

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

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Liu, X.-Y. *et al.* *J. Am. Chem. Soc.* **2016**, *138*, 9357-9360.

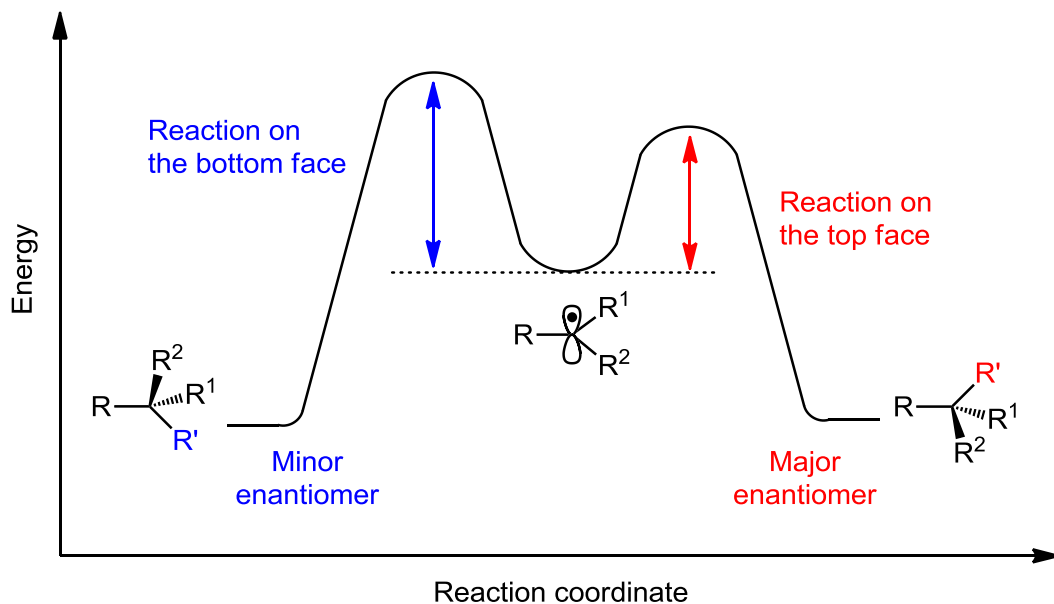
Contents

- Introduction
- The strategies for enantioselective radical process
- The dual-catalytic strategy to asymmetric radical aminotrifluoromethylation of alkenes
- Summary

The Carbon-Centred Radical

The targets:

- ✓ The clean, environmentally friendly methods for radical formation.
- ✓ The high reactivity and potential to form byproducts (in low yields).
- ✓ *Stereoselective reactions to produce predominantly one isomer.*

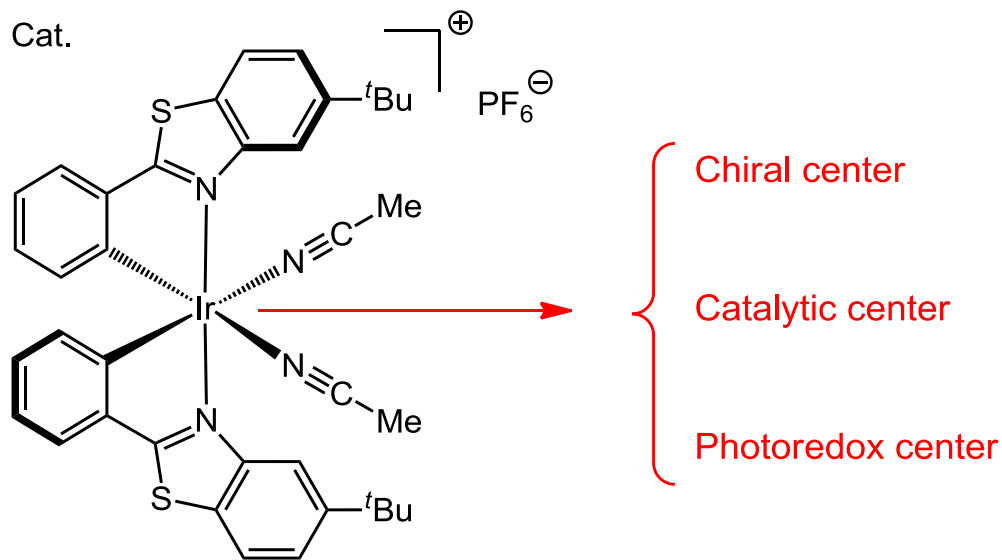
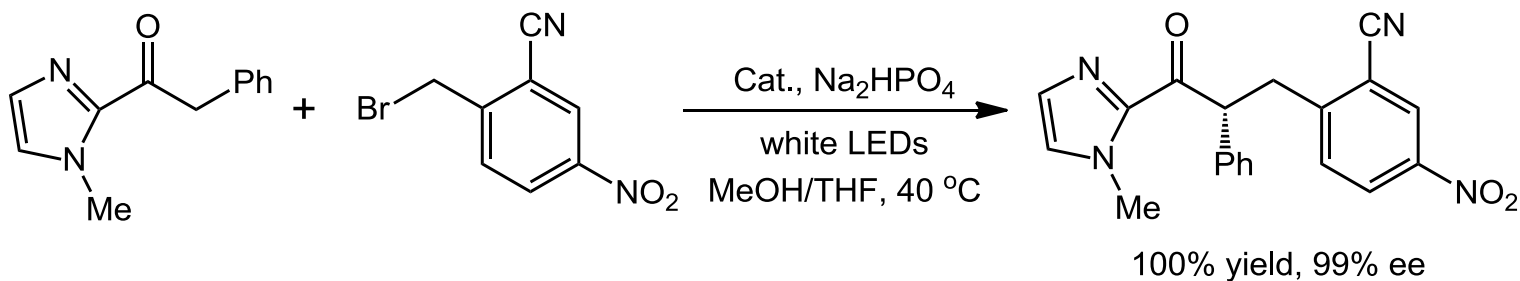


◆ How to control them?

- ✓ Complex-controlled strategy
- ✓ Reagent-controlled strategy
- ✓ *Radical relay strategy*

