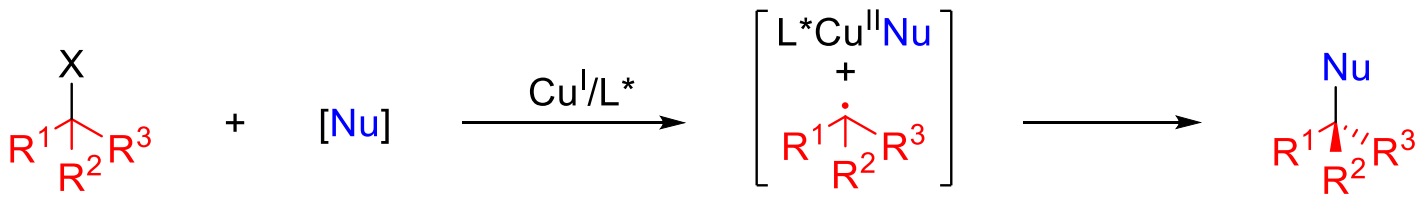
铜催化消旋(类)卤代烷烃的不对称 C(sp^3)-C键偶联反应



汇报人：许正帅

指导老师：麻生明 教授

2022年10月08日

01 背景介绍

02

- 光促进的不对称C(sp^3)-C键偶联反应
  - ✓ 光和光催化剂引发自由基参与的偶联反应
  - ✓ 光和铜络合物引发自由基参与的偶联反应
- 铜络合物引发自由基参与的不对称C(sp^3)-C键偶联反应

03 总结与展望

01 背景介绍

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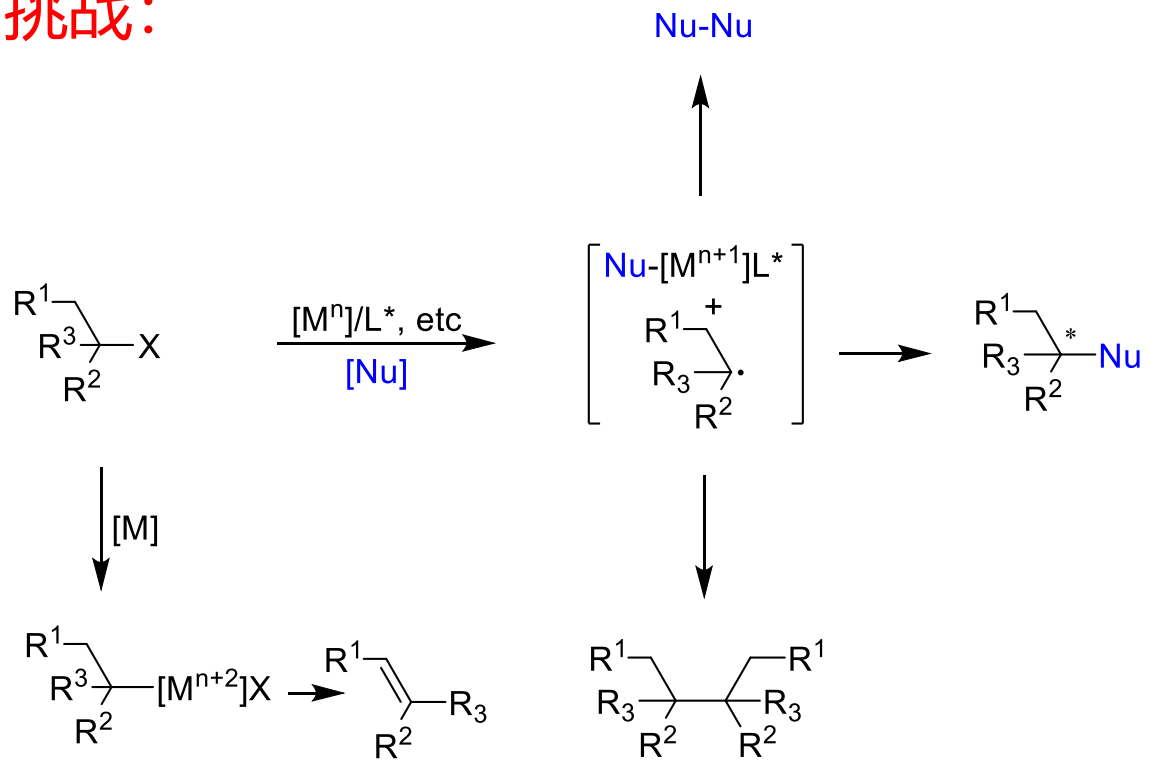
03 总结与展望

壹

背景介绍

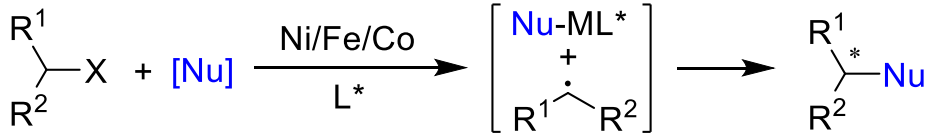
过渡金属催化消旋(类)卤代烷烃不对称C(sp^3)-C偶联反应的挑战及进展：

挑战：



- 易发生消除反应
- 易发生自偶联
- 烷基自由基活性高，对映选择性控制困难

进展：



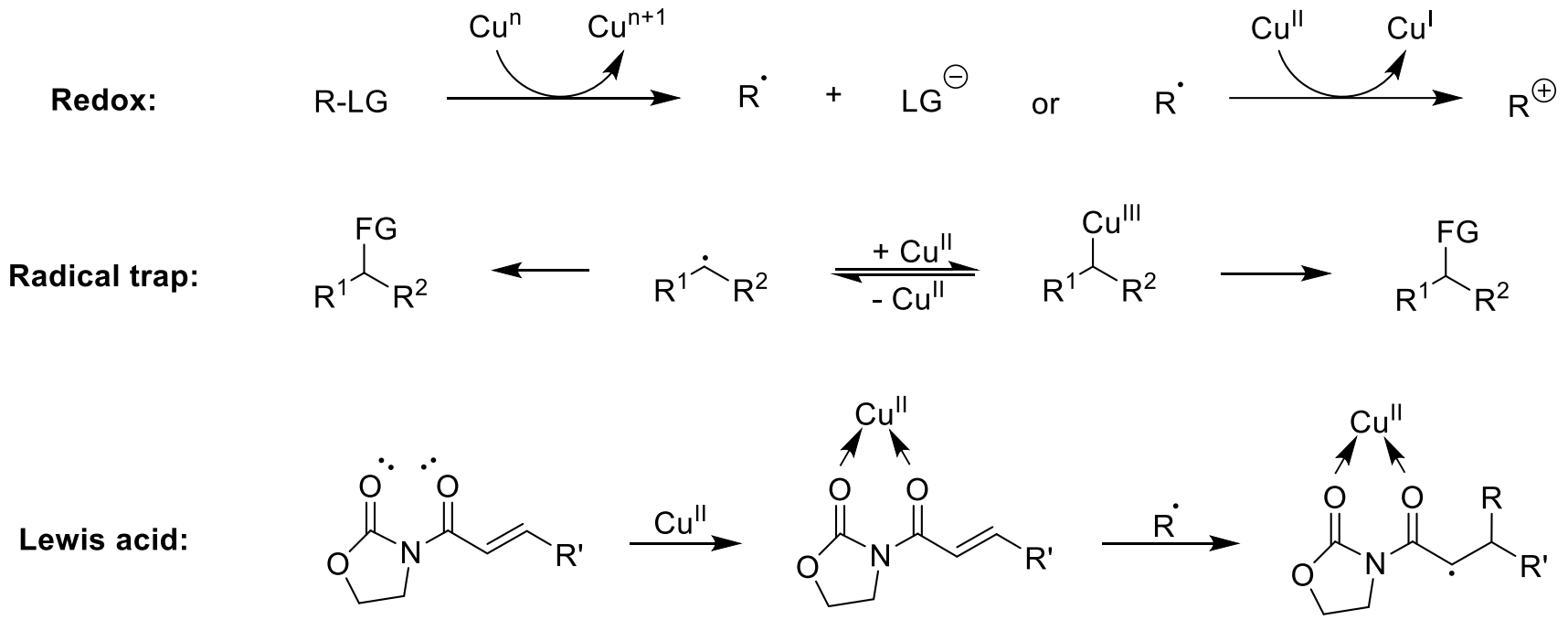
[Nu] = R-[B], R-[Mg], R-[Si], R-[Zn], R-[Zr], etc.

- 亲和试剂多为有机金属试剂
- 一般为消旋二级(类)卤代烷烃

壹

背景介绍

在自由基反应中，铜催化剂的作用：

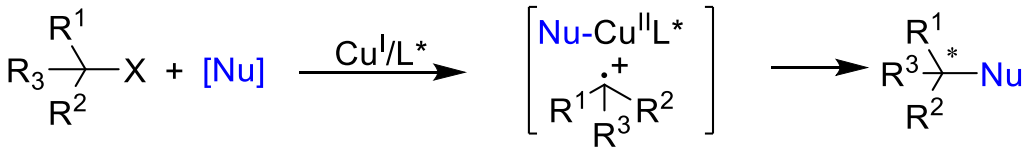


a) X.-Y. Liu, et al, *Acc. Chem. Res.* **2020**, *53*, 170; b) X.-Y. Liu, et al, *ACS Catal.* **2021**, *11*, 7978; c) X.-Y. Liu et al., *J. Am. Chem. Soc.* **2022**, *doi.org/10.1021/jacs.2c06718*

壹

背景介绍

铜催化消旋(类)卤代烷烃不对称C(sp^3)-C偶联反应面临的挑战：



挑战：

- 烷基自由基活性高，对映选择性控制困难
- 易发生β-H消除
- 易发生烷基自由基或亲核试剂的自偶联
- 铜催化剂的还原性较弱，难以活化烷基卤化物

目前已报道的解决方法：

- 使用光引发自由基，促进反应进行
- 提高配体的给电子能力，促进反应进行

a) X.-Y. Liu, et al, *Acc. Chem. Res.* **2020**, *53*, 170−181; b) X.-Y. Liu, et al, *ACS Catal.* **2021**, *11*, 7978−7986; c) X.-Y. Liu et al., *J. Am. Chem. Soc.* **2022**, *doi.org/10.1021/jacs.2c06718*

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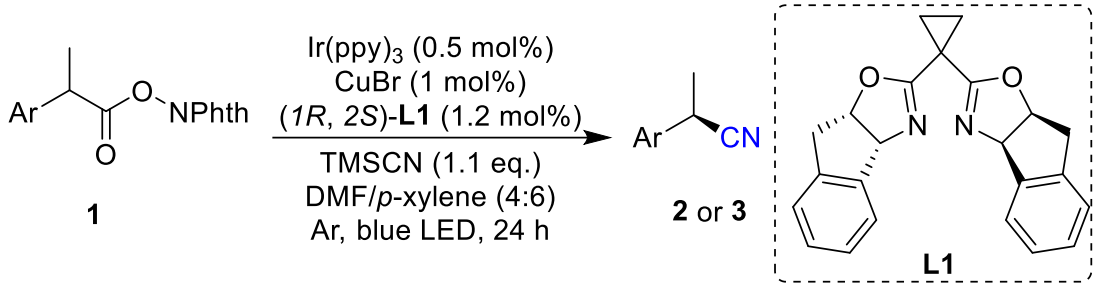
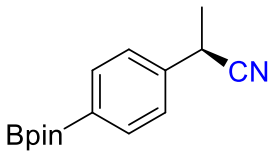
  - ✓ 光和铜络合物引发自由基参与的偶联反应
- 铜络合物引发自由基参与的不对称C(sp^3)-C键偶联反应

03 总结与展望

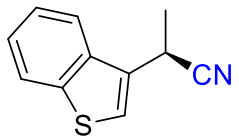
贰 光和光催化剂引发自由基参与的偶联反应 ——和TMSCN的偶联

底物适用范围实例：

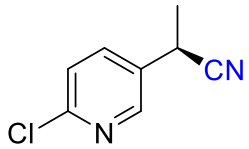




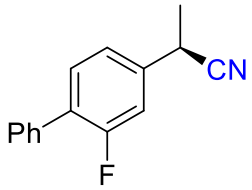
2k, 38%, 94% ee



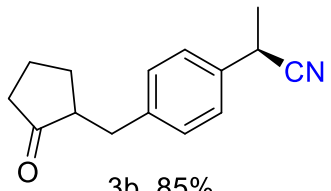
2x, 67%, 88% ee



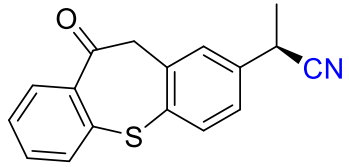
2y, 71%, 90% ee



3a, 92%, 92% ee



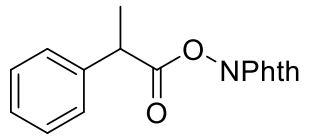
3b, 85%
(dr = 1:1, 86% ee/86% ee)



3e, 79%, 88% ee

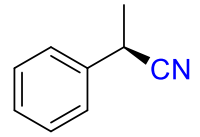
合成应用：

a) scale-up reaction (0.27 mol scale)



1d

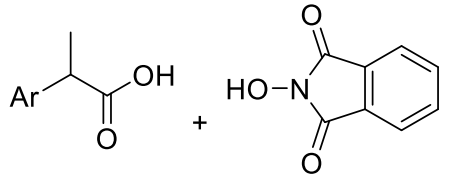
Ir(ppy)3 (0.13 mol%)
CuBr (0.26 mol%)
(1R, 2S)-L1 (0.26 mol%)
TMSCN (1.35 eq.)
DMF/toluene (1:1)
Ar, blue LED, r.t., 4.5 d



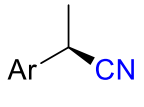
2d

34.3 g, 95% yield
88% ee

b) One-pot reactions



1) DMAP (5 mol%)
DCC (1.0 eq.)
DCM, 0 °C
2) standard condition

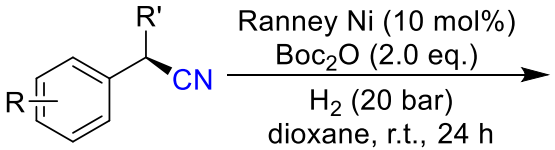


3a
94% yiled
91% ee

3b
85% yield
dr 1:1, 86%/86% ee

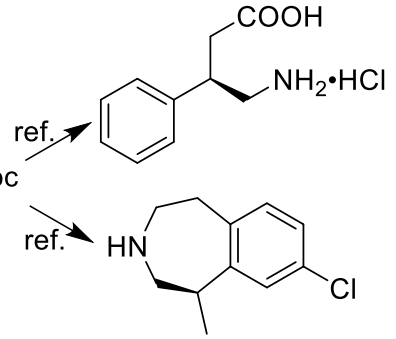
3e
52% yield
89% ee

c) drug molecules synthesis



R = H, R' = CH_2CO_2Et, 90% ee
R = *m*-Cl, R' = Me, 91% ee

92% yield, 89% ee
85% yield, 91% ee

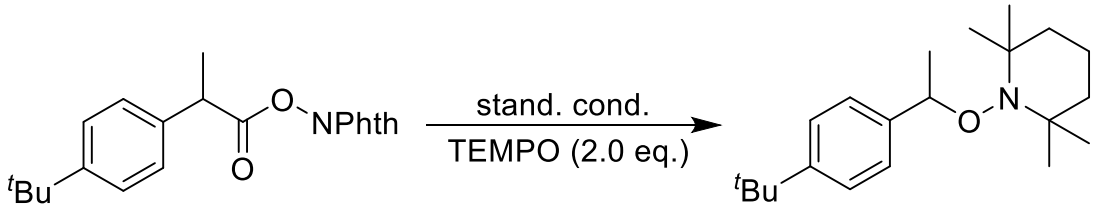


Z. Lin, G. Liu, et al., *J. Am. Chem. Soc.* **2017**, *139*, 15632.

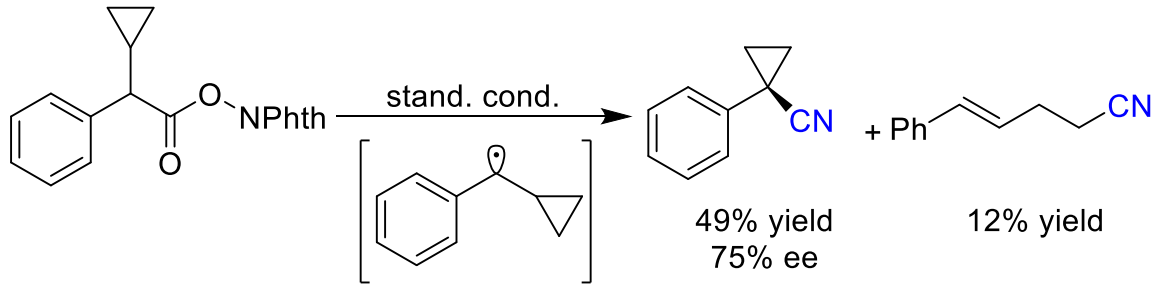
贰 光和光催化剂引发自由基参与的偶联反应 ——和TMSCN的偶联

控制实验：

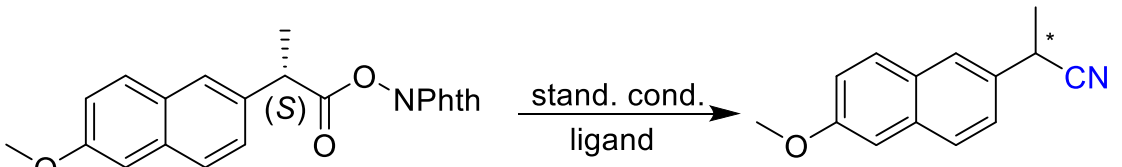
a)



b)

