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# Enantioselective Copper-Catalyzed Intermolecular Trifluoromethylation of Alkenes *via* Radical Process

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Checker: Hong-Qiang Shen

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Wu, L., Wang, F., Wan, X., Wang, D., Chen, P., Liu, G.  
*J. Am. Chem. Soc.* **2017**, 139, 2904–2907.

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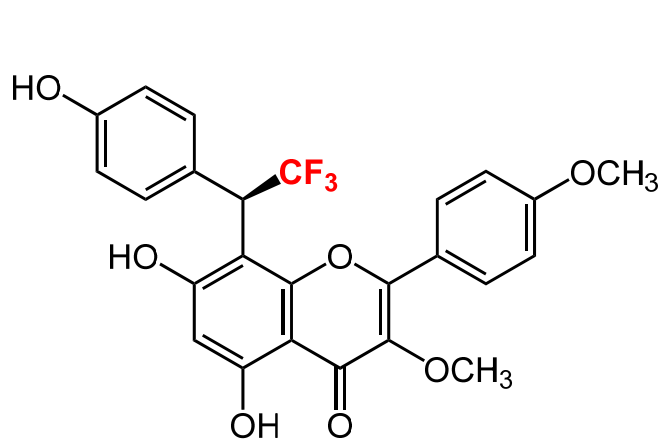
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4 Summary

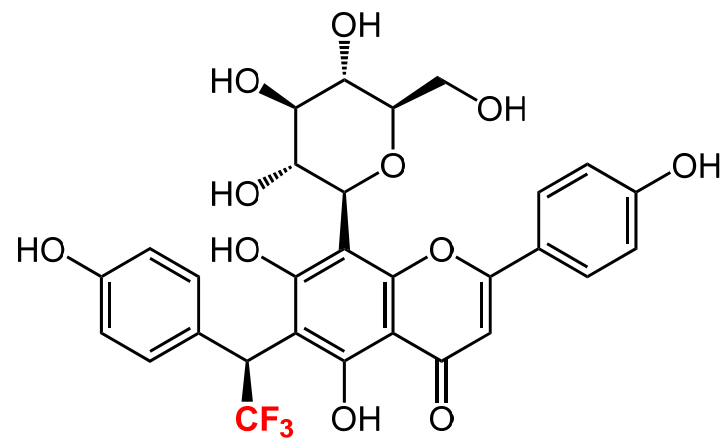
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# Introduction

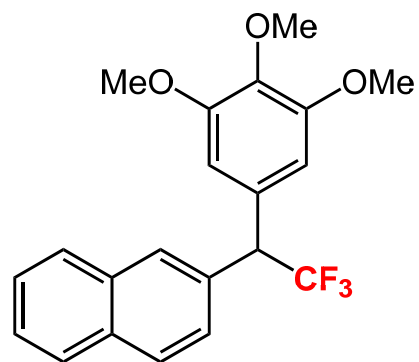
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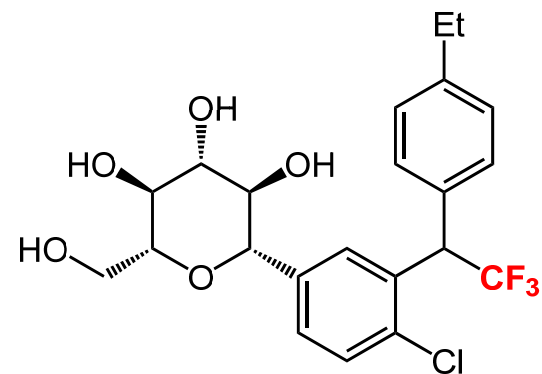
Haplopappin (CF<sub>3</sub>)



Cucumerin A (CF<sub>3</sub>)

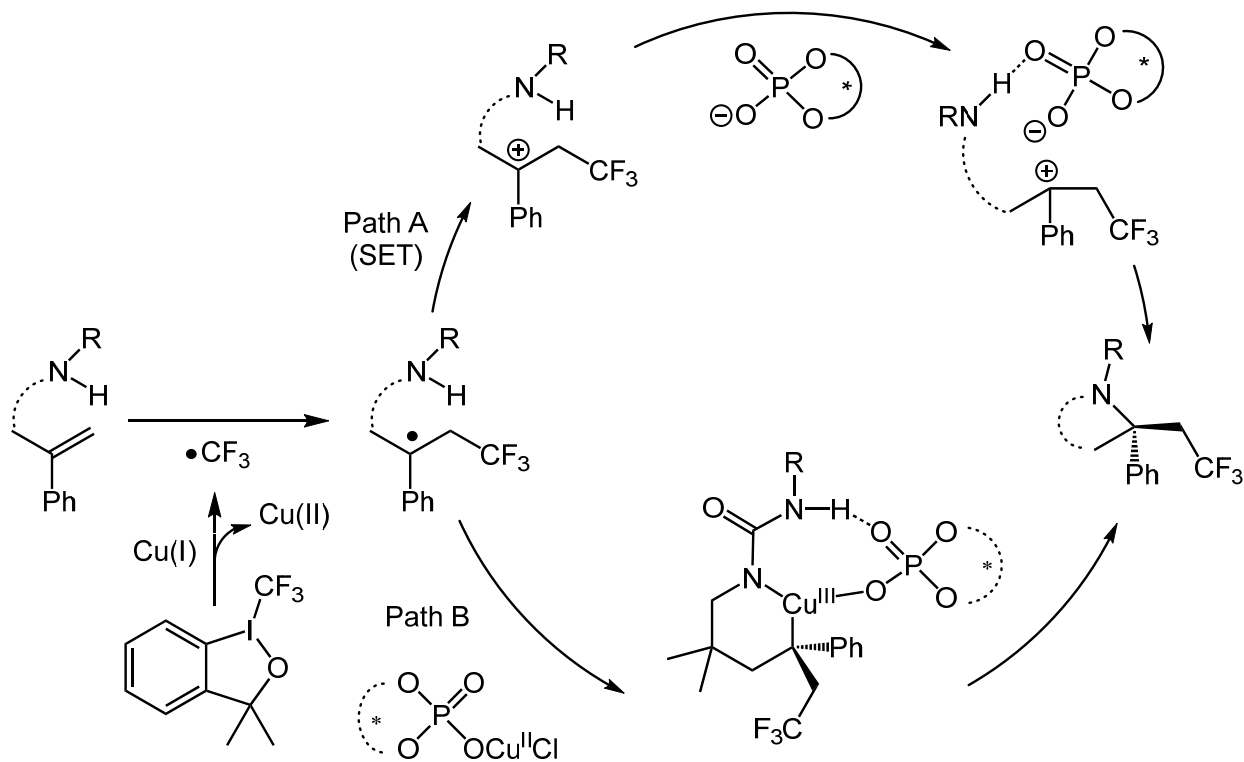
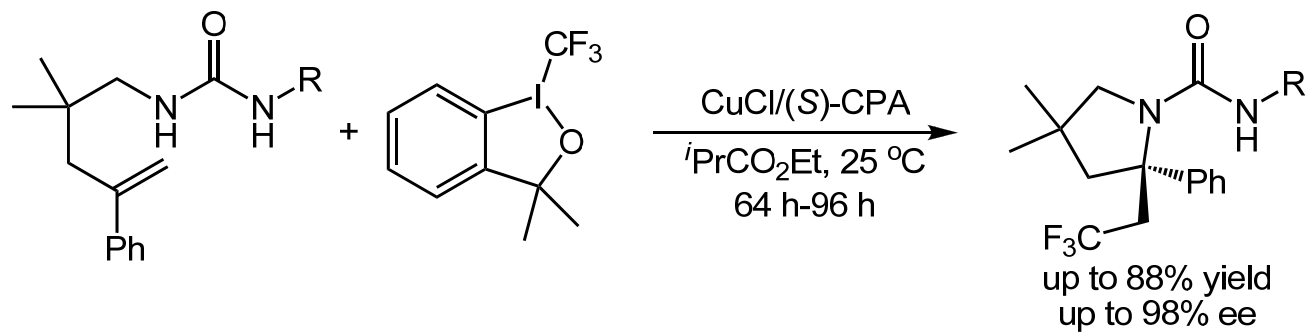


Antitubulin polymerization agent (CF<sub>3</sub>)



