Literature Report VIII

Rhodium-Catalyzed Enantio- and Regioselective Allylation of Indoles with *gem*-Difluorinated Cyclopropanes

Reporter: Yan-Jiang Yu
Checker: Hao-Dong Chen

Yang, H.; Lu, G.; Xia, Y.
Angew. Chem. Int. Ed. **2024**, *63,* e202403602

2024-04-29

CV of Prof. Xia Ying

Group's goal:

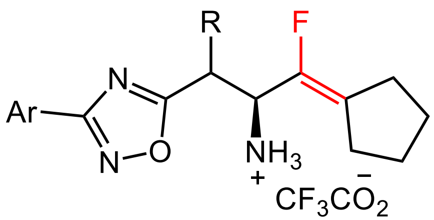
- Transition Metal Catalyzed Small Ring Chemistry
- Asymmetric Catalysis
- Organic Fluorine Chemistry

Background:

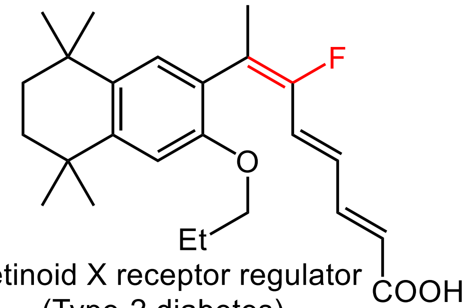
- **2006-2010** B.S., Beijing Institute of Technology
- **2010-2015** Ph.D., Peking University
- **2015-2016** Postdoc., The University of Texas at Austin
- **2016-2019** Postdoc., The University of Chicago
- **2019-Now** Professor, Sichuan University

Contents

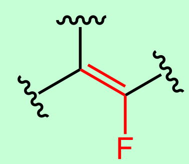
Introduction

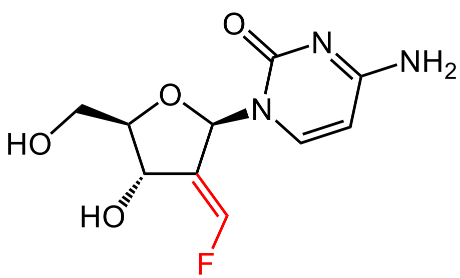


Dipeptidyl peptidase inhibitors
(Type 2 diabetes)

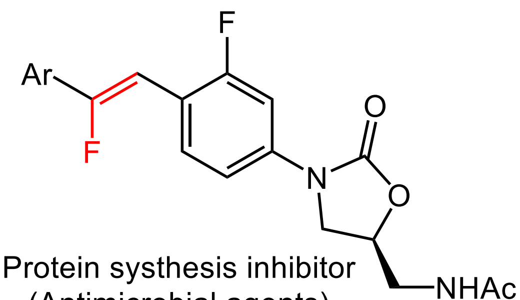


Retinoid X receptor regulator
(Type 2 diabetes)





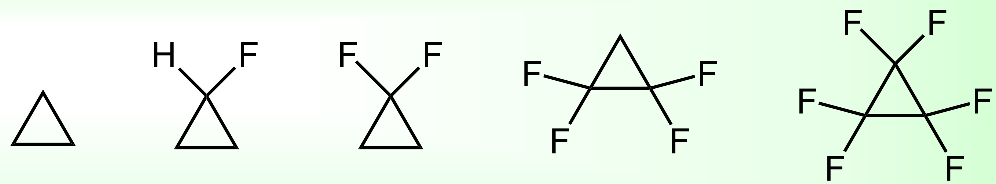
Ribonucleotide reductase inhibitor
(Anti-cancer)



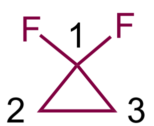
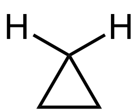
Protein systhesis inhibitor
(Antimicrobial agents)

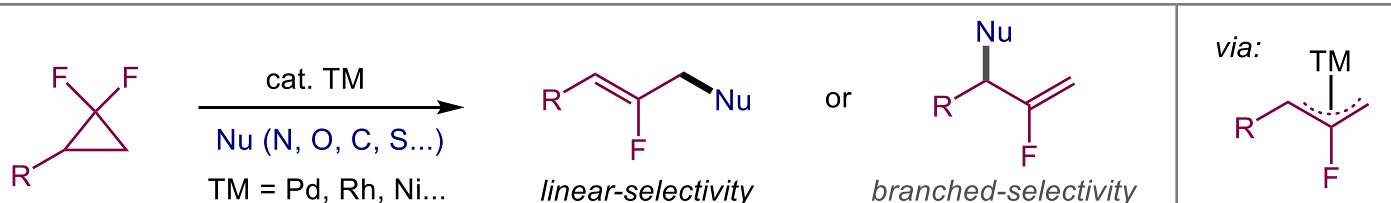
Qi, S.; Yang, J.; Zhang, J. *Chin. J. Chem.* **2024**, *42*, 823

Introduction



Ring-strain Energy (kcal/mol)	27.1	32.9	42.4	54.0	62.0

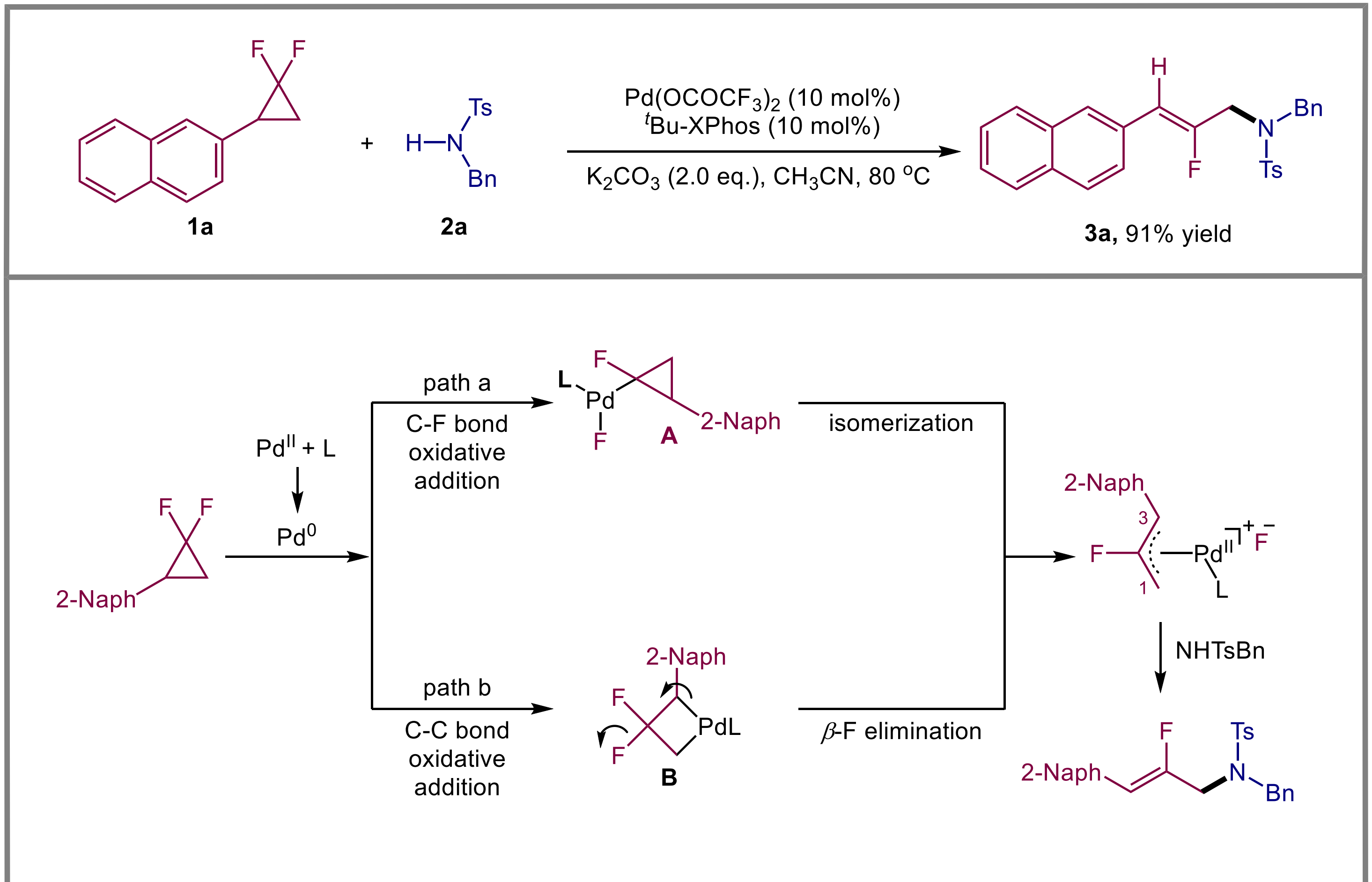
Cyclopropane	Ring-strain Energy	Bond Length	Bond Angle
	42.4 kcal/mol	r(C1-C2) 1.477 Å	∠C2-C1-C3 63.3°
		r(C2-C3) 1.550 Å	∠F-C1-F 109.6°
	27.1 kcal/mol	r(C-C) 1.515 Å	∠C-C-C 60.0°
			∠H-C-H 114.5°



