Activation by One Electron Oxidation

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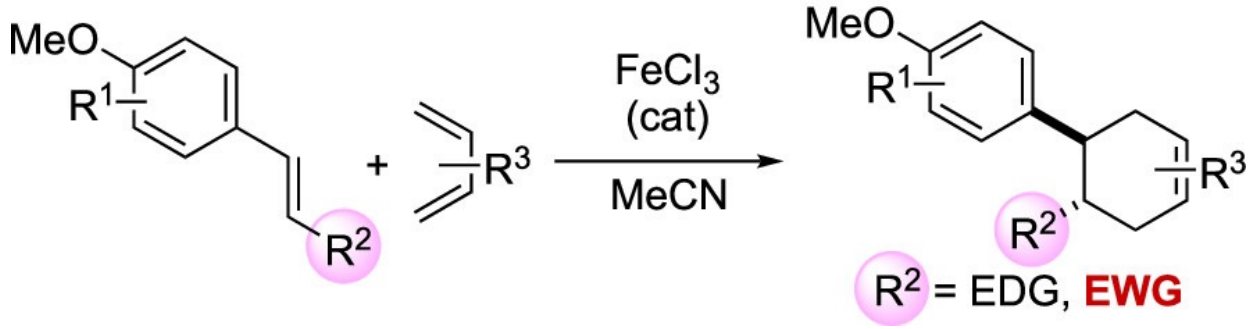
2021/12/17

Introduction

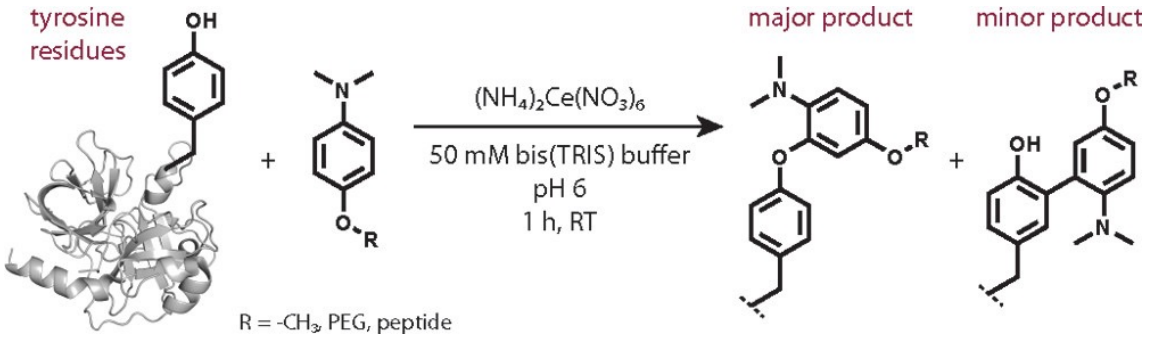
Examples of one electron oxidation

- Initiating cycloaddition



Ishihara, K. *et al. J. Am. Chem. Soc.* **2019**, *141*, 1877-1881

- Bioconjugation



Francis, M. et al. *J. Am. Chem. Soc.* **2011**, *133*, 16970–16976

Contents

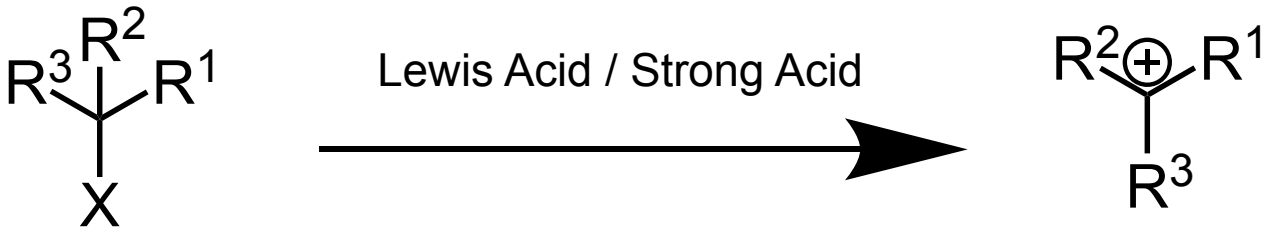
- Mesolytic Cleavage of Radical Cation
- Oxidative S_NAr Pathway
- Application to Biomolecular
- Summary

Contents

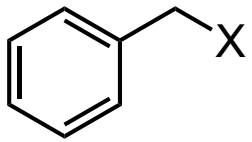
Mesolytic Cleavage of Radical Cation

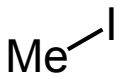
- Conventional Alkylation Strategies

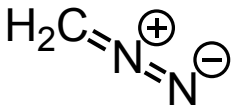
➢ Strong acids or Lewis acids required for generating carbocation。

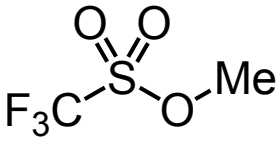


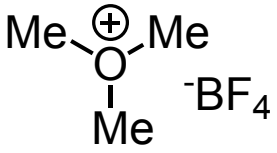
➢ Alkylation reagents are very reactive.





