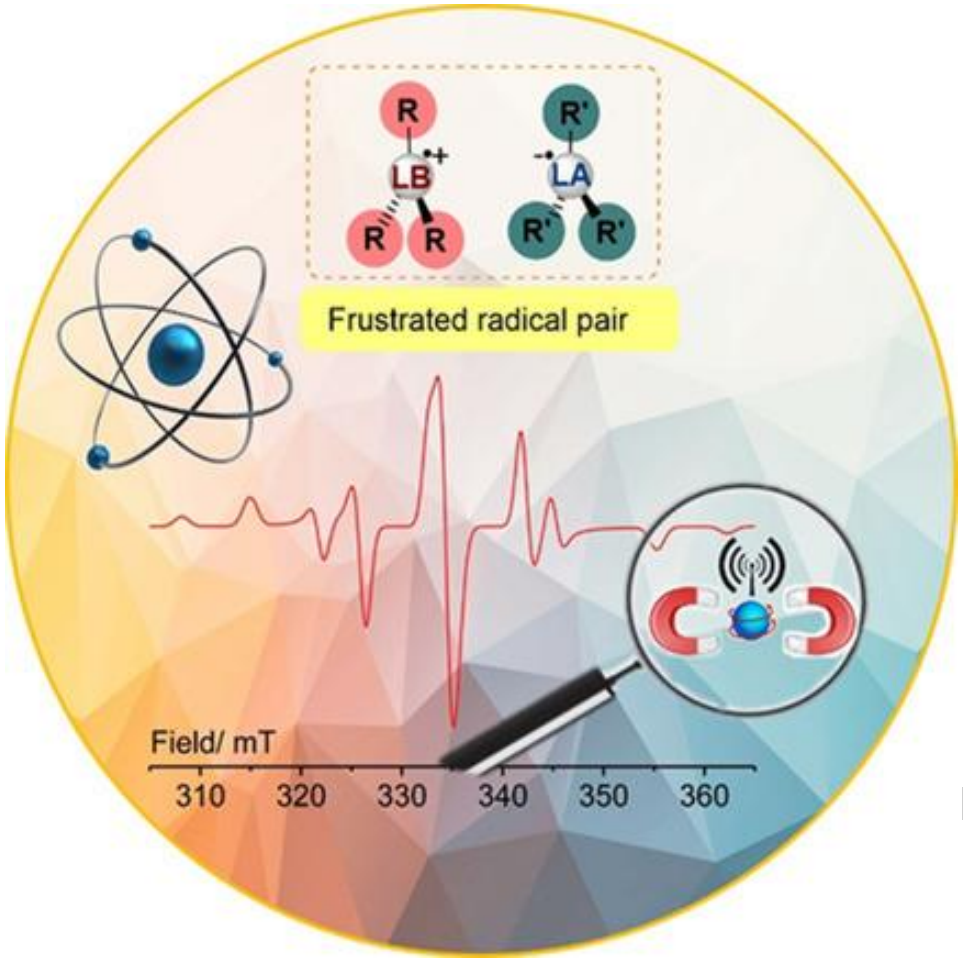
Article

Coupling of unactivated alkyl electrophiles using frustrated ion pairs



Nature 636, 108–114 (2024)

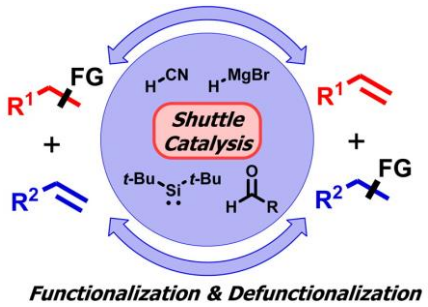
Wang Jing, 2025/01/18

ETH zürich

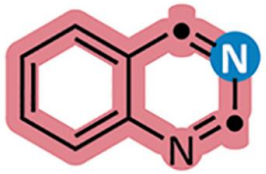
2003-2008	BSc in Biology and a MSc in Chemical Biology, ETH Zürich
2008-2012	PhD in organic synthesis, **Prof. Erick M. Carreira**., ETH Zürich
2012-2014	Postdoc., California Institute of Technology, **Prof. Robert H. Grubbs**
2014-2018	Group Leader , Max-Planck-Institut für Kohlenforschung
2018-now	Full Professor of Synthetic Organic Chemistry, ETH Zürich

Prof. Dr. Bill Morandi

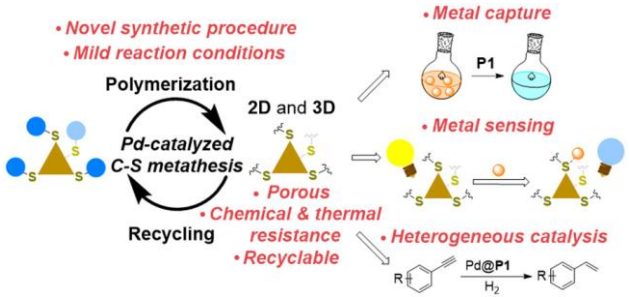
Shuttle catalysis/Metathesis reactions/Amination/Alkene/alkyne functionalization/C-O activation



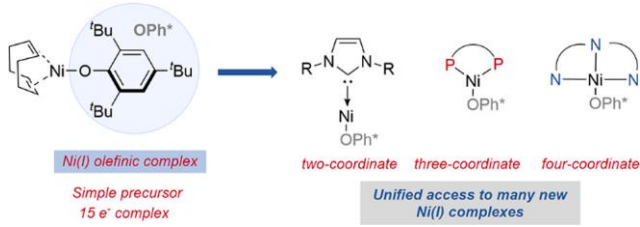
Molecular editing



Materials

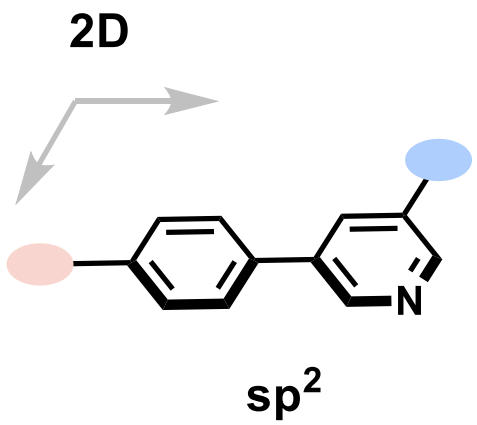


Organometallic and Mechanistic Studies



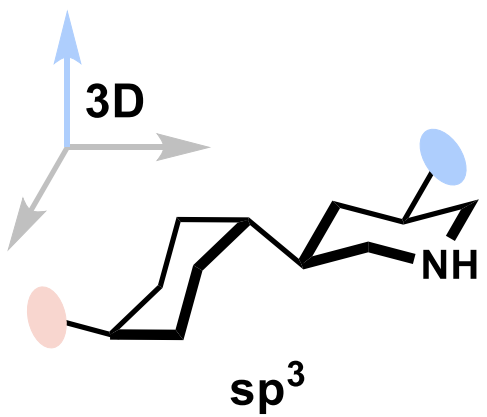
Background

The construction of C(sp³)-C(sp³) bond



Escaping flatland

- Improved solubility
- Reduced off-target



Traditional organometallic reagent cross-couplings

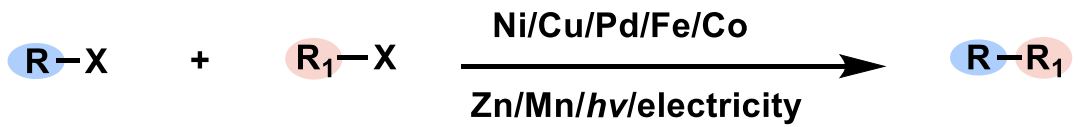
electrophile nucleophile

X = halogen or pseudohalogen;

[M] = Li, MgX, ZnX, $B(OR)_2$, SnR_3, SiR_3, $ZrCp_2Cl$, AlR_2.....

Represent chemist: G.C. Fu

Cross-electrophile coupling reactions (XECs)



electrophile electrophile

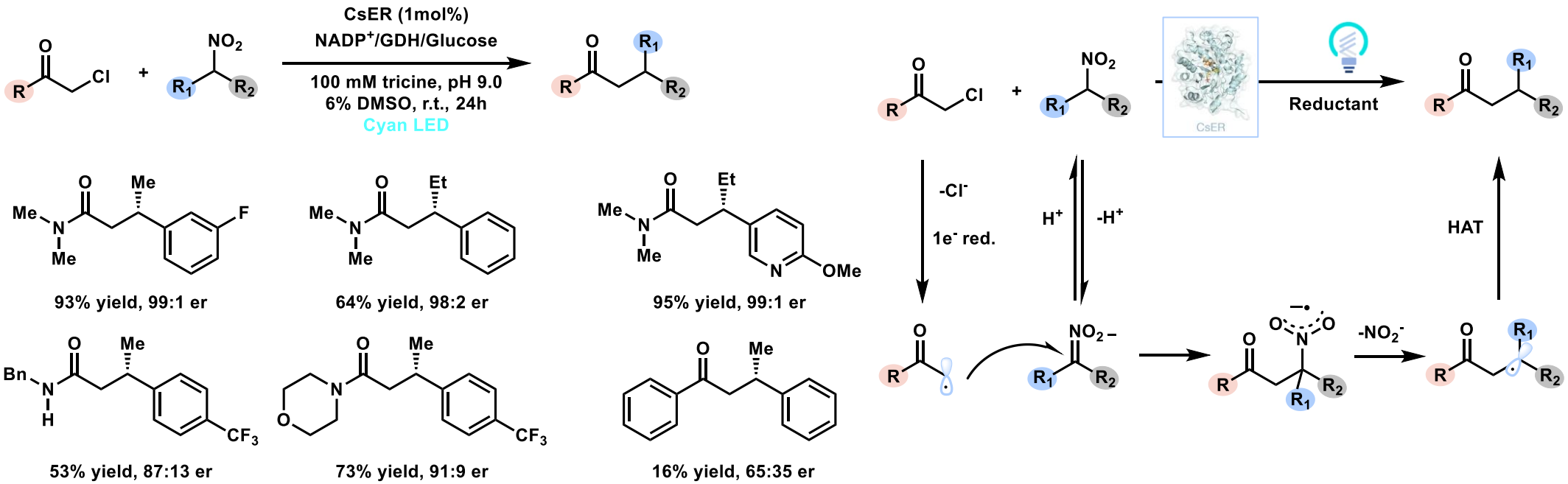
X = halogen or pseudohalogen;

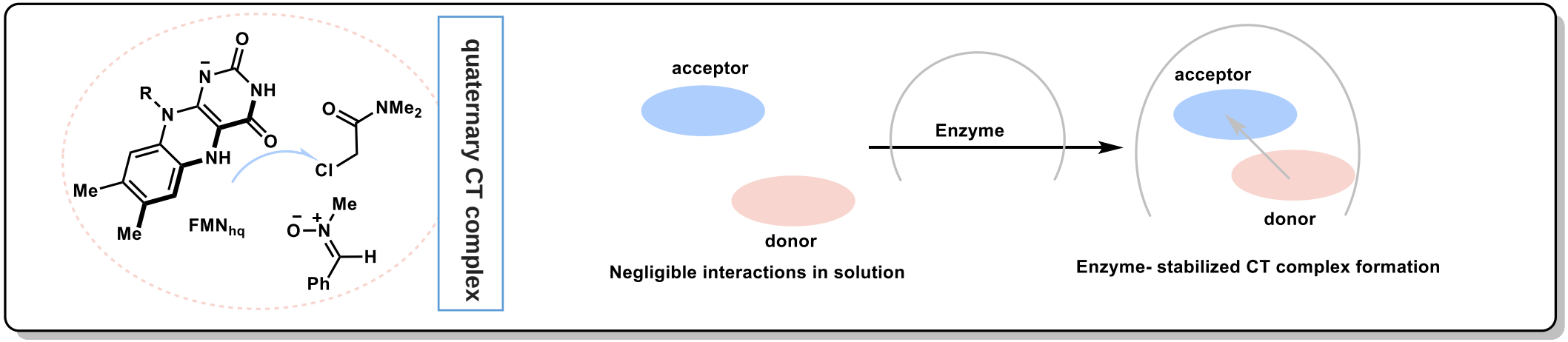
Represent chemists: Gong, Weix, D. MacMillan, P.S. Baran

Ref: J. Am. Chem. Soc. **2023**, 145, 14, 7736–7742; *J. Med.Chem.* **2009**, 52, 21, 6752-6756; *Organometallics* **2022**, 41, 6, 667–679.

The construction of C(sp³)-C(sp³) bond

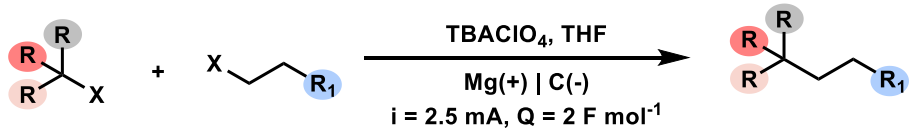
- Enzyme catalysis, *Todd K. Hyster*, *Nature* **610**, 302–307 (2022)

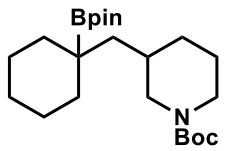




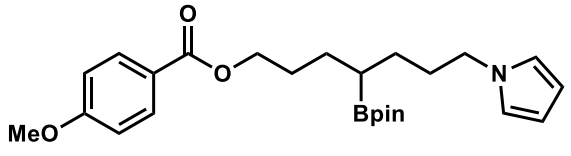
The construction of C(sp³)-C(sp³) bond

- Electrochemistry, *Song Lin*, *Nature* **604**, 292–297 (2022)

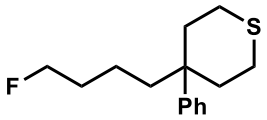




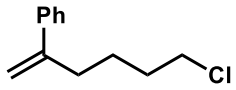
84% yield



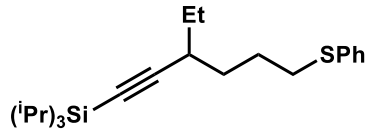
76% yield



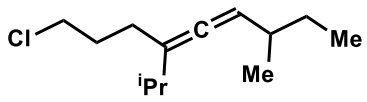
85% yield



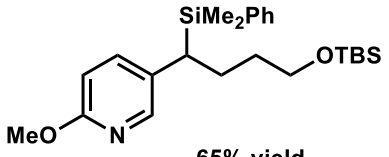
53% yield



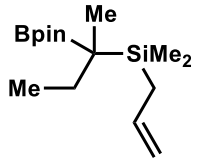
53% yield



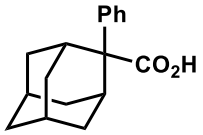
23% yield



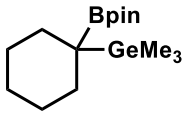
65% yield



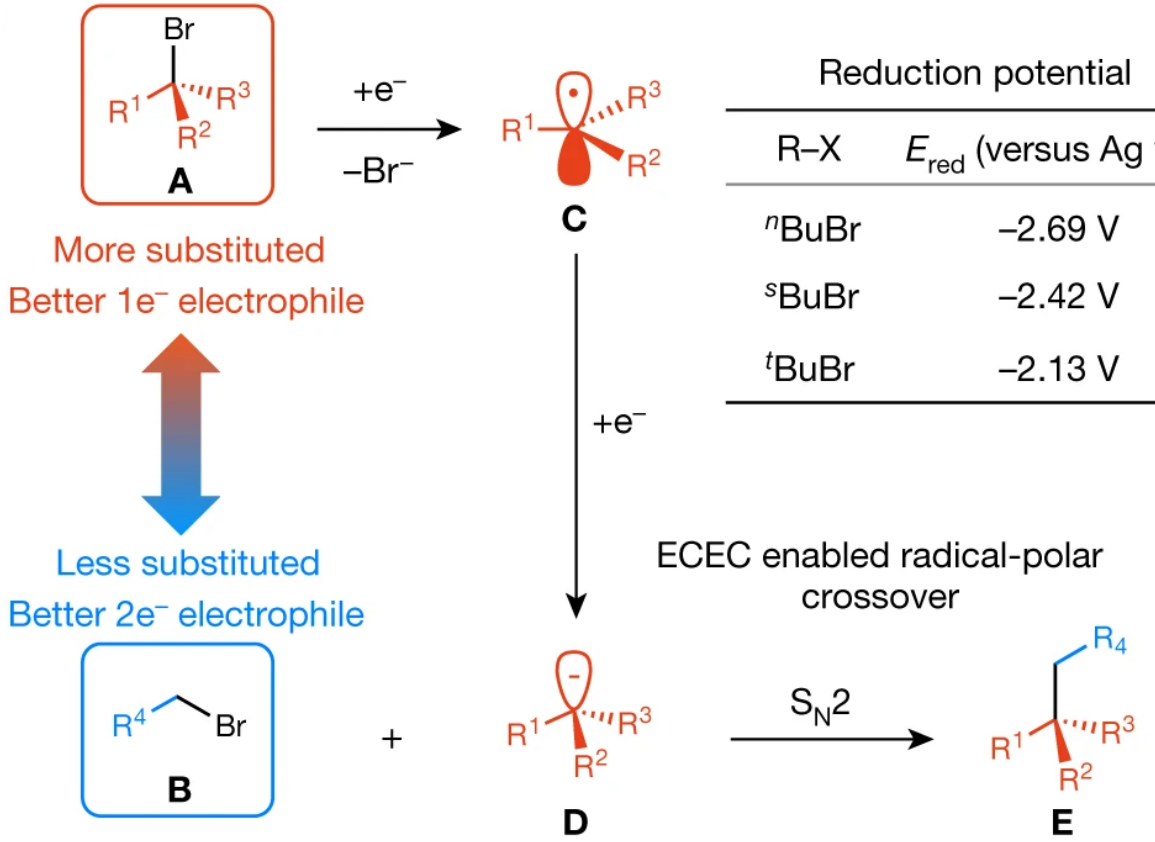
46% yield



83% yield



85% yield



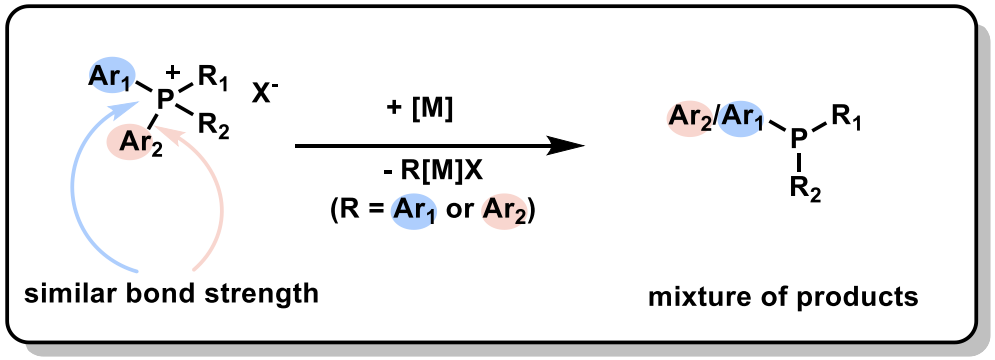
Reduction potential

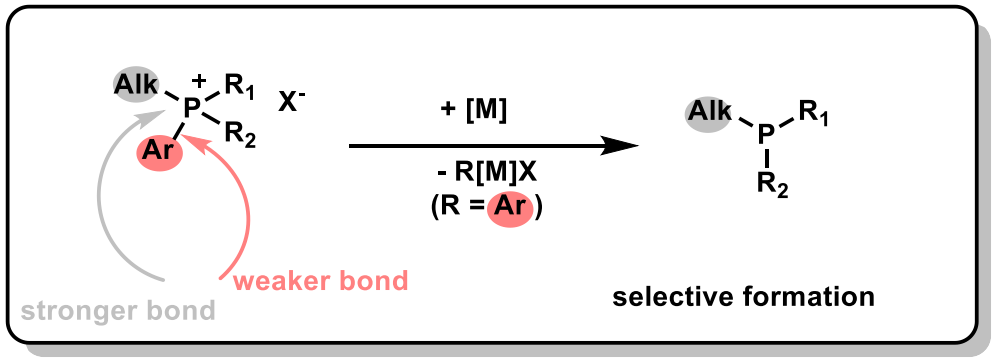
R–X	E_{red} (versus Ag wire)
^{n}BuBr	–2.69 V
^{s}BuBr	–2.42 V
^{t}BuBr	–2.13 V

This work

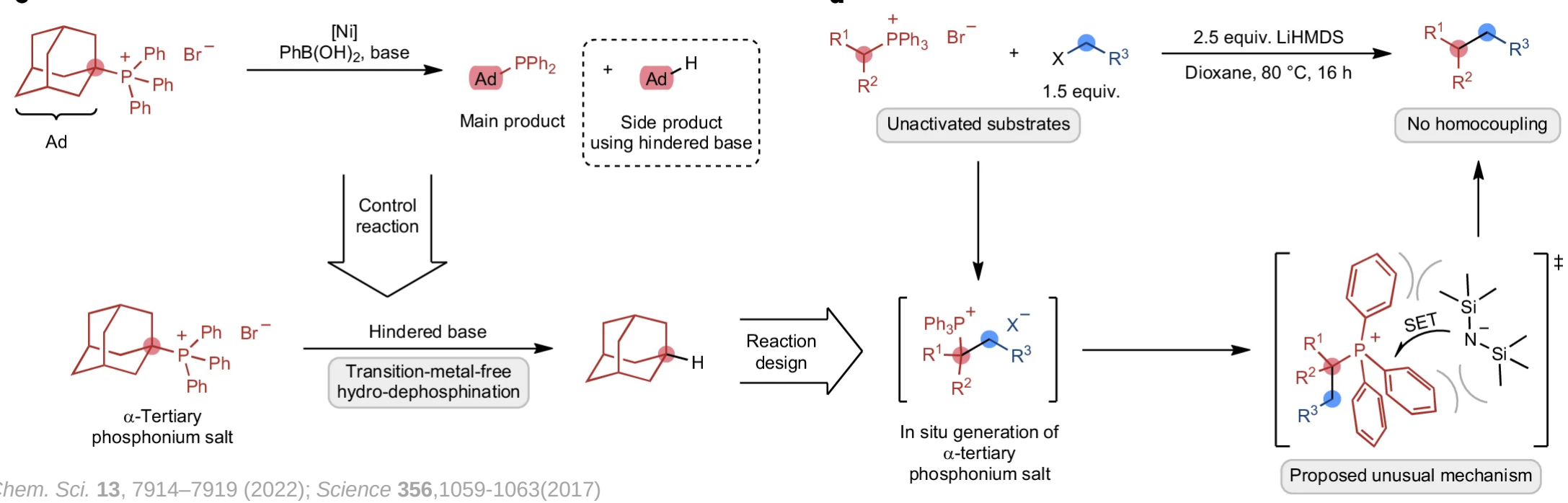
The construction of C(sp³)-C(sp³) bond

C–P metathesis reactions





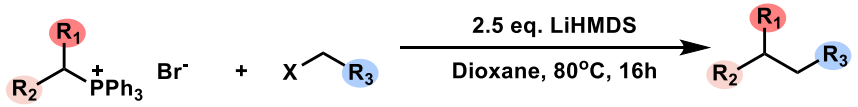
This work: transition-metal-free C(*sp*³)–C(*sp*³) coupling of unactivated substrates enabled by a frustrated ion pair

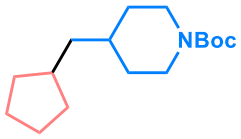


Ref: Chem. Sci. **13**, 7914–7919 (2022); *Science* **356**,1059-1063(2017)

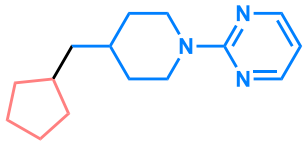
Scope of the reaction

Scope of the coupling reaction

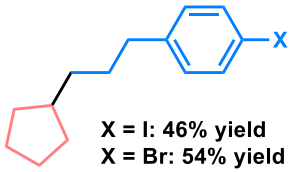




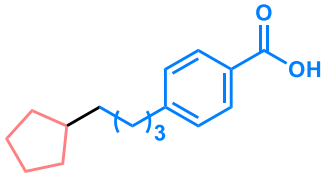
64% yield



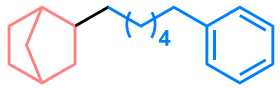
76% yield



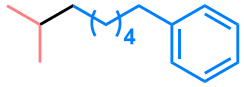
X = I: 46% yield
X = Br: 54% yield
X = Bpin: 84% yield



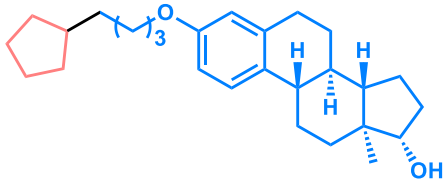
37% yield



68% yield, dr = 9:1

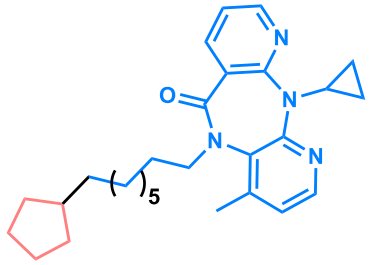


64% yield



Oestradiol derivative

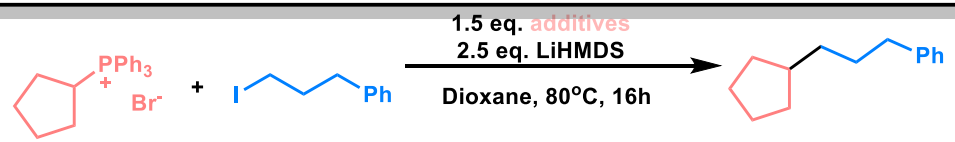
61% yield



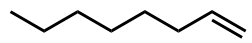
Nerirapine derivative

16% yield

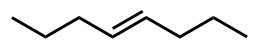
Additive compatibility screen



no additive : 97% yield



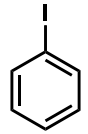
96% yield



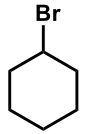
88% yield

91% yield

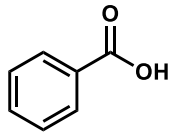
97% yield



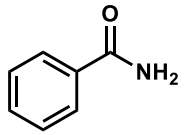
86% yield



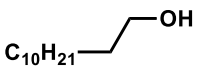
81% yield



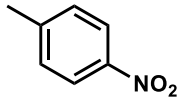
79% yield



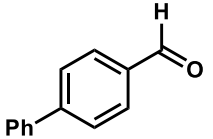
99% yield



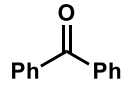
98% yield



trace



trace



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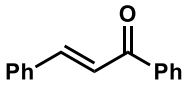
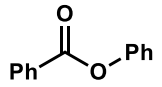


12% yield



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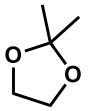
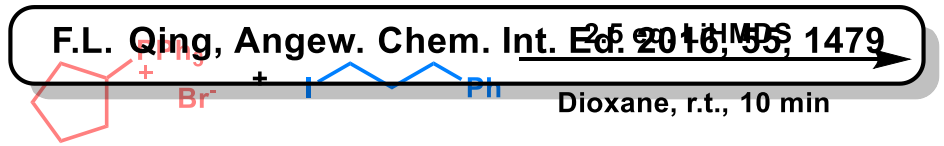


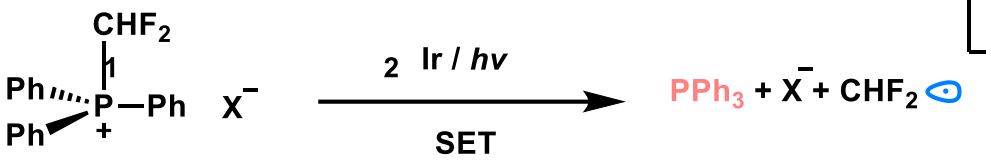
0% yield

What are the products from cleavage of the C–P bond?

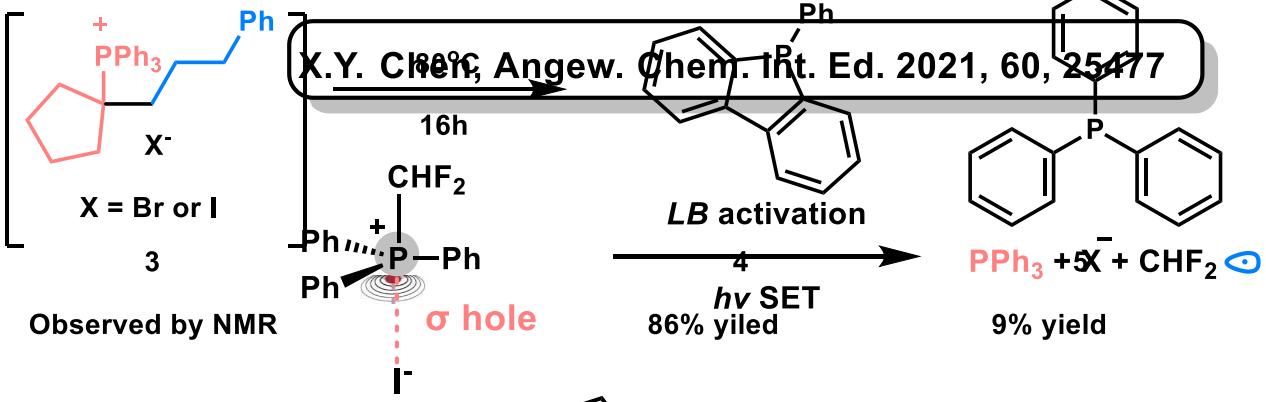
Reaction monitoring by NMR spectroscopy

F.L. Qing, Angew. Chem. Int. Ed. 2016, 55, 1479

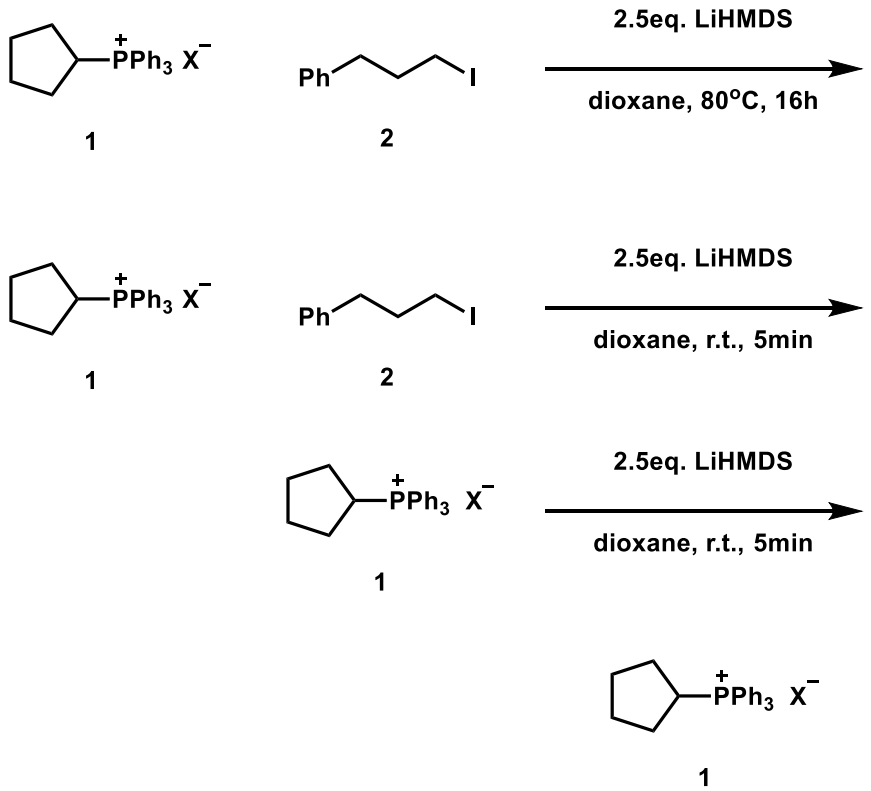


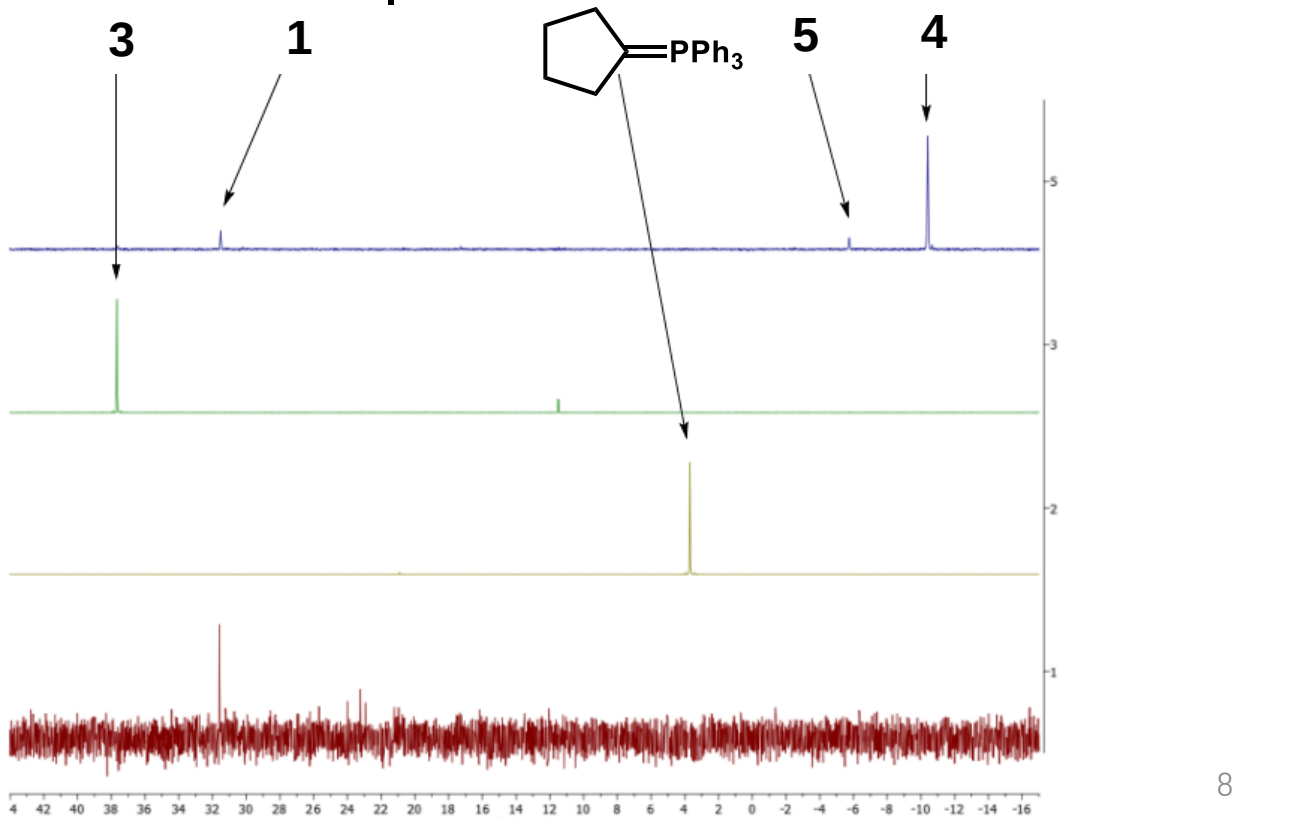


X.Y. Chen, Angew. Chem. Int. Ed. 2021, 60, 25477



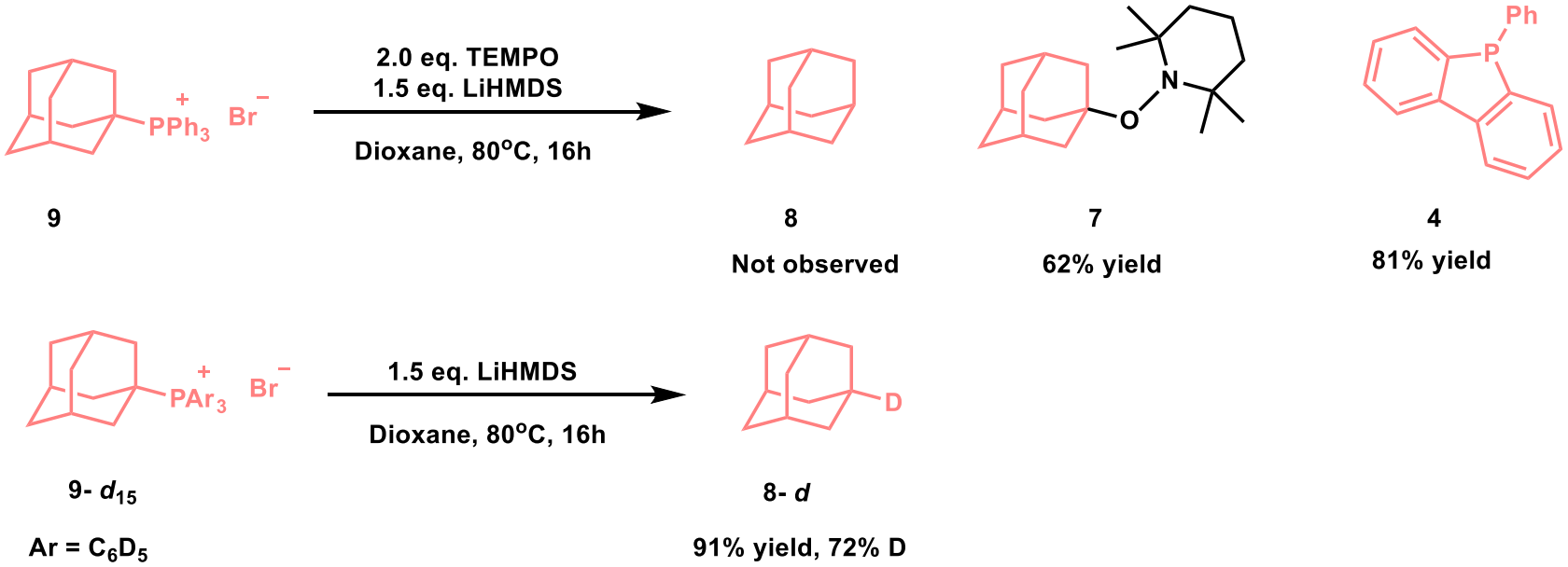
Observed by NMR

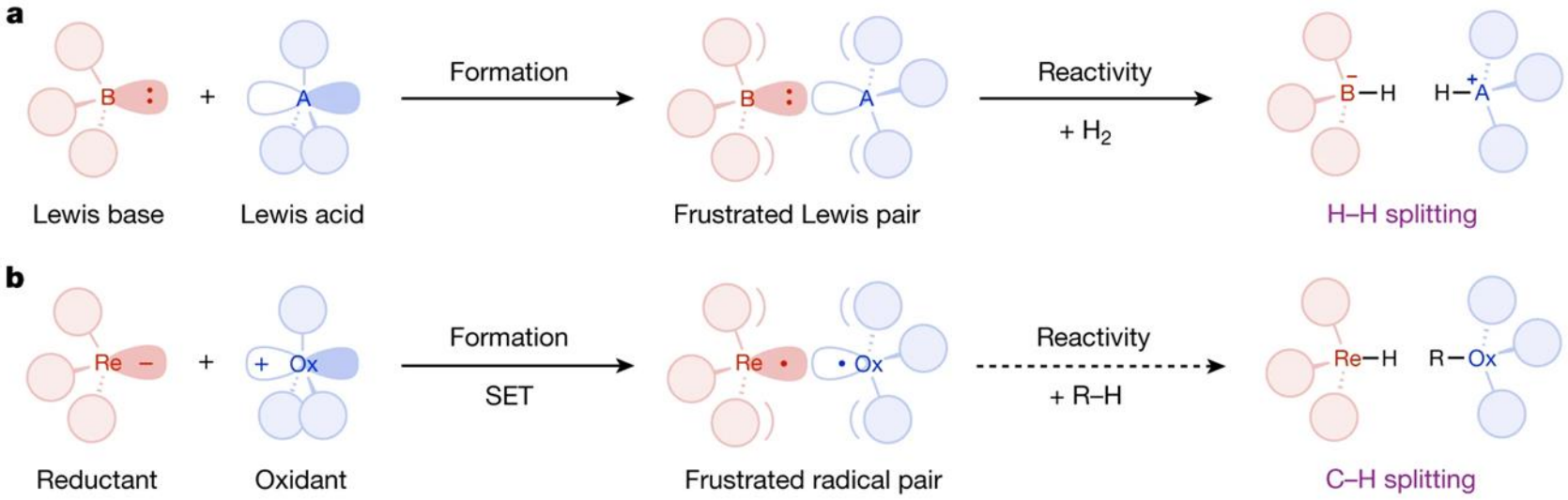




How does the HAT process occur?

Reaction inhibition by TEMPO and deuteration experiment

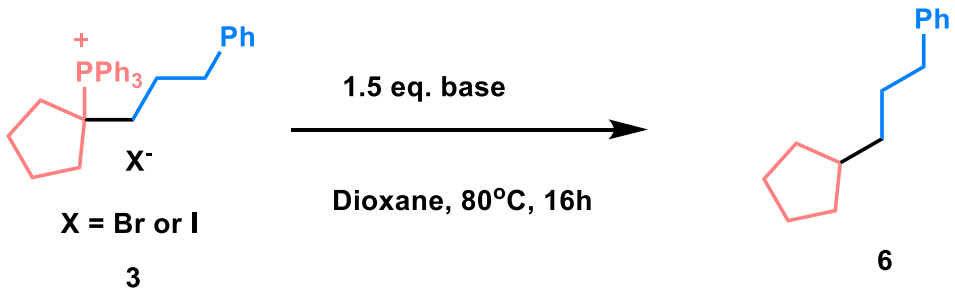




Ref: Nature 619, 514–520 (2023).

What is the role of base?

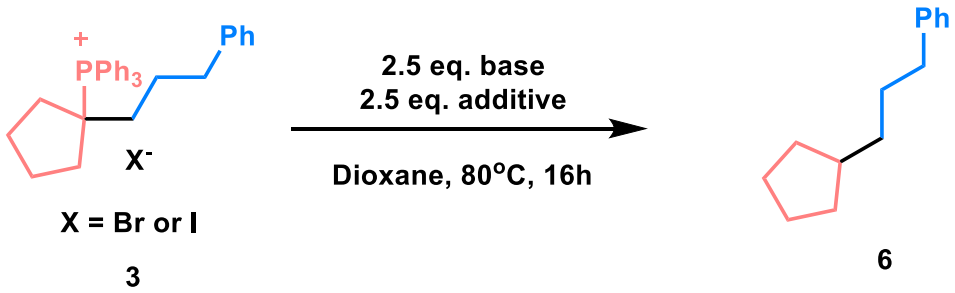
Effect of the base size



	LiHMDS	LiN(*i*-Pr)$_2$	LiN(Me)$_2$	LiNH$_2$
yield	72%	37%	25%	13%
% V_{bur}	68.1	58.8	35.1	13.8

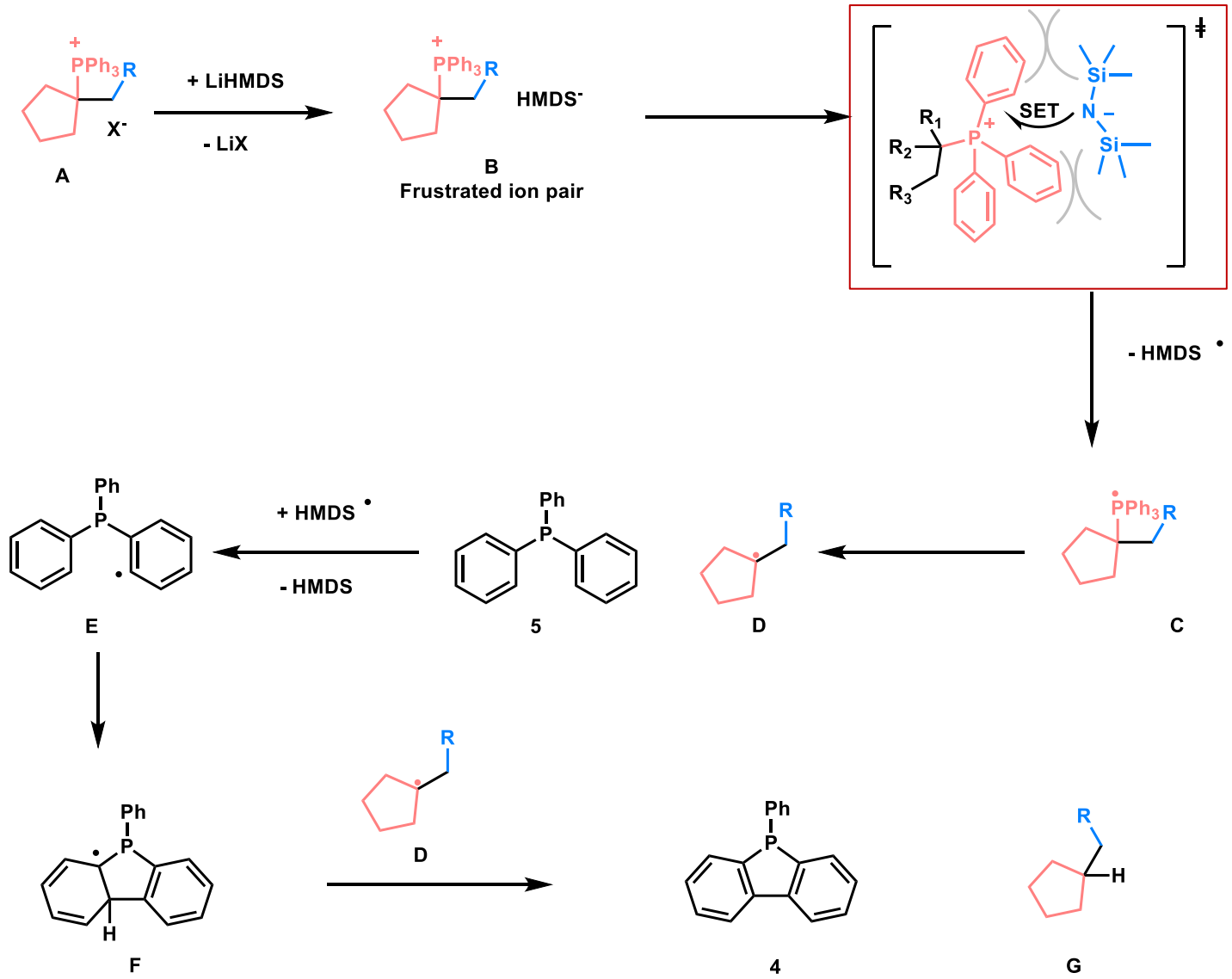
%V_{bur}, percent buried volume

Effect of the additives on the reaction yield



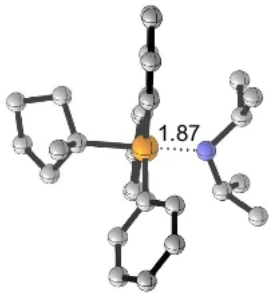
Entry	base	additive	yield (%)
1	LiHMDS	-	96
2	KHMDS	-	18
3	NaHMDS	-	43
4	LiHMDS	KCl	quant.
5	LiHMDS	12-crown-4	0
6	LiHMDS	12-crown-4 (1.0eq)	13
7	LiHMDS	18-crown-6	75

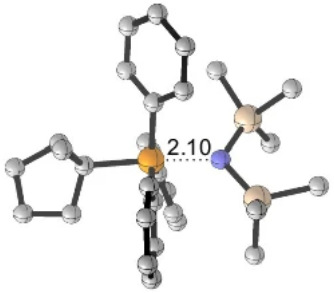
Proposed mechanism of the C–P cleavage

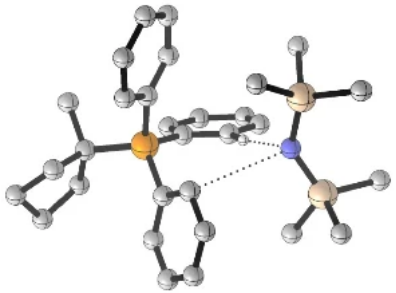


What's the structure of the frustrated ion pair?

Steric frustration leads to atypical ion pair geometry:



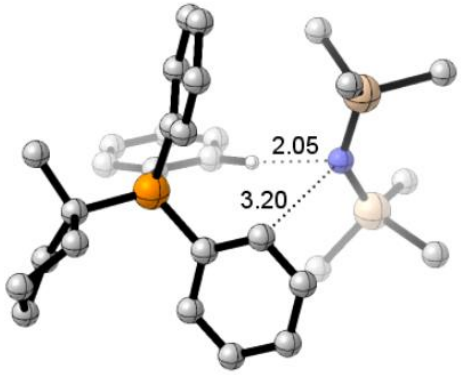




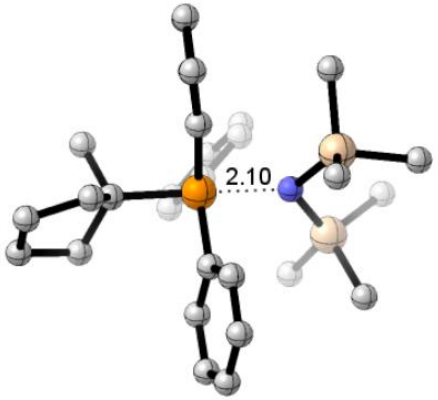
	H	**B′**	**B**
Anion:	$N(i\text{-}Pr)_2$	HMDS	HMDS
Interaction:	P–N (d(P–N) = 1.87 Å)	P–N (d(P–N) = 2.10 Å)	Aryl–anion (d(P–N) = 4.47 Å)
Relative ΔG:	–	21.7	0
Distortion energy:	59.2	55.1	1.8
Interaction energy:	–107.3	–75.7	–38.4
	–48.1	–20.6	–36.6

Steric frustration

Steric relief

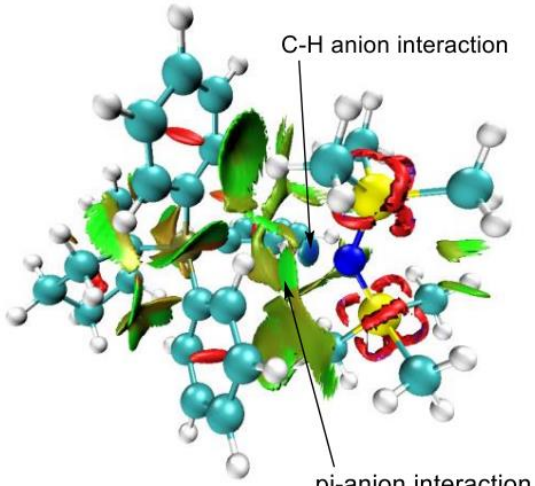


B
0.0 kcal/mol

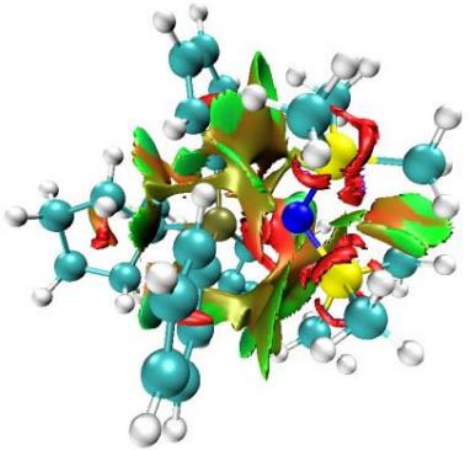


B'
21.7 kcal/mol

B NCI plot of B



C NCI plot of B'



What's the structure of the frustrated ion pair?

The excitation of charge-transfer complex:
Calculated B: 348nm
Calculated B': 272nm
Measured: 380nm and 515nm

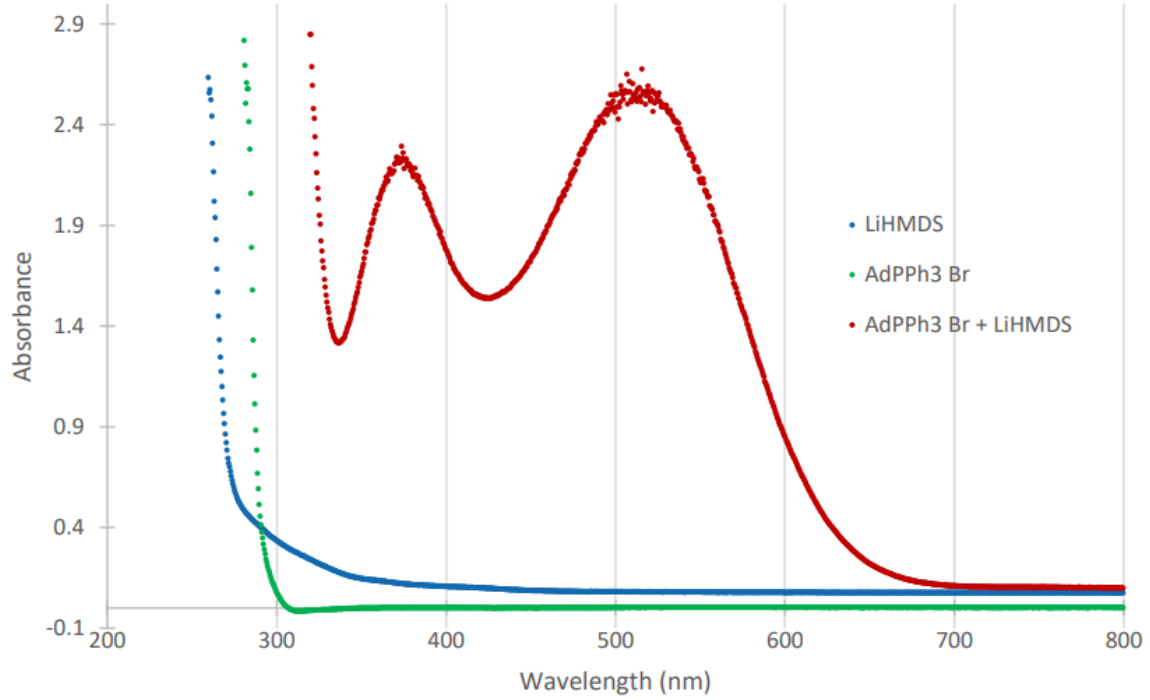
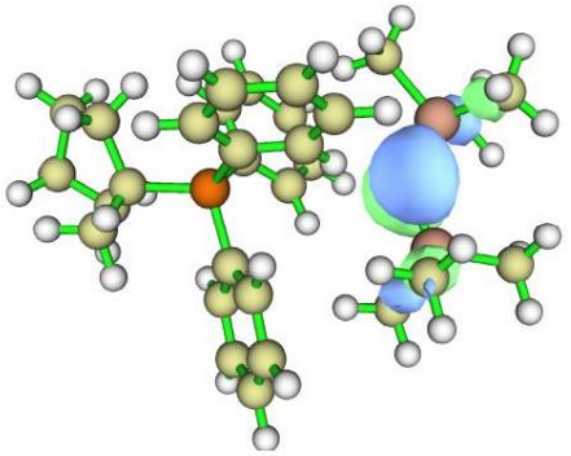


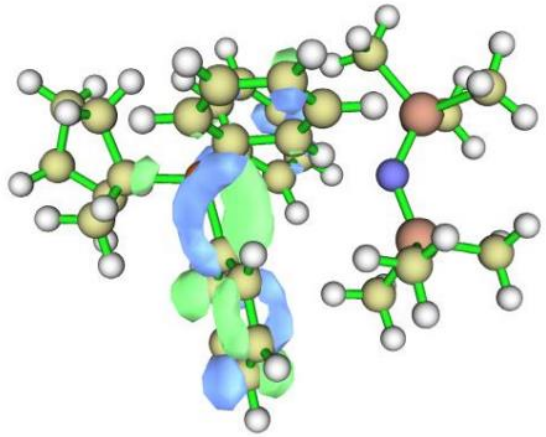
Figure S9. UV/Vis spectra of **9** (AdPPh3 Br), LiHMDS, and the mixture of the two compounds.

The UV/Vis spectrum shows the appearance of two charge-transfer bands when the colorless starting materials **9** and LiHMDS are mixed.

A Frontier orbitals of B.



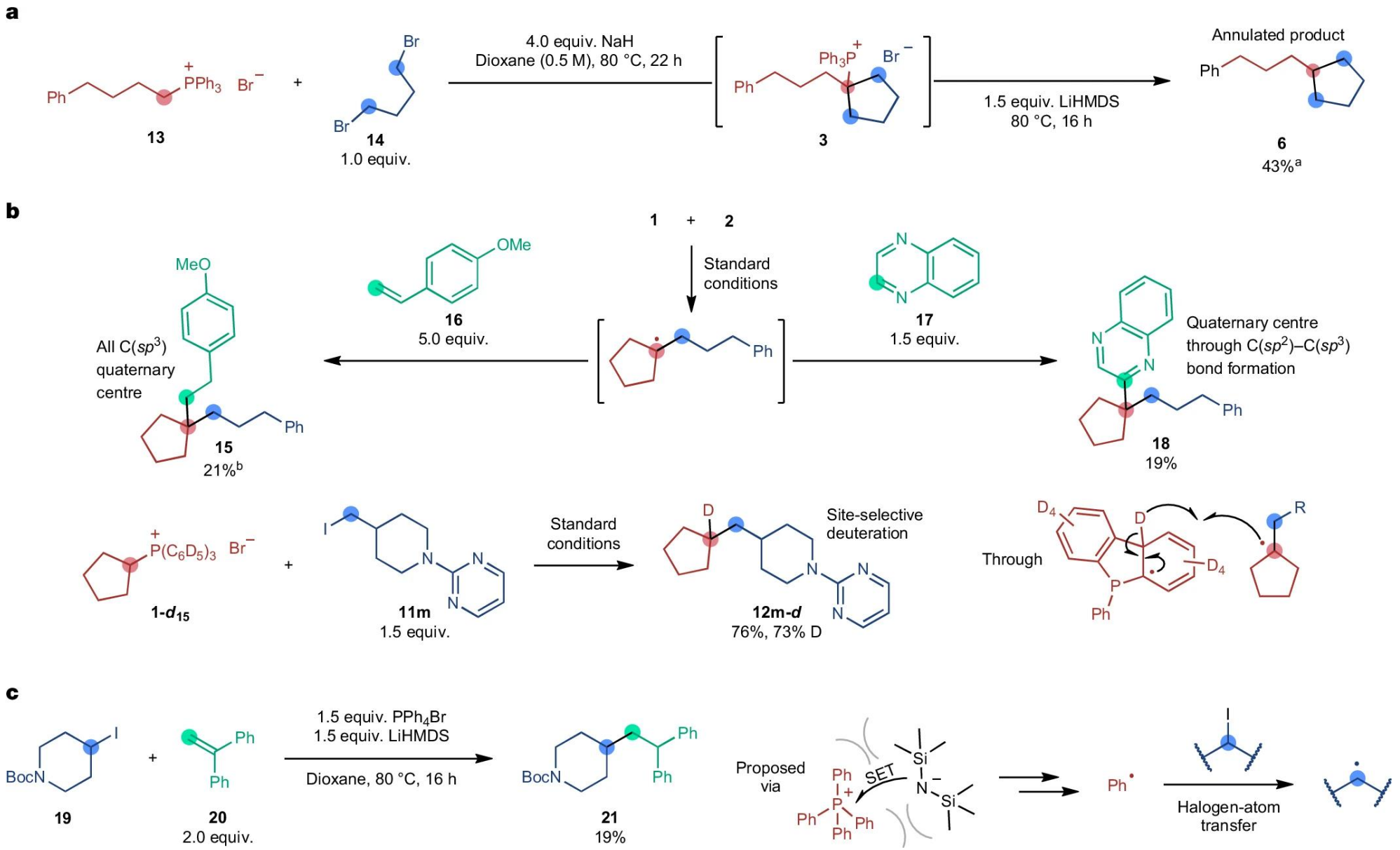
HOMO



LUMO

Electron transfer would proceed from anion to cation

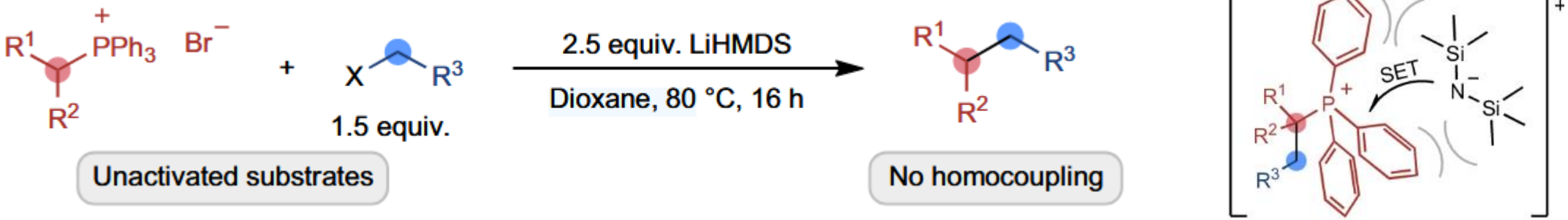
Mechanistically informed extensions of the reaction scope



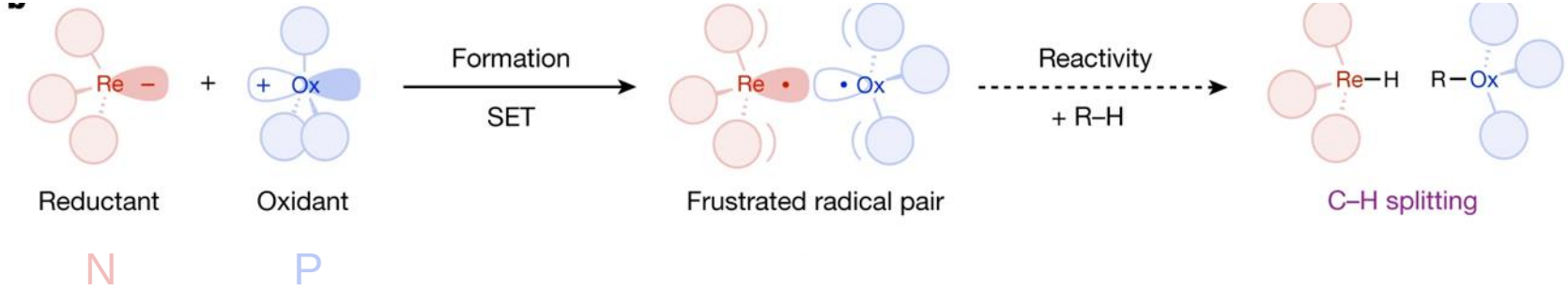
Summary

Frustrated radical pair in C(sp³)-C(sp³) bond formation

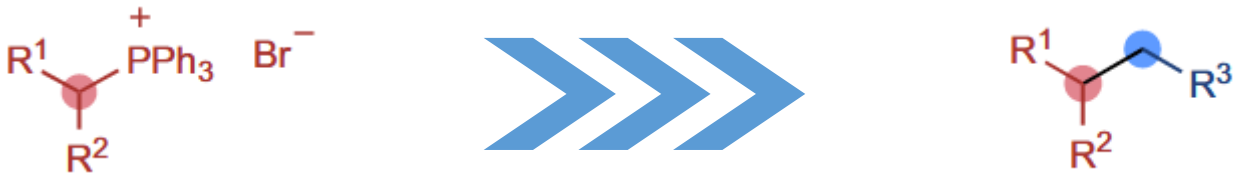
- **A distinct, transition-metal-free platform to form C(sp³)–C(sp³) bonds without the need for activating or stabilizing groups on the coupling partners.**



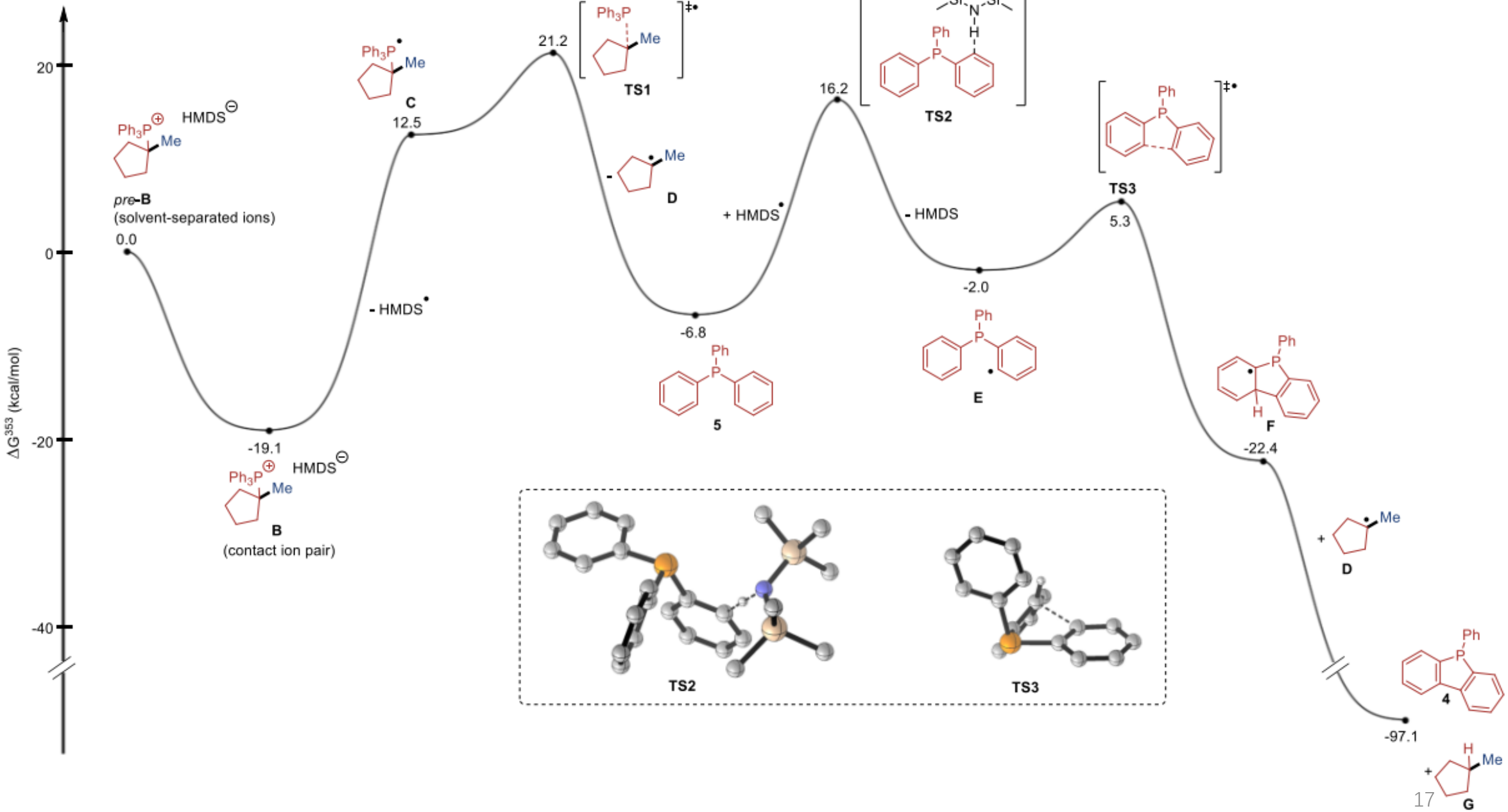
- **Expanding the spectrum of available FRP types**

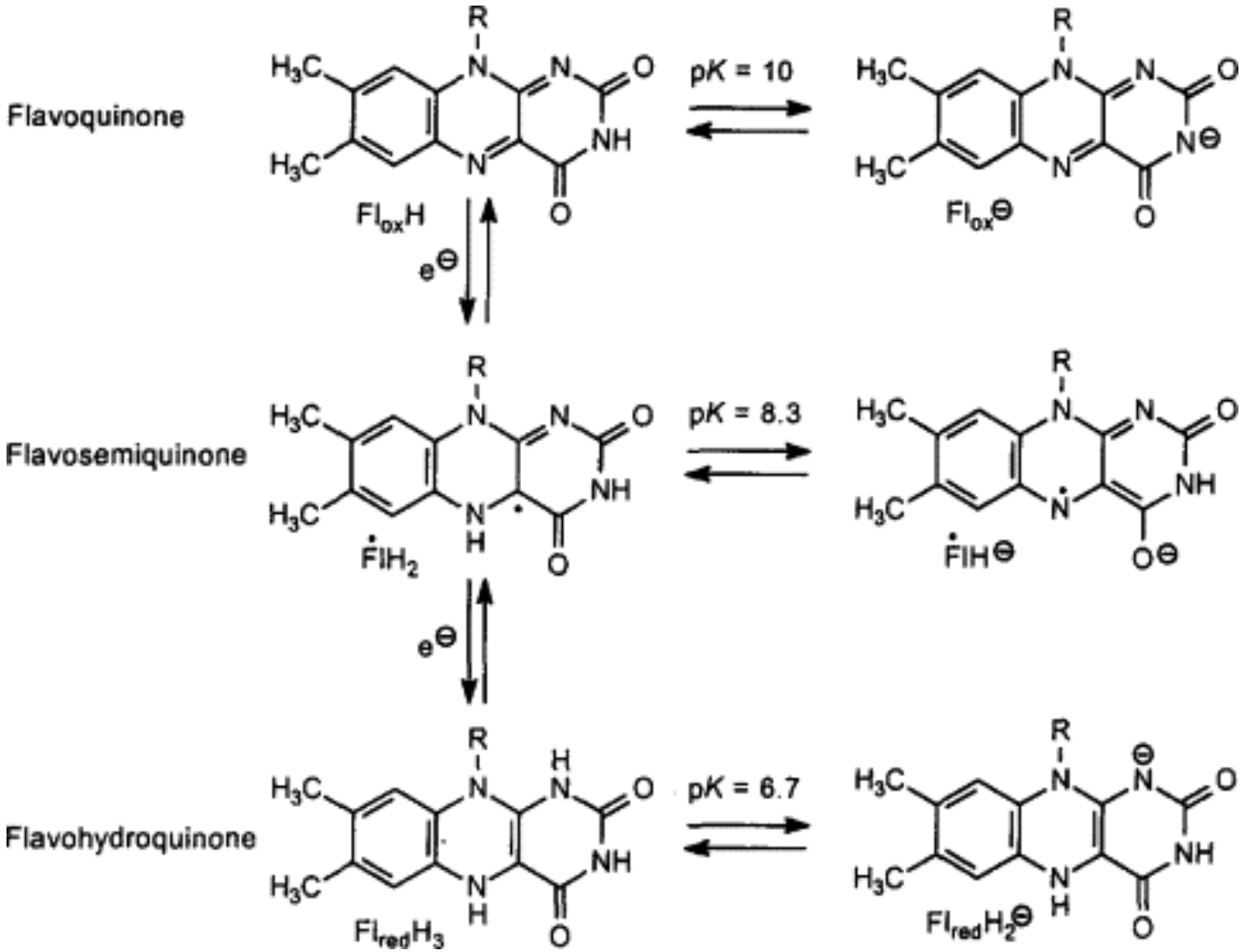


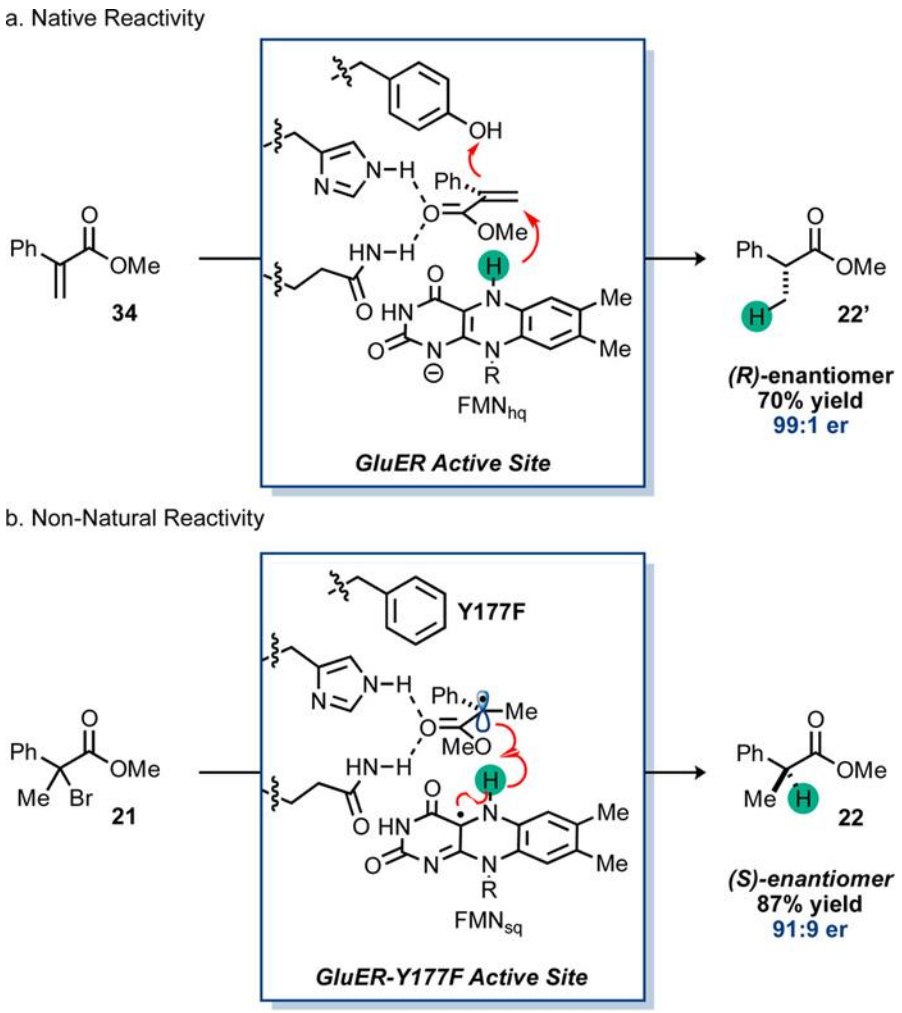
- **From "byproduct" to "Product"**



Thanks for your attention!


ΔG353 (kcal/mol)
20
0
-20
-40
pre-B
(solvent-separated ions)
0.0
HMDS
-19.1
B
(contact ion pair)
12.5
C
- HMDS
21.2
TS1
-6.8
D
5
+ HMDS
16.2
TS2
-2.0
- HMDS
E
TS3
5.3
F
-22.4
D
4
-97.1
G
TS2
TS3


Flavoquinone
Flavosemiquinone
Flavohydroquinone
pK = 10
pK = 8.3
pK = 6.7
e⊖
e⊖


a. Native Reactivity
34
GluER Active Site
22'
(R)-enantiomer
70% yield
99:1 er
b. Non-Natural Reactivity
21
Y177F
GluER-Y177F Active Site
22
(S)-enantiomer
87% yield
91:9 er