Palladium-Catalyzed Arylhalogenation of Alkenes

Reporter: Bo Song
Checker: Yue Ji
Date: 2015/10/20

Toste, F. D. *et al.*
J. Am. Chem. Soc. **2015**, *137*, 12207.

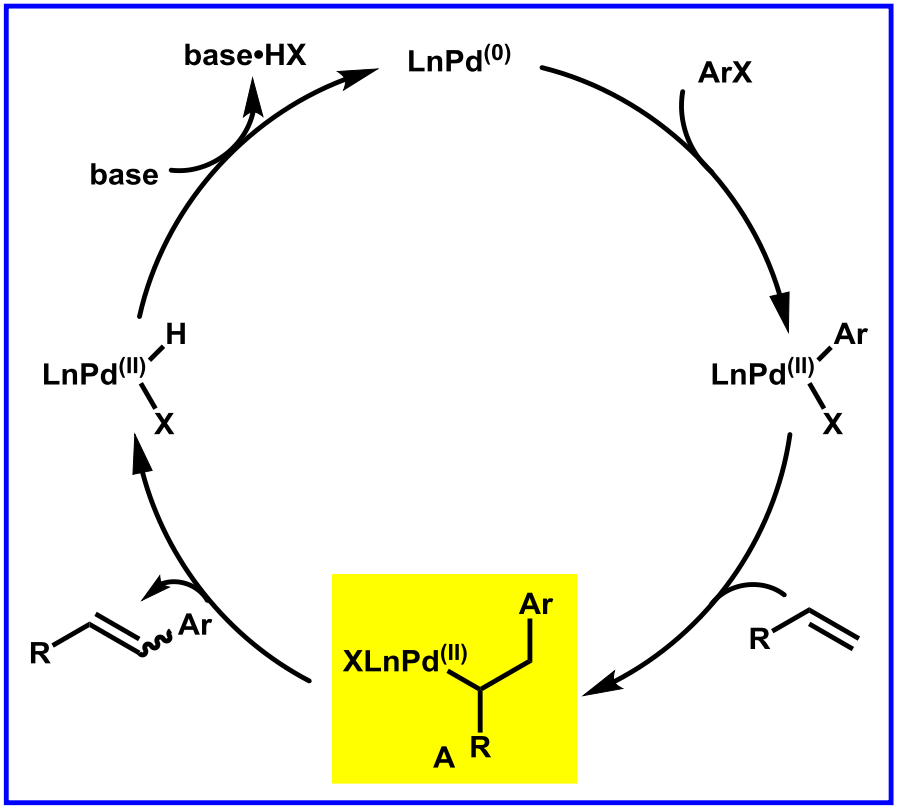
F. Dean Toste
University of California

Contents

- Introduction
- Pd-Catalyzed 1,1 and 1,2-Arylhalogenation
- Pd-Catalyzed Enantioselective 1,1 and 1,2-Arylfluorination
- Summary

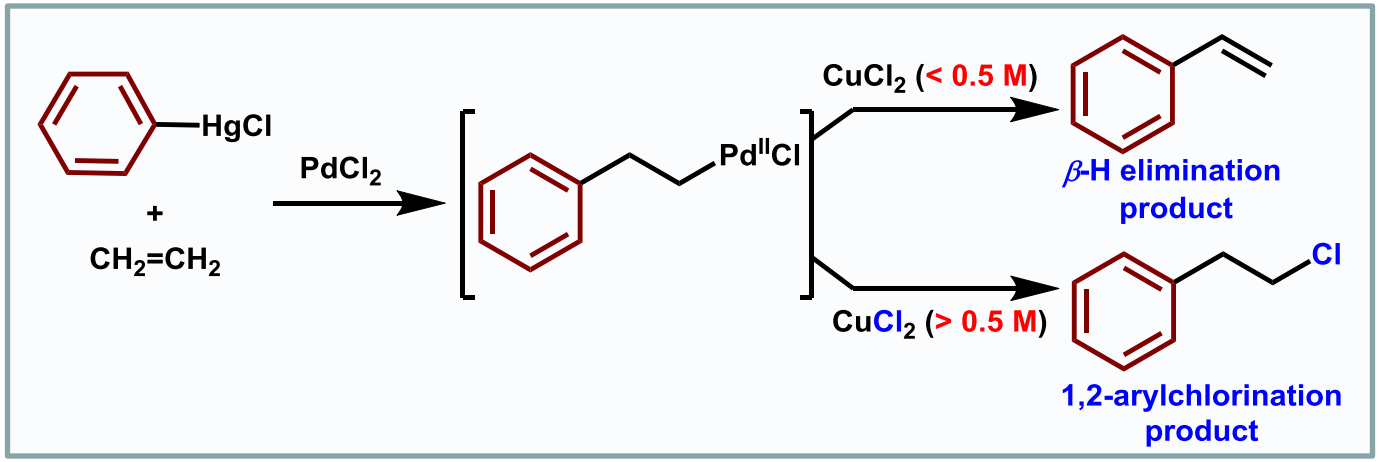
Introduction

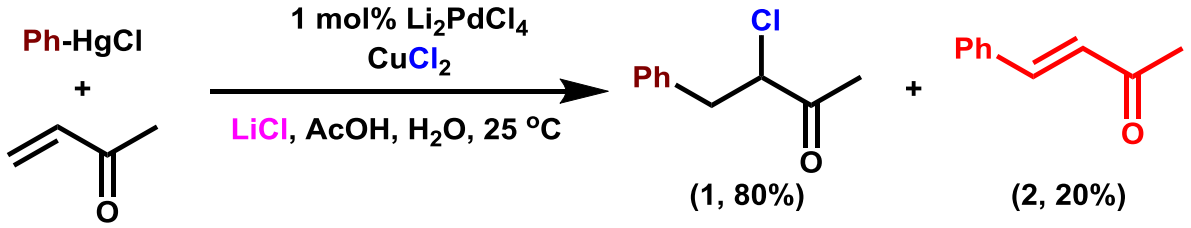
Mizoroki-Heck Reaction (沟吕木-赫克反应)



Mizoroki, T. *et al. Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
Heck, R. F. *et al. J. Org. Chem.* **1972**, *37*, 2320.

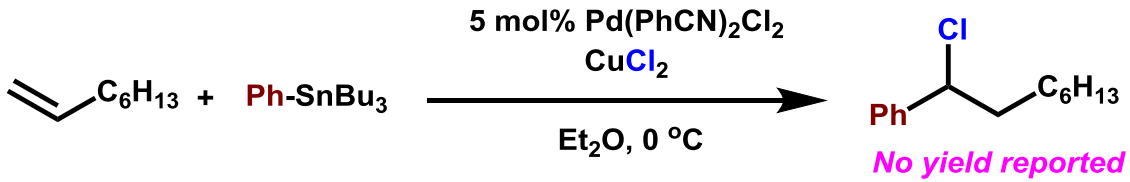
Introduction



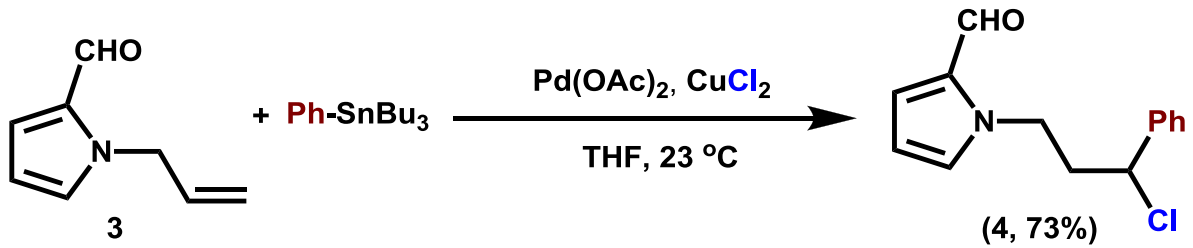


Heck, R. F. *et al. J. Am. Chem. Soc.* **1968**, *90*, 5538.

Introduction

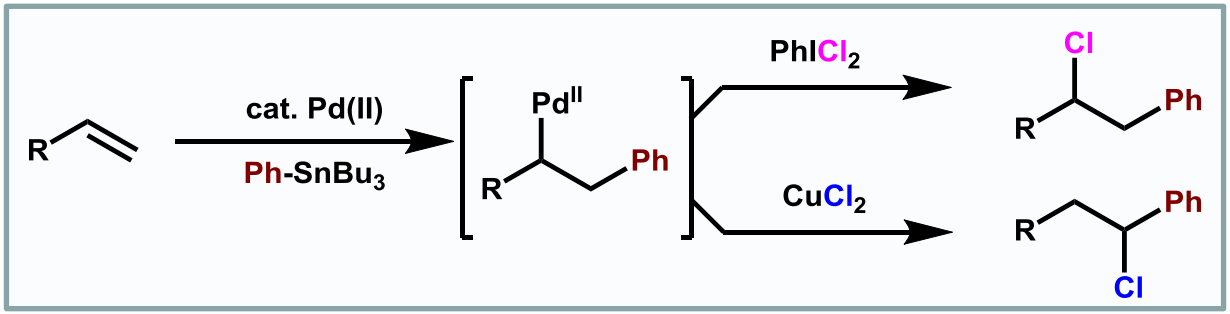


Yoshida, Z. *et al. J. Org. Chem.* **1986**, *51,* 4089.



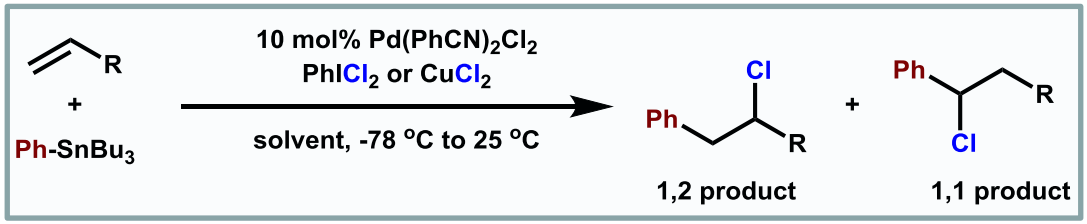
Jung, K. W. *et al. J. Org. Chem.* **2002**, *67*, 7127.