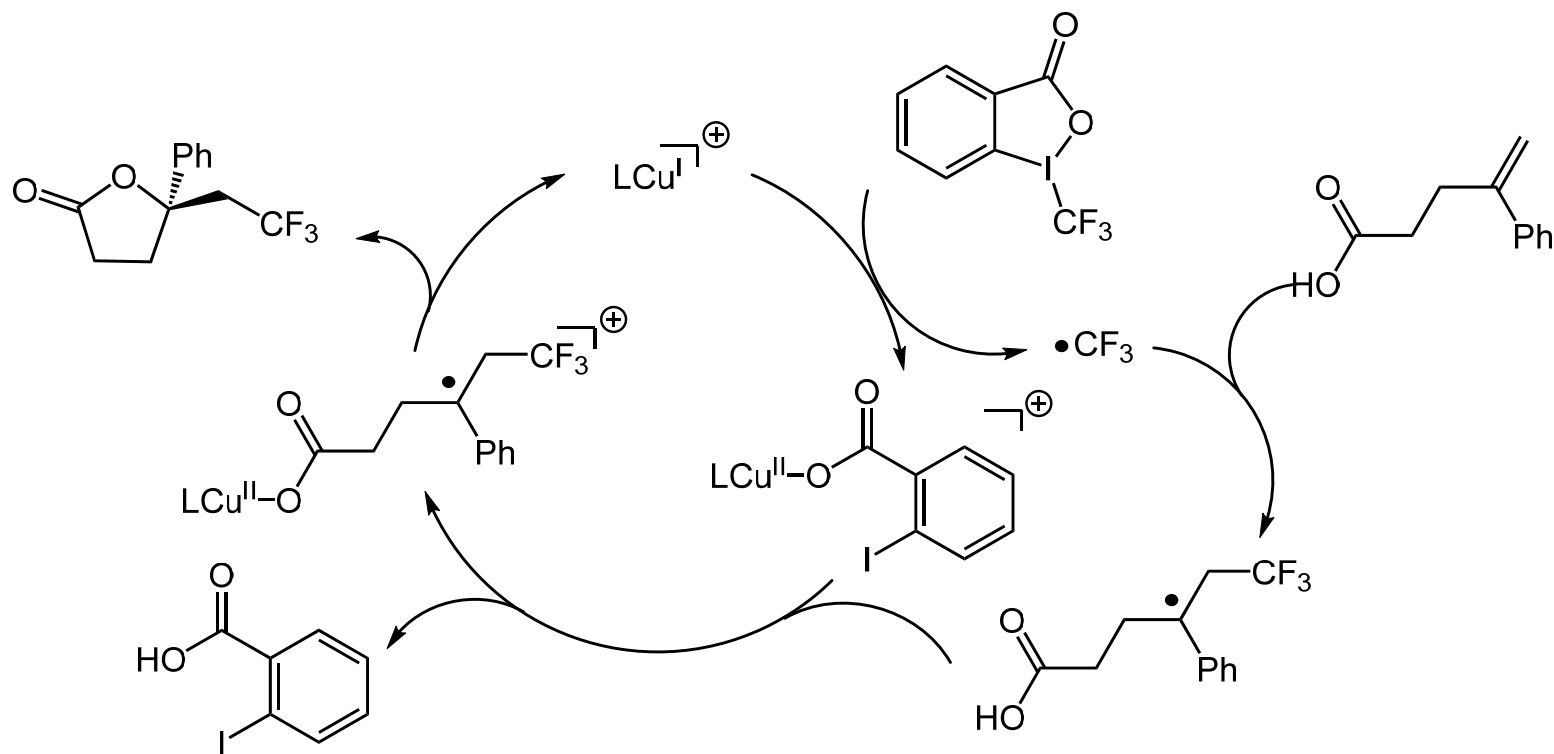
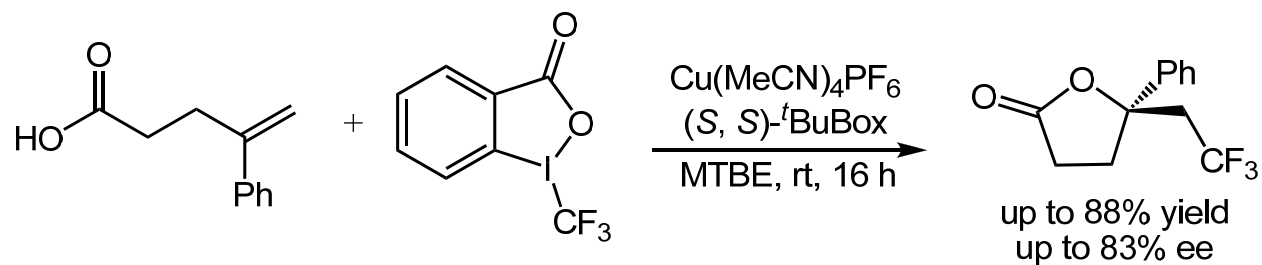
SGLT2 inhibitor (CF<sub>3</sub>)

# Introduction

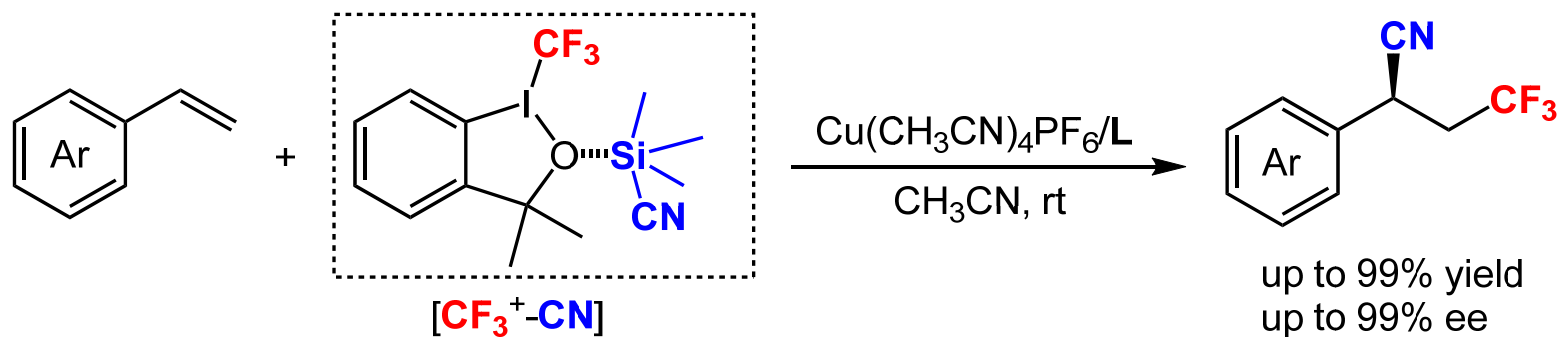


Liu, X.-Y. *et al.* *J. Am. Chem. Soc.* **2016**, *138*, 9357.

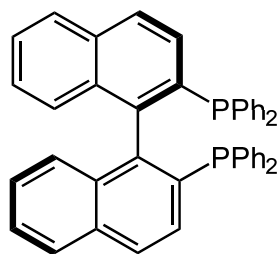
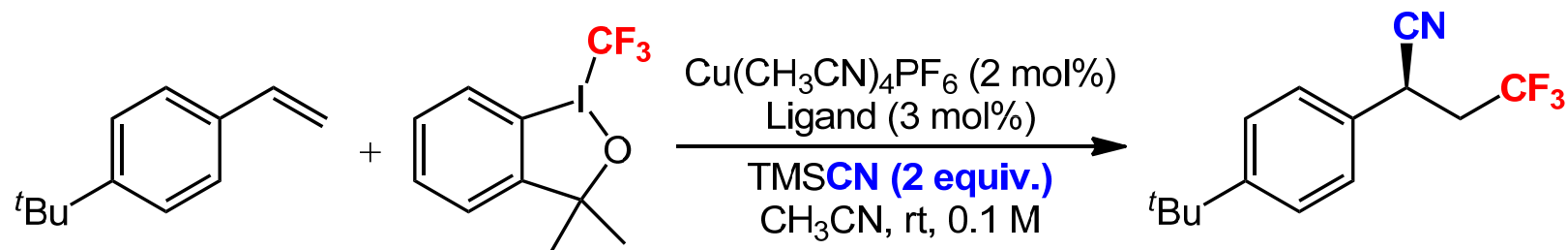
# Introduction



