Frustrated Radical Pairs (FRPs)

Discovery, Reactivities and Applications

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Supervisors: Prof. Zhang Junliang

Dr. Yang Junfeng

2025.03.28

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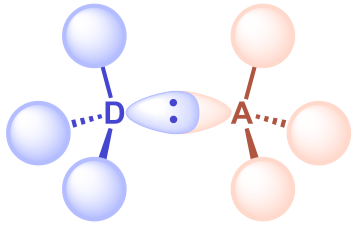
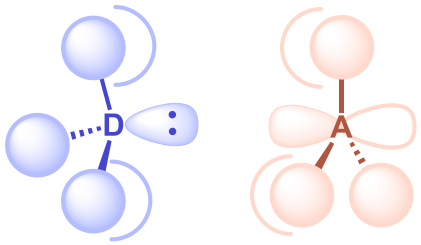
Introduction



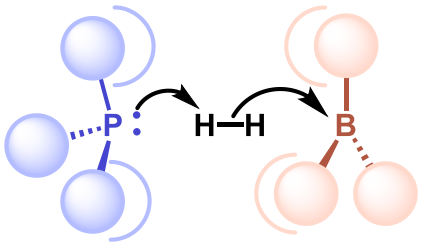
Common Lewis Pair
Lewis acid/base adduct

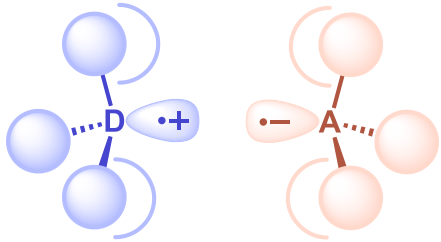
Weakened Lewis acidic or basic reactivities



Frustrated Lewis Pair
(FLP)

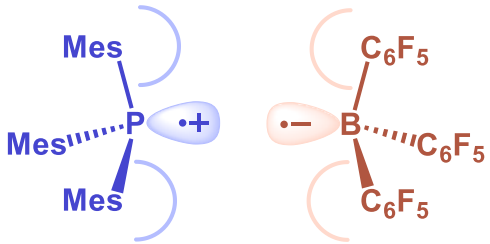
Coexistence of strong Lewis acidic and basic reactivities





Frustrated Radical Pair
(FRP)

Coexistence of two radical-type oxidant and reductant

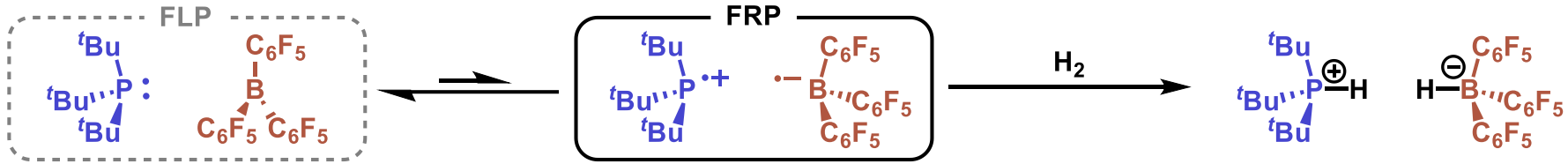


Frustrated (adj.): feeling annoyed or less confident because you cannot achieve what you want

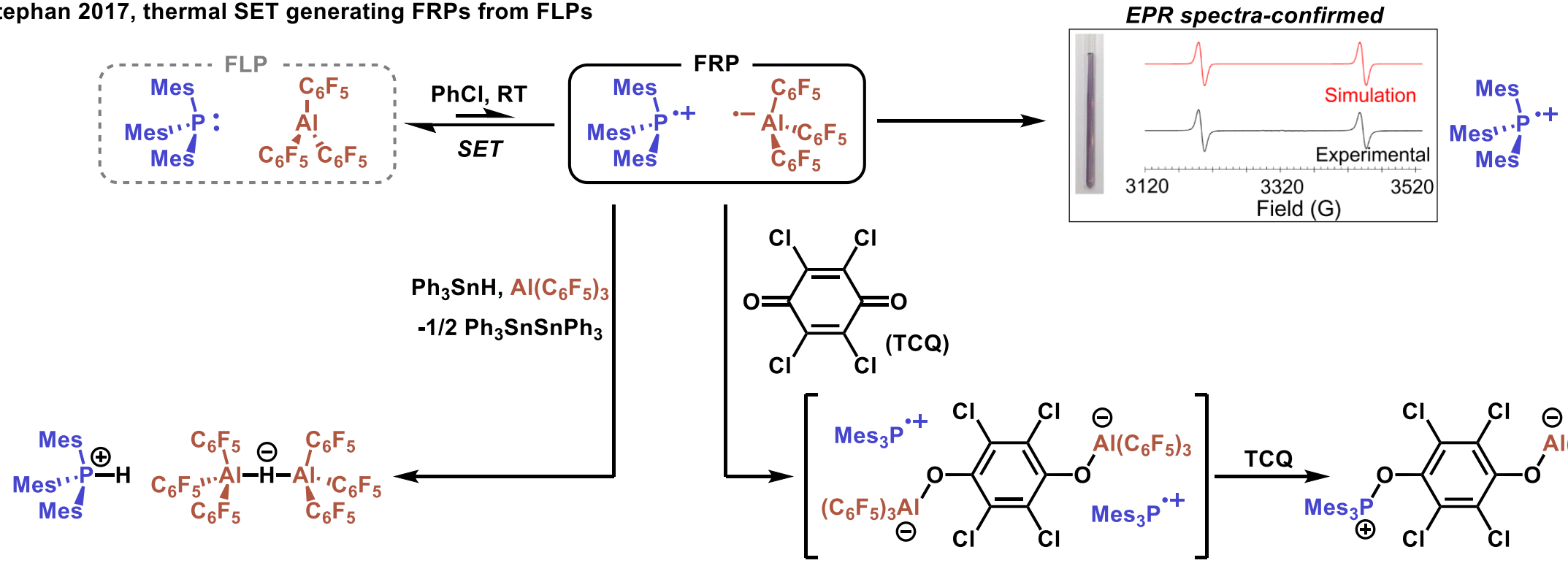
Melen, R. L., et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 53; Lin, S., et al. *J. Am. Chem. Soc.* **2023**, *145*, 19478; Jiao, N., et al. *Chin. J. Chem.* **2024**, *42*, 1157.

Generation of FRPs

Piers 2011, proposed mechanism



Stephan 2017, thermal SET generating FRPs from FLPs

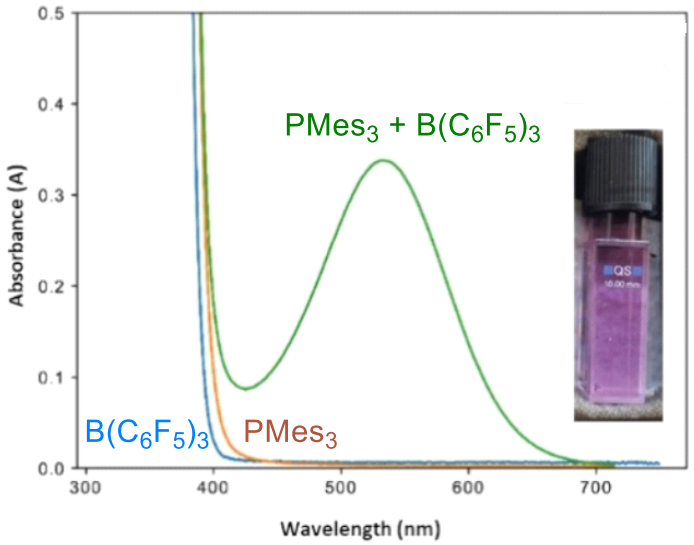


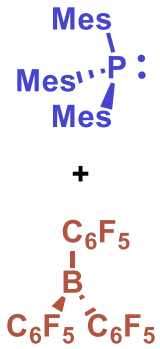
Piers, W. E.; et al. *Inorg. Chem.* **2011**, *50*, 12252; Stephan, D. W., et al. *Chem* **2017**, *3*, 259.

Generation of FRPs

Slootweg 2020, photochemical SET generating FRPs from FLPs

UV-vis spectra





no light

Toluene, RT

violet (FLP)

no light

Toluene, 30 K

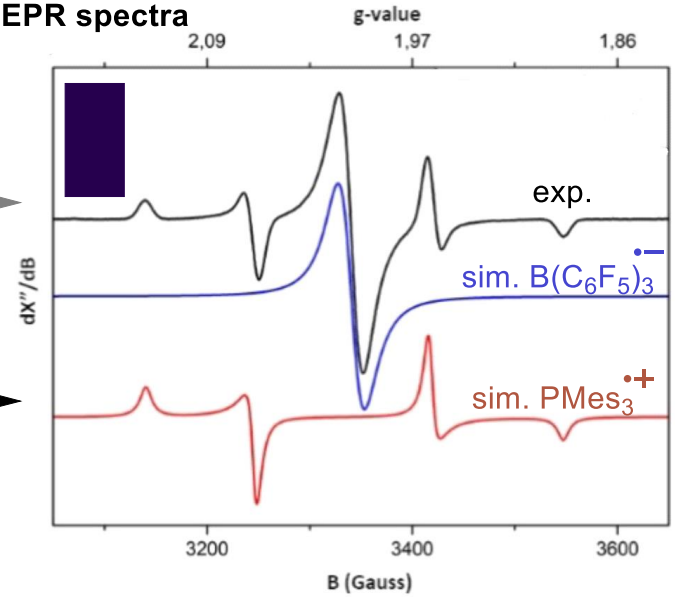
SET

390-500 nm light

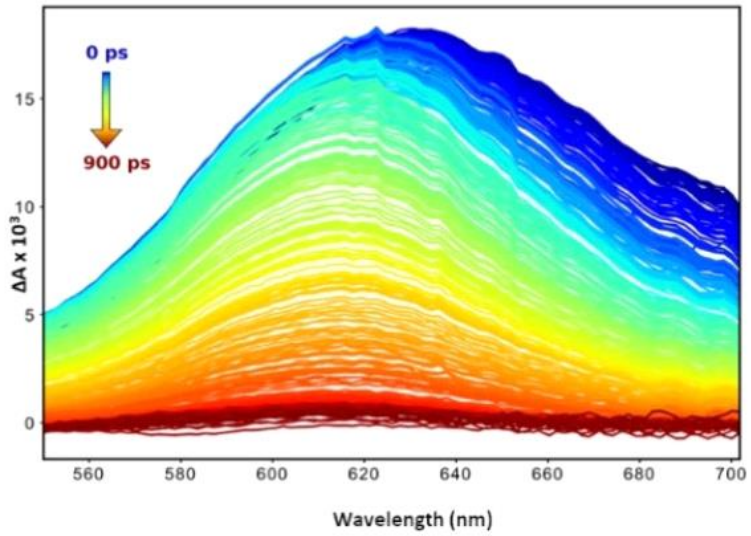
Toluene, 30 K

dark purple (FRP)

EPR spectra



Transient absorption spectra



530 nm, < 200 fs short laser pulse

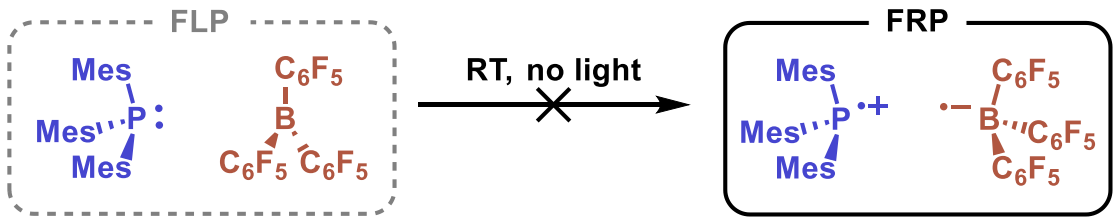
Toluene, RT

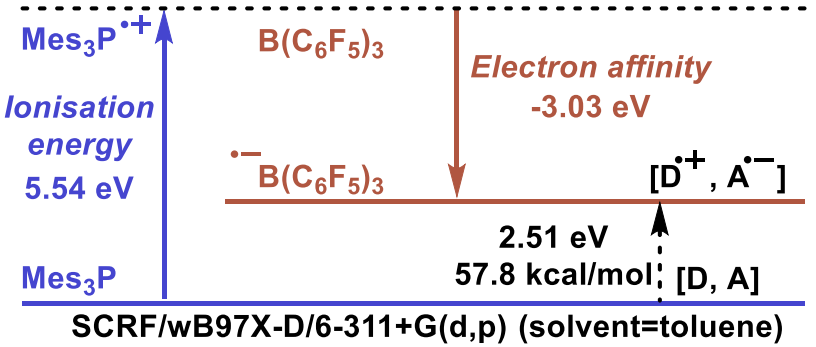
- **NO FRP generation without light at RT**
- **Photochemical SET forming FRP**
- **237 ps lifetime of FRP $Mes_3P^{\cdot+}/B(C_6F_5)_3^{\cdot-}$ (unstable)**

Slootweg, J. C., et al. *Chem. - Eur. J.* **2020**, *26*, 9005.

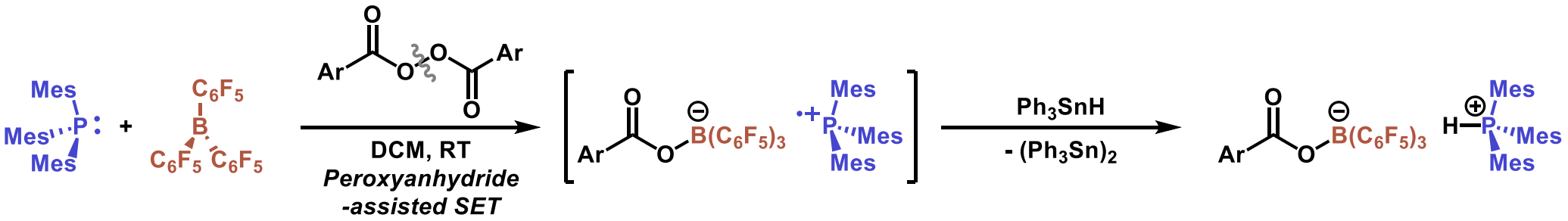
Generation of FRPs

Slootweg 2020

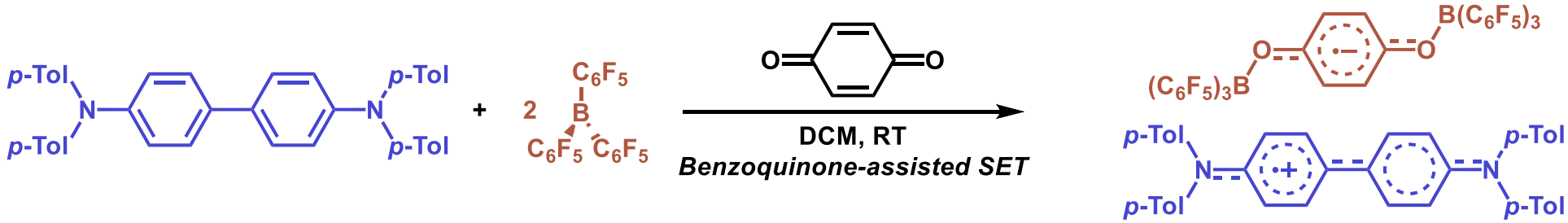




Stephan 2018, substrate-assisted SET generating FRPs from FLPs

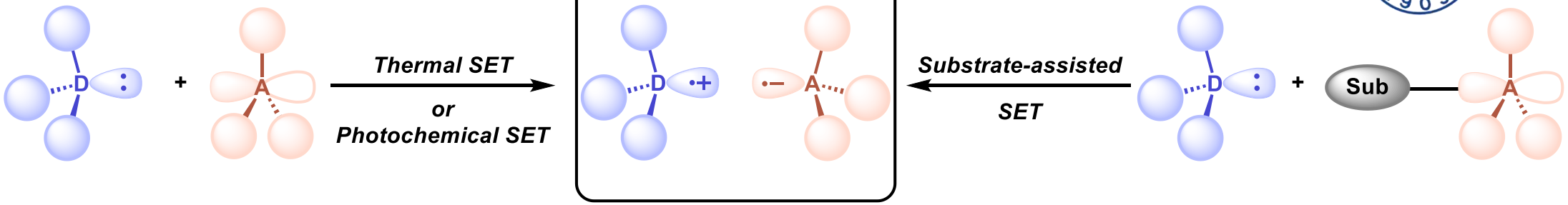


Wang 2023, substrate-assisted SET generating FRPs from FLPs

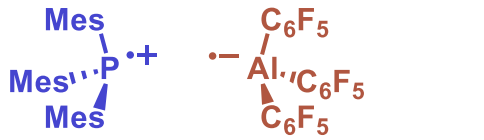


Slootweg, J. C., et al. *Chem. - Eur. J.* **2020**, *26*, 9005; Stephan, D. W., et al. *Chem. Commun.* **2018**, *54*, 7431; Wang, X., et al. *CCS Chemistry* **2023**, *5*, 334.

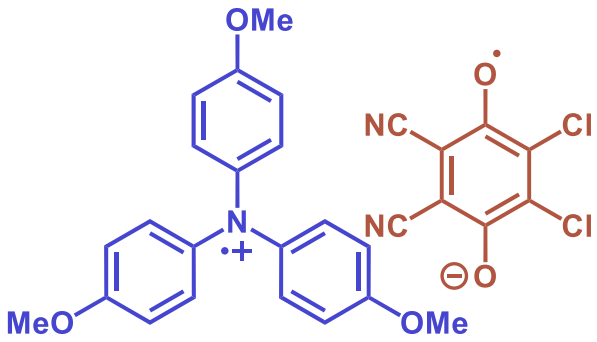
Generation of FRPs



Thermal SET

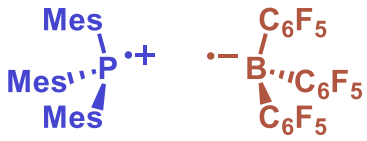


Stephan 2017

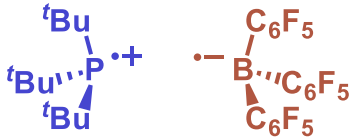


Slootweg 2025, isolable

Photochemical SET

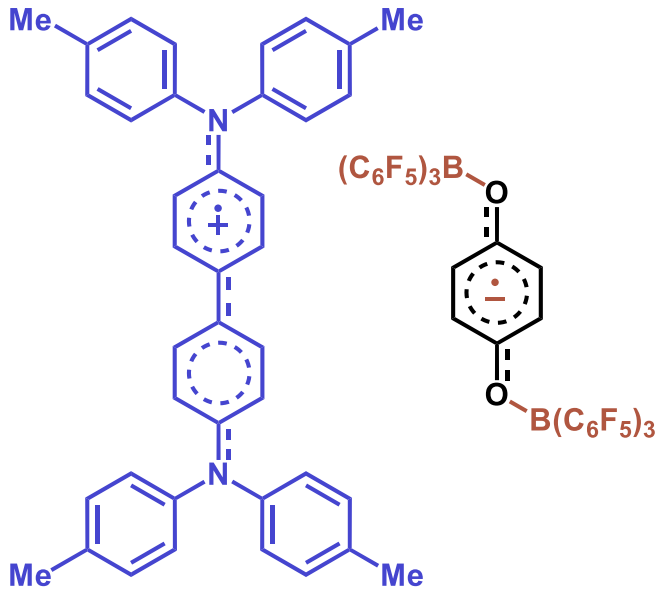


Slootweg 2020



Slootweg 2020

Substrate-assisted SET

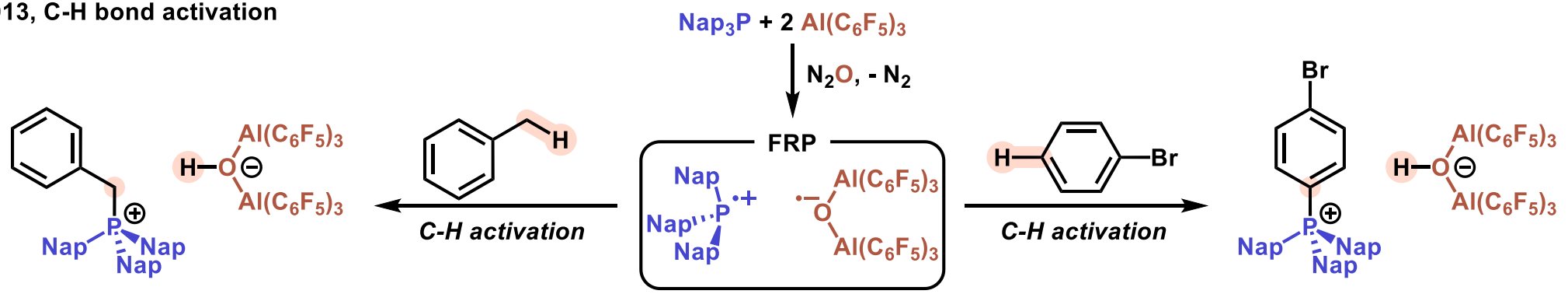


Wang 2023

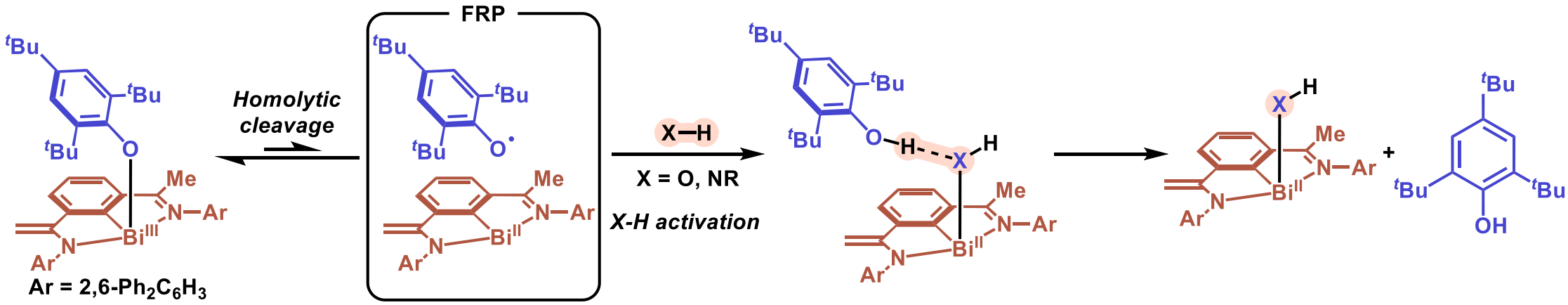
Stephan, D. W., et al. *Chem* **2017**, *3*, 259; Slootweg, J. C., et al. *Chem. - Eur. J.* **2025**, *31*, e202403885; Slootweg, J. C., et al. *Chem. - Eur. J.* **2020**, *26*, 9005; Wang, X., et al. *CCS Chemistry* **2023**, *5*, 334.

Reactivities of FRPs

Stephan 2013, C-H bond activation



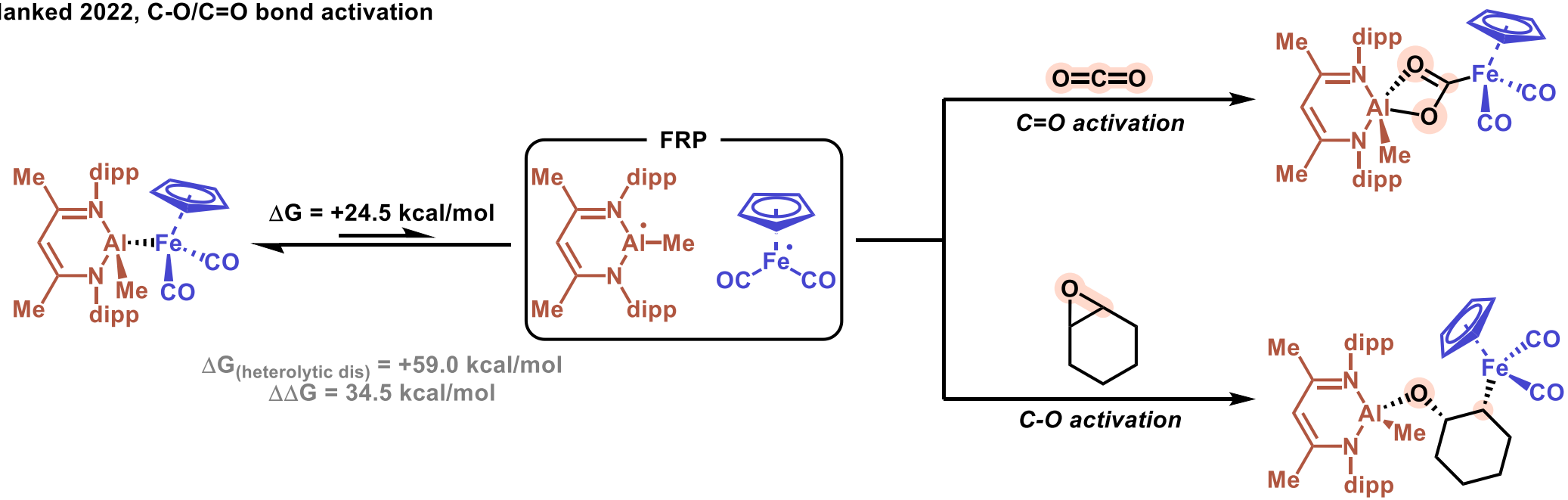
Cornella 2022, O-H/N-H bond activation



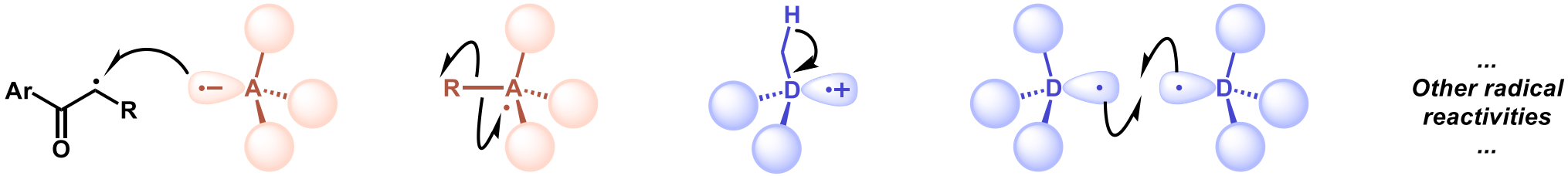
Stephan, D. W., et al. *J. Am. Chem. Soc.* **2013**, *135*, 6446; Cornella, J., et al. *J. Am. Chem. Soc.* **2022**, *144*, 16535.

Reactivities of FRPs

Manked 2022, C-O/C=O bond activation



Other reactivities (typical radical reactivities)



SET *α-scission* *Elimination* *Dimerization*

Mankad, N. P., et al. *J. Am. Chem. Soc.* **2022**, *144*, 3210.

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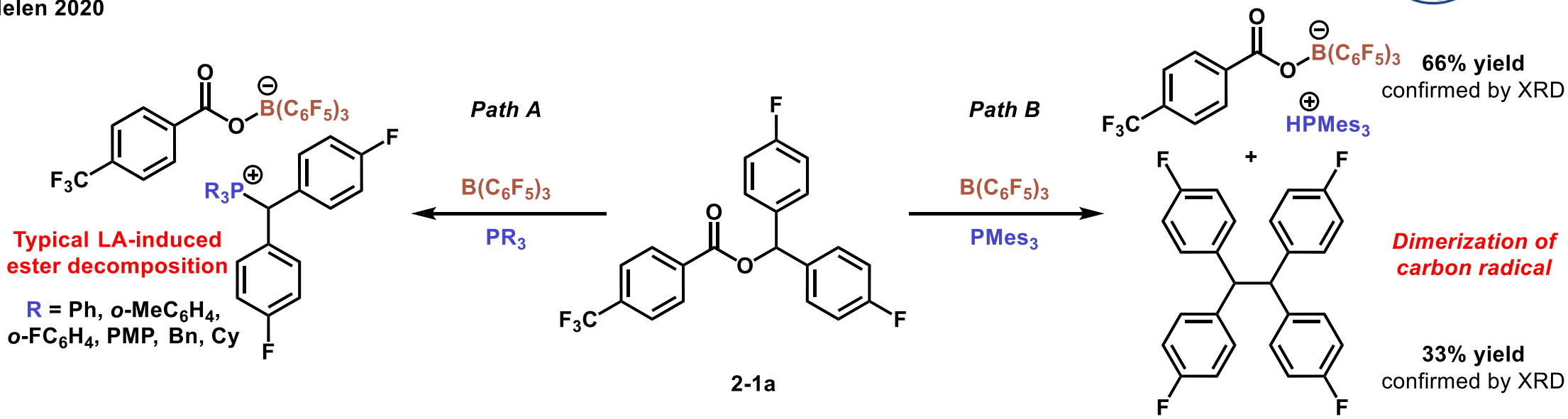
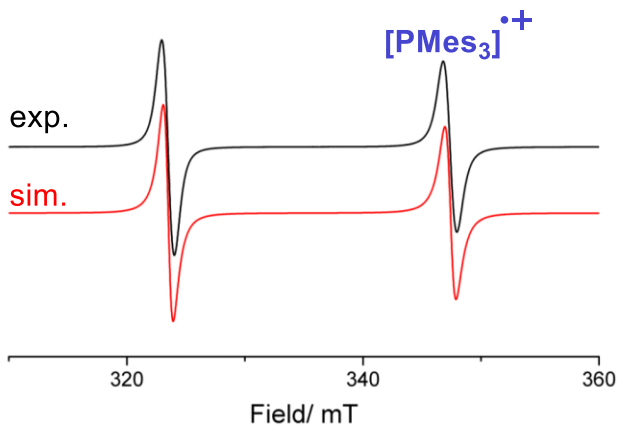
FRPs in Alkene Functionalization

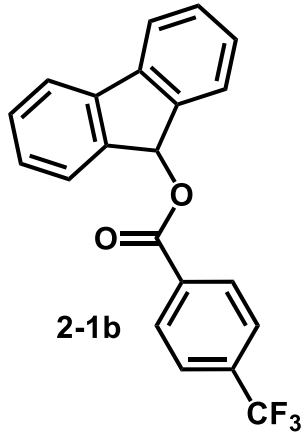
Melen 2020

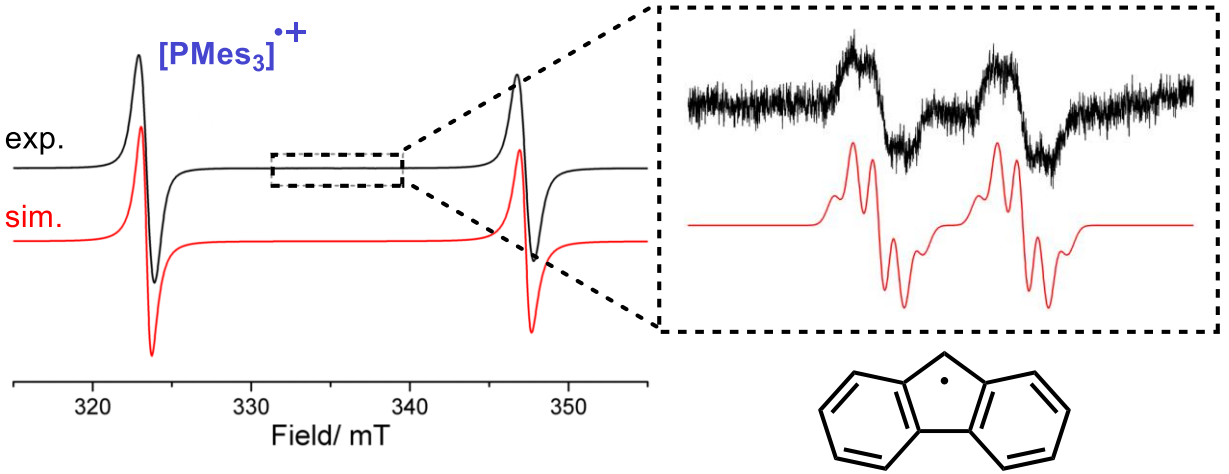


EPR spectra



2-1a + $B(C_6F_5)_3$ + $PMes_3$





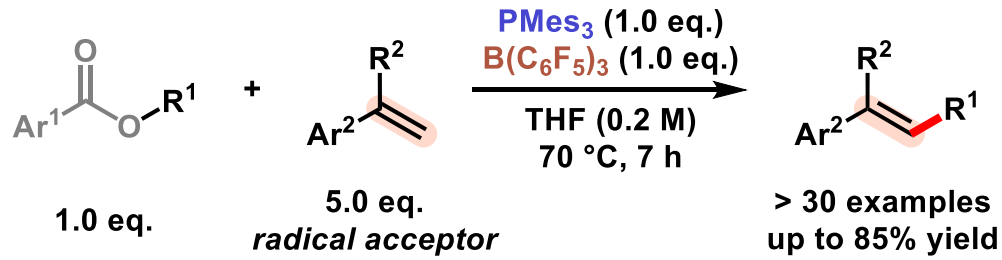
2-1b + $B(C_6F_5)_3$ + $PMes_3$

Stablized carbon radical

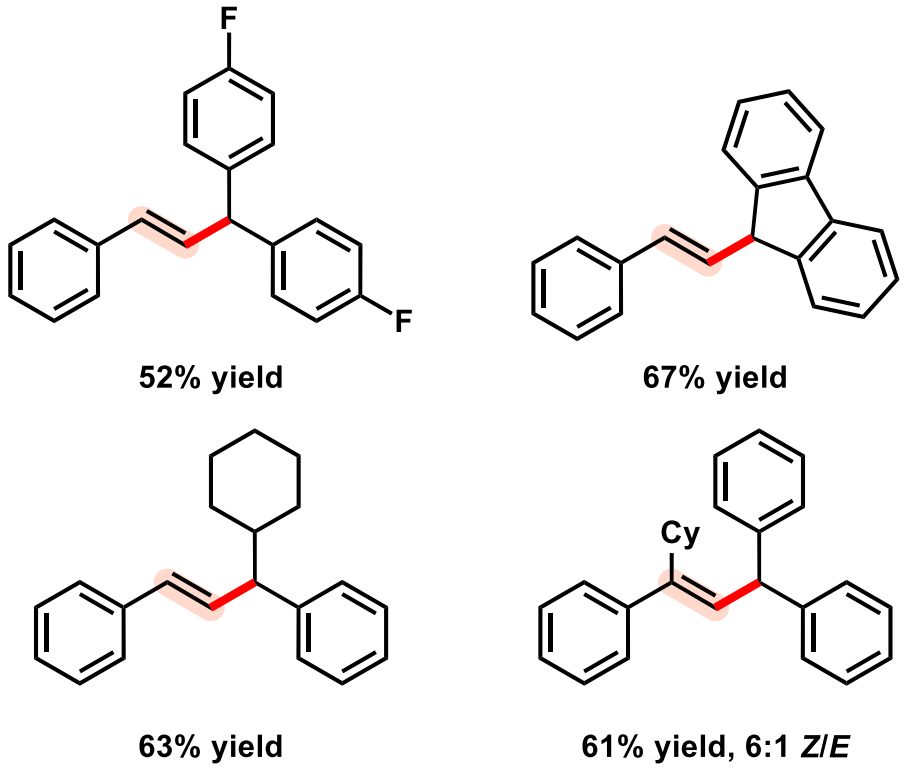
Melen, R. L., et al. *Cell Reports Physical Science* **2020**, *1*.

What would happen if a radical acceptor were used?

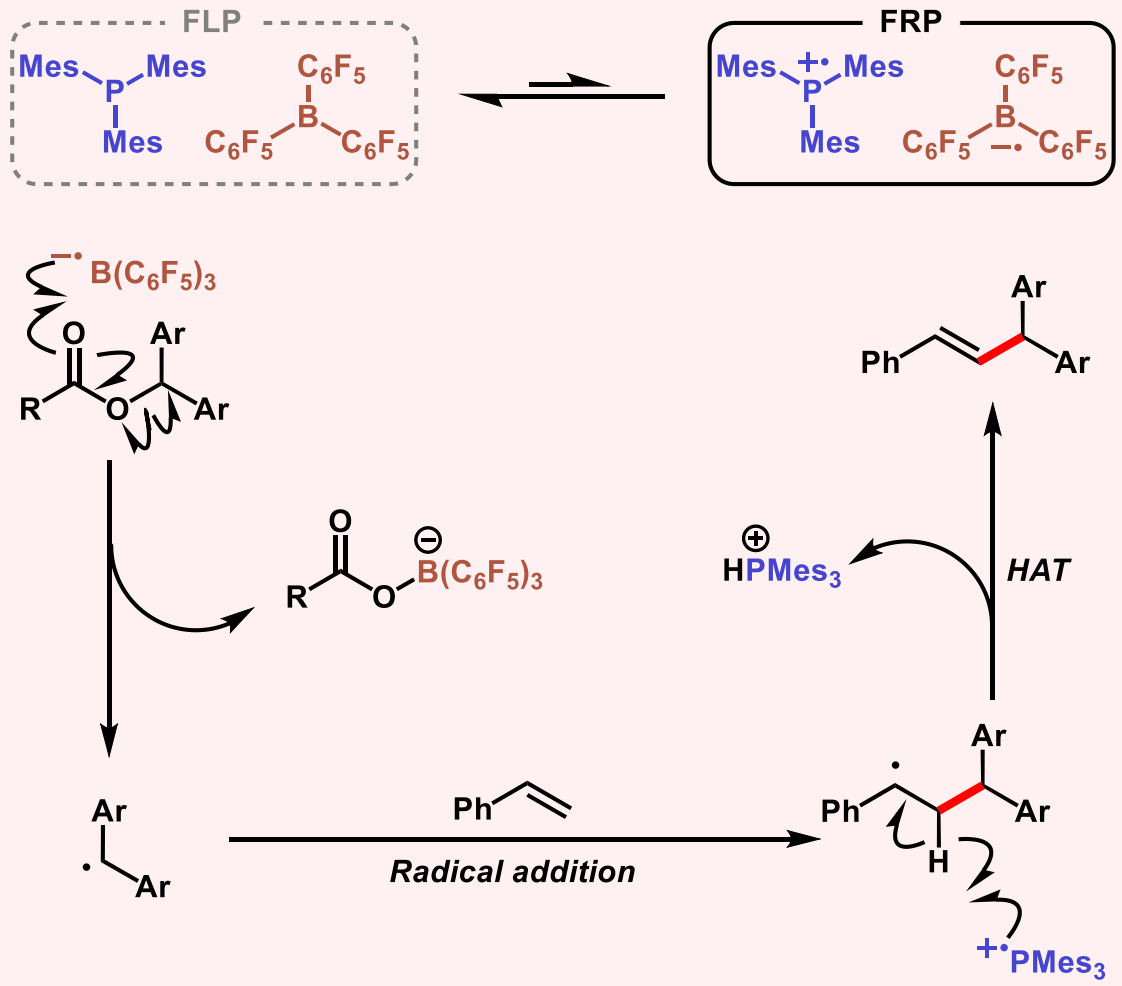
FRPs in Alkene Functionalization



Selected substrates



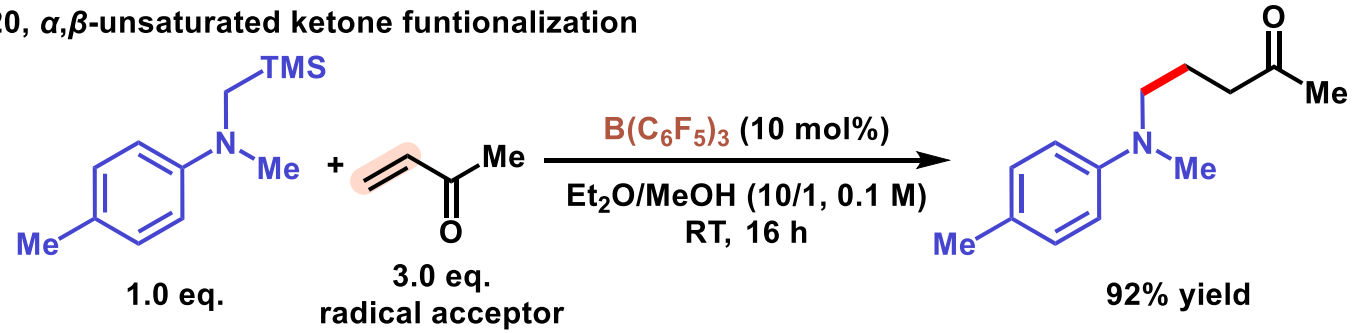
Proposed mechanism



Melen, R. L., et al. *Cell Reports Physical Science* **2020**, *1*.

FRPs in Alkene Functionalization

Ooi 2020, *α,β*-unsaturated ketone funtionalization

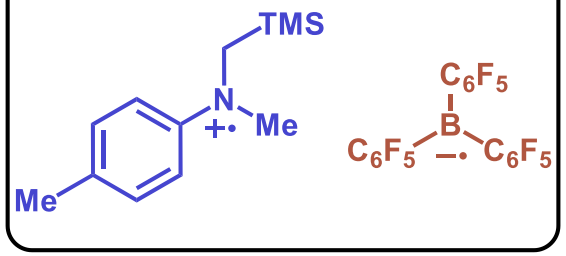


1.0 eq.

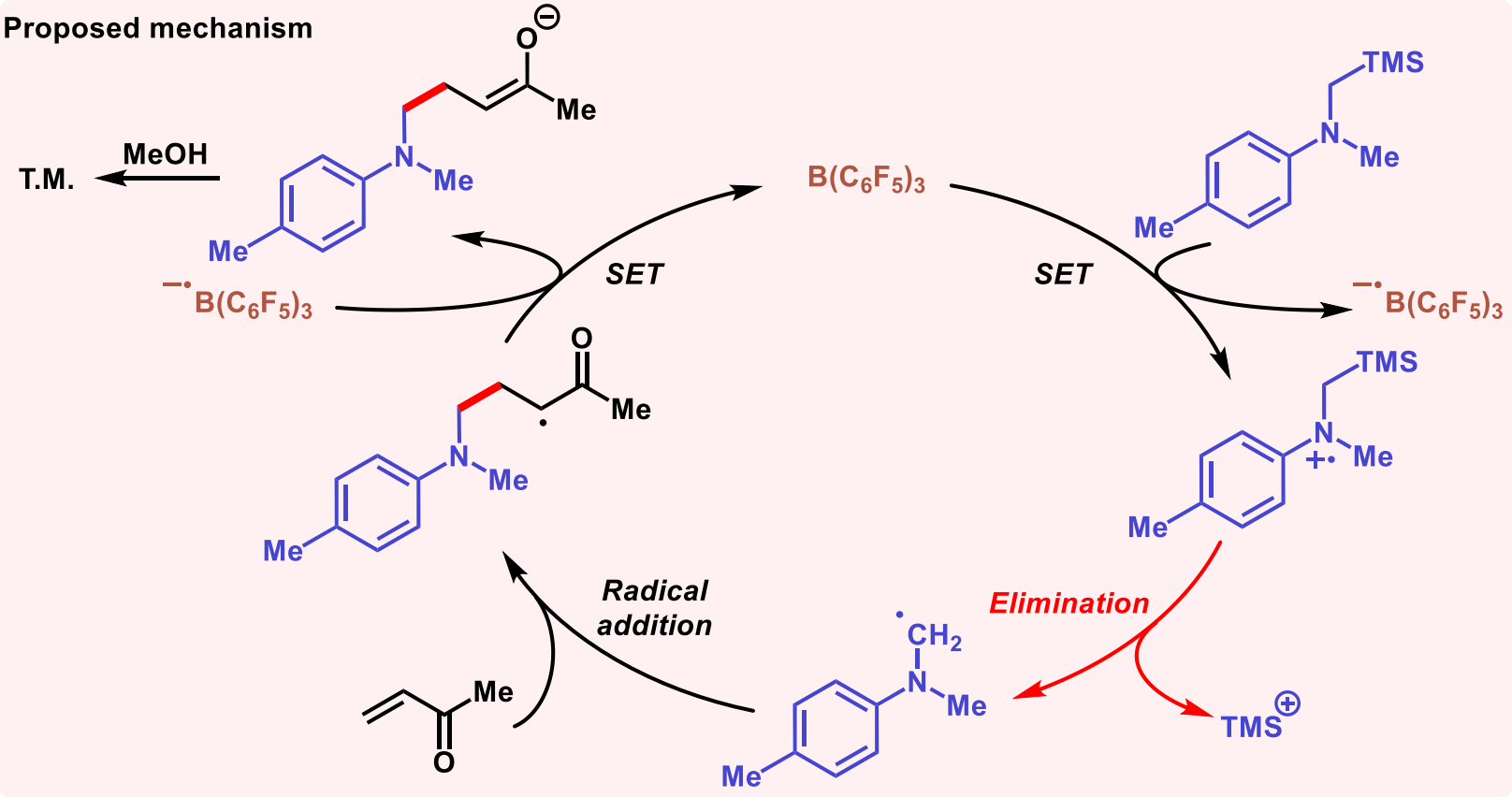
3.0 eq. radical acceptor

92% yield

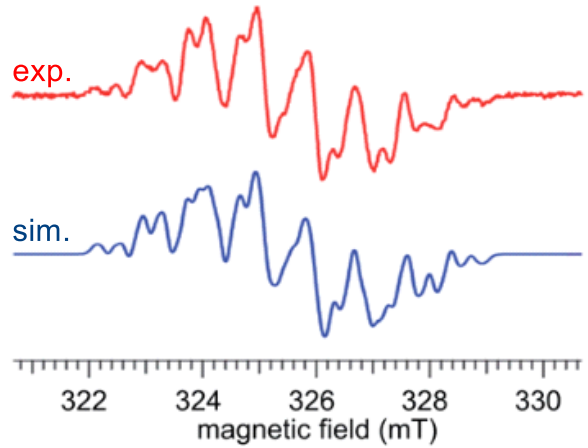
FRP

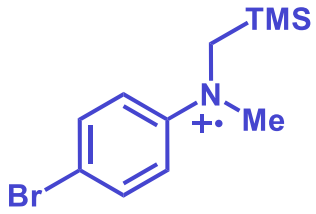


Proposed mechanism



EPR experiment



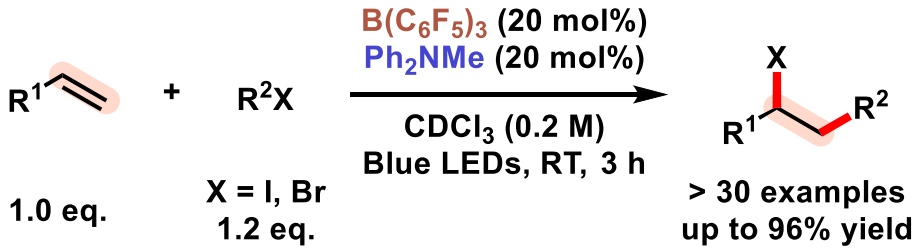


in DCM

Ooi, T., et al. *Chem. Sci.* **2020**, *11*, 4305.

FRPs in Alkene Functionalization

Zhang 2023, FRP-catalyzed alkene carbon halogenation

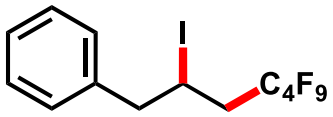


1.0 eq.

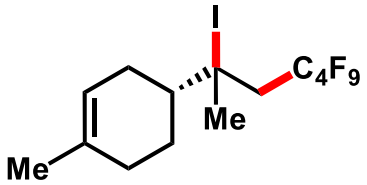
X = I, Br
1.2 eq.

> 30 examples
up to 96% yield

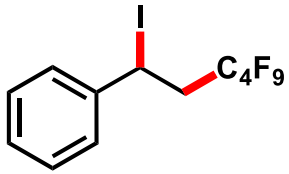
Selected substrates



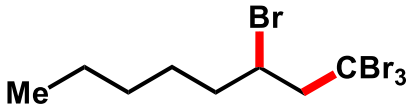
95% yield



95% yield

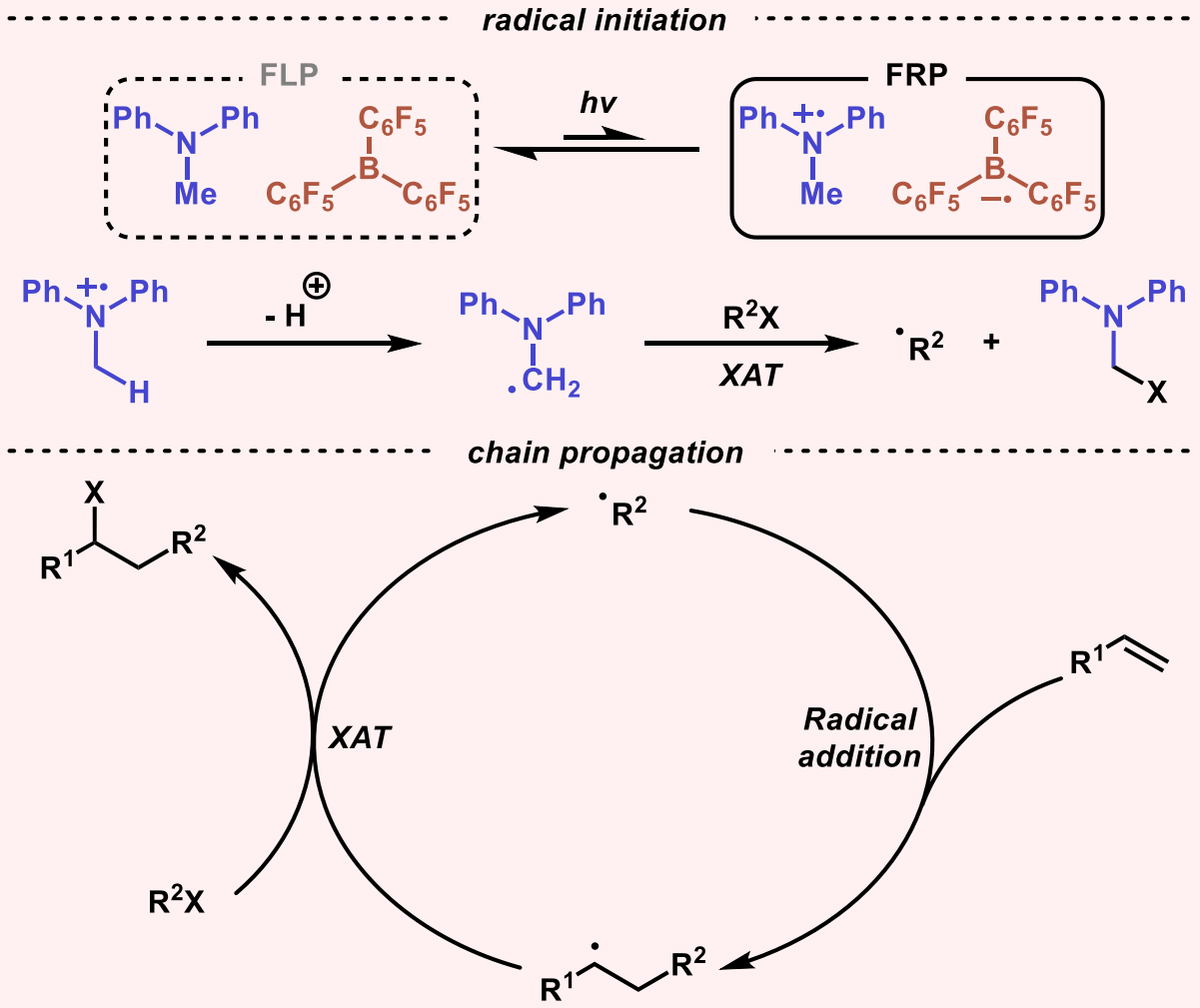


82% yield



59% yield

Proposed mechanism

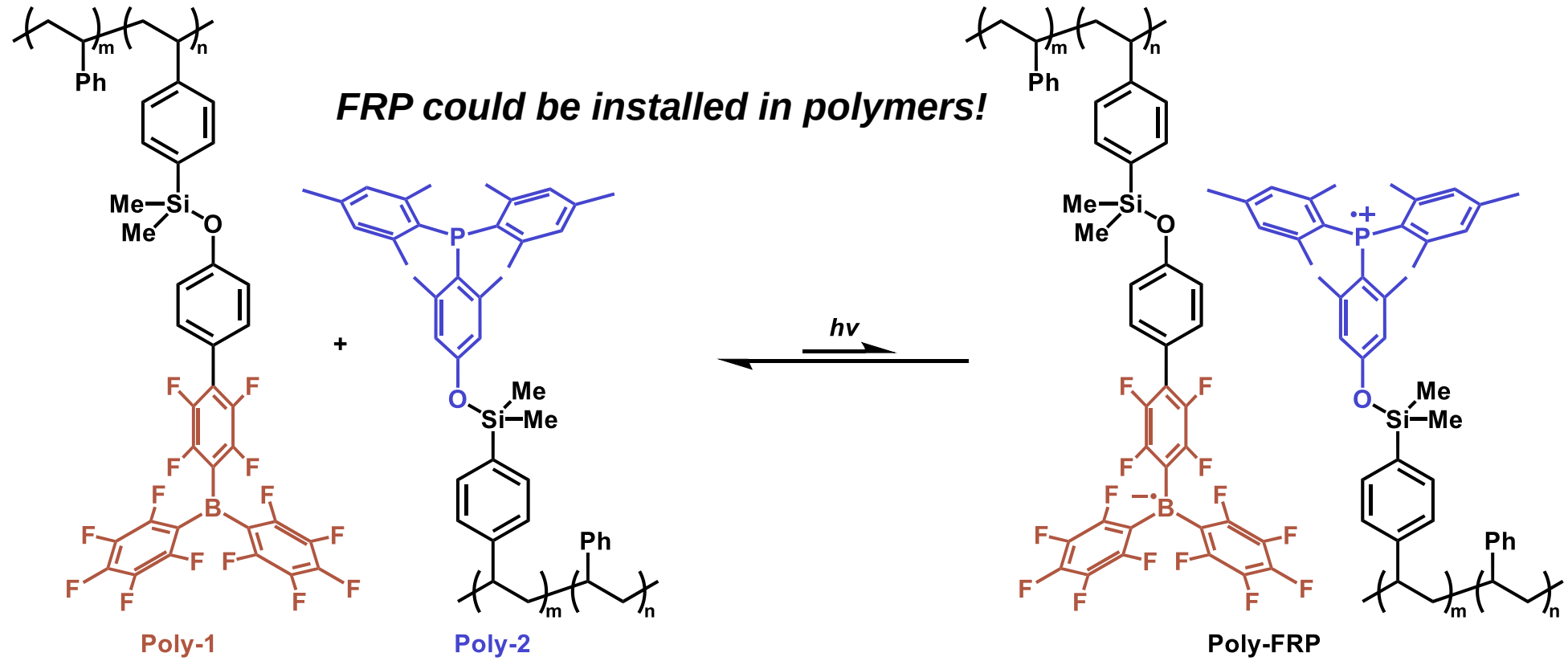


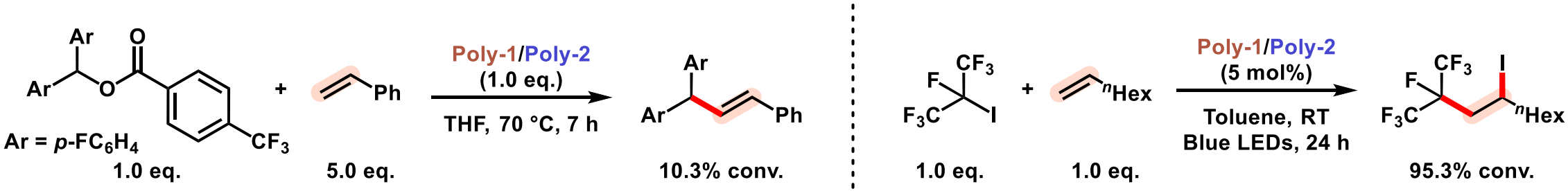
Zhang, Y., et al. *Org. Chem. Front.* **2023**, *10*, 3861.

FRPs in Alkene Functionalization

Shaver 2023

FRP could be installed in polymers!





Shaver, M. P., et al. *J. Am. Chem. Soc.* **2023**, *145*, 24294.

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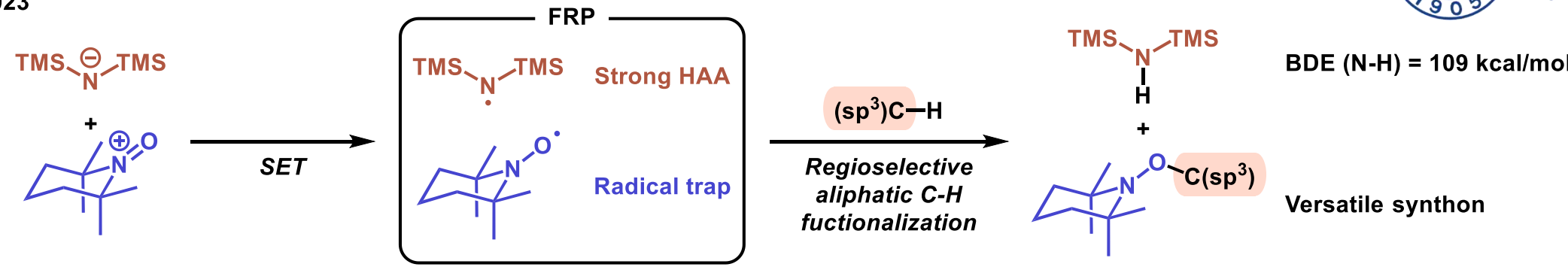
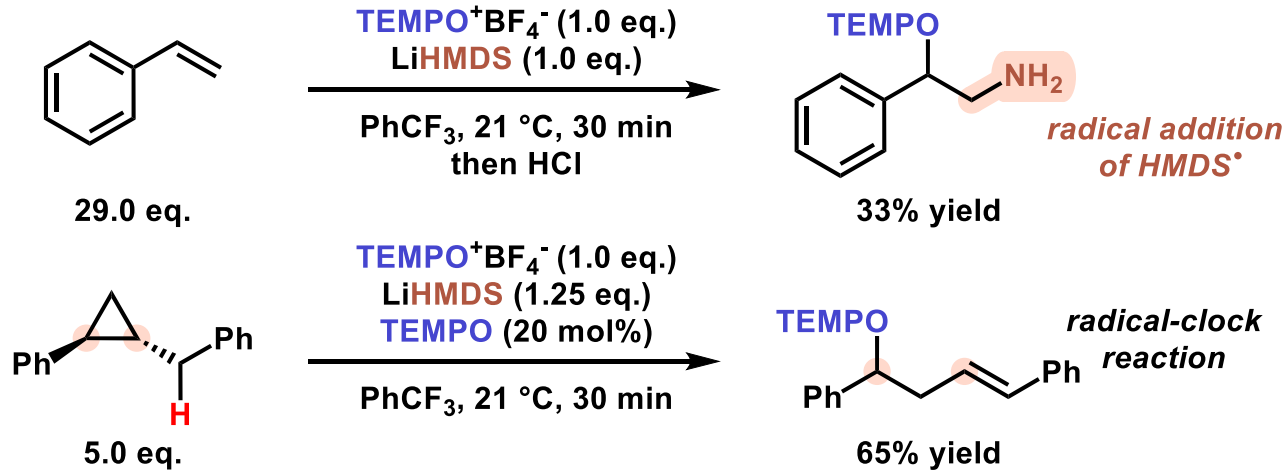
FRPs in sp^3 C-H Activation

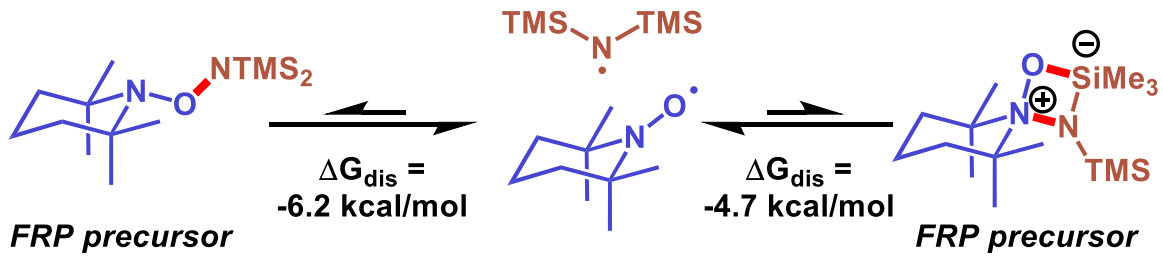
Lin 2023



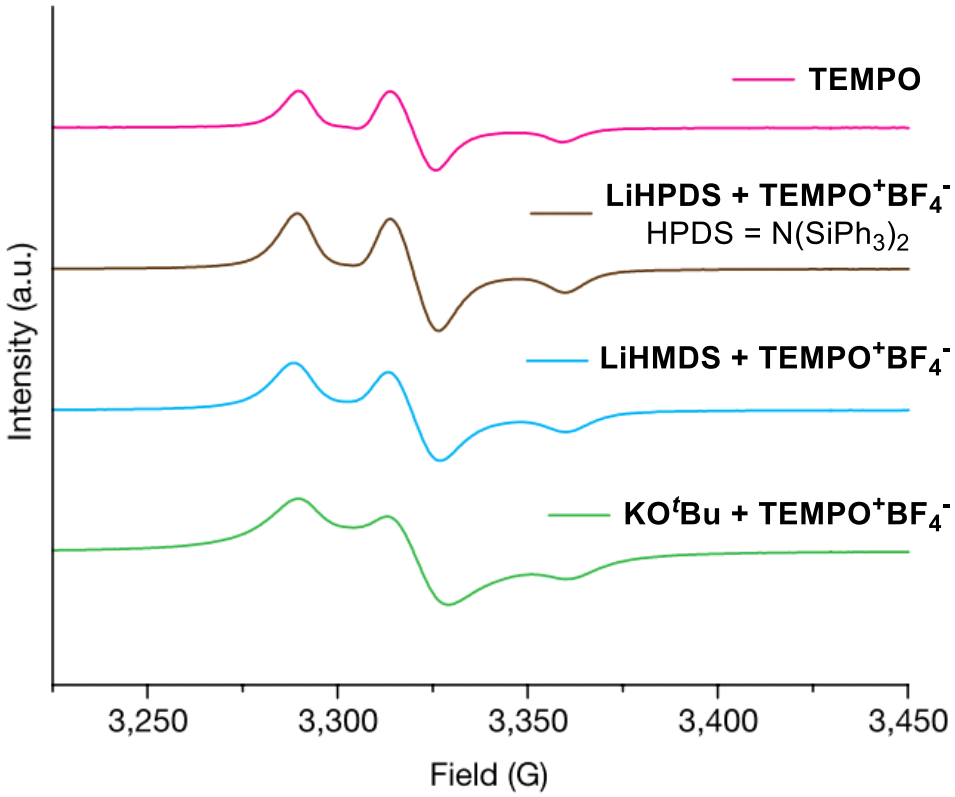
Mechanism experiment



DFT calculation

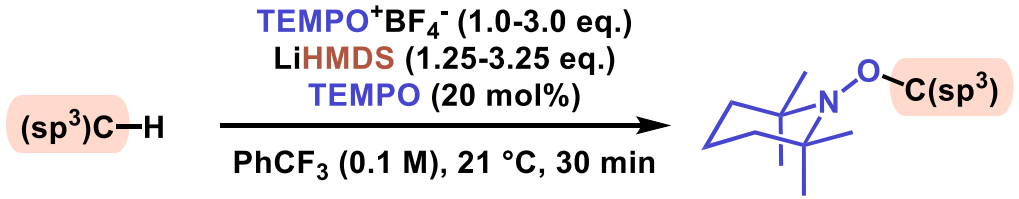


EPR spectra



Lin, S., et al. *Nature* **2023**, *619*, 514.

FRPs in sp^3 C-H Activation

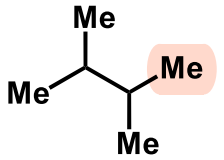


x eq.

> 40 examples
up to 87% yield

Selected substrates

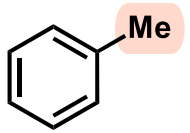
with TEMPO+BF4- (1.0 eq.)
LiHMDS (1.25 eq.)
x = 5.0, 42% yield
x = 20.0, 60% yield



with TEMPO+BF4- (1.0 eq.)
LiHMDS (1.25 eq.)

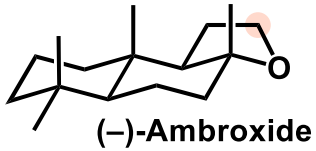
x = 20.0, 60% yield, 12:1 rr

good site selectivities!



with TEMPO+BF4- (1.0 eq.)
LiHMDS (1.25 eq.)

x = 5.0, 70% yield

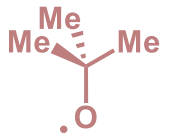


(–)-Ambroxide

with TEMPO+BF4- (2.0 eq.)
LiHMDS (2.25 eq.)

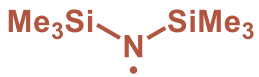
x = 1.0, 66% yield, 1:1 dr

Divergent site selectivities



^{t}BuO•

%V_{bur}(3.5 Å) = 35



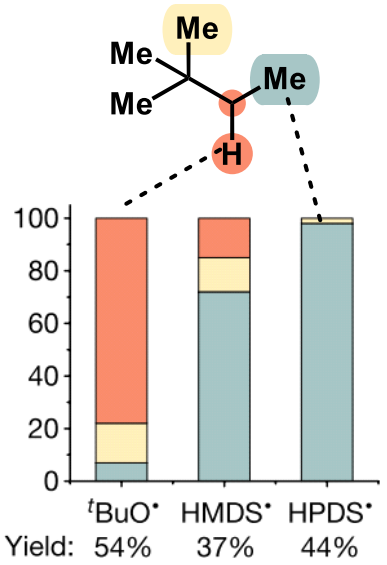
HMDS•

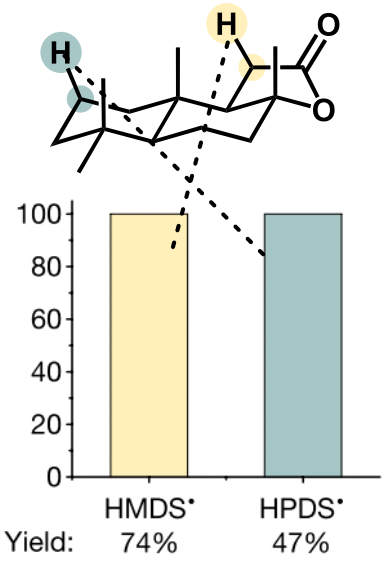
%V_{bur}(3.5 Å) = 52

HPDS•

%V_{bur}(3.5 Å) = 66

Increasing steric hindrance



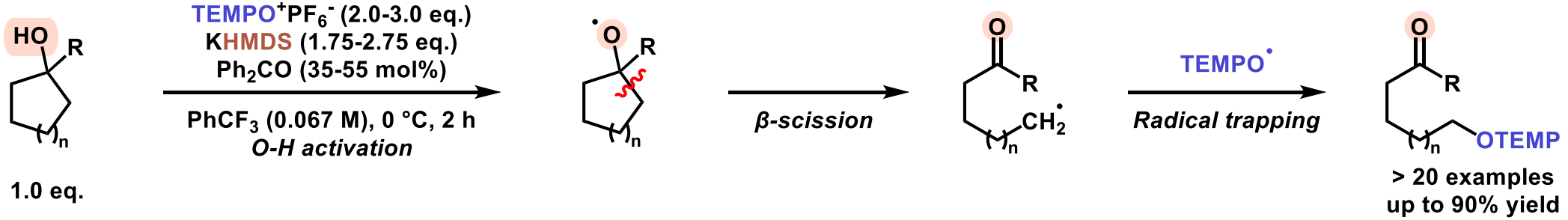


Lin, S., et al. *Nature* **2023**, *619*, 514.

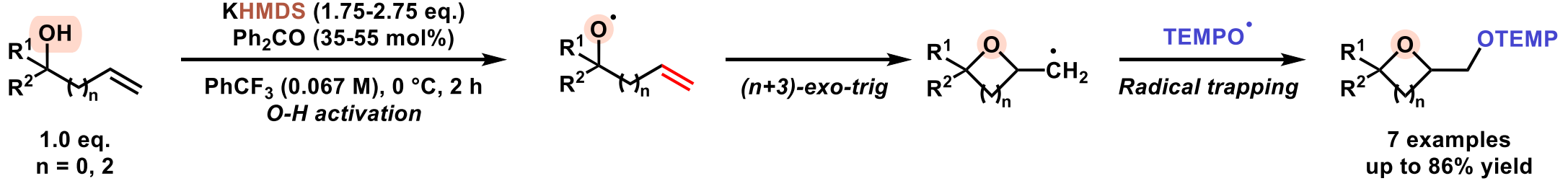
FRPs in sp^3 C-H Activation

Lin 2024

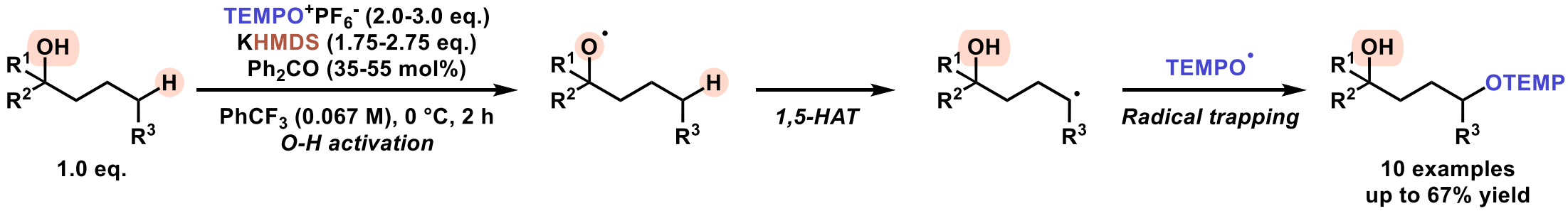
Generating carbon radical through β-scission



Generating carbon radical through n-exo-trig

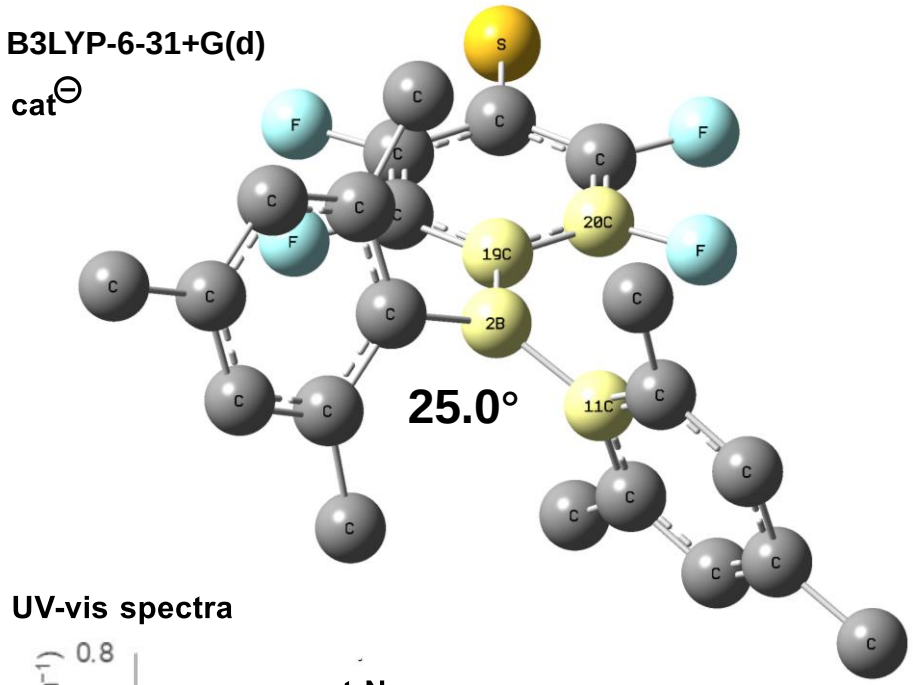


Generating carbon radical through 1,5-HAT

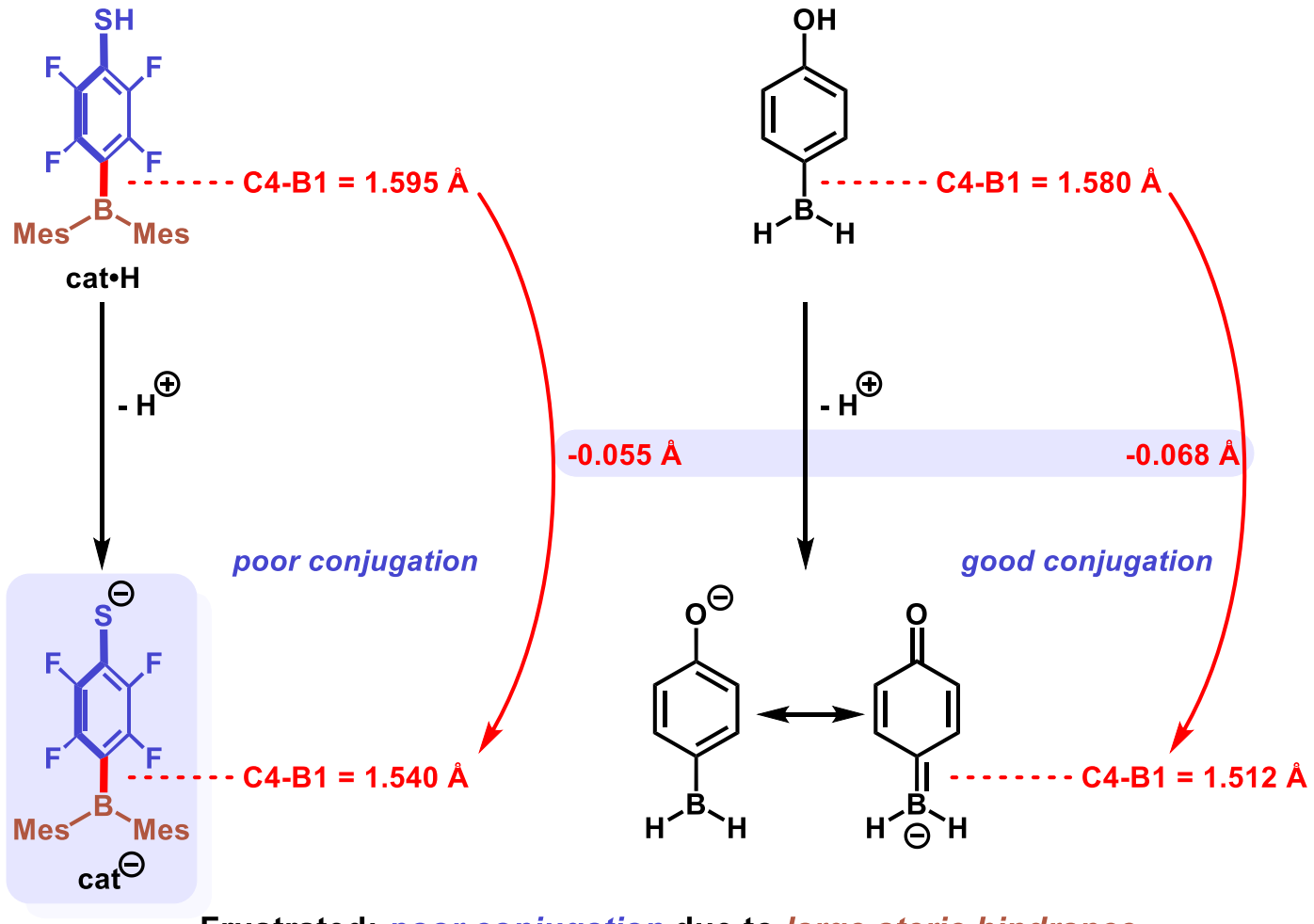


Lin, S., et al. *J. Am. Chem. Soc.* **2024**, *146*, 19696.

FRPs in sp³ C-H Activation



An intramolecular FLP generating through deprotonation



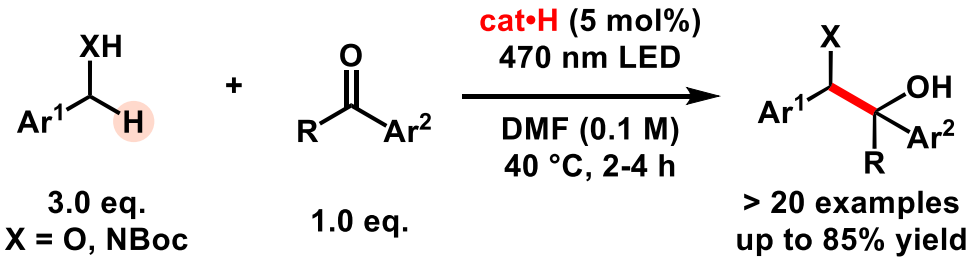
Frustrated: ***poor conjugation*** **due to** ***large steric hindrance***

Ooi, T., et al. *J. Am. Chem. Soc.* **2024**, *146*, 20425.

An intramolecular FRP from an intramolecular FLP

FRPs in sp³ C-H Activation

Ooi 2024, Intramolecular FRPs

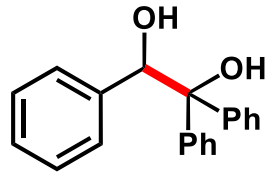


3.0 eq.
X = O, NBoc

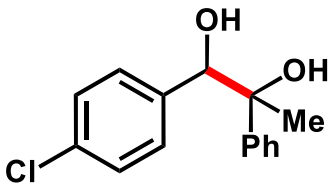
1.0 eq.

> 20 examples
up to 85% yield

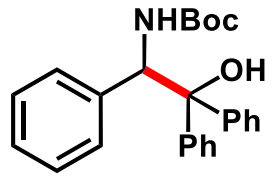
Selected substrates



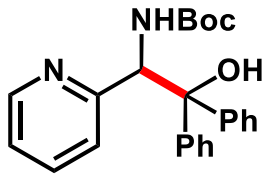
48% yield



36% yield, 1.1:1 dr

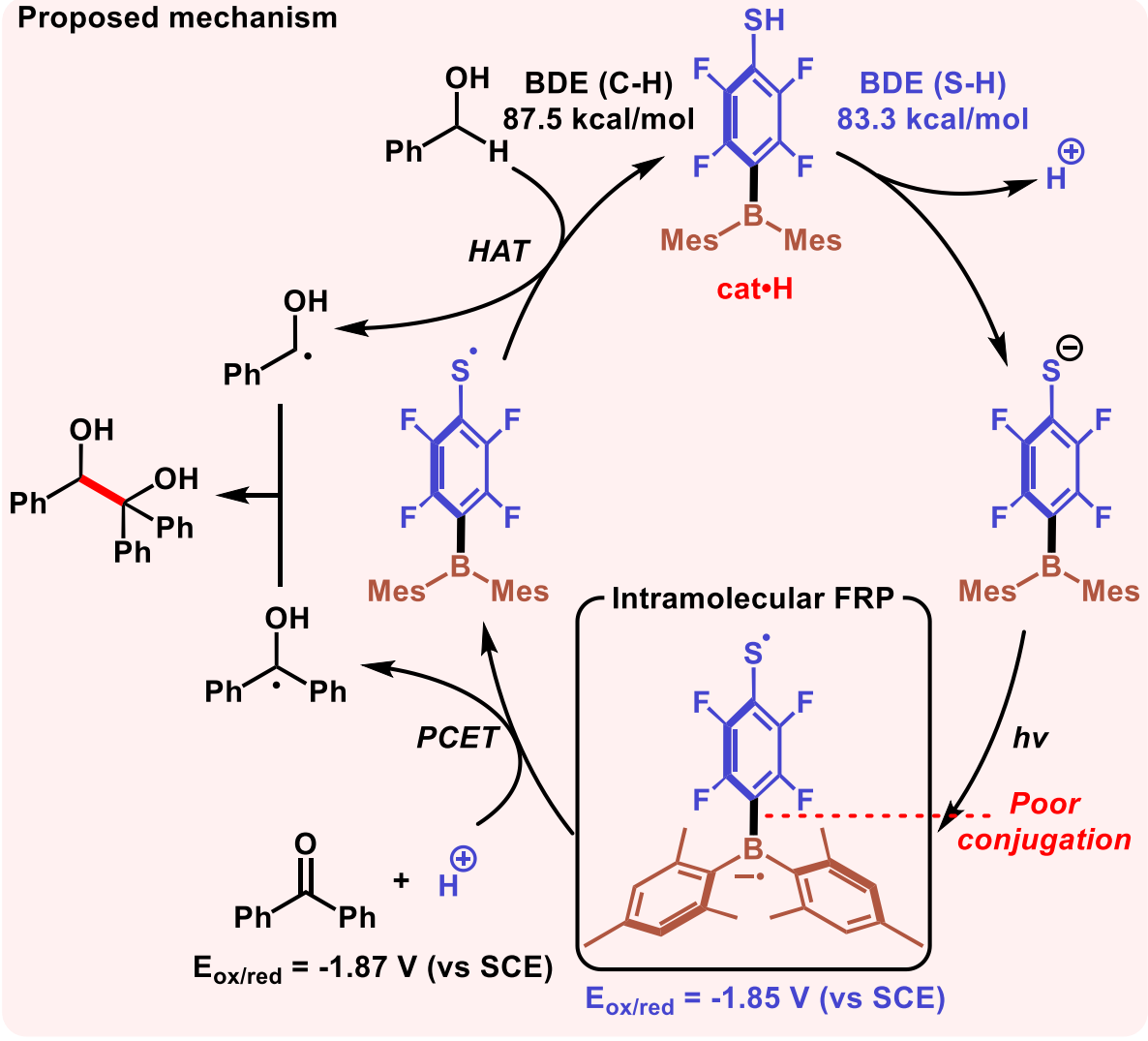


77% yield



42% yield

Proposed mechanism

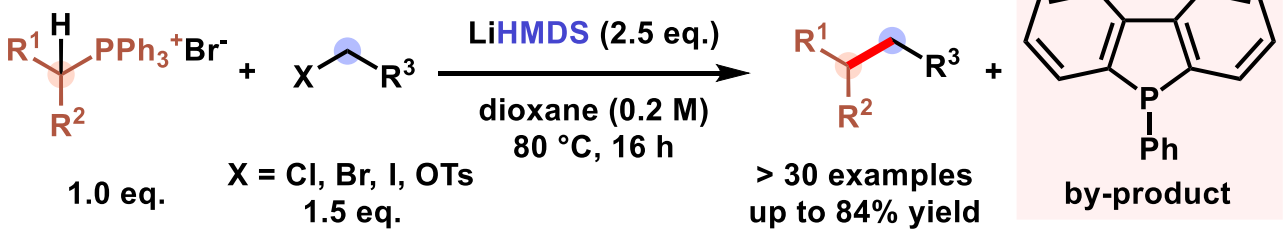


Ooi, T., et al. *J. Am. Chem. Soc.* **2024**, *146*, 20425.

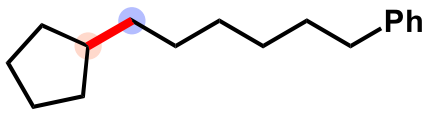
Content

FRPs in Cross Coupling

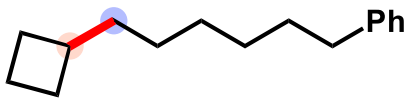
Morandi 2024



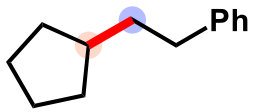
Selected substrates



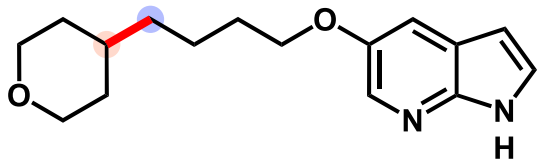
X = I, 81% yield
X = Br, 79% yield



X = Br, 73% yield

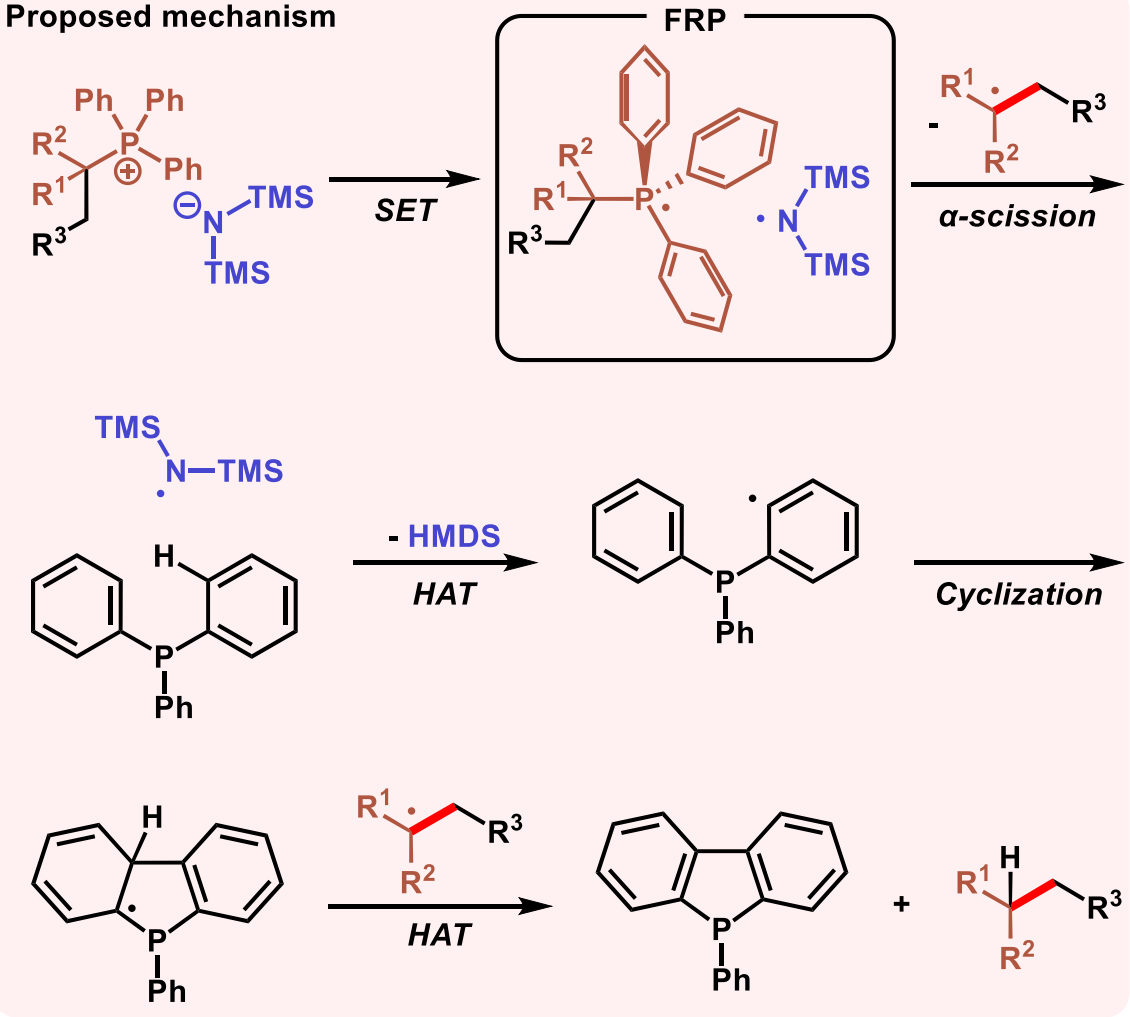


X = Cl, 32% yield
X = OTs, 62% yield



X = Br, 33% yield

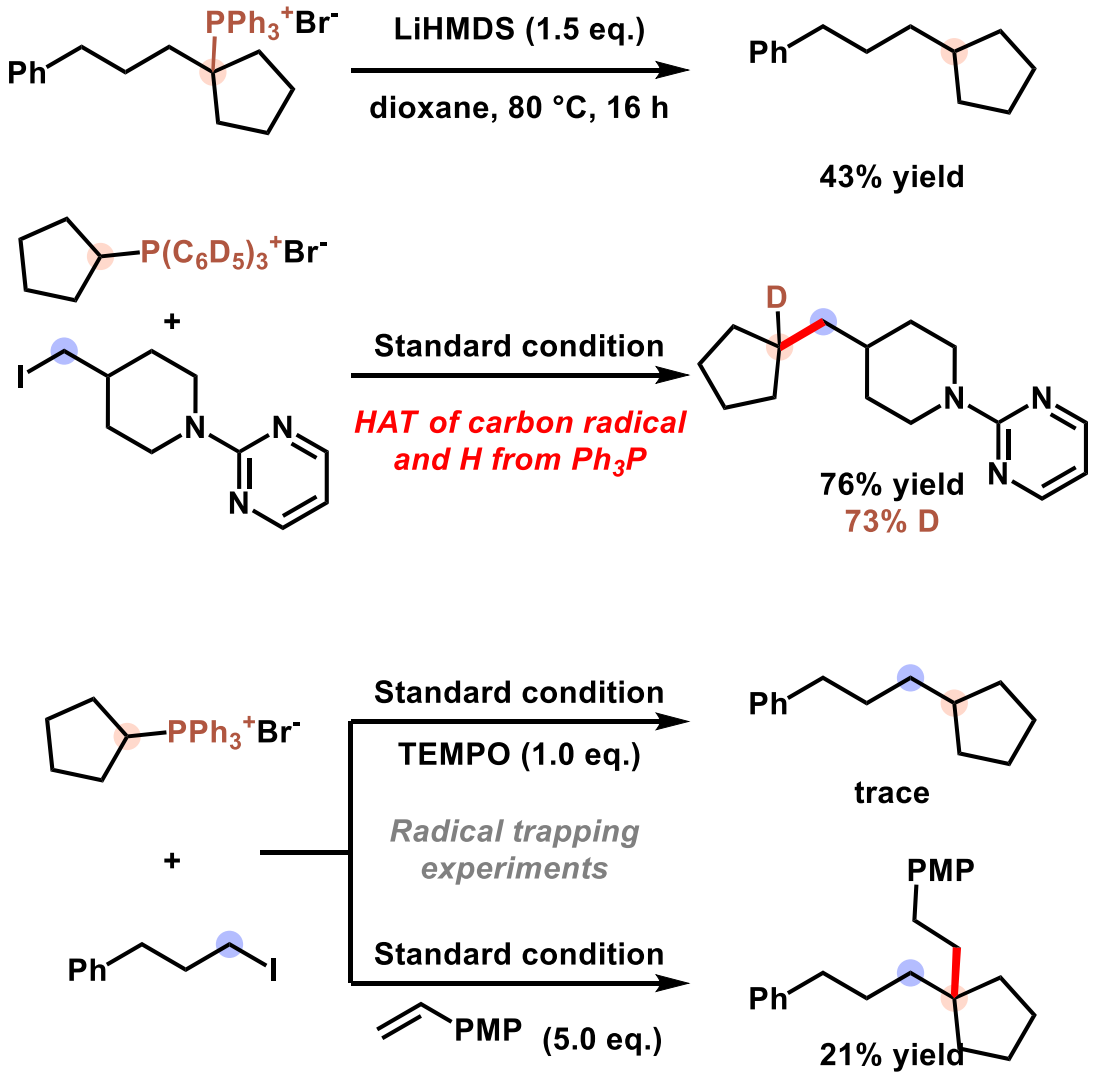
Proposed mechanism



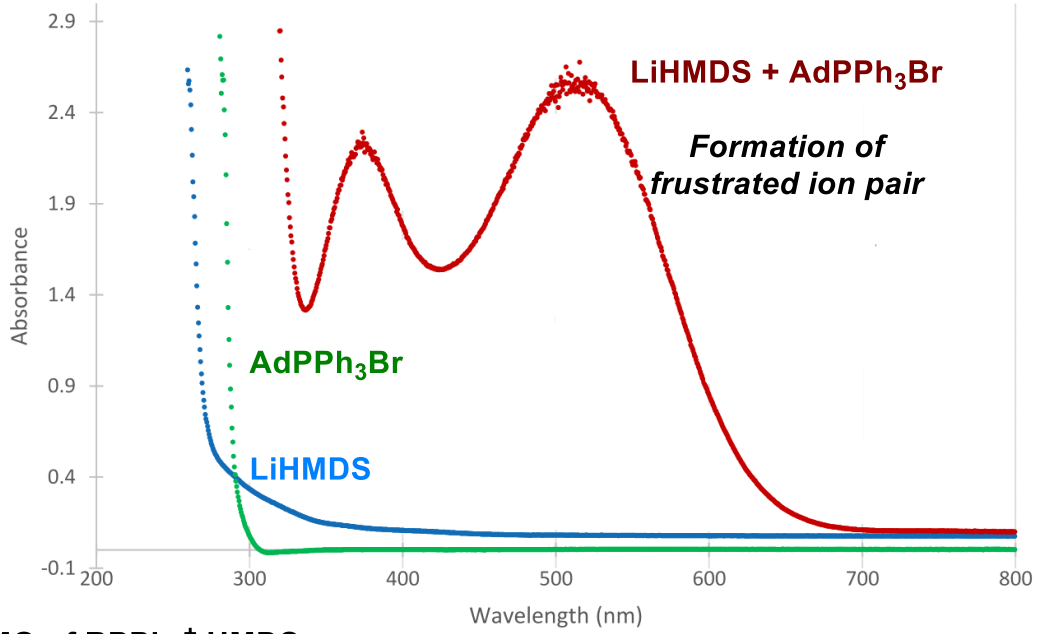
Morandi, B., et al. *Nature* **2024**, *636*, 108.

FRPs in Cross Coupling

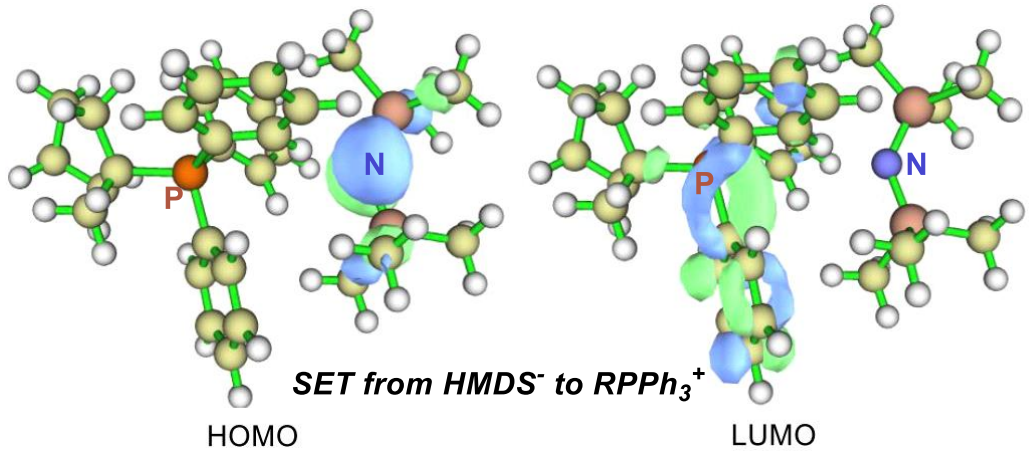
Mechanistic experiments



UV-vis spectra



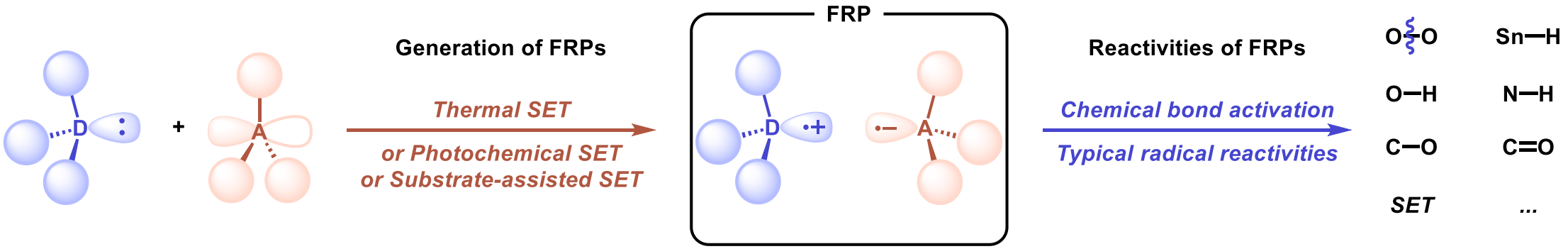
FMO of $RPPh_3^+$ $HMDS^-$



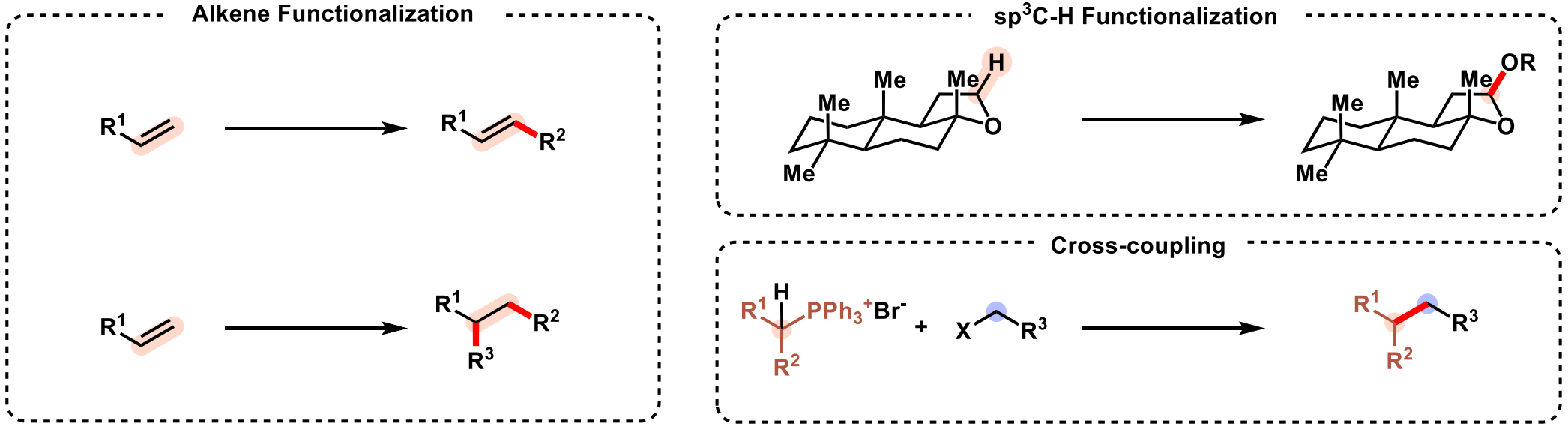
Morandi, B., et al. *Nature* **2024**, *636*, 108.

Content

Summary

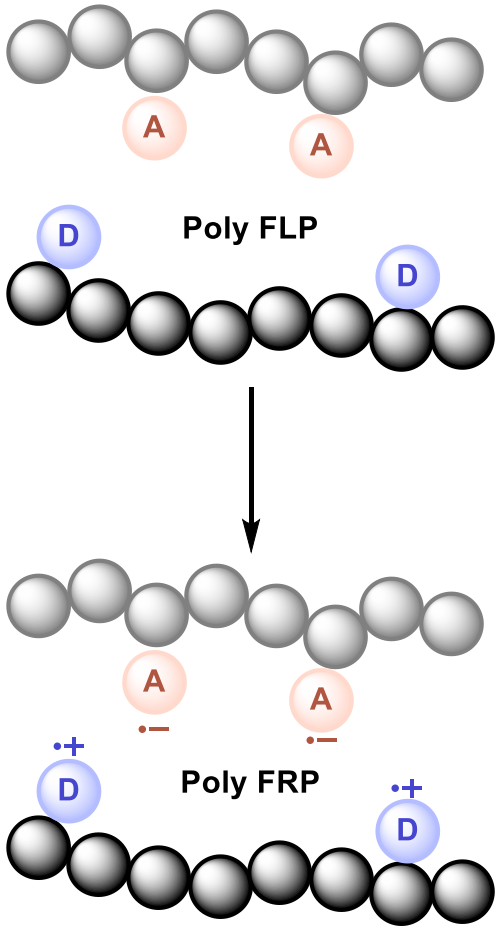


FRPs in Organic Synthesis

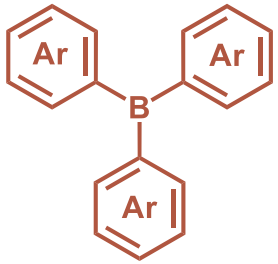


Outlook

FRPs in Organic Materials



New FRPs



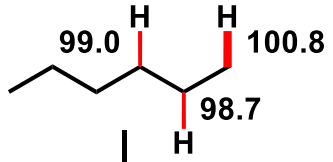
New functional group on FRPs

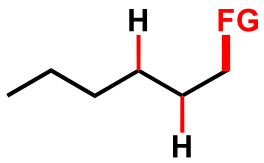
B	C	N	O
Al	Si	P	S
Ga	Ge	As	Se
In	Sn	Sb	Te

New element in FRPs

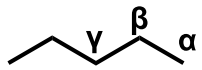
Enhanced Selectivities

BDE (kcal/mol)





Lin 2023



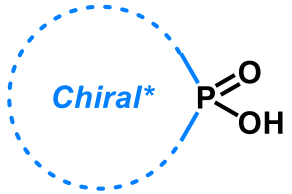
C-H functionalization

TEMPO/HMDS, α : β : γ = 1.1 : 3.4 : 1

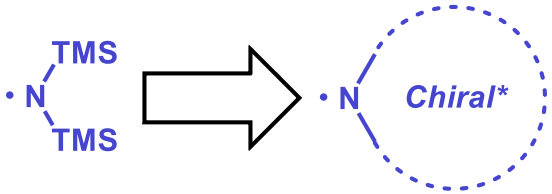
TEMPO/HPDS, α : β : γ = 14 : 18 : 1

TEMPO/O^{t}Bu, α : β : γ = 3.9 : 9.4 : 1

Asymmetric Transformations



Asymmetric catalysis



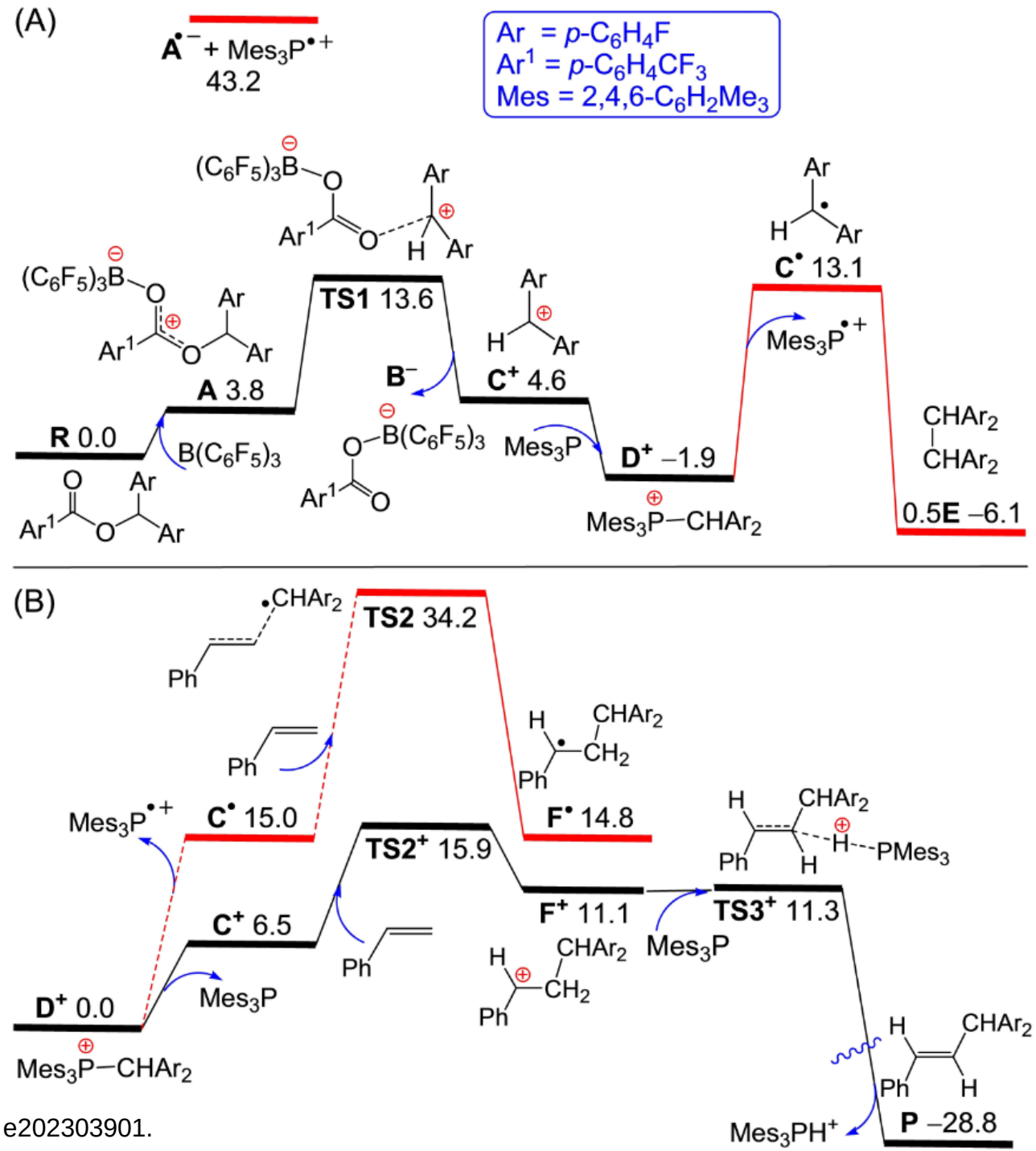
Enatioselective HAT
or
Kinetic resolution

Hu, P., et al. *Science* **2024**, *383*, 537; Lin, S., et al. *Nature* **2023**, *619*, 514.

復旦大學

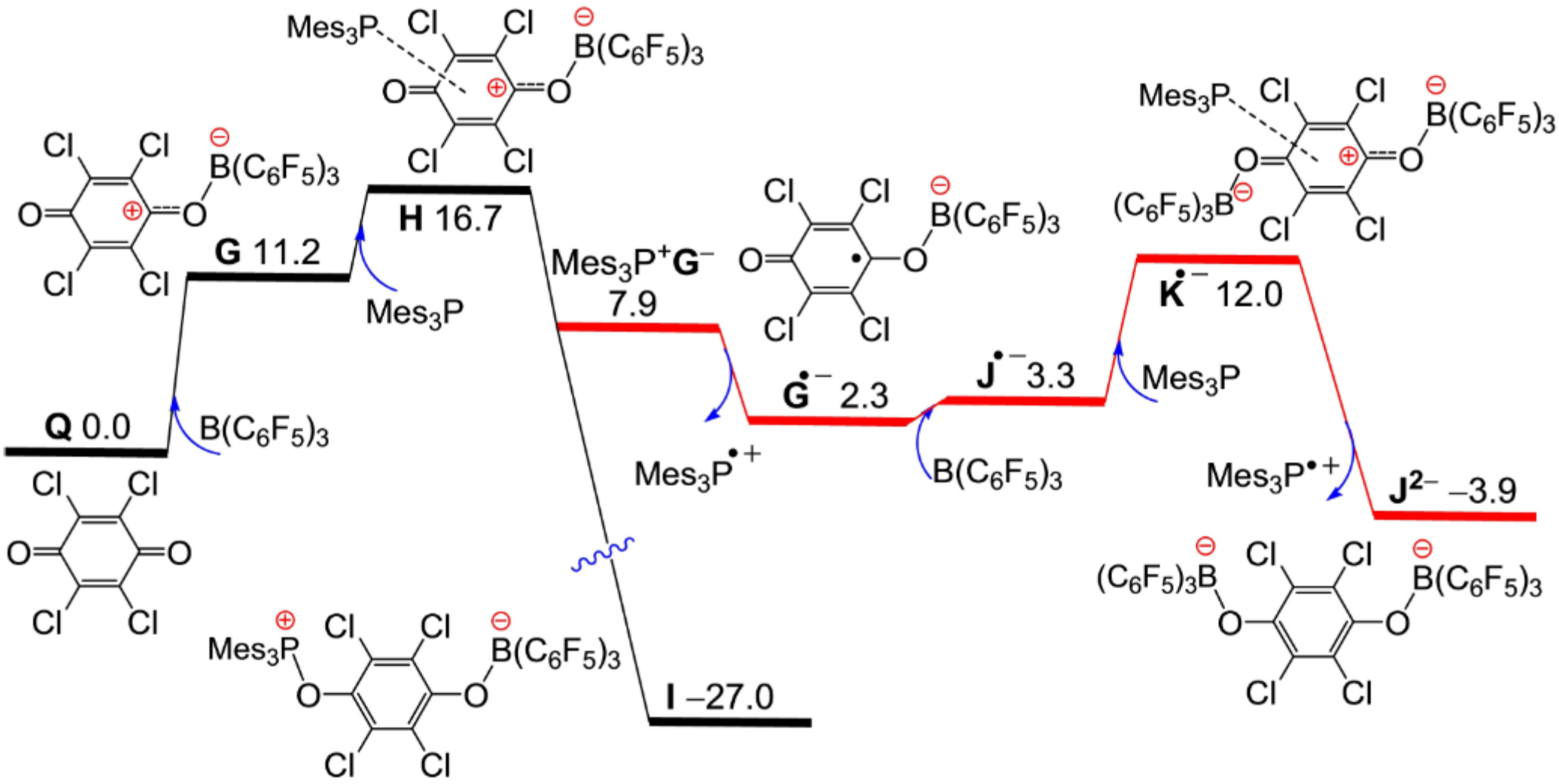
Thanks for listening !

Appendix



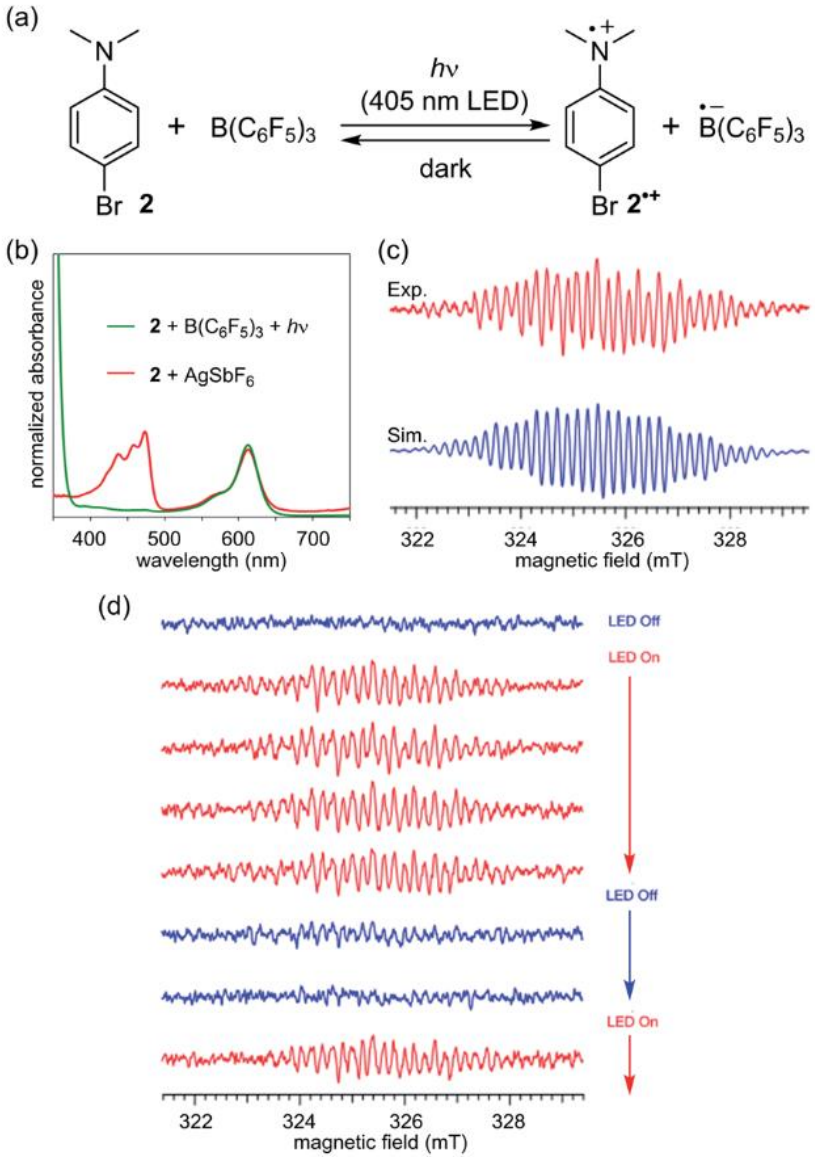
Grimme, S., et al. *Chem. - Eur. J.* **2024**, *30*, e202303901.

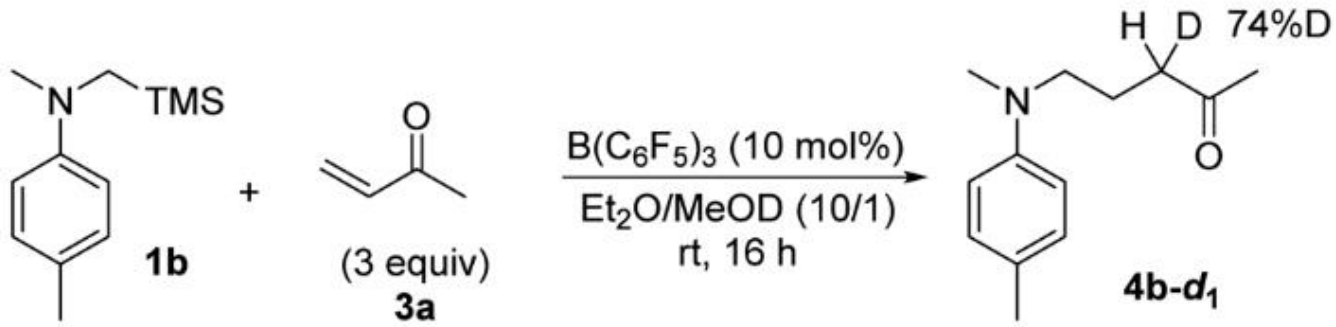
Appendix



Grimme, S., et al. *Chem. - Eur. J.* **2024**, *30*, e202303901.

Appendix

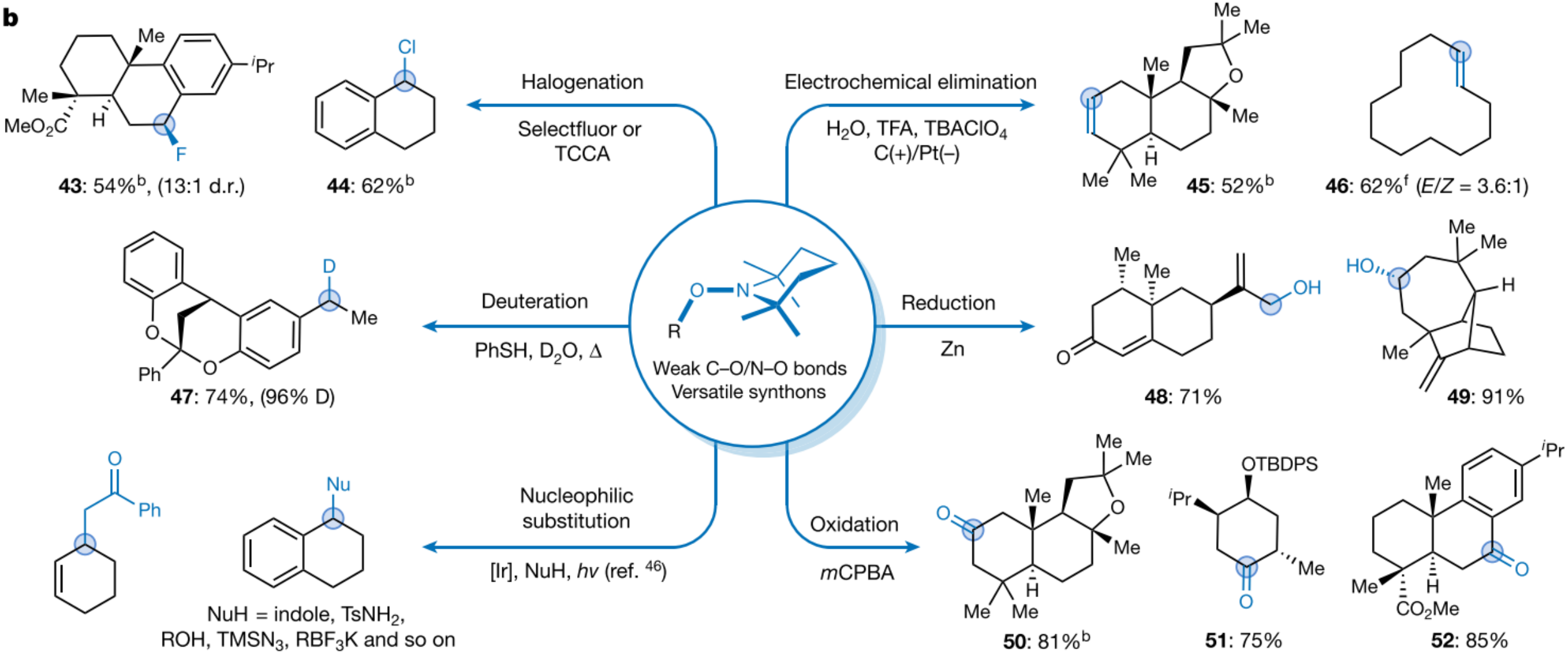




Scheme 1 Deuterium incorporation experiment.

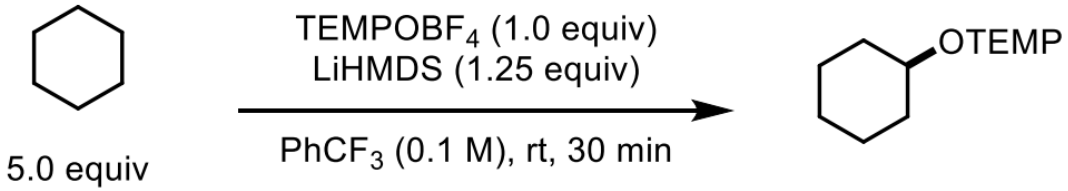
Ooi, T., et al. *Chem. Sci.* **2020**, *11*, 4305.

Appendix



Lin, S., et al. *Nature* **2023**, *619*, 514.

Appendix



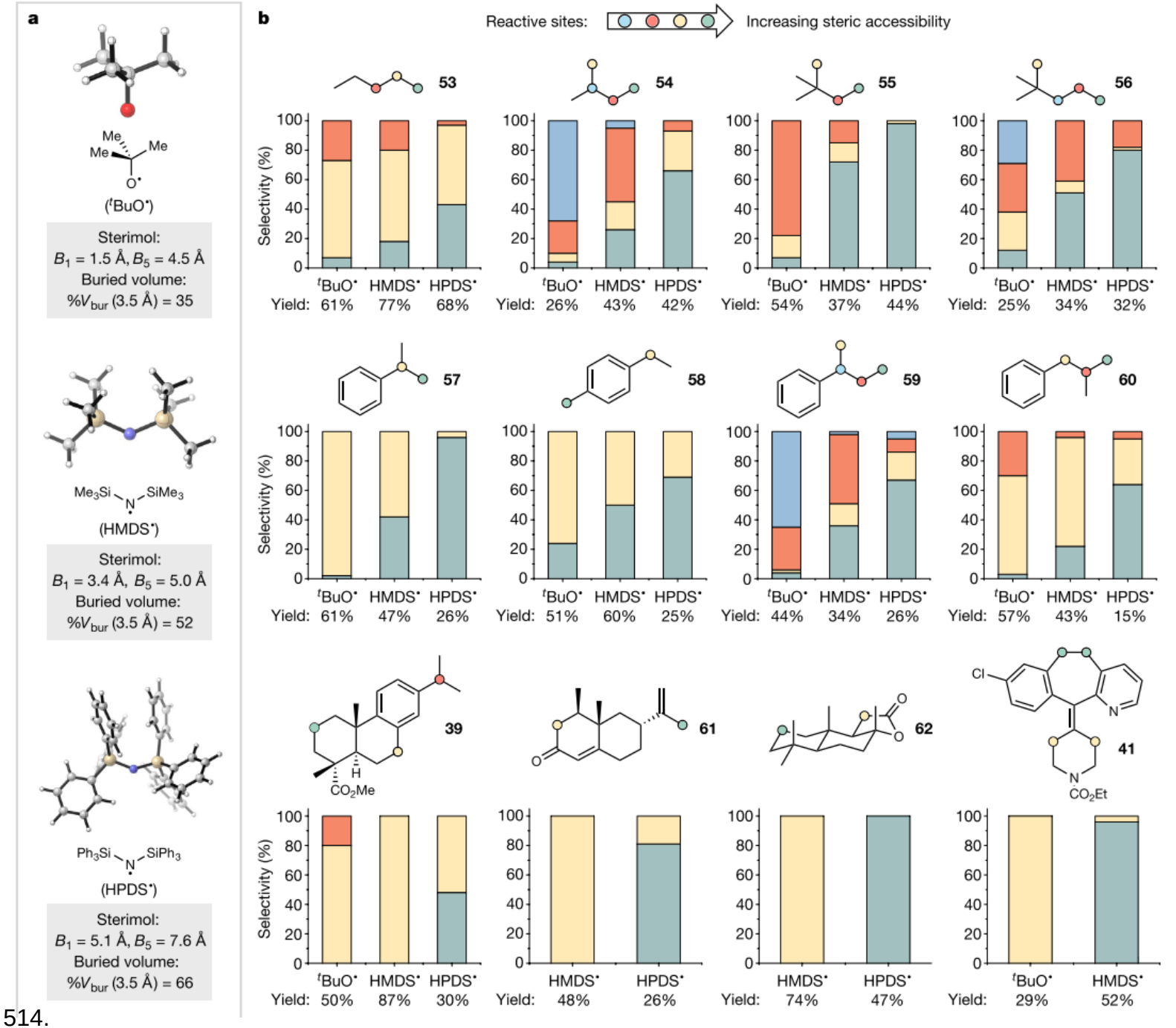
Entry	Deviations from standard conditions	Yield
1	none	67%
2	1 equiv of cyclohexane	35%
3	1 equiv of LiHMDS	59%
4	rapid addition of LiHMDS solution	51%
5	0 °C	59%
6	0.2 M in $PhCF_3$	63%
7	ClO_4^-, PF_6^-, OTf^- instead of BF_4^-	22–57%
8	C_6H_6, PhCl instead of $PhCF_3$	56–64%
9	0.2 equiv of TEMPO additive	**74%**
10	no LiHMDS	0%

Optimizations were performed on a 0.2 mmol scale. Yields were determined by quantitative ^1H NMR analysis using mesitylene internal standard. TEMP=2,2,6,6-tetramethyl-1-piperidinyl.

In all cases, the addition of a small amount of TEMPO (0.2 equiv.) was found to help improve the reaction yield, presumably by facilitating trapping of the alkyl radical at the initial stage of reaction with increased concentration of the radical coupling partner

Lin, S., et al. *Nature* **2023**, *619*, 514.

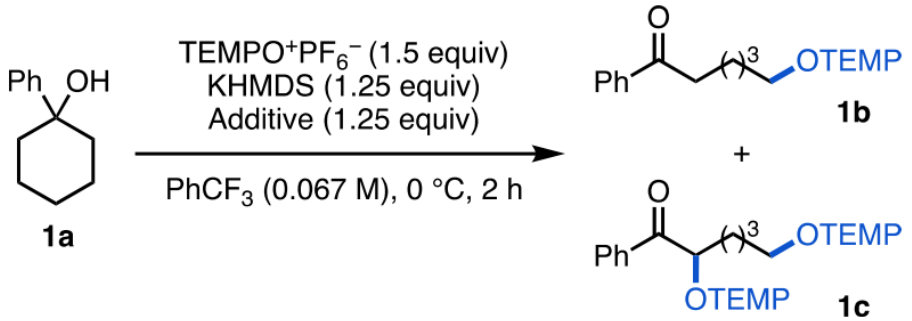
Appendix



Lin, S., et al. *Nature* **2023**, *619*, 514.

Appendix

Table 1. Conditions Explored for Reaction Optimization[a]



Entry	Additive	Yield of **1b**	Yield of **1c**
1	none	14%	18%
2	THF	13%	12%
3	18-crown-6	3%	2%
4	Ph3N	9%	13%
5	pyridine	7%	9%
6	1,10-phen	9%	1%
7	HMPA	9%	8%
8	benzophenone	32%	ND
9	benzophenone[b]	57%	2%
10[c]	**benzophenone**	**72%**	**2%**

[a]Optimization was conducted on a 0.1 mmol scale. Yield was determined by ^{1}H NMR using mesitylene internal standard. [b]0.25 equiv of benzophenone. [c]2.5 equiv of $TEMPO^+PF_6^-$, 2.25 equiv of KHMDS, 0.45 equiv of benzophenone.

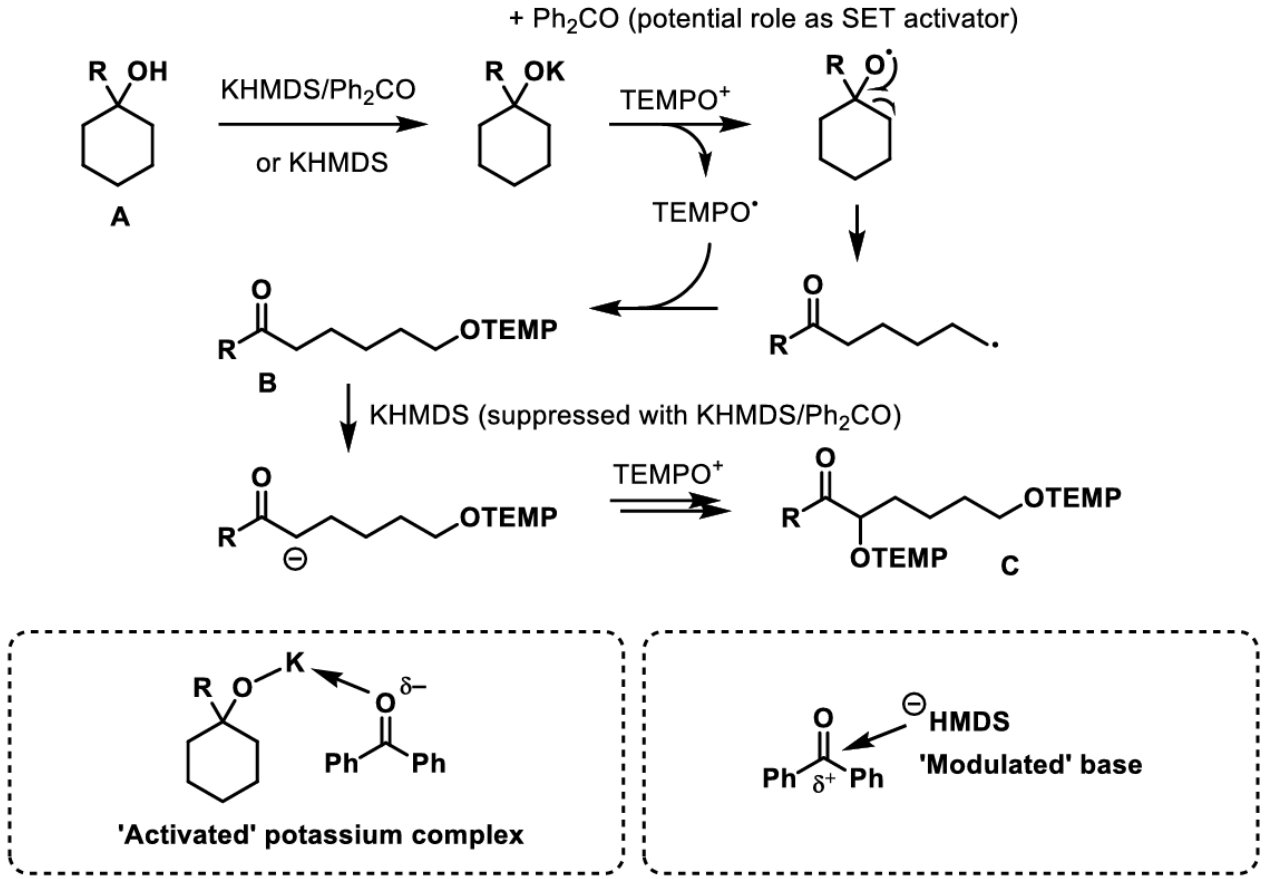
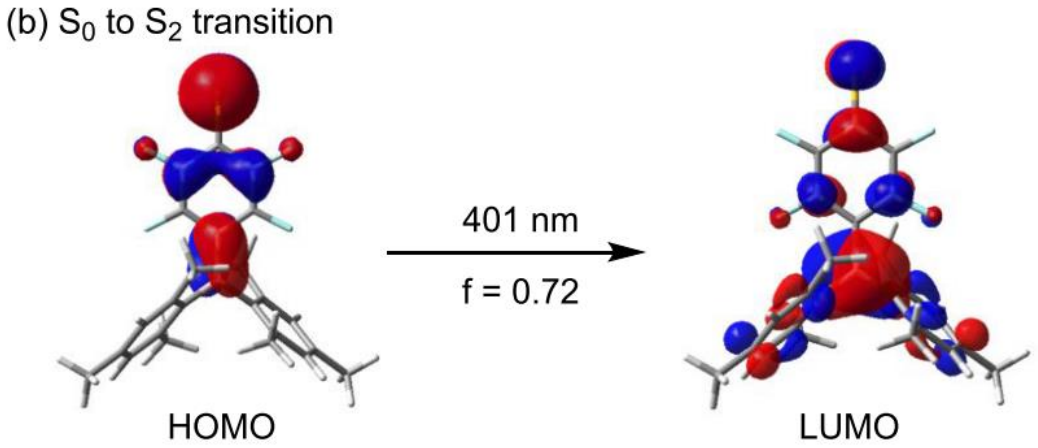
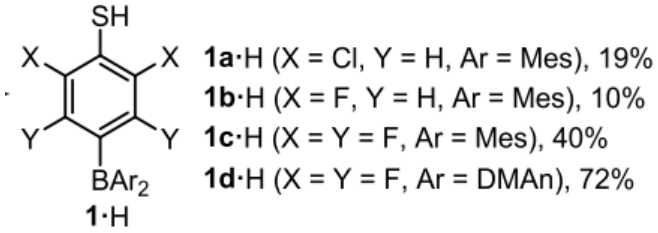


Figure S25. Proposed role of the benzophenone additive.

Appendix





1a·H (X = Cl, Y = H, Ar = Mes), 19%
1b·H (X = F, Y = H, Ar = Mes), 10%
1c·H (X = Y = F, Ar = Mes), 40%
1d·H (X = Y = F, Ar = DMAn), 72%

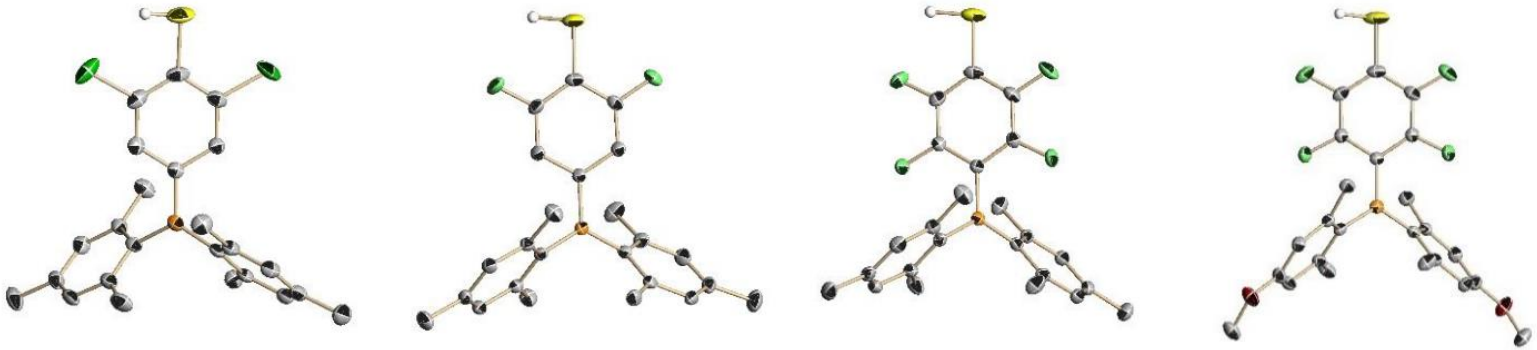
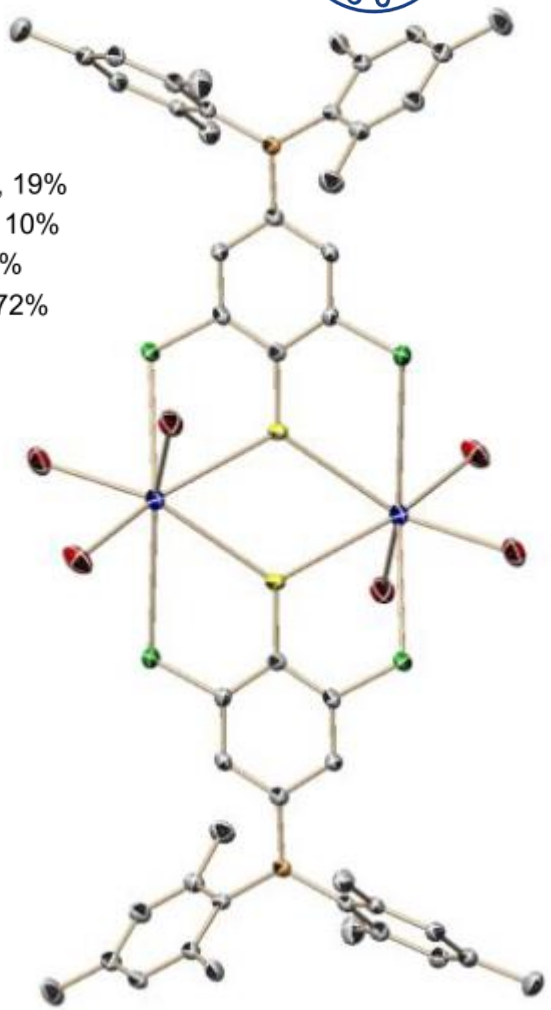


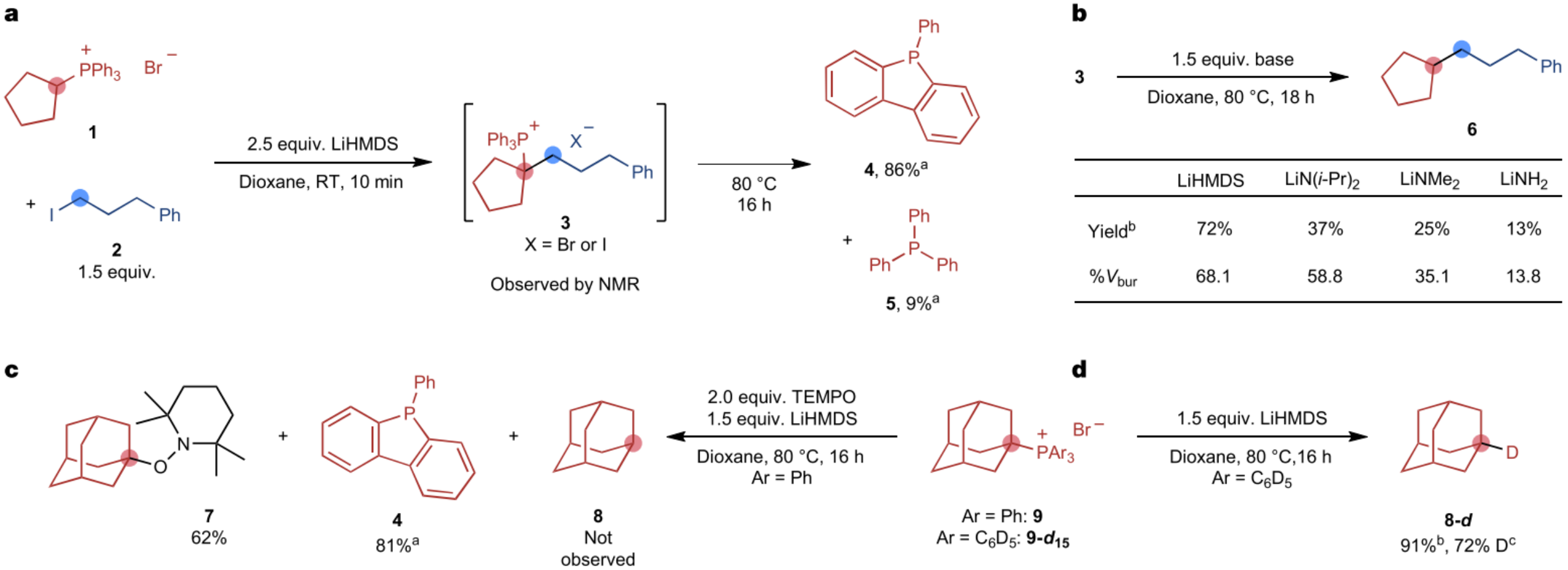
Figure S8. ORTEP drawing of **1a**·H, **1b**·H, **1c**·H, and **1d**·H (thermal ellipsoids were set to 50%).



·$[\mathbf{1a}\cdot K(THF)_3]_2$

Ooi, T., et al. *J. Am. Chem. Soc.* **2024**, *146*, 20425.

Appendix



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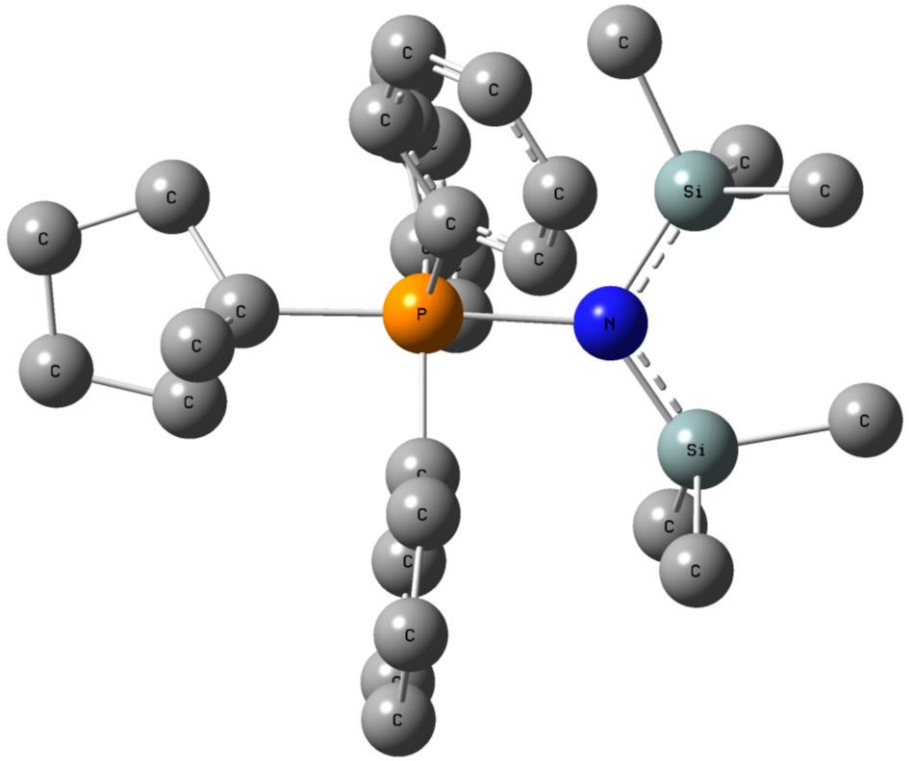
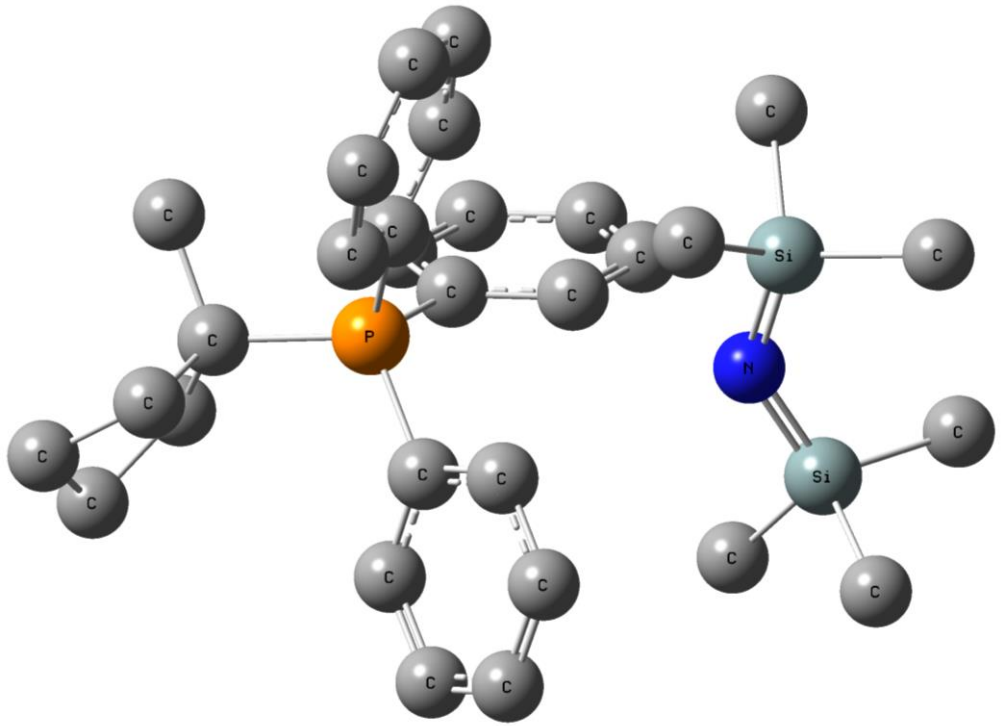
Appendix



P-N Adduct
P-N = 2.10 Å
ΔG = 21.7 kcal/mol
$E_{distortion}$ = 55.1 kcal/mol
$E_{interaction}$ = -75.7 kcal/mol



Frustrated Ion Pair
P-N = 4.47 Å
ΔG = 0 kcal/mol
$E_{distortion}$ = 1.8 kcal/mol
$E_{interaction}$ = -38.4 kcal/mol

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Appendix

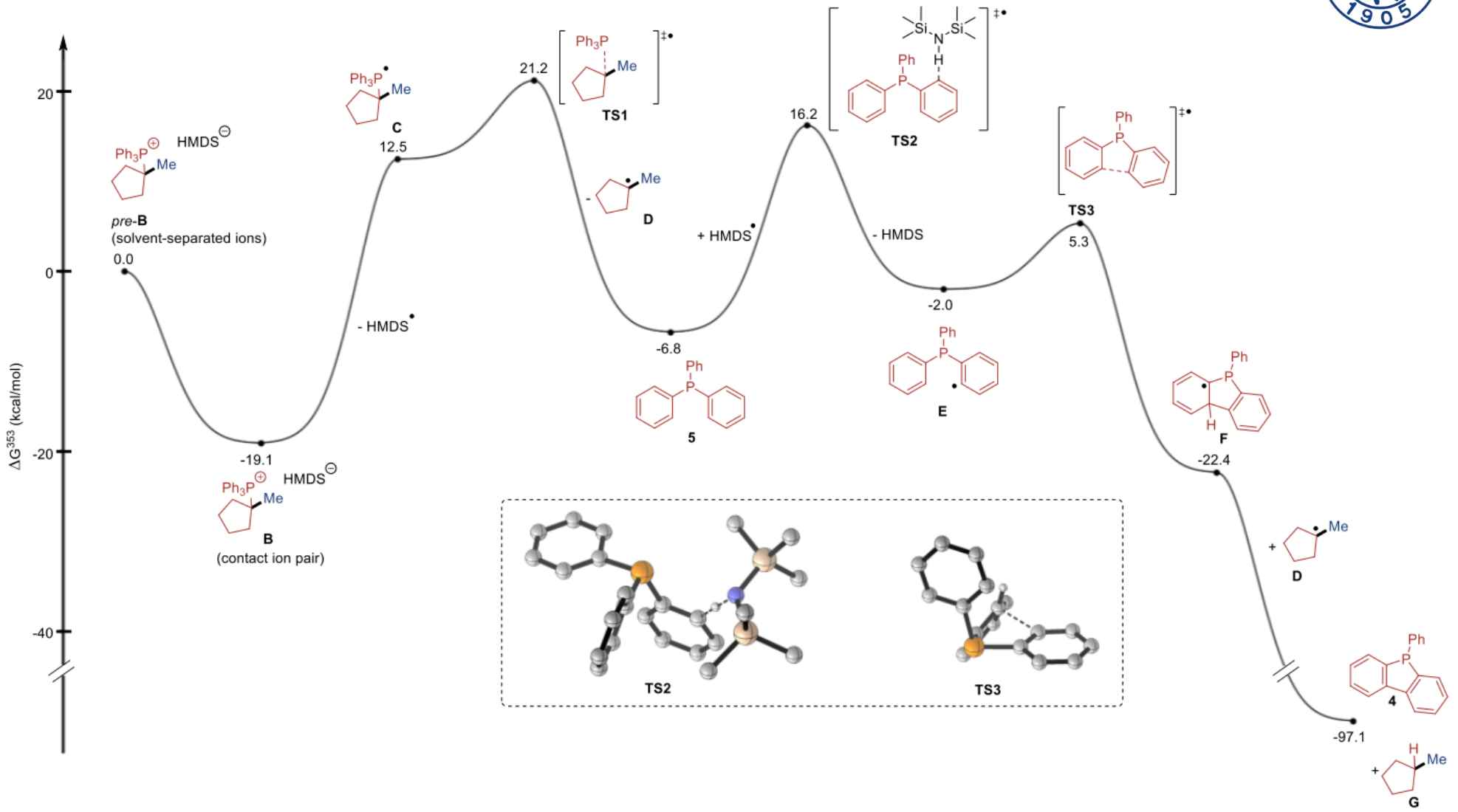

Figure S10. Calculated free energy diagram at the PW6B95-D3(BJ)/SMD(dioxane)-def2qzvpp//PBE0-D3(BJ)/SMD(dioxane)-def2tzvp level of theory. The optimized geometries of the transition states **TS2** and **TS3** are shown. Most hydrogen atoms have been omitted for clarity.

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