Literature Report VII

Tunable Synthesis of Monofluoroalkenes and *Gem*-Difluoroalkenes *via* Solvent-Controlled Rhodium-Catalyzed Arylation of 1-Bromo-2,2-difluoroethylene

Reporter: Hao Tang

Checker: Jian Chen

Xu, W.-Y.; Xu, Z.-Y.; Zhang, Z.-K.; Gong, T.-J.; Fu, Y.*
Angew. Chem. Int. Ed. **2023**, e202310125

2023-09-18

CV of Prof. Yao Fu

Background:

- **1996-2000** B.S., University of Science and Technology of China
- **2000-2005** Ph.D., University of Science and Technology of China
- **2005-2010** Associate Professor, University of Science and Technology of China
- **2010-now** Professor, University of Science and Technology of China

Research:

- Theoretical and Computational Organic Chemistry;
- Green Organic Synthesis Methodology.
- Biomass Catalytic Conversion;

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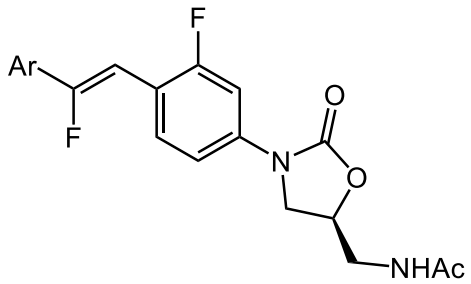
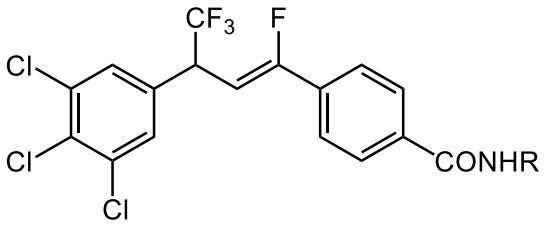
2 Solvent-Controlled Tunable Synthesis of Fluoroalkenes

3 Summary

Introduction



protein synthesis inhibitors



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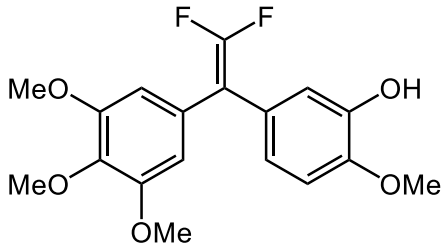
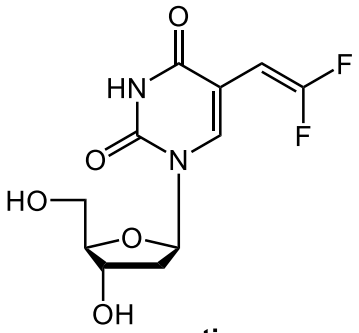


antitubulin agent



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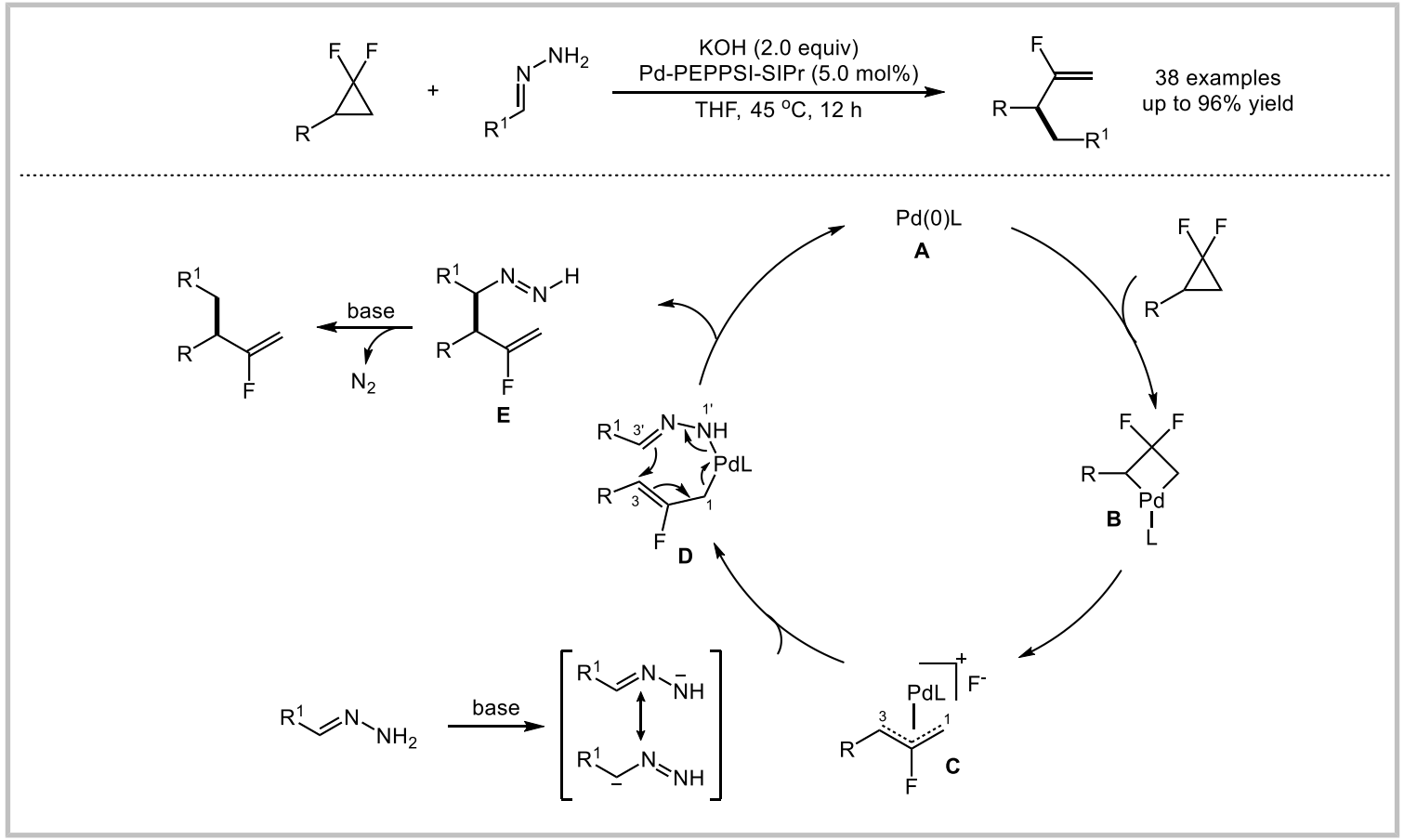
Introduction

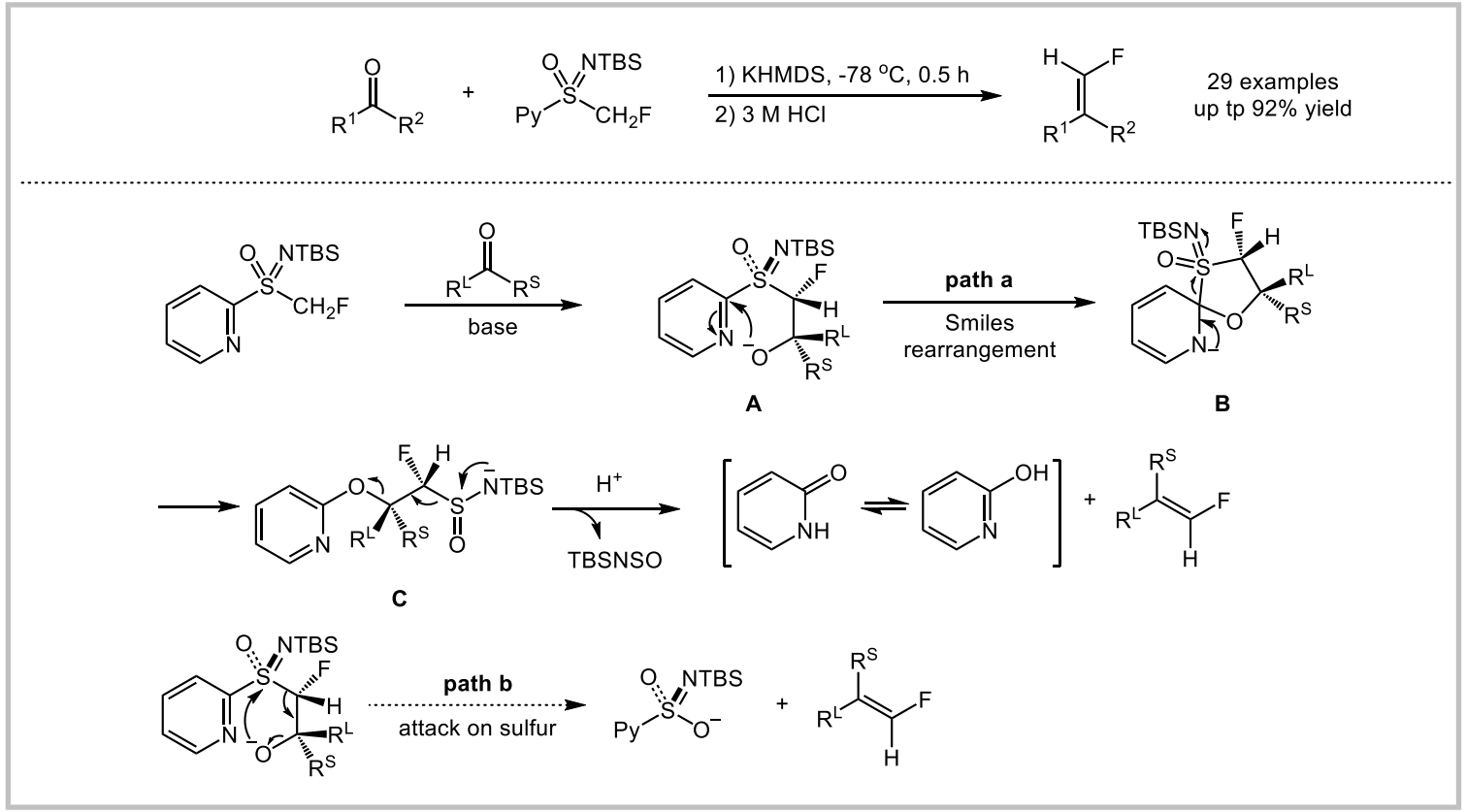
Fluoroalkenes Synthesis *via* Activation of *gem*-Difluorinated Cyclopropanes



Xu, J.; Ahmed, E.-A.; Xiao, B.; Lu, Q.-Q.; Wang, Y.-L.; Yu, C.-G.; Fu, Y.* *Angew. Chem. Int. Ed.* **2021**, *60*, 13098