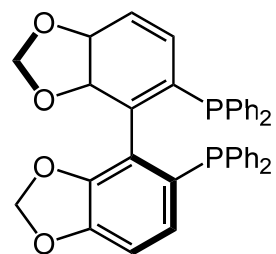
# Cyanotrifluoromethylation of Alkenes



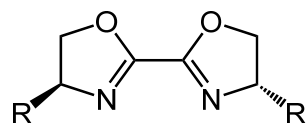
# Evaluation of the Ligand



L1 34%, 1% ee



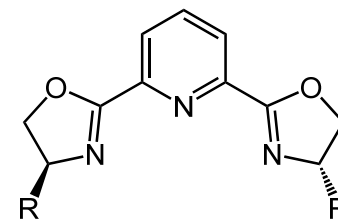
L2 29%, 0% ee



L3 R = Me, 19%, 2% ee

L4 R = Ph, 26%, 0% ee

L5 R = *t*Bu, 13%, 7% ee

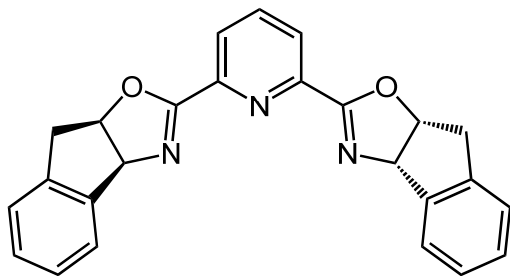


L6 R = Me, 78%, 10% ee

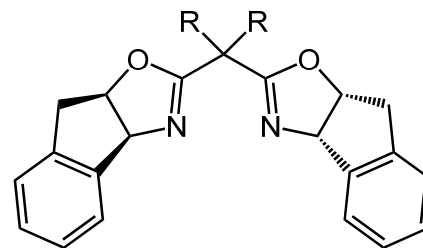
L7 R = *i*Pr, 79%, 48% ee

L8 R = Ph, 67%, 43% ee

L9 R = Bn, 77%, 21% ee



L10 74%, 55% ee



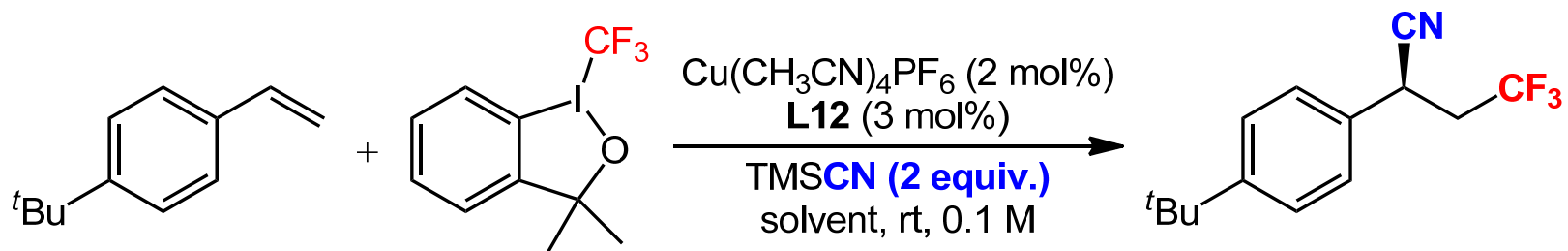
L11 R = H, 78%, 37% ee

L12 R =  $(\text{CH}_2)_2$ , 86%, 97% ee

L13 R = Me, 76%, 91% ee

L14 R =  $(\text{CH}_2)_4$ , 81%, 94% ee

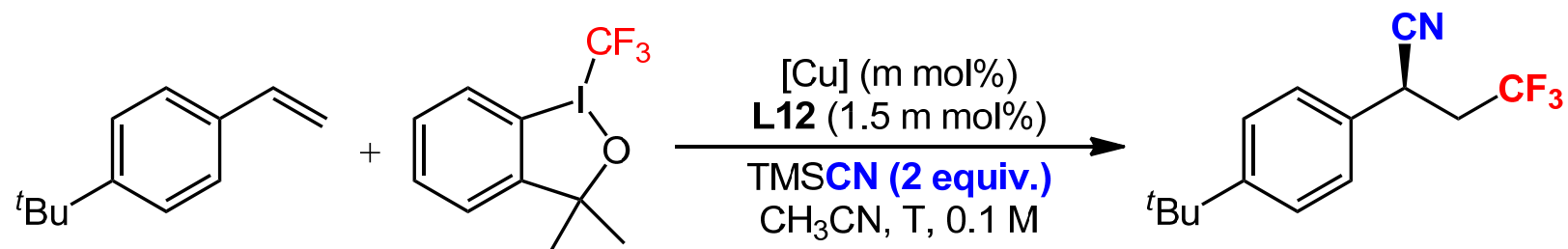
# Evaluation of the Solvent



entry	solvent	yield (%)	ee (%)
1	DCM	75	95
2	$\text{CHCl}_3$	71	96
3	THF	75	96
4	DMSO	86	96
5	MeOH	75	95
6	EtOAc	86	96
<b>7</b>	<b><math>\text{CH}_3\text{CN}</math></b>	<b>86</b>	<b>97</b>

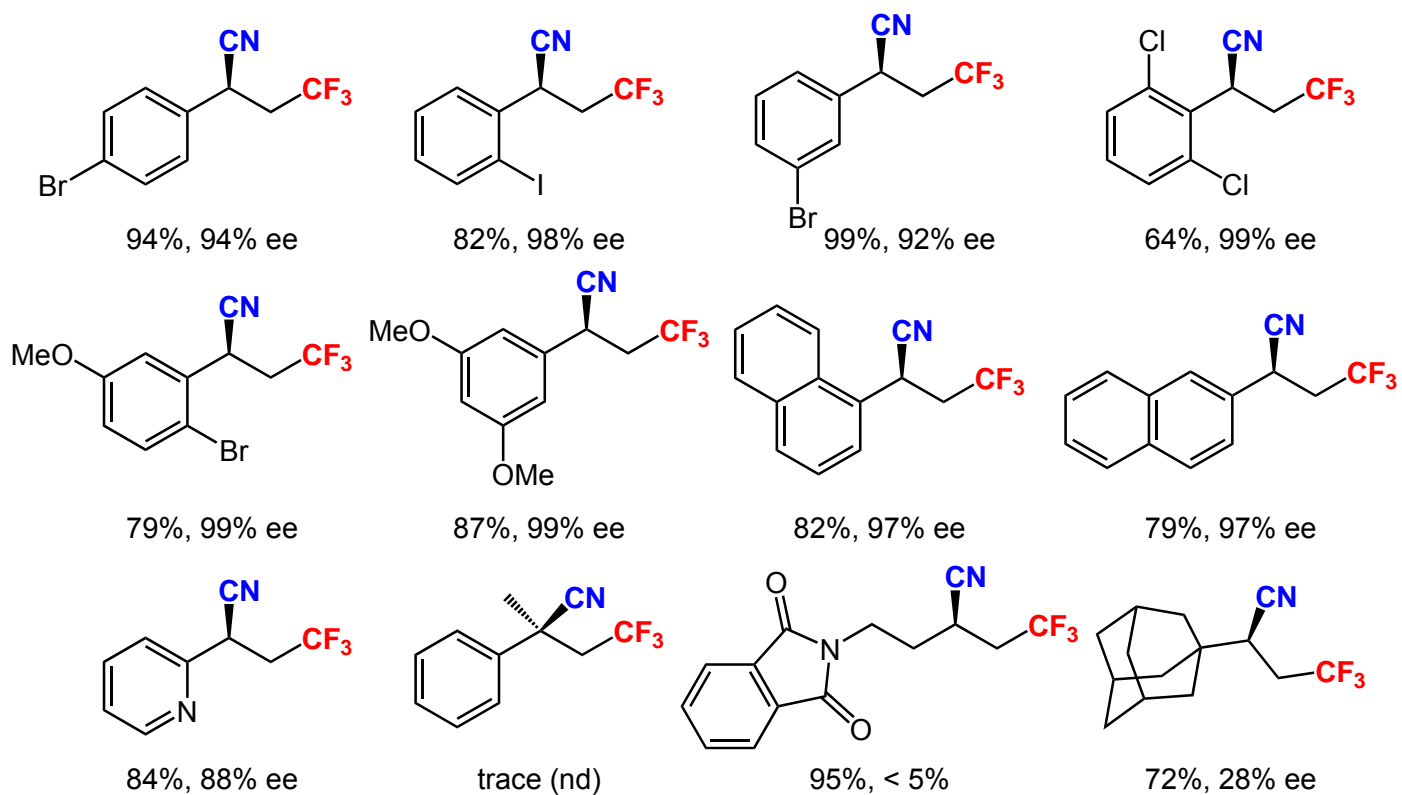
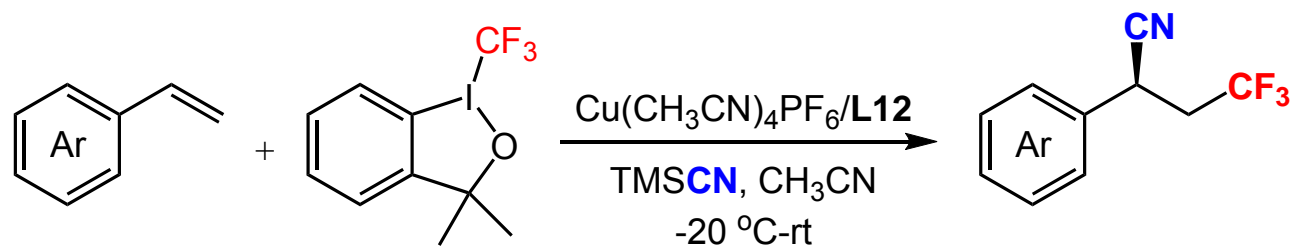