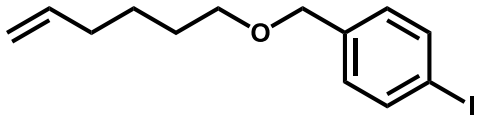
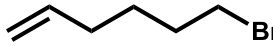
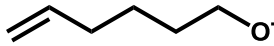
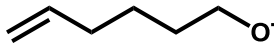
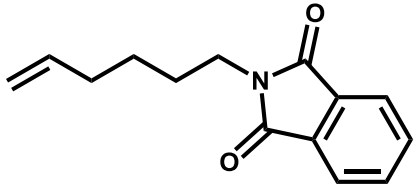
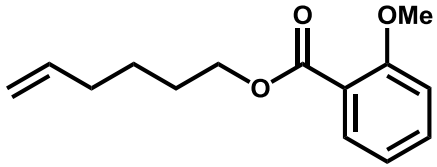
Pd-Catalyzed 1,2- and 1,1-Arylchlorination



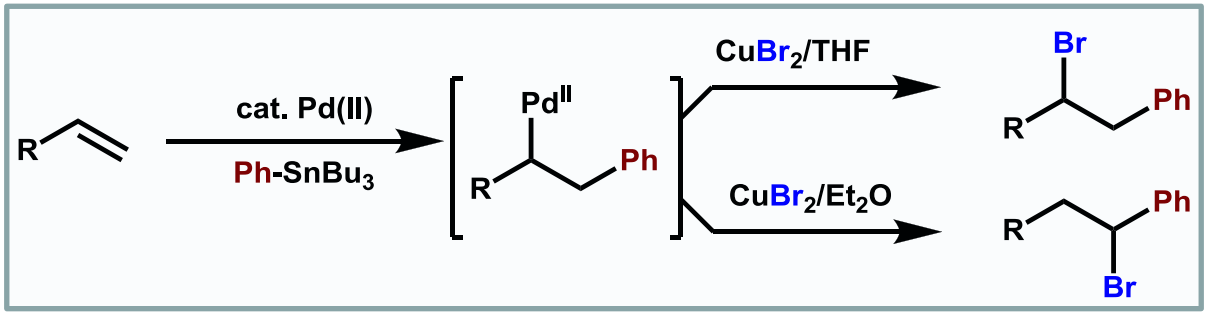
Sanford, M. S. *et al. J. Am. Chem. Soc.* **2008**, *130*, 2150.

Pd-Catalyzed 1,2- and 1,1-Arylchlorination



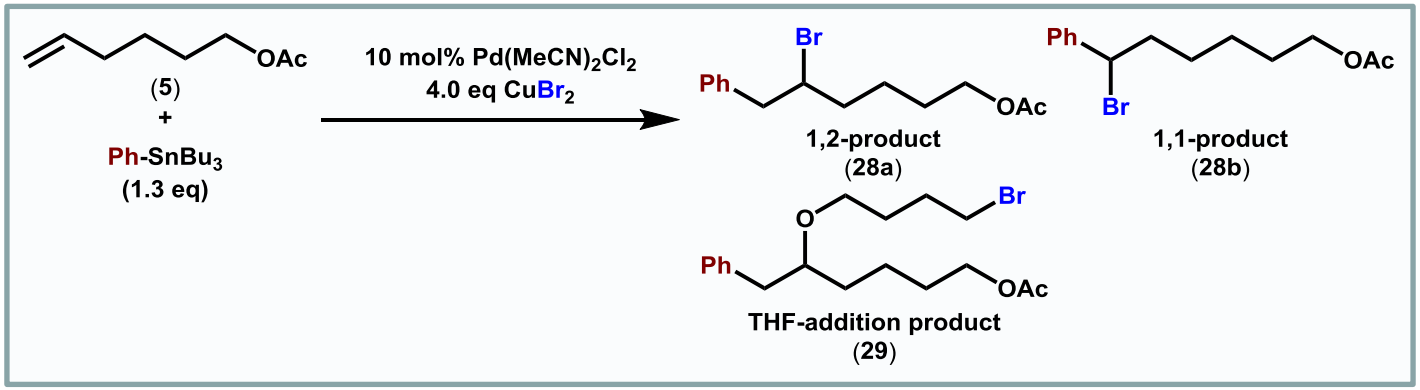
entry	substrates	$PhICl_2$: yield $CuCl_2$: yield	1,2:1,1 1,2:1,1
1		72% 53%	8:1 <1:20
2		84% 54%	13:1 <1:20
3		96% 71%	9:1 <1:20
4		92% 66%	11:1 <1:20
5		85% 71%	6:1 <1:20
6		86% 41%	8:1 <1:20

Pd-Catalyzed 1,2- and 1,1-Arylbromination



Sanford, M. S. *et al. J. Am. Chem. Soc.* **2010**, *132*, 8419.

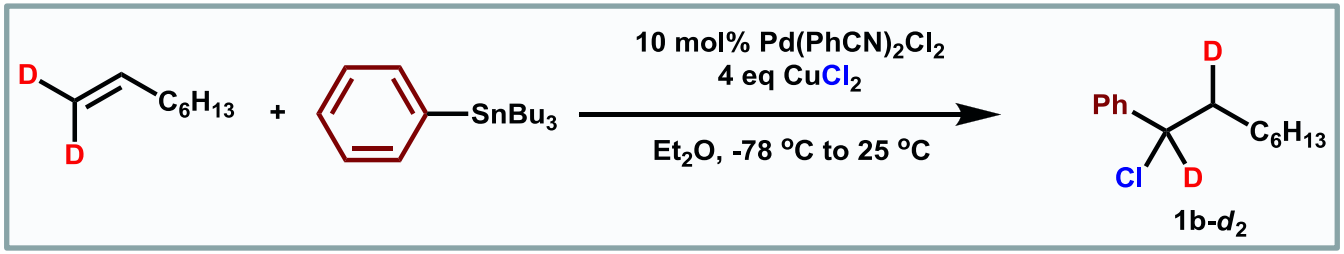
Pd-Catalyzed 1,2- and 1,1-Arylbromination

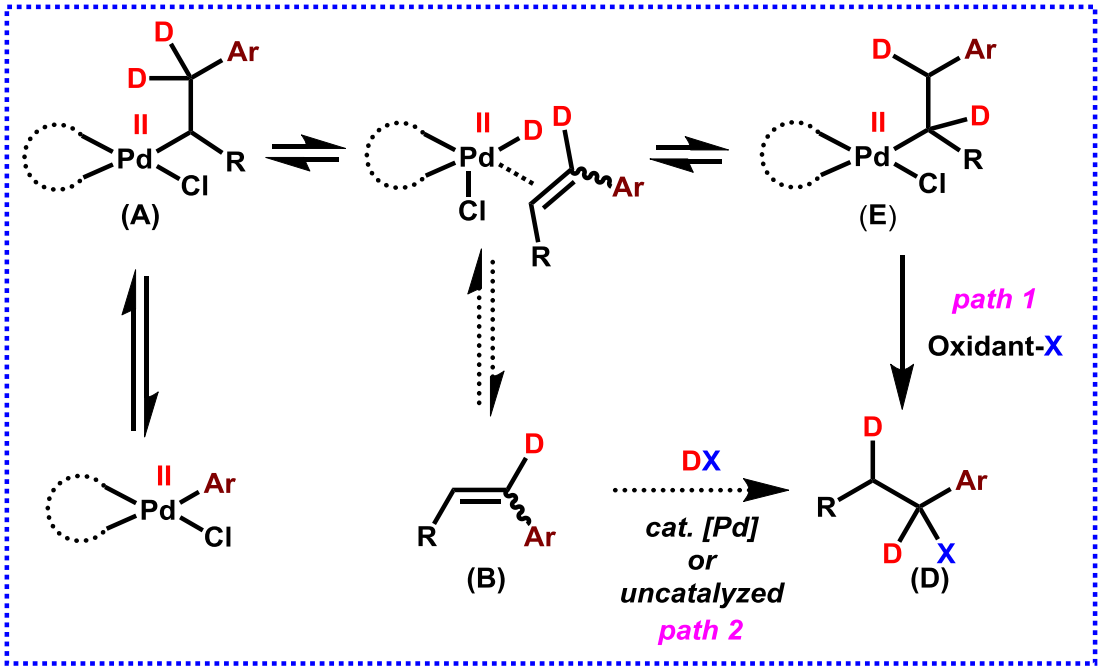


entry	solvent	t (°C)	yield (%)[a]	**28a**:**28b**[a]
1	dioxane	25	29	1:>20
2	C_6H_6	25	24	1:13
3	AcOH	25	16	1:>20
4	CH_2Cl_2	25	27	1:>20
5	Et_2O	25	46	1:>20
6	Et_2O	-78 to 25	82	1:>20
7	THF	25	25	1:>20
8	THF	-78 to 25	49 (17)	3:1
9[b]	THF	-78 to 25	50 (5)	10:1
10[b]	THF	-78 to 25	80% (20)	10:1

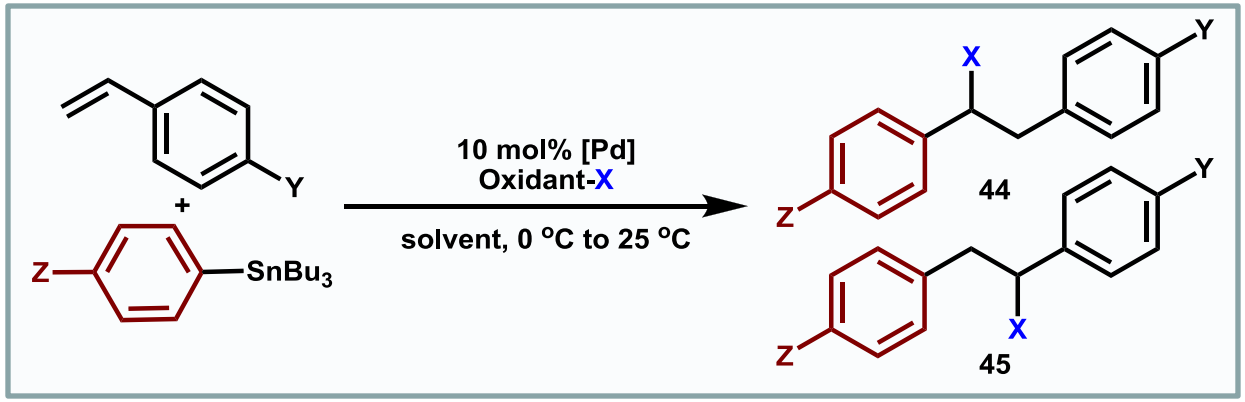
[a] Yield and ratio of isomers determined by ^{1}H NMR of crude reaction mixture. The yield of **29** is shown in parentheses where applicable. [b] Concentration of reactions was 0.032 M for entries 1-8, 0.064 M for entry 9 and 0.128 M for entry 10.