Zeiger, D. N.; Liebman, J. F. *J. Mol. Structure* **2000**, *556*, 83
Dolbier, W. R.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071

Introduction

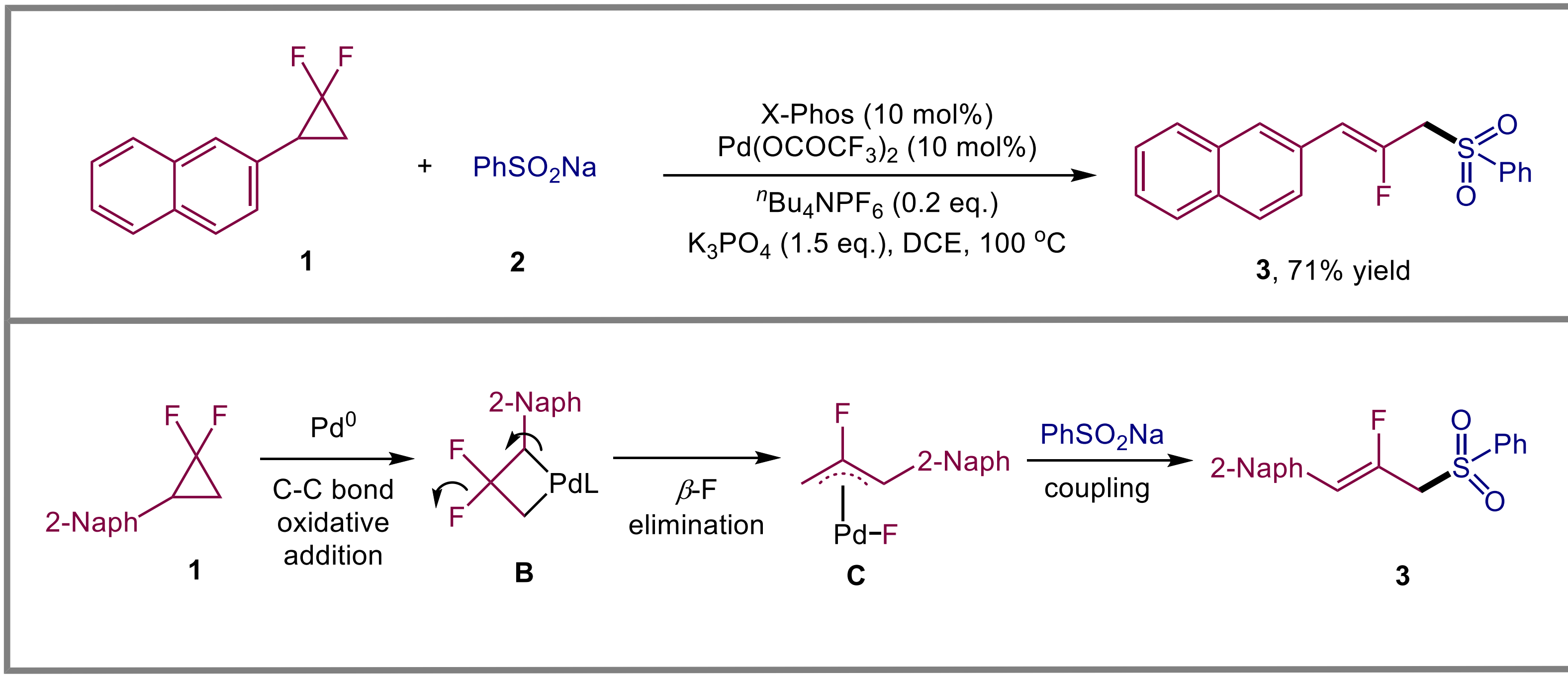
Pd-catalyzed ring opening of *gem*-DFCPs to form C-N bond (linear-selectivity)



Xu, J.; Xiao, B.; Yu, C.-G.; Fu, Y. *Angew. Chem. Int. Ed*. **2015**, *54*, 8231

Introduction

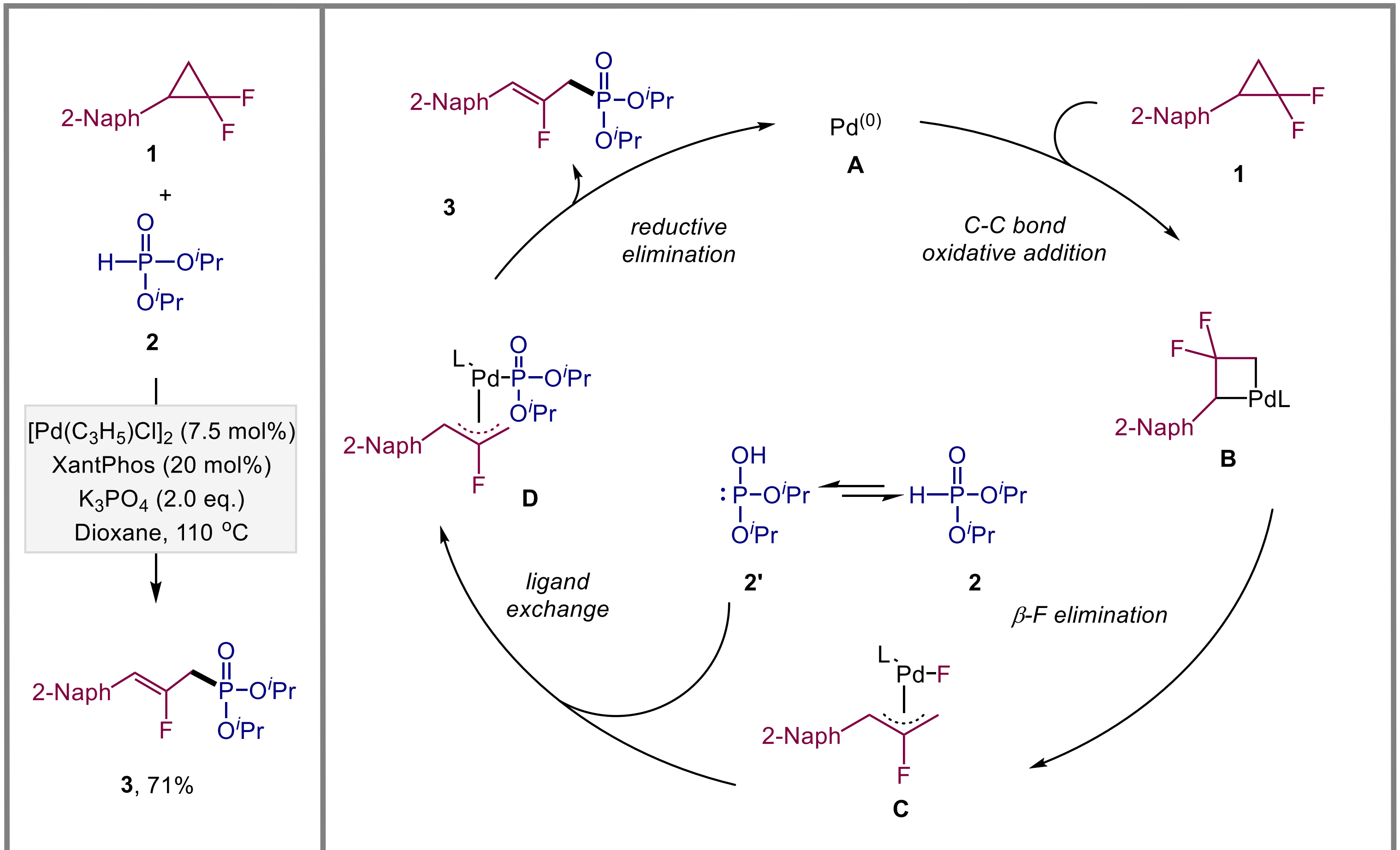
Pd-catalyzed ring opening of *gem*-DFCPs
to form C-S bond (linear-selectivity)