# Evaluation of the Catalyst and Temperature

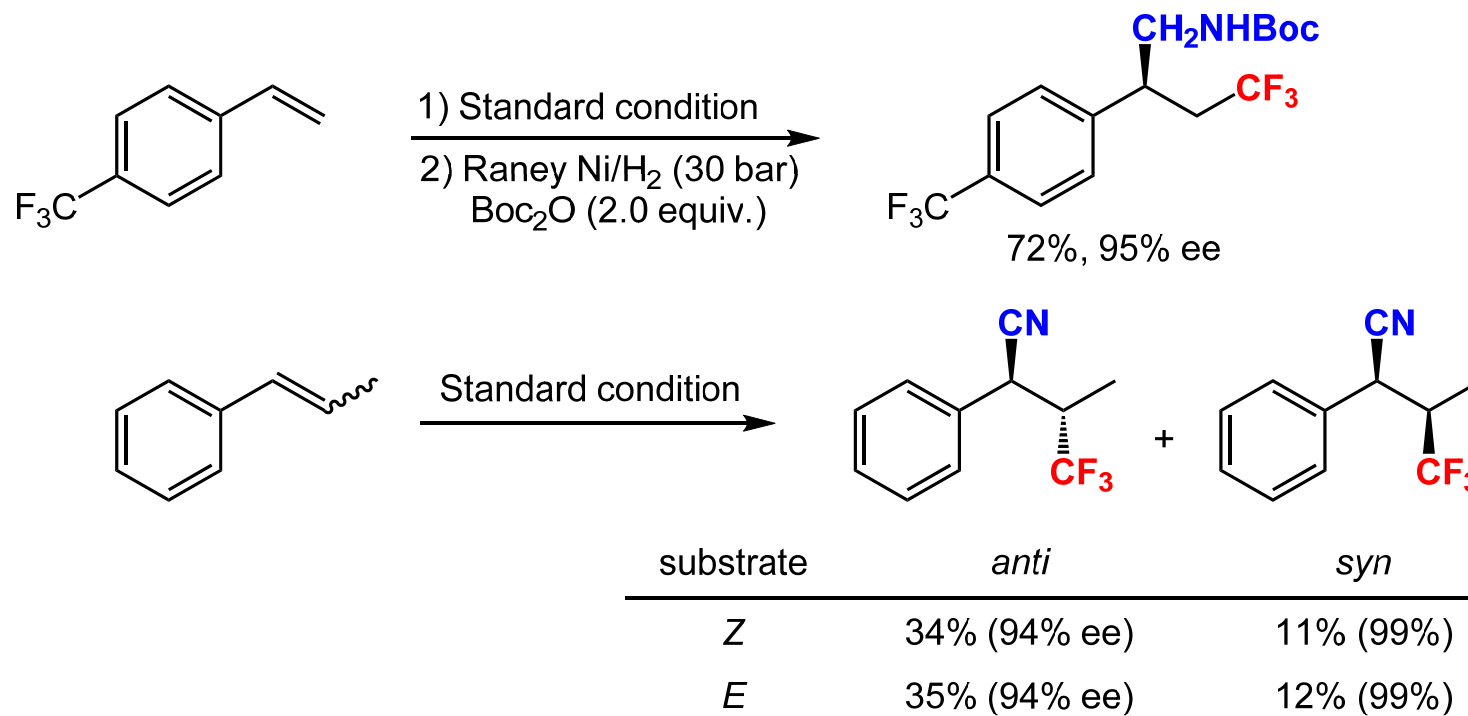


entry	[Cu]	m	T (°C)	yield (%)	ee (%)
1	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	2	rt	86	97
2	CuI	2	rt	83	96
3	CuBr	2	rt	79	94
4	Cu(OAc) <sub>2</sub>	2	rt	81	91
5	Fe(acac) <sub>2</sub>	2	rt	-	-
6	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	5	rt	86	97
<b>7</b>	<b>Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub></b>	<b>1</b>	<b>rt</b>	<b>91</b>	<b>97</b>
8	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	1	40	80	96

# Substrate Scope

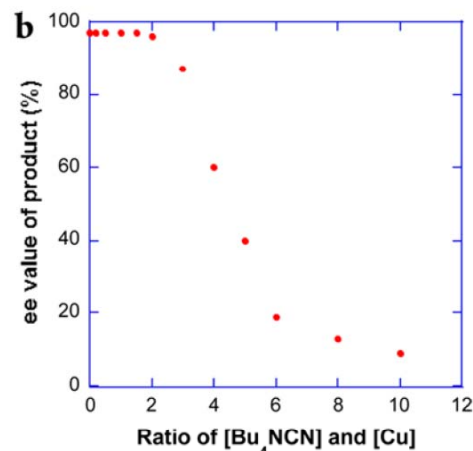
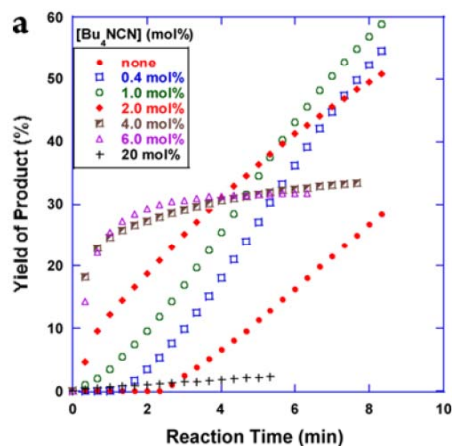


# Transformation Experiments



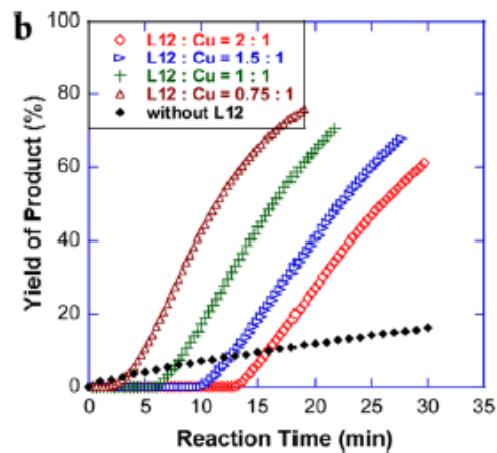
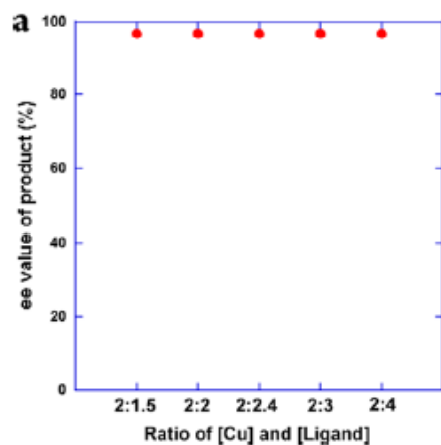
# Mechanism Study

