Literature Report 13

Copper-Catalyzed Enantioselective Dehydro-Diels-Alder Reaction

Reporter: Han Wang
Checker: Shan-shan Xun
Date: 2025.01.13

Chen, H.-H.; Chen, Y.-B.; Ye, L.-W.; Zhou, B.* *Angew. Chem. Int. Ed.* **2024**, *63*, e202411709.

CV of Dr. Bo Zhou (周波)

Background:

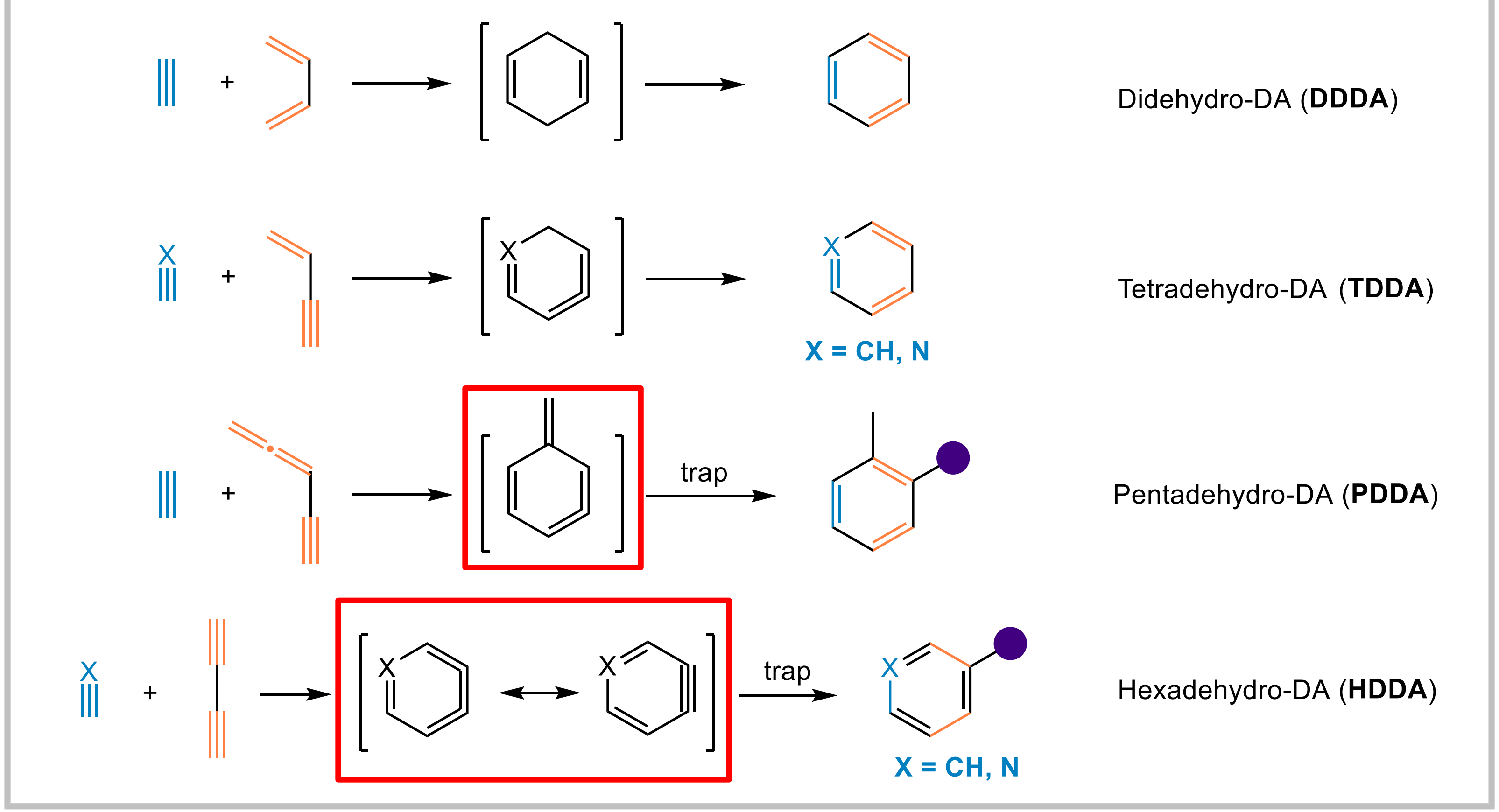
- **2009-2013** B.S., Wuhan University of Technology
- **2013-2016** M.S., Xiamen University (Prof. L.-W. Ye)
- **2016-2019** Ph.D., Xiamen University (Prof. L.-W. Ye)
- **2019-2022** Postdoc., The University of Chicago (Prof. G. Dong)
- **2022-present** Associate Prof., Xiamen University

Research:

- ✓ **Organic Synthesis Methodology**
- ✓ **Design and Synthesis of Functional Molecules**
- ✓ **Medicinal Chemistry**

Contents

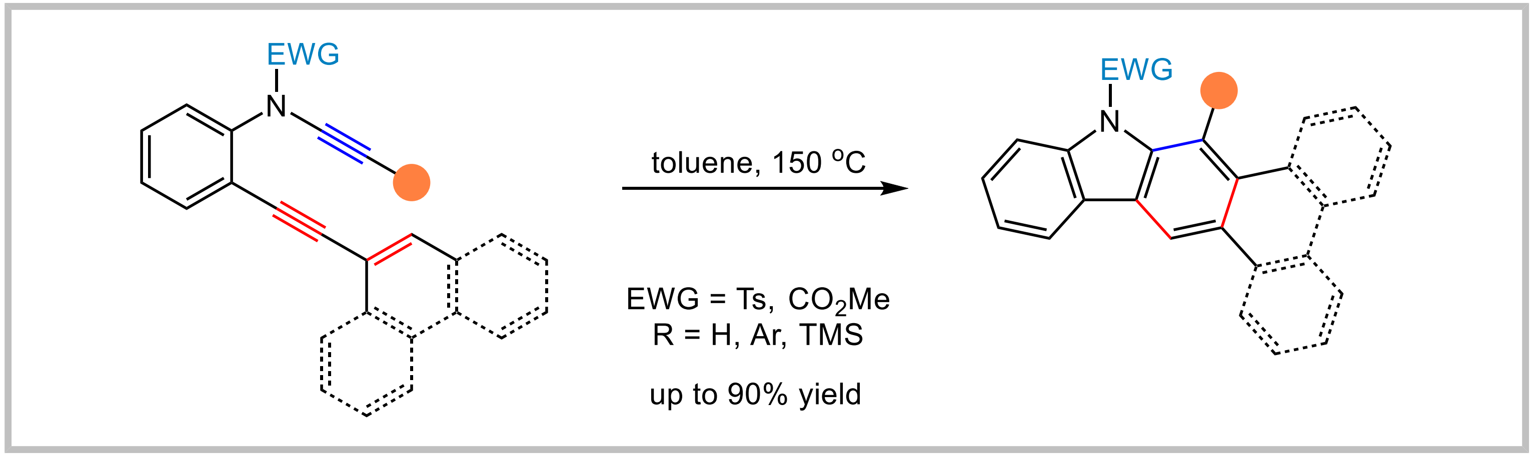
Introduction



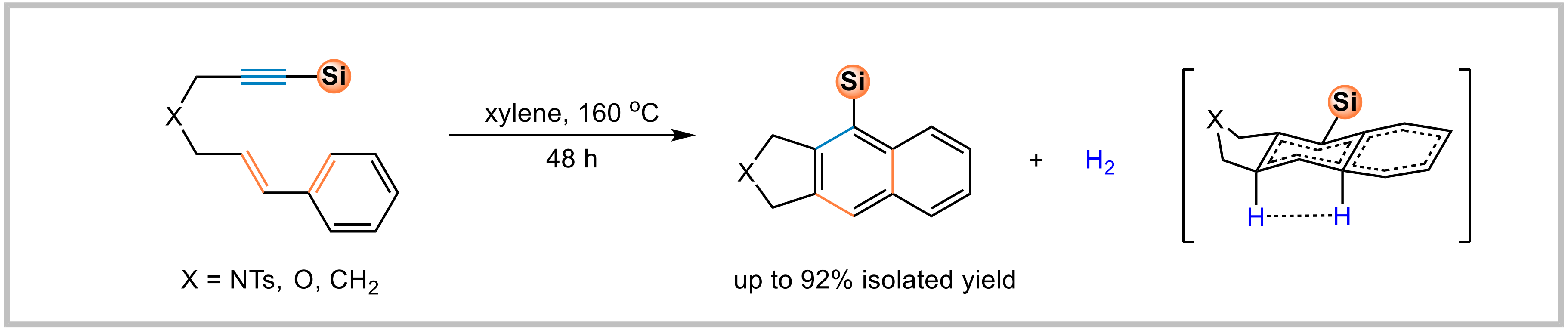
- Heat Promoted
- Base Promoted
- Transition Metal Catalyzed
- Photochemically Initiated

Hoye, T. R. *et al. Chem. Rev.* **2021**, *121*, 2413.

