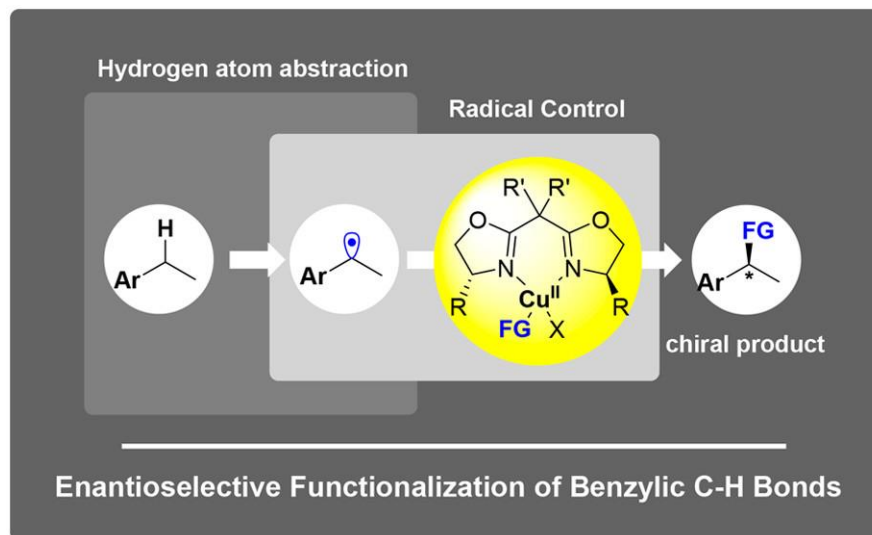


Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations



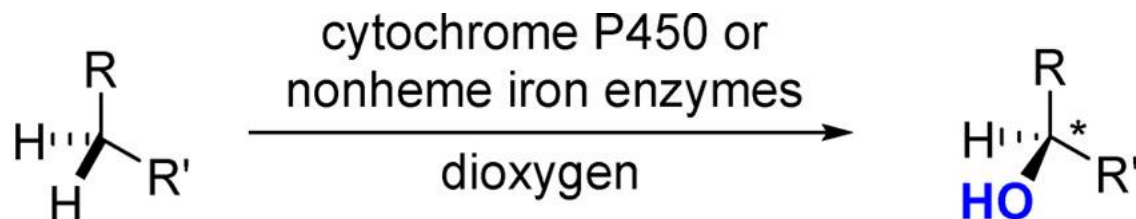
Reporter: Xin-Hang Jiang

Supervisor: *Prof. Yong Huang*

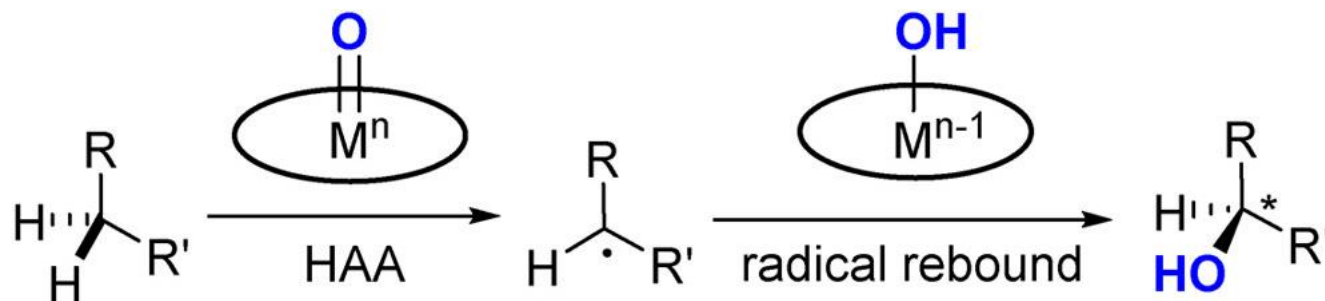
Date: 2019. 01. 14

1.1 Enzymatic oxygenases & halogenases: regio- & enantioselectivity.

Oxidation of sp^3 C–H Bonds by Cytochrome P450 or Non-heme Iron Enzymes.



metal–oxo intermediates abstracting H, then radical rebounding.

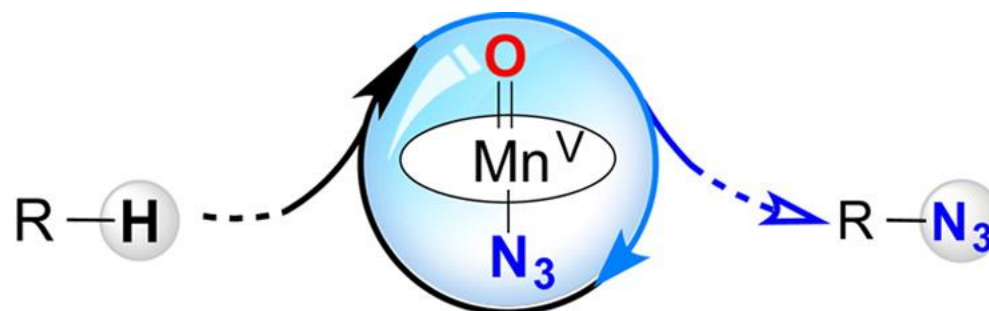


2. Meunier, B.; de Visser, S. P.; Shaik, S. *Chem. Rev.* **2004**, 104, 3947– 3980.

3. Butler, A.; Sandy, M. *Nature* **2009**, 460, 848– 854.

1.2 Bio-inspired catalysts designing for sp³ C-H functionalization.

1.2.1 Manganese-Catalyzed Late-Stage Aliphatic C-H Azidation.



- *NaN₃ (aq.) as the azide source*

- *Late-stage functionalization*

- *Enantioselective*



mimicking the core motif of P450, such as metalloporphyrin and tetradentate aminopyridine-coordinated metal (e.g., Mn, Fe, etc.) complexes, often less enantioselective than the enzyme catalysis

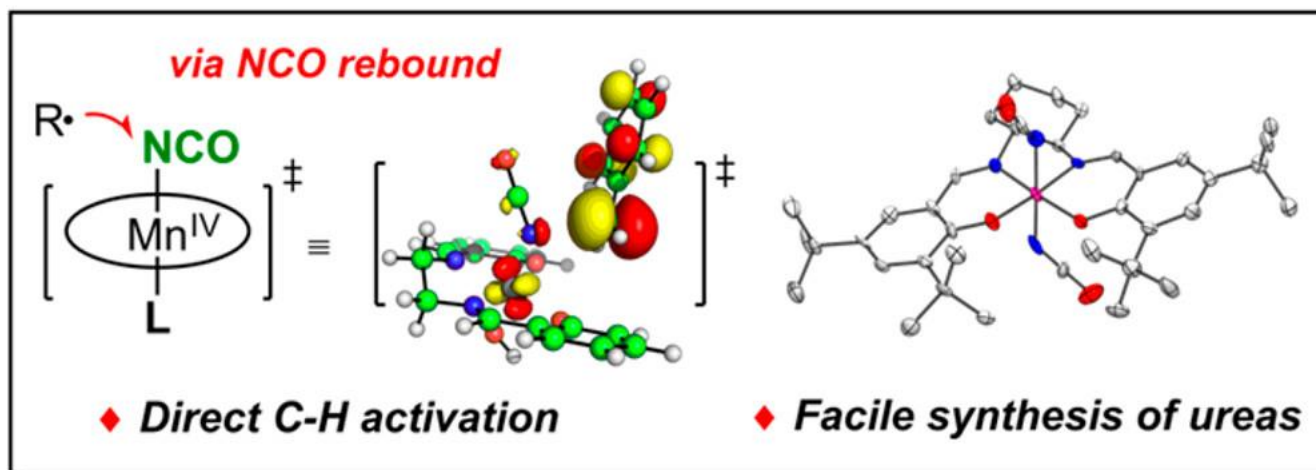
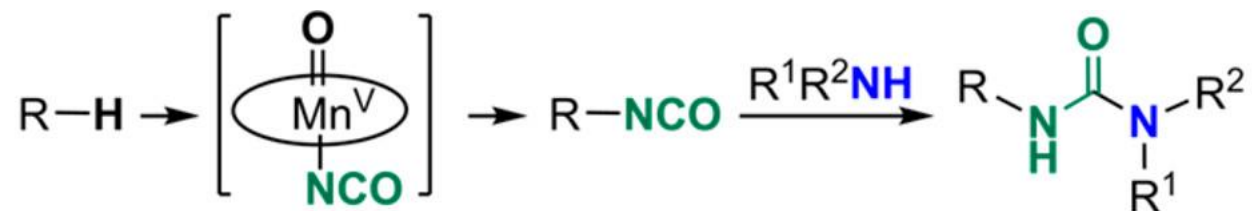
4. Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, 40, 1950– 1975.

5. Huang, X.; Groves, J. T. *Chem. Rev.* **2018**, 118, 2491– 2553.

6. Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015**, 137, 5300– 5303.

1.2 Bio-inspired catalysts designing for sp³ C-H functionalization.

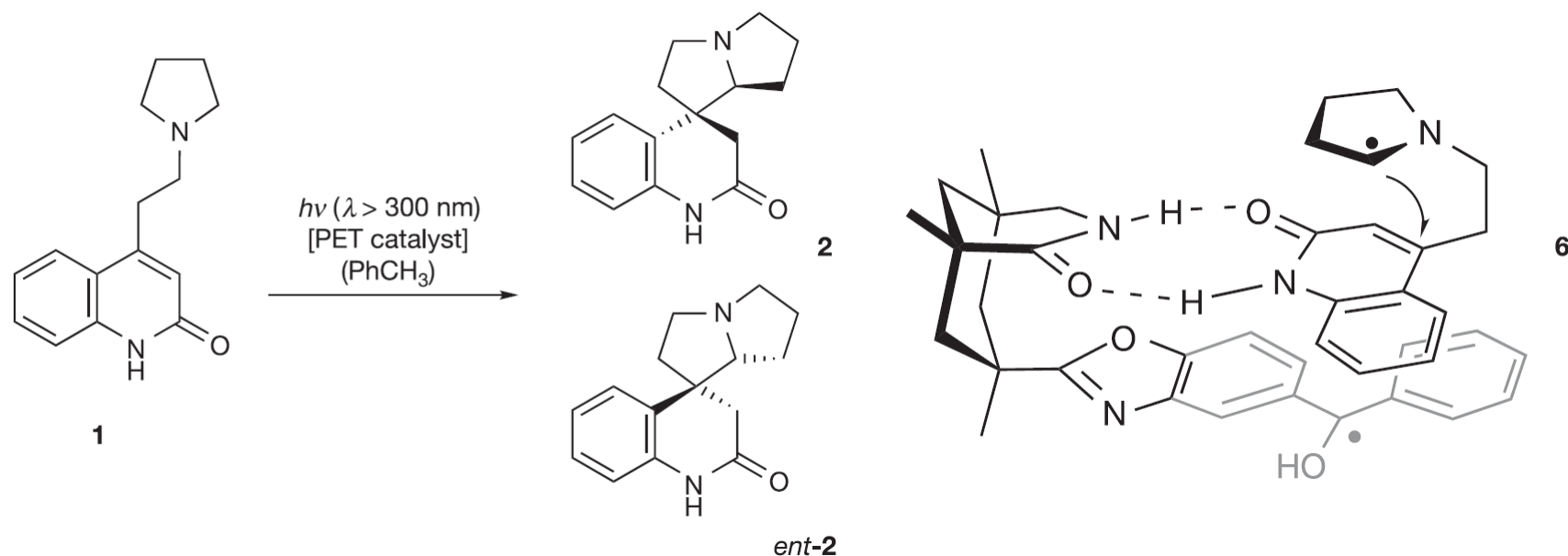
1.2.2 Alkyl Isocyanates via Manganese-Catalyzed C-H Activation.



mimicking the core motif of P450, such as metalloporphyrin and tetradentate aminopyridine-coordinated metal (e.g., Mn, Fe, etc.) complexes, often less enantioselective than the enzyme catalysis

1.3 Chiral organocat. or LA for asymmetric radical C-H functionalization.

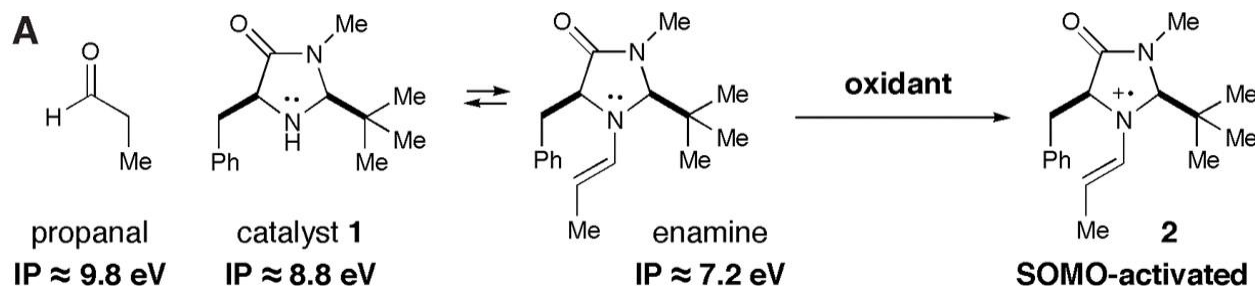
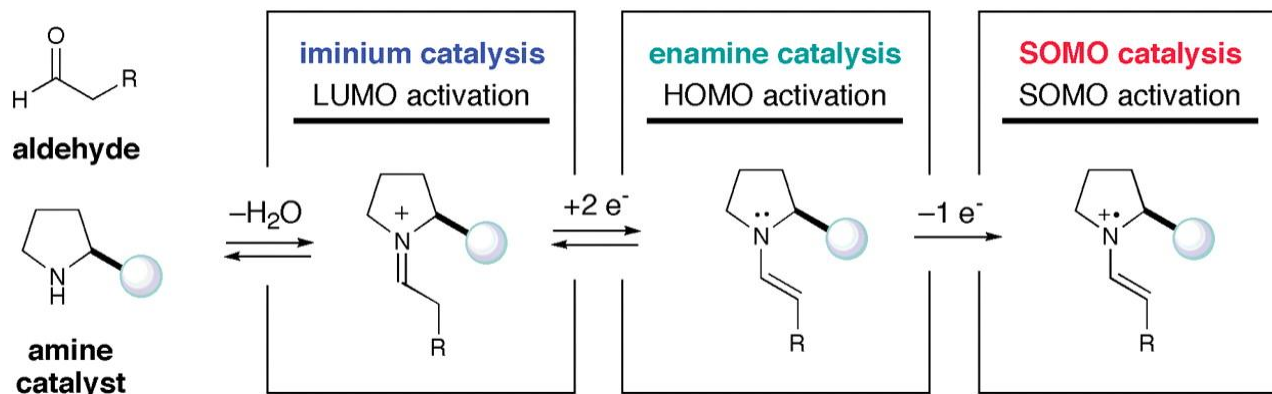
1.3.1 Photoinduced electron transfer catalysed cyclization.



