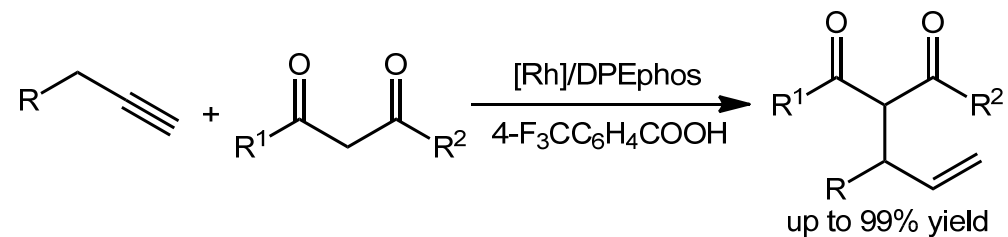


Dong, V. M. et al. *J. Am. Chem. Soc.* **2015**, 137, 8392.

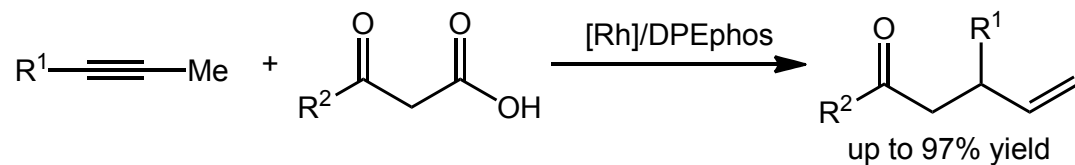


Breit, B. et al. *Chem. Eur. J.* **2016**, 22, 6547.

Formation of Csp³-C Bond *via* Rh- π -allyl Species

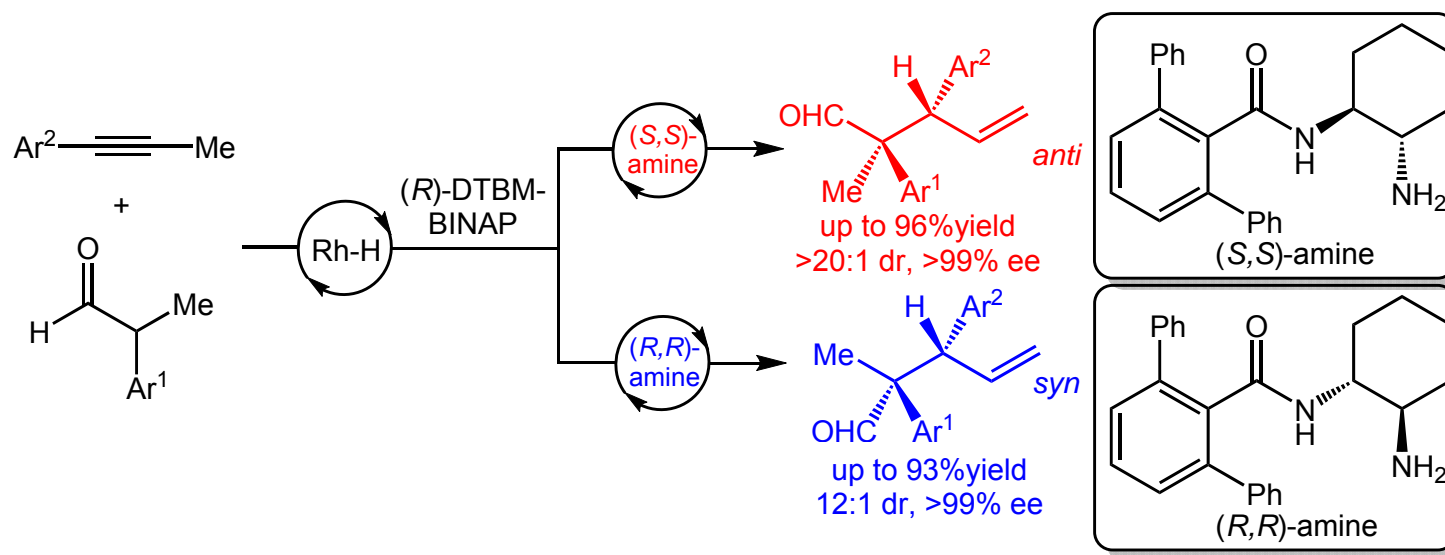


Breit, B. et al. *Org. Lett.* **2016**, *18*, 124.



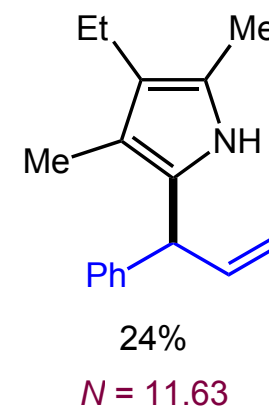
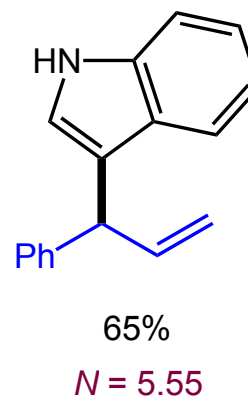
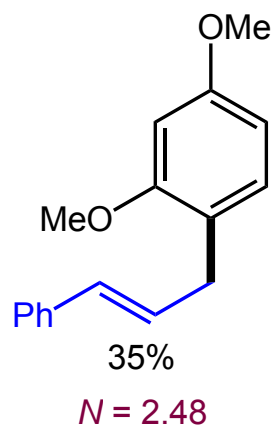
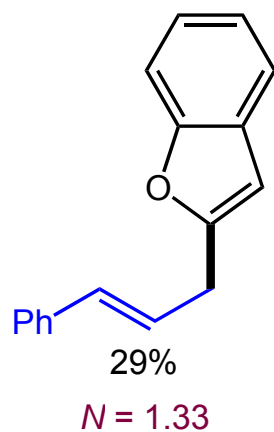
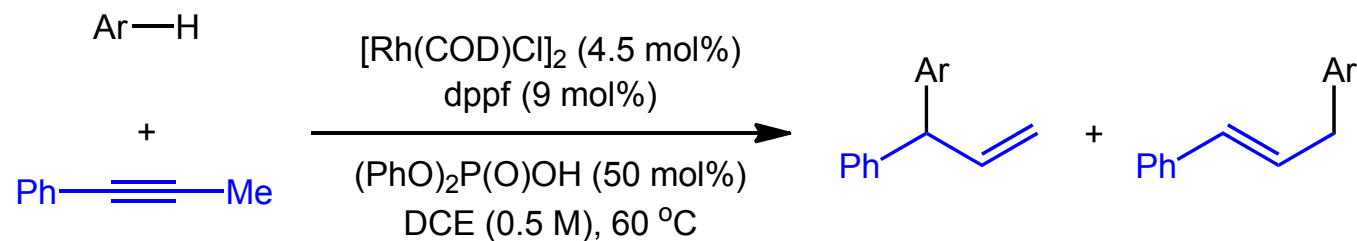
Dong, V. M. et al. *Chem. Commun.* **2016**, *52*, 5840.