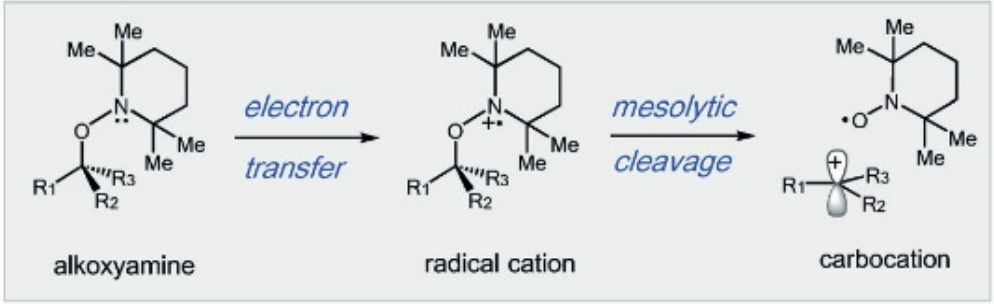




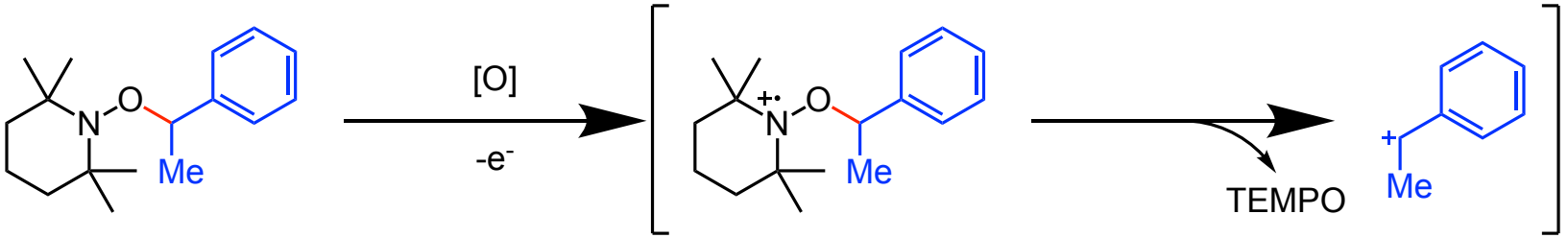


Mesolytic Cleavage of Radical Cation

- Previous works



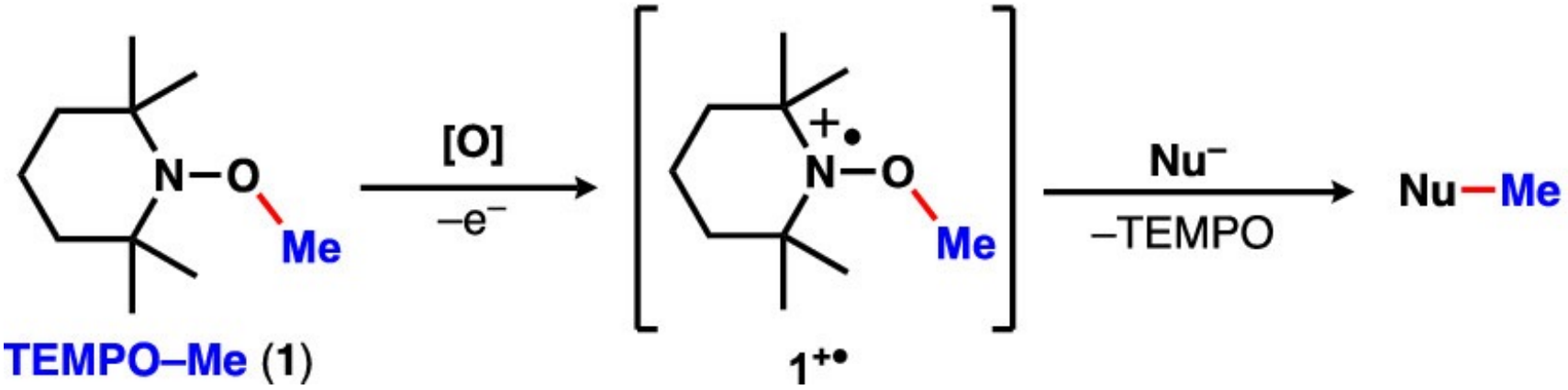
Knowles, R. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 9969-9973.



Ciampi, S., Coote, M. *et al. J. Am. Chem. Soc.* **2018**, *140*, 766–774.

- Generating carbocation by mesolytic cleavage of radicalcation
- Under mild conditions without Lewis/strong acid

Electrochemically activated methylation

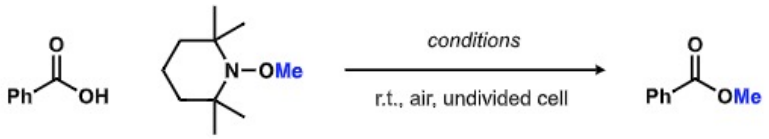


- Stable and unreactive in neutral form without electrochemical stimuli.

Coote, M., *et al. J. Am. Chem. Soc.* **2019**, *141*, 15450−15455

Optimization

Table 2. Electrochemical Methylation of Benzoic Acid Using TEMPO–Me: Influence of Reaction Parameters[a]