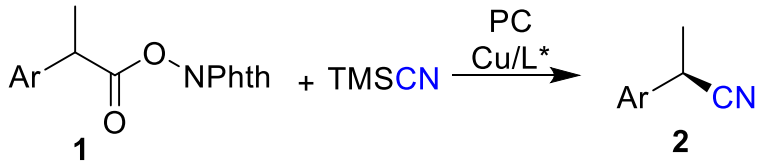


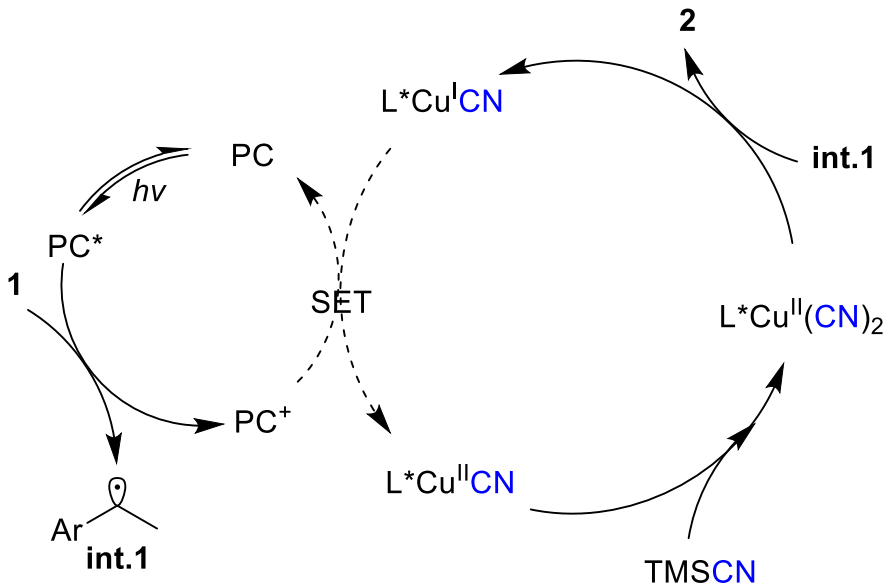
c)



with (1*R*, 2*S*)-**L1**, (*R*)-**11**, 84% yield, 87% ee
with (1*S*, 2*R*)-**L1**, (*S*)-**11**, 85% yield, -88% ee

可能的反应机理：





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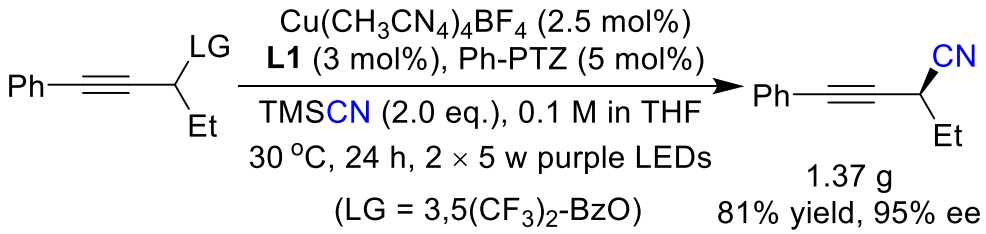
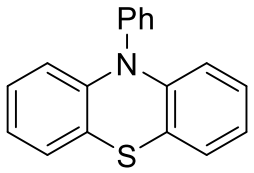
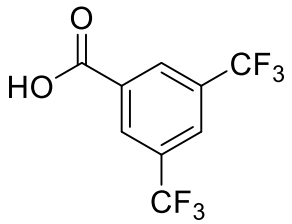
克级反应：

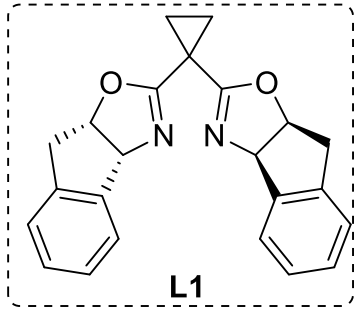




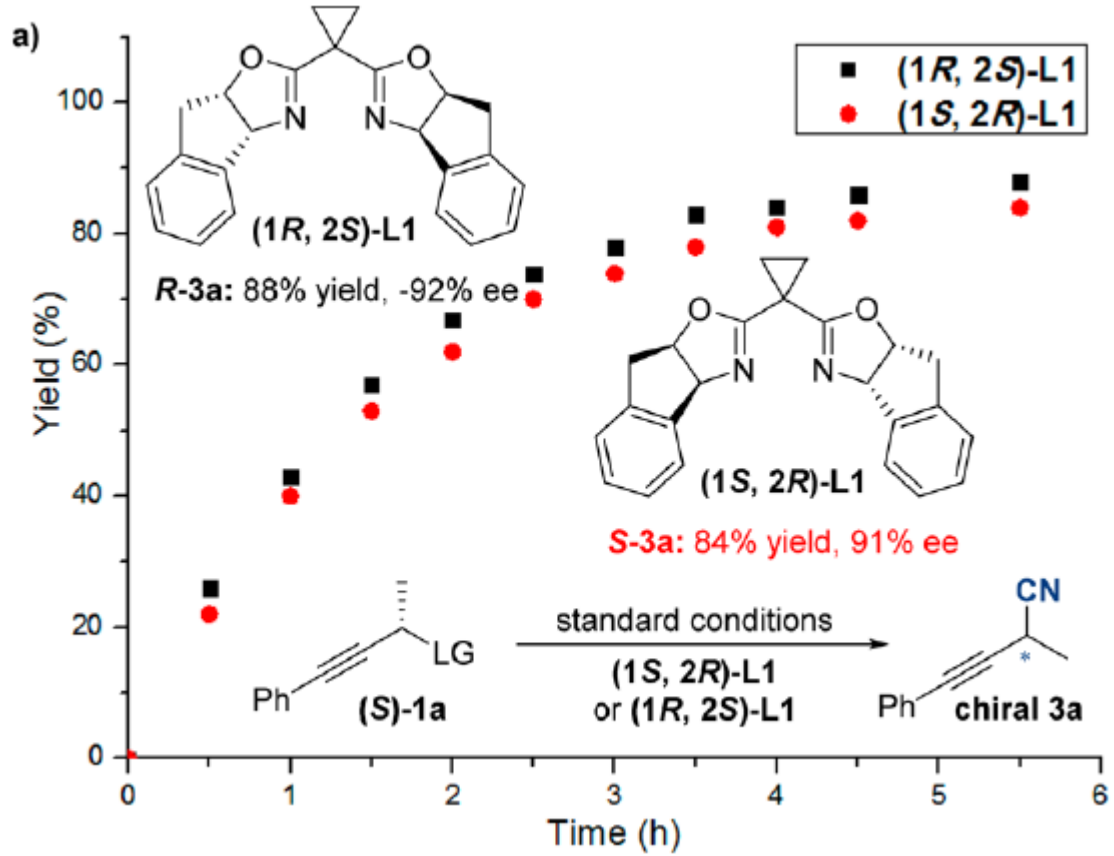
Recoverd Ph-PTZ:
91% yield



Recoverd acid:
85% yield



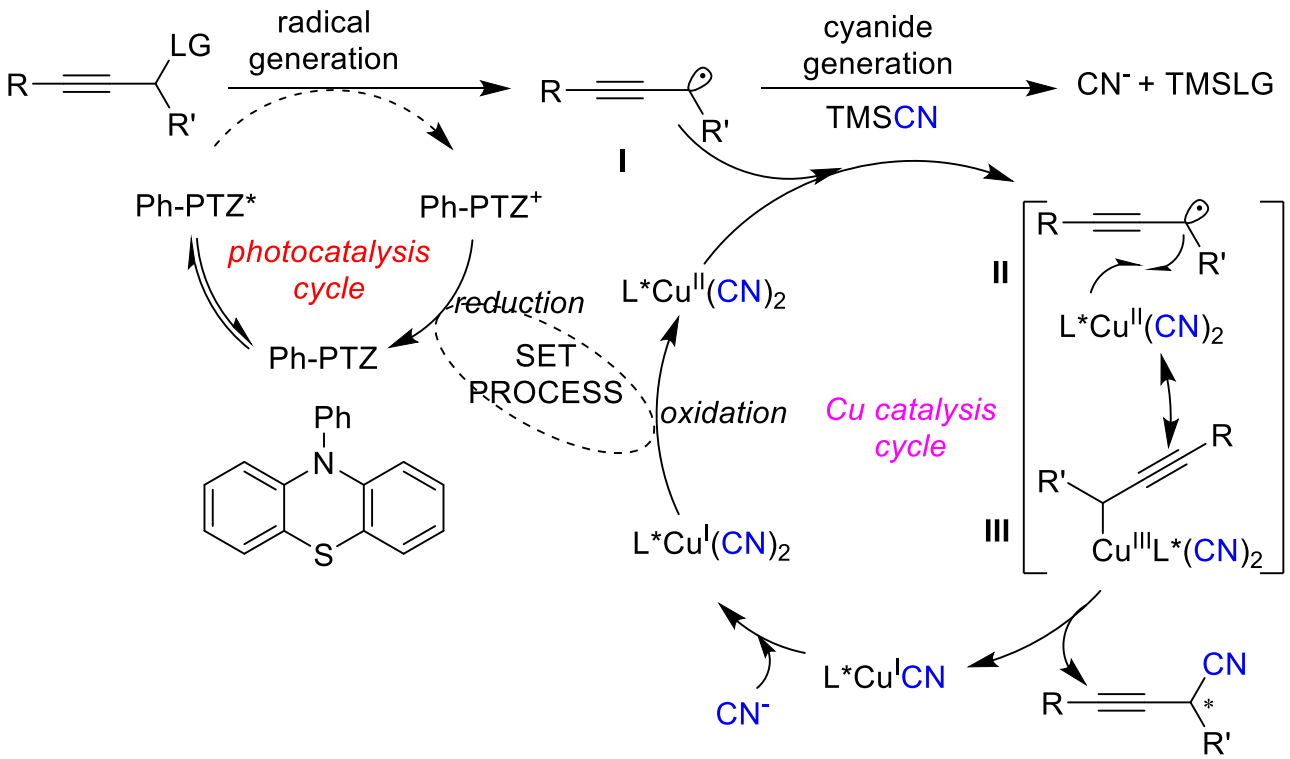
控制实验：



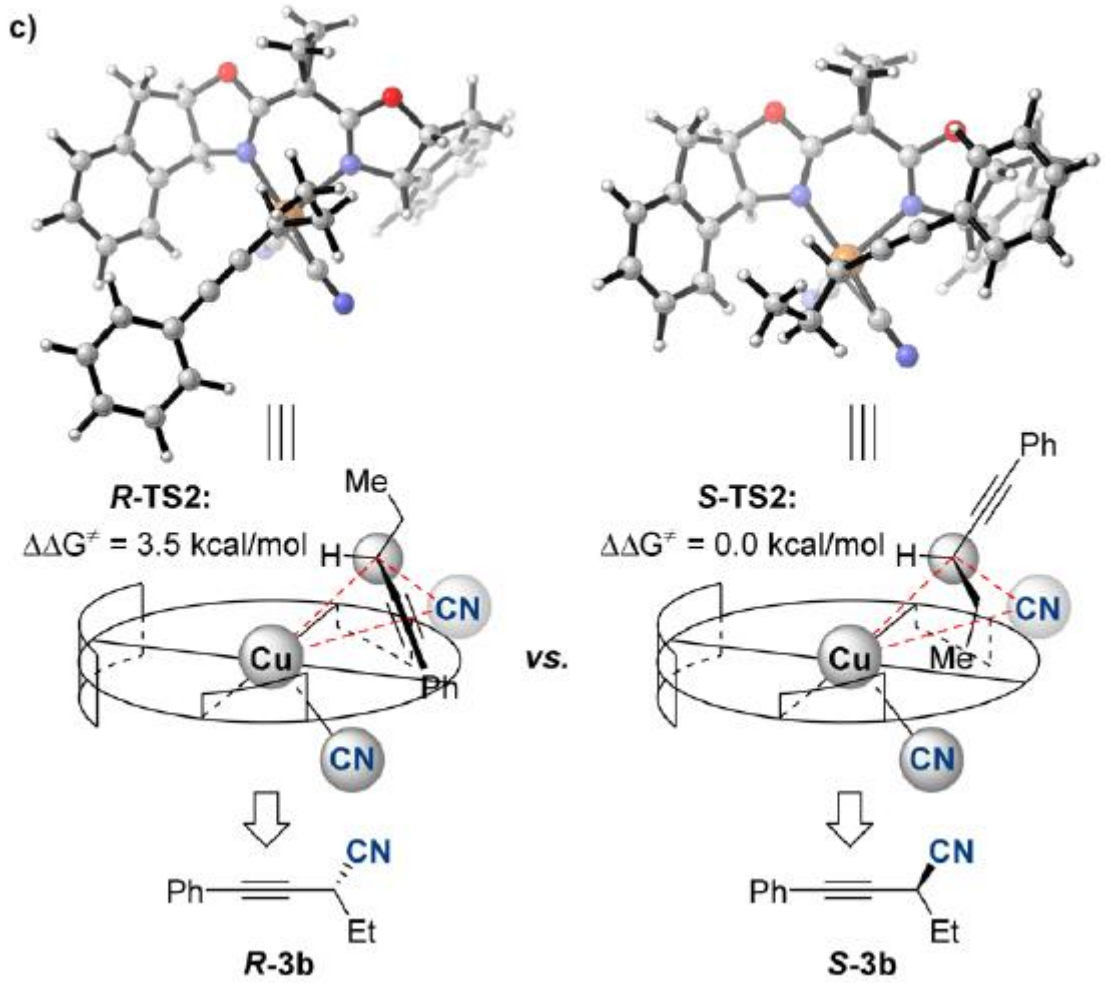
L.-Q. Lu, Y. Lan, W.-J. Xiao et al., *J. Am. Chem. Soc*. **2019**, *141*, 6167.

贰 光和光催化剂引发自由基参与的偶联反应 ——和TMSCN的偶联

可能的反应机理：



可能的立体控制模型：



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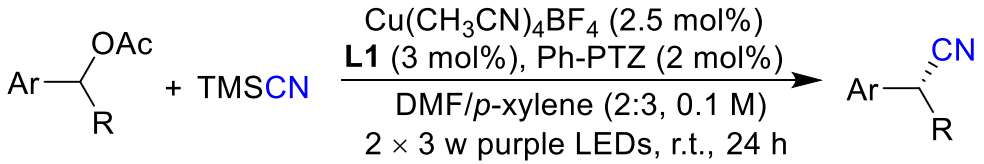
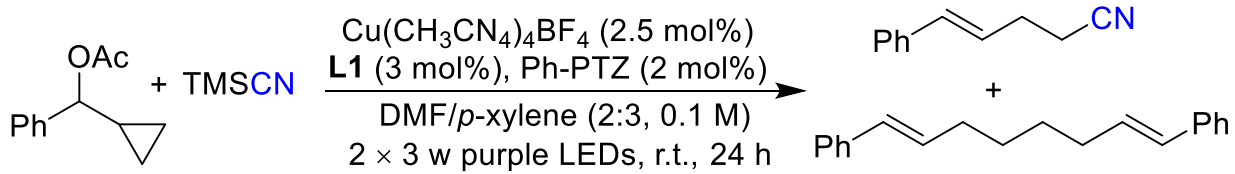


22 examples
up to 93% yield
up to 92% ee

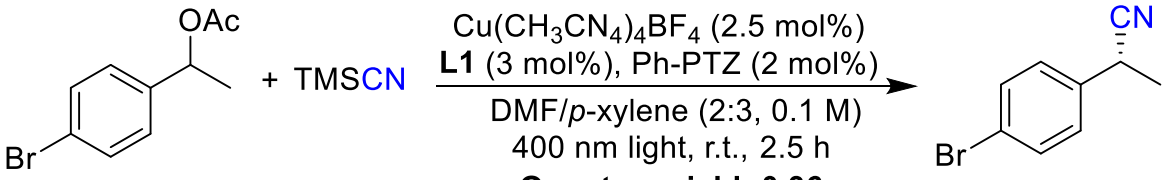
控制实验：

a) Radical clock experiment



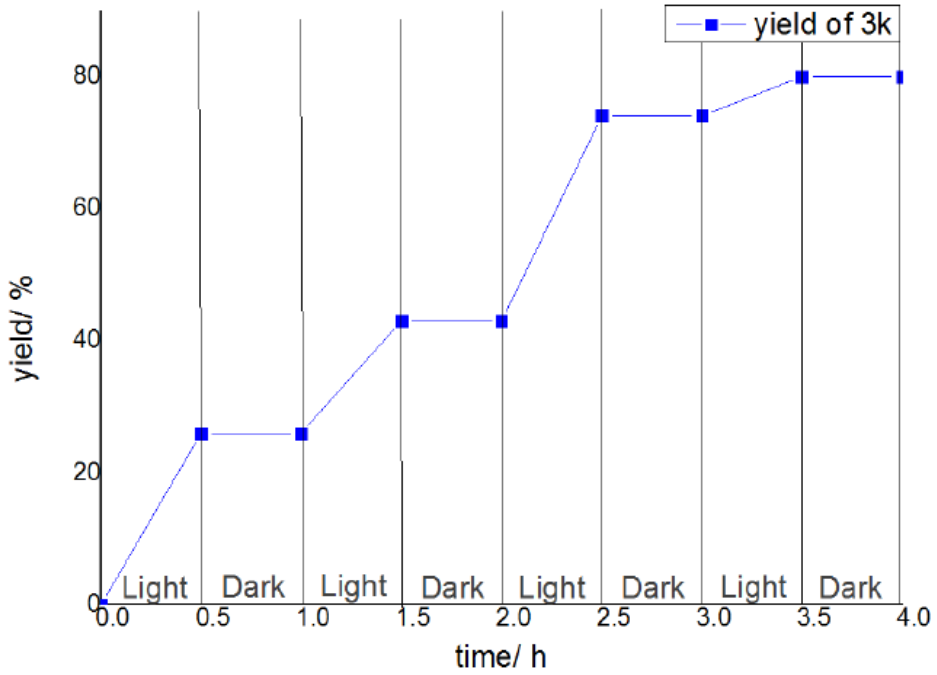
Detected by GC-MS

b) Quantum yield determination



3k, 1% yield

c) Light/dark experiment



Y. Cheng, L.-Q. Lu, W.-J. Xiao et al., *Chin. J. Chem.* **2020**, *38*, 1671.

01 背景介绍

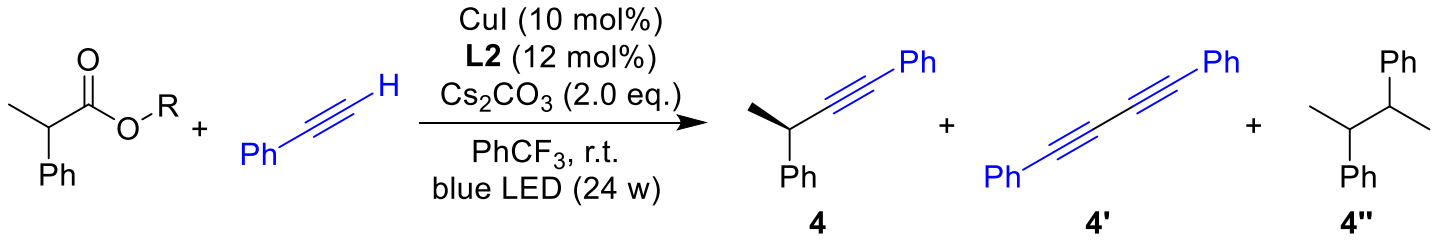
02

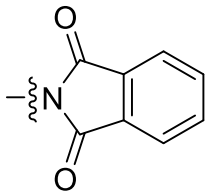
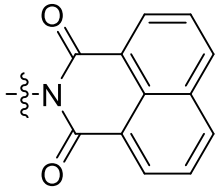
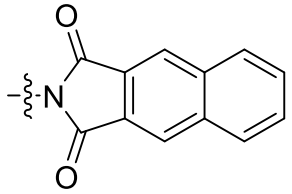
- 光促进的不对称C(sp^3)-C键偶联反应
  - ✓ 光和光催化剂引发自由基参与的偶联反应
  - ✓ 光和铜络合物引发自由基参与的偶联反应
- 铜络合物引发自由基参与的不对称C(sp^3)-C键偶联反应

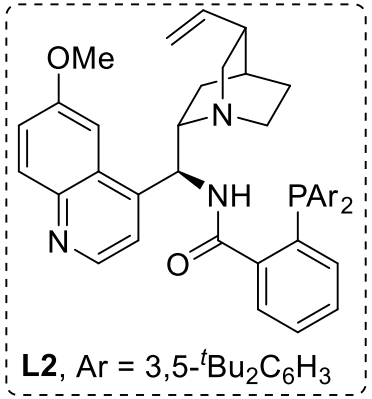
03 总结与展望

贰 光和铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

离去基团对反应的影响：



R	yield of **4**	yield of **4'**	yield of **4''**
	21%	30%	12%
	30%	trace	trace
	37%	trace	trace

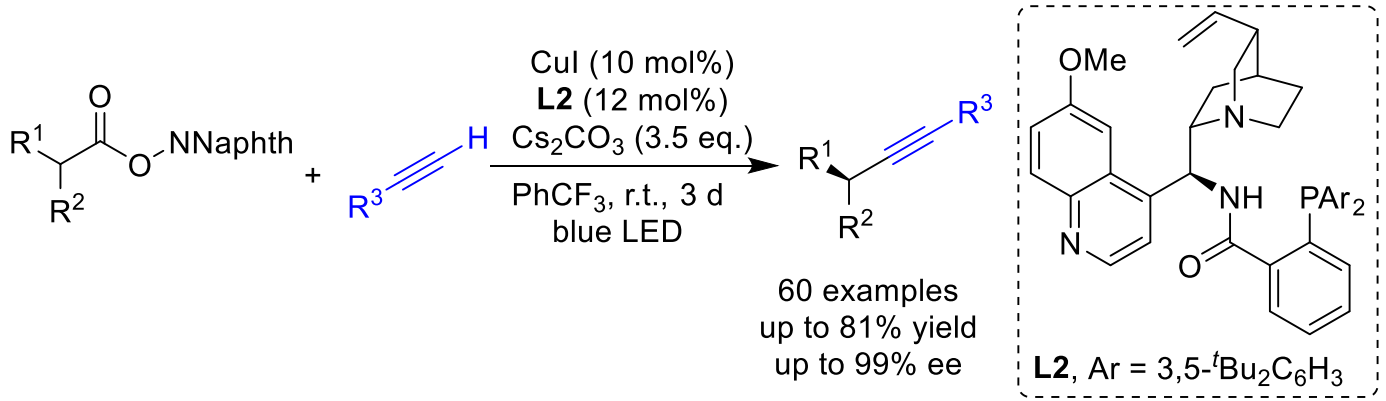


L2, Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$

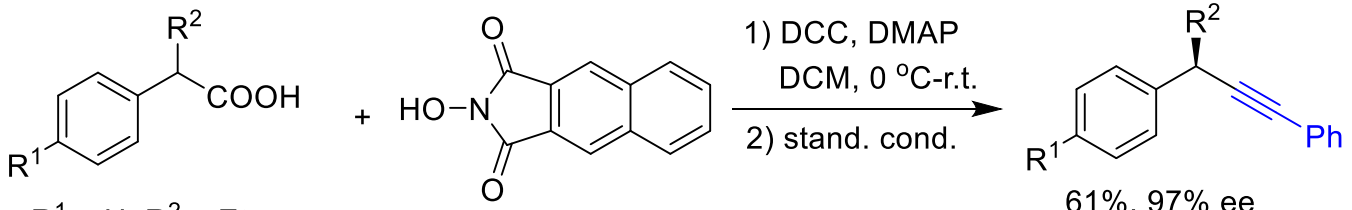
X.-Y. Liu et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 16926.

贰 光和铜络合物引发自由基参与的偶联反应 ——和末端炔烃的偶联

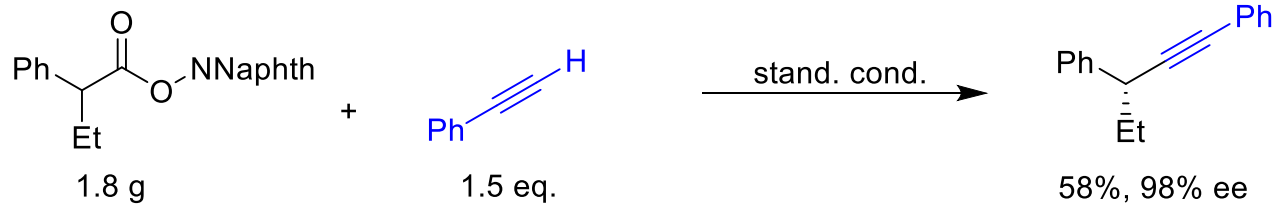
底物适用范围考察及规模放大实验：



One-pot synthesis



Large-scale sythesis

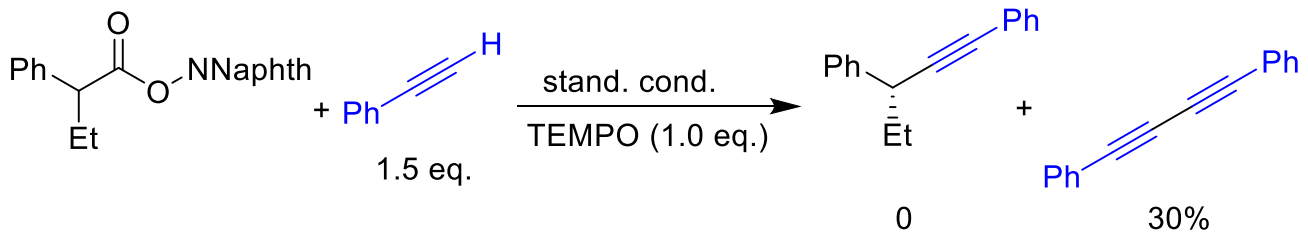


X.-Y. Liu et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 16926.

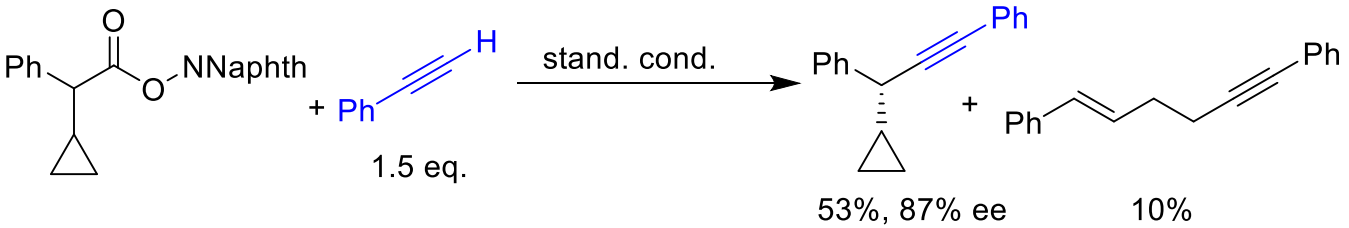
贰 光和铜络合物引发自由基参与的偶联反应 ——和末端炔烃的偶联

控制实验：

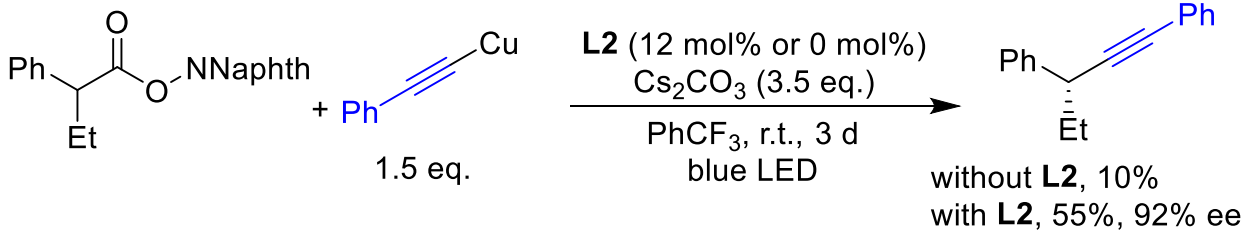
a) TEMPO inhibiting experiment



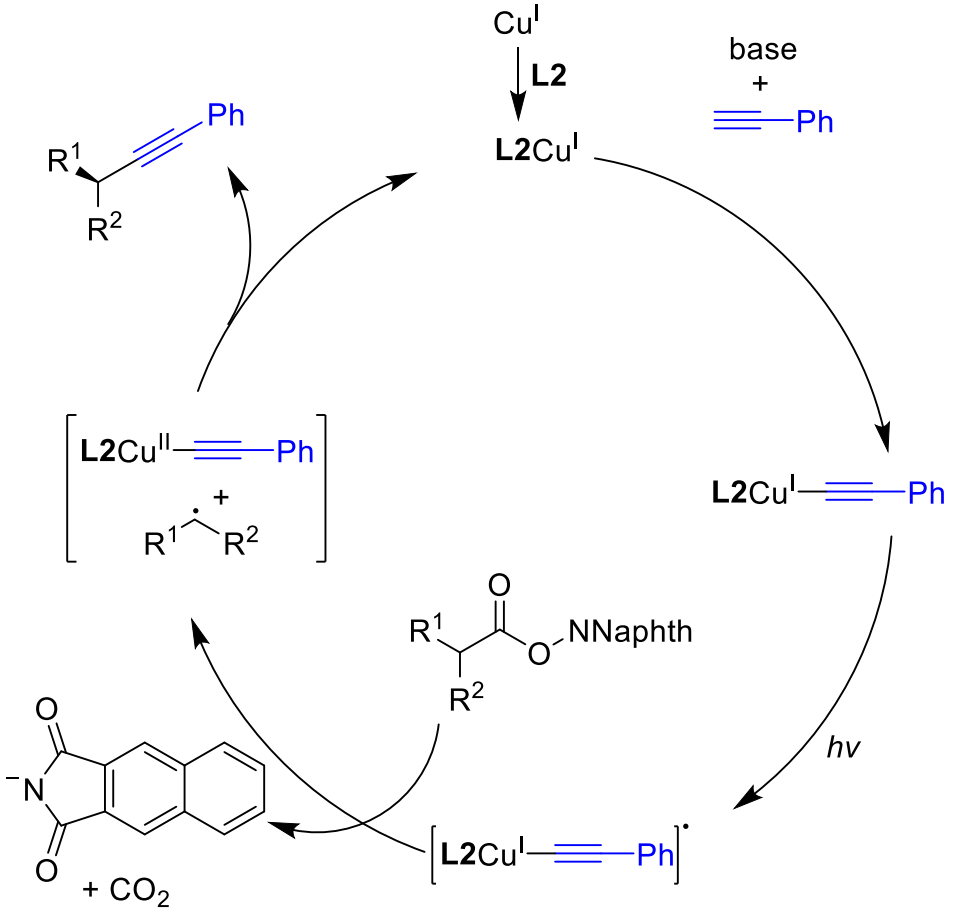
b) Radical clock experiment



c) Reaction with stoichiomeric copper acetylide and ligand effect

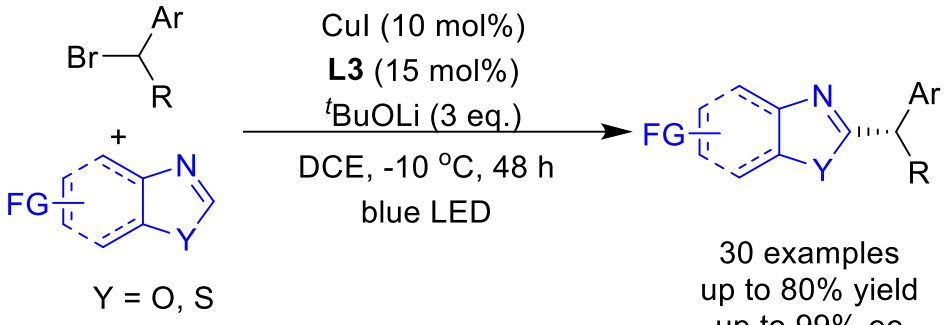


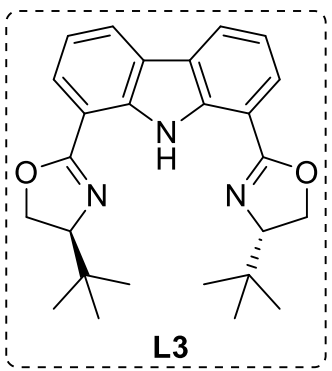
可能的反应机理：

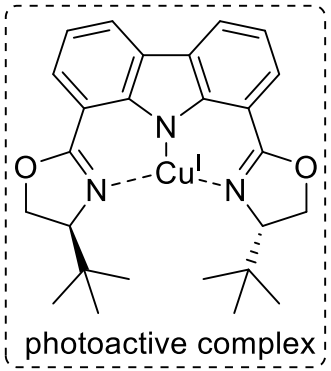


X.-Y. Liu et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 16926.

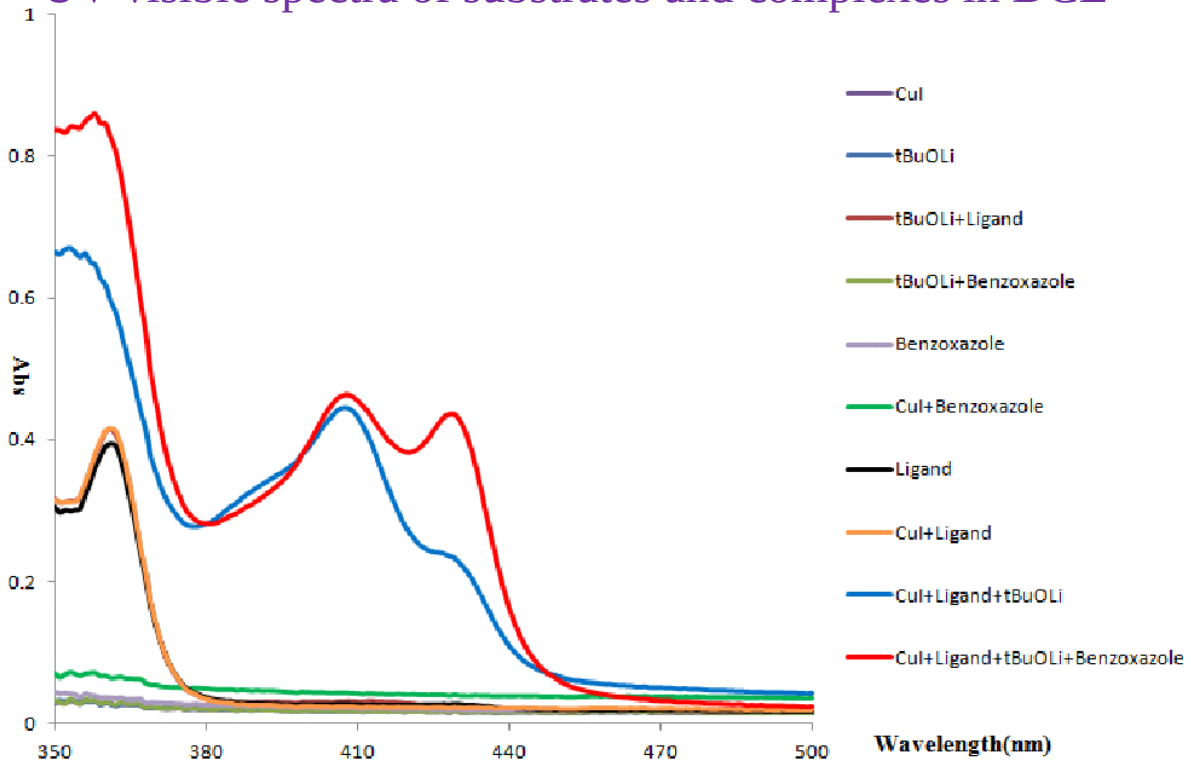
贰 光和铜络合物引发自由基参与的偶联反应 ——和杂环化合物的偶联

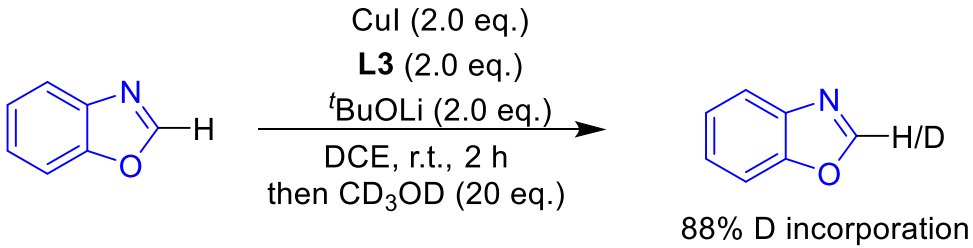


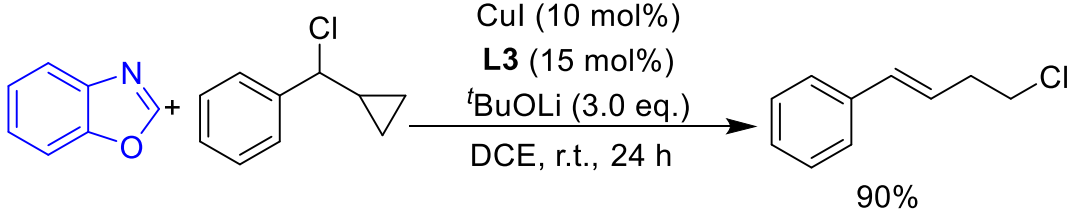




UV-visible spectra of substrates and complexes in DCE



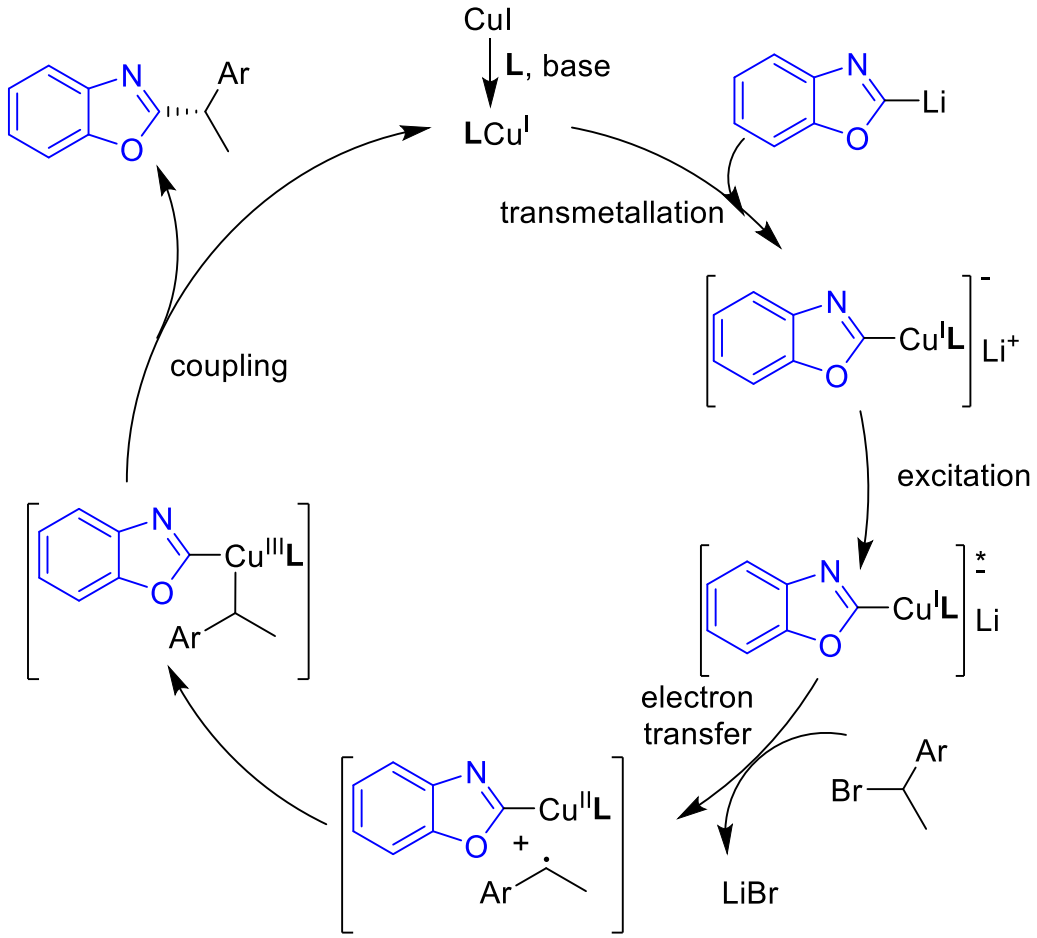




G. Zhang et al., *Angew. Chem. Int. Ed*. **2021**, *60*, 2130.

贰 光和铜络合物引发自由基参与的偶联反应 ——和杂环化合物的偶联

可能的反应机理：



G. Zhang et al., *Angew. Chem. Int. Ed*. **2021**, *60*, 2130.

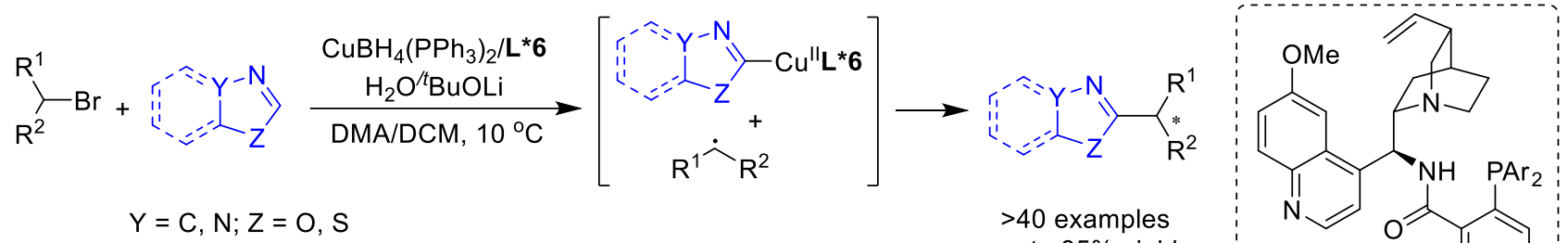
01 背景介绍

02

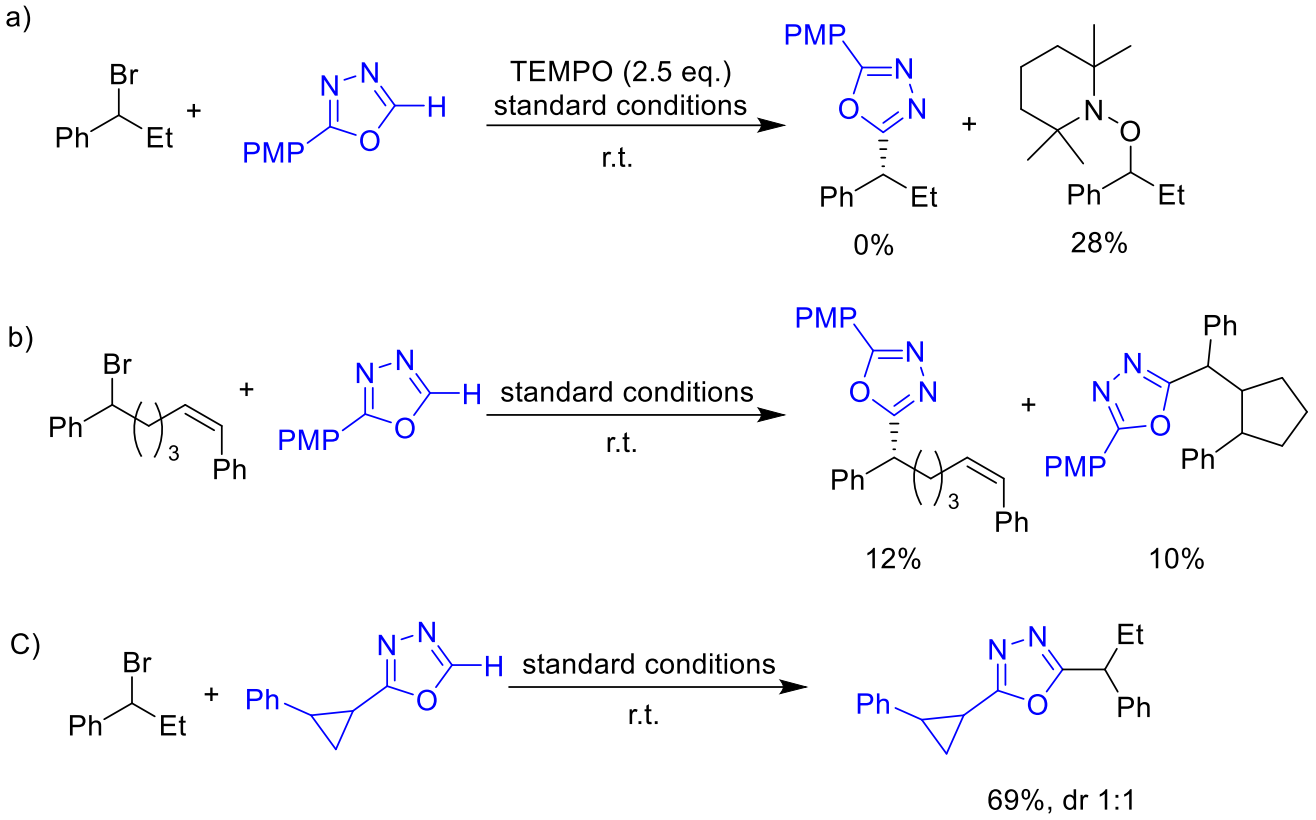
- 光促进的不对称C(sp^3)-C键偶联反应
  - ✓ 光和光催化剂引发自由基参与的偶联反应
  - ✓ 光和铜络合物引发自由基参与的偶联反应
- 铜络合物引发自由基参与的不对称C(sp^3)-C键偶联反应

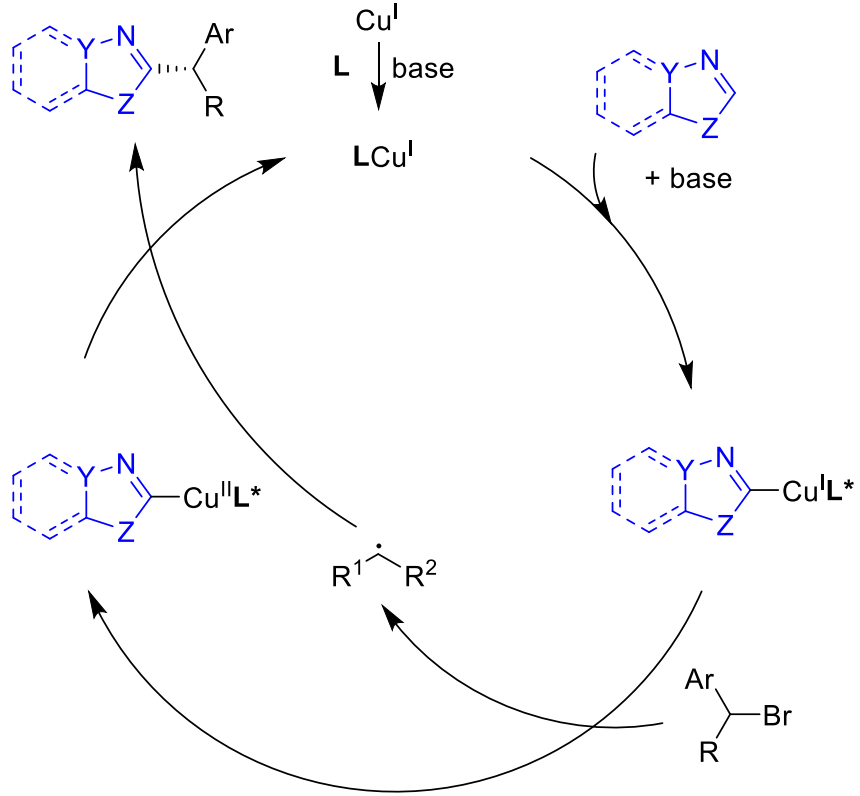
03 总结与展望

贰 铜络合物引发自由基参与的偶联反应——和杂环化合物的偶联



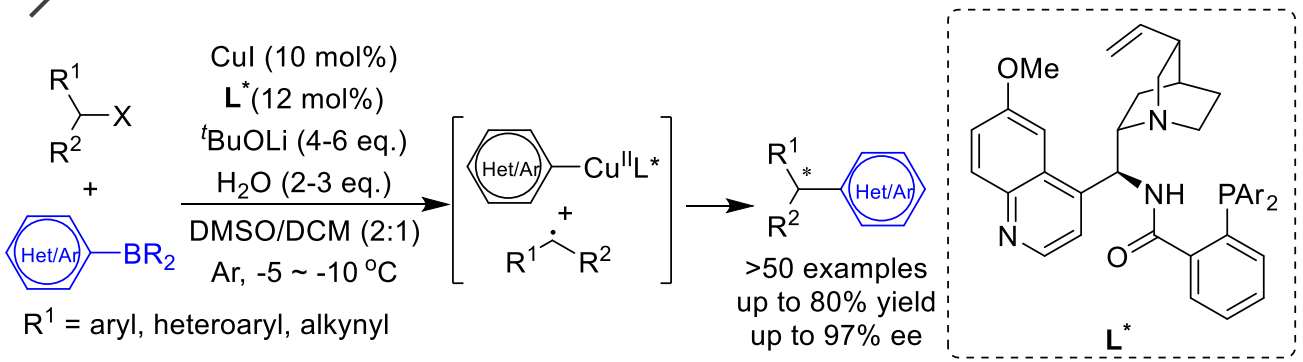
控制实验及可能的反应机理：





X.-Y. Liu et al., *Angew. Chem. Int. Ed.* **2021**, *60*, 380.

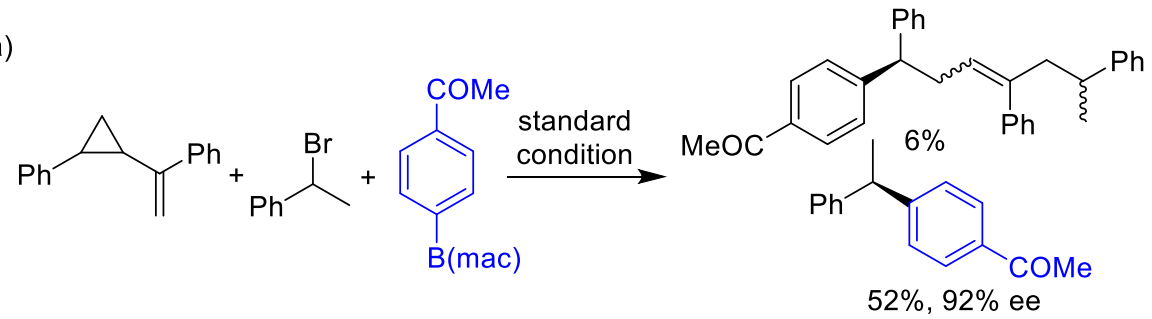
贰 铜络合物引发自由基参与的偶联反应——和硼酸酯的偶联



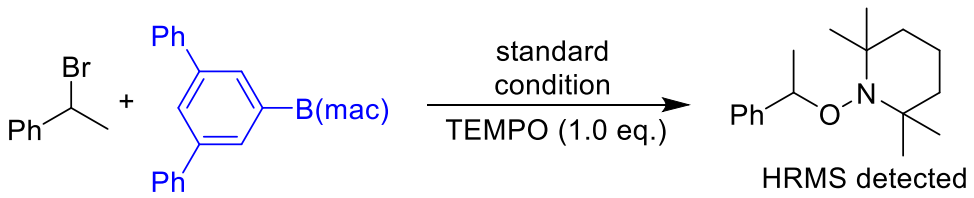
R^1 = aryl, heteroaryl, alkynyl

控制实验：

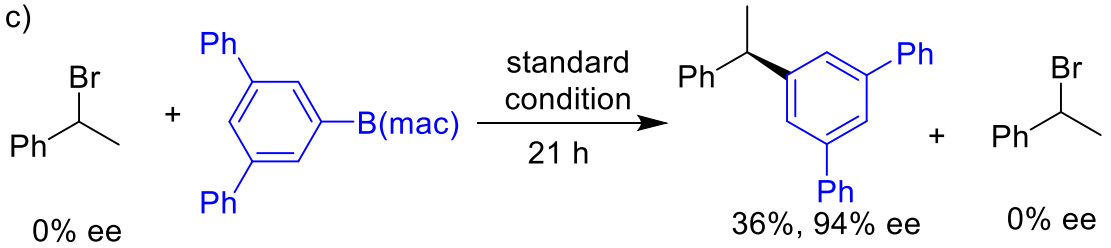
a)



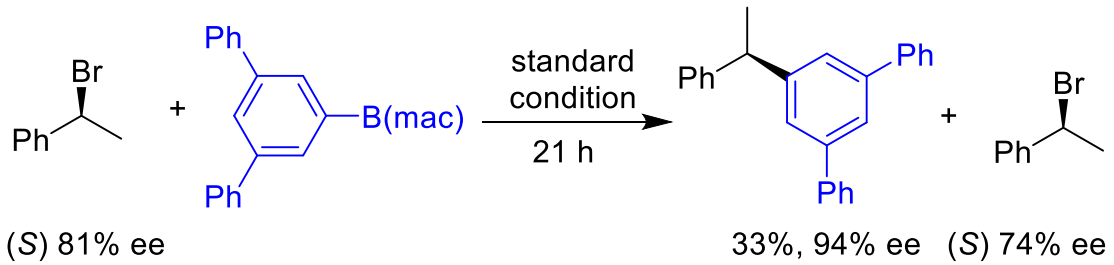
b)



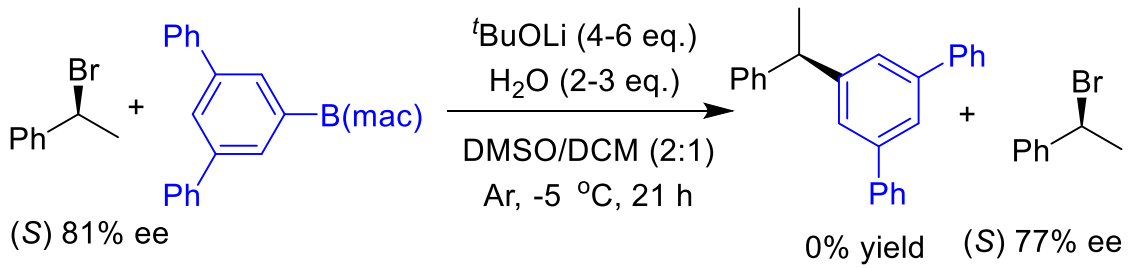
c)



d)



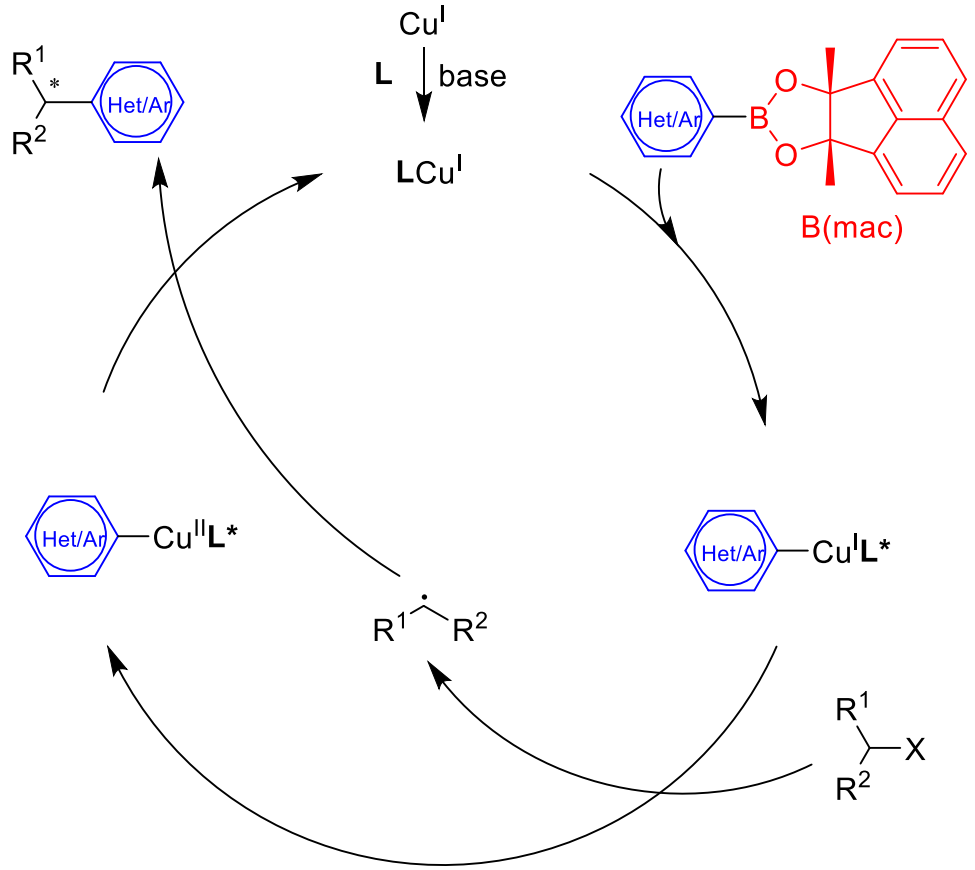
e)



Z.-L. Li, X.-Y. Liu et al., *J. Am. Chem. Soc.* **2020**, *142*, 19652.

贰 铜络合物引发自由基参与的偶联反应——和硼酸酯的偶联

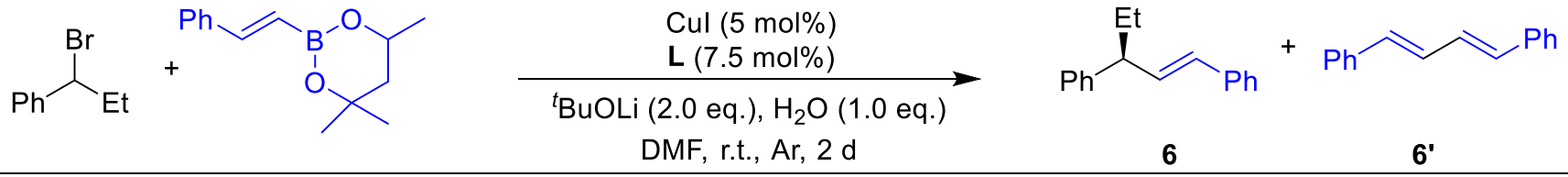
可能的反应机理：

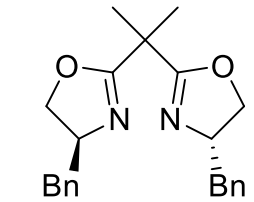


Z.-L. Li, X.-Y. Liu et al., *J. Am. Chem. Soc*. **2020**, *142*, 19652.

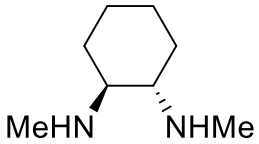
贰 铜络合物引发自由基参与的偶联反应——和硼酸酯的偶联

配体筛选：

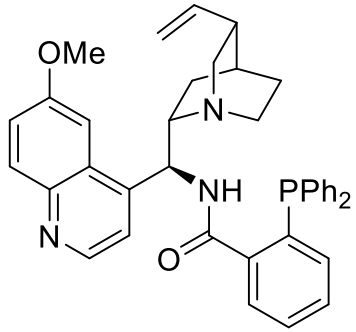




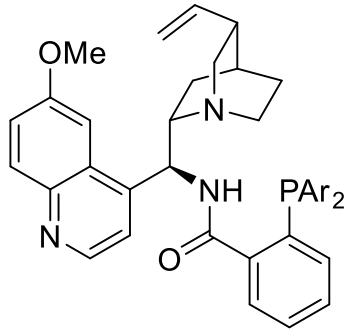
6, trace
6', 29%



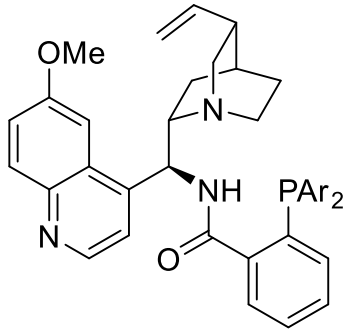
6, trace
6', 81%



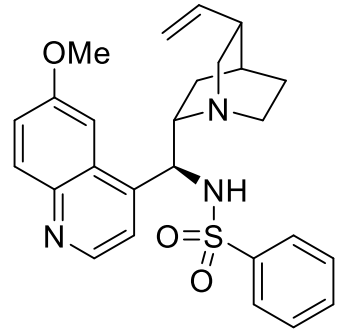
6, 13%, 32% ee
6', 62%



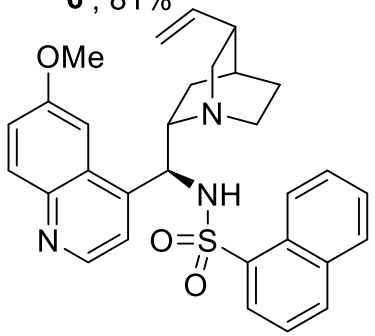
Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$
6, 29%, 43% ee
6', 35%



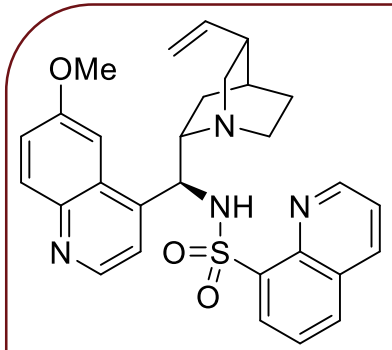
Ar = 2,6-Me$_2$C$_6$H$_3$
6, 28%, 46% ee
6', 32%



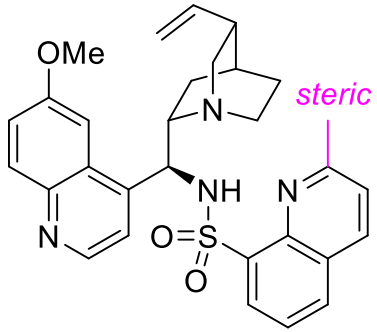
6, 4%, 50% ee
6', 80%



6, 3%, 31% ee
6', 77%



6, 57%, 16% ee
6', 15%

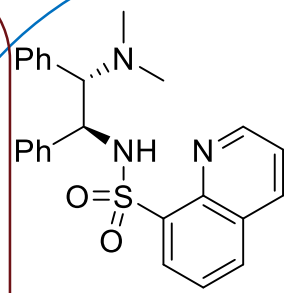


steric effect

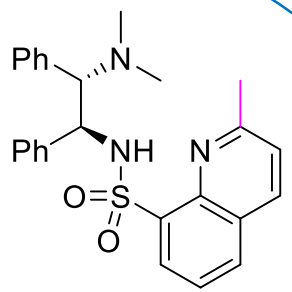
L7 *hemilabile ligand*

6, 57%, 91% ee
6', 26%

-20 °C, 4 d:
6, 77%, 95% ee
6', 8%



-20 °C, 4 d:
6, 55%, -14% ee
6', 10%



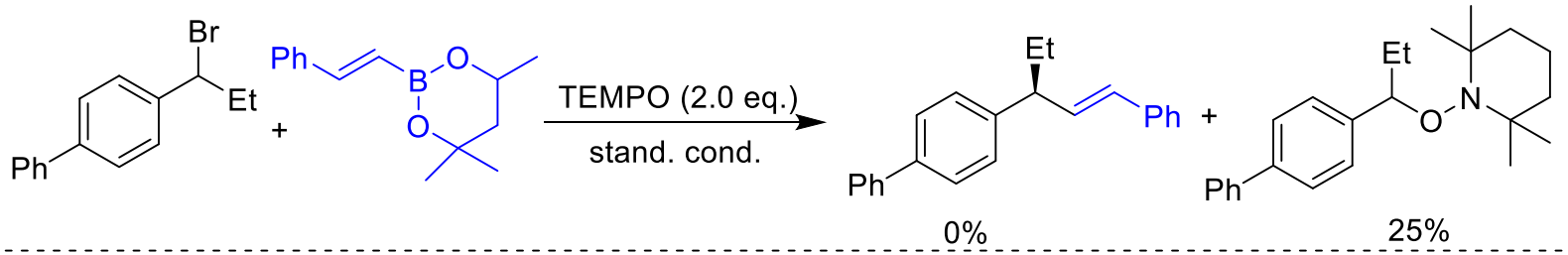
-20 °C, 4 d:
6, 51%, -96% ee
6', 34%

Z.-L. Li, X.-Y. Liu et al., *J. Am. Chem. Soc.* **2022**, *144*, 6442.

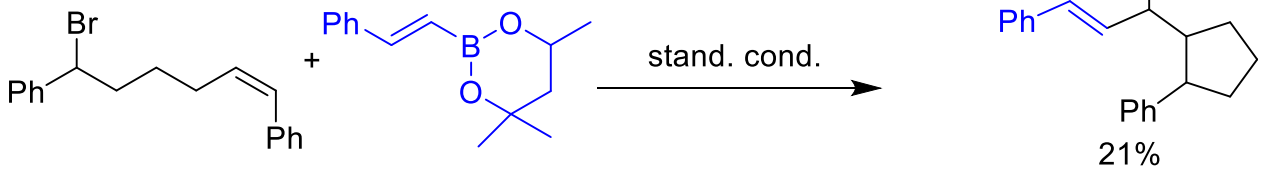
贰 铜络合物引发自由基参与的偶联反应——和硼酸酯的偶联

机理探究实验：

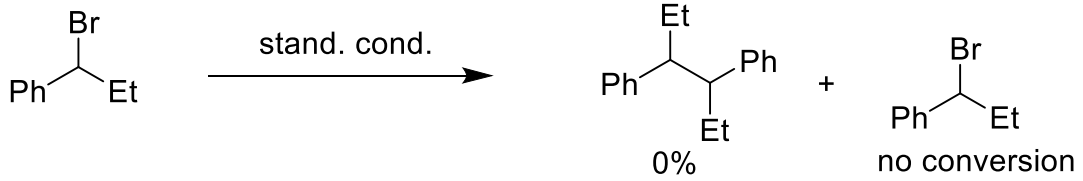
a) Radical trap experiment



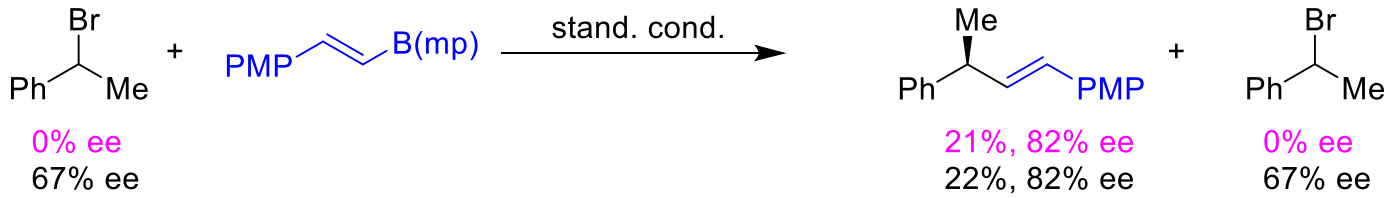
b) Radical clock experiment



c) Effect of nucleophile on reaction initiation



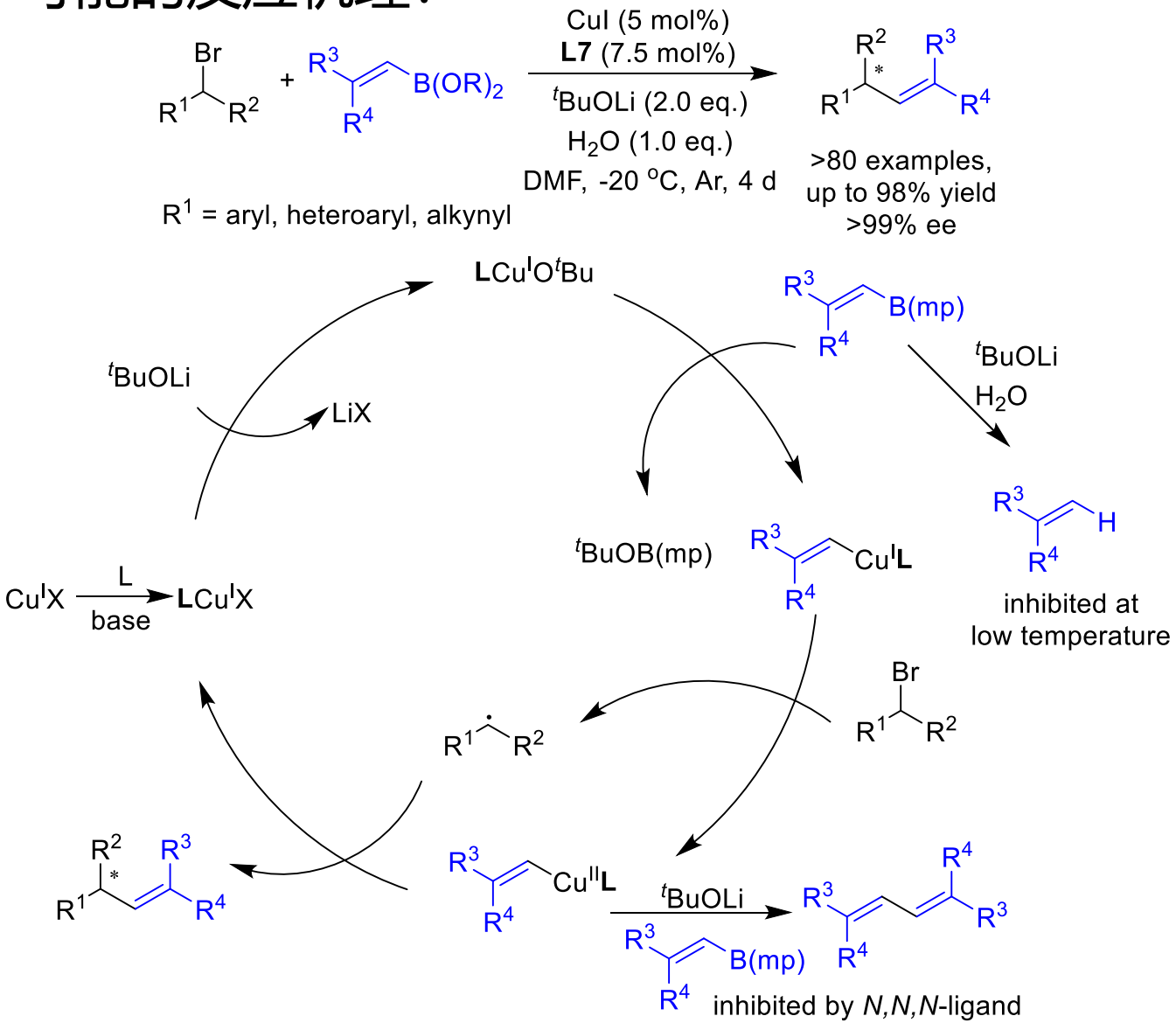
d) Enantiopurity of recovered alkyl bromdie



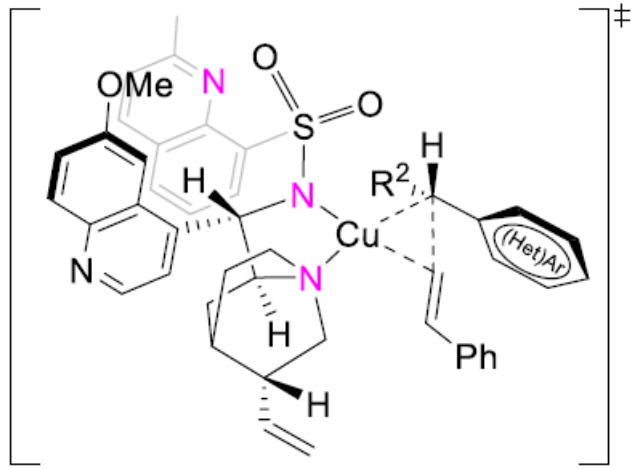
Z.-L. Li, X.-Y. Liu et al., *J. Am. Chem. Soc*. **2022**, *144*, 6442.

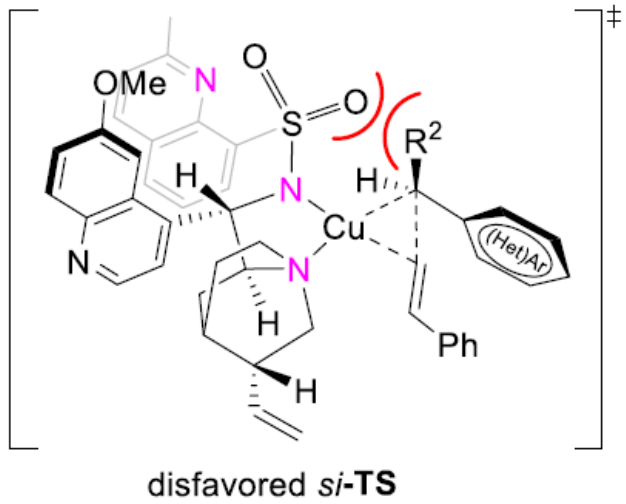
贰 铜络合物引发自由基参与的偶联反应——和硼酸酯的偶联

可能的反应机理：



可能的Cu^{III}中间体及过渡态：

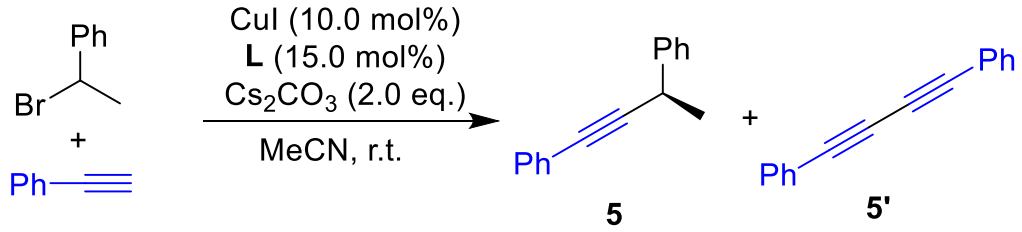




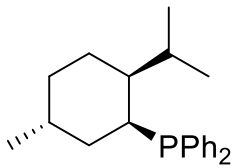
Z.-L. Li, X.-Y. Liu et al., *J. Am. Chem. Soc.* **2022**, *144*, 6442.

贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

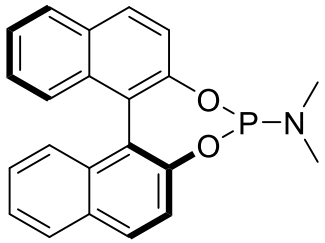
配体筛选：



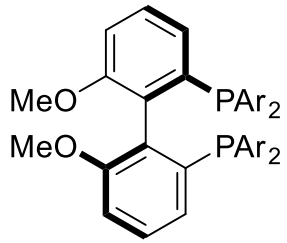
5 **5'**



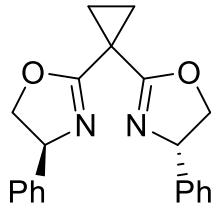
5 trace, **5'** 22%



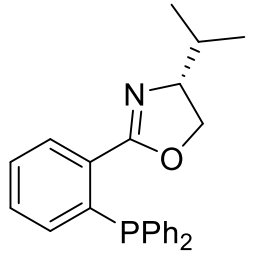
5 trace, **5'** trace



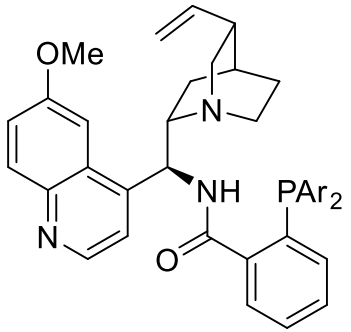
Ar = 3,5-^{t}Bu-4-OMe-C_6H_2
5 trace, **5'** trace



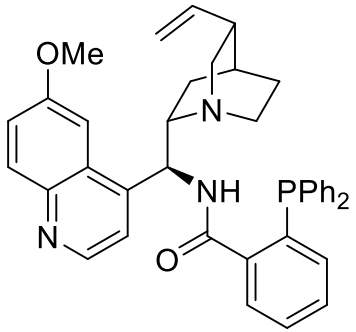
5 trace, **5'** 52%



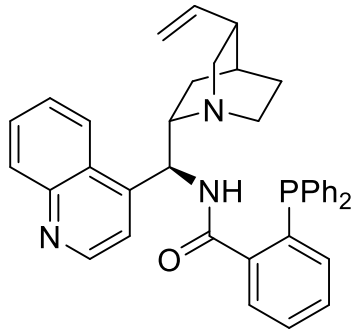
5 trace, **5'** 32%



L2, Ar = 3,5-^{t}Bu$_2$$C_6H_3$
5 90%, 94% ee



L3
5 81%, 50% ee

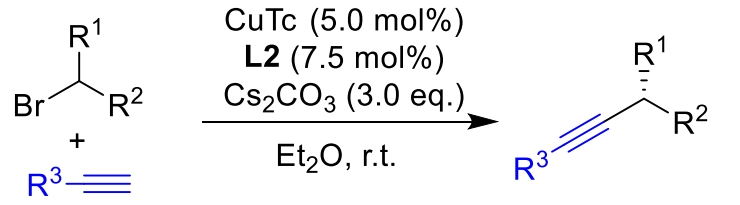


L4

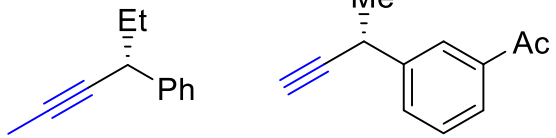
X.-Y. Liu et al., *Nat. Chem.* **2019**, *11* , 1158.

贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

底物拓展：

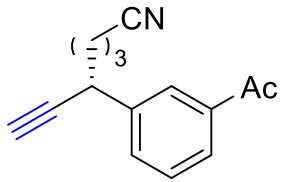


> 120 examples
up to 99% ee

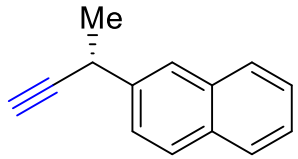


88%, 97% ee

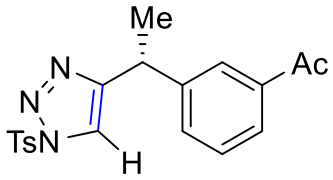
96%, 96% ee



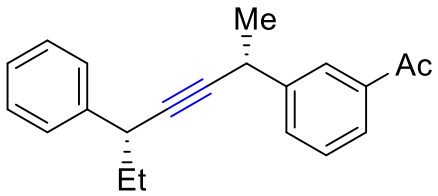
77%, 95% ee



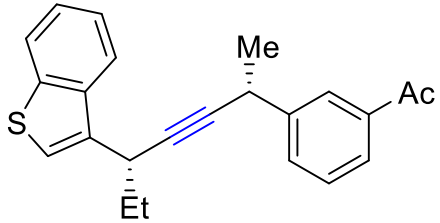
71%, 93% ee



81%, 95% ee



68%, 95% ee, dr > 20:1



49%, 95% ee, dr > 20:1

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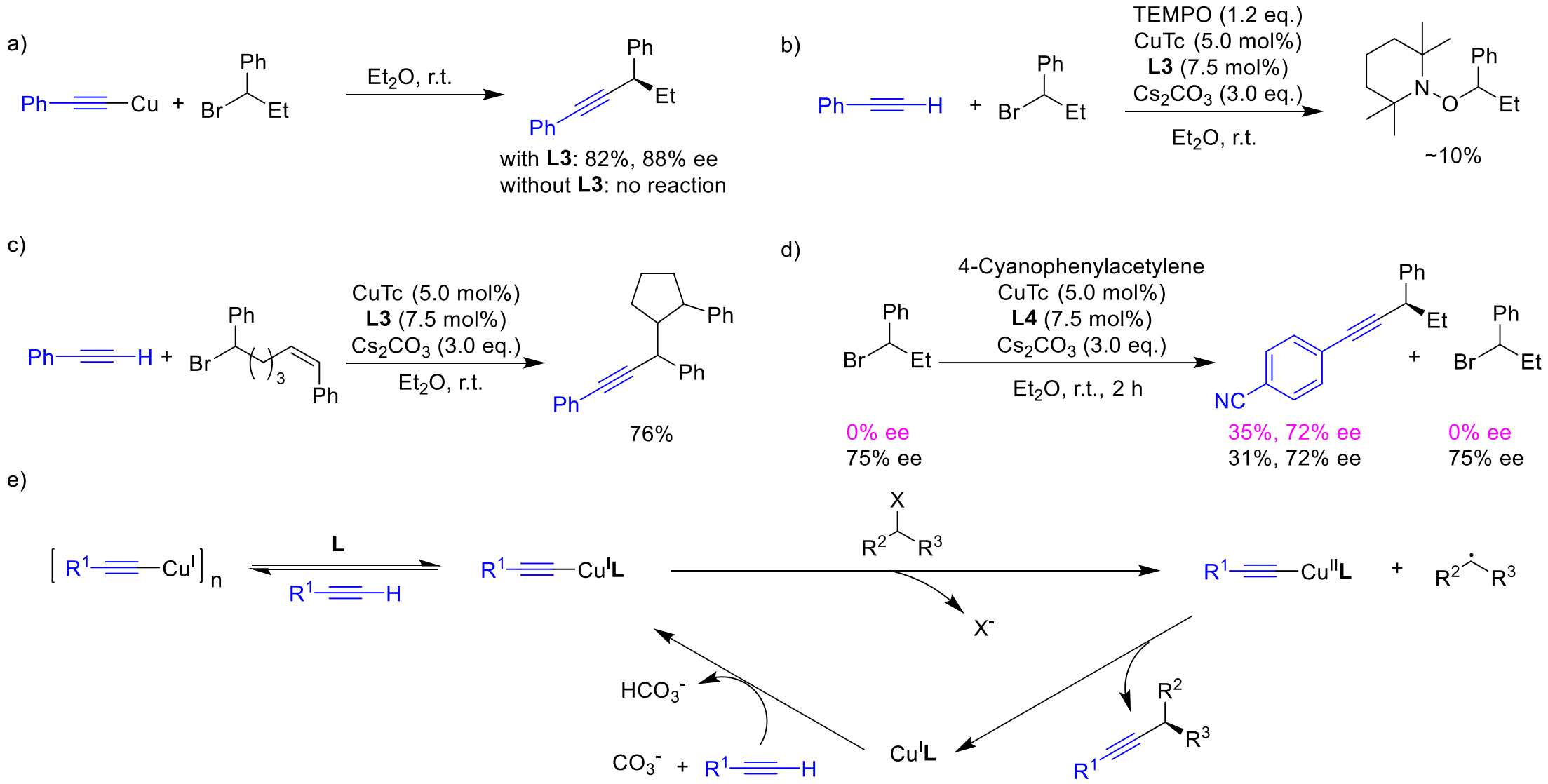
贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

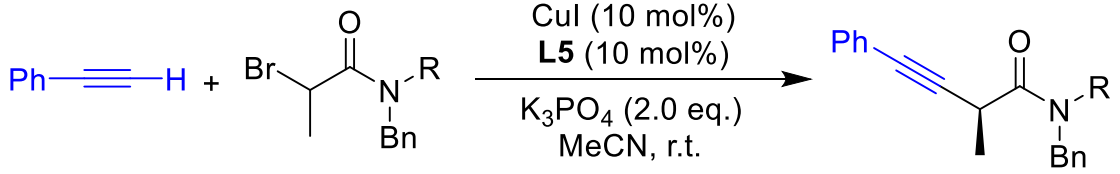
控制实验及可能的反应机理：

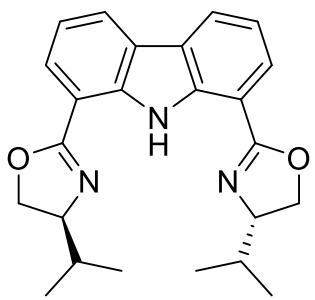


贰

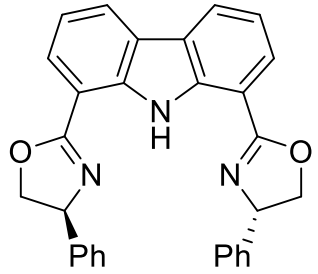
铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

配体考察：

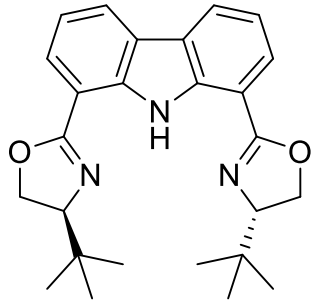




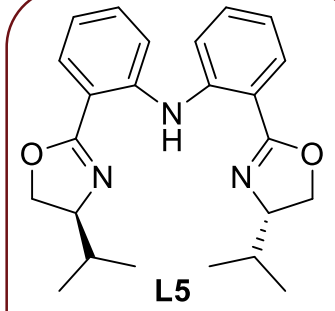
R = Ph
67%, 13% ee



R = Ph
86%, 13% ee

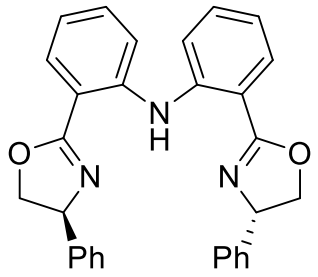


R = Ph
55%, 3% ee

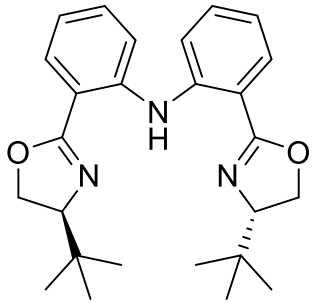


L5

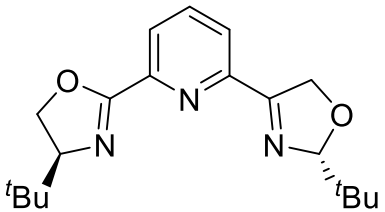
R = Ph
80%, 76% ee
R = Mes, -10 °C
84%, 94% ee



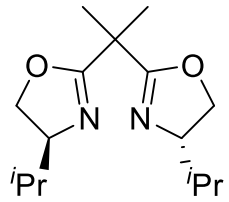
R = Ph
60%, 40% ee



R = Ph
0, -



R = Ph
0, -

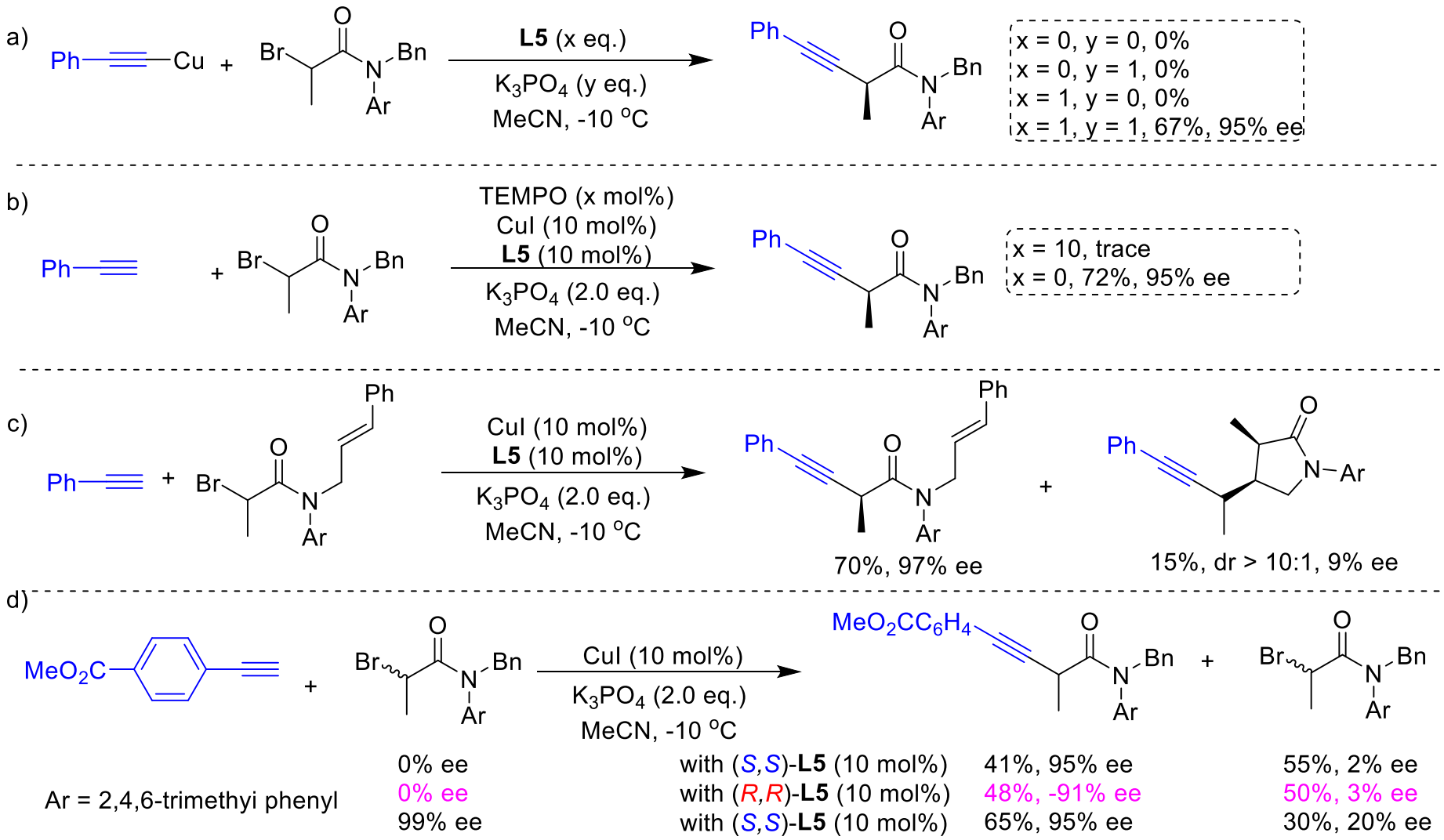


R = Ph
0, -

G. Zhang et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 13998.

贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

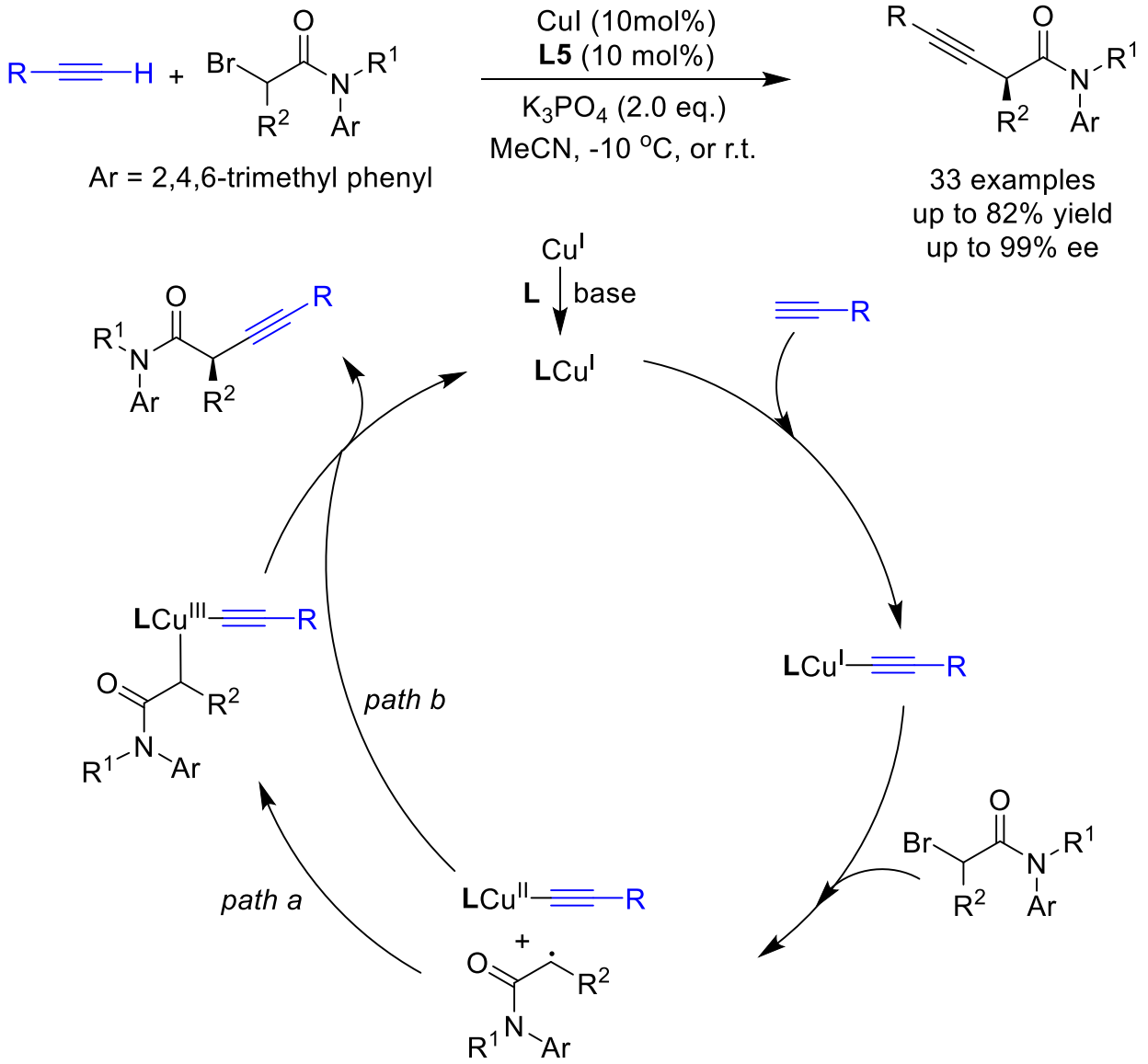
控制实验：



G. Zhang et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 13998.

贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

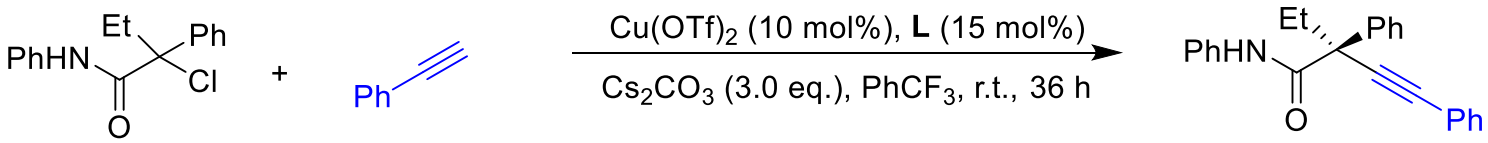
可能的反应机理：

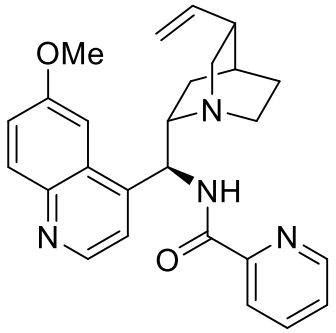


G. Zhang et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 13998.

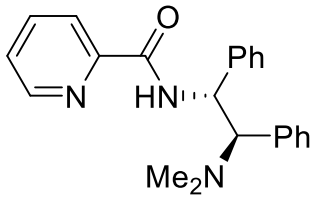
贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

配体筛选：

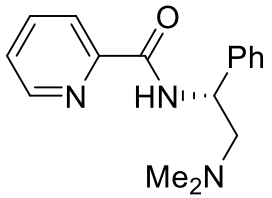




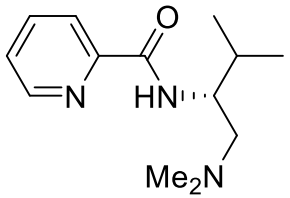
65%, 41% ee



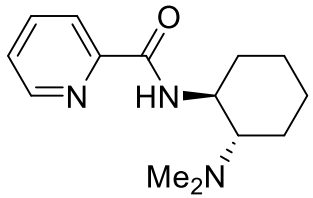
62%, -51% ee



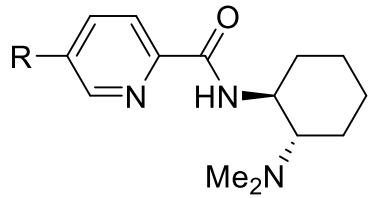
74%, 55% ee



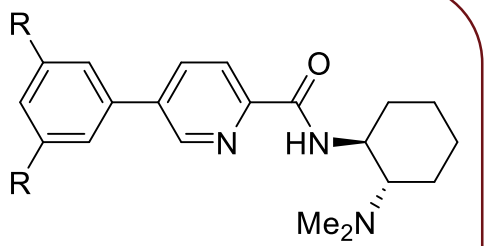
66%, 42% ee



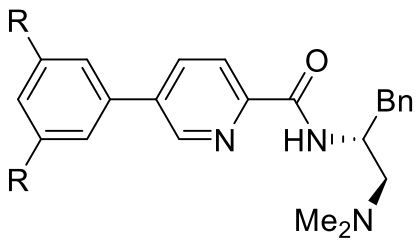
81%, 61% ee



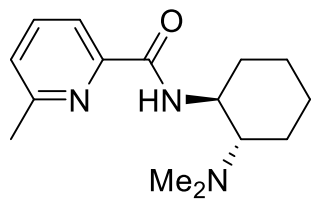
R = Ph, 83%, 72% ee
R = 1-Np, 80%, 78% ee
R = 9-An, 80%, 81% ee



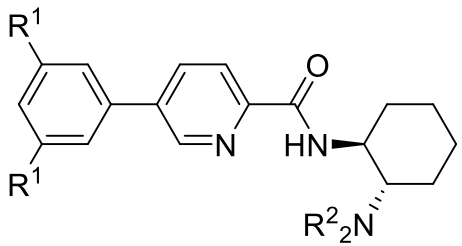
R = Ph, 76%, 82% ee
R = 1-Np, 72%, 85% ee
R = 4-^{t}BuPh, 80%, 86% ee



R = 4-^{t}BuPh, 84%, 85% ee



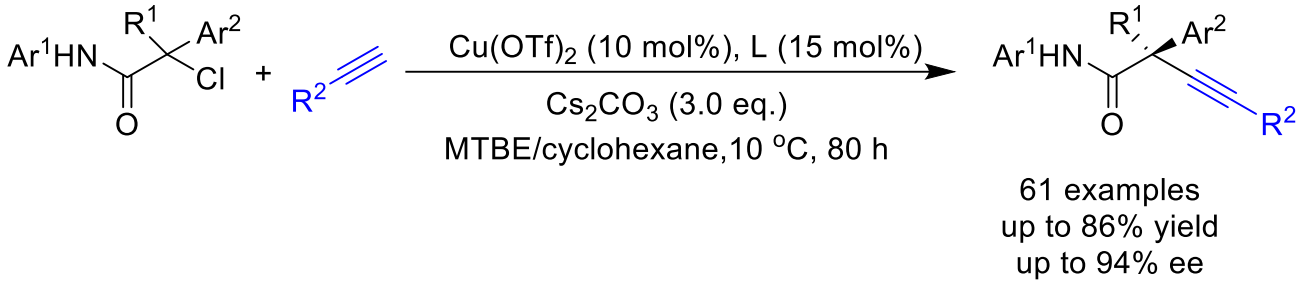
21%, 17% ee



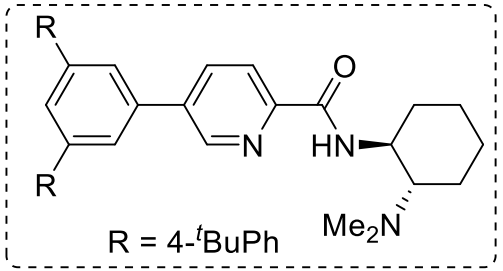
R^1, R^2 = 4-^{t}BuPh, (C_2H_4), 21%, 37% ee
R^1, R^2 = 4-^{t}BuPh, Bn, 12%, 0% ee

贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

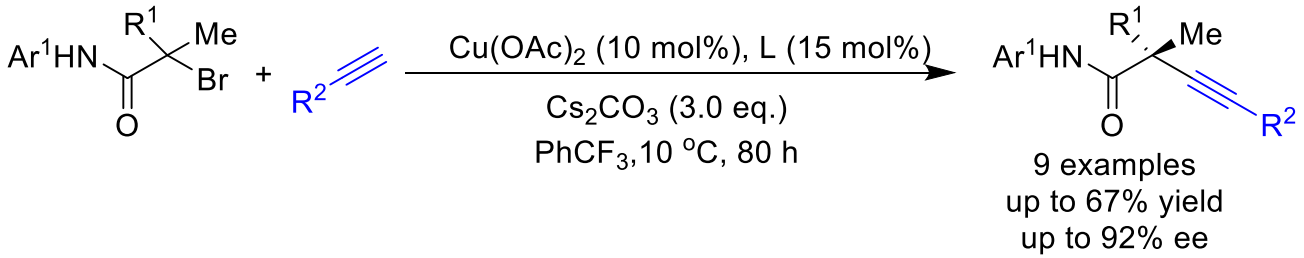
底物适用范围考察：



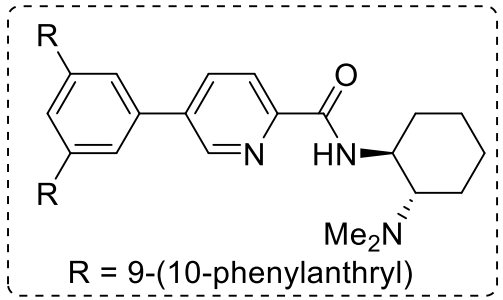
61 examples
up to 86% yield
up to 94% ee



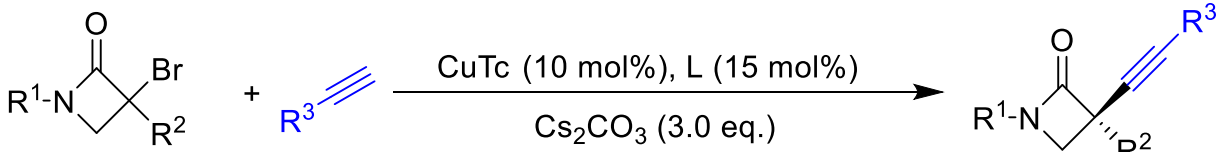
R = 4-^{t}BuPh



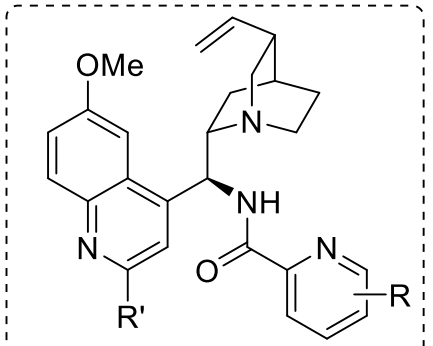
9 examples
up to 67% yield
up to 92% ee



R = 9-(10-phenylanthryl)



17 examples
up to 90% yield
up to 92% ee



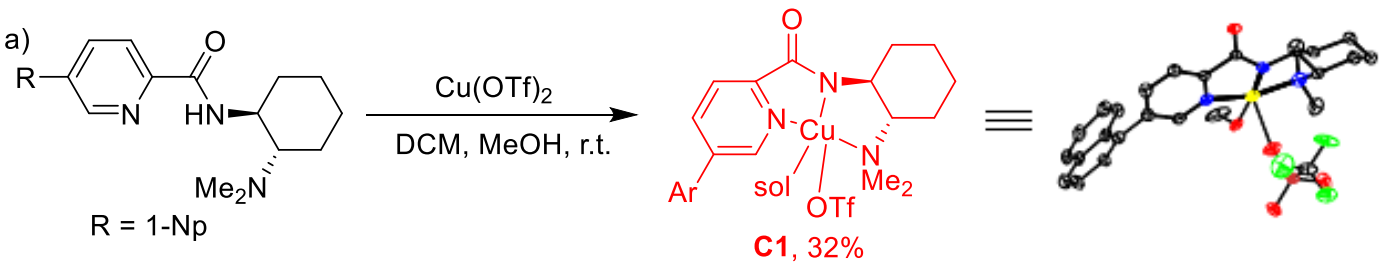
R = H, R' = 5-CF_3
R = 3,5-Me_2Ph, R' = 5-CF_3
R = H, R' = 1-isoquinolinyl

Q.-S. Gu, X. Hong, X.-Y. Liu et al., *Nat. Chem.* **2022**, *14* , 949.

贰 铜络合物引发自由基参与的偶联反应——和末端炔烃的偶联

控制实验：

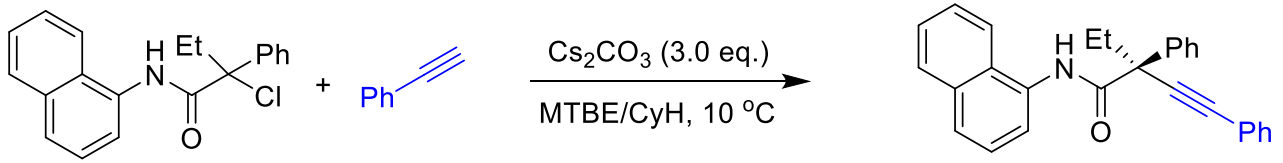
a)



R = 1-Np

C1, 32%

b)



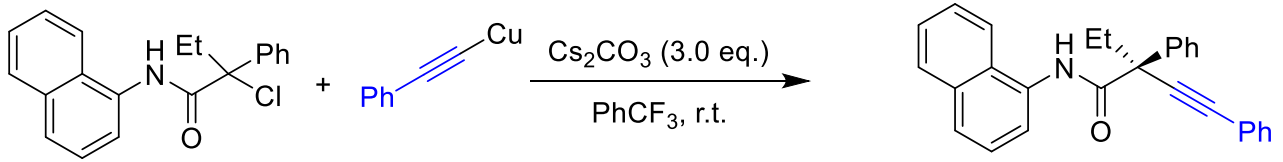
E2

11

with **C1**: 75%, 89% ee

with $Cu(OTf)_2$/**L**: 50%, 88% ee

c)

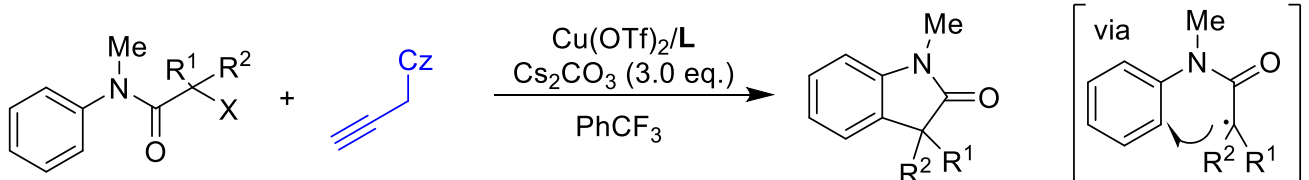


11

with **L**: 20%, 88% ee

without **L**: 0%

d)



X = Cl, R^1 = Et, R^2 = Ph

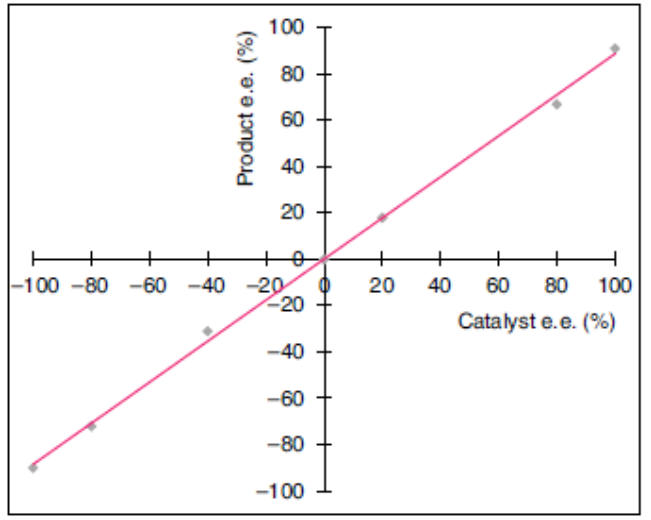
X = Br, R^1 = Ph = Me

Cz:9-carbazolyl

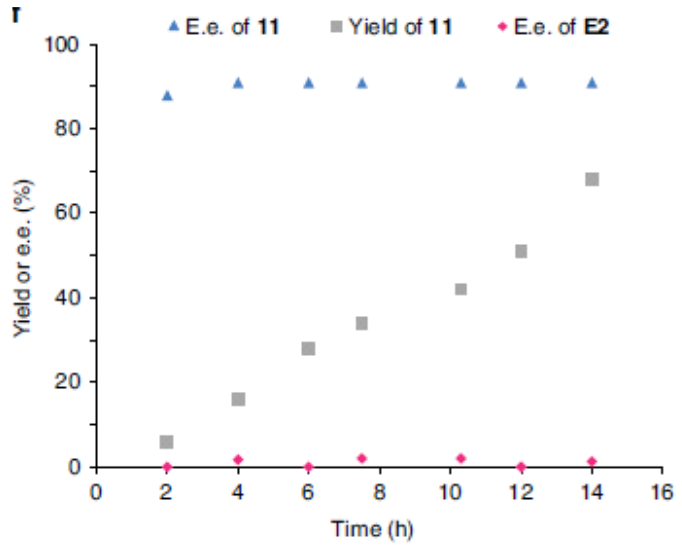
90 °C, 30%

50 °C, 45%

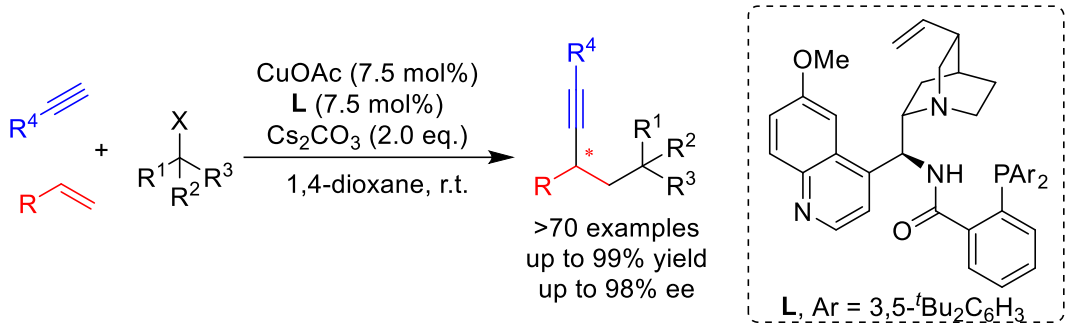
e)



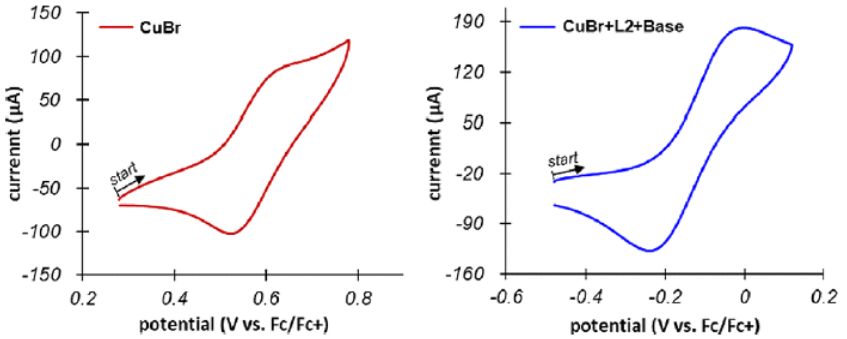
f)



贰 铜络合物引发自由基参与的偶联反应——机理探究



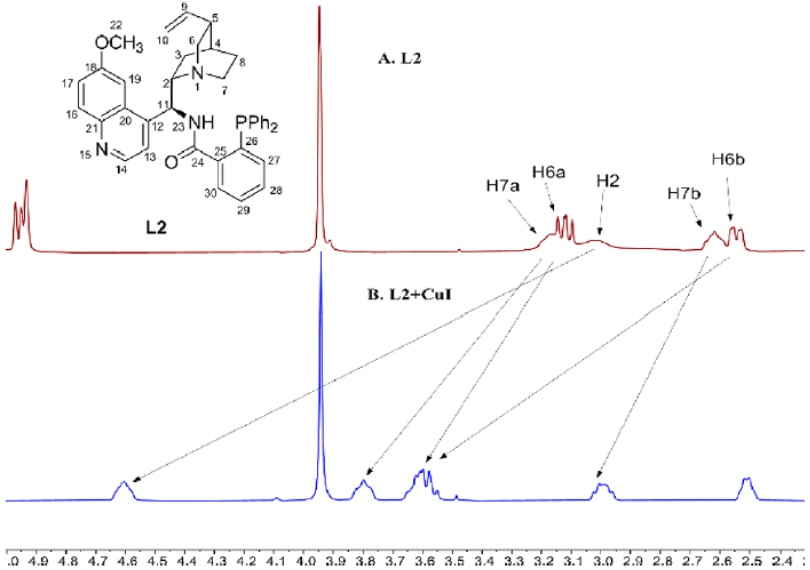
实验探究配体对金属铜电性的影响：



CuBr: +0.6 V　　L2 CuBr: -0.1 V

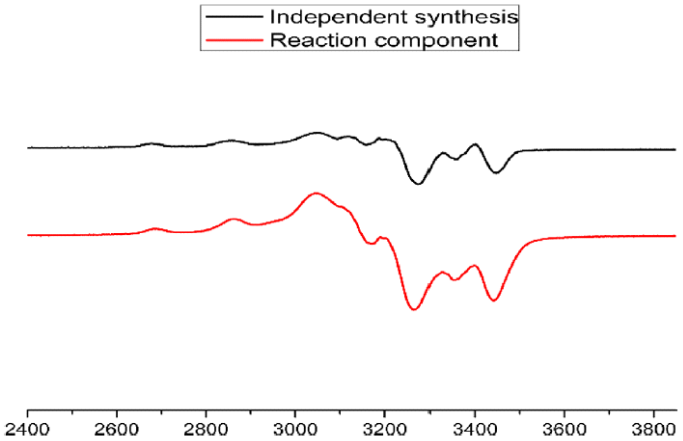
Cyclic voltammograms of CuBr (red) and the **L2** CuBr complex (blue). Conditions: 10 mM in CH_3CN with 0.1 M Bu_4NPF_6 as electrolyte and a 100 mV/s scan rate using a glassy carbon working electrode and a Pt counter electrode. Potentials were calibrated with Fc as an internal standard.

实验探究配体和金属铜的配位模式：



^{1}H NMR Studies of the **L2** CuI Complex. Red: ^{1}H NMR of **L2**. Blue: ^{1}H NMR of **L2** Cu^I.

实验探究反应体系中金属铜的价态：



X-band EPR spectrum (9.26 GHz, 100 K). Black: a mixture of $Cu(OAc)_2$, **L2**, and 4-Cyanophenylacetylene. Red: a reaction component of the standard model carboalkynylation reaction.

X.-Y. Liu et al., *J. Am. Chem. Soc.* **2020**, *142*, 9501.

01 背景介绍

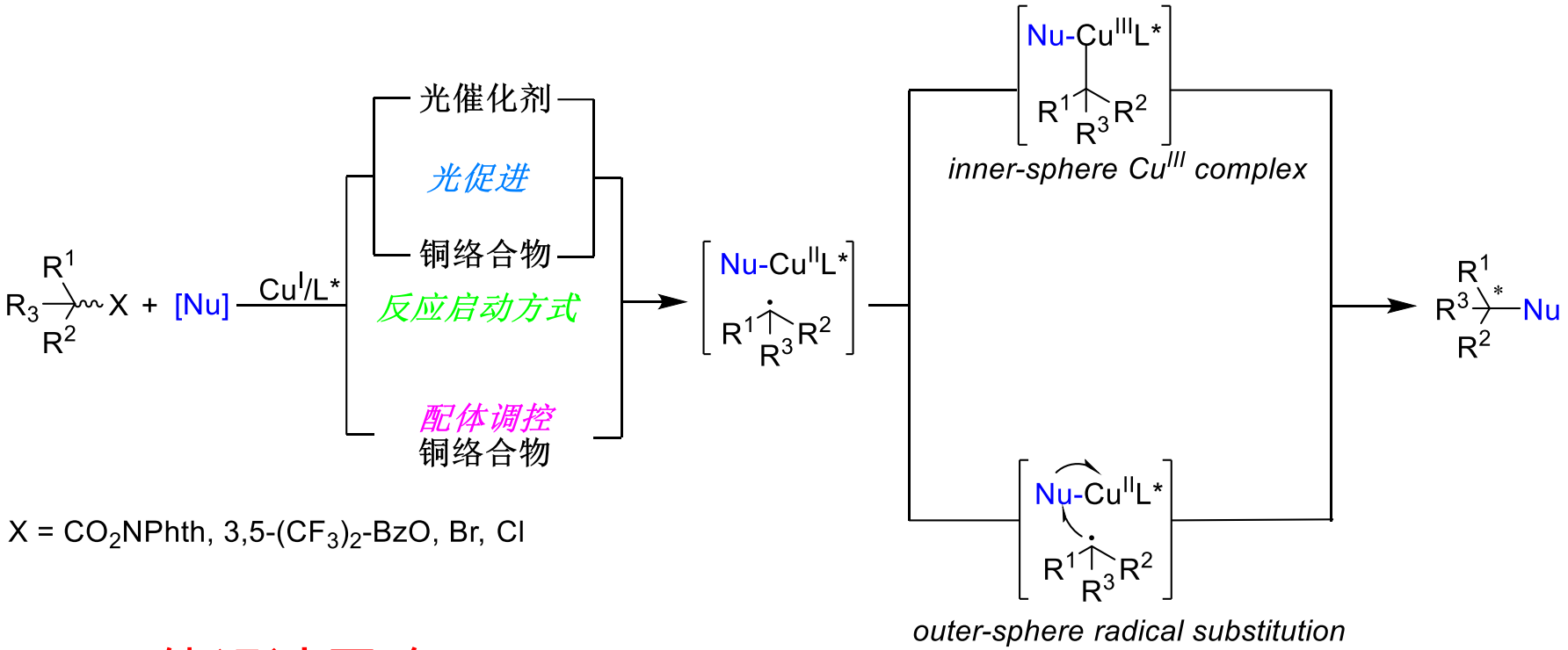
02

- 光促进的不对称C(sp^3)-C键偶联反应
  - ✓ 光和光催化剂引发自由基参与的偶联反应
  - ✓ 光和铜络合物引发自由基参与的偶联反应
- 铜络合物引发自由基参与的不对称C(sp^3)-C键偶联反应

03 总结与展望

叁 总结与展望

总结：



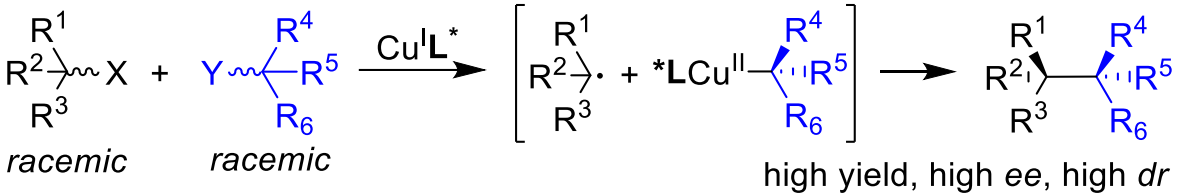
配体设计思路：

- 富电子配体来提高铜催化剂的还原能力以促进反应的进行
- 能够高效控制高活性前手性烷基自由基的对映选择性偶联

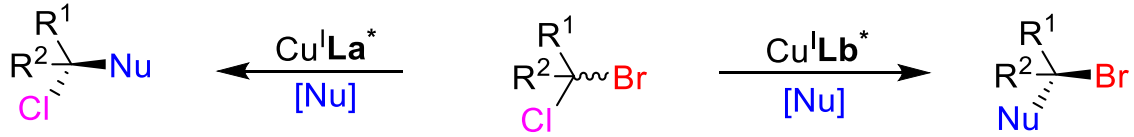
叁 总结与展望

展望：

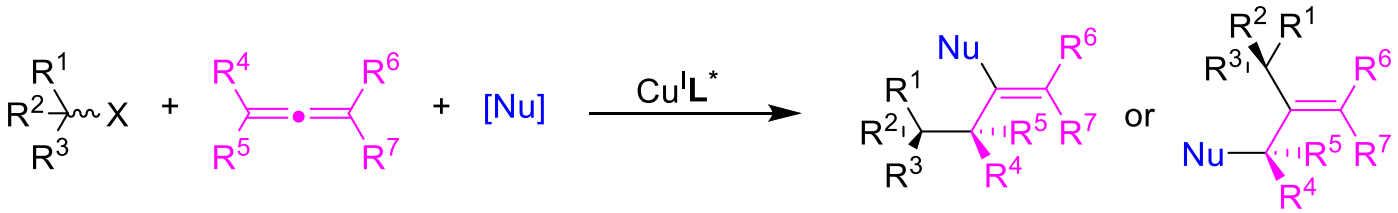
- 实现多手性中心复杂分子的构建



- 实现卤原子的选择性不对称偶联



- 实现联烯参与的三组分不对称偶联



谢谢大家！

恳请各位老师批评指正！