## Extra cyanide effect on the reaction rates (a) and ee values (b)



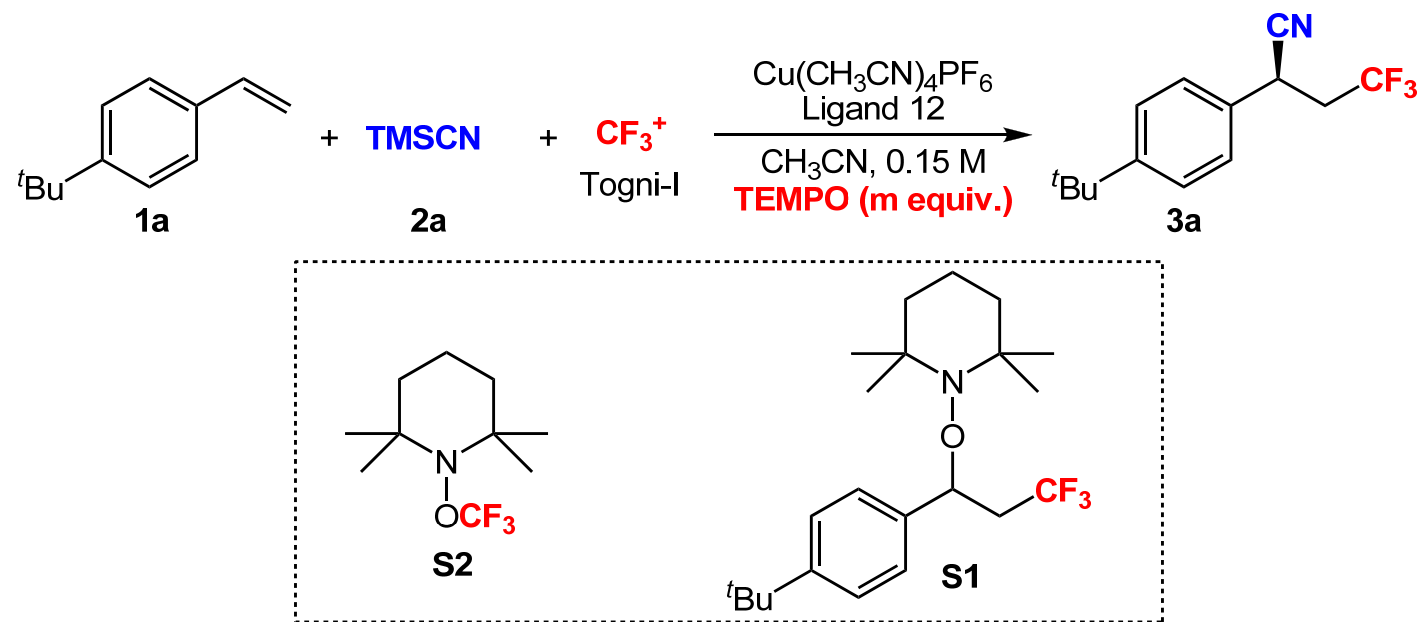
extraneous cyanide  
induction period

## Ligand effect on the ee values (a) and reaction rates (b)



the ligand effect on  
the induction period

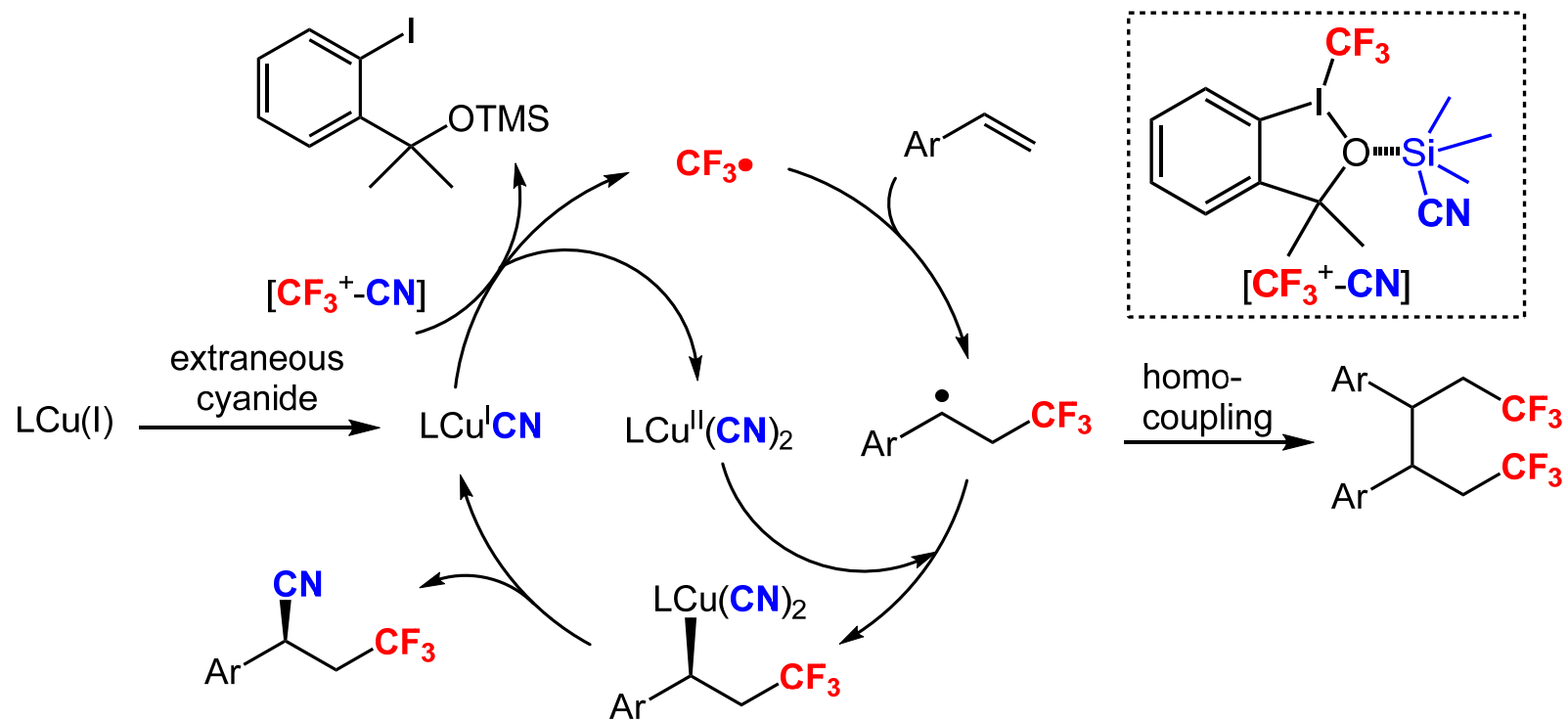
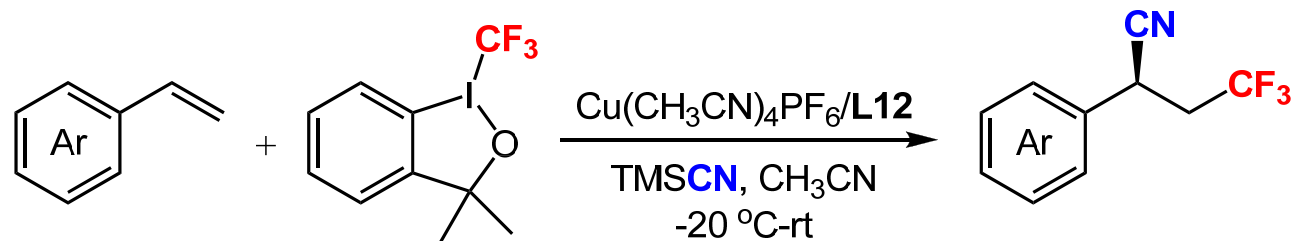
# Mechanism Study



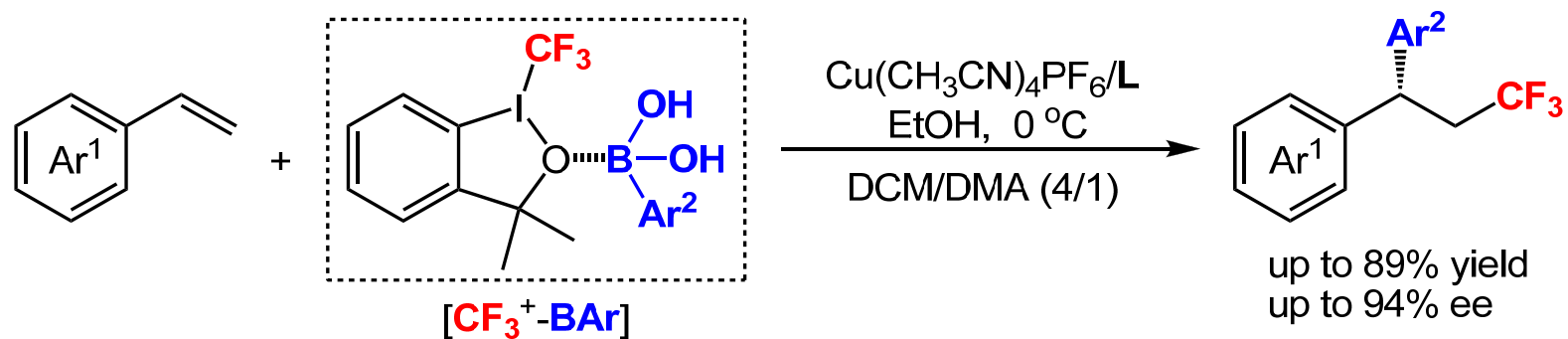
Yield of the product (%)

entry	m	<b>3a</b>	<b>S1</b>	<b>S2</b>
1	0.5	25	20	19
2	1.0	trace	14	23
3	2.0	no	10	34

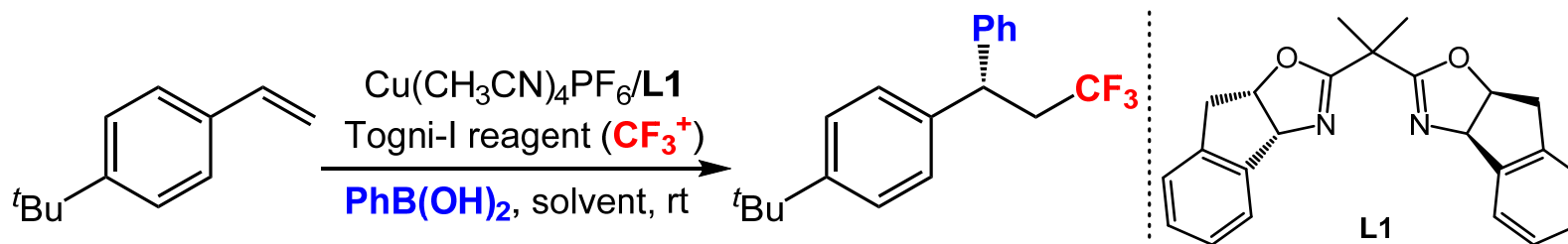
# Proposed Mechanism



# Trifluoromethylarylation of Styrenes



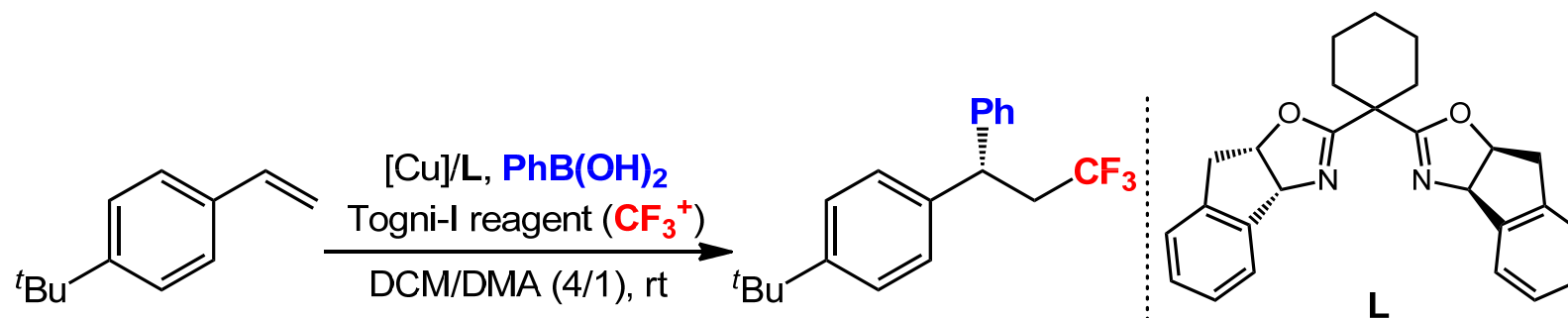
# Evaluation of the Solvent



entry	solvent	yield (%)	ee (%)
1	DMA	37	58
2	DCM	16	72
3	DMF	16	62
4	CH <sub>3</sub> CN	10	76
5	Toluene	24	62
<b>6</b>	<b>DCM/DMA (4/1)</b>	<b>71</b>	<b>79</b>
7	DCM/DMA (1/1)	80	68
8	DCM/DMA (1/4)	51	62



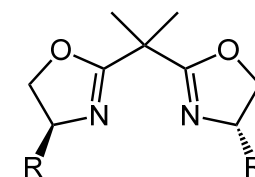
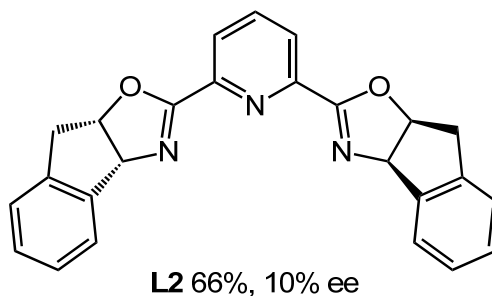
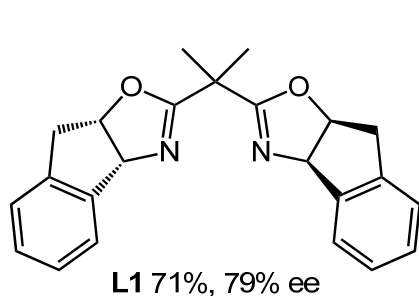
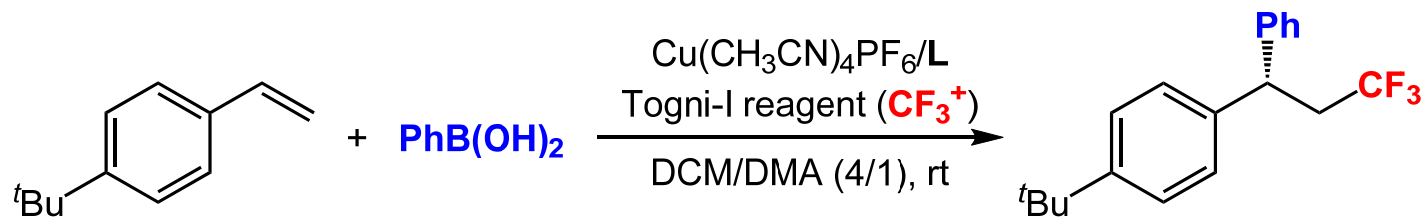
# Evaluation of the Catalyst



entry	[Cu]	yield (%)	ee (%)
1 <sup>a</sup>	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	71	79
<b>2</b>	<b>Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub></b>	<b>80</b>	<b>80</b>
3	CuCl	72	62
4	CuBr	54	32
5	CuBr·SMe <sub>2</sub>	72	79
6	Cu(OAc) <sub>2</sub>	51	76
7	CuCl <sub>2</sub>	67	65