Formation of Csp³-C Bond *via* Rh- π -allyl Species



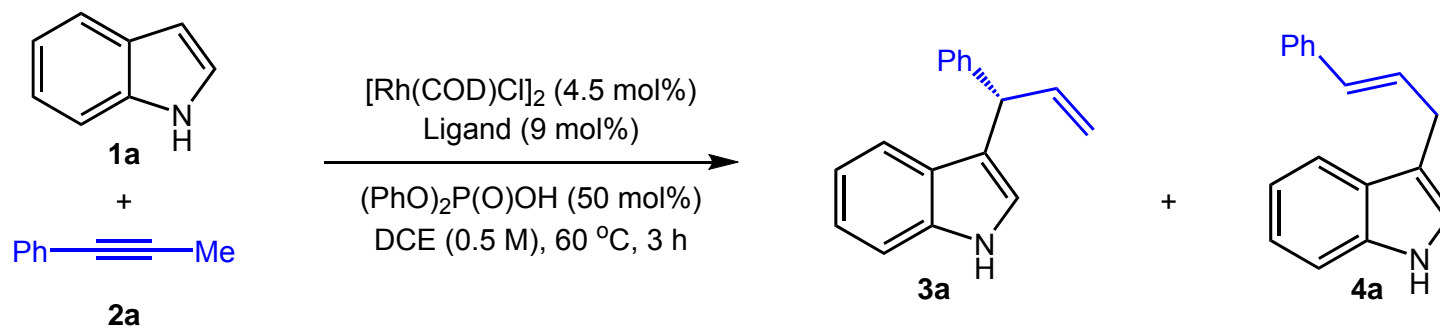
Dong, V. M. et al. *J. Am. Chem. Soc.* **2017**, 139, 1029.

Alkyne Hydroarylation—Nucleophilicity Effects

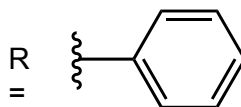
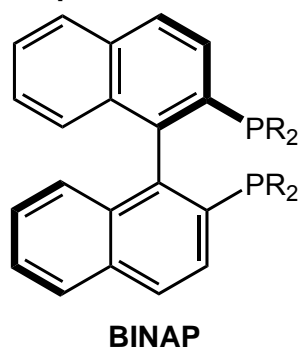


Mayr, H et al. *J. Phys. Org. Chem.* **2008**, *21*, 584-595.

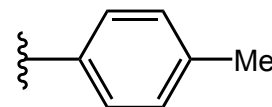
Alkyne Hydroarylation—Ligand Effects



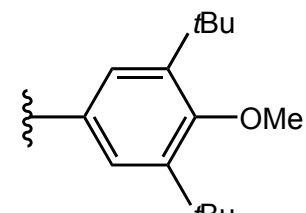
a) Phosphine Substituent



Ph (L1)
5%
20% ee



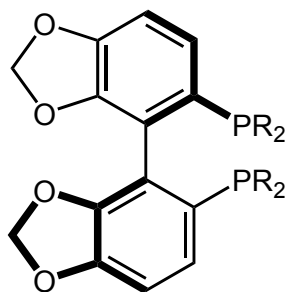
Tol (L2)
13%
28% ee



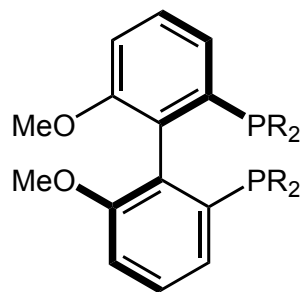
DTBM (L3)
81%
93% ee

increasing bulk

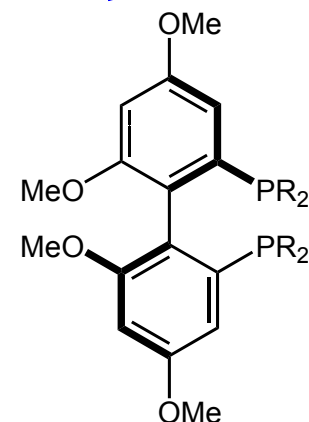
b) Ligand Scaffold, R = DTBM



SEGPHOS (L4), 31%, 90% ee

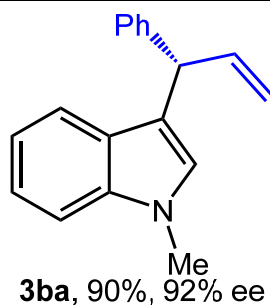
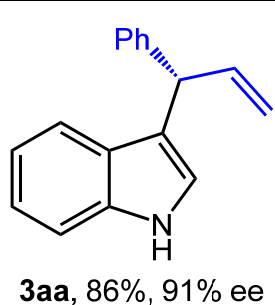
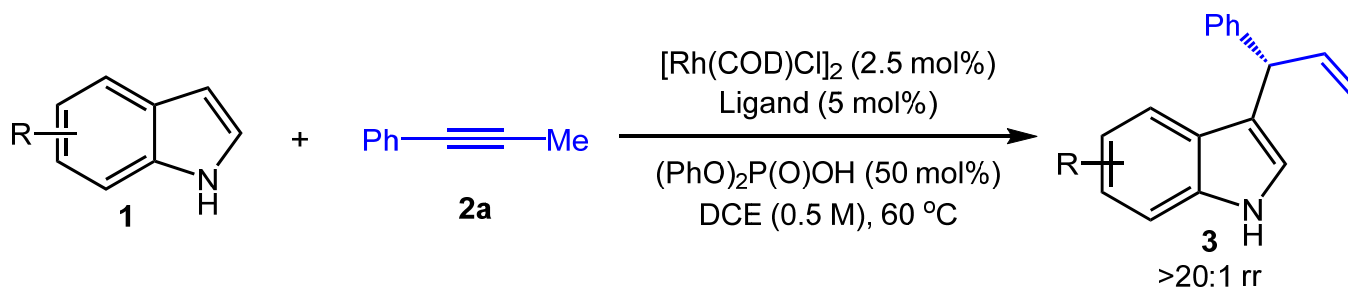


MeO-BIPHEP (L5), 18%, 89% ee

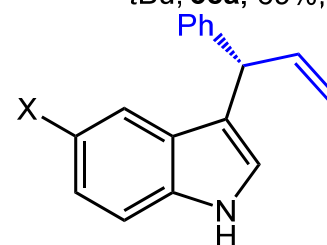
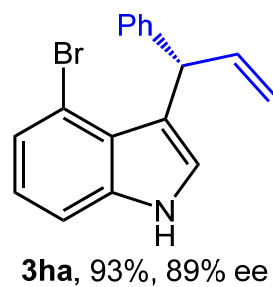
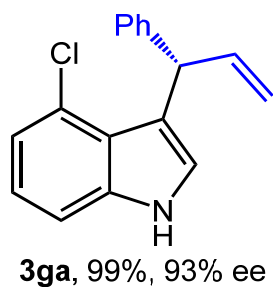
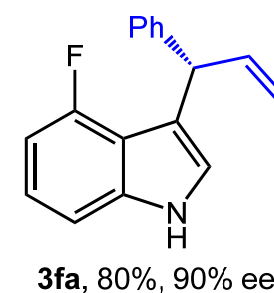


GARPPOS (L6), 23%, 96% ee

Alkyne Hydroarylation—Various Indoles



R Me, **3ca**, 95%, 69% ee
 Ph, **3da**, 72%, 92% ee
 = *t*Bu, **3ea**, 69%, 86% ee



5-Me **3ia**, 87%
 89% ee

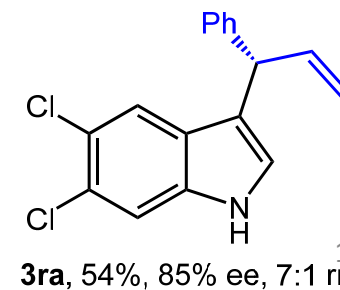
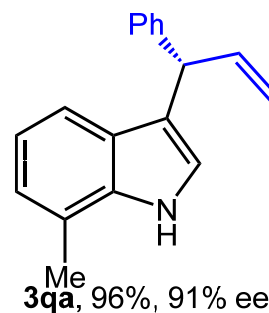
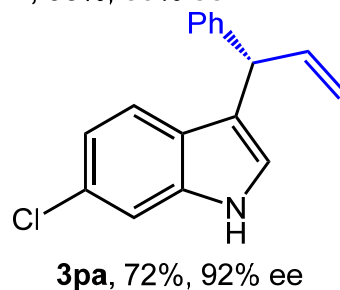
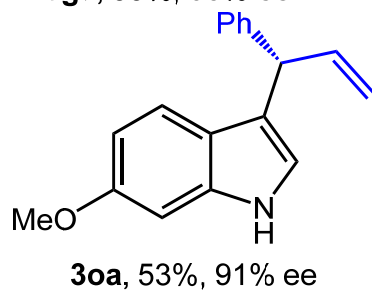
5-OH **3ja**, 90%
 90% ee