Heat Promoted

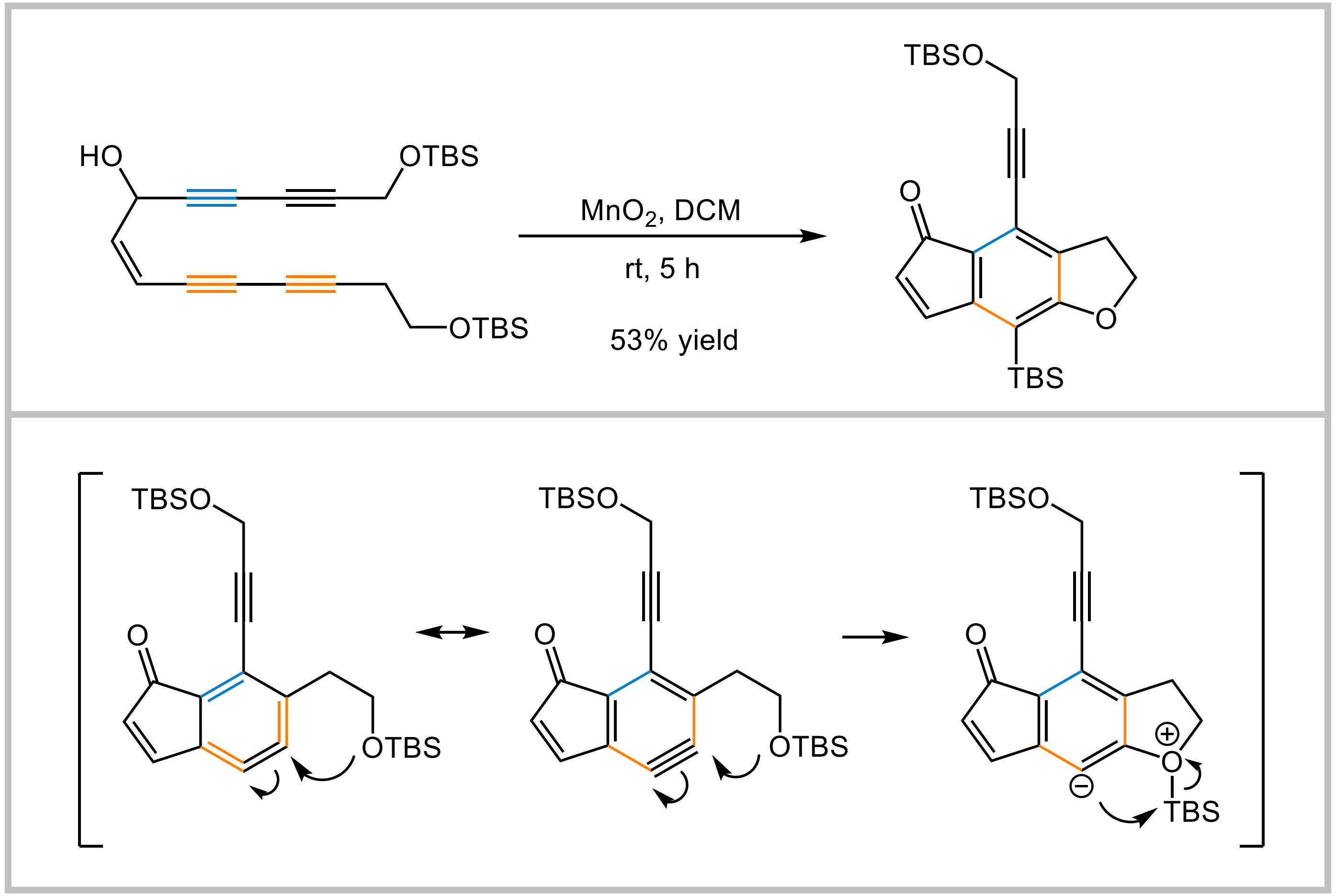


Saá, C. *et al. Org. Lett.* **2005**, *7,* 2213.



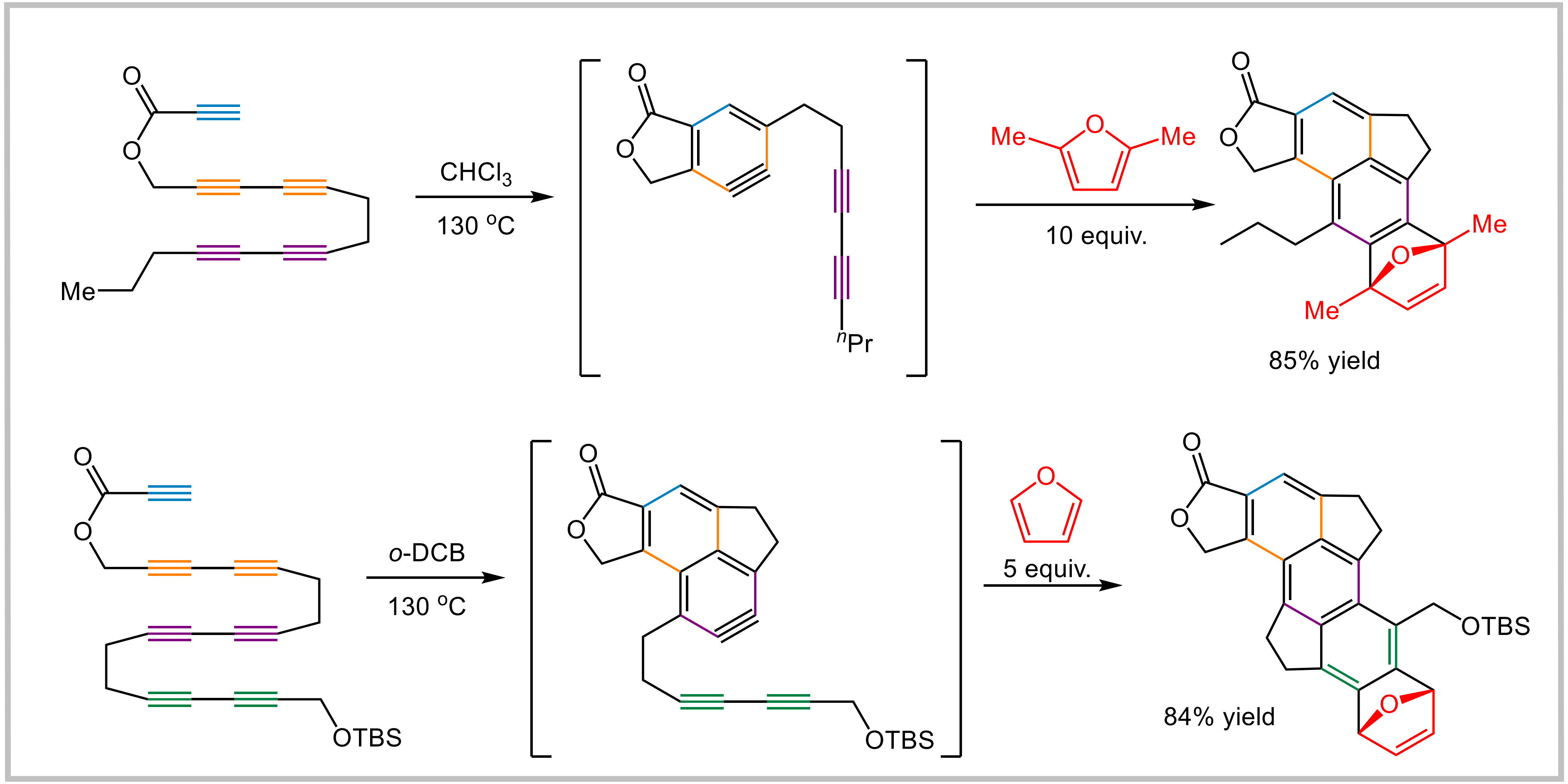
Matsubara, S. *et al. Org. Lett.* **2011**, *13,* 5390.

Heat Promoted



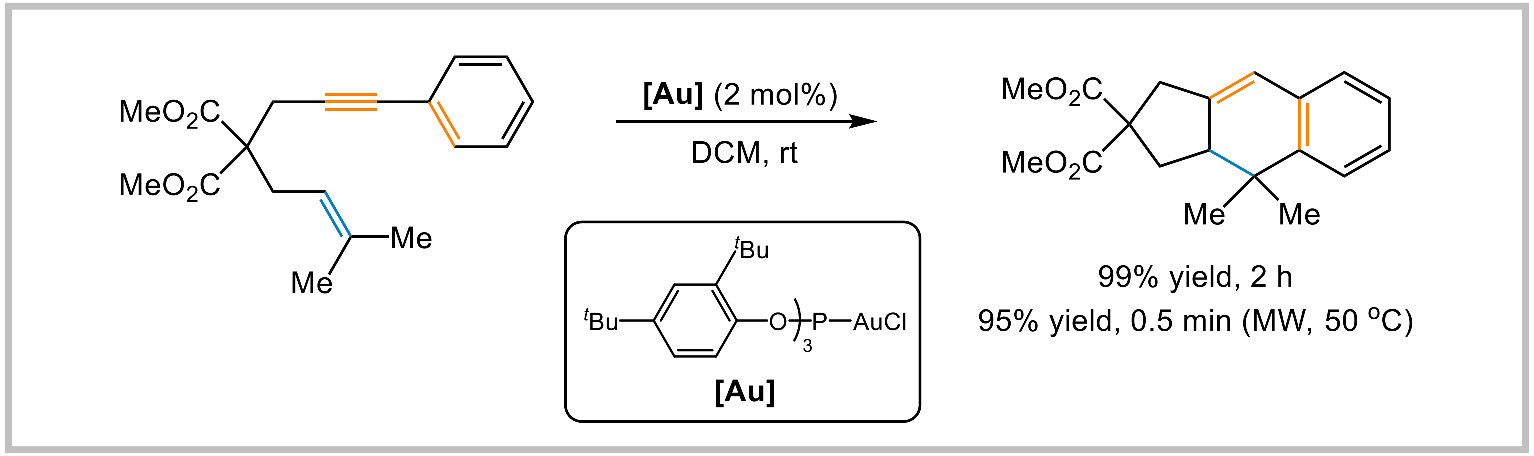
Woods, B. P. *et al. Nature* **2012**, *490,* 208.

Heat Promoted

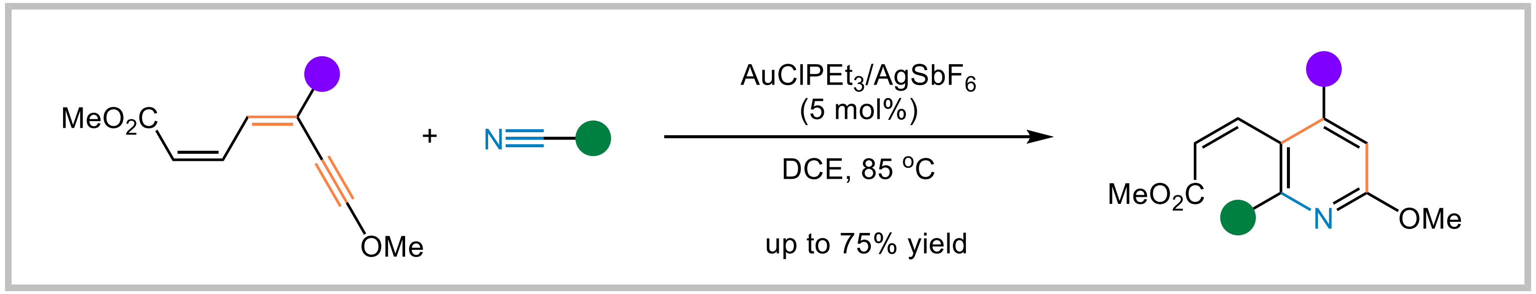


Hoye, R. T. *et al. Nat. Chem.* **2018**, *10*, 838.