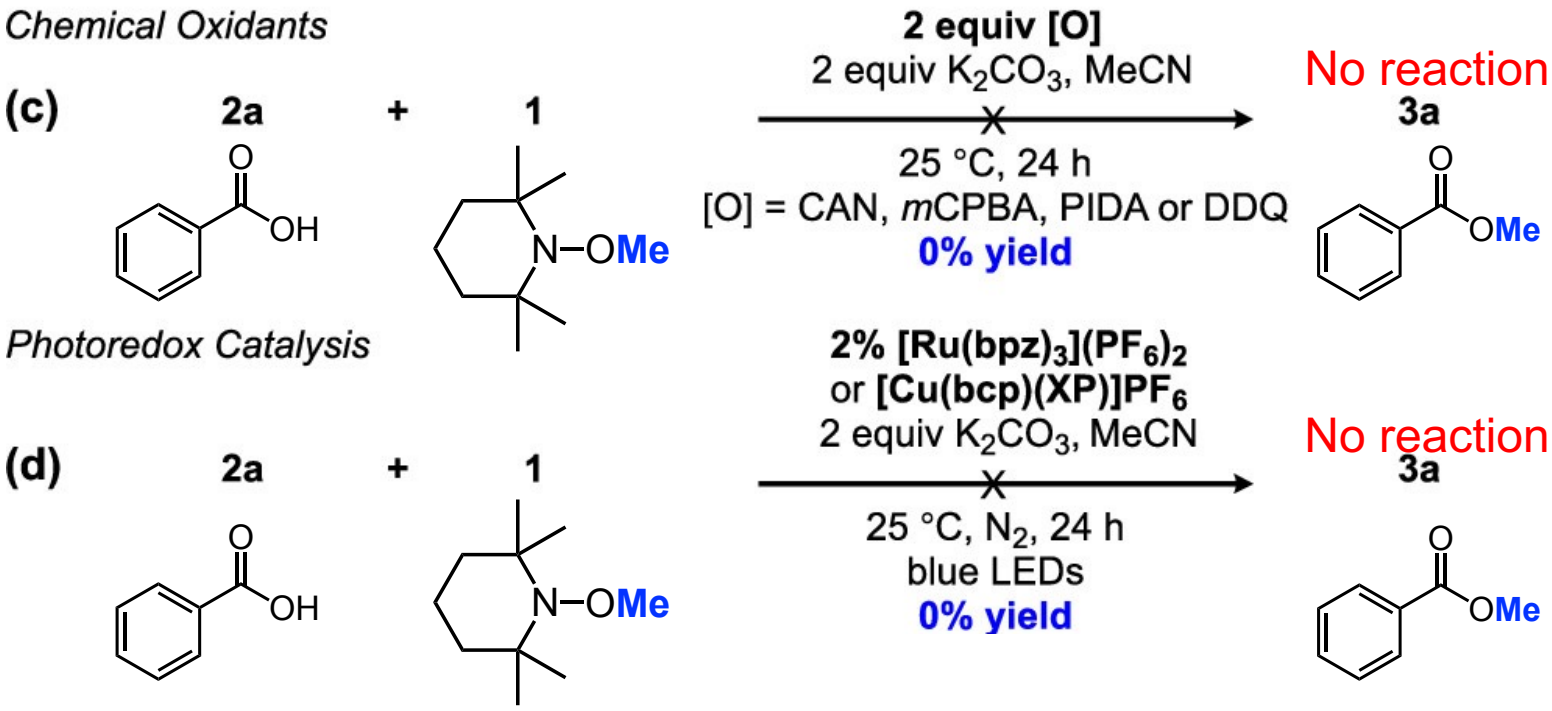
2a 1 3a

entry	electrolyte	solvent	base (eq)		electrolytic conditions (mA)	F·mol^{-1}	isolated yield (%)[b]
1	Bu_4NBF_4	MeCN	**Cs_2CO_3**	(1.1)	10	12.2	0 (13)[c]
2	Bu_4NBF_4	MeCN	**K_2CO_3**	(1.1)	10	12.2	0 (21)[c]
3	Bu_4NBF_4	MeCN	**2,6-(t-Bu)$_2C_5H_3N$**	(1.1)	10	12.2	37
4	Bu_4NBF_4	**CH_2Cl_2**	2,6-(t-Bu)$_2C_5H_3N$	(1.1)	10	12.2	22
5	Bu_4NBF_4	**THF**	2,6-(t-Bu)$_2C_5H_3N$	(1.1)	10	12.2	0
6	Bu_4NBF_4	**DMSO**	2,6-(t-Bu)$_2C_5H_3N$	(1.1)	10	12.2	0
7	**Bu_4NPF_6**	MeCN	2,6-(t-Bu)$_2C_5H_3N$	(1.1)	10	12.2	44
8	**Bu_4NClO_4**	MeCN	2,6-(t-Bu)$_2C_5H_3N$	(1.1)	10	12.2	51
9	Bu_4NClO_4	MeCN	2,6-(t-Bu)$_2C_5H_3N$	**(0.25)**	10	12.2	50
10	Bu_4NClO_4	MeCN	2,6-(t-Bu)$_2C_5H_3N$	**(0.10)**	10	12.2	51
11	Bu_4NClO_4	MeCN	none		10	12.2	22
12	Bu_4NClO_4	MeCN	2,6-(t-Bu)$_2C_5H_3N$	(0.10)	**5**	**6.1**	46
13	Bu_4NClO_4	MeCN	2,6-(t-Bu)$_2C_5H_3N$	(0.10)	**15**	**18.3**	25
14	Bu_4NClO_4	MeCN	2,6-(t-Bu)$_2C_5H_3N$	(0.10)	10	6.7	91[d]

[a]Reactions consisted of **2a** (0.5 mmol), **1** (0.55 mmol, 1.1 equiv), and base (stated equivalents) in an electrolyte solution (10 mL; 0.1 M) electrolyzed in a 10 mL undivided cell at room temperature open to air for 18 h using an IKA Electrasyn 2.0 and two graphite electrodes, unless otherwise specified. [b]Yield with respect to **2a**. [c]Yield obtained when the cell polarity was reversed every 10 min. [d]2.0 equiv of **1**.

Coote, M., *et al. J. Am. Chem. Soc.* **2019**, *141*, 15450−15455

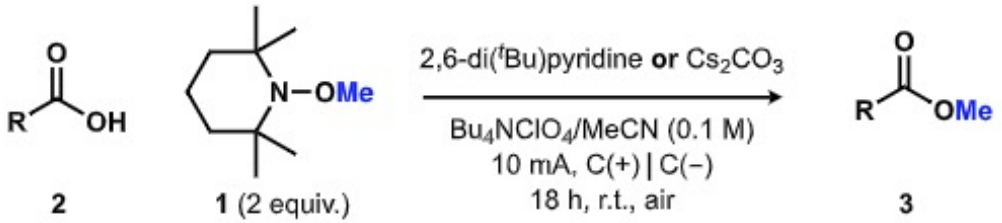
Optimization



- Neither stoichiometric oxidants nor PC facilitated methylation
  - ➢ Electrochemistry is crucial for this reaction

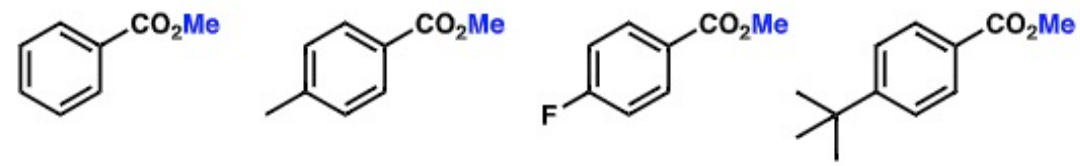
Coote, M., *et al. J. Am. Chem. Soc.* **2019**, *141*, 15450−15455

Substrate scope

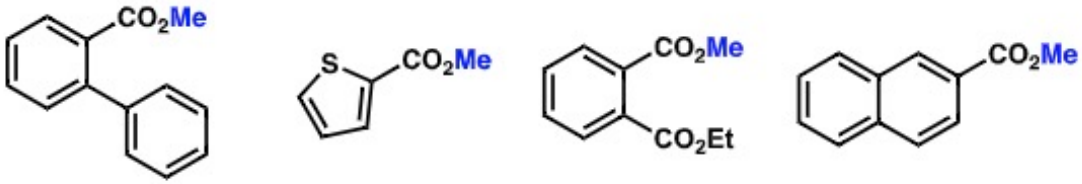


2 1 (2 equiv.) 3

undivided cell: 0.5 mmol **2**, 2,6-di(^{t}Bu)pyridine (10 mol%)

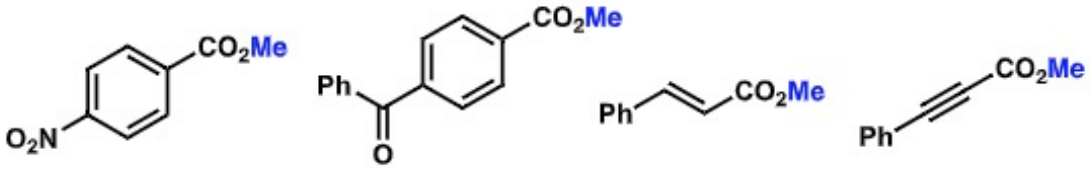


3a[a] 91% **3b**[a] 97% **3c**[a] 60% **3d** 86% yield



3e 73% yield **3f** 92% yield **3g** 57% yield **3h** 65% yield

divided cell: 1.0 mmol **2**, Cs_2CO_3 (1.1 equiv.)