5-CO₂Me **3ka**, 64%
 86% ee

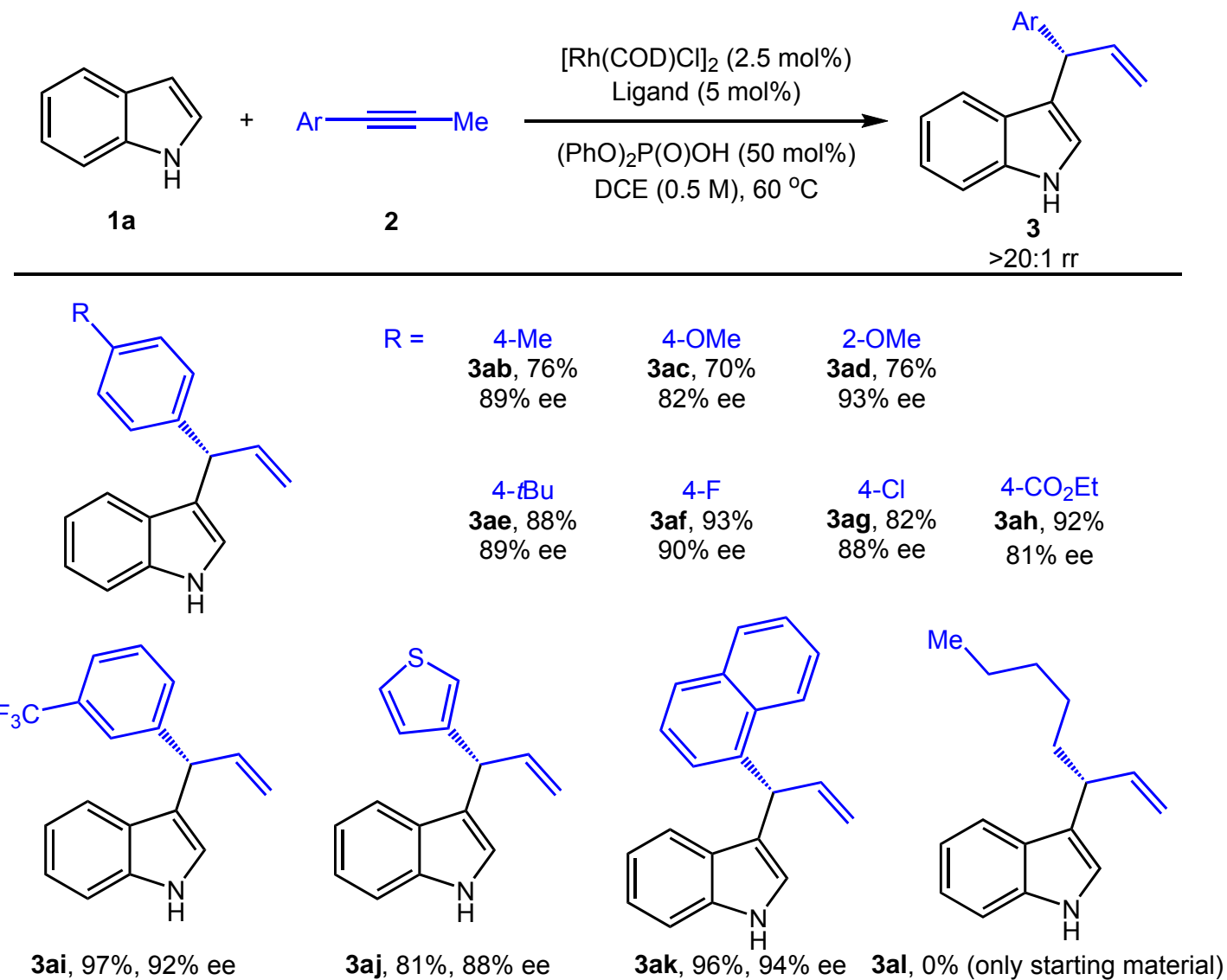
5-OMe **3la**, 81%
 90% ee

5-F **3ma**, 71%
 85% ee

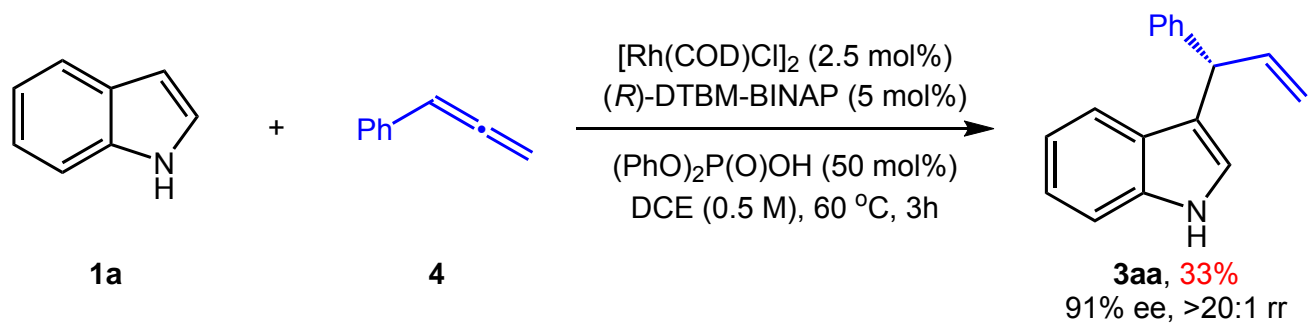
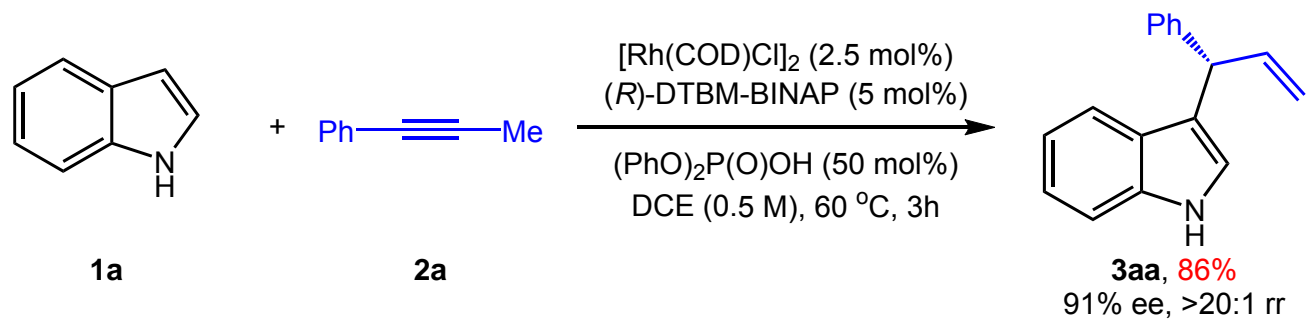
5-Bpin **3na**, 69%
 94% ee