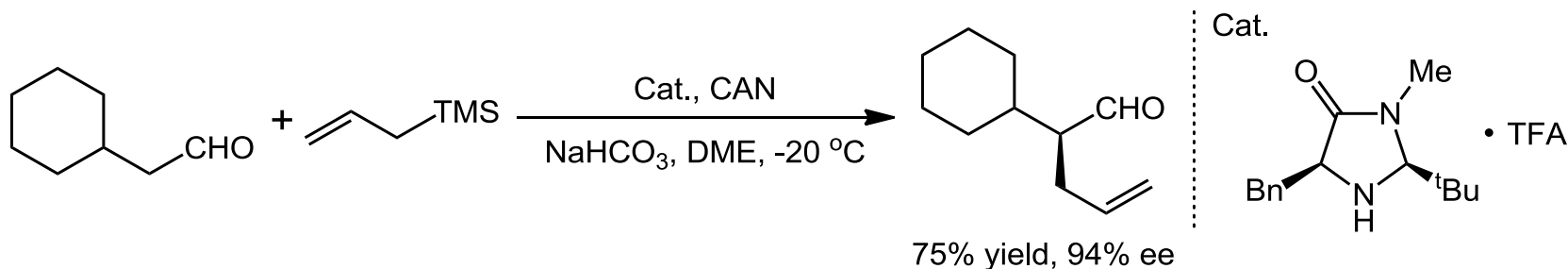
The Complex-Controlled Strategy

◆ Lewis acid catalysis



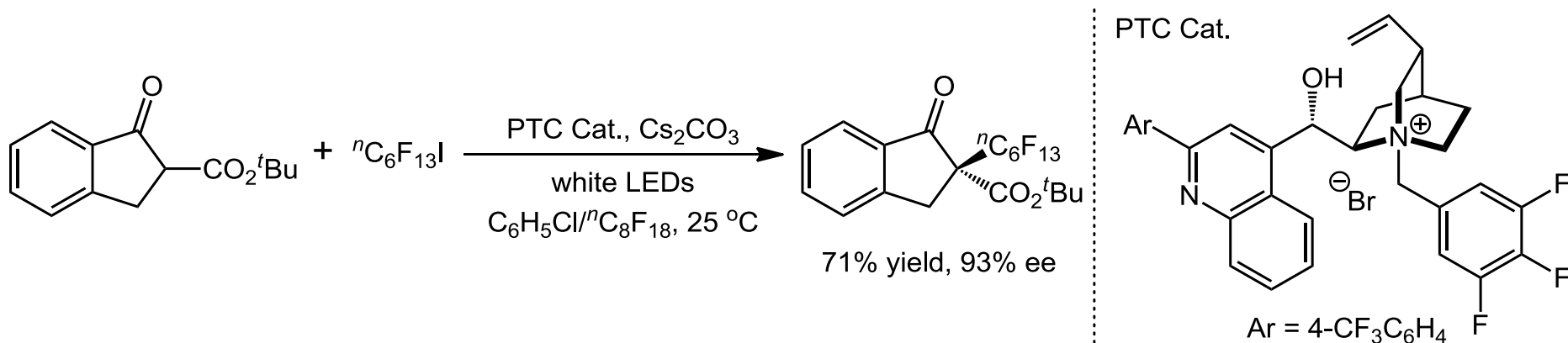
The Complex-Controlled Strategy

◆ SOMO catalysis



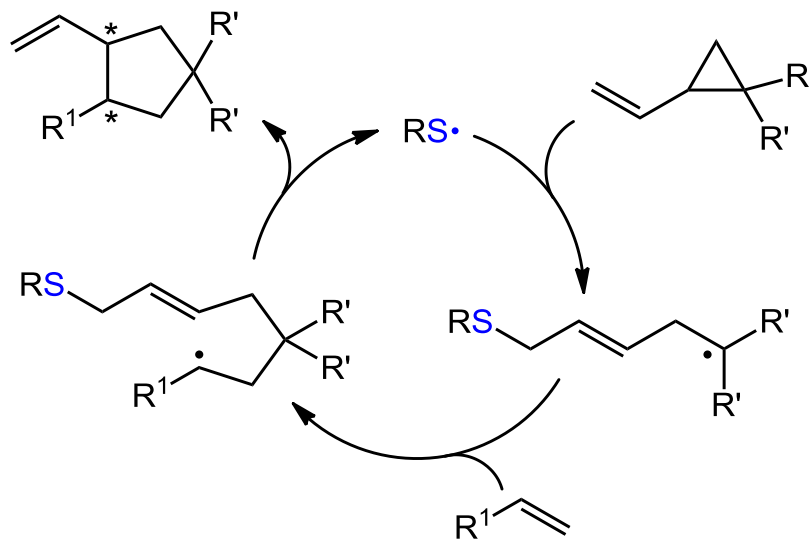
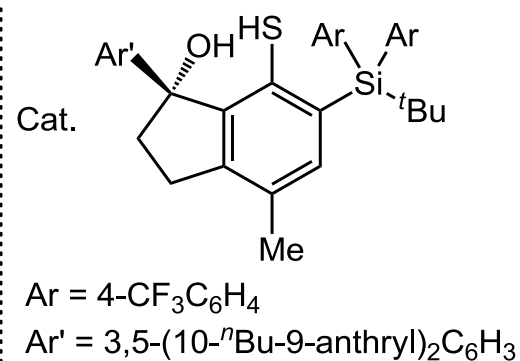
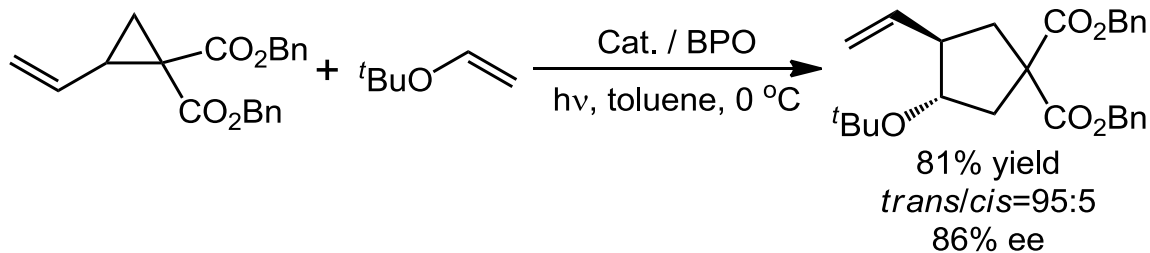
MacMillan, D. W. C. *et al. Science* **2007**, 316, 582.

◆ Phase transfer catalysis



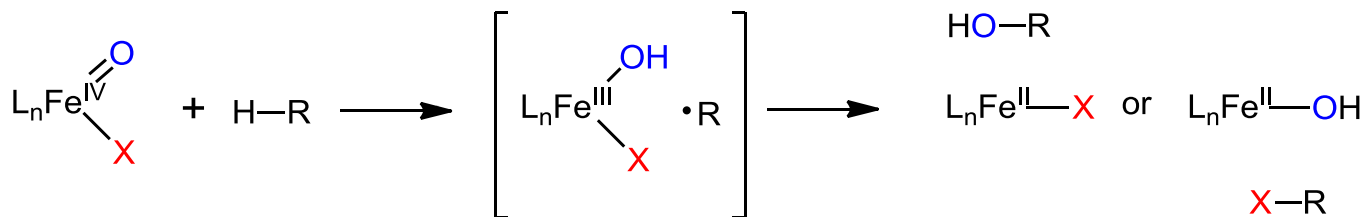
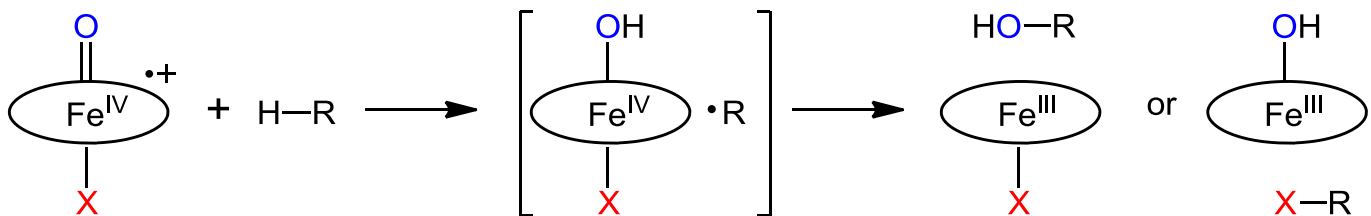
Melchiorre, P. *et al. J. Am. Chem. Soc.* **2015**, 137, 5678.

