Asymmetric Cu-Catalyzed C(sp^3)-C(sp) Coupling by Liu's group

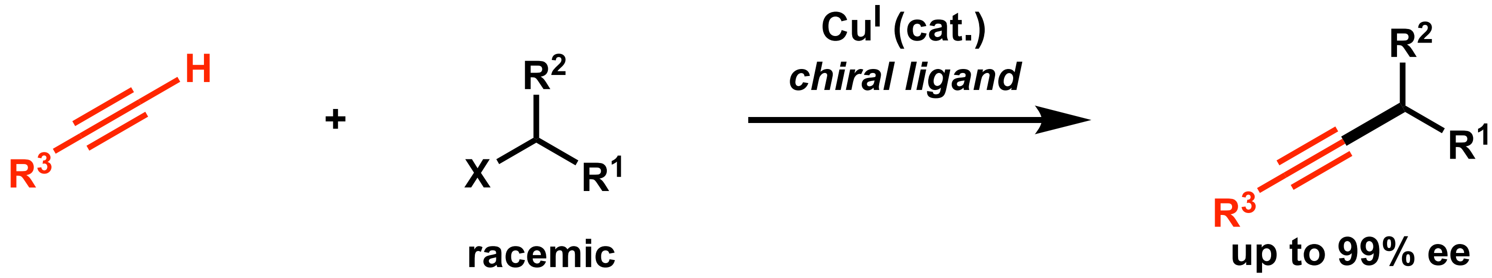
2020.05.20

Toshiya Nagai

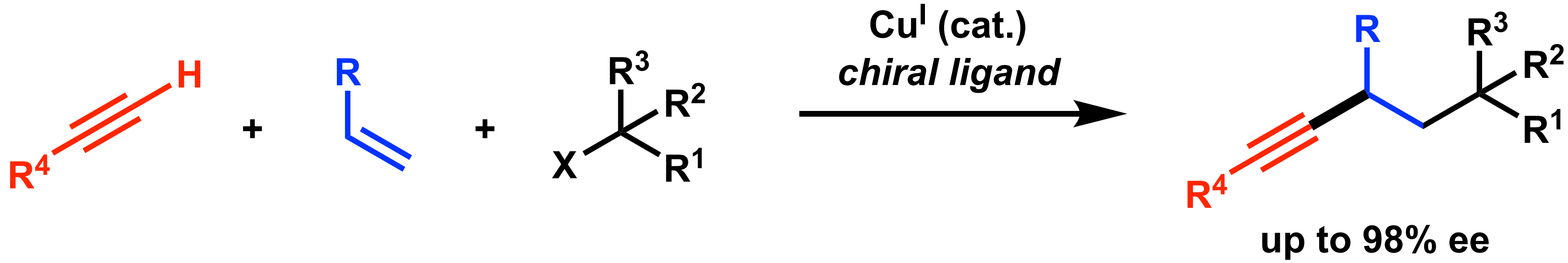
Contents

1. **Introduction**

2. **Asymmetric *Cu*-Catalyzed C(*sp*^{3})-C(*sp*) Coupling** [1)]



3. **Asymmetric *Cu*-Catalyzed Radical 1,2-Carboalkynylation of Alkenes** [2)]



1) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.
2) Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

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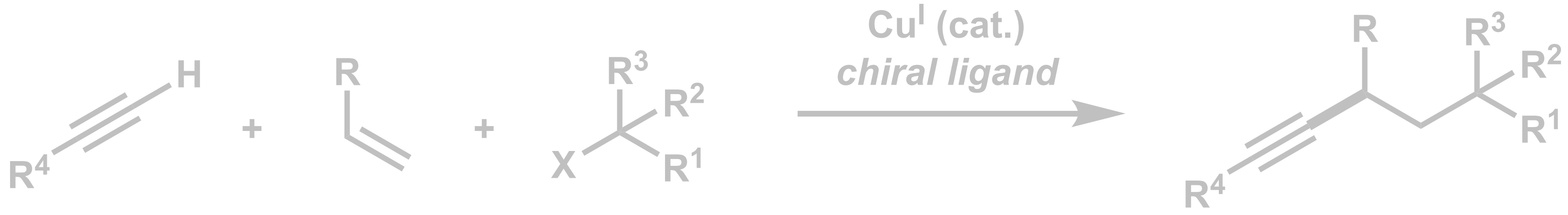
3. Asymmetric *Cu*-Catalyzed Radical 1,2-Carboalkynylation of Alkenes [2)]



1) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.
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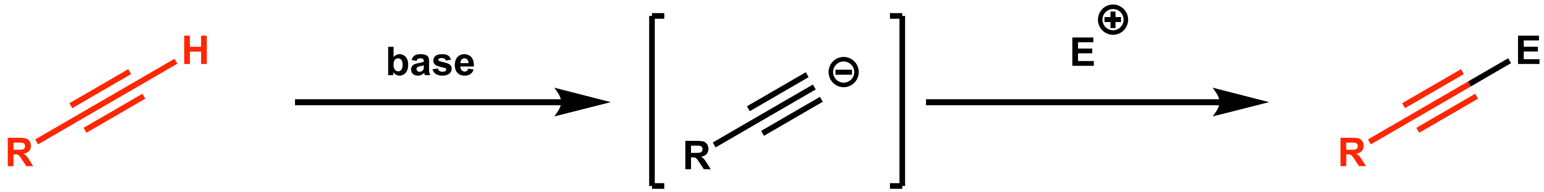
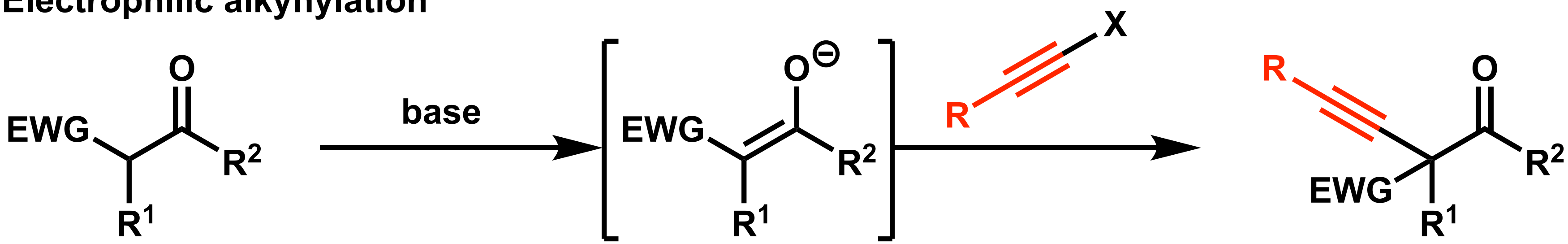
Alkynylations-1

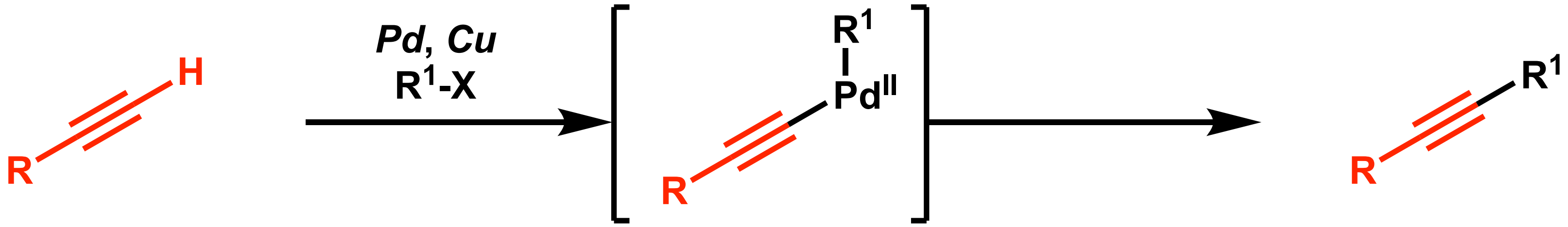
1. Nucleophilic alkynylation



2. Electrophilic alkynylation

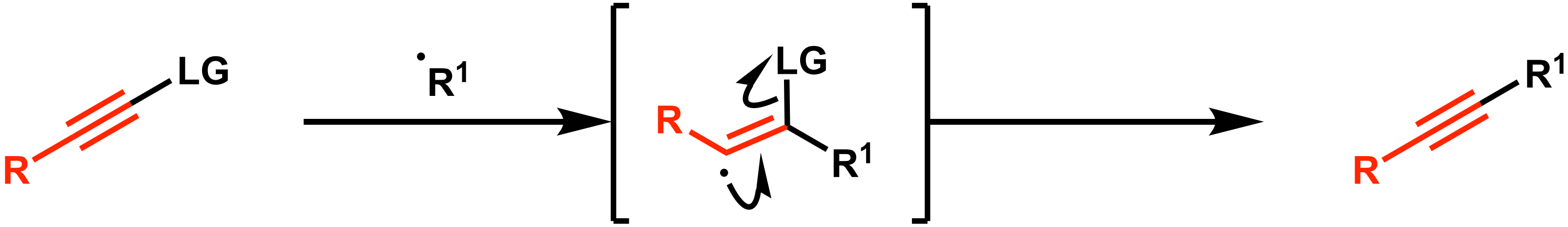


3. Sonogashira-type cross-coupling

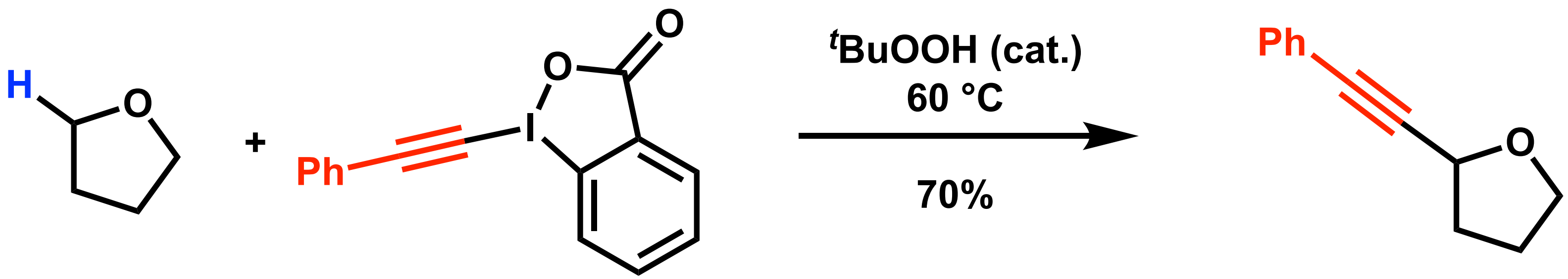


Alkynylation-2

4. Radical alkynylation



1)