Alkyne Hydroarylation—Various Alkynes

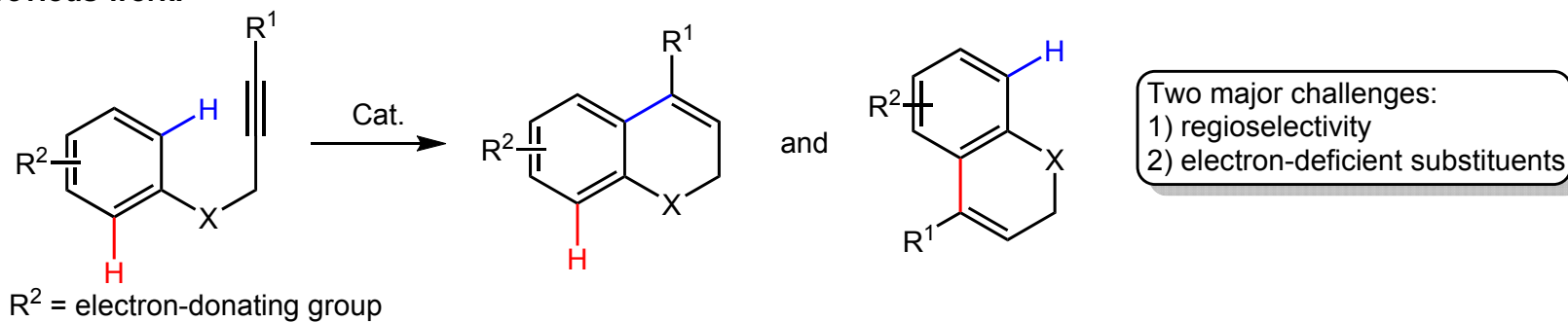


Phenylallene Hydroarylation



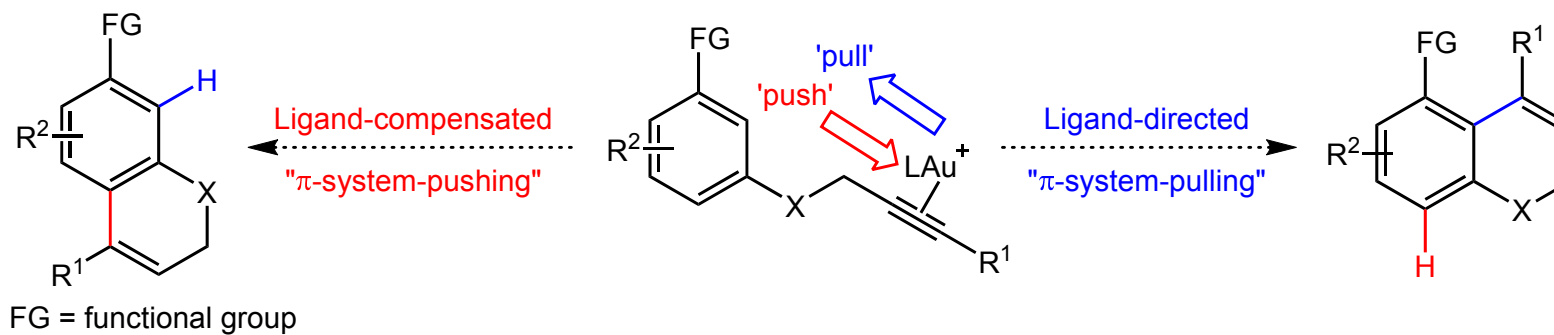
Hydroarylation and Cascade Cyclization

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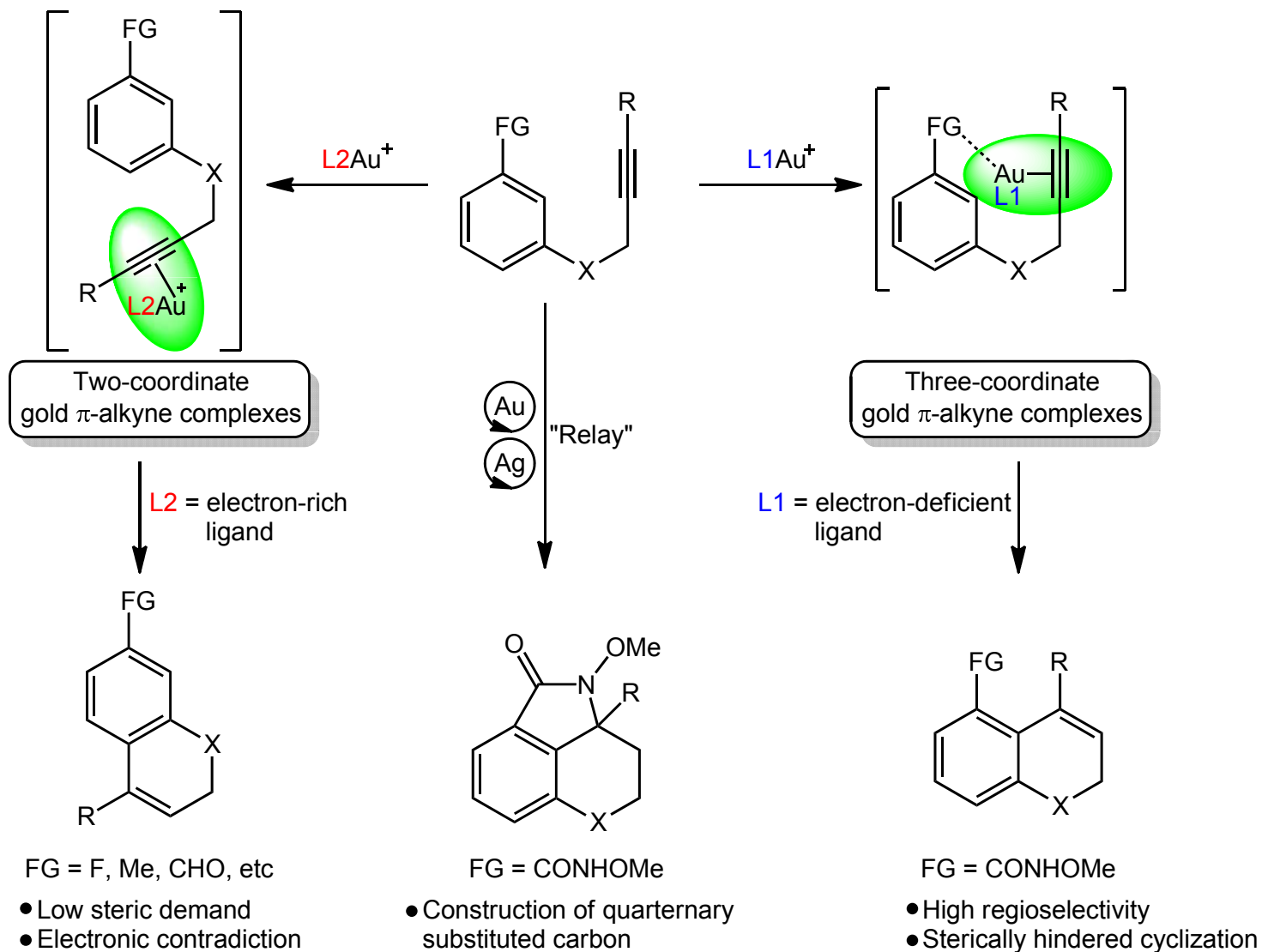


Echavarren, A. M. et al. *Chem. Eur. J.* **2006**, *11*, 3155-3164.