The Reagent-Controlled Strategy

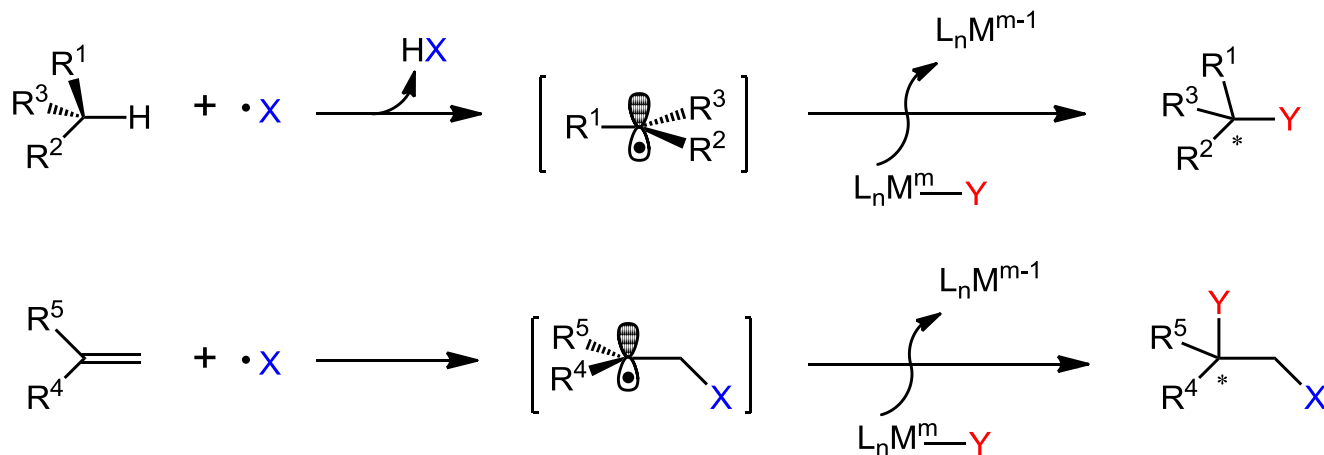


Enzymatic and Biomimetic C–H Functionalization

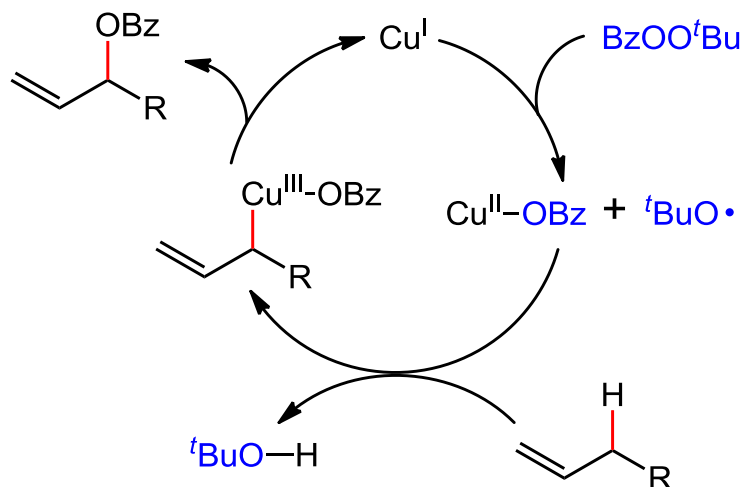
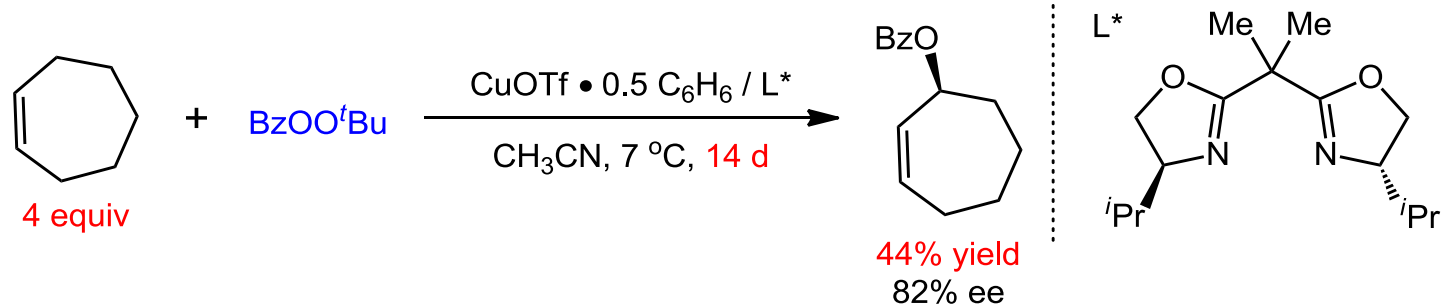
Radical rebound



Radical relay

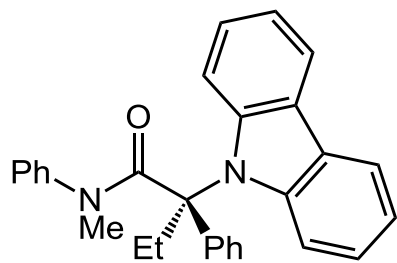
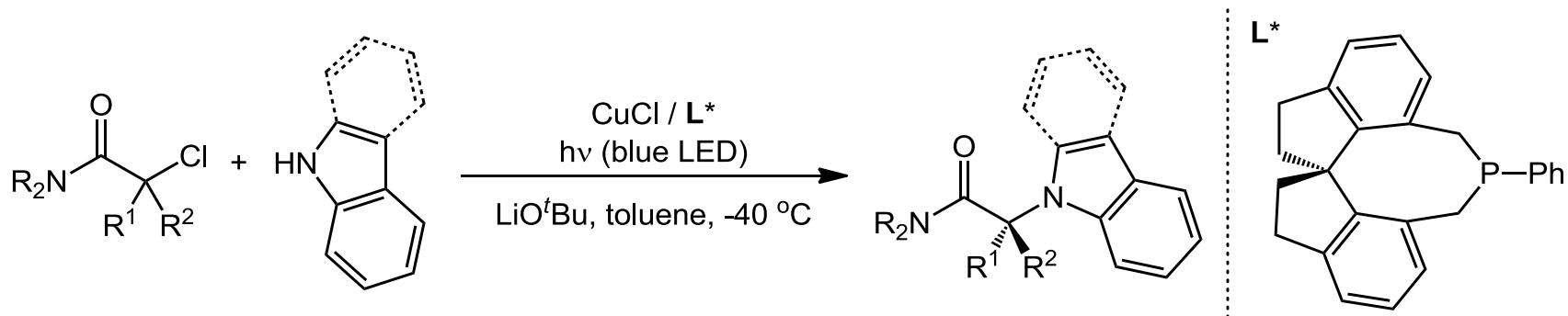


Kharasch-Sosnovsky Allylic Oxidation

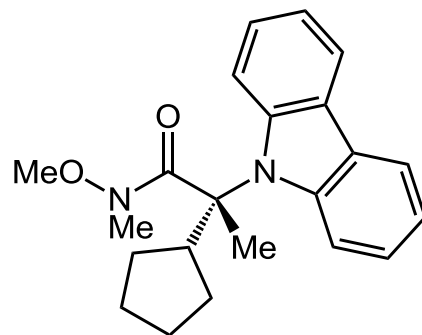


Kharasch, M. S. and Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, *80*, 756;
Pfaltz, A. *et al. Tetrahedron Lett.* **1995**, *36*, 1831.

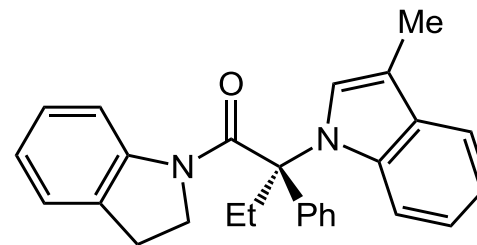
Radical Relay Strategy – Amination



79% yield, 94% ee

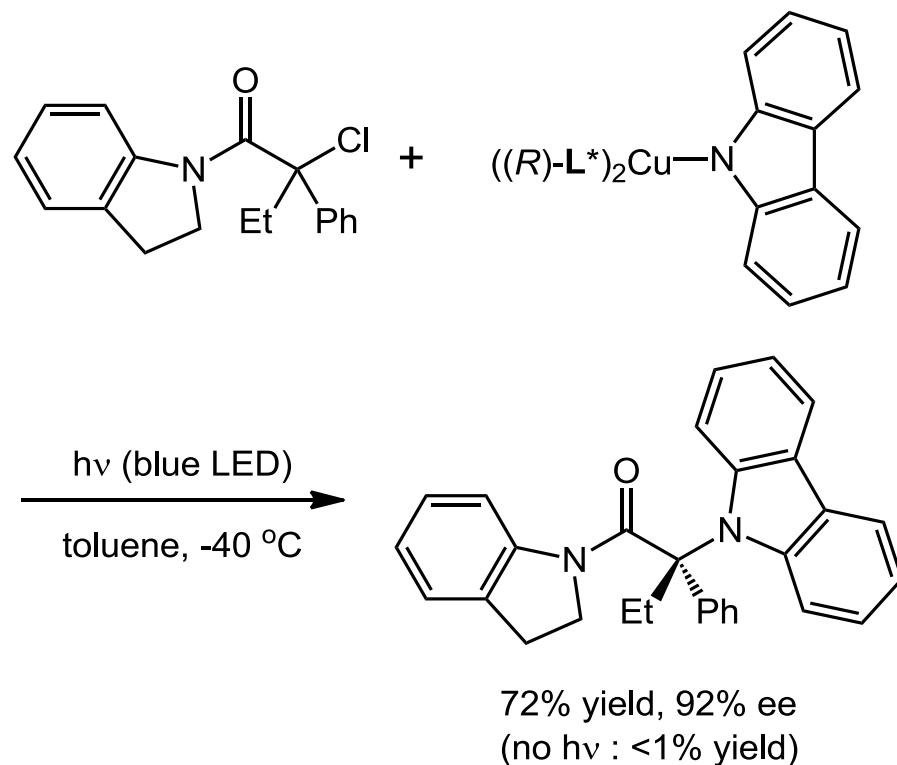
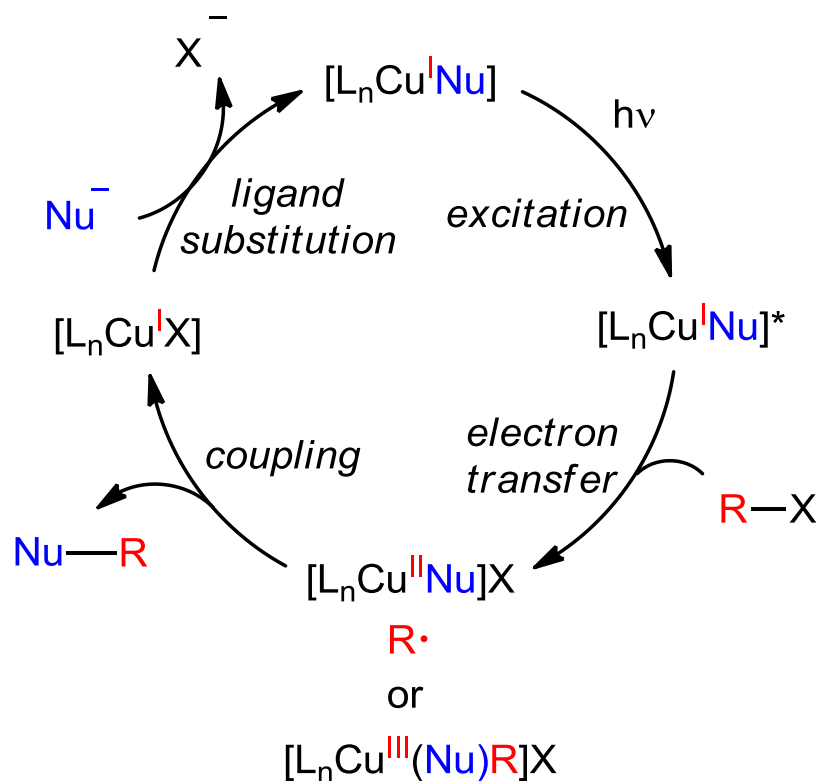


73% yield, 95% ee

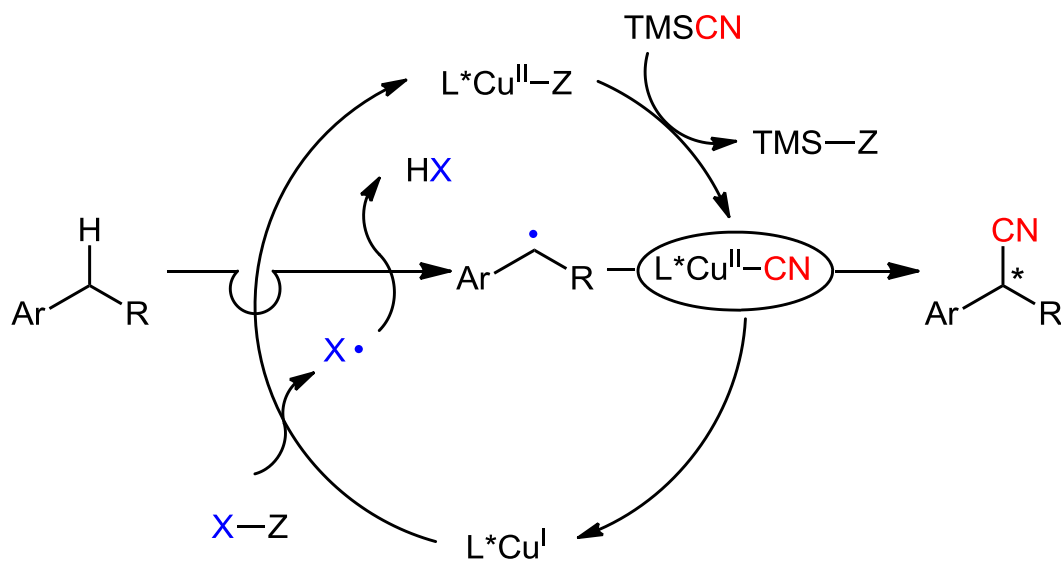
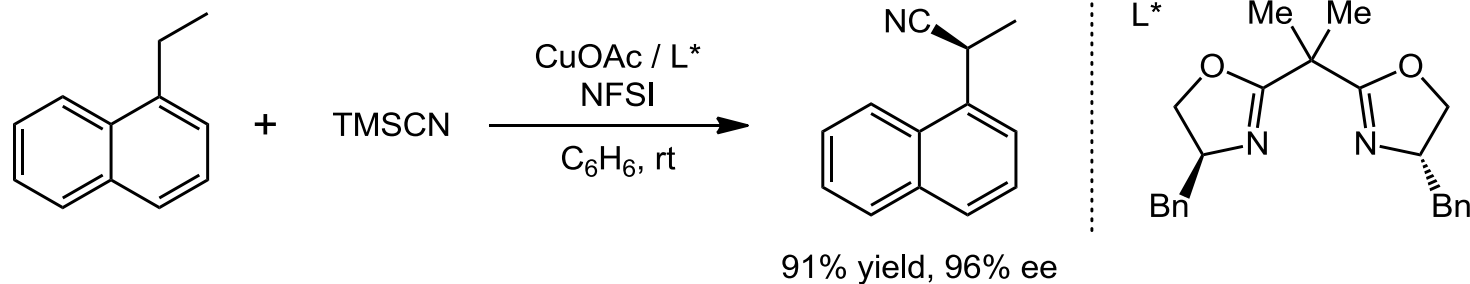


79% yield, 92% ee

Radical Relay Strategy – Amination

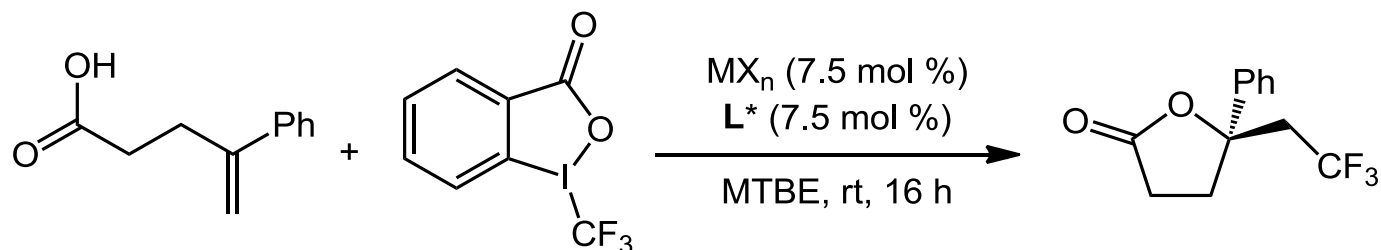


Radical Relay Strategy – Cyanation

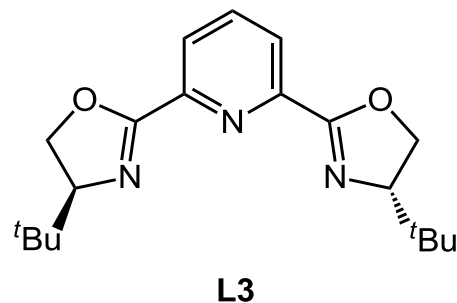
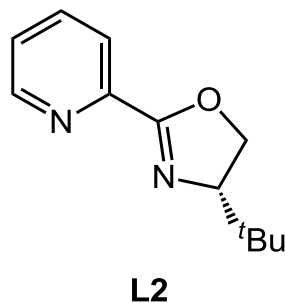
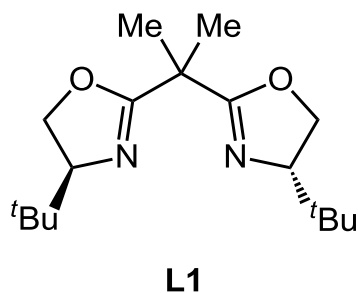


Entry	Oxidant	Yield (%)
1	(^t BuO) ₂	0
2	^t BuONO	0
3	^t BuOOH	0
4	BzOO ^t Bu	0
5	Oxone	0
6	K ₂ S ₂ O ₈	0
7	PhI(OAc) ₂	0
8	SelectFluor	0

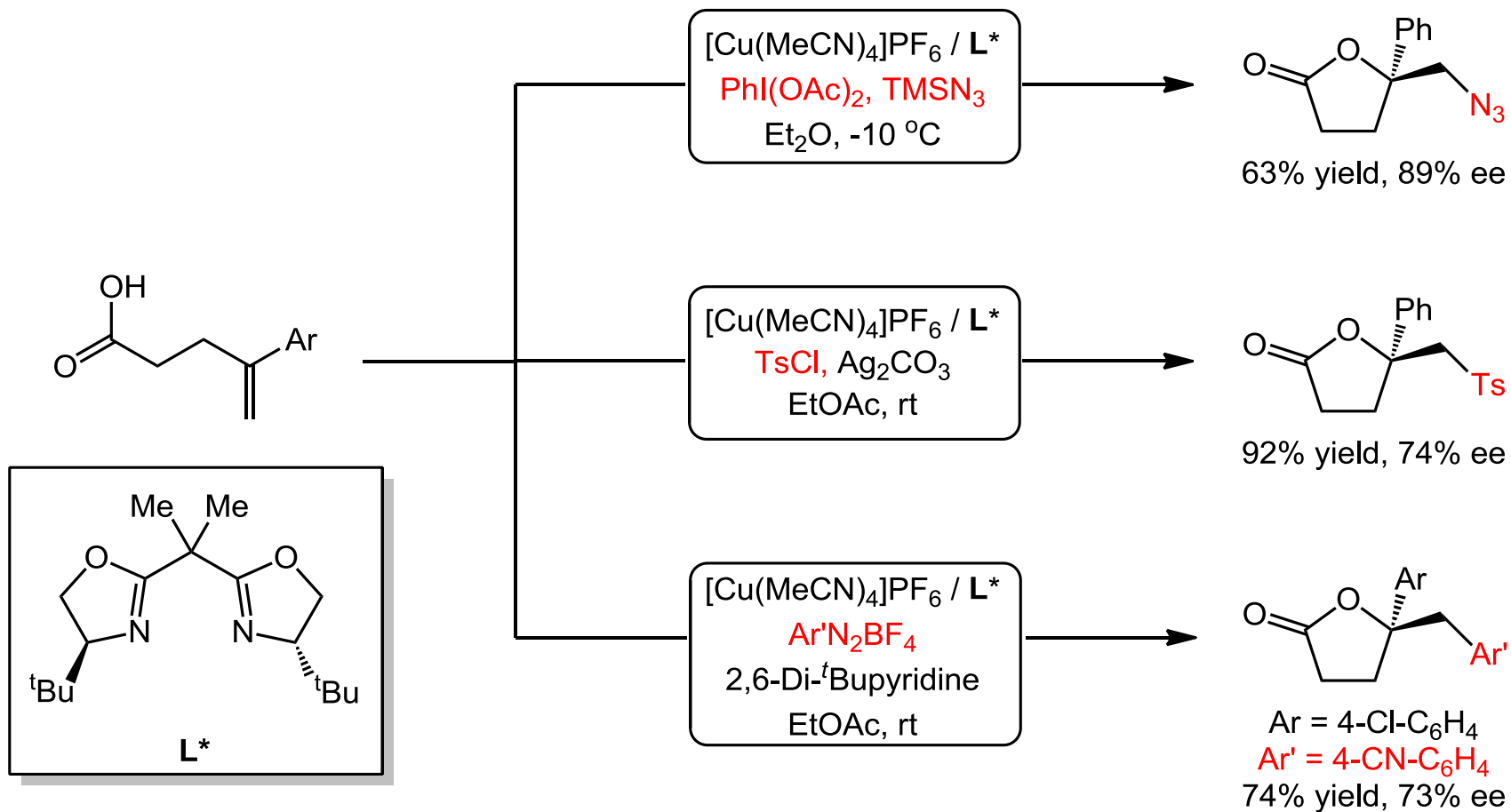
Radical Relay Strategy - Oxytrifluoromethylation