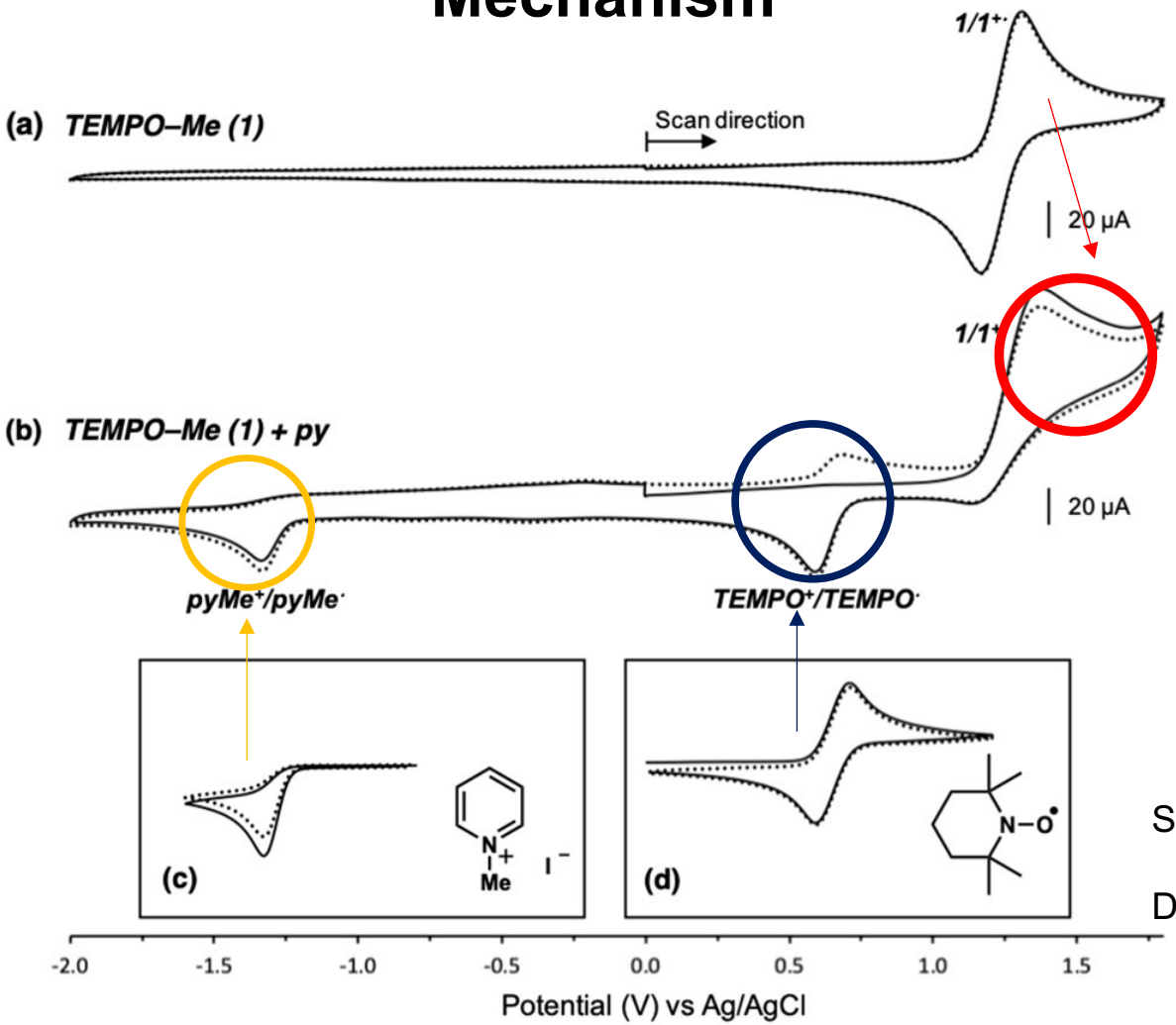


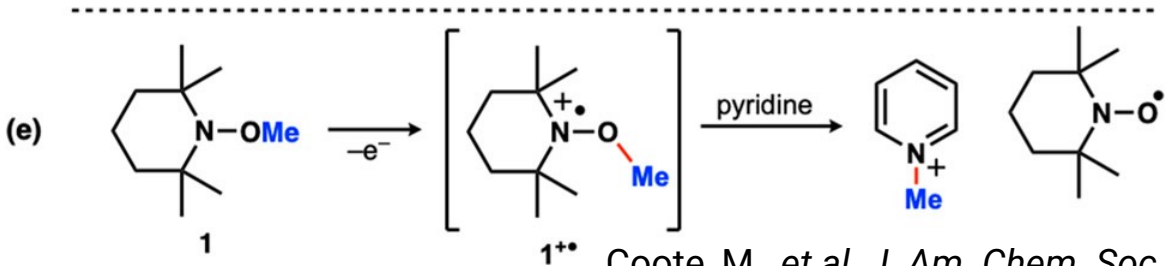
3i 65% yield **3j** 59% yield **3k** 59% yield **3l** 91% yield

- Methylation achieved in moderate to high yield
- Bearing functional groups susceptible to reduction
  → divided cells

Coote, M., *et al. J. Am. Chem. Soc.* **2019**, *141*, 15450−15455

Mechanism



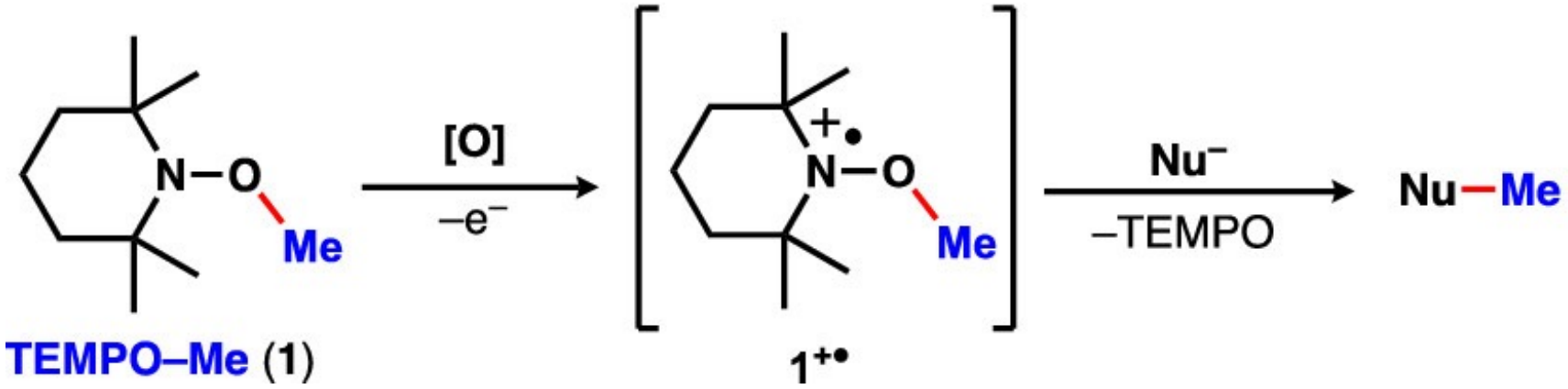


Solid line: Scan 1

Dotted line: Scan 2

Coote, M., *et al. J. Am. Chem. Soc.* **2019**, *141*, 15450−1545

Short Summary



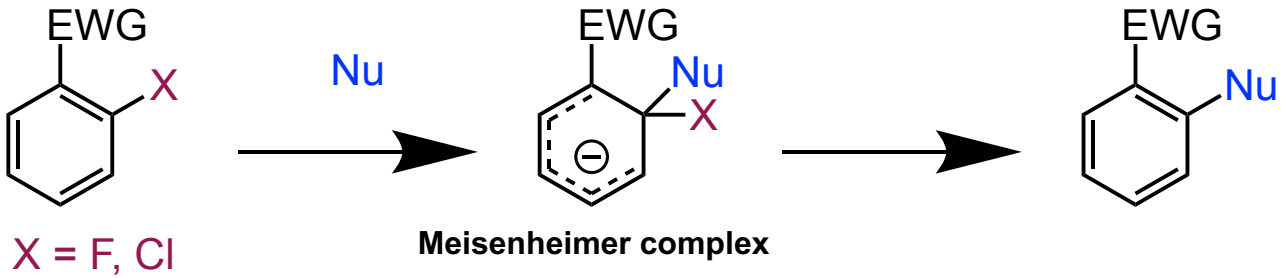
- Electrochemically activated methylation under mild condition.
- TEMPO-Me is stable in neutral form.
- There is still some room for improvement of the substrate scope and the reactivity of the donor.