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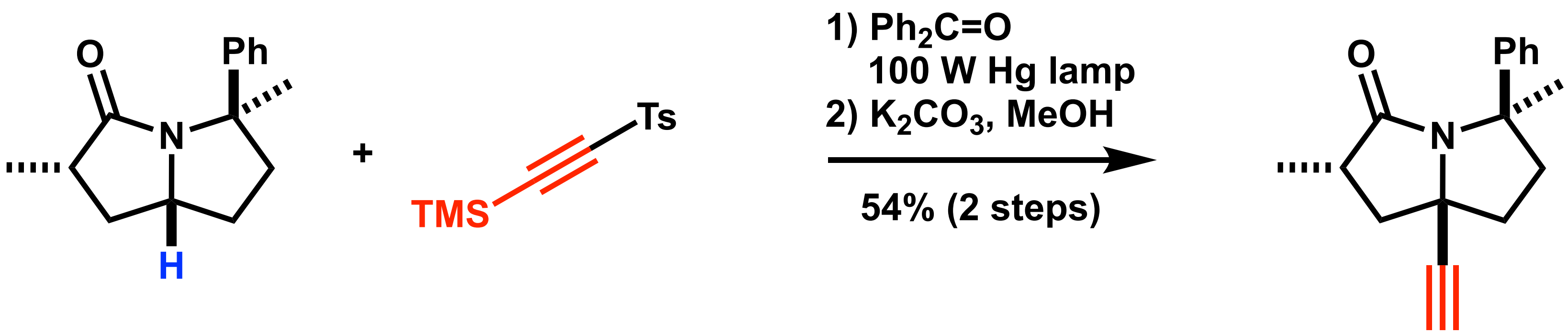
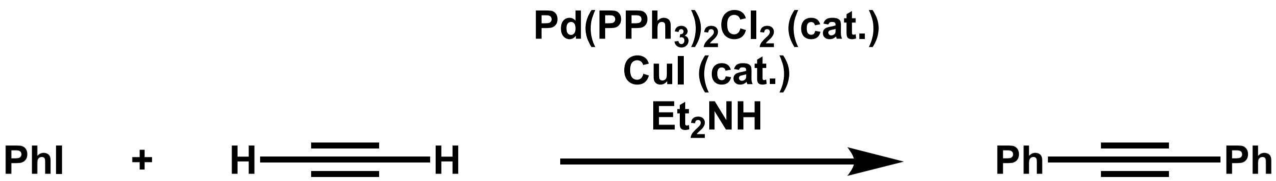
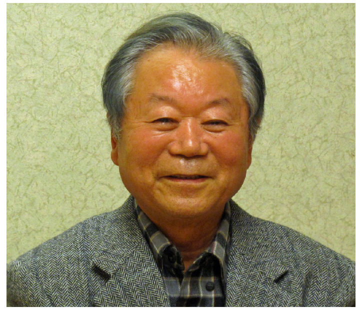


1) Zhang, R.-Y.; Xi, L.-Y.; Zhang, L.; Liang, S.; Chen, S.-Y.; Yu, X.-Q. *RSC Adv.* **2014**, *4*, 54349.
2) a) Yoshioka, S.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2015**, *17*, 90.
b) Hoshikawa, T.; Kamijo, S.; Inoue, M. *Org. Biomol. Chem.* **2013**, *11*, 164.

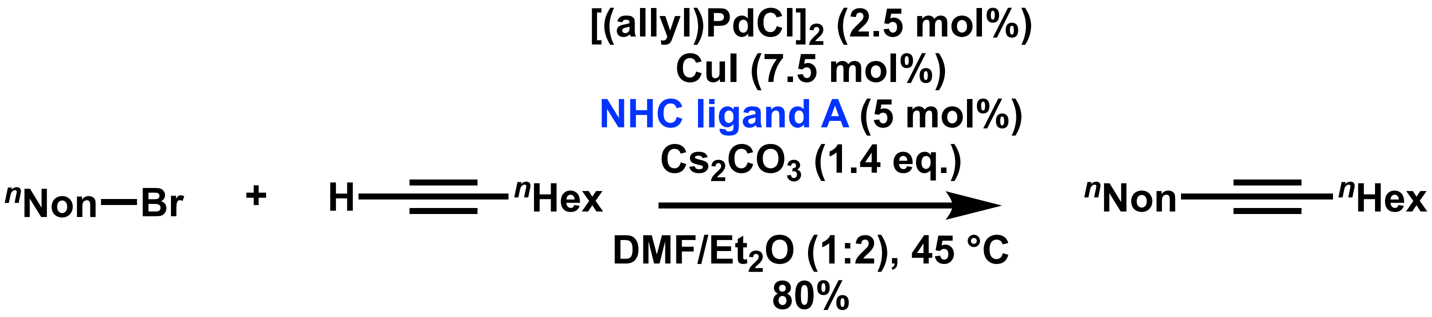
Sonogashira-type Cross-coupling

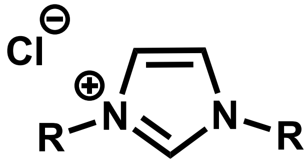
1) Original Sonogashira cross-coupling (*sp* + *sp*^{2})





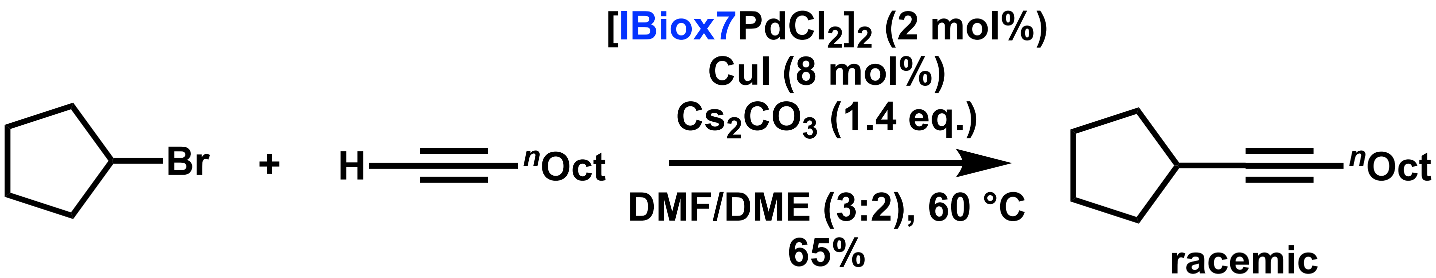
2) Cross-coupling of alkyne and primary alkyl halide (*sp* + *sp*^{3})

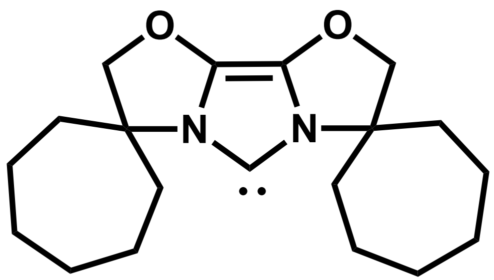




NHC ligand A
(R = 1-adamantyl)

3) Cross-coupling of alkyne and secondary alkyl halide (*sp* + *sp*^{3})





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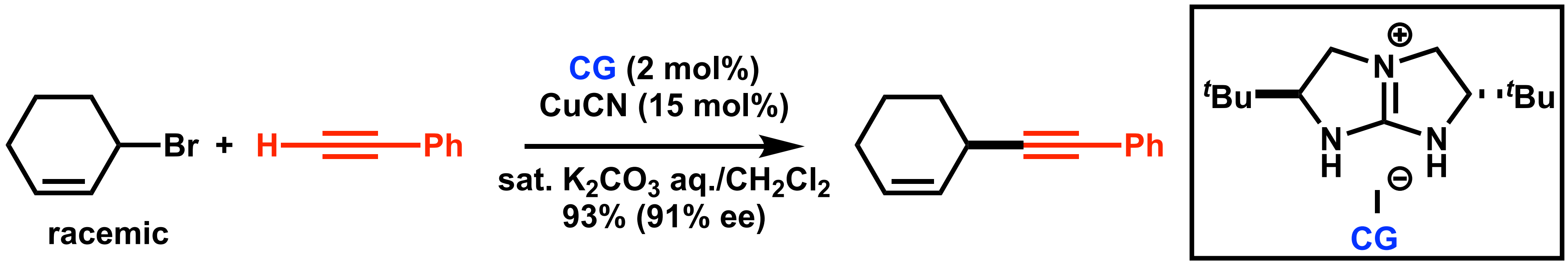
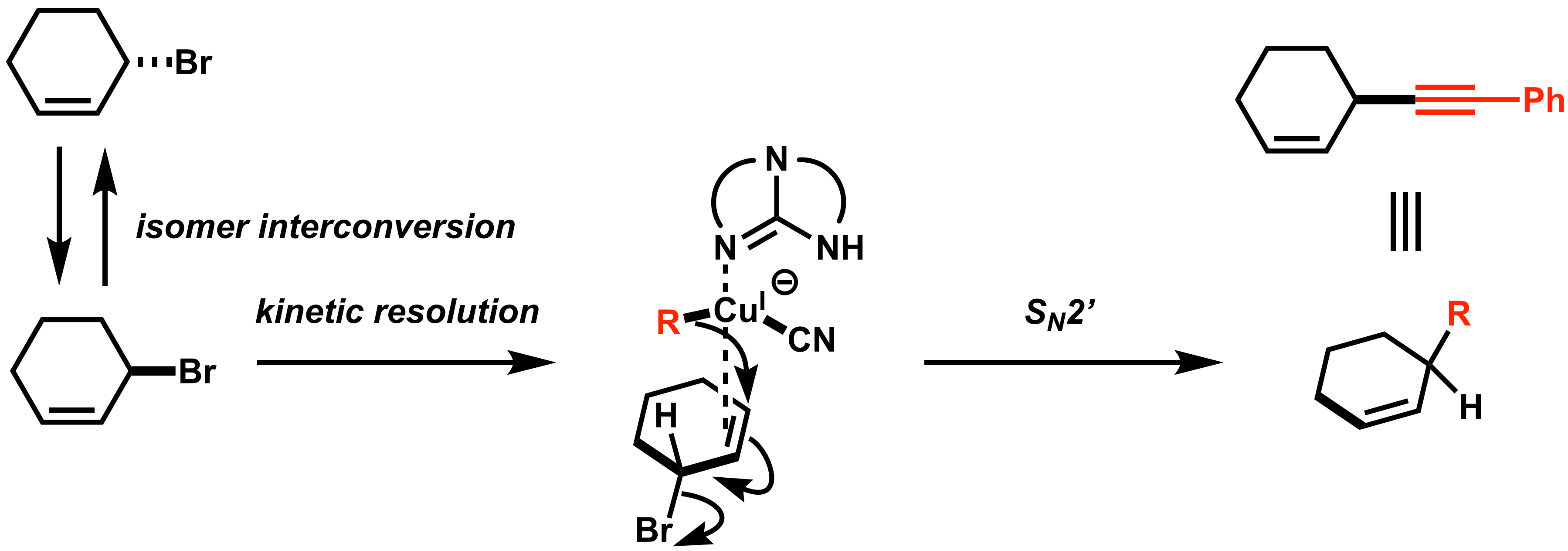
1) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. 2) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. 3) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925.

Asymmetric *Cu*-Catalyzed S_N2' reaction by Tan's group



proposed reaction mechanism



1) Cui, X.-Y.; Ge, Y.; Tan, S. M.; Jiang, H.; Tan, D.; Lu, Y.; Lee, R.; Tan, C.-H. *J. Am. Chem. Soc.* **2018**, *140*, 8448.

