

Cu催化的偶联反应

--Liu Group



1852946 · Shenghan Cai

作者介绍



Prof. Xin-Yuan Liu

工作经历

- 2018年1月-至今 教授，南方科技大学化学系
- 2012年9月-2017年12月 副教授，南方科技大学化学系
- 2010年4月-2012年8月 博士后，美国斯克普斯研究所，香港大学。导师：Carlos F. Barbas III, 支志明
- 2004年7月-2005年8月 研究助理，中科院上海有机化学研究所。导师：赵刚

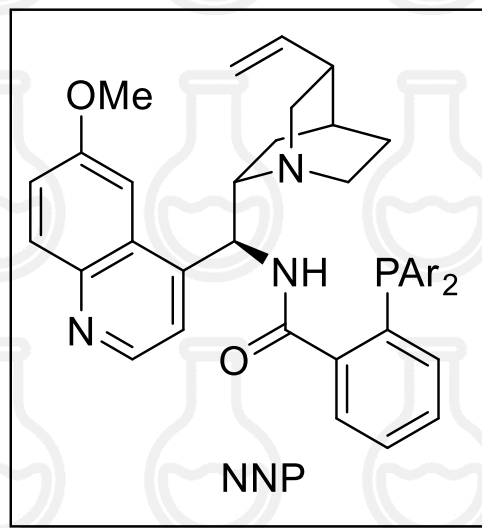
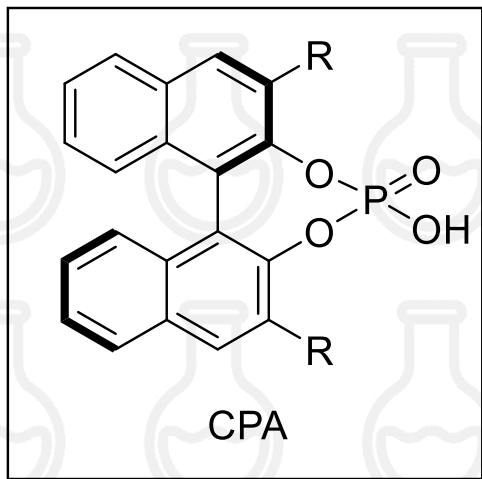
教育经历

- 2005年9月-2010年3月 博士，香港大学化学系，导师：支志明
- 2001年9月-2004年6月 硕士，中国科学院上海有机化学研究所与安徽师范大学联合培养，导师：朱仕正 王绍武
- 1997年9月-2001年6月 学士，安徽师范大学

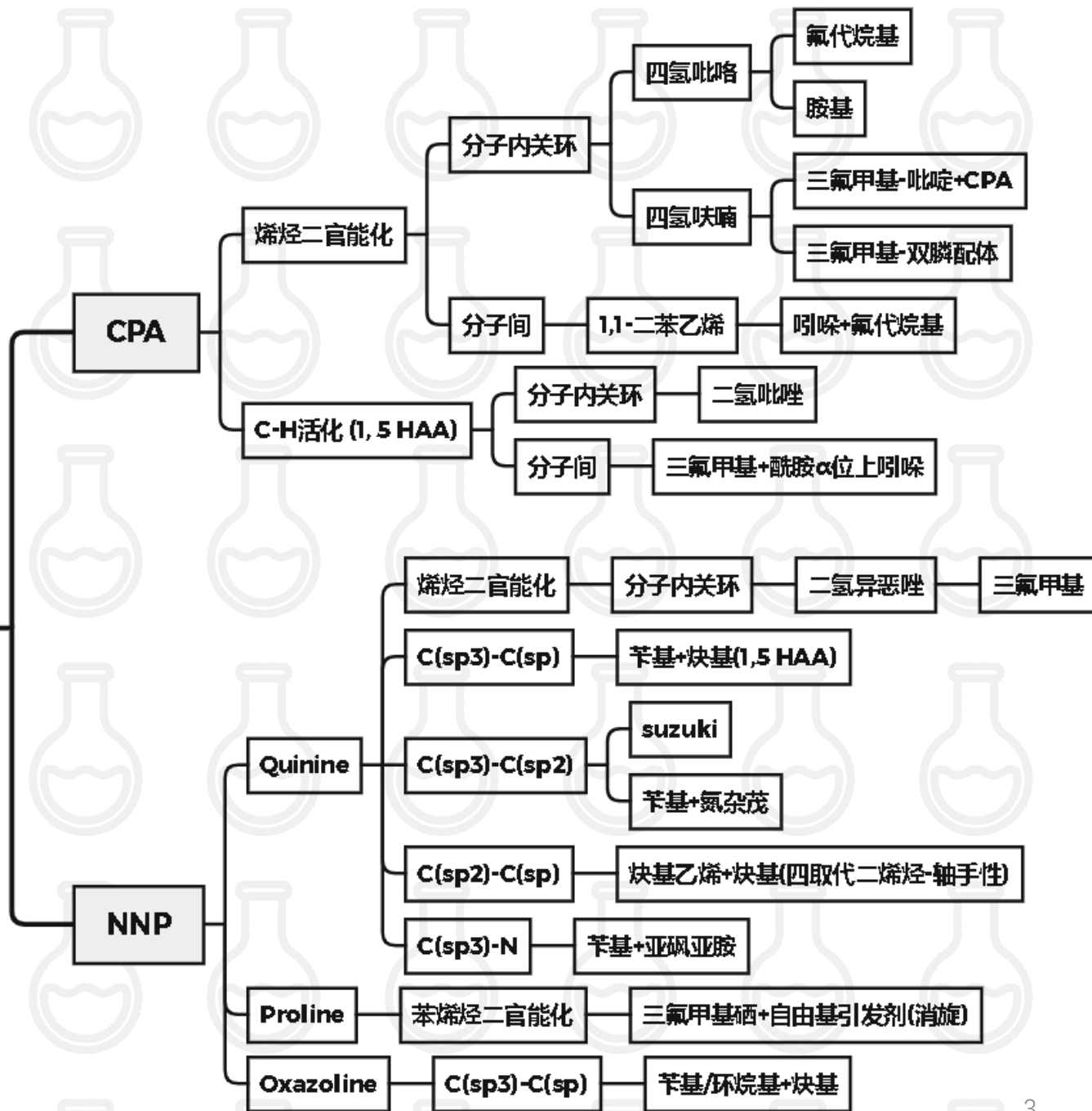
研究兴趣

- 自由基不对称化学
- 自由基迁移化学
- 有机氟化学

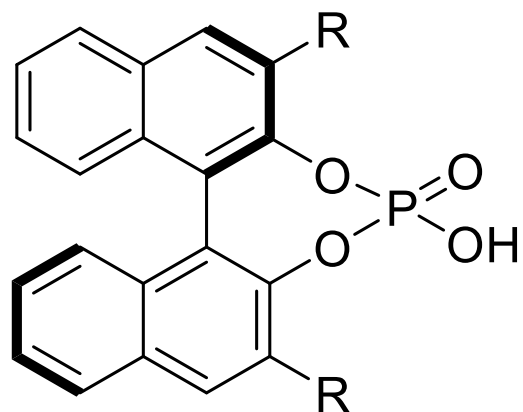
研究简介



Liu Group



CPA+Cu(I)



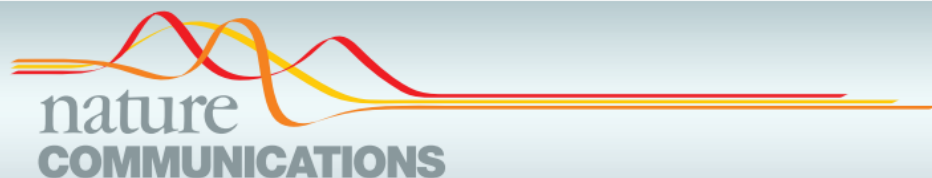
Part I

A Dual-Catalytic Strategy To Direct Asymmetric Radical Aminotrifluoromethylation of Alkenes

Jin-Shun Lin,^{†,‡} Xiao-Yang Dong,[†] Tao-Tao Li,[†] Na-Chuan Jiang,[†] Bin Tan,[†] and Xin-Yuan Liu^{*,†}

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ARTICLE

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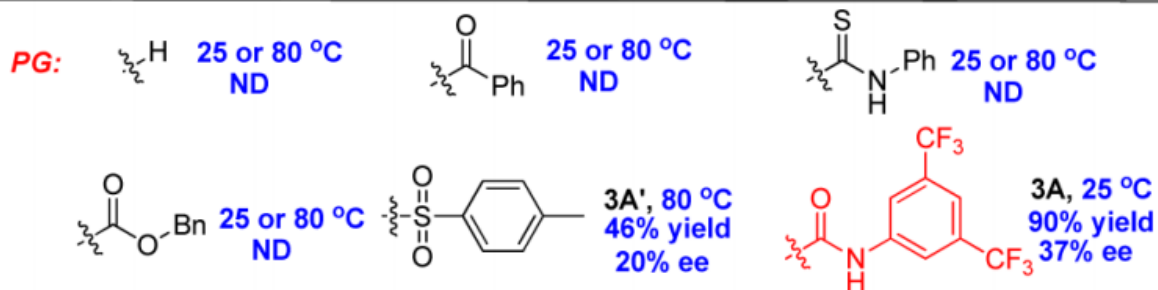
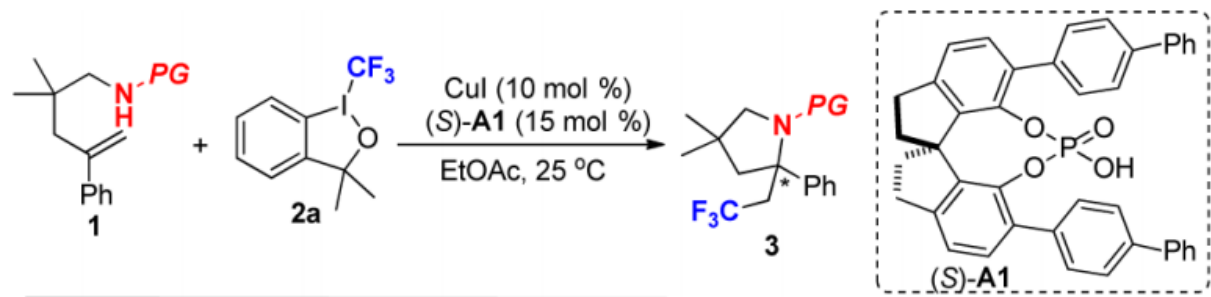
OPEN

Catalytic asymmetric radical aminoperfluoroalkylation and aminodifluoromethylation of alkenes to versatile enantioenriched-fluoroalkyl amines

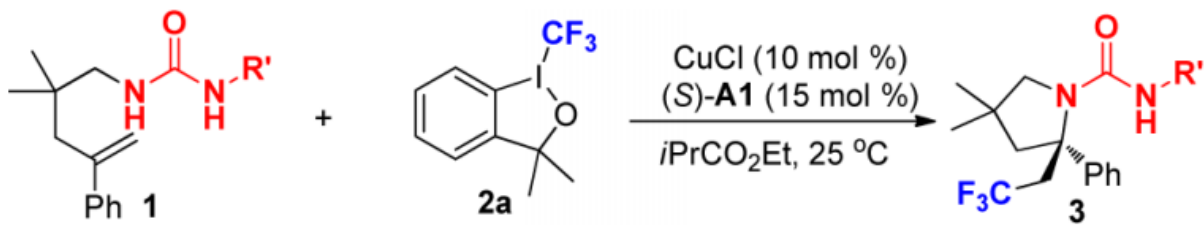
Jin-Shun Lin^{1,*}, Fu-Li Wang^{1,*}, Xiao-Yang Dong^{1,*}, Wei-Wei He¹, Yue Yuan¹, Su Chen¹ & Xin-Yuan Liu¹

内容相似，使用自由基引发剂不同

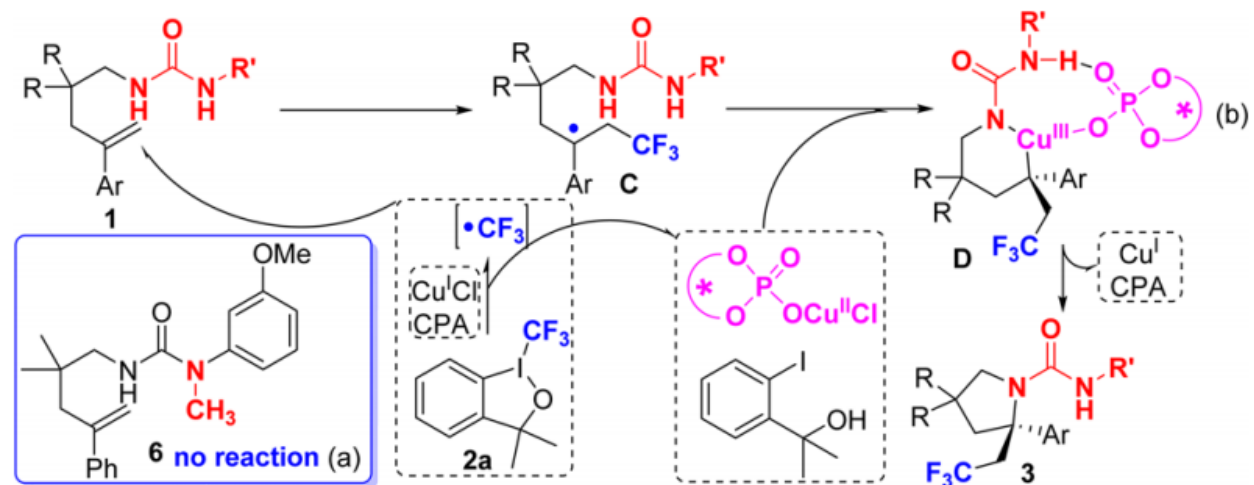
JACS:
Togni 试剂
Nat comm:
烷基磺酰氯



Two acidic N–H as both the nucleophile and directing group



yield: 85%
ee: 91%



胺作为底物可能存在的问题:

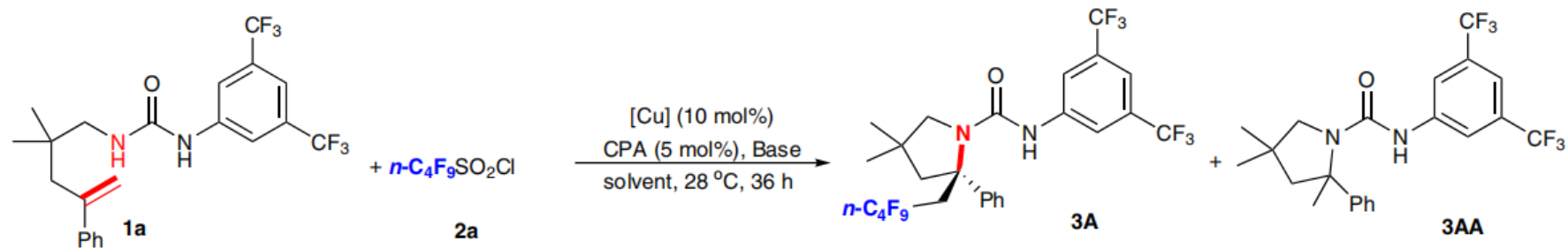
- 易被氧化
- 造成金属催化剂中毒

解决方案:

- 带有吸电子的保护基团同时确保所需的N的亲核性
- 提供两个酸性的N–H，与CPA形成氢键提升立体选择性

偕二甲基效应:

- 分子链中亚甲基上的氢被大体积烷基取代后，该处键角变小，分子链末端两个反应基团相互靠近，有利于分子内环化反应



自由基引发剂

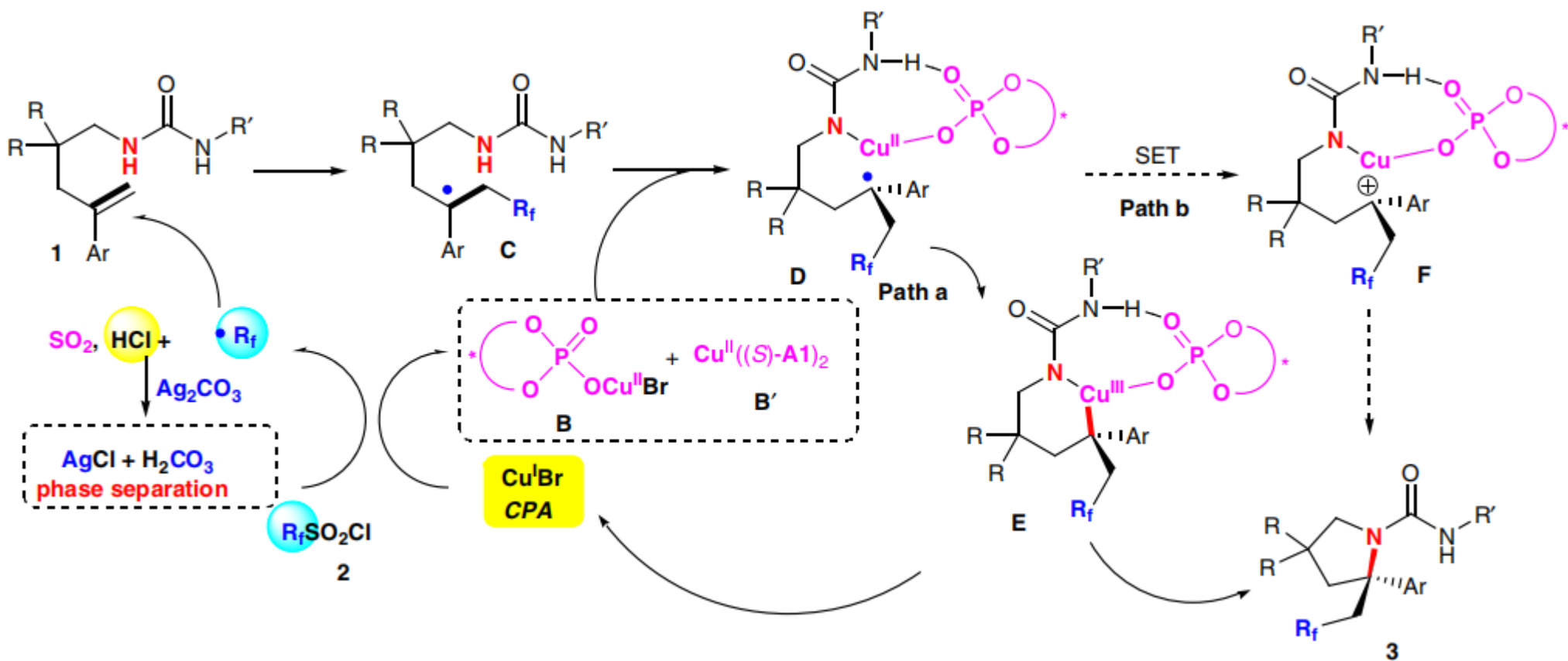
$n\text{-C}_4\text{F}_9\text{SO}_2\text{Cl}$

$\text{MeO}_2\text{CCF}_2\text{SO}_2\text{Cl}$

$\text{HCF}_2\text{SO}_2\text{Cl}$

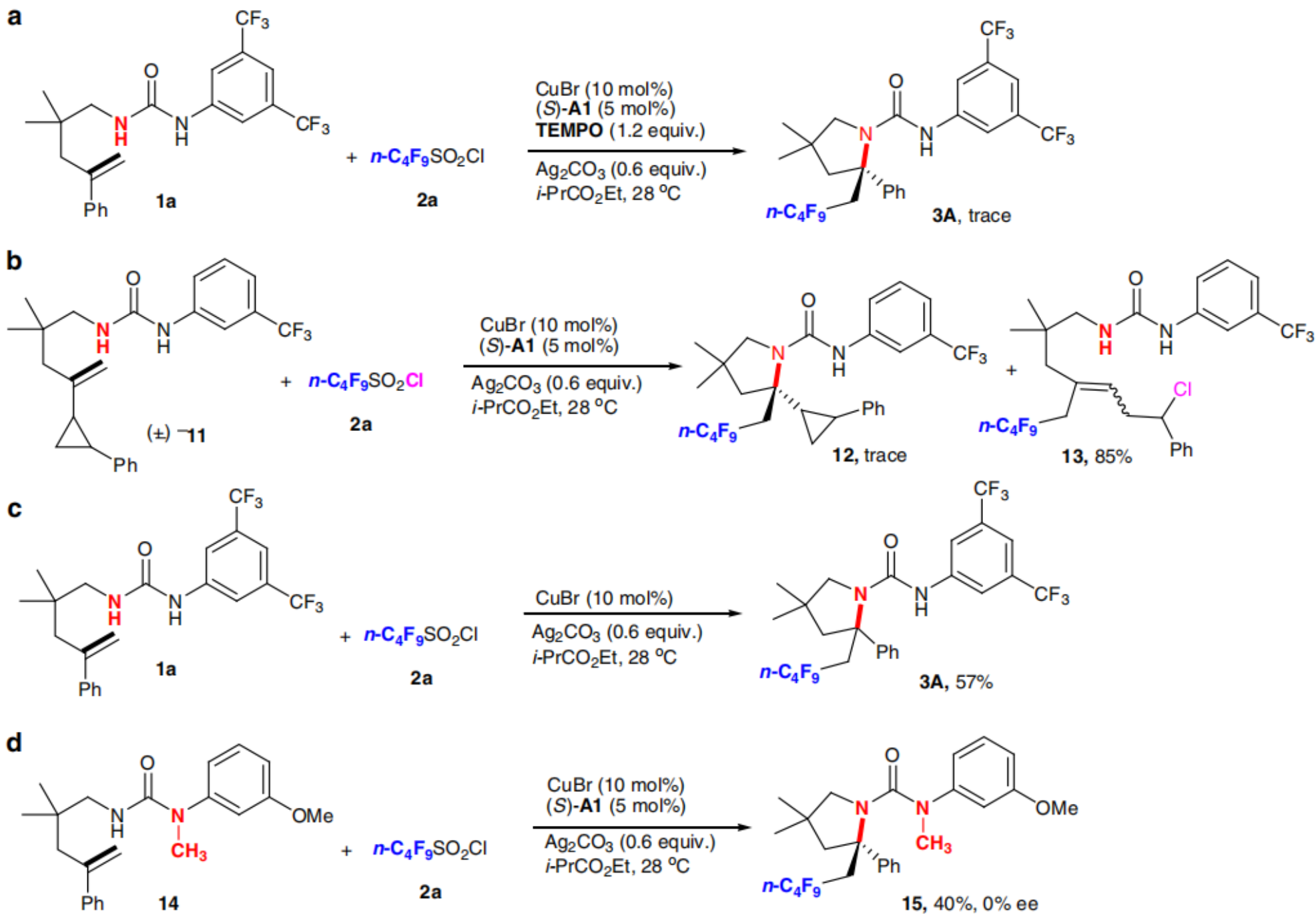
$\text{CF}_3\text{SO}_2\text{Cl}$

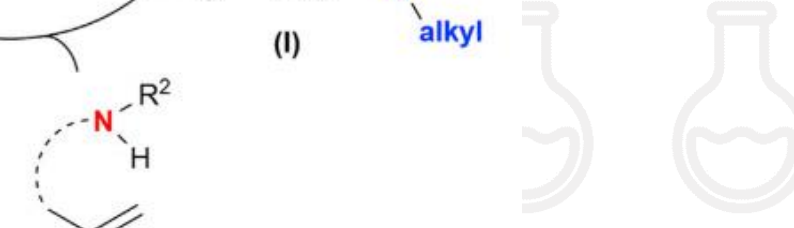
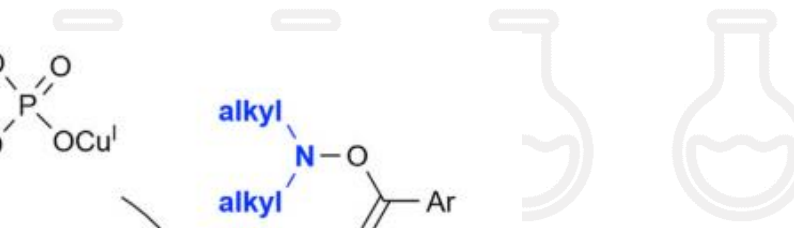
[Cu]	Base (x equiv.)	CPA	Solvent	Yield (%)		ee (%) [*]
				3A [†]	3AA [†]	
CuBr	Ag ₂ CO ₃ (0.6)	(S)-A1	<i>i</i> -PrCO ₂ Et	98	0	99



机理研究

- TEMPO捕获
- 自由基钟开环
- 无CPA无ee
- 底物无N-H无ee

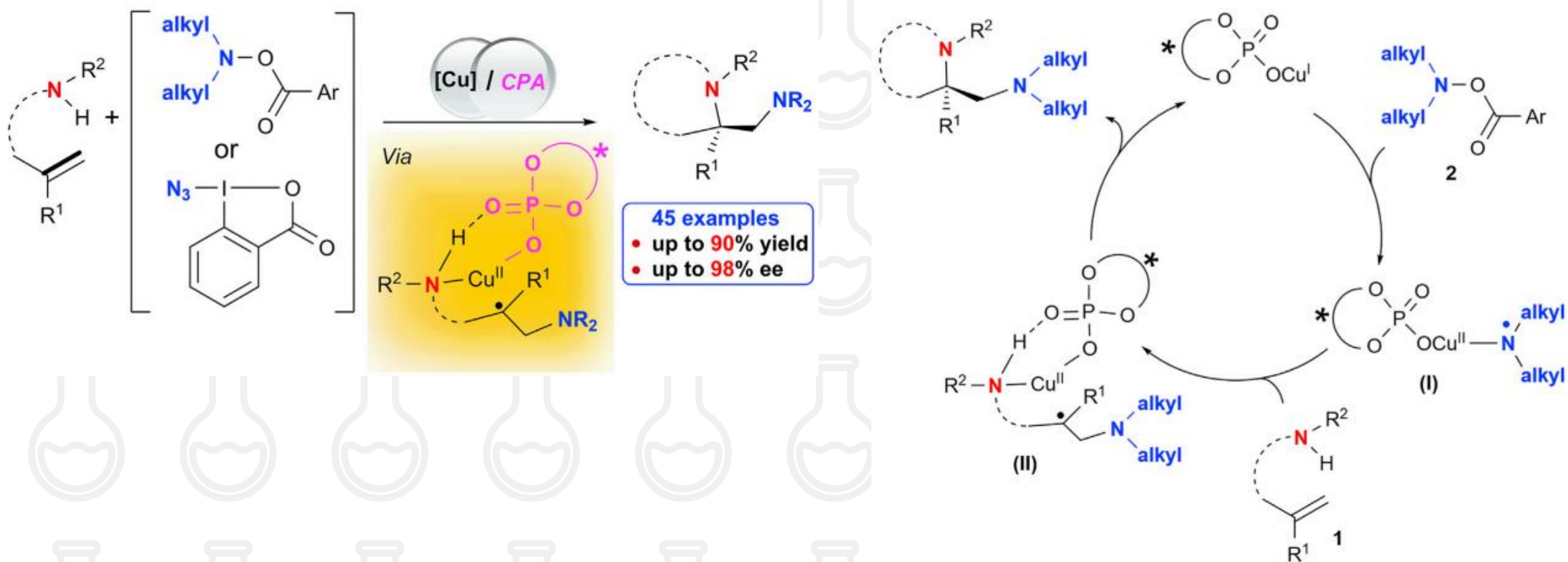


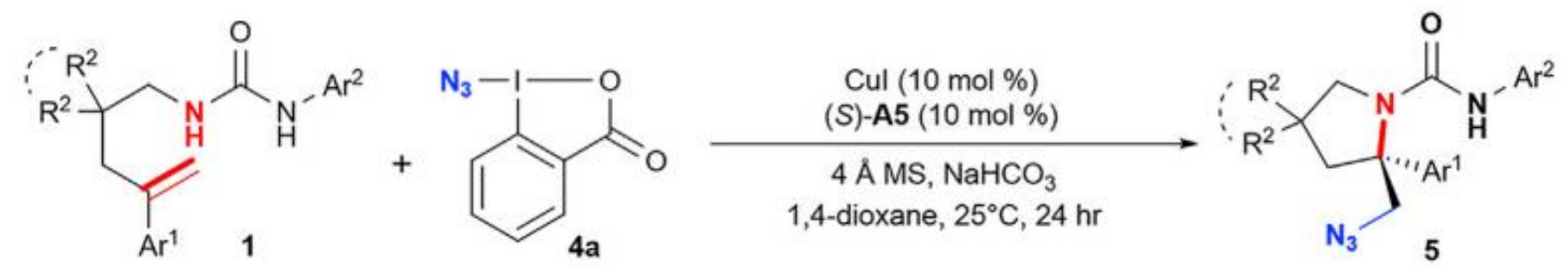
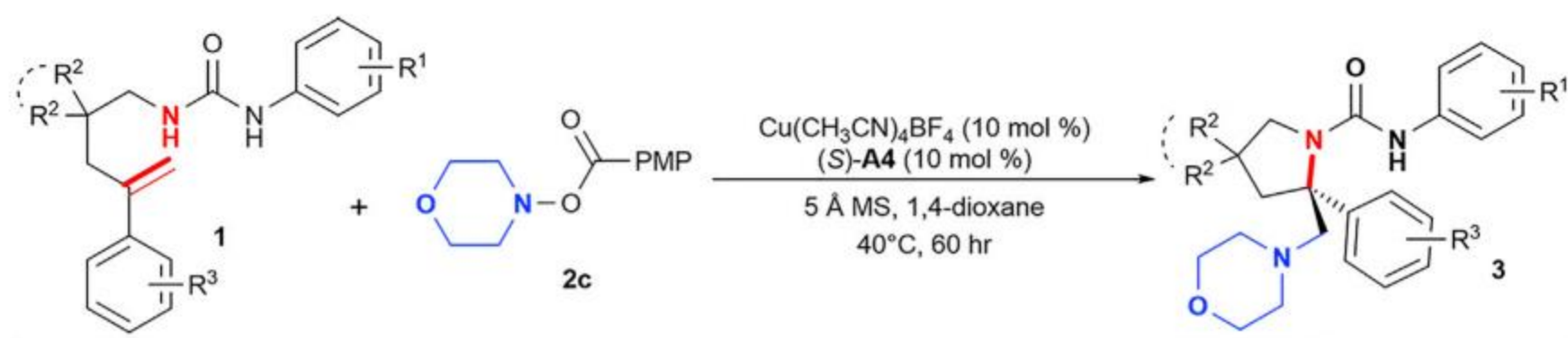
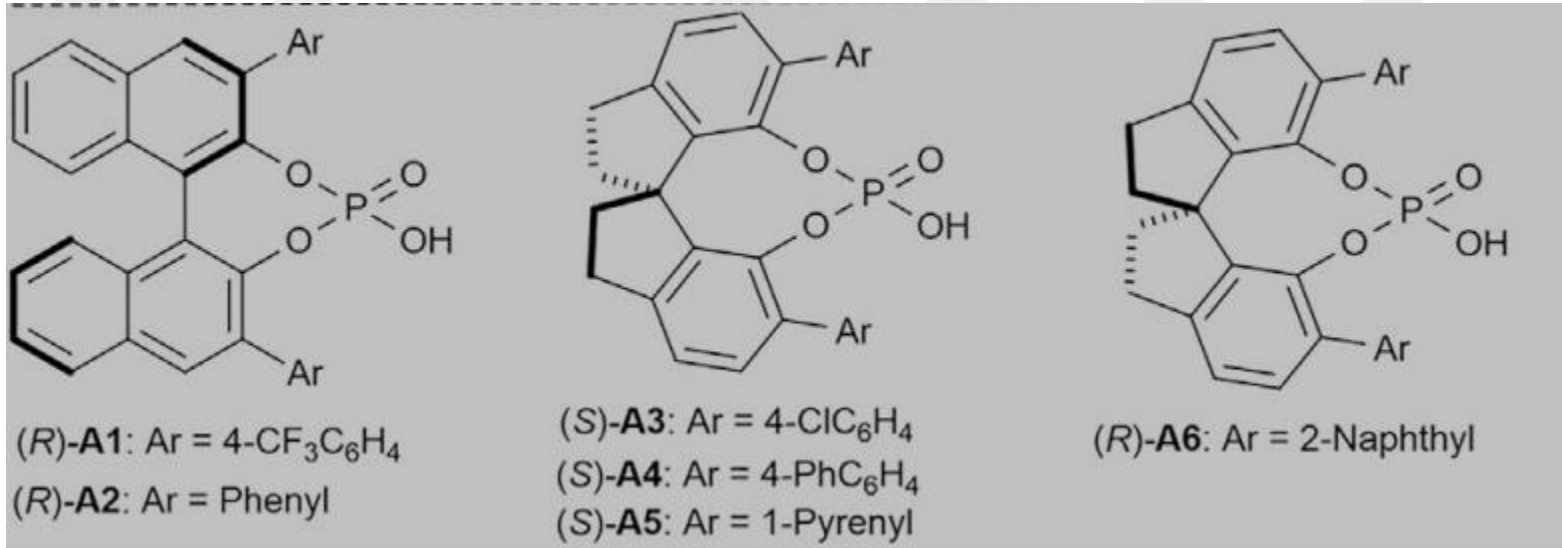


Article

Catalytic Asymmetric Radical Diamination of Alkenes

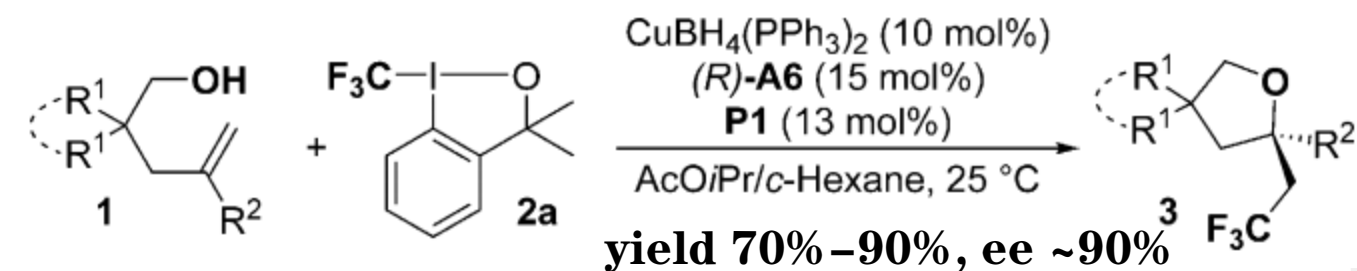
Fu-Li Wang,^{1,2,3} Xiao-Yang Dong,^{1,3} Jin-Shun Lin,^{1,3} Yang Zeng,¹ Guan-Yuan Jiao,¹ Qiang-Shuai Gu,¹ Xian-Qi Guo,¹ Can-Liang Ma,¹ and Xin-Yuan Liu^{1,4,*}



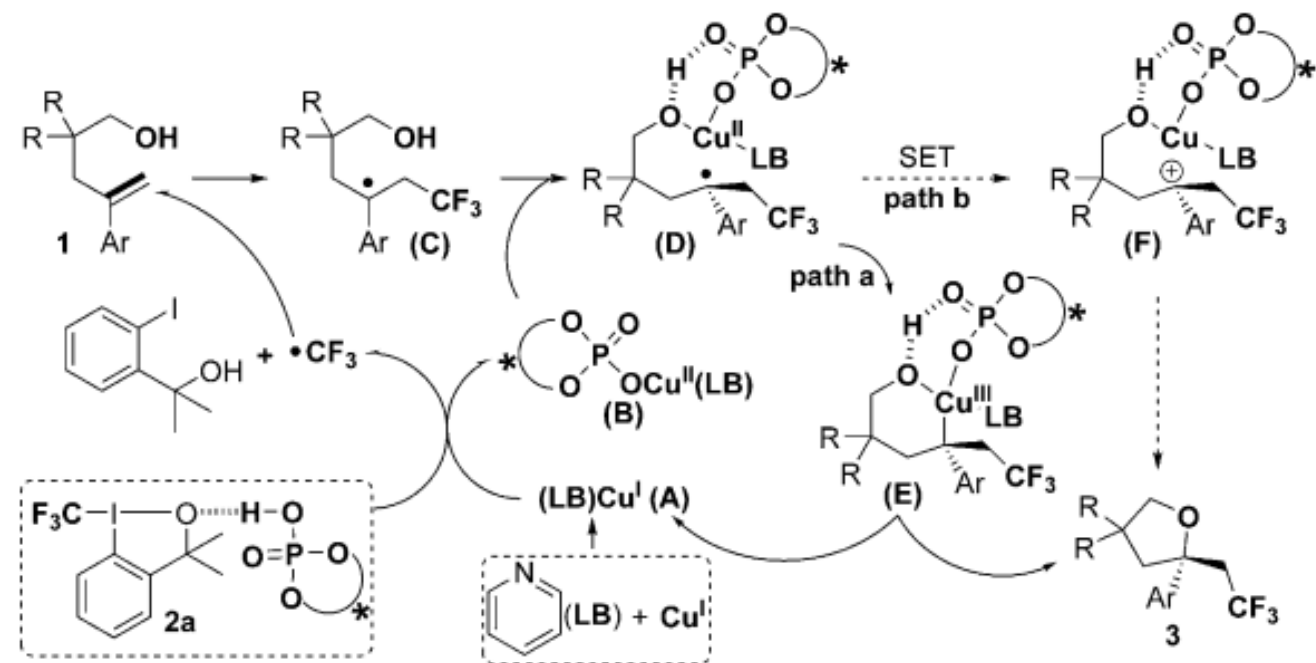
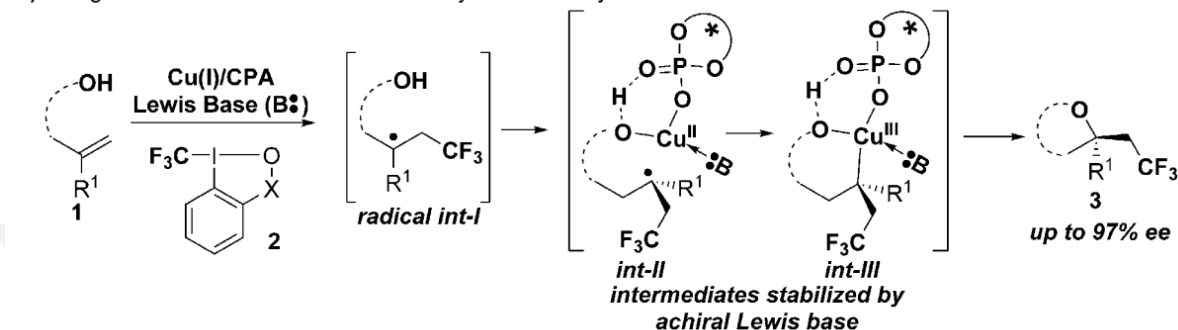


Achiral Pyridine Ligand-Enabled Enantioselective Radical Oxytrifluoromethylation of Alkenes with Alcohols

Yong-Feng Cheng⁺, Xiao-Yang Dong⁺, Qiang-Shuai Gu⁺, Zhang-Long Yu, and Xin-Yuan Liu^{*}



e) Design: Achiral Lewis base effect in oxytrifluoromethylation with CPA



直接使用原有的关环形成四氢吡咯的反应条件ee低可能是由于-OH作为氢键中H的供体，与CPA形成的氢键比尿素中N-H中形成的氢键弱

加入非手性的路易斯碱(吡啶)，提高中间体Int-II与Int-III的稳定性，改善OA与RE的反应活性，提高立体选择性。

吡啶的作用：(ee 21%→93%)