<sup>a</sup> L1

# Evaluation of the Ligand

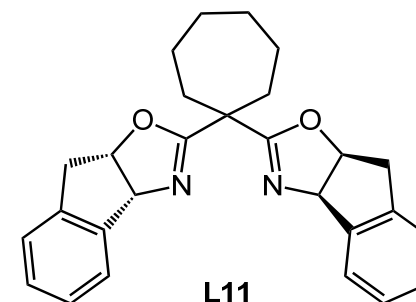
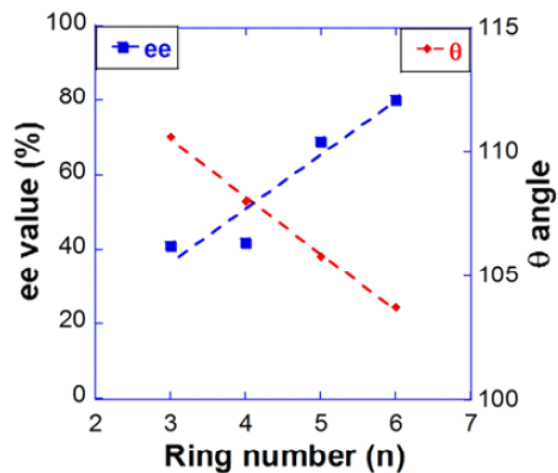
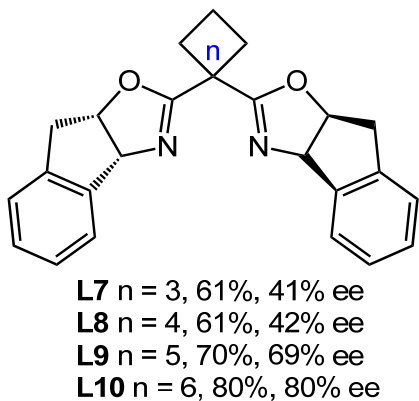


**L3** R = Ph, 88%, -4% ee

**L4** R = Cy, 69%, -48% ee

**L5** R = Bn, 89%, -46% ee

**L6** R = *t*Bu, 49%, 0



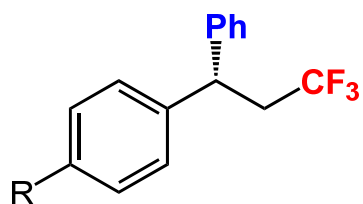
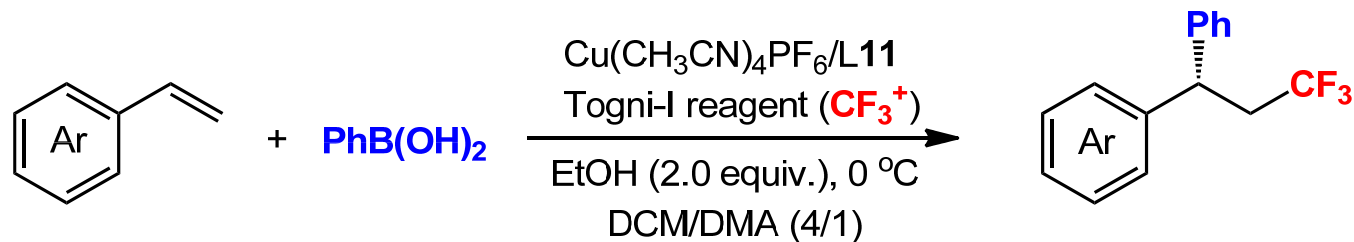
85%, 83% ee

77%, 89% ee (0 °C)

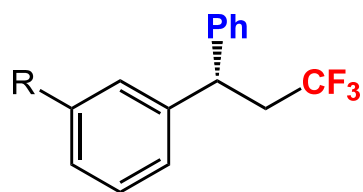
84%, 89% ee (0 °C, 2.0 equiv. EtOH)

82%, 89% ee (0.2 mmol)

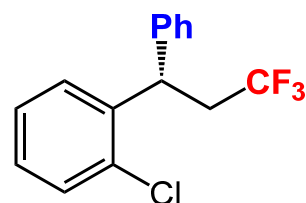
# Substrate Scope



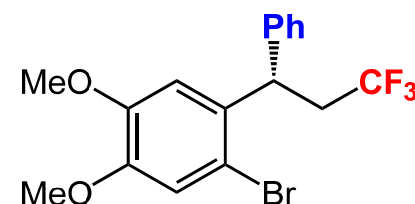
R = CO<sub>2</sub>Me, 82%, 90% ee  
R = CN, 78%, 83% ee  
R = NO<sub>2</sub>, 72%, 85% ee



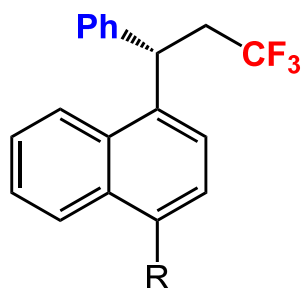
R = F, 68%, 88% ee  
R = OMe, 77%, 90% ee



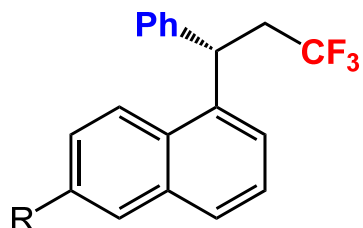
63%, 90% ee



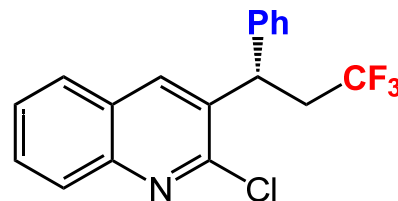
53%, 90% ee



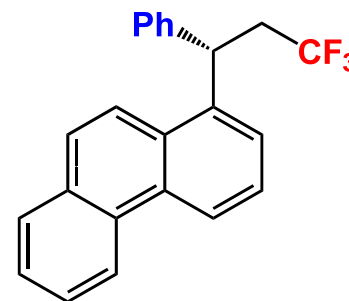
R = H, 87%, 93% ee  
R = F, 74%, 92% ee



R = H, 82%, 90% ee  
R = OAc, 33%, 88% ee

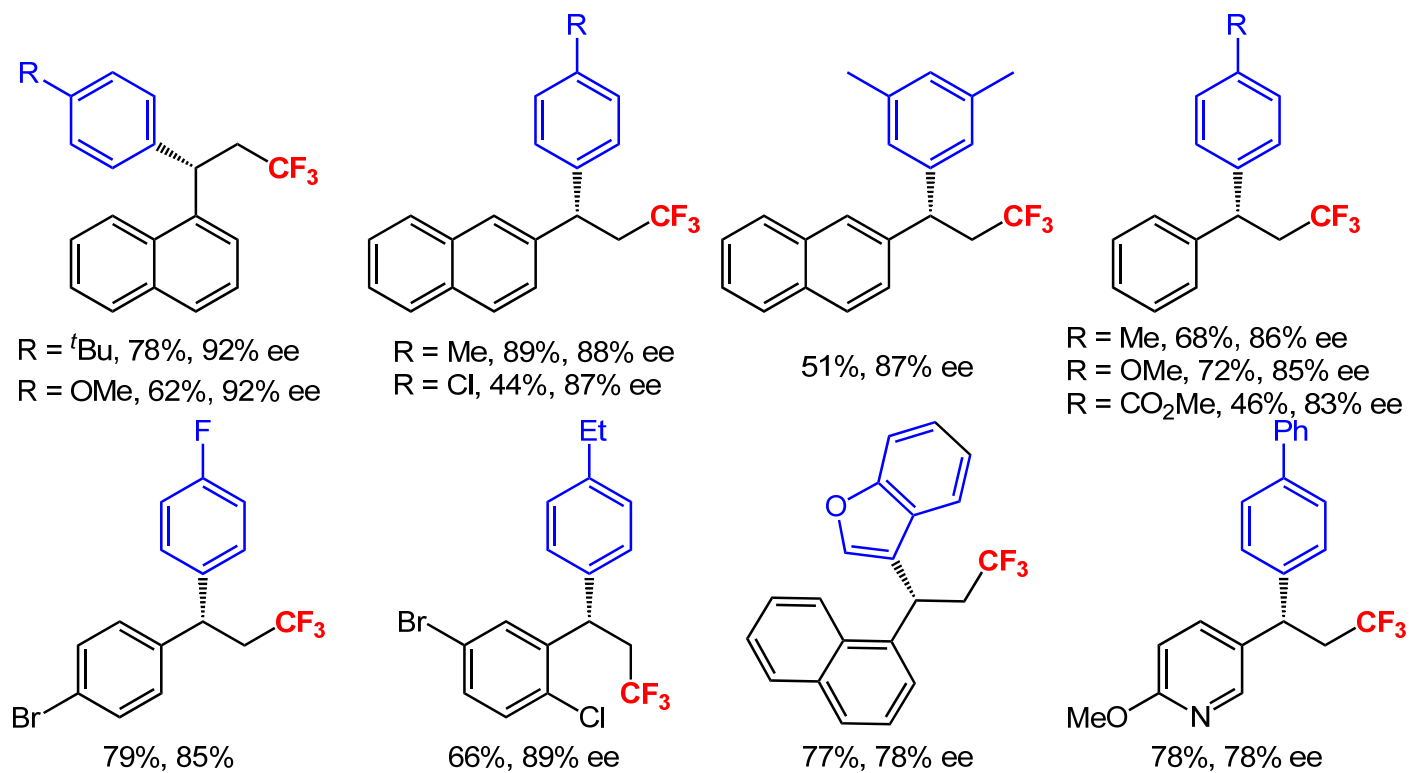
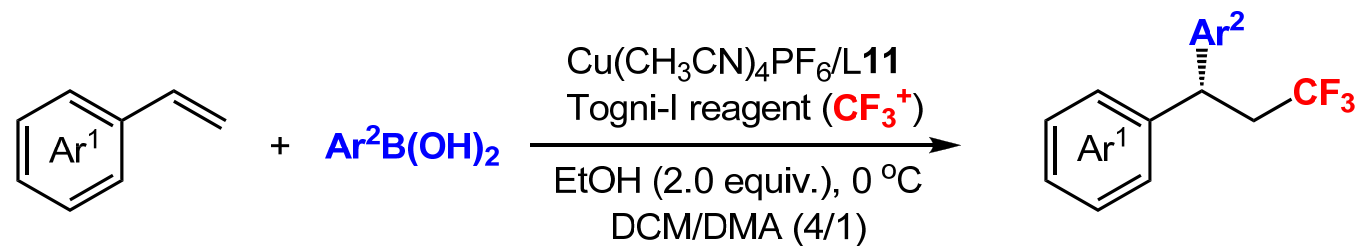