Transition-Metal Catalyzed

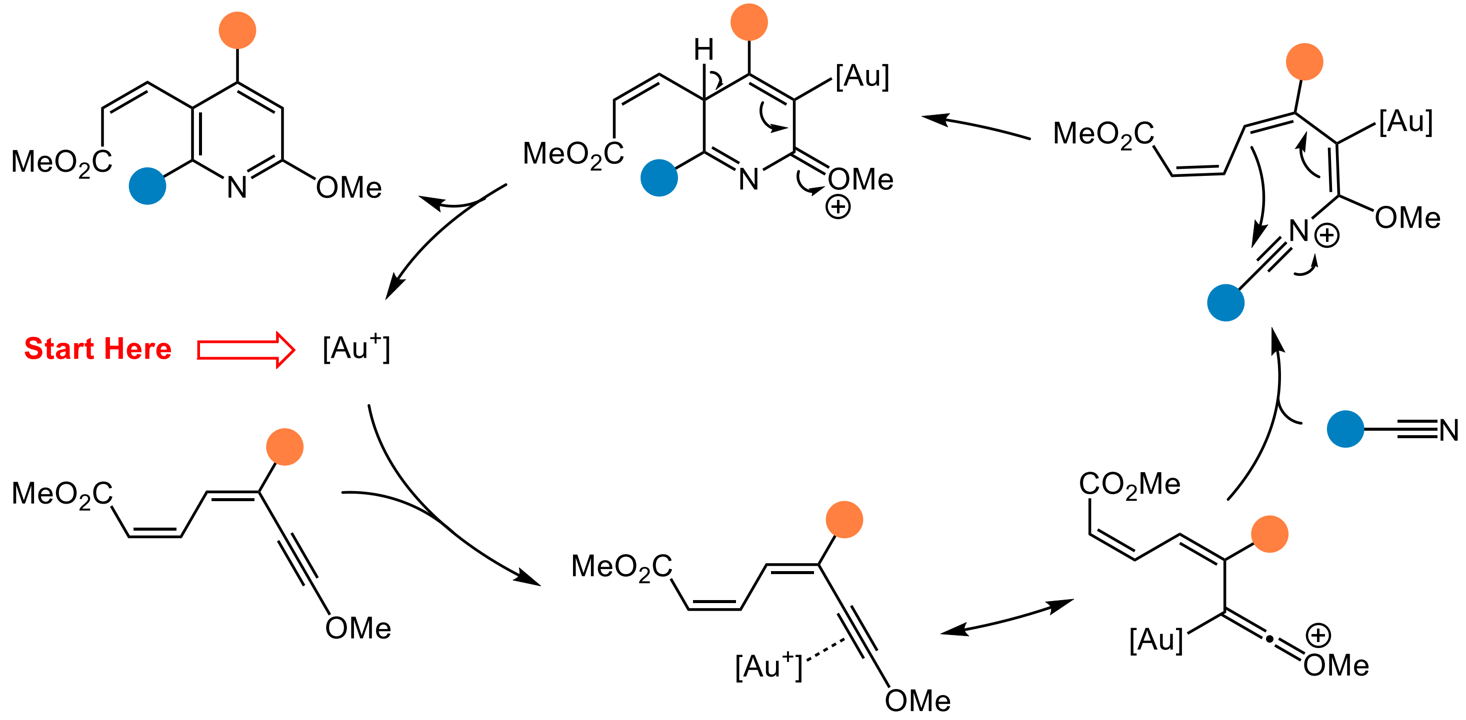


Echavarren, A. M. *et al. J. Am. Chem. Soc.* **2008**, *130,* 269.



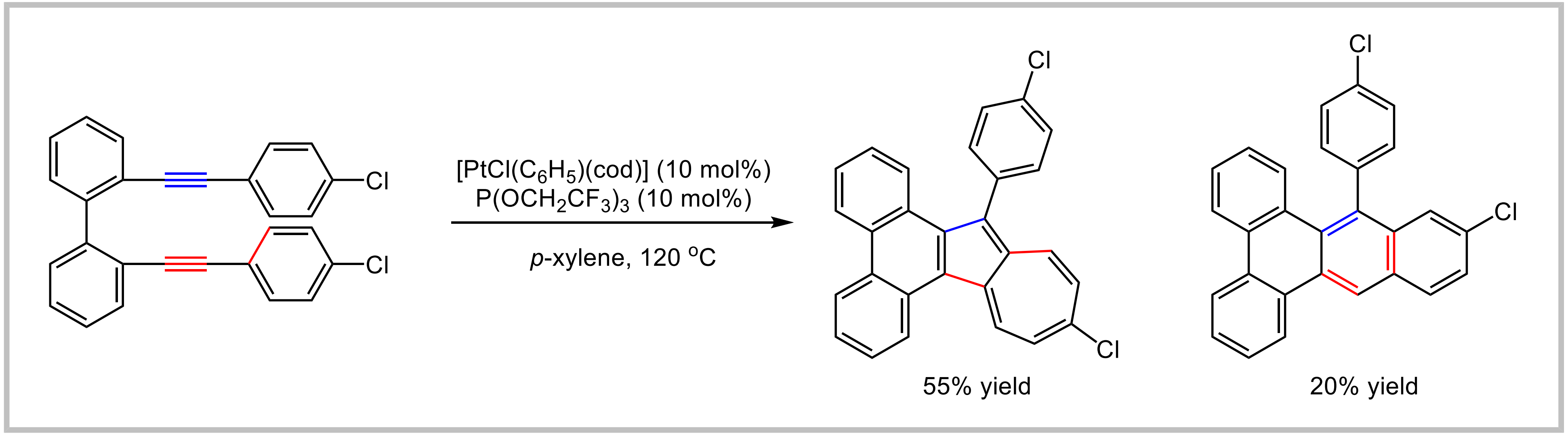
Aguilar, E. *et al. J. Am. Chem. Soc.* **2008**, *130, 2764*.

Transition-Metal Catalyzed

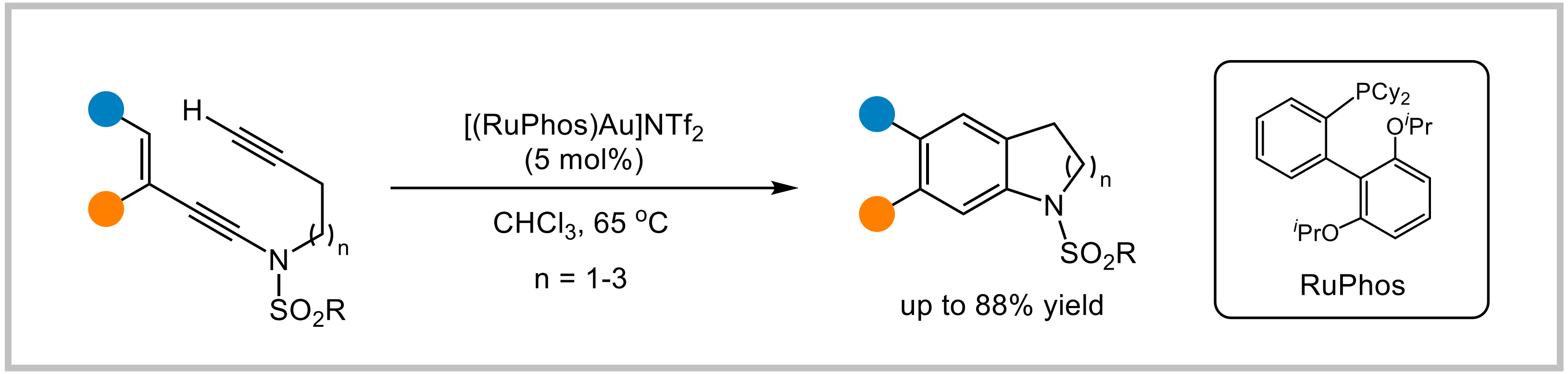


Aguilar, E. *et al. J. Am. Chem. Soc.* **2008**, *130, 2764*.

Transition-Metal Catalyzed

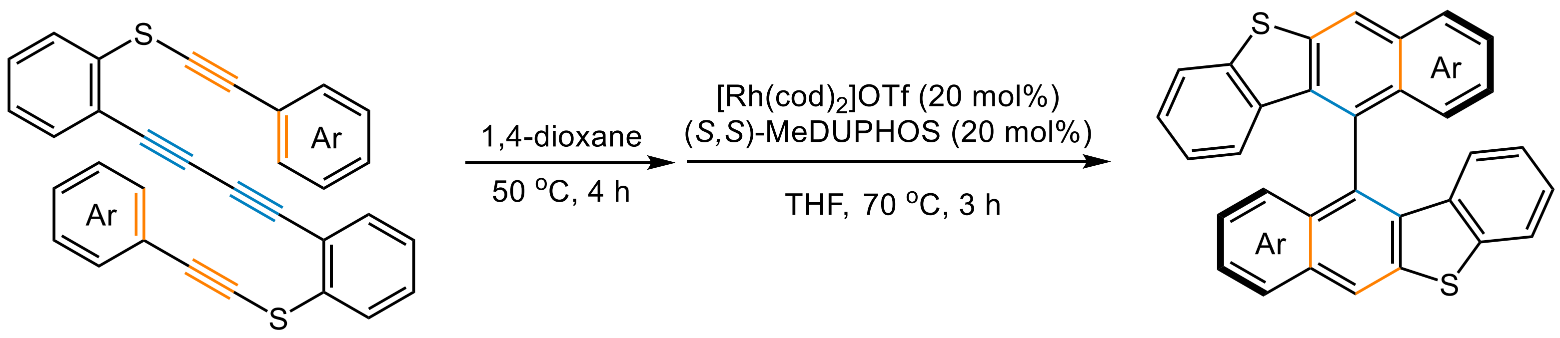


Murakami, M. *et al. Angew. Chem. Int. Ed.* **2013**, *52,* 6492.



Gagosz, F. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 13603.