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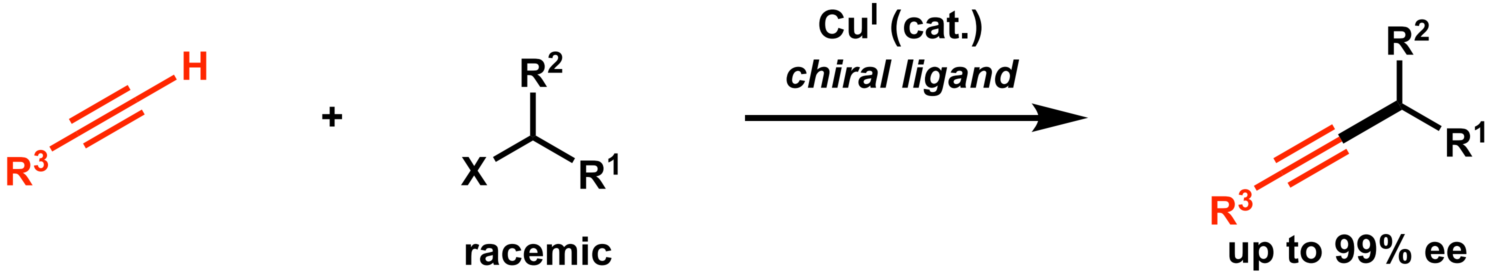

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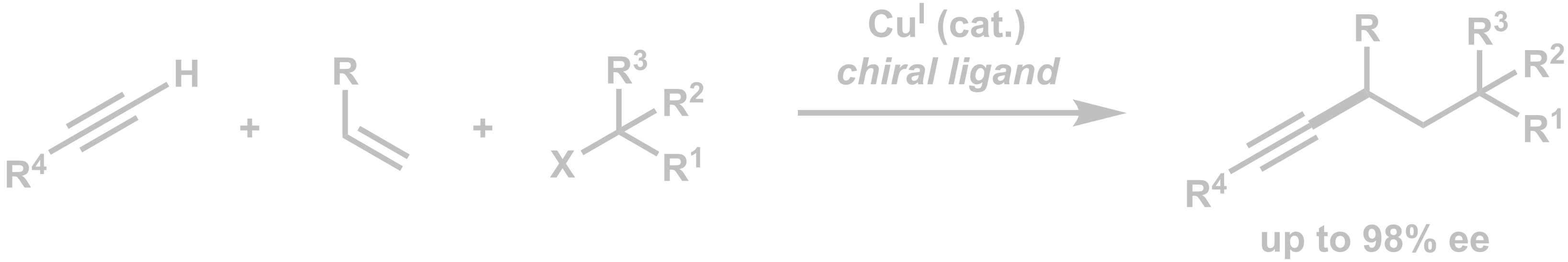

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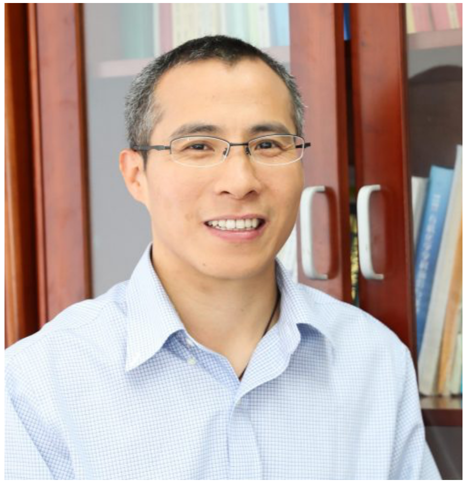
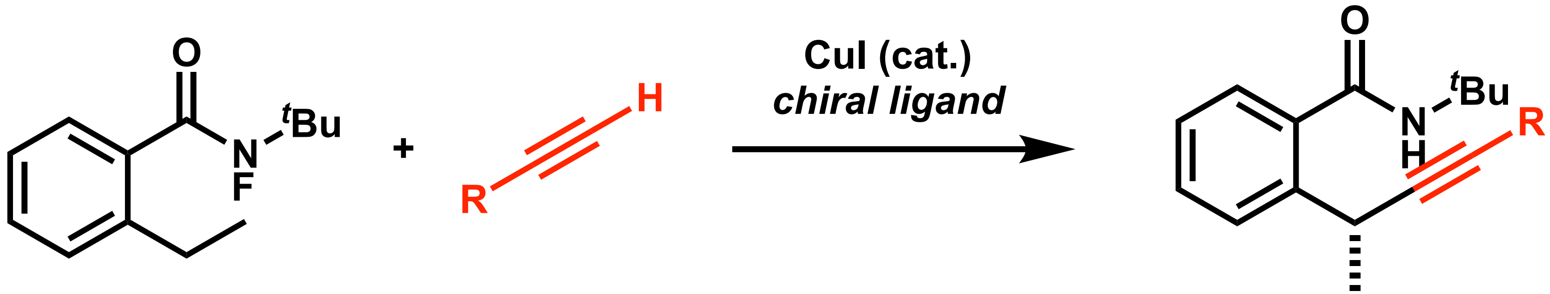
Prof. Xin-Yuan Liu



Career:
1997-2001 : B.S., Anhui Normal University
2001-2004 : M.S., Anhui Normal University (Prof. Shizheng Zhu) and Shanghai Institute of Organic Chemistry (Prof. Shaowu Wang)
2005-2010 : Ph D., The University of Hong Kong (Prof. Chi-Ming Che)
2010-2012 : Postdoc, the Scripps Research Institute (Prof. Carlos F. Barbas III) and The University of Hong Kong (Prof. Chi-Ming Che)
2012-2017 : Associate Professor, Southern University of Science and Technology
2018- : Full Professor, Southern University of Science and Technology

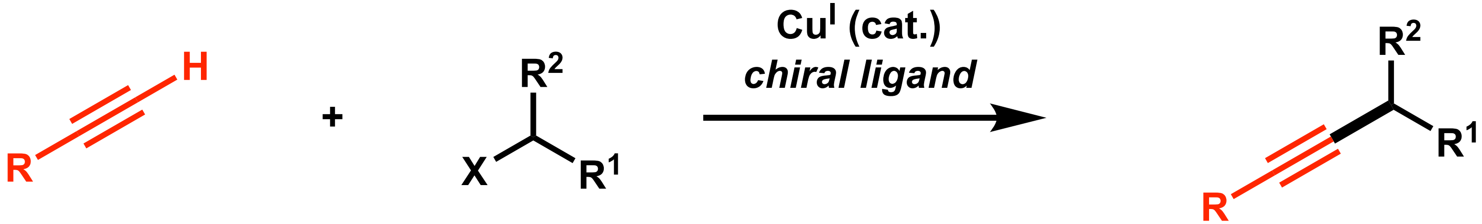
Research topic: Transition-metal catalysis, asymmetric catalysis, radical chemistry

1. Asymmetric C-H functionalization



up to 94% ee

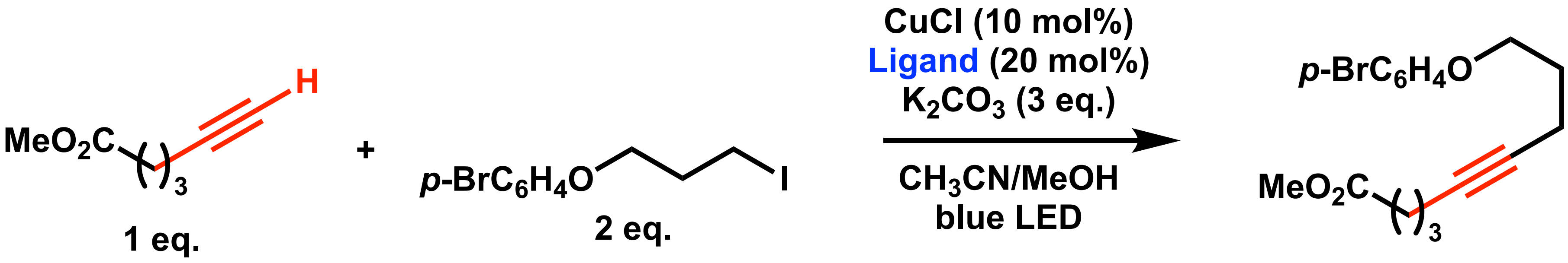
2. Enantioconvergent cross-coupling

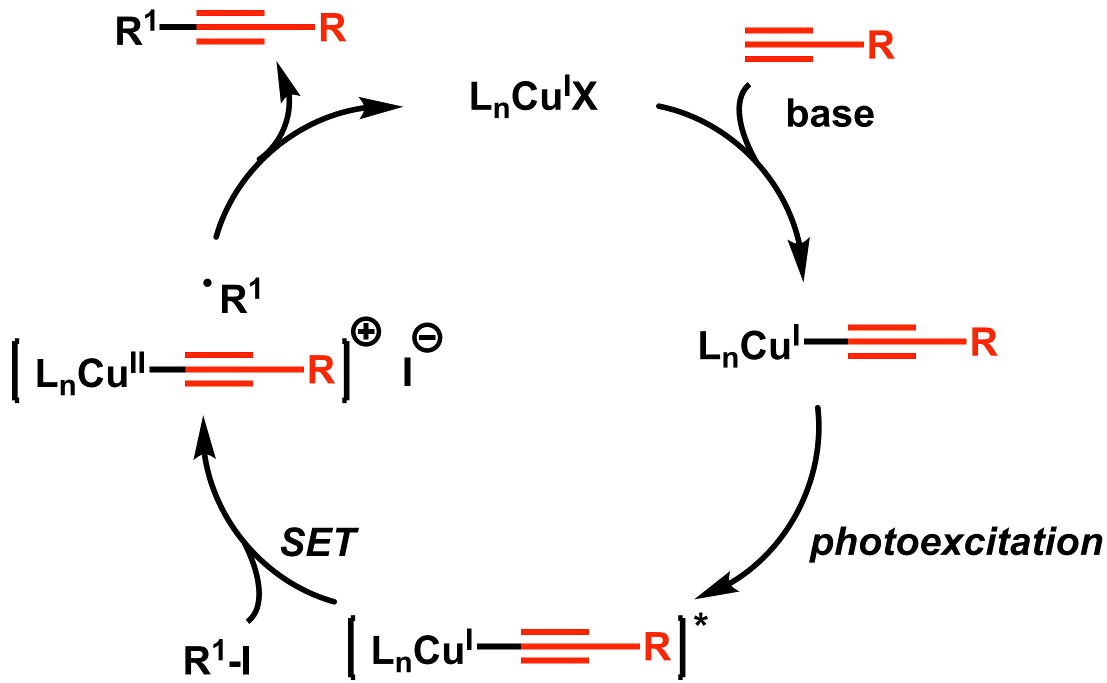


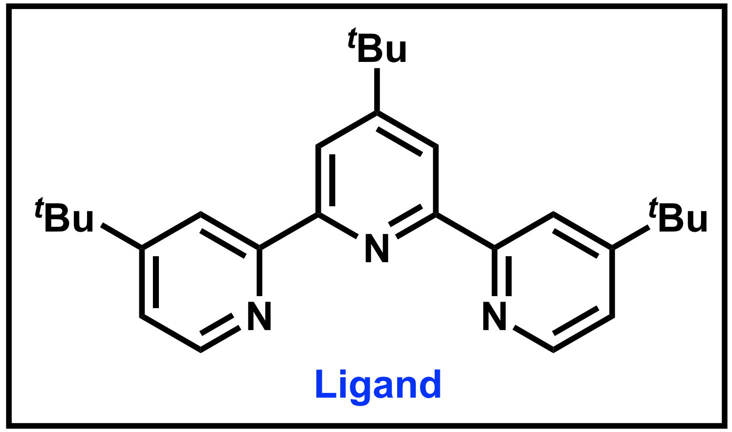
racemic

up to 99% ee

Photoinduced *Cu*-Catalyzed Coupling of Terminal Alkyne and Alkyl Iodide by Lalic's group



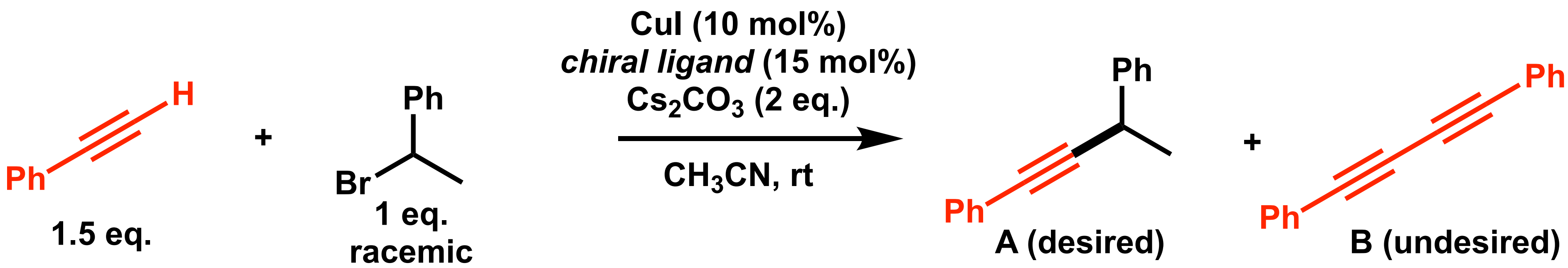


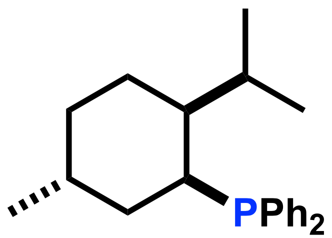


If the proper chiral ligand is used, the enantioselective radical addition would occur without photoirradiation, to realize the assymmetric cross-coupling??