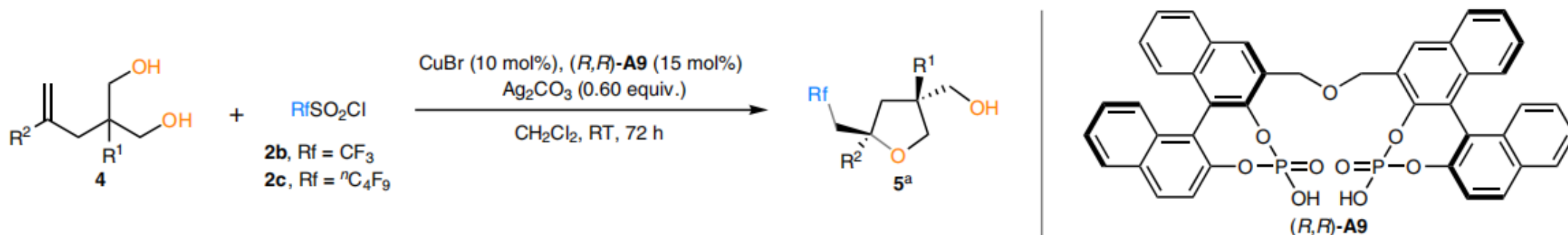
Cu的配体、促进脱质子

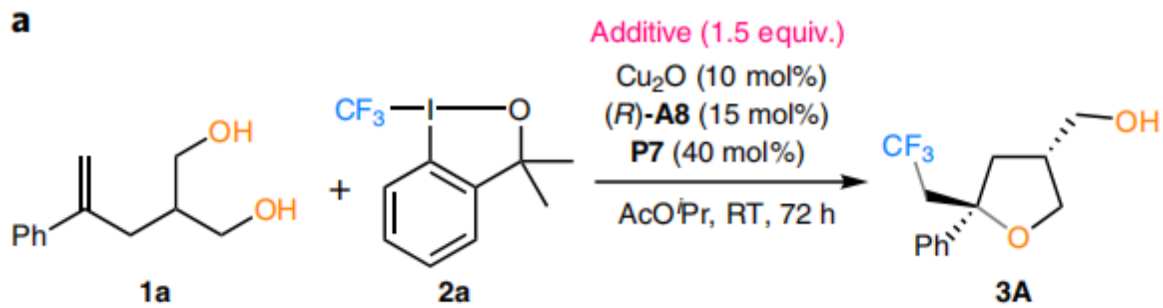


Catalytic enantioselective desymmetrizing functionalization of alkyl radicals via Cu(I)/CPA cooperative catalysis

Yong-Feng Cheng^{1,2,5}, Ji-Ren Liu^{3,5}, Qiang-Shuai Gu^{2,4,5}, Zhang-Long Yu^{1,2,5}, Jian Wang^{1,2}, Zhong-Liang Li^{2,4}, Jun-Qian Bian^{1,2}, Han-Tao Wen^{1,2}, Xiao-Jing Wang^{1,2}, Xin Hong³✉ and Xin-Yuan Liu^{1,2}✉

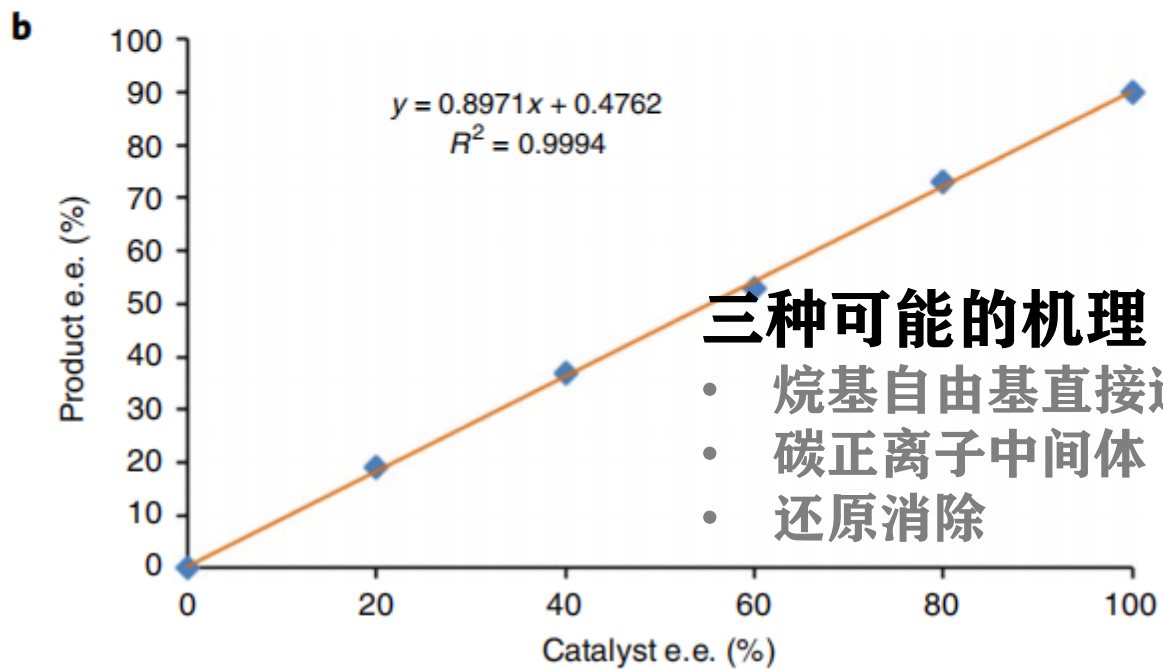
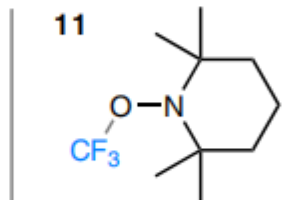
dr>20:1, **ee**>90%





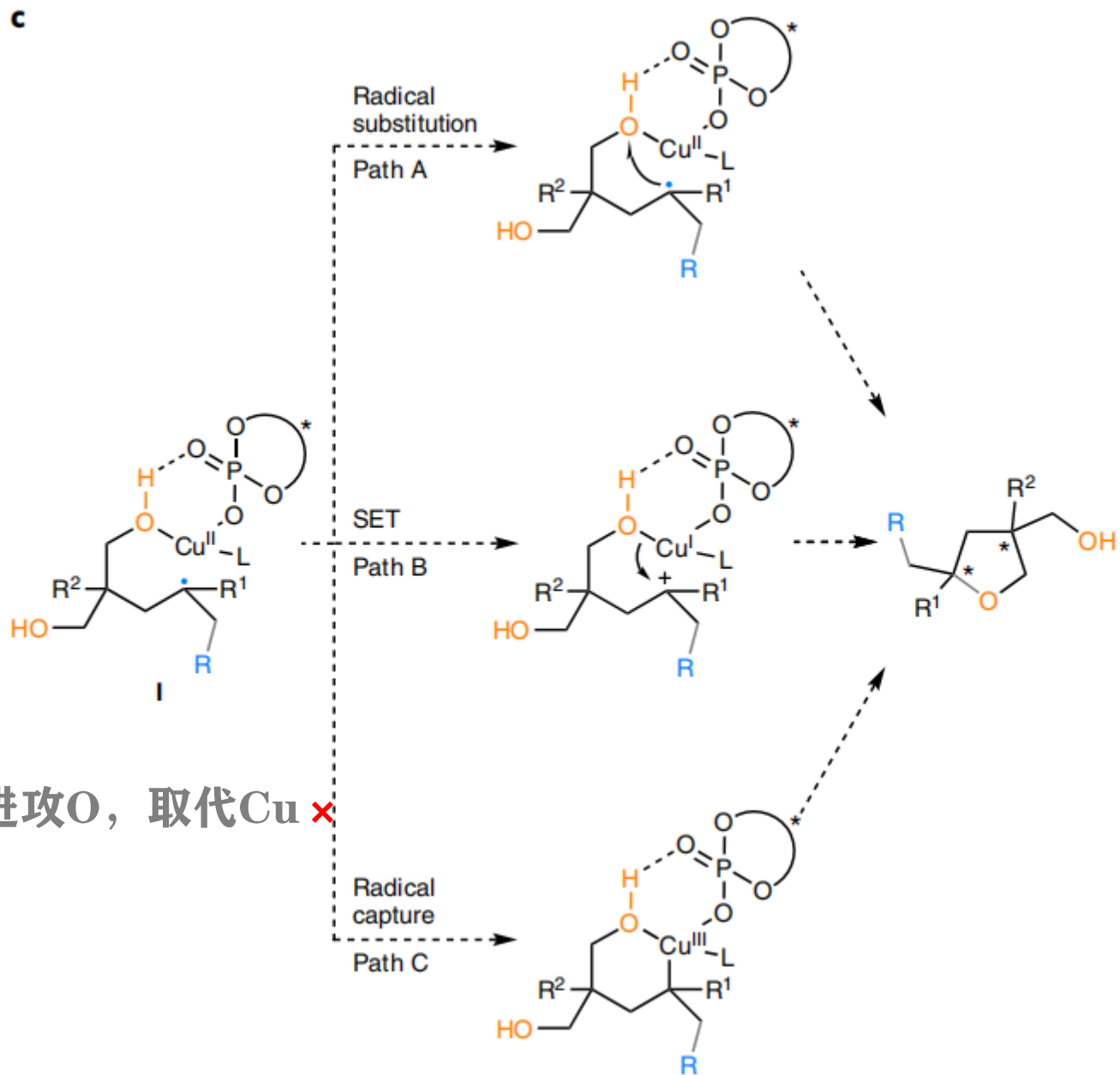
TEMPO: 3A (trace) + 11 (5%)

BHT: 3A (16%)



三种可能的机理

- 烷基自由基直接进攻O, 取代Cu \times
- 碳正离子中间体
- 还原消除



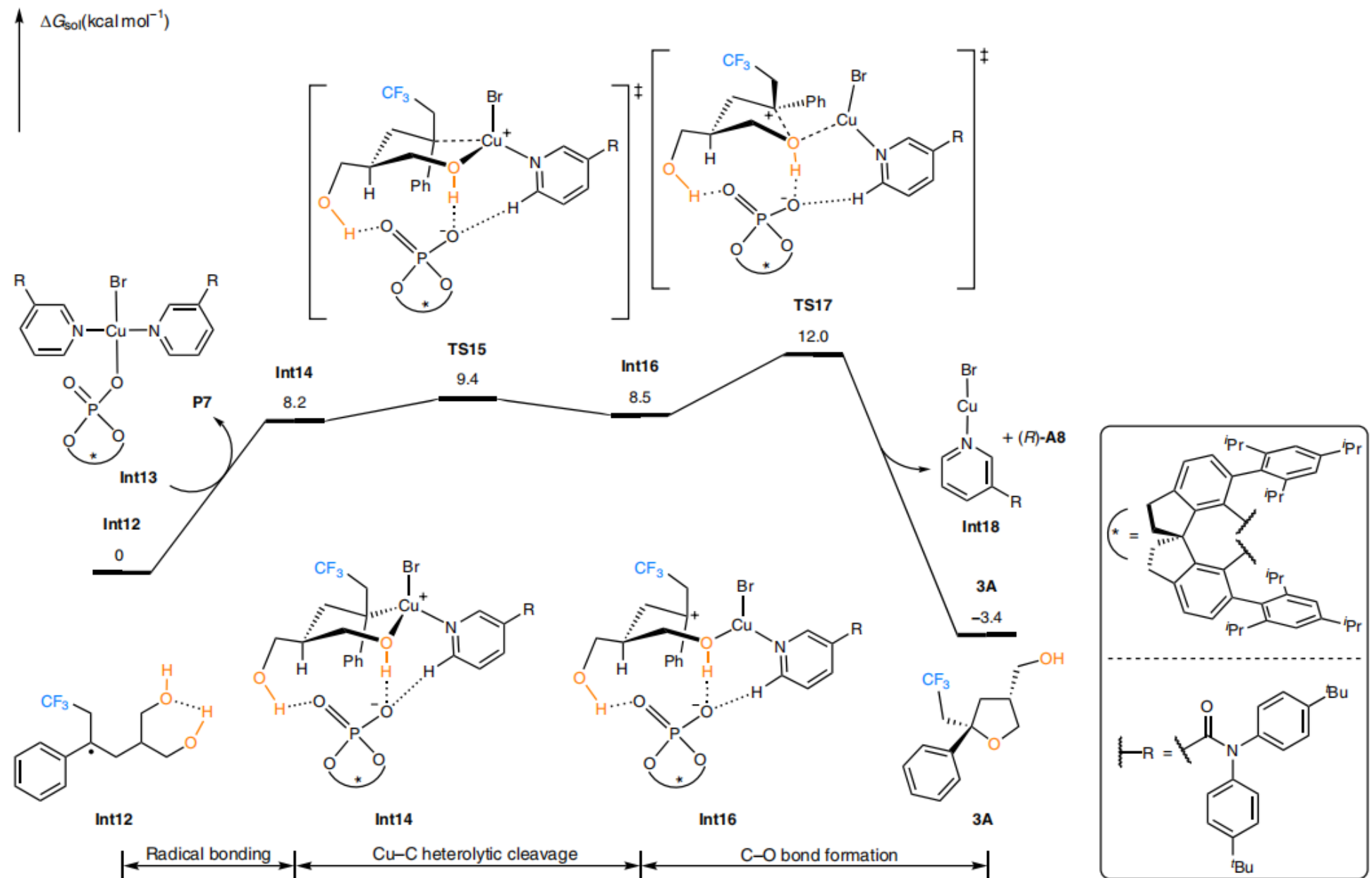
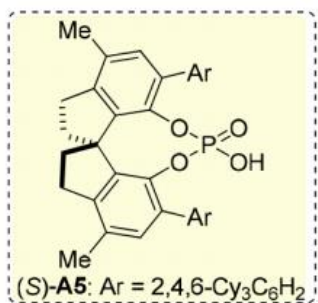
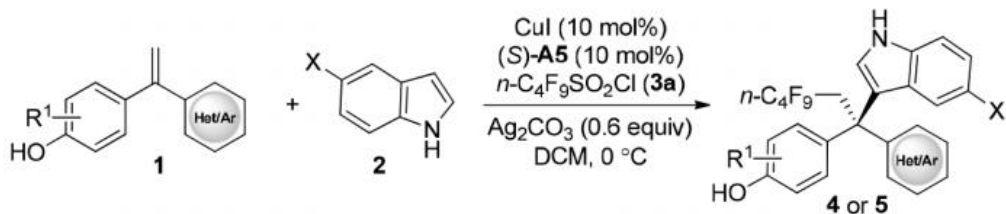


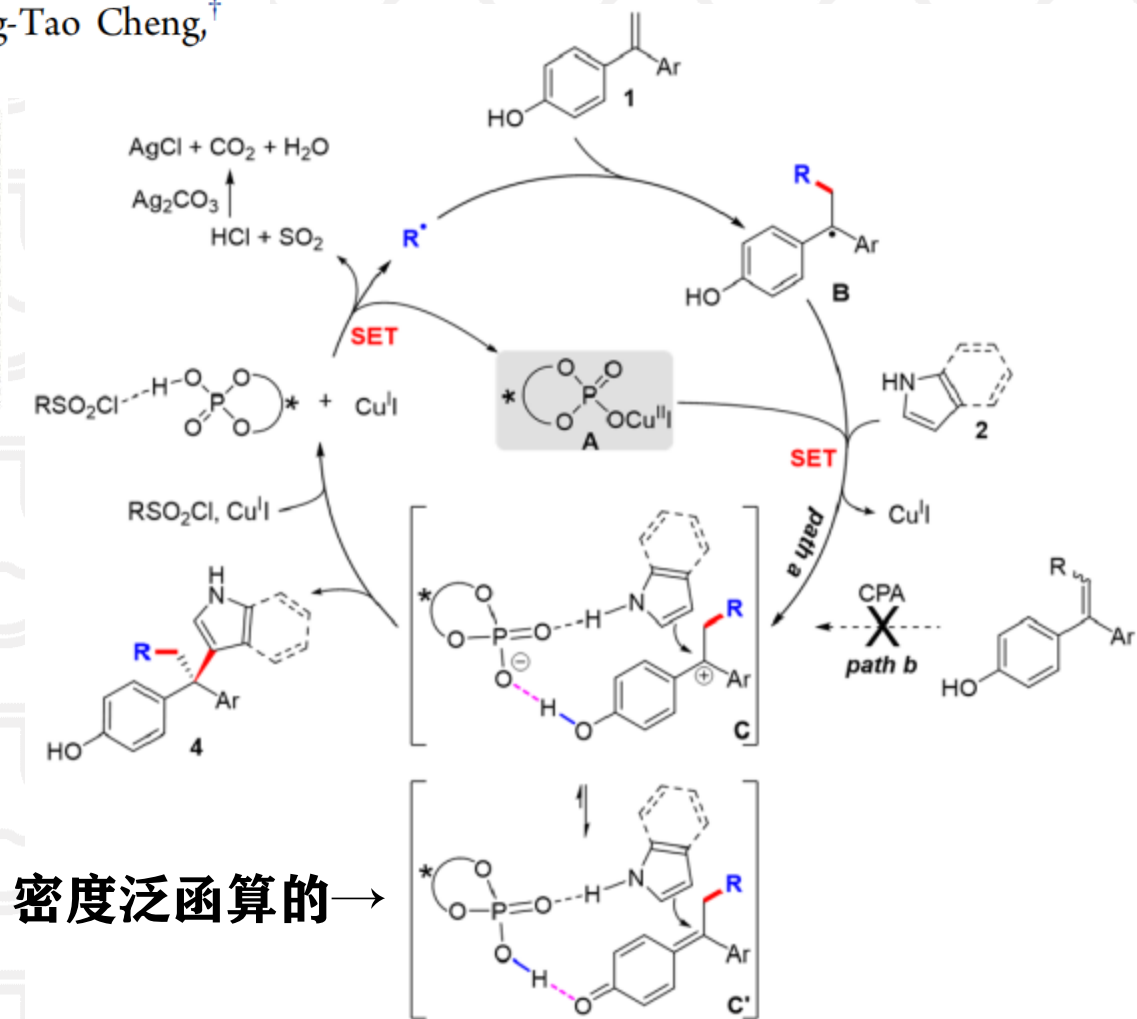
Fig. 4 | DFT-computed free energy profile of the favoured C-O bond formation process. Computational studies were performed at the B3LYP-D3(BJ)/6-311+G(d,p)-SDD-SMD(Propyl Ethanoate)//B3LYP-D3(BJ)/6-31G(d)-LANL2DZ level of theory. This process involves sequential radical bonding, Cu-C bond heterolytic cleavage and C-O bond formation.