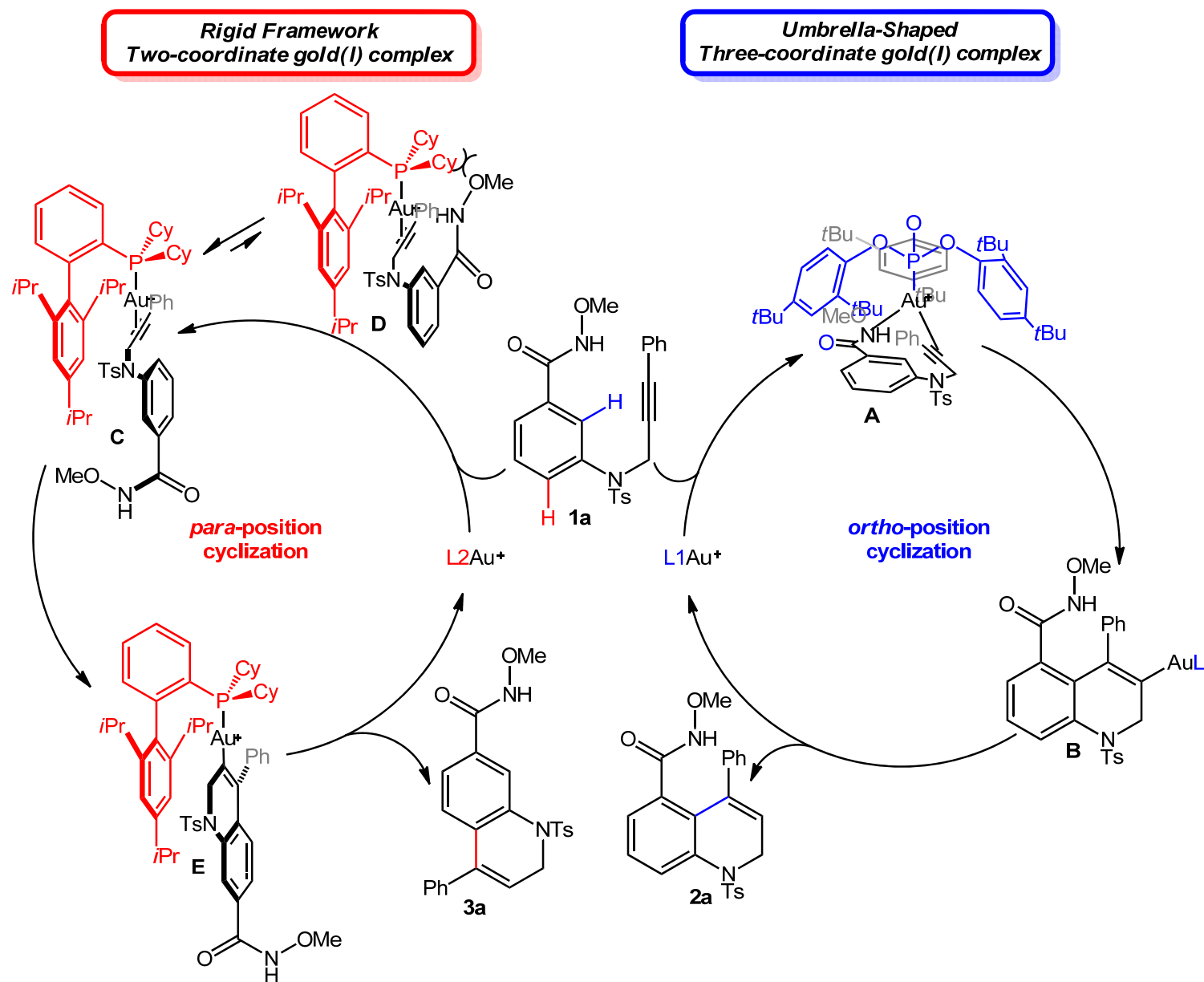
Jiang's concept:



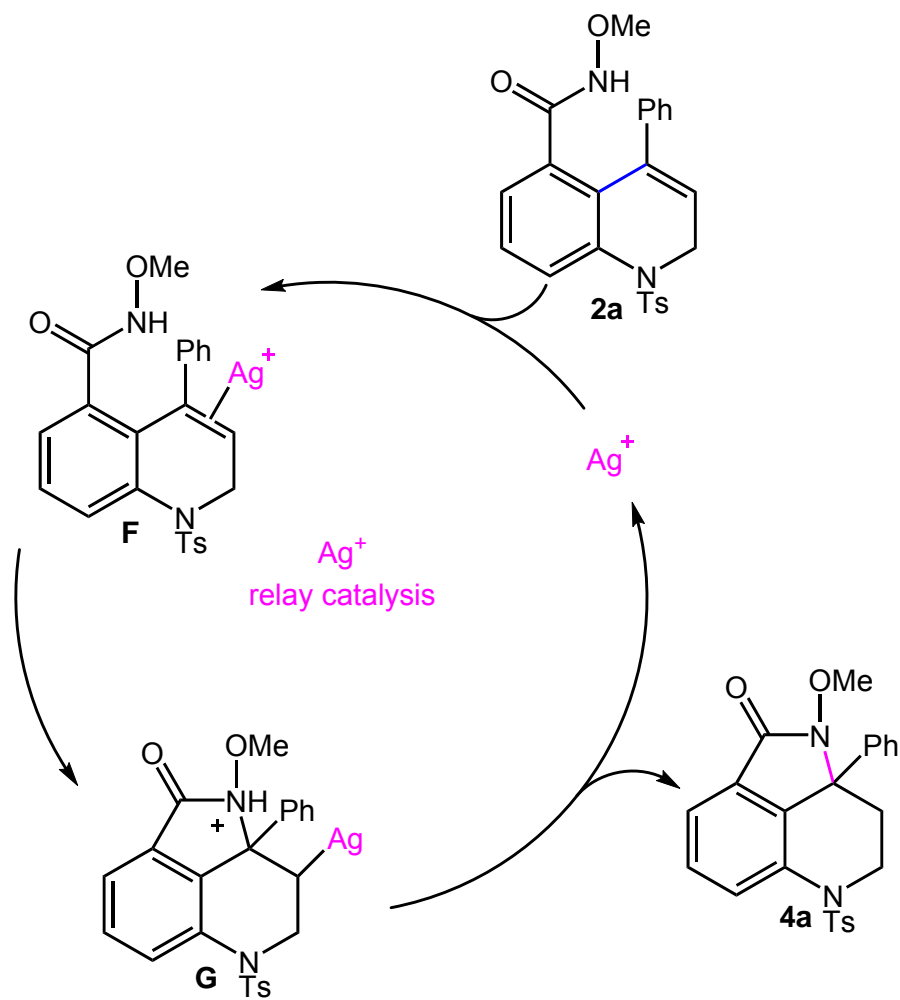
Hydroarylation and Cascade Cyclization



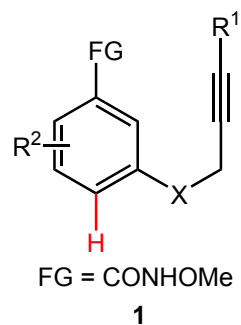
Proposed Mechanism



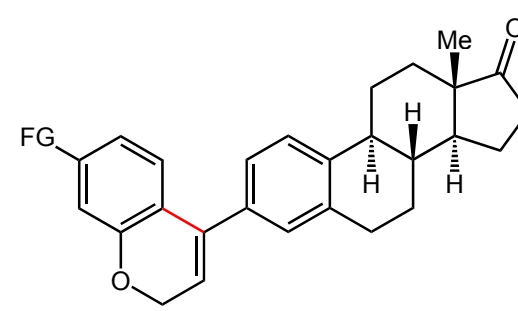
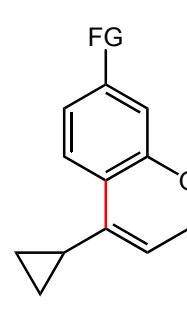
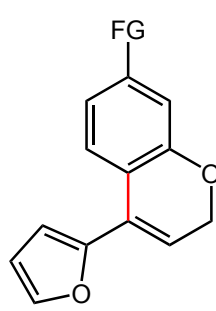
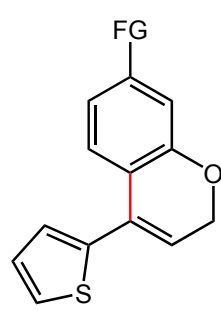
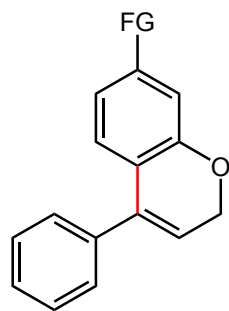
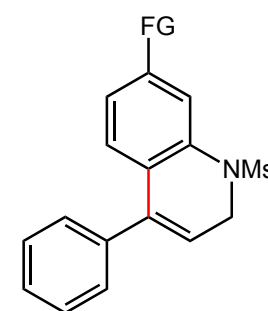
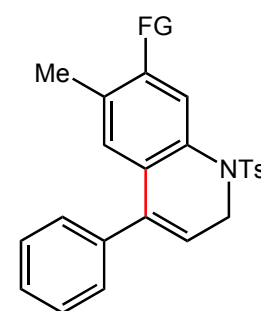
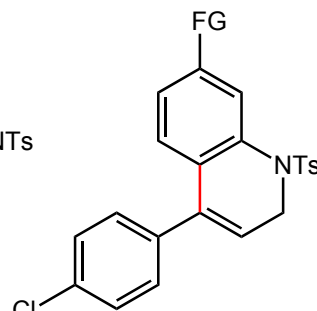
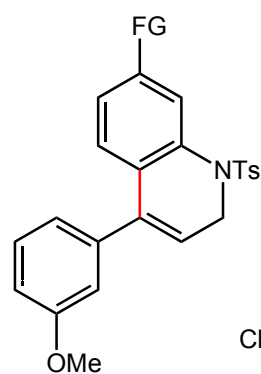
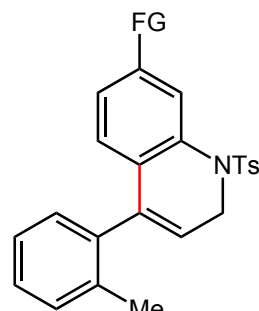
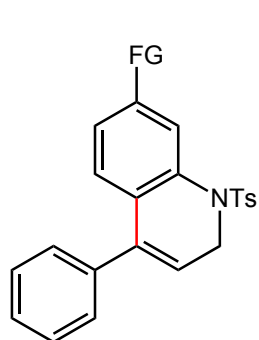
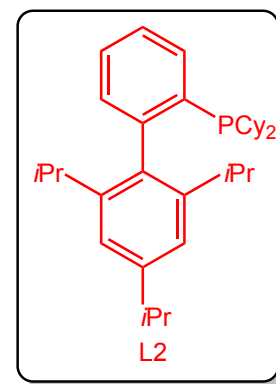
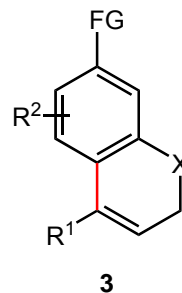
Proposed Mechanism



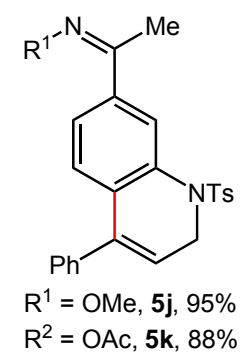
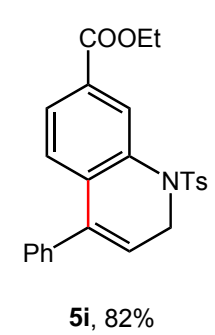
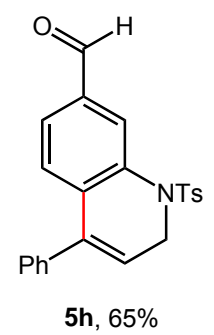
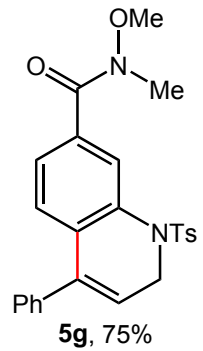
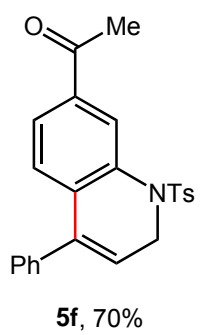
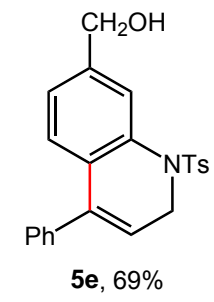
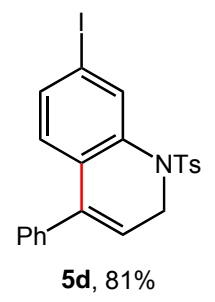
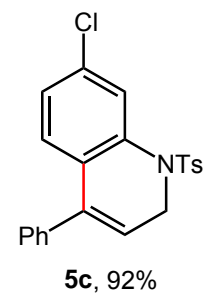
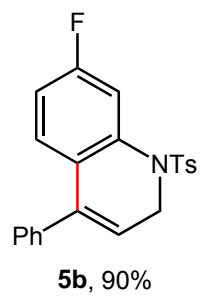
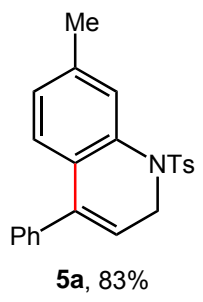
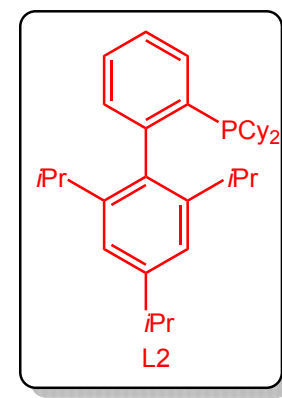
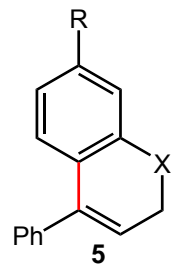
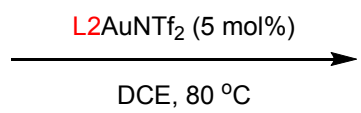
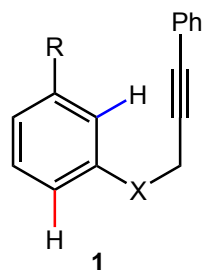
para-Position Cyclization



L2AuNTf₂ (5 mol%)

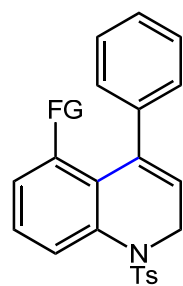
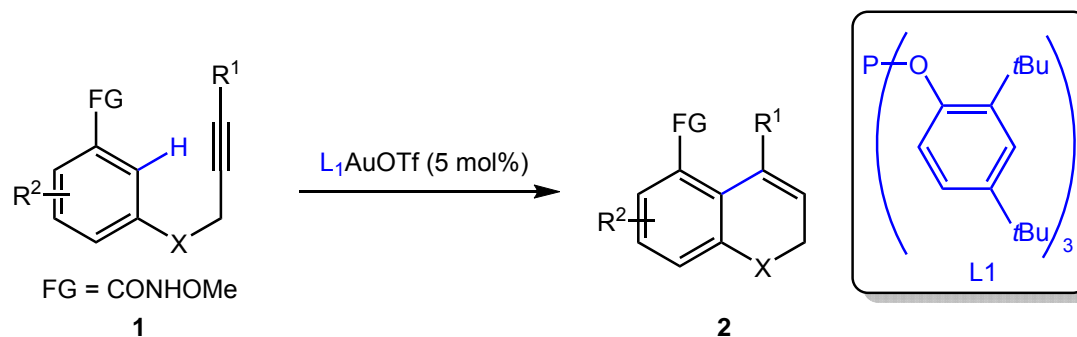


para-Position Cyclization

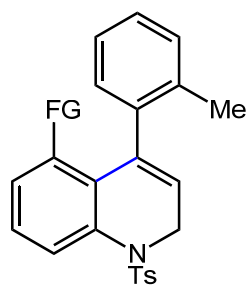


R¹ = OMe, **5j**, 95%
R² = OAc, **5k**, 88%

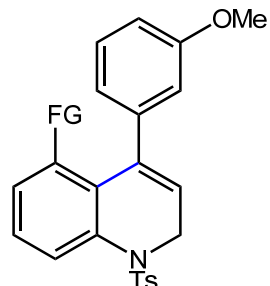
ortho-Position Cyclization



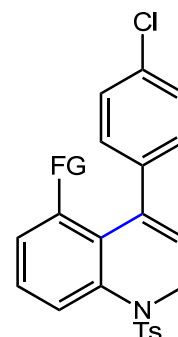
2a, 61%
o:p = 5.6:1



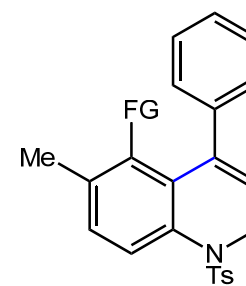
2b, 68%
o:p = 10.1:1



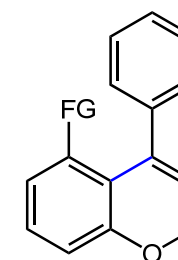
2c, 70%
o:p = 12.2:1



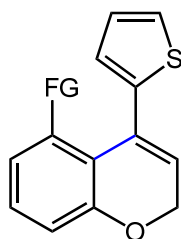
2d, 64%
o:p = 4.5:1



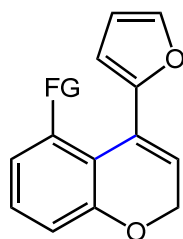
2e, 61%
o:p = 4.0:1



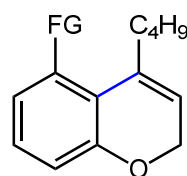
2f, 81%
o:p > 20:1



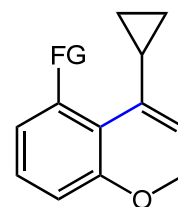
2g, 78%
o:p > 20:1



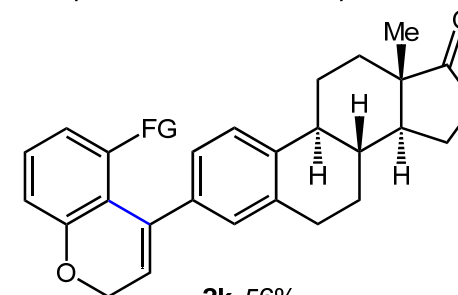
2h, 66%
o:p > 20:1



2i, 76%
o:p > 20:1

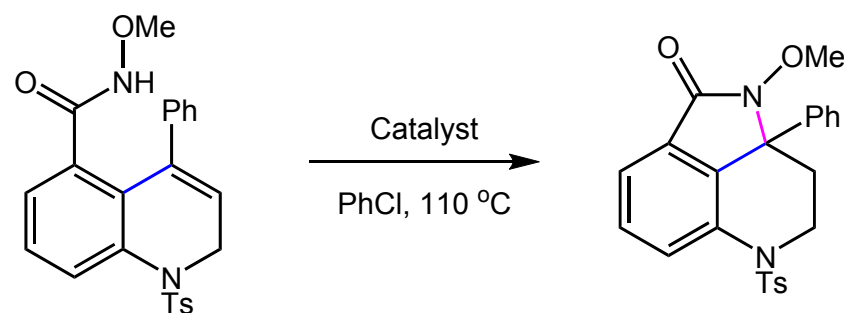


2j, 62%
o:p > 20:1



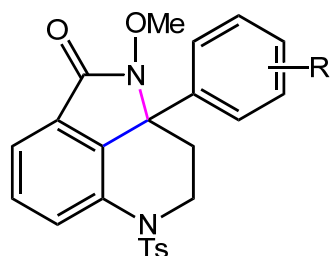
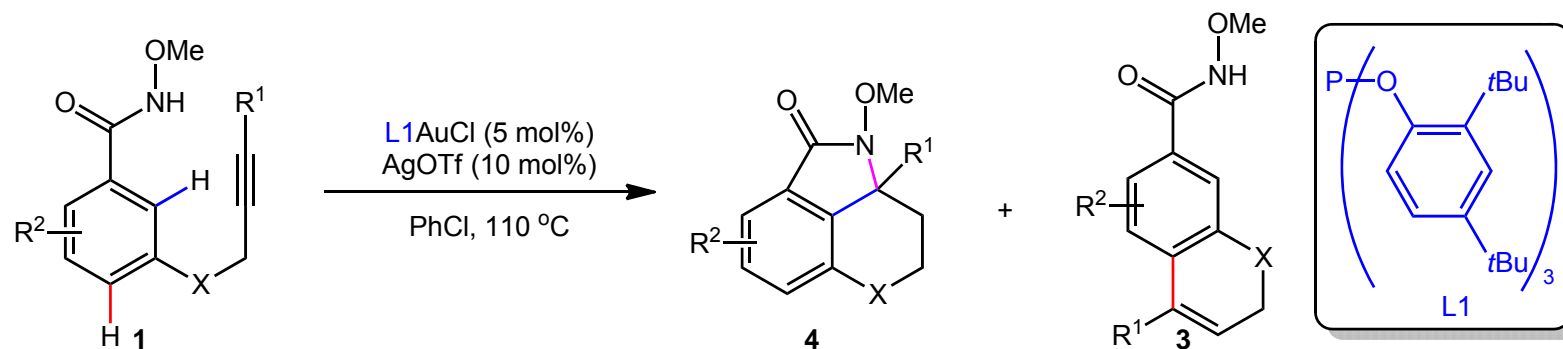
2k, 56%
o:p > 20:1

Au/Ag Relay Cascade Cyclization

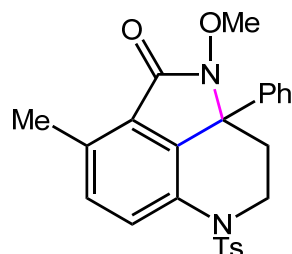


Cat.	Yield
(2,4- <i>t</i> Bu ₂ C ₆ H ₃ O) ₃ PAuOTf (5 mol%)	0%
(2,4- <i>t</i> Bu ₂ C ₆ H ₃ O) ₃ PAuCl (5 mol%) /AgOTf (10 mol%)	80%
AgOTf (10 mol%)	85%

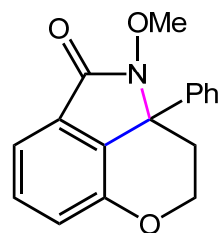
Au/Ag Relay Cascade Cyclization



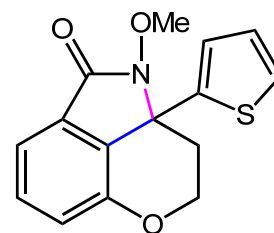
$\text{R} = \text{H}$, **4a**, 65%, **4:3** = 5.9:1 $\text{R} = 4\text{-Br}$ **4c**, 61%, **4:3** = 4.0:1
 $\text{R} = 3\text{-OMe}$, **4b**, 80%, **4:3** > 20:1 $\text{R} = 4\text{-Cl}$ **4d**, 67%, **4:3** = 4.6:1



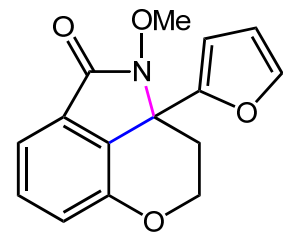
4e, 65%, **4:3** = 4.5:1



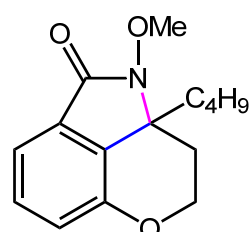
4f, 83%, **4:3** > 20:1



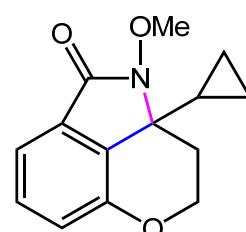
4g, 75%, **4:3** > 20:1



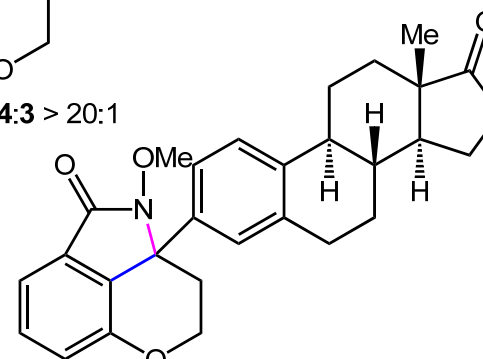
4h, 70%, **4:3** > 20:1



4i, 85%, **4:3** > 20:1

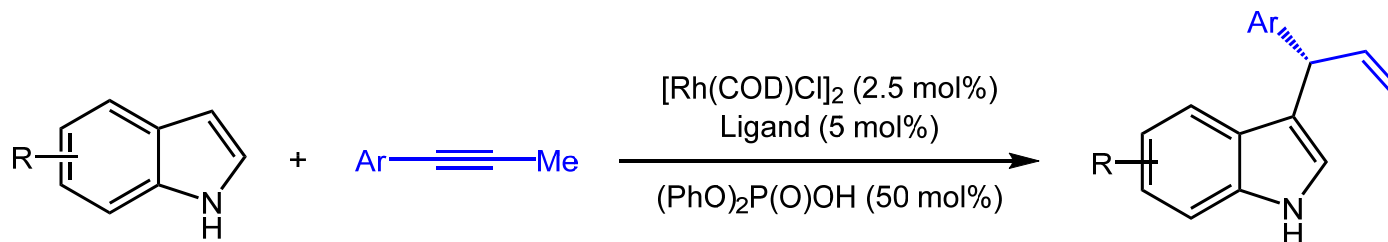


4j, 68%, **4:3** > 20:1

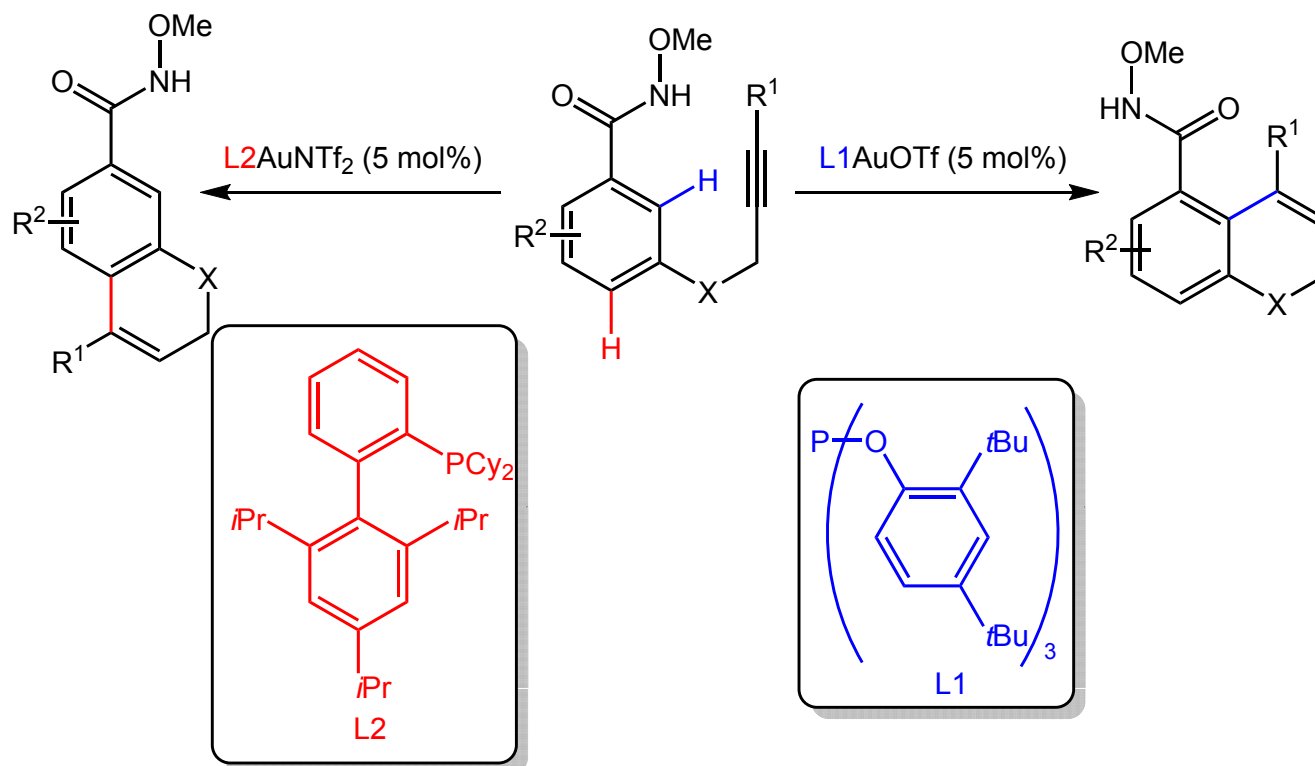


4k, 65%, **4:3** > 20:1

Summary



Dong, V. M. et al. *J. Am. Chem. Soc.* **2017**, *139*, 10641.



Jiang, X. et al. *J. Am. Chem. Soc.* **2016**, *138*, 5218.

The First Paragraph

Aryl and heteroaryl rings can be used to increase nonbonding and electrostatic interactions between a small molecule and its macromolecule target. Among the top selling therapeutics, more than half contain aryl structures. Given the relevance of chirality in medicine, inventing enantioselective tools for introducing aromatic nucleophiles warrants pursuit. The hydroarylation of alkynes is a modern strategy for functionalizing aryl structures, where two simple functional groups are coupled with high atom economy. To date, however, this approach has been limited to generating achiral olefins.

The First Paragraph

Classic alkyne hydroarylations generate achiral vinylated arenes via mechanisms that involve alkyne activation with π -acids or arene activation to access aryl-metal species. **In contrast, we imagined using metal-hydride catalysis to couple arenes with alkynes to form allylated products.** In this communication, we disclose a regio- and enantioselective alkyne hydroheteroarylation using indoles.

The Last Paragraph

We have demonstrated a regio- and enantioselective way to hydrofunctionalize alkynes using indoles. The use of Rh-hydride catalysis to isomerize alkynes has enabled access to a complementary hydrohetero-arylation motif. Moreover, our study demonstrates the potential of generating C–C bonds under mild conditions using both aromatic and heteroaromatic motifs. Given these promising results, our future studies will focus on enantio- and regioselective coupling using other classes of aromatic nucleophiles.

Acknowledgment

Thanks for your attention