65%, 88% ee

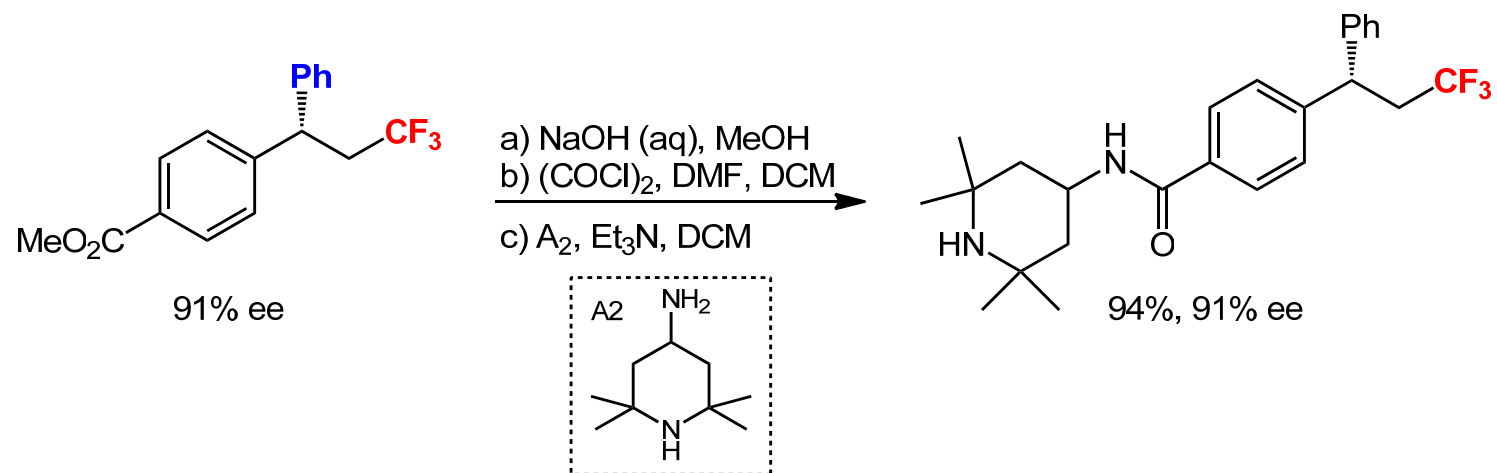
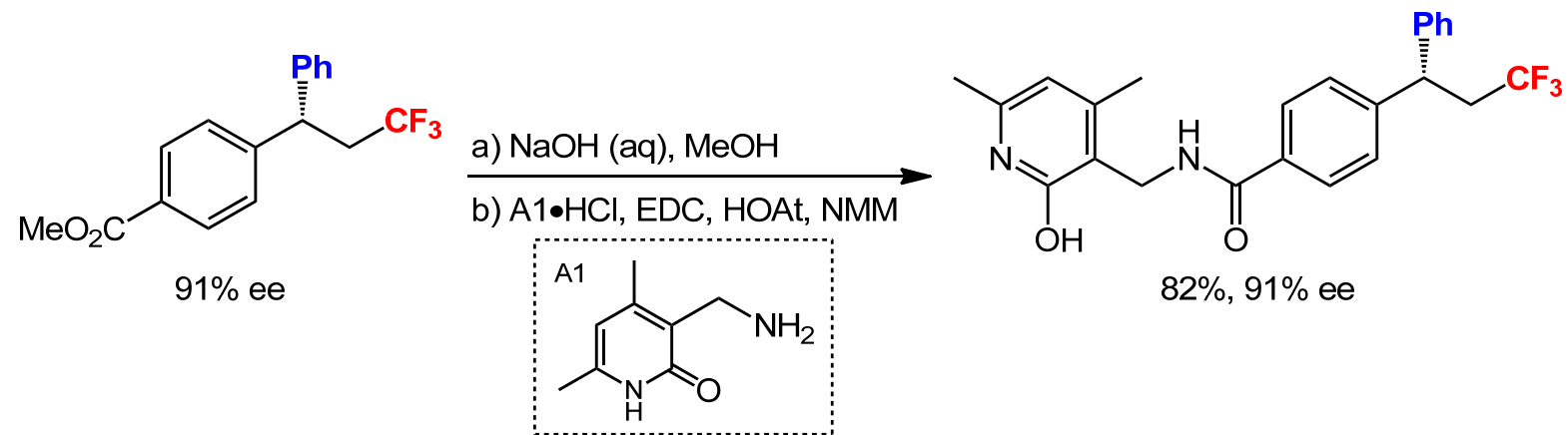