Coote, M., *et al. J. Am. Chem. Soc.* **2019**, *141*, 15450−15455

Contents

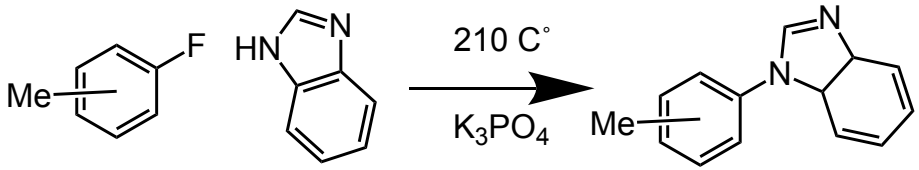
Oxidative S_NAr Pathway

- Common S_NAr pathway



Cannot be applied to electron-rich arenes

- Attempts to facilitate S_NAr with electron neutral/rich arenes

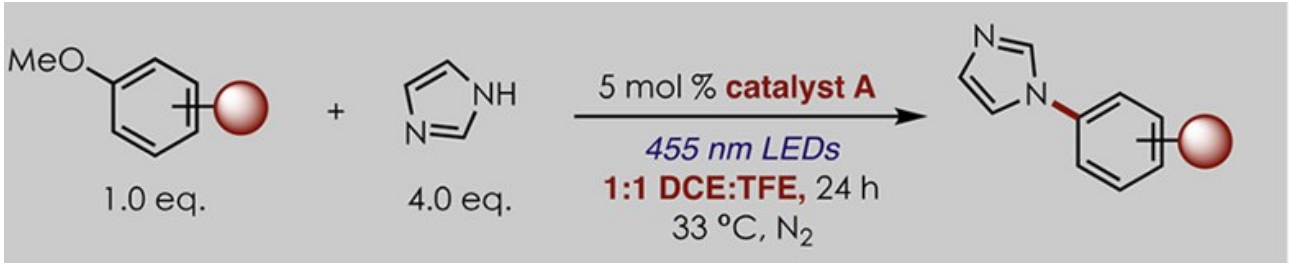


High temperature is needed

Diness, F. & Fairlie, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 8012-8016

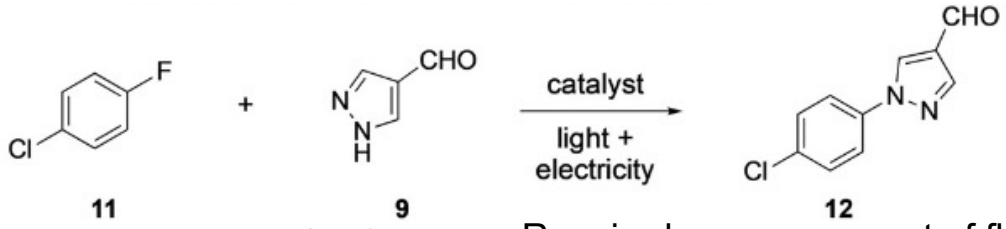
Oxidative S_NAr Pathway

- Previous reports
  - Substitution at C–OMe



Nicholas. T., & Nicewicz. D. *J. Am. Chem. Soc.* **2017**, *139*, 16100–16104

  - Defluorinative substitution

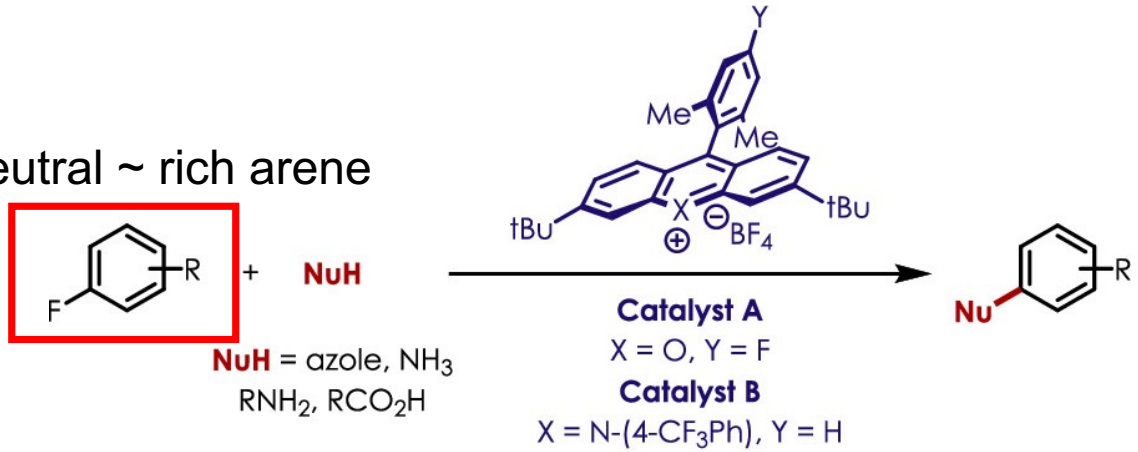


Required excess amount of fluoroarene

Huang, H., & Lambert, T. H. *Angew. Chem. Int. Ed.* **2020**, *59*, 658-662

Oxidative S_NAr Pathway

Electron neutral ~ rich arene

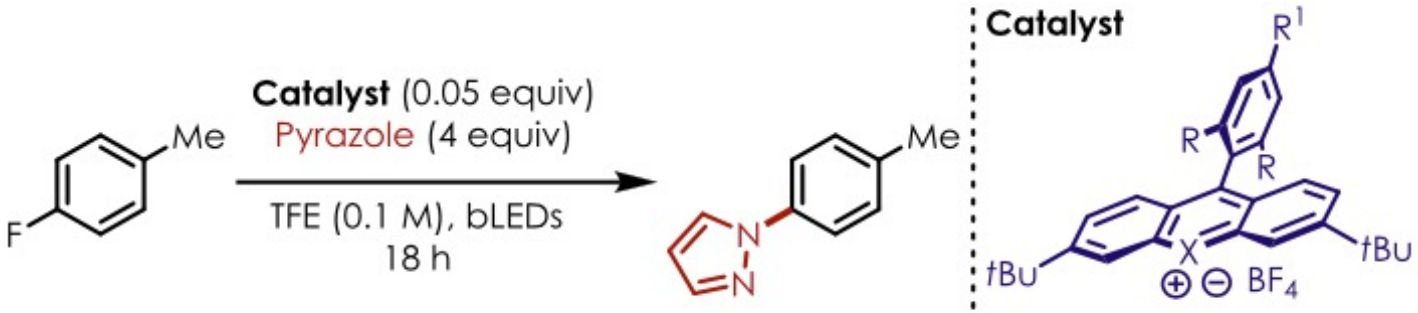


- S_NAr reaction with electron rich or neutral arene under mild condition
- Amine or carboxylic acid can be used as nucleophile