Experiments for Mechanistic Research

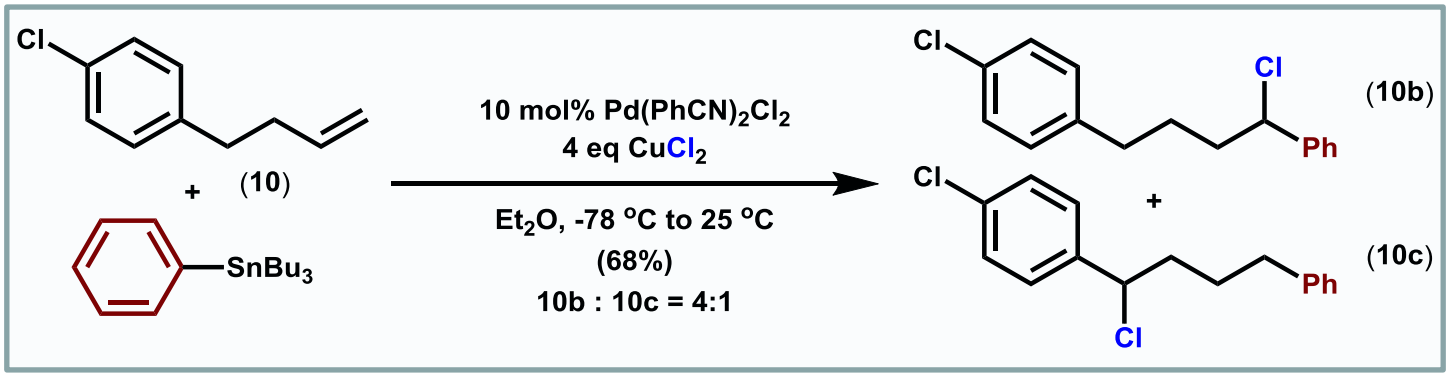




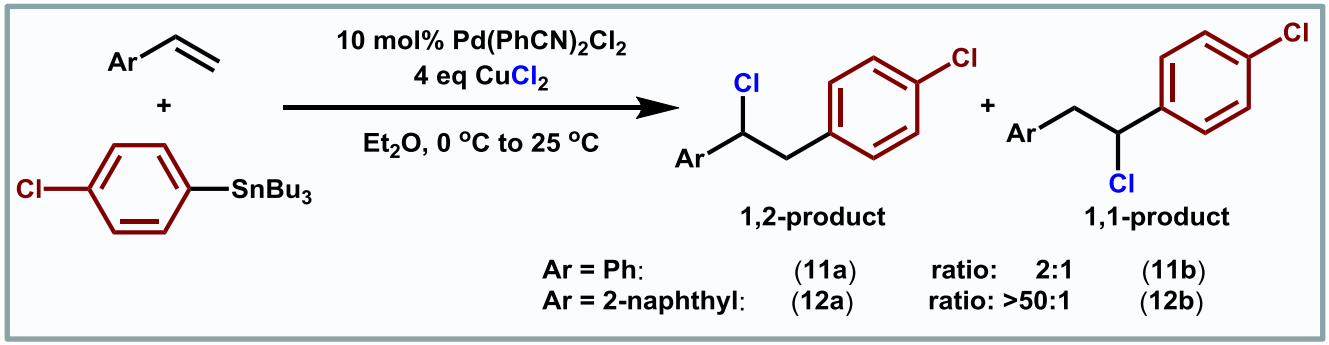
Experiments for Mechanistic Research

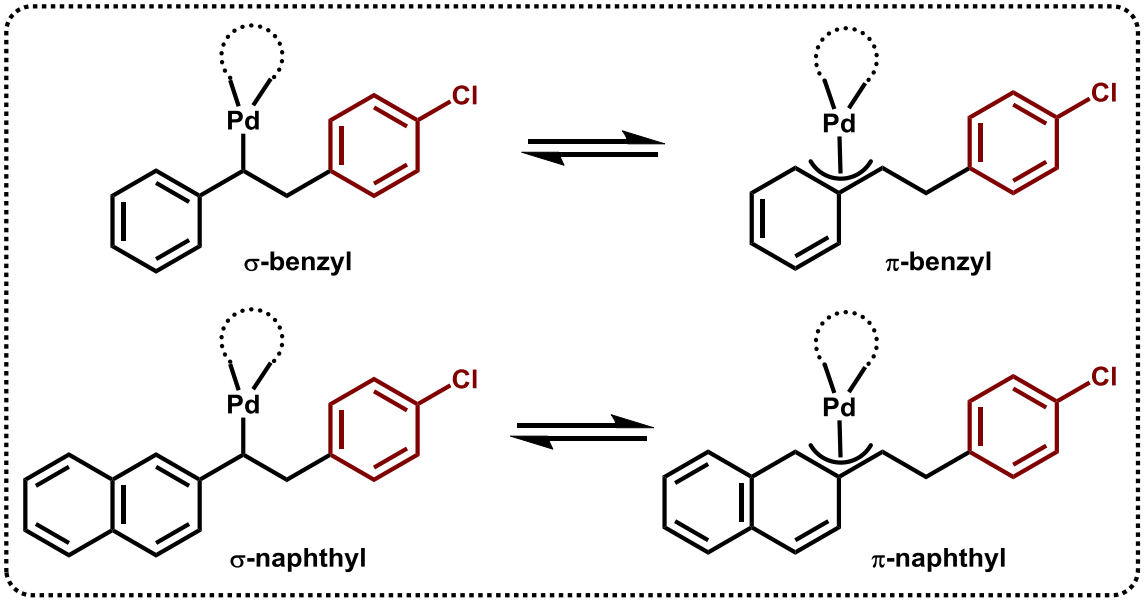


entry	X	Y	Z	yield	ratio 1,2:1,1
1	Cl	F	H	48%	1.4:1
2	Cl	H	F	50%	2.2:1
3	Br	F	H	69%	9:1
4	Br	H	F	50%	24:1



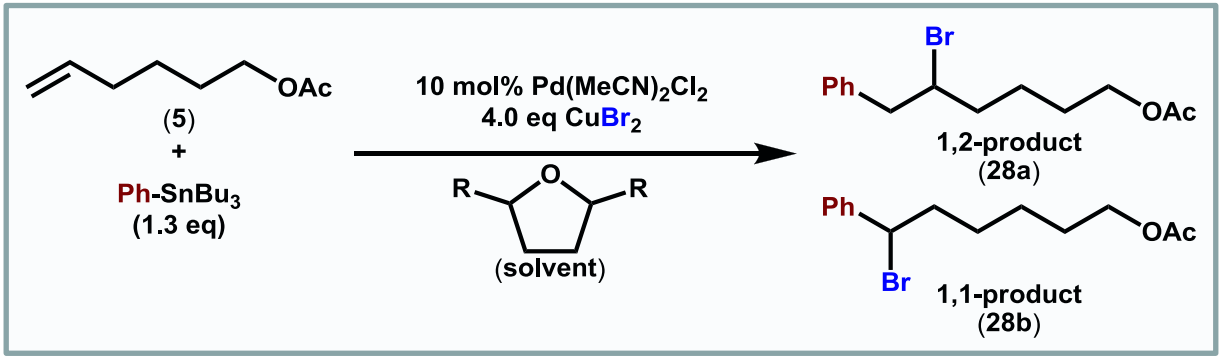
Experiments for Mechanistic Research





Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2006**, *128*, 1828.

Effect of Substituted THF on the Selectivity

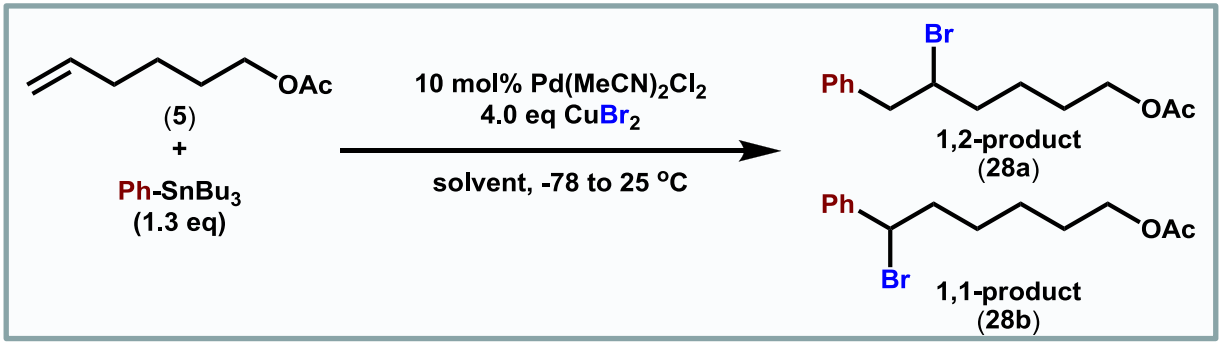


entry	solvent	yield (%)[a]	**28a**:**28b**[a]
1	THF	80	15:1
2	Me-THF[b]	37	1.5:1
3	Me_2-THF[c]	57	1.8:1

[a] Yield and ratio of isomers determined by ^{1}H NMR of crude reaction mixture. [b] Me-THF, 2-methyltetrahydrofuran.[c] Me_2-THF, 2,5-dimethyltetrahydrofuran

Me-THF and Me_2-THF are expected to have very similar polarity but significantly poorer coordinating capabilities than THF. Thus, this result suggests that THF coordination (to either Pd or Cu) may play a key role in switching the selectivity.

Effect of Aprotic Solvents on the Selectivity

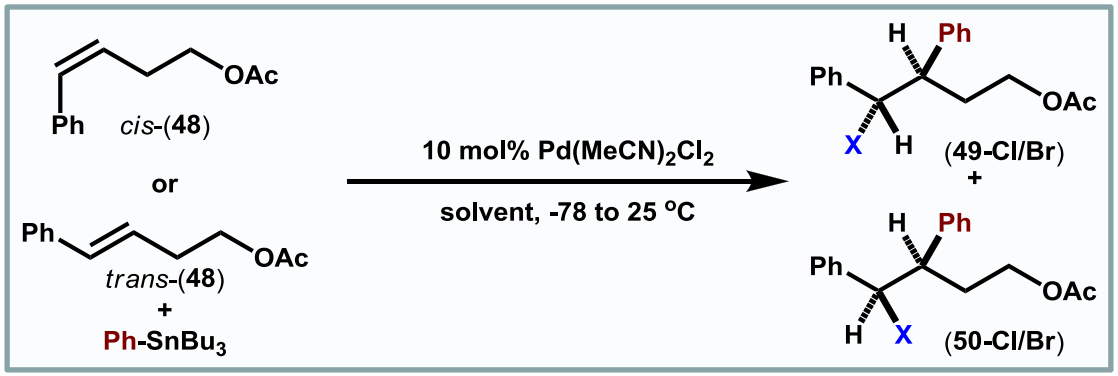


entry	solvent	ε	yield (%)[a]	**28a**:**28b**[a]
1	THF	7.58	49	3.4:1
2	1,2-Dimethoxyethane	7.2	14	>20:1
3	EtOAc	6.02	63	1:8
4	$CHCl_3$	4.81	45	1:>20
5	Et_2O	4.33	82	1:24
6	Anisole	4.33	23	1:>20
7	$^{i}Pr_2O$	3.9	76	1:5.9
8	MTBE	2.6	56	1:>20
9	Dioxane	2.25	30	1:20

[a] Yield and ratio of isomers determined by ^{1}H NMR of crude reaction mixture.

Polar coordinating solvents are likely to enhance the solubility of $CuBr_2$, which should increase the rate of oxidative bromination relative to that of β–hydride elimination.

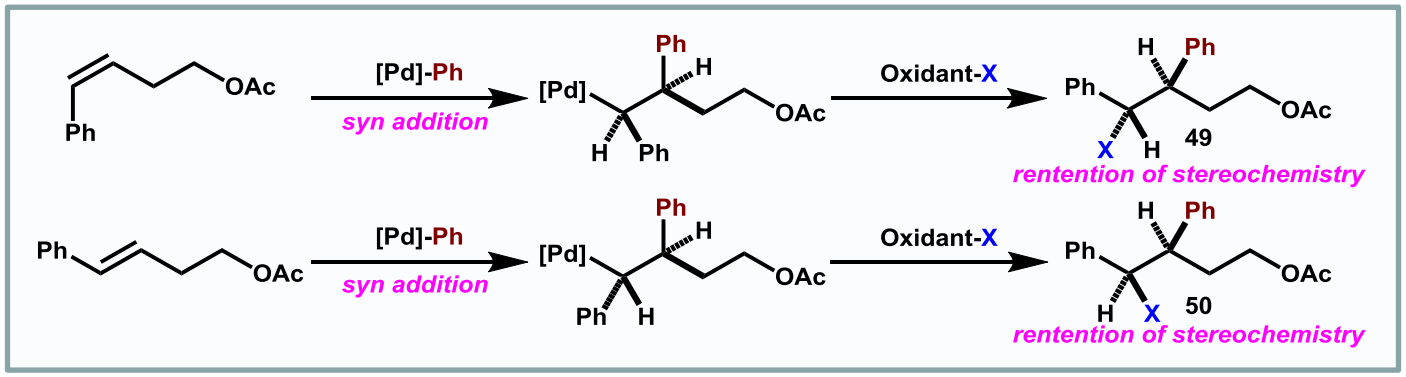
Mechanistic Research for Stereochemistry

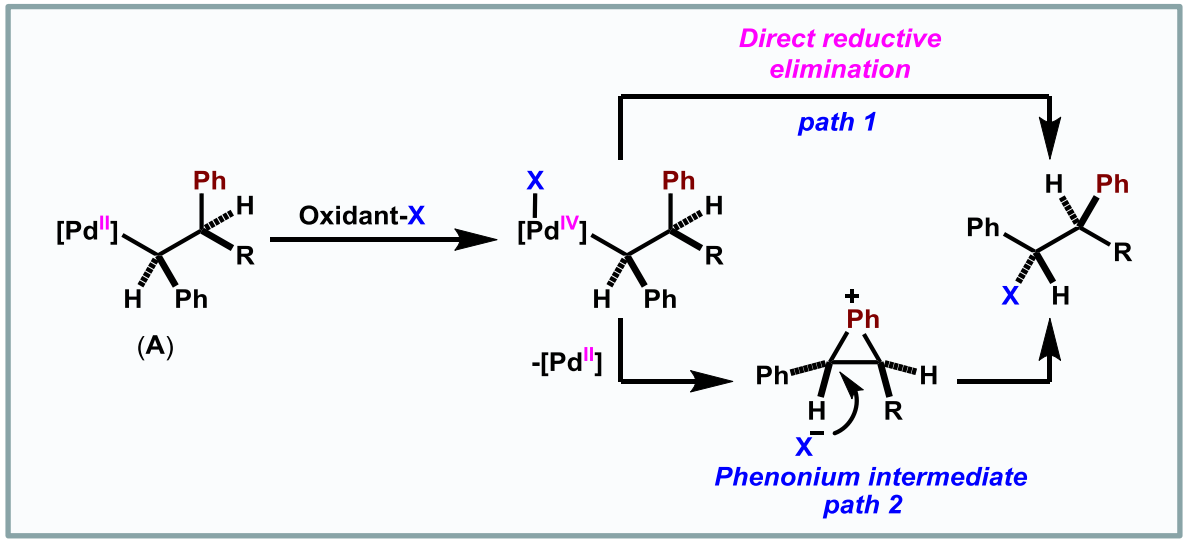


entry	substrate	oxidant	solvent	yield (%)[a]	**49**:**50**[a]
1	*cis*-**48**	$PhICl_2$	CH_2Cl_2	40%	12:1
2	*cis*-**48**	$CuCl_2$	Et_2O	51%	>30:1
3	*cis*-**48**	$CuBr_2$	Et_2O	41%	5:1
4	*trans*-**48**	$PhICl_2$	CH_2Cl_2	21%	1:1.6
5	*trans*-**48**	$CuCl_2$	Et_2O	45%	1:8
6	*trans*-**48**	$CuBr_2$	Et_2O	9%	1:8

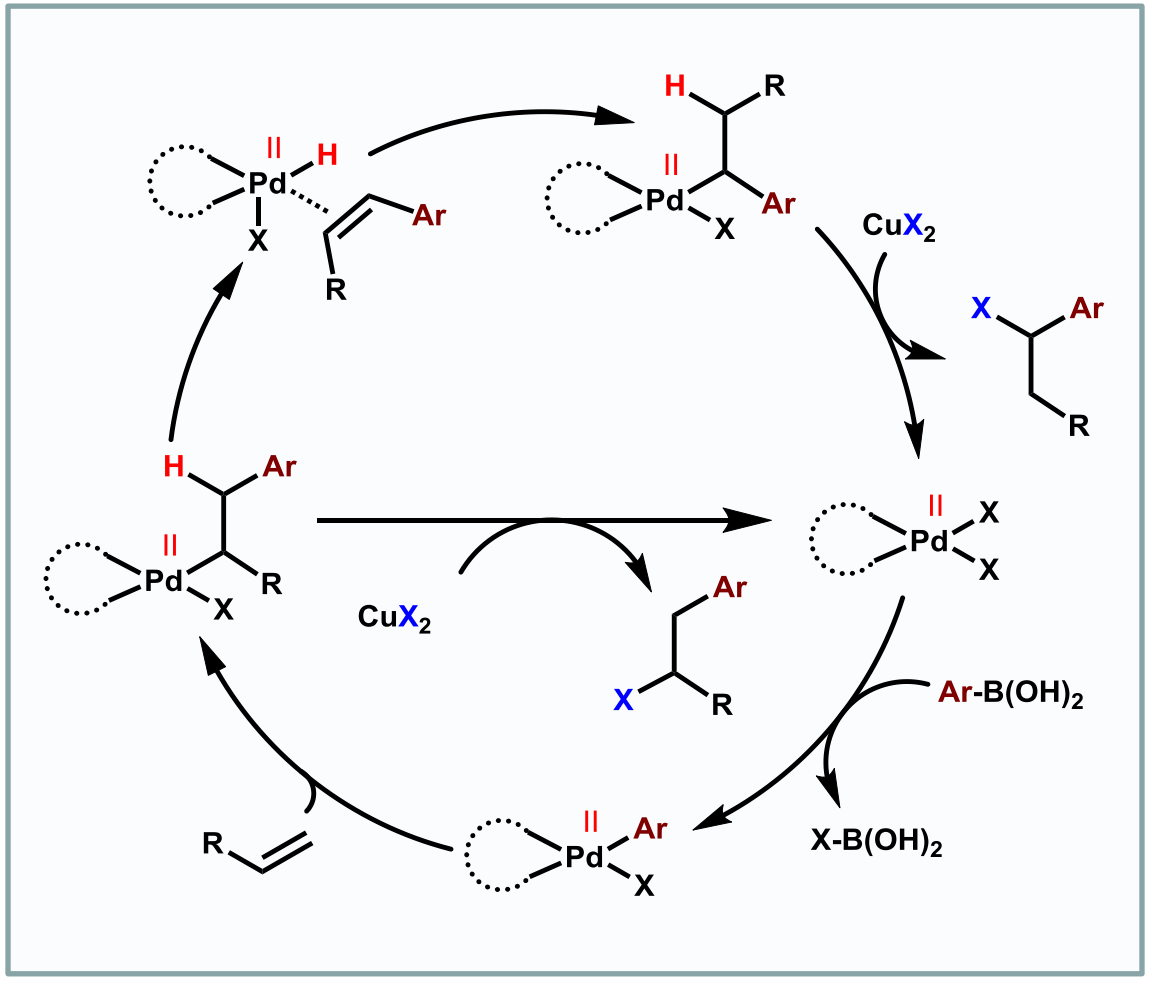
[a] Yield and ratio of isomers determined by ^1H NMR of crude reaction mixture.