77%, 90% ee

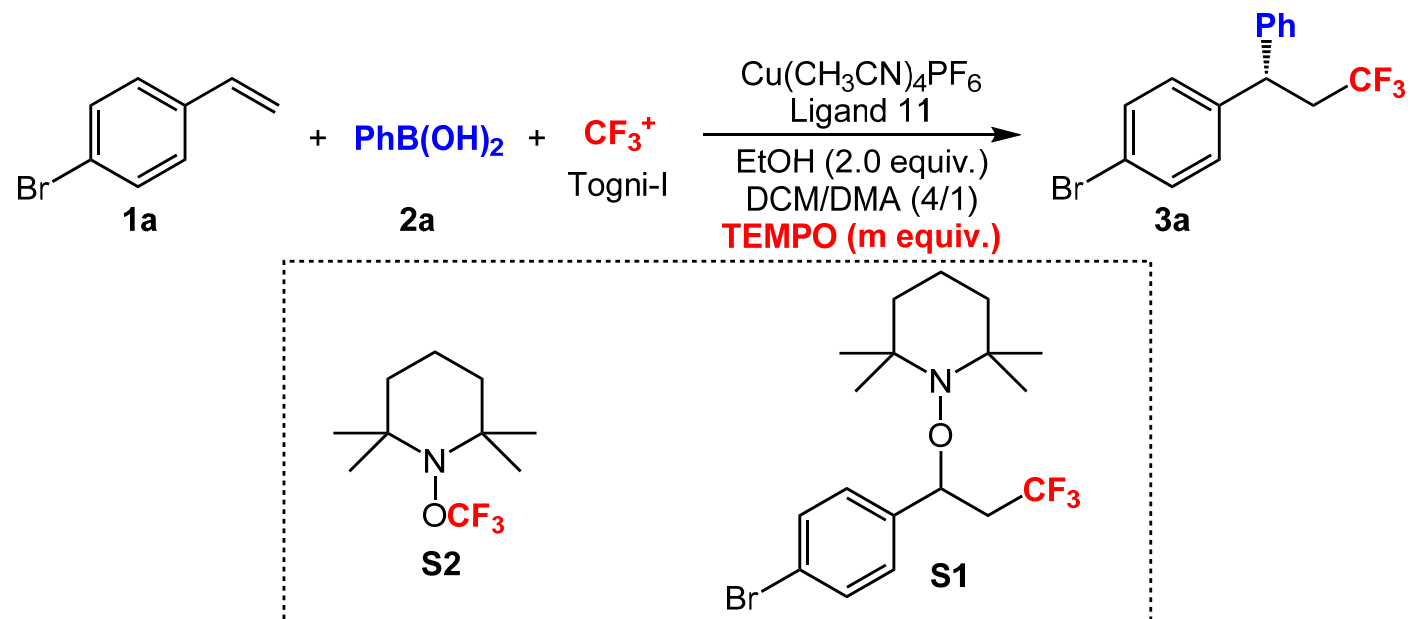
# Substrate Scope



# Transformation Experiments



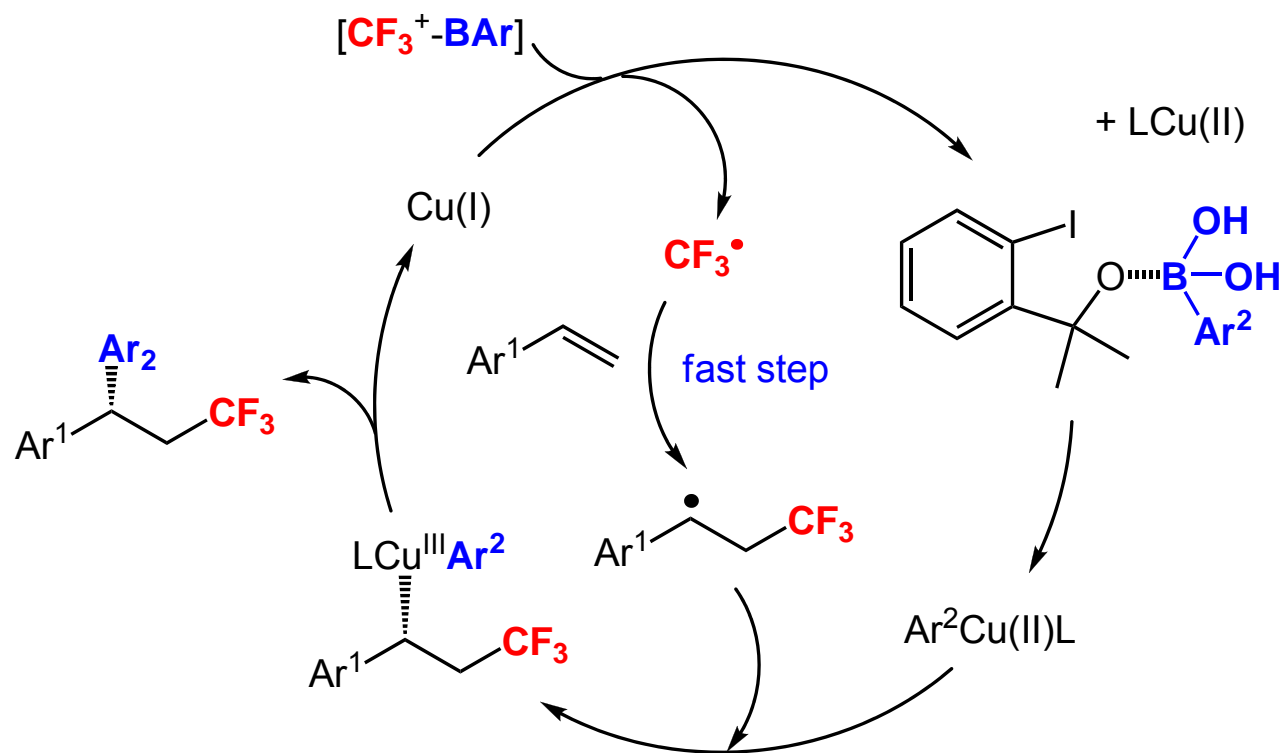
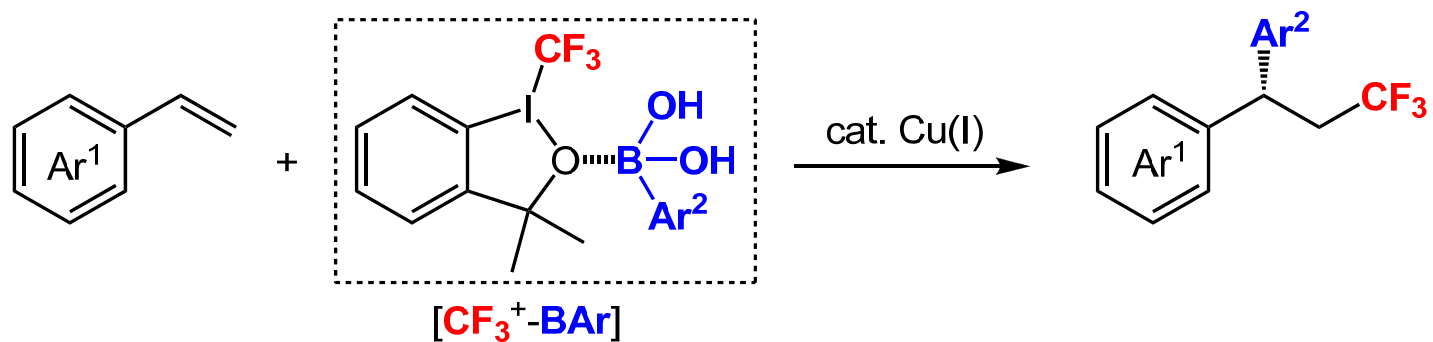
# Mechanistic Study



Yield of the product (%)

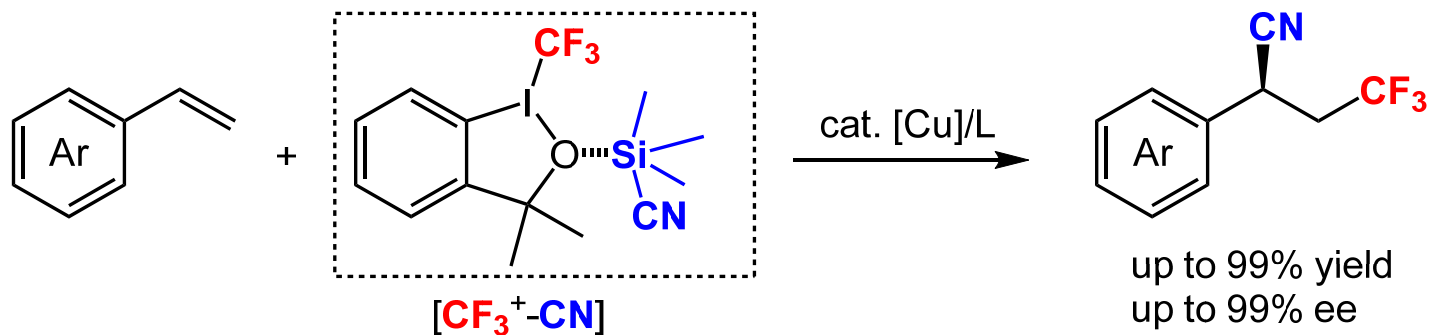
entry	<i>m</i>	<b>3a</b>	<b>S1</b>	<b>S2</b>
1	0.5	46	8	8
2	0.8	28	10	31
3	2.0	no	12	94

# Proposed Mechanism



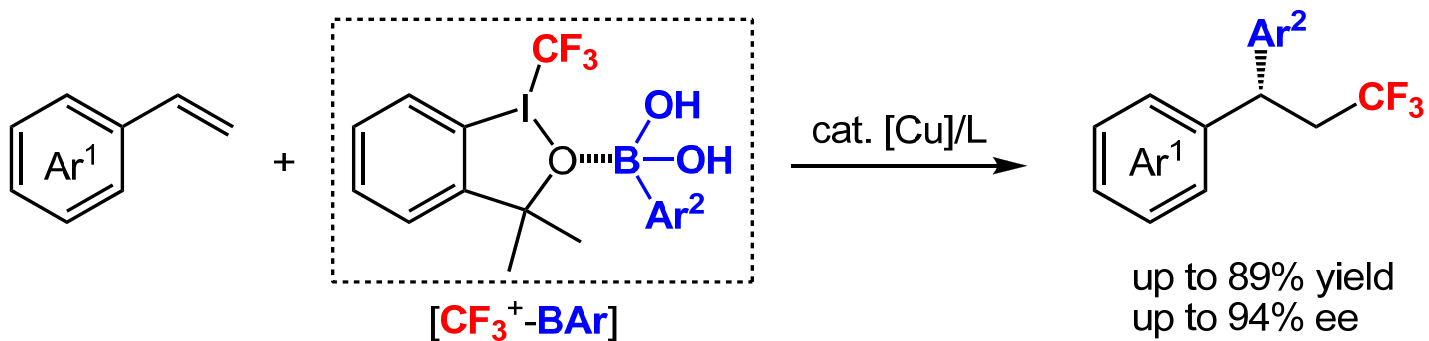
# Summary

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Liu, G. *et al.* *J. Am. Chem. Soc.* **2016**, 138, 15547.

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Liu, G. *et al.* *J. Am. Chem. Soc.* **2017**, 139, 2904.

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# The first paragraph

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Tertiary stereocenters with two aryl substituents are important core structures in natural products and bioactive compounds, such as Haplopappin and Cucumerin A. Thus, many efforts have made toward the enantioselective synthesis of 1,1-diarylalkanes, including asymmetric hydrogenation, nucleophilic addition of activated alkenes, and cross-coupling reactions with chiral benzylic electrophiles or nucleophiles. Recently, Fu and co-workers reported an elegant Ni-catalyzed asymmetric radical transformation (ART), which enabled the synthesis of optically active 1,1-diarylalkanes from achiral benzylic electrophiles and aryl zinc reagents.

# The last paragraph

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In summary, we have developed a copper-catalyzed enantioselective trifluoromethylarylation of alkenes. **The present process serves as a versatile, efficient, and convenient approach for the rapid access of chiral CF<sub>3</sub>-containing diarylalkane derivatives.** A broad range of substrates with various functional groups exhibit good to excellent enantioselectivity. Future efforts will focus on the exploring mechanistic details and new asymmetric radical transformations based on this chemistry.