Nicewicz, D. *et al. J. Am. Chem. Soc.* **2020**, *142* , 17187-17194

Optimization (Heteroarene)

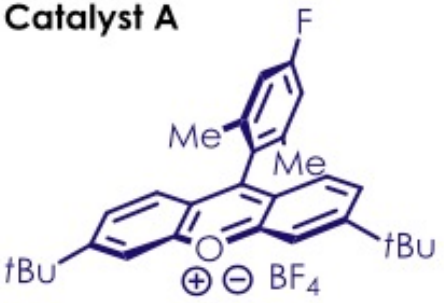
Table 1. Catalyst Development for Fluorotoluene S_NAr



entry	R	R^1	X	$E^*_{1/2}{}^{red}$ (V)[a]	yield[b]
1	Me	Me	NPh	+2.10	0%
2	Cl	H	NPh	+2.21	8%
3	Me	Me	O	+2.51	<5%
4	Cl	H	O	+2.66	35%
5	Me	F	O	+2.57	55%

[a]Saturated calomel electrode (SCE) as reference. [b]Yield determined by ^{1}H NMR using HMDSO as an internal standard.

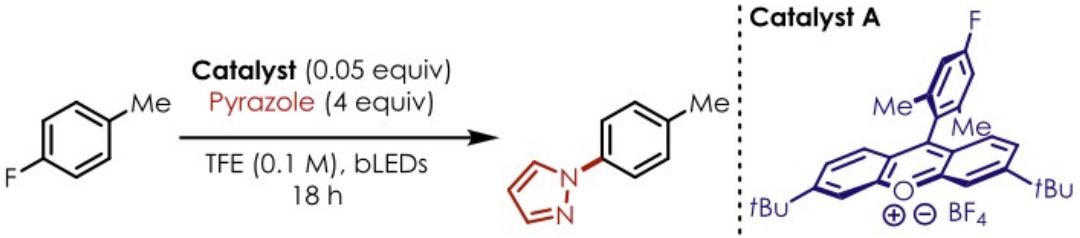
Catalyst A



Nicewicz, D. *et al. J. Am. Chem. Soc.* **2020**, *142* , 17187-17194

Optimization (Heteroarene)

Table 2. Optimization of Fluorotoluene S_NAr using Pyrazole



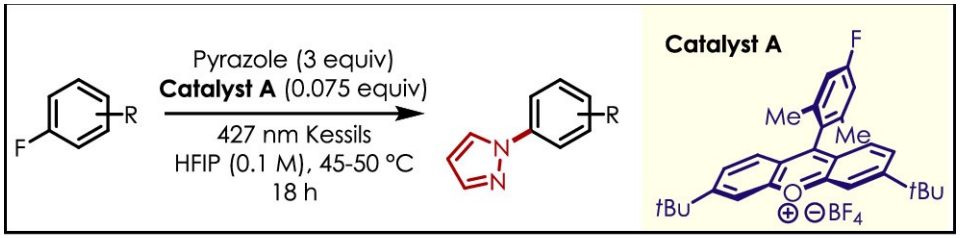
entry	deviations from the above conditions	yield[a]
1	none	55%
2	DCM	4%
3	MeCN	10%
4	HFIP as solvent	72%
5	3 equiv of pyrazole	68%
6	2 equiv of pyrazole	51%
7	1 equiv of pyrazole	45%
8	0.01 equiv of catalyst	48%
9	0.075 equiv of catalyst; HFIP	72%
10	456 nm Kessils	63%
11	427 nm Kessils	62%
12	427 nm Kessils with foil barrier	82%

[a]Yield determined by ^1H NMR using HMDSO as an internal standard

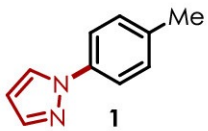
Using HFIP as solvent gave higher yield

Nicewicz, D. *et al. J. Am. Chem. Soc.* **2020**, *142* , 17187-17194

Substrate Scope (Heteroarene)



Arene Scope


1
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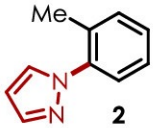
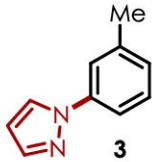
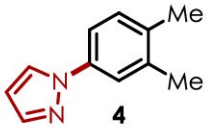

2
69%


3
23%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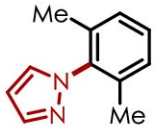
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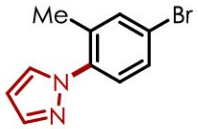
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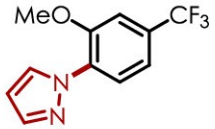
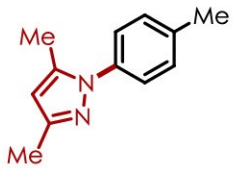
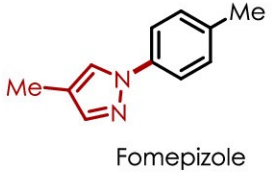
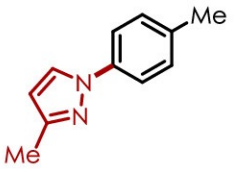

7
44%

Azole Scope[b]


8
29%


9
63%
Fomepizole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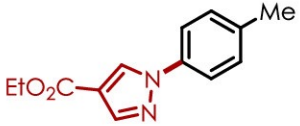
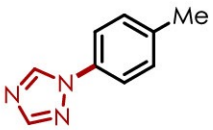

11
56%[c]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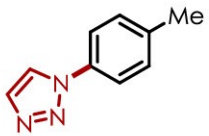
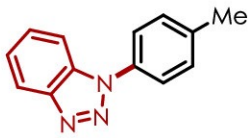
36%