Ni, J.; Nishonov, B.; Zhang, A. *J. Org. Chem.* **2019**, *84*, 13646

Introduction

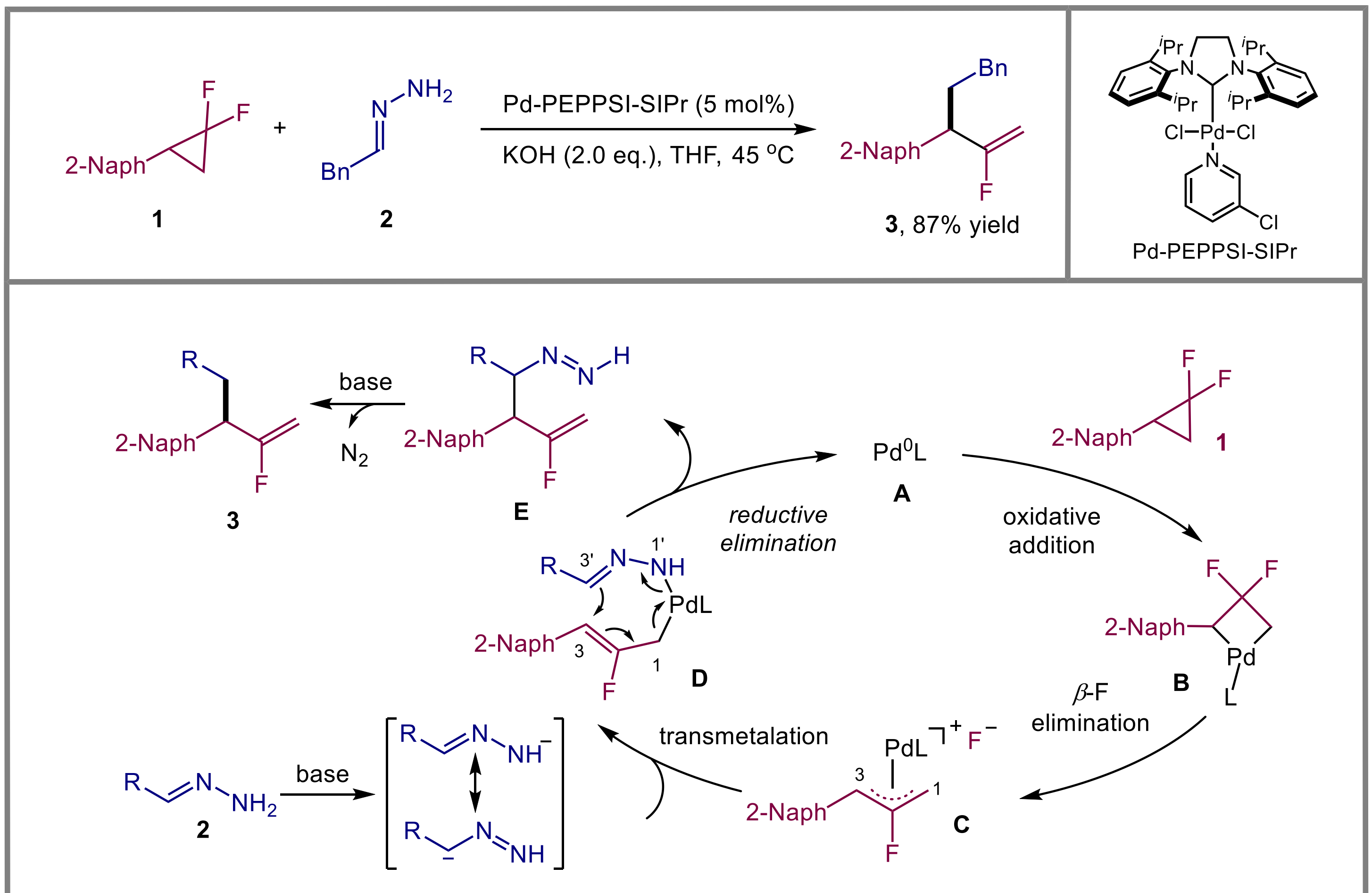
Pd-catalyzed ring opening of *gem*-DFCPs to form C-P bond (linear-selectivity)



Sun, J.; X.-W.; Wu, X.-X. *Org. Lett.* **2023**, *25*, 5220

Introduction

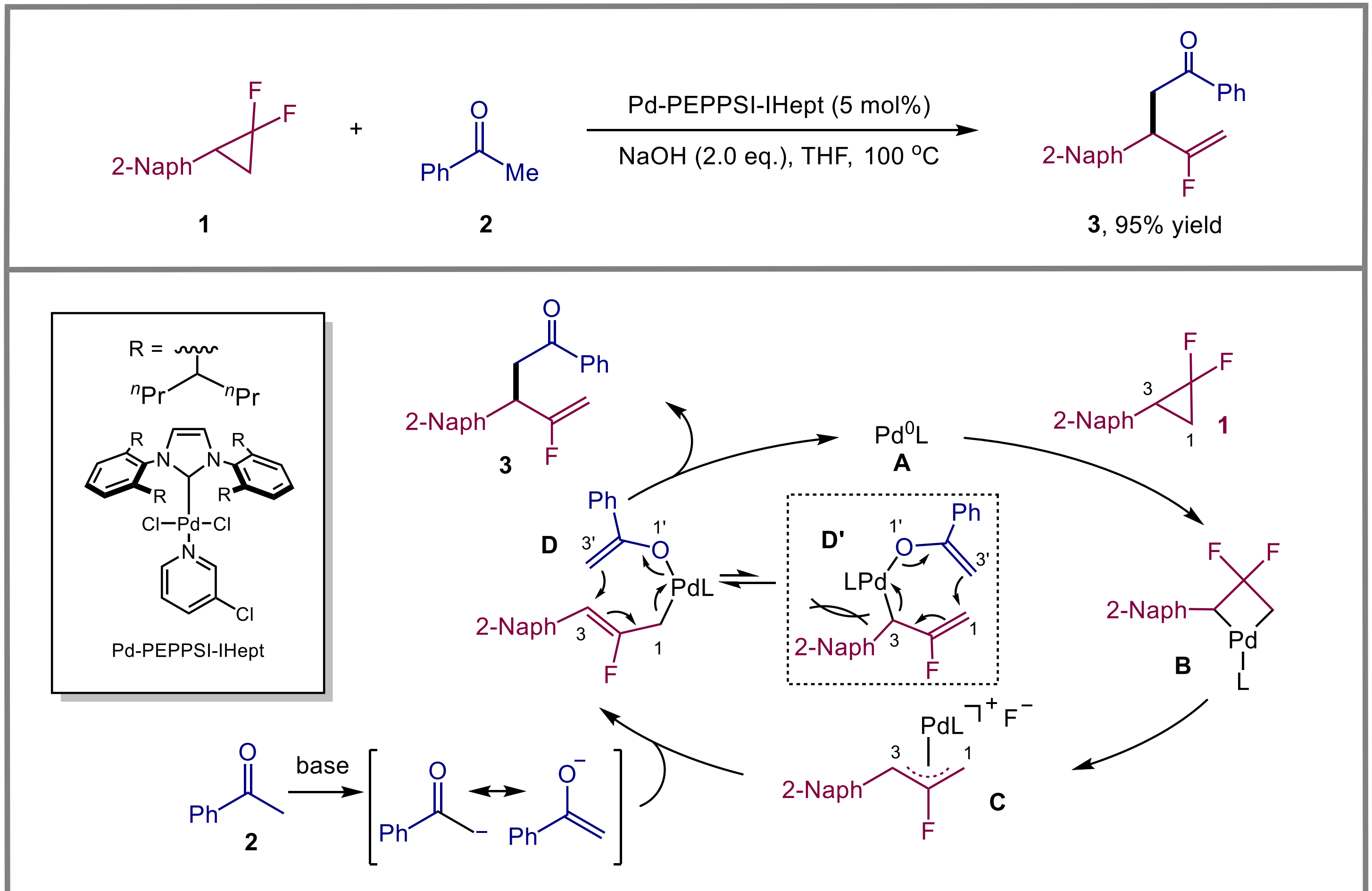
Pd-catalyzed ring opening of *gem*-DFCPs to form C-C bond (branched-selectivity)



