Reactivity of *gem*-difluoroallene

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Supervisor: Prof. Shengming Ma
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Date: 2024.3.29

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Introduction: F

- About 20% of marketed drugs and 30% of agrichemicals contain one or more fluorine atoms!

- Introduced F can modify:

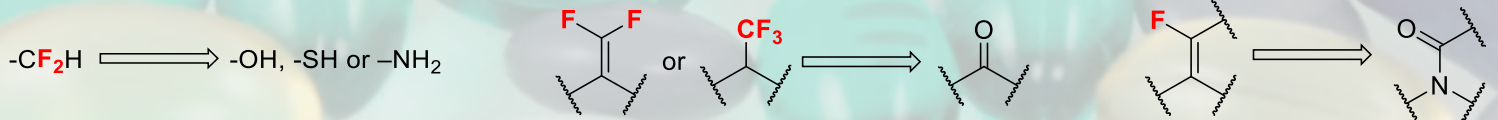
pK$_a$
Hydrogen bonding
Electrostatic
Interactions
Conformation
Lipophilicity
……

Tuning

Selectivity
Potency
Membrane Permeability
pharmacokinetic properties
Metabolic stability
……

- Bioisosterism: the capacity of atoms or functional groups with similar sizes or shapes to be interchanged without substantially altering biological behavior such as binding affinity

C-F(1.35 Å): between C-H (1.09 Å) and C-O (1.43 Å)

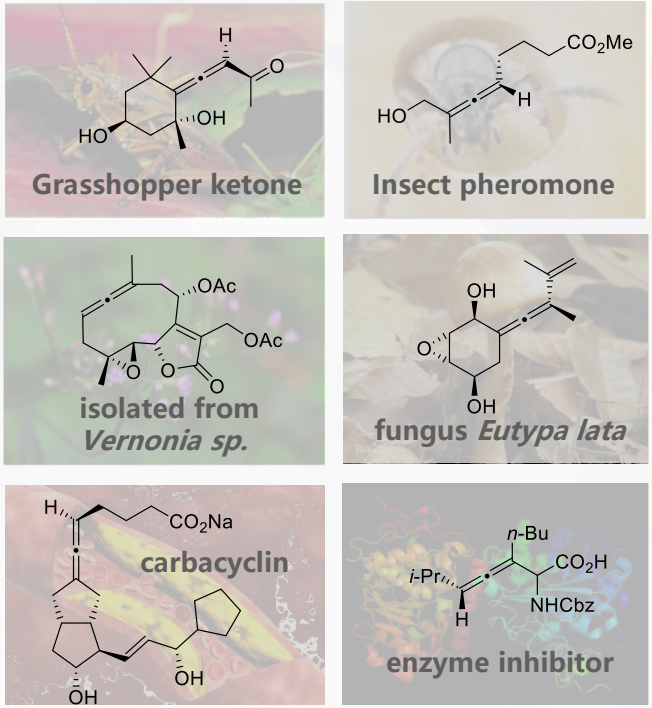


- …

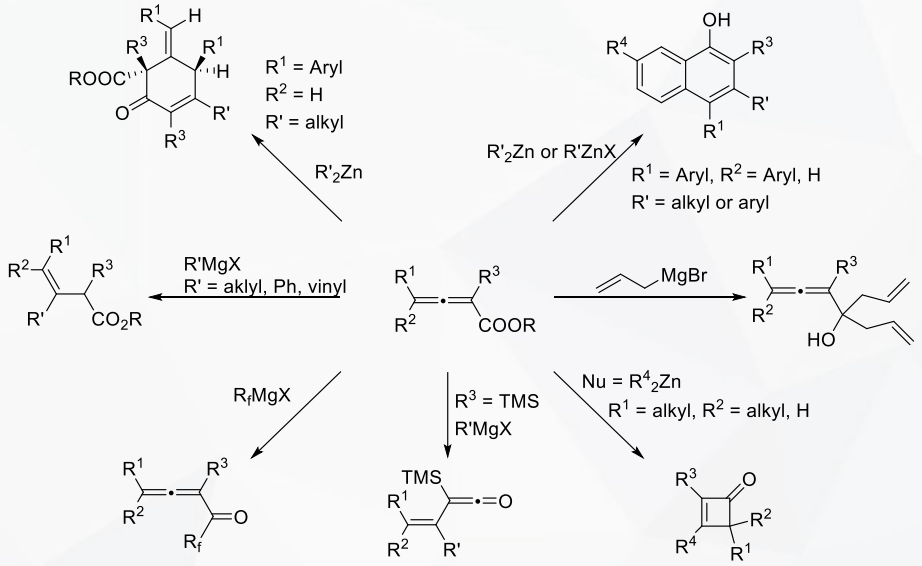
a) K. Müller, et al. *Science* **2007**, *317*, 1881. b) E. P. Gillis, et al. *J. Med. Chem.* **2015**, *58*, 8315.
c) S. Caron. *Org. Process Res. Dev.* **2020**, *24*, 470. d) V. Gouverneur, et al. *Chem. Soc. Rev.* **2008**, *37*, 320.

Introduction: allene

Allenic Natural Products and Pharmaceuticals



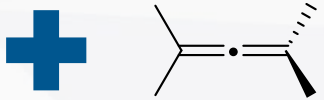
Allene as multifunctional synthon



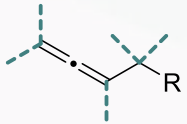
Examples of Nucleophilic Addition and Cyclization of allenoic acids

a) A. Hoffmann-Röder & N. Krause. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196. b) S. Ma. *Acc. Chem. Res.* **2009**, *42*, 1679.
c) S. Ma. *Acc. Chem. Res.* **2003**, *36*, 701. d) S. Ma., et al. *Acc. Chem. Res.* **2014**, *47*, 989.

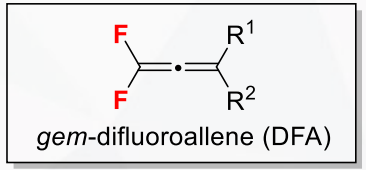
Introduction: *gem*-difluoroallene (DFA)



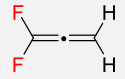
Potential Fluorinating synthons



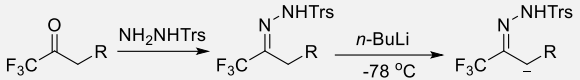
fluoro-allene



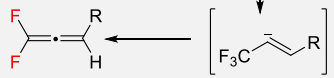
Synthesis of DFA



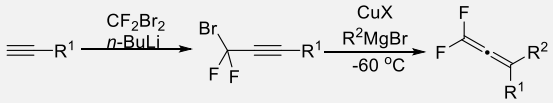
- Hard to synthesize
- No substituents



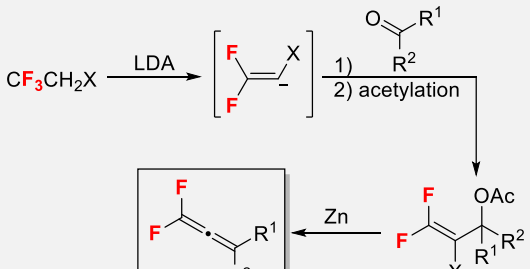
Xu's method



Hammond's method

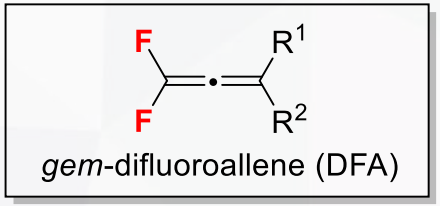


Ichikawa's general method

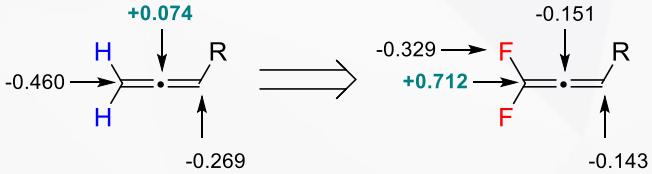


a) W. H. Knoth & D. D. Coffman. *J. Am. Chem. Soc.* **1960**, *82*, 3872. b) Y. Xu, et al. *J. Fluorine Chem.* **1989**, *44*, 161.
c) G. B. Hammond, et al. *J. Org. Chem.* **2000**, *65*, 6547. d) J. Ichikawa, et al. *Org. Synth.* **2016**, *93*, 352.

Introduction: *gem*-difluoroallene (DFA)



NBO (natural bond order) of allene and DFA



LUMO coefficient of DFA

$F_2C{=}C{=}CH_2$ (α β γ)	α	β	γ
LUMO Coefficient:	0.275	0.581	**0.693**

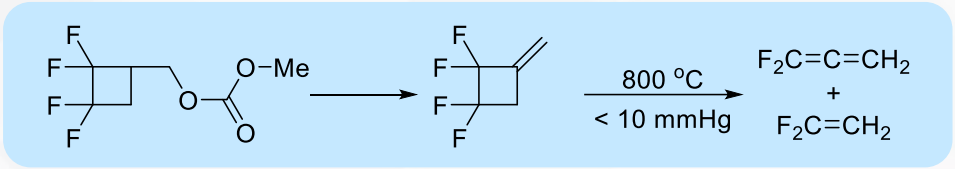
- The electrostatic distribution is different from that of general allenes
- LUMO concentrate on C^{γ}

Different reactivity and selectivity !

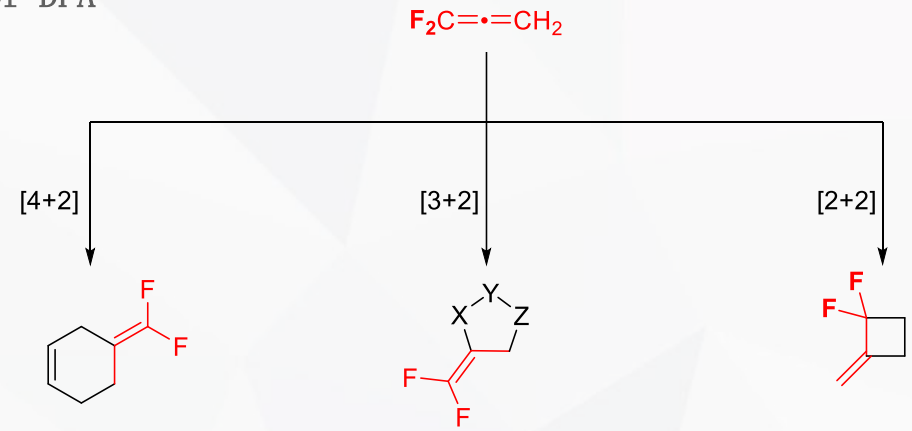
a) Z. Shi, et al. *Nat. Synth.* **2022**, *1*, 227. b) J. Ichikawa, et al. *Chem. Lett.* **2012**, *41*, 1619.

Contents

Cycloadditions: Preliminary studies of DFA



Cycloadditions of DFA



Experimental results & calculations

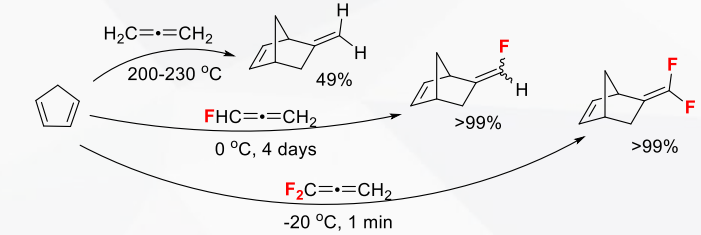
- Reactivity
- Regio-selectivity
- …

a) J. L. Anderson, et al. U.S. Patent 2733278, **1956**. b) W. R. Dolbier, Jr. *Acc. Chem. Res.* **1991**, *24*, 63.

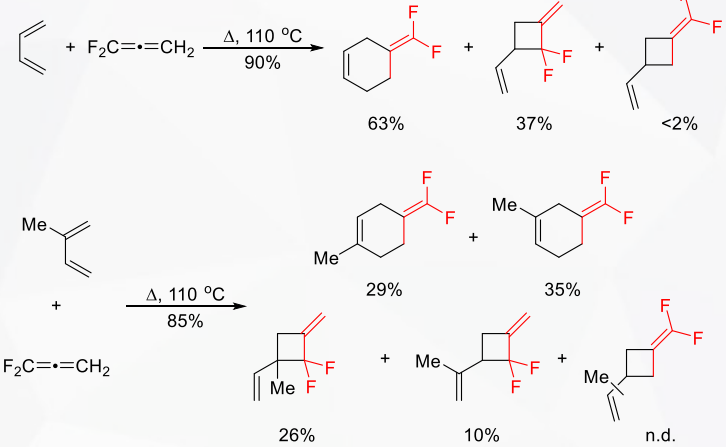
Cycloadditions: [4+2] & [2+2]

Dolbier

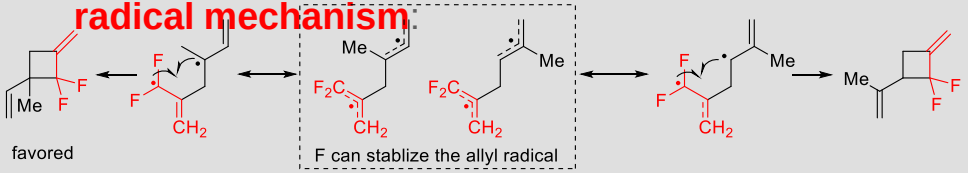
Comparison of reactivity in D-A reaction

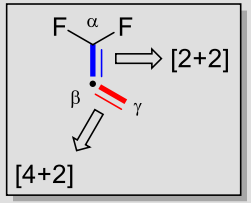


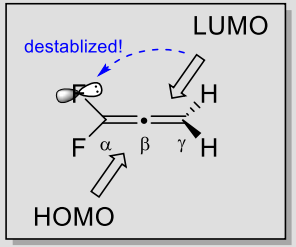
Acyclic diene:



- [4+2]: Greater reactivity than general allene. Regio-specifically reacted at $C^{\beta}=C^{\gamma}$, but bad orientation effect, underwent **concerted mechanism**.
- [2+2]: mainly reacted at $C^{\alpha}=C^{\beta}$, with relatively good orientation effect, underwent **stepwise di-radical mechanism**.





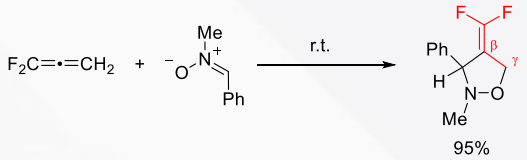


a) W. R. Dolbier, Jr. *Acc. Chem. Res.* **1991**, *24*, 63. b) W. R. Dolbier, Jr., et al. *J. Org. Chem.* **1984**, *49*, 13, 2381.
c) W. R. Dolbier, Jr., et al. *Tetrahedron Lett.* **1978**, *26*, 2231. d) K. N. Houk, et al. *J. Am. Chem. Soc.* **1978**, *100*, 6908.

Cycloadditions: [3+2] 1,3-dipolar cycloadditions

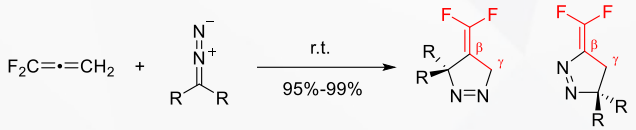
[3+2]: obeys Woodward-Hoffmann rules, undergoes **concerted, suprafacial-suprafacial mechanism** with $HOMO^{dipole}$ to $LUMO^{DFA}$ FMO interaction, like [4+2].

Nitrone as dipole:

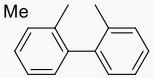


95%

Diazomethane as dipole:

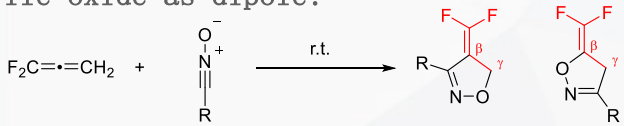


ratio of regioisomers

R = Me	61%	39%
R = 	28%	72%
R = Ph	14%	86%

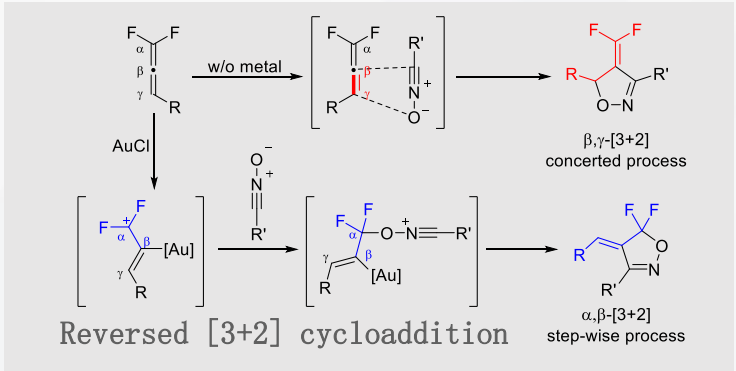
Mes = 2,4,6-trimethylbenzo-

Nitrile oxide as dipole:



ratio of regioisomers

R = Ph (75%)	56%	44%
R = Mes (94%)	>99%	

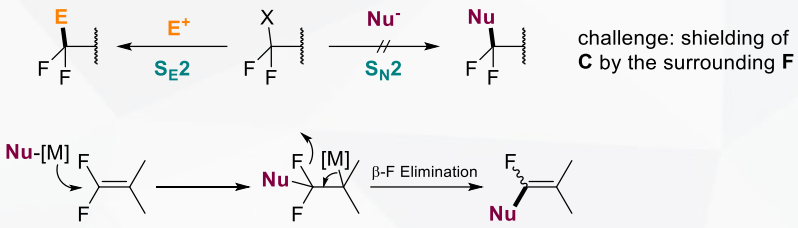


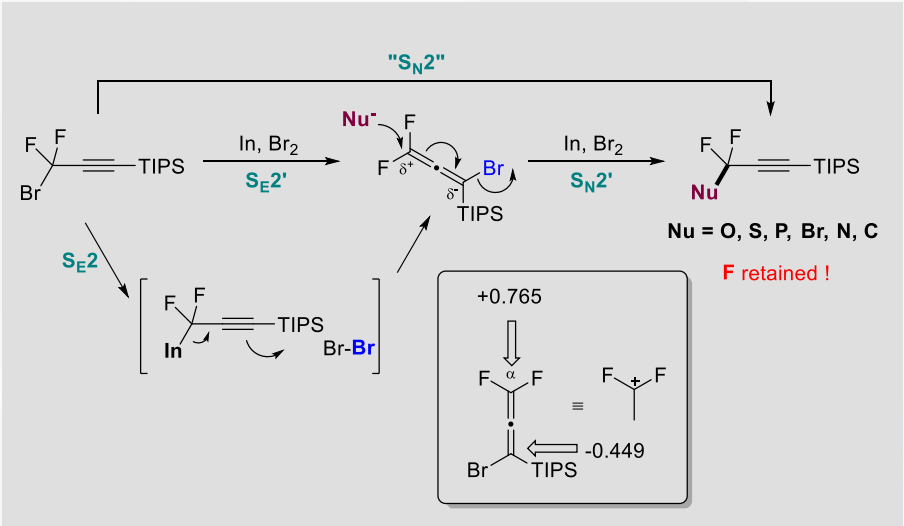
a) W. R. Dolbier, Jr. *Acc. Chem. Res.* **1991**, *24*, 63. b) W. R. Dolbier, Jr., et al. *Isr. J. Chem.* **1985**, *26*,115.
c) W. R. Dolbier, Jr. *Tetrahedron Lett.* **1990**, *46*, 7991. d) K. Fuchibe, J. Ichikawa, et al. *Org. Lett.* **2023**, *25*, 7258.

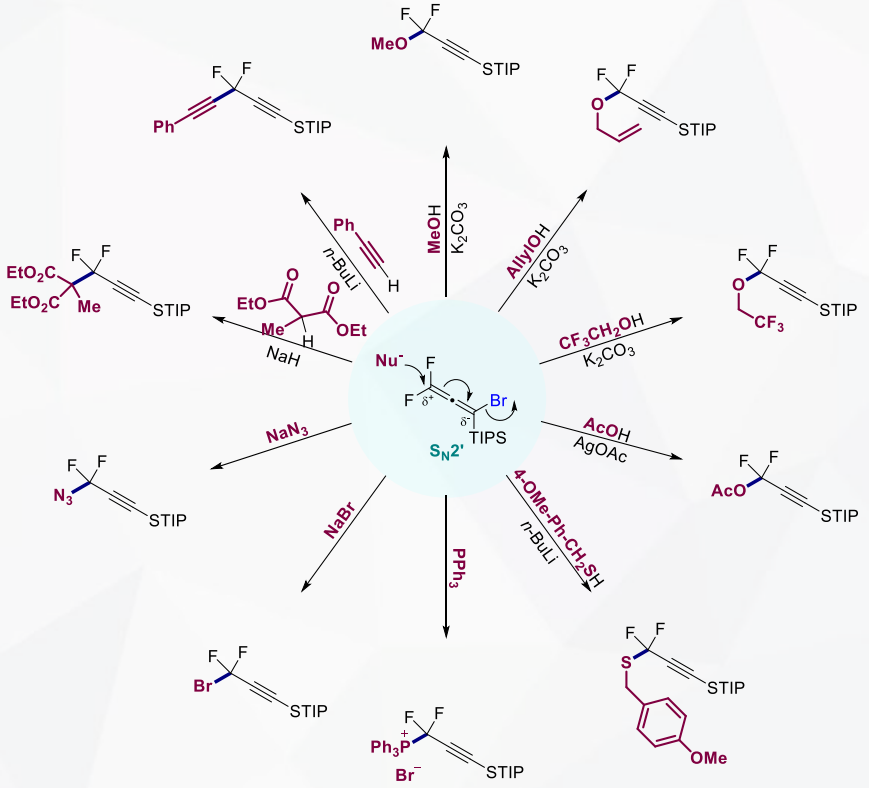
Contents

Bond forming at α-site: S_N2'-type substitution

Hammond





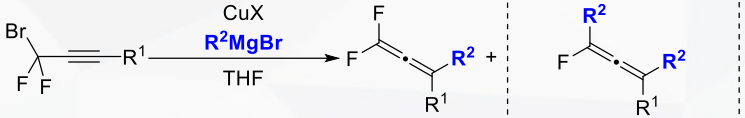


G. B. Hammond, et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 7404.

Bond forming at α-site: F substitution (S_NV)

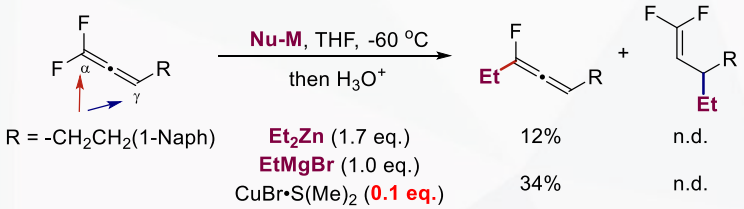
Hammond & Ichikawa

Observed in optimization & scope studies in Hammond's work:

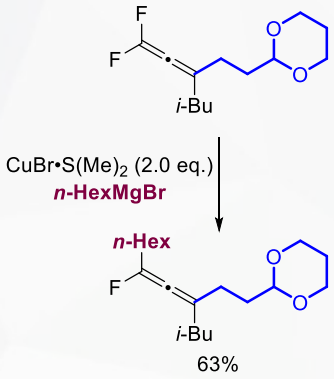


second nucleophilic attack

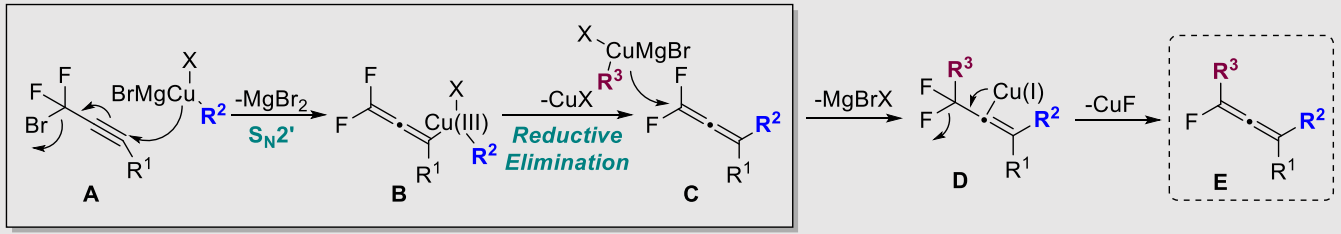
In optimization of Ichikawa's work:



Experimental evidence:



Proposed mechanism



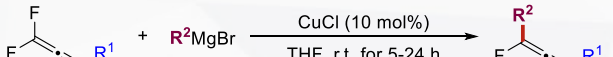
S_NV: Nucleophilic vinylic substitution

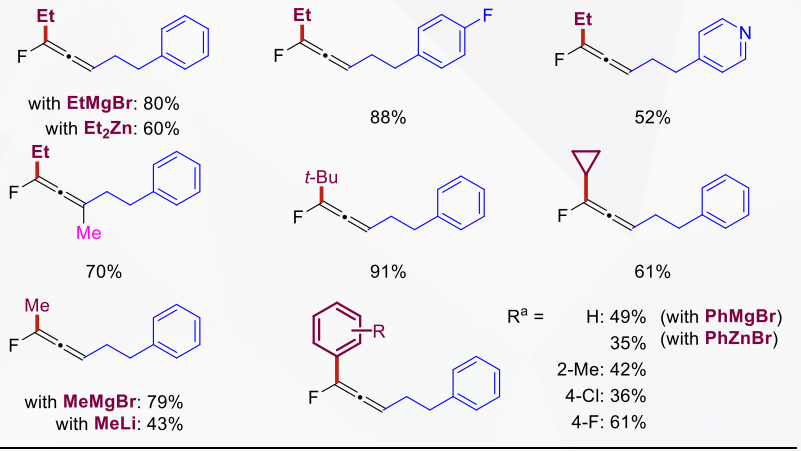
a) G. B. Hammond, et al. *Org. Lett.* **2006**, *8(3)*, 479. b) J. Ichikawa, et al. *Chem. Lett.* **2012**, *41*, 1619.

Bond forming at α-site: F substitution (S_NV)

Wu

More in-depth study by Wu's group

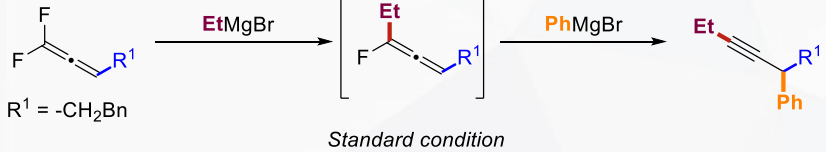




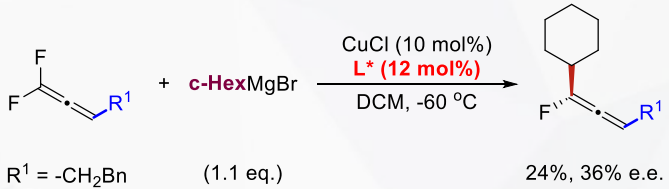
[a] -60°C

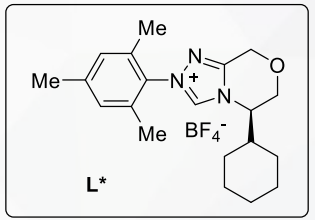
Application

- Tandem & step-by-step further nucleophilic attack



- Asymmetric trails



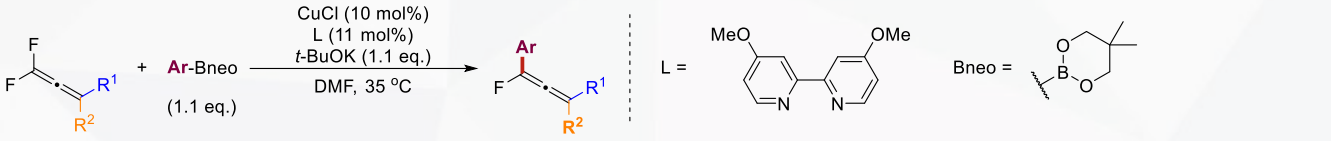


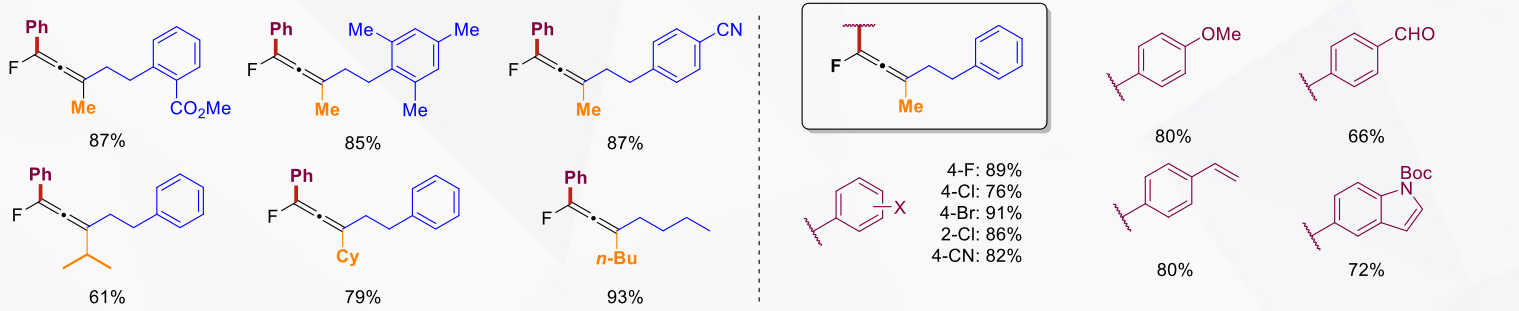
T. Wu, et al. *Eur. J. Org. Chem.* **2024**, *27*, e202300869.

Bond forming at α-site: F substitution (S_NV)

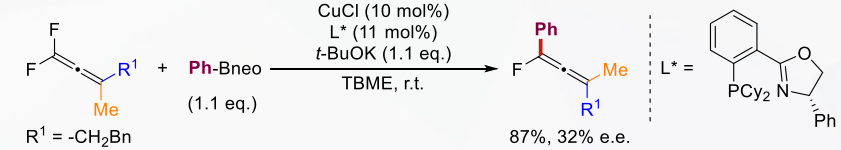
Wu

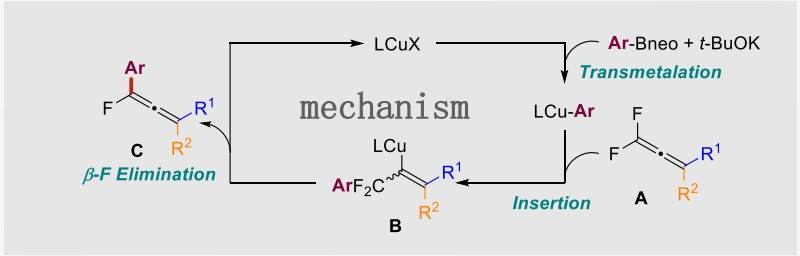
Defluoroarylation with aryl boronic esters





Asymmetric trails:



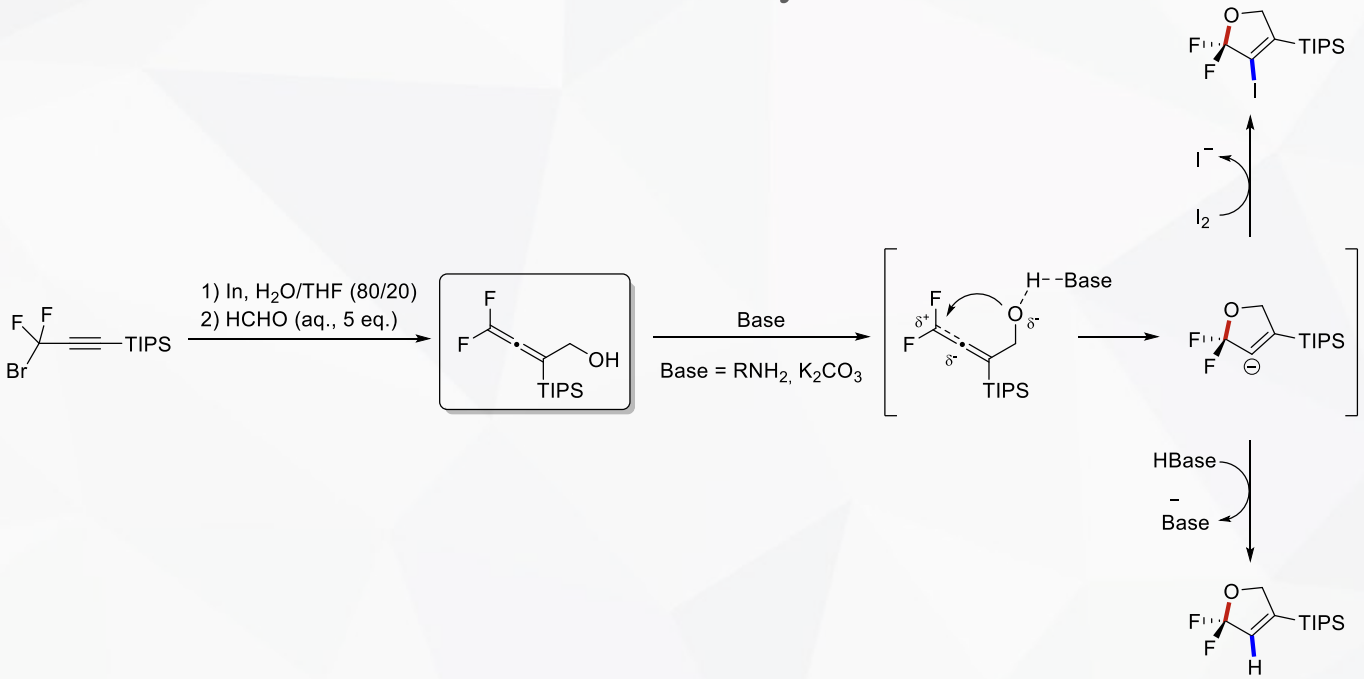


T. Wu, et al. *Org. Lett.* **2023**, *25*, 4546.

Bond forming at α-site: Addition

Hammond

Intramolecular cyclization

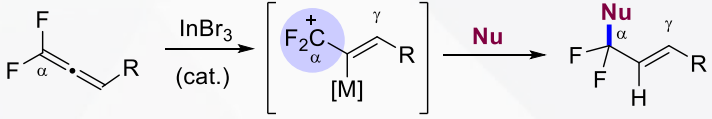


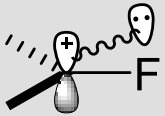
a) G. B. Hammond, et al. *J. Org. Chem.* **2000**, *65*, 6547. b) G. B. Hammond, et al. *J. Org. Chem.* **2008**, *73*, 2886.

Bond forming at α-site: Addition

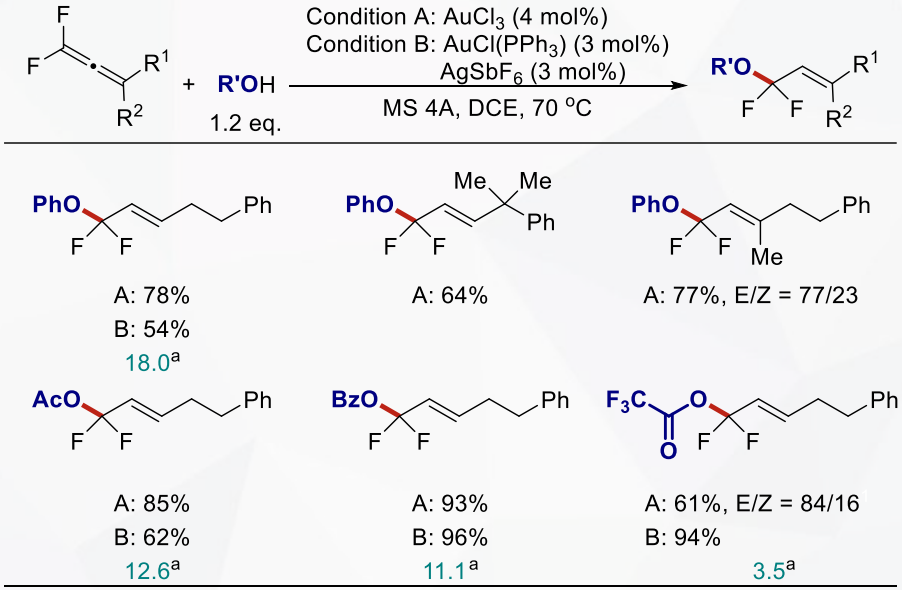
Ichikawa

Intermolecular addition





α -Cation stabilizing effect



[a] pKa of R'OH in DMSO

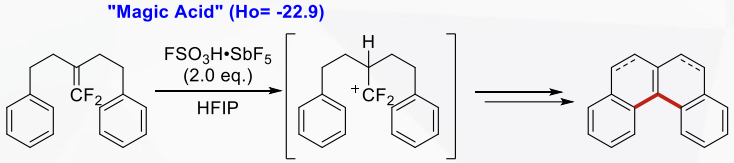
J. Ichikawa, et al. *J. Fluorine Chem.* **2020**, *232*, 109452.

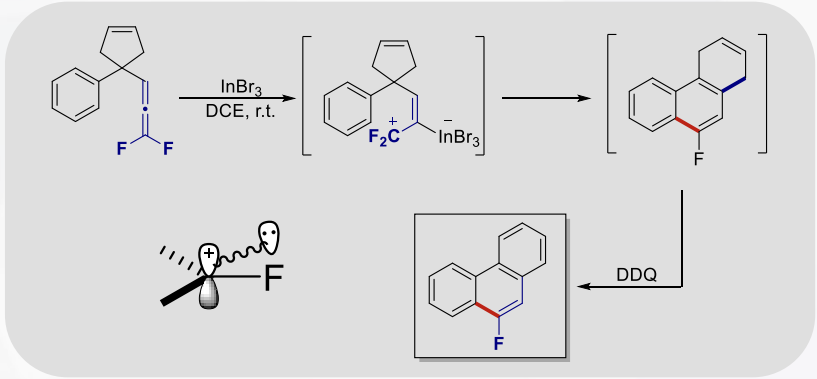
Bond forming at α-site: F-C type domino synthesis of PAHs

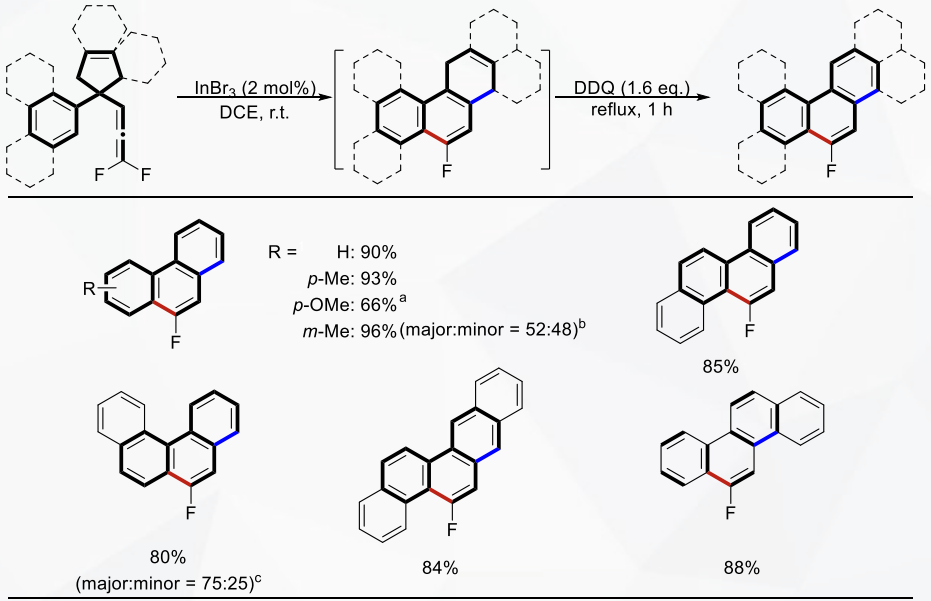
Ichikawa

Friedel-Crafts type cyclization to form polycyclic aromatic hydrocarbons (PAHs): domino synthesis

Previous work:







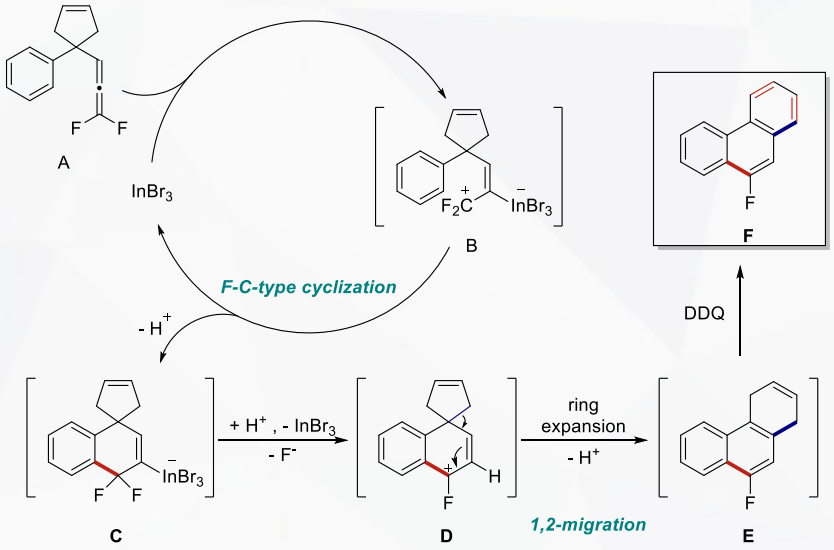
[a] 10 mol% $InBr_3$. [b] major product was reacted at *p*-site of Me, while minor product was at *o*-site.
[c] minor product was formed by sequential cyclization at the *ipso* position and a double ring expansion

J. Ichikawa, et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 7825.

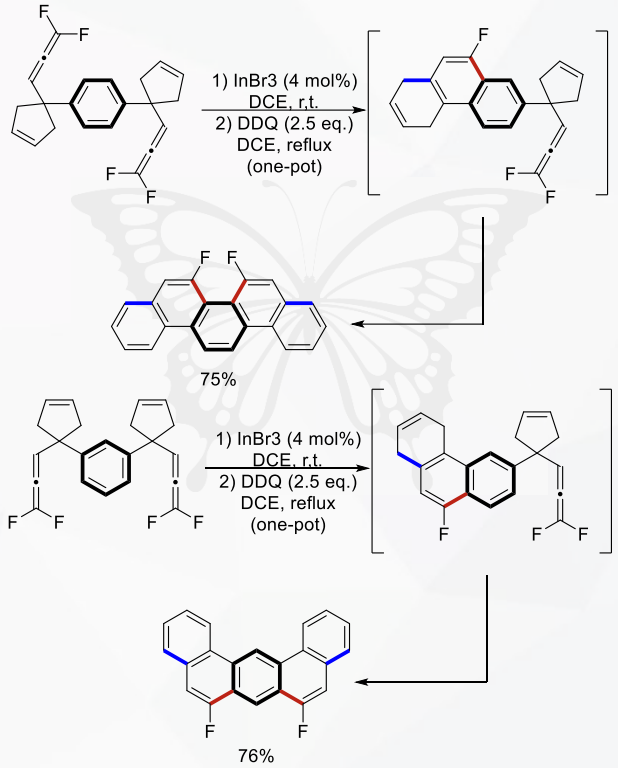
Bond forming at α-site: F-C type domino synthesis of PAHs

Ichikawa

Proposed mechanism



Tandem synthesis of difluoro-PAHs

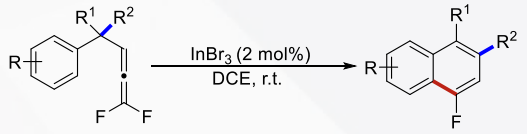


a) J. Ichikawa, et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 7825. b) J. Ichikawa, et al. *J. Fluorine Chem.* **2017**, *203*, 173.

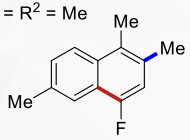
Bond forming at α-site: F-C type domino synthesis of PAHs

Ichikawa

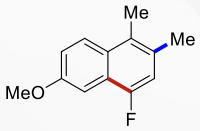
Synthesis of 1-fluoro-naphthalenes (acyclic substrates at benzyl site)



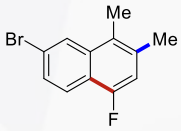
$R^1 = R^2 = Me$



85%

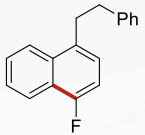


56%

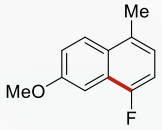


74%

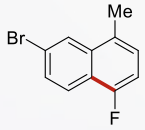
$R^1 \neq R^2 = H$



83%

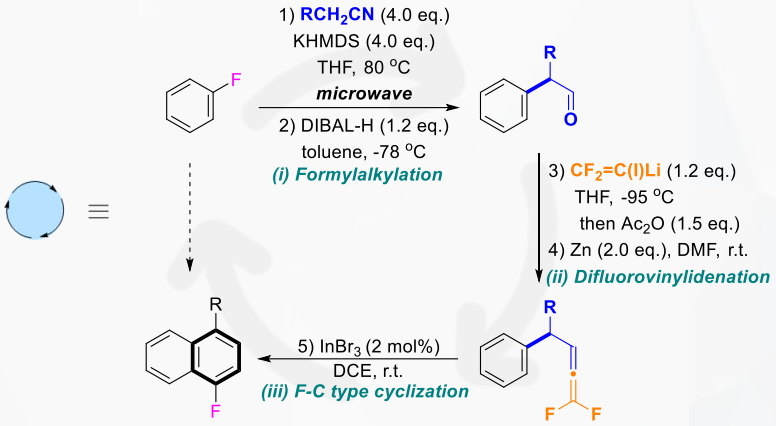


65%

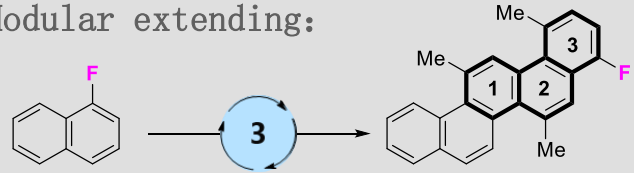


74%

Benzene Ring Extension



Modular extending:

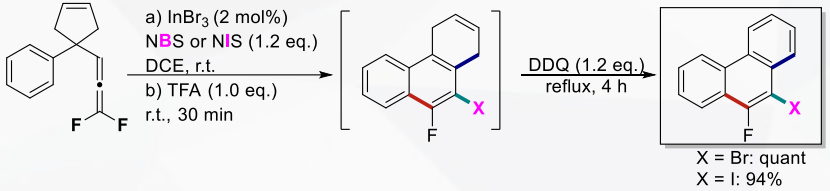


a) J. Ichikawa, et al. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 942. b) J. Ichikawa, et al. *J. Chem. Asian J.* **2017**, *12*, 2359.

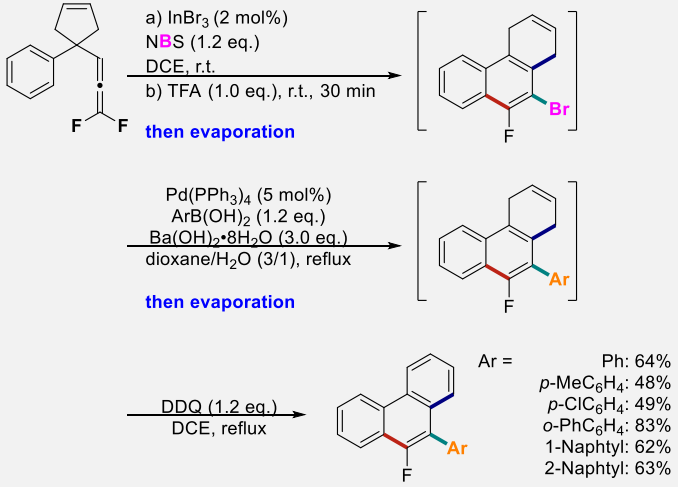
Bond forming at α-site: F-C type domino synthesis of PAHs

Ichikawa

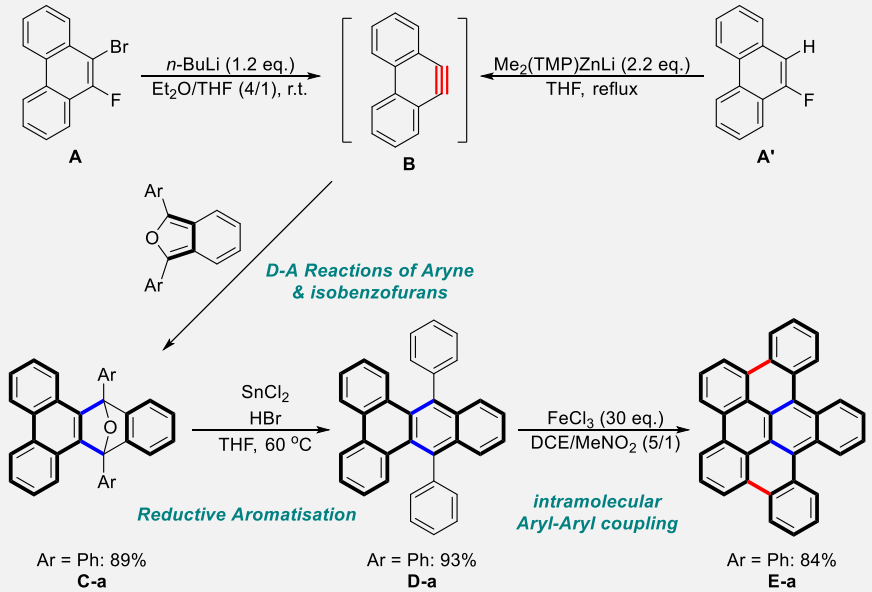
Halogenation of the intermediate:



Sequential synthesis of PAHs



As Aryne Precursors: expanding the π-systems



a) J. Ichikawa, et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 7825. b) J. Ichikawa, et al. *Chem. Asian J.* **2020**, *15*, 1384.

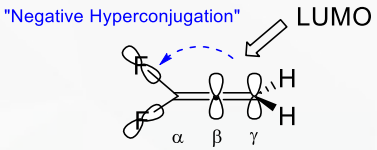
Contents

Bond forming at γ-site

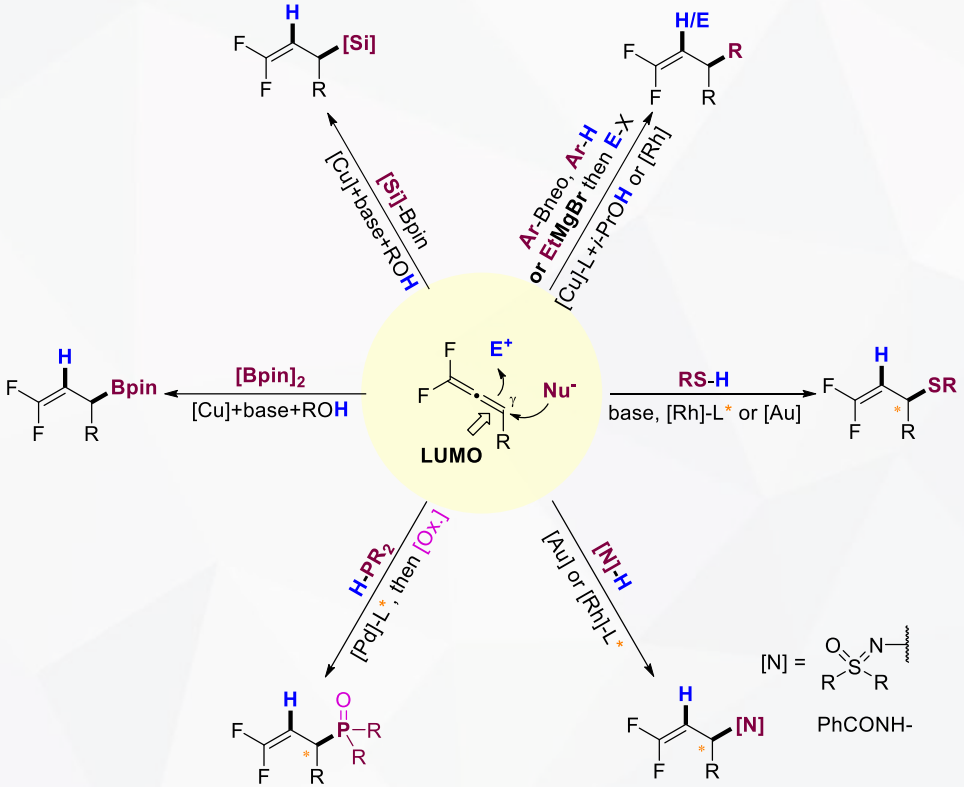
Possibility for nucleophilic addition at γ-site:

$F_2C{=}C{=}CH_2$ (α β γ)	α	β	γ
Coefficient of LUMO:	0.275	0.581	0.693

- LUMO is concentrated on π^*-$C^{\beta}{=}C^{\gamma}$
- Fluorine substituents can lower the energy of the LUMO



FMO-controlled nucleophilic additions!

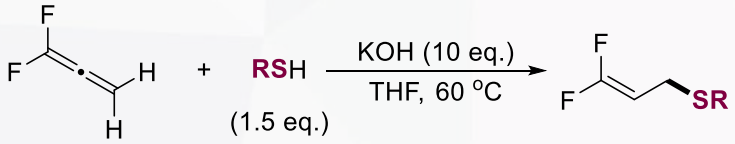


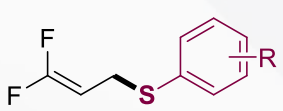
a) K. N. Houk, et al. *J. Am. Chem. Soc.* **1978**, *100*, 6908. b) J. Ichikawa, et al. *Chem. Lett.* **2012**, *41*, 1619.
c) W. R. Dolbier, Jr., et al. *Tetrahedron Lett.* **1978**, *26*, 2231.

Bond forming at γ-site: [S] as nucleophiles

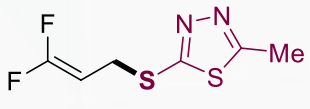
Huang

First reported nucleophilic addition with DFA

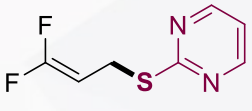




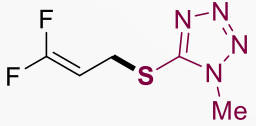
R = H: 89%
4-Me: 91%
4-Cl: 85%
2-NH_2: 81%[a]



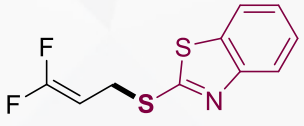
92%



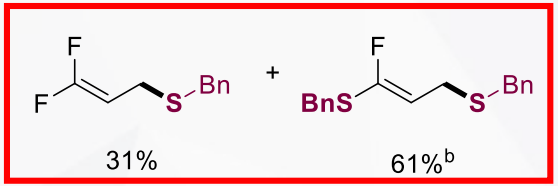
94%



85%



87%



31%

61%[b]

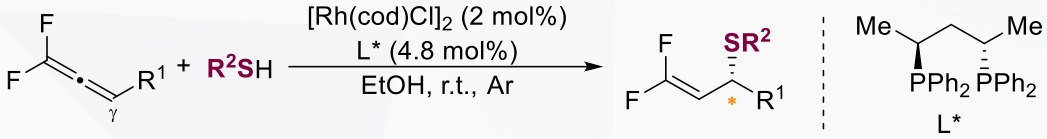
[a] Et_3N (100 eq.) instead of KOH. [b] KOH (100 eq.), byproduct was formed through further addtion followed by dehydrofluorination.

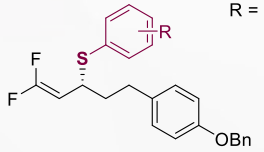
W. Huang, et al. *J. Fluorine Chem.* **1995**, *70*, 5.

Bond forming at γ-site: [S] as nucleophiles

Shi

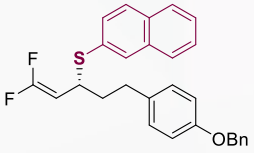
Regio- & enantioselective nucleophilic addition



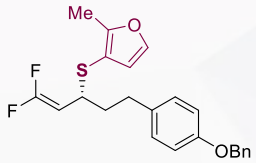


R =

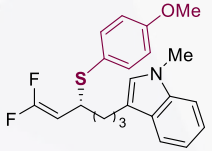
H: 76% (16/1 r.r.), 90% e.e.
4-Me: 78% (>20/1 r.r.), 94% e.e.
3-Me: 92% (13/1 r.r.), 91% e.e.
4-F: 91% (19/1 r.r.), 92% e.e.
4-Cl: 79% (>20/1 r.r.), 91% e.e.
4-Br: 80% (>20/1 r.r.), 90% e.e.
4-COOMe: 75% (>20/1 r.r.), 88% e.e.



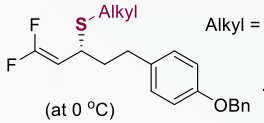
76% (19/1 r.r.), 93% e.e.



83% (>20/1 r.r.), 95% e.e.

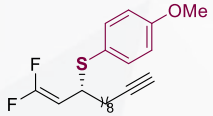


79% (>20/1 r.r.), 90% e.e.

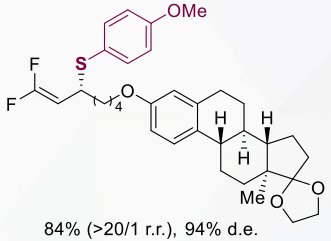


Alkyl =

-Bn: 65% (>20/1 r.r.), 90% e.e.
-CH_2CH_2Ph: 62% (13/1 r.r.), 92% e.e.
-*n*-Hex: 64% (7/1 r.r.), 86% e.e.
-$CH_2CH_2CO_2Me$: 70% (4/1 r.r.), 91% e.e.



85% (>20/1 r.r.), 93% e.e.



84% (>20/1 r.r.), 94% d.e.

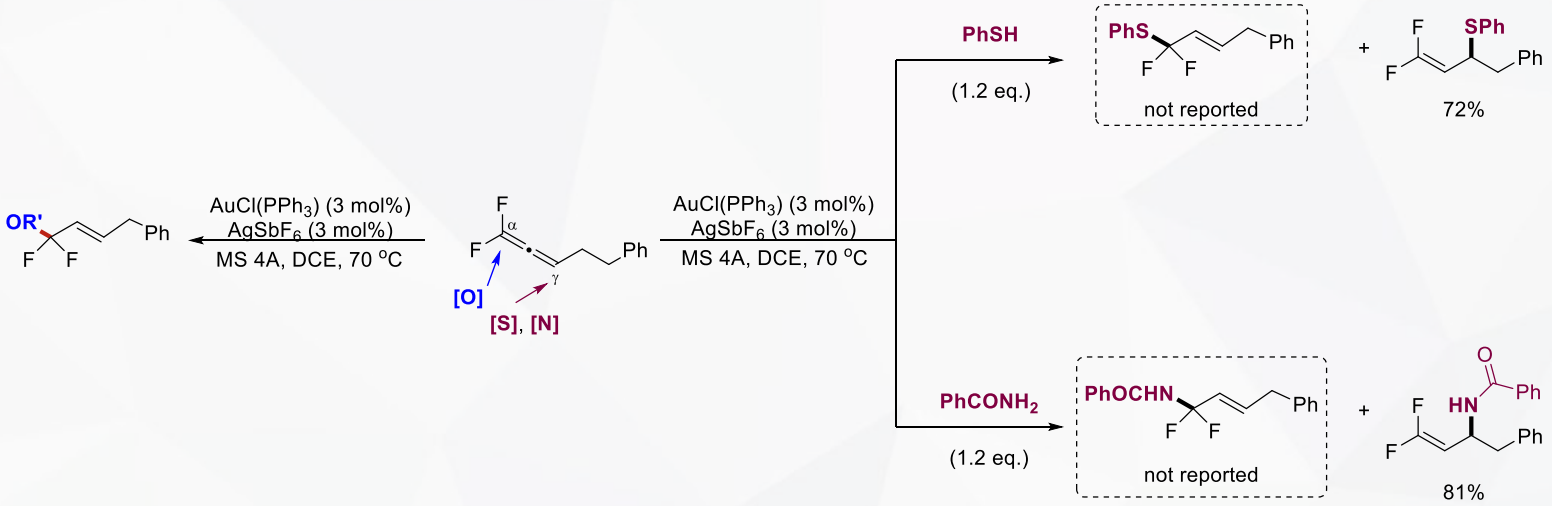
r.r. = regioisomeric ratio of γ/β. e.e. = enantiomeric excess. d.e. = diastereometric excess.

Z. Shi, et al. *Nat. Synth.* **2022**, *1*, 227.

Bond forming at γ-site: [S] & [N] as nucleophiles

Ichikawa

Different selectivity under [Au]-condition



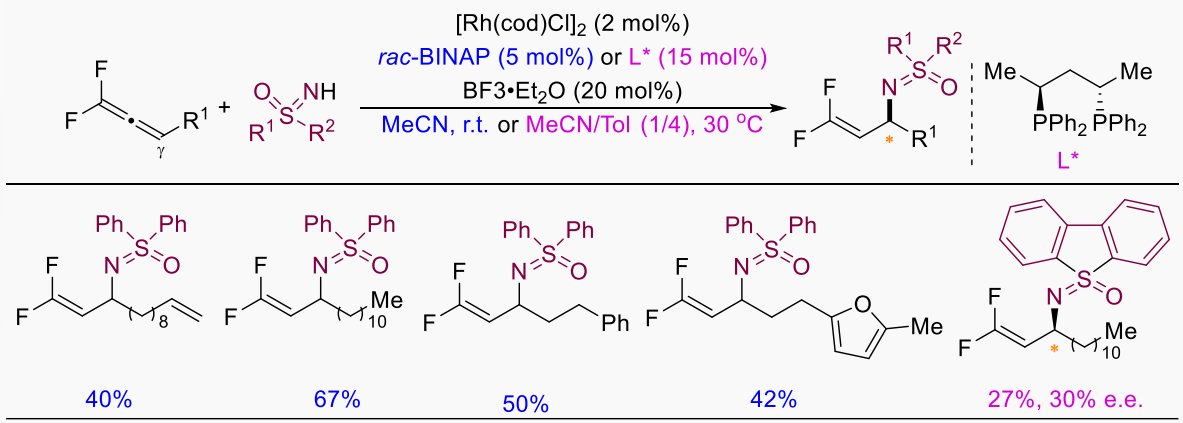
J. Ichikawa, et al. *J. Fluorine Chem.* **2020**, *232*, 109452.

Bond forming at γ-site: [N] as nucleophiles

Gao

Sulfoximines as nucleophiles

Challenges:
low nucleophilicity

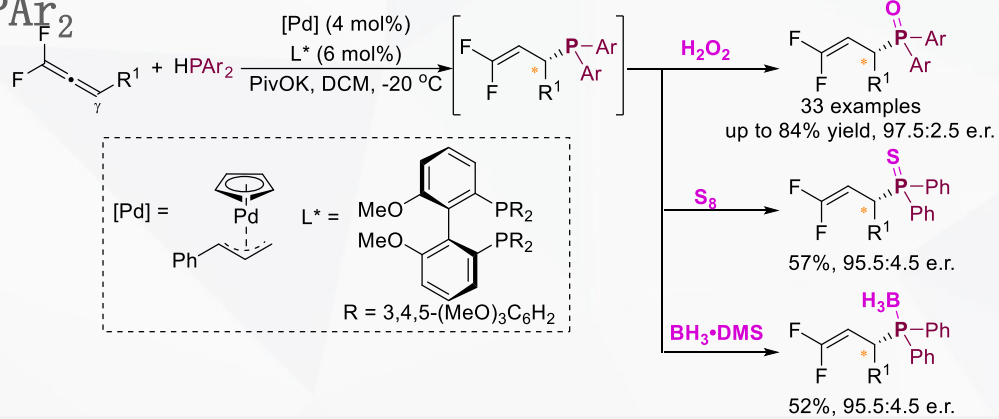


B. Gao, et al. *Org. Lett*. **2023**, *25*, 2756.

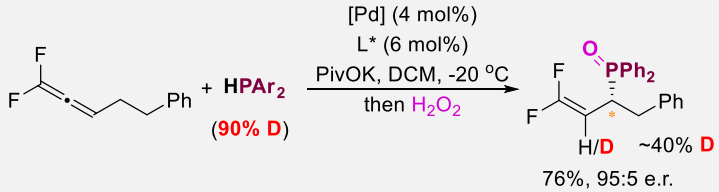
Bond forming at γ-site: [P] as nucleophiles

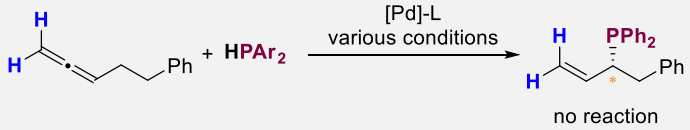
Li

Enantioselective nucleophilic addition of $HPAr_2$



Mechanism studies:



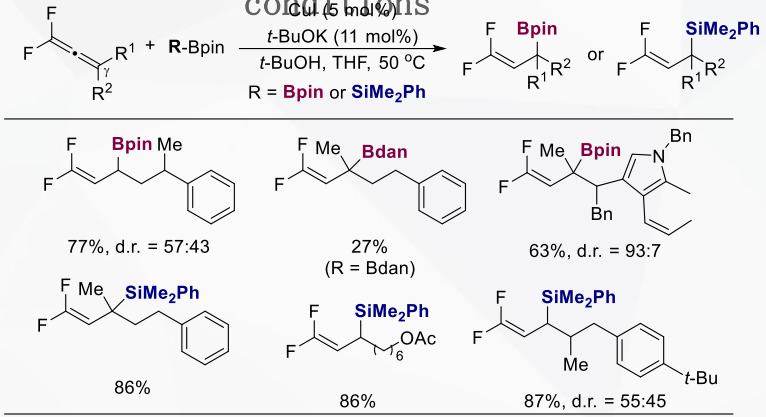


X. Li, et al. *Org. Lett.* **2023**, *25*, 5957.

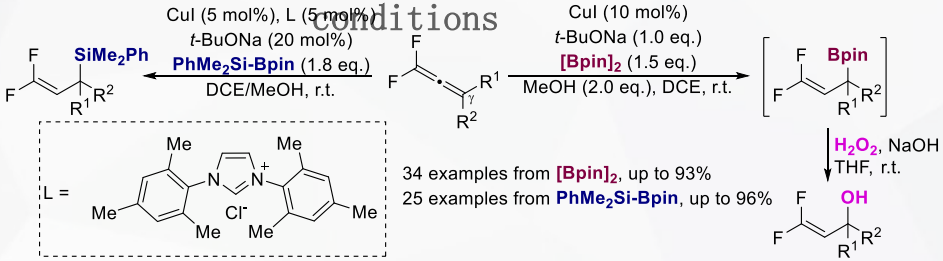
Bond forming at γ-site: [B] & [Si] as nucleophiles

Xu & Feng

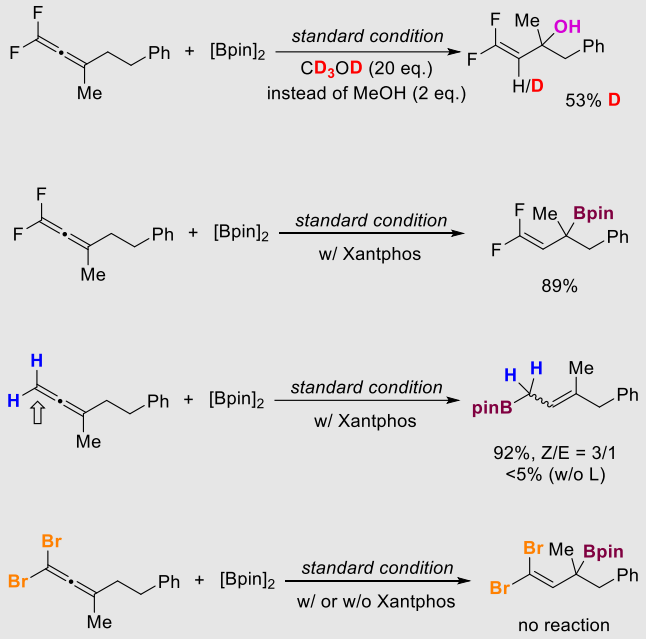
Xu's conditions



Feng's conditions



Mechanism studies

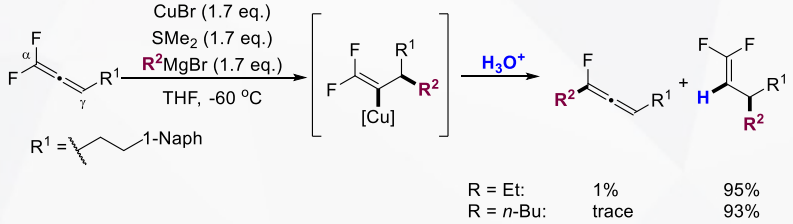


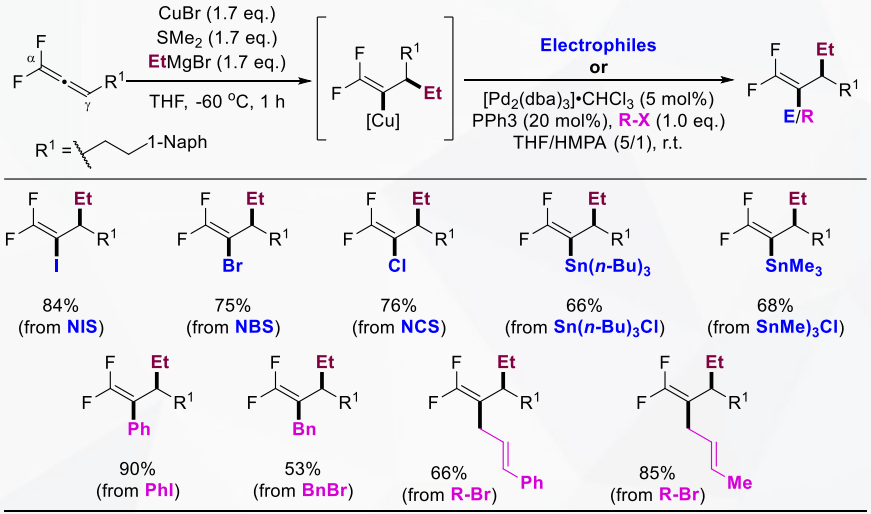
a) Y. Xu, et al. *Eur. J. Org. Chem.* **2021**, 4054. b) C. Feng, et al. *Cell. Rep. Phys. Sci.* **2021**, *2*, 100461.

Bond forming at γ-site: [C] as nucleophiles

Ichikawa

EtMgBr: Three component coupling



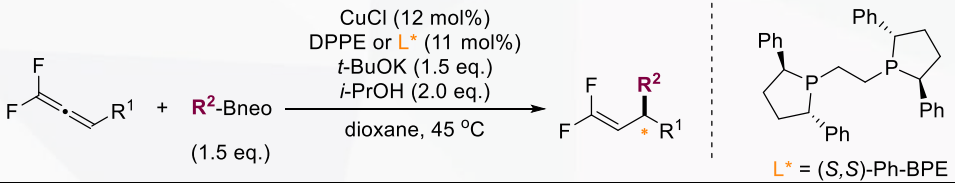


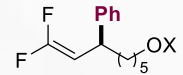
J. Ichikawa, et al. *Chem. Lett.* **2012**, *41*, 1619.

Bond forming at γ-site: [C] as nucleophiles

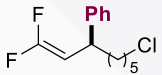
Cheng

Cu-catalyzed hydro-arylation

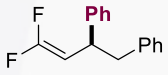




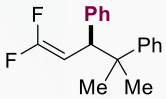
X = Bn: 89%
TBS: 83%
H: 73%



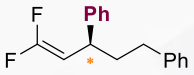
76%



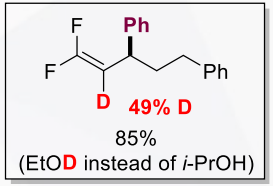
81%



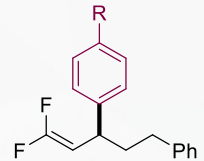
0%



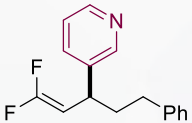
70%, 89:11 e.r.



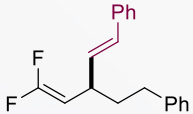
85%
(EtOD instead of *i*-PrOH)



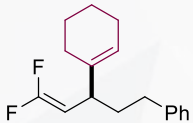
R = Me: 91%
$CON(Me)_2$: 87%
CHO: 52%
Br: 90%



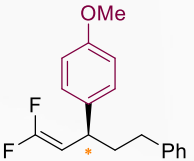
74%



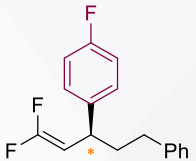
91%



71%



54%, 89:11 e.r.



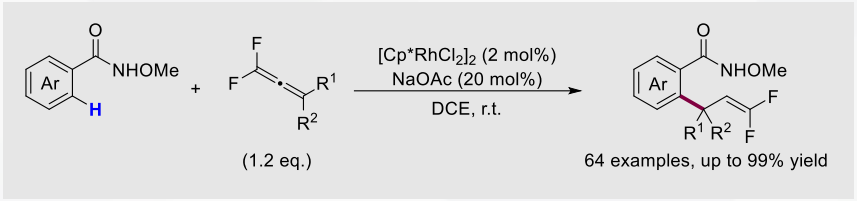
58%, 89:11 e.r.

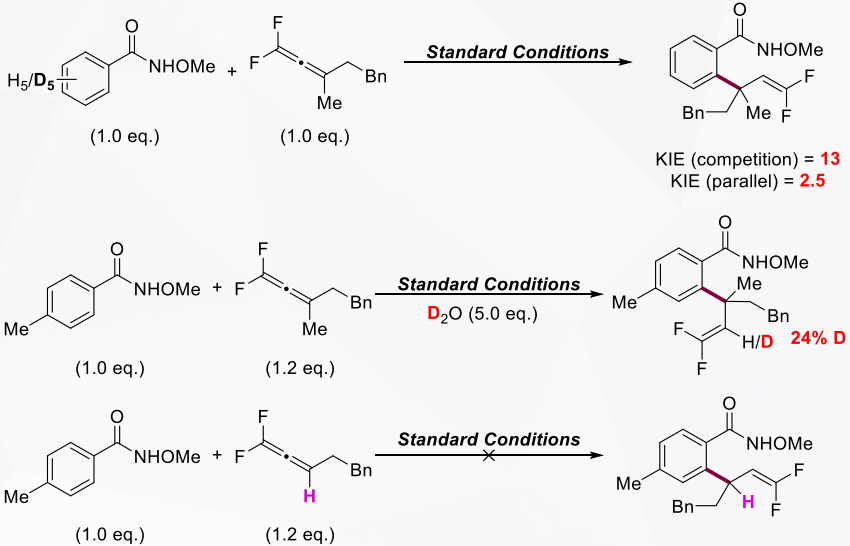
L. Cheng, et al. *Org. Lett.* **2024**, *26*, 525.

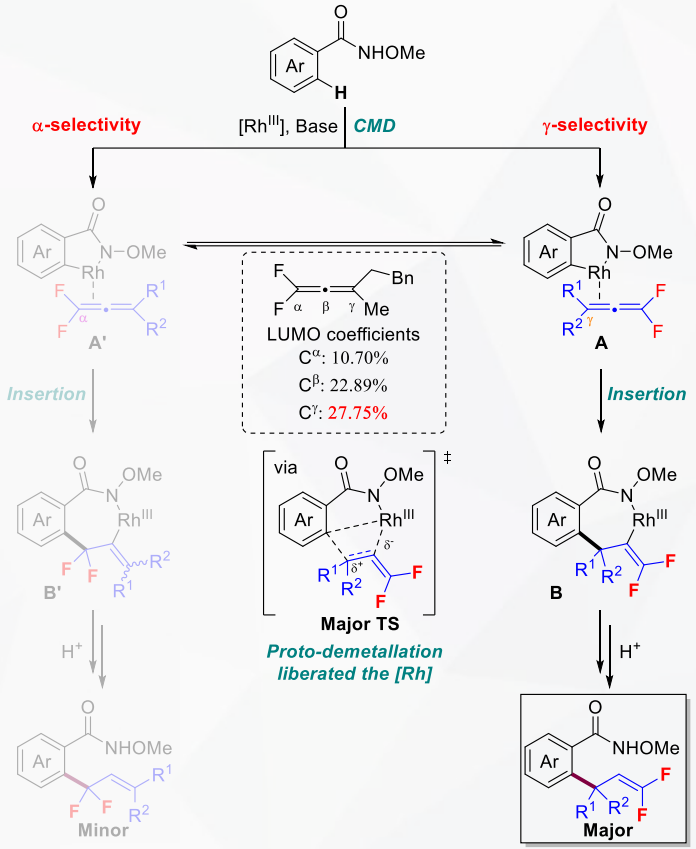
Bond forming at γ-site: [C] as nucleophiles

Feng

Regioselective C–H functionalization

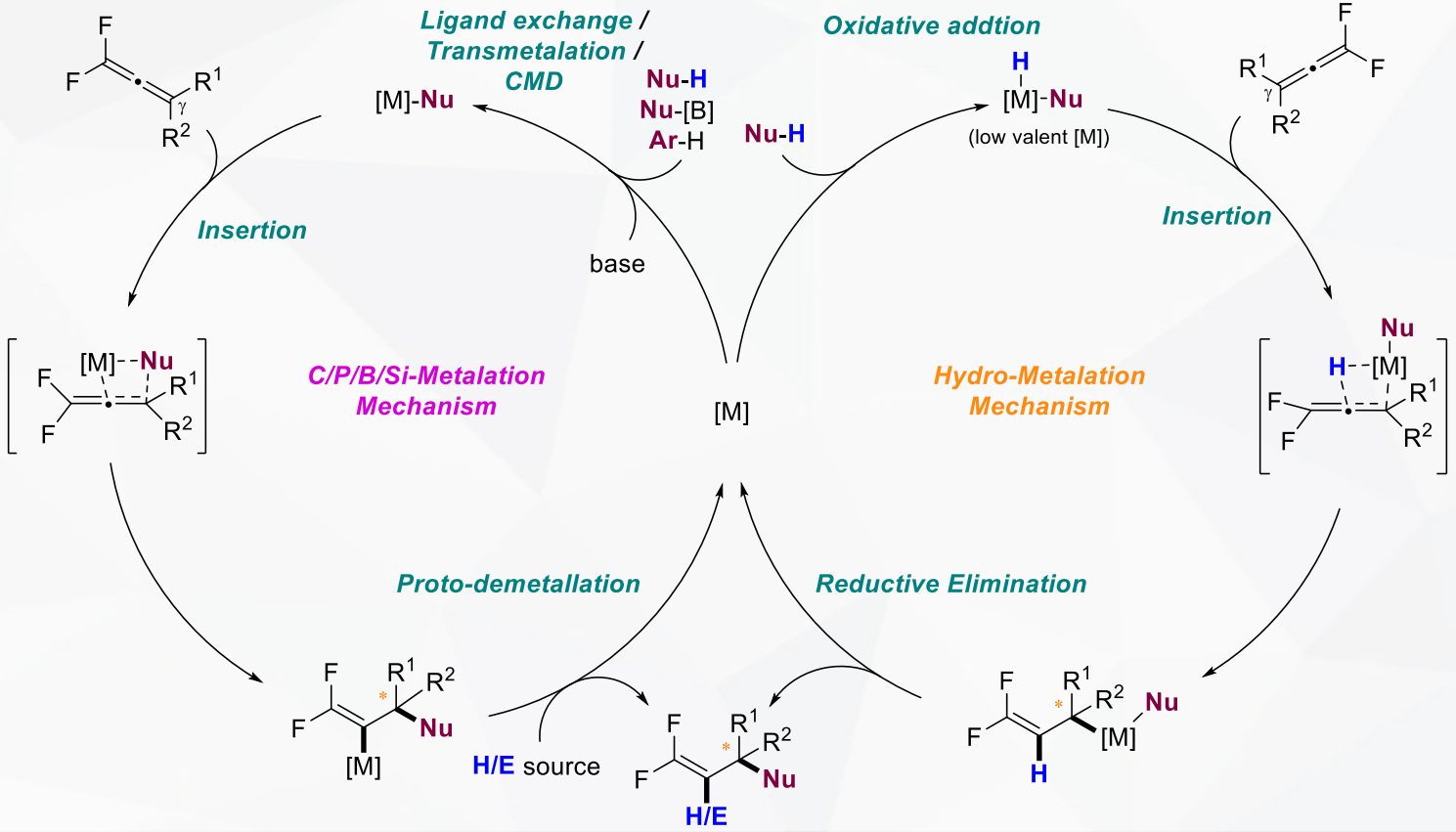






P. J. Walsh & C. Feng, et al. *Cell. Rep. Phys. Sci*. **2021**, *3*, 101117.

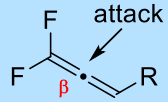
Bond forming at γ-site: plausible mechanisms



Contents

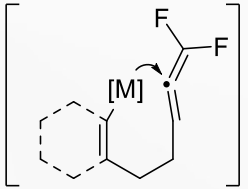
Bond forming at β-site: challenges and strategies

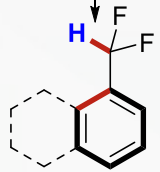
$F_2C{=}C{=}CH_2$ (α β γ)	α	β	γ
Coefficient of LUMO:	0.275	0.581	0.693
Electrostatic Charge:	+0.272	−0.067	−0.341



Difficult to attack at β-site!

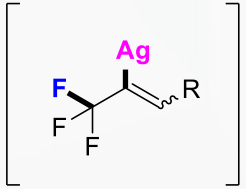
- LUMO for nucleophilic addition
- Positive charge



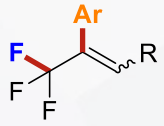


Cyclization

Ag-F



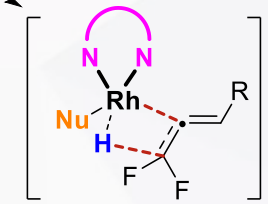
[Pd]-Ar

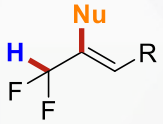


E or *Z*

F-nucleophilic addition

Rh-L, Nu-H



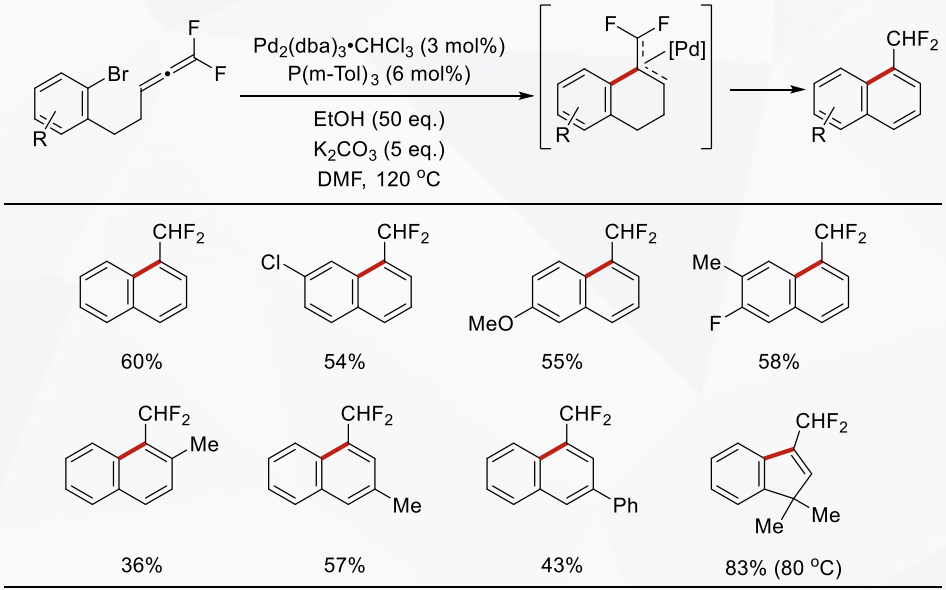


Ligand control

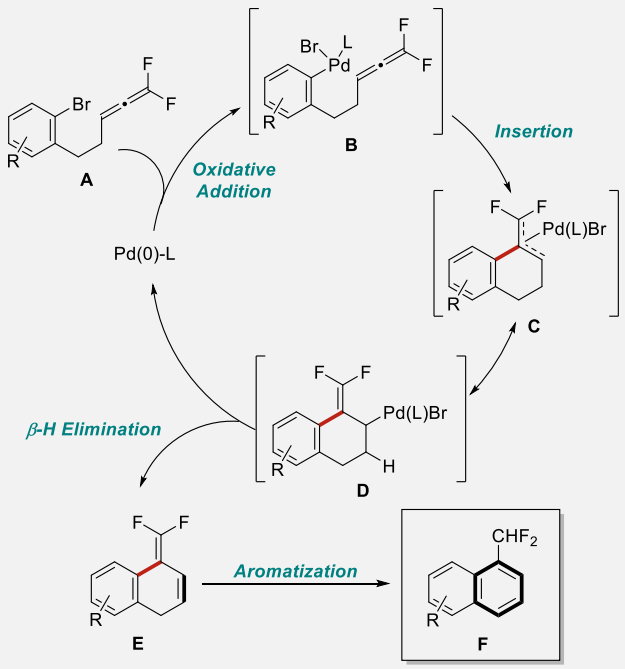
J. Ichikawa, et al. *Chem. Lett.* **2012**, *41*, 1619.

Bond forming at β-site: **Cyclization**

Ichikawa



Proposed catalytic cycle

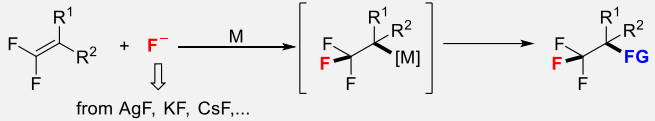


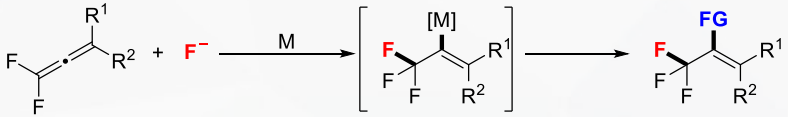
J. Ichikawa, et al. *Org. Biomol. Chem.* **2019**, *17*, 5047-5054.

Bond forming at β-site: F-nucleophilic addition strategy

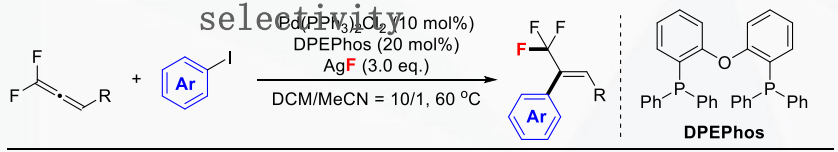
Shi & Lou

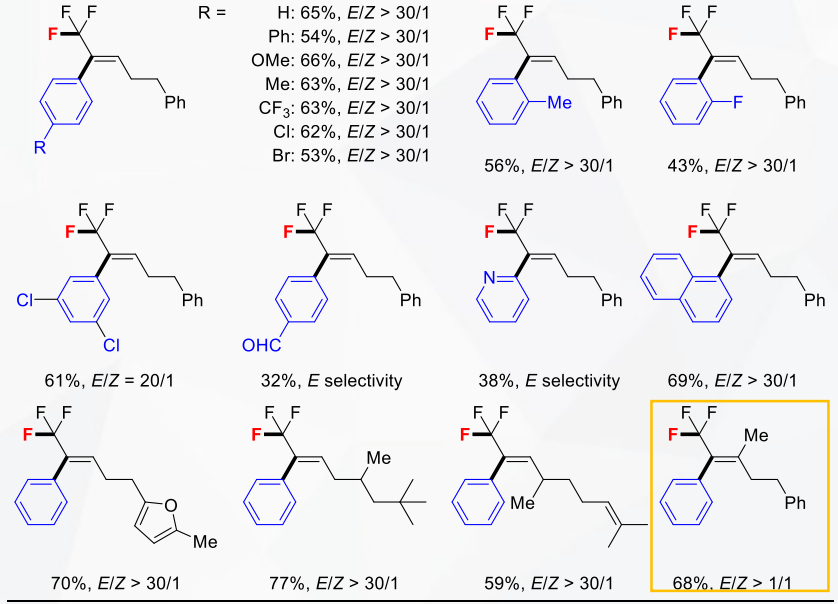
F-nucleophilic addition of difluoro-olefins





Shi's work: *E*-selectivity

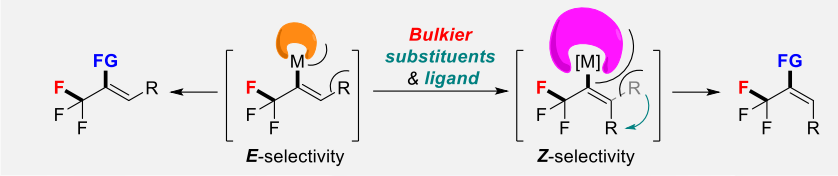




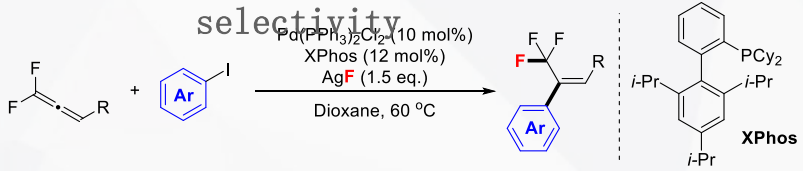
a) Z. Shi, et al. *Green Synth. Catal.* **2020**, *1*, 134. b) D. Xu, S. Lou, et al. *Org. Biomol. Chem.* **2023**, *21*, 8979.

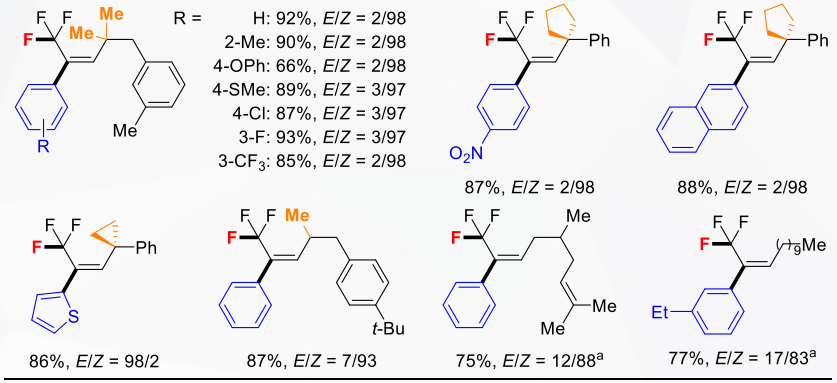
Bond forming at β-site: F-nucleophilic addition strategy

Shi & Lou



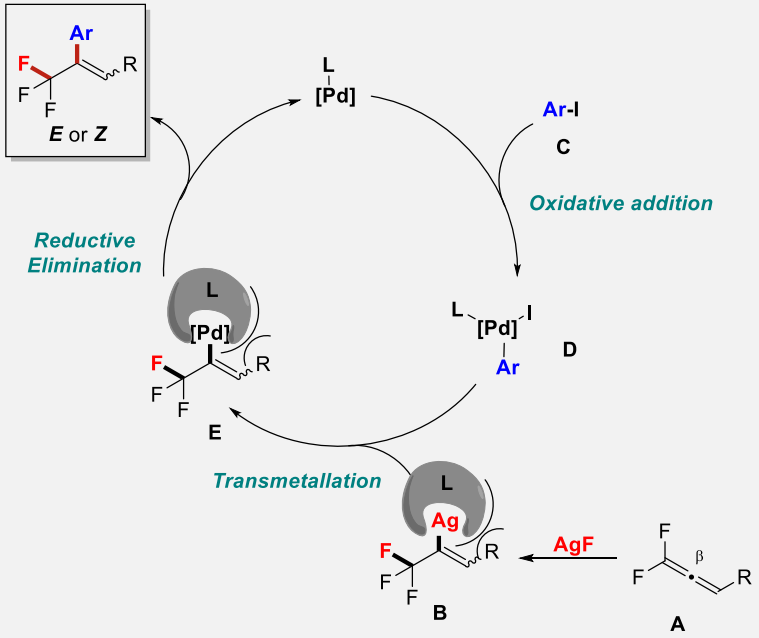
Lou's work: *Z*-selectivity





[a] 100 °C, XPhos (20 mol%).

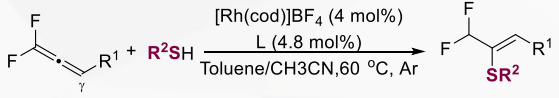
Proposed mechanism

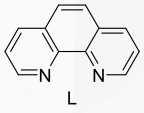


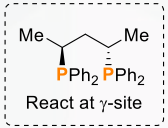
a) Z. Shi, et al. *Green Synth. Catal.* **2020**, *1*, 134. b) D. Xu, S. Lou, et al. *Org. Biomol. Chem.* **2023**, *21*, 8979.

Bond forming at β-site: **Ligand control strategy**

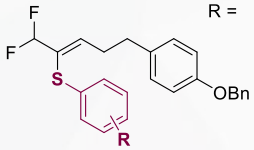
Shi



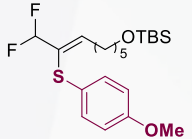




R =

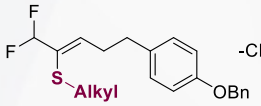


H: 71% (>20/1 r.r.), *E*/*Z* = 83/17
4-Me: 72% (>20/1 r.r.), *E*/*Z* = 86/14
3-Me: 77% (>20/1 r.r.), *E*/*Z* = 83/17
4-F: 75% (>20/1 r.r.), *E*/*Z* = 82/18
4-Cl: 64% (>20/1 r.r.), *E*/*Z* = 90/10
4-Br: 77% (>20/1 r.r.), *E*/*Z* = 81/19
4-COOMe: 77% (>20/1 r.r.), *E*/*Z* = 95/5

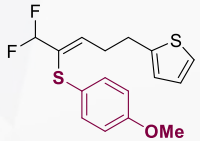


74% (>20/1 r.r.), *E*/*Z* = 86/14

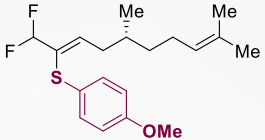
Alkyl* =



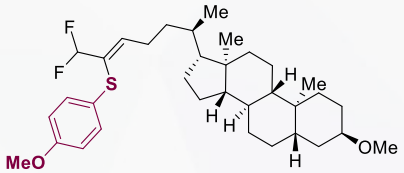
-Bn: 58% (>20/1 r.r.), *E*/*Z* = 82/18
-CH_2CH_2Ph: 66% (>20/1 r.r.), *E*/*Z* = 85/15
-*n*-Hex: 68% (>20/1 r.r.), *E*/*Z* = 91/9
-$CH_2CH_2CO_2Me$: 71% (>20/1 r.r.), *E*/*Z* = 89/11



63% (>20/1 r.r.), *E*/*Z* = 86/14



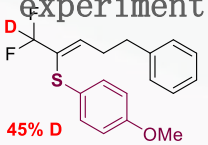
61% (>201 r.r.), *E*/*Z* = 94/6



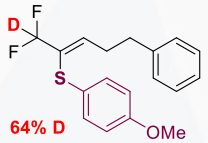
67% (16/1 r.r.), *E*/*Z* = 90/10

r.r. = regioisomeric ratio of β/γ.* CF_3COOH (40 mol%) in DCM/EtOH (1/3)

Isotopic labelling experiments



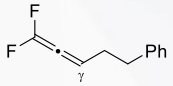
45% D



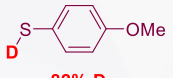
64% D

[Rh(cod)]BF_4 (4 mol%)
L^N (4.8 mol%)
Toluene/CH_3CN,60 °C, Ar
63%

[Rh(cod)]BF_4 (4 mol%)
L^N (4.8 mol%)
Toluene-d_8/CH_3CN,60 °C, Ar
61%



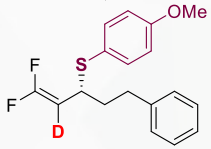
+



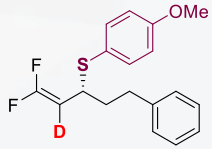
82% D

[Rh(cod)Cl_2]$_2$ (2 mol%)
L^P (4.8 mol%)
EtOH, r.t., Ar
87%, 94% e.e.

[Rh(cod)Cl_2]$_2$ (2 mol%)
L^P (4.8 mol%)
EtOH-d_6, r.t., Ar
90%, 94% e.e.



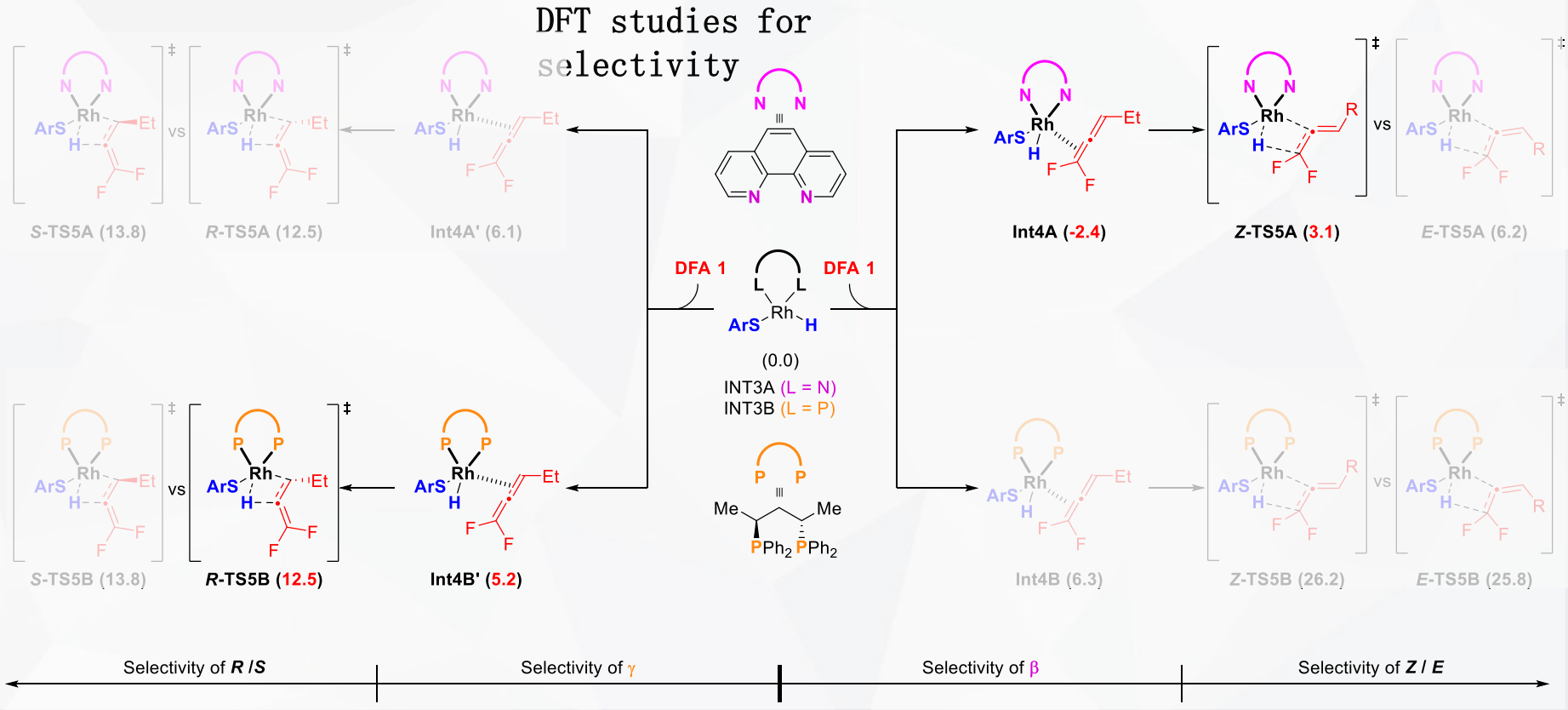
10% D



94% D

Bond forming at β-site: **Ligand control strategy**

Shi



Z. Shi, et al. *Nat. Synth.* **2022**, *1*, 227.

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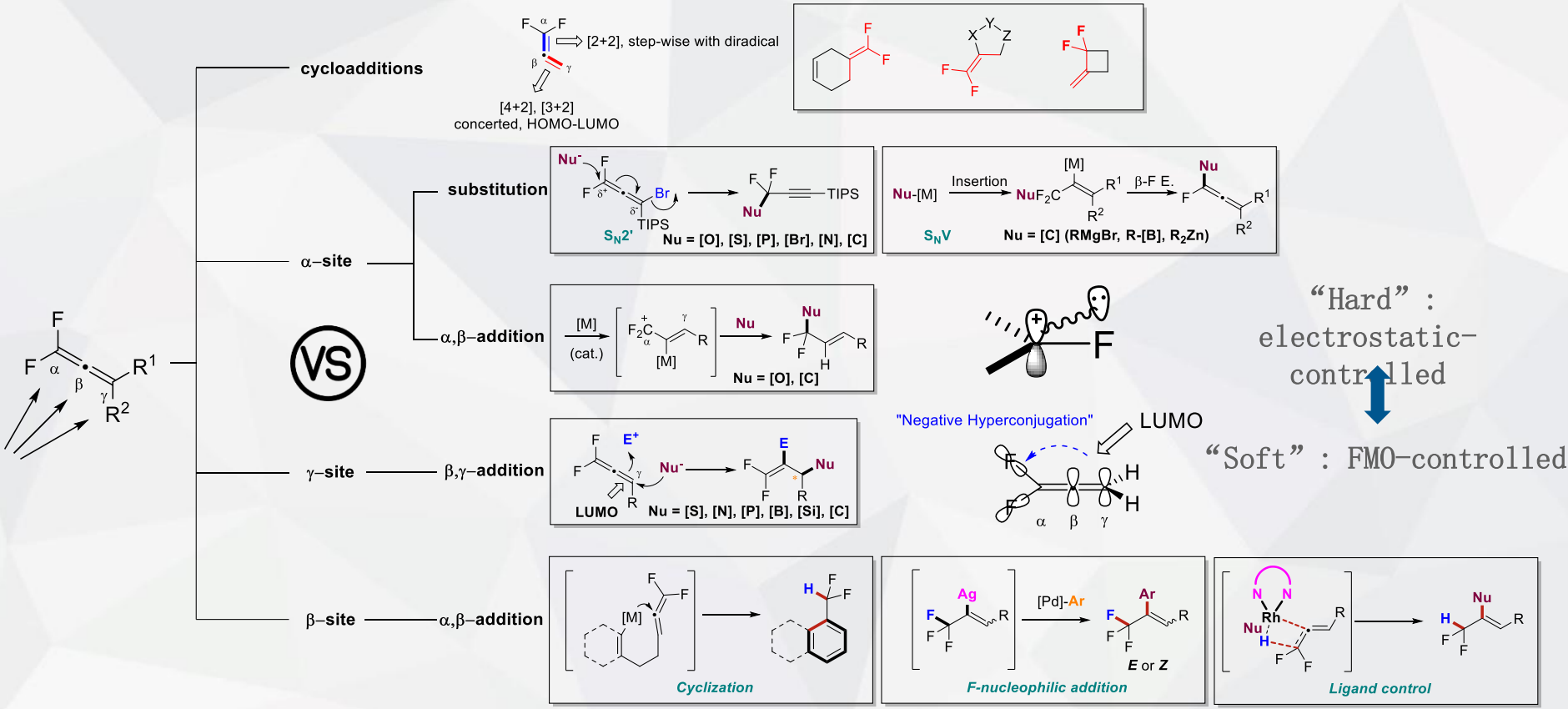
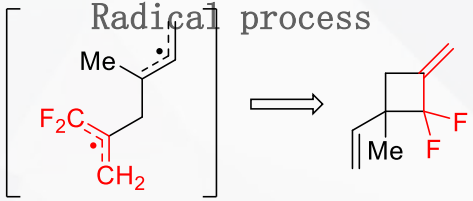
Conclusion


cycloadditions
[2+2], step-wise with diradical
[4+2], [3+2]
concerted, HOMO-LUMO
α–site
substitution
Nu = [O], [S], [P], [Br], [N], [C]
Nu-[M]
Insertion
β-F E.
Nu = [C] (RMgBr, R-[B], R2Zn)
α,β–addition
Nu = [O], [C]
VS
"Negative Hyperconjugation"
LUMO
"Hard" : electrostatic-controlled
"Soft" : FMO-controlled
γ–site
β,γ–addition
Nu = [S], [N], [P], [B], [Si], [C]
β–site
α,β–addition
Cyclization
F-nucleophilic addition
E or Z
Ligand control

Outlook

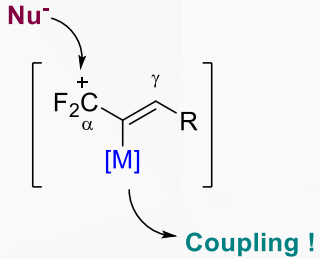
How to develop **β-selectivity?**

More strategies to stabilize intermediates: Radical process

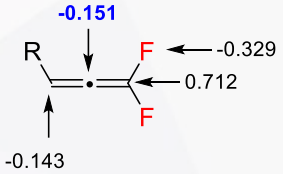


F can stablize the allyl radical

MCR: difluoro-alkylation reagent



Electrophilic Addition

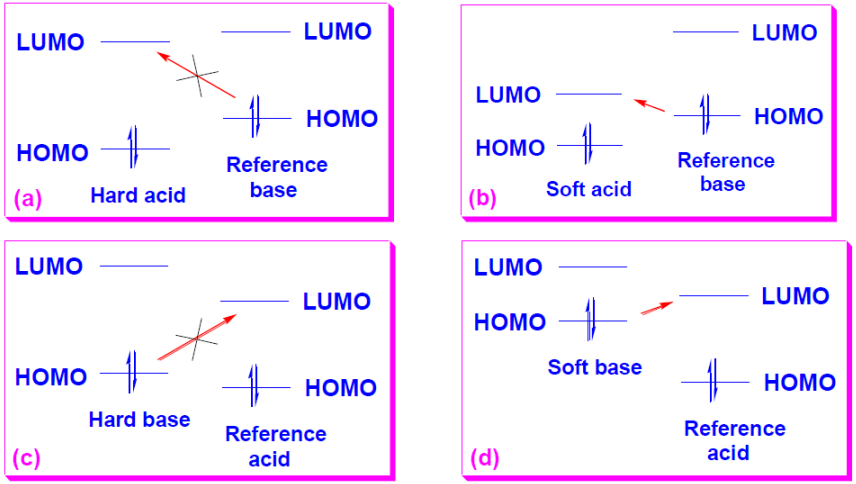


New Catalyst and substrate design

Thank you!

Appendix: HSAB and HMO

Theory of Lewis (HSAB) acid–base interactions
(Klopman, G. *J. Am. Chem. Soc.* 1968, *90*, 223.)



Hard acid—hard base: electrostatic interaction
Soft acid—soft base: covalent interaction

Combining Pearson's and Klopman's Ideas

- *Hard* Lewis acids:

- Atomic centers of small ionic radius
- Net positive charge
- Species do not contain electron pairs in their valence shells
- Low electron affinity
- Likely to be strongly solvated
- High energy LUMO

- *Soft* Lewis acids:

- Large radius
- Low or partial (delta+) positive charge
- Electron pairs in their valence shells
- Easy to polarize and oxidize
- Low energy LUMOs, but large magnitude LUMO coefficients

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Appendix: DDQ 氧化