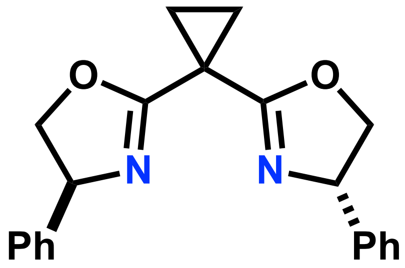
Hazra, A.; Lee, M. T.; Chiu, J. F.; Lalic, G. *Angew. Chem. Int. Ed.* **2018**, *57*, 5492.

Investigation of Chiral Legand-1

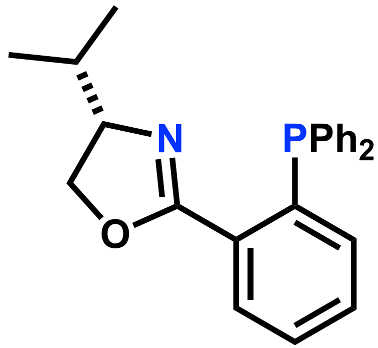




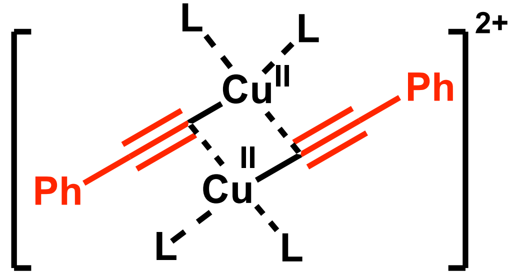
A: trace, B: 22%



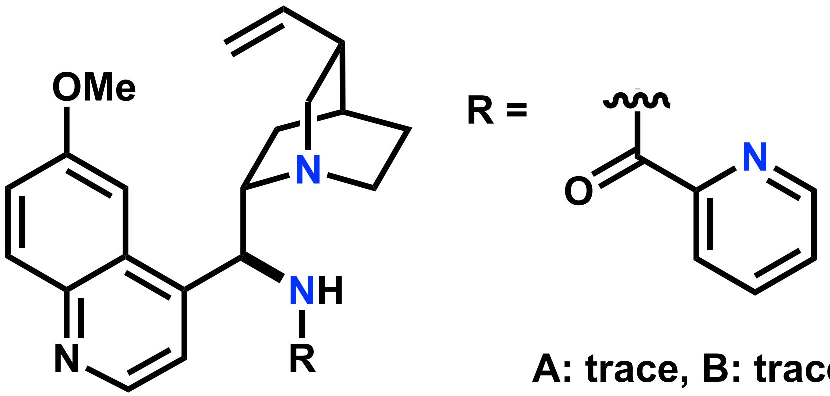
A: trace, B: 52%



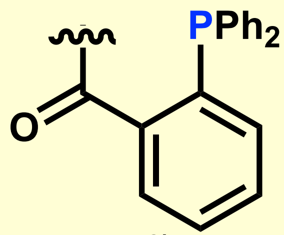
A: trace, B: 34%



intermediate of Glaser reaction



A: trace, B: trace



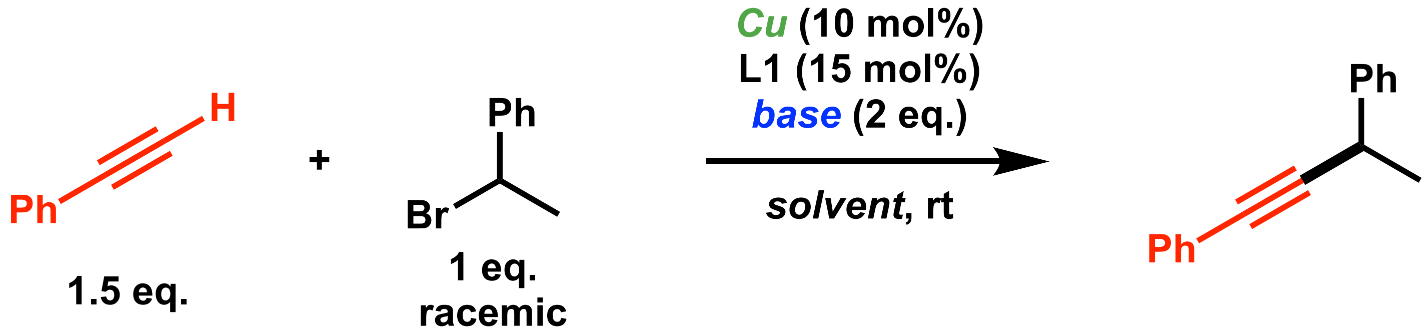
L1[2)]

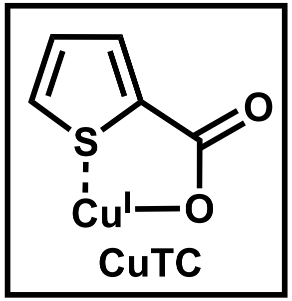
A: 81% (50% ee)

To inhibit Glaser reaction, the legand should be
- bulky
- multidentate

1) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.
2) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. *J. Am. Chem. Soc.* **2011**, *133*, 1710.

Optimization of Reaction Condition



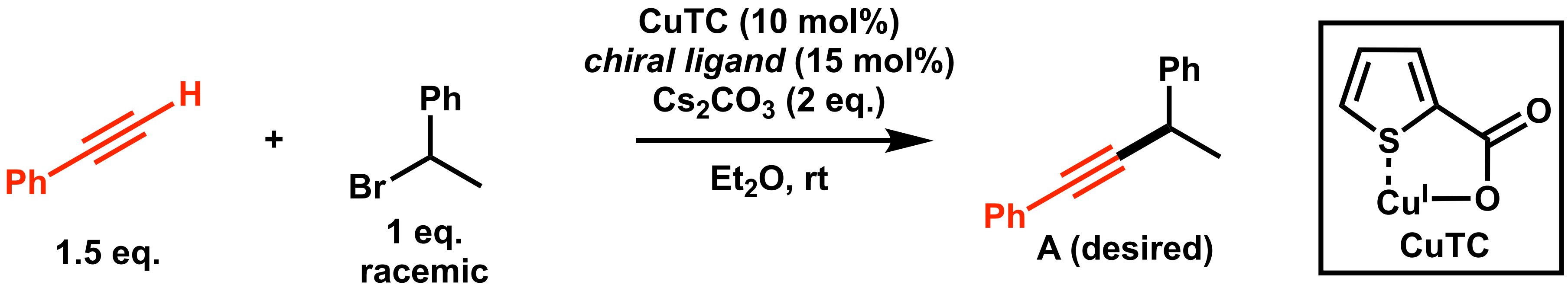


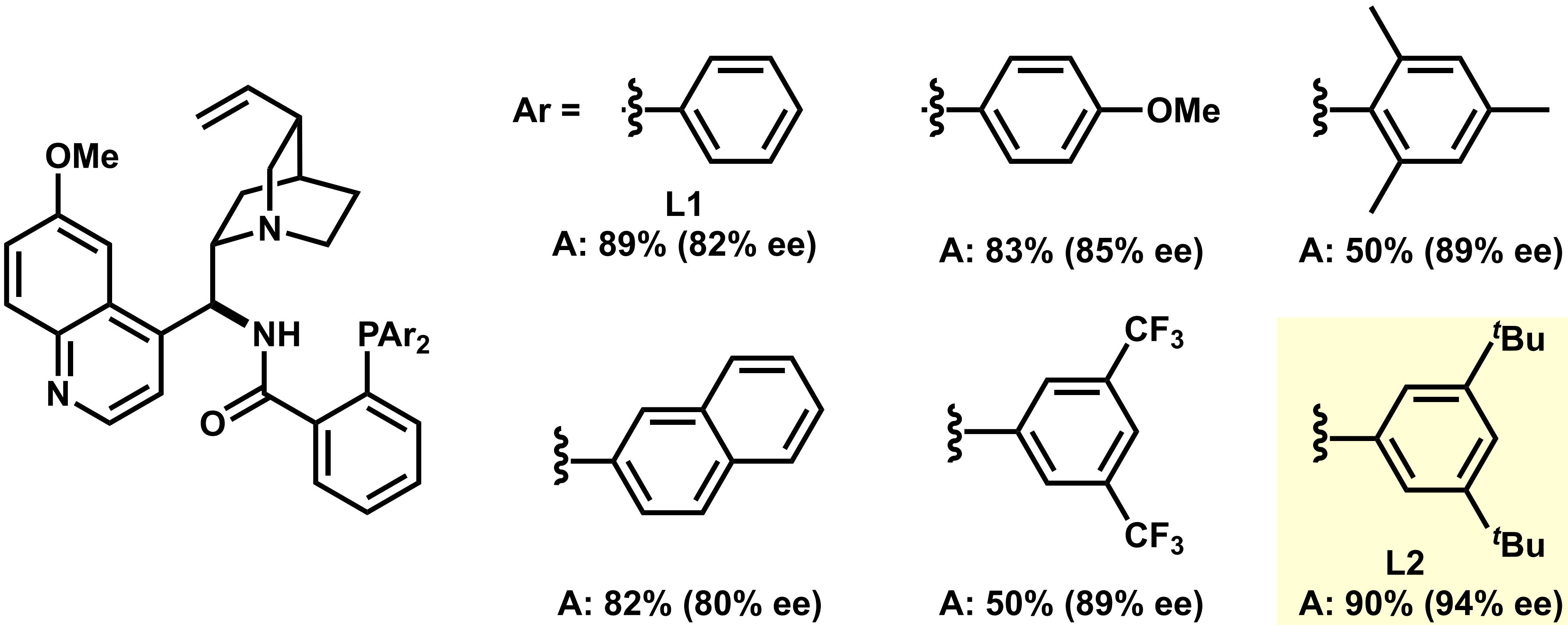
entry	*Cu*	*base*	*solvent*	yield (ee)
1	CuI	Cs_2CO_3	CH_3CN	81% (50% ee)
2	CuI	Cs_2CO_3	EtOAc	85% (72% ee)
3	CuI	Cs_2CO_3	*t*-BuOMe	83% (78% ee)
4	CuI	Cs_2CO_3	toluene	65% (79% ee)
5	CuI	Cs_2CO_3	THF	79% (73% ee)
6	CuI	Cs_2CO_3	MeOH	81% (53% ee)
7	CuI	Cs_2CO_3	Et_2O	87% (81% ee)

entry	*Cu*	*base*	*solvent*	yield (ee)
8	CuI	Cs_2CO_3	CH_2Cl_2	65% (61% ee)
9	CuI	Cs_2CO_3	DCE	52% (54% ee)
10	CuCl	Cs_2CO_3	Et_2O	83% (82% ee)
11	CuBr	Cs_2CO_3	Et_2O	84% (82% ee)
12	CuTC	Cs_2CO_3	Et_2O	89% (82% ee)
13	CuTC	K_3PO_4	Et_2O	88% (81% ee)
14	CuTC	NaOH	Et_2O	87% (81% ee)

Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.