Cu/Chiral Phosphoric Acid-Catalyzed Asymmetric Three-Component Radical-Initiated 1,2-Dicarbofunctionalization of Alkenes

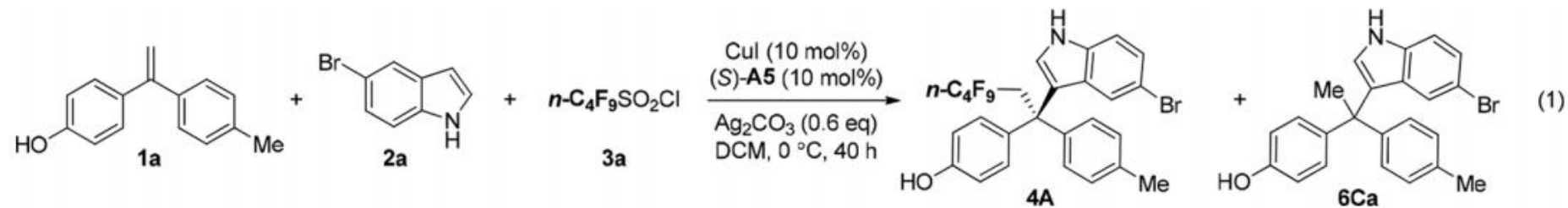
Jin-Shun Lin,^{†,§} Tao-Tao Li,^{†,§} Ji-Ren Liu,^{||,§} Guan-Yuan Jiao,[†] Qiang-Shuai Gu,[‡] Jiang-Tao Cheng,[†] Yu-Long Guo,[†] Xin Hong,^{*,||} and Xin-Yuan Liu^{*,†,||}



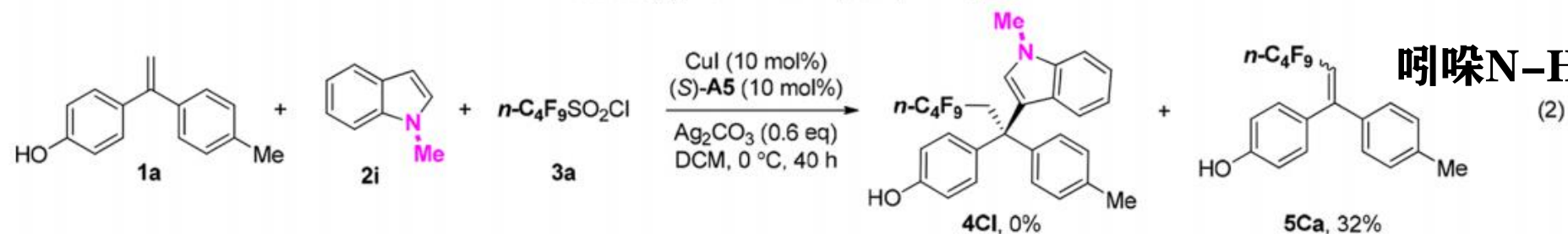
yield 80%–95%, ee ~95%



Scheme 4. Mechanistic Study

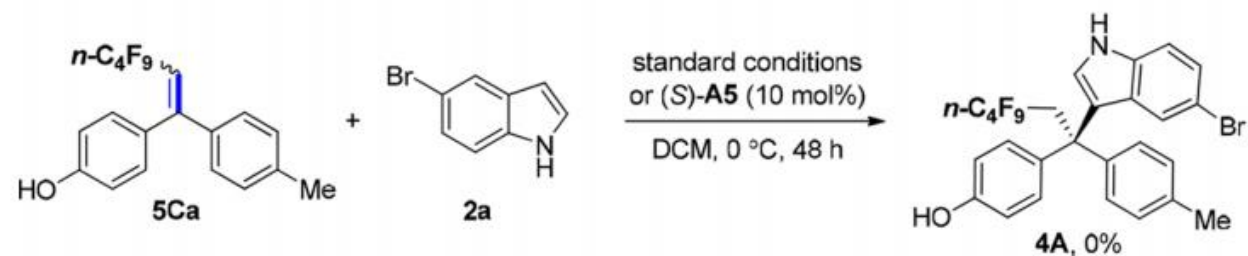


TEMPO (1.2 equiv): **4A**, 0% + $n\text{-C}_4\text{F}_9\text{O-N}$ (detected by GC-MS)
 without Cul: **4A**, 0%; **6Ca**, 56%
 without (S)-A5: *rac*-**4A**, 50%; **6Ca**, 48%



吡啶N-H与CPA作用

(2)

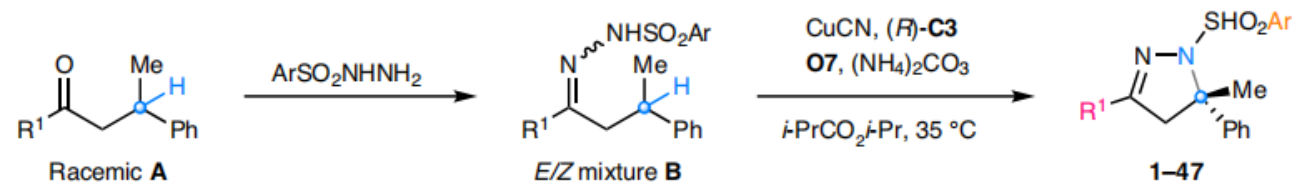


排除CPA给5Ca质子形成C+

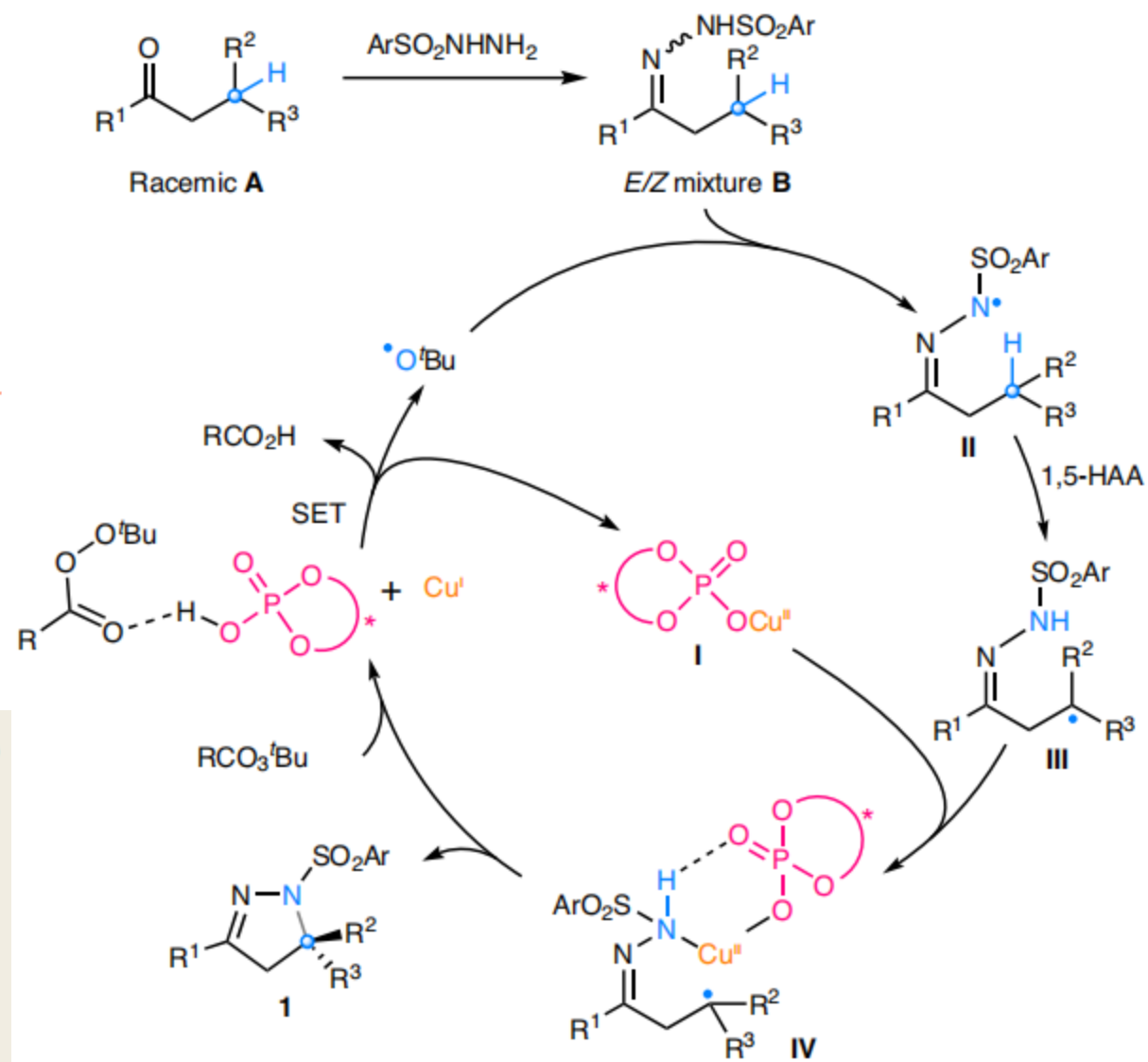
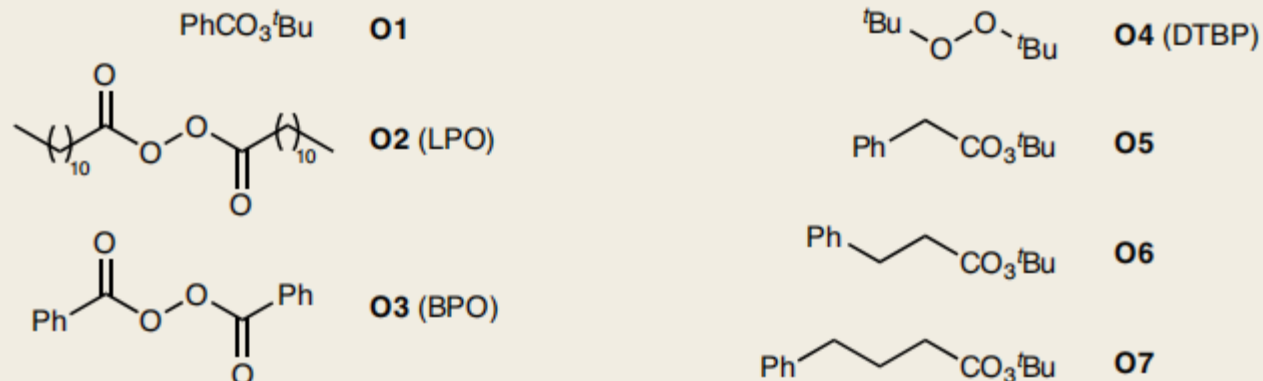


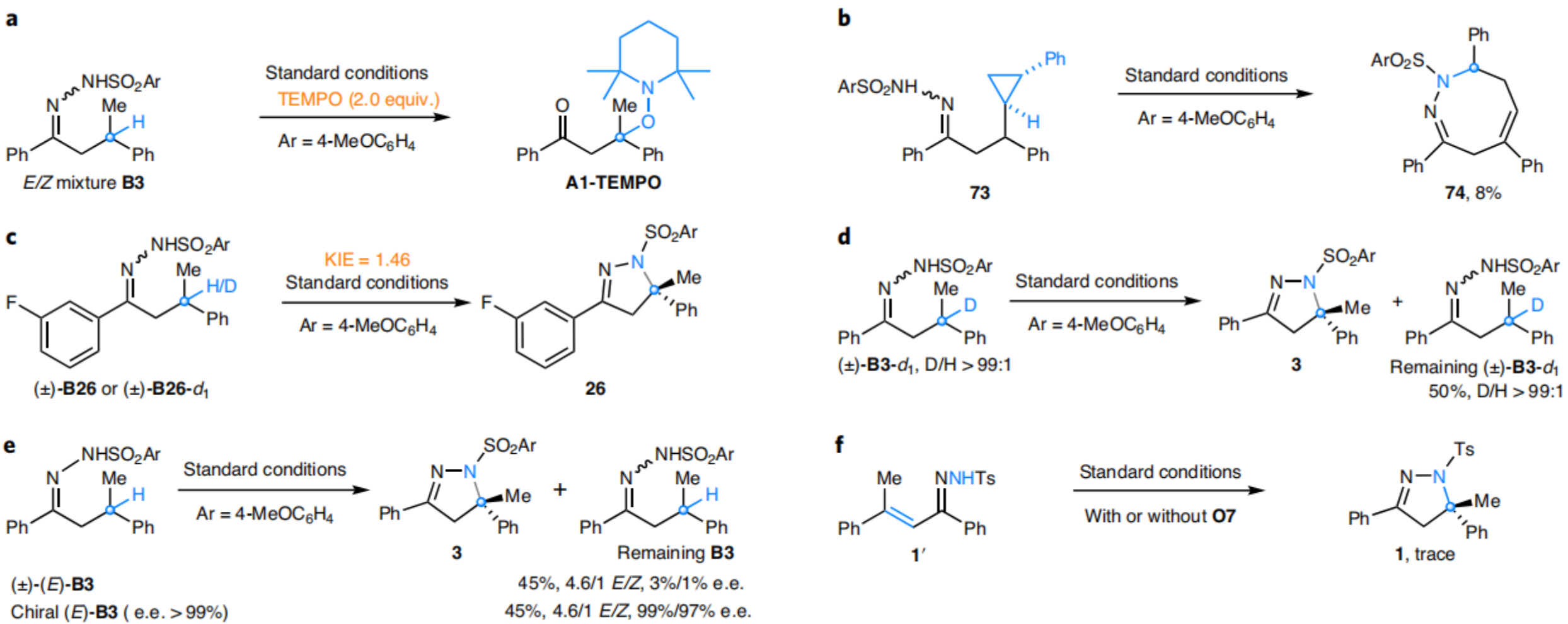
Cu-catalysed intramolecular radical enantioconvergent tertiary β -C(sp^3)-H amination of racemic ketones

Chang-Jiang Yang^{1,4}, Chi Zhang^{1,4}, Qiang-Shuai Gu^{2,4}, Jia-Heng Fang¹, Xiao-Long Su³, Liu Ye², Yan Sun¹, Yu Tian¹, Zhong-Liang Li² and Xin-Yuan Liu¹✉



少量碳酸铵的加入有利于提升产率





机理研究

- a. TEMPO捕获 b. 自由基钟开环 f. 1' 不能转化为1, 不是分子内的Micheal加成
- c. 同位素效应: 1,5 HAA非决速, 有其他反应参与
- d. 同位素标记原料回收D/H不变, 未观察到H交换, 分子内的1,5 HAA快速且不可逆
- e. 原料回收基本ee不变, suggesting that the kinetic resolution or dynamic kinetic resolution of racemic tertiary C - H bonds is unlikely

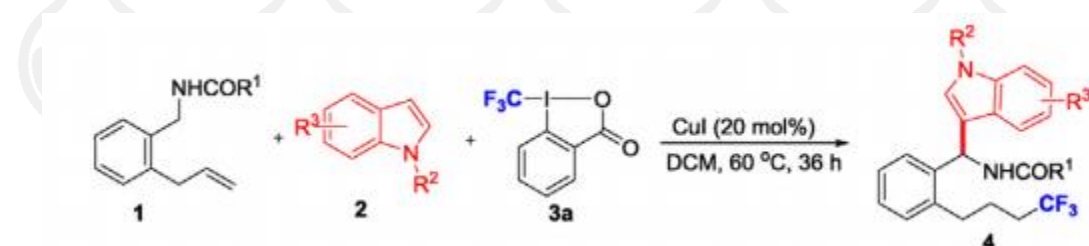
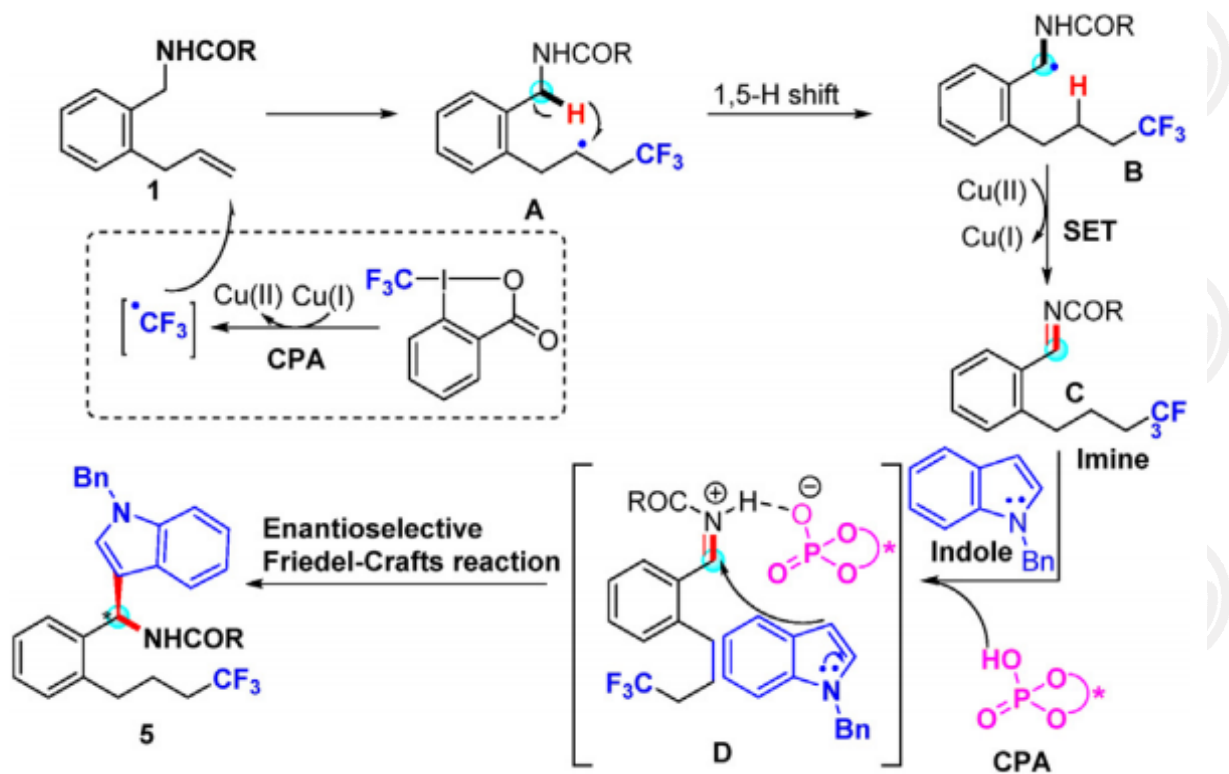


ELSEVIER

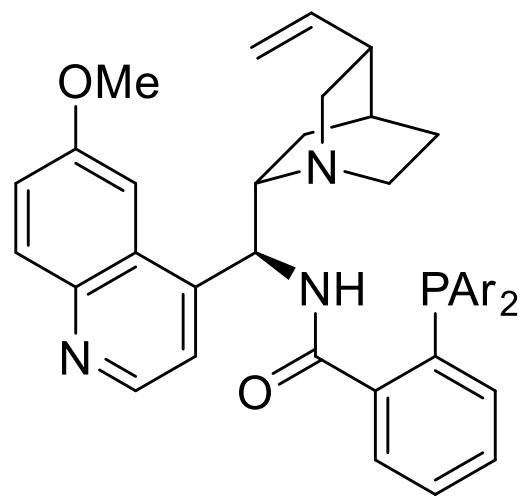


Enantioselective α -C-H functionalization of amides with indoles triggered by radical trifluoromethylation of alkenes: Highly selective formation of C—CF₃ and C—C bonds

Taotao Li^{a,b,c}, Peng Yu^c, Yi-Meng Du^c, Jin-Shun Lin^c, Yonggang Zhi^{a,b,**}, Xin-Yuan Liu^{c,*}



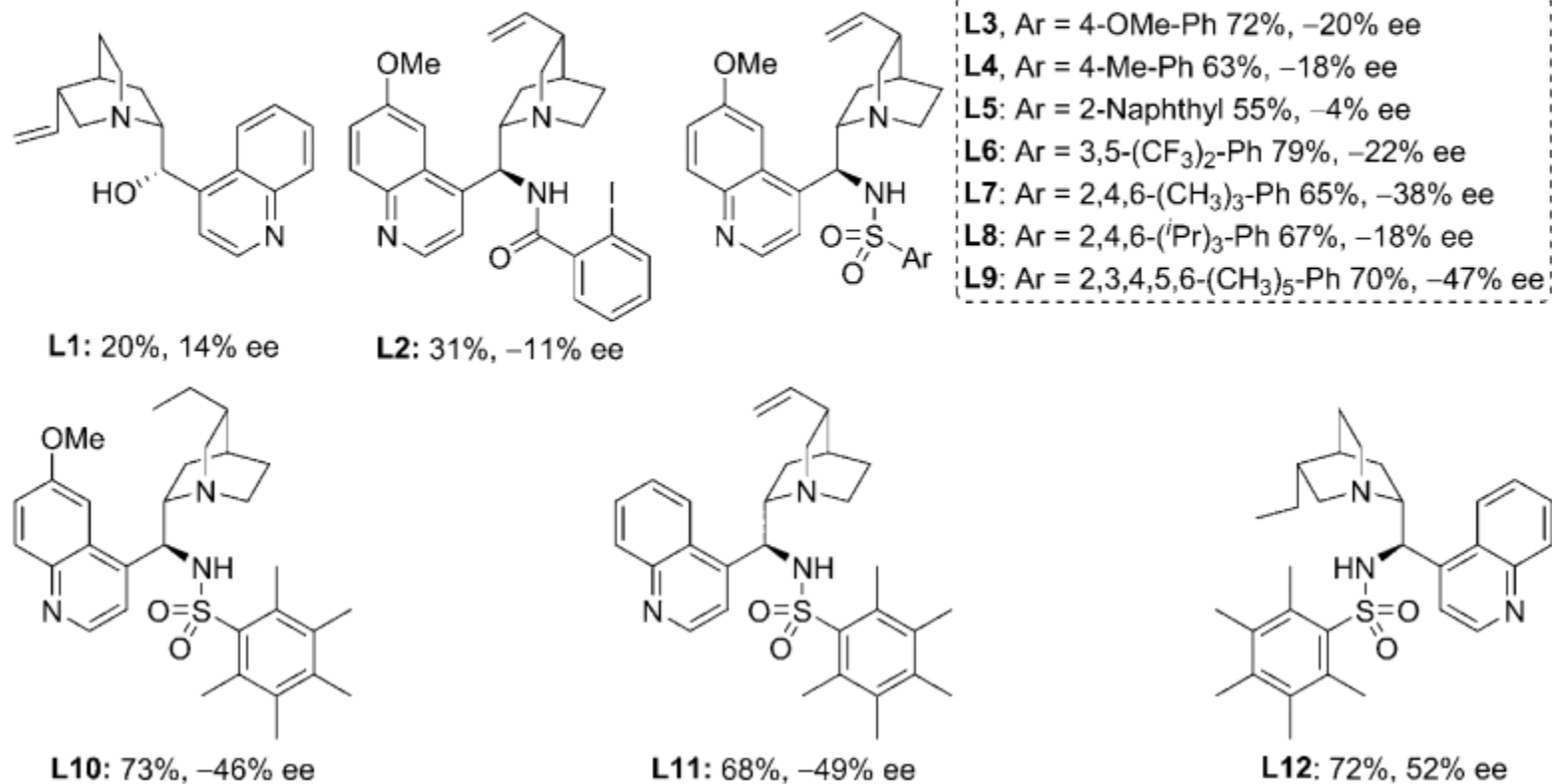
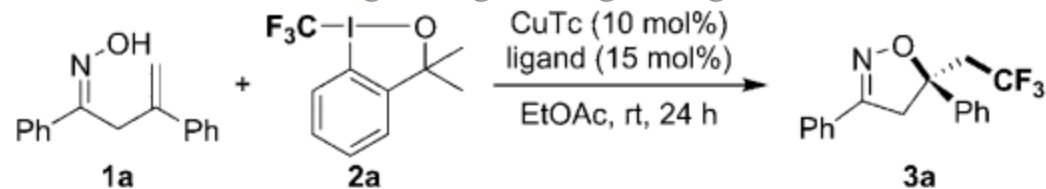
NNP+Cu(I)



Part 2

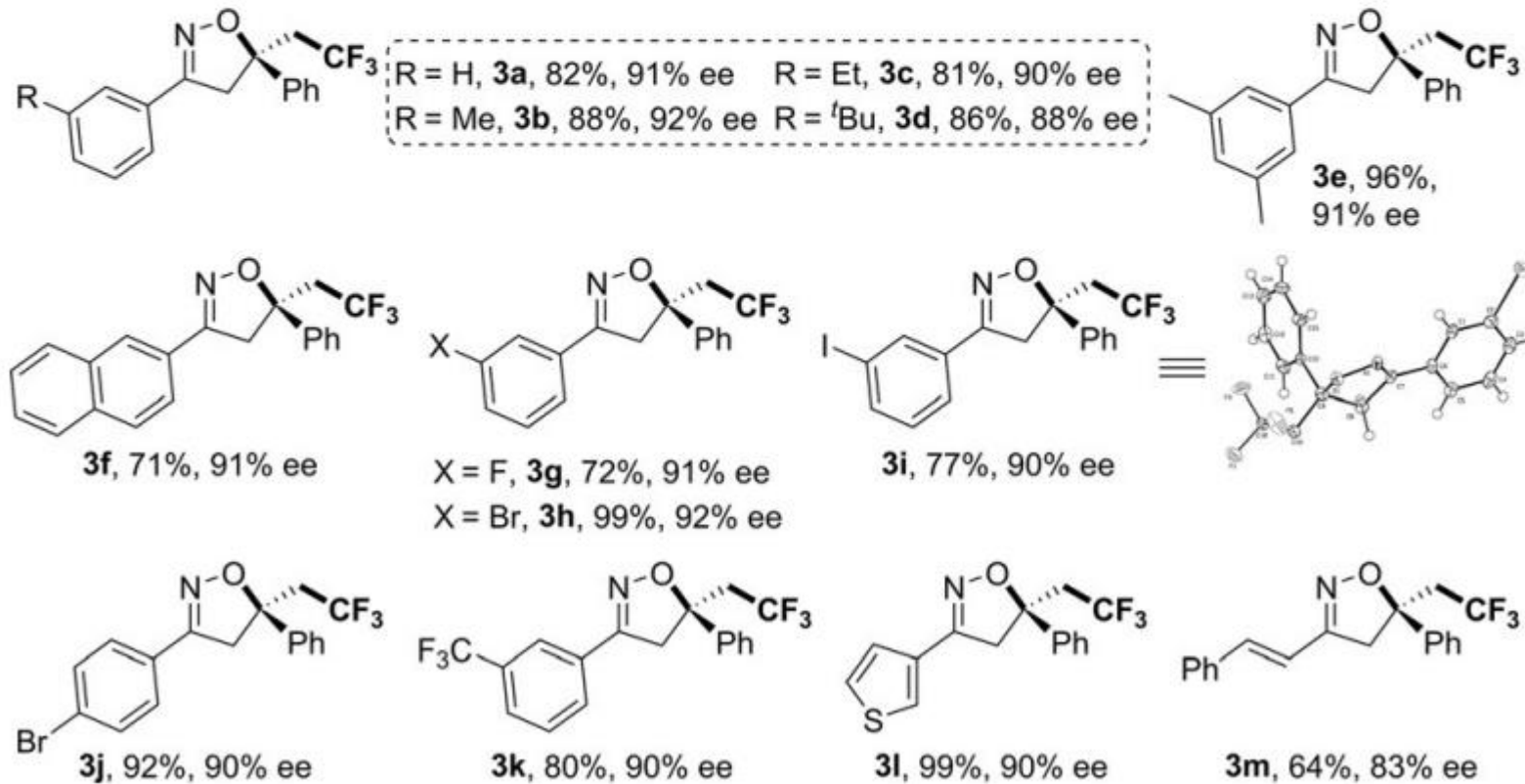
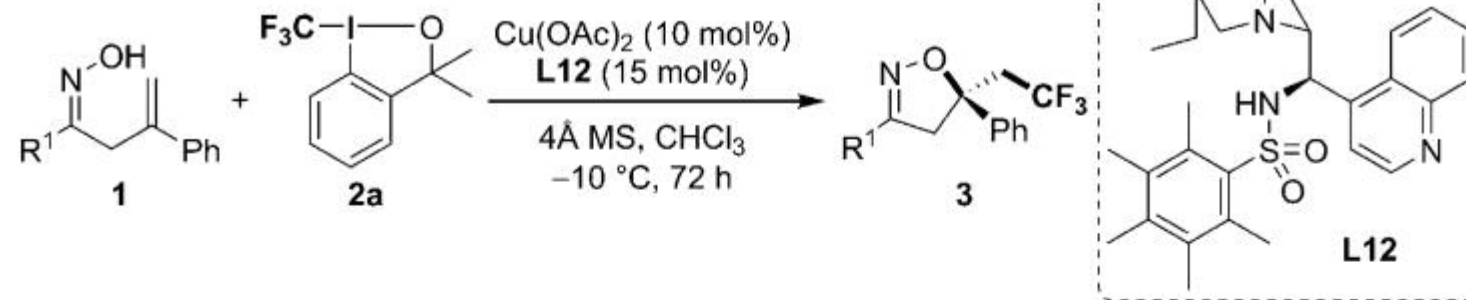
A Copper Catalyst with a Cinchona-Alkaloid-Based Sulfonamide Ligand for Asymmetric Radical Oxytrifluoromethylation of Alkenyl Oximes

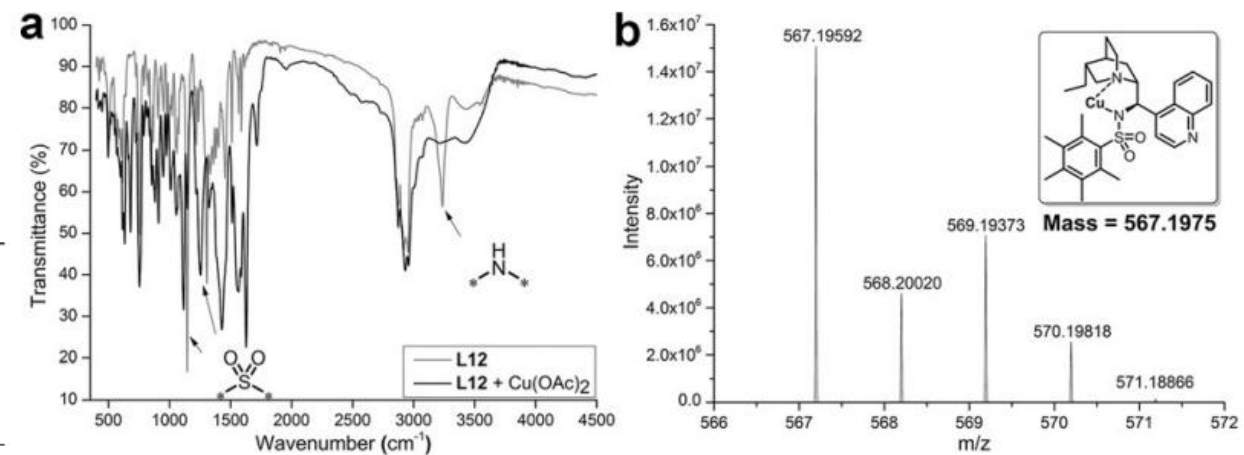
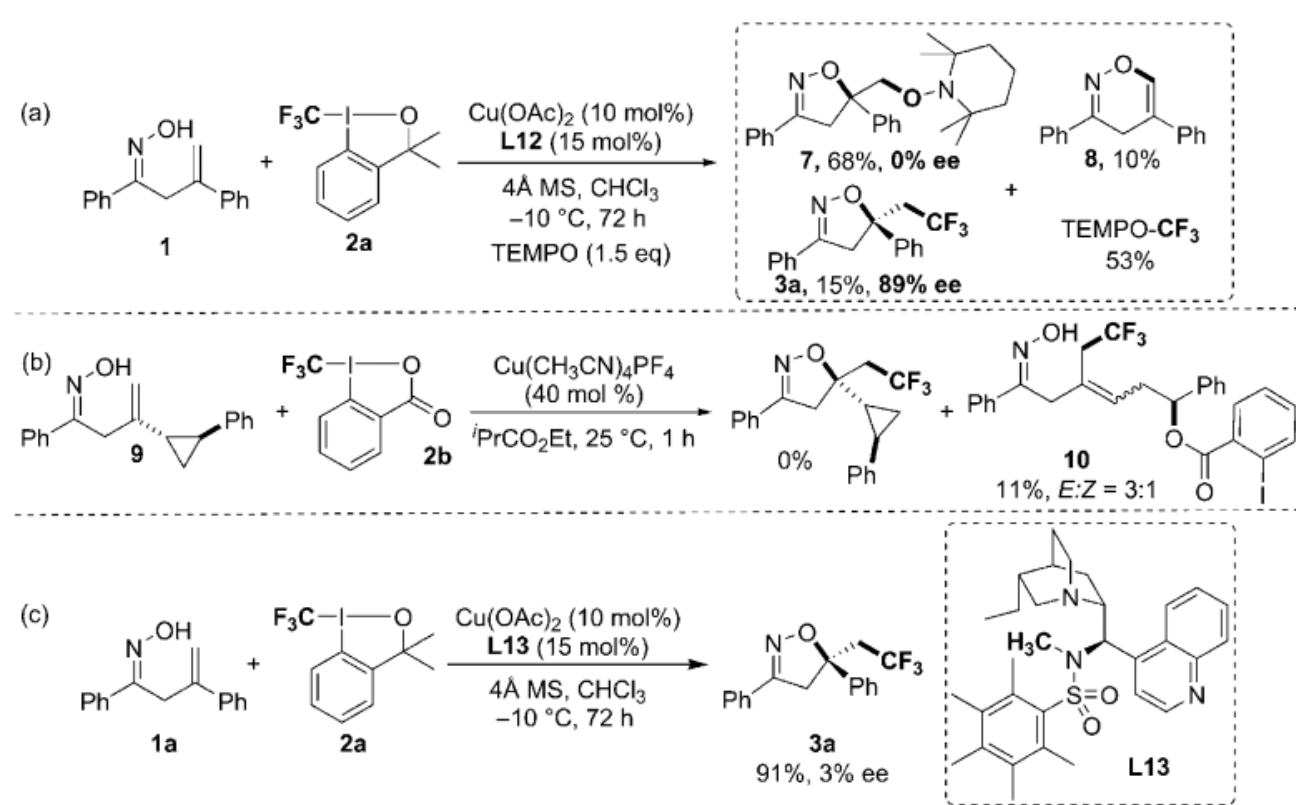
Xi-Tao Li, Qiang-Shuai Gu, Xiao-Yang Dong, Xiang Meng, and Xin-Yuan Liu*



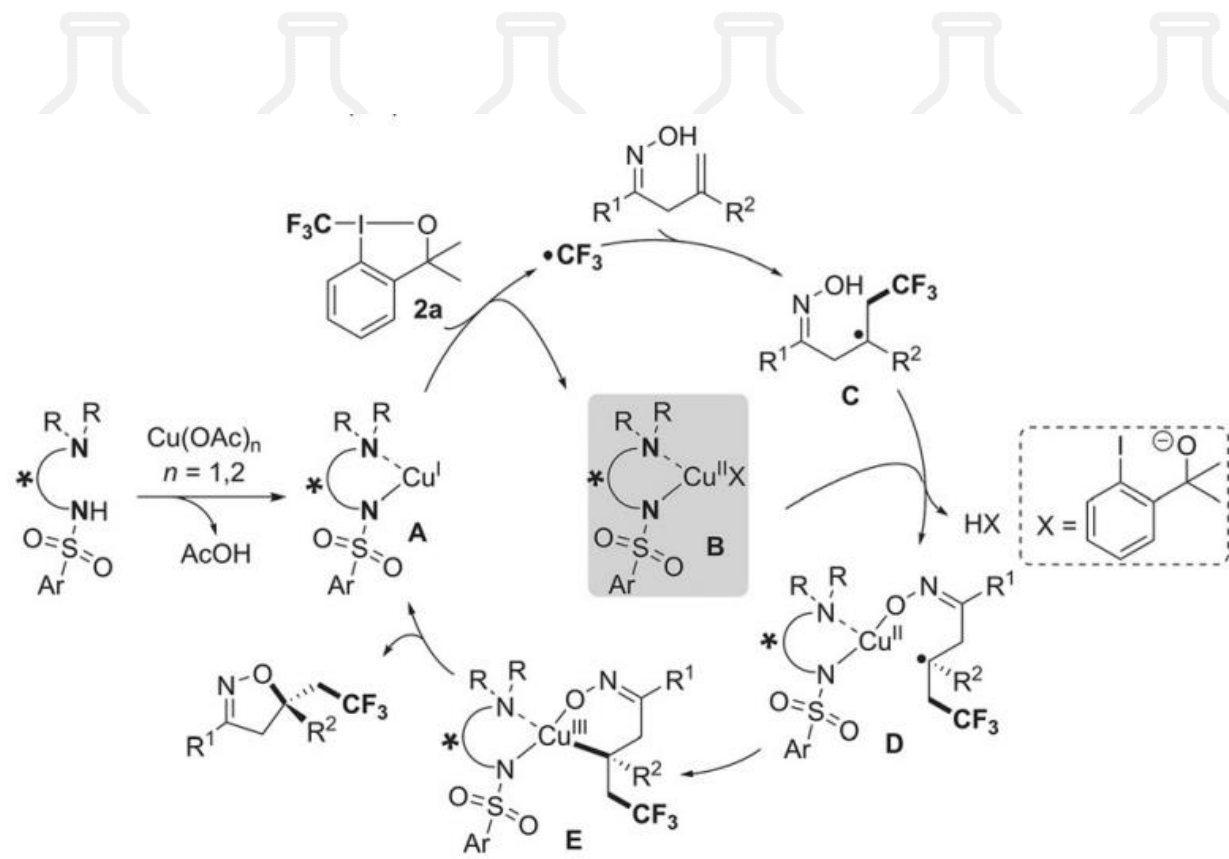
L1,L2 ee较低可能原因:

- 配体中羟基或酰胺中H的酸度低
- L3-L12添加磺酰基, 配体更易脱H后与Cu配位

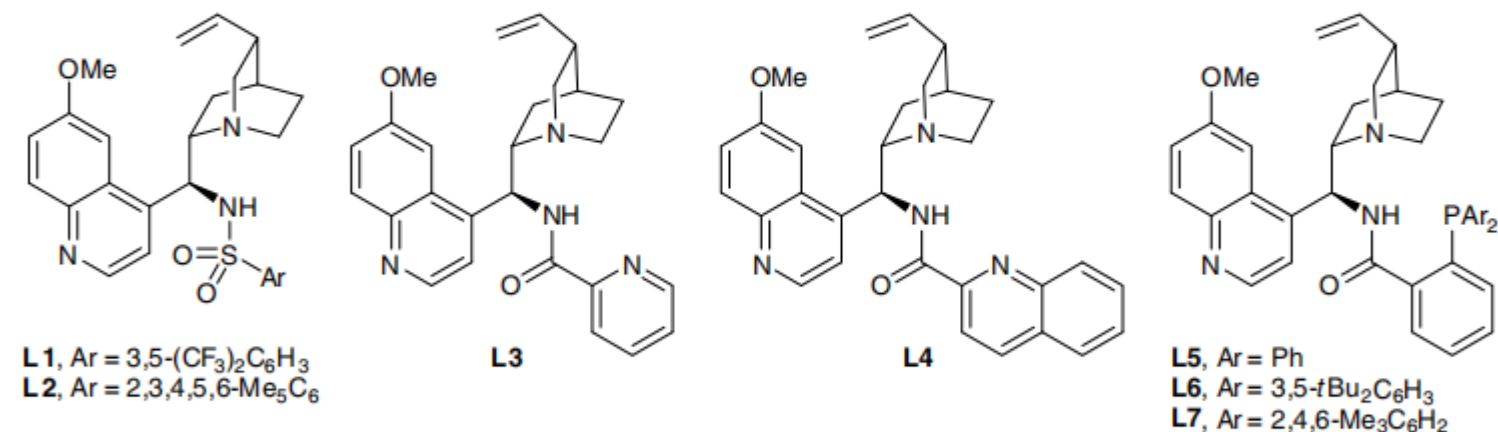
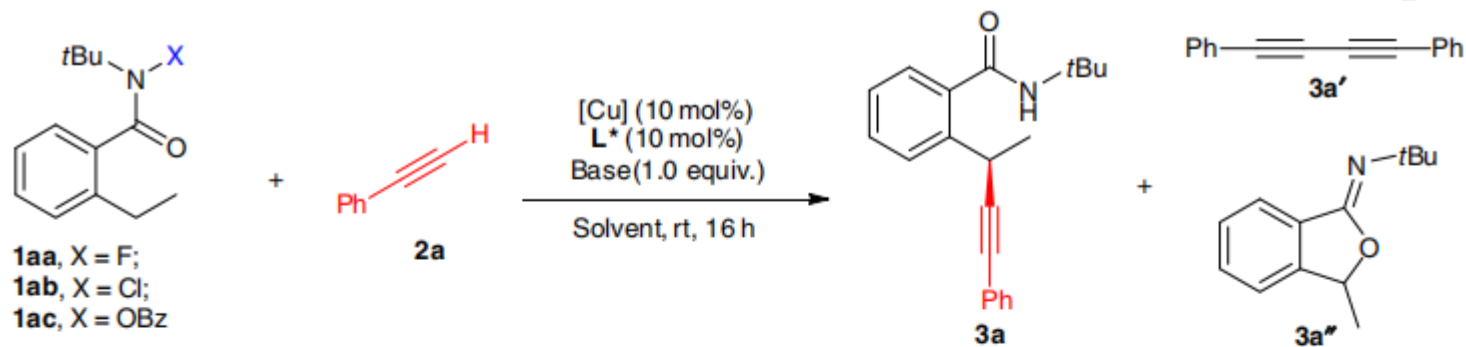




a. L12加入Cu后N-H峰消失
(c)中L12配体中无N-H, 产物ee非常低



Copper-catalyzed enantioselective Sonogashira-type oxidative cross-coupling of unactivated C(sp³)–H bonds with alkynes

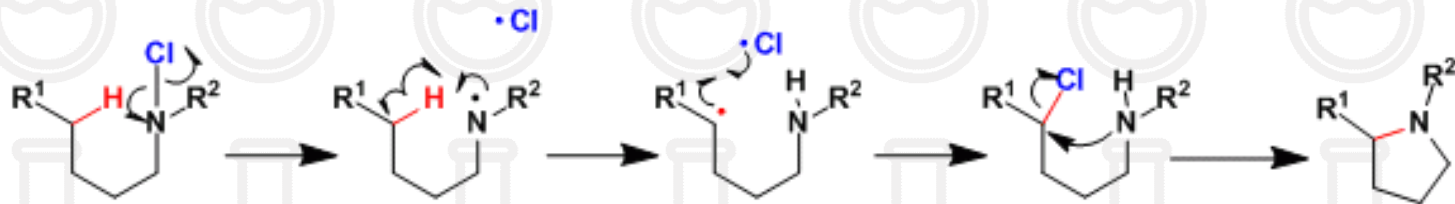


1	[Cu]	Base	L*	Solvent	Yield (%; 3a , 3a' , 3a'') ^b	Ee (%) ^c
1aa	CuI	Cs ₂ CO ₃	L1	Dichloromethane (DCM)	– ^d , 0, 0	–
1aa	CuI	Cs ₂ CO ₃	L2	DCM	– ^d , 0, 0	–
1aa	CuI	Cs ₂ CO ₃	L3	DCM	<5, 0, 0	6
1aa	CuI	Cs ₂ CO ₃	L4	DCM	8, 0, 0	74
1aa	CuI	Cs ₂ CO ₃	L5	DCM	53, 0, – ^d	68
1aa	CuI	Cs ₂ CO ₃	L6	DCM	15, 0, 0	51

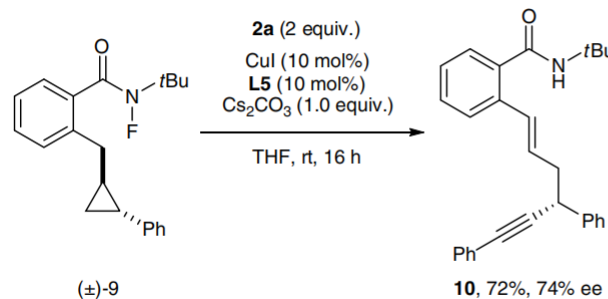
Cu(I)可以还原底物，但和炔基偶联后，NN配体+Cu(I)无法与底物反应

在原有的配体上增加一个胺/磷，提高配体电子密度，提升Cu(I)+L*的还原能力

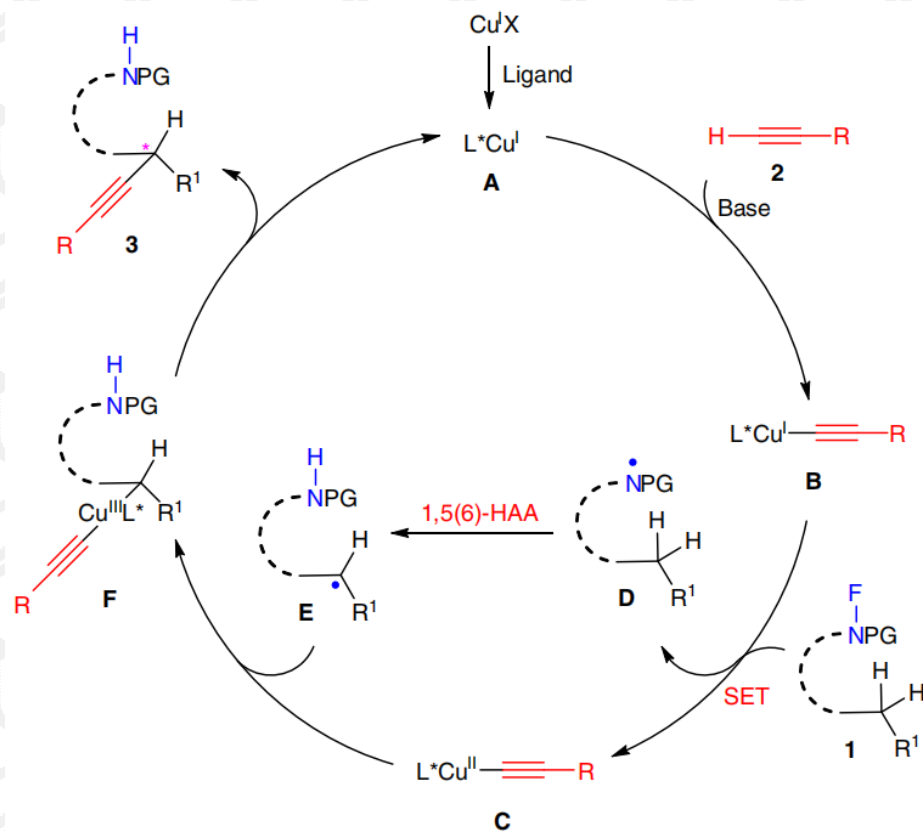
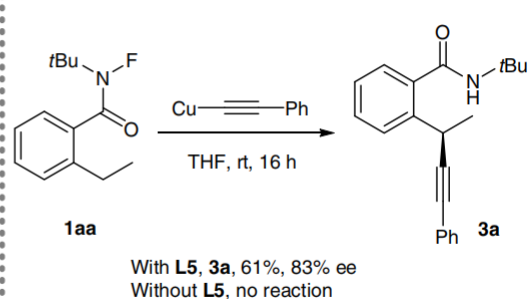
Hofmann-Löffler-Freytag Reaction



a Radical-clock experiment



b Experiments on the effect of chiral ligand

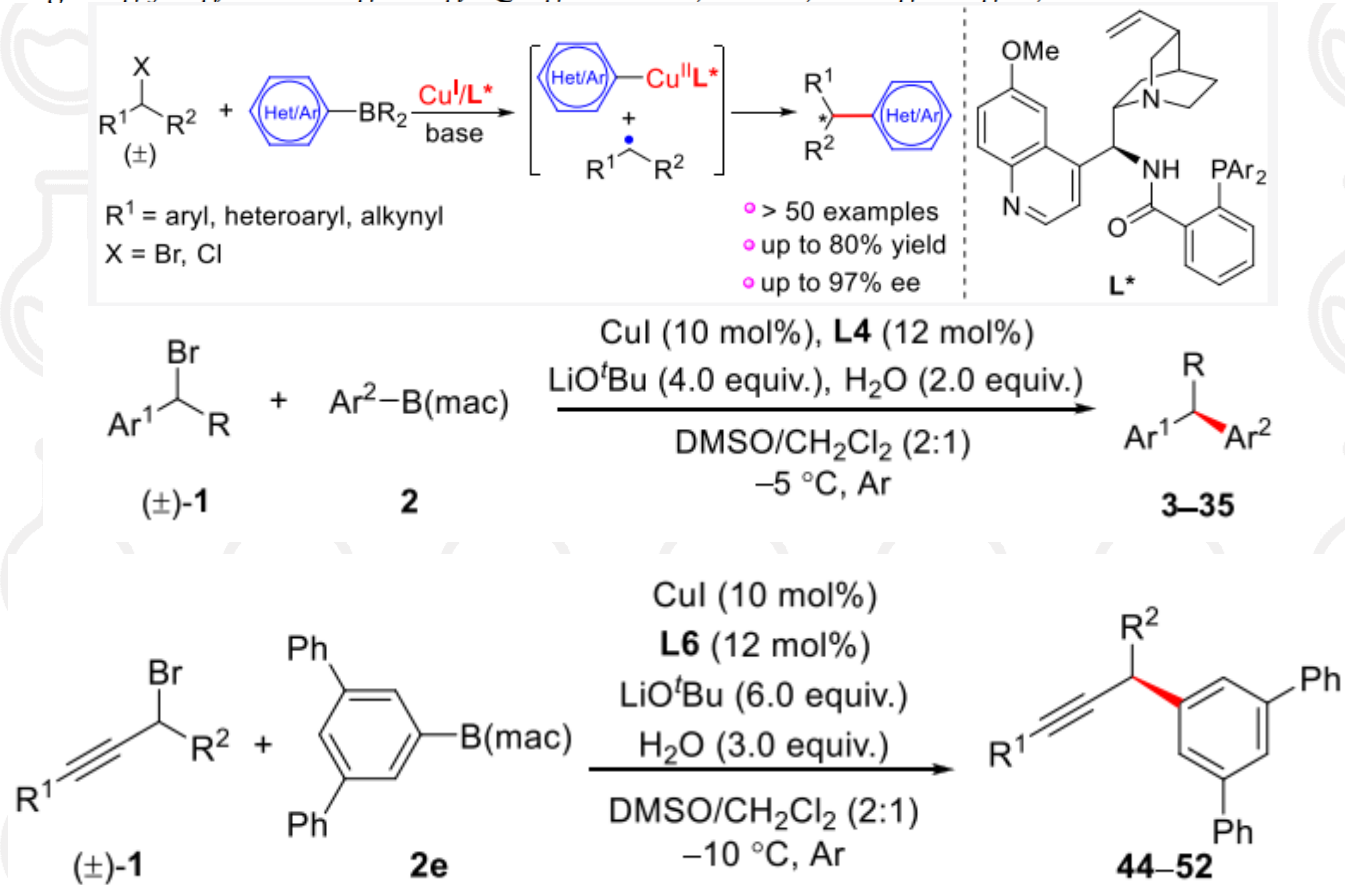


机理研究

- TEMPO捕获
- 自由基钟开环
- 无配体不反应
- 同位素效应(苜位KIE=1.16(分子间)/1.94(分子内)): 1,5 HAA非决速, 有其他反应参与

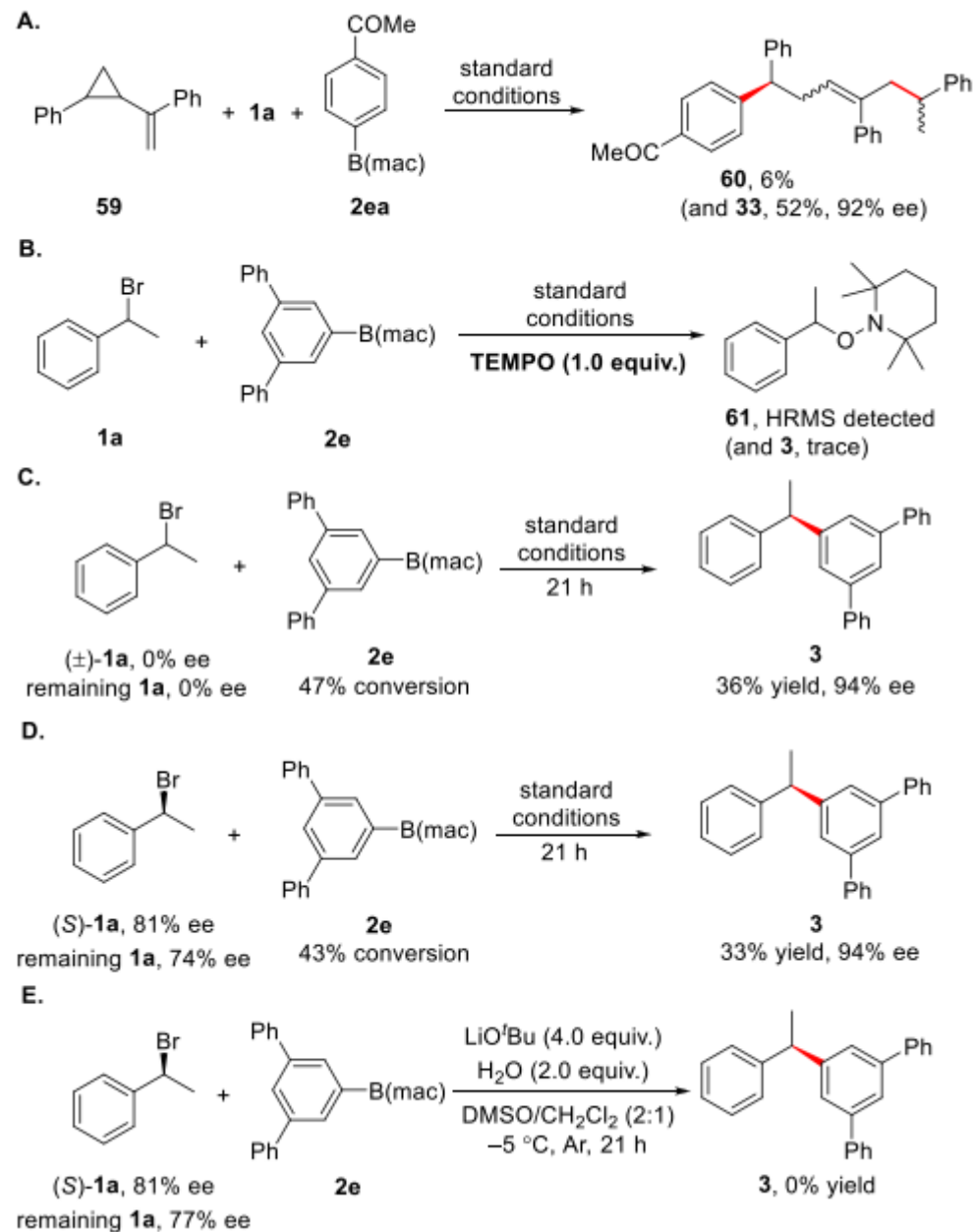
Copper-Catalyzed Enantioconvergent Radical Suzuki–Miyaura C(sp³)–C(sp²) Cross-Coupling

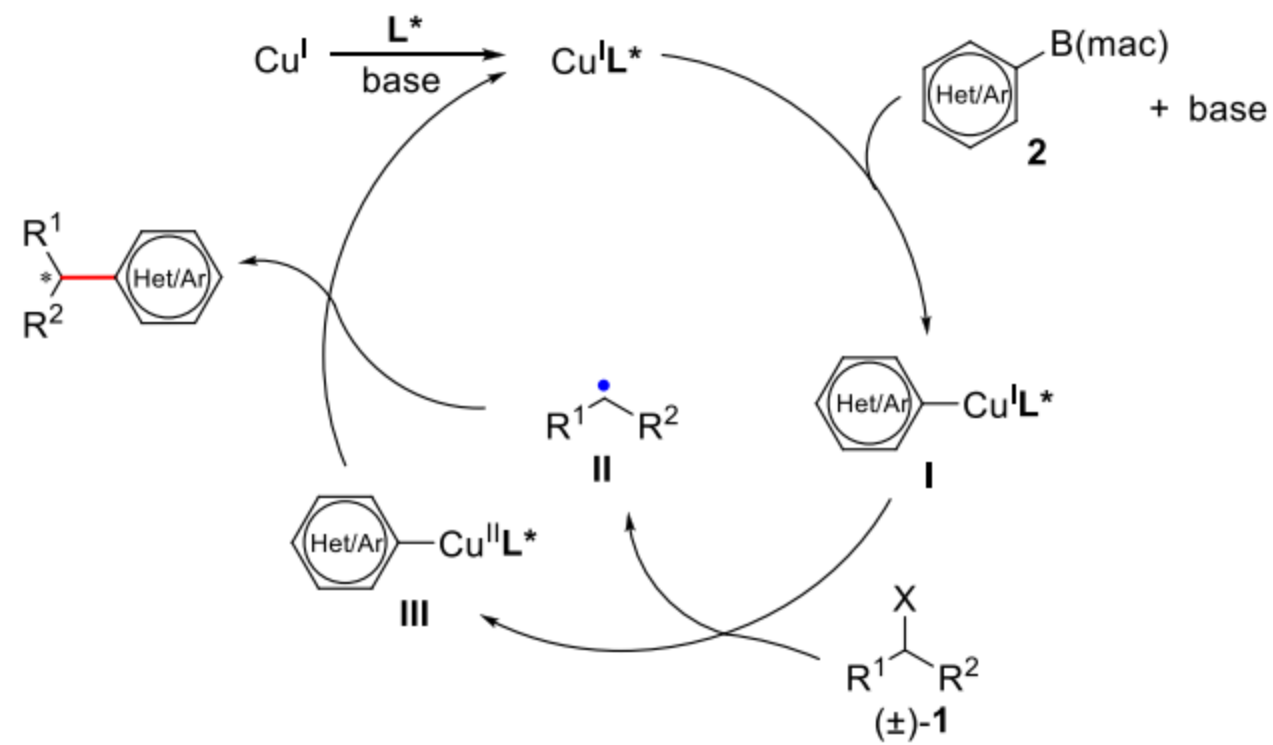
Sheng-Peng Jiang, Xiao-Yang Dong, Qiang-Shuai Gu, Liu Ye, Zhong-Liang Li,* and Xin-Yuan Liu*



加水后，从不反应变为 yield=39% , ee=30%
水能够促进LiOtBu的溶解以及配体交换过程

Scheme 3. Mechanistic Study

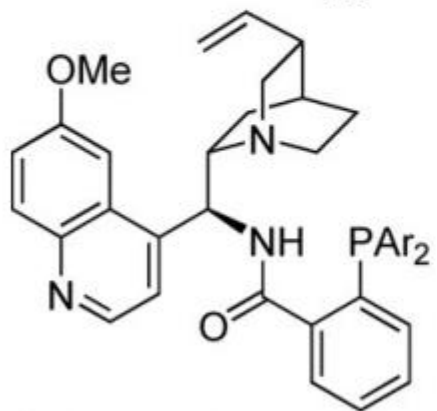
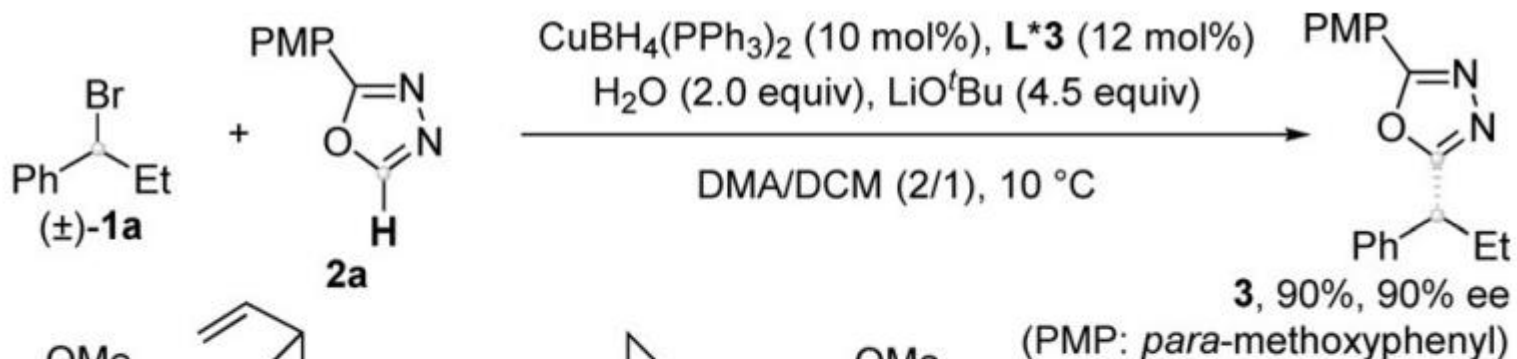




Copper-Catalyzed Enantioconvergent Cross-Coupling of Racemic Alkyl Bromides with Azole C(sp²)-H Bonds

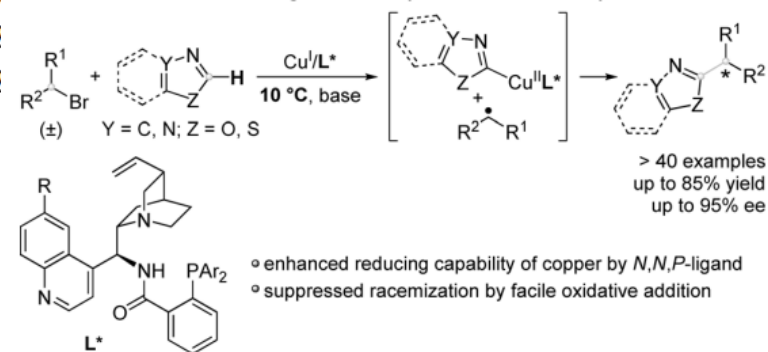
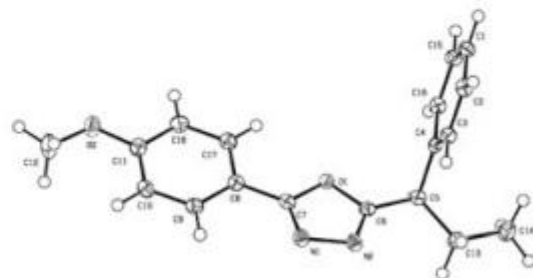
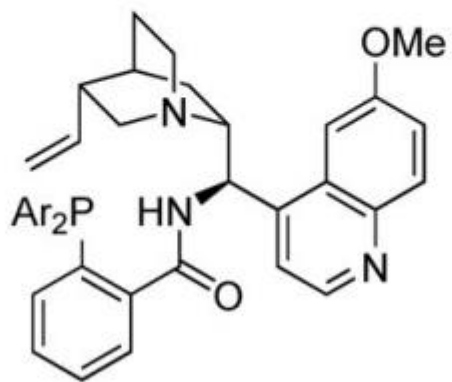
Xiao-Long Su[†], Liu Ye[†], Ji-Jun Chen[†], Xiao-Dong Liu[†], Sheng-Peng Jiang, Fu-Li Wang, Lin Liu, Chang-Jiang Yang, Xiao-Yong Chang, Zhong-Liang Li, Qiang-Shuai Gu, and Xin-Yuan Liu*

苜位卤代烃+氮杂茂

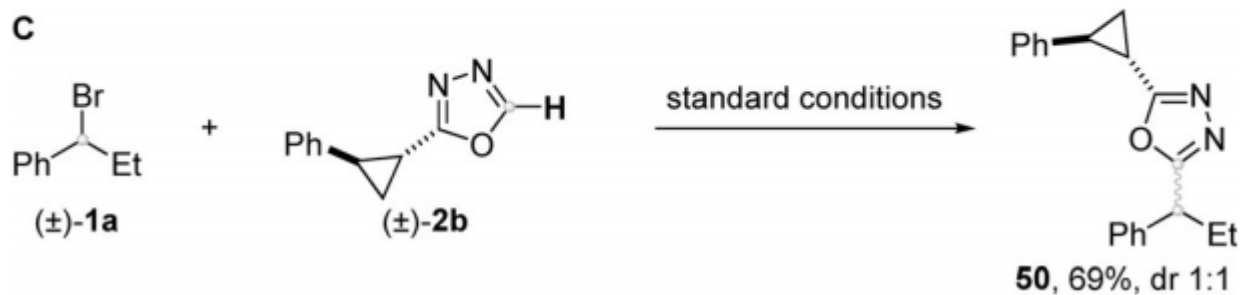
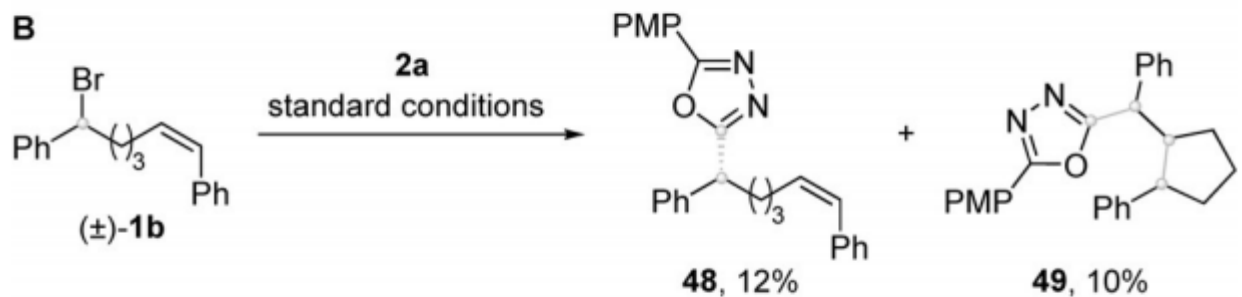
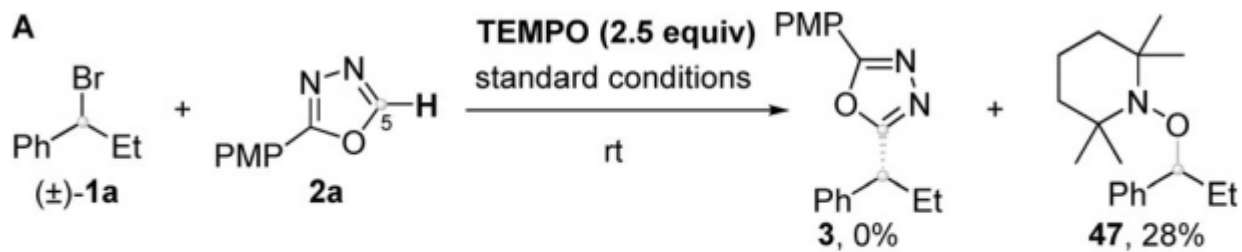


L***2**, Ar = 3,5-(OMe)₂-C₆H₃

L***3**, Ar = 9-Phen

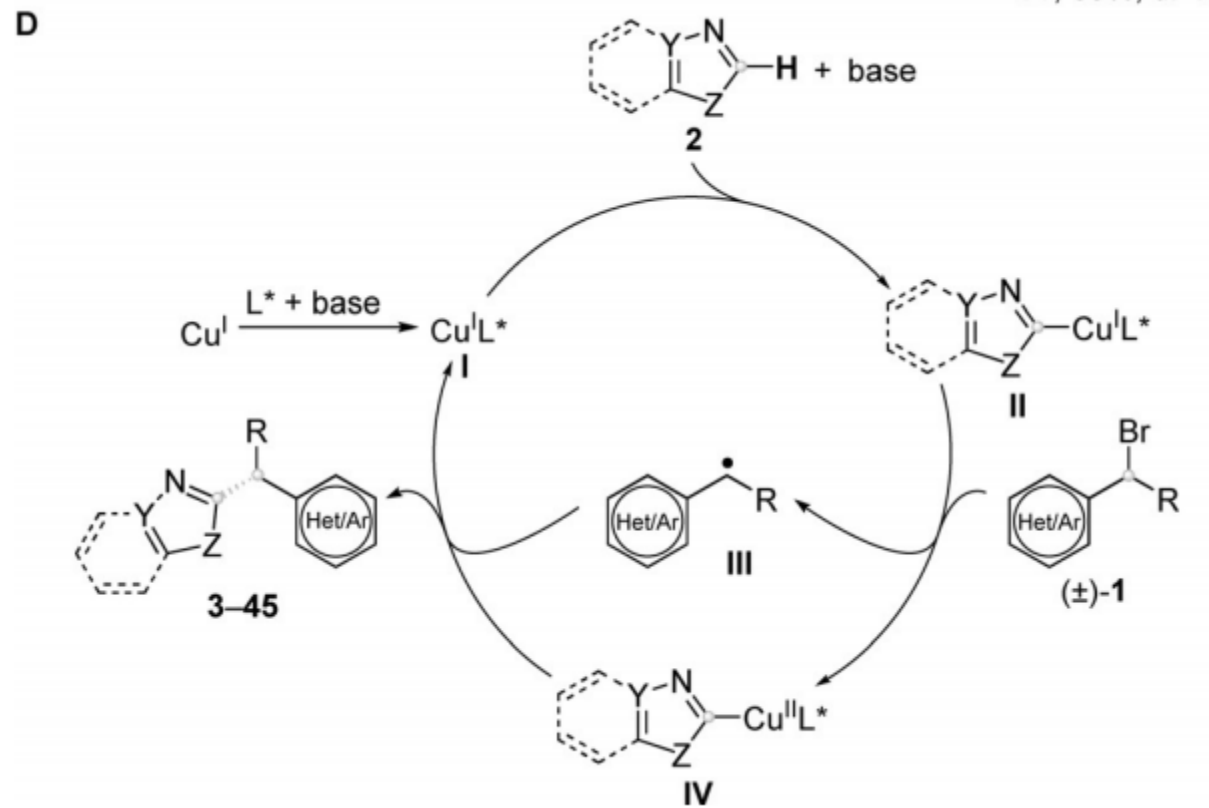


- enhanced reducing capability of copper by *N,N,P*-ligand
- suppressed racemization by facile oxidative addition



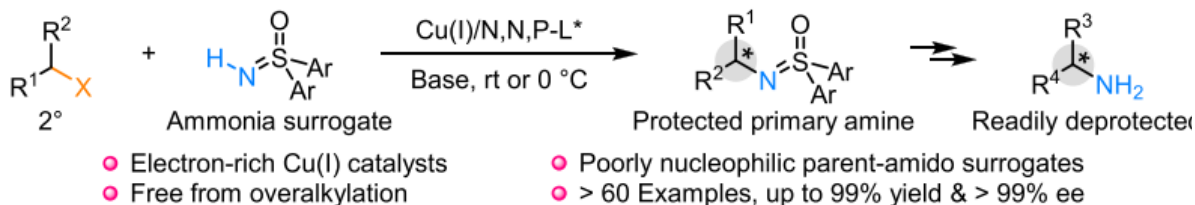
B: (±)-1b环化副产物(5-exo-trig)->烷基自由基

C: 自由基钟，未开环，应该不是唑环直接与自由基加成



Enantioconvergent Cu-Catalyzed Radical C–N Coupling of Racemic Secondary Alkyl Halides to Access α -Chiral Primary Amines

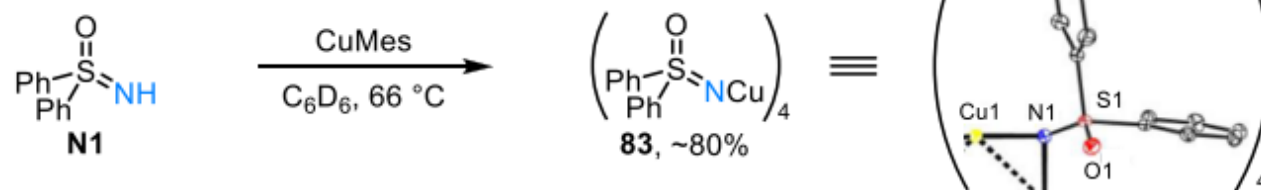
Yu-Feng Zhang,[§] Xiao-Yang Dong,[§] Jiang-Tao Cheng,[§] Ning-Yuan Yang, Li-Lei Wang, Fu-Li Wang, Cheng Luan, Juan Liu, Zhong-Liang Li, Qiang-Shuai Gu, and Xin-Yuan Liu*



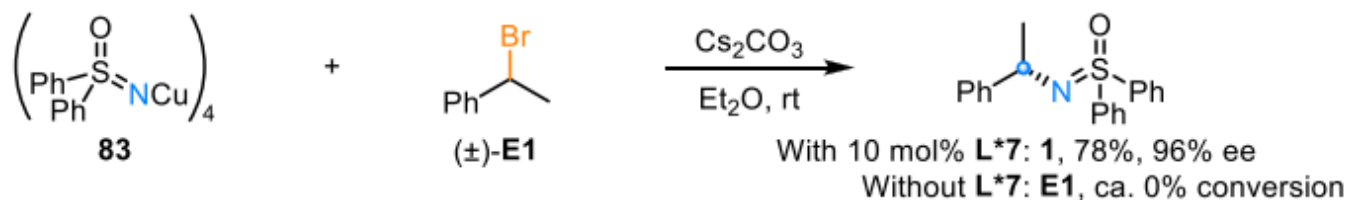
苄基溴/氯, 炔丙基溴, 酰基 α 溴代
CV循环图证明第一个中间体是亚砷亚胺
的配合物

Scheme 5. Mechanistic Investigations

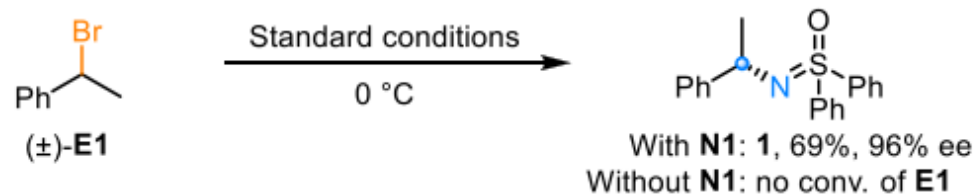
A. Preparation of Cu(I)-sulfoximinato complex



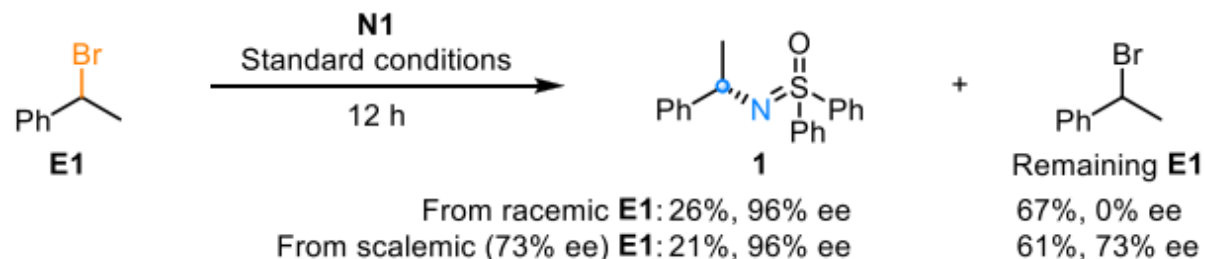
B. Reaction of Cu(I)-sulfoximinato complex



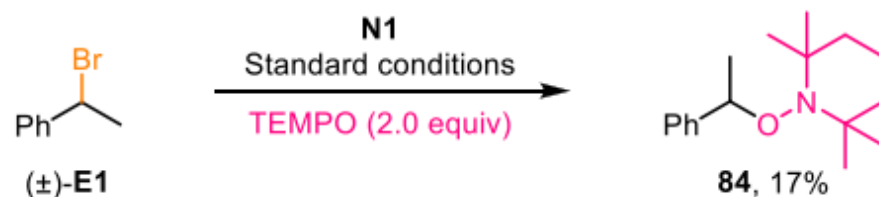
C. Effect of nucleophile on reaction initiation



D. Enantiopurity of recovered alkyl bromide



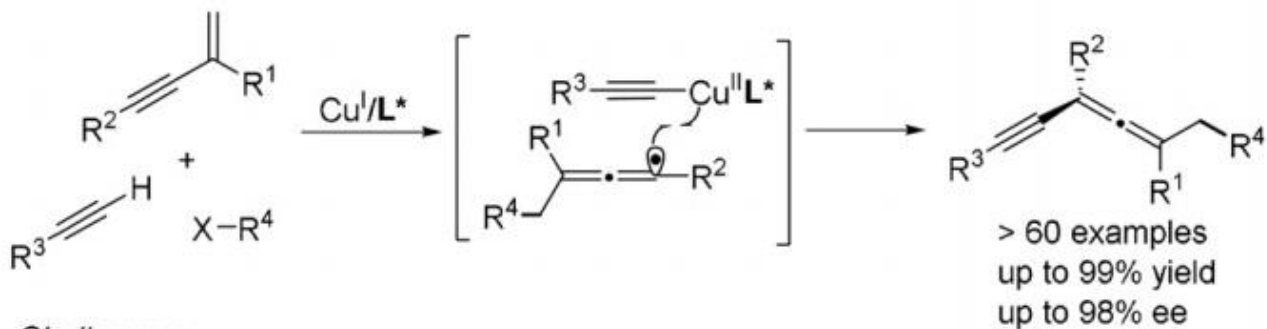
E. Radical trap experiment



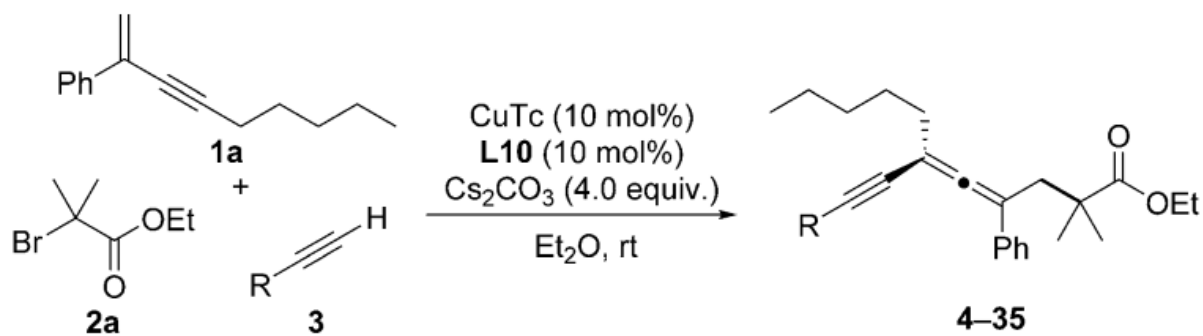
Copper-Catalyzed Asymmetric Coupling of Allenyl Radicals with Terminal Alkynes to Access Tetrasubstituted Allenes

Xiao-Yang Dong⁺, Tian-Ya Zhan⁺, Sheng-Peng Jiang, Xiao-Dong Liu, Liu Ye, Zhong-Liang Li, Qiang-Shuai Gu, and Xin-Yuan Liu*

C. This Work on Enantiocontrol of Allenyl Radical to Access Tetrasubstituted Chiral Allenes

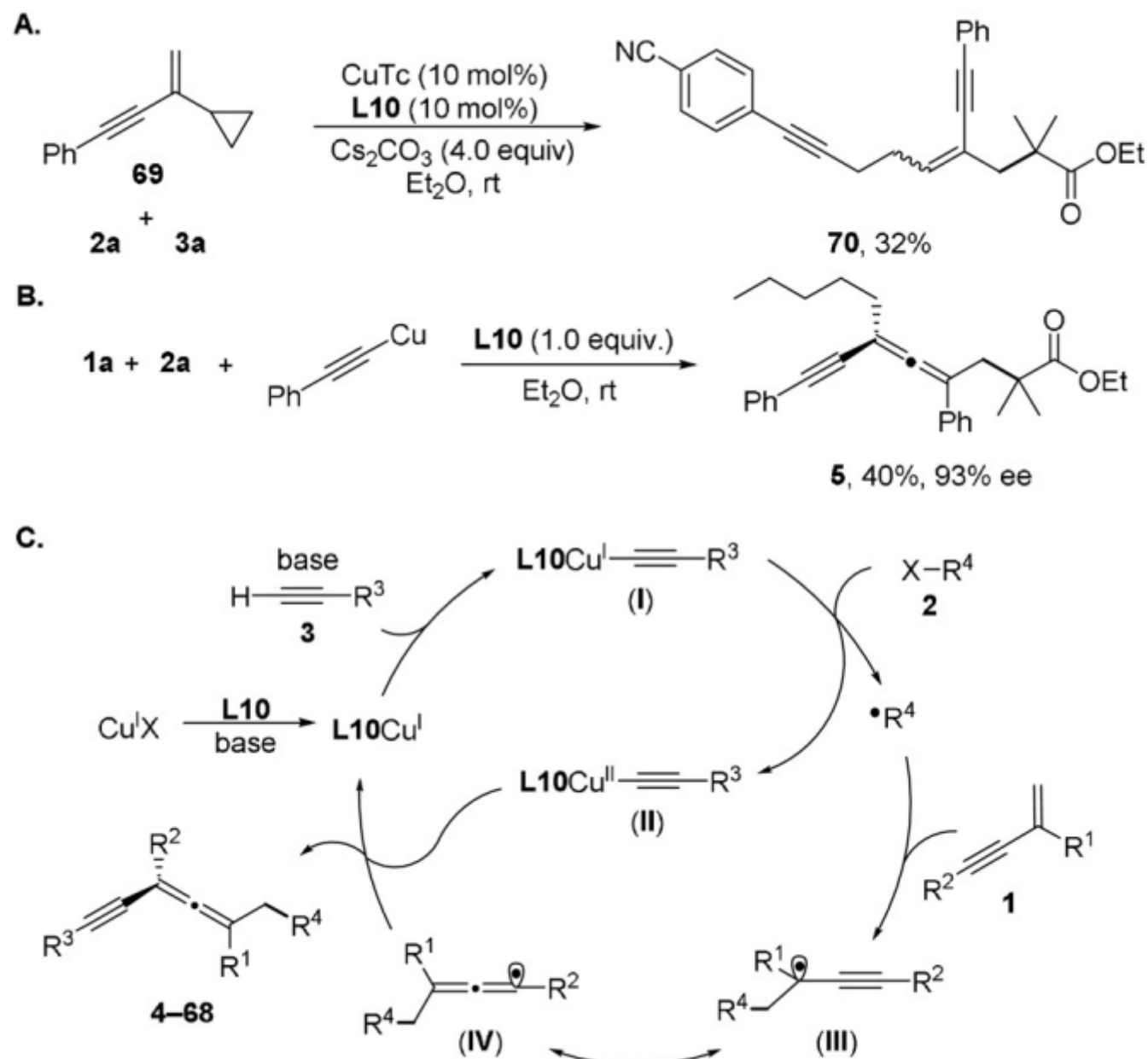


1. 高活性的炔丙基自由基的手性控制
2. 合适的配体
3. 副反应 (如卤代烃和炔丙基偶联, 炔丙基自偶联等)



R-X	Product	R-X	Product
 2b	 60, 81%, 93% ee	 2g	 65, 86%, 90% ee
 2c	 61, 91%, 89% ee	 2h	 66, 77%, 91% ee
 2d	 62, 88%, 91% ee	 2i	 67, 64%, 83% ee
 2e	 63, 33%, 89% ee	 2i	 68, 71%, 80% ee ^[b]
 2f	 64, 85%, 98% ee		

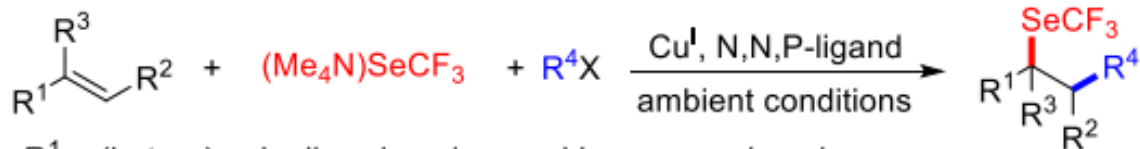
直接使用炔基铜作为反应物，可以得到 ee 高产物，说明其可能为中间体



Copper-Catalyzed Radical 1,2-Carbotrifluoromethylselenolation of Alkenes under Ambient Conditions

Jiao Yu, Ning-Yuan Yang, Jiang-Tao Cheng, Tian-Ya Zhan, Cheng Luan, Liu Ye, Qiang-Shuai Gu, Zhong-Liang Li,* Guo-Qiang Chen,* and Xin-Yuan Liu*

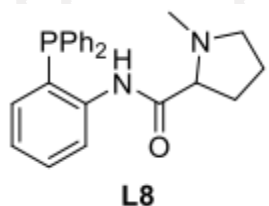
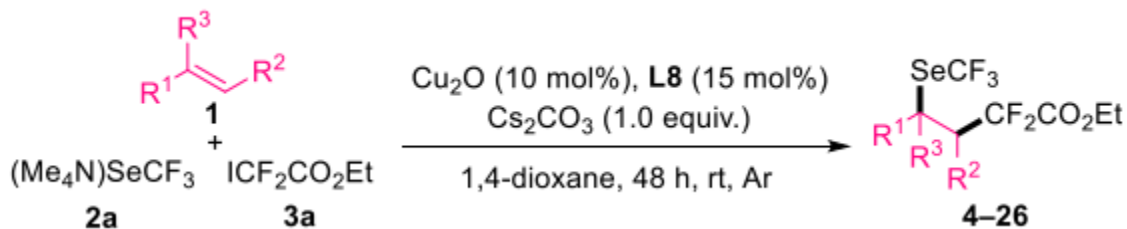
(B) This Work on Diverse Radical 1,2-Carbotrifluoromethylselenolation of Alkenes with Readily Available (Me₄N)SeCF₃ under Ambient Conditions



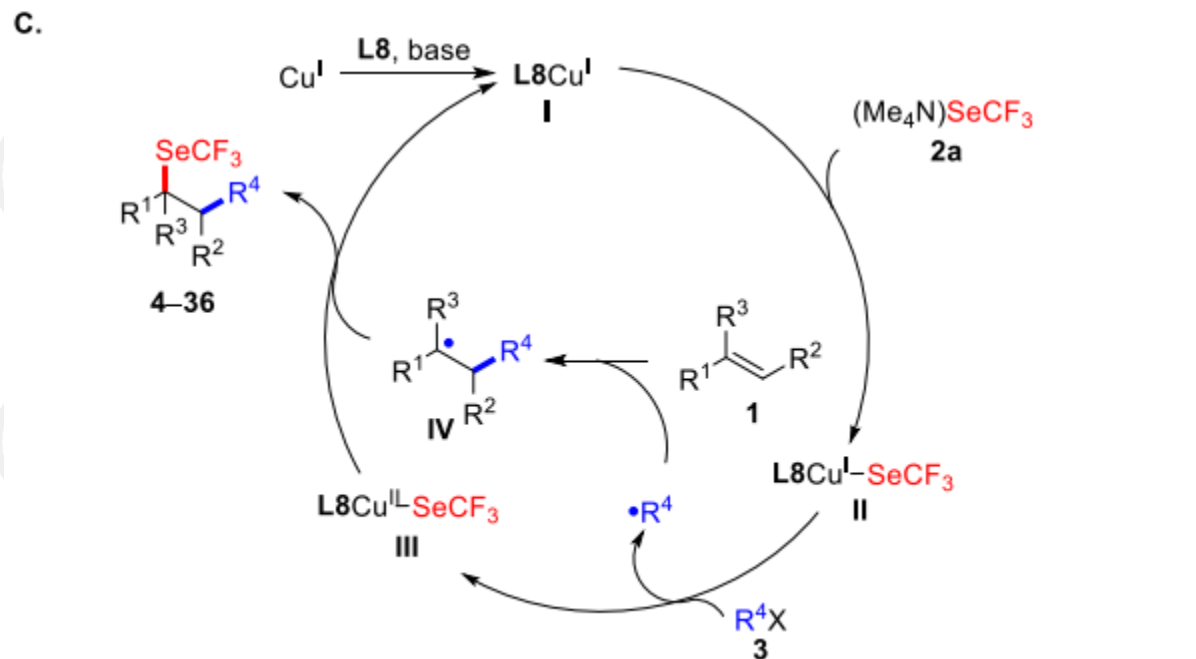
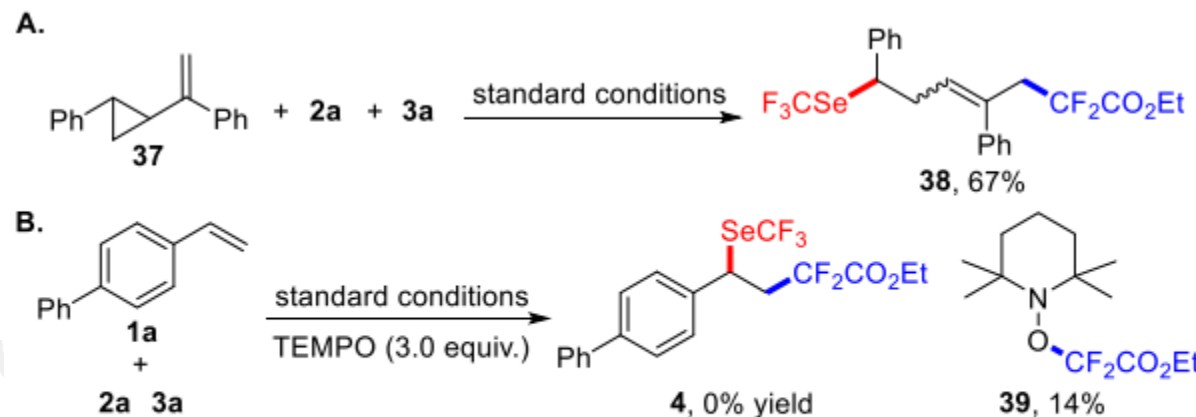
R¹ = (hetero)aryl, alkynyl, amino, and benzyloxycarbonyl

R² = H, alkyl; R³ = H, alkyl, Ph

R⁴ = CF₂CO₂Et, C₄F₉, CCl₂CF₃, C(CH₃)₂CO₂^tBu



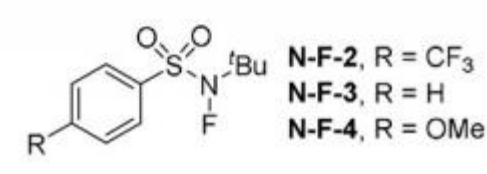
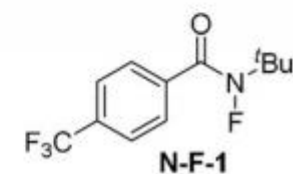
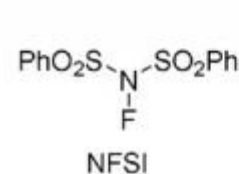
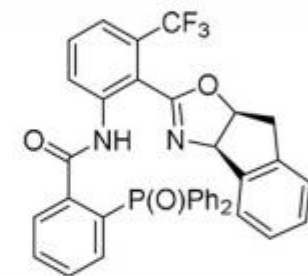
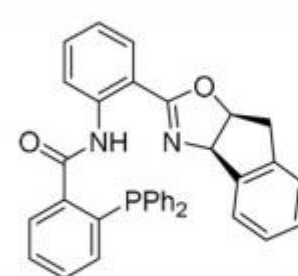
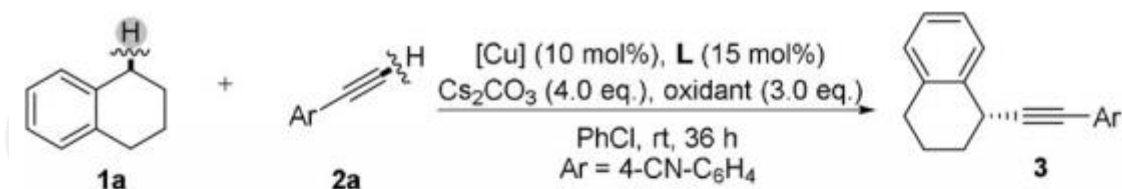
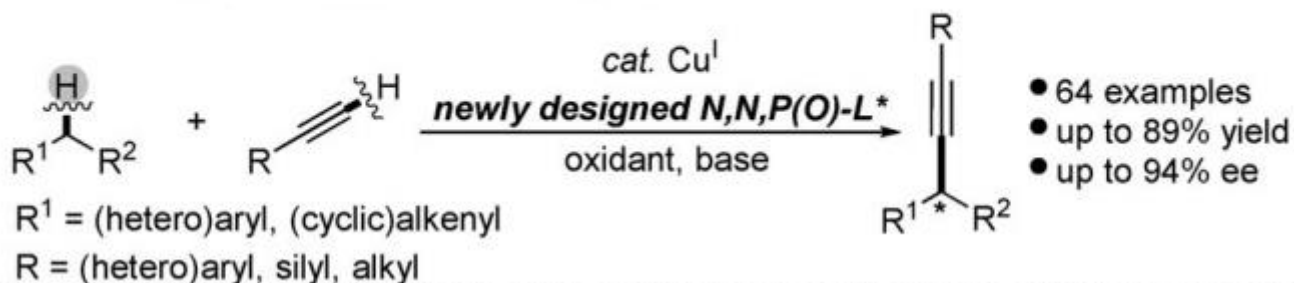
基于脯氨酸改造的非手性的
NNP配体



Copper-Catalyzed Intermolecular Enantioselective Radical Oxidative C(sp³)–H/C(sp)–H Cross-Coupling with Rationally Designed Oxazoline-Derived N,N,P(O)-Ligands

Lin Liu, Kai-Xin Guo, Yu Tian, Chang-Jiang Yang, Qiang-Shuai Gu, Zhong-Liang Li, Liu Ye,* and Xin-Yuan Liu*

c) This work: rational ligand design for realizing the challenging intermolecular asymmetric oxidative C(sp³)–H/C(sp)–H cross-coupling



难点:

- 需要氧化剂拔H以提高HAA的效率
- Cu催化体系中，末端炔烃、手性配体与强氧化剂难以兼容

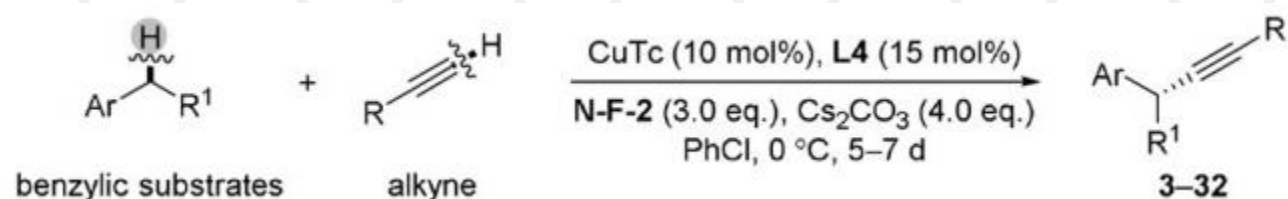
原有的基于奎宁的NNP配体

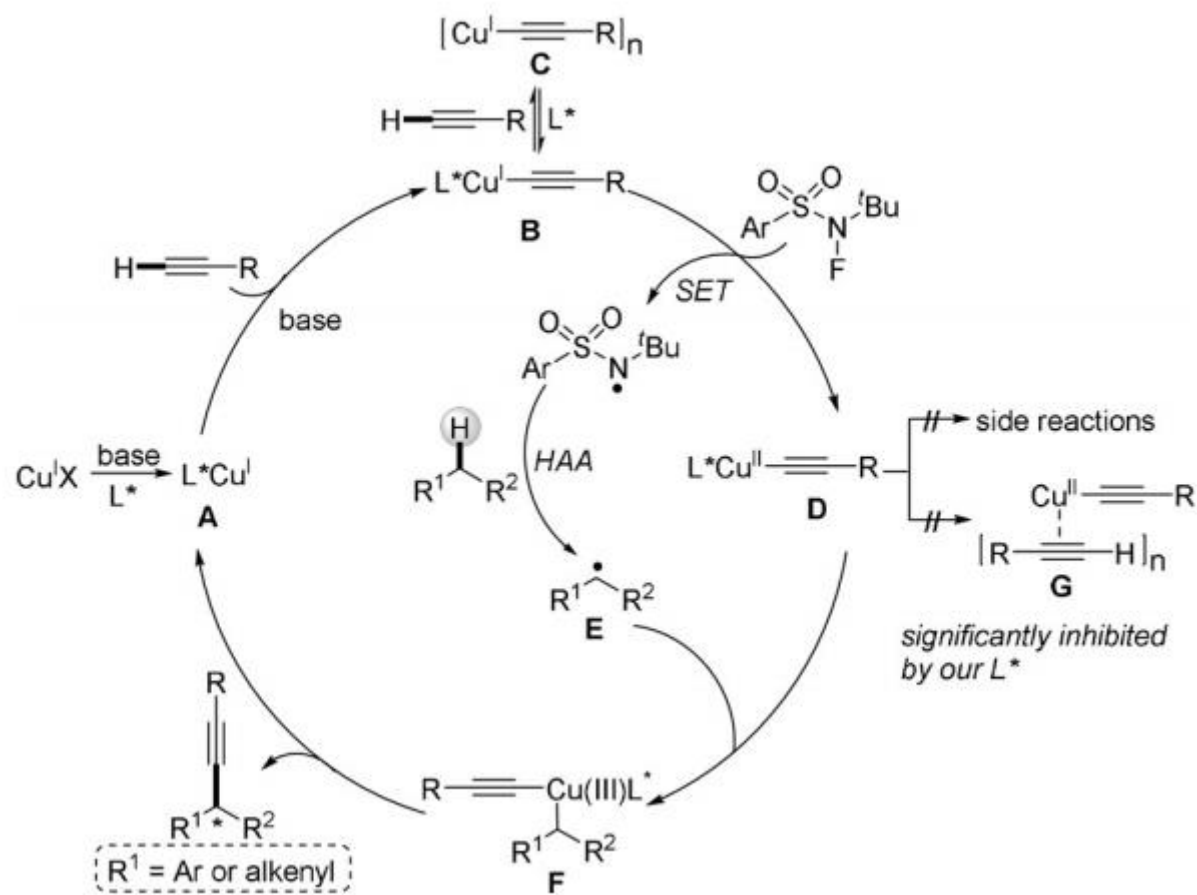
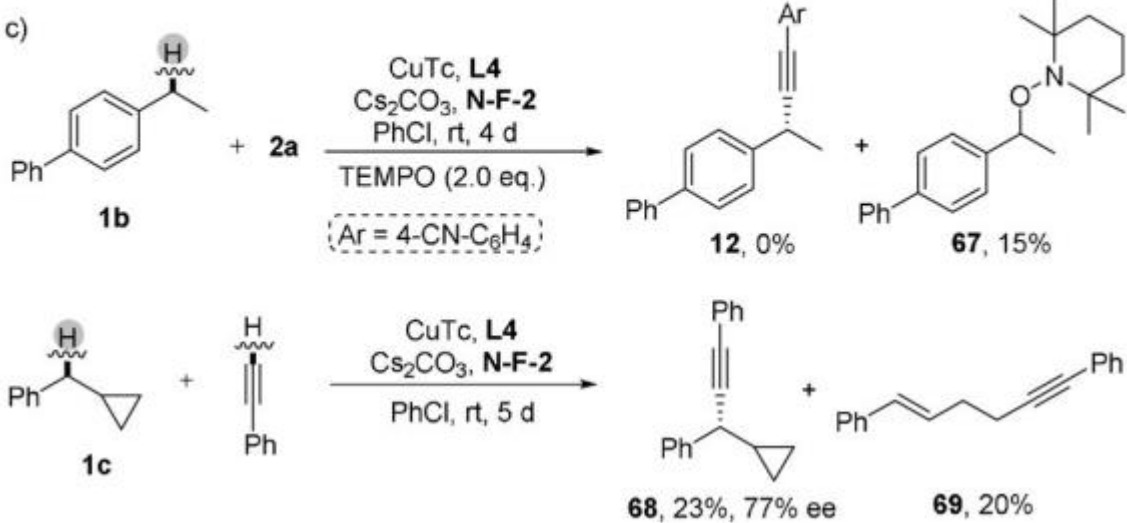
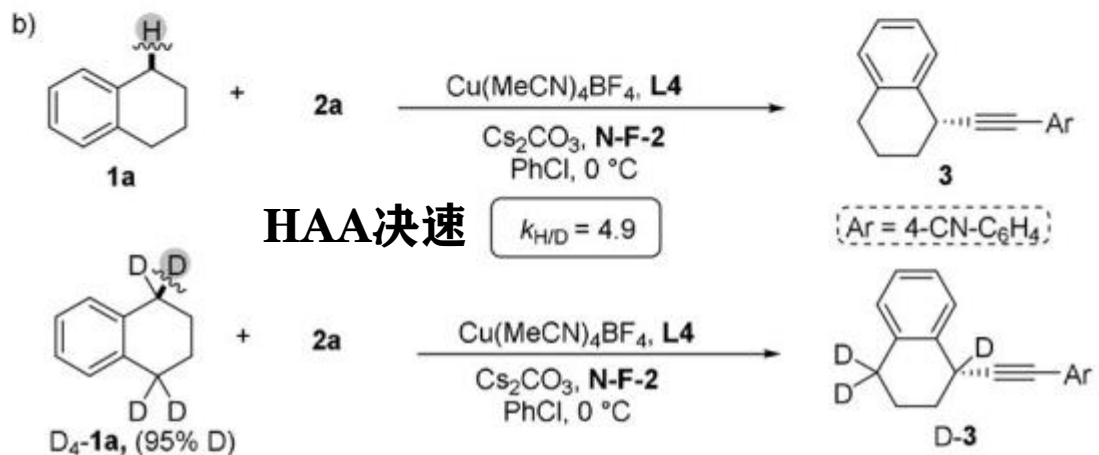
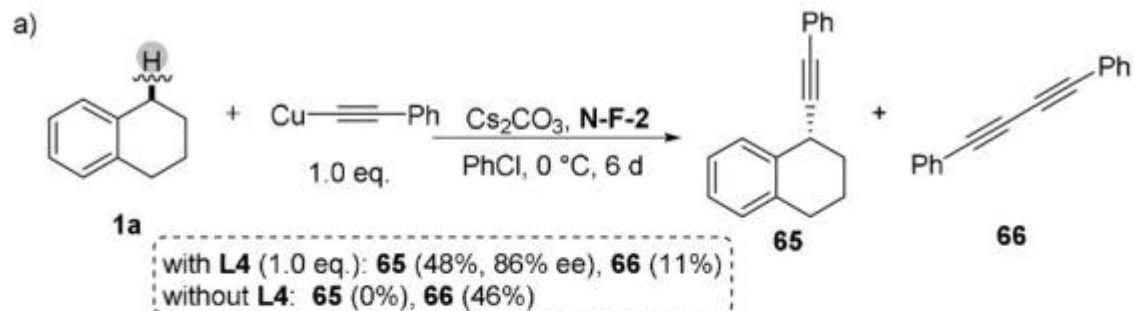
- 与强氧化剂（如NFSI）不能共存，迅速分解
- 与稍弱氧化剂，反应性较差

开发新的基于噁唑啉环的NNP配体

保证结构稳定的同时，具有合适的电子密度，可以使(炔烃–Cu(I)–L*)有很好的还原性

磷谱确认，在氧化剂的作用下L4→L5





末端炔烃过量时，易在体系中聚合，加入 NNP(O)能够有效减少聚合。

谢谢



1852946 · Shenghan Cai