harnessing carbon-centered radical, moderate enantioselectivity

1.3 Chiral organocat. or LA for asymmetric radical C-H functionalization.

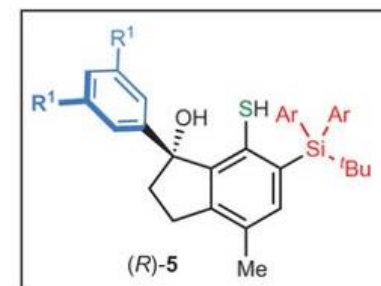
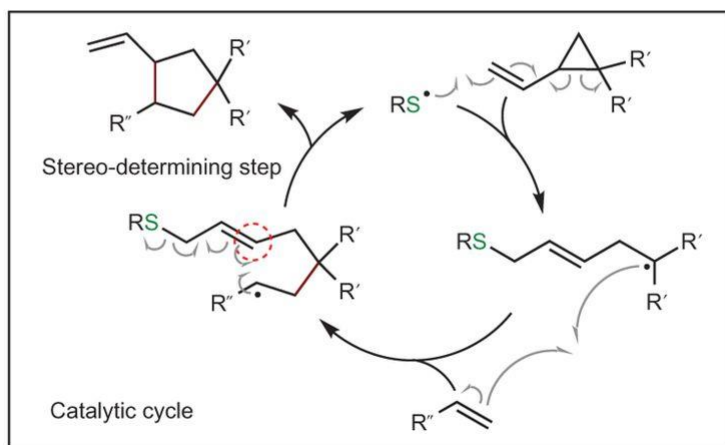
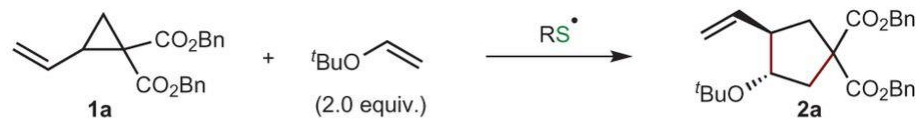
1.3.2 Enantioselective Organocatalysis Using SOMO Activation.



harnessing carbon-centered radical, high enantioselectivity

1.3 Chiral organocat. or LA for asymmetric radical C-H functionalization.

1.3.3 An organic thiyl radical catalyst for enantioselective cyclization.

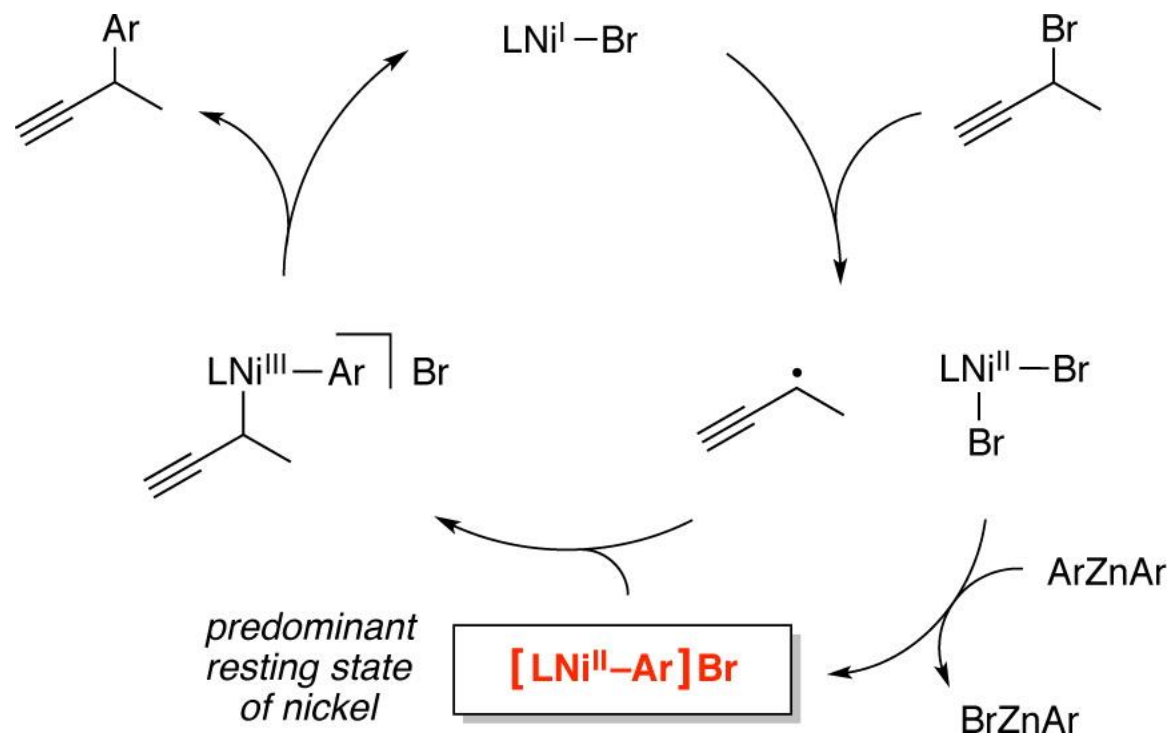


Ar = 4-CF₃C₆H₄, R₁ = 10-Bu-9-anthryl;
 Yield: 95%, 95:5 dr, 86% e.e.

harnessing carbon-centered radical, good enantioselectivity

1.4 Transitionmetal-catalyzed redox systems for C-H functionalizations.

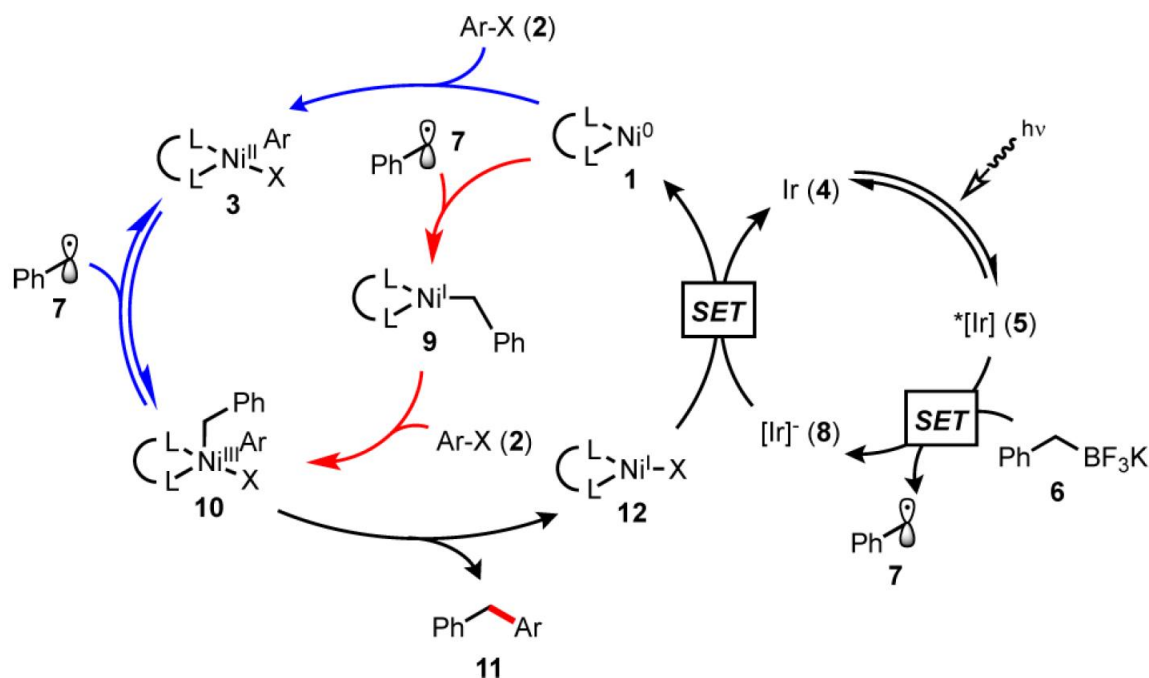
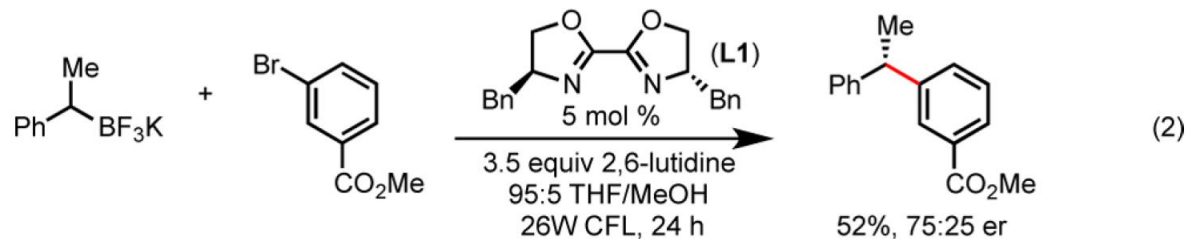
1.4.1 Nickel-Catalyzed Negishi Arylations of Propargylic Bromides.



the enantioselective induction of the radical species was controlled by the formation of an R-Ni(III)-R' species

1.4 Transitionmetal-catalyzed redox systems for C-H functionalizations.

1.4.2 Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals.

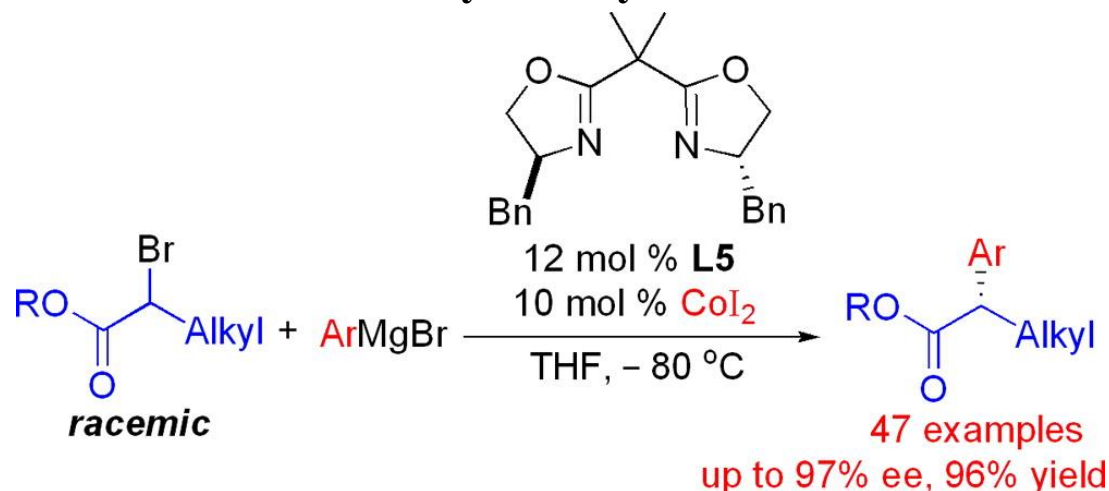


1.4 Transitionmetal-catalyzed redox systems for C-H functionalizations.

1.4.3 Iron-Catalyzed Enantioselective Cross-Coupling Reactions.



1.4.4 Cobalt-Bisoxazoline-Catalyzed Asymmetric Kumada Cross-Coupling.

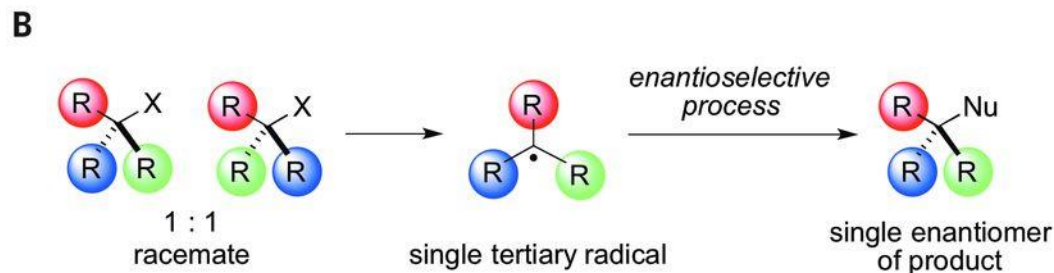
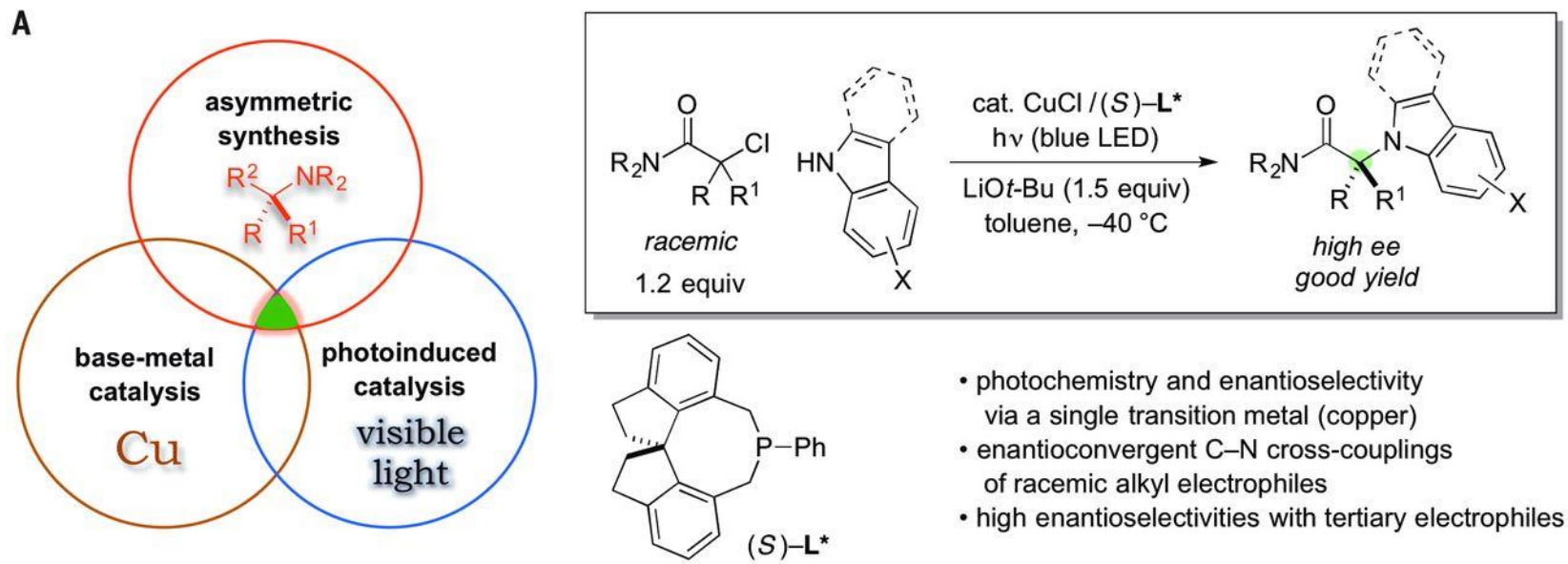


13. Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, 137, 7128–7134.

14. Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, 136, 17662–17668.

1.4 Transitionmetal-catalyzed redox systems for C-H functionalizations.

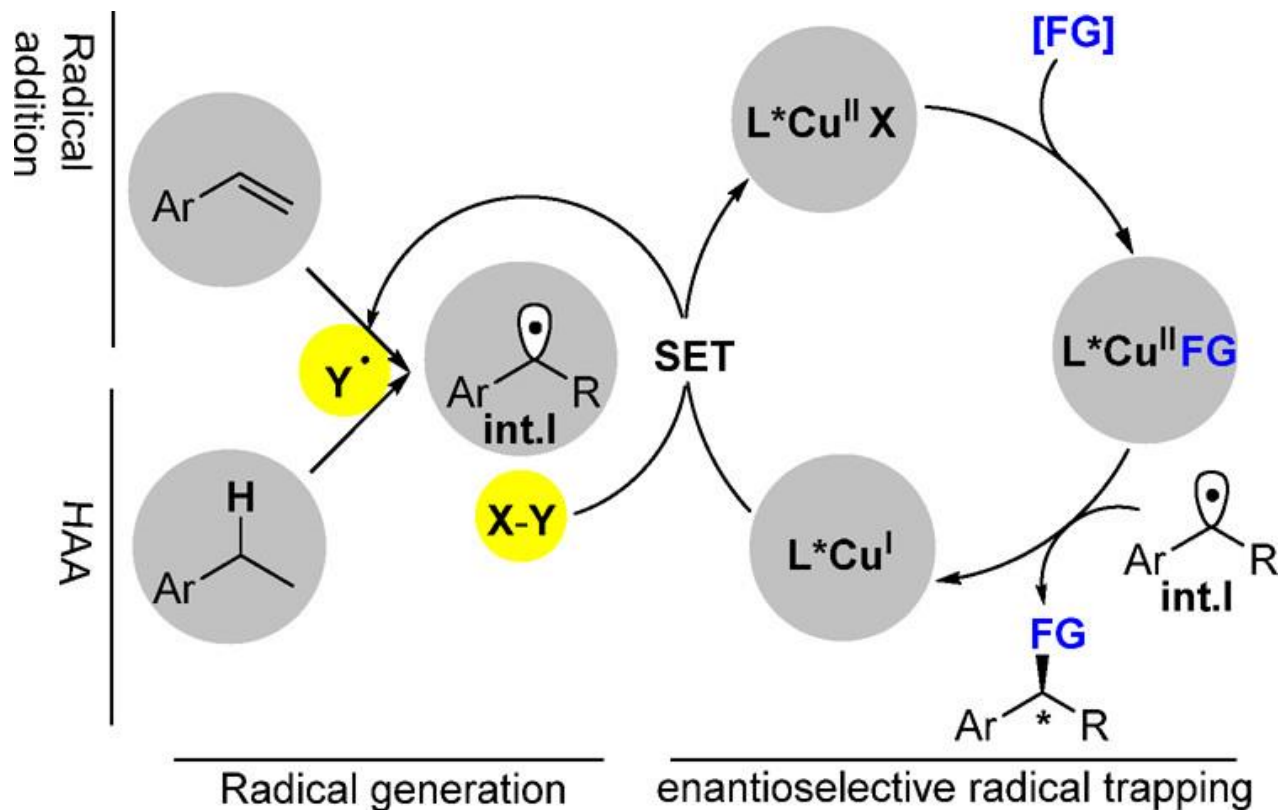
1.4.5 Asymmetric Copper-Catalyzed C-N Cross-Couplings Induced by Visible Light..



How to apply the appealing strategy to asymmetric functionalizations of sp^3 C–H bonds?

1.5 Copper catalyzed asymmetric radical transformations (ARTs).

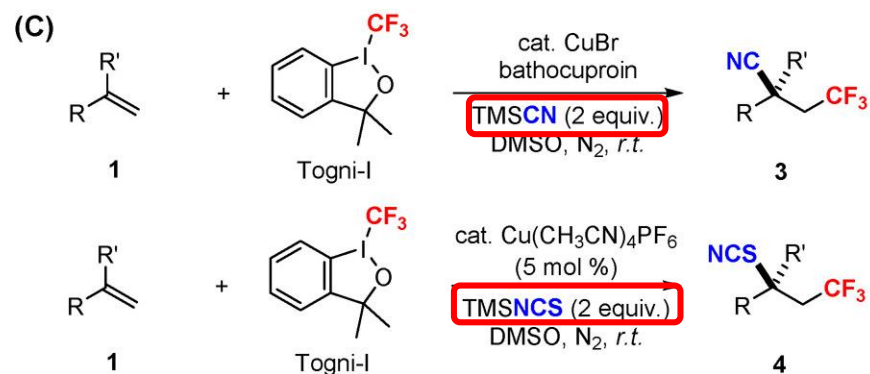
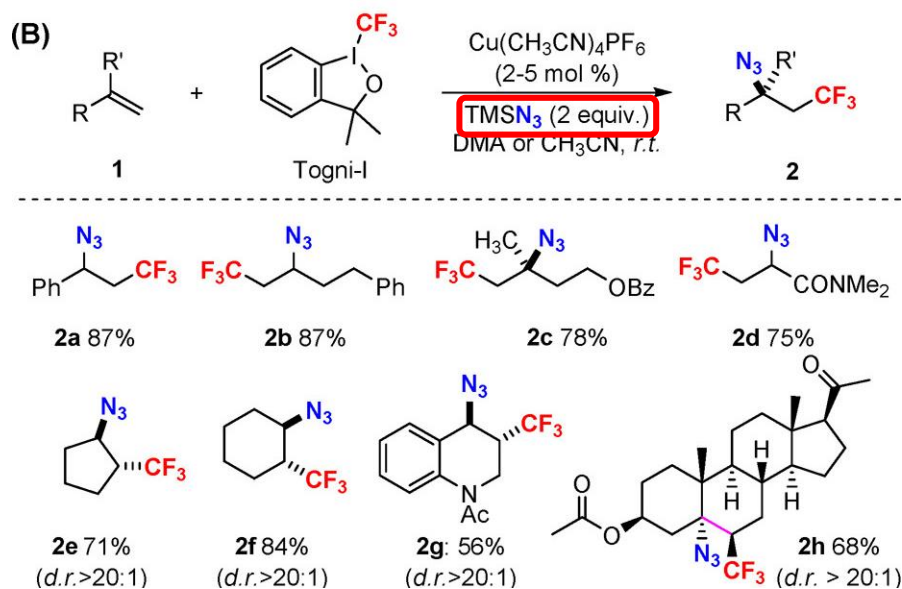
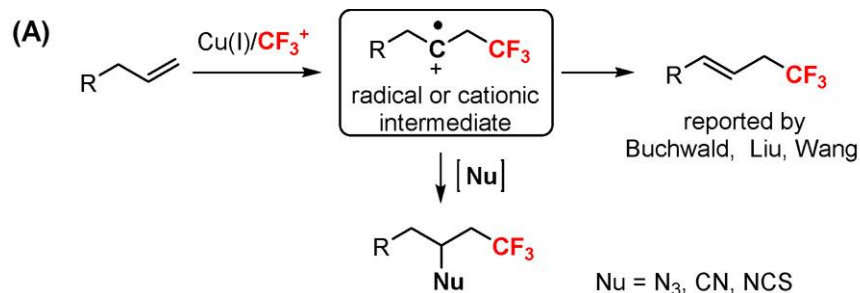
Copper-Catalyzed ARTs through a Radical Relay Process



the initially generated radical undergoes hydrogen atom abstraction (HAA) or addition to the alkene to generate a new carbon-centered radical

2 Cu-cat. intermolecular difunctionalization of alkenes.

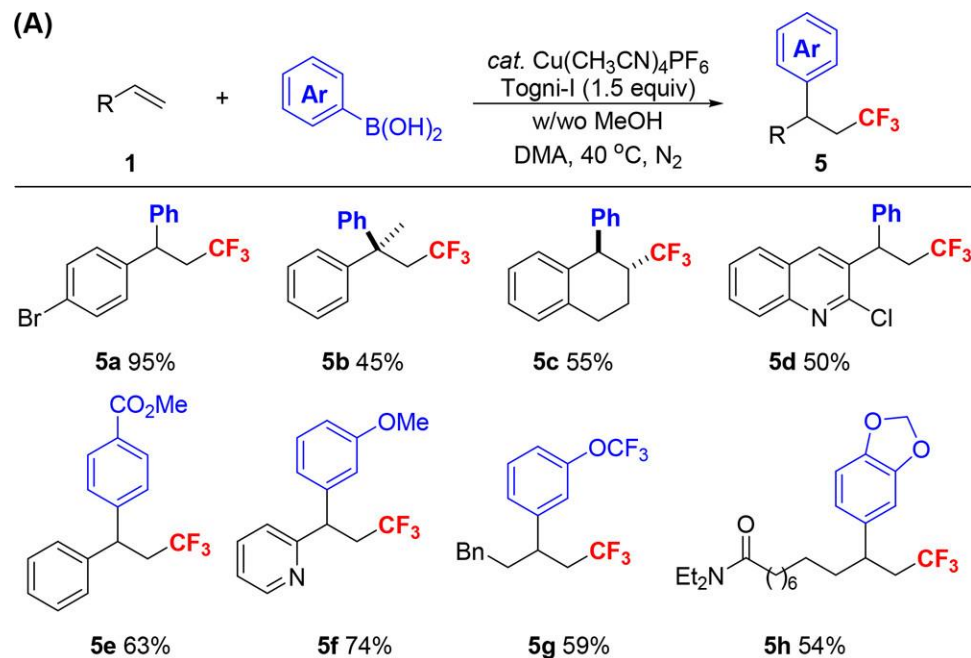
2.1 azidotrifluoromethylation, trifluoromethyl-cyanation and -thiocyanation.



the silyl reagents, alkynes, allenes, and enynes

2 Cu-cat. intermolecular difunctionalization of alkenes.

2.2 Cu-cat. intermolecular trifluoromethylarylation of alkenes.

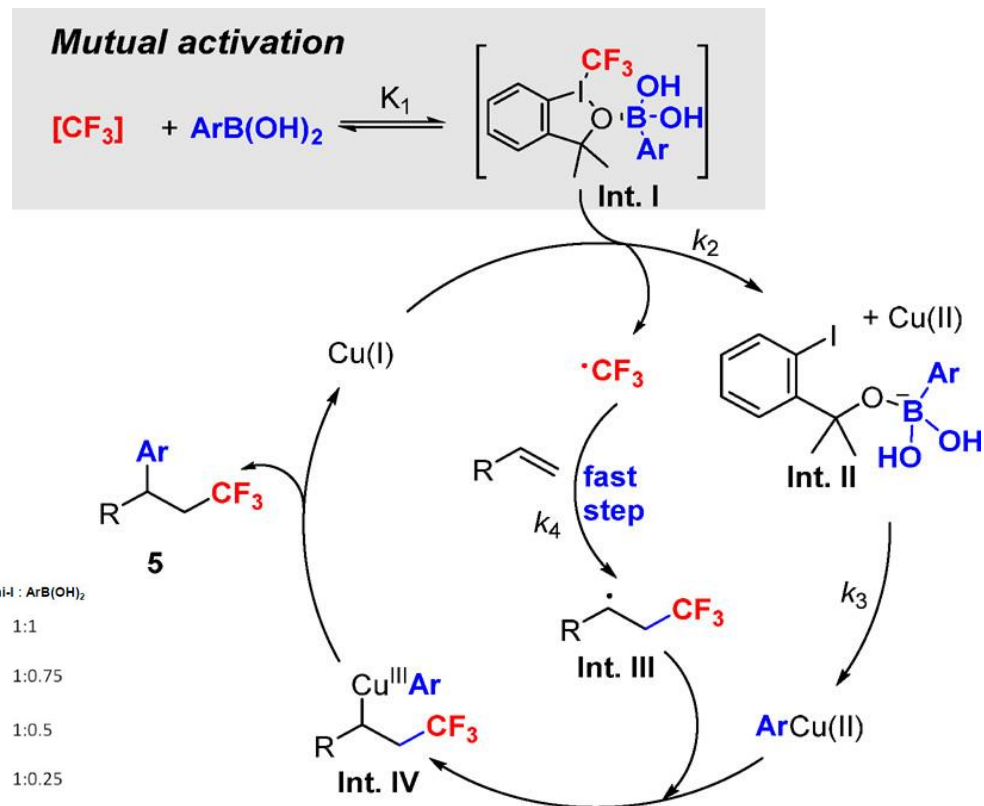
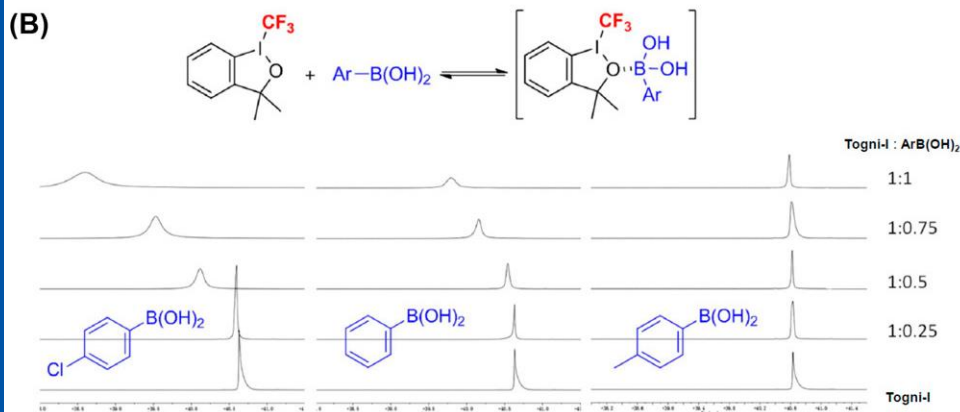


Togni-I reagent, ArB(OH)_2

2 Cu-cat. intermolecular difunctionalization of alkenes.

2.2 Possible Mechanism for the Trifluoromethylarylation of Alkenes.

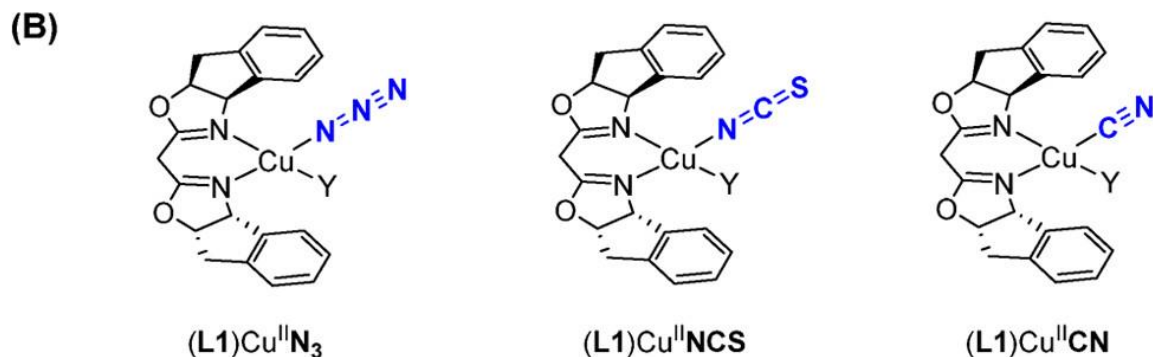
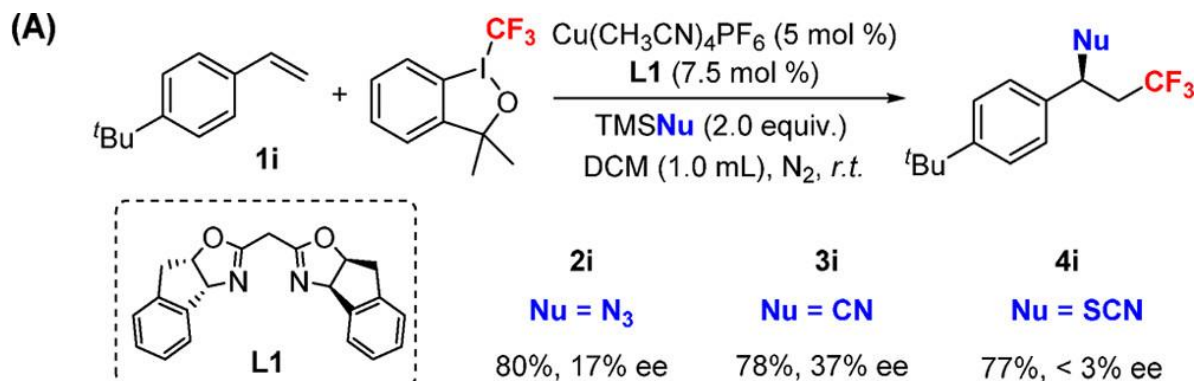
mutual activation,
 facilitating the oxidation,
 strong base to activate
 ArB(OH)_2



reflecting a promising approach to achieving asymmetric radical transformations

3 Enantioselective Cu-cat. difunctionalization of styrenes.

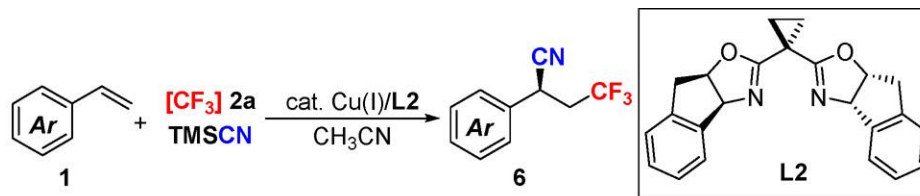
3.1 Initial examination of the feasibility of asymmetric versions.



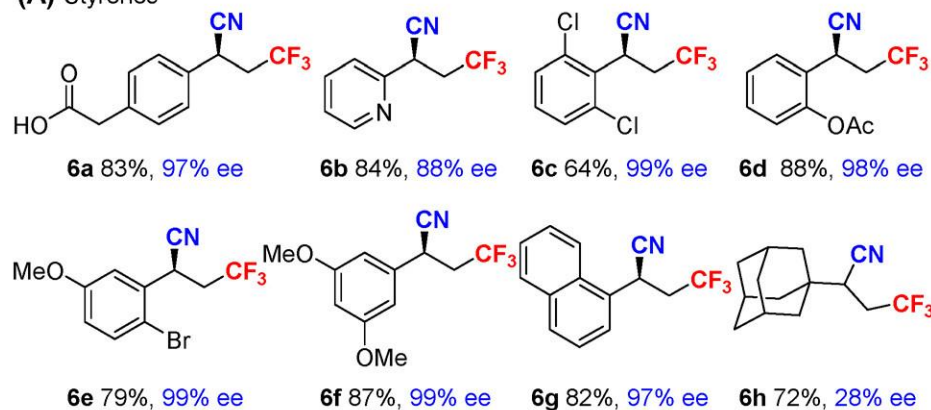
the cyanation exhibiting promising enantioselectivity, the strong coordinating ability.

3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.1.1 Enantioselective Trifluoromethylation of Alkenes.



(A) Styrenes

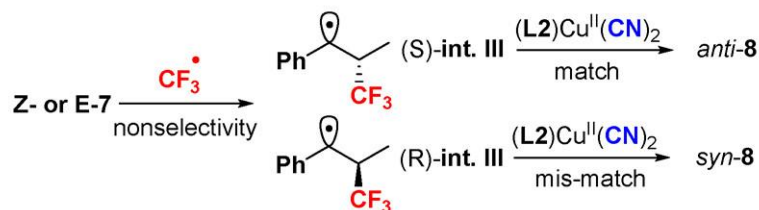
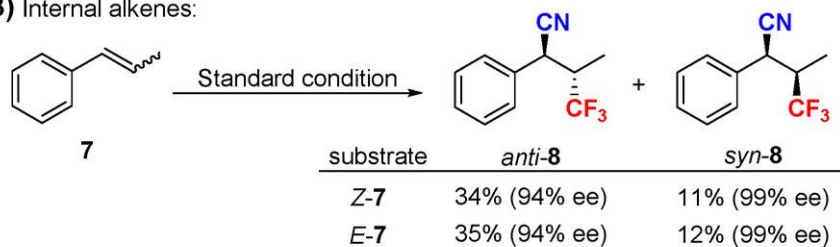


bisoxazolines being proven to be good ligands

3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.1.1 Enantioselective Trifluoromethylation of Alkenes.

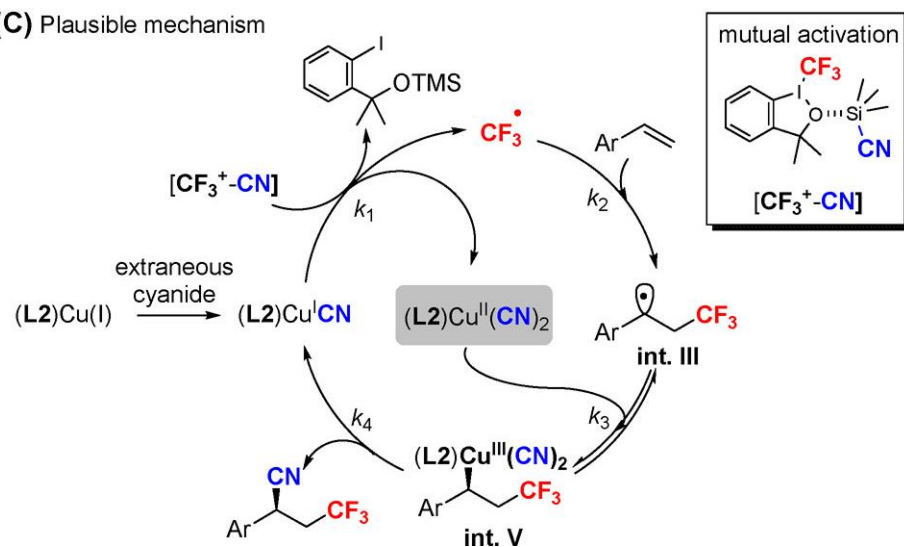
(B) Internal alkenes:



**E or Z-internal alkene,
nonselective addition,
match or mismatch.**

**induction period,
concentration of cyanide,
ligand acceleration.**

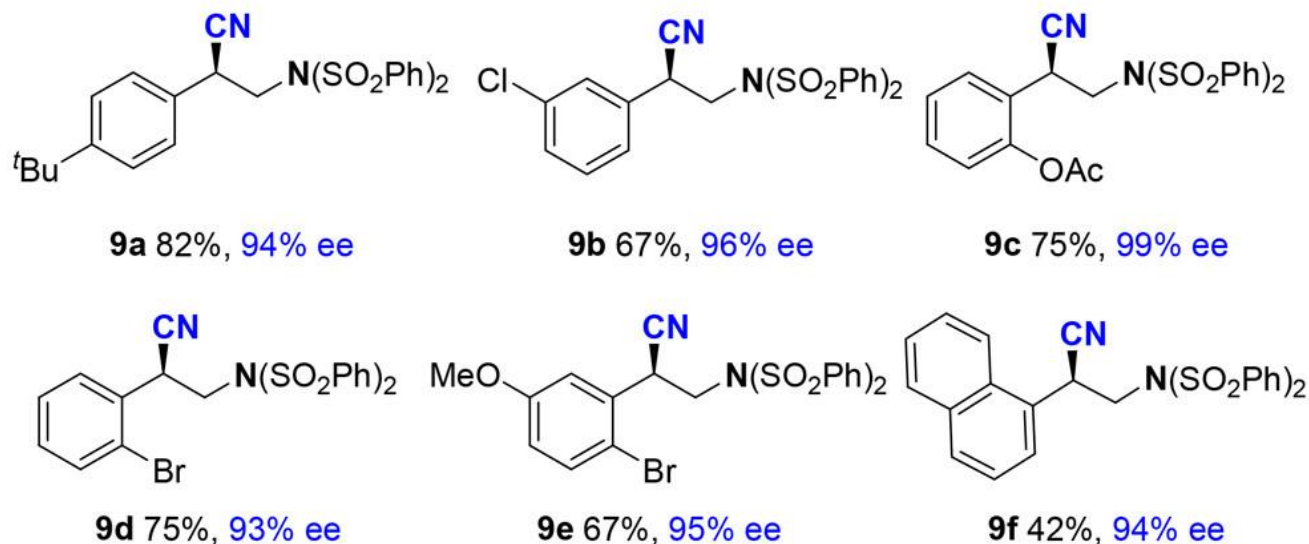
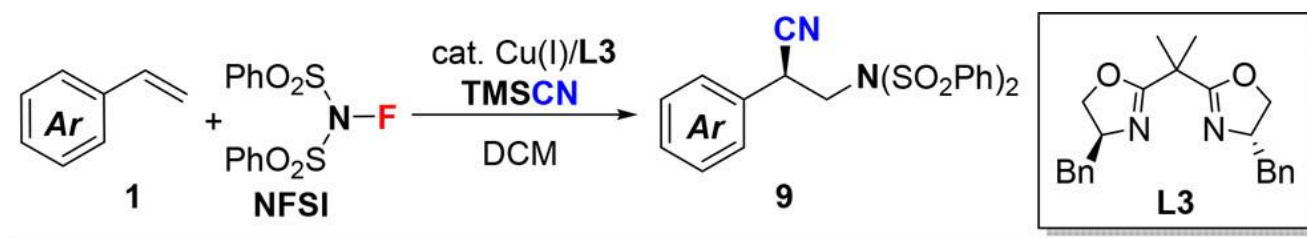
(C) Plausible mechanism



(L2)Cu^I(CN) being proposed to be the active catalytic species.

3 Enantioselective Cu-cat. difunctionalization of styrenes.

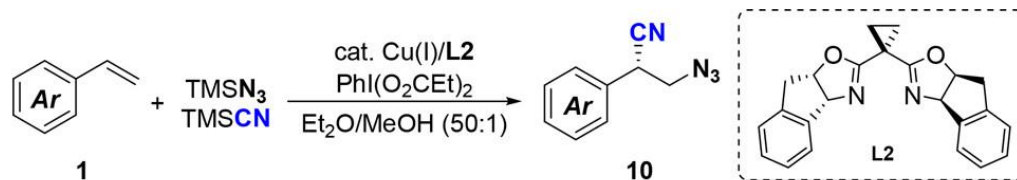
3.1.2 Enantioselective Aminocyanation of Styrenes.



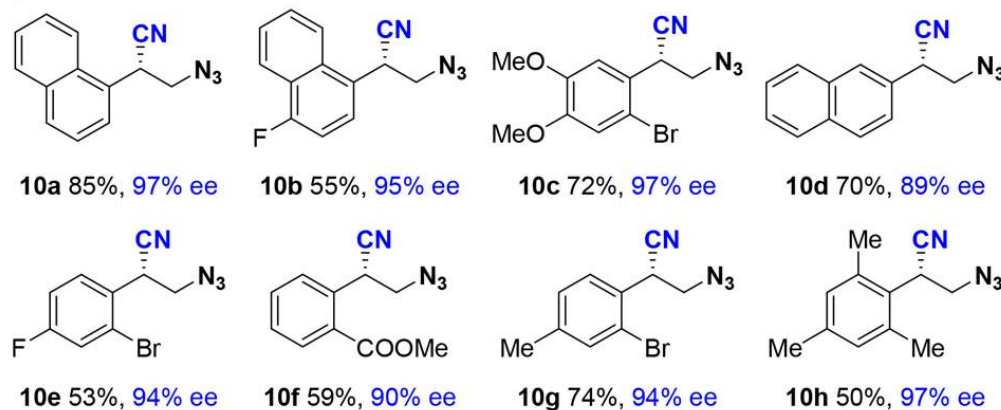
deprotection of the sulfonyl group in 9 resulting in significant erosion of the enantiopurity

3 Enantioselective Cu-cat. difunctionalization of styrenes.

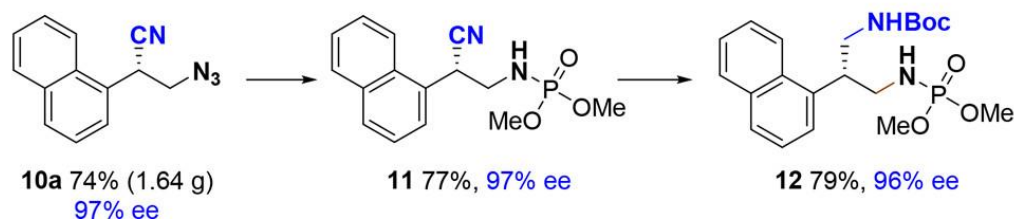
3.1.3 Enantioselective Azidocyanation of Styrenes.



(A)

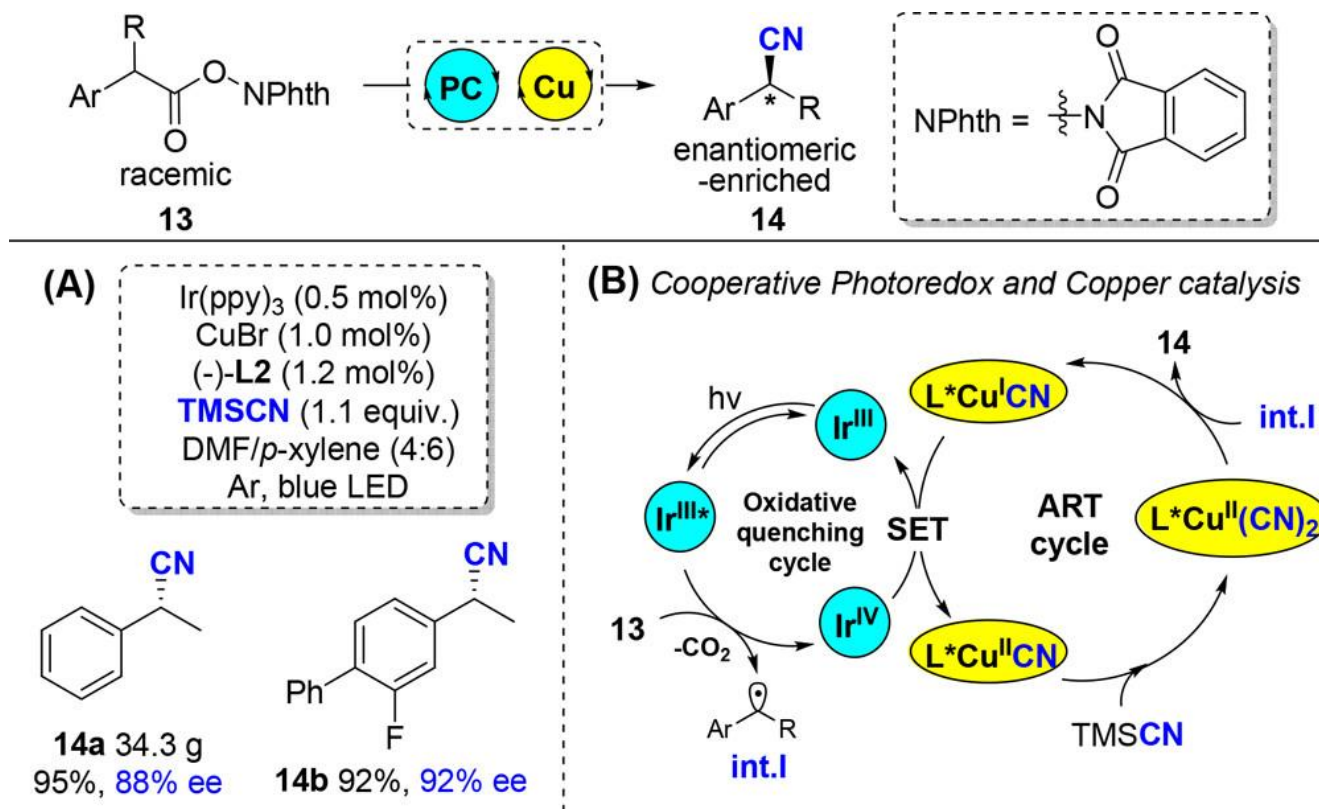


(B) Synthetic application



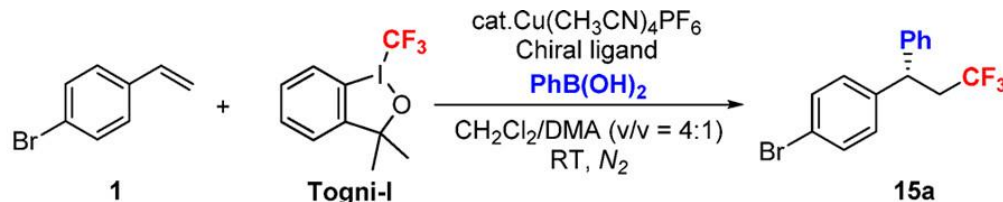
3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.1.4 Enantioselective Decarboxylative Cyanation with Cooperative Catalysis.

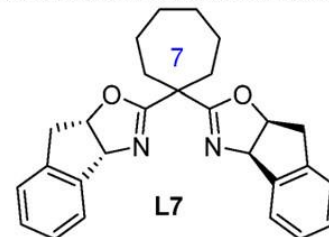
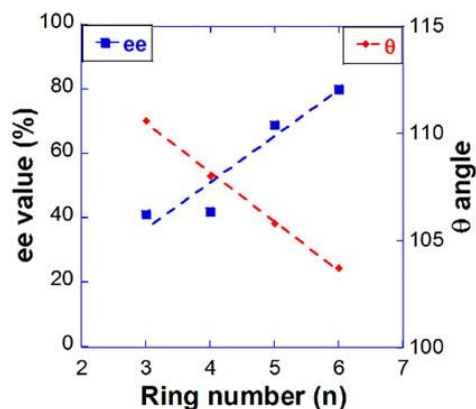
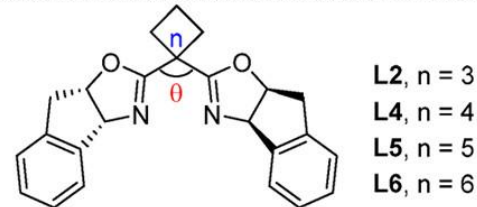


3 Enantioselective Cu-cat. difunctionalization of styrenes.

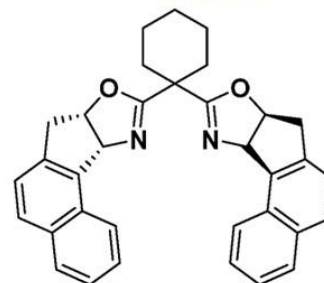
3.2 Enantioselective Copper-Catalyzed Arylation of Styrenes.



(A)



85%, 83% ee
84%, 89% ee^a

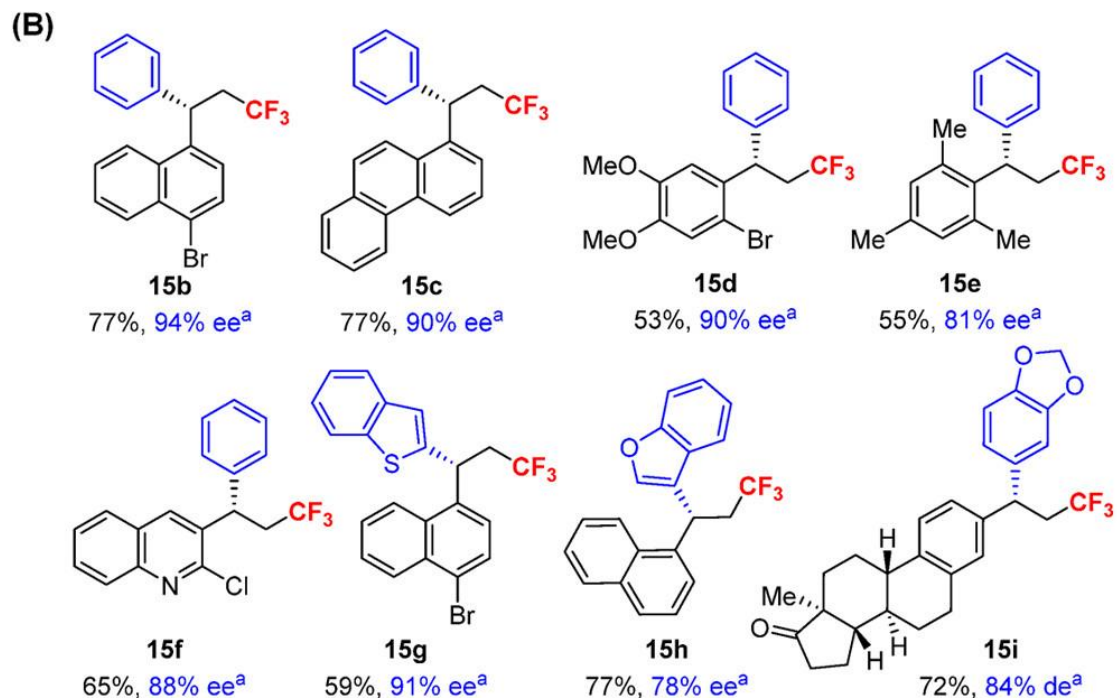


30%, 5% ee

a correlation between the enantiomeric excess and the bite angle of the Box ligand

3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.2 Enantioselective Copper-Catalyzed Arylation of Styrenes.

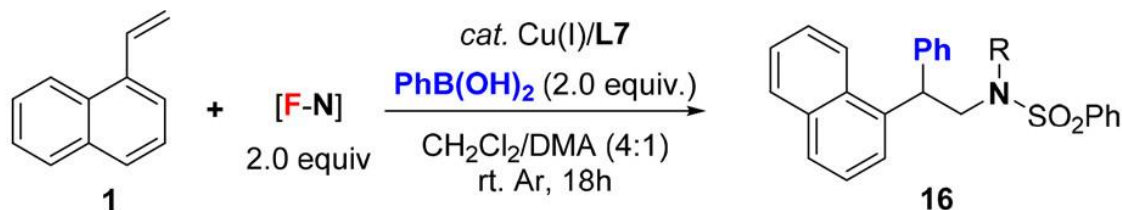


^aThe reaction using L7 and EtOH (2.0 equiv.) was conducted at 0 °C.

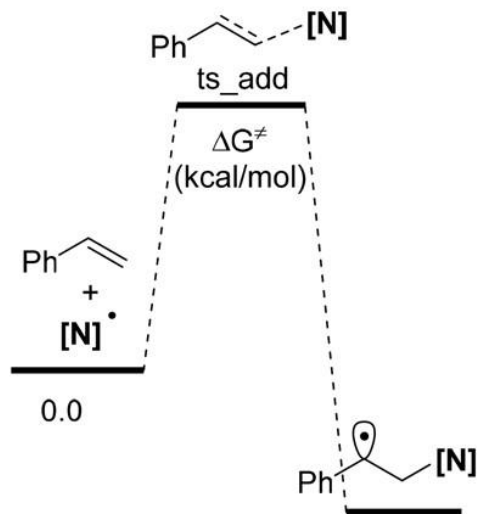
chiral 1,1-diarylethane moieties in natural products and bioactive molecules

3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.3 DFT Calculations for the Amino Radical Addition Process.

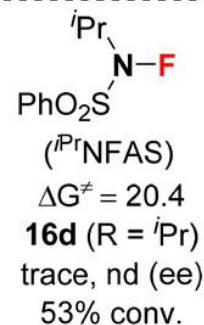
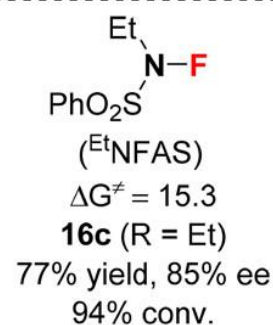
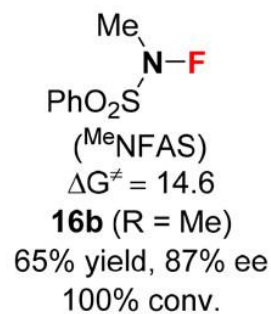


(A) DFT calculation:



UB3LYP 6-31G(D) for C, H, N, O, S

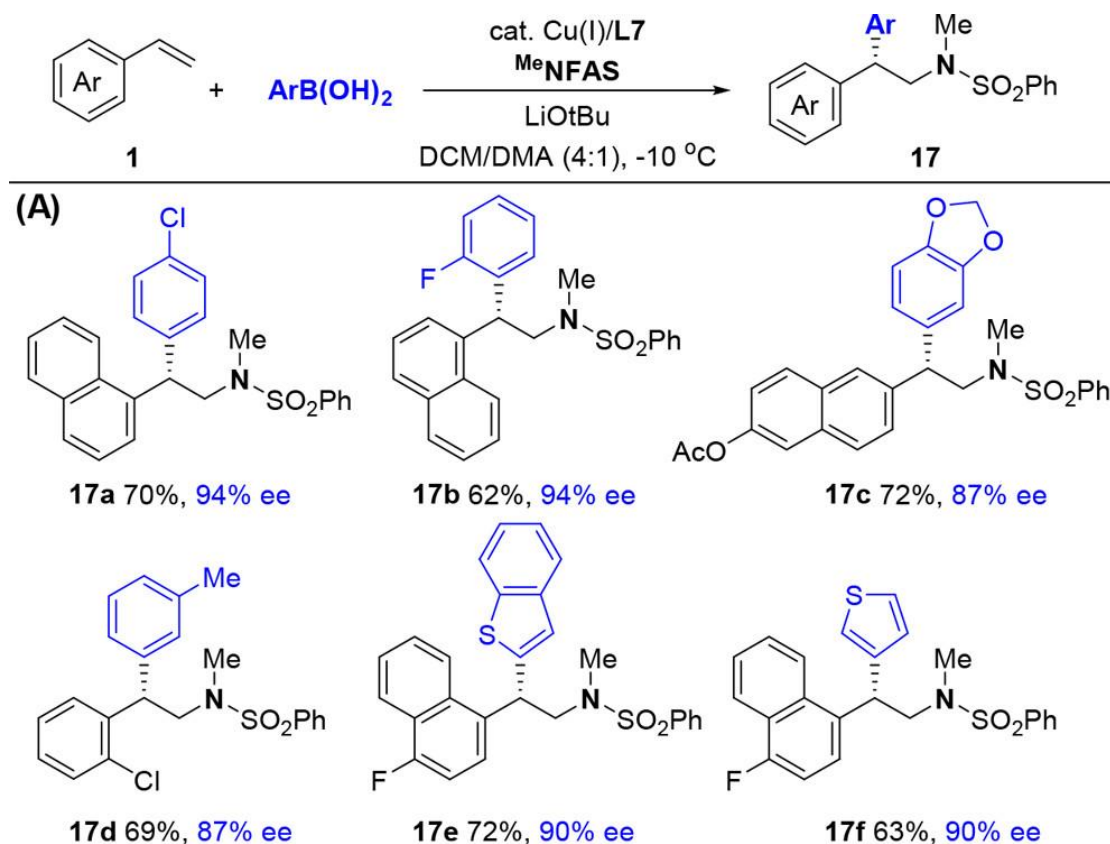
(B) $\text{PhO}_2\text{S-N-F}$



the rate of formation of the ArCu(II) and benzylic radical generation, compatibility

3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.3 Enantioselective Aminoarylation of Styrenes.

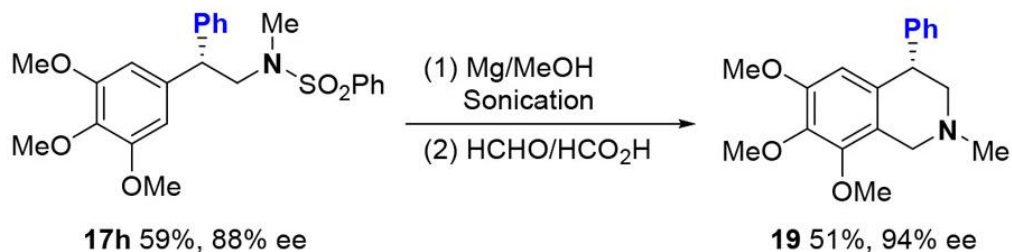
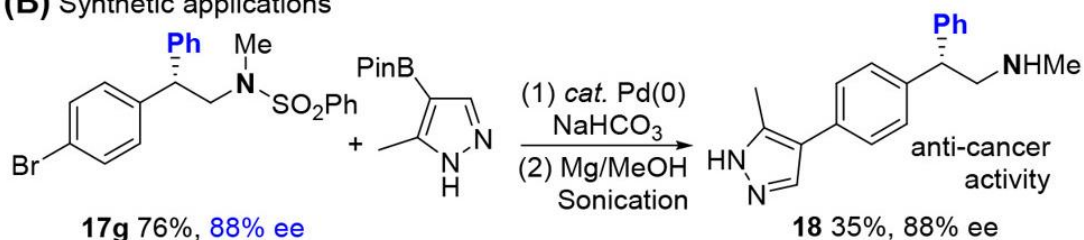


featuring good functional group tolerance

3 Enantioselective Cu-cat. difunctionalization of styrenes.

3.3 Enantioselective Aminoarylation of Styrenes.

(B) Synthetic applications

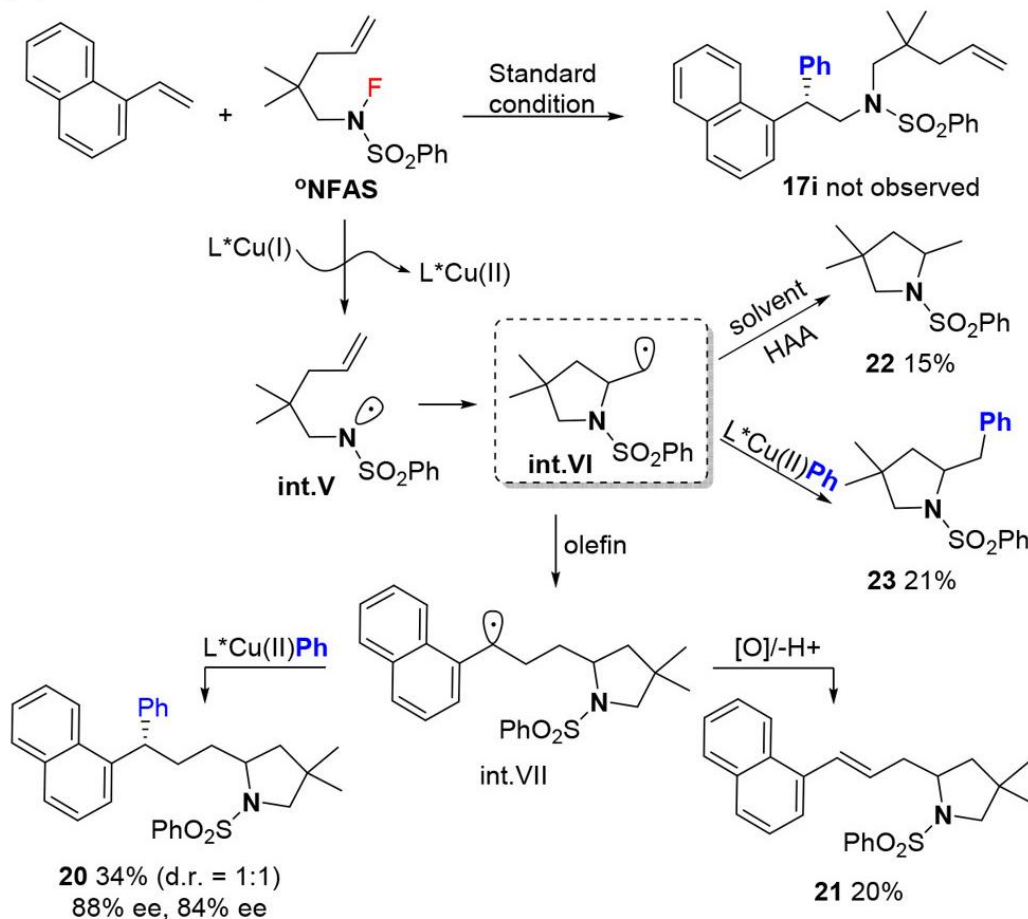


being easily deprotected to afford the corresponding free amines in high yields with retention of the enantiopurity

3 Enantioselective Cu-cat. difunctionalization of styrenes.

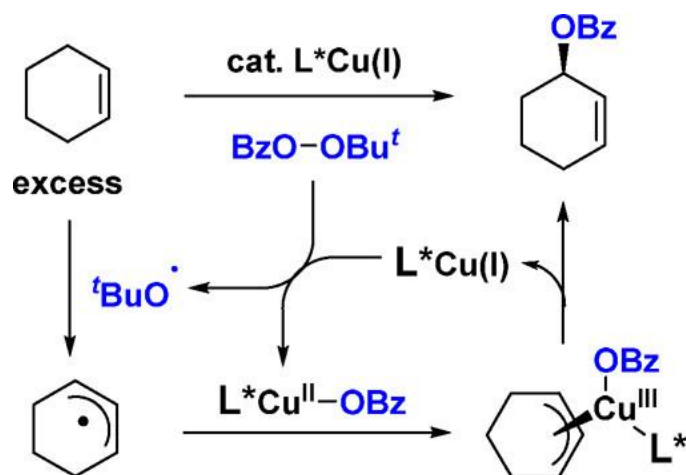
3.3 Enantioselective Aminoarylation of Styrenes.

(C) Mechanistic studies



4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

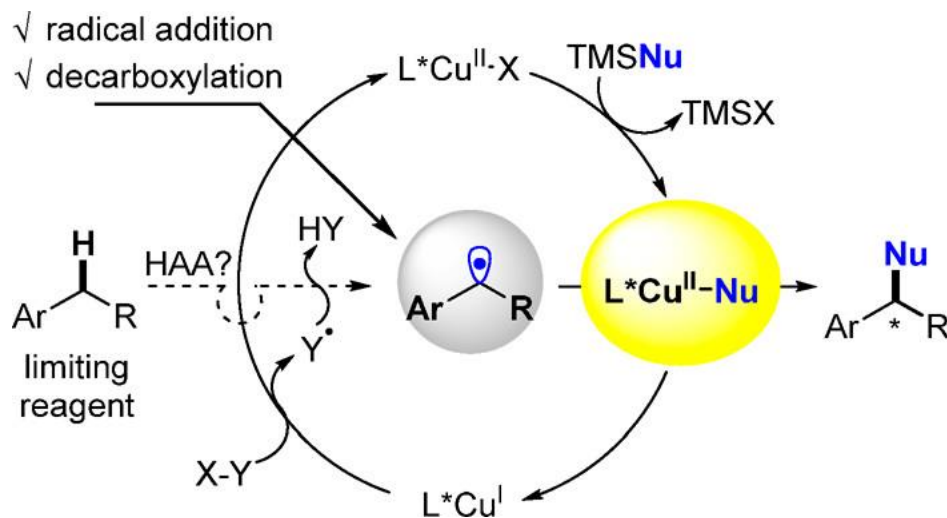
Kharasch–Sosnovsky Reaction.



a large excess of the alkene, enantioselective reaction being limited to cyclic alkenes

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

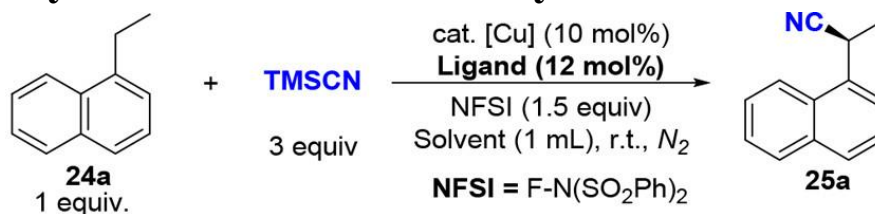
Enantioselective Functionalization of Benzylic C-H Bonds.



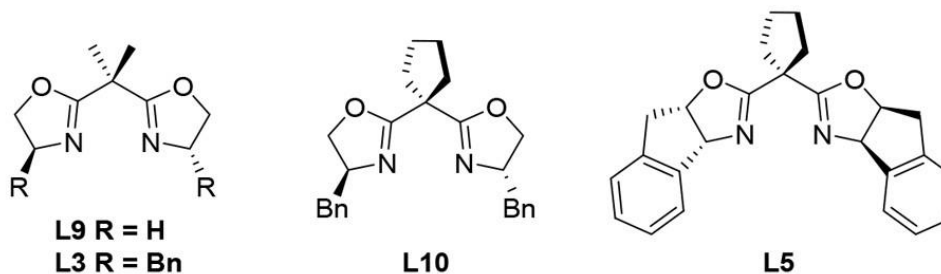
HAA of a benzylic C-H bond, compatibility with the trapping process

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.1 Copper-Catalyzed Enantioselective Cyanation of Benzylic C-H Bonds.



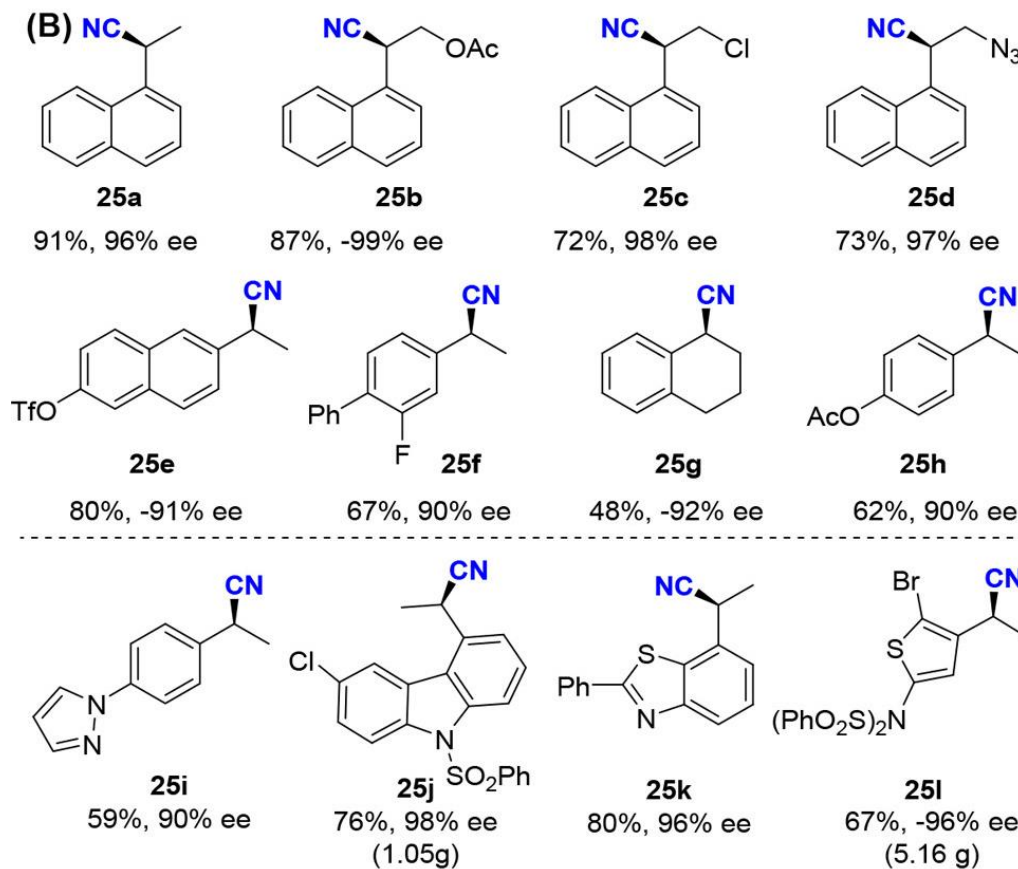
(A) Entry	Cu Source	Ligand	Solvent	Yield (ee)
1	[Cu(MeCN) ₄]PF ₆	L9	MeCN	5% (N/A)
2	[Cu(MeCN) ₄]PF ₆	L9	PhCl	12% (N/A)
3	CuOAc	L9	PhCl	25% (N/A)
4	CuOAc	L3	PhCl	75% (94%)
5	CuOAc	L3	PhH	91% (96%)
6	CuOAc	L10	PhH	84% (95%)
7	CuOAc	L5	PhH	71% (-97%)



bisulfonimidyl radicals for HAA(ineffective oxygen-centered radicals), solvent effect.

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

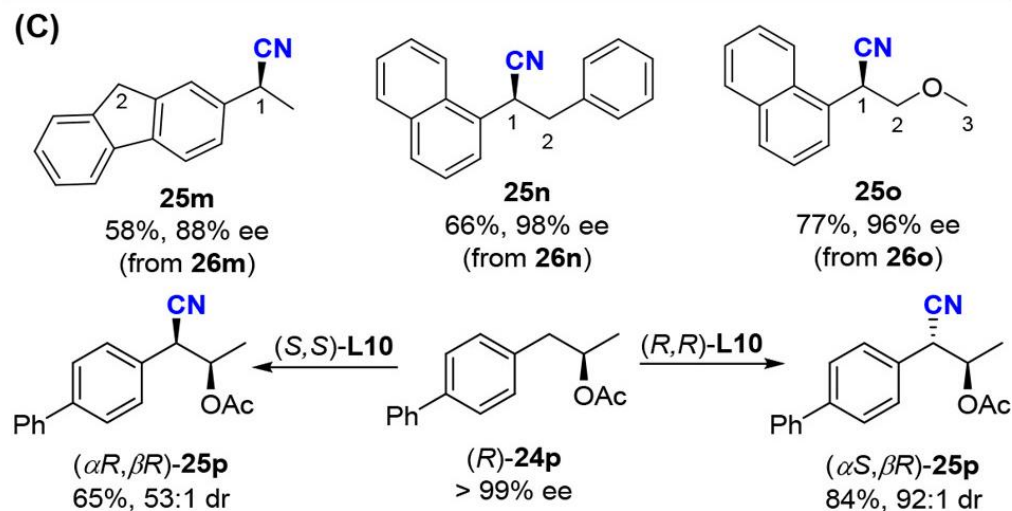
4.1 Copper-Catalyzed Enantioselective Cyanation of Benzylic C-H Bonds.



broad substrate scope

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.1 Copper-Catalyzed Enantioselective Cyanation of Benzylic C-H Bonds.

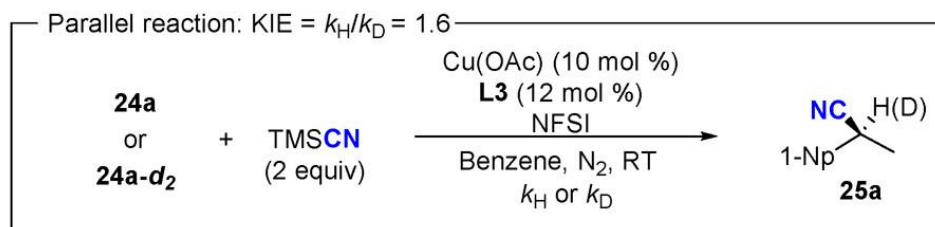
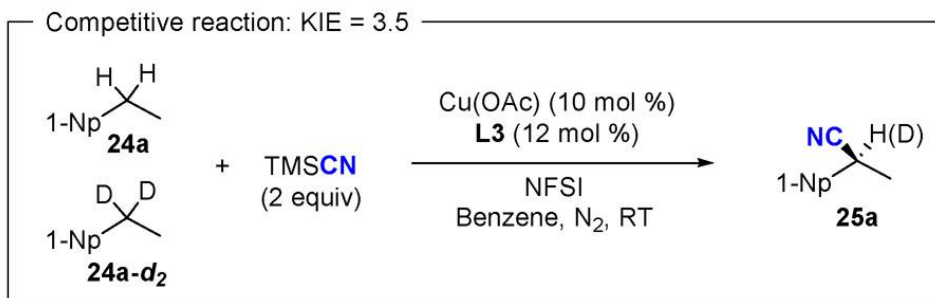


great site selectivity at the C-1 benzylic position,
 excellent diastereoselectivities indicating the chiral catalyst determined stereoselectivity
 rather than the substrates.

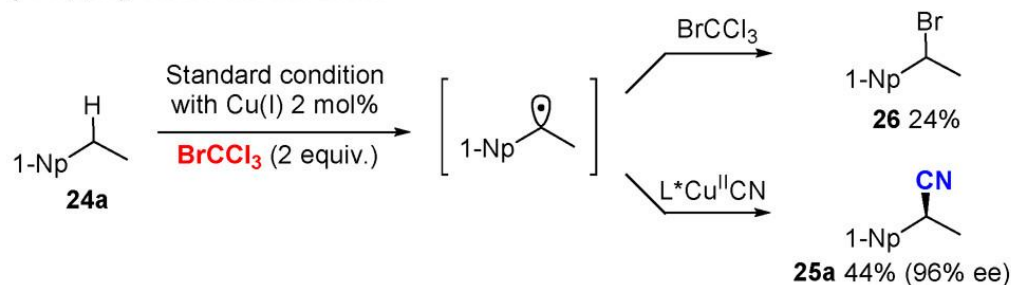
4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.1 Mechanistic Studies of Enantioselective Benzylic C-H Bond Cyanation.

(A) Kinetic isotopic effect experiments



(B) Trapping radical intermediates

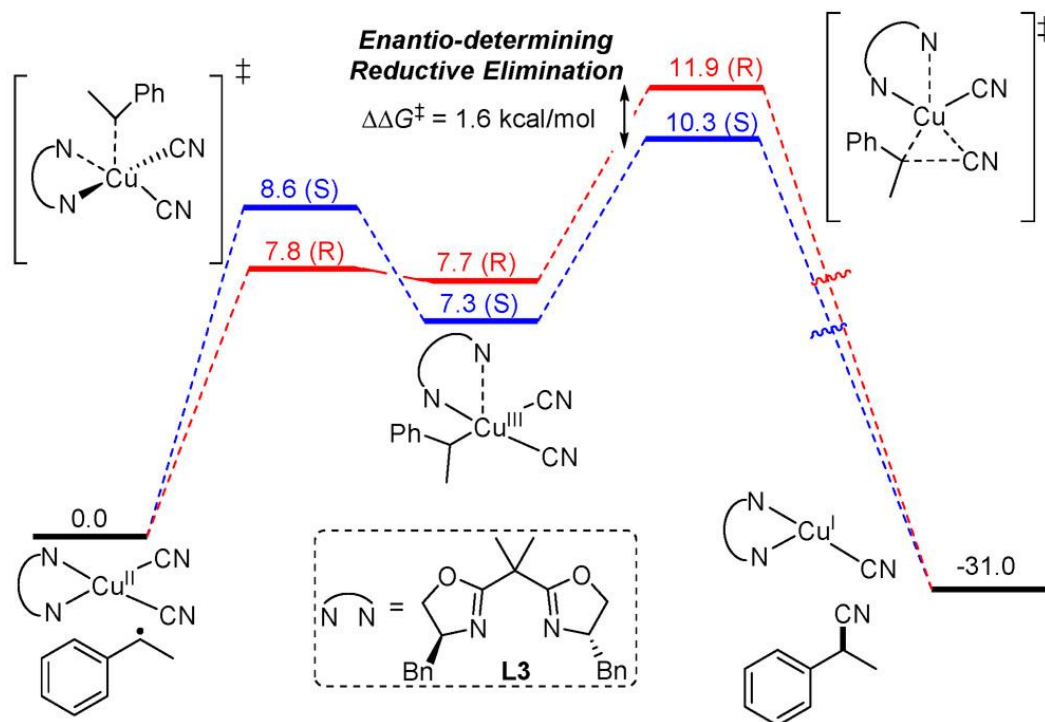


C-H bond cleavage being partially involved in RDS, benzylic radical

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.1 Mechanistic Studies of Enantioselective Benzylic C-H Bond Cyanation.

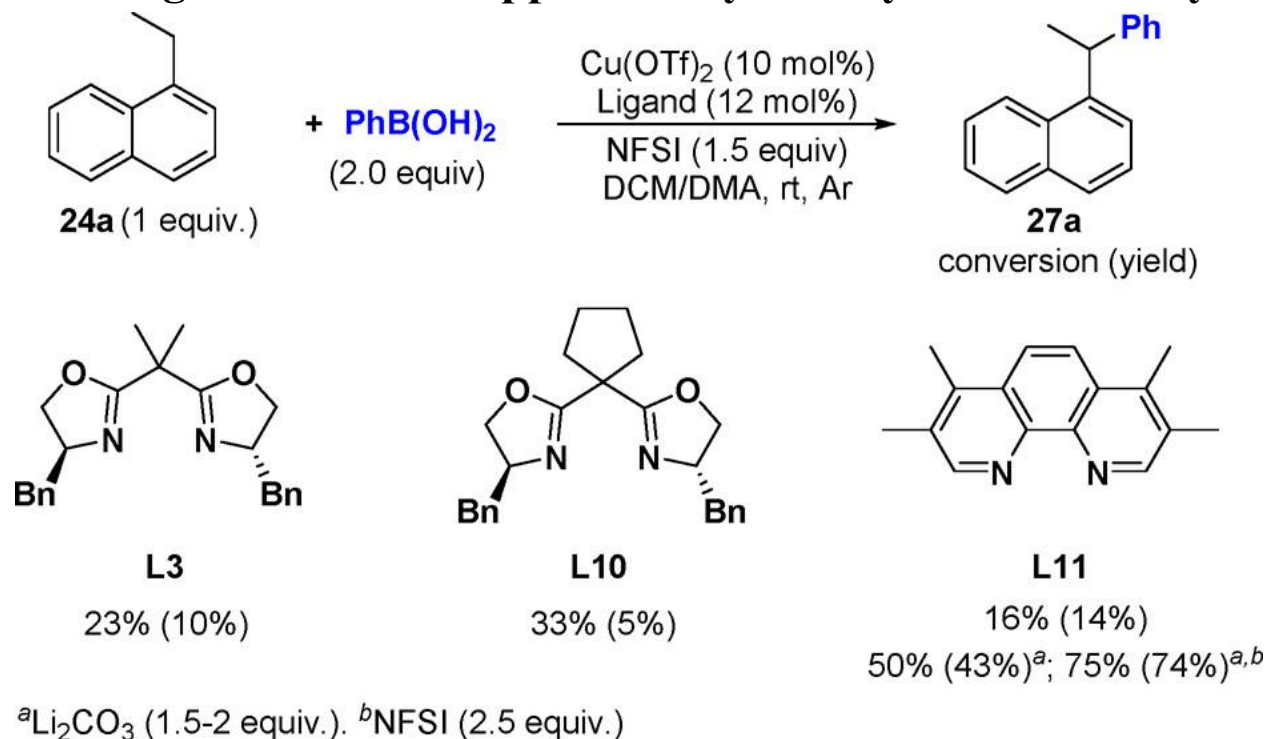
(C) DFT calculations



suggesting that the formation of the Cu(III) complex was reversible, and the reductive elimination from the Cu(III) intermediate was the enantioselectivity-determining step

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.2 Evaluation of Ligands for the Copper-Catalyzed Arylation of Benzylic C-H Bonds.

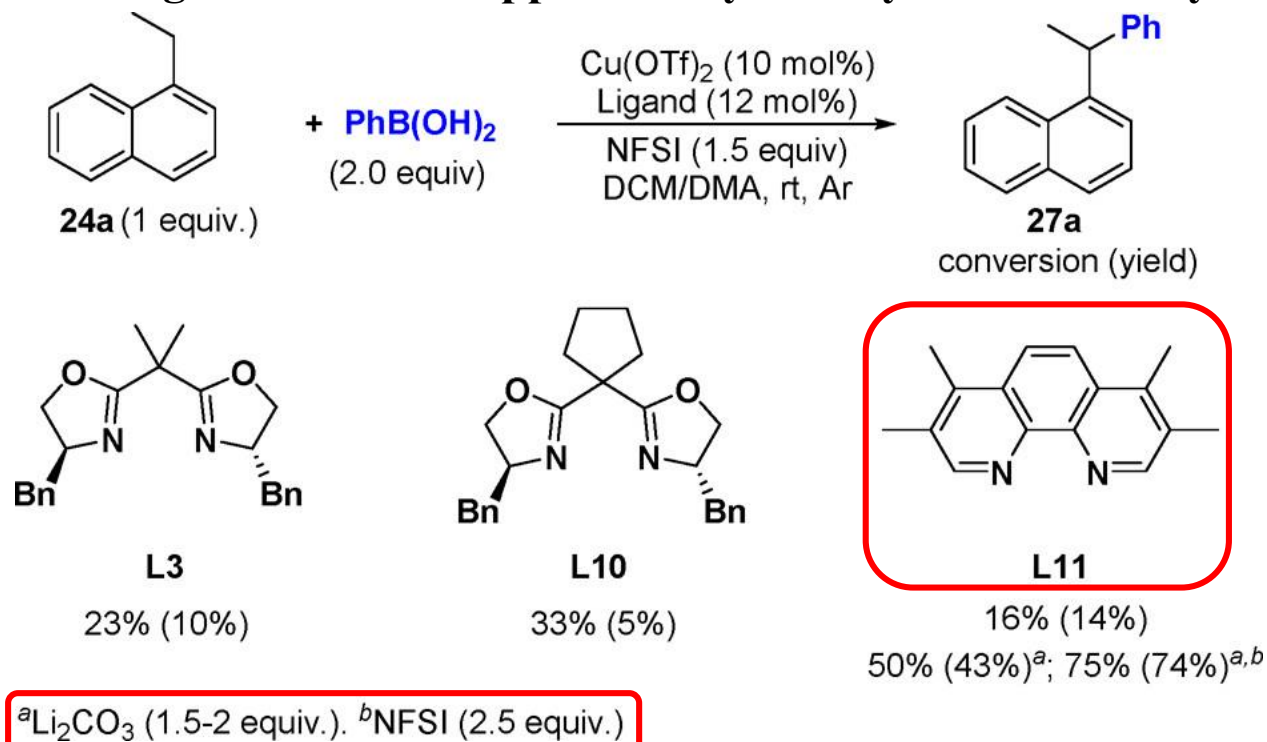


using the Box/Cu(I) system: low yields with poor enantioselectivities, benzylic amination and fluorination products as side products; indicating the inefficient benzylic radical trapping, which being resulted from slow transmetalation;

solution: less hindered achiral ligand L11, Li₂CO₃, loading of NFSI.

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.2 Evaluation of Ligands for the Copper-Catalyzed Arylation of Benzylic C-H Bonds.

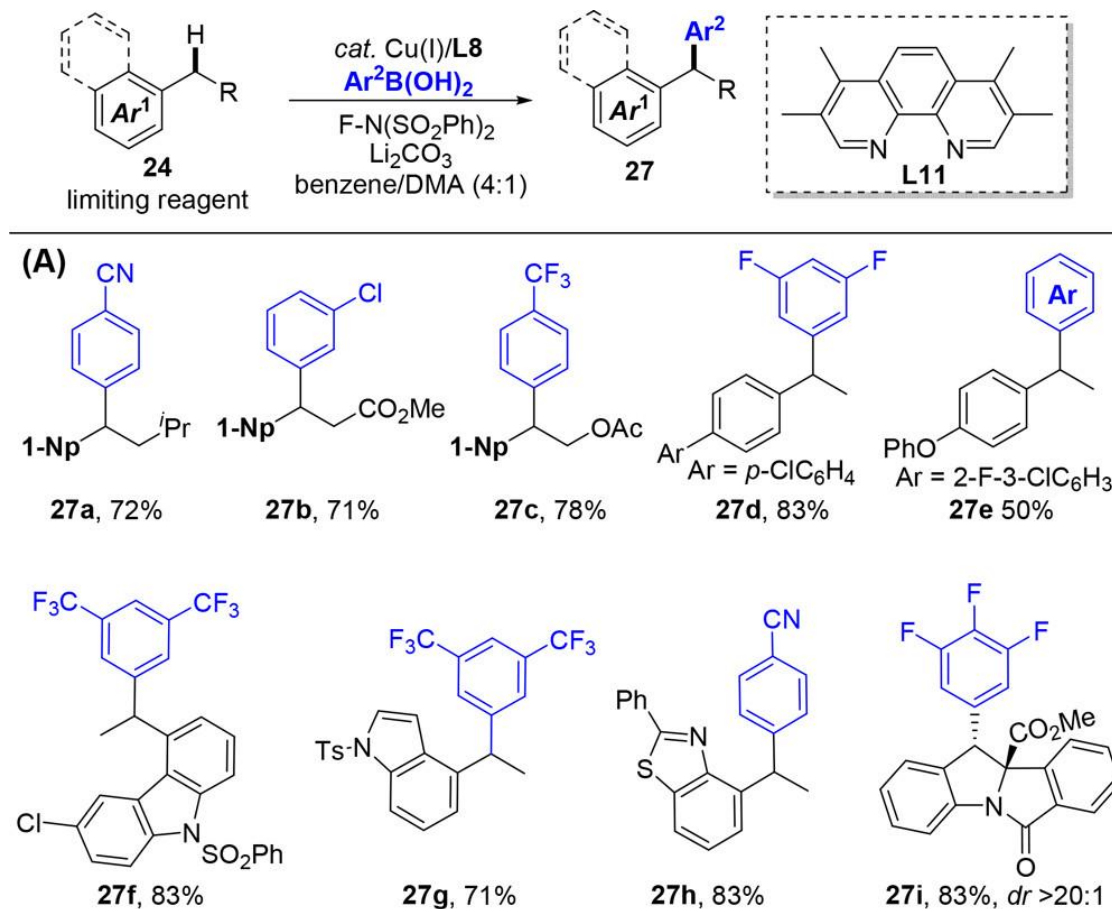


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4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.2 Copper-Catalyzed Arylation of Benzylic C-H Bonds.

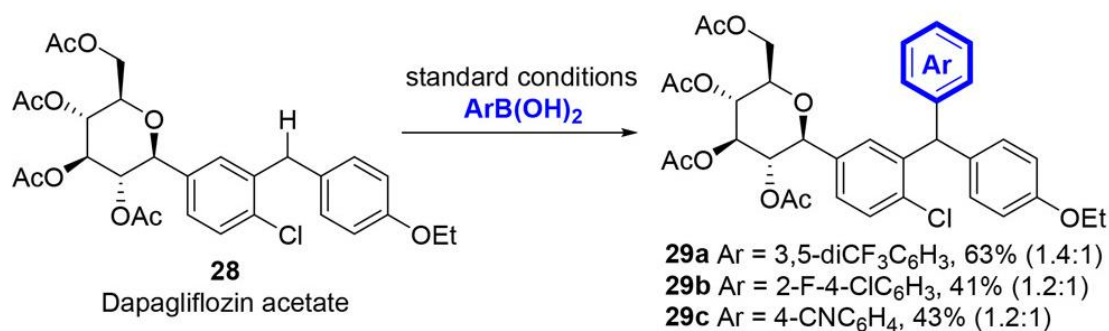


broad substrate scope, but electron-rich ArB(OH)₂ derivatives were less reactive.

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

4.2 Copper-Catalyzed Arylation of Benzylic C-H Bonds.

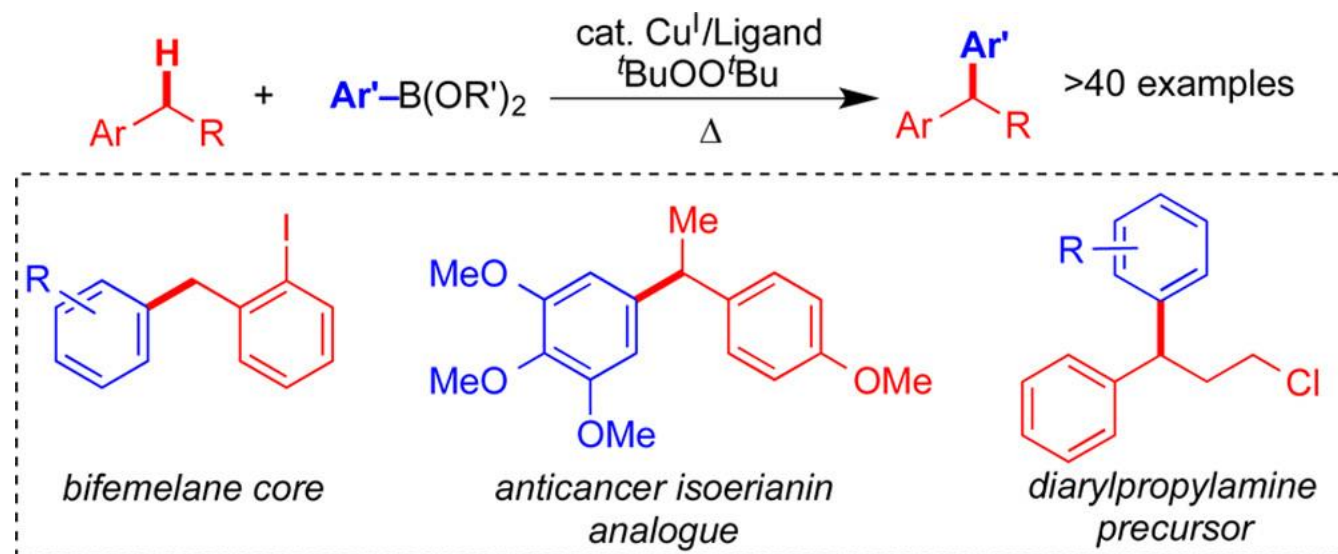
(B) Late-stage arylation of C-H bonds in bioactive molecules



application for the late-stage arylation of benzylic C-H bonds in bioactive molecules

4 Cu-cat. Enantioselective Functionalization of Benzylic C-H Bonds.

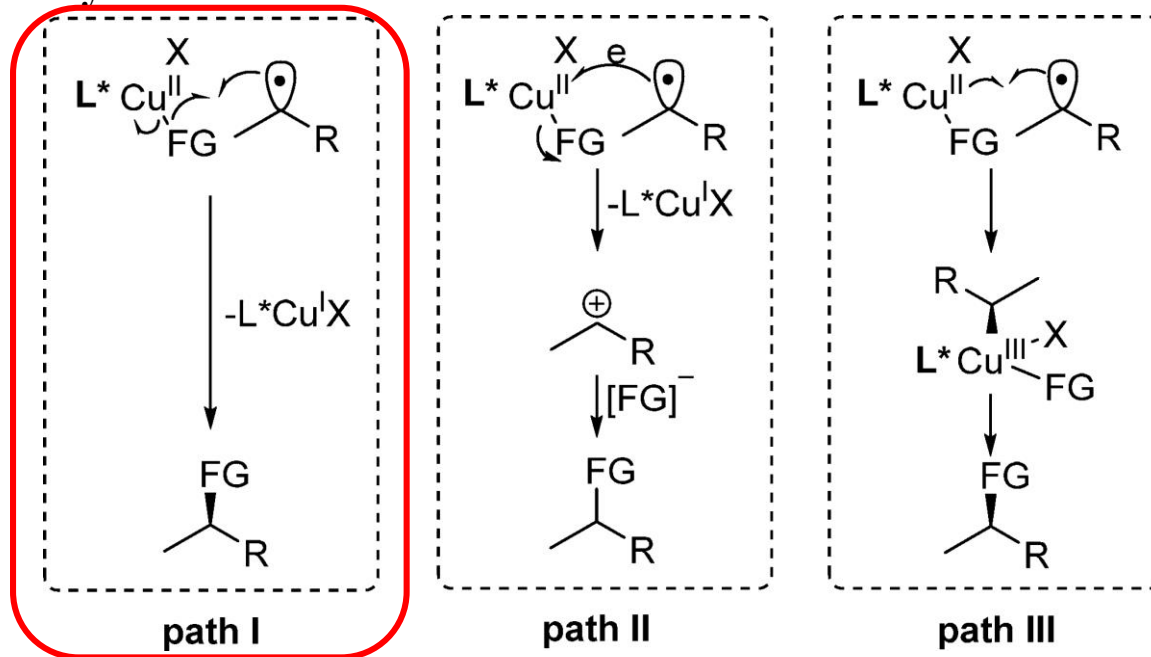
4.3 Cu-Catalyzed Oxidative Arylation of Inexpensive Alkylarenes.



using tert-butyl peroxide as an oxidant
 (oxygen-centered radical for HAA),
simple alkyl arenes,
electron-rich arylboronic acids,
an excess of the alkyl arene for a satisfactory yield.

5 Summary and Perspectives.

Pathways of Possible Reactions between Carbon Radical and Copper(II) Species.

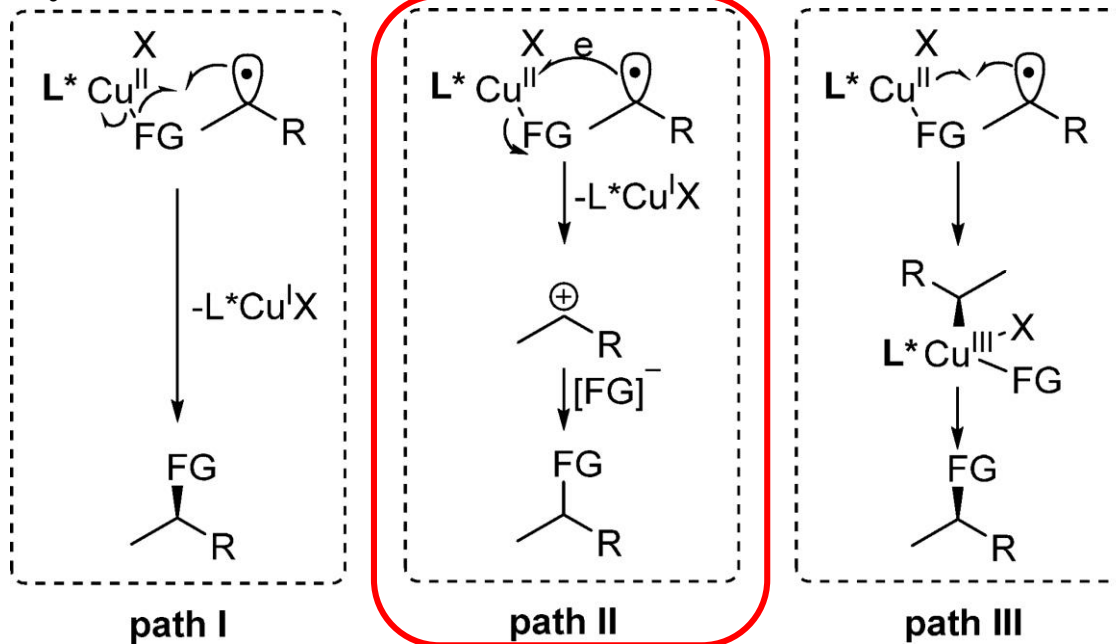


outer-sphere ligand transfer
(path I)

CuBr: racemic benzyl bromide

5 Summary and Perspectives.

Pathways of Possible Reactions between Carbon Radical and Copper(II) Species.



outer-sphere ligand transfer
(path I)

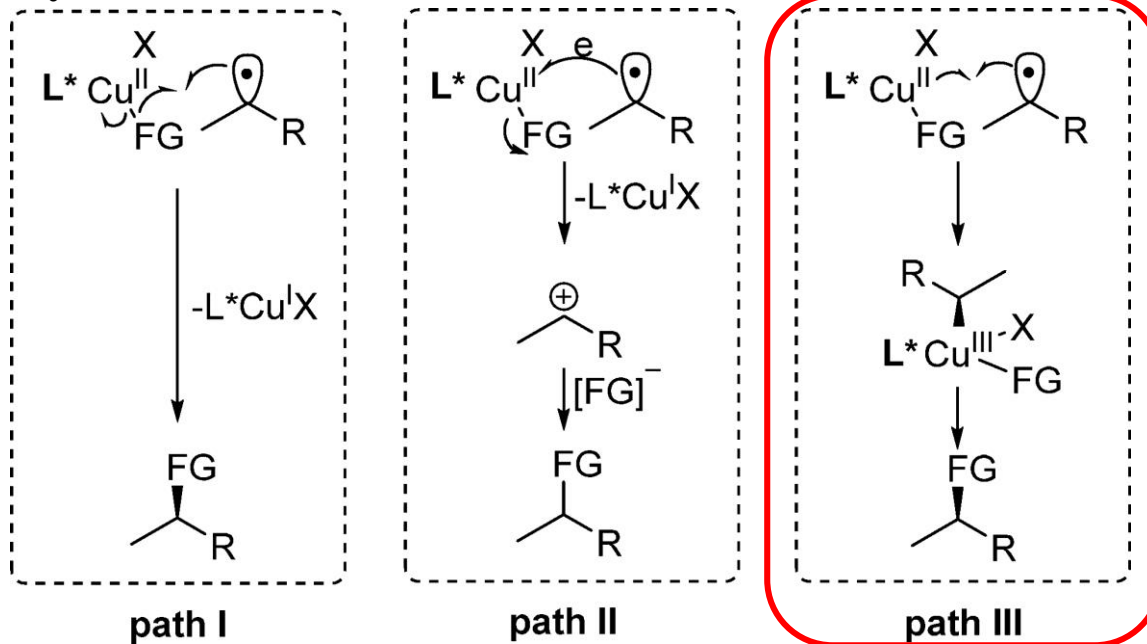
carbocation intermediate
(path II)

CuBr: racemic benzyl bromide

NFSI: racemic benzylic amination

5 Summary and Perspectives.

Pathways of Possible Reactions between Carbon Radical and Copper(II) Species.



**radical relay process
(path III)**
 (L*)RCu^{III}IFG,
 reductive elimination

outer-sphere ligand transfer
(path I)

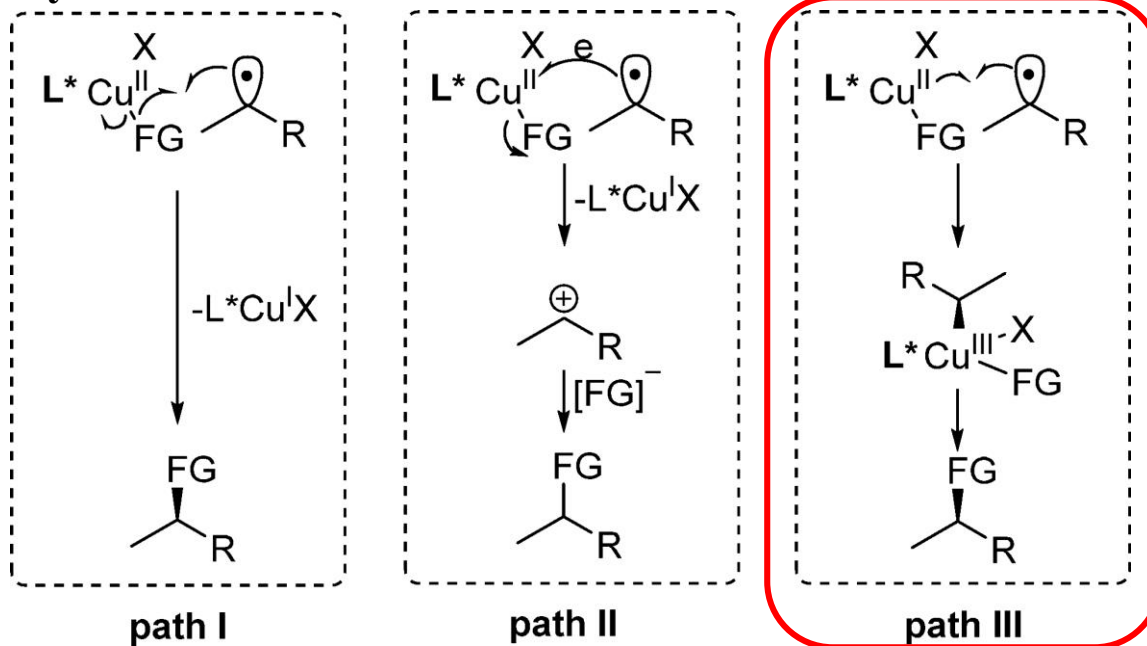
carbocation intermediate
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Pathways of Possible Reactions between Carbon Radical and Copper(II) Species.



**radical relay process
(path III)**
 (L*)RCu^{III}FG,
 reductive elimination

outer-sphere ligand transfer
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carbocation intermediate
(path II)

CuBr: racemic benzylic bromide

NFSI: racemic benzylic amination

**Limitations: poor enantioselectivity for non-benzylic radicals, tertiary benzylic radicals;
 further extensions to intermolecular asymmetric oxygenation and amination;
 limited asymmetric benzylic C–H cyanation, limited HAA mediator.**

Thank you!