Introduction

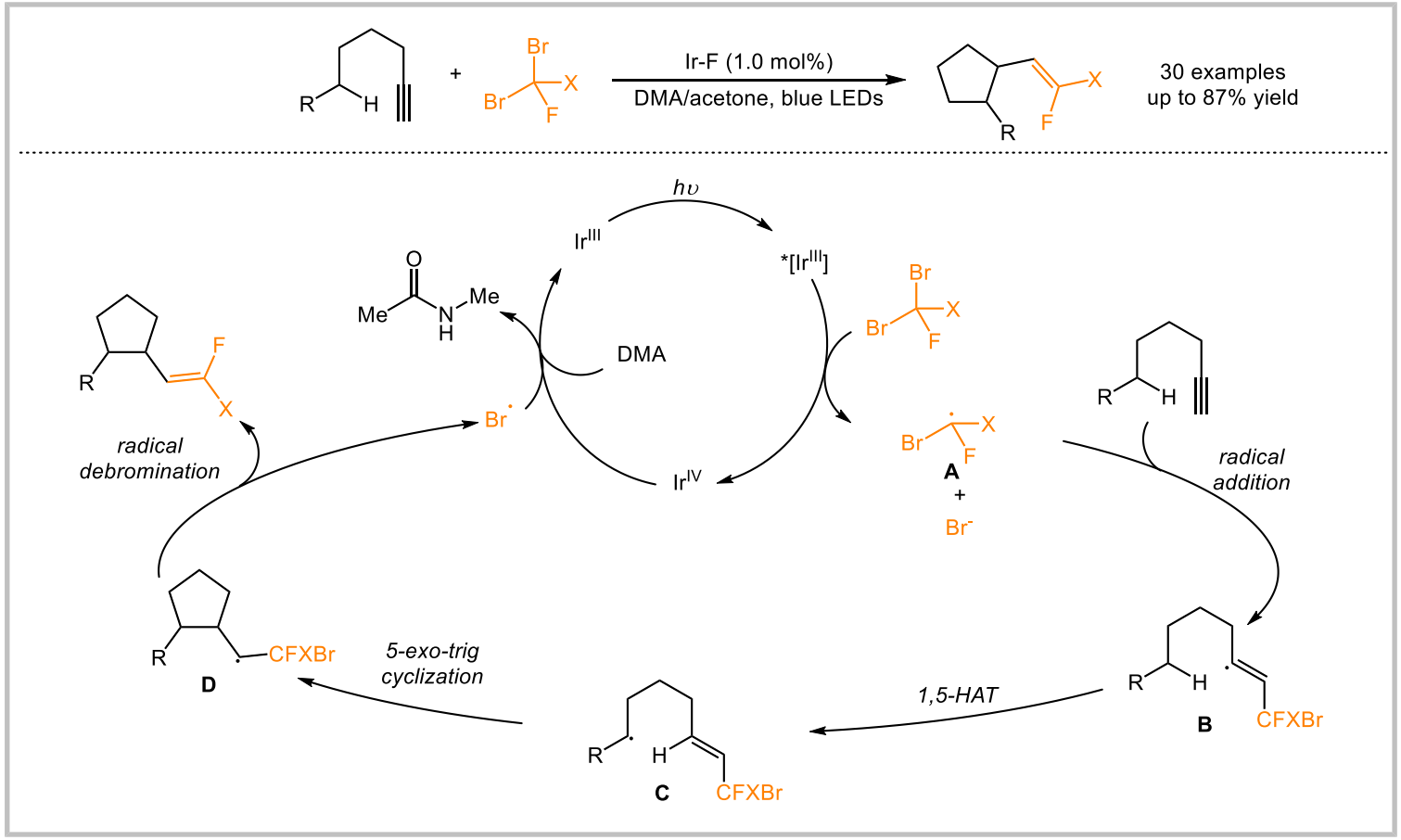
Fluoroalkenes Synthesis *via* Fluorosulfoximines



Liu, Q.; Shen, X.; Ni, C.; Hu, J.* *Angew. Chem. Int. Ed.* **2017**, *56*, 619

Introduction

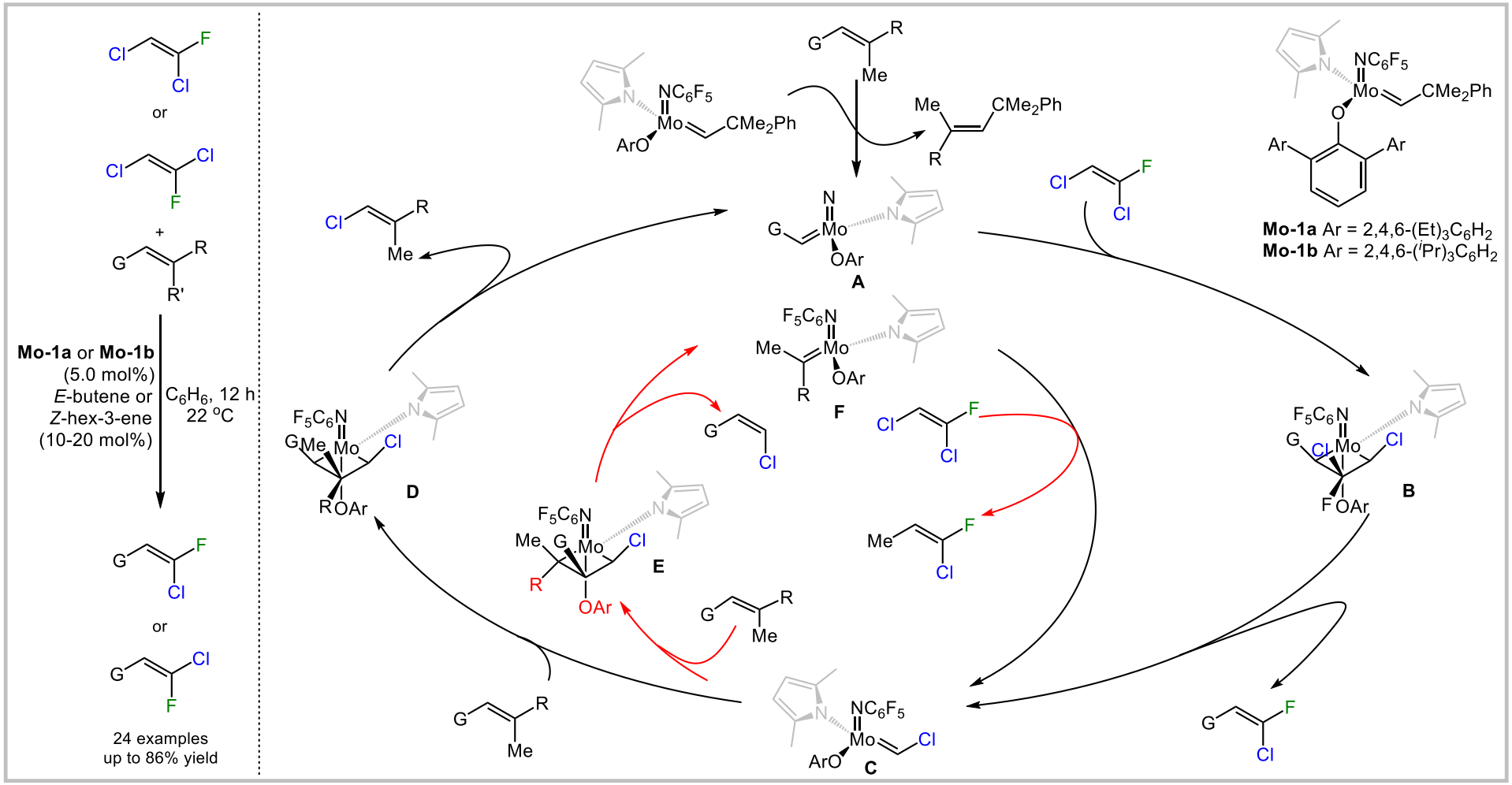
Fluoroalkenes Synthesis *via* Metallaphotoredox-Catalysis



Xu, P.; Daniliuc, C. G.; Bergander, K.; Stein, C.; Studer, A.* *ACS Catal.* **2022**, *12*, 11934

Introduction

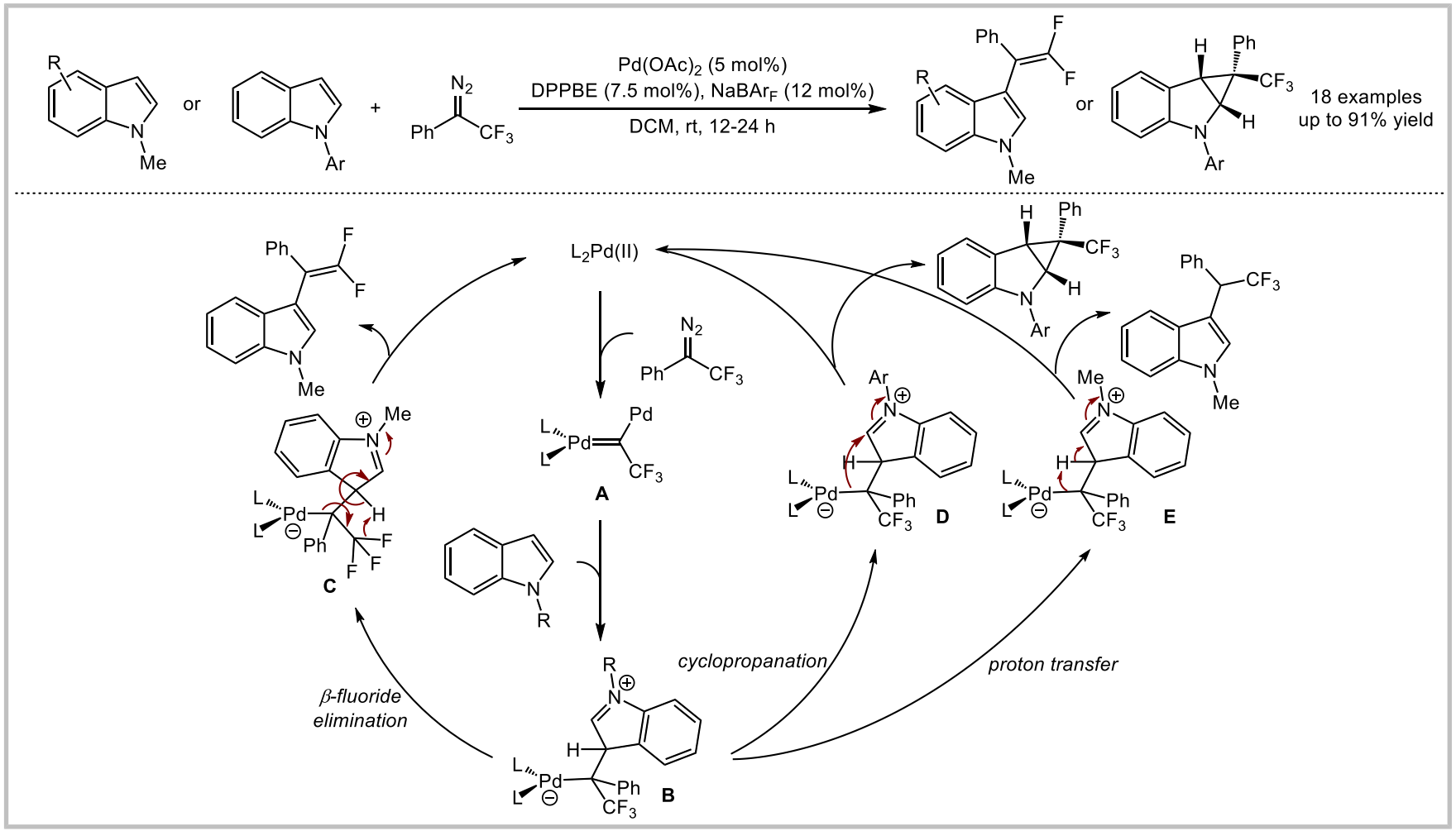
Fluoroalkenes Synthesis *via* Olefin Metathesis



Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H.* *Nat. Chem.* **2022**, *14*, 463