Mechanistic Research for Stereochemistry

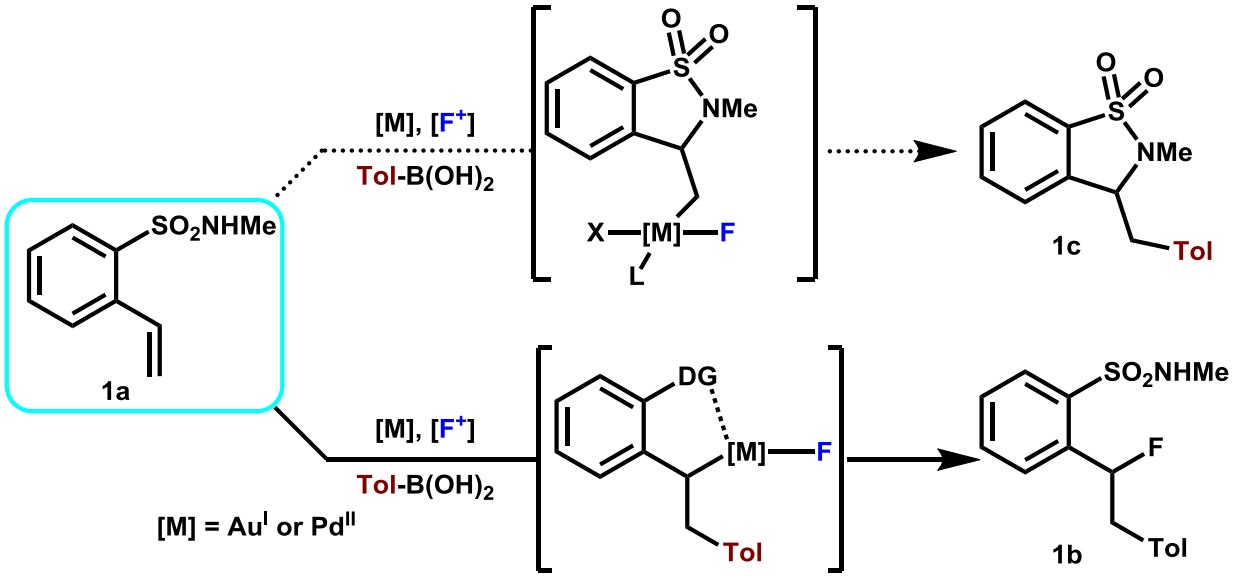


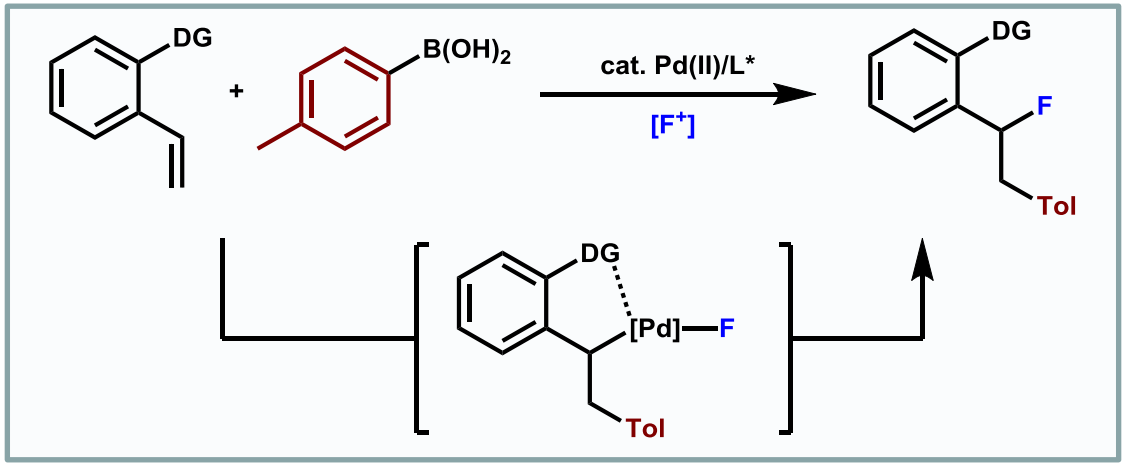


Proposed Mechanism for Arylhalogenation



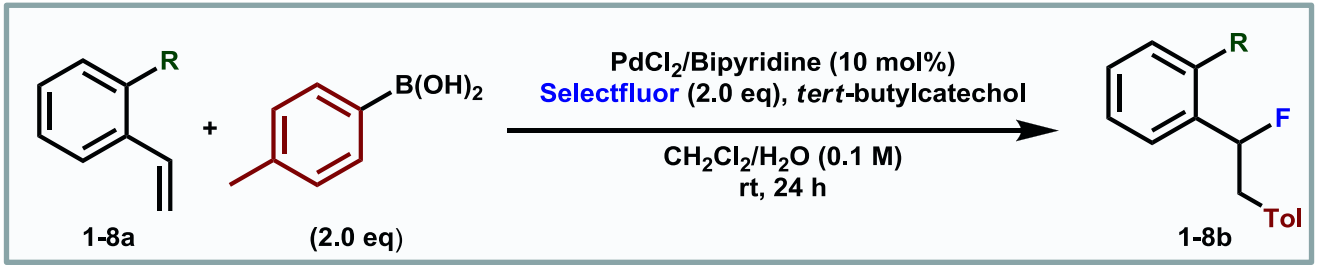
Pd-Catalyzed Enantioselective 1,2-Arylfluorination

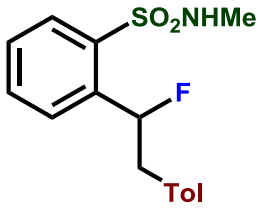




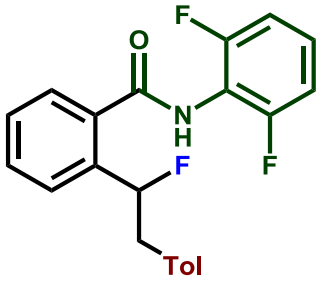
Toste, F. D. *et al. J. Am. Chem. Soc.* **2014**, *136*, 4101.

Screening of Suitable Directing Group

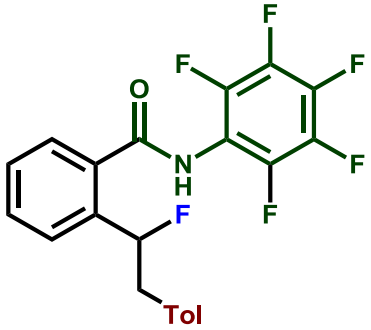




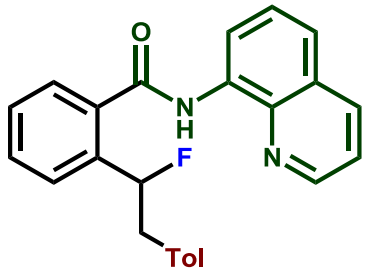
1b, 57%



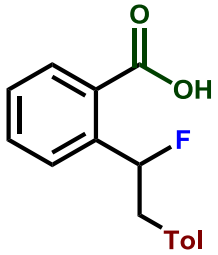
2b, 55%



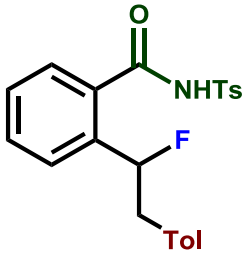
3b, 45%



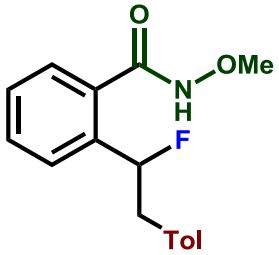
4b, 54%



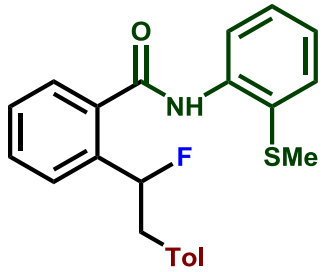
5b, 0%



6b, 0%

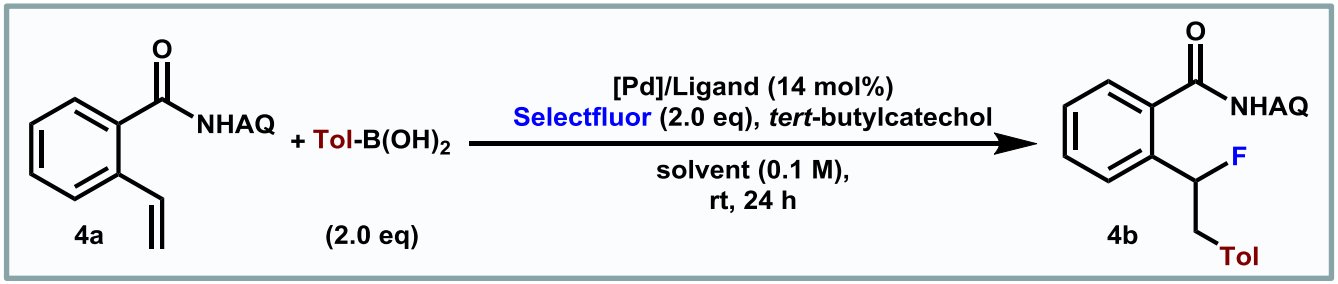


7b, 0%

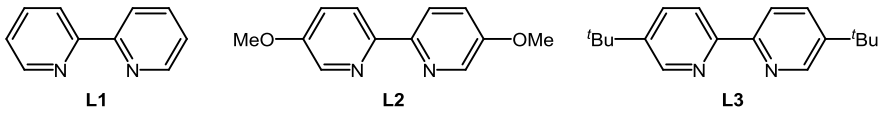


8b, 0%

Pd-Catalyzed 1,2-Arylfluorination

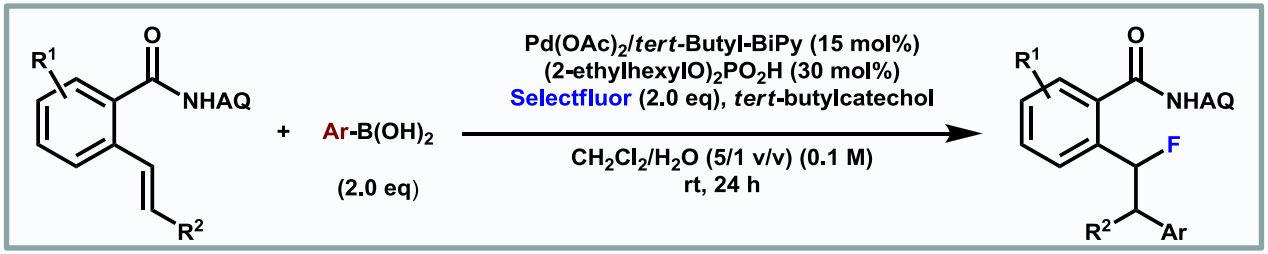


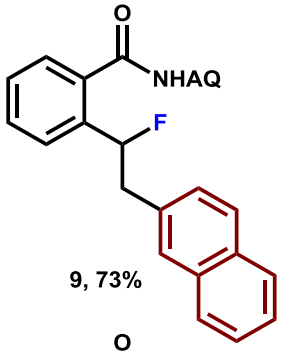
entry	[Pd]	ligand	solvent	additive[b]	yield (%)[c]
1	$PdCl_2$	**L1**	CH_2Cl_2/H_2O (1/0.1)	--	54
2	$Pd(OAc)_2$	**L1**	CH_2Cl_2/H_2O (1/0.1)	--	67
3	$PdBr_2$	**L1**	CH_2Cl_2/H_2O (1/0.1)	--	54
4	$Pd(TFA)_2$	**L1**	CH_2Cl_2/H_2O (1/0.1)	--	61
5	$Pd(OAc)_2$	**--**	CH_2Cl_2/H_2O (1/0.1)	--	0
6	$Pd(OAc)_2$	**L2**	CH_2Cl_2/H_2O (1/0.1)	--	56
7	$Pd(OAc)_2$	**L3**	CH_2Cl_2/H_2O (1/0.1)	--	76
8	$Pd(OAc)_2$	**L3**	CH_2Cl_2	--	23
9	$Pd(OAc)_2$	**L3**	CH_2Cl_2/H_2O (1/0.2)	--	82
10	$Pd(OAc)_2$	**L3**	CH_2Cl_2/H_2O (1/0.2)	P1 (0.3 eq)	91(86)[d]
11	$Pd(OAc)_2$	**L3**	CH_2Cl_2/H_2O (1/0.2)	P1 (0.5 eq)	82
12	$Pd(OAc)_2$	**L3**	CH_2Cl_2/H_2O (1/0.2)	P2 (0.3 eq)	74



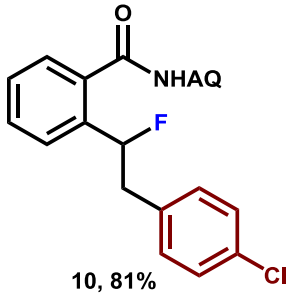
[b] P1: bis(2-ethylhexyl) hydrogen phosphate; P2: dibenzyl hydrogen phosphate. [c] Determined by correlation between HPLC-Ms and crude ^{1}H-NMR analysis. [d] Isolated yield.

Substrate Scope for AQ Directing Group

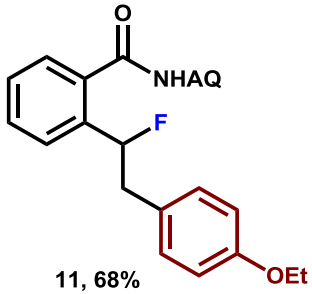




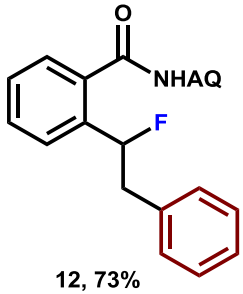
9, 73%



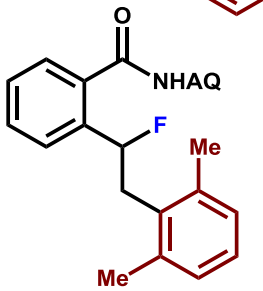
10, 81%



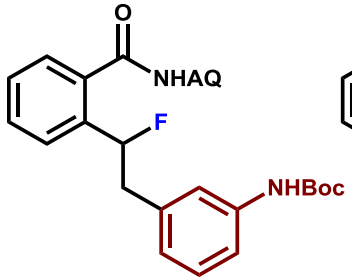
11, 68%



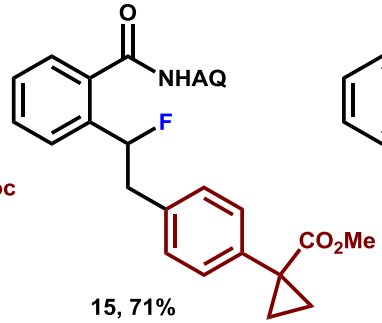
12, 73%



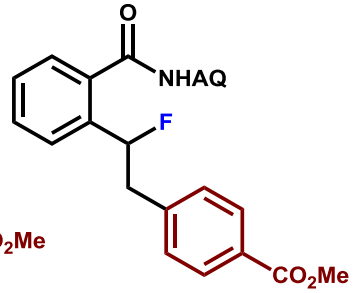
13, 45%



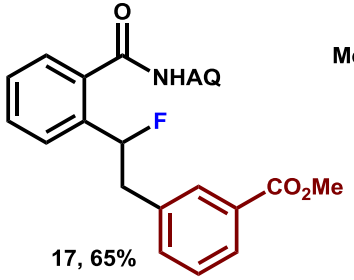
14, 62%



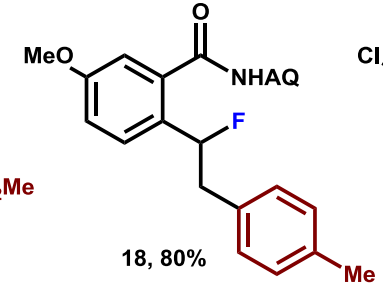
15, 71%



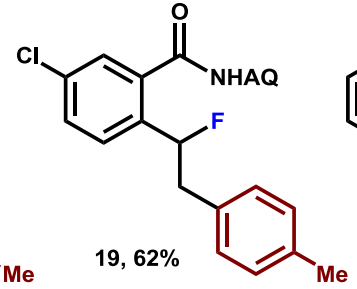
16, 43%



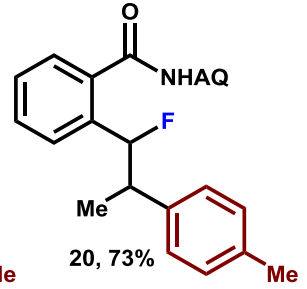
17, 65%



18, 80%

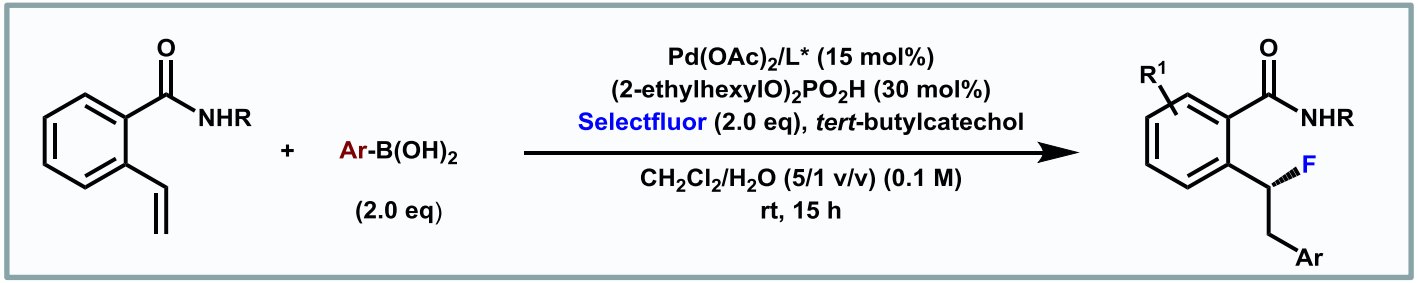


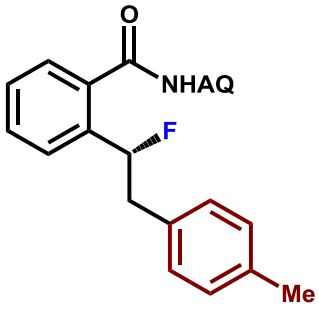
19, 62%



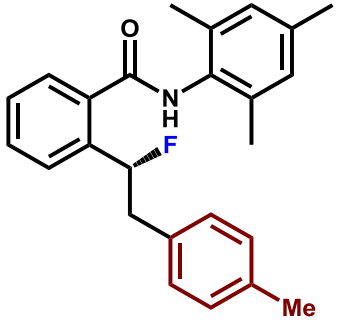
20, 73%

Substrate Scope for Enantioselective Arylfluorination

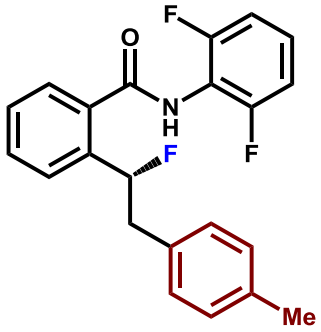




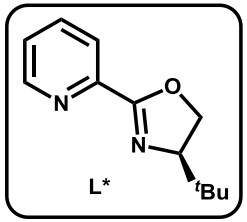
4b, 15%, 81% ee

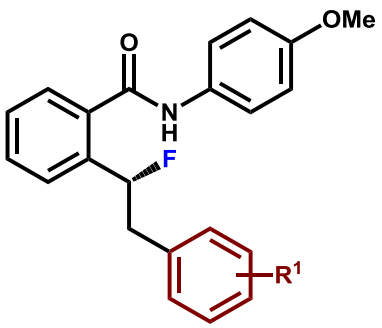


22, 72%,
76% ee

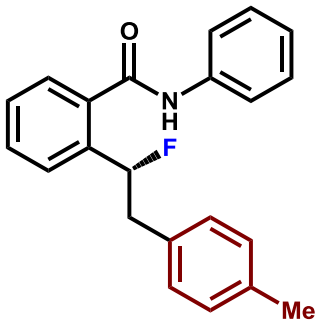


2b, 67%, 78% ee

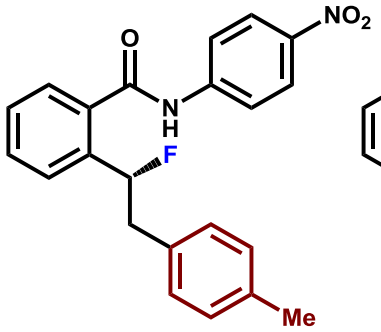




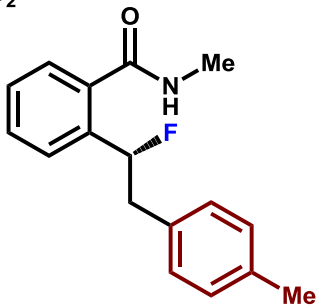
26 (R^1 = 4-Me), 74%, 96% ee
27 (R^1 = 4-Cl), 83%, 91% ee
28 (R^1 = 4-OEt), 71%, 83% ee
29 (R^1 = 3-F), 71%, 87% ee
30 (R^1 = 2,6-$(Me)_2$), 66%, 60% ee
31 (R^1 = H), 77%, 94% ee
32 (R^1 = Br), 60%, 90% ee



23, 76%, 96% ee

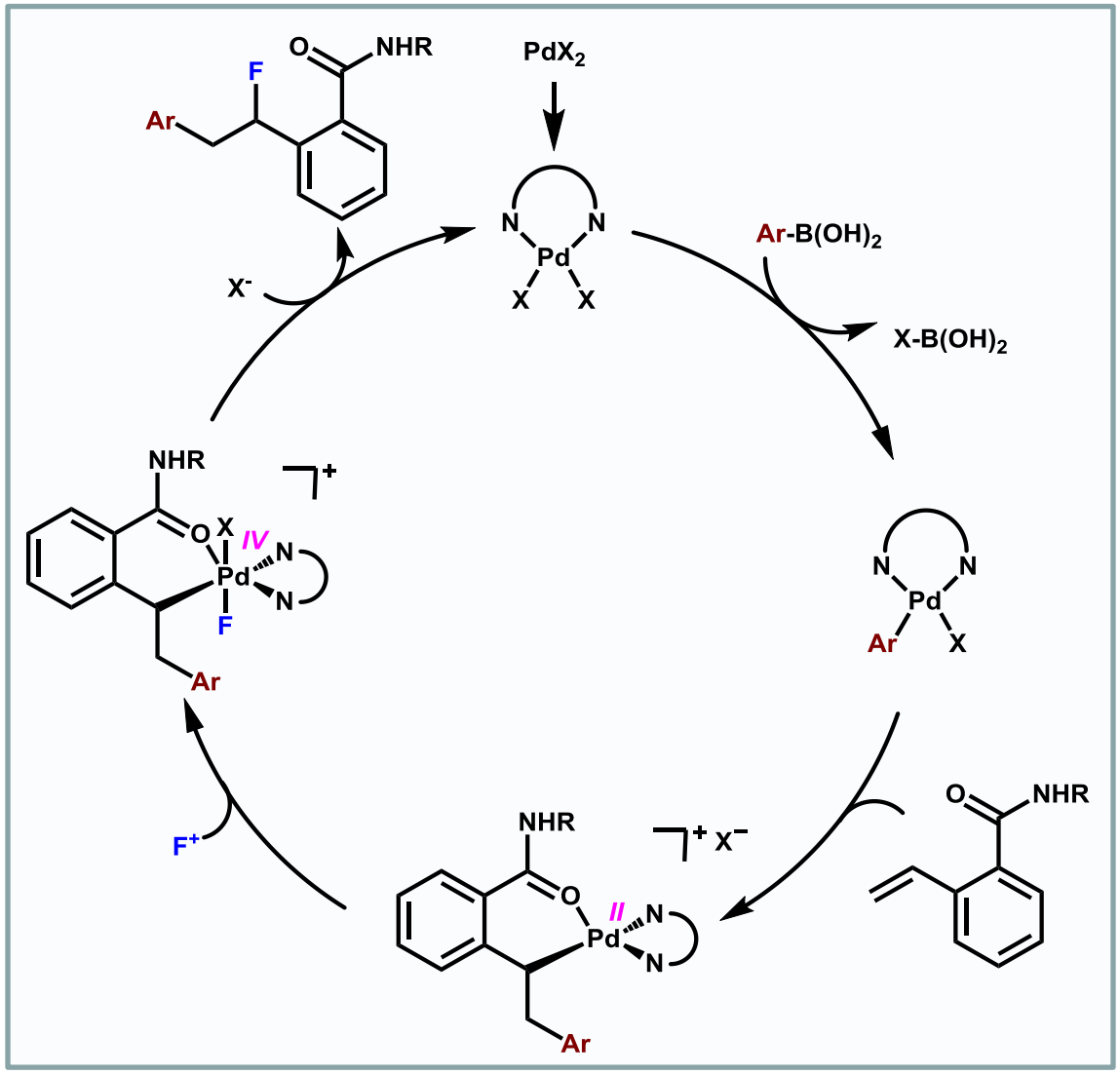


24, 73%, 93% ee

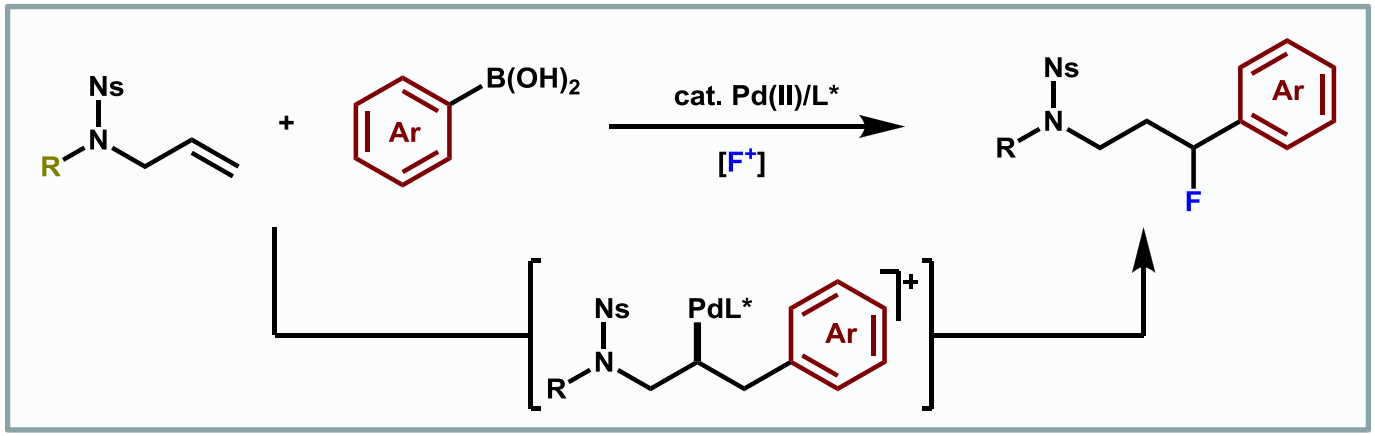


25, 47%, 92% ee

Proposed Mechanism for 1,1-Arylfluorination

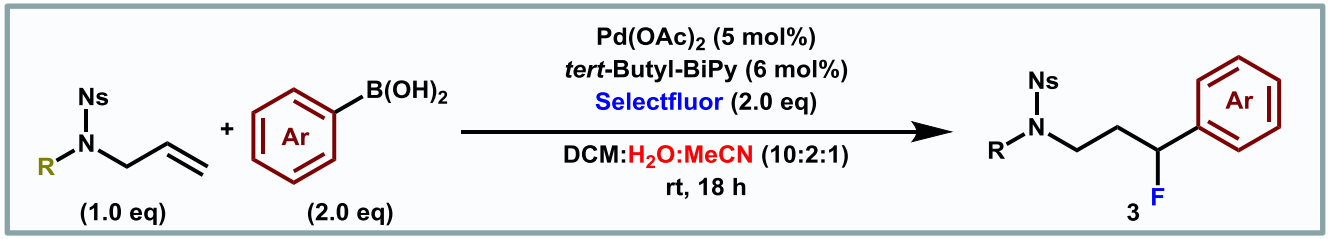


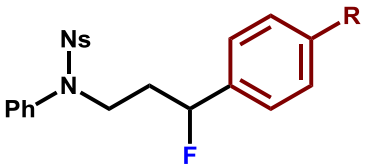
Pd-Catalyzed Enantioselective 1,1-Arylfluorination



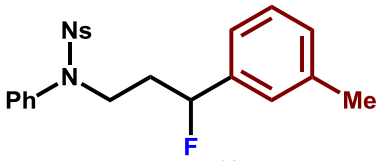
Toste, F. D. *et al. J. Am. Chem. Soc.* **2015**, *137*, 12207.

Substrate Scope

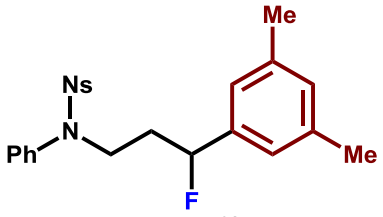




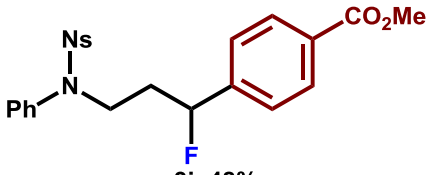
3a (R = H), 75%
3b (R = Me), 77%
3c (R = ^{t}Bu), 67%
3d (R = F), 68%
3e (R = Cl, 80%
3f (R = Br), 78%



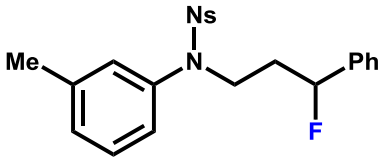
3g, 69%



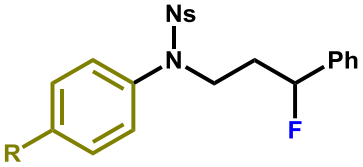
3h, 60%



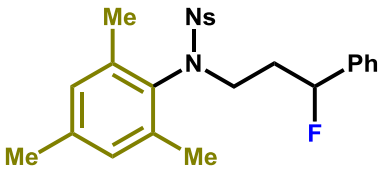
3i, 48%



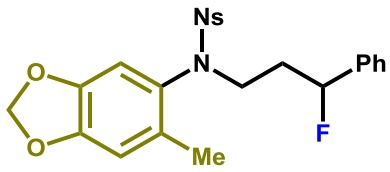
3j, 70%



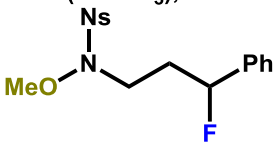
3k (R = MeO), 65%
3l (R = F), 72%
3m (R = F), 72%
3n (R = CF_3), 67%



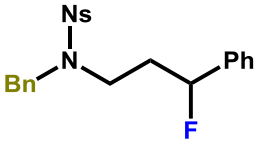
3o, 80%



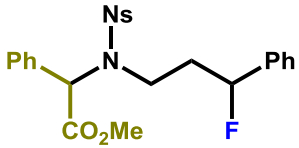
3p, 66%



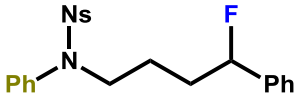
3q, 71%



3r, 68%

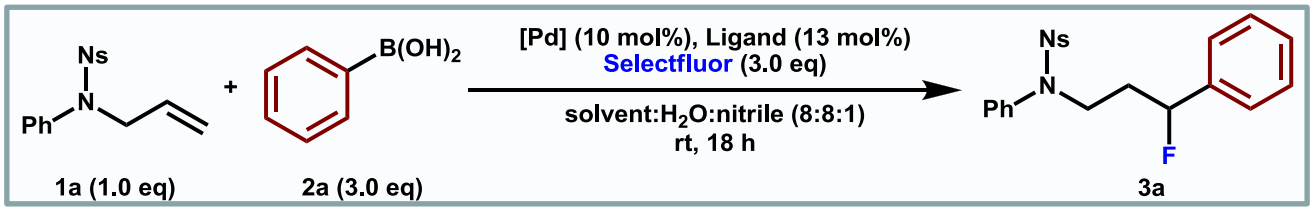


3s, 77%
(dr = 1.8 : 1)

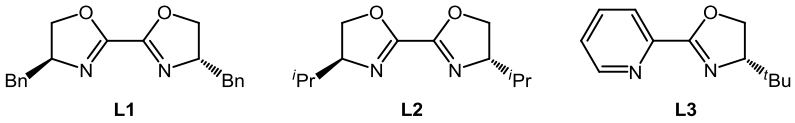


3t, 60%

Pd-Catalyzed Enantioselective 1,1-Arylfluorination

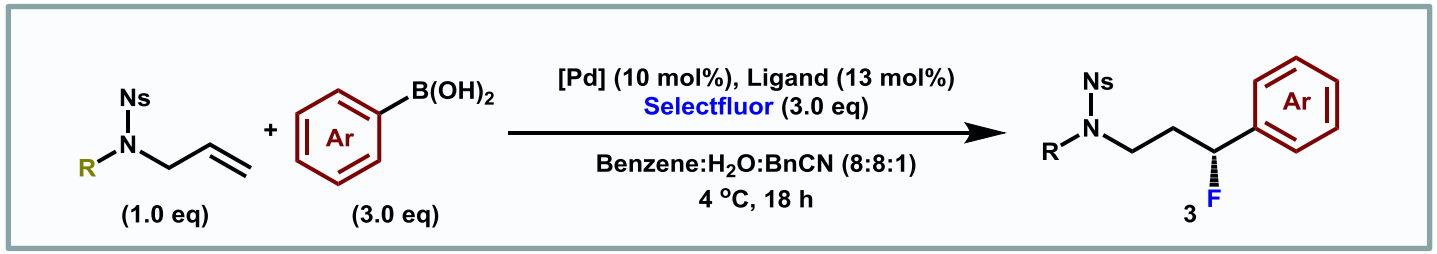


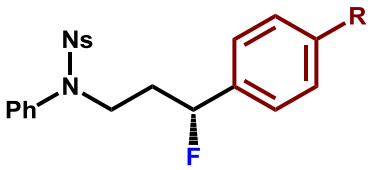
entry[a]	[Pd]	ligand	solvent	nitrile	ee (%)[b] (yield)[c]
1	$Pd(OAc)_2$	**L1**	CH_2Cl_2/H_2O	--	--
2	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	--	(trace)
3	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	MeCN	66(68%)
4	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	^{i}PrCN	82
5	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	BnCN	84
6	$Pd(MeCN)_2Cl_2$	**L2**	CH_2Cl_2/H_2O	BnCN	81
7	$Pd(MeCN)_2Cl_2$	**L3**	CH_2Cl_2/H_2O	BnCN	55
8	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2	BnCN	80
9	$Pd(MeCN)_2Cl_2$	**L1**	Benzene/H_2O	BnCN	87
10[d]	$Pd(MeCN)_2Cl_2$	**L1**	Benzene/H_2O	BnCN	90(46%)



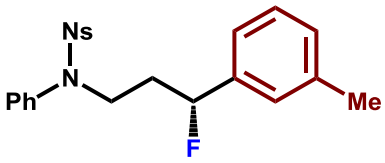
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Selectfluor (0.3 mmol); Cat., 10 mol %; ligand, 13 mol %; solvent, 0.8 mL; H_2O, 0.8 mL; nitrile, 0.1 mL; rt, 18 h. [b] ee determined by chiral HPLC. [c] ^{1}H NMR yields in parentheses. [d] The reaction was carried out at 4 ^{o}C for 18 h, isolated yield in parentheses.

Substrate Scope

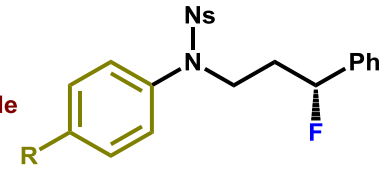




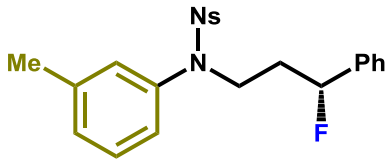
3a (R = H), 46%, 90% ee
3c (R = ^{t}Bu), 47%, 88% ee



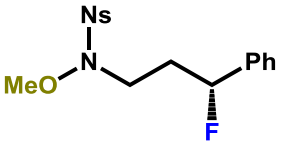
3g, 56%, 89% ee



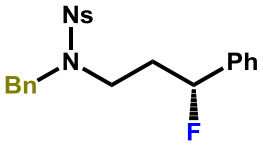
3k (R = MeO), 51%, 91% ee
3l (R = F), 48%, 87% ee



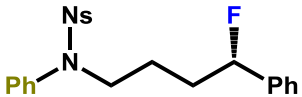
3n, 43%, 90% ee



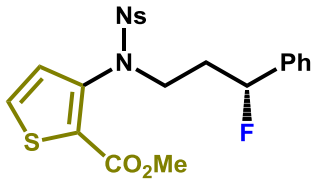
3q, 55%, 81% ee



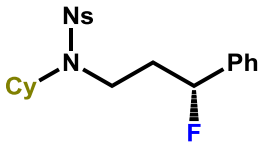
3r, 54%, 84% ee



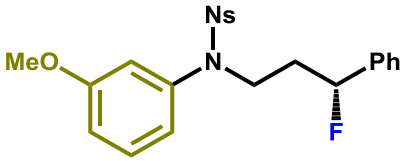
3t, 42%, 66% ee



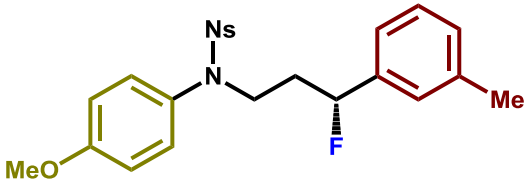
3u, 35%, 81% ee



3v, 52%, 83% ee



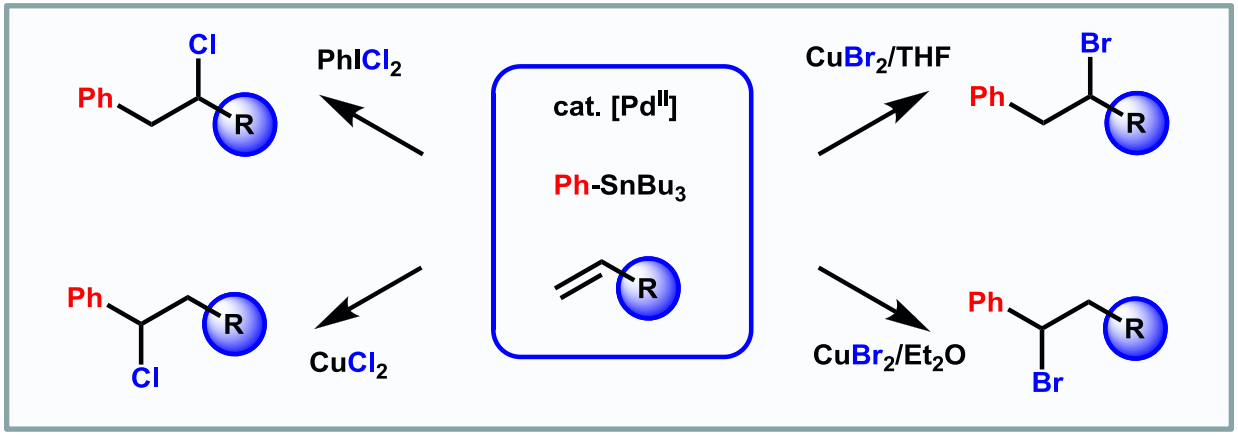
3w, 56%, 86% ee

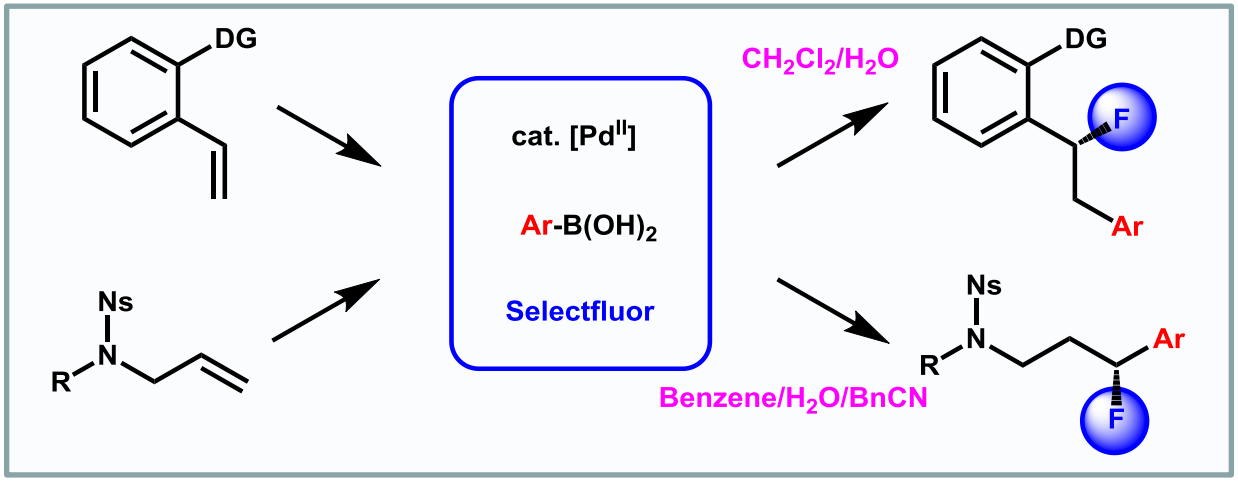


3x, 50%, 91% ee

Toste, F. D. *et al. J. Am. Chem. Soc.* **2015**, *137*, 12207.

Summary


Cl
Ph
R
PhICl2
cat. [PdII]
Ph-SnBu3
R
CuBr2/THF
Br
Ph
R
Ph
R
Cl
CuCl2
CuBr2/Et2O
Ph
R
Br


DG
cat. [PdII]
Ar-B(OH)2
Selectfluor
CH2Cl2/H2O
DG
F
Ar
Ns
N
R
Ns
N
R
Ar
F
Benzene/H2O/BnCN

The unique properties engendered by fluorine have inspired a number of strategies for the enantioselective construction of C−F bonds employing either electrophilic or nucleophilic fluorine sources. The difunctionalization of alkenes has emerged as an attractive strategy for the simultaneous formation of C−F and C−X (X = C, N, P, etc.) bonds. However, while great progress has been made in fluorocyclization of alkenes, intermolecular difunctionalization of alkenes as a means for enantioselective construction of C−F bonds remains challenging. We recently reported a palladium-catalyzed asymmetric 1,2-fluoroarylation of styrenes with boronic acids and Selectfluor as the fluorine source. Key to this transformation was the placement of a directing group on the alkene, which disfavored the oxidative Heck reaction and allowed for C−F bond formation via a high-valent palladium intermediate. In contrast, Sanford has described the 1,2 or 1,1-arylchlorination/bromination of alkenes with arylstannanes in the absence of a directing group on the alkene. Inspired by these reports, we have developed a catalytic enantioselective 1,1-arylfluorination of alkenes with arylboronic acids and Selectfluor.

In conclusion, we have disclosed a palladium-catalyzed 1,1-fluoroarylation of unactivated amino-alkenes by a three-component coupling of alkenes, arylboronic acids, and Selectfluor. Moreover, the reaction was extended to an asymmetric transformation that generated chiral benzylic fluorides in good to excellent enantioselectivies. This method promises to serve as a powerful strategy for the difunctionalization of alkenes to provide chiral fluorinated molecules.