Phosphorus-Fluoride Exchange (PFEx)

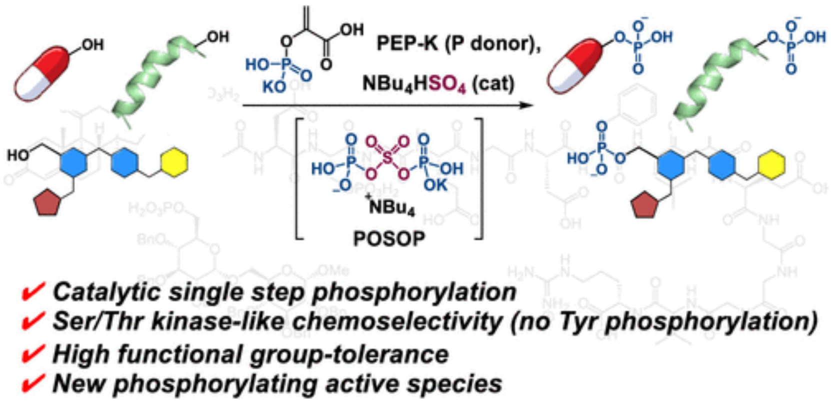
~Another good reaction for click chemistry~

2022/11/10(Thr) M2 Tomoyuki Fukuta

Table of contents

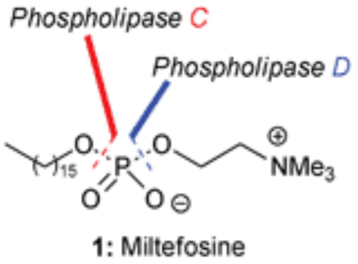
Introducing Phosphorus group provides divergent features.

Phosphate



Kanai, M *et. al. ACS Cent. Sci.* **2020**, *6*, 2, 283−292

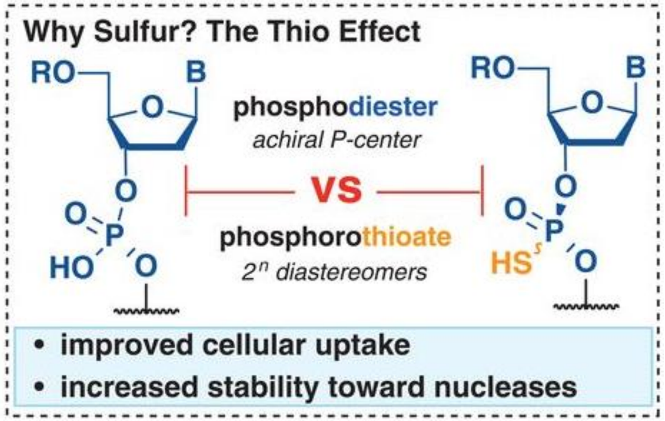
Phosphinate (P-C bond)



✓ Strong tolerance toward hydrolysis

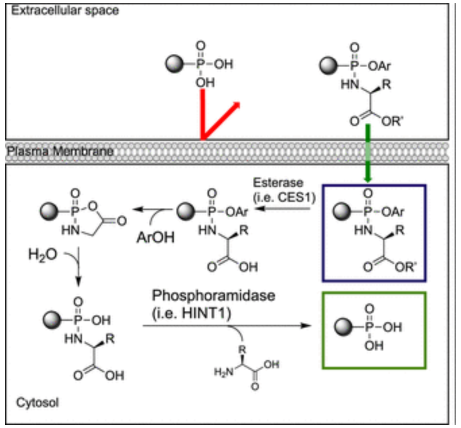
Org. Biomol. Chem., **2013**, *11*, 119-129

Thiophosphate (P-S bond)



Baran, P. et. Al .Nat. Chem. **2021**, *12*, 2760.

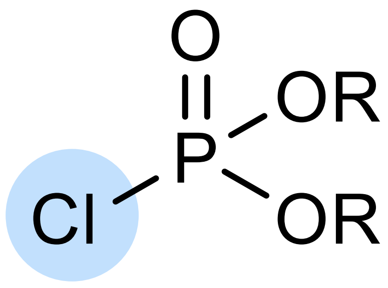
Phosphoamidate (P-N bond)

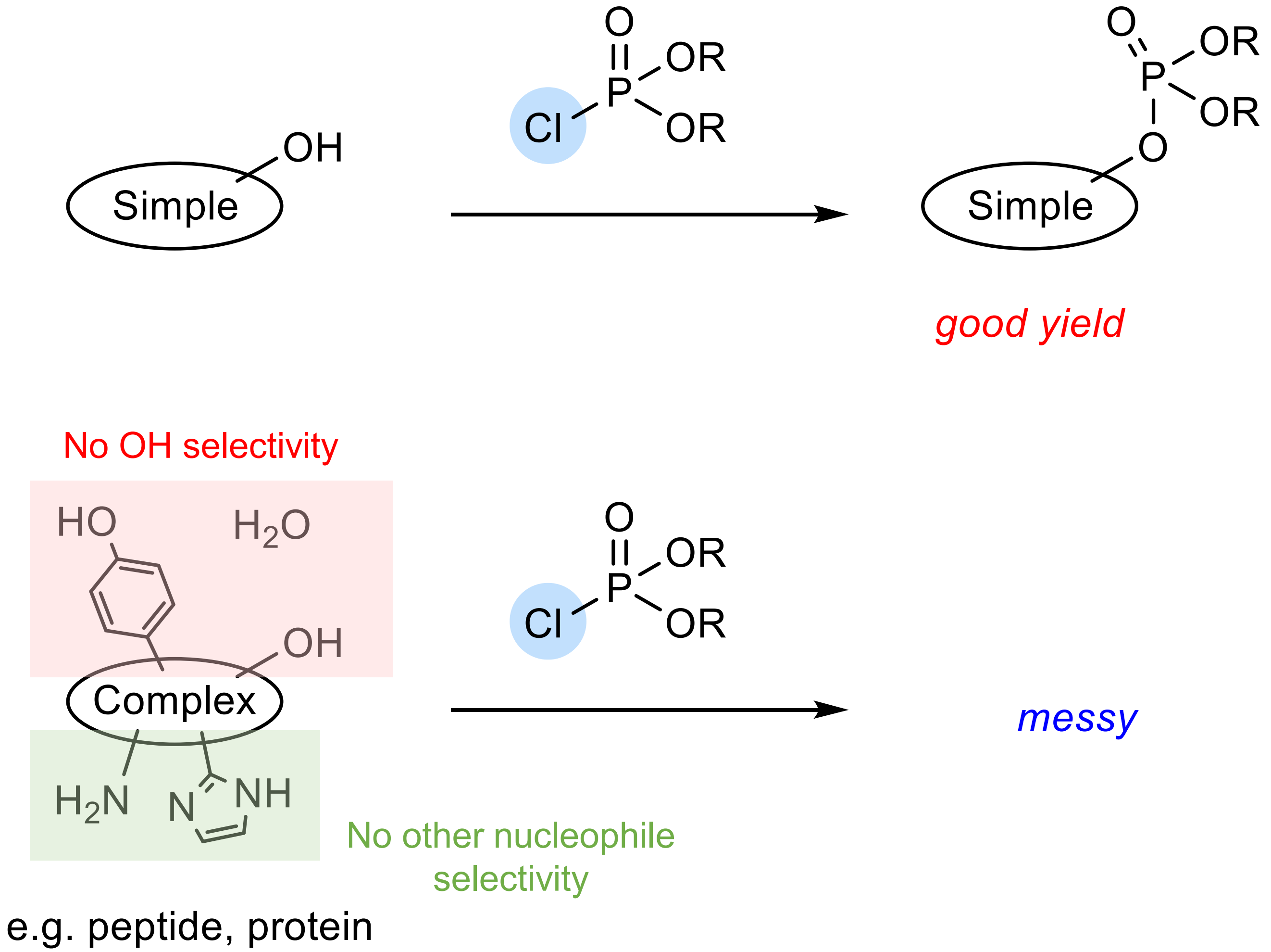


ACS Med. Chem. Lett. 2020, 11, 9, 1704−1710

P(V) reagents are desirable for complex substates

Traditional P(V) reagents

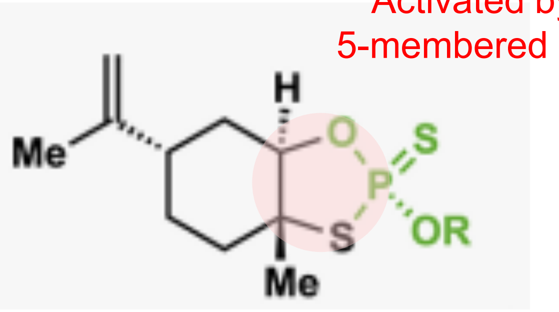




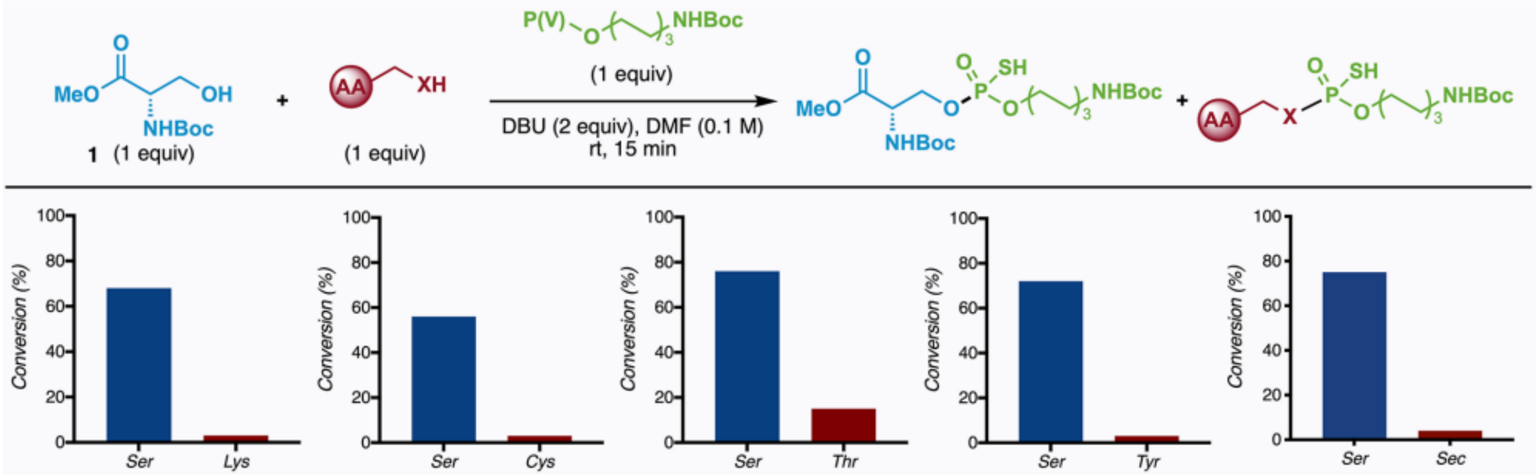
Recent advances of P(V) reagents for bioconjugation

PSI reagents

Activated by
5-membered ring

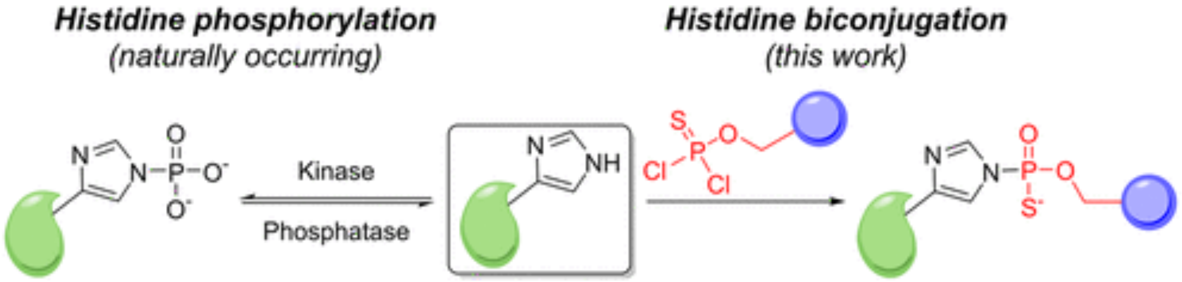


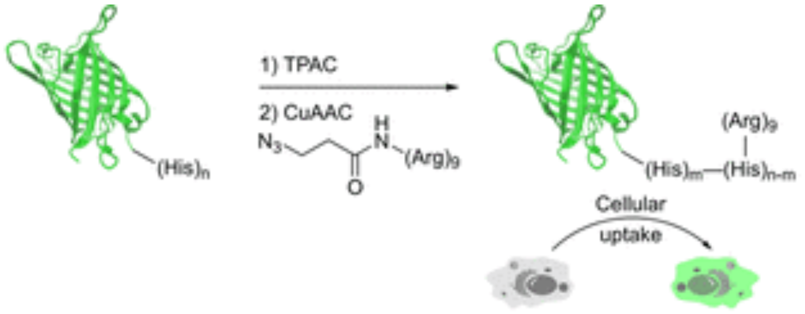
See Fujiyoshi-san's Lit 2021.7.29 in detail



Baran, P. *et. al. J. Am. Chem. Soc.* **2020**, *142*, 41, 17236−17242

Chlorothiophosphate



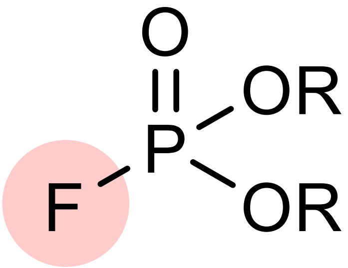


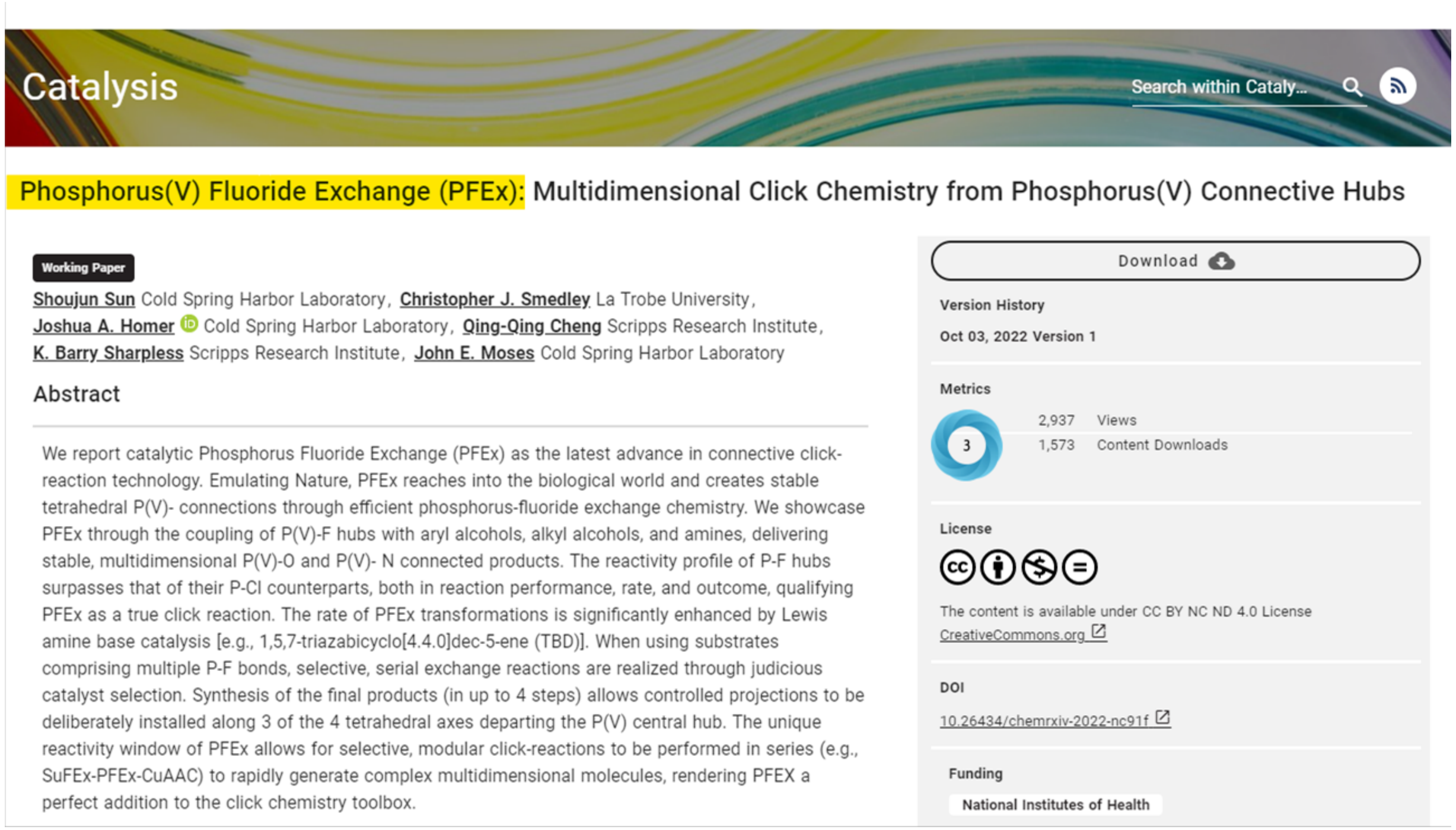
High His-selectivity in protein substrates

J. Am. Chem. Soc. **2019**, *141*, 18, 7294−7301

K.B. Sharpless suggests the utility of "PFEx".

K.B. Sharpless





Catalysis

Search within Cataly...

Phosphorus(V) Fluoride Exchange (PFEx): Multidimensional Click Chemistry from Phosphorus(V) Connective Hubs

Working Paper

Shoujun Sun Cold Spring Harbor Laboratory, Christopher J. Smedley La Trobe University, Joshua A. Homer Cold Spring Harbor Laboratory, Qing-Qing Cheng Scripps Research Institute, K. Barry Sharpless Scripps Research Institute, John E. Moses Cold Spring Harbor Laboratory

Abstract

We report catalytic Phosphorus Fluoride Exchange (PFEx) as the latest advance in connective click-reaction technology. Emulating Nature, PFEx reaches into the biological world and creates stable tetrahedral P(V)- connections through efficient phosphorus-fluoride exchange chemistry. We showcase PFEx through the coupling of P(V)-F hubs with aryl alcohols, alkyl alcohols, and amines, delivering stable, multidimensional P(V)-O and P(V)- N connected products. The reactivity profile of P-F hubs surpasses that of their P-Cl counterparts, both in reaction performance, rate, and outcome, qualifying PFEx as a true click reaction. The rate of PFEx transformations is significantly enhanced by Lewis amine base catalysis [e.g., 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)]. When using substrates comprising multiple P-F bonds, selective, serial exchange reactions are realized through judicious catalyst selection. Synthesis of the final products (in up to 4 steps) allows controlled projections to be deliberately installed along 3 of the 4 tetrahedral axes departing the P(V) central hub. The unique reactivity window of PFEx allows for selective, modular click-reactions to be performed in series (e.g., SuFEx-PFEx-CuAAC) to rapidly generate complex multidimensional molecules, rendering PFEX a perfect addition to the click chemistry toolbox.

Download

Version History

Oct 03, 2022 Version 1

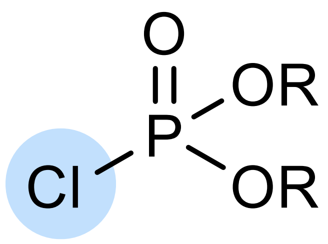
DOI

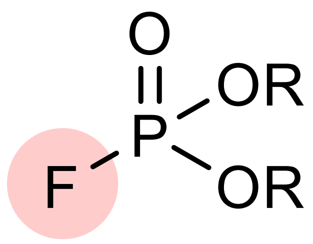
10.26434/chemrxiv-2022-nc91f

Funding

National Institutes of Health

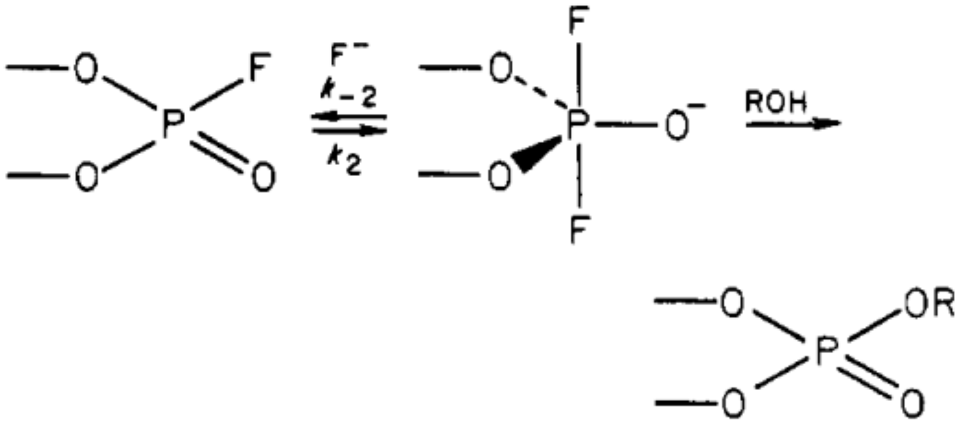
Comparison between P(V)-F and P(V)-Cl





less stable	stable
Good leaving group (Cl)	Poor leaving ability (F)
React w/o activation	Activation is required (F^- or imidazole)

Activation by CsF



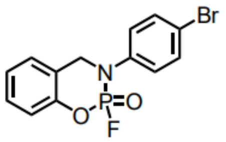
Application of P(V)-F was limited.

J. Chem. Soc. Chem. Commun., **1981**, 101-103

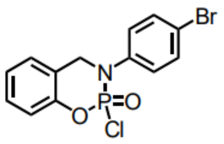
J. Am. Chem. Soc. **1984**, *106*, 4, 1060−1065

Feature of P(V)-F compounds

Comparison of Stability/Reactivity : F vs Cl



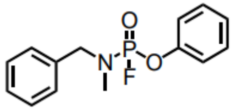
10a



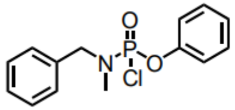
8a

Conditions	10a 1 h	10a 3 h	10a 24 h	8a 1 h	8a 3 h	8a 24 h
Buffer (pH = 7.4), r.t.	Stable	Stable	Stable	Stable	Stable	Stable
Buffer (pH = 8.8), r.t.	Stable	Stable	Stable	Stable	Stable	Stable
EtOH, r.t.	Stable	Stable	Stable	New compounds identified	New compounds identified	Degraded

Stable | New compounds identified | Degraded



12a



11a

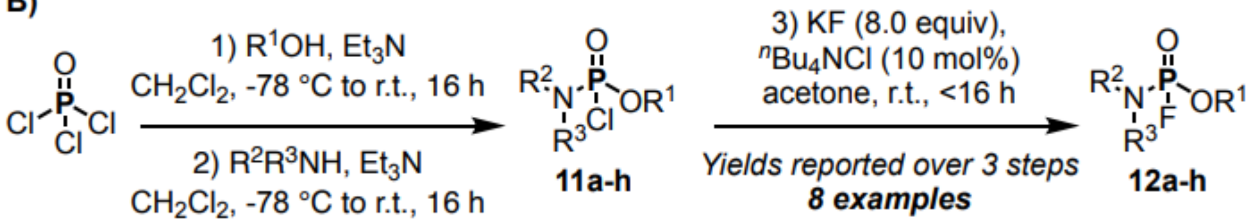
Conditions	12a 1 h	12a 3 h	12a 24 h	11a 1 h	11a 3 h	11a 24 h
Buffer (pH = 7.4), r.t.	Stable	Stable	Stable	Stable	Stable	Stable
Buffer (pH = 8.8), r.t.	Stable	Stable	Stable	Stable	Stable	New compounds identified
EtOH, r.t.	Stable	Stable	Stable	Stable	Stable	New compounds identified

Stable | New compounds identified | Degraded

P(V)-F bond is relatively stable, which means low reactivity.

Synthesis

B)



Synthesis of P(V)-F compound is well-investigated, but the application is limited.

Selectivity of P(V)-Cl and P(V)-F ; *O* or *N* ?

TABLE II

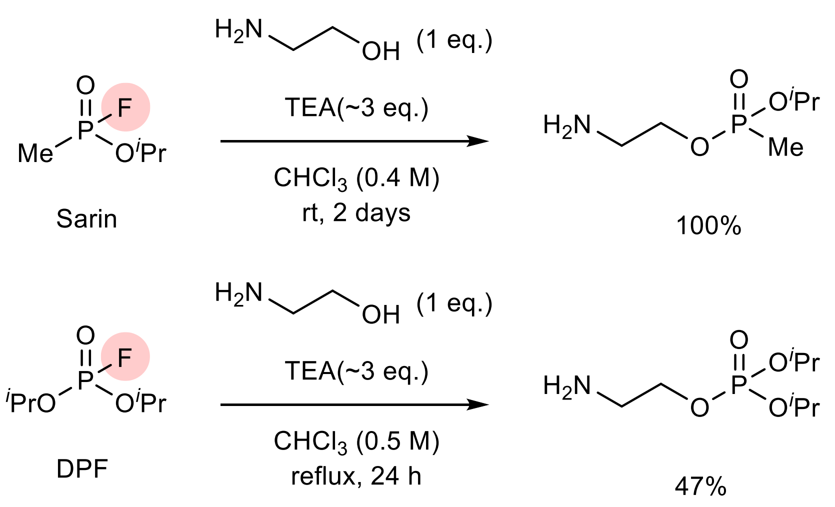
Product yields from the phosphylation of ethanolamine

Phosphylating agent	X	Y	Z	% reaction*	% yield of product: Nuclear magnetic resonance N—P	O—P	Isolation N—P	O—P
Sarin	*i*-PrO	CH_3	F	100	0	92	0	71
DFP	*i*-PrO	*i*-PrO	F	47	0	47	0	26
Chlorosarin	*i*-PrO	CH_3	Cl	100	84	8	70	4
DClP	*i*-PrO	*i*-PrO	Cl	100	92	4	65	0
Tabun	EtO	NMe_2	CN	95	72	23	70	15
TEPP	EtO	EtO	$OP(O)(OEt)_2$	88	66	†	65	0

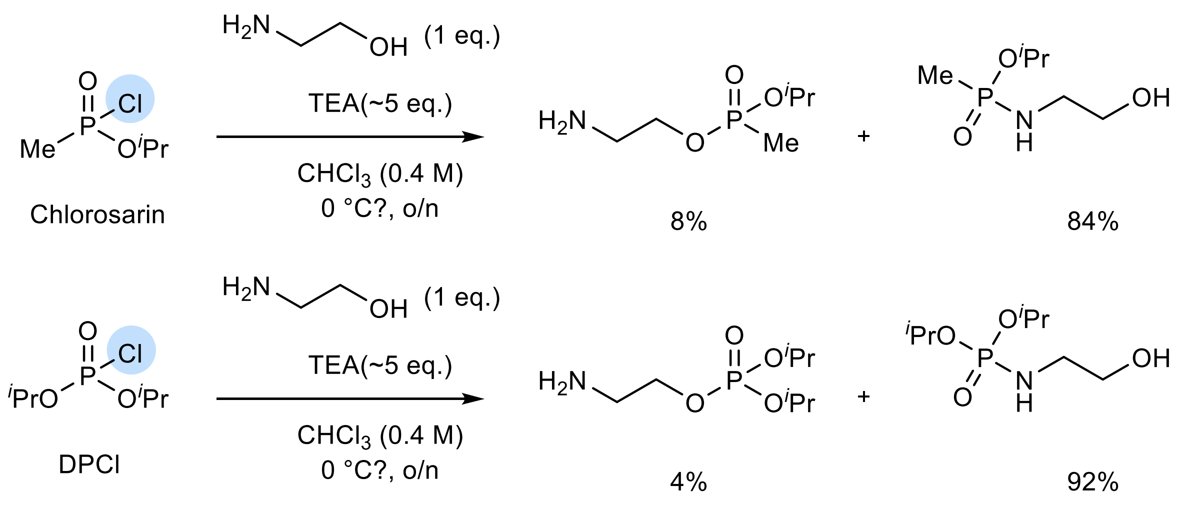
Structure: X—P(→O)(—Z)—Y

*Based on the residual phosphylating agent, as determined by n.m.r.
†*O*-Phosphorylation cannot be excluded because of interference from diethyl phosphoric acid.

O-selective

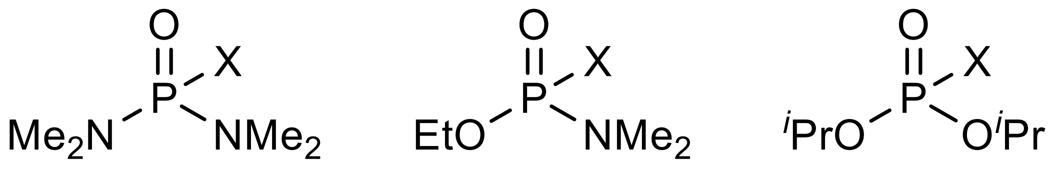


Predominant reaction w/ N



Weinberger, W. A. *et. al. Can. J. Chem.* **1967**, *45*, 495.

Mechanistic study for the difference between P(V)-Cl and P(V)-F



1 **2** **3**

X = Cl, OP(O)RR', CN, F

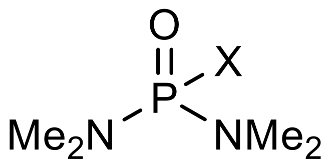
π interaction between p(Y)-d(P)

= Electrophilicity of P-center
1 < **2** < **3**

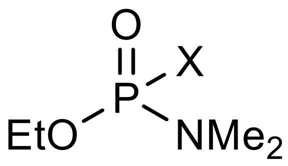
How selectivity changes?

Weinberger, W. A. *et. al*. *Can. J. Chem.* **1970**, *48*, 1351.

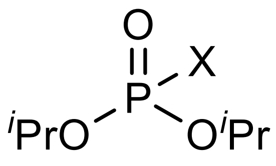
Mechanistic study for the difference between P(V)-Cl and P(V)-F



1



2



3

X = Cl, OP(O)RR', CN, F

π interaction between p(Y)-d(P)

= Electrophilicity of P-center
1 < **2** < **3**

How selectivity changes?

TABLE 4
Variation in selectivity with phosphylating agent (RR′P(O)X)

	R	R′	Sum of Hammett σ values of R and R′	Selectivity $\left(\ln \frac{\text{yield P—N}}{\text{yield P—O}}\right)$ X = Cl	OP(O)RR′	CN	F
1	Me_2N	Me_2N	−1.2	1.8	—	—	—
2	Me_2N	EtO	−0.85	2.04	—	1.15	< −4
3	Pr^iO	Pr^iO	−0.57	3.13	2.68	−1.27	< −4
	Pr^iO	Me	−0.46	2.35	2.37	< −4	< −4
	Me	Me	−0.34	1.39	0.02	—	—
			P—X Bond Energy (kcal) (21)	80	96	80.5*	120

*Value for P—CH_3.

As for P(V)-Cl

More active P produced more P-N product.

As for the leaving group (X)

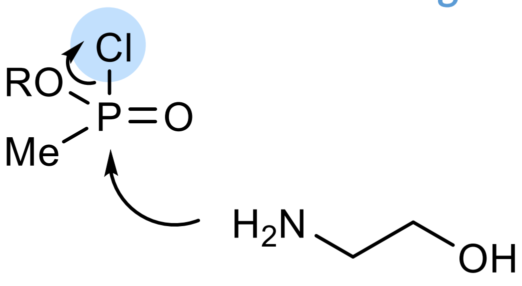
Poorer leaving ability, more P-O product.

Weinberger, W. A. *et. al. Can. J. Chem.* **1970**, *48*, 1351.

Mechanistic study for the difference between P(V)-Cl and P(V)-F

S_N2 reaction

Good leaving ability

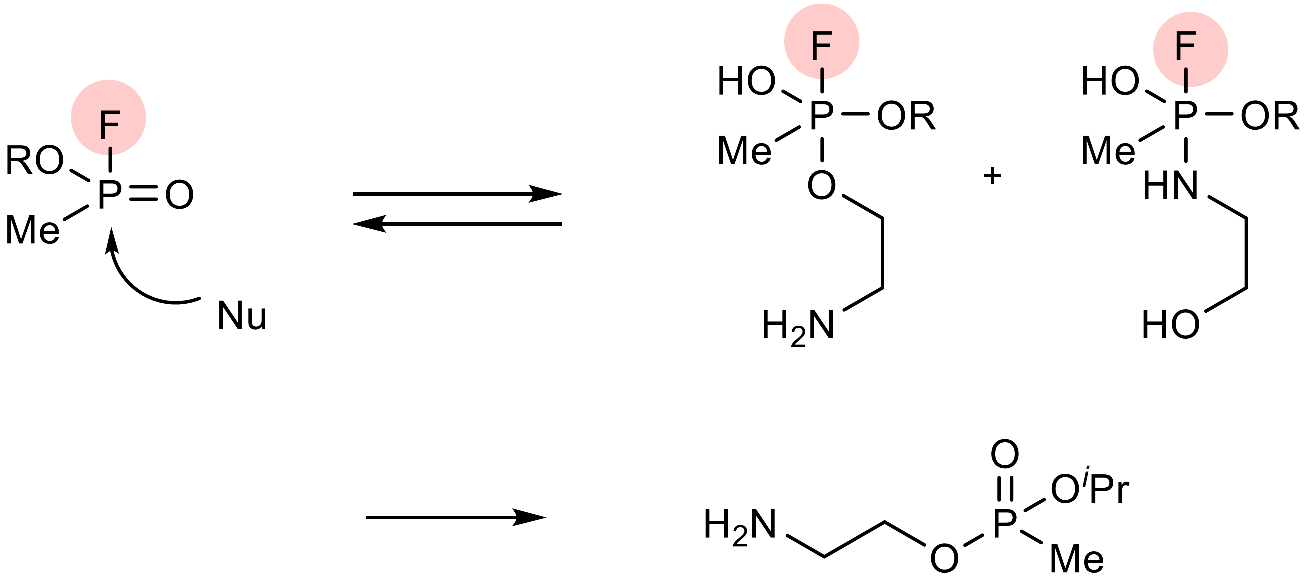


More nucleophilic

Follow the equation

$$v = k[Nu][PCl]$$

Addition-Elimination

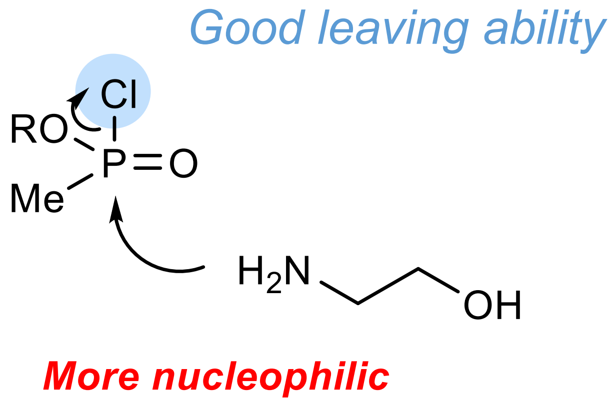


thermodynamically stable

Weinberger, W. A. *et. al. Can. J. Chem.* **1970**, *48*, 1351.

Mechanistic study for the difference between P(V)-Cl and P(V)-F

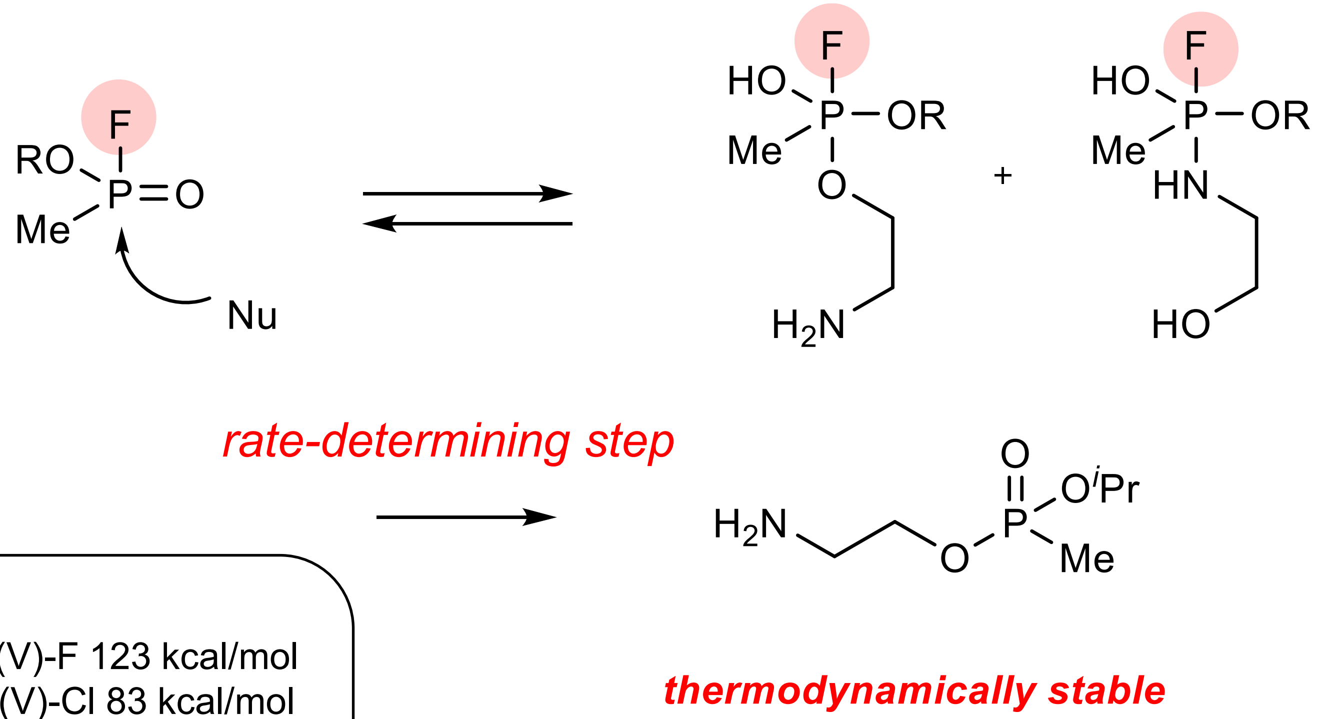
S_N2 reaction



Follow the equation

$$v = k[Nu][PCl]$$

Addition-Elimination



P(V)-F 123 kcal/mol
P(V)-Cl 83 kcal/mol

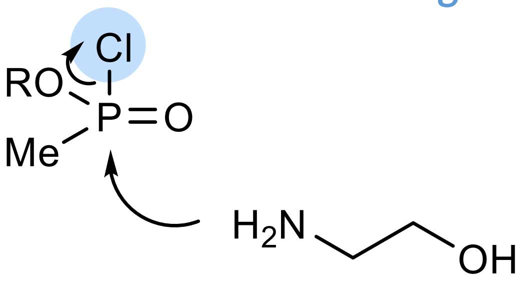
P(V)-N 50-70 kcal/mol
P(V)-O ~100 kcal/mol

Weinberger, W. A. *et. al. Can. J. Chem.* **1970**, *48*, 1351.

Mechanistic study for the difference between P(V)-Cl and P(V)-F

S_N2 reaction

Good leaving ability

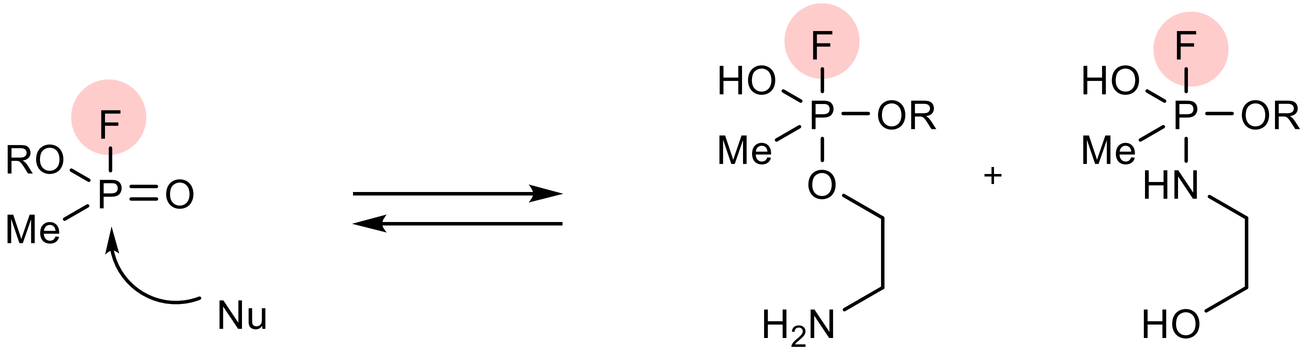


More nucleophilic

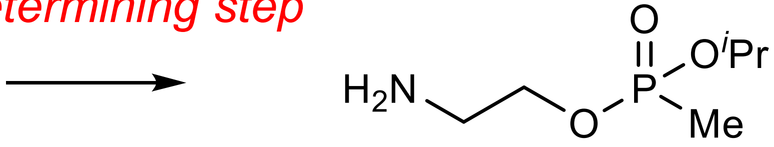
Follow the equation

$$v = k[Nu][PCl]$$

Addition-Elimination



rate-determining step



P(V)-F 123 kcal/mol
P(V)-Cl 83 kcal/mol

P(V)-N 50-70 kcal/mol
P(V)-O ~100 kcal/mol

Si(VI)-F 136 kcal/mol

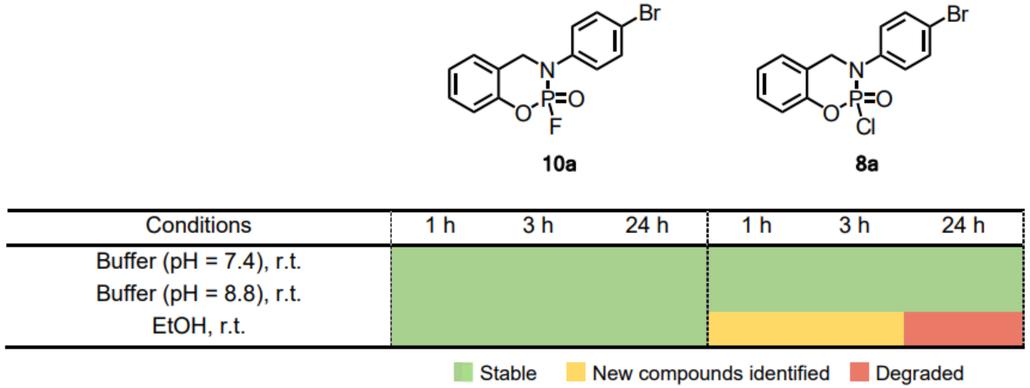
thermodynamically stable

Is P(V)-F compound applicable to click chemistry like SuFEx?

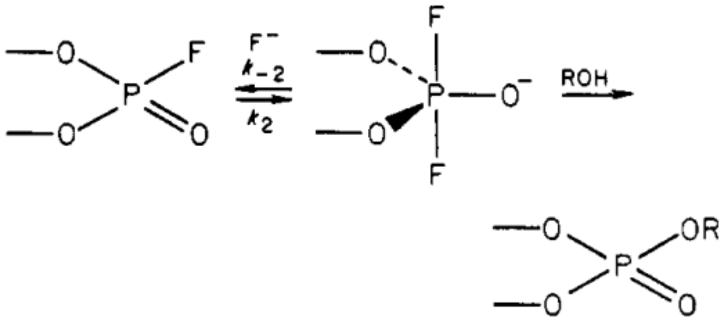
Weinberger, W. A. *et. al. Can. J. Chem.* **1970**, *48*, 1351.

Short summary

P(V)-F is stable reagent

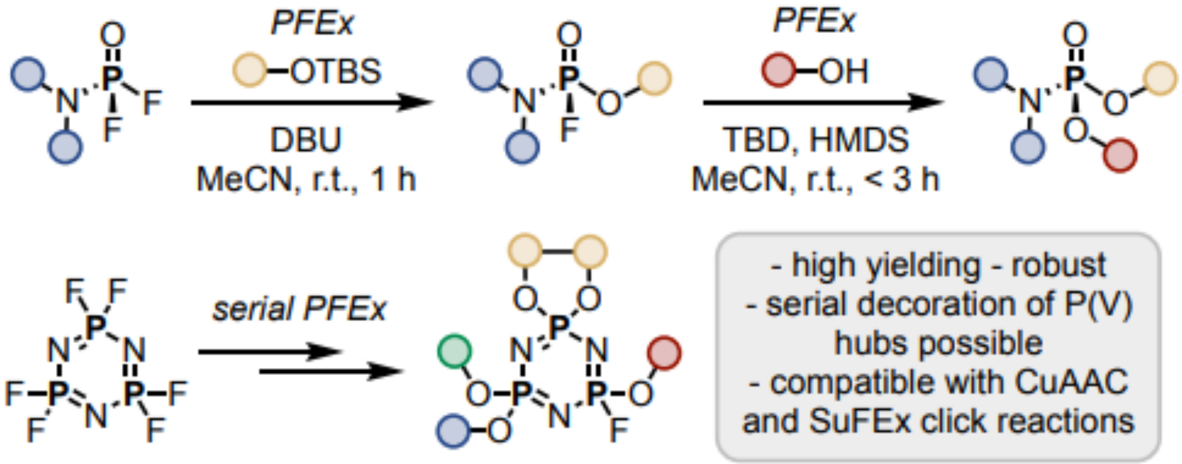


traditional activation method



J. Am. Chem. Soc. **1984**, *106*, 4, 1060–1065

PFEx



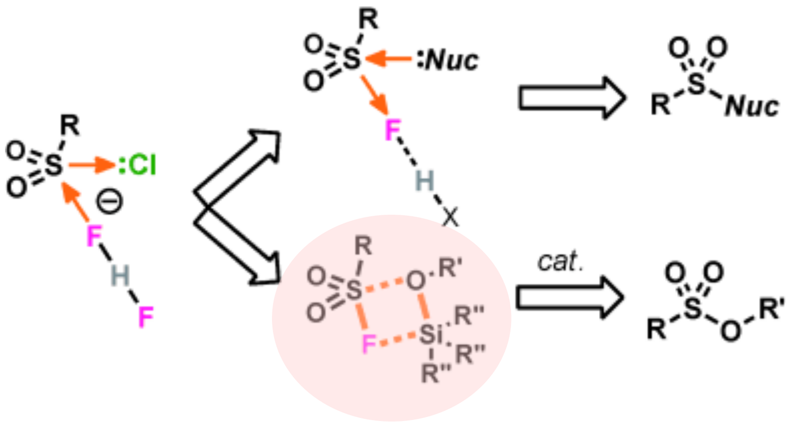
Activation by Silicon

P(V)-F 123 kcal/mol
P(V)-O ~100 kcal/mol
Si(VI)-F 136 kcal/mol

Table of contents

Initial trial of “PFEx” drawing insight from classical SuFEx

SuFEx

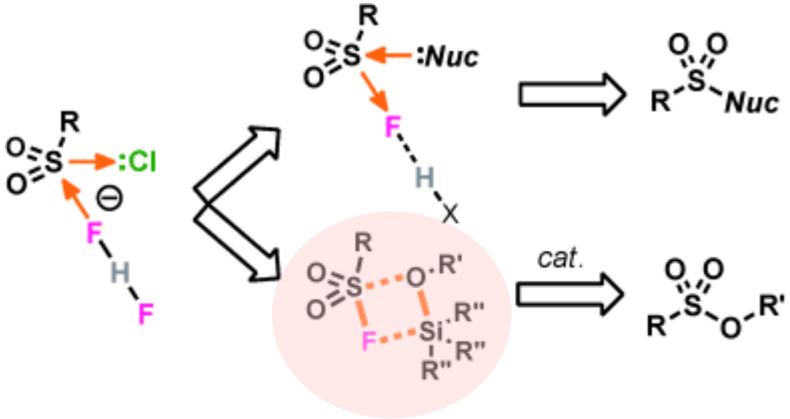


- ✓ Developed by K.B. Sharpless *et al* in 2014
- ✓ Si mediates very fast reactions of S-F as electrophiles.

Sharpless, K. B. *et. al. Angew. Chem. Int. Ed*. **2014**,*53*, 9430 – 9448

Initial trial of “PFEx” drawing insight from classical SuFEx

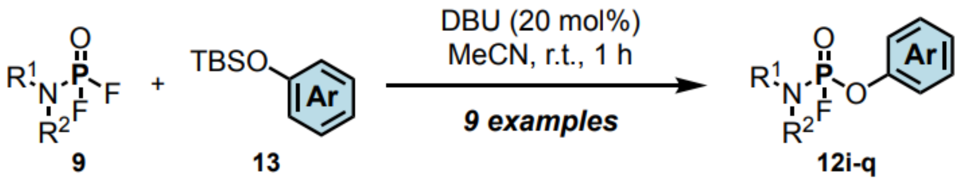
SuFEx

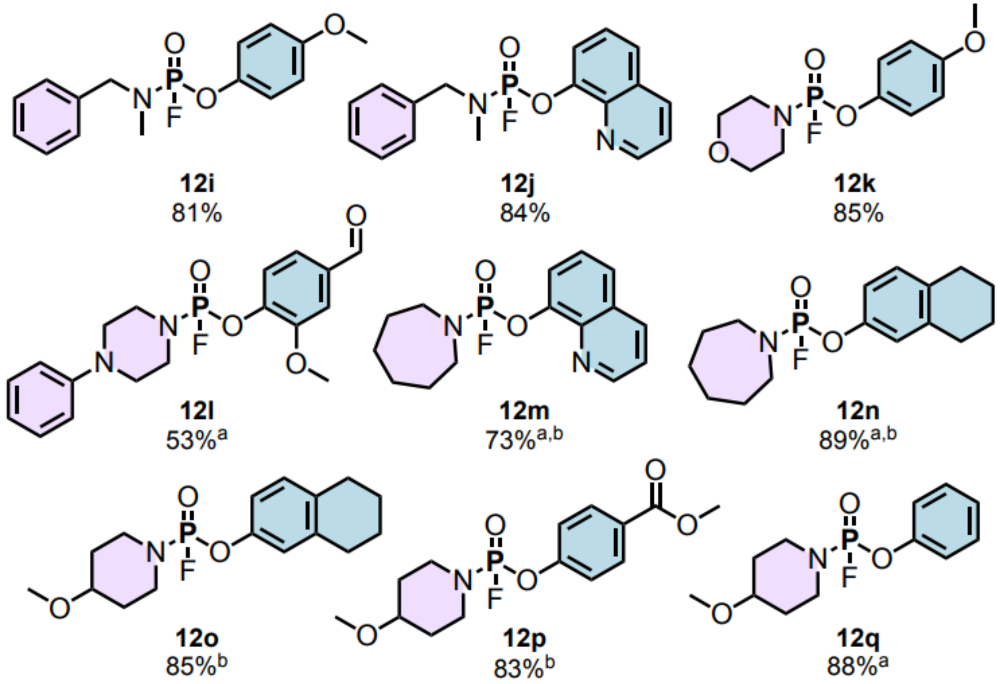


- ✓ Developed by K.B. Sharpless *et al* in 2014
- ✓ Si mediates very fast reactions of S-F as electrophiles.

Sharpless, K. B. *et. al. Angew. Chem. Int. Ed.* **2014**,*53*, 9430 – 9448

PFEx (This work)

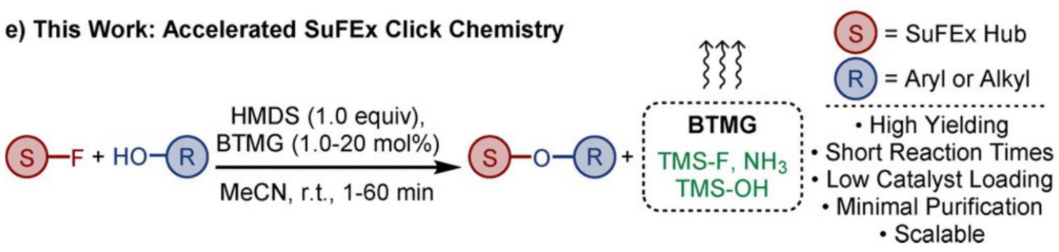




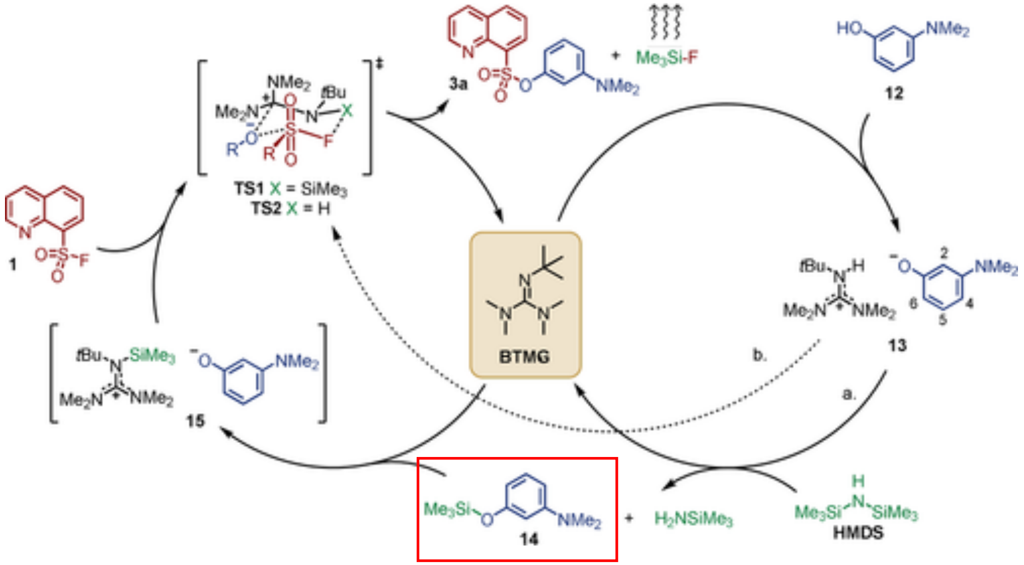
PFEx successfully occurred in good yields using various Ar-Si ester.

Accelerated SuFEx click chemistry

Accelerated SuFEx (ASCC); external Si additives



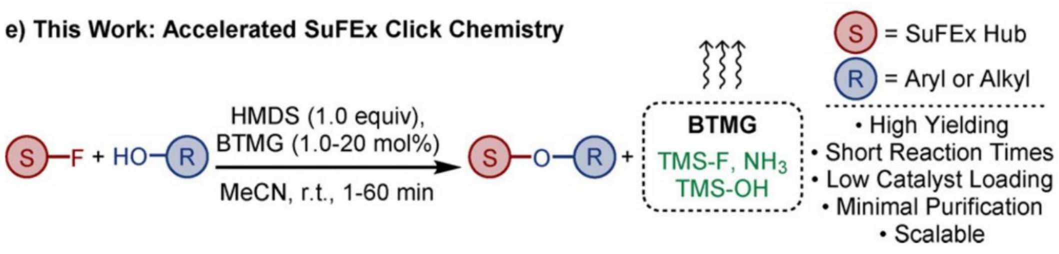
Moses, *et. al. Angew. Chem. Int. Ed.* **2022**, *1*, e202112375.



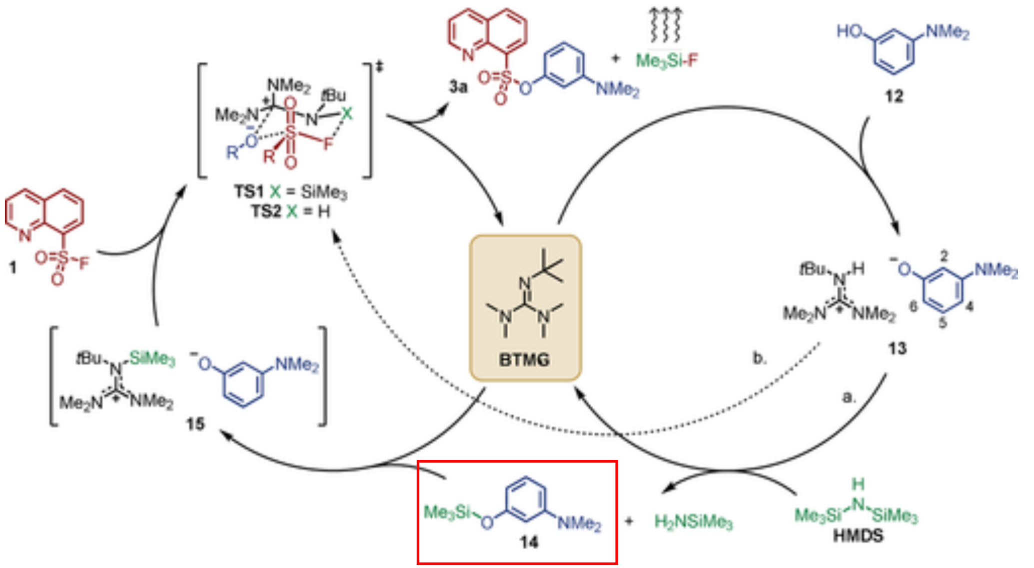
In situ generation of Silyl ester

Accelerated SuFEx click chemistry

Accelerated SuFEx (ASCC); external Si additives

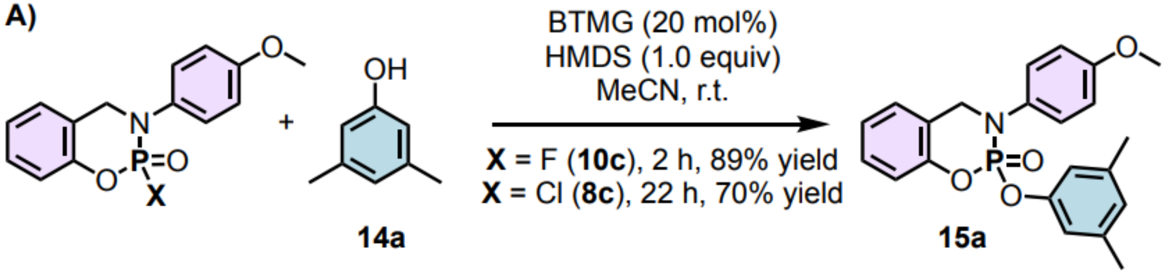


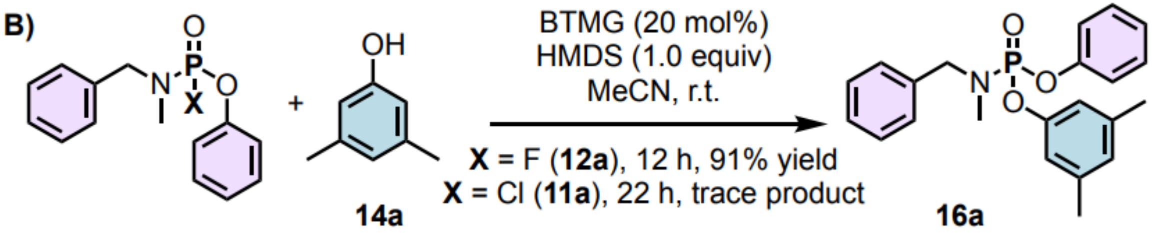
Moses, *et. al. Angew. Chem. Int. Ed.* **2022**, *1*, e202112375.



In situ generation of Silyl ester

Employed ASCC conditions to PFEx

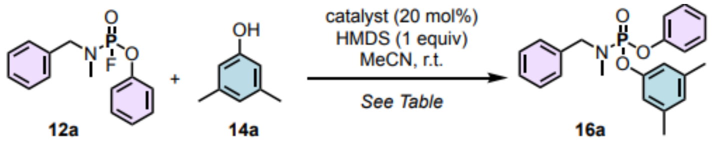




Demonstrate the superiority of P(V)-F over P(V)-Cl

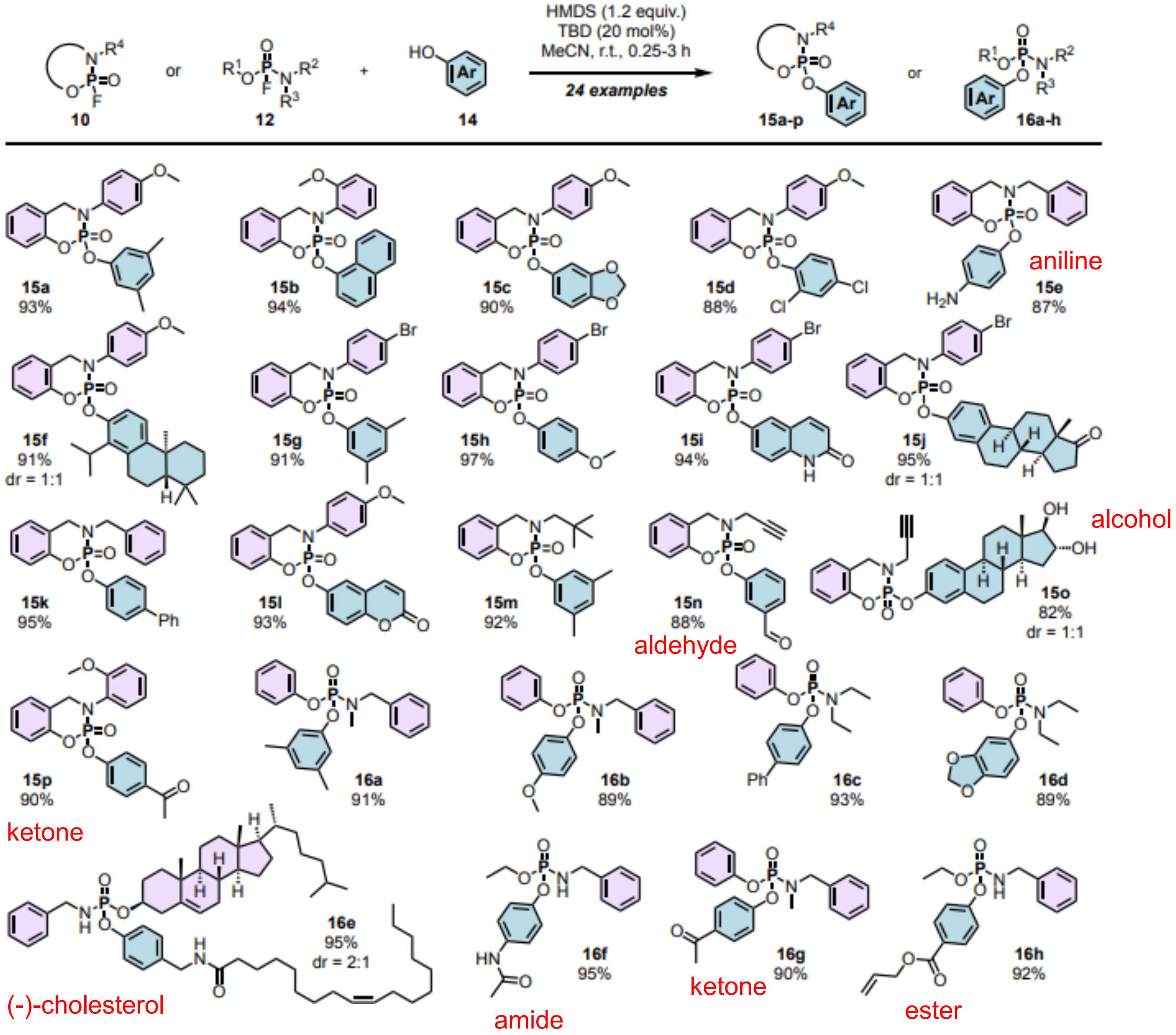
Optimization for PFEx

Base screening

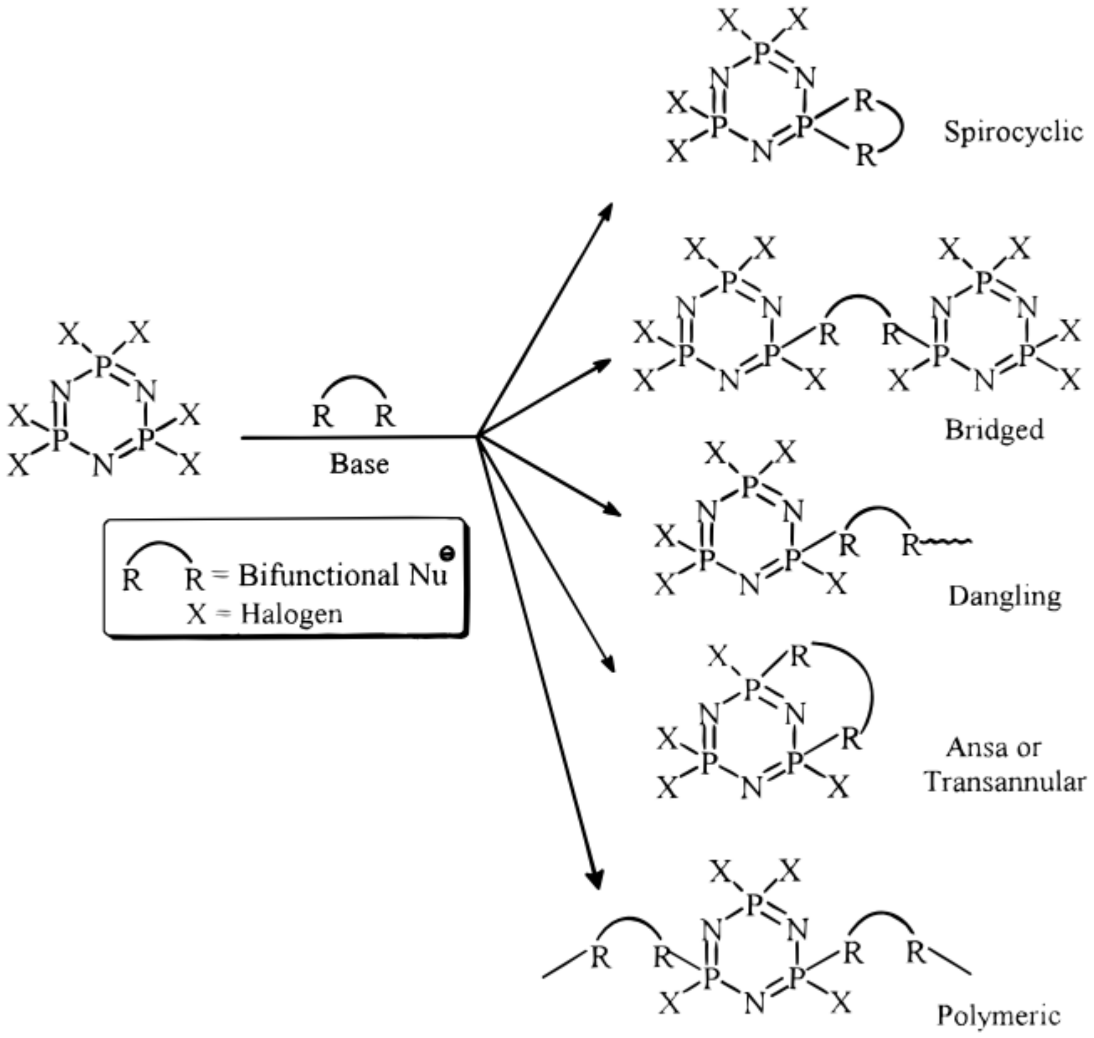


Entry	Catalyst	pK_aH (MeCN)	Time (h)	Conversion (%)[a]
1	P_4-^{t}Bu	42.7	1	>99
2	P_2-^{t}Bu	33.5	1.5	>99
3	TBD	26.2	5	>99
4	BTMG	~26	14	91
5	DBU	24.3	14	80
6	P_1-^{t}Bu	26.9	14	10
7	TMG	23.7	14	9
8	DPG	18.8	14	Trace
9	BEMP	27.5	14	66
10	MTBD	25.0	14	64
11	DMAP	18.0	14	0
12[b]	TBD	26.2	2	>99
13[c]	TBD	26.2	7	16
14[d]	TBD	26.2	7	20

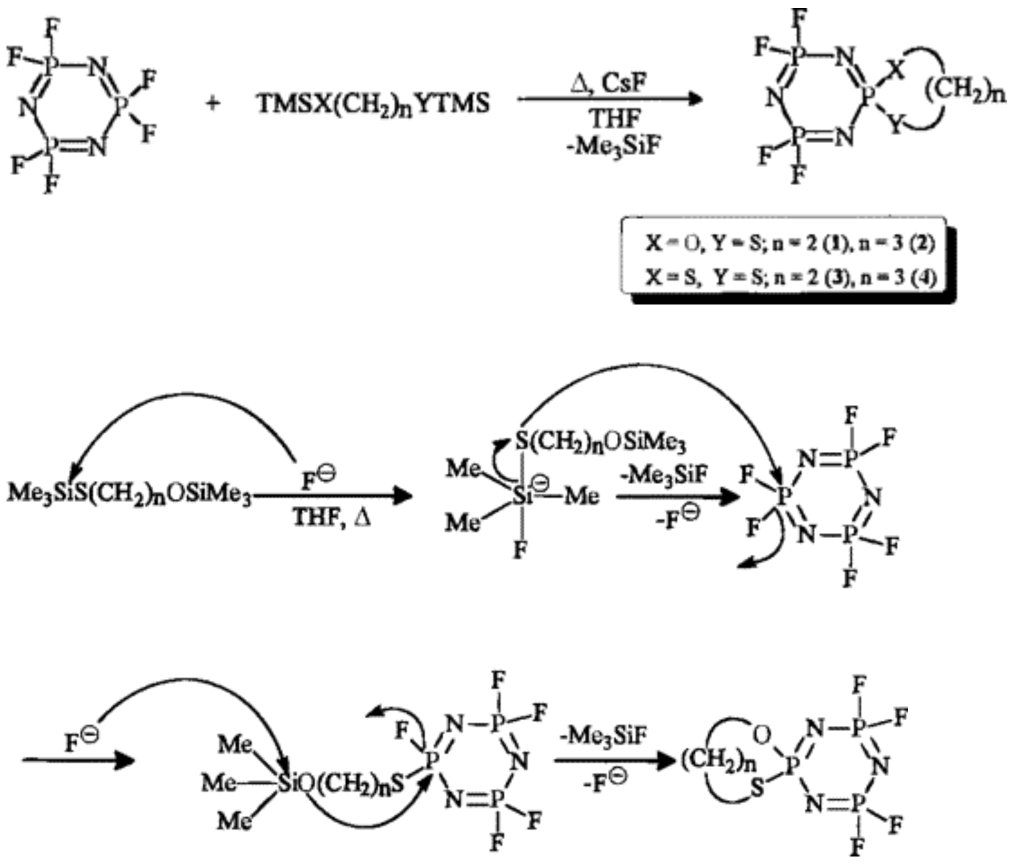
Stronger base is necessary for deprotonation of phenol.



Polyfluorinated organophosphorus compounds

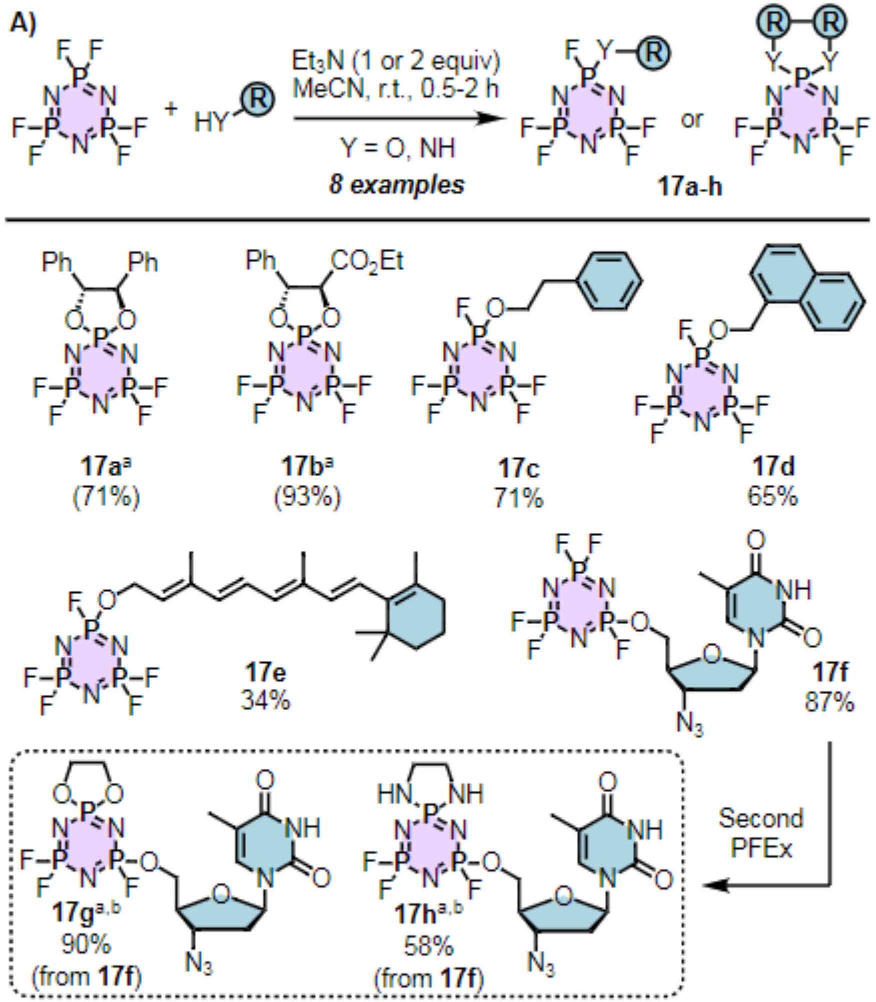


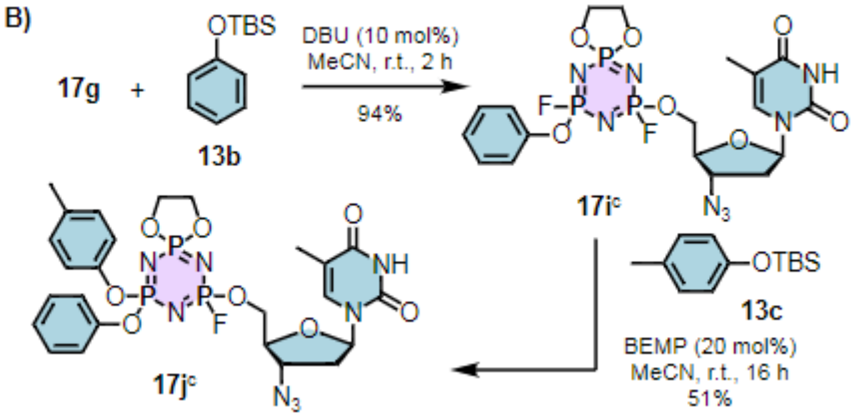
Activation by CsF



Inorg. Chem. **1996**, *35*, 10, 2915–2929

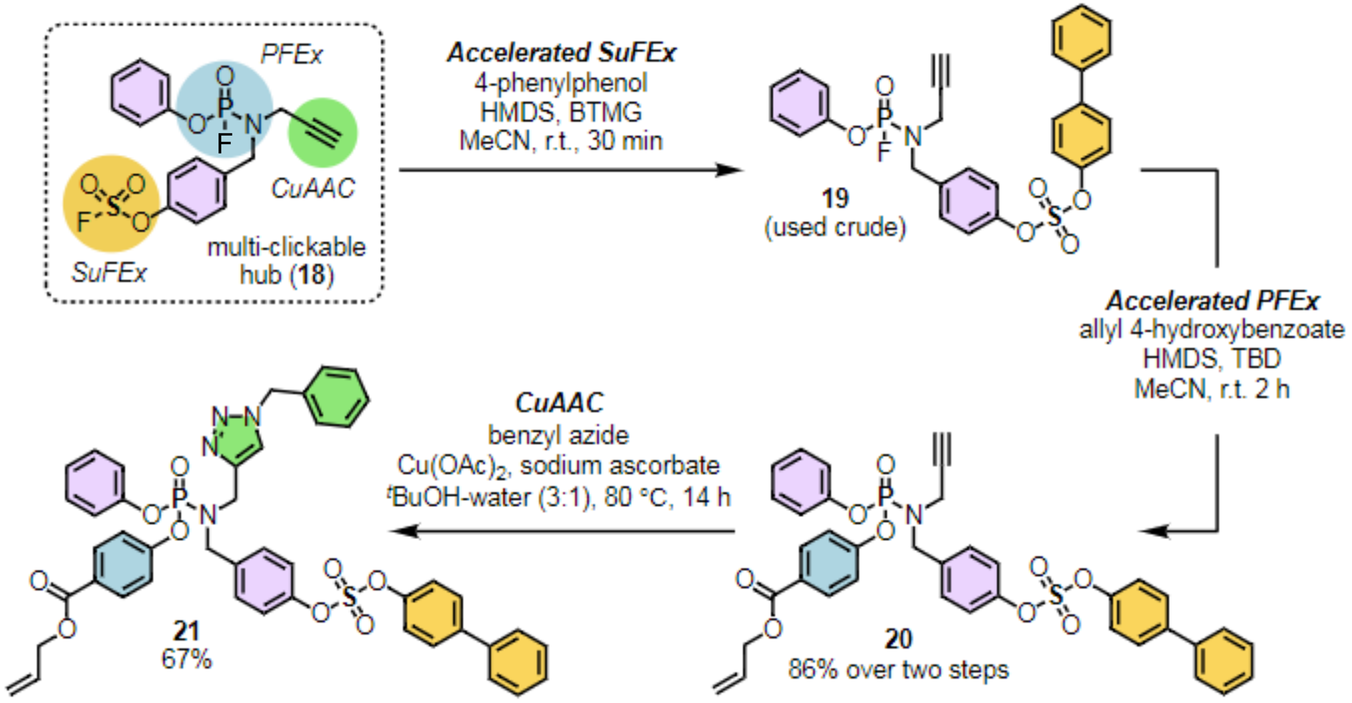
Polyfluorinated organophosphorus compounds





With substrates comprising multiple P-F bonds an opportunity for diversity orientated clicking is presented.

The orthogonal reactivity between PFEx and other click reactions



The striking difference in reactivity between P-F and S-F clickable hubs creates a window of opportunity for orthogonal connective chemistry.

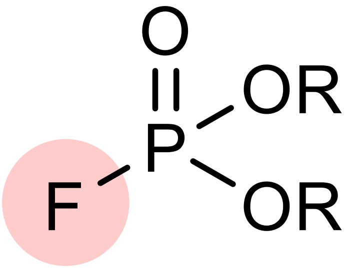
Reason?

bond	ΔH_{bond} (kJ/mol)
P–H	322
P–P	201
P–F	490.
P–Cl	326
P–Br	264

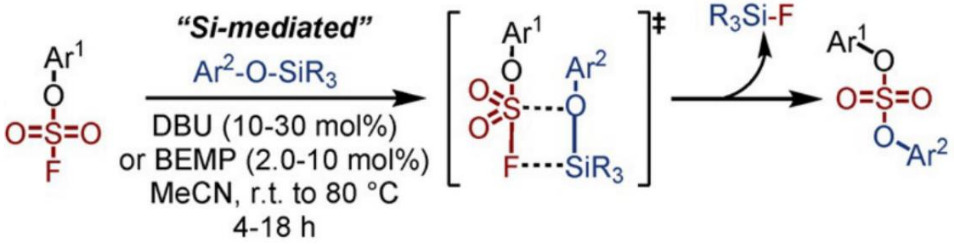
bond	ΔH_{bond} (kJ/mol)
S–H	347
S–S	266
S=S	425
S–F	327
S–Cl	253
S–Br	218

bond	ΔH_{bond} (kJ/mol)
Si–H	393
Si–Si	340.
Si–O	452
Si–F	565
Si–Cl	381
Si–Br	310.

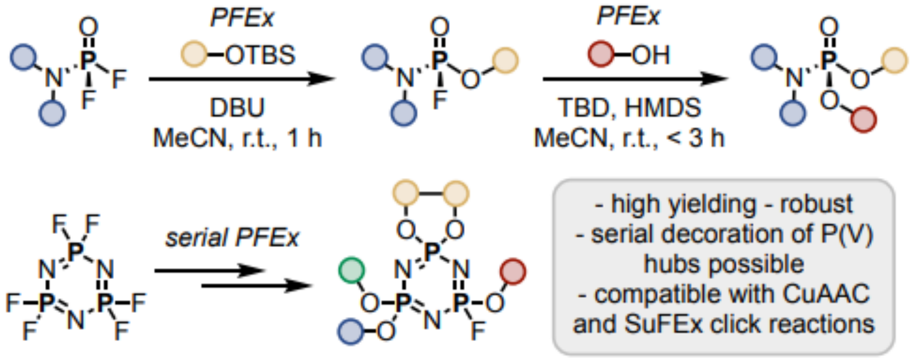
Short summary



- ✓ P(V)-F derivatives are stable but once activated, show sharp reactivity.
- ✓ PFEx is orthogonal over other click reactions.



Angew. Chem. Int. Ed. **2022**, *1*, e202112375.



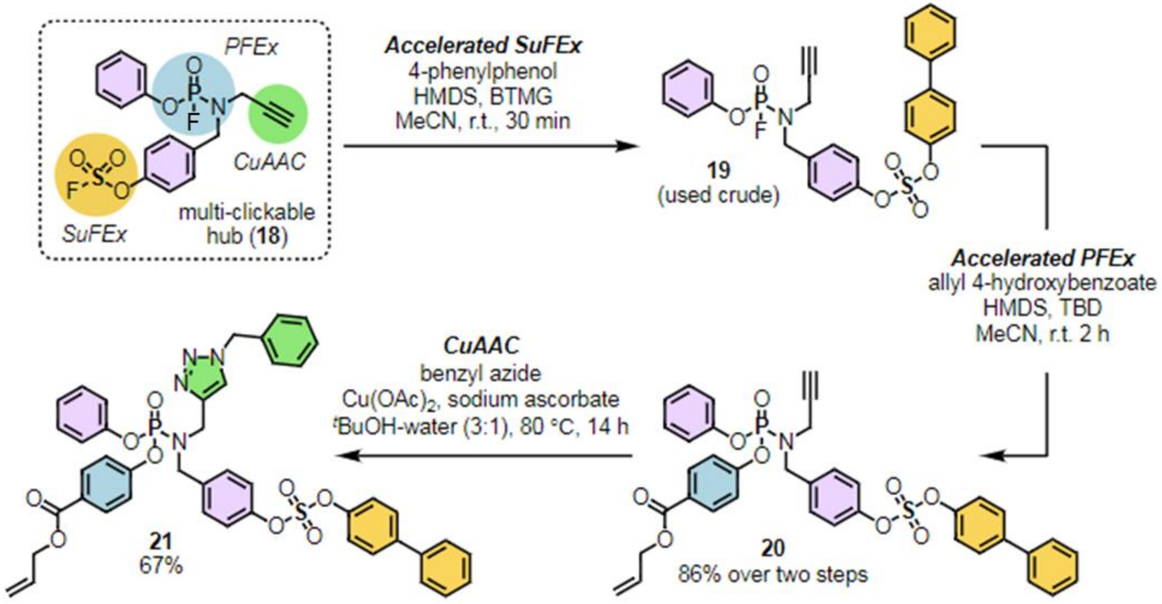
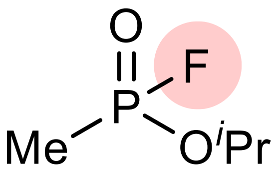


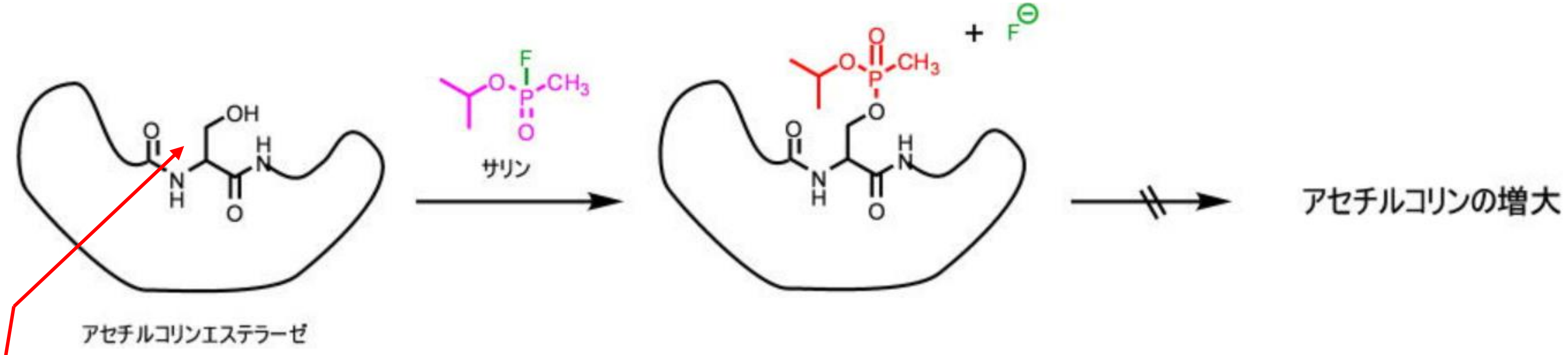
Table of contents



Sarin

P(V)-F shows activated serine-selective reactivity.

Mechanism of action; Irreversible phosphonylation of Ser



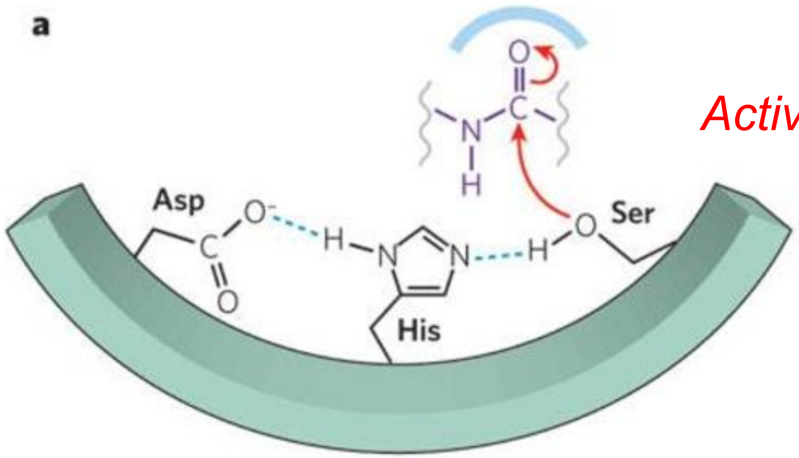
http://molecules.a.la9.jp/acetylcholine%20esterase.html

Serine at Catalytic triad

…. A set of three coordinated amino acids in the active site of enzymes

…. Found in Serine hydrolases (SHs)

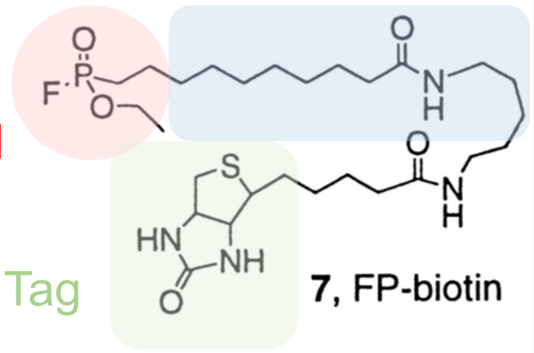
Ex) Serine esterase
Serine protease
Phospholipase



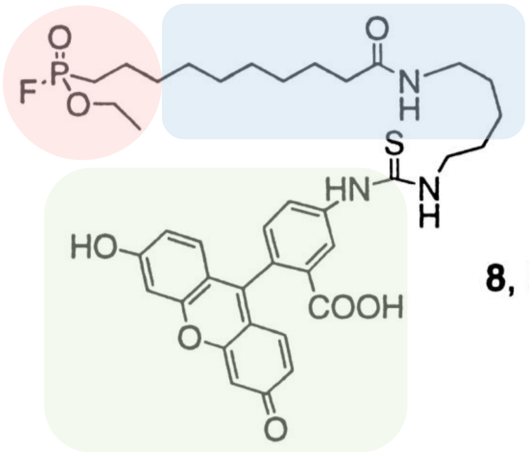
Activated Serine

https://www.chegg.com/homework-help/questions-and-answers/amino-acid-serine-form-catalytic-triad-amino-acid-cysteine-form-catalytic-dyad-q18222430

Activity-based protein profiling (ABPP) for SHs

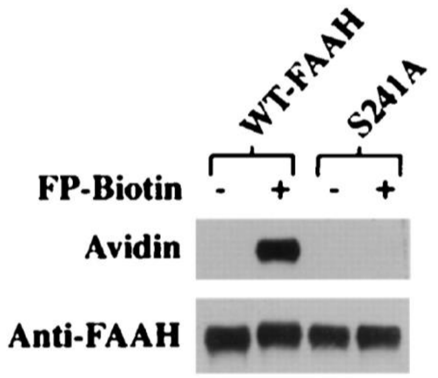


7, FP-biotin

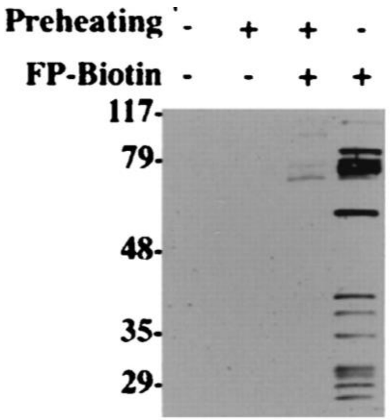


8, FP-fluorescein

Active-Ser selective



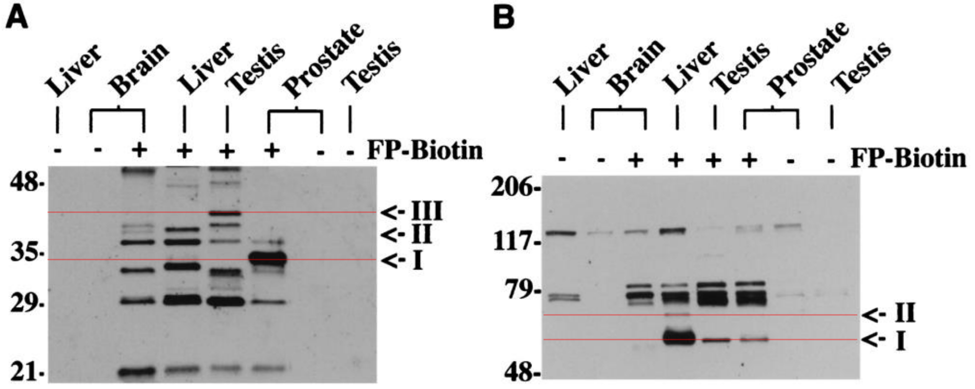
No reaction w/ denatured proteins



Soluble fractions of rat testis
>10 testicular proteins detected

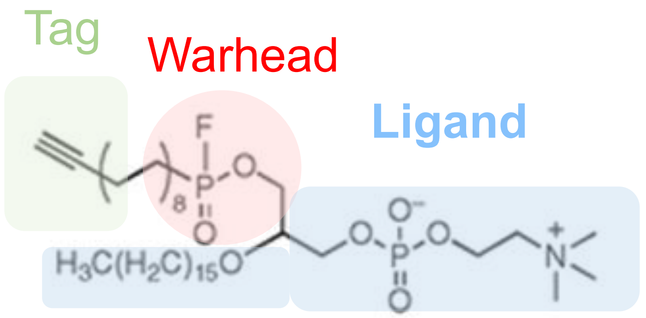
Preheating ; 80°C, 5 min

Identification of SH activity enzyme from rat tissues

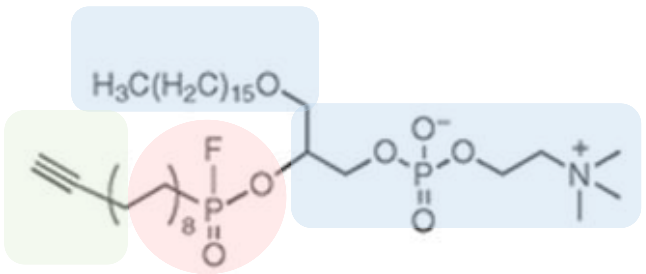


Cravatt, B. F. *et. al.* *Proc. Natl. Acad. Sci. U.S.A.* **1999**, 96, 14694.

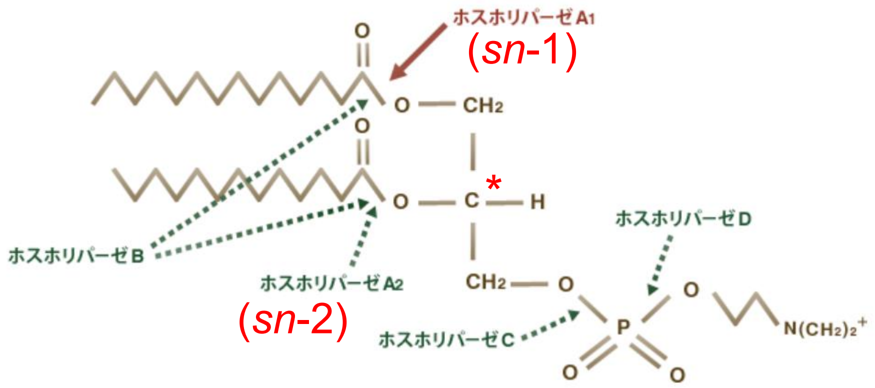
Phospholipase-selective probe



***sn*-1 selective probe, 1**

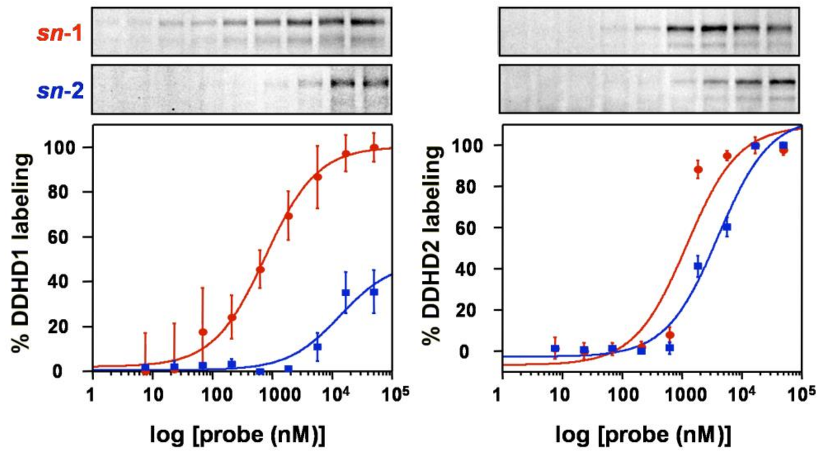


***sn*-2 selective probe, 2**

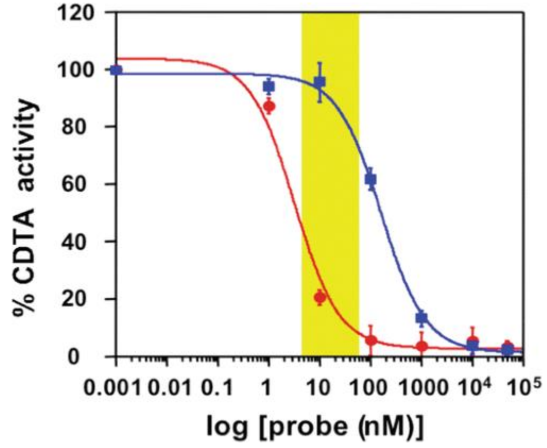


https://www.mfc.co.jp/product/kouso/phospholipase/index.html

Reactivity of 1 and 2 with poorly-investigated lipase



Good features for identification of CDTA

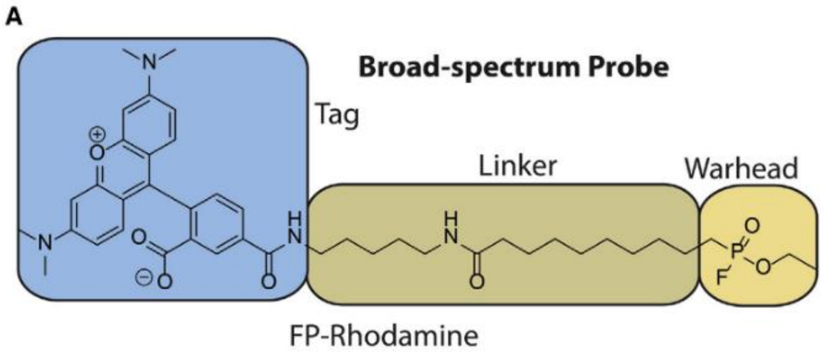


Red : probe 1
Blue : probe 2

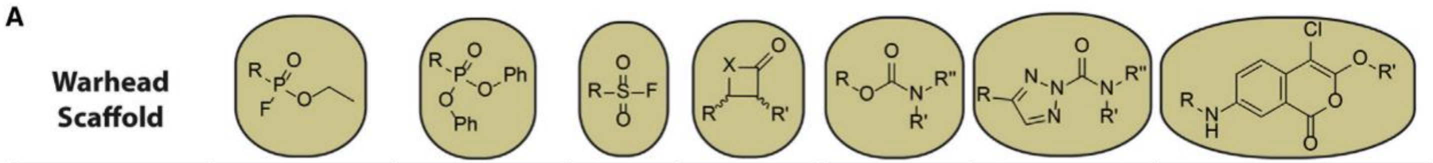
IC_{50}
Probe1 : 3 nM
(Probe2 : 165 nM)

Cravatt, B. F. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 10, 3264−3265.

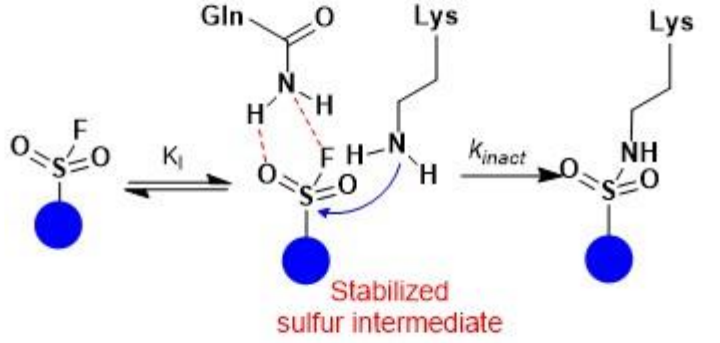
Further application of ABPP and perspective of P(V)-F



Cell Chem. Biol. **2020**, *27*, 937.



Warhead	Fluoro-phosphonate	Diphenyl-phosphonate	Sulfonyl Fluoride	β-lactam β-lactone	Carbamate	Triazole Urea	4-chloro-isocoumarin
Synthetic Tractability	Difficult	Moderate	Easy	Moderate	Easy	Easy	Easy
Serine Selectivity	High	High	Poor	Poor	Moderate	Moderate	High
Hydrolase Preference	Broad-spectrum	Proteases	Proteases	β-lactamases	Lipases	Peptidases, Lipsases	Broad
Diversity of Leaving Group	Fluoride	Broad	Fluoride	N.A.	Broad	Broad	Chloride



https://sites.rutgers.edu/moschitto-lab/research/

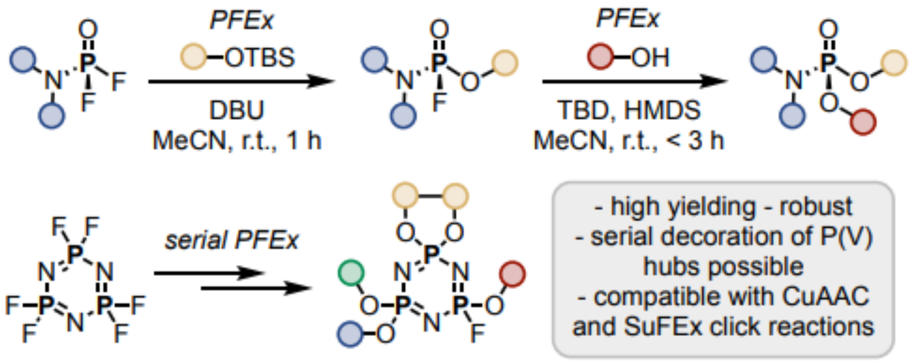
SuFEx for divergent application

- ✓ React with Ser/ Tyr/ Lys/His

- ✓ Target identification and validation
- ✓ Mapping of enzyme binding site (other than SH)
- ✓ Covalent drugs

P(V)-F could be another CR with high selectivity toward O.

Summary



PFEx

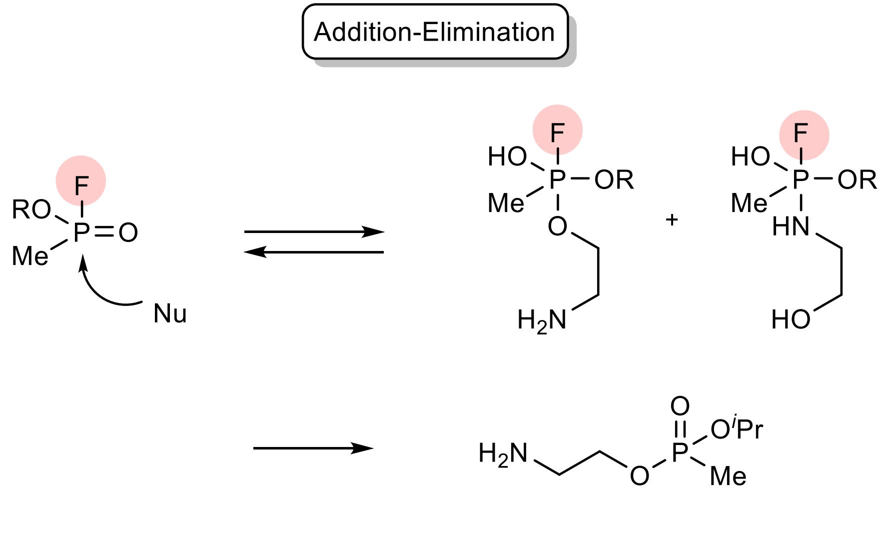
.... is another good reaction for click chemistry

.... the transformation proceeds smoothly like SuFEx

.... original feature derived from *P* ; Selectivity toward *O*

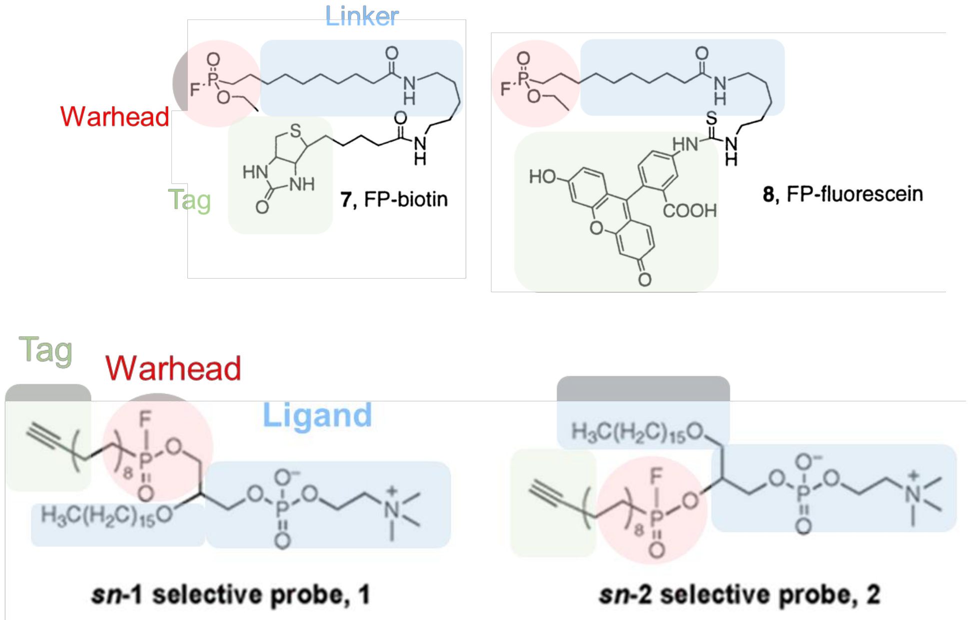
.... further development (activation by LA or H network) is desired

Phosphorus-oriented selectivity



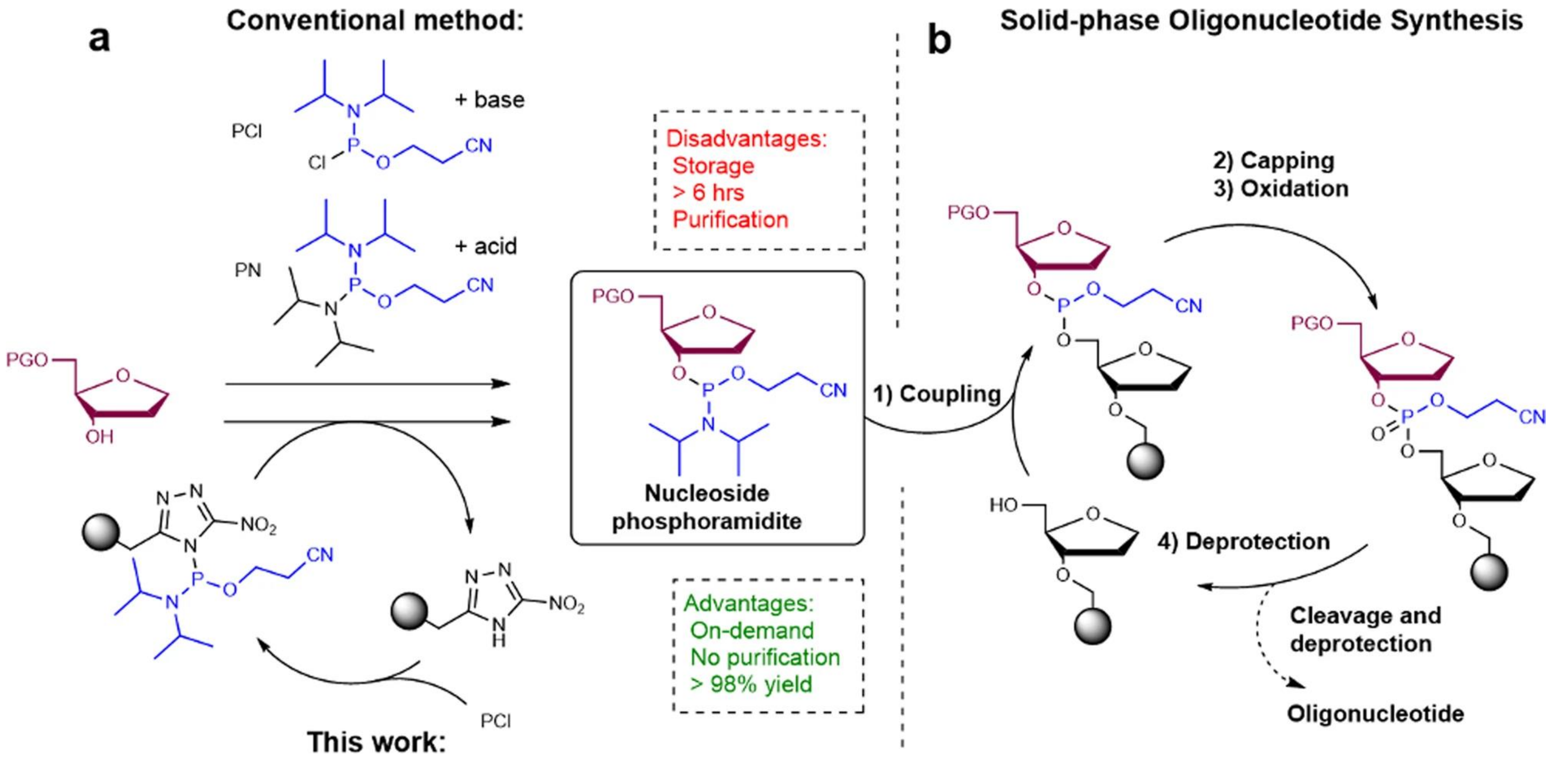
thermodynamically stable

Preliminary example of labeling



Appendix

Trivalent Phosphoryl reagent ; P(III) reagents

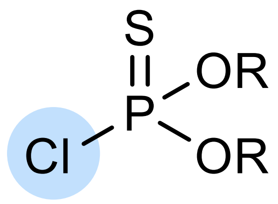


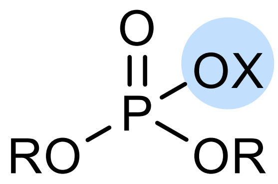
Nat. Chem. **2021**, *12*, 2760.

✓ Alcohol-selective phosphorylation over Amine

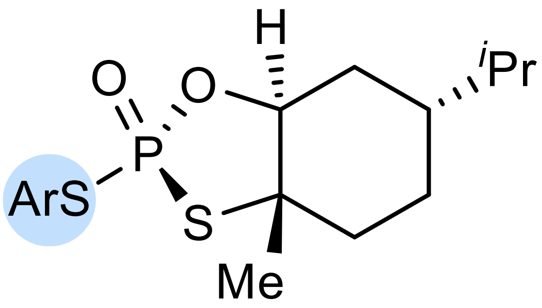
✗ Containing oxidation steps ✗ No-selectivity among OH

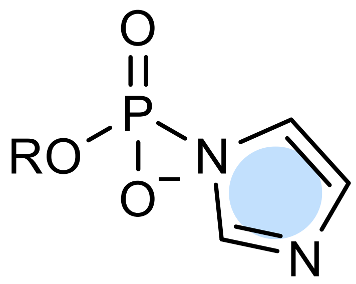
P(V) reagents are desirable for protein labeling (w/o oxidation step)





X=nitorobenzene etc.





Warning in case of handing P(V)-F compounds

General Procedure A:

To a solution of the desired substituted phosphoramidic dichloride (1.00 equiv) in acetone (0.125 M) was added KF (8.00 equiv). The reaction mixture was rapidly stirred at room temperature for 3 h and then filtered through Celite®. The solvent was removed under reduced pressure to give the desired phosphoramidic difluoride. The shelf-life of these compounds is limited (up to 3 days at -20 °C) and so they should be converted to the more stable phosphoramidofluoridates as soon as possible.

***Caution!** Substituted phosphoramidic difluorides are assumed to be extremely toxic and should only be handled in a well-ventilated fume cupboard with concentrated NaOH on hand to quench any spills and wash glassware.*

Raw data of Mechanistic study

TABLE 1

Reaction conditions and products from the reaction of ethanolamine with phosphylating agents

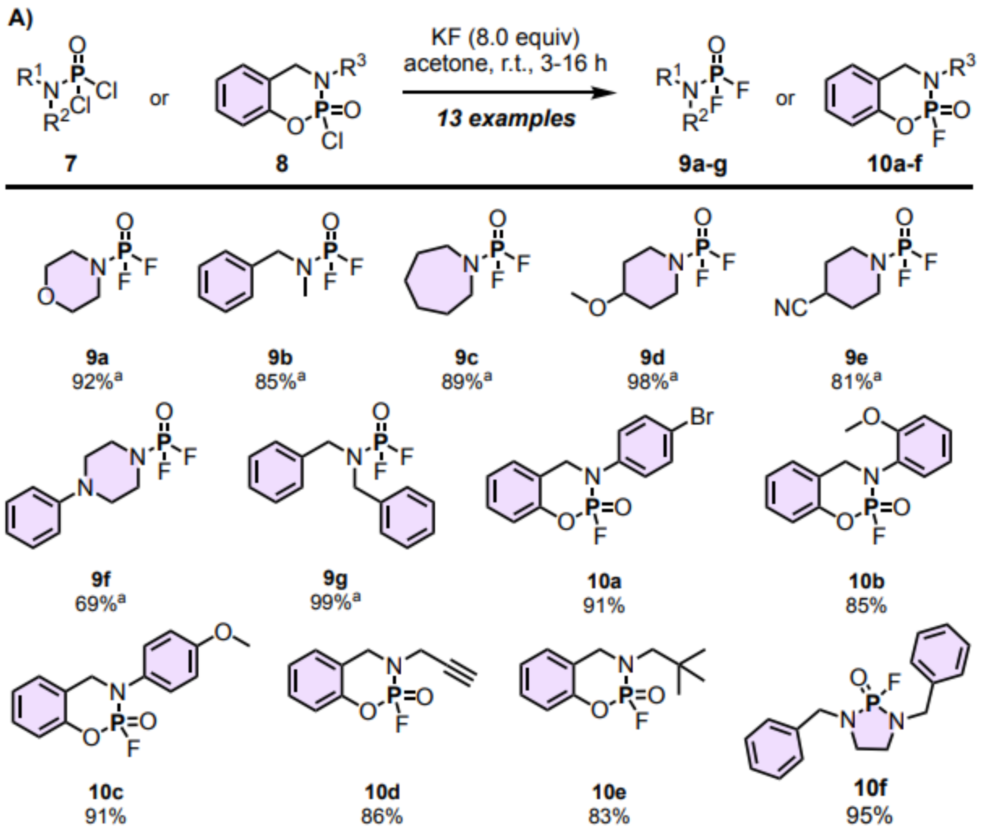
Phosphylating agent (RR′P(O)X)			Chemical shift (p.p.m.)	^{31}P Chemical shifts (p.p.m.) and % material at end of reaction				Reaction conditions	
R	R′	X		*N*-Phosphyl derivative	*O*-Phosphyl derivative	RR′P(O)OH	Other products	Time (h)	Temperature†
Me_2N	Me_2N	Cl	−29.7	−23.6 (22%)	−19.0 (3.5%)			24	R.T.
EtO	Me_2N	Cl	−16.9	−18.8 (84%)	−11.1 (11%)		−30.9 (2%), −7.2 (3%)	28	R.T.
EtO	Me_2N	OP(O)RR′	0	−18.6 (4%)			+12.7 (1%)	24	Reflux
EtO	Me_2N	F	−5.2*		−11.9 (13%)			120	R.T.
Pr^iO	Pr^iO	OP(O)RR′	+15	−7.9 (44%)	+2.0 (3%)	+2.0 (50%)	+9.6 (3%)	72	R.T.
Pr^iO	Pr^iO	CN	+24.2	−8.1 (22%)	+2.5 (78%)			56	R.T.
Pr^iO	CH_3	OP(O)RR′	−20.5	−32.5 (43%)	−29.9 (4%)	−19.8 (53%)		72	R.T.
Pr^iO	CH_3	CN	−10.5		−29.6 (95%)	−19.8 (5%)		48	R.T.
CH_3	CH_3	Cl	−62.0	−41.1 (61%)	−55.7 (15%)	−33.3 (21%)		2	R.T.
CH_3	CH_3	OP(O)RR′	−51.5	−39.0 (22%)	−54.4 (19%)	−33.9 (59%)		24	R.T.

*Doublet.
†R.T. stands for room temperature.

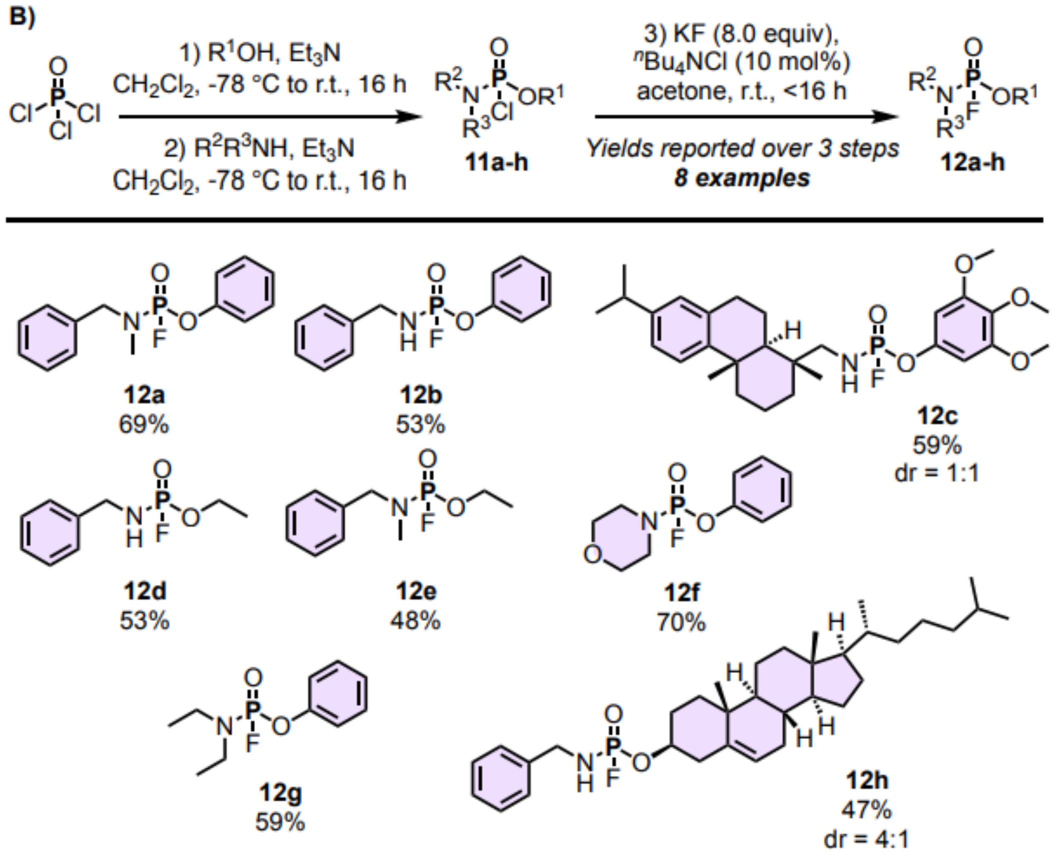
Weinberger, W. A. *et. al. Can. J. Chem.* **1970**, *48*, 1351.

Synthesis of P(V)-F compounds

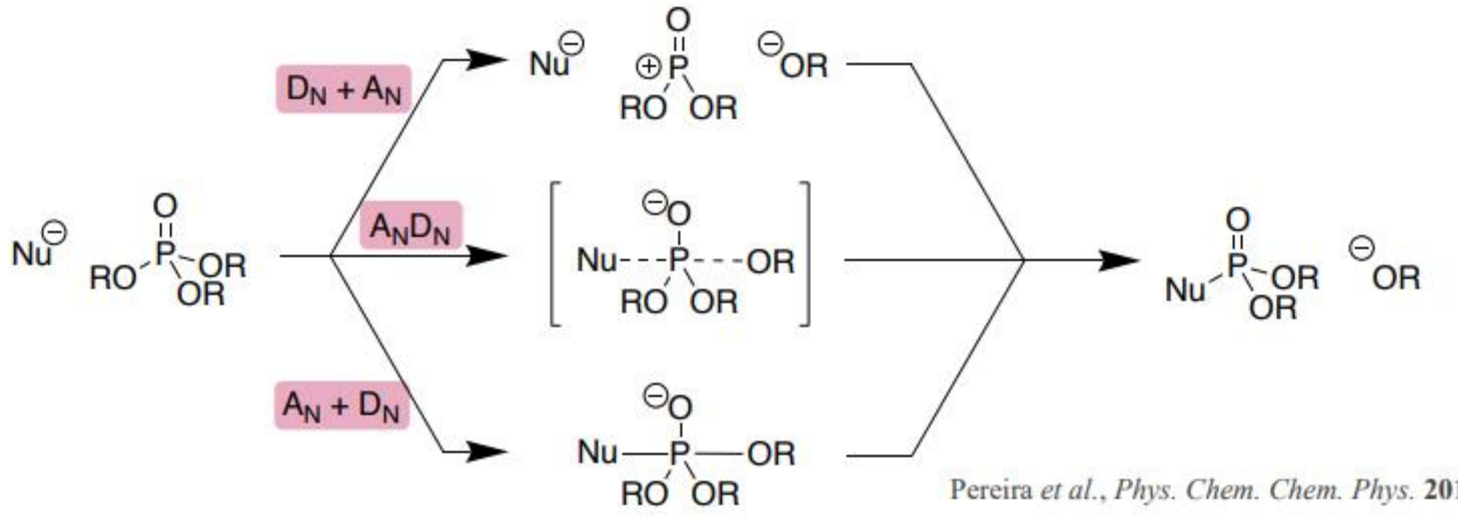
Phosphoramidic difluoride



Phosphoramidofluoridate



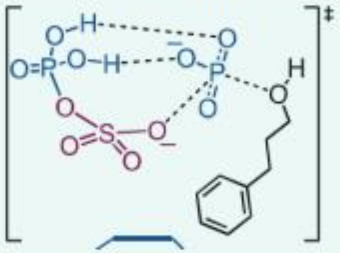
Reaction mechanism of phosphoryl transfer



Pereira *et al.*, *Phys. Chem. Chem. Phys.* **2016**, *18*, 18255

A_ND_N

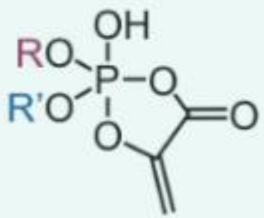
POSOP transition state



Domon, K.; Fujiyoshi, K.; Kanai, M.; *et al.* *ACS Cent. Sci.* **2020**, *6*, 283

$A_N + D_N$

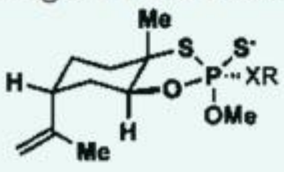
R_2PEP intermediate



Fujiyoshi, K.; Motomu, K.; *et al.* *Synlett* **2021**, *32*, 1135

$A_N + D_N$

ψ reagent intermediate

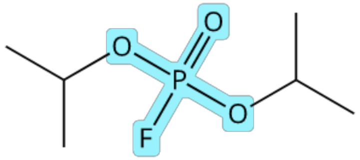


INT1
(TBP)

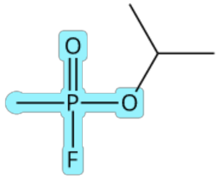
Vantourout, J.; Baran, P.; *et al.* *J. Am. Chem. Soc.* **2020**, *142*, 17236

Phosphorous Fluoride derivatives

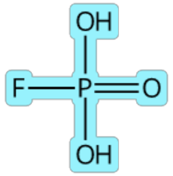
Representative P(V)-F derivatives



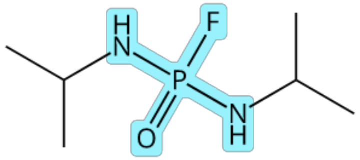
Diisopropyl fluorophosphate



Sarin

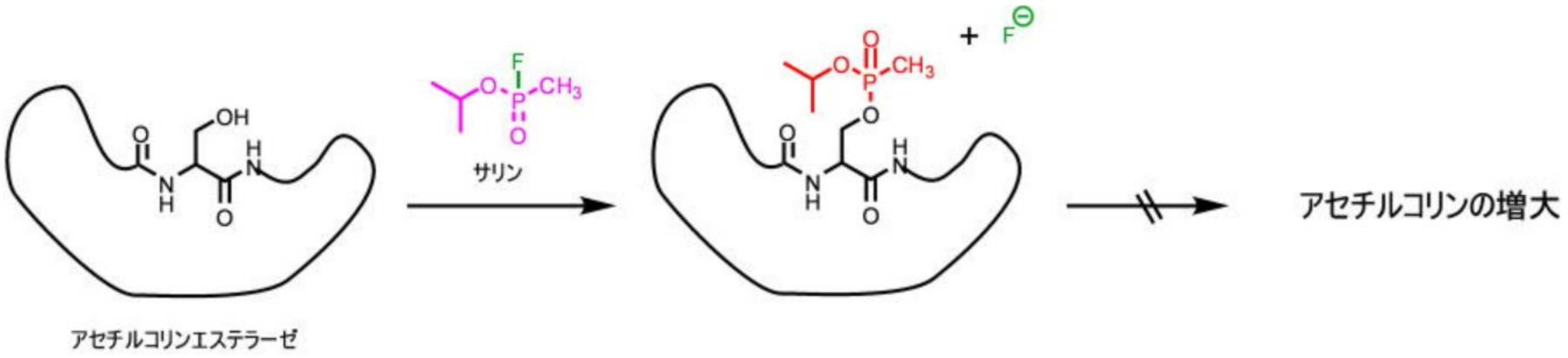


Phosphorofluoridic acid



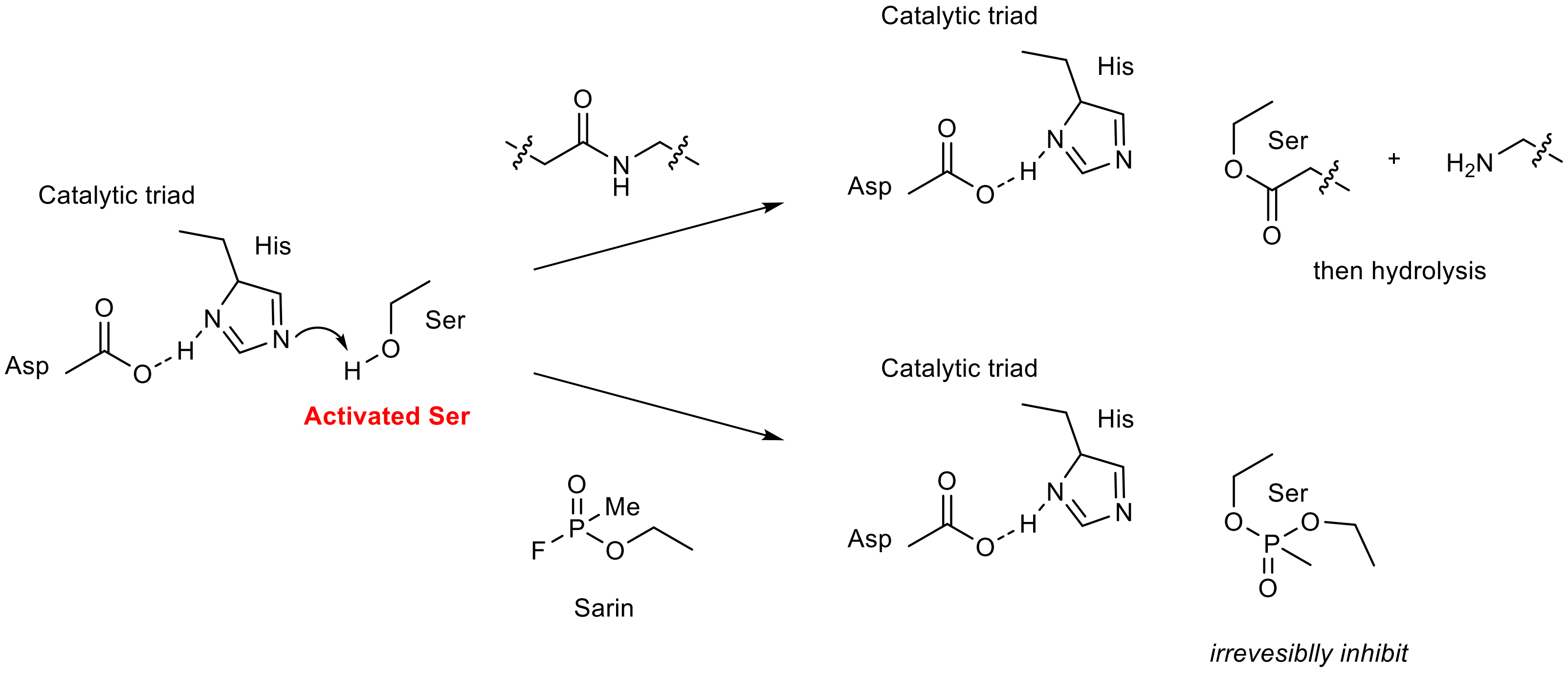
Mipafox

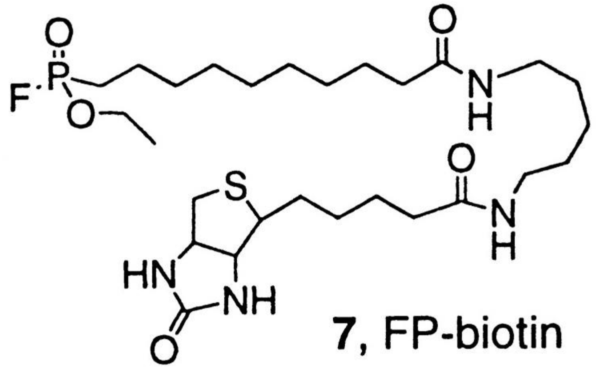
Mechanism of action; Irreversible phosphorylation of Ser



http://molecules.a.la9.jp/acetylcholine%20esterase.html

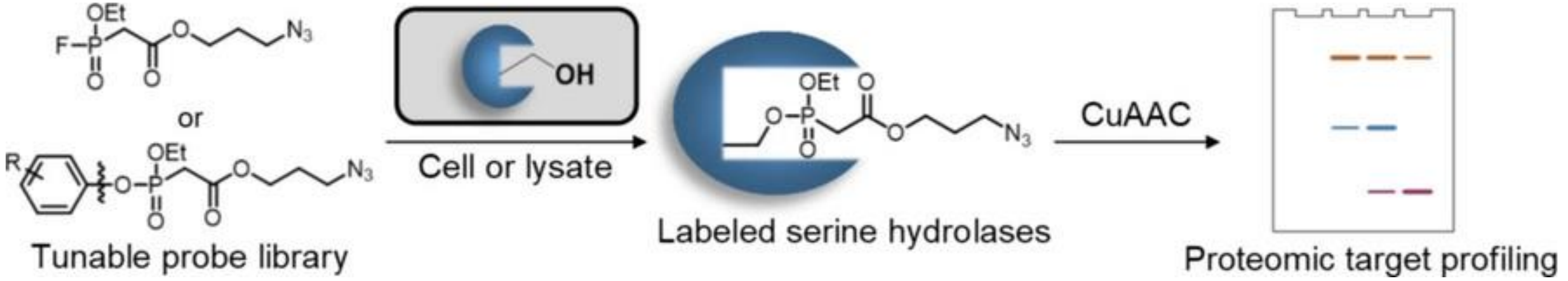
Serine hydrolases

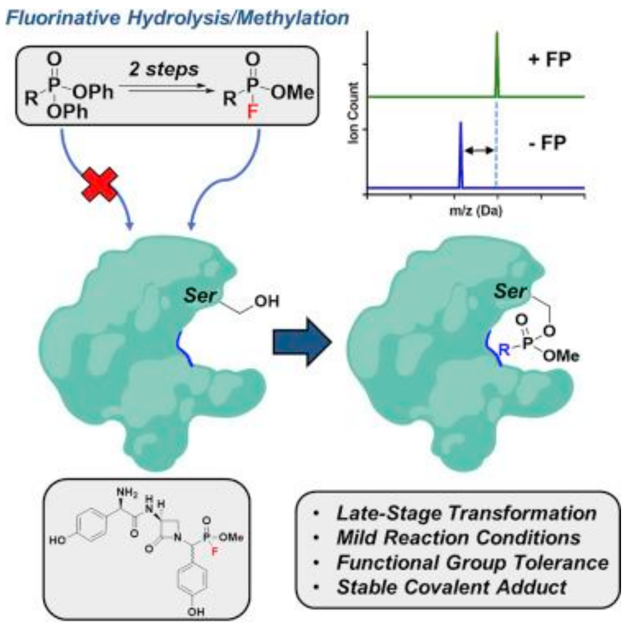




7, FP-biotin

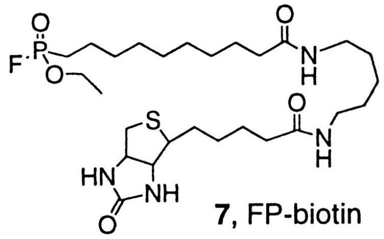
PF probeとしての活用法





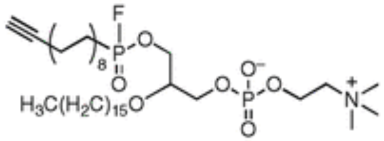
https://www.sciencedirect.com/science/article/pii/S2451945619300753

FP probe for detection of Serine hydrase

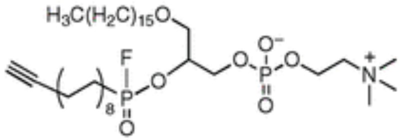


7, FP-biotin

Cravatt, B. F. *et. al.*
Proc. Natl. Acad. Sci. U.S.A.
1999, 96, 14694.

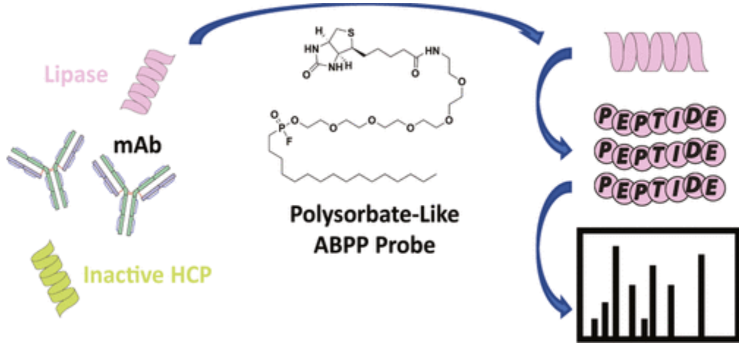


***sn*-1 selective probe, 1**



***sn*-2 selective probe, 2**

Cravatt, B. F. *et. al.*
J. Am. Chem. Soc. **2010**,
132, 10, 3264−3265.



Li, N. *et. al.*
Anal. Chem. **2022**, *94*, 24,
8625−8632.

- ✓ SH selective
- ✓ Broad reactivity across the SH class

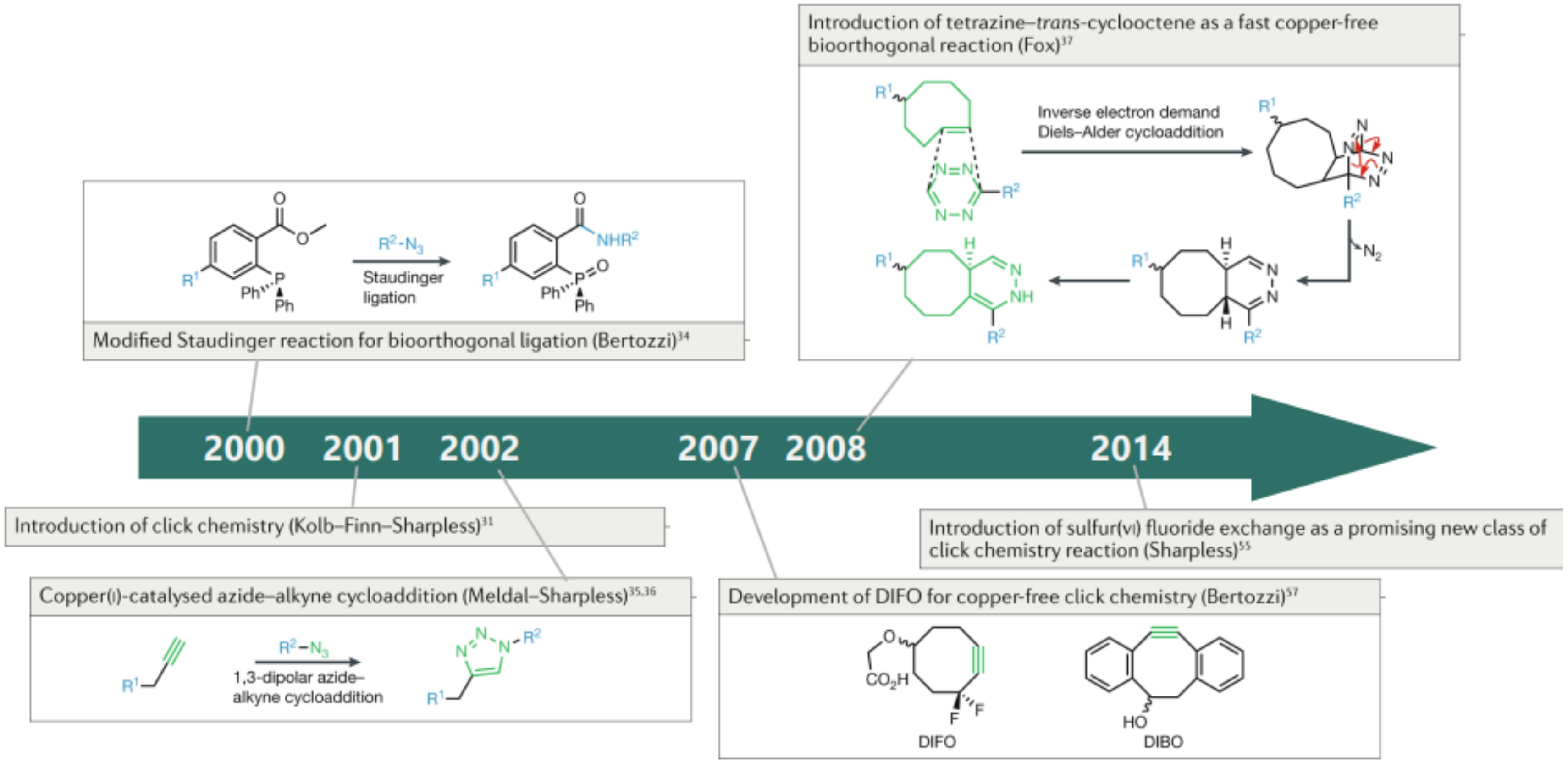
The broad-spectrum serine hydrolase probe

more selective for reacting with phospholipases (over other SHs)

In cell lysate

Serine protases
Phospholipases

SuFEx



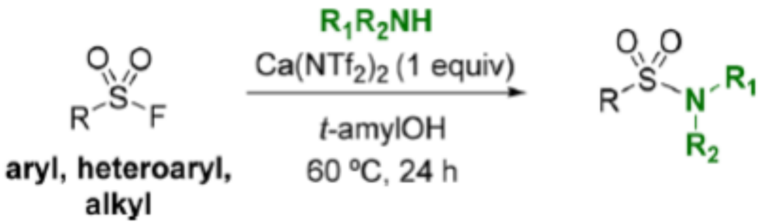
Nat. Rev. Chem. **2018**, *2*, 202.

- ***Robust connection***
- ***High functional group tolerance***
- ***Fast kinetics***
- ***Easy operation***

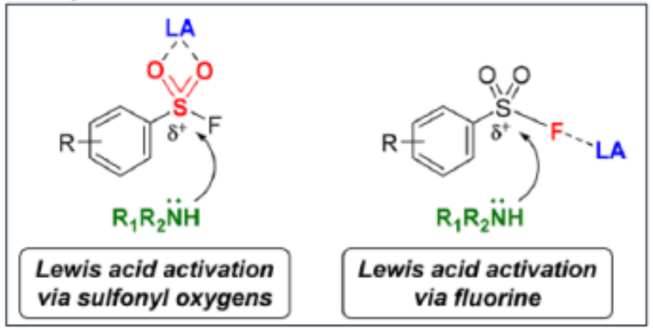
4

SuFEx

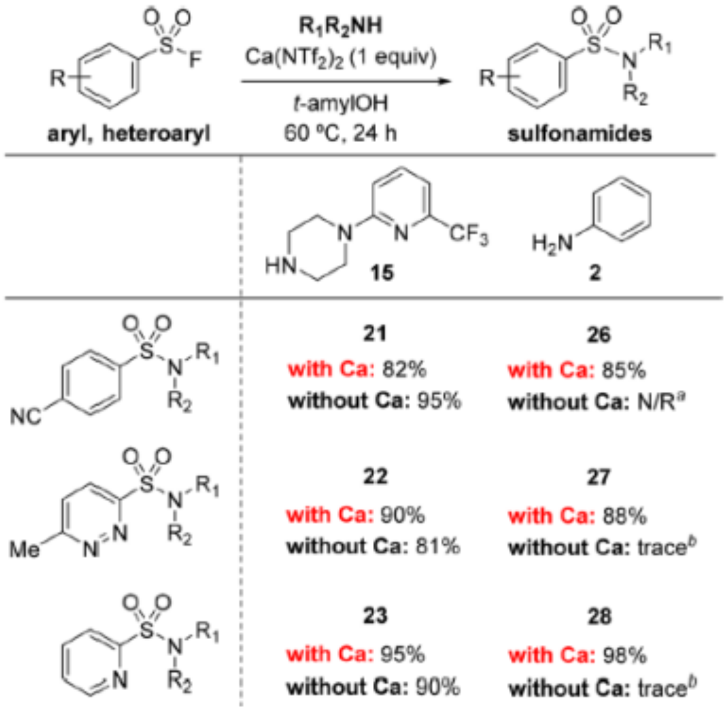
Activation with $Ca(NTf)_2$ (Lewis acid)



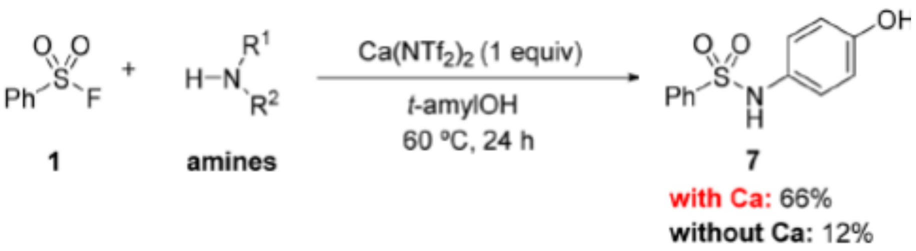
Proposed mode of activation

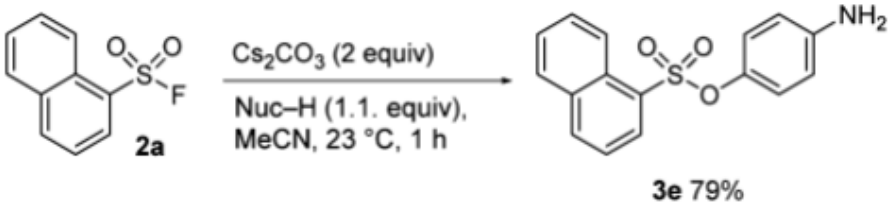


Effect of Ca salt



Selectivity of nucleophile

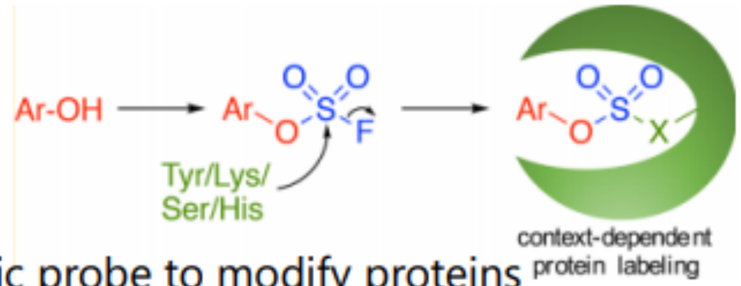




JOC **2017**, *82*, 2294.

Am Ende, C. W.; Ball, N. D. *et al. Org. Lett.* **2018**, *20*, 3943. 8

RSO_2F in Biological Context



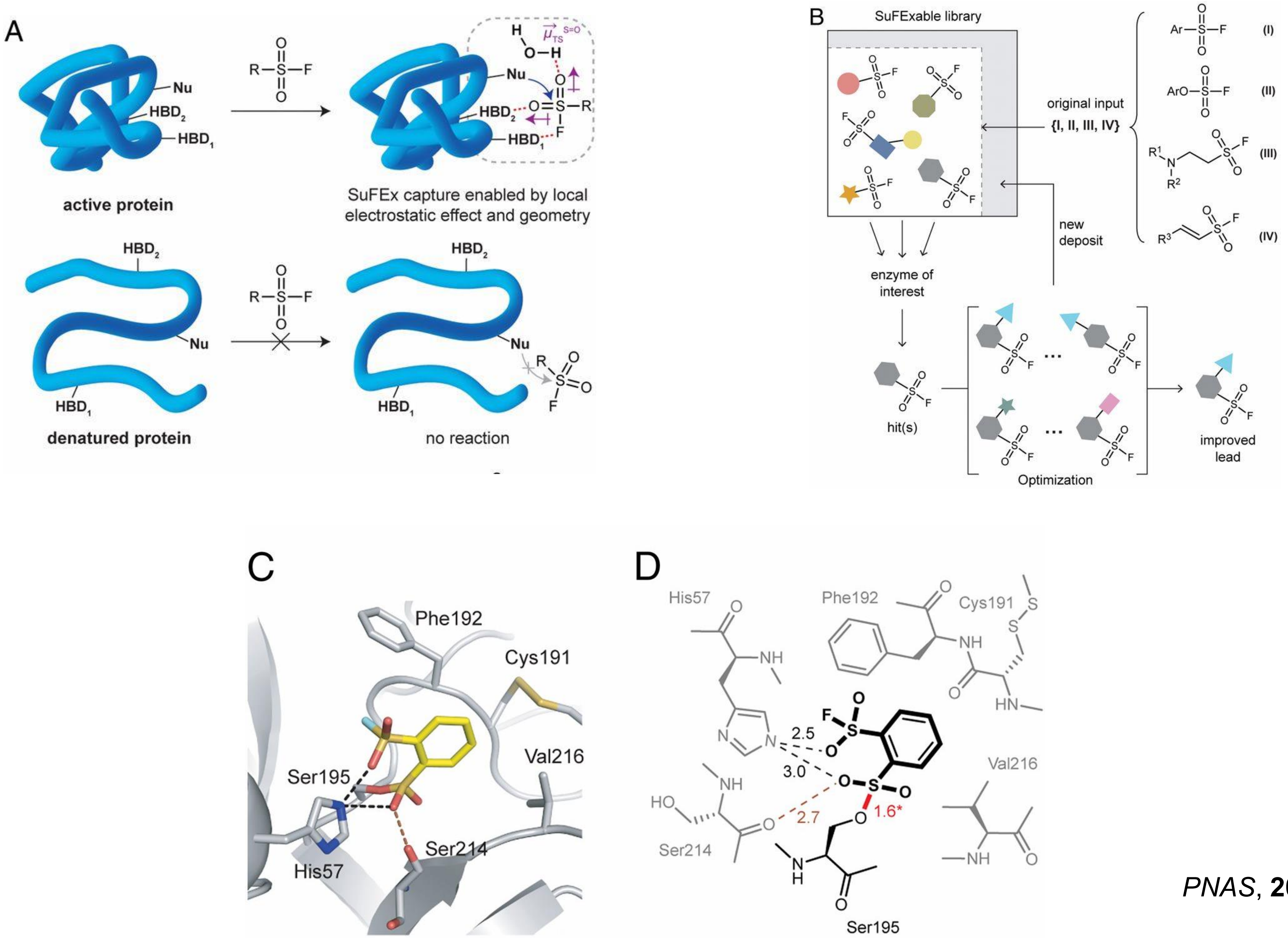
electrophilic probe to modify proteins

H+ mediated switch-on
-> specificity to microenvironment

- Activation of S-F in special environment
- Proximity driven reaction
- Ser, Tyr, Lys, Thr, His, Cys

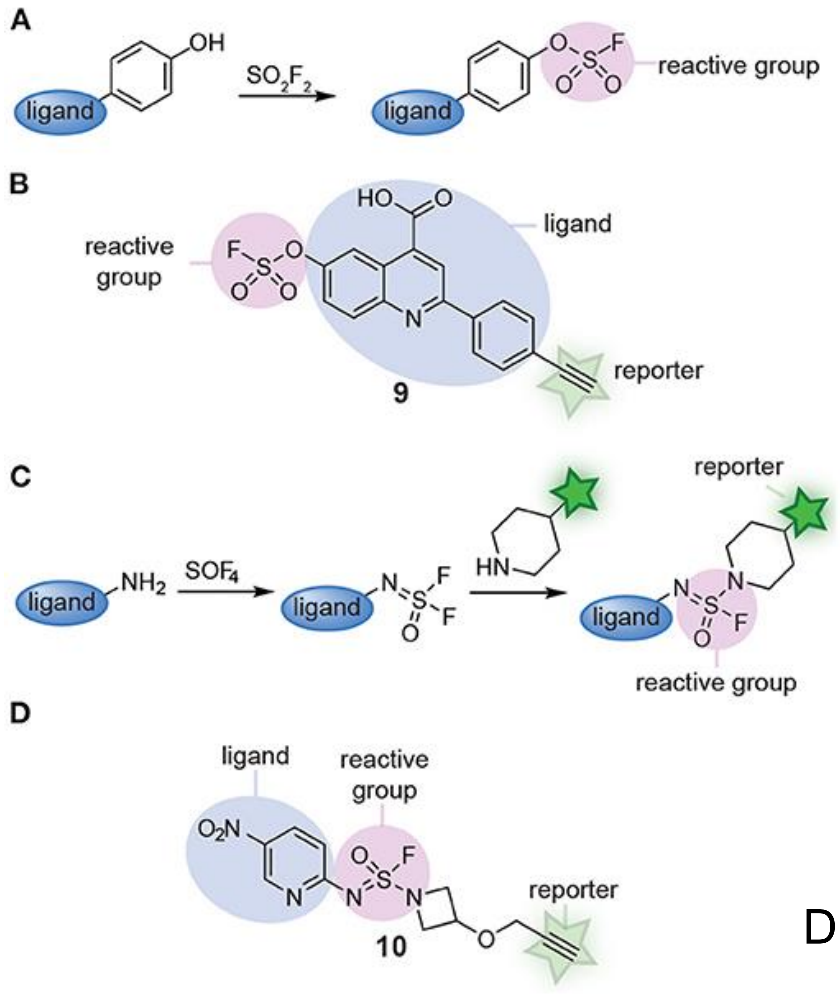
<u>Examples</u>
- Covalent drugs
- Target identification and validation
- Mapping of enzyme binding sites, substrates and protein–protein interactions.
- Late-stage functionalization (LSF) of bioactive molecules

SuFEx for activity-based protein profiling



PNAS, **2019**, *116*, 18809.

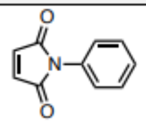
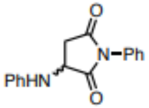
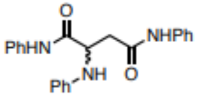
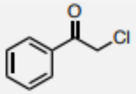
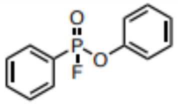
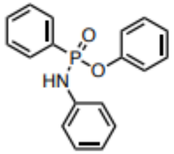
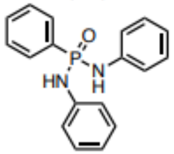
SuFEX



Dual use of SuFEx and PFEx

https://reader.elsevier.com/reader/sd/pii/S2451945620302816?token=F14E2FBC6E423E1AA1B10EF1491C38F1431A101FB2BA2C1CFE2C3085395BDDB771A028B451B020A53A3B3DB9C4E36E37&originRegion=us-east-1&originCreation=20221107124339

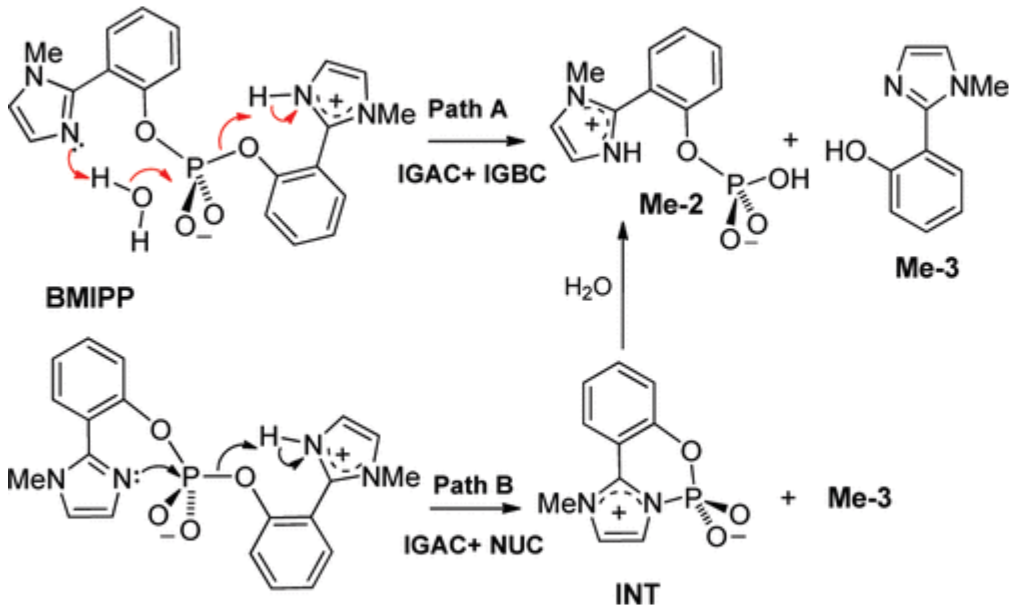
アニリンとrefluxするとPFも反応してしまう

Entry	Electrophile	% remaining SM	Product (% HPLC yield)	Analytical method
7	 (xii) maleimide	0	 (27)  (73)	LC-MS
8	 (xiii) α-chloroketone	0	Unidentified mixture	LC-MS
9	 (xiv) fluorophosphorate	11	 (55)  (34)	LC-MS

*"Refluxing aniline" test was performed by heat the neat mixture of respective electrophiles (1.0 mmol) with 1.3 mL aniline at 184 ºC.

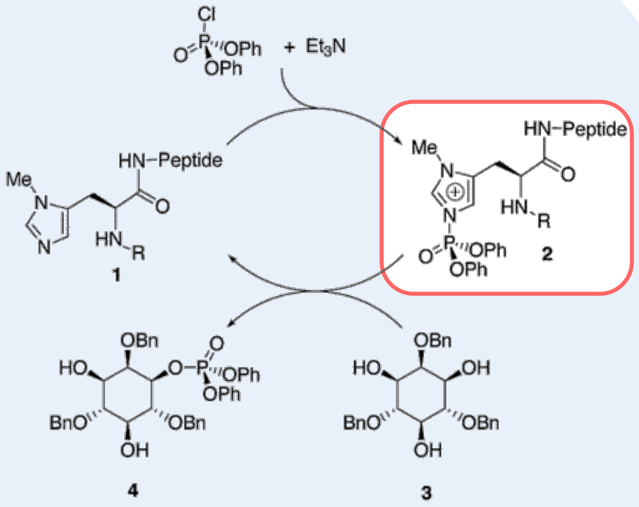
PNAS, **2019**, *116*, 18809.

Imidazole acts as nucleophilic catalyst

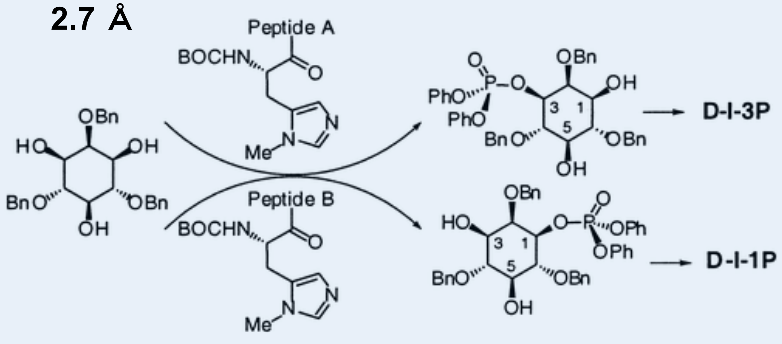


https://pubs.acs.org/doi/10.1021/ja1034733

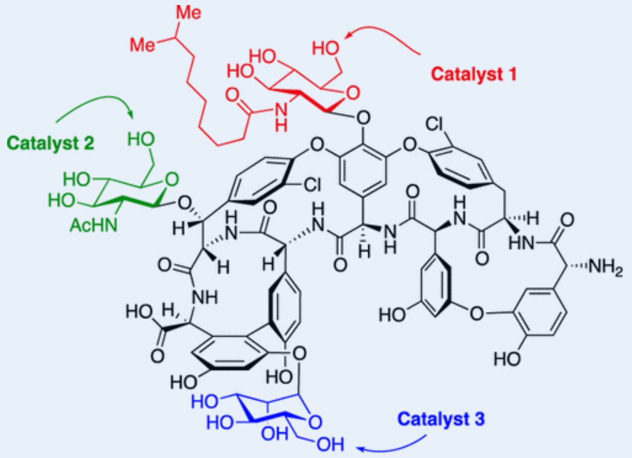
Selective-phosphorylation using imidazole as a nucleophilic catalyst



Miller, S. J. *et. al. J. Am. Chem. Soc.* **2001**, *123*, 41, 10125−10126



Miller, S. J. *et. al. J. Am. Chem. Soc.* **2002**, *124*, 39, 11653−11656



Miller, S. J. *et. al.J. Am. Chem. Soc.* **2013**, *135*, 33, 12414−12421

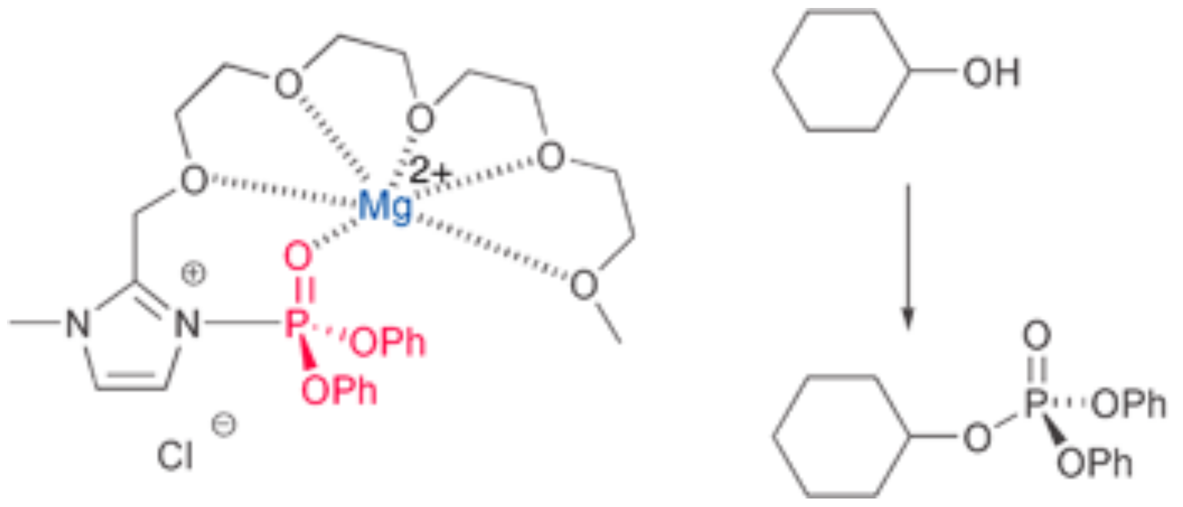
Kinase mimic catalyst for asymmetric phosphorylation of inositol

Site-selective phosphorylation of the enantiotopic 1- and 3-positions of the inositol ring

Site-selective phosphorylation of three distinct hydroxyl groups within the complex glycopeptide

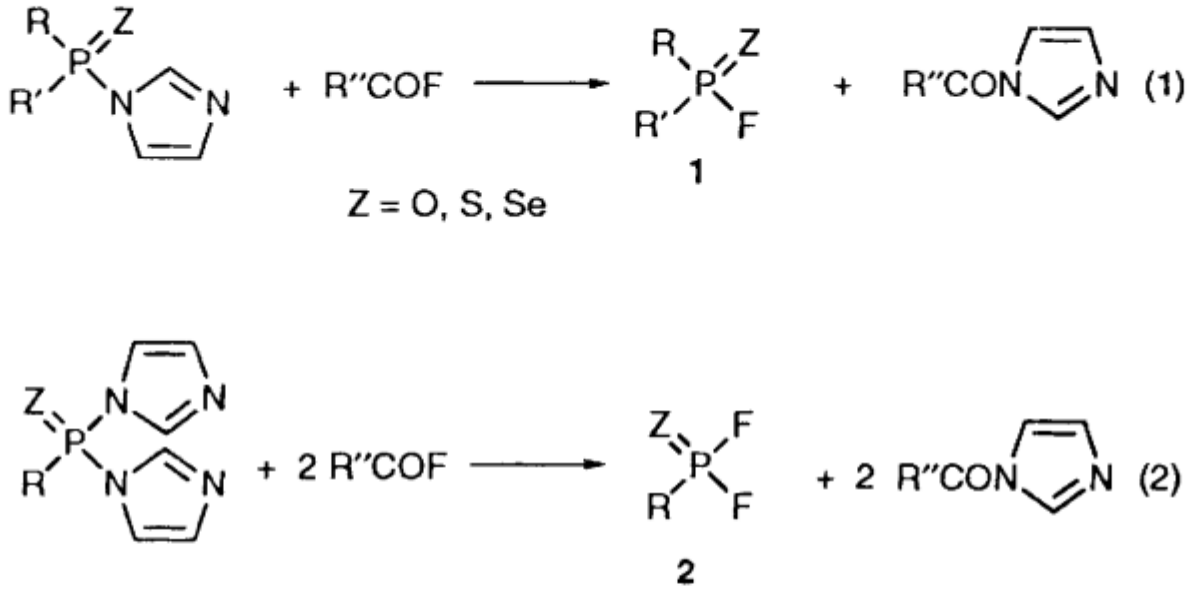
今回の話題

内在性のMgを使ってこういうactivation



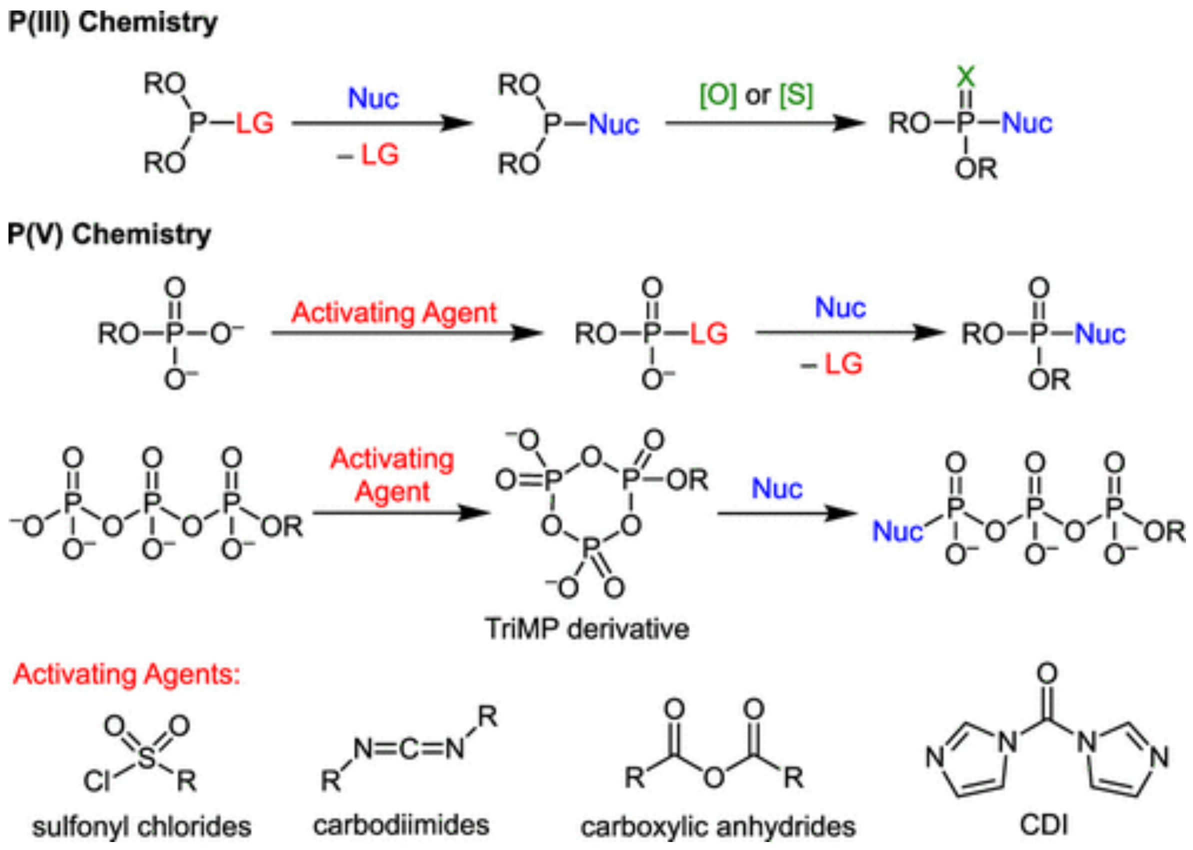
https://pubs.rsc.org/en/content/articlelanding/2005/cc/b506344b

Other synthetic method for P(V)-F



J. Chem. Soc., Perkin Trans. 1, **1994**, 817-820

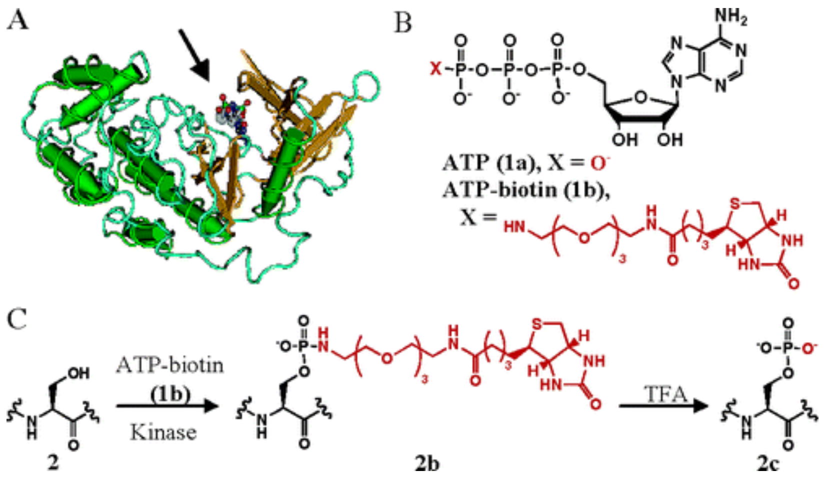
Activating reagent for minimal-protection phosphate



J. Am. Chem. Soc. **2022**, *144*, 17, 7517–7530

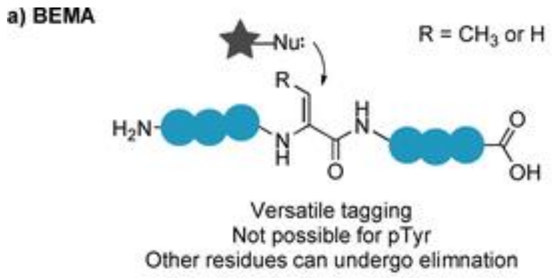
リン酸化体を釣ってくる方法

内在性のキナーゼを使ってbiotinを導入



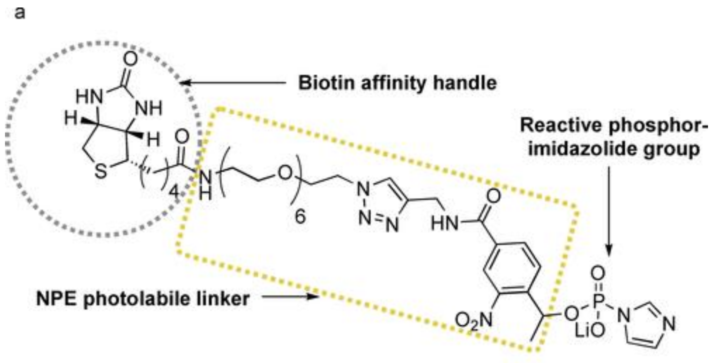
https://pubs.acs.org/doi/10.1021/ja066828o

塩基でデヒドロアラニンにしてチオールあなどの1,4-付加
（phosphotyrosineには使えない）



https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/cbic.202200407

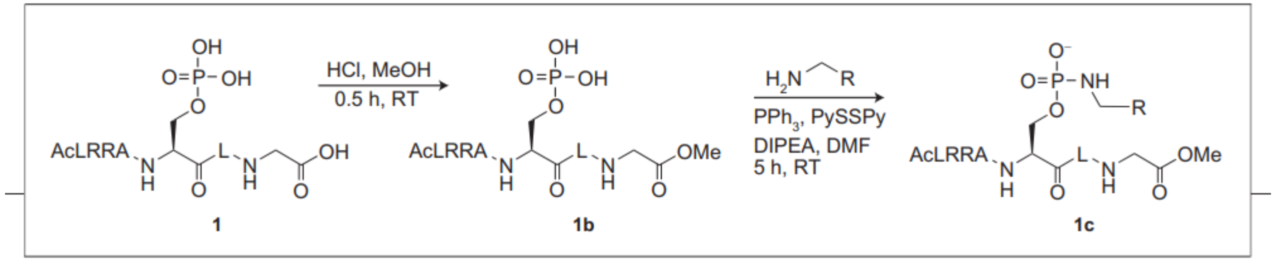
Phosphoimidazole (pyrophosphorylation)



btNPE-imidazolide (1)

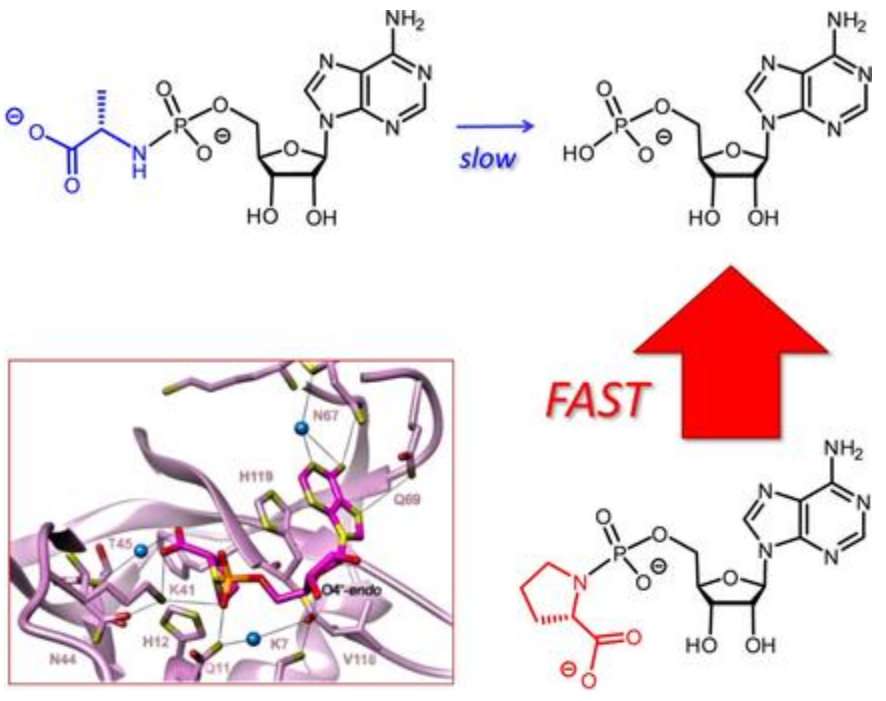
https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/cbic.202200407

樹脂を使ってリン酸基にアミンを縮合する方法

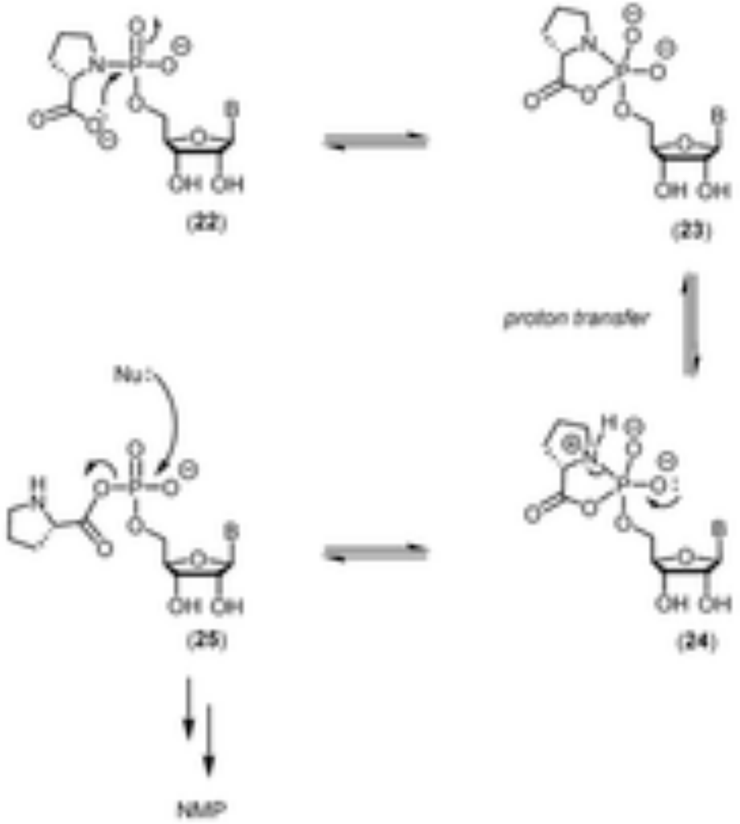


https://pubs.acs.org/doi/pdf/10.1021/cb6003564

P-N化合物の特性



A



レムデシビルなどのプロドラックのphophateのマスキング保護基として使われている

Phosphoryl amidazeで切ってたけど、これにすると酵素非依存で放出される

https://onlinelibrary.wiley.com/doi/10.1002/anie.202008665

Bond dissociation energy

Average Bond Enthalpies

bond	ΔH_{bond} (kJ/mol)
C–H	413
C–C	347
C=C	614
C≡C	839
C–N	305
C=N	613
C≡N	891
C–O	358
C=O	743
C≡O	1072
C–F	485
C–Cl	339
C–Br	276
C–I	238
C–Si	318
C–P	264
C–S	259
C=S	573

bond	ΔH_{bond} (kJ/mol)
N–H	391
N–N	163
N=N	418
N≡N	941
N–O	201
N=O	607
N–F	272
N–Cl	200.
N–Br	243

bond	ΔH_{bond} (kJ/mol)
O–H	467
O–O	146
O=O	495
O–F	185
O–Cl	203
O–Br	156
O–S	364
O=S	522
O–P	335
O=P	544

bond	ΔH_{bond} (kJ/mol)
H–H	432
H–F	565
H–Cl	427
H–Br	363
H–I	295
F–F	154
Cl–Cl	239
Br–Br	193
I–I	149

bond	ΔH_{bond} (kJ/mol)
Si–H	393
Si–Si	340.
Si–O	452
Si–F	565
Si–Cl	381
Si–Br	310.

bond	ΔH_{bond} (kJ/mol)
P–H	322
P–P	201
P–F	490.
P–Cl	326
P–Br	264

bond	ΔH_{bond} (kJ/mol)
S–H	347
S–S	266
S=S	425
S–F	327
S–Cl	253
S–Br	218

https://www.chegg.com/homework-help/questions-and-answers/using-standard-enthalpy-formation-data-show-standard-enthalpy-formation-hf-g-used-determin-q37373914