Introduction

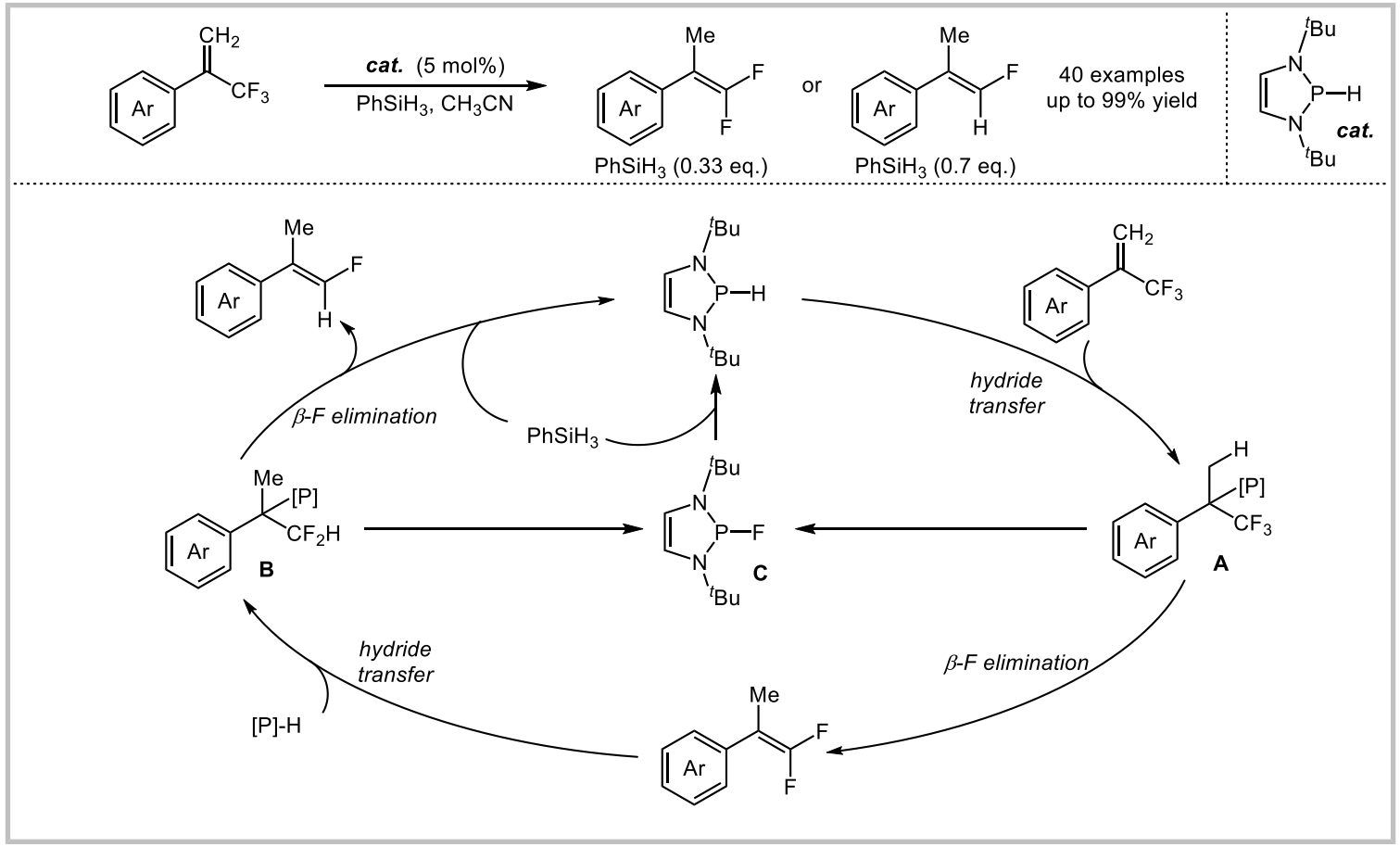
Fluoroalkenes Synthesis *via* Difluorocarbene Intermediates



Yang, Z.; Möller, M.; Koenigs, R. M.* *Angew. Chem. Int. Ed.* **2020**, *59*, 5572

Introduction

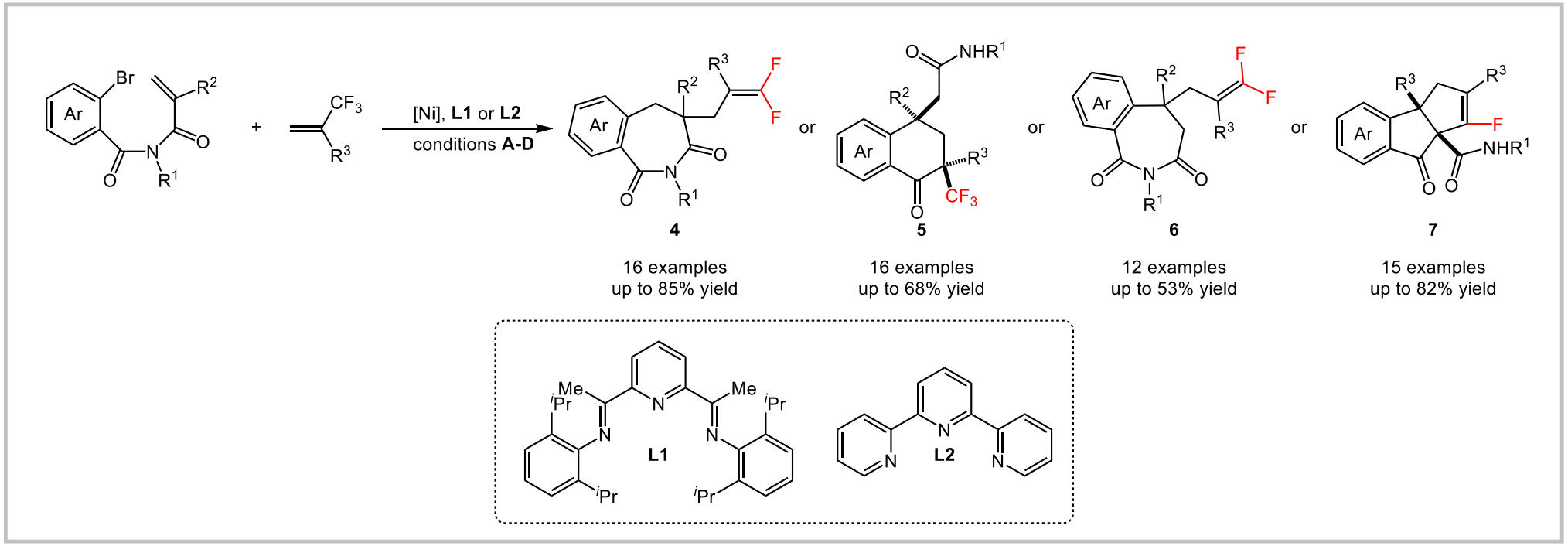
Fluoroalkenes Synthesis *via* Diazaphospholene-Catalysis



Zhang, J.; Yang, J.-D.; Cheng, J.-P.* *Nat. Commun.* **2021**, *12*, 2835

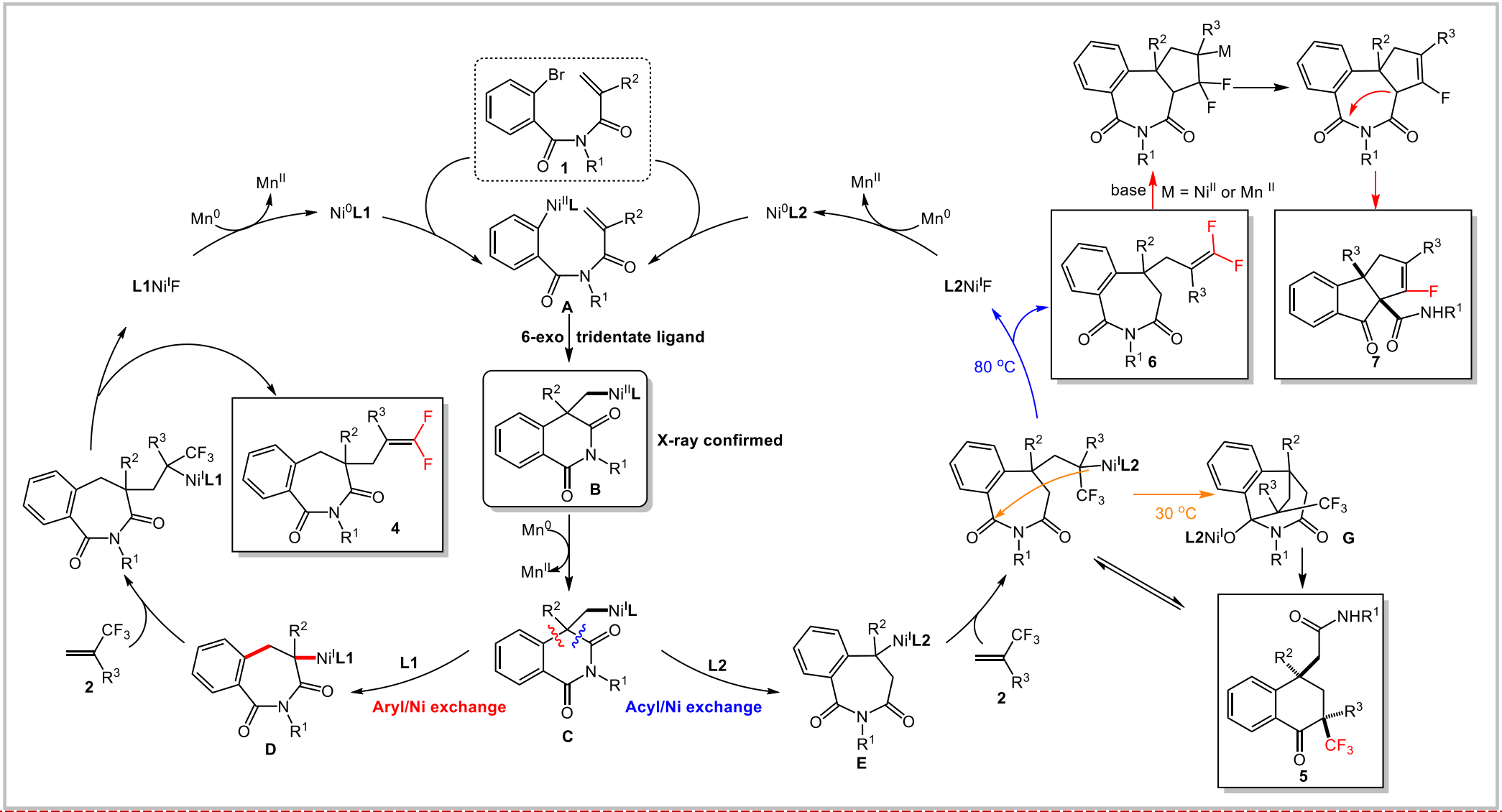
Introduction

Fluoroalkenes Synthesis *via* Nickel-Catalysis



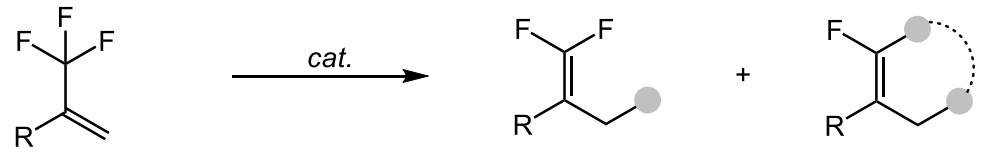
Ping, Y.; Li, X.; Pan, Q.; Kong, W.* *J. Am. Chem. Soc.* **2022**, *144*, 11626