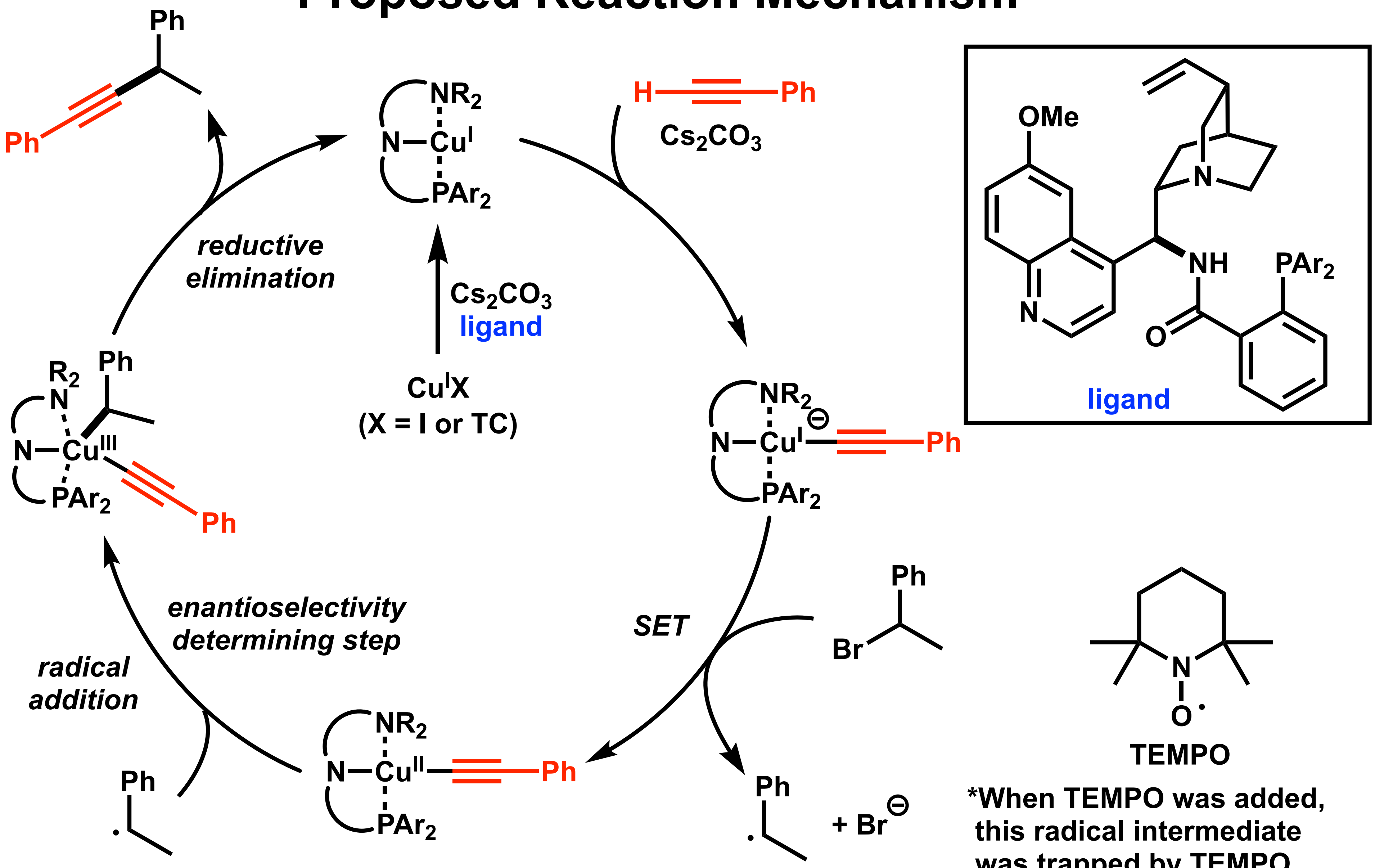
Investigation of Chiral Legand-2





Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.

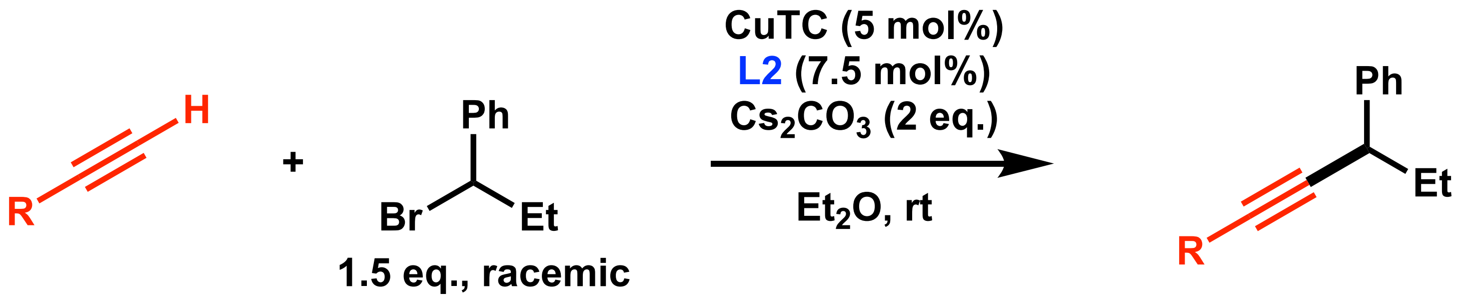
Proposed Reaction Mechanism

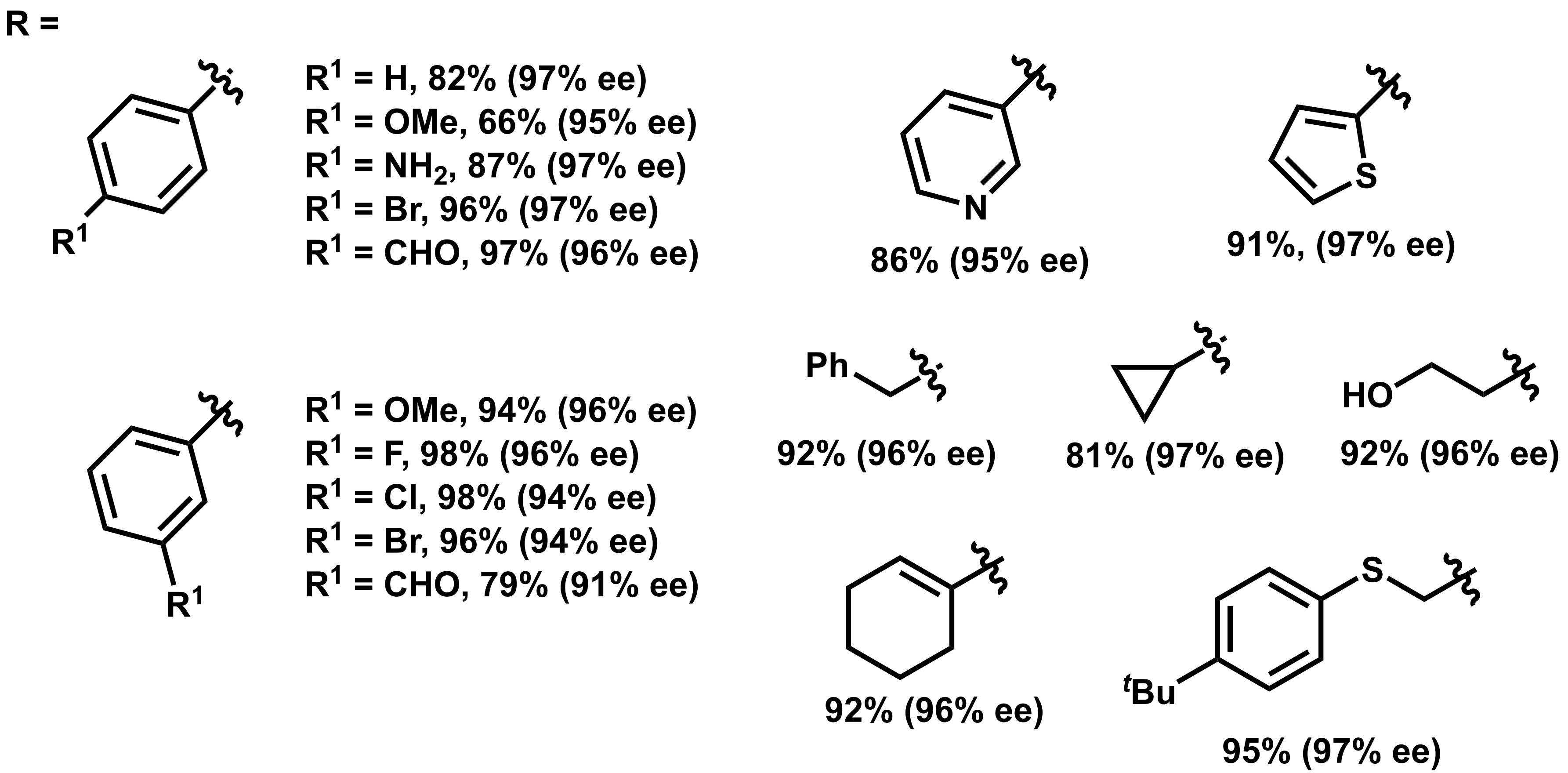


*When TEMPO was added, this radical intermediate was trapped by TEMPO.

Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.

Substrate Scope of Alkynes





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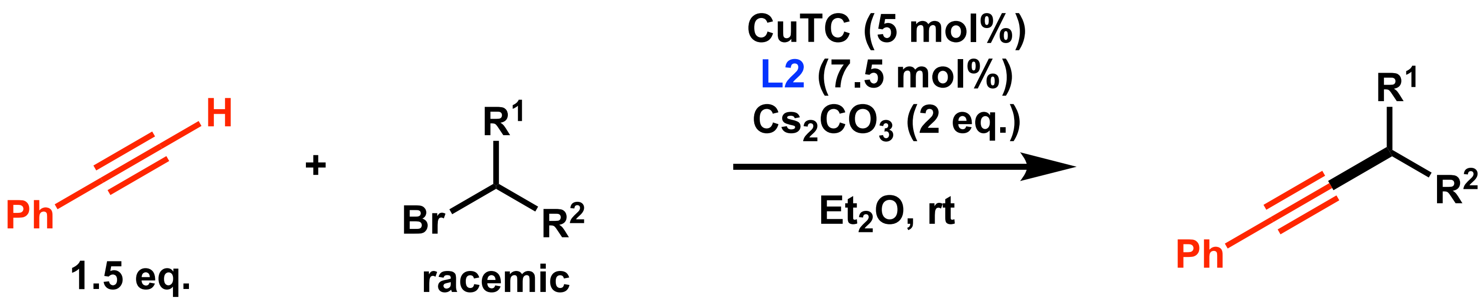
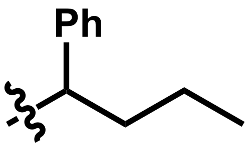
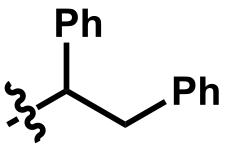
Substrate Scope of Alkyl Halides

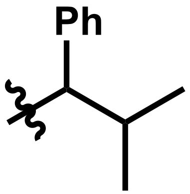




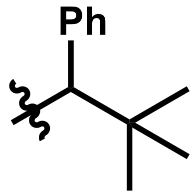
77% (96% ee)



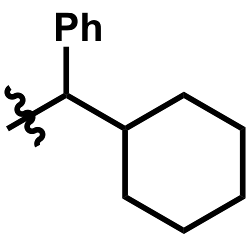
62% (92% ee)



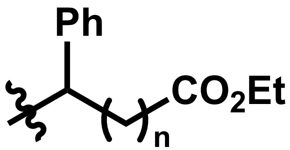
81% (98% ee)*



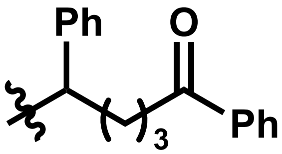
30% (96% ee)



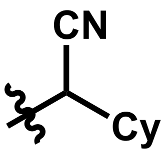
82% (98% ee)*



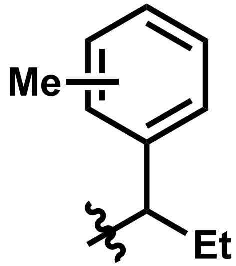
n = 1, 34% (92% ee)
n = 2, 86% (86% ee)



84% (92% ee)



61% (77% ee)**

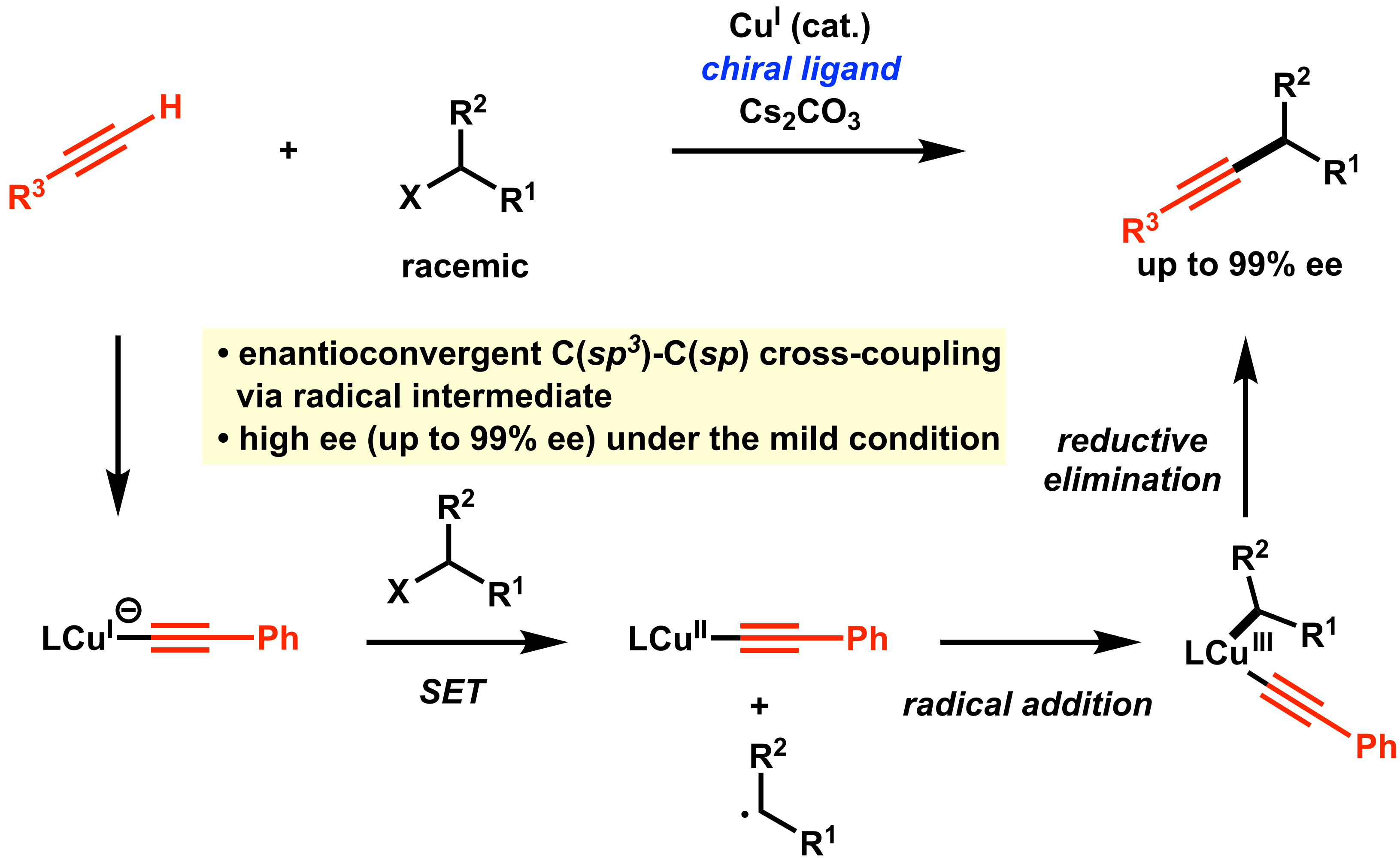


4-Me, 85% (96% ee)
3-Me, 79% (93% ee)
2-Me, 43% (95% ee)*

*L1 (7.5 mol%) was used, in stead of L2.
**alkyne (1 eq.), alkyl halide (1.5 eq.), –40 °C

Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.

Summary-1



- enantioconvergent C(sp^3)-C(sp) cross-coupling via radical intermediate
- high ee (up to 99% ee) under the mild condition

Next task: three-component coupling reaction by radical traping

Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.

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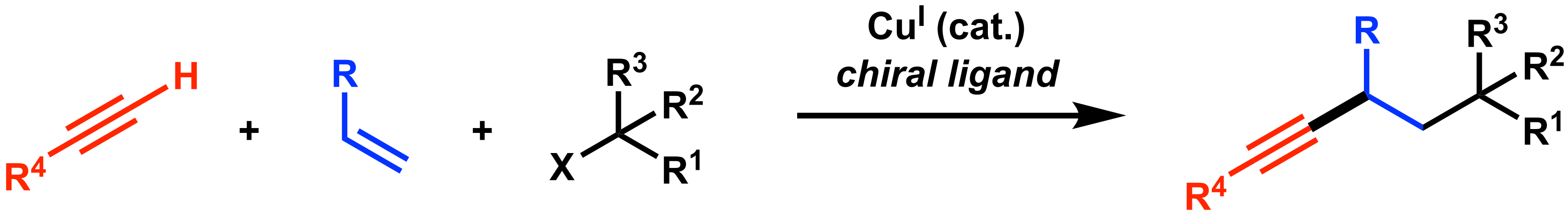
racemic

up to 99% ee

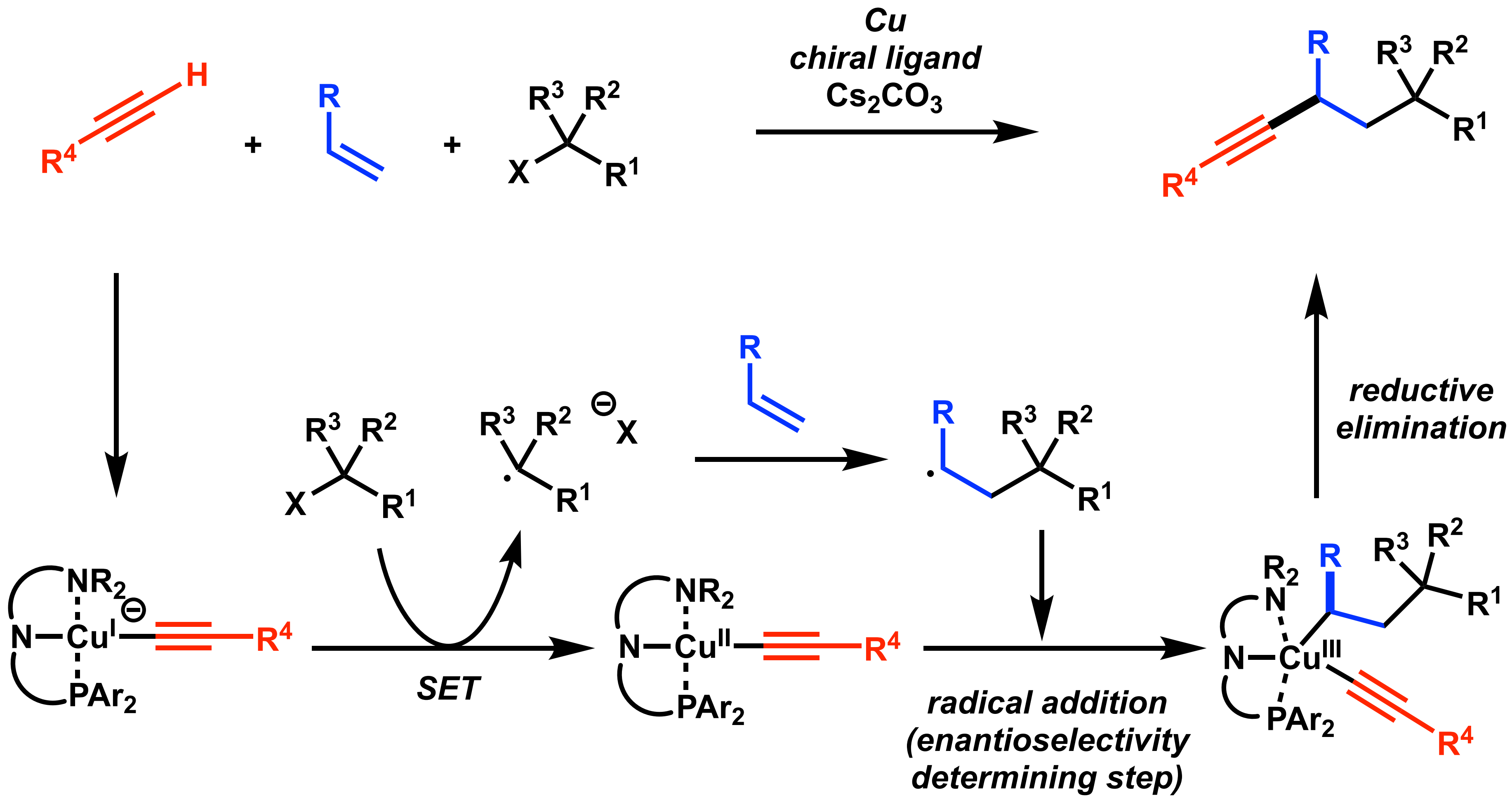
3. Asymmetric *Cu*-Catalyzed Radical 1,2-Carboalkynylation of Alkenes [2)]



up to 98% ee

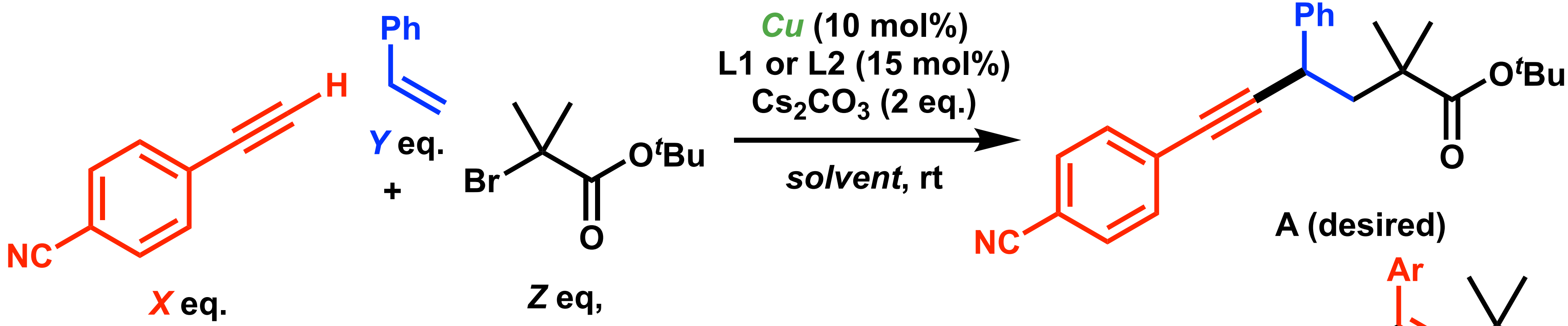
1) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. *Nature Chemistry* **2019**, *11*, 1158.
2) Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

Asymmetric *Cu*-Catalyzed Radical 1,2-Carboalkynylation of Alkenes

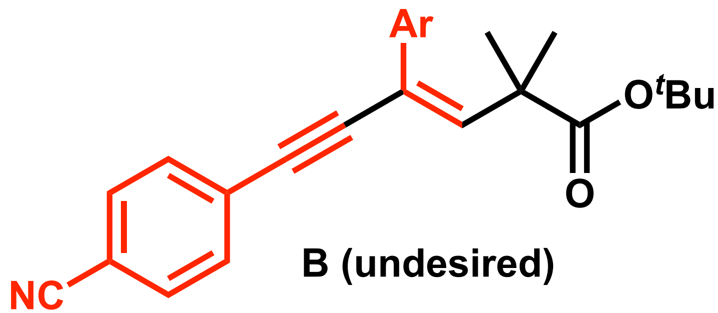


Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y.
J. Am. Chem. Soc. **2020**, in press.

Optimization of Reaction Condition

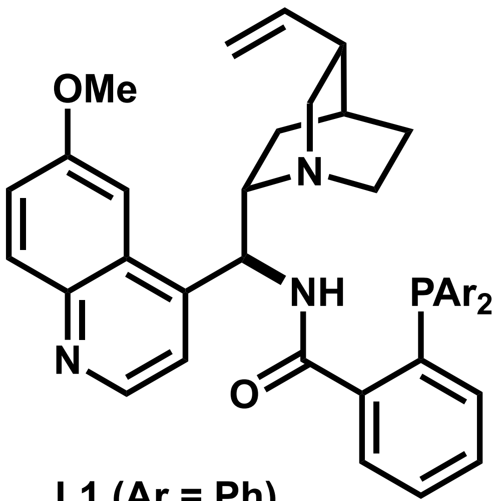


A (desired)



B (undesired)

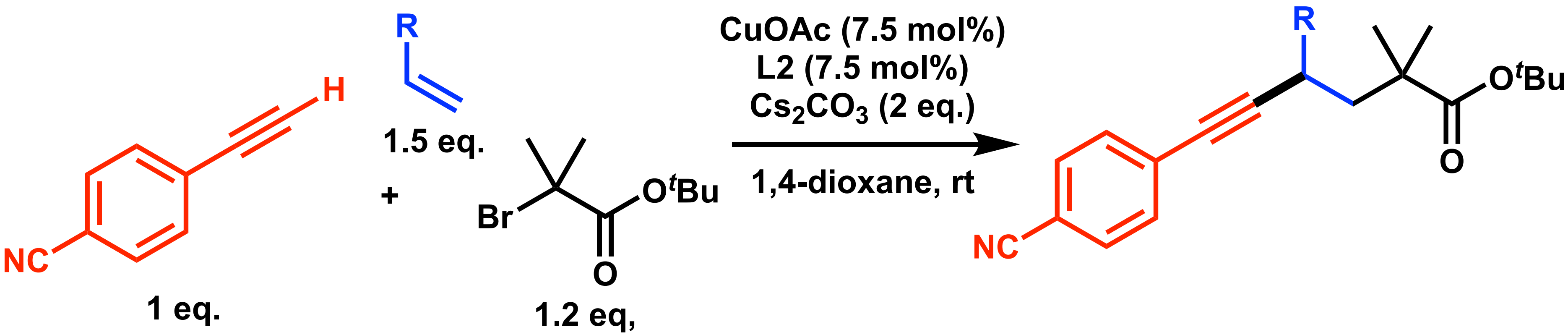
entry	*Cu*	*ligand*	*X*	*Y*	*Z*	*solvent*	A% (% ee)	B%
1	CuI	L1	1.5	1	1.2	Et_2O	42 (72)	16
2	CuI	L1	1.5	1	1.2	1,4-dioxane	50 (70)	12
3	CuI	L2	1.5	1	1.2	1,4-dioxane	66 (94)	32
4	CuI	L2	1	1.5	1.2	1,4-dioxane	76 (94)	8
5	CuTC	L2	1	1.5	1.2	1,4-dioxane	67 (94)	8
6	CuOAc	L2	1	1.5	1.2	1,4-dioxane	76 (94)	4



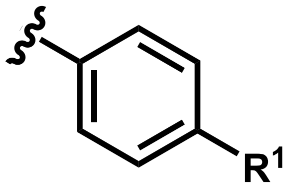
L1 (Ar = Ph)
L2 (Ar = 3,5-$^tBu_2C_6H_3$)

Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

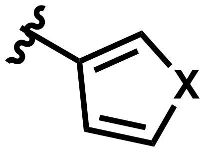
Substrate Scope of Alkenes



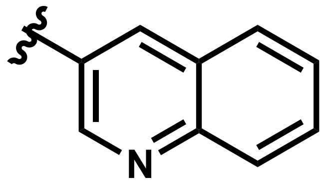
R =



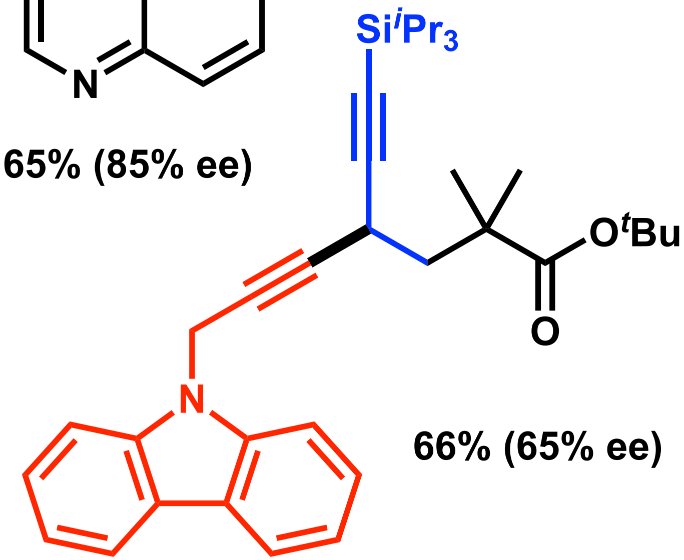
R^1 = H, 71% (93% ee)
R^1 = OMe, 72% (91% ee)
R^1 = F, 82% (92% ee)
R^1 = Cl, 66% (90% ee)
R^1 = Br, 72% (92% ee)



X = O, 60% (85% ee)
X = S, 70% (92% ee)



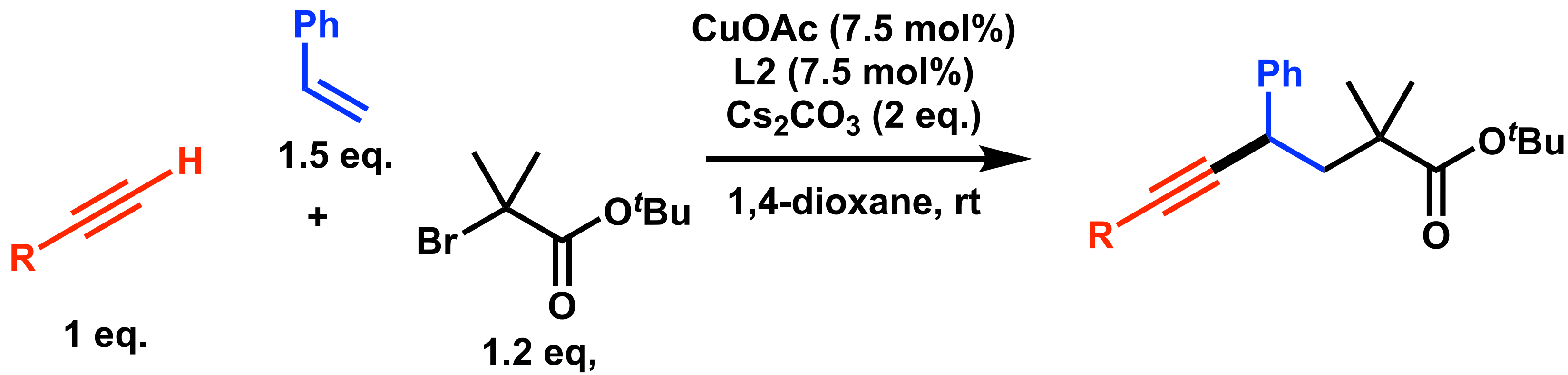
65% (85% ee)



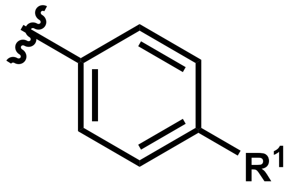
66% (65% ee)

Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

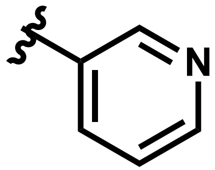
Substrate Scope of Alkynes



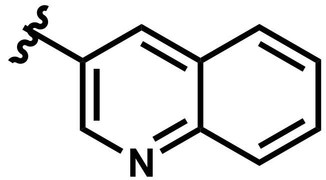
R =



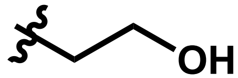
R^1 = H, 82% (96% ee)
R^1 = OMe, 82% (95% ee)
R^1 = F, 82% (95% ee)
R^1 = Cl, 77% (95% ee)
R^1 = CHO, 71% (95% ee)



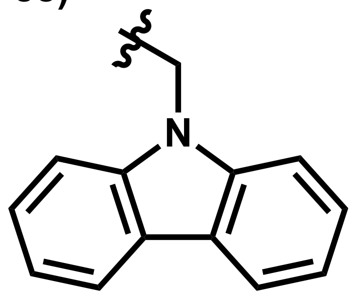
53% (96% ee)



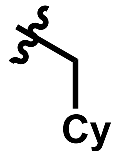
65% (85% ee)



90% (97% ee)



85% (96% ee)

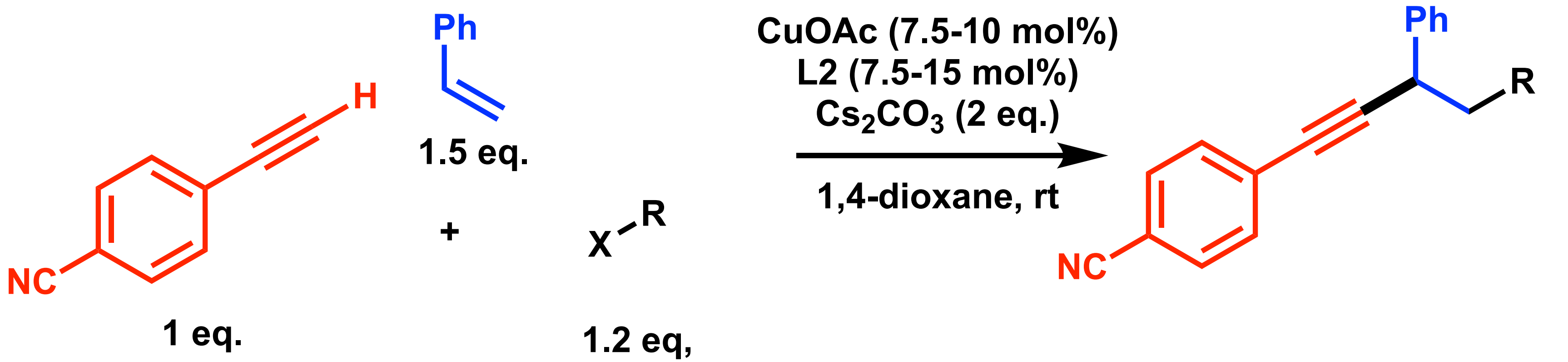


72% (95% ee)

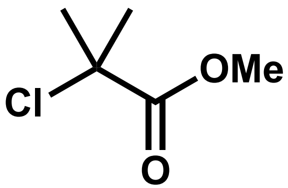
90% (96% ee)

Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

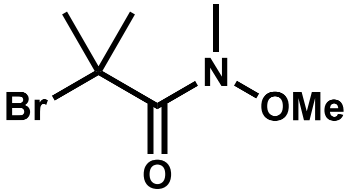
Substrate Scope of Alkyl Radical Precursors



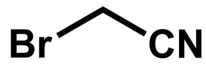
R-X =



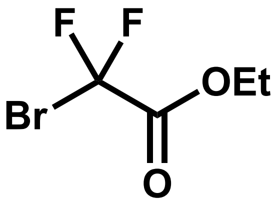
51% (93% ee)



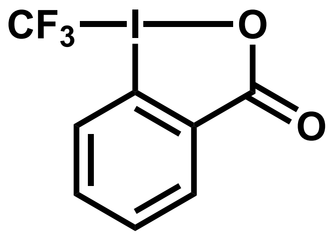
74% (94% ee)



70% (95% ee)