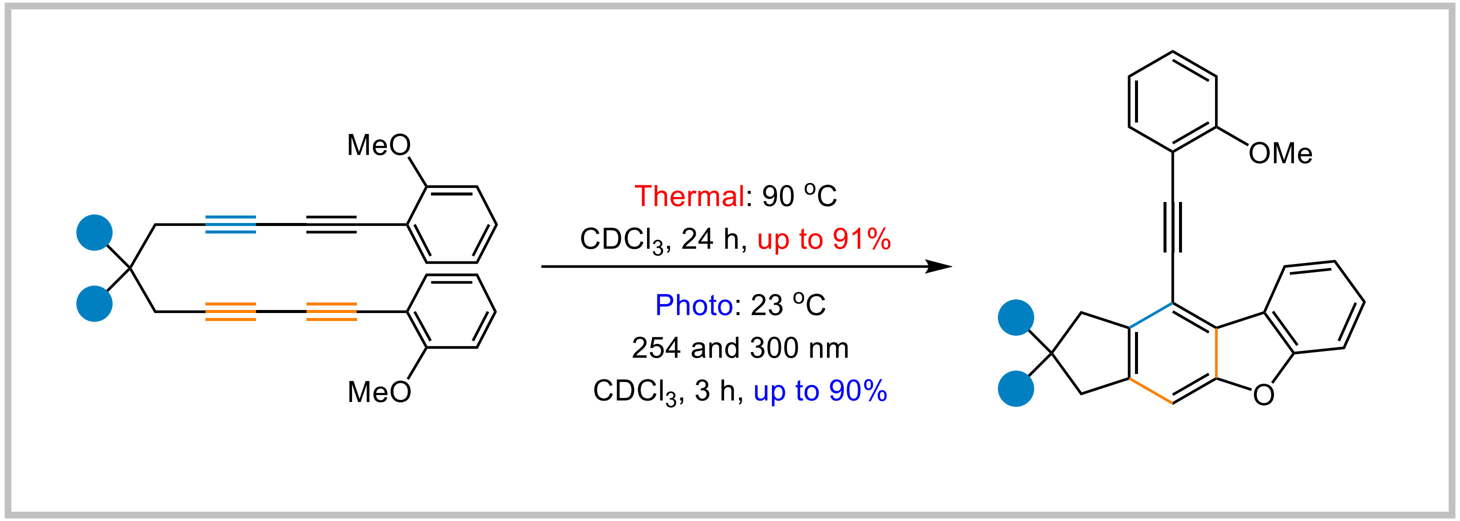
Transition-Metal Catalyzed



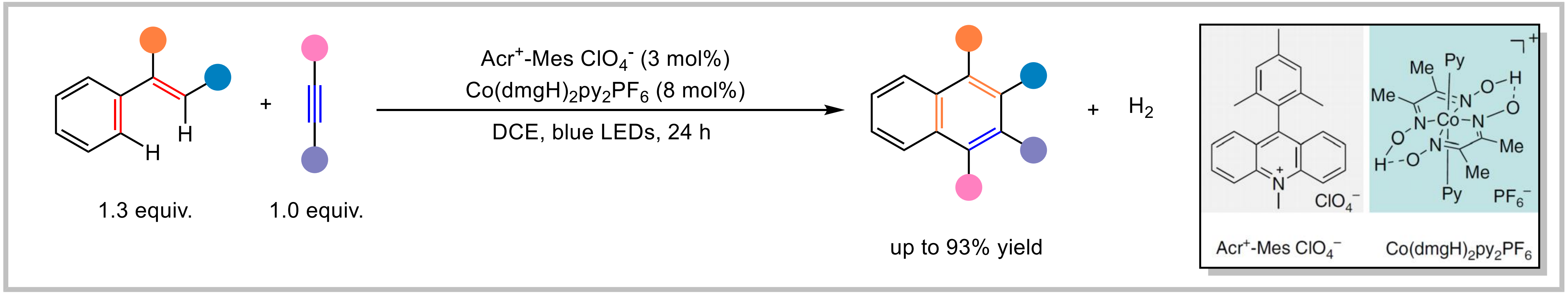
Entry	Ar	Yield [%]	Ee [%]
1	*p*-MeC_6H_4	96	93
2	*p*-ClC_6H_4	66	90
3	*p*-$MeOC_6H_4$	96	81
4	*o*-MeC_6H_4	53	90
5	1-naphthyl	54	>99

Shibata, T. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 15862.

Photochemical Initiated

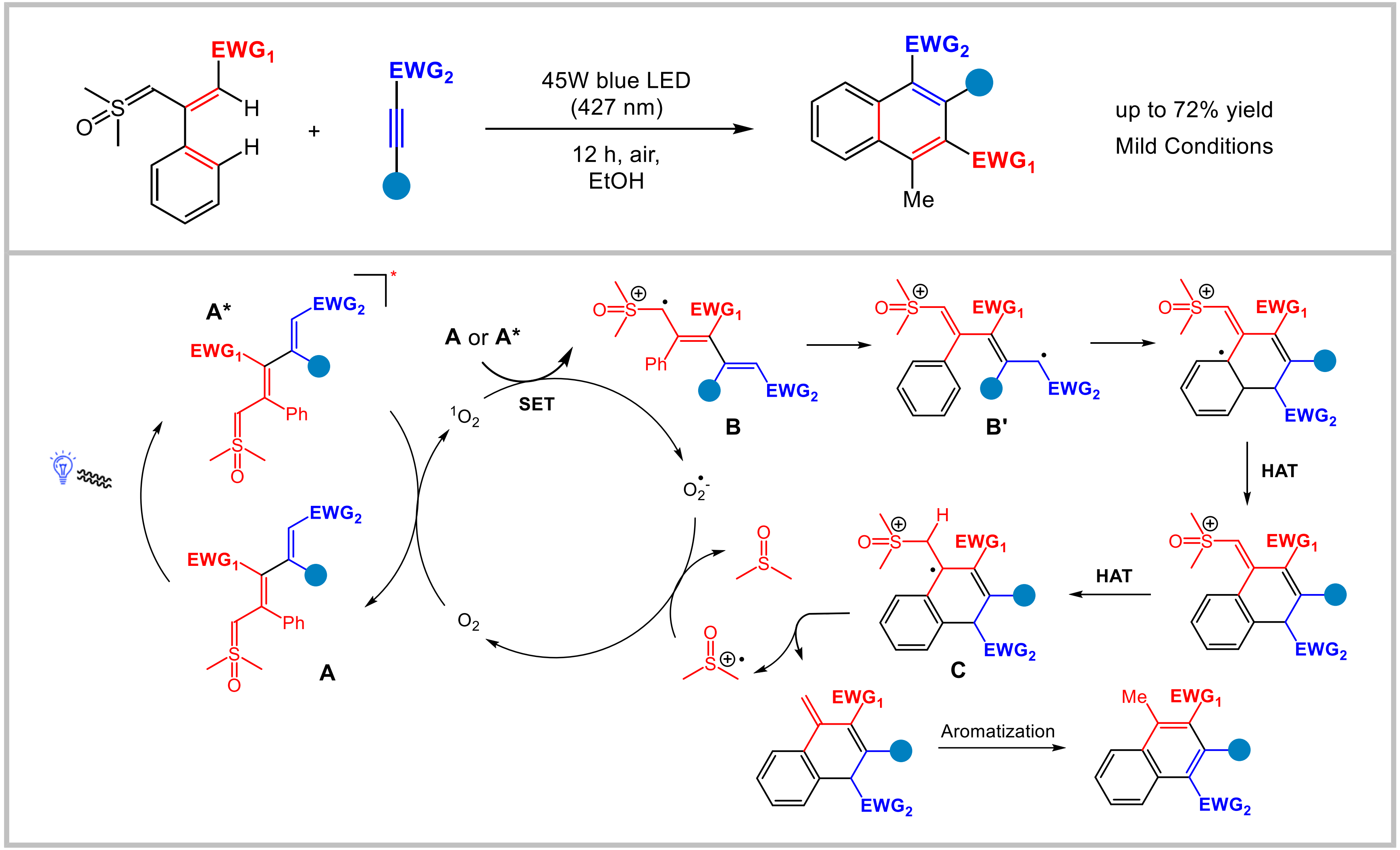


Hoye, R. T. *et al. J. Am. Chem. Soc.* **2017**, *139,* 8400.



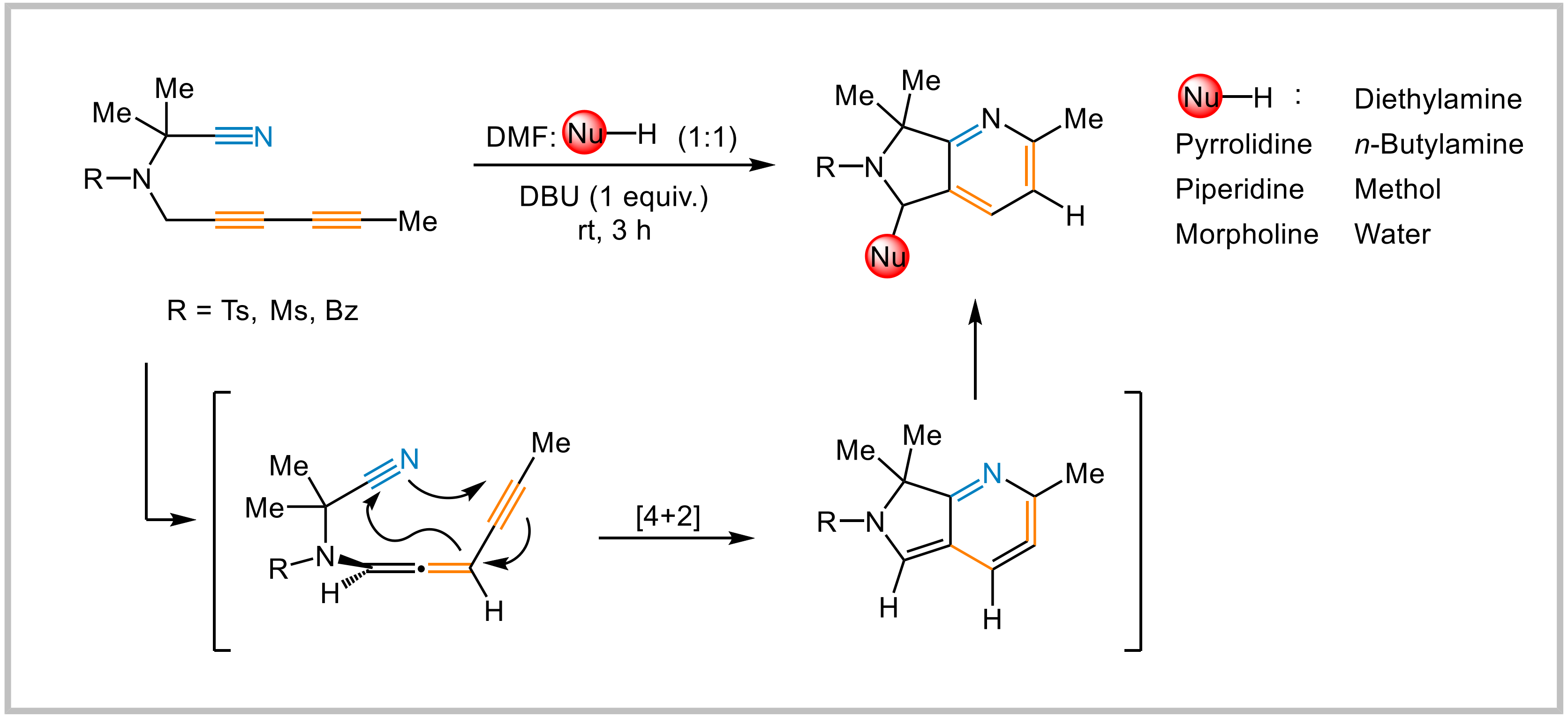
Lei, A. *et al. Nat. Commun.* **2018**, *9,* 1225.

Photochemical Initiated



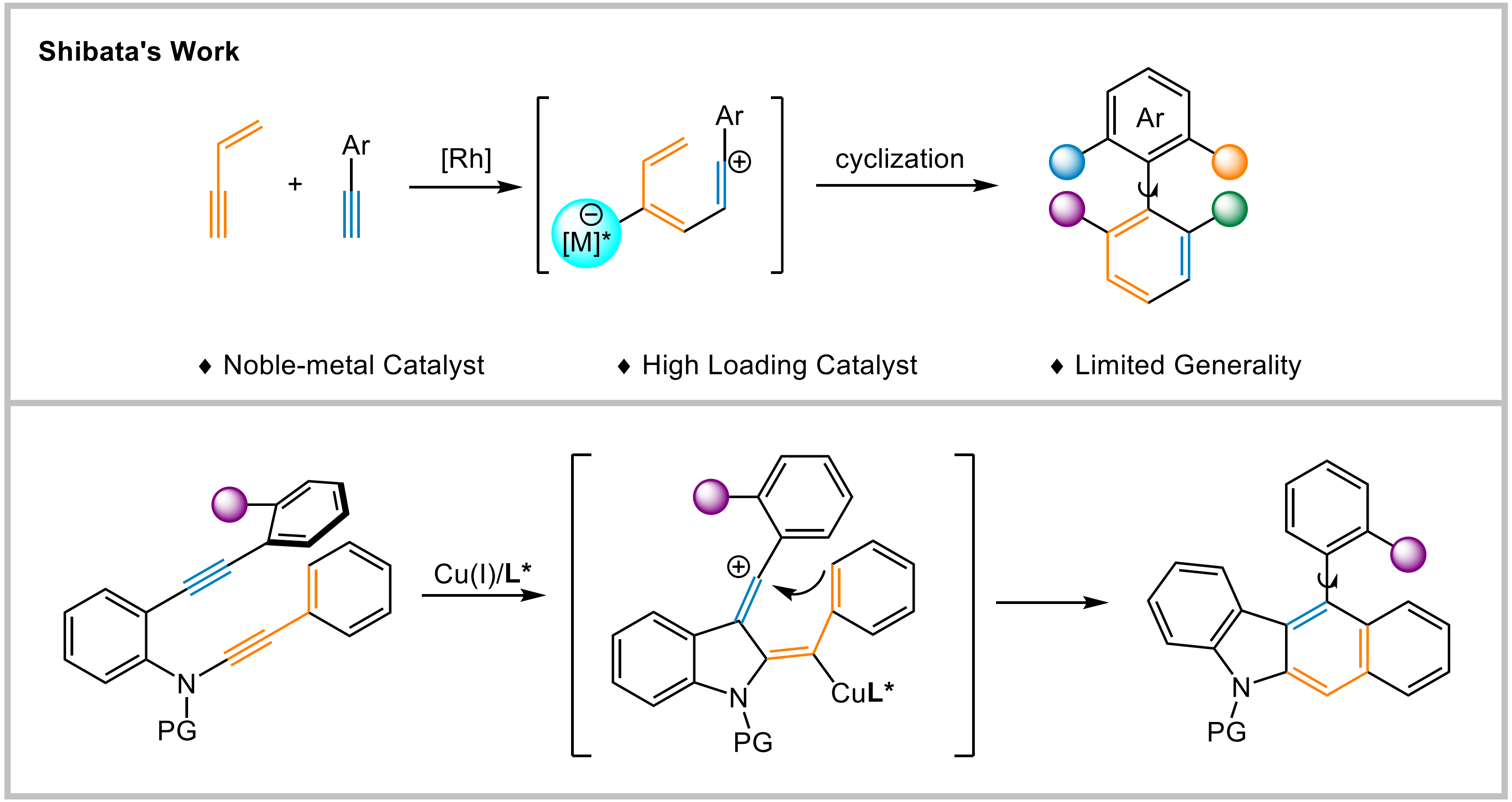
Vaitla, J. *et al. JACS Au* **2024**, *4*, 1073.

Base Promoted

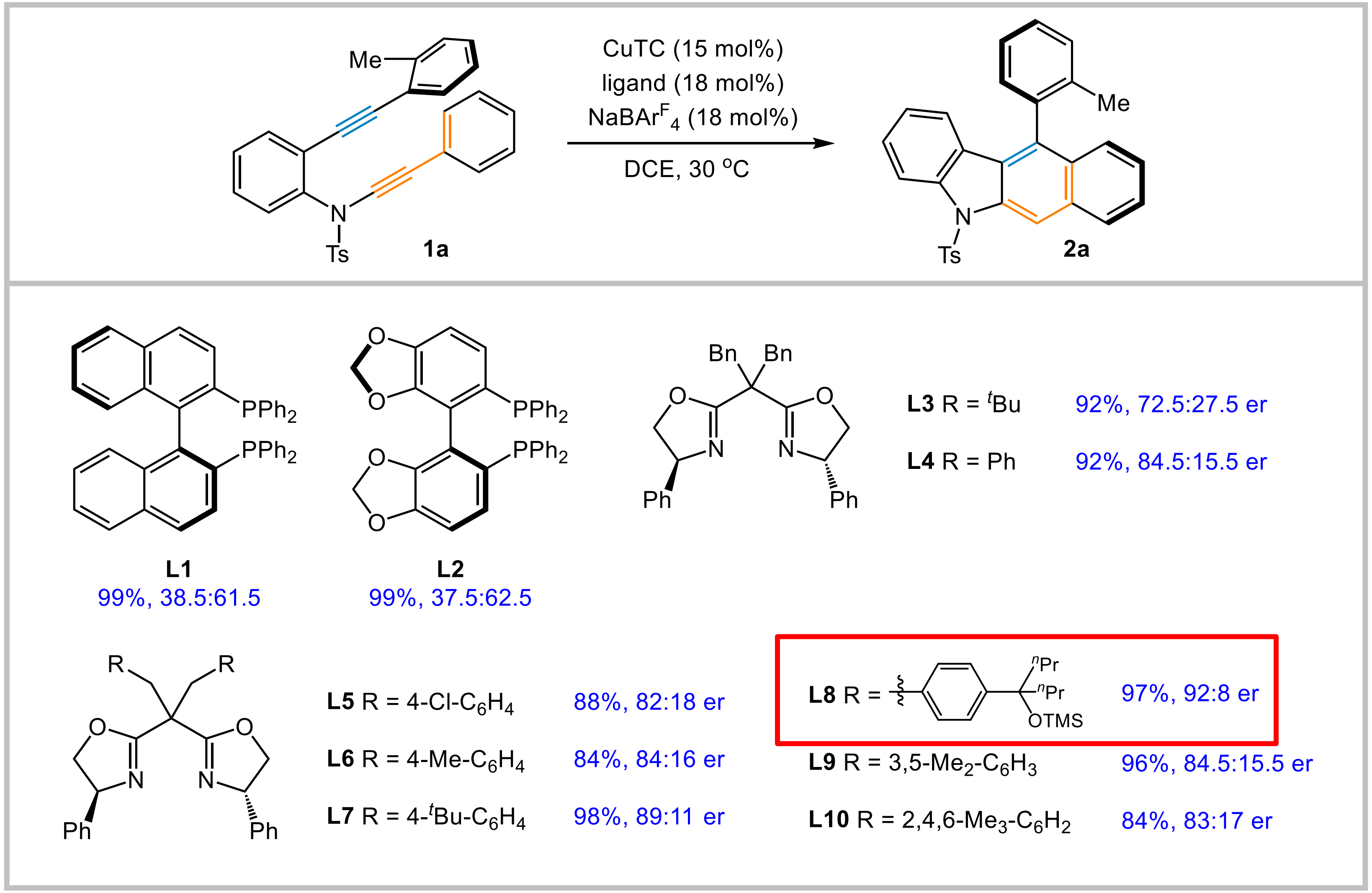


Hoye, T. R. *et al. Nature* **2016**, *532,* 484.