Introduction

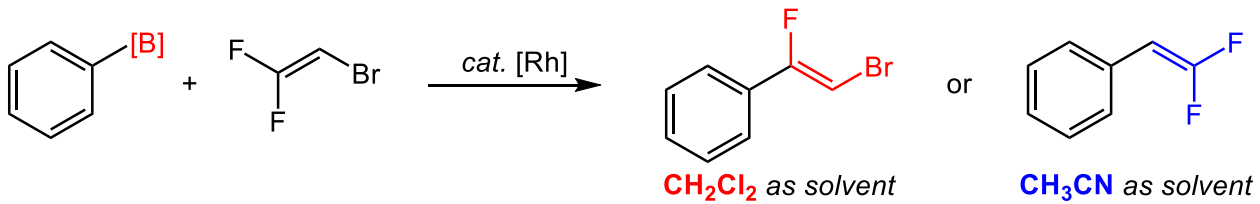


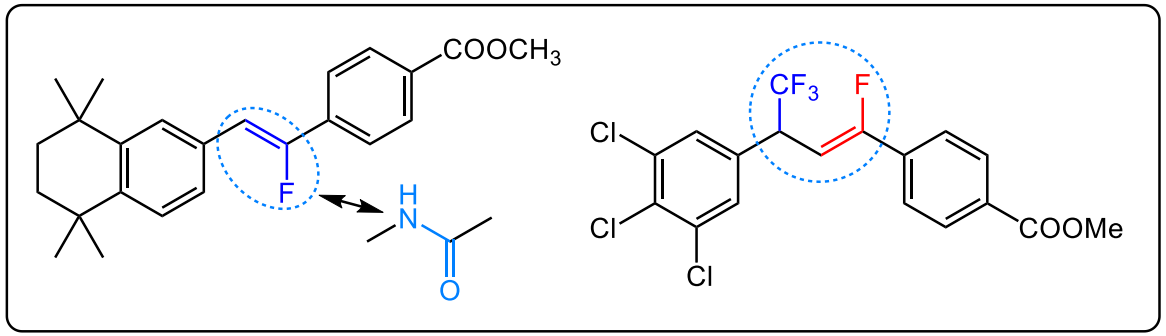
Introduction

Successive C-F bond functionalization of trifluoromethyl alkenes

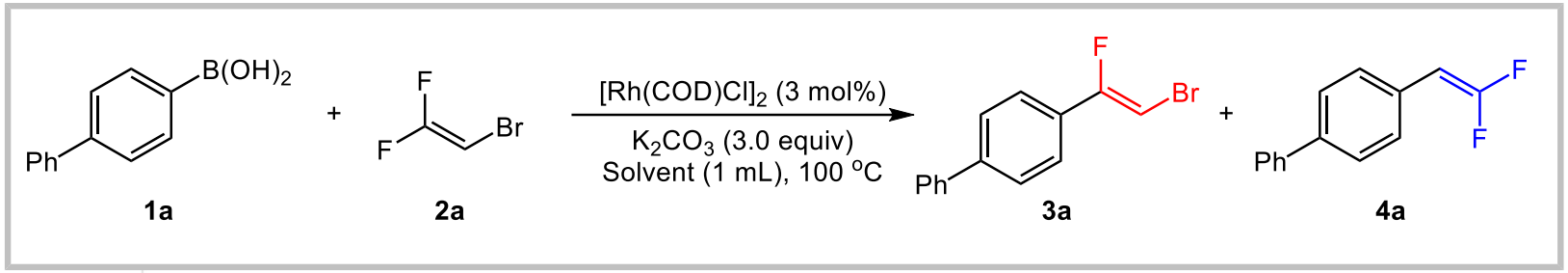


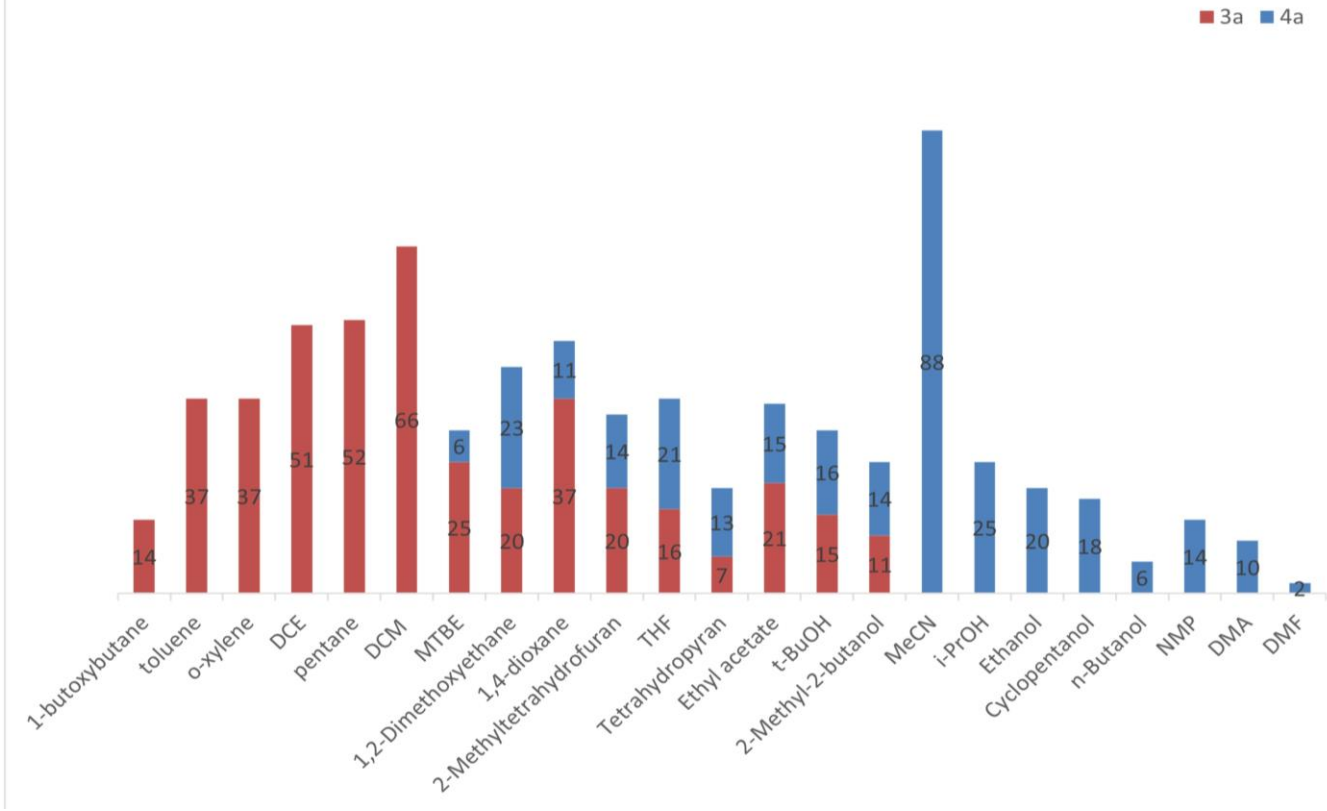
Solvent-controlled tunable synthesis of monofluoroalkenes and gem-difluoroalkenes



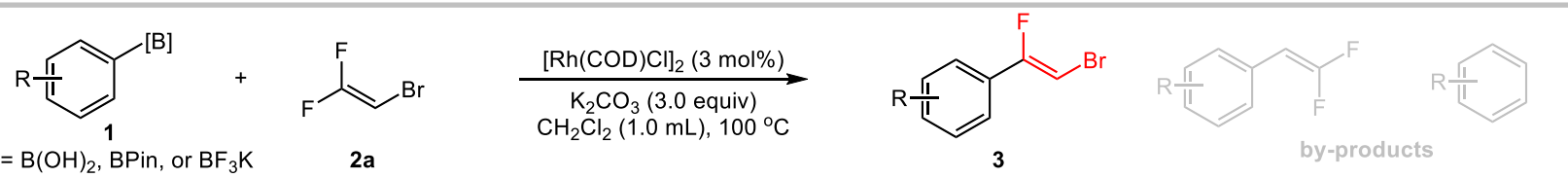


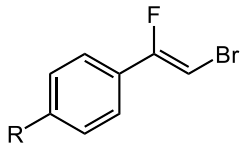
Optimization of the Reaction Conditions



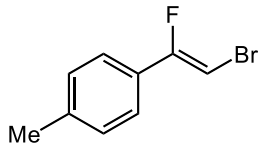


Substrate Scope

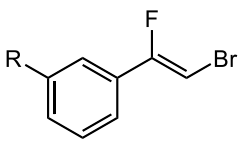




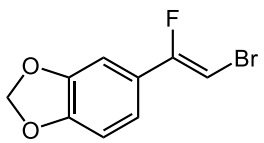
3a, R = Ph, 61%, >20:1 r.r.
3b, R = ^{t}Bu, 68%, >20:1 r.r.
3c, R = OCF_3, 59%, >20:1 r.r.
3d, R = TMS, 63%, >20:1 r.r.
3e, R = OBn, 61%, 15:1 r.r.
3f, R = SEt, 56%, >20:1 r.r.
3g, R = morpholine, 62%, 20:1 r.r.
3h, R = CH_2OH, 72%, 5:1 r.r.
3i, R = F, 86%, >20:1 r.r.
3j, R = Cl, 74%, 12:1 r.r.
3k, R = Br, 71%, 13:1 r.r.
3l, R = $COOCH_3$, 36%, 4:1 r.r.



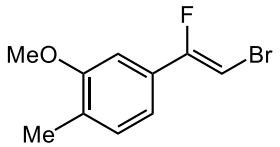
3m, 58%, >20:1 r.r.



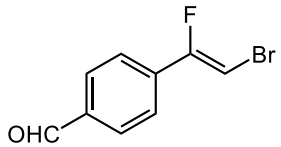
3n, R = O^{i}Pr, 61%, 17:1 r.r.
3o, R = Br, 34%, 6:1 r.r.



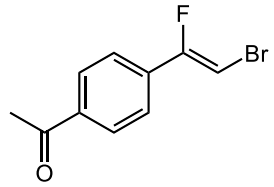
3p, 42%, >20:1 r.r.



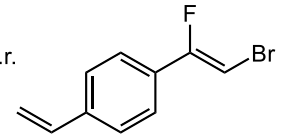
3q, 91%, 20:1 r.r.



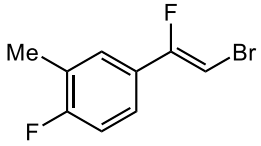
3r, 56%, 4.5:1 r.r.



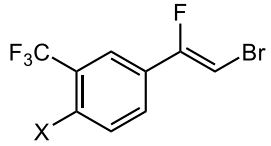
3s, 61%, 4:1 r.r.



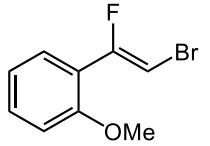
3t, 48%, 20:1 r.r.



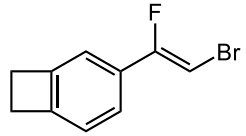
3u, 62%, >20:1 r.r.



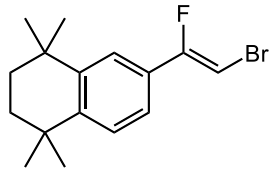
3v, X = F, 45%, 12:1 r.r.
3w, X = Cl, 42%, 10:1 r.r.



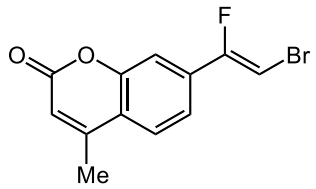
3x, 83%, 20:1 r.r.



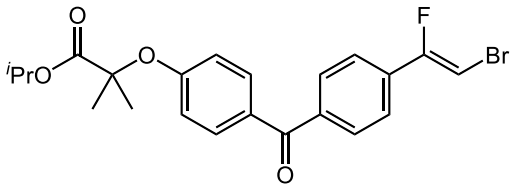
3y, 60%, >20:1 r.r.



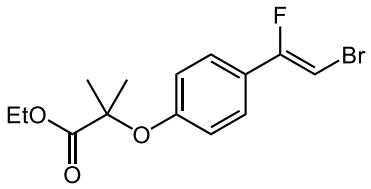
3z, 84%, 18:1 r.r.



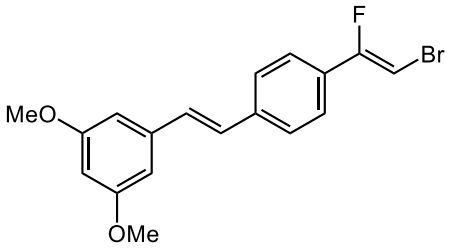
3aa, 53%, 10:1 r.r.
from **4-Methylcumarin**



3ab, 46%, 10:1 r.r.
from **Fenofibrate derivate**

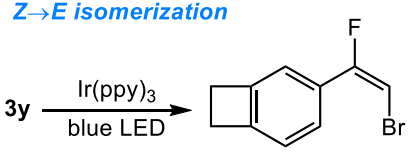


3ac, 73%, >20:1 r.r.
from **Clofibrate derivate**



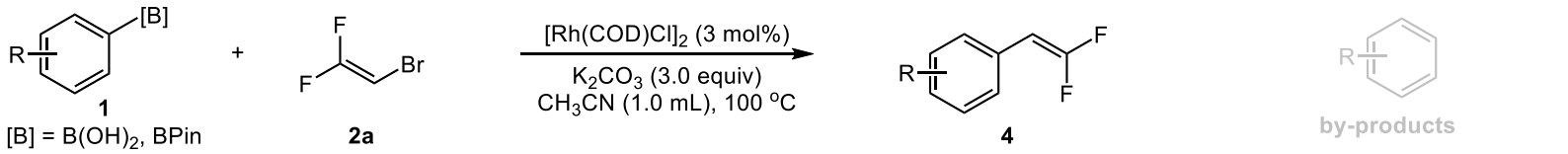
3ad, 47%, 10:1 r.r.
from **Pterostilbene**

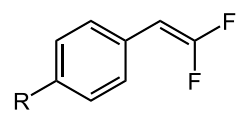
Z→E isomerization



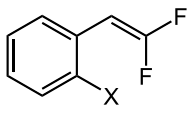
3y', *E*/*Z* = 2.6:1

Substrate Scope

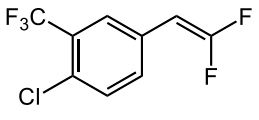




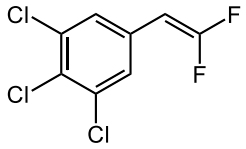
4a, R = Ph, 86%
4b, R = TMS, 67%
4c, R = $COOCH_3$, 70%
4d, R = OMe, 75%
4e, R = SEt, 70%
4f, R = I, 64%
4g, R = Br, 60%
4h, R = morpholine, 76%
4i, R = NPh_2, 53%
.



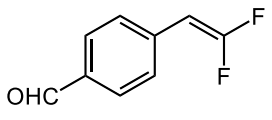
X = Cl, **4j**
X = COOEt, **4k**



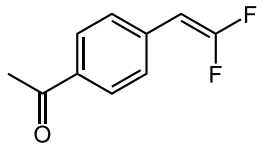
4l, 67%



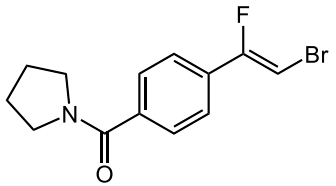
4m, 55%



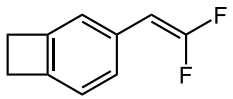
4n, 71%



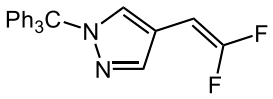
4o, 70%



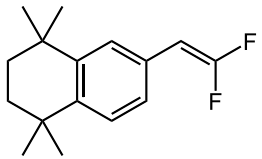
4p, 56%



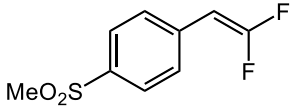
4q, 70%



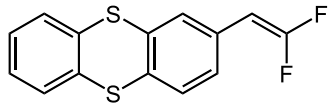
4r, 65%



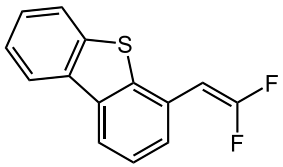
4s, 50%



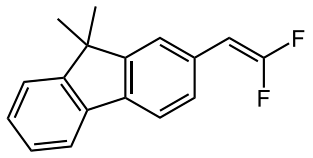
4t, 52%



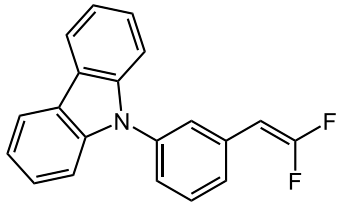
4u, 56%



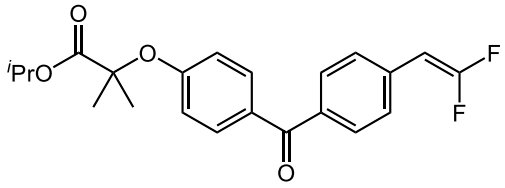
4v, 80%



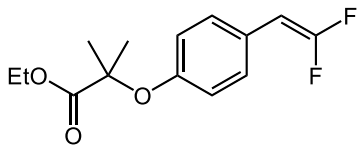
4aa, 40%



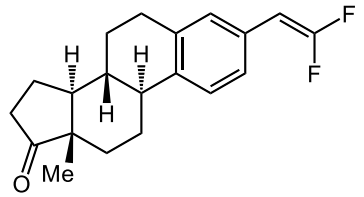
4ab, 77%



4ac, 85%
from **Fenofibrate derivate**

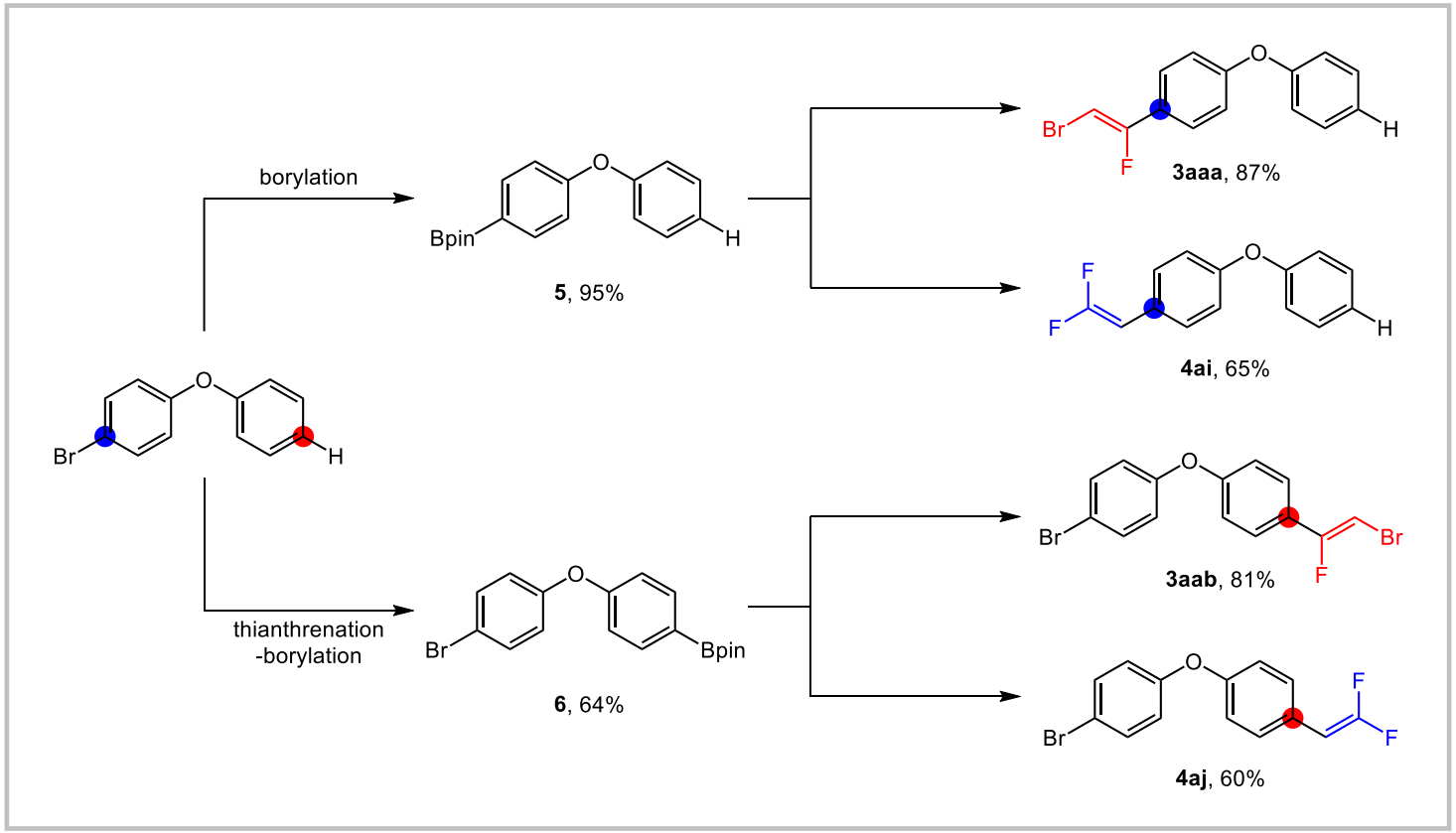


4ad, 44%
from **Clofibrate derivate**

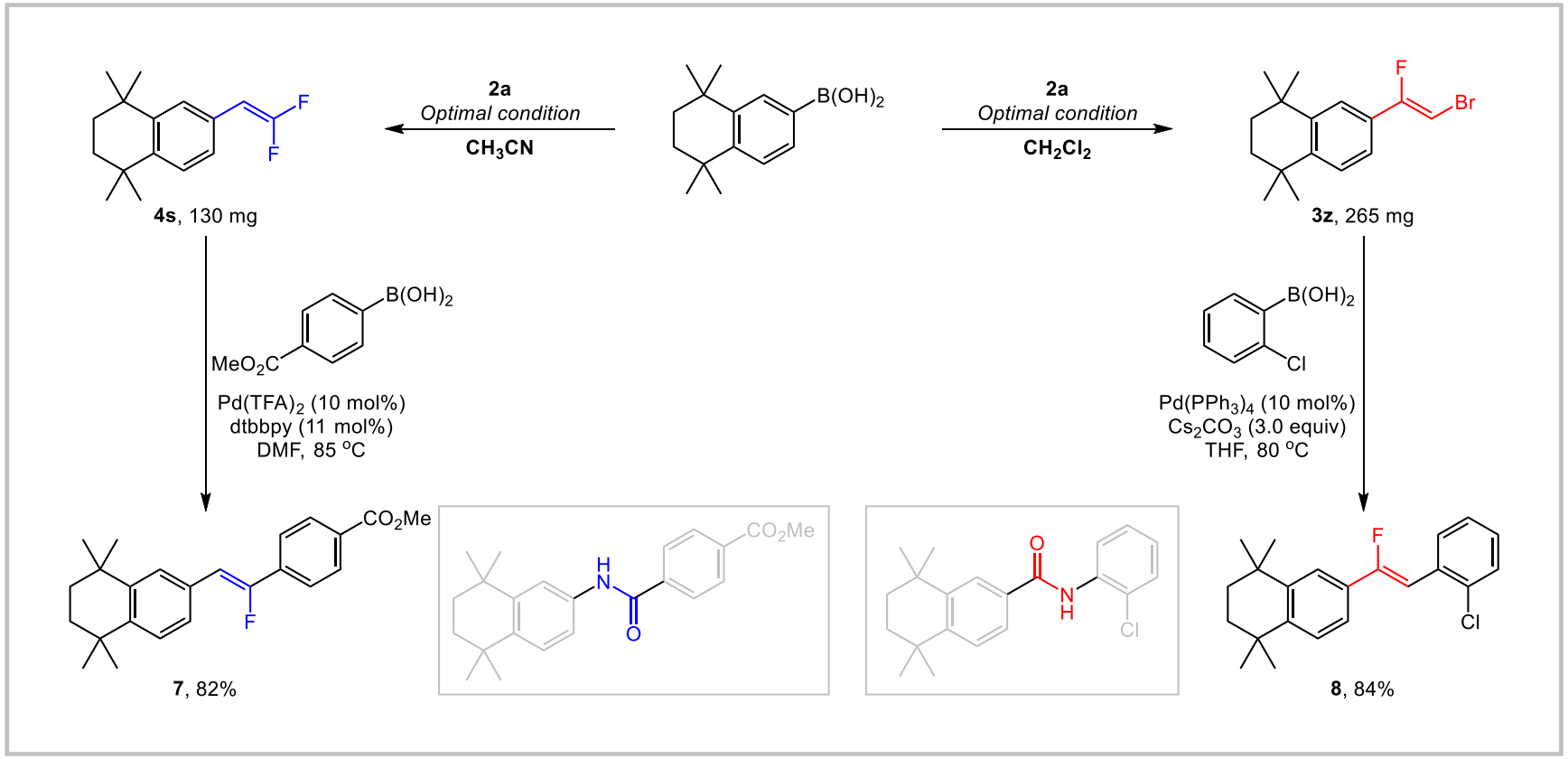


4ae, 64%
from **Estrone derivate**

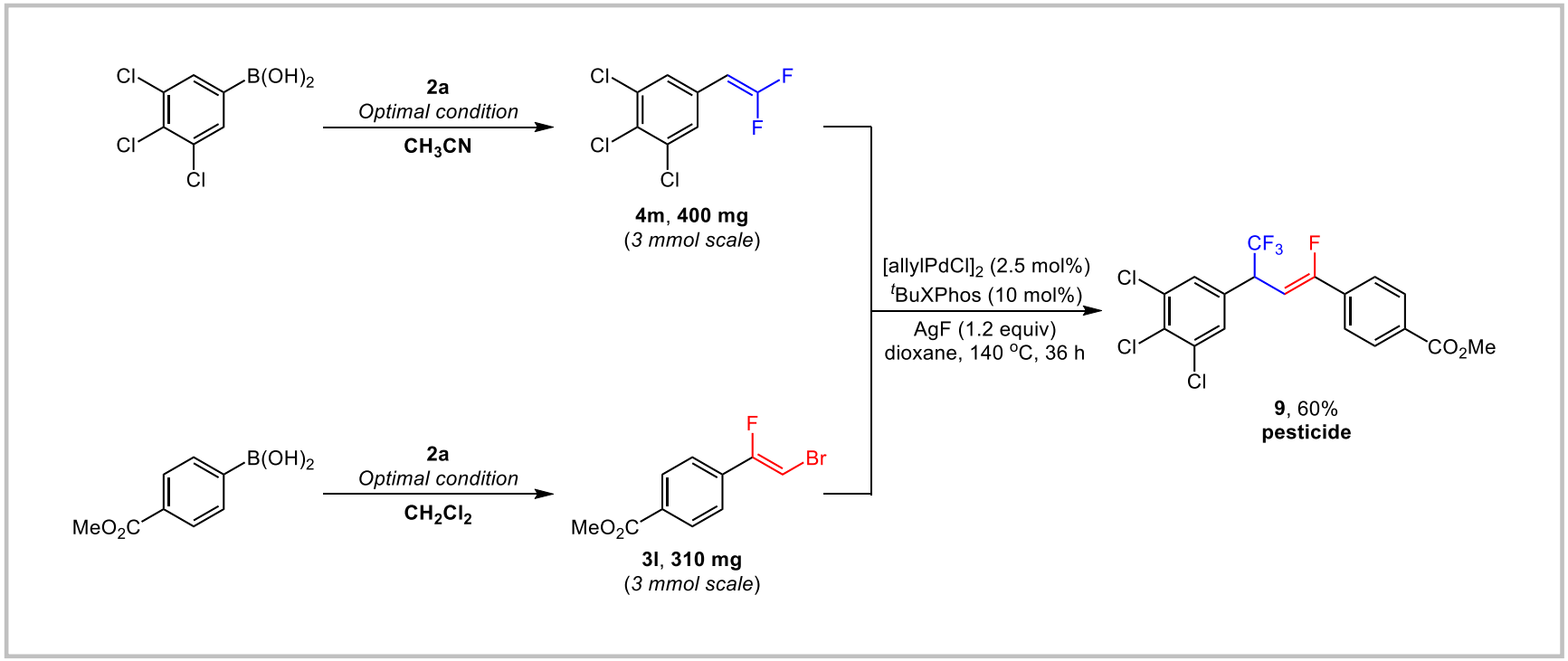
Divergent Synthesis



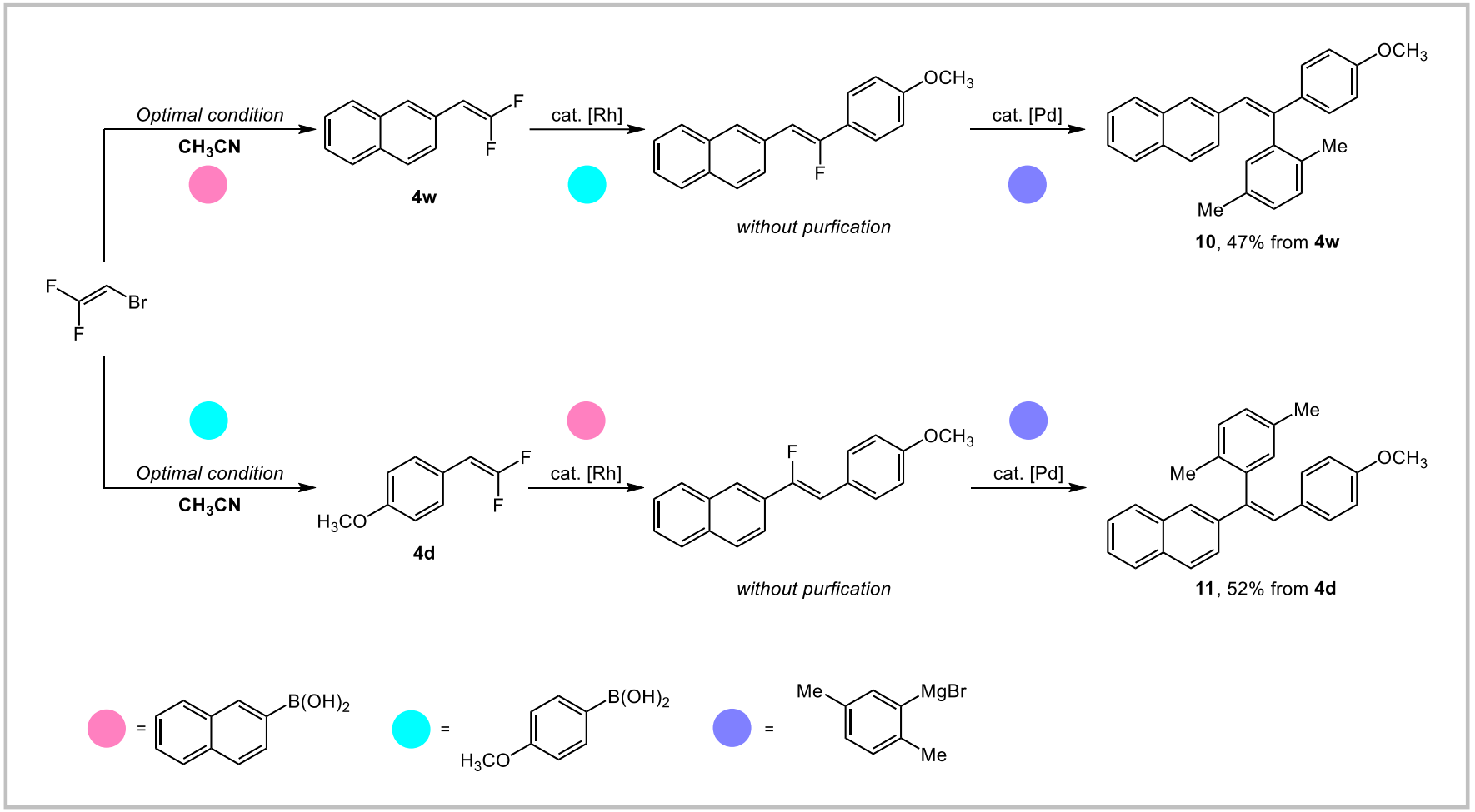
Synthesis of Bioactive Amide Analogues



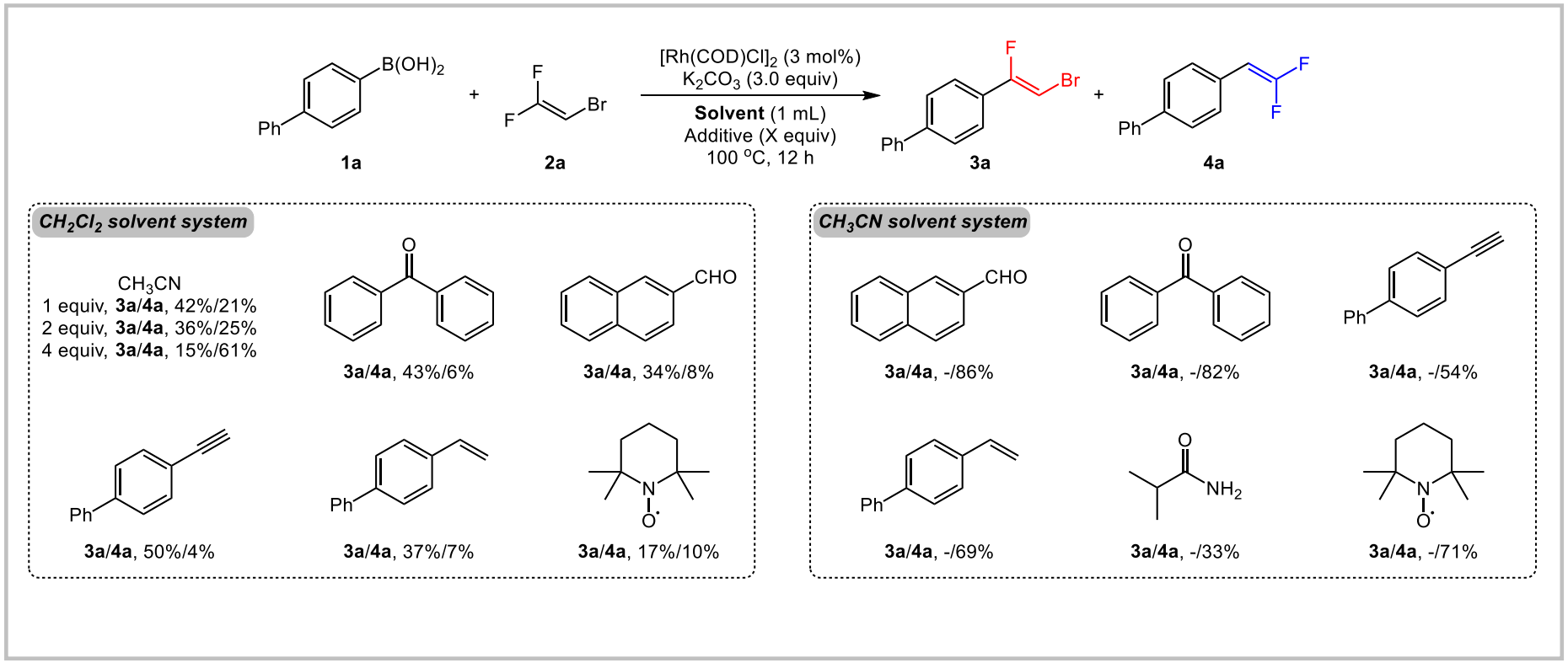
Synthesis of Pesticide



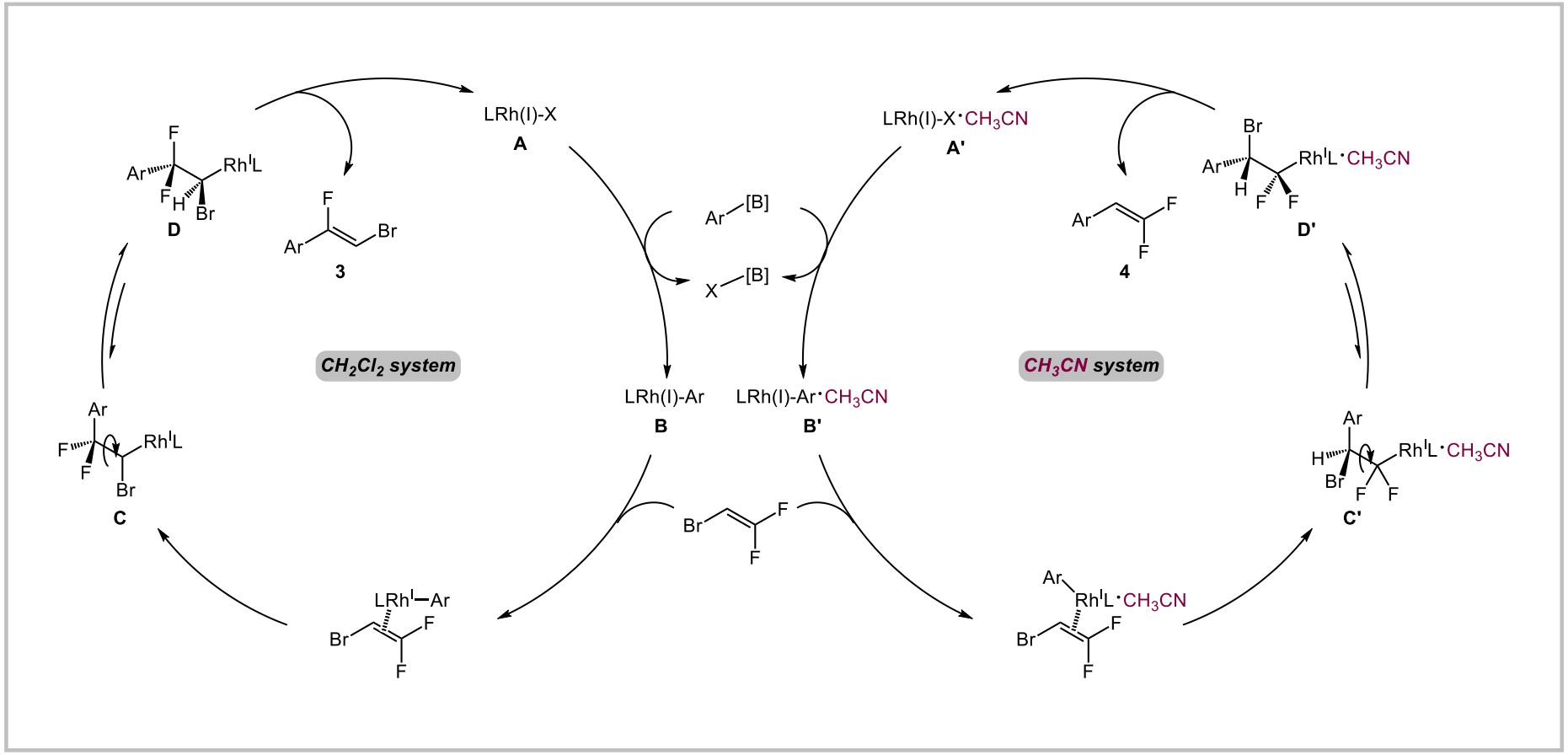
Iterative Synthesis Triaryl-Substituted Ethylene Compounds



Control Experiments

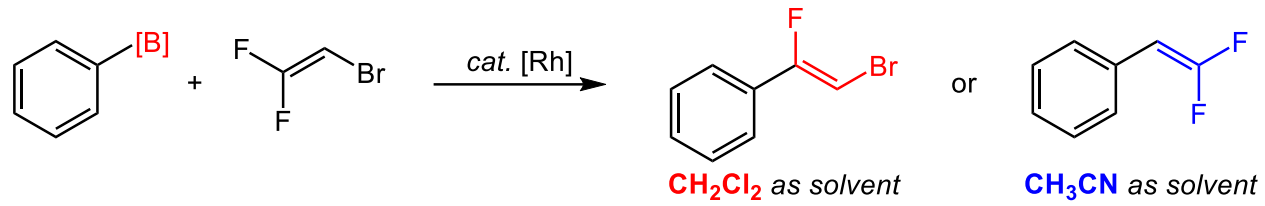


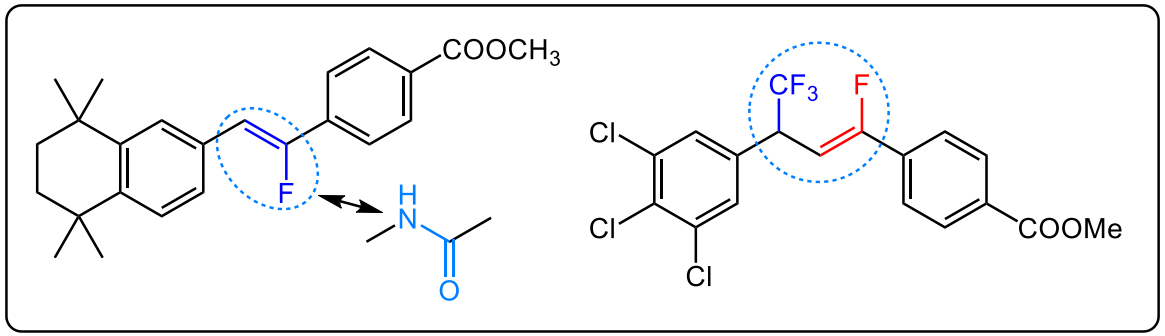
Proposed Mechanism



Summary

Solvent-controlled tunable synthesis of monofluoroalkenes and gem-difluoroalkenes





- Diversified synthesis
- Solvent-controlled
- Without an extra ligand
- Readily available substrates
- High-value fluorinated alkene compounds

Writing Strategy

The First Paragraph

Value of Organofluorine Compounds

↓

Developed Synthetic Methods

↓

The Necessity to Develop New Approach

- Organofluorine compounds play an important role in the fields of organic synthesis, medicine, agrochemicals and materials because the introduction of fluorine-containing groups into organic compounds can lead to unique lipid solubility, metabolic stability, and binding properties to biological targets.
- Since fluorine-containing compounds are extremely rare in nature, organofluorine compounds are only artificially accessible by fluorination of organic compounds⋯fully demonstrating that the development of diverse transformation reactions of fluorine building blocks is vital for the synthesis of fluorinecontaining organic compounds.
- Despite rapid progress in a myriad of methodologies, access to vital subunits of organofluorine compounds cannot satisfy the growing demand.

Writing Strategy

Last paragraph

Summary of This Work

- In conclusion, we present an example of Rh(I)-catalyzed tunable defluorinated or debrominated arylation of 1-bromo-2,2-difluoroethylene by switching the reaction solvent without the need for additional ligands. When dichloromethane was used as the solvent, selective defluorination products were obtained.

Highlights of The Current Method

- On the other hand, when acetonitrile was used as the solvent, the strong coordination between acetonitrile and the rhodium catalyst led to the formation of debromination products. ⋯ The resulting monofluoroalkenes and *gem*-difluoro-alkenes can be employed in the synthesis of pharmaceutical analogs.

Outlook of This Work

- We believe that this reaction will be a valuable addition to the toolbox of synthetic chemists. Further investigations to determine the detailed reaction mechanism and the application of this reaction are underway in our laboratory.

Representative Examples

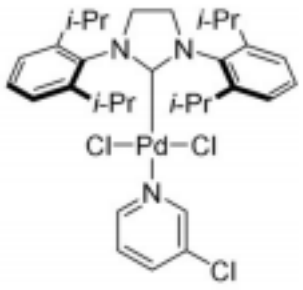
- Among many important fluorine-containing motifs, monofluoroalkenes and *gem*-difluoroalkenes, as mimics of amide and carbonyl groups, respectively, have received extensive attention in the field of drug design and development. (*v*. 模仿；*n*. 善于模仿的人/物)

- On the basis of our ongoing interest in the synthesis and application of fluoroalkenes, we described a tunable strategy that enables the synthesis of monofluoroalkenes and gem-difluoroalkenes. (*adj*. 可调谐的, 可调音的)

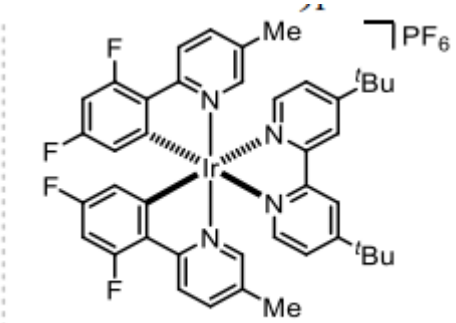
- Next, we sought more detailed insight about the mechanism of the reaction. (引出机理研究)

Acknowledgement

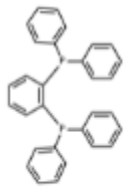
Thanks for your attention



Pd-PEPPSI-SIPr



[Ir(dF(Me)ppy)$_2$(dtbpy)]PF$_6$ (**Ir-F**)



3D Mol 相似结构

CBNumber: CB6682332
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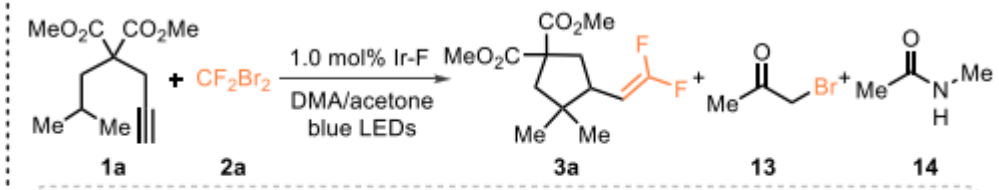
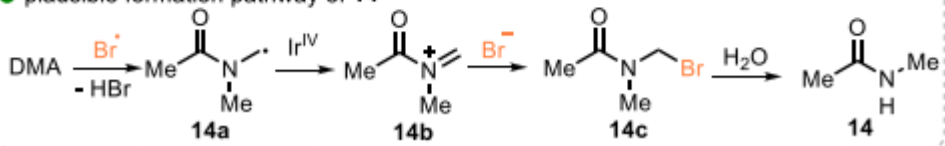
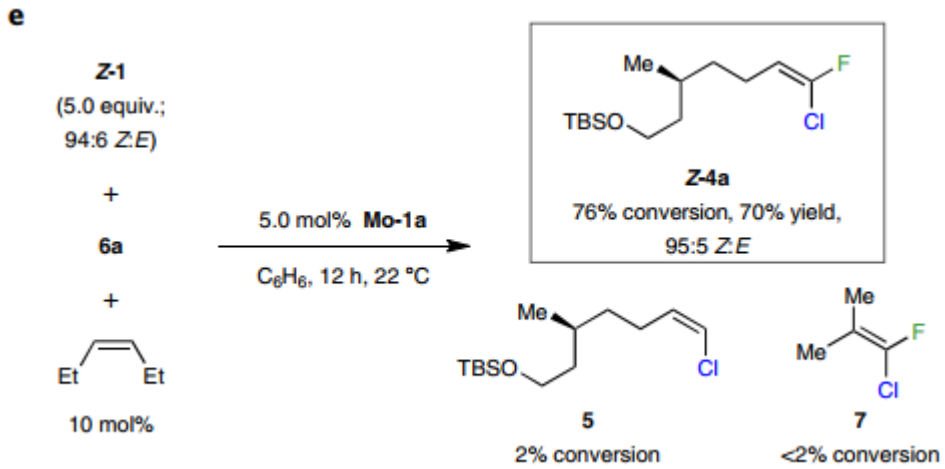
中文名称: 1,2-双(二苯基膦基)苯
MF: C30H24P2
MW: 446.47
CAS: 13991-08-7
Book指数: 8级

d) Detection of by-products via GCMS analysis

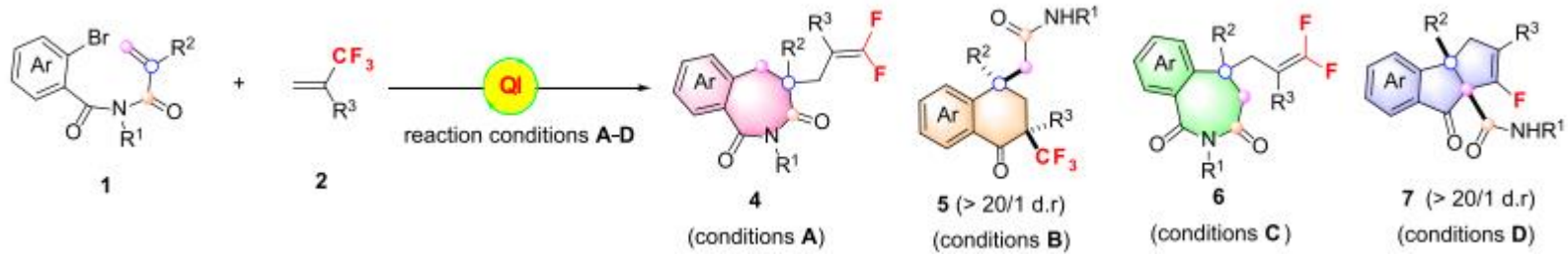


● plausible formation pathway of **14**



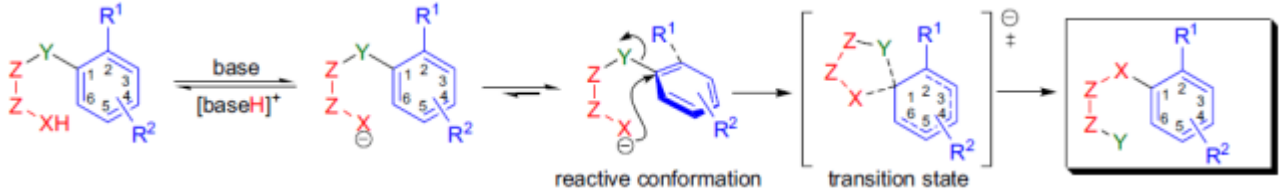


In the event, with 10 mol% of a *Z*-1,2-disubstituted olefin, the reaction takes place readily and with exceptional stereochemical control.

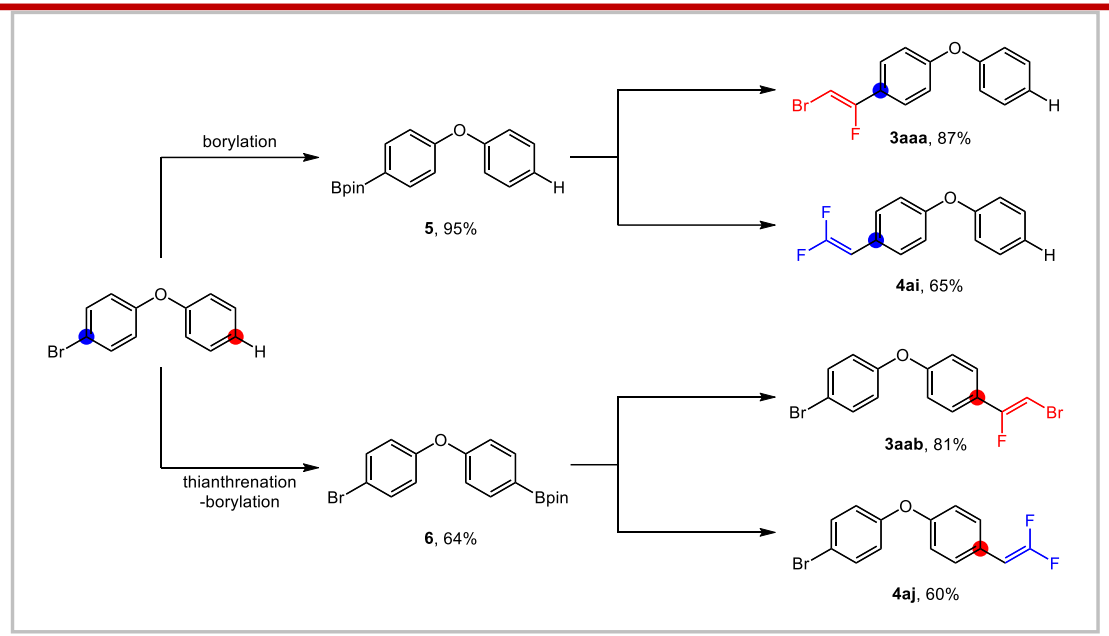


[a]Reaction conditions: (A) **1** (0.1 mmol), **2** (0.3 mmol), $NiBr_2$(DME) (10.0 mol %), **L4** (20.0 mol %), Mn^0 (0.3 mmol), LiO^tBu (0.1 mmol), DMSO (2 mL), 4 Å MS (20 mg), 80 °C, 48 h; (B) **1** (0.1 mmol), **2** (0.2 mmol), $Ni(acac)_2$ (10.0 mol %), **L6** (20.0 mol %), Mn^0 (0.3 mmol), $MnBr_2$ (0.1 mmol), 4 Å MS (20 mg), DMSO (1 mL), THF (1 mL), 25 °C, 48−72 h; (C) **1** (0.1 mmol), **2** (0.2 mmol), $Ni(acac)_2$ (10.0 mol %), **L6** (20.0 mol %), Mn^0 (0.2 mmol), KI (0.2 mmol),4 Å MS (20 mg), DMSO (0.2 mL), THF (1.8 mL), 80 °C, 36−48 h; (D) 1 (0.1 mmol), **2** (0.2 mmol), $Ni(acac)_2$ (10.0 mol %), **L6** (20.0 mol %), Mn^0 (0.3 mmol), $MnBr_2$ (0.2 mmol), 4 Å MS (20 mg), DMSO (2 mL), THF (2 mL), 80 °C, and 48−96 h. (R^3 = 4-CN-C_6H_4).

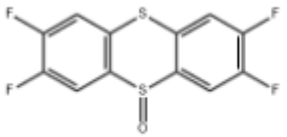
Smilies Rearrangement



Acknowledgement



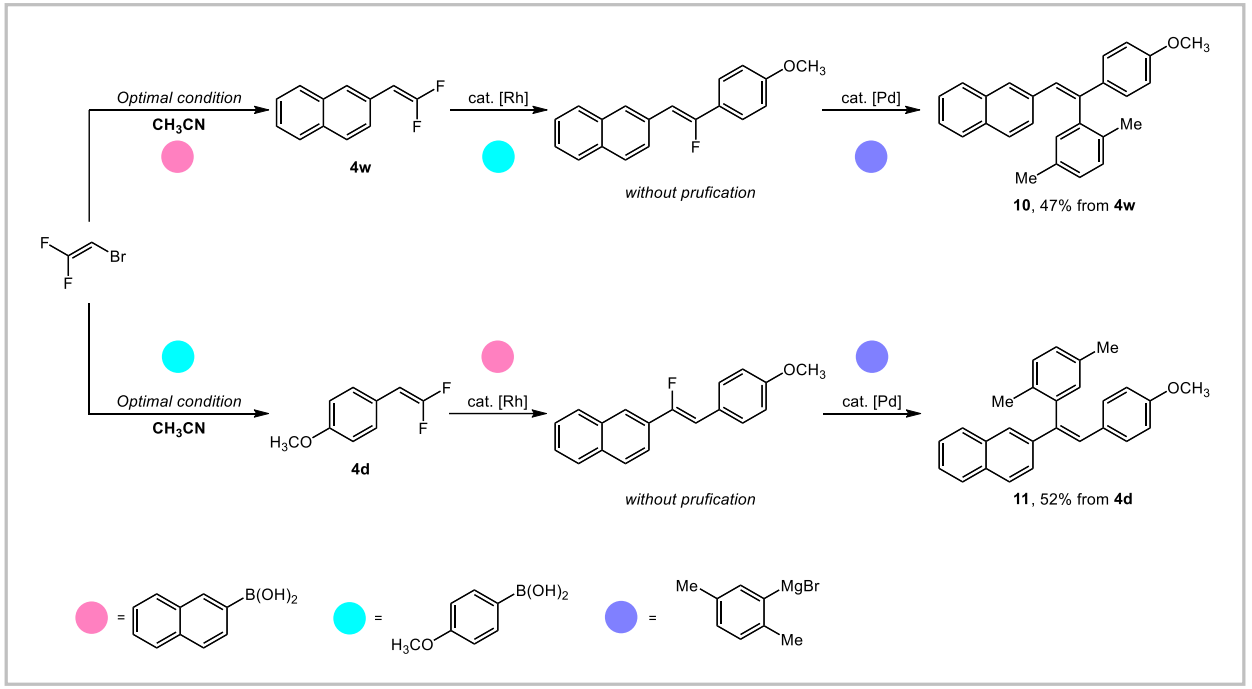
Scheme 4. Divergent synthesis. a) B_2pin_2 (1.1 equiv), $Pd(dba)_2$ (2 mol%), DPEphos (4 mol%), NaOAc (1.2 equiv), dioxane, 110 °C, 12 h. b) 1.2,3,7,8-Tetrafluoro-thianthrene-S-oxide, $(CF_3CO)_2O$ (1.5 equiv), HBF_4OEt_2 (1.1 equiv), CH_3CN, 0–25 °C, 16 h. c) Pyridine (5.0 equiv), B_2pin_2 (2.5 equiv), $Ru(bpy)_3(PF_6)_2$ (2.0 mol%), CH_3CN, blue LED 60 W, 25 °C, 16 h. d) aryl boronic ester (0.10 mmol, 1.0 equiv), 1-bromo-2,2-difluoroethylene in toluene (6.0 equiv, 0.60 mmol), $[Rh(COD)Cl]_2$ (3 mol%), K_2CO_3 (3.0 equiv), dichloromethane (1.0 mL), 100 °C, 12 h, isolated yield. e) aryl boronic ester (0.10 mmol, 1.0 equiv), 1-bromo-2,2-difluoroethylene in toluene (6.0 equiv, 0.60 mmol), $[Rh(COD)Cl]_2$ (3 mol%), K_2CO_3 (3.0 equiv), acetonitrile (1.0 mL), 100 °C, 12 h, isolated yield.



3D Mol 相似结构

CBNumber: CB05848717
英文名称: tetrafluorothianthrene S-oxide
中文名称: tetrafluorothianthrene S-oxide
MF: C12H4F4OS2
MW: 304.28
CAS: 2320491-72-1
Book指数: 2级

Acknowledgement



Scheme 5. Synthetic transformations and applications. a) $[Rh(COD)Cl]_2$ (5 mol%), BINAP (6 mol%), KOH (3.0 equiv), dioxane, 70°C, 12 h. b) $Pd(PPh_3)_4$, Et_2O, 30°C, 2 h.