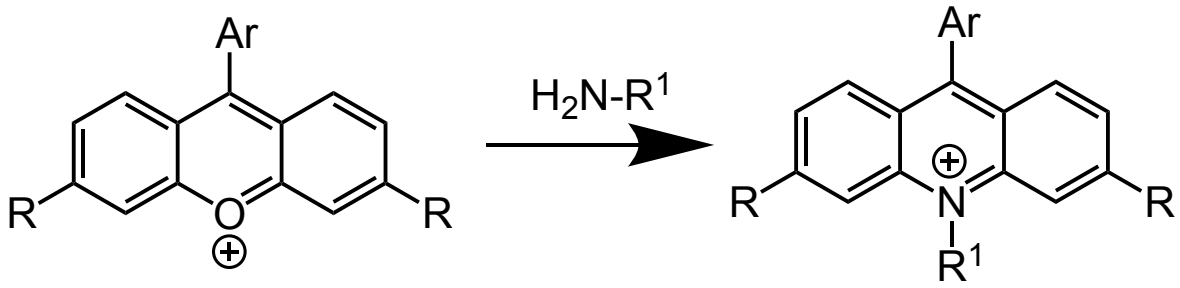

13
82%


14
84%

Nicewicz, D. *et al. J. Am. Chem. Soc.* **2020**, *142* , 17187-17194

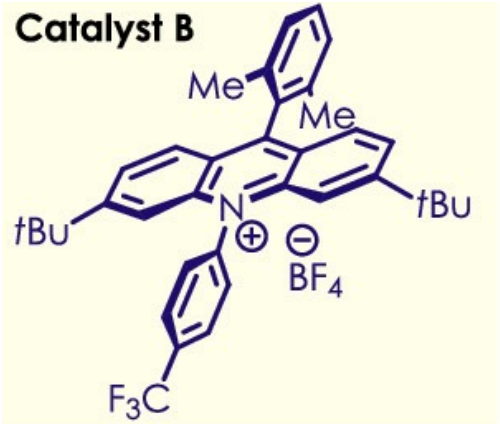
Optimization (Amine, Carboxylic acid)

- Xanthylium salt catalyst is not compatible with amine as nucleophile

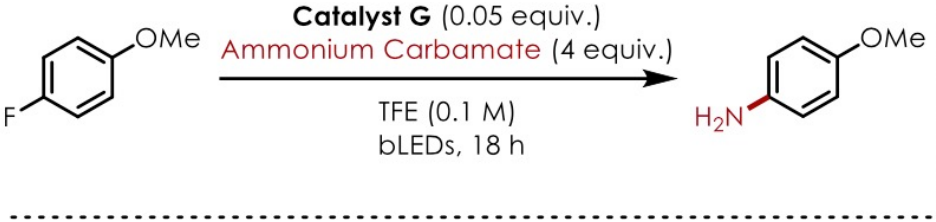


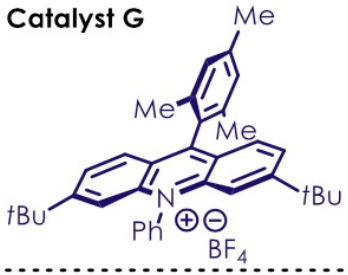
Nicewicz, D. *et al. Synlett.* **2019**, *30*, 827-832

- Using acridinium salt catalyst (Catalyst B) instead



Optimization (Amine, Carboxylic acid)

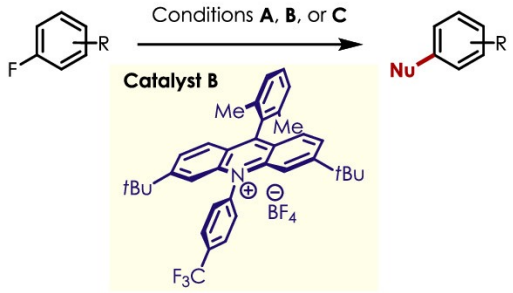




Entry	Deviations from above conditions	Yield[a]
1	None	<5%
2	TFE:DCE (2:1)	29%
3	TFE:DCE (1:1)	48%
4	TFE:DCE (1:2)	64%
5	TFE:DCE (1:3)	74%
6	1 equiv. ammonium carbamate; TFE:DCE (1:3)	18%
7	2 equiv. ammonium carbamate; TFE:DCE (1:3)	50%
8	3 equiv. ammonium carbamate; TFE:DCE (1:3)	54%
9	5 equiv. ammonium carbamate; TFE:DCE (1:3)	72%
10	0.03 equiv **Catalyst G**; TFE:DCE (1:3)	57%
11	0.05 equiv **Catalyst B**; TFE:DCE (1:3)	72%
12	0.05 equiv **Catalyst H**; TFE:DCE (1:3)	48%
13	0.05 equiv **Catalyst I**; TFE:DCE (1:3)	55%
14	0.05 equiv **Catalyst J**; TFE:DCE (1:3)	43%

[a]Yield determined by ^{1}H NMR using HMDSO as an internal standard

Substrate Scope (Amine, Carboxylic acid)



Condition A

Nu = H_2N

Catalyst B (0.05 equiv)
Ammonium Carbamate (4 equiv)
3:1 DCE:TFE (0.1 M)
427 nm Kessils, 18 h
45-50 °C

Condition B

Nu =

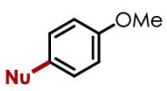
Catalyst B (0.05 equiv)
2-(aminomethyl)pyridine (3 equiv)
TFE (0.1 M), 427 nm Kessils
18 h, 45-50 °C

Condition C

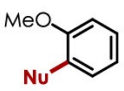
Nu =

Catalyst B (0.05 equiv)
Benzoic Acid (4 equiv)
$NaHCO_3$ (2 equiv)
TFE (0.1 M), 456 nm Kessils
18 h, 45-50 °C

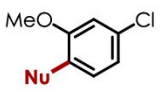
Arene Scope



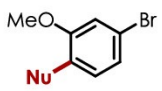
17
A-78%
B-69%
C-43%



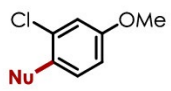
18
A-54%
B-70%
C-46%



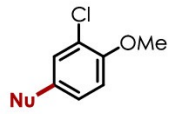
19
A-57%
B-52%
C-65%



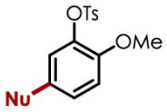
20
A-50%
B-52%
C-57%



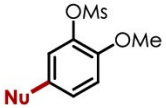
21
A-55%
B-83%
C-90%



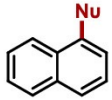
22
A-52%
B-55%[b]
C-28%



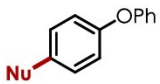
23
A-46%
B-41%
C-28%



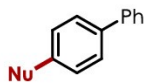
24
A-52%
B-37%
C-27%



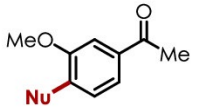
25
A-40%
B-82%
C-32%[c]



26
A-59%
B-76%
C-28%



27
A-37%
B-61%
C-N.R.



28
A-26%
B-17%
C-35%

[a]Average isolated yields are reported (0.3−0.5 mmol, n = 2); 45−50 °C represents the ambient temperature of the light setup using external fan cooling. [b]Eleven percent C−O substitution product. [c]0.10 equiv of Catalyst B used. [d]Ratio determined by ^{1}H NMR. [e]Nine percent disbustitution observed. [f]3 equiv of benzyl amine as nucleophile [g]Isolated yield (0.150 mmol, n = 1). [h]Yield determined by ^{1}H NMR using HMDSO as an internal standard. [i]Isolated yield (0.050 mmol, n = 1). [j]0.075 equiv of Catalyst B used. [k]DCE used as in place of TFE. [l]4 equiv of carboxylic acid and 2 equiv of $NaHCO_3$ employed.

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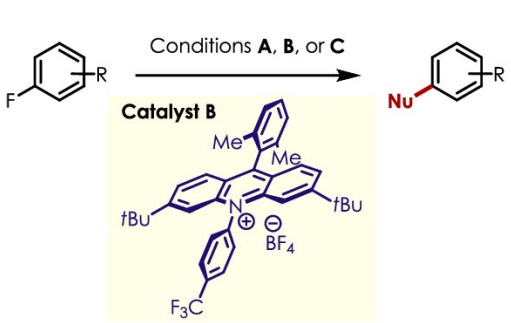
Substrate Scope (Amine, Carboxylic acid)



Condition A

Nu = H_2N

Catalyst B (0.05 equiv)
Ammonium Carbamate (4 equiv)
3:1 DCE:TFE (0.1 M)
427 nm Kessils, 18 h
45-50 °C

Condition B

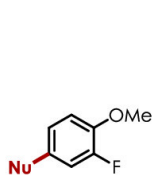
Nu =

Catalyst B (0.05 equiv)
2-(aminomethyl)pyridine (3 equiv)
TFE (0.1 M), 427 nm Kessils
18 h, 45-50 °C

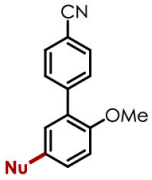
Condition C

Nu =

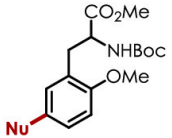
Catalyst B (0.05 equiv)
Benzoic Acid (4 equiv)
$NaHCO_3$ (2 equiv)
TFE (0.1 M), 456 nm Kessils
18 h, 45-50 °C



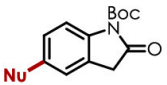
29
A-65%, 1.2:1 (C1:C3)[d]
B-65%, 1:1.9 (C1:C3)[d]
C-41%[e], 1.5:1 (C1:C3)[d]



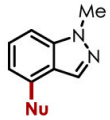
30
A-62%
B-75%
C-25%[c]



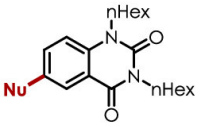
31
A-66%
B-61%
C-31%[c]



32
A-48%
B-73%[f]
C-N.R.

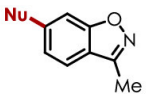


33
A-N.R.
B-58%[f,g]
C-28%[h]

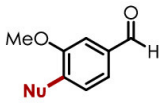


34
A-48%
B-24%
C-44%[i]

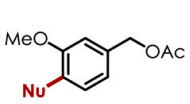
35
A-N.R.
B-N.R.
C-24%



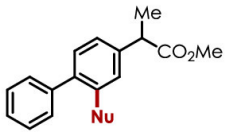
36
A-14%[h]
B-18%[f,g]
C-N.R.



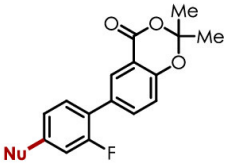
37
A-32%
B-N.R.
C-N.R.



38
A-N.R.
B-N.R.
C-53%



Flurbiprofen methyl ester
39
A-N.R.
B-N.R.
C-25%[j]

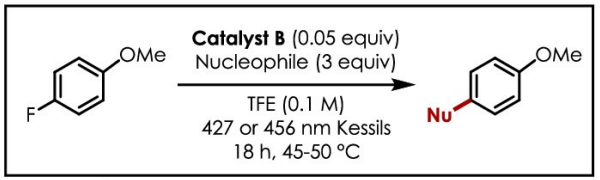


Diflunisal acetonide
40
A-N.R.
B-16%[j]
C-18%[j], 2.2:1 (C1:C3)[d]

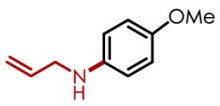
[a]Average isolated yields are reported (0.3−0.5 mmol, $n = 2$); 45−50 °C represents the ambient temperature of the light setup using external fan cooling. [b]Eleven percent C−O substitution product. [c]0.10 equiv of Catalyst B used. [d]Ratio determined by ^{1}H NMR. [e]Nine percent disbustitution observed. [f]3 equiv of benzyl amine as nucleophile [g]Isolated yield (0.150 mmol, $n = 1$). [h]Yield determined by ^{1}H NMR using HMDSO as an internal standard. [i]Isolated yield (0.050 mmol, $n = 1$). [j]0.075 equiv of Catalyst B used. [k]DCE used as in place of TFE. [l]4 equiv of carboxylic acid and 2 equiv of $NaHCO_3$ employed.

Nicewicz, D. *et al. J. Am. Chem. Soc.* **2020**, *142* , 17187-17194

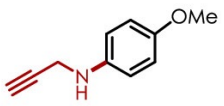
Substrate Scope (Amine, Carboxylic acid)



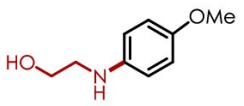
Nucleophile Scope



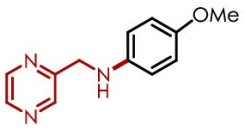
41
42%



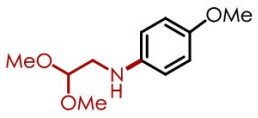
42
57%



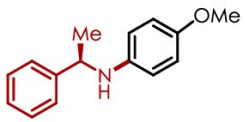
43
58%



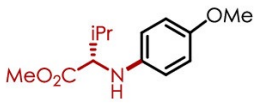
44
70%



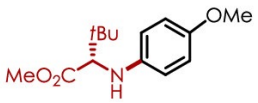
45
70%



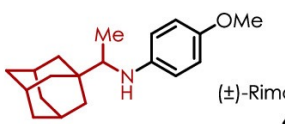
46
66%



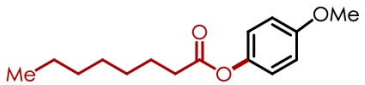
47
50%



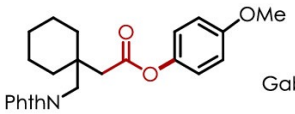
48
55%



(±)-Rimantadine
49
43%[k]



50
63%[g,l]



Gabapentin Phthalimide
51
39%[l]

[a]Average isolated yields are reported (0.3−0.5 mmol, n = 2); 45−50 °C represents the ambient temperature of the light setup using external fan cooling. [b]Eleven percent C−O substitution product. [c]0.10 equiv of Catalyst B used. [d]Ratio determined by ^{1}H NMR. [e]Nine percent disbustitution observed. [f]3 equiv of benzyl amine as nucleophile [g]Isolated yield (0.150 mmol, n = 1). [h]Yield determined by ^{1}H NMR using HMDSO as an internal standard. [i]Isolated yield (0.050 mmol, n = 1). [j]0.075 equiv of Catalyst B used. [k]DