

Recent advances in the use of phosphoranyl radical

2021/10/28

M1 Tomoyuki Fukuta

Today's Contents

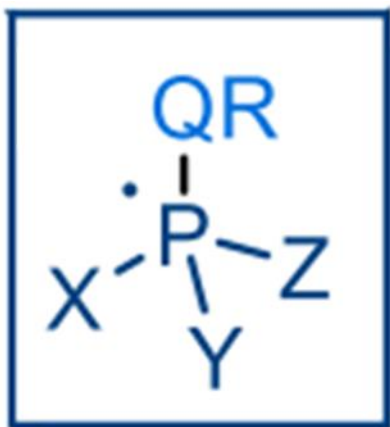
1. Introduction: What is phosphoranyl radical?

2. Application

- *O*-radical trap (C1 synthon)
- unique C-O bond activation
- catalytic α -scission pathway
(hydroamination with sulfonamides)

3. Summary

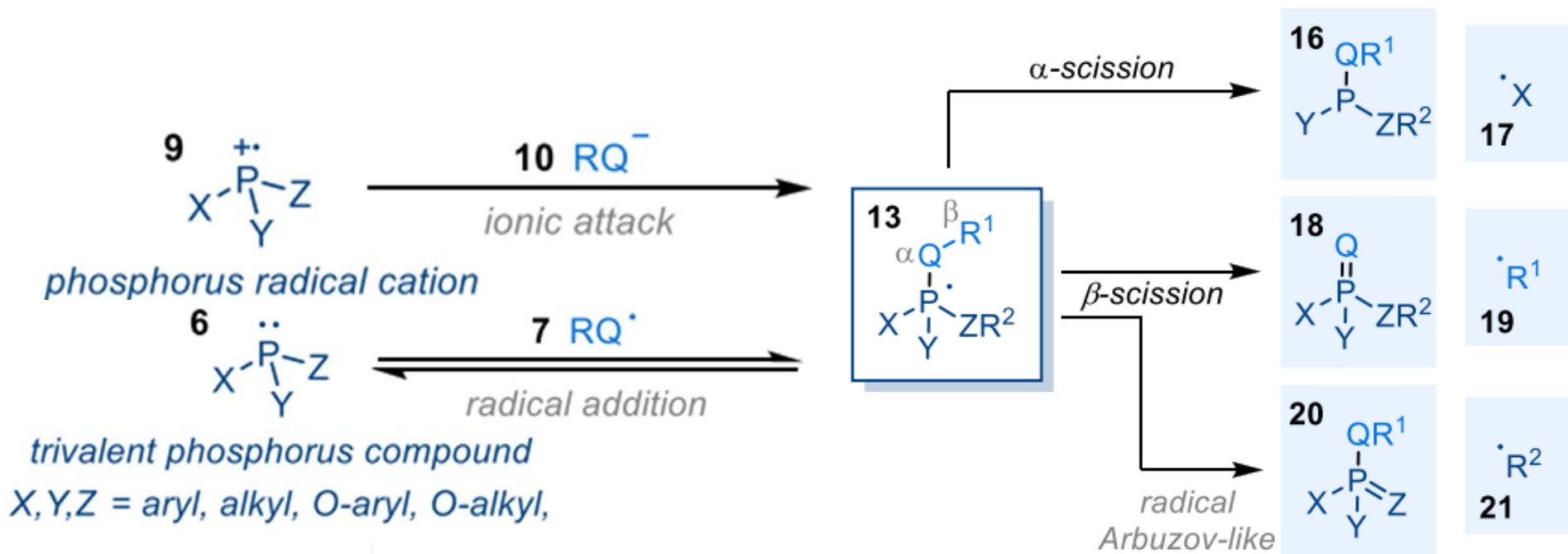
What is phosphoranyl radical?



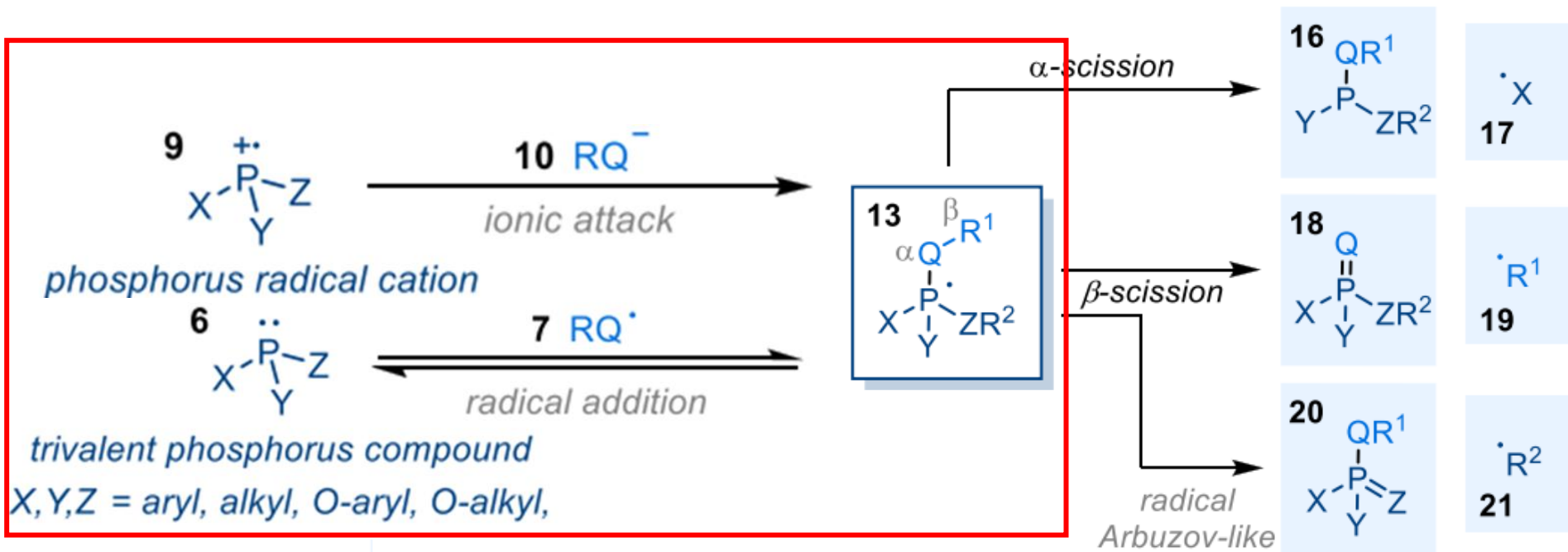
*phosphoranyl
radical*

- ✓ One of the *P*-centered radicals
- ✓ First detection by ESR in 1960.
- ✓ Mediator to generate valuable radicals
- ✓ Advancing field accelerated by photocatalyst

Overview of phosphoranyl Radical Reactivity

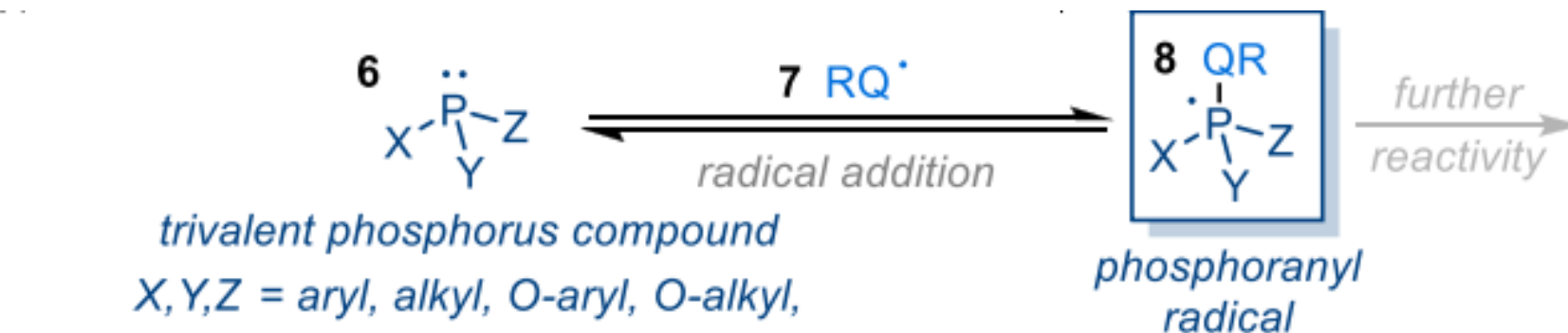


Overview of phosphoranyl Radical Reactivity



Formation of phosphoranyl radical

□ Radical addition



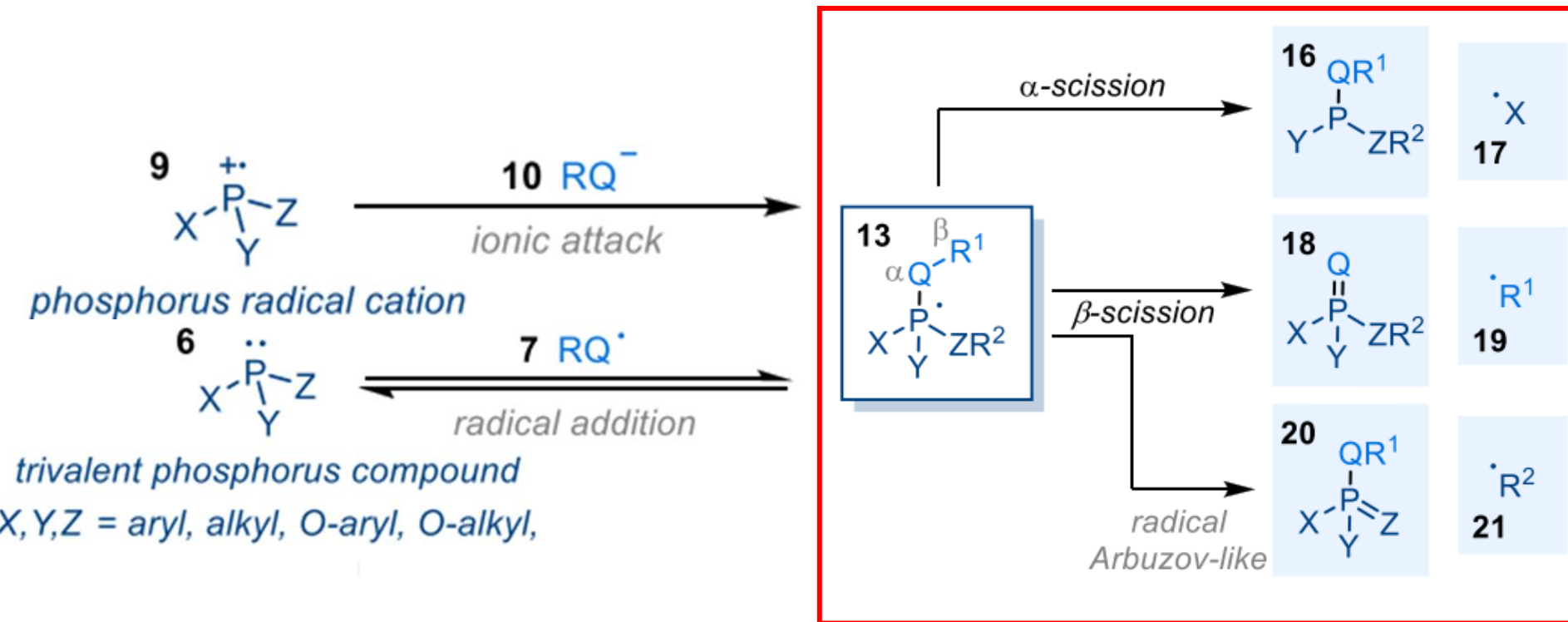
1) irreversible		2) reversible		3) no addition	
$\text{RQ}^\bullet = \text{RO}^\bullet$	TMSO^\bullet	$\text{RQ}^\bullet = \text{Et}^\bullet$	Me^\bullet	Bn^\bullet	$t\text{Bu}^\bullet$
Ph^\bullet	$\text{X}_3\text{P}^\bullet\text{H}$	$\text{Me}_2\text{N}^\bullet$	$\text{F}_3\text{C}^\bullet$	$i\text{Pr}^\bullet$	
BzO^\bullet	RS^\bullet	$\text{F}_5\text{C}_2^\bullet$			

✓ Mainly determined by **stability of radical**



Selective reaction (P-O bond formation)

Overview of phosphoranyl Radical Reactivity



- ✓ Scission occurs in the weakest bond in phosphoranyl radical.
- ✓ Strong P=O bond formation can be a driving force for β -scission.

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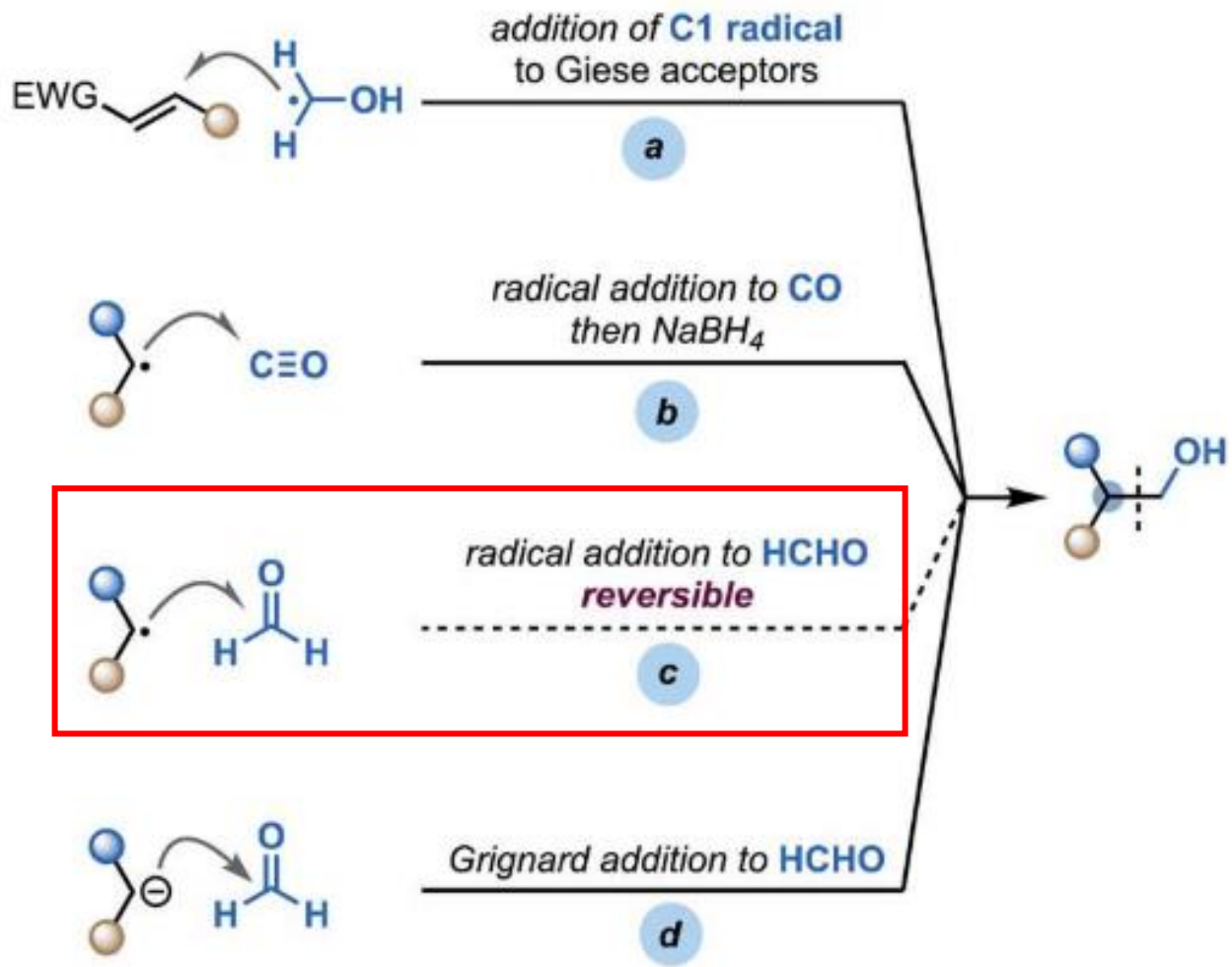
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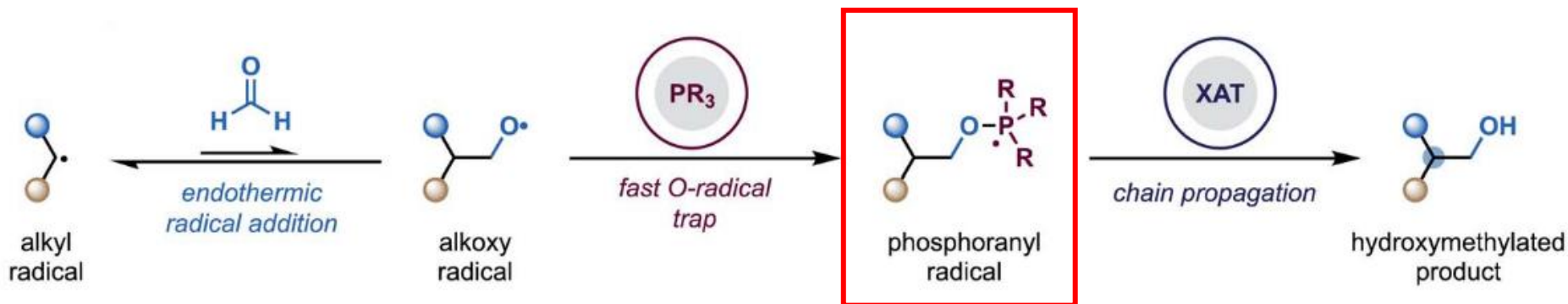
3. Summary

C1 synthon

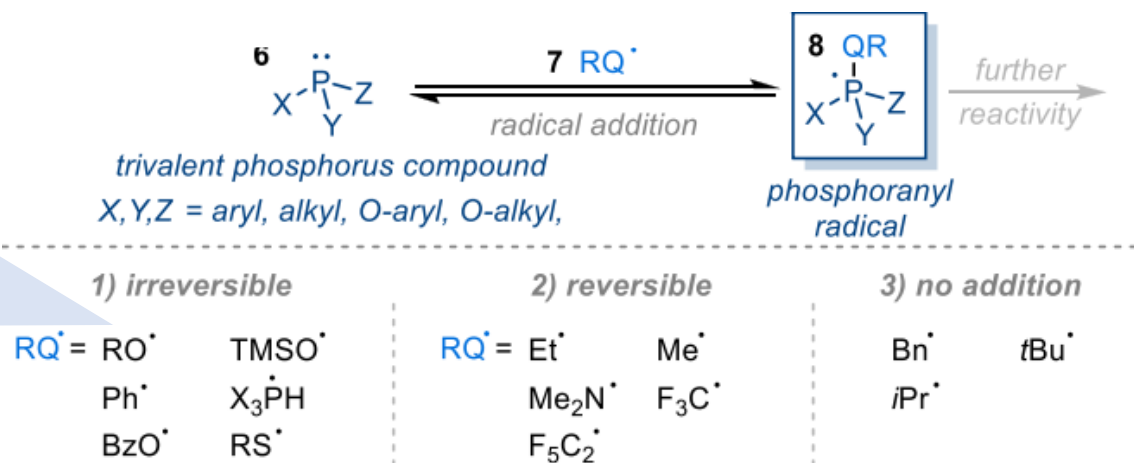
□ Conventional approaches for hydromethylation



Application to C1 synton

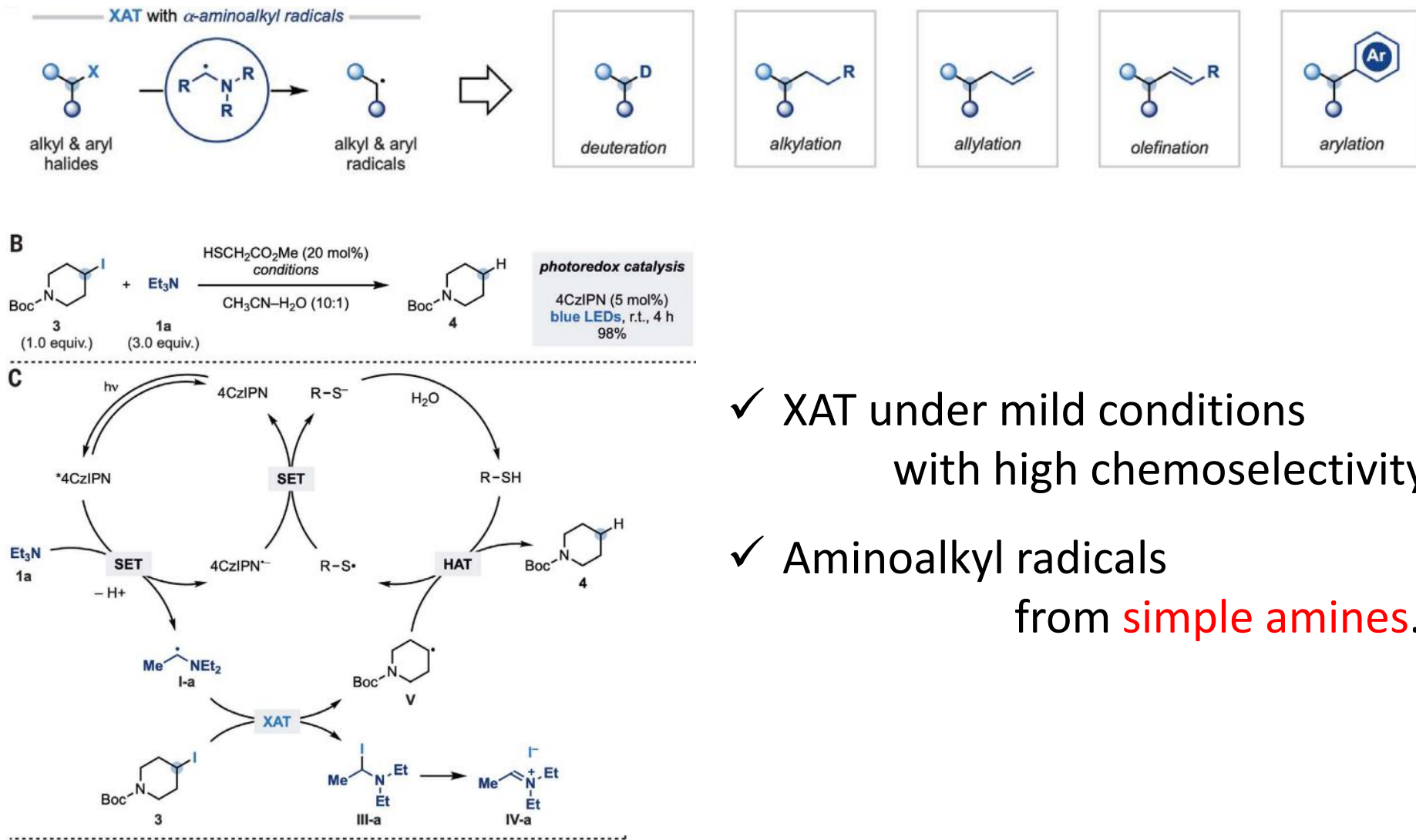


high reactivity
to O-centered
radical



Halogen-Atom Transfer using aminoalkyl radical

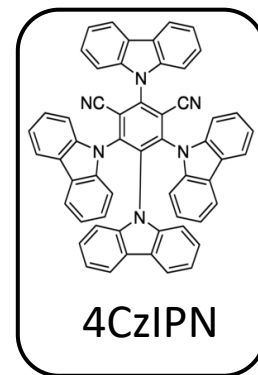
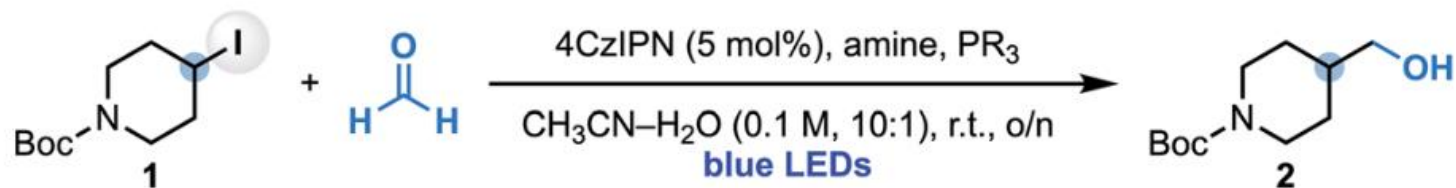
Previous report



- ✓ XAT under mild conditions with high chemoselectivity
- ✓ Aminoalkyl radicals from **simple amines**.

Optimization

B) Reaction optimization

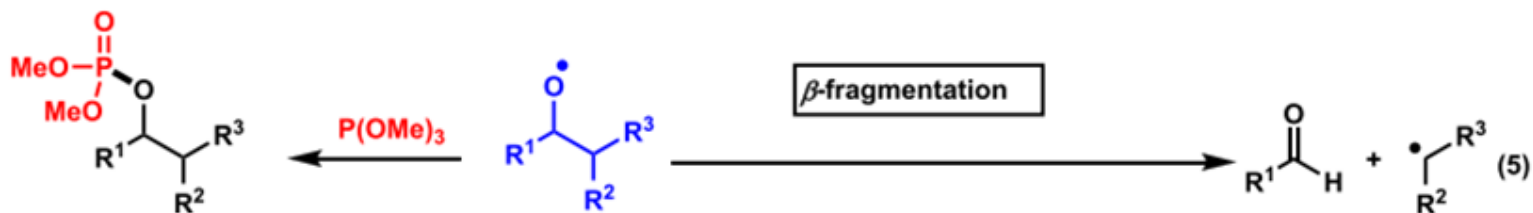
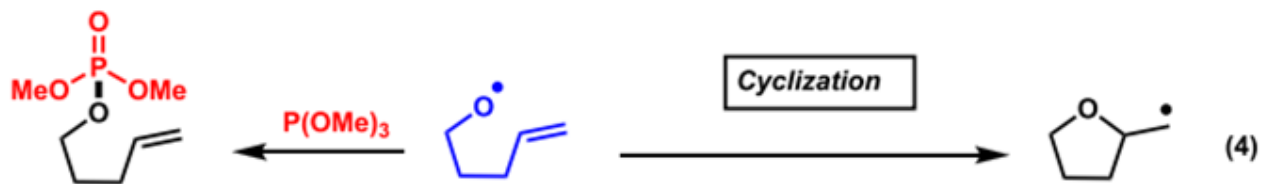
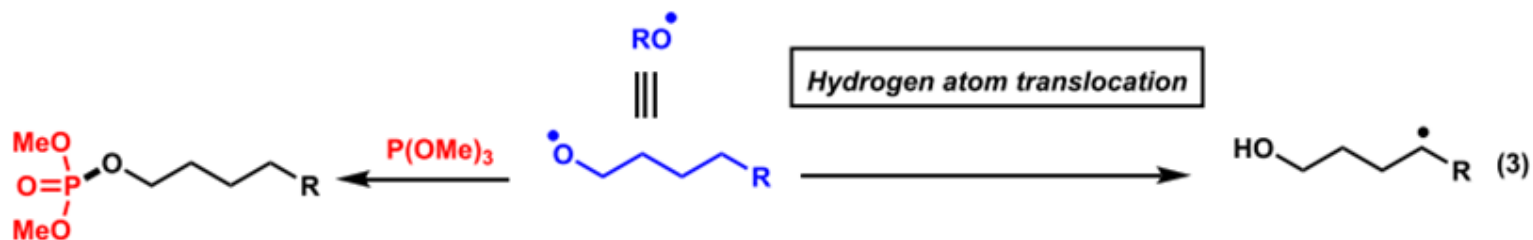


entry	HCHO source	amine	PR ₃	yield (%)
1	HCHO _n (4.0 equiv.)	Et ₃ N (2.0 equiv.)	–	27
2	HCHO _n (4.0 equiv.)	<i>i</i> -Pr ₂ NEt (2.0 equiv.)	–	35
3	HCHO _n (4.0 equiv.)	TMP (2.0 equiv.)	–	–
4	HCHO _n (4.0 equiv.)	Ph ₃ N (2.0 equiv.)	–	–
5	HCHO _n (4.0 equiv.)	<i>i</i> -Pr ₂ NEt (2.0 equiv.)	PPh ₃ (2.0 equiv.)	60
6	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (2.0 equiv.)	PPh ₃ (2.0 equiv.)	61
7	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	PPh ₃ (3.0 equiv.)	86
8	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	P(<i>p</i> -F-C ₆ H ₄) ₃ (3.0 equiv.)	86
9	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	P(<i>p</i> -CF ₃ -C ₆ H ₄) ₃ (3.0 equiv.)	76
10	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	P(<i>p</i> -OMe-C ₆ H ₄) ₃ (3.0 equiv.)	70
11	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	PCy ₃ (3.0 equiv.)	65
12	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	P(OEt ₃) (3.0 equiv.)	40
13	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	BPh ₃ (3.0 equiv.)	–
14	HCHO _{aq} (10.0 equiv.)	<i>i</i> -Pr ₂ NEt (3.0 equiv.)	P(OPh) ₃ (3.0 equiv.)	74

*E_{red} = -1.04 V vs SC

Leonori, D. *et al. Chem. Sci.*, 2021, 12, 10448.

Trapping transient O-radical

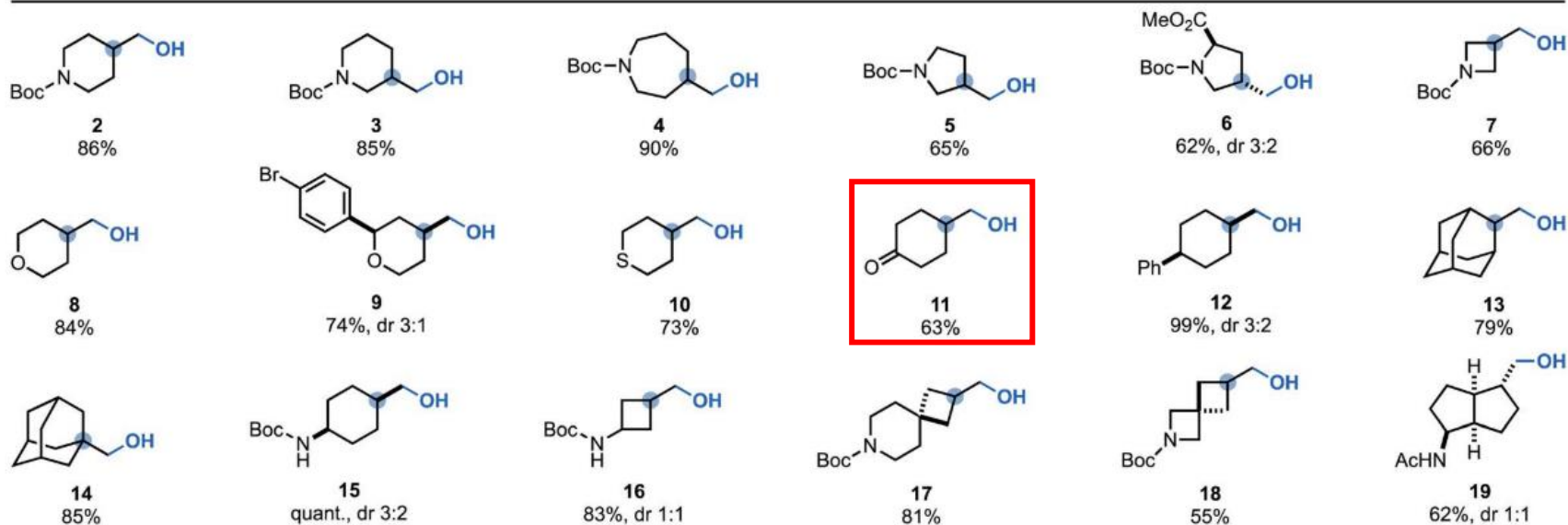
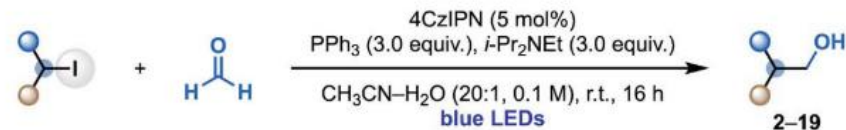


Lakhdar, S. *et al. Org. Lett.* **2020**, *22*, 4404–4407.

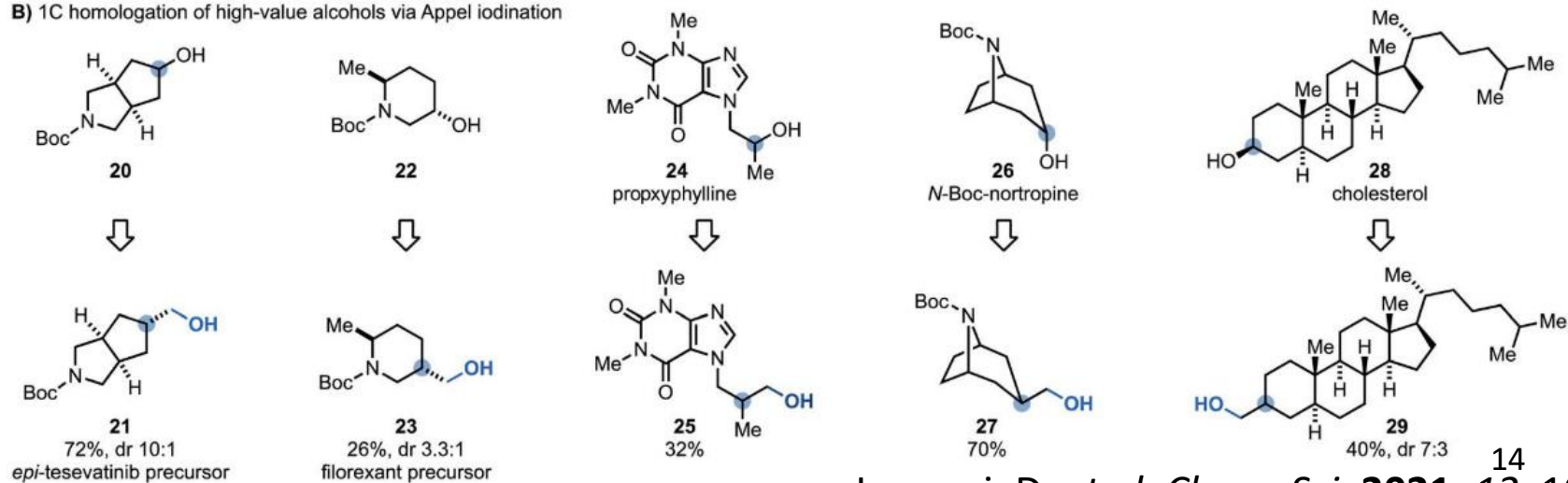
- ✓ Trapping is diffusion-controlled rate
- ✓ O-selective trap (Addition of C-radical is reversible.)

Substrate scope

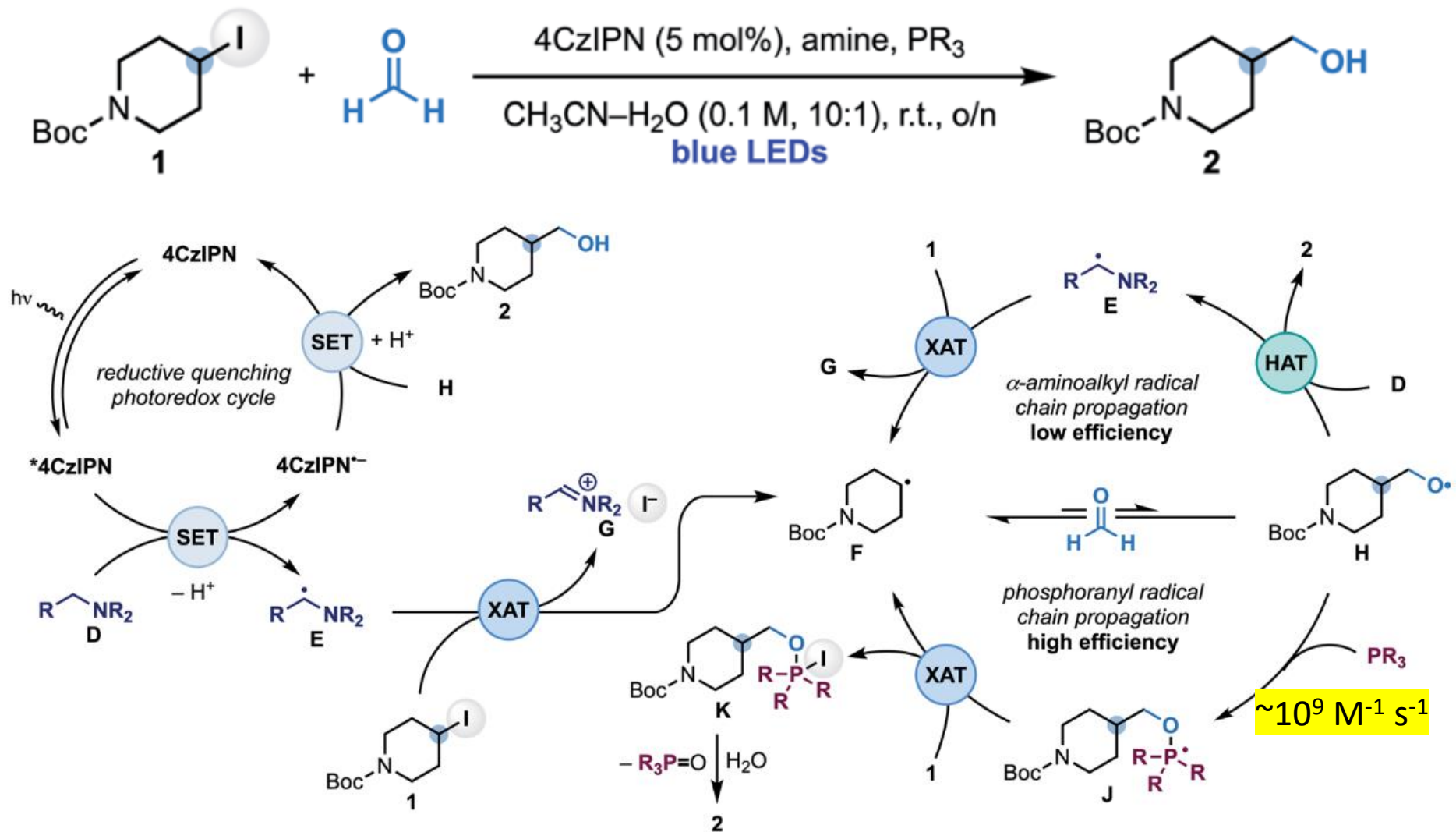
A) Alkyl iodide scope



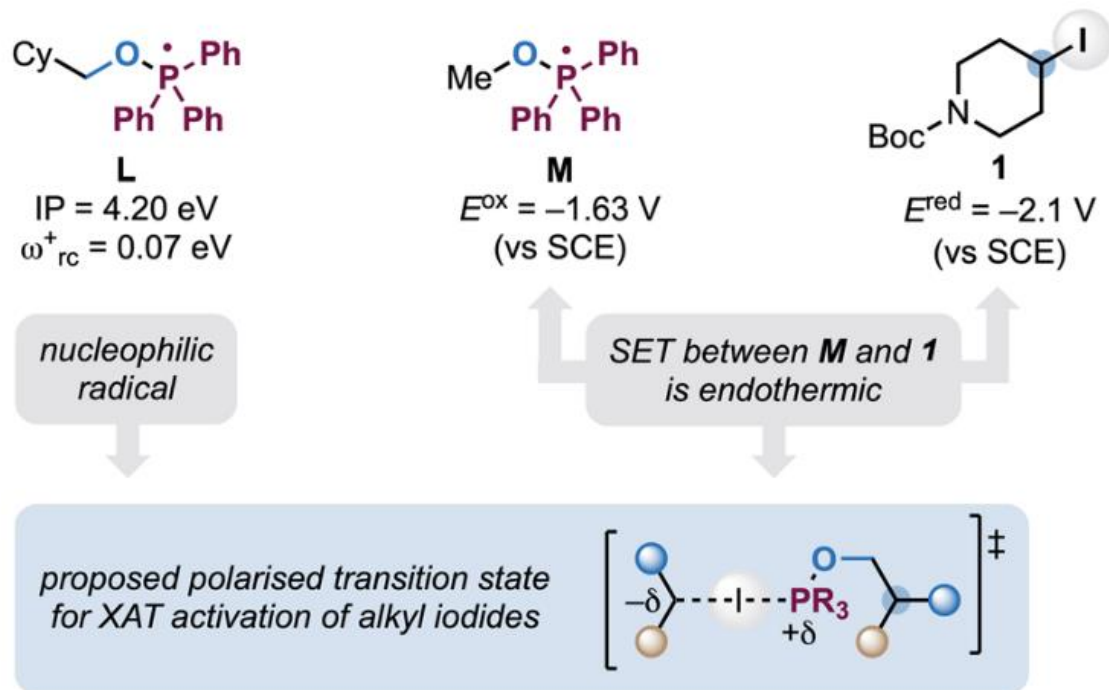
B) 1C homologation of high-value alcohols via Appel iodination



Proposed mechanism

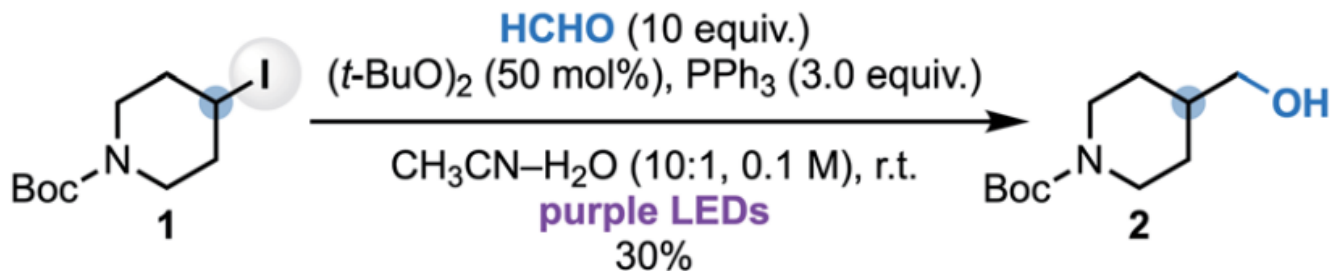


XAT by phosphoranyl radical

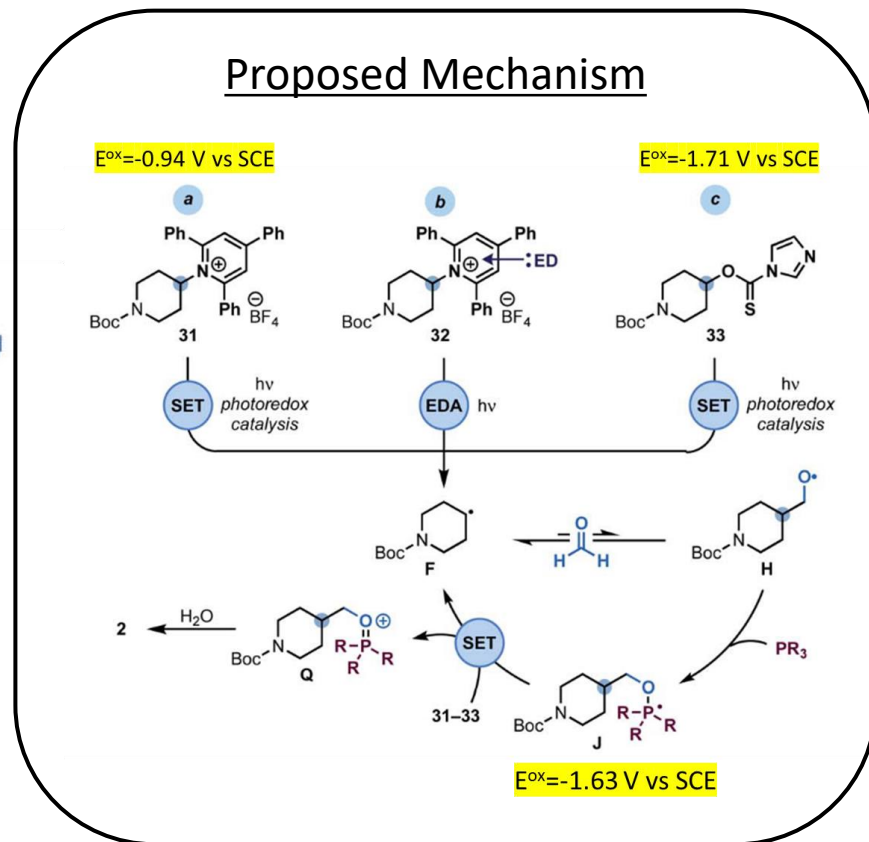
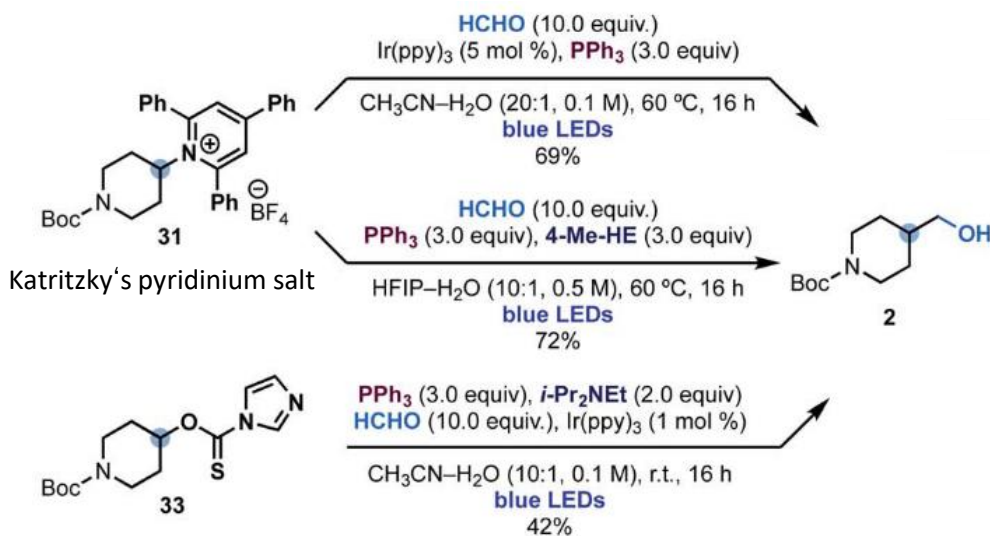


Supporting evidence of XAT by phosphoranyl radical

E) Reactivity under “reductant-free” conditions

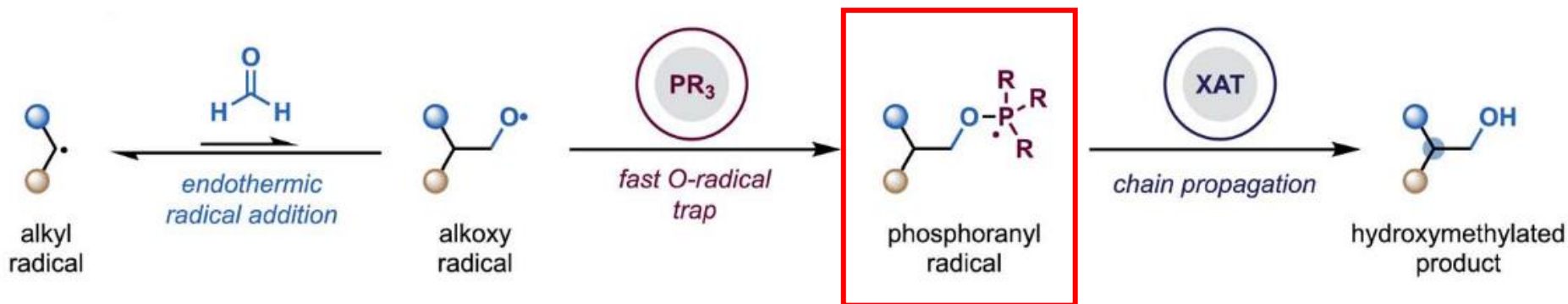


SET by phosphoranyl radical



- ✓ Application to other alkyl radical precursors
- ✓ Sustain a chain propagation by phosphoranyl radical

Short summary



- ✓ New approach for C1 synthon (hydromethylation)
- ✓ Overcome the unfavored addition **by trapping O radical with PPh_3**
- ✓ New reactivity of phosphoranyl radical ; XAT, SET

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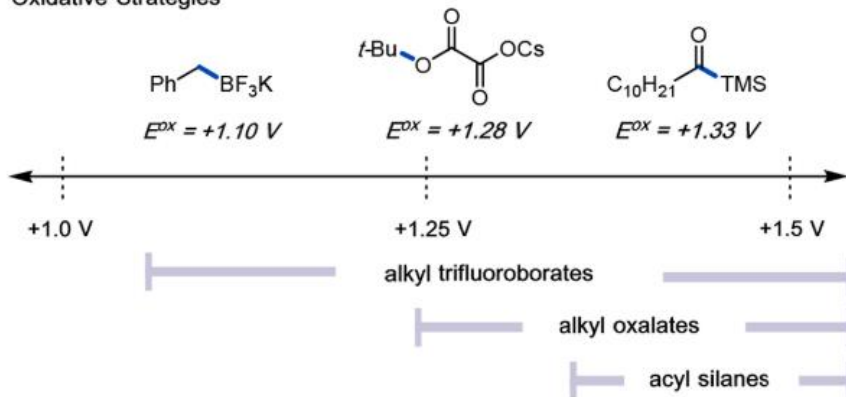
3. Summary

Deoxygenation by Photocatalyst

A. Voltage-gated SET activation strategies for functionalization of C-O bonds



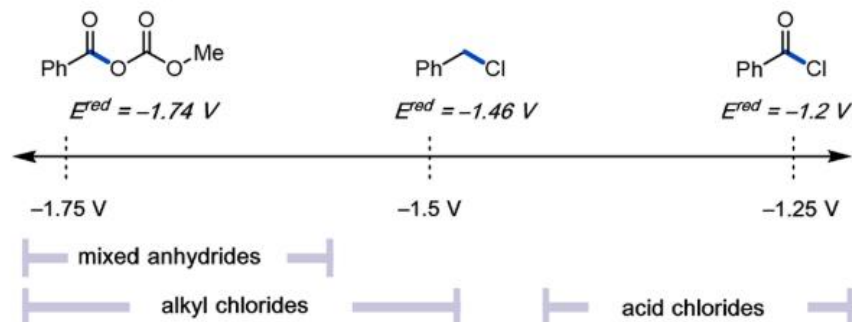
Oxidative Strategies



$$[\text{Ir}(\text{dFCF}_3\text{ppy})_2\text{dtbbpy}]^+ (\text{III})^*/(\text{II}) = +1.21 \text{ V}$$

$$\text{Acr}^+-\text{Mes} (P^*)/(P^{*-}) = +2.06 \text{ V}$$

Reductive Strategies



$$[\text{fac-Ir}(\text{ppy})_3] (\text{III})^*/(\text{IV}) = -1.73 \text{ V}$$

$$[\text{Ru}(\text{bpy})_3]^+ (\text{II})/(\text{I}) = -1.33 \text{ V}$$

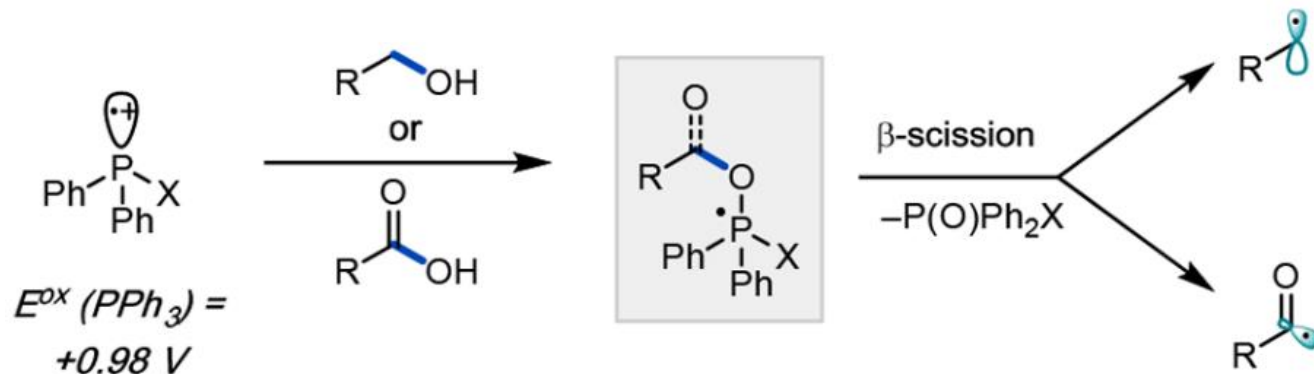
- × Activation methods depend on the substrate
- × **Multistep** conversion to activate C-O bonds
- × Substrate limitation



Single strategy applicable to various substrate is required.

Deoxygenation via phosphoranyl radical

This Work – phosphine radical mediator (X = Ph or OEt)

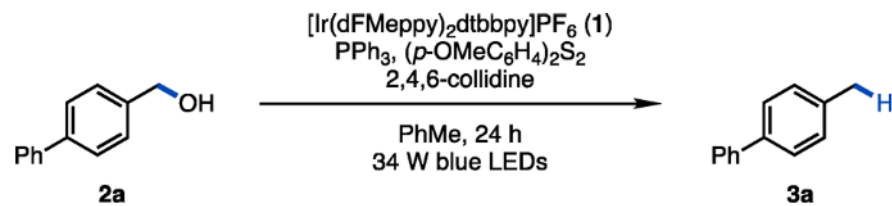


- access to valuable phosphoranyl radical under mild conditions
- activation of C–O bonds independent of substrate redox potentials

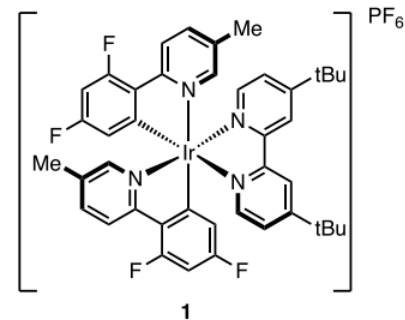
- ✓ Unique C-O bond activation using phosphine & Photoredox cat.
- ✓ **Single** strategy to activate various alcohols and carboxylic acids

Deoxygenation via phosphoranyl radical

Table 1. Reaction Evaluation of Benzylic Alcohols



entry	deviation from standard conditions ^a	% yield ^b
1	none	>99%
2	no PPh_3	0%
3	no light	0%
4	no $[\text{Ir}]$ 1	0%
5	no $(p\text{-OMeC}_6\text{H}_4)_2\text{S}_2$	4%
6	ACN (0.1M), no $(p\text{-OMeC}_6\text{H}_4)_2\text{S}_2$	80%
7	2,6-lutidine (1.0 equiv)	79%
8	no base	32%
9	Ph_2POEt (1.2 equiv)	91%
10	TRIP-SH (20 mol %)	59%
11	TRIP ₂ S ₂ (10 mol %)	93%
12	$[\text{Ir}(\text{dFCF}_3\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ (2 mol %)	75%

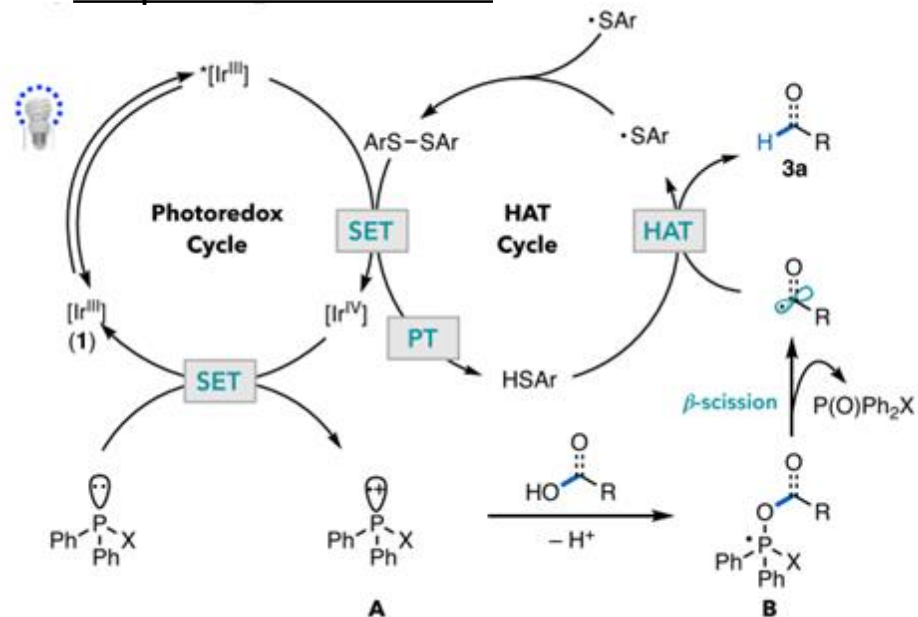


$E_{\text{red}} = 0.97$ vs SCE

cf. PPh_3

$E_{1/2} = 0.98$ V vs SCE

Proposed mechanism



Substrate scope ①

Table 2. Benzylic Alcohol Scope^a

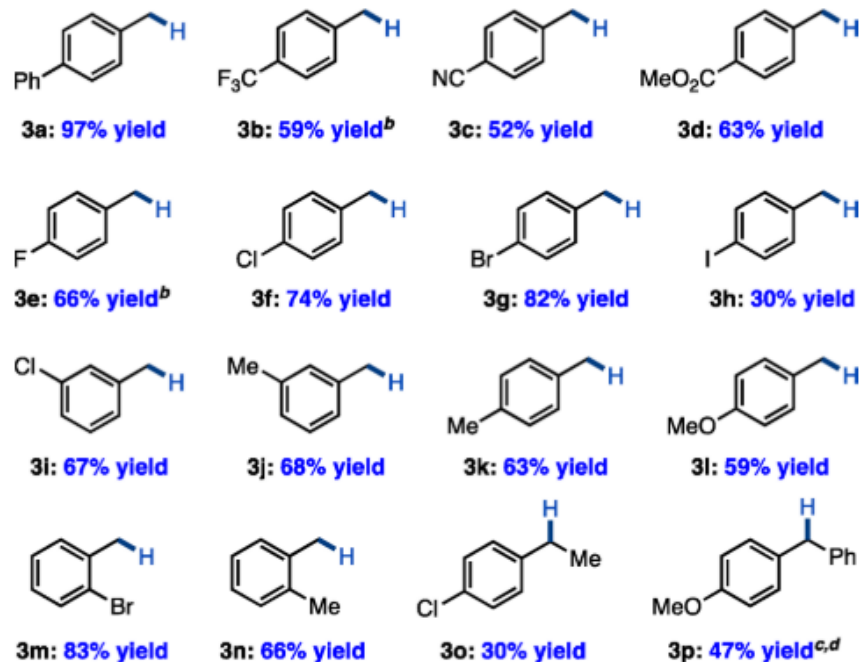
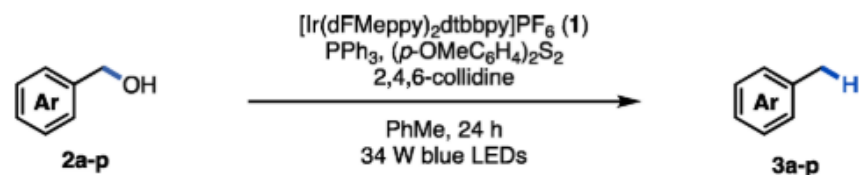
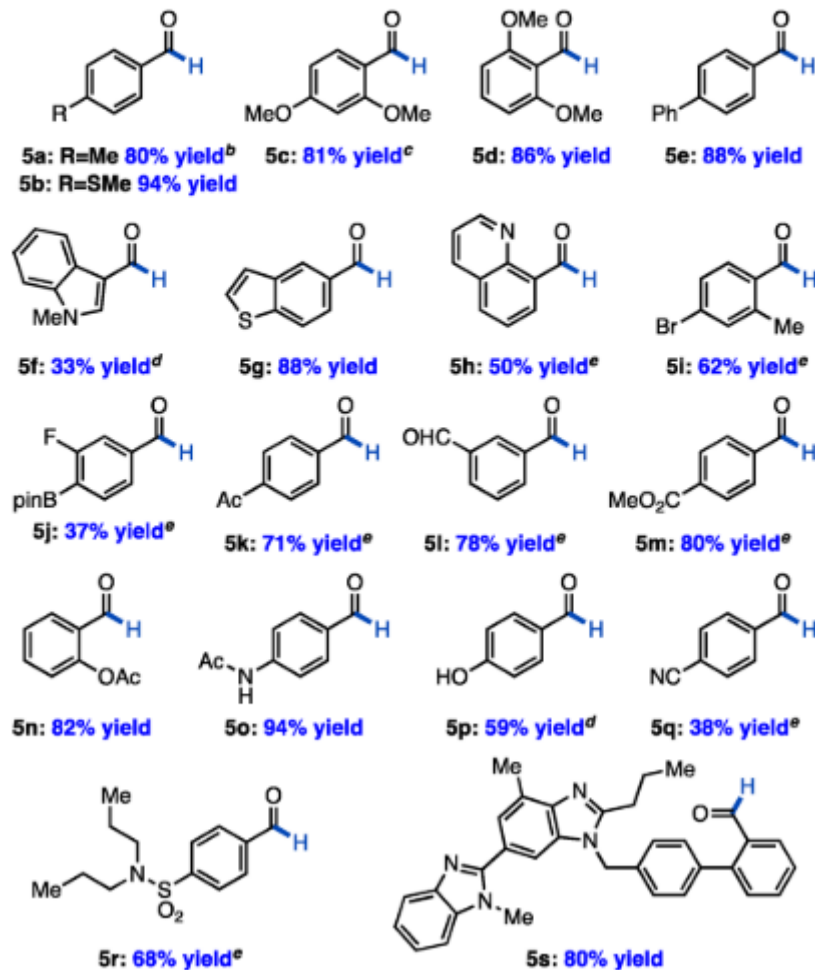
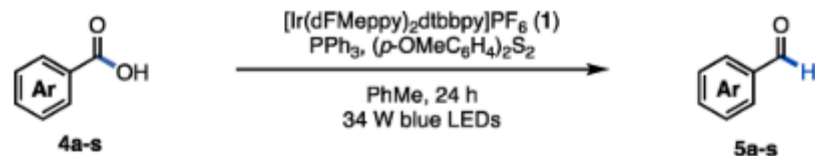
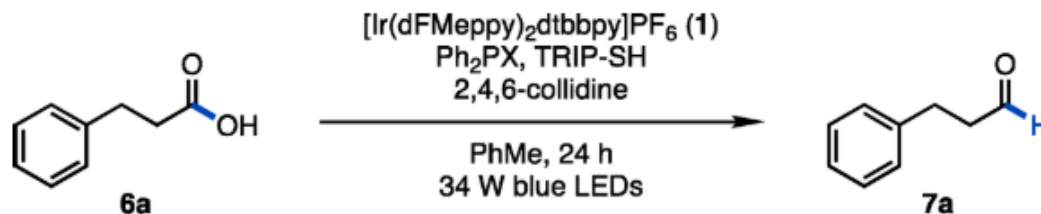


Table 3. Aromatic Acid Scope^a



Deoxygenation of aliphatic carboxylic acid

Table 4. Aliphatic Acid Optimization



entry	Ph_2PX , [M] ^a	% yield ^b
1	PPh_3 , 0.1M	4%
2	Ph_2POEt , 0.1M	43%
3	Ph_2POEt , 0.02M	60%
4	Ph_2POEt , 0.0133M	68%
5	PPh_3 , 0.0133M	8%

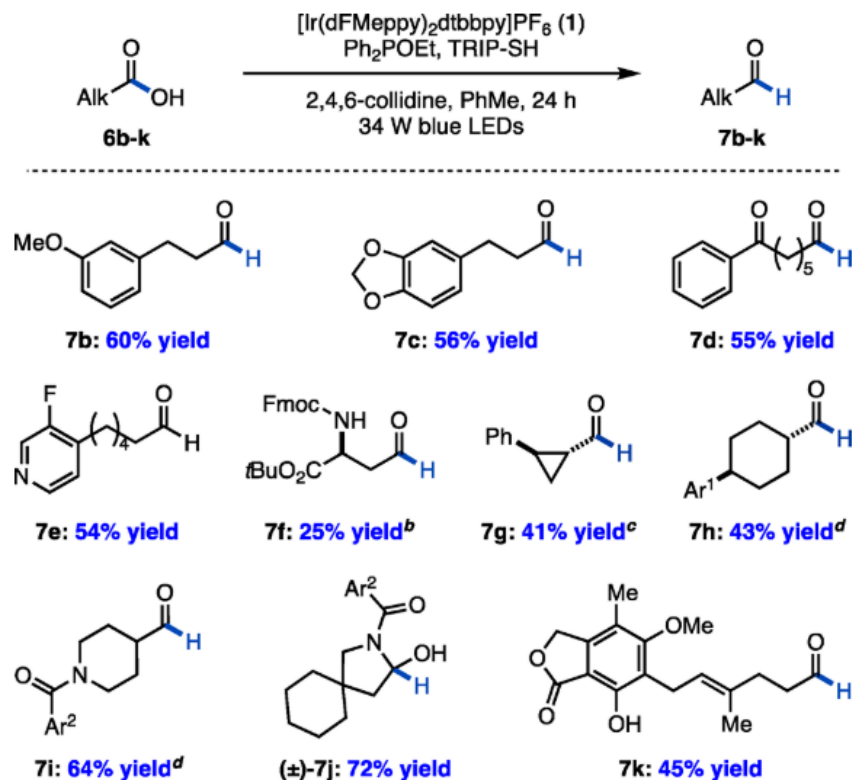
Z_3P	E^{OX} vs Ag/Ag^+
PPh_3	1.19
$\text{PPh}_2(\text{OMe})$	1.21
$\text{PPh}(\text{OMe})_2$	1.49
$\text{P}(\text{OMe})_3$	1.87

- ✓ Tune Ph_2PX to avoid over-oxidation
- ✓ Dilute conditions help β -scission bfr oxi.

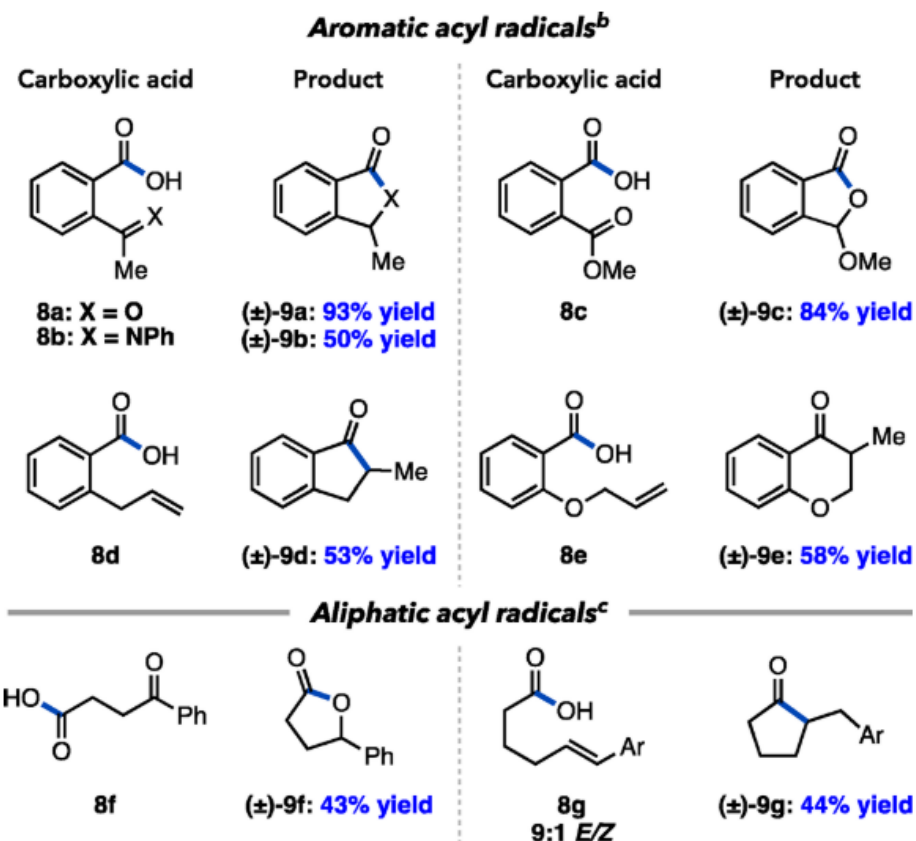
J. Phys. Org. Chem. **2013**, 26, 1090–1097

Substrate scope ②

Table 5. Aliphatic Acid Scope^a



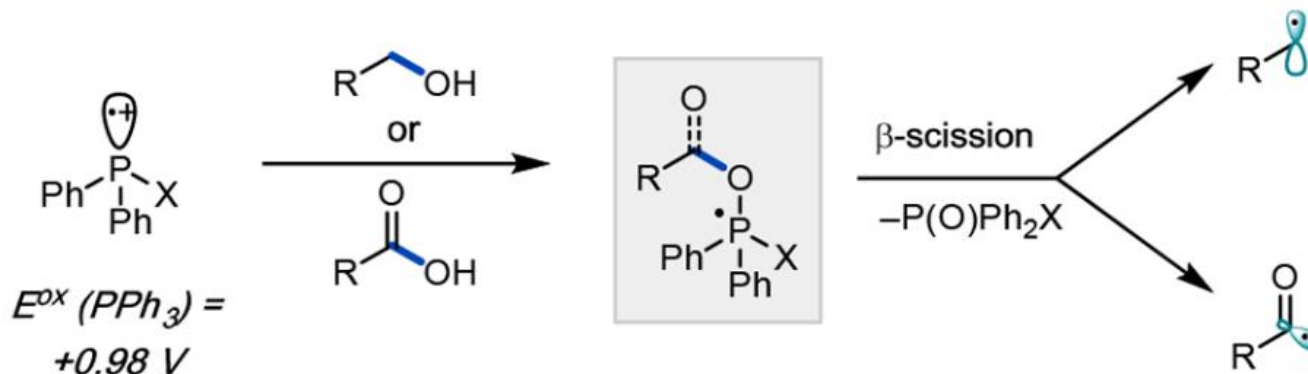
Scheme 1. Intramolecular Cyclizations^a



✓ intramolecular cyclization (Aromatic & Aliphatic)

Short summary

This Work – phosphine radical mediator (X = Ph or OEt)



- access to valuable phosphoranyl radical under mild conditions
- activation of C–O bonds independent of substrate redox potentials

- ✓ Unique C-O bond activation approach
- ✓ Access the corresponding radical from **alcohol** and **carboxylic acid**
(Aromatic & Aliphatic)
- ✓ Tunable mediator ($\text{PPh}_3 \rightarrow \text{PPh}_2\text{OEt}$)

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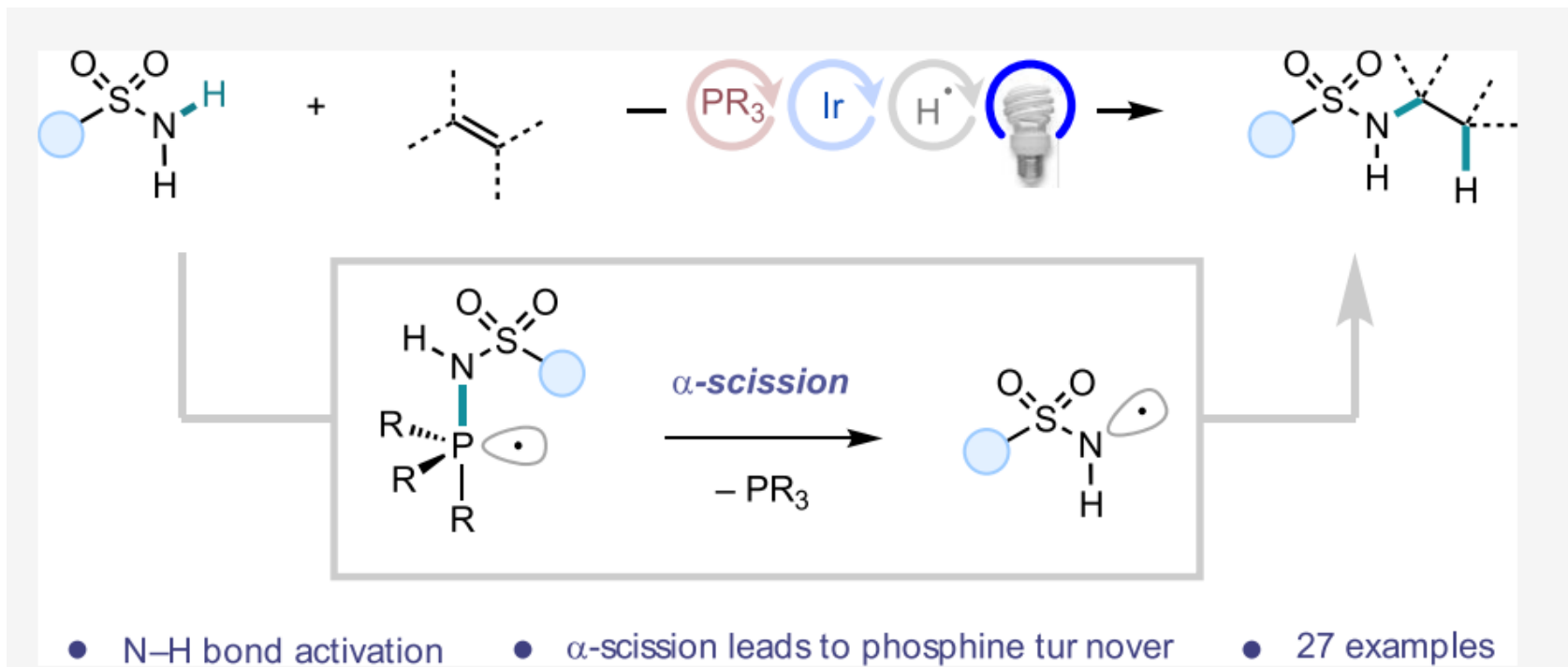
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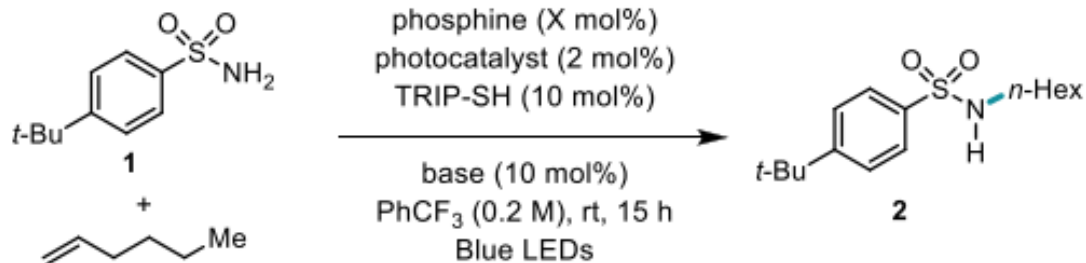
Anti-Markovnikov Hydroamination of Olefin

□ JACS ASAP paper



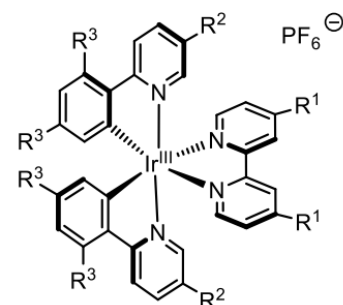
- ✓ New synthetic approach using α -scission
- ✓ Dual catalytic system; phosphine & photoredox cat.

Optimization



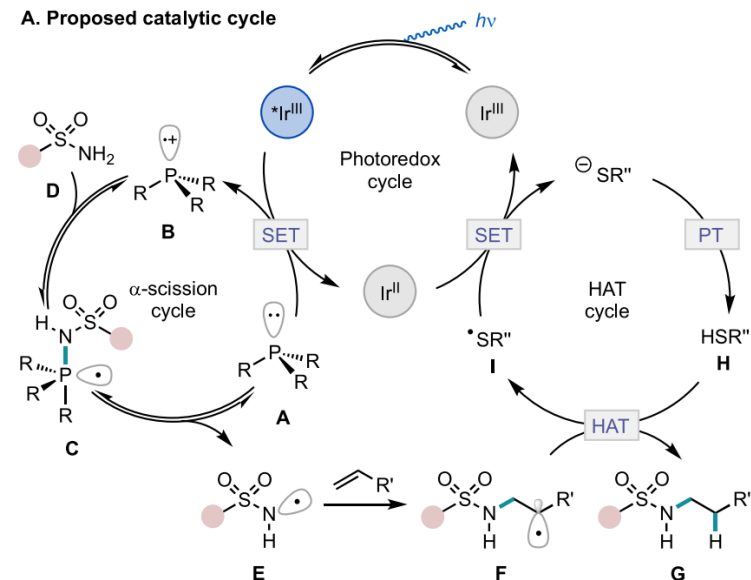
entry ^a	phosphine (mol%)	base	photocatalyst	yield (%) ^b
1	PPh ₃ (10 mol%)	Lutidine	3	12
2	P(4-MeOC ₆ H ₄) ₃ (10 mol%)	Lutidine	3	12
3	P(4-CF ₃ C ₆ H ₄) ₃ (10 mol%)	Lutidine	3	0
4	PMe ₃ (10 mol%)	Lutidine	3	34
5	PEt ₃ (10 mol%)	Lutidine	3	41
6	P(<i>t</i> -Bu) ₃ (10 mol%)	Lutidine	3	37
7	PCy ₃ (10 mol%)	Lutidine	3	46
8	PCy ₃ (10 mol%)	none	3	46
9	PCy ₃ (10 mol%)	NBu ₄ OP(O)(OBu) ₂	3	32
10	PCy ₃ (5 mol%)	none	3	60
11	PCy ₃ (2.5 mol%)	none	3	63
12 ^c	PCy ₃ (2.5 mol%)	none	3	87
13	PCy ₃ (2.5 mol%)	none	4	0
14	PCy ₃ (2.5 mol%)	none	5	49
15	PCy ₃ (2.5 mol%)	none	6	10
16^d	PCy₃ (2.5 mol%)	none	3	79

2.0 equiv of olefin (entry 12)



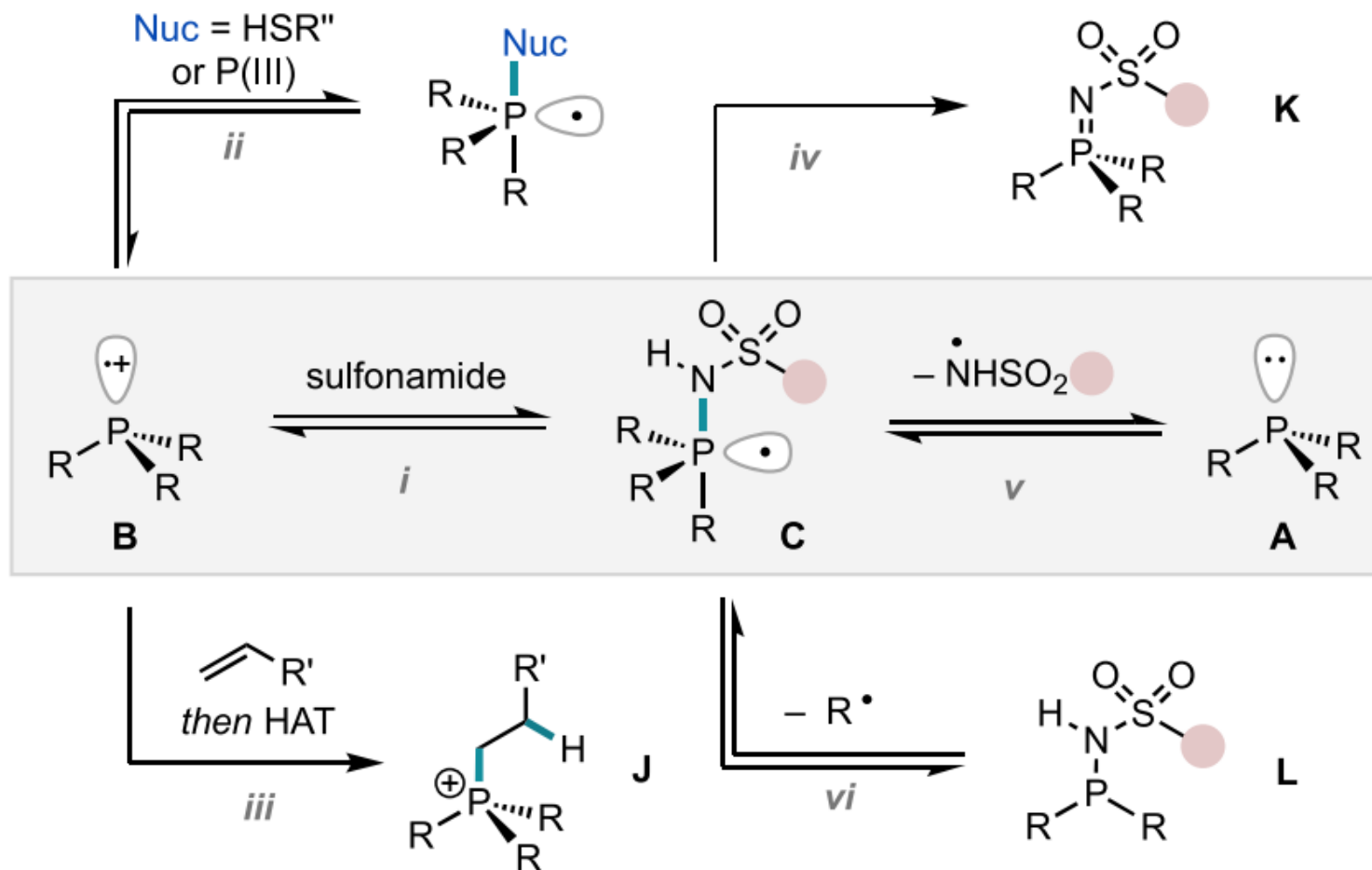
- 3: R¹ = *t*-Bu, R² = Me, R³ = F
Ir^{II}/*Ir^{III} = +0.97 V vs SCE
- 4: R¹ = *t*-Bu, R² = H, R³ = H
Ir^{II}/*Ir^{III} = +0.66 V vs SCE
- 5: R¹ = *t*-Bu, R² = CF₃, R³ = F
Ir^{II}/*Ir^{III} = +1.21 V vs SCE
- 6: R¹ = CF₃, R² = CF₃, R³ = F
Ir^{II}/*Ir^{III} = +1.65 V vs SCE

A. Proposed catalytic cycle

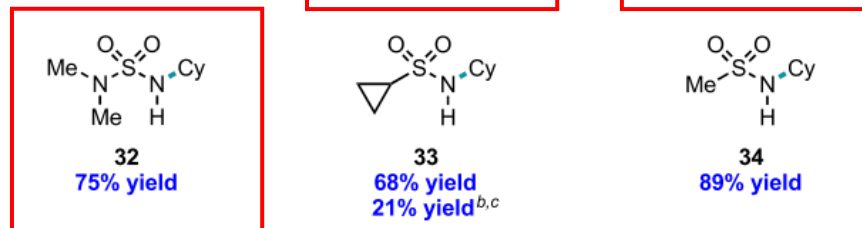
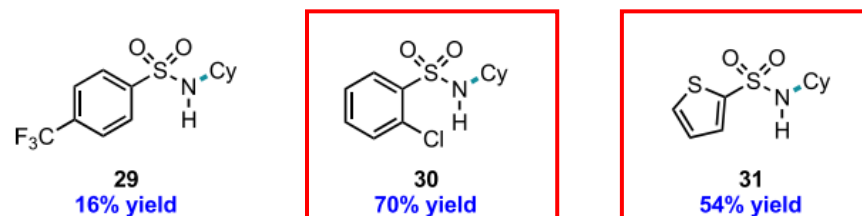
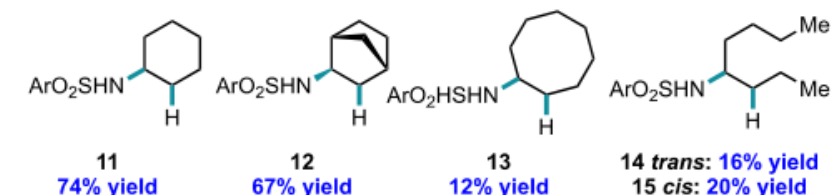
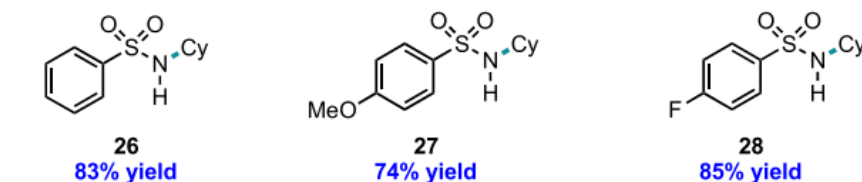
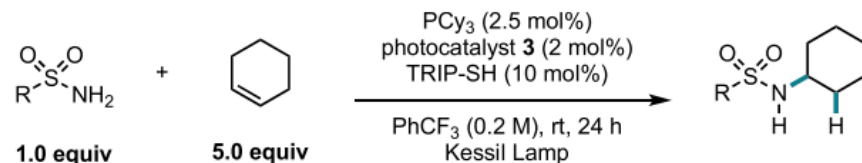
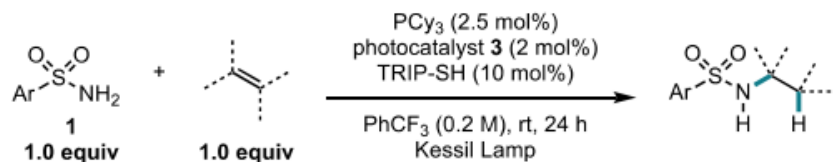


Optimization

B. Phosphine speciation pathways



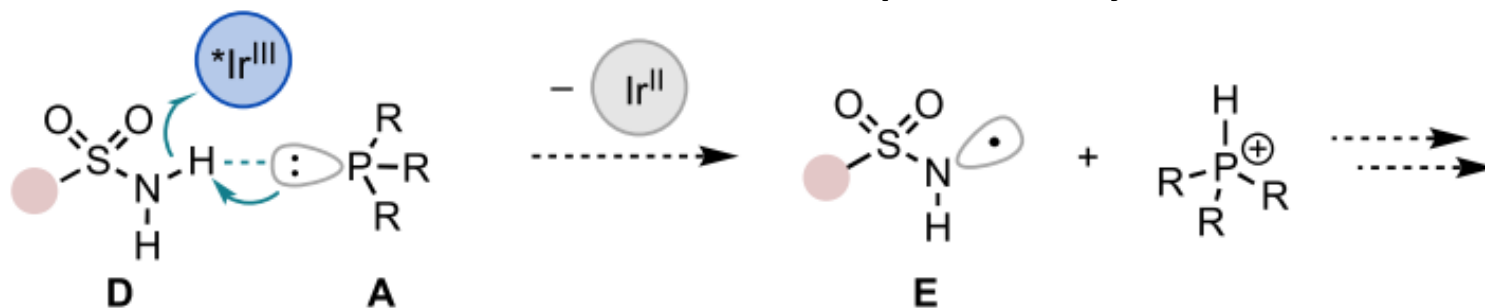
Substrate scope



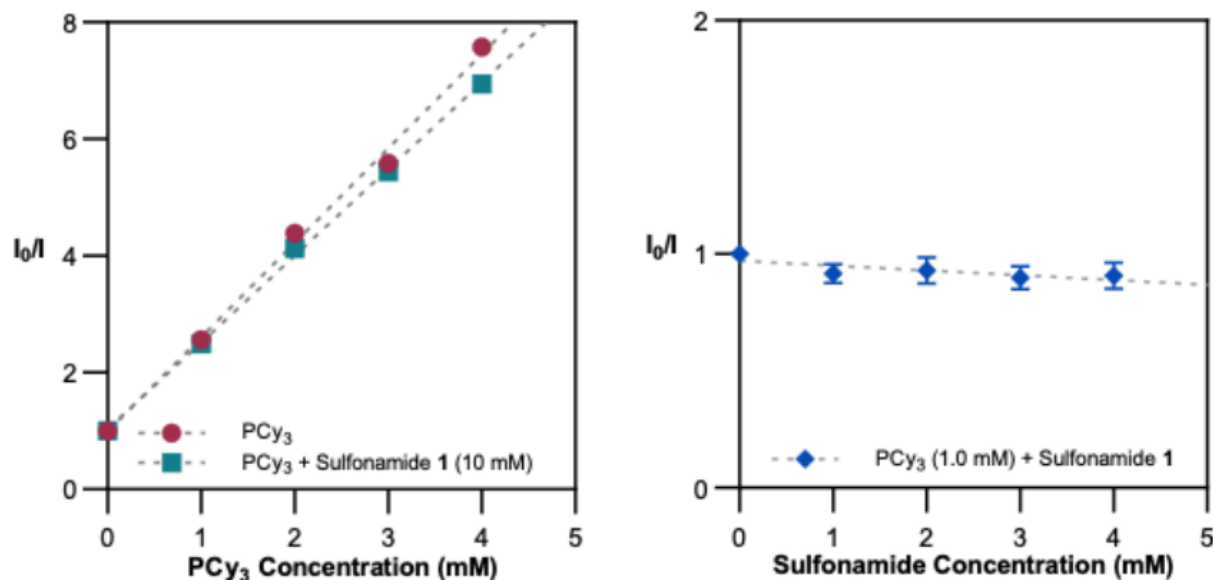
✓ Medically relevant motifs

Mechanistic study①

Alternative mechanism; PCET pathway



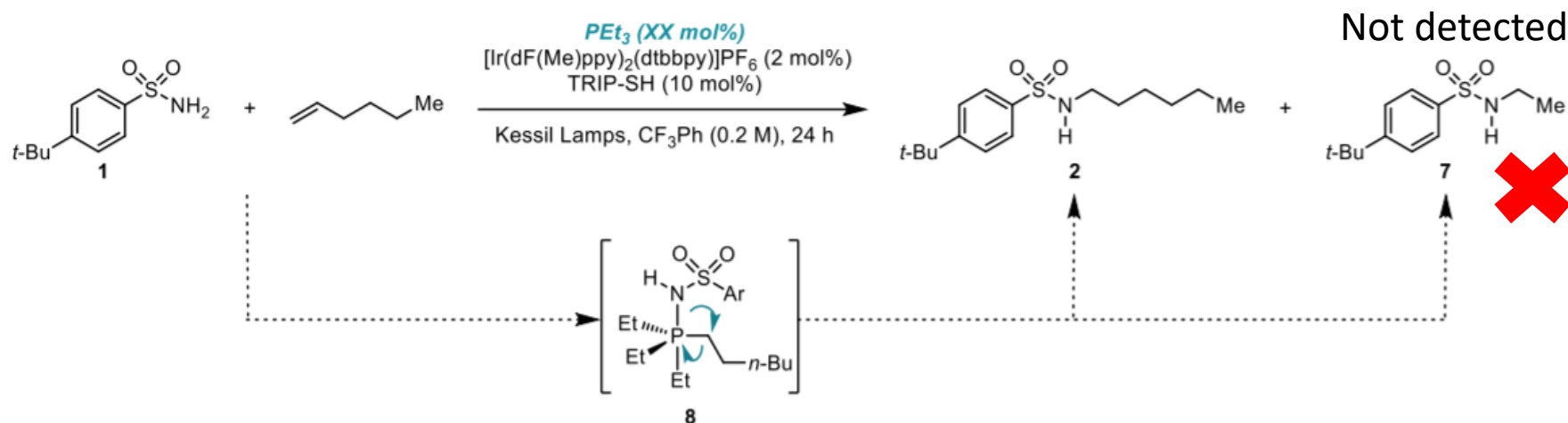
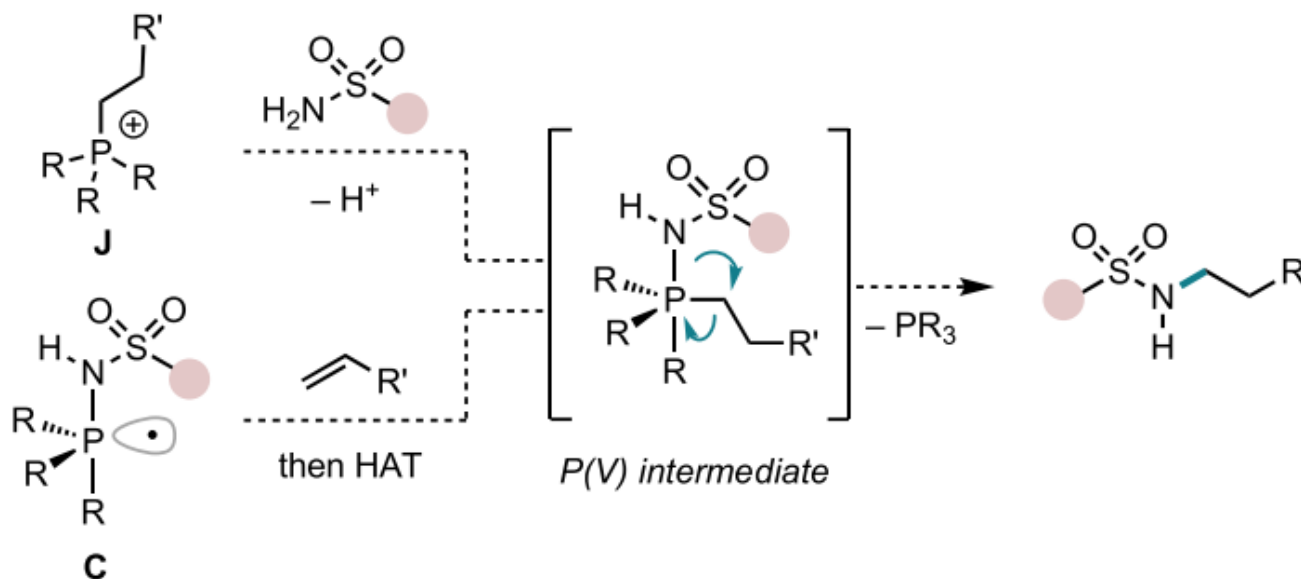
C. Stern–Volmer luminescence quenching experiments



✓ PCET pathway is **not operative**.

Mechanistic study②

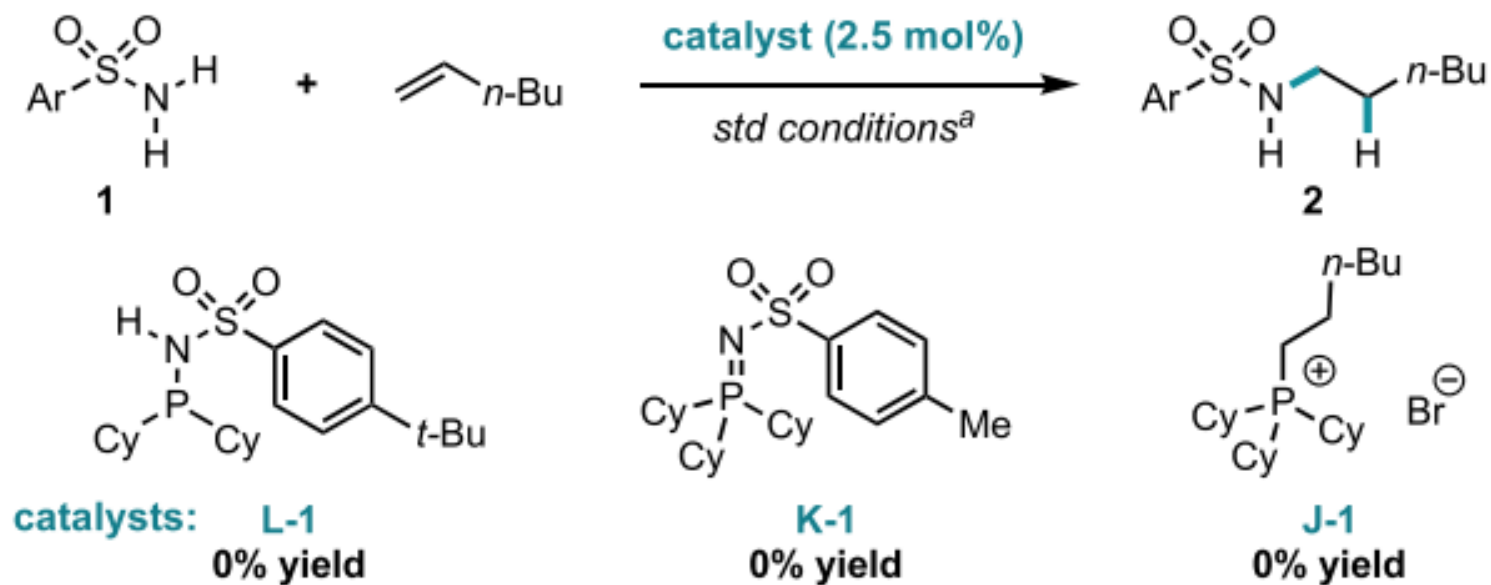
Alternative mechanism; reductive elimination



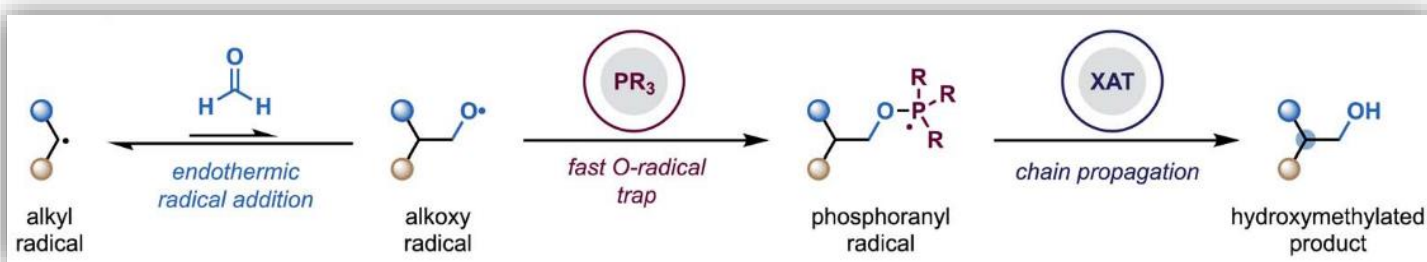
Mechanistic study^③

□ Catalytic performance of by-products

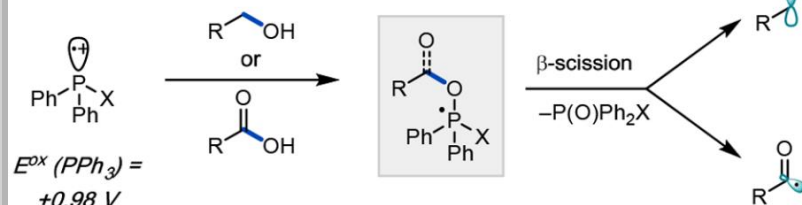
D. Catalytic performance of isolated P-derived byproducts



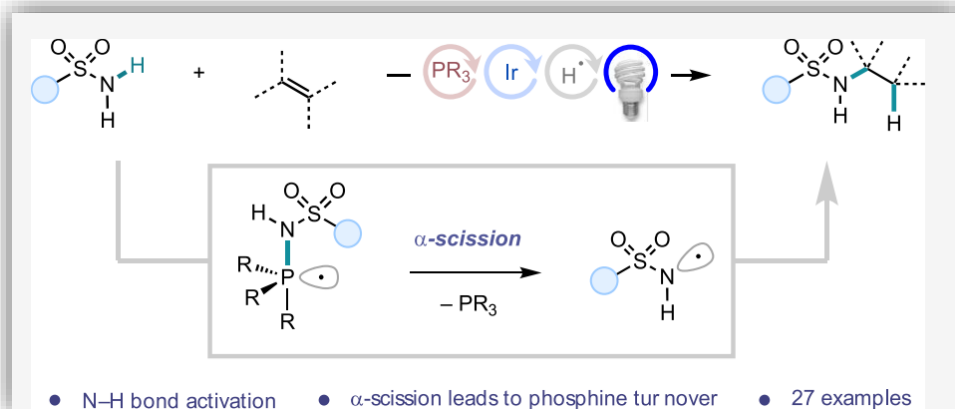
Summary



This Work – phosphine radical mediator (X = Ph or OEt)



- access to valuable phosphoranyl radical under mild conditions
- activation of C–O bonds independent of substrate redox potentials



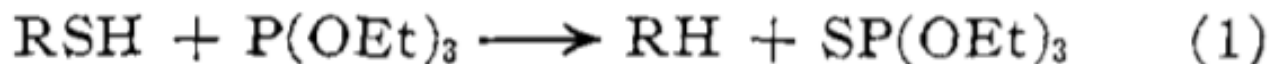
- ✓ Tunable mediator to generate valuable radicals
- ✓ Quickly advancing area in synthetic chemistry
- ✓ Open up a new innovative radical reactivity!

Appendix

History of phosphoranyl radical

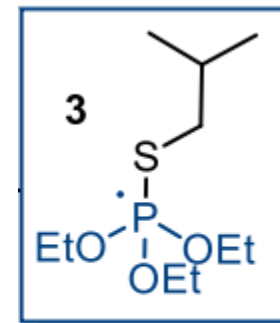
Early reaction via Phosphoranyl Radical (1950s)

Hoffmann and co-workers² recently have reported a remarkable reaction between mercaptans and trialkyl phosphites occurring at elevated temperatures, or photochemically at room temperature.



tures, or photochemically at room temperature.

- ✓ Proposed as an intermediate of desulfurization rxn.
- ✓ Later, *P*-centered radical was detected by ESR.



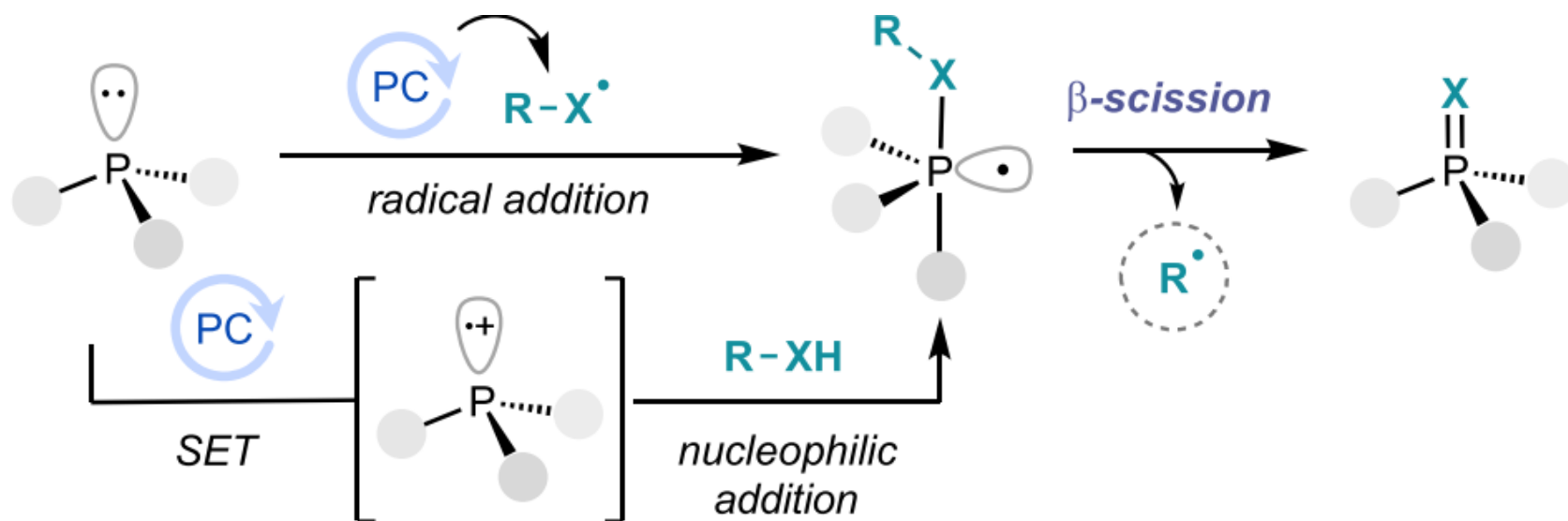
phosphoranyl
radical

Hoffmann, F. W. *et al.* *J. Am. Chem. Soc.* **1956**, 78, 6414–6414.

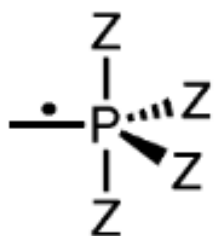
Walling, C. *et al.* *J. Am. Chem. Soc.* **1957**, 79, 5326–5326.

Brief history of phosphoranyl radical

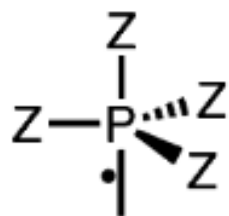
- Before the development of photoredox catalyst
 - × Hard to generate radicals in **mild conditions**
 - × **Further oxidation** under stoichiometric conditions
- Photoredox catalyst mediated reaction (2000s~)



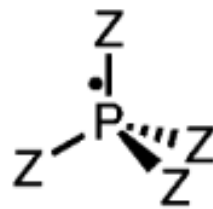
Structure of phosphoranyl radical



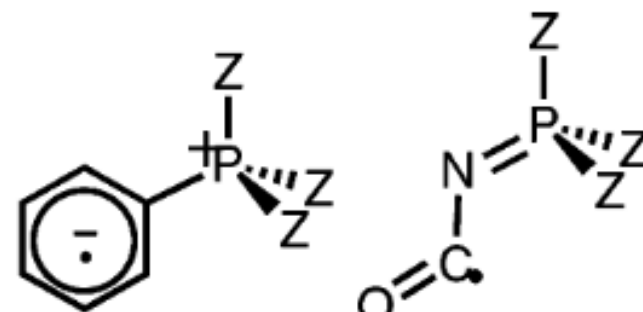
I TBP_e



II TBP_a

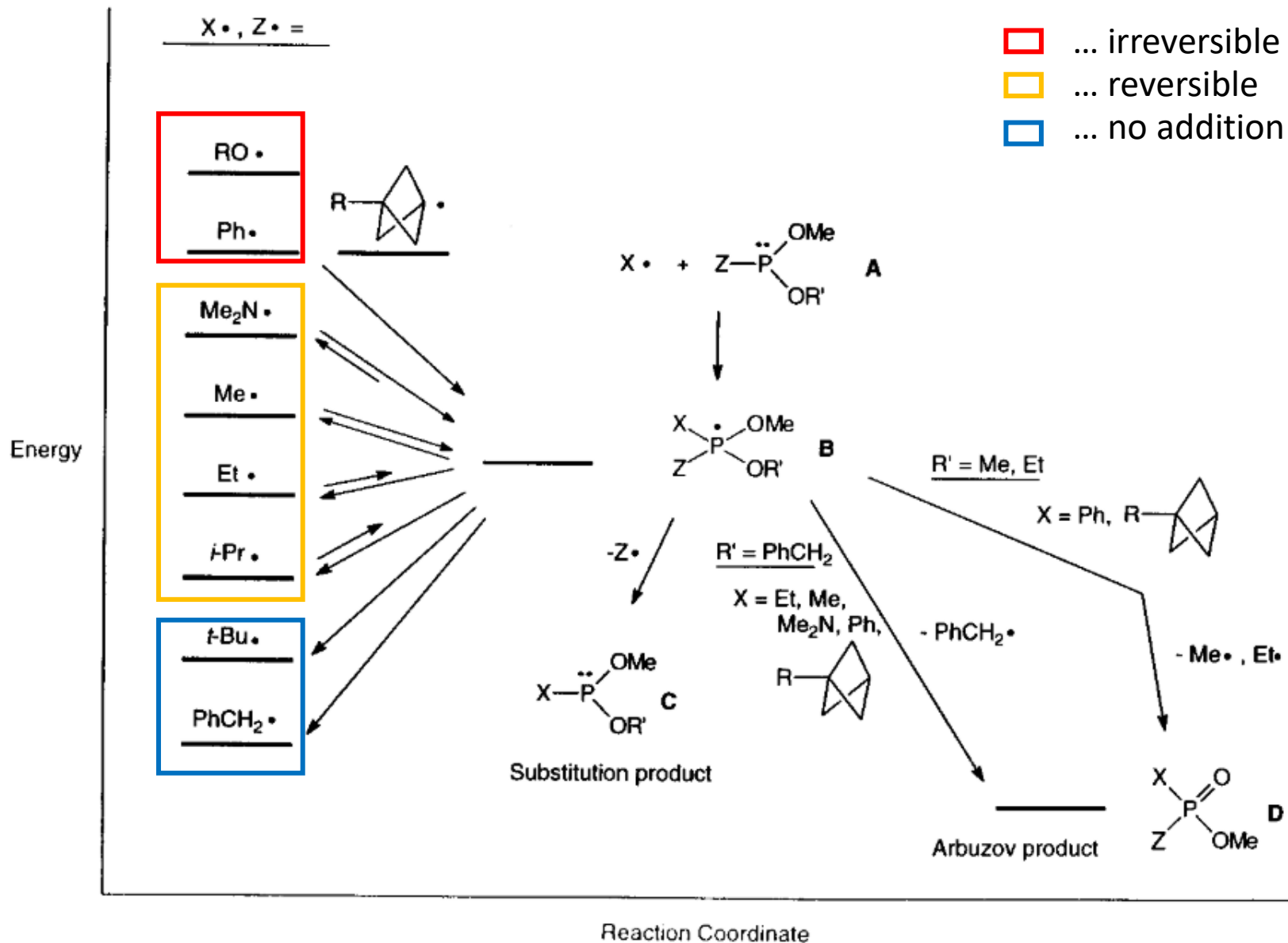


III σ^*



IV ligand π

Radical stability explains the reactivity



Today's Contents

1. Introduction: What is phosphoranyl radical?

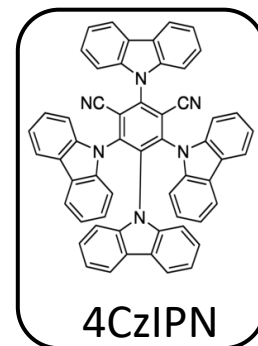
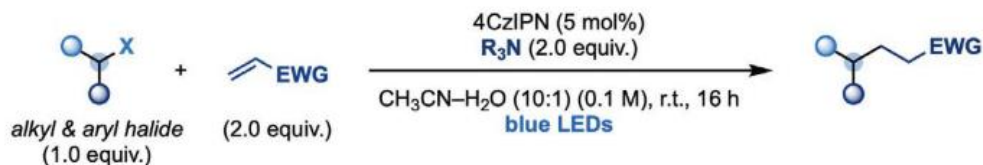
2. Application

- *O*-radical trap (C1 synthon)
- unique C-O bond activation
- catalytic α -scission pathway
(hydroamination with sulfonamides)

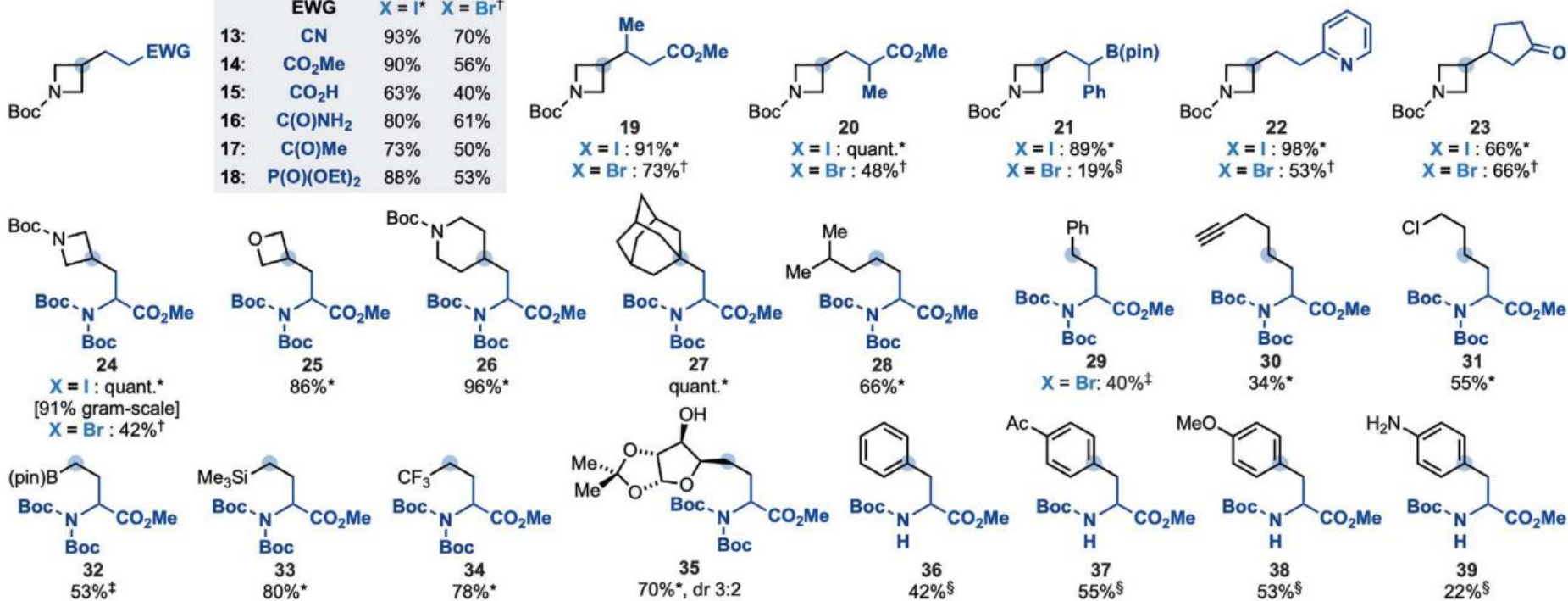
3. Summary

Halogen-Atom Transfer using aminoalkyl radical

Previous report



EWG	X = I*	X = Br [†]
13: CN	93%	70%
14: CO ₂ Me	90%	56%
15: CO ₂ H	63%	40%
16: C(O)NH ₂	80%	61%
17: C(O)Me	73%	50%
18: P(O)(OEt) ₂	88%	53%



Halogen-Atom Transfer using aminoalkyl radical

Previous report

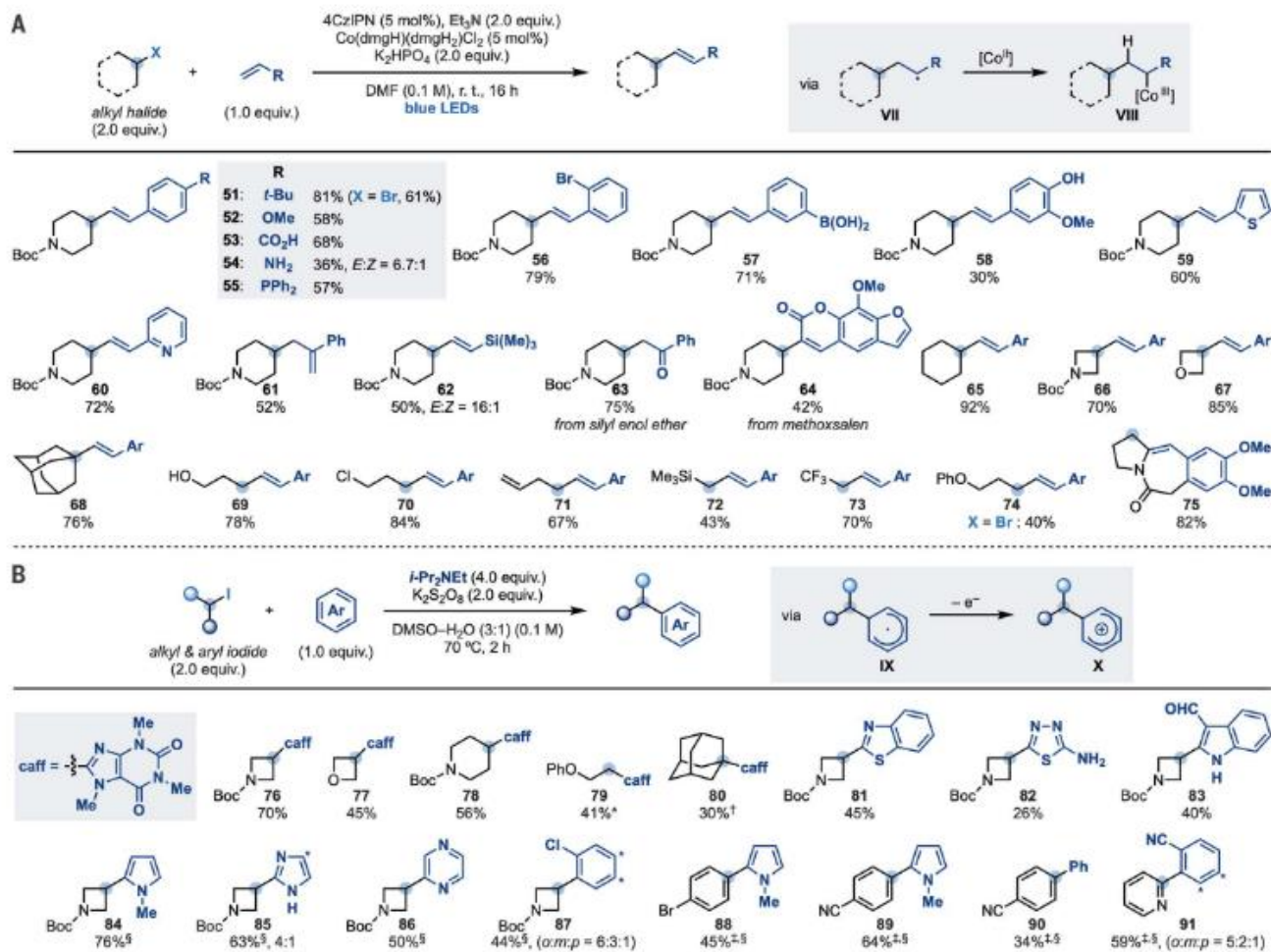
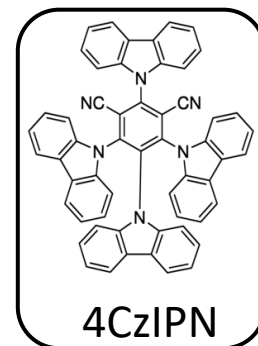
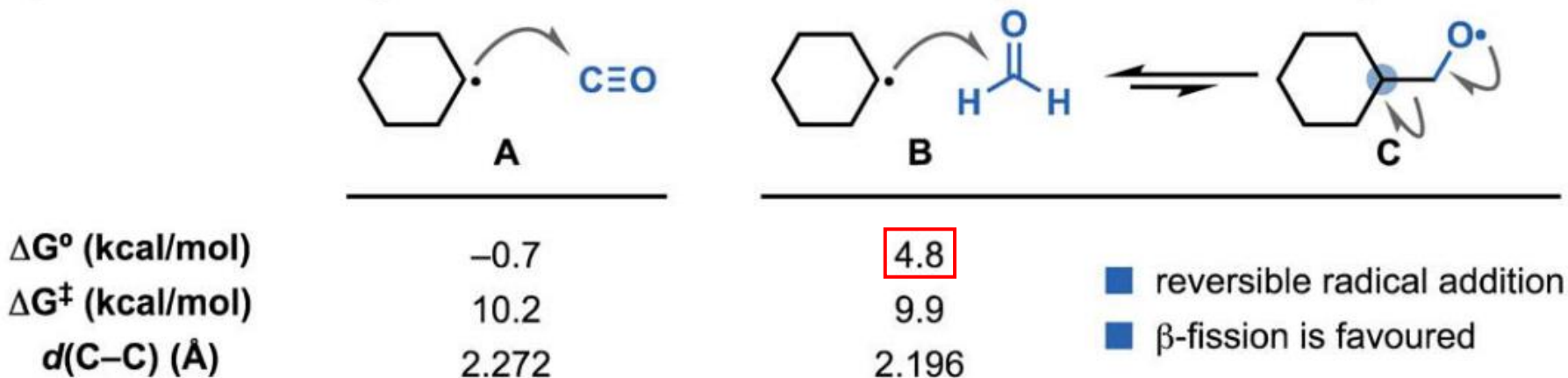


Fig. 4. Application to olefinations and arylations. (A) Scope for olefination of alkyl iodides and alkyl bromides. dmg, dimethylglyoximate; DMF, dimethylformamide. (B) Scope for the C–H alkylation and arylation of aromatics. All yields are isolated. ***1c** was used as the amine. †Me₃N was used as the amine. ‡tBu₃N was used as the amine. §The reaction was run with 50 equiv of the arene. DMSO, dimethyl sulfoxide. Asterisks in structures indicate the position of the minor constitutional isomer.

Application to C1-synton

□ Addition to formaldehyde is reversible and endothermic.

C) Mechanistic challenges in radical addition to **HCHO** vs **CO** [B3LYP-D3/def2-TZVP]



Chem. Sci., 2021, 12, 10448.

Trapping reagent Phos. vs Borane

	radical	X ₃ M	<i>k</i> , M ⁻¹ s ⁻¹	source
P	<i>t</i> -BuO•	Ph ₃ P	1.9 × 10 ⁹	laser photolysis
	MeO•	Ph ₃ P	5.1 × 10 ⁹	pulse radiolysis
	<i>t</i> -BuO•	P(OEt) ₃	8.1 × 10 ⁸	ESR competition with cyclopentane ^{a,b}
	<i>t</i> -BuO•	PEt ₃	1.2 × 10 ⁹	ESR competition with P(OEt) ₃ ^c
B	<i>t</i> -BuO•	Ph ₃ B	1.0 × 10 ⁸	laser photolysis
	<i>t</i> -BuO•	<i>n</i> -Bu ₃ B	1.5 × 10 ⁸	ESR competition with cyclopentane ^{a,d}
	<i>t</i> -BuO•	<i>i</i> -Bu ₃ B	5.1 × 10 ⁶	ESR competition with cyclopentane ^{a,d}
	<i>t</i> -BuO•	<i>sec</i> -Bu ₃ B	1.5 × 10 ⁶	ESR competition with cyclopentane ^{a,d}
	<i>t</i> -BuO•	(MeBO) ₃	1.0 × 10 ⁷	ESR competition with cyclopentane ^{a,d}

Small, R. D. et al. *J. Am. Chem. Soc.* **1979**, *101*, 14, 3780–3785.

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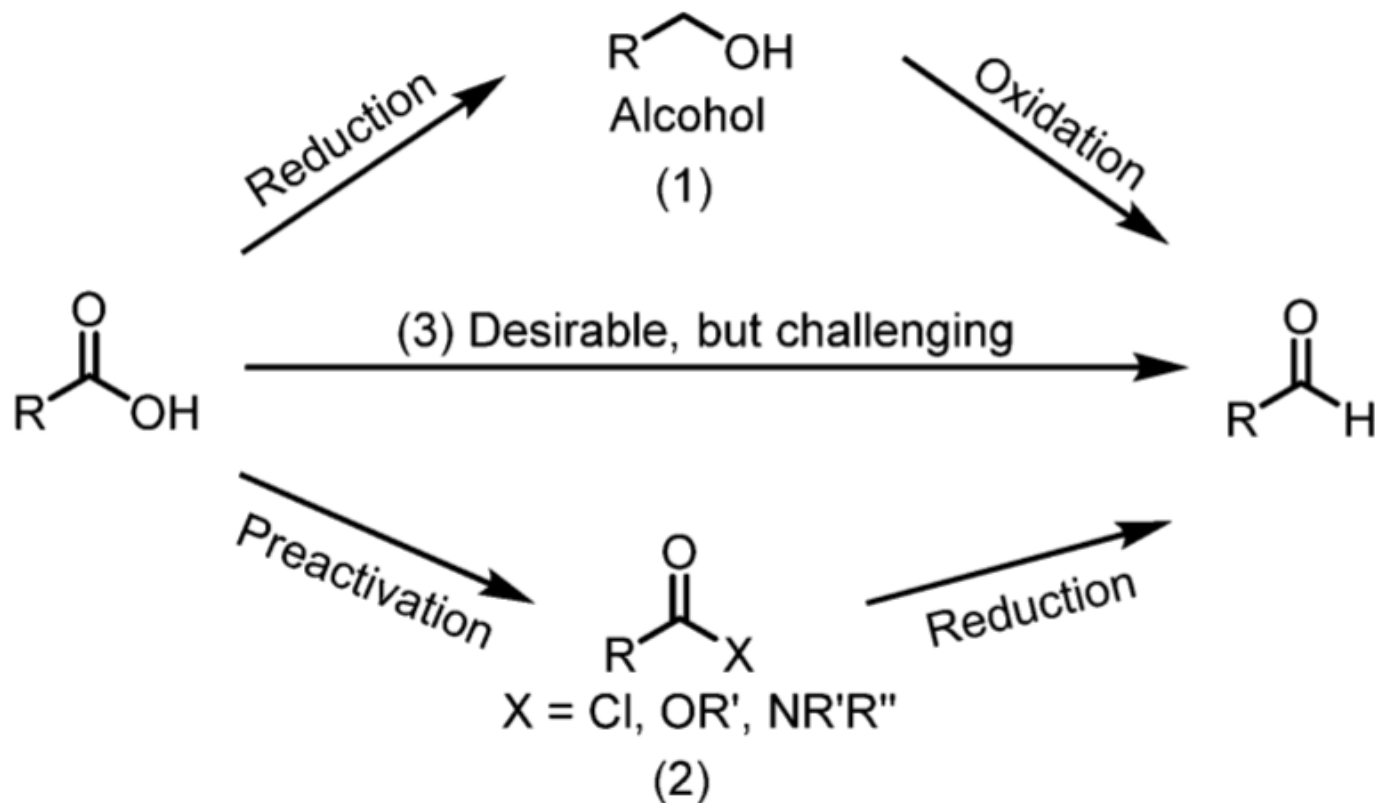
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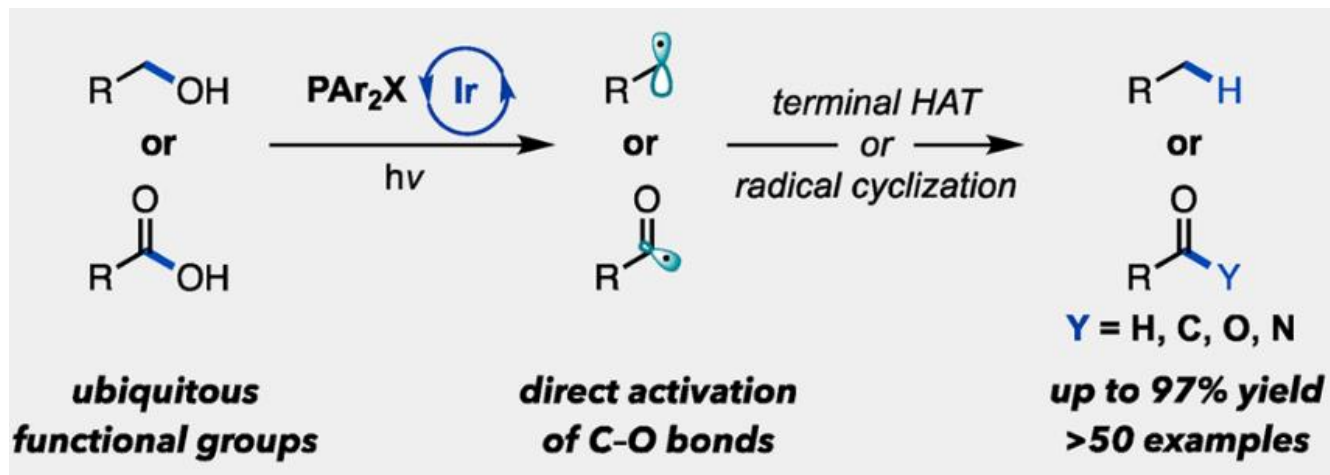
Direct reduction of carboxylic acid to aldehyde

A) Classic synthesis of aldehydes from carboxylic acids



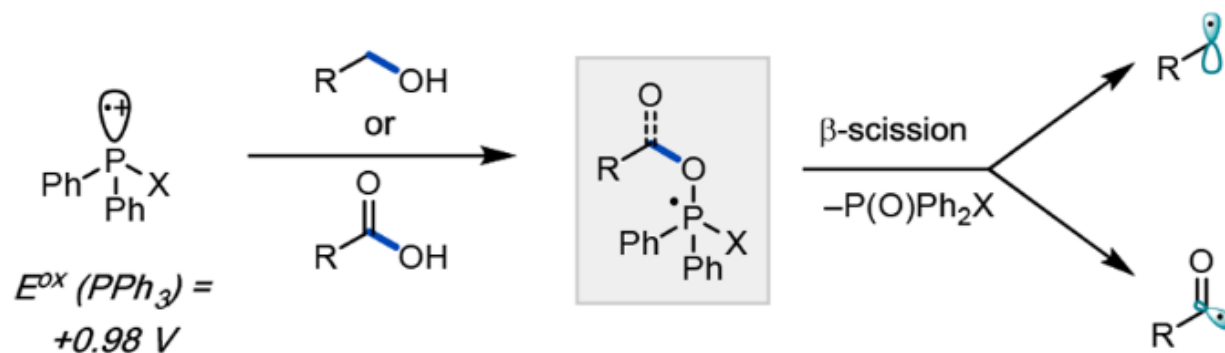
Non-substrate-specific strategy is required.

Deoxygenation reaction

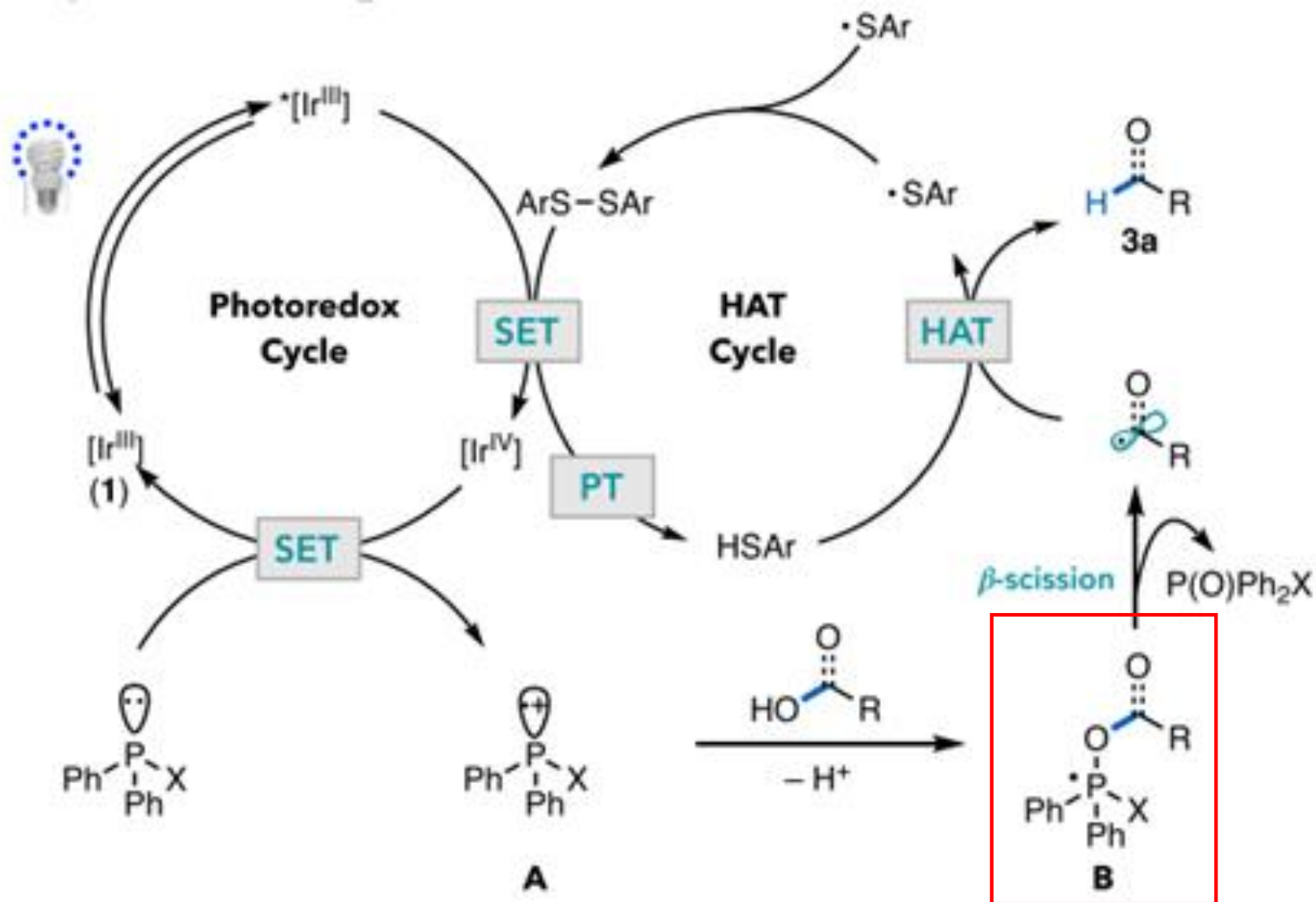


C-O bond activation via phosphoranyl radical

C. This Work – phosphine radical mediator (X = Ph or OEt)

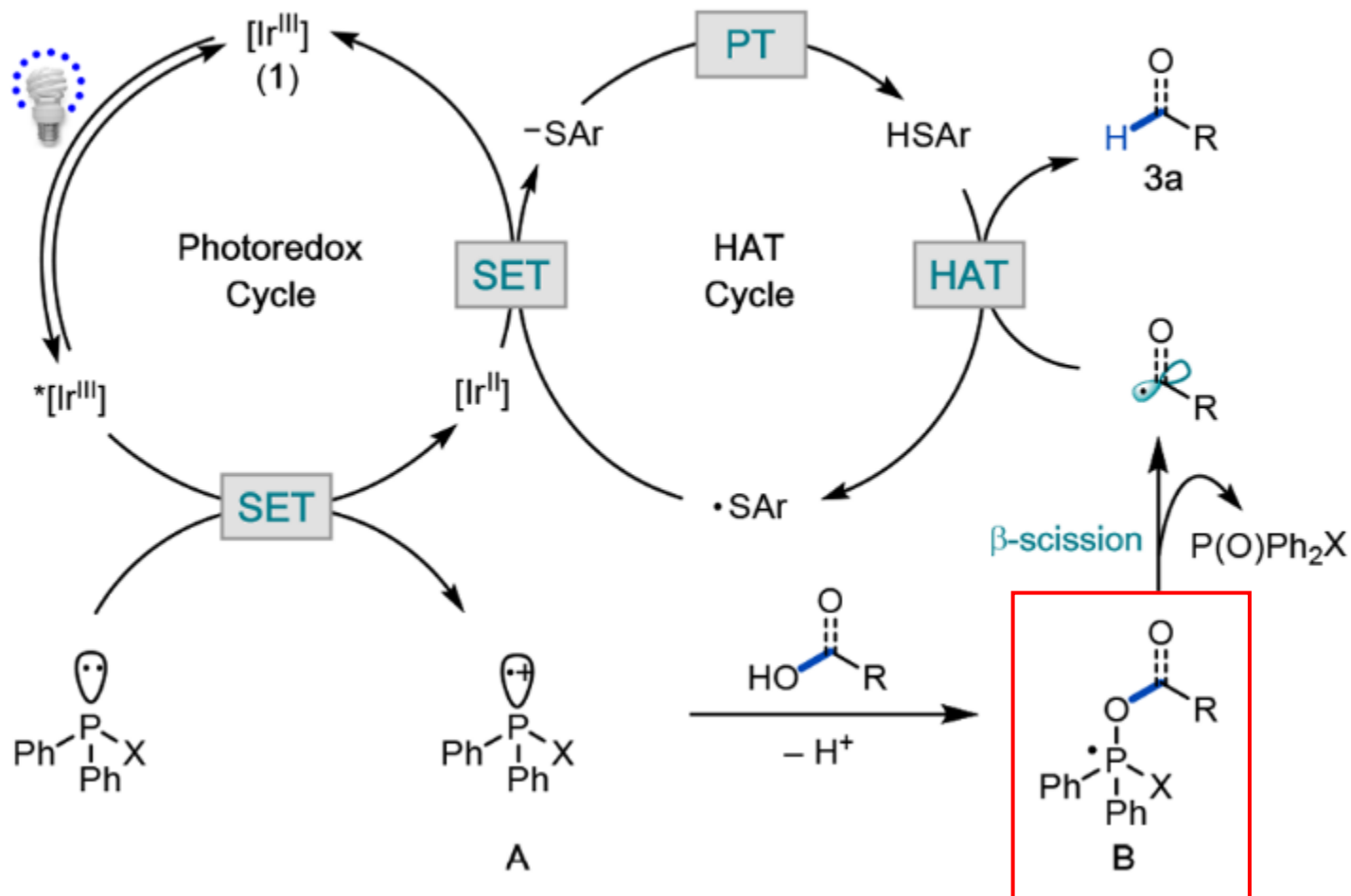


Proposed mechanism in the presence of ArSSAr



Proposed mechanism

D. Mechanistic proposal



Today's Contents

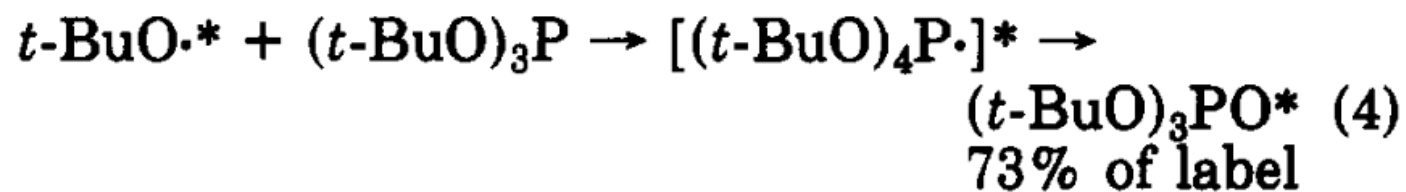
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Memory effect



Phosphine screening