Lv, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2021**, *60*, 13098

Introduction

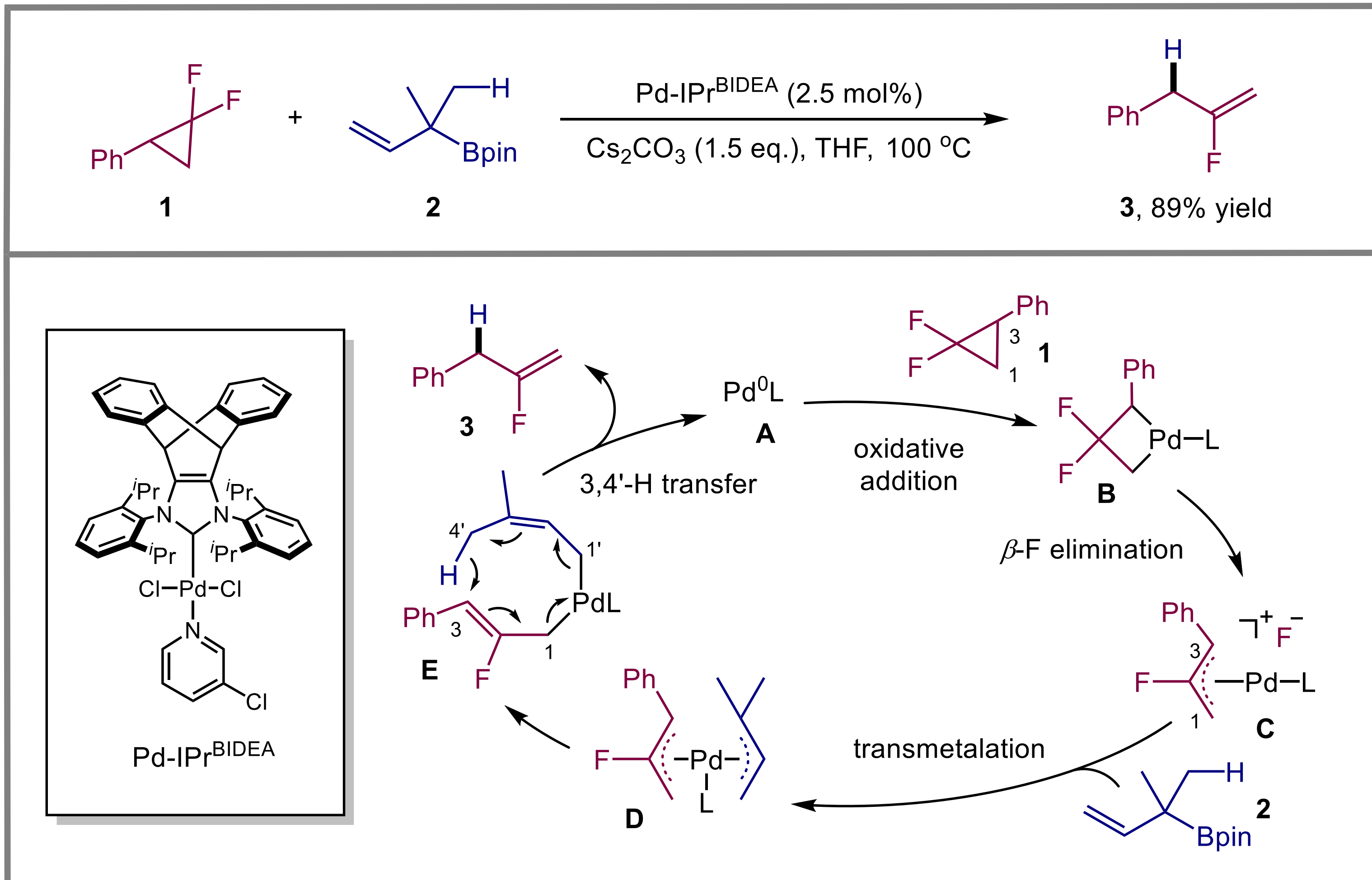
Pd-catalyzed ring opening of *gem*-DFCPs (branched-selectivity)



Lv, L.; Yan, X.; Li, Z. *Chem. Sci.* **2021**, *12*, 15511

Introduction

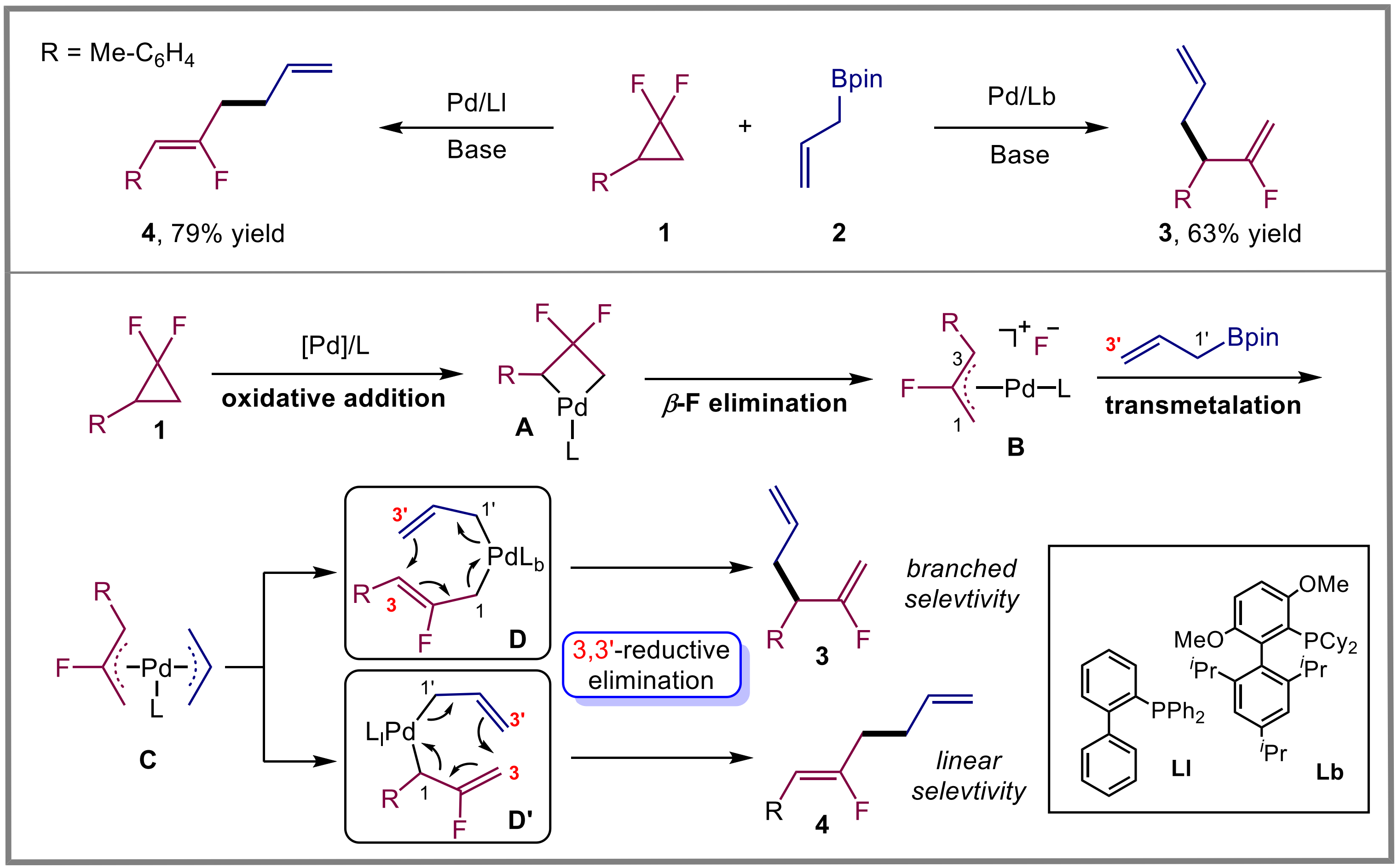
Pd-catalyzed ring opening of *gem*-DFCPs (branched-selectivity)



Qian, H.; Cheng, Z.; Li, Z. *J. Am. Chem. Soc.* **2024**, *146*, 24

Introduction

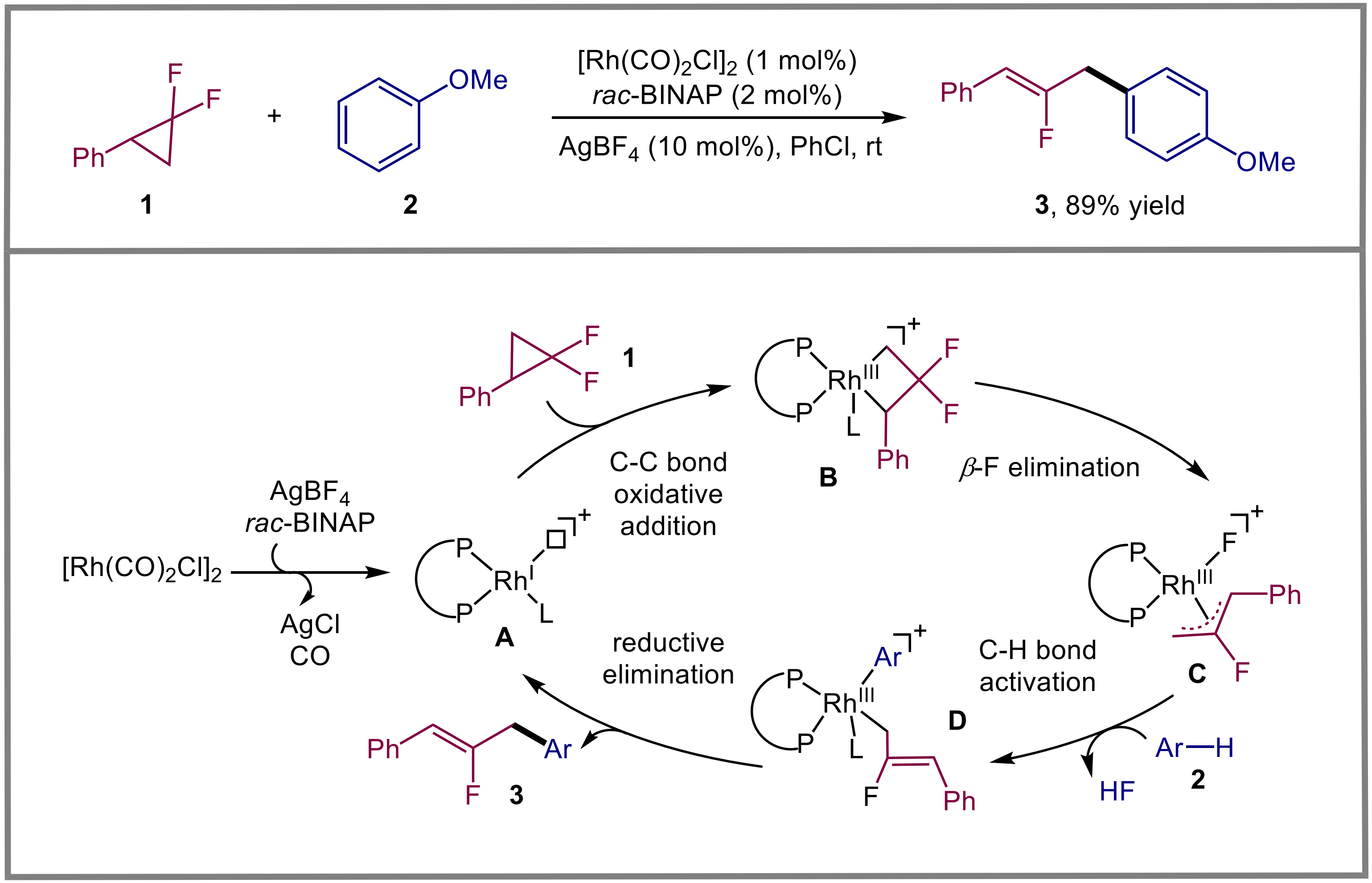
Pd-catalyzed ring opening of *gem*-DFCPs (branched-selectivity or linear-selectivity)