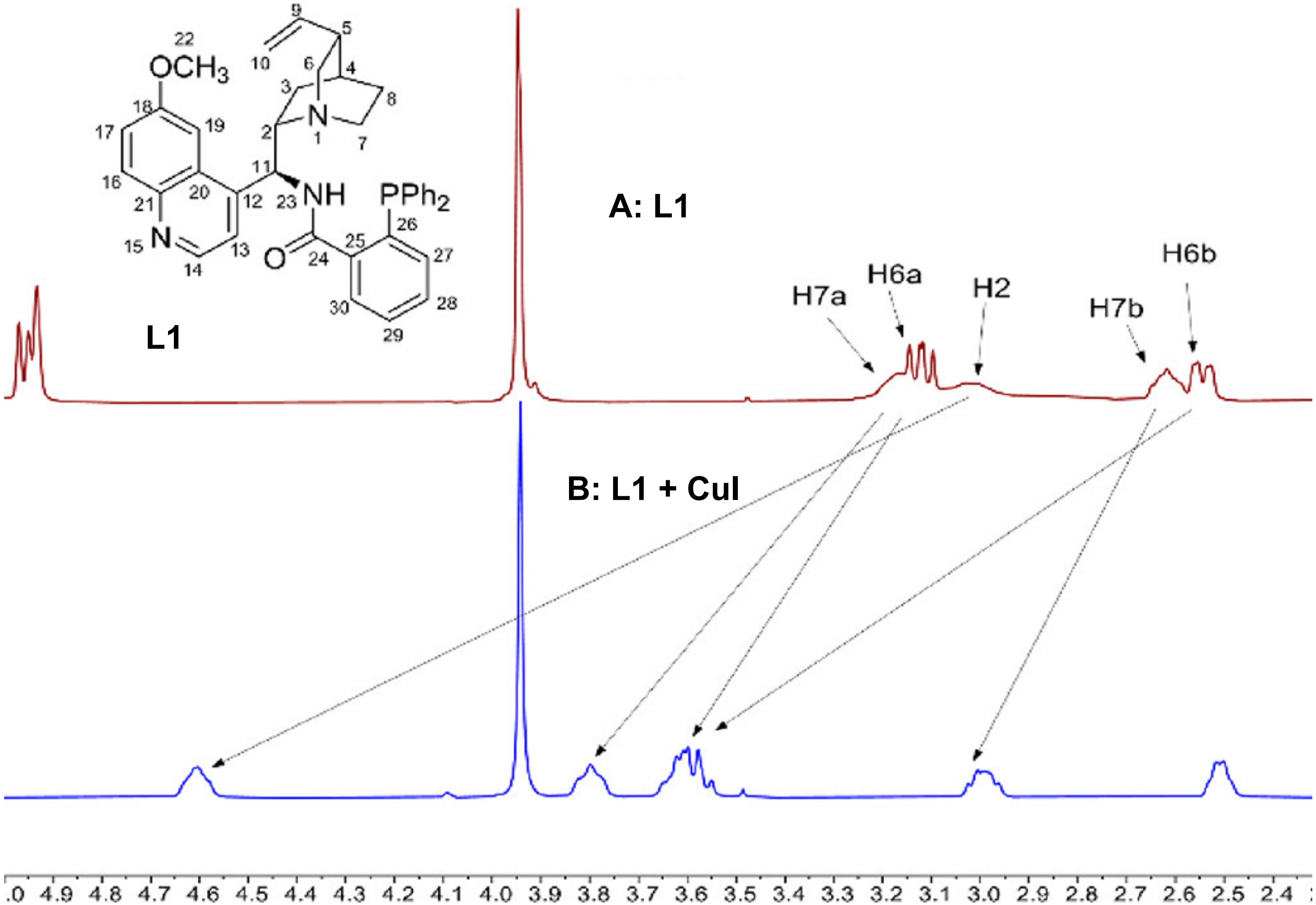
53% (92% ee)



71% (96% ee)

Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

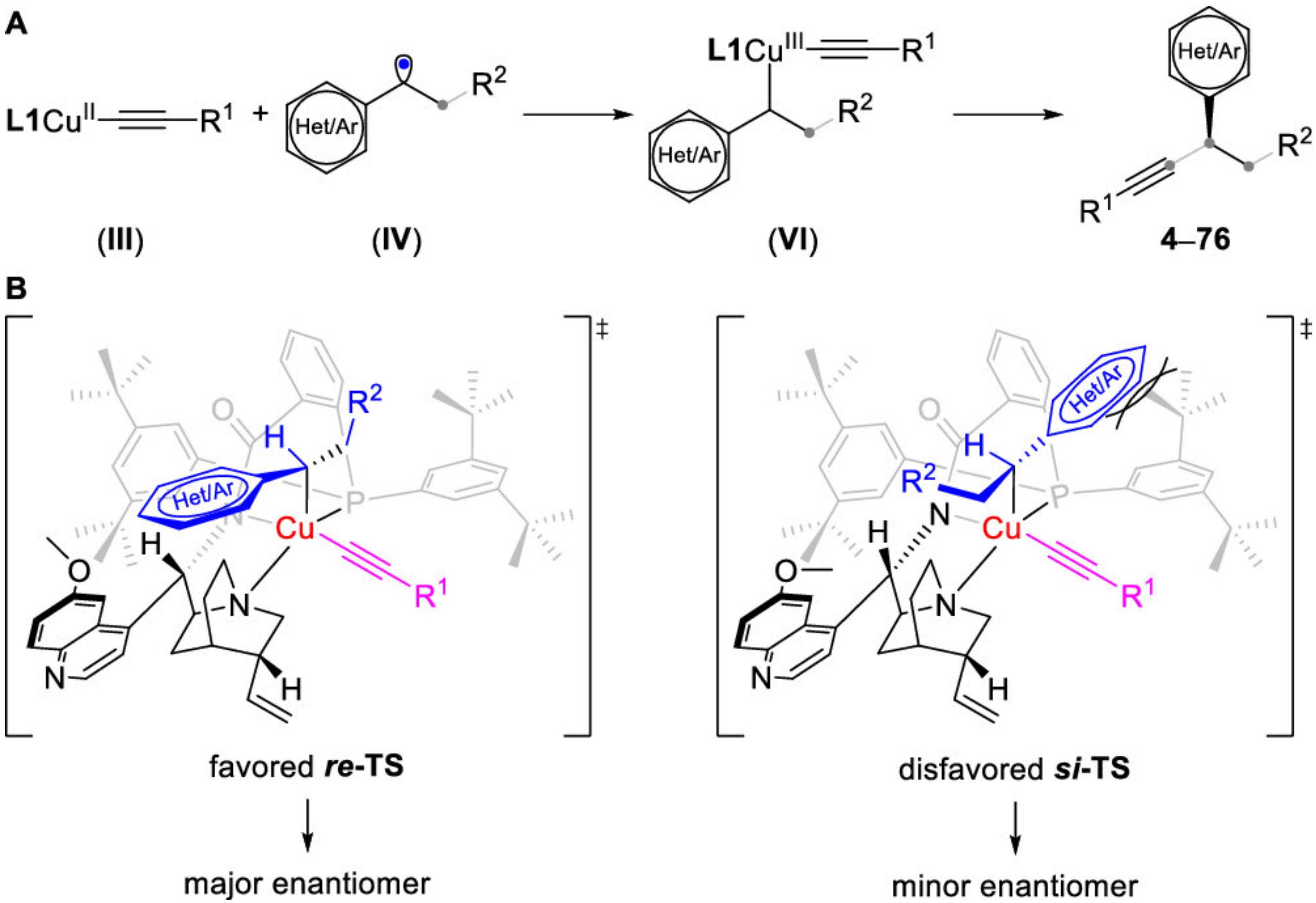
1H-NMR Study of The Cu^{I} complex



Protons adjacent to the quinuclidine nitrogen shifted to downfield by mixing L1 and CuI.
The ^{31}P-NMR experiments also showed the downfield shift (+2.4 ppm). –> L1 worked as a multidentate ligand.

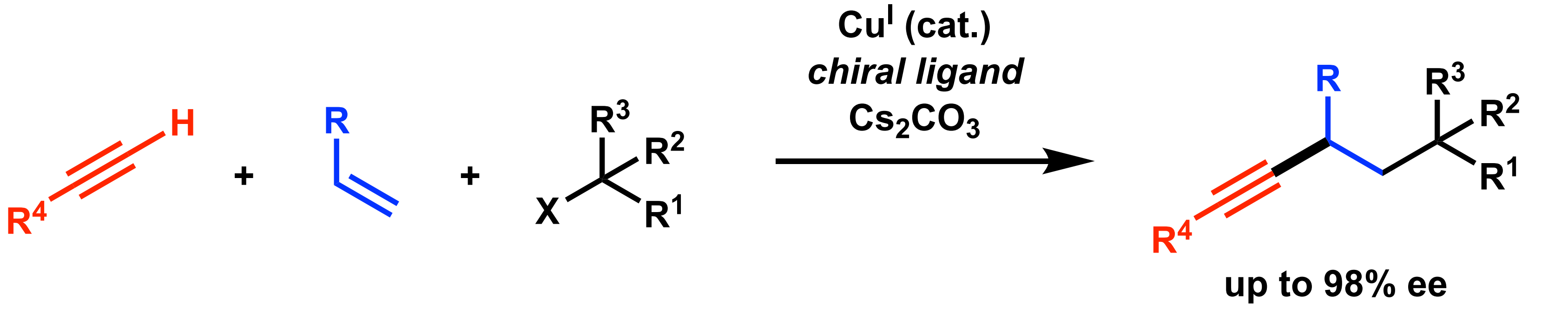
Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

Proposed Enantioselectivity

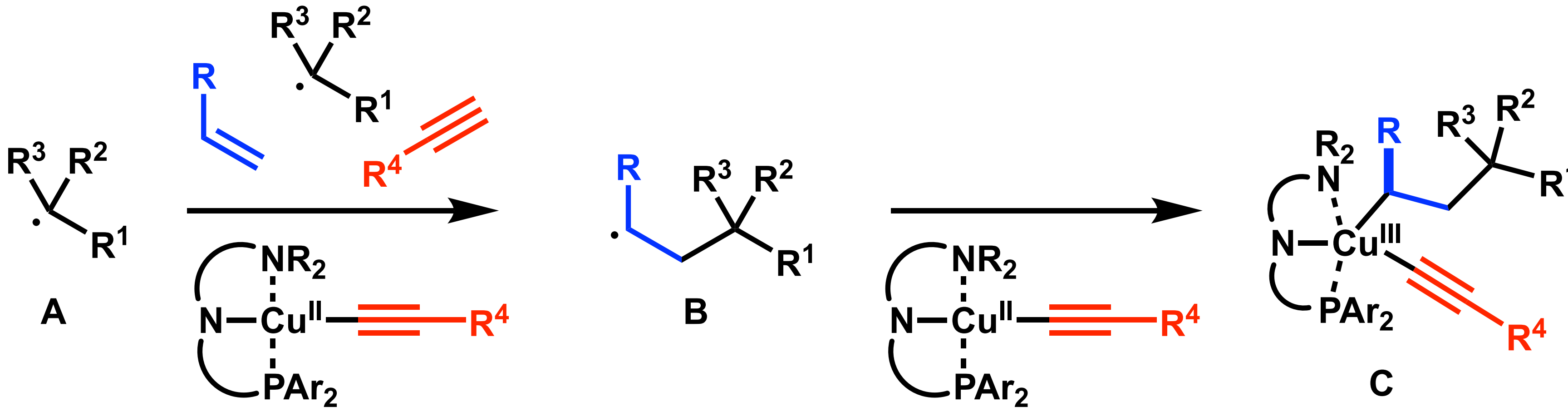


Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.

Summary-2



<chemoselective addition>



A –> B

- **The bulky tertiary radical reacts with alkene or alkyne.**
- **The transition state leading to alkyl radical would be more stable than that of vinyl radical.**

B –> C

- **The relatively stable benzyl radical reacts with Cu^{II} complex.**

Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, in press.