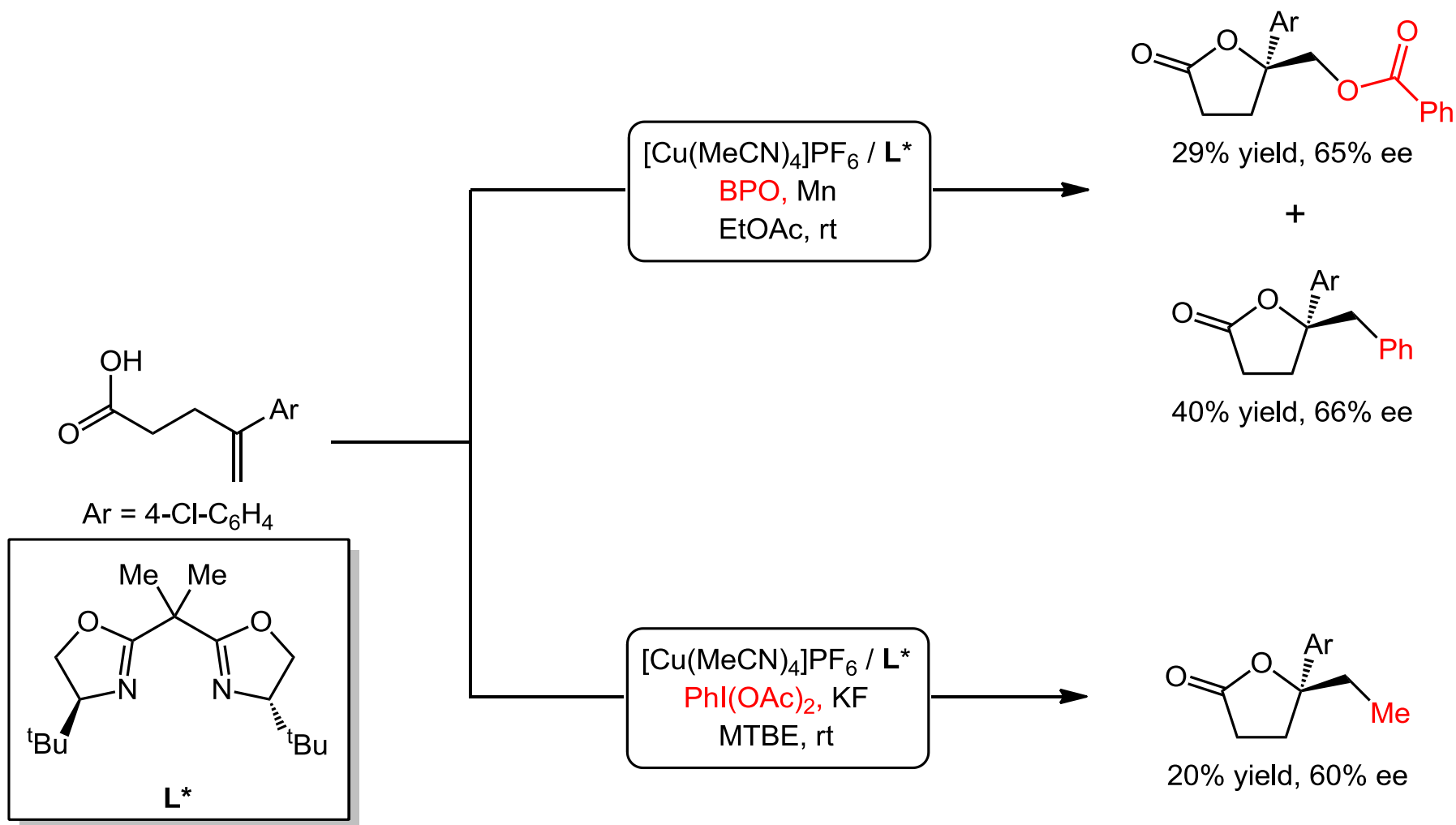
Entry	MX_n	L^*	Yield (%)	Ee (%)
1	$[\text{Cu}(\text{MeCN})_4]\text{PF}_6$	L1	85	81
2	$[\text{Cu}(\text{MeCN})_4]\text{PF}_6$	L2 or L3	<2	--
3	CuI	L1	<2	--
4	CuCl	L1	66	-21
5	$\text{Cu}(\text{OTf})_2$, $\text{Zn}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$	L1	<2	--



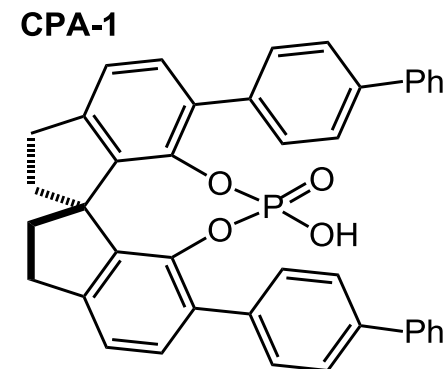
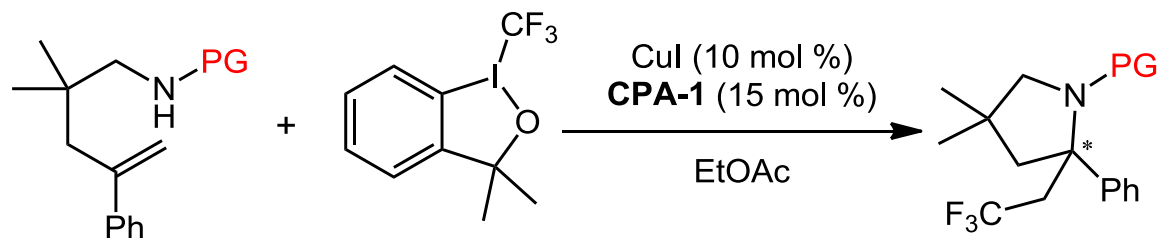
Radical Relay Strategy - Oxyfunctionalization



Radical Relay Strategy - Oxyfunctionalization



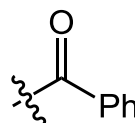
Asymmetric Radical Aminotrifluoromethylation



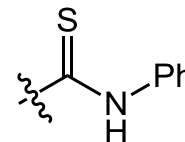
PG:



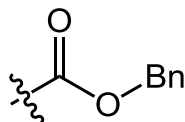
80 °C, ND



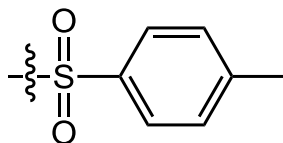
80 °C, ND



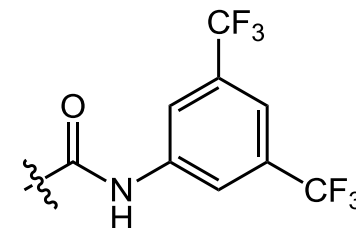
80 °C, ND



80 °C, ND

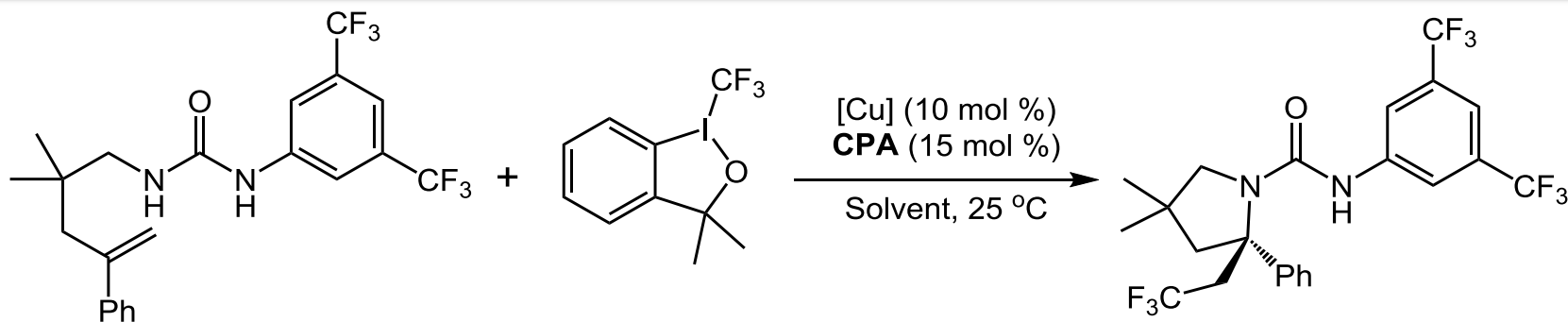


80 °C, 46% yield, 20% ee

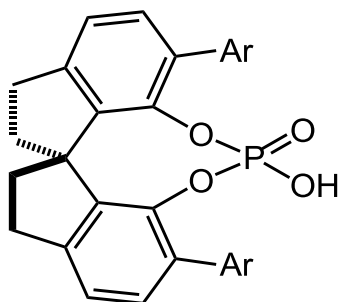


25 °C, 90% yield, 37% ee

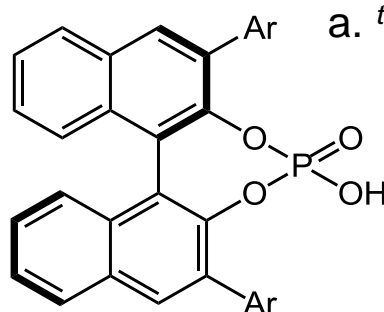
Screening of Reaction Conditions



Entry	[Cu]	CPA	Solvent	Yield (%)	Ee (%)
1 ^a	Cu(MeCN) ₄ PF ₆	--	MTBE	17	0
2	CuI	CPA-1	EtOAc	90	37
3	CuI	CPA-2	EtOAc	91	15
4	CuI	CPA-3	EtOAc	92	8
5	CuI	CPA-4	EtOAc	51	18
6	CuI	CPA-5	EtOAc	90	34



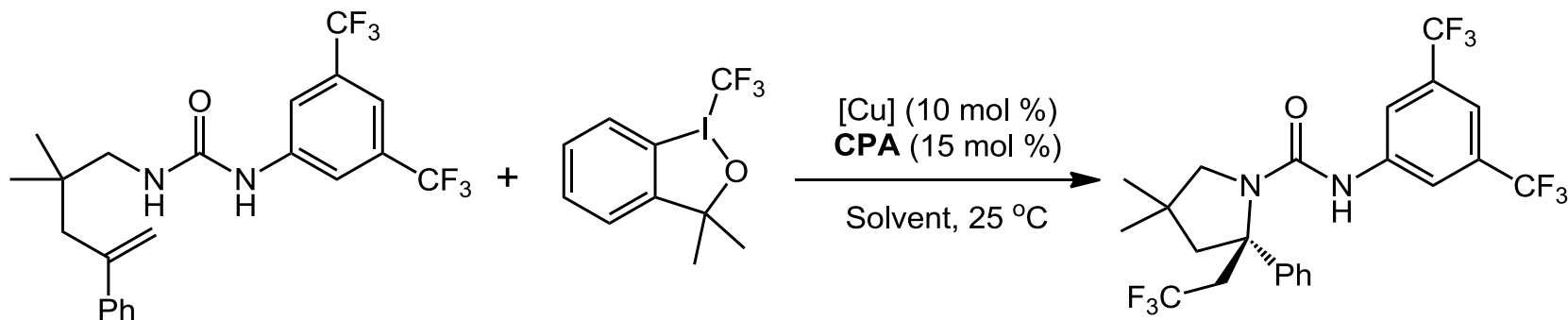
CPA-1: Ar = 4-PhC₆H₄
CPA-2: Ar = 4-ClC₆H₄
CPA-3: Ar = 1-Naphthyl



CPA-4: Ar = 4-NO₂C₆H₄
CPA-5: Ar = 2-Naphthyl

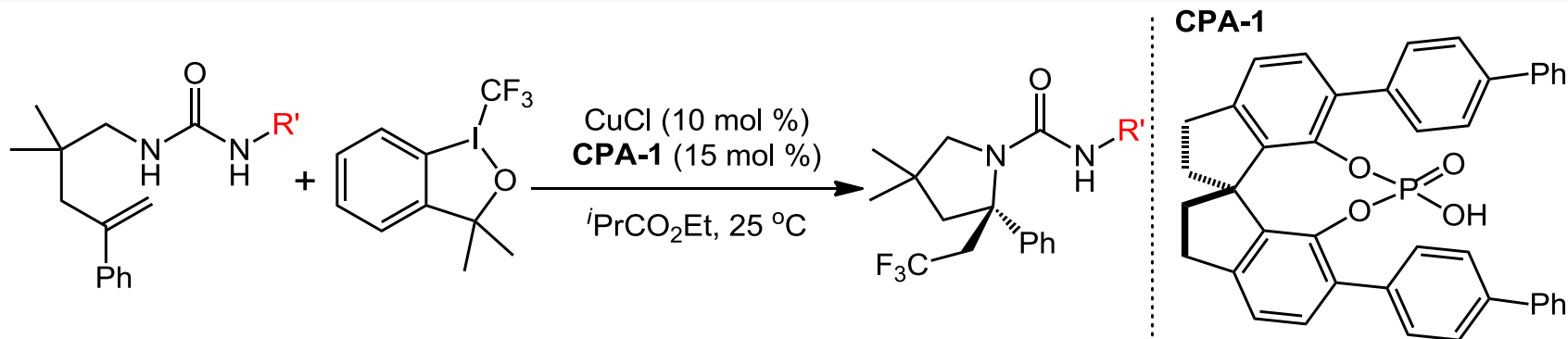
a. ^tBuBox ligand was used.

Screening of Reaction Conditions



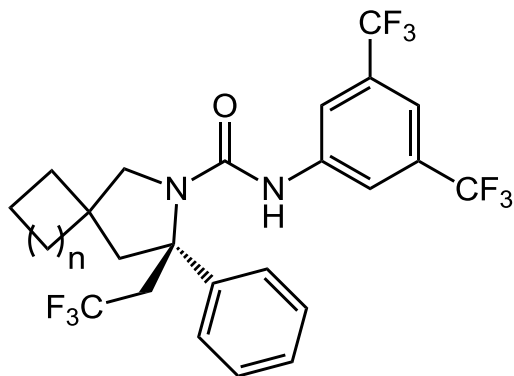
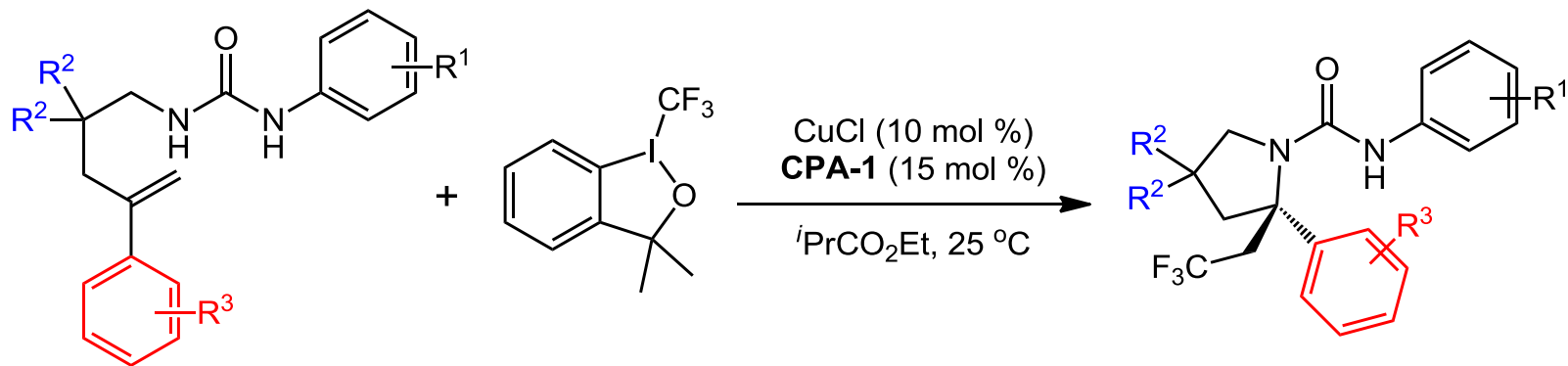
Entry	[Cu]	CPA	Solvent	Yield (%)	Ee (%)
7	CuCl	CPA-1	EtOAc	85	81
8	CuOAc	CPA-1	EtOAc	85	80
9	Cu(MeCN) ₄ PF ₆	CPA-1	EtOAc	60	43
10	CuCl	CPA-1	DCM	93	78
11	CuCl	CPA-1	MeCN	17	0
12	CuCl	CPA-1	MTBE	55	84
13	CuCl	CPA-1	<i>i</i> PrCO ₂ Et	85	91
14	--	CPA-1	<i>i</i> PrCO ₂ Et	--	--
15	CuCl	--	<i>i</i> PrCO ₂ Et	trace	--

Substrate Scope of Different Urea Groups

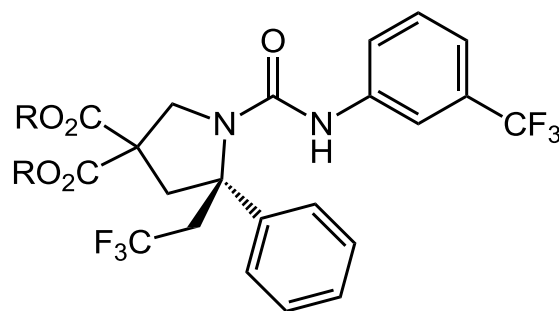


Entry	R'	Yield (%)	Ee (%)
1	3,5-(CF ₃) ₂ C ₆ H ₃	80	91
2	4-CF ₃ C ₆ H ₄	71	91
3	3-CF ₃ C ₆ H ₄	70	97
4	4-FC ₆ H ₄	72	96
5	3-ClC ₆ H ₄	78	97
6	4-BrC ₆ H ₄	83	92
7	3-MeC ₆ H ₄	69	98
8	3-MeOC ₆ H ₄	88	91
9	2-BrC ₆ H ₄	50	90

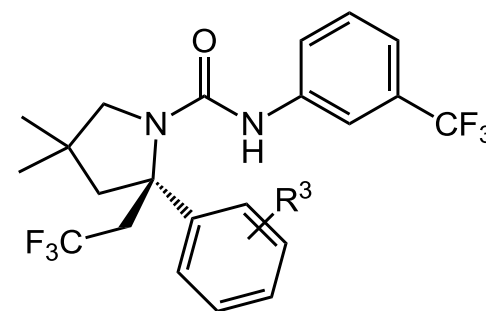
Substrate Scope of Tethers and Alkenyl Moieties



$n = 1$, 78% yield, 88% ee
 $n = 2$, 65% yield, 89% ee
 $n = 3$, 68% yield, 87% ee
 $n = 4$, 71% yield, 88% ee

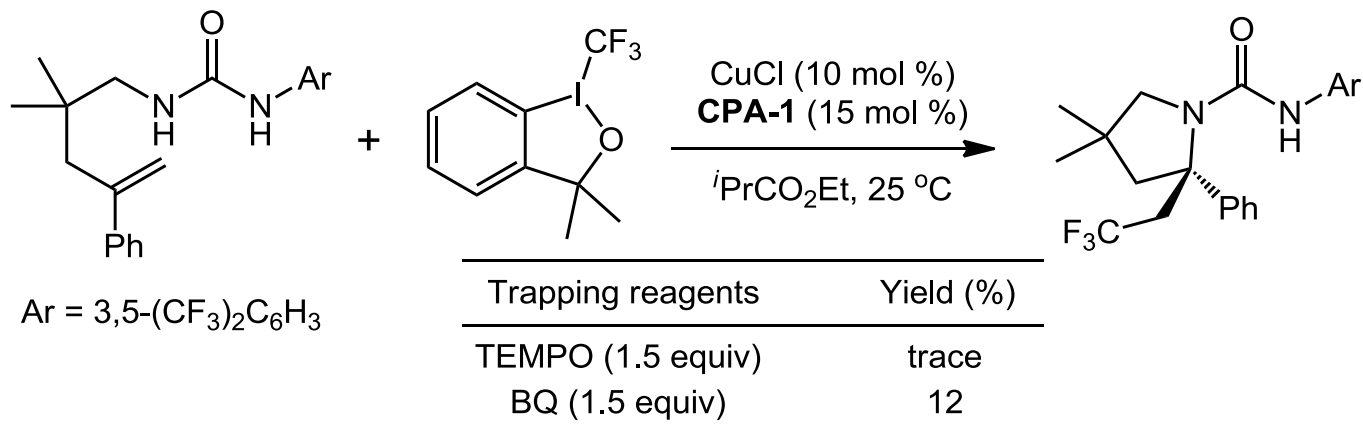


$R = \text{Et}$, 60% yield, 95% ee
 $R = t\text{Bu}$, 54% yield, 88% ee

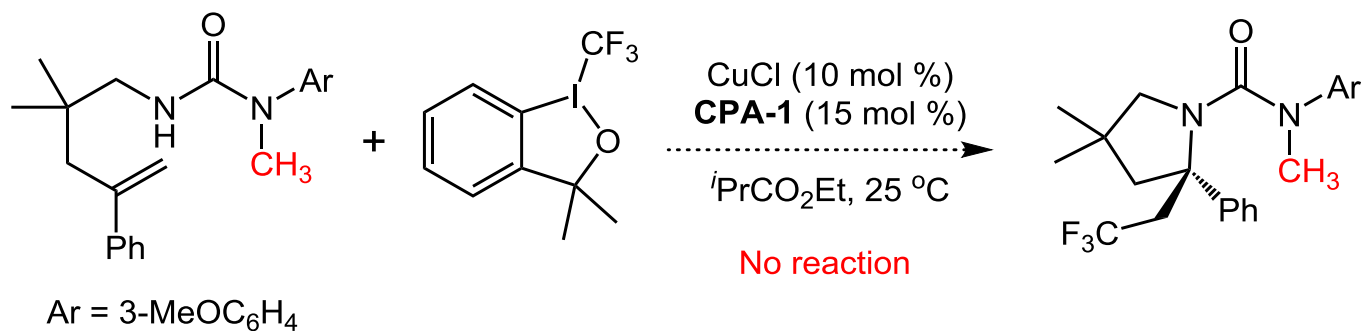


$R^3 = 3\text{-OMe}$, 76% yield, 94% ee
 $R^3 = 3\text{-Ph}$, 64% yield, 90% ee
 $R^3 = 3\text{-F}$, 55% yield, 96% ee

Mechanistic Studies

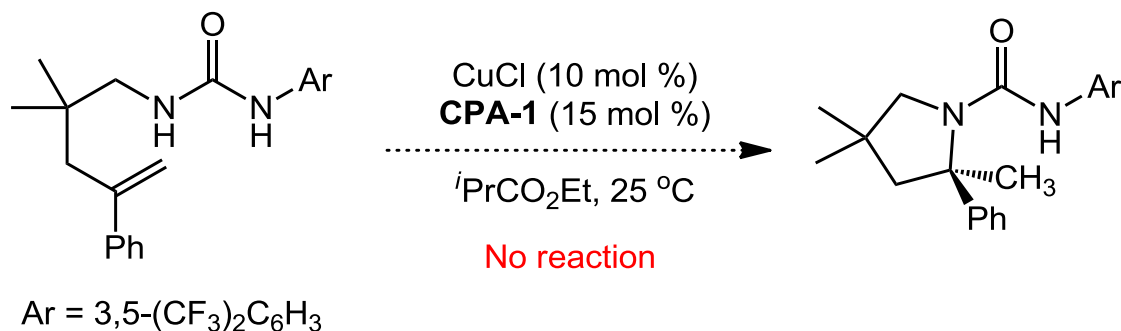


➤ The CF₃ radical is likely involved as the reactive species under the current reaction conditions.

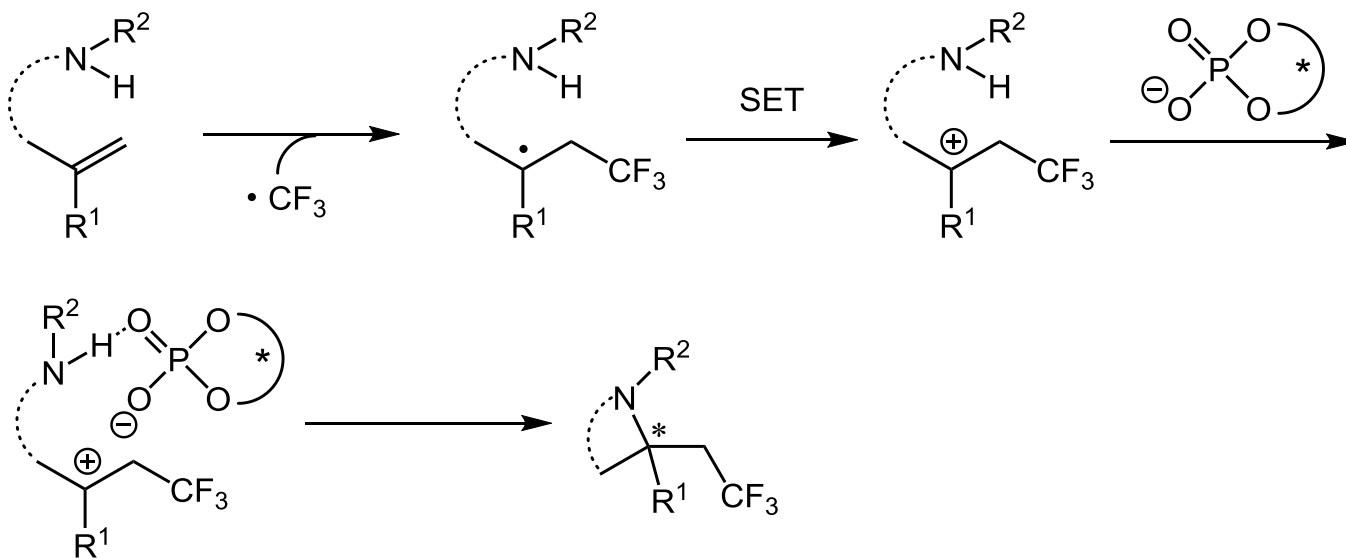


➤ The urea with two acidic N-H at the appropriate positions plays a crucial role in asymmetric induction.

Mechanistic Studies

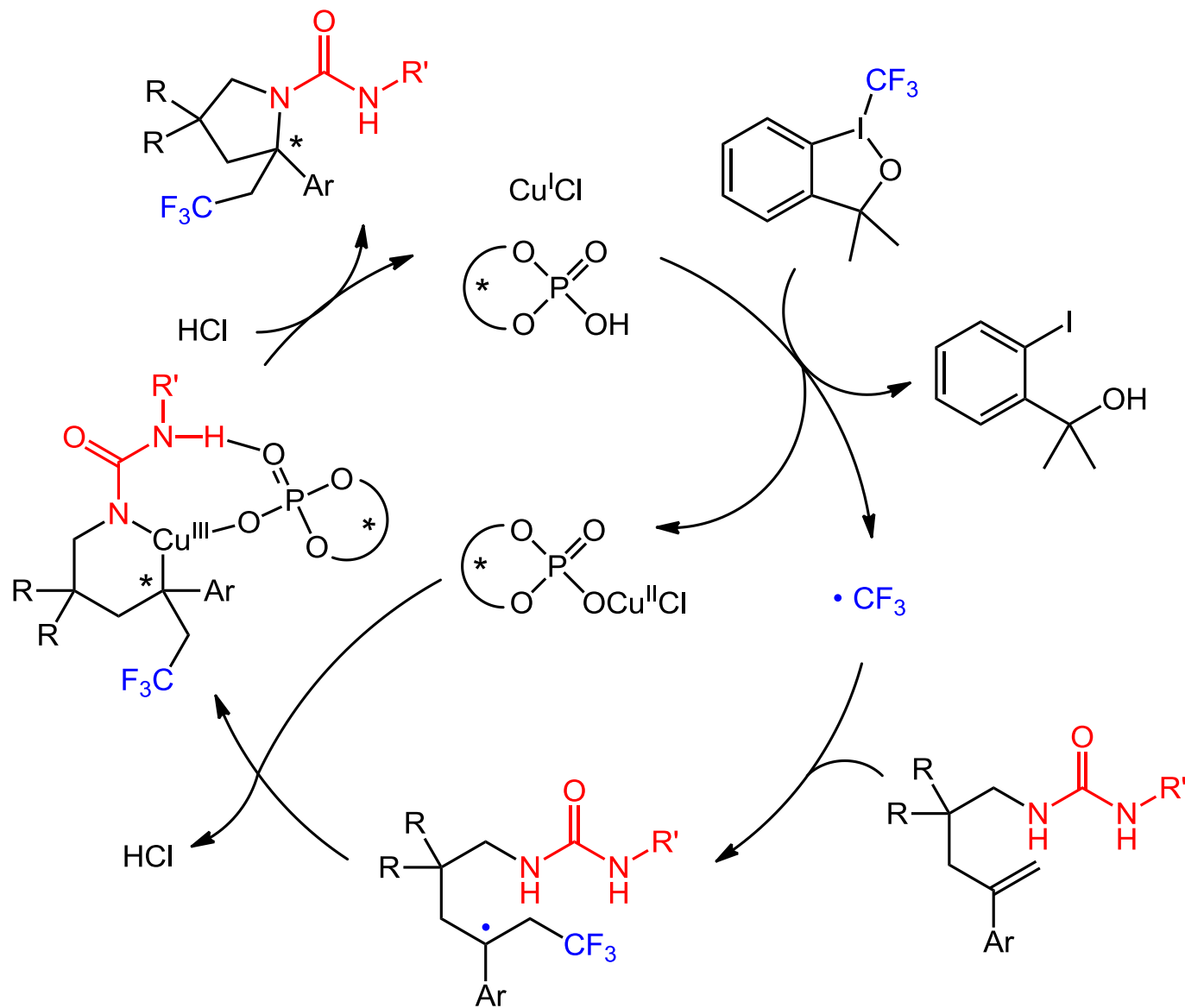


➤ A mechanism involving aminocupration followed by homolysis of the C–Cu bonds and subsequent coupling of a CF₃ radical is possibly unlikely.



➤ Single-electron oxidation to the corresponding carbocation by Cu(II) through ion pairing cannot be ruled out at the present stage.

Mechanistic Proposal



Summary

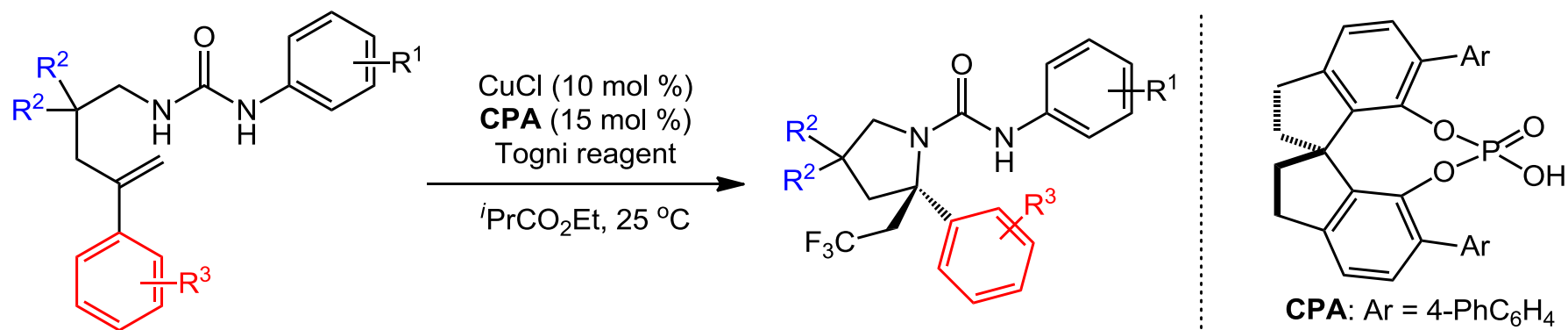
➤ A brief introduction: the strategies for enantioselective radical process.

✓ Complex-controlled strategy

✓ Reagent-controlled strategy

✓ *Radical relay strategy*

➤ The dual-catalytic strategy to asymmetric radical aminotrifluoromethylation.



The increasing importance of chiral CF_3 -containing heterocycles in pharmaceuticals and agrochemicals as well as materials development has spurred vast efforts in the development of new catalytic asymmetric methods for their synthesis. In particular, since the pioneering studies on Cu(I)-catalyzed deprotonative radical trifluoromethylation of olefins carried out by the research groups of Buchwald, Liu and Fu, and Wang, direct radical difunctionalization of alkenes and alkynes has received increasing attention in recent years. Although great endeavors have been devoted to various racemic versions of radical trifluoromethylation of alkenes, the development of catalytic asymmetric methods has proven a formidable challenge, largely because of the intrinsic reactivity of the involved odd-electron species. To address this challenge, Buchwald has more recently championed the copper-catalyzed enantioselective intramolecular oxytrifluoromethylation of alkenes with carboxylic acids in the presence of chiral bis(oxazoline) ligands, providing efficient access to CF_3 -containing lactones with good enantioselectivities (74–83% ee).

However, difunctionalization-type radical trifluoromethylation reactions with other types of nucleophiles, to the best of our knowledge, still remain unknown. In the past several years, we and others have successfully developed the racemic Cu(I)-catalyzed radical aminotrifluoromethylation of alkenes, offering an efficient way to construct useful trifluoromethyl azaheterocycles. Unfortunately, our initial attempts to the use of Cu(I)/bis(oxazoline) catalysis, as inspired by Buchwald's work, to achieve asymmetric aminotrifluoromethylation of N-alkenylurea with Togni's reagent met with very low yield and enantioselectivity. Clearly, a conceptually different approach is still very desirable to achieve highly efficient asymmetric radical aminotrifluoromethylation of alkenes.

In summary, we have developed the first catalytic asymmetric radical aminotrifluoromethylation of alkenes. The overall process serves as a novel, efficient, and simple approach for straightforward access to diversely substituted CF₃-containing pyrrolidines bearing an α -tertiary stereocenter with excellent efficiency, remarkable enantioselectivity, and excellent functional group tolerance. Critical to the success of this process is not only the introduction of a Cu(I)/phosphoric acid dual-catalytic system but also the use of urea with two acidic N-H as both the nucleophile and directing group. The highly enantioenriched and diversely functionalized products can be easily transformed into other useful chiral CF₃-containing building blocks.