Wu, L.; Liang, Y.; Shi, Z. *Chin. J. Chem.* **2022**, *40*, 2345

Introduction

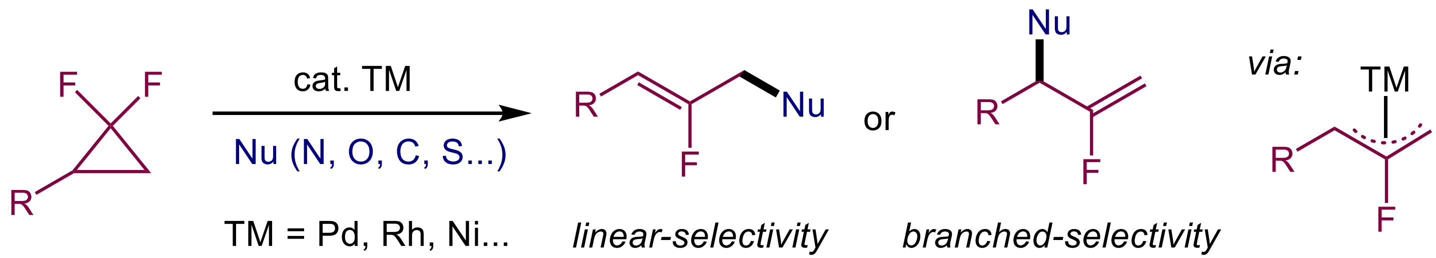
Rh-catalyzed ring opening of *gem*-DFCPs (linear-selectivity)



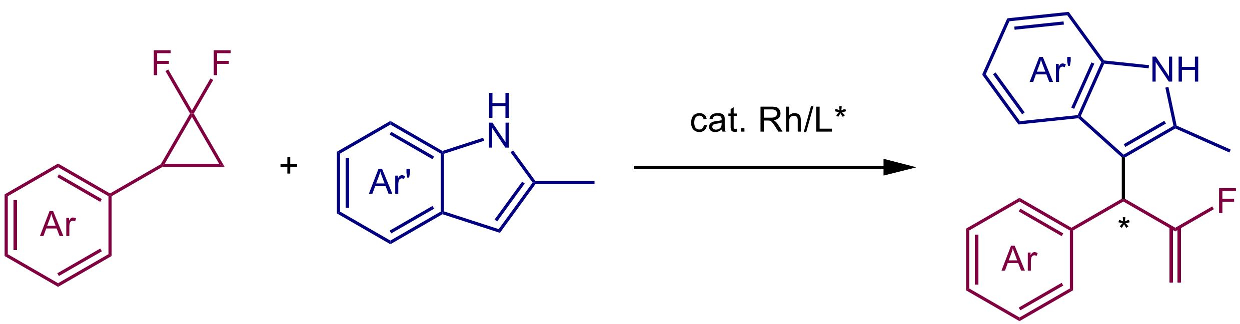
Jiang, Z.-T.; Huang, J.; Xia, Y. *Angew. Chem. Int. Ed.* **2021**, *60*, 10626

Project Synopsis

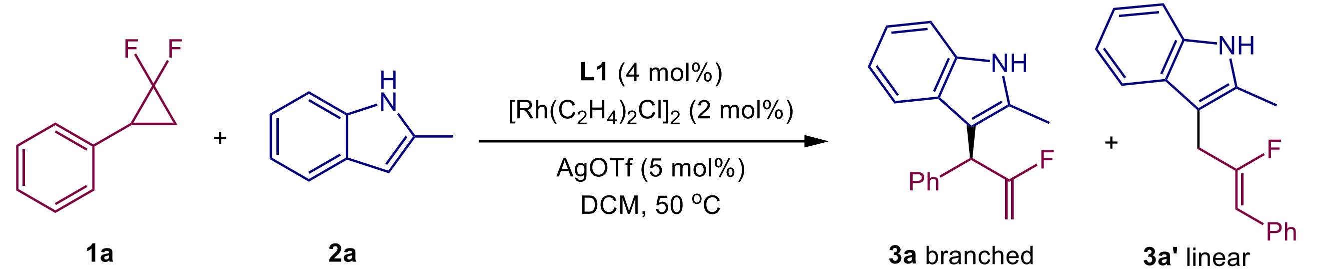
Racemic or Achiral mono-Fluoroalkenes (Well-developed)



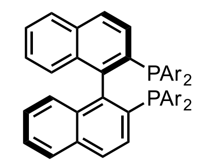
The Collection of Enantioenriched mono-Fluoroalkenes



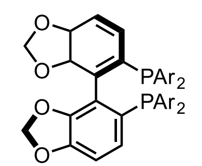
Optimization of Reaction Conditions



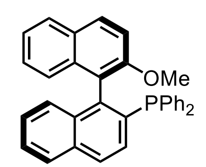
Entry	Variations	Yield (%)	b/l	Ee (%)
1	none	93 (92)	38:1	93
2	no AgOTf	0	-	-
3	$AgPF_6$	53	25:1	89
4	$AgBF_4$	56	25:1	69
5	**L2**	86	11:1	31
6	**L3**	82	9:1	31
7	**L4**	72	4:1	15
8	**L5**	86	1:1	48
9	**L6**	15	26:1	93
10	**L7**	0	-	-
11	PhCl	91	31:1	91
12	DCE	91	29:1	85
13	THF, **L2**	36	1:1.3	29



L1 (*R*)-DTBM-BINAP
L2 (*R*)-BINAP
L3 (*R*)-tol-BINAP
L4 (*R*)-xyl-BINAP

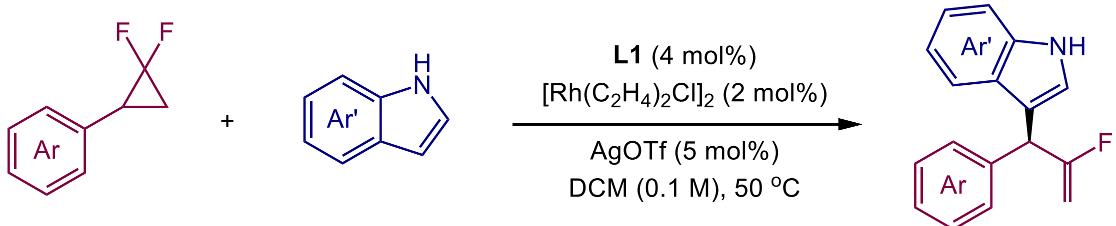


L5 (*R*)-SegPhos
L6 (*R*)-DTBM-SegPhos

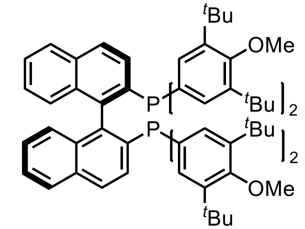


L7

Substrate Scope

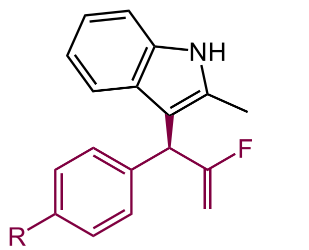


1 + 2a → 3

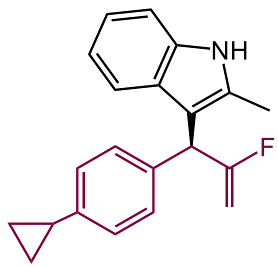


L1

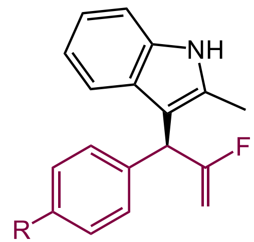
A: Scope of gem-DFCPs



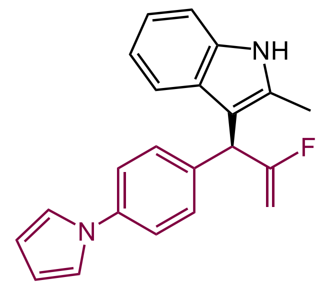
3a, R = H, 93% ee, 92% yield
3b, R = Me, 91% ee, 57% yield



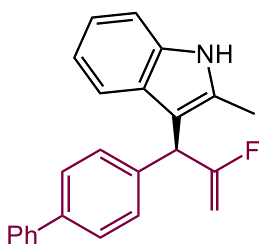
3c, 89% ee, 68% yield



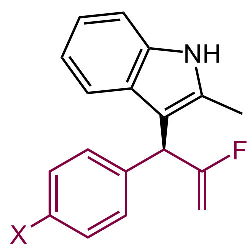
3d, R = OPh, 91% ee, 85% yield
3e, R = OAc, 96% ee, 95% yield



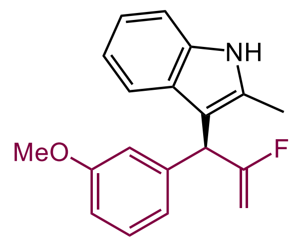
3f, 93% ee, 96% yield



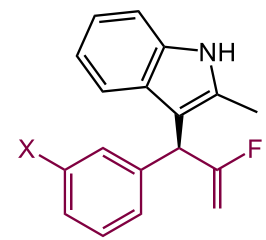
3g, 93% ee, 93% yield



3h, X = F, 93% ee, 92% yield
3i, X = Cl, 96% ee, 55% yield
3j, X = Br, 95% ee, 49% yield



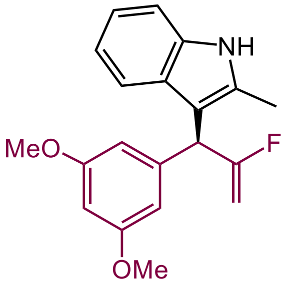
3k, 91% ee, 95% yield



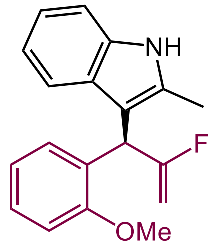
3l, X = F, 96% ee, 53% yield
3m, X = Cl, 95% ee, 88% yield
3n, X = Br, 97% ee, 95% yield

Substrate Scope

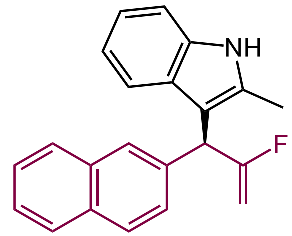
A: Scope of gem-DFCPs



3o, 91% ee, 60% yield

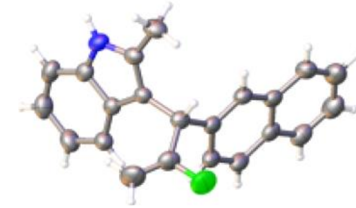


3p, 83% ee, 70% yield

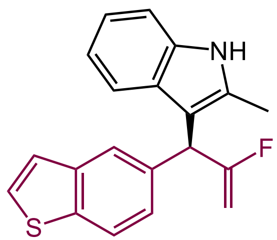


3q, 91% ee, 83% yield

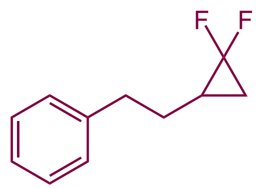
≡



X-ray of 3q

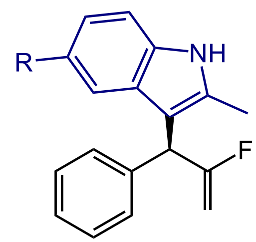


3r, 91% ee, 95% yield

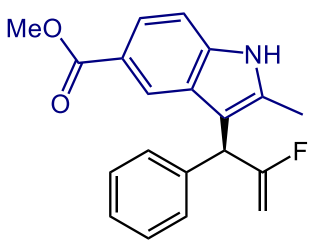


unsuccessful substrate
50 °C or 90 °C

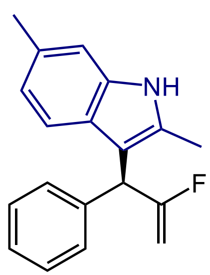
B: Scope of Indoles



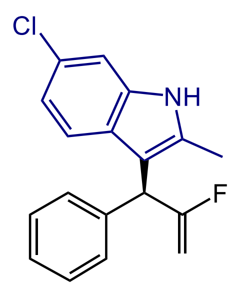
3s, X = Me, 92% ee, 86% yield
3t, X = OMe, 93% ee, 94% yield
3u, X = Cl, 91% ee, 66% yield
3v, X = F, 95% ee, 66% yield



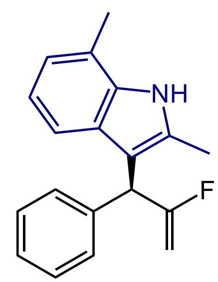
3w, 94% ee, 62% yield



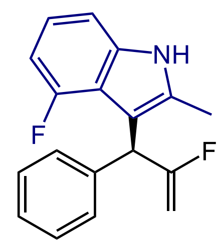
3x, 90% ee, 85% yield



3y, 93% ee, 39% yield



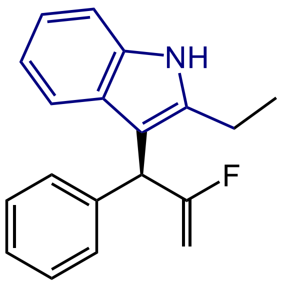
3z, 85% ee, 46% yield



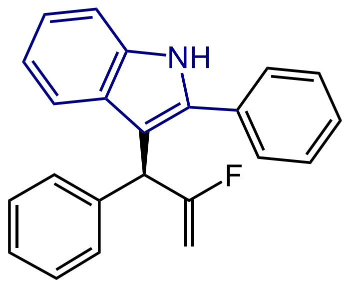
3aa, 90% ee, 55% yield

Substrate Scope

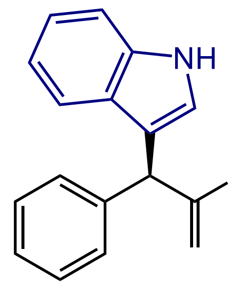
B: Scope of Indoles



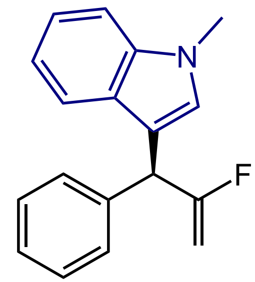
3ab, 94% ee, 81% yield



3ac, 85% ee, 60% yield

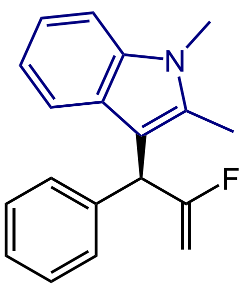


3ad, 73% ee, 7% yield
81% ee, 70% yield (*R*)-BINAP

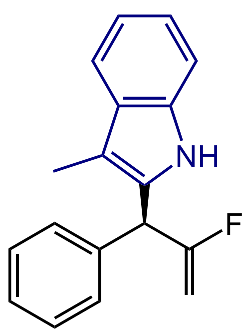


3ae, 95% ee, 5% yield

73% ee, 46% yield
b/l = 4:1, (*R*)-SegPhos

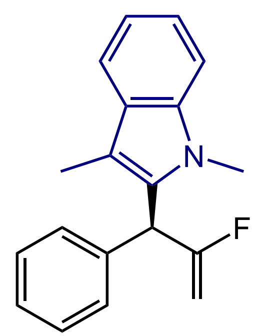


3af, 95% ee, 90% yield



3ag, 41% ee, 15% yield

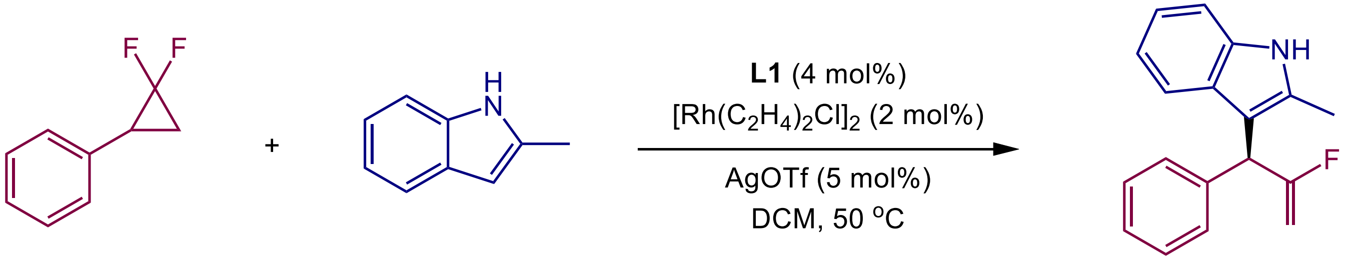
89% ee, 77% yield
b/l = 6:1, (*R*)-BINAP



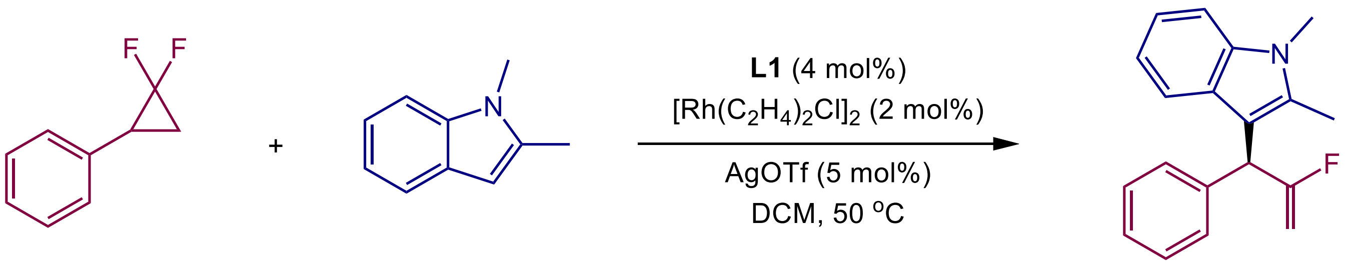
3ah, no reaction

99% ee, 51% yield
b/l = 14:1, (*R*)-BINAP

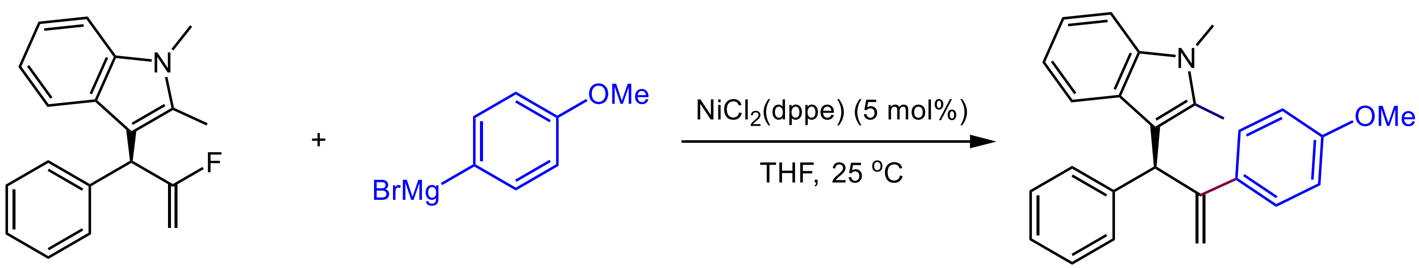
Synthetic Application



1a **2a** 1 mmol **3a**, 93% ee, 92% yield



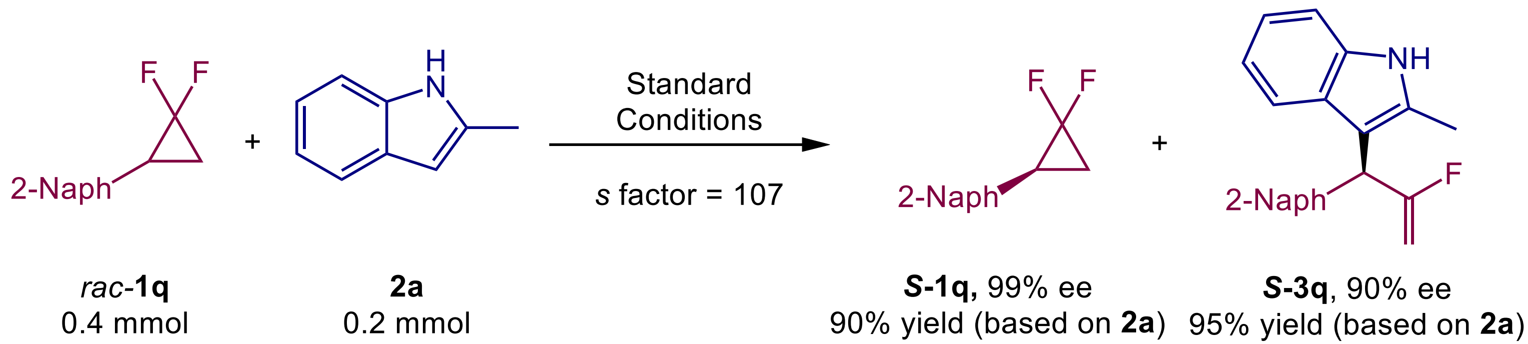
1a **2o** 1 mmol **3af**, 88% ee, 90% yield



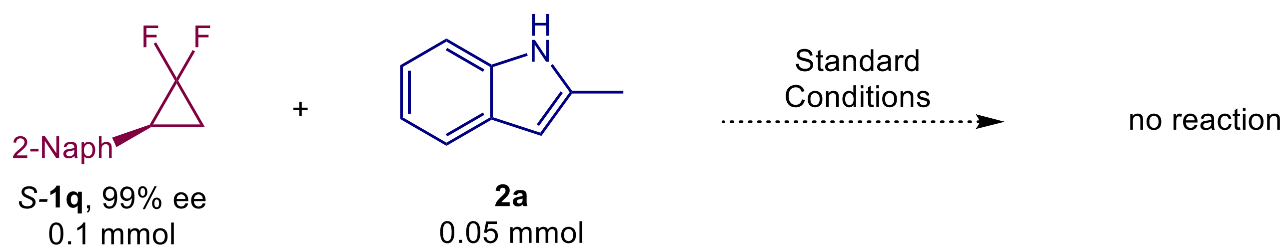
3af, 90% yield **4**, 98% ee, 54% yield

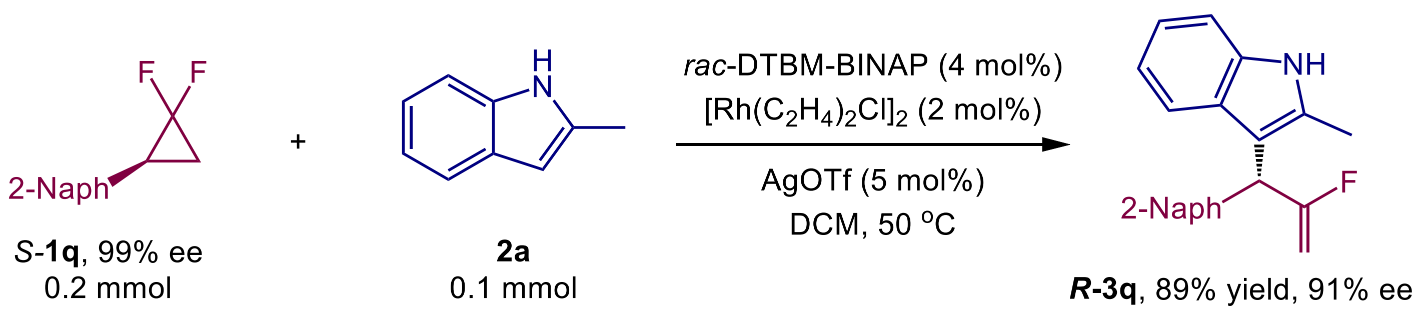
Mechanistic Studies

Recycled the Remaining gem-DFCP

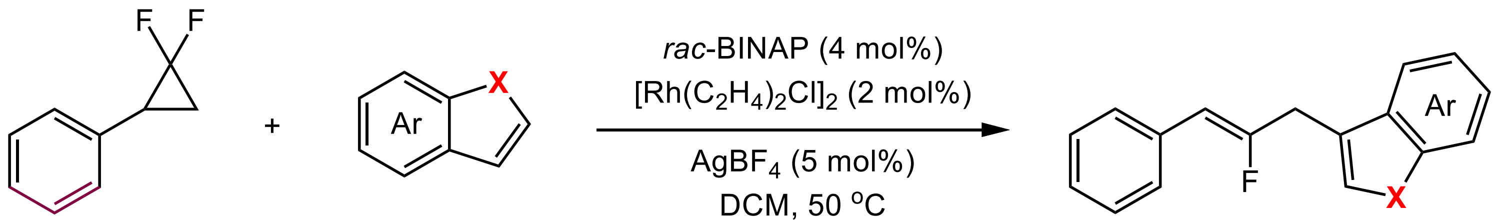


Reaction of Recovered Enantiopure gem-DFCP





Mechanistic Studies

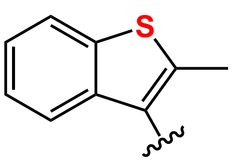


1a

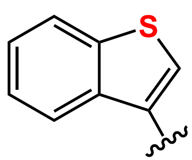
X = O or S
2r-2u

5a-5d

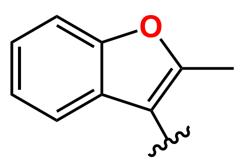
Other Aromatic Heterocycles



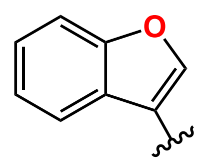
5a 64% yield



5b 39% yield

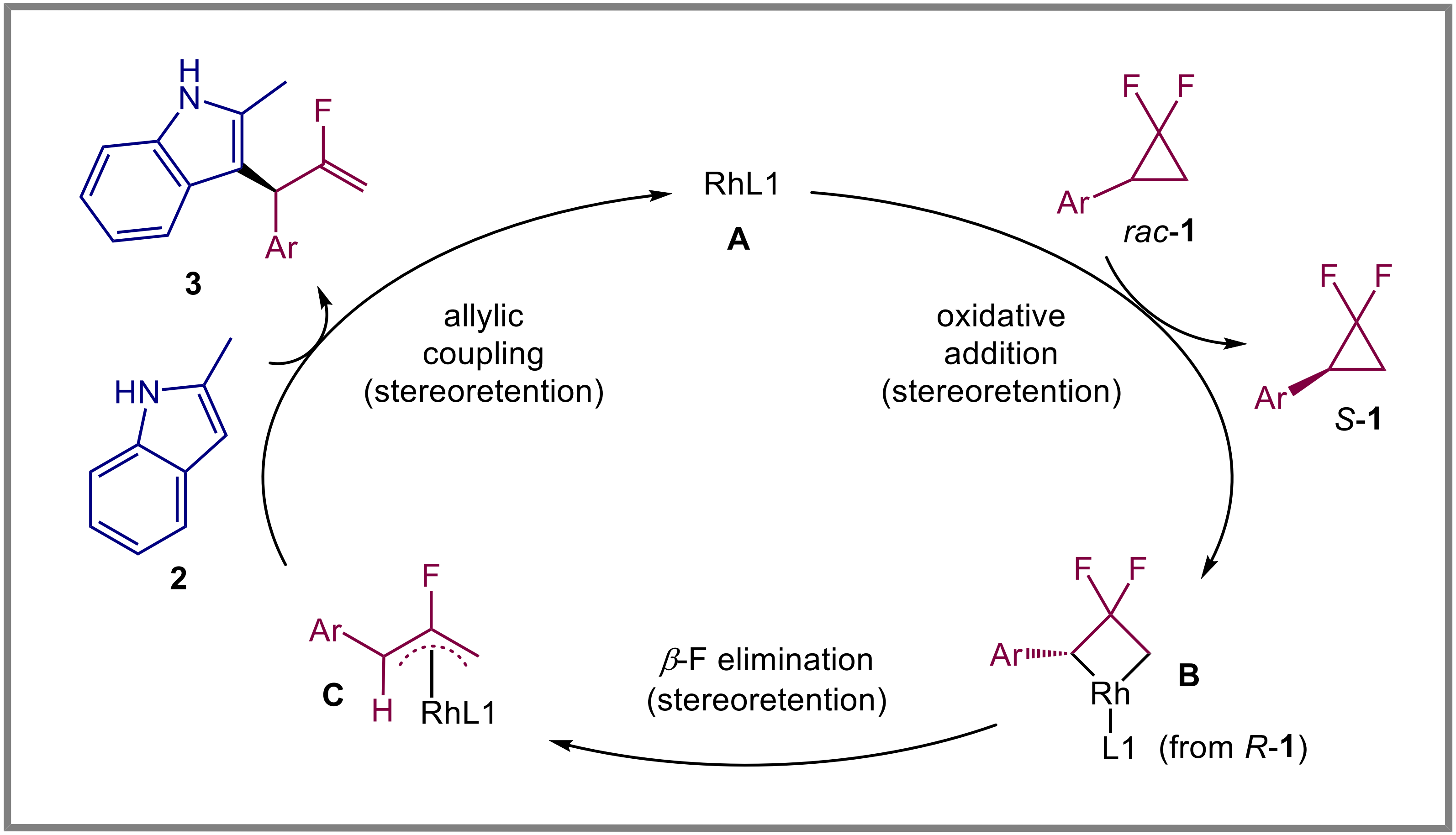


5c 26% yield

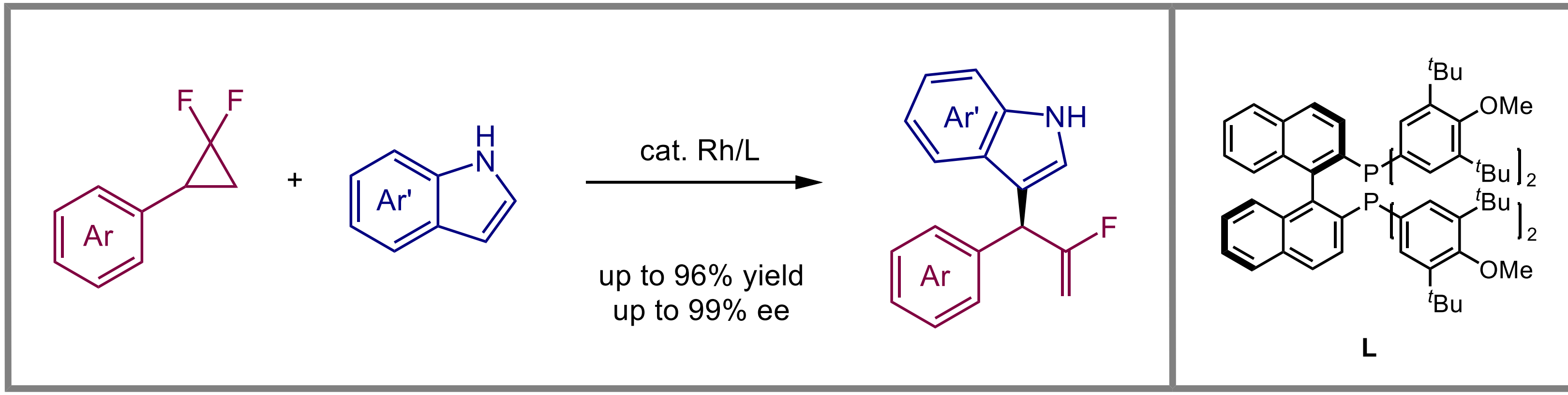


5d 33% yield

Proposed Mechanism



Summary



- Exclusive Branched-selectivity
- Excellent Enantioselectivity
- Good Functional Group Tolerance
- Indole C2 and C3 Fluoroallylation

The First Paragraph

Writing strategy

The importance of mono-fluoroalkenes compounds

↓

The synthesis of mono-fluoroalkenes

↓

Rh-catalyzed asymmetric allylic Of *gem*-DFCPs

- Organofluorine compounds occupy a significant place in pharmaceutical chemistry and material science. Among various fluorinated motifs, the mono-fluoroalkenes have consistently attracted attention from the synthetic community.
- Despite these significant achievements that have been made in the synthesis of racemic or achiral mono-fluoroalkenes, a strategy for the collection of enantioenriched *α*-mono-fluoroalkenes using *gem*-DFCPs as fluoroallyl surrogates has not yet been realized.
- Herein, we disclosed the first Rh-catalyzed branched-regioselective and enantioselective allylic coupling between *gem*-DFCPs and indoles.

The Last Paragraph

Writing strategy

Summary of this work

- In conclusion, we have developed an efficient access to highly branched and enantioselective allylic coupling of indoles with *gem*-DFCPs using rhodium catalysis. This reaction is the first example with high enantioselectivity and high branchedregioselectivity in the ring opening coupling of *gem*-DFCPs, to afford C2 and C3 fluoroallylated products.

Outlook of this work

- Further study on the understanding of the stereochemistry and the origin of the branched regioselectivity is currently underway in our laboratory.

Representative Examples

A strategy for the collection of enantioenriched *α*-mono-fluoroalkenes using *gem*-DFCPs as fluoroallyl surrogates has not yet been realized. (代用品，代理，替代物)

Taking together, the efficient kinetic resolution process (*via* oxidative addition) and the high stereospecificity of the allylation process with L1 as the bulky ligand account for the observed high enantioselectivity of the reaction.(总的来看，综合起来；表意是“所讨论的想法是通过组合多个因素组成的”)

While more investigations are required to understand the origin of the branched selectivity, this observation underscores the privileged nucleophilicity of indoles in controlling the regioselectivity (underscore, *vt*. 强调，着重说明； underscores, *n*. 下划线，底线)

Thanks
for your attention