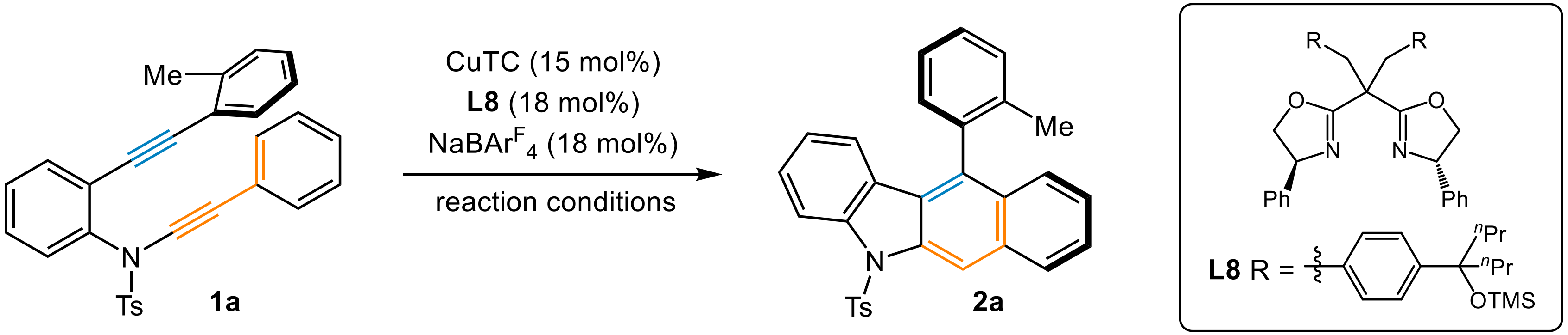
Prospect


Shibata's Work
Ar
[Rh]
Ar
[M]*
cyclization
Ar
♦ Noble-metal Catalyst
♦ High Loading Catalyst
♦ Limited Generality
N
PG
Cu(I)/L*
N
PG
CuL*
N
PG

Optimization of the Reaction Conditions

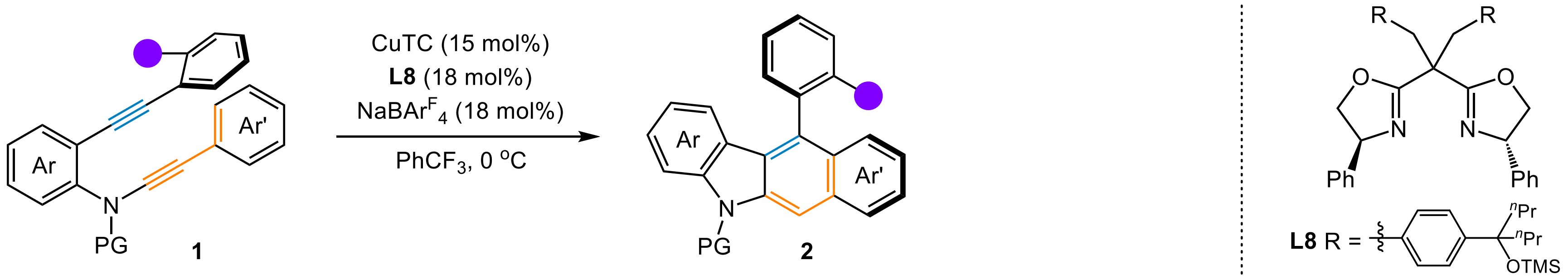


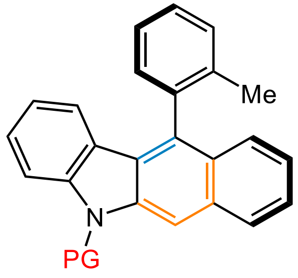
Optimization of the Reaction Conditions



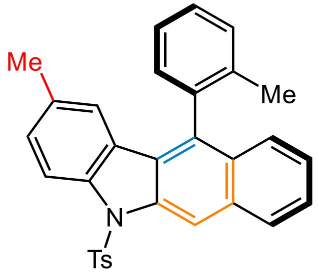
Entry	Reaction Conditions	Yield [%]	Er
1	DCE, 30 ºC, 4 h	97	92:8
2	DCM, 30 ºC, 3 h	98	93.5:6.5
3	THF, 30 ºC, 30 h	17	50.5:49.5
4	Toluene, 30 ºC, 3 h	97	94:6
5	$PhCF_3$, 30 ºC, 2 h	99	94.5:5.5
6	$PhCF_3$, 0 ºC, 90 h	99	96:4

Reaction Scope

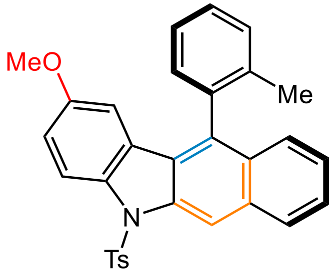




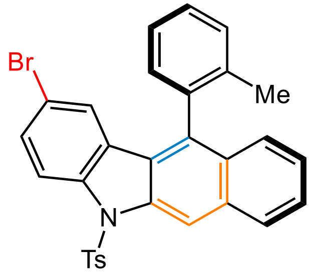
2a, PG = Ts, 99%, 96:4 er (84 h)
2b, PG = Mbs, 98%, 96:4 er (96 h)
2c, PG = SO_2Ph, 98%, 96.5:3.5 er (96 h)
2d, PG = Bs, 96%, 96:4 er (120 h)
2e, PG = Ns, 85%, 94.5:5.5 er (120 h)
2f, PG = Ms, 52%, 96:4 er (144 h)



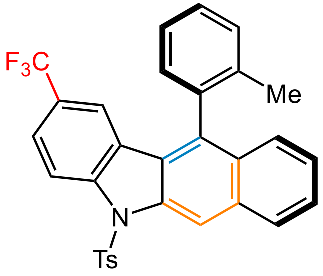
2g, 99%, 96.5:3.5 er (136 h)



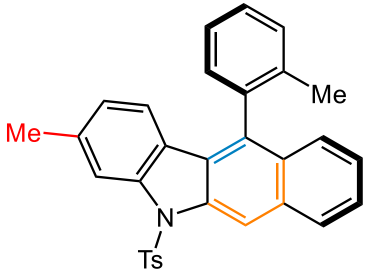
2h, 88%, 96:4 er (138 h)



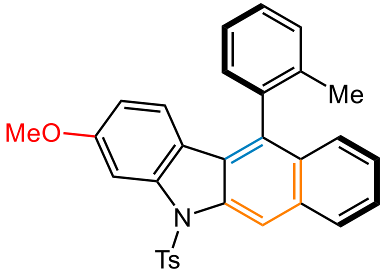
2i, 99%, 97.5:2.5 er (95 h)



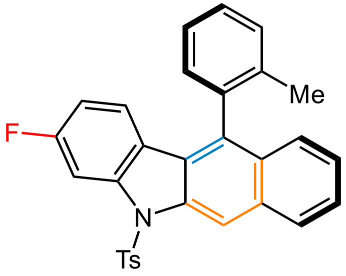
2l, 90%, 95:5 er (90 h)



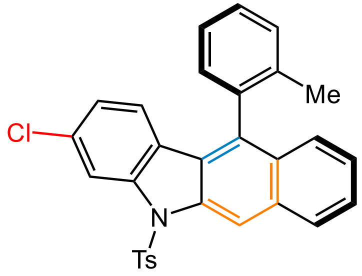
2m, 96%, 96:4 er (108 h)



2n, 92%, 96:4 er (131 h)

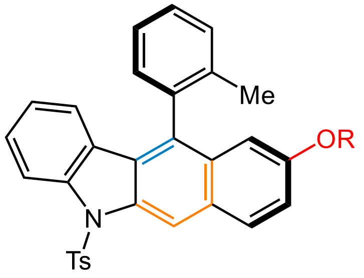


2o, 99%, 95.5:4.5 er (108 h)

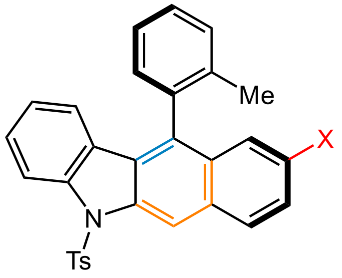


2p, 96%, 95:5 er (123 h)

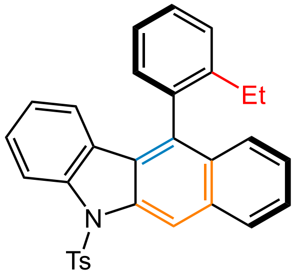
Reaction Scope



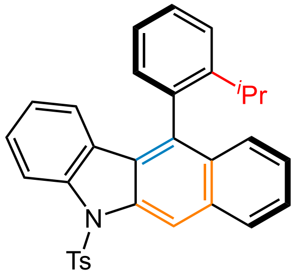
2q, R = Me, 82%, 92:8 er (57 h)
2r, R = TBS, 75%, 92.5:7.5 er (74 h)
2s, R = Tf, 93%, 99:1 er (42 h)



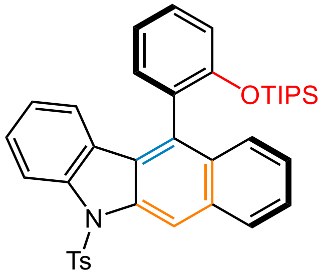
2t, R = F, 97%, 97.5:2.5 er (42 h)
2u, R = Cl, 99%, 97.5:2.5 er (69 h)
2v, R = Br, 96%, 97:3 er (33 h)



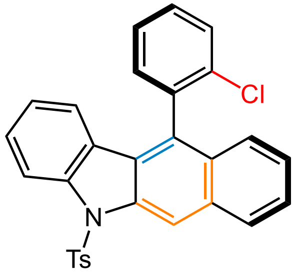
2w, 93%, 96:4 er (90 h)



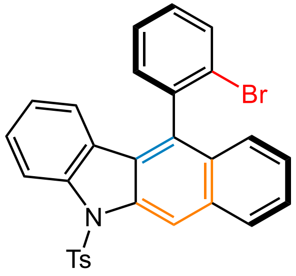
2x, 94%, 96:4 er (108 h)



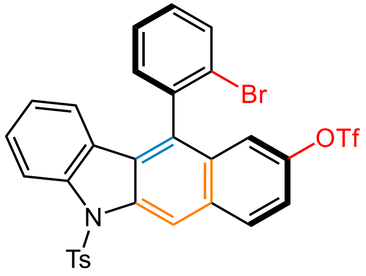
2y, 91%, 96:4 er (89 h)



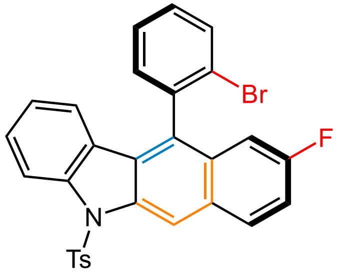
2z, 95%, 95:5 er (108 h)



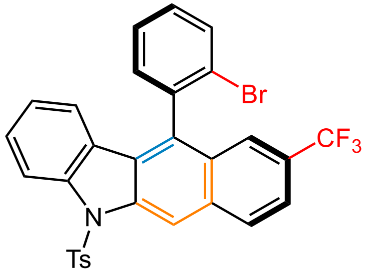
2aa, 96%, 95:5 er (144 h)



2ab, 82%, 97:3 er (90 h)

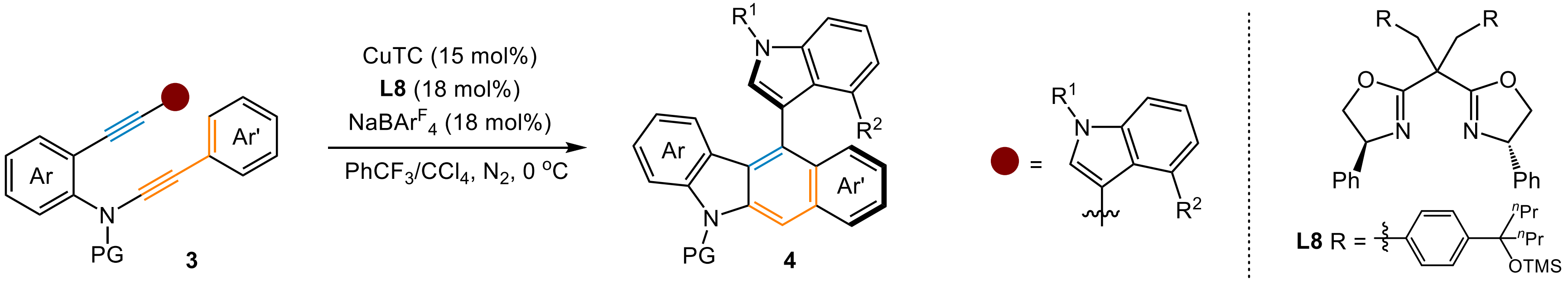


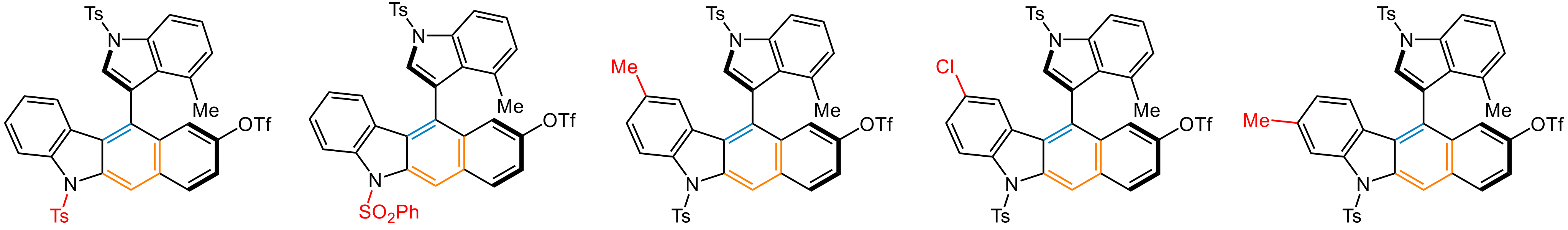
2ac, 96%, 97:3 er (95 h)



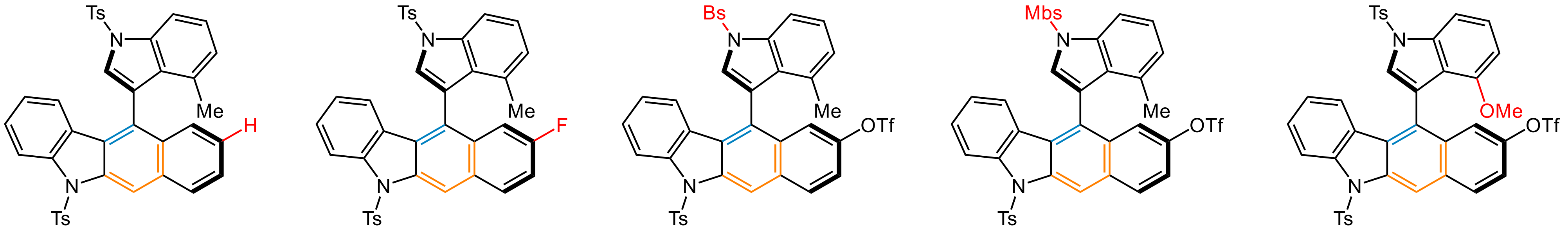
2ad, 98%, 98:2 er (120 h)

Reaction Scope



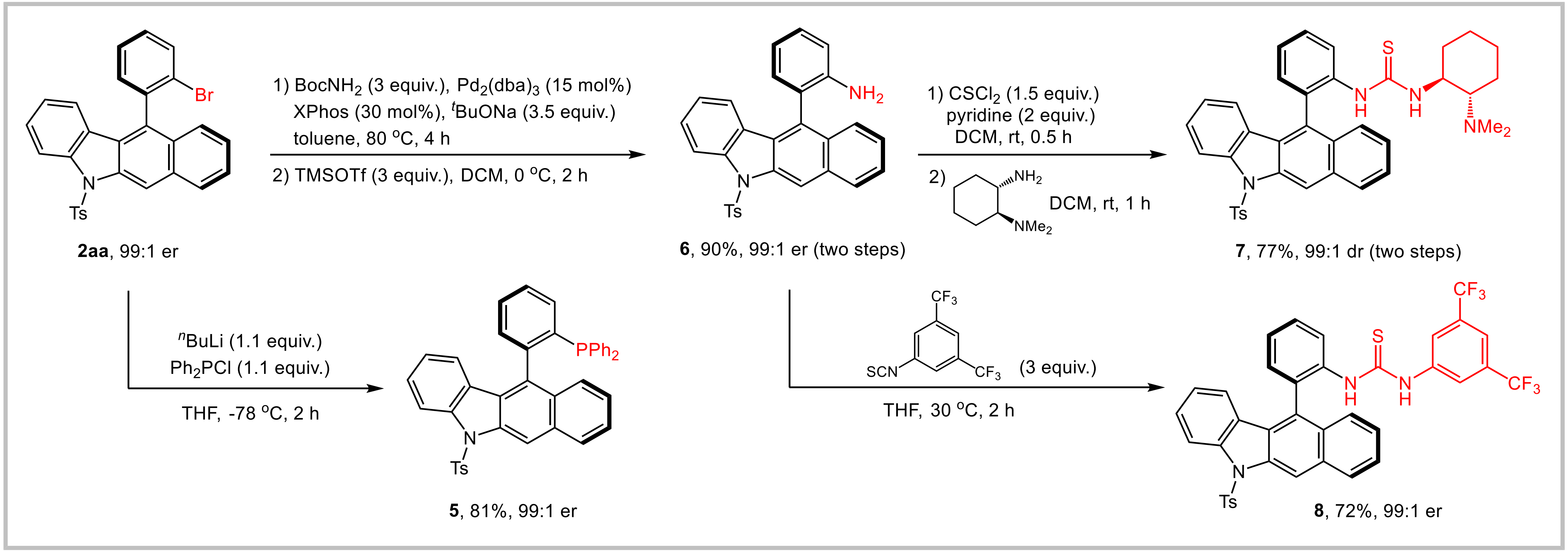


4a, 99%, 95:5 er (48 h) | **4b**, 98%, 93:7 er (39 h) | **4c**, 98%, 95:5 er (41 h) | **4d**, 98%, 96:4 er (44 h) | **4e**, 97%, 95:5 er (43 h)

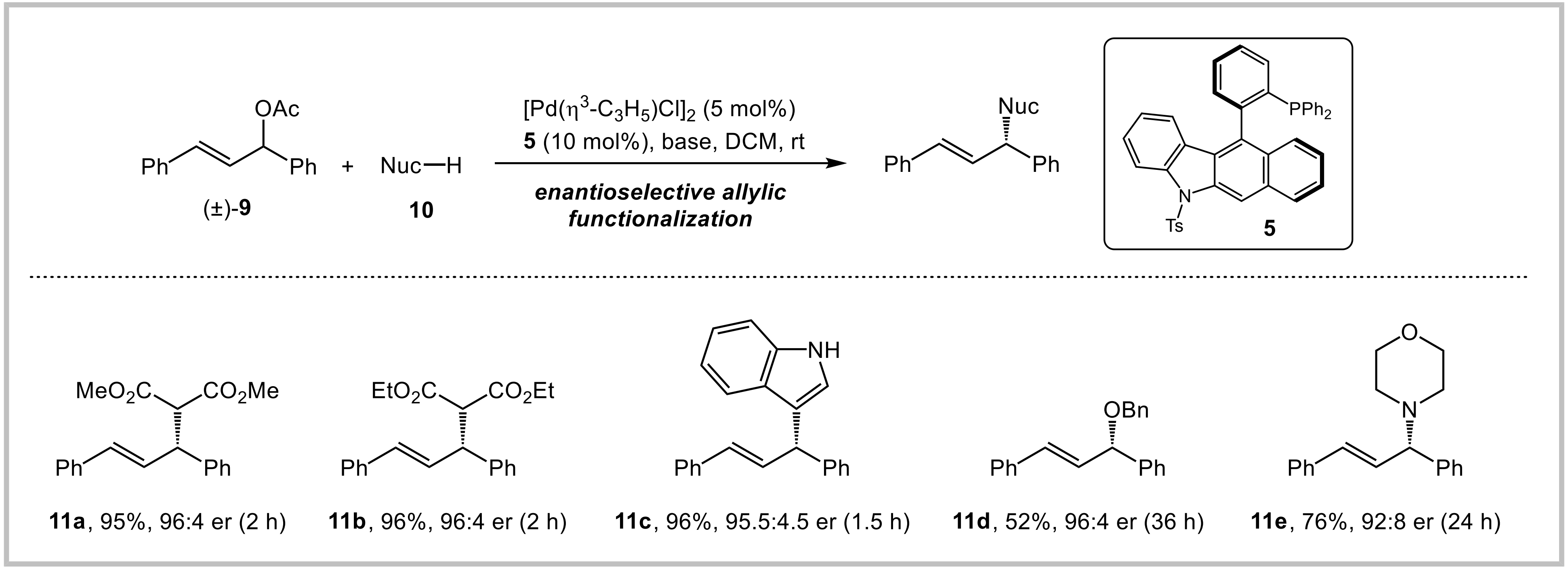


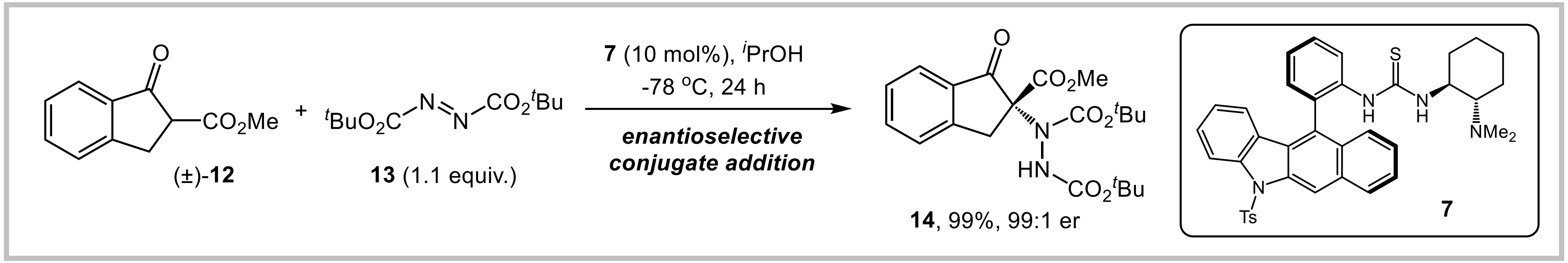
4f, 95%, 89:11 er (44 h) | **4g**, 95%, 93.5:6.5 er (47 h) | **4h**, 97%, 95:5 er (54 h) | **4l**, 98%, 95:5 er (29 h) | **4m**, 95%, 91:9 er (42 h, 15 °C)

Synthesis of Chiral Ligand and Organocatalyst

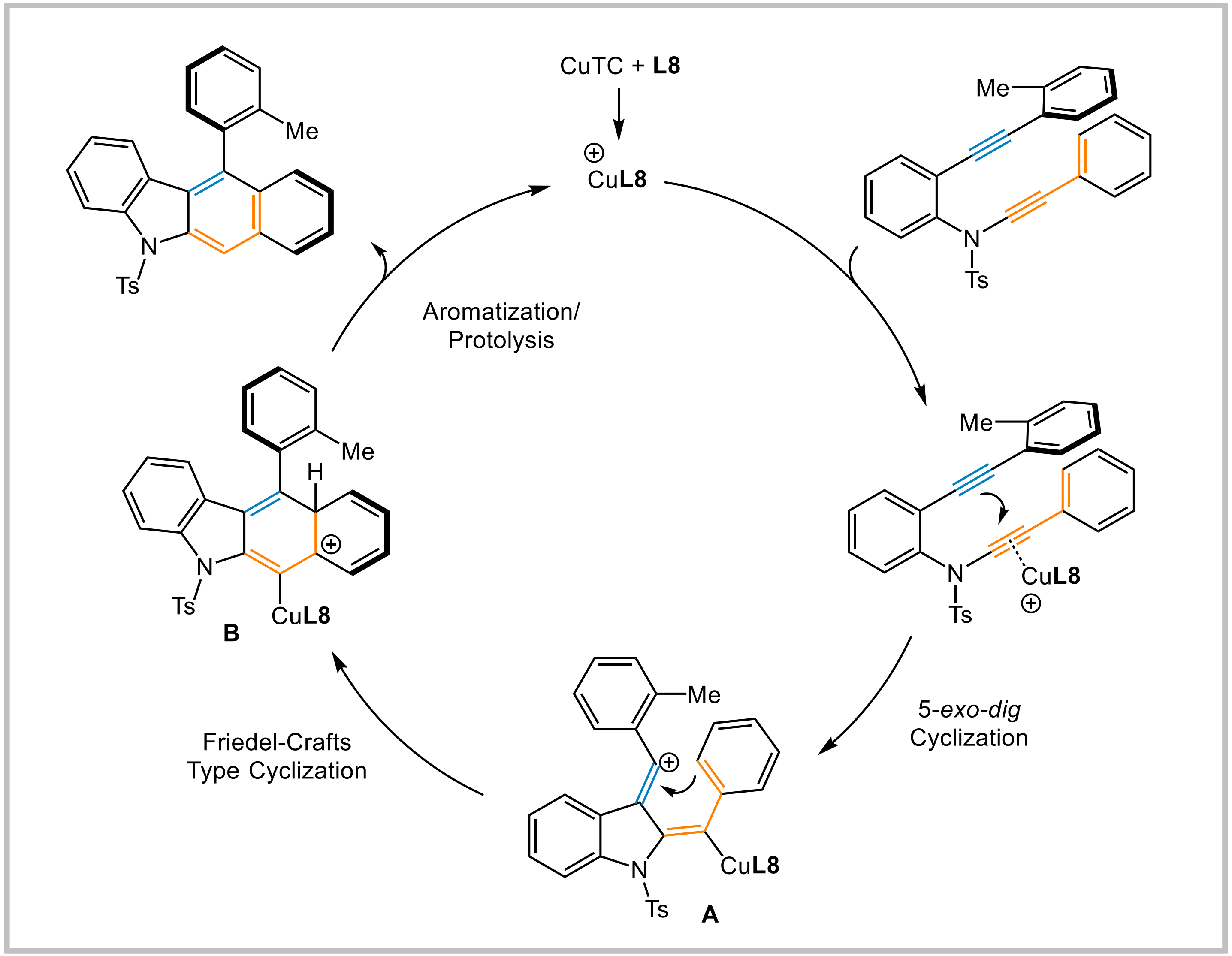


Application in Asymmetric Catalysis



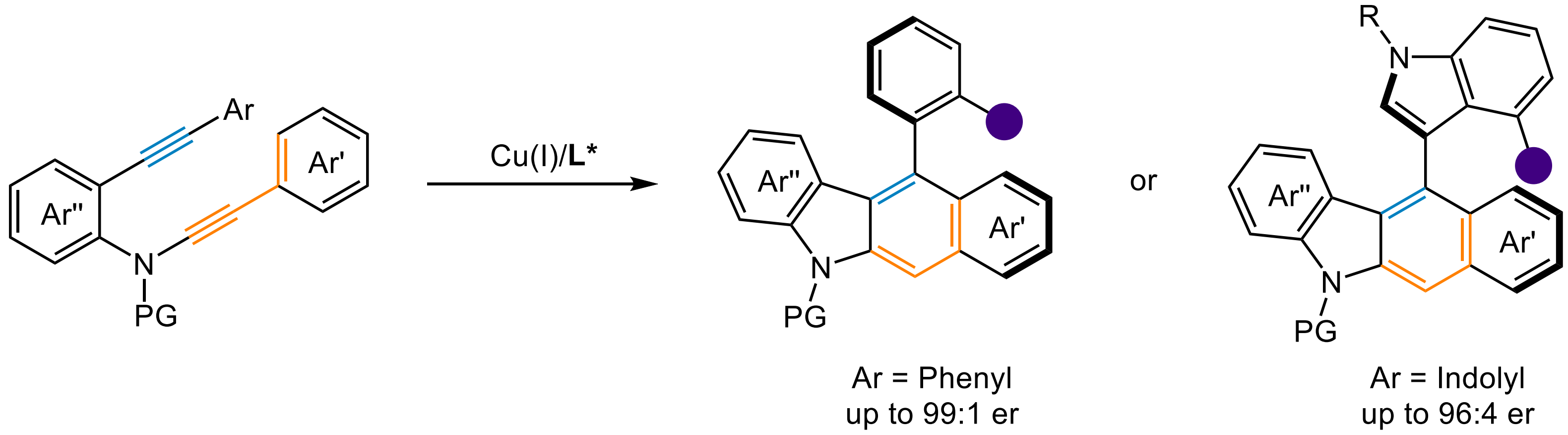


Plausible Reaction Mechanism



Summary

Copper Catalyzed Enantioselective DDA Reaction *via* Diyne Cyclization



- Enantioselective Dehydro-Diels-Alder Reaction;
- Non-noble Metal Catalysis under Mild Conditions;
- Effective Enantiocontrol of Vinyl Cations.;
- Further Derivatizations Enabled Synthesis of Ligand and Catalysts.

Chen, H.-H.; Chen, Y.-B.; Gao, J.-Z.; Ye, L.-W.; Zhou, B.* *Angew. Chem. Int. Ed.* **2024**, *63*, e202411709.

Writing Strategy

➢The First Paragraph

DDA反应的介绍

↓

DDA反应目前的发展和挑战

♣ The dehydro-Diels-Alder (DDA) reaction refers to the special Diels-Alder reaction involving at least one alkyne moiety, which has been developed as an important approach towards aromatic compounds. Compared with traditional D-A reaction, the incorporation of triple bonds enables higher variability for this transformation, such as the reactions of 1,3-dienes with alkynes, 1,3-enynes with alkenes or alkynes, 1,3-diynes with alkenes or alkynes, as well as hetero-DDA reaction.

♣ During the past decades, thermal, base-promoted, transition metal-catalyzed, photochemically initiated and microwave-assisted protocols have been established to facilitate the DDA reaction. However, the enantio-selective DDA reaction still remains challenging, possibly due to the competitive thermal reaction. In 2018, the only catalytic asymmetric example of DDA reaction was reported by Shibata and co-workers. By using 20 mol% of Rh(I) catalyst and chiral bisphosphine ligand, axially chiral bis(benzocarbazole) derivatives were synthesized through the atroposelective reaction of alkynyl sulfides

Writing Strategy

➢The Last Paragraph

总结工作
工作的特点

↓

介绍工作的意义
及展望

- ♣ In conclusion, a copper-catalyzed enantioselective DDA reaction has been disclosed via the effective enantiocontrol of vinyl cations, leading to the atom-economical construction of axially chiral phenyl and indolyl carbazoles. This reaction represents the first example of non-noble metalcatalyzed enantioselective DDA reaction, as well as a breakthrough in enantioselective 1,6-diyne cyclization. Importantly, the scala-bility and further derivatizations enabled the synthesis of new axially chiral phosphine ligand and organocatalyst, which have been proven to be applicable in asymmetric catalysis.
- ♣ We believe these findings will expand the repertoire of enantioselective D-A-type reactions and stimulate further explorations into axially chiral functional molecules. Efforts to examine more chiral induction models to develop broadly useful asymmetric transformations of vinyl cations are ongoing in our laboratory.

Representative Examples

- The enantiocontrol for the transformations of vinyl cations is difficult because of their high reactivities and almost barrierless conversions. Consequently, it is **pivotal** to establish an effective chiral induction model. (adj. 核心的;关键性的)

- To enhance the synthetic utility, the tolerance of various functional groups and their transformations into chiral catalysts, ligands, and other functional molecules are **requisite**. (adj./n. 必需的/必需的事物)

Acknowledgement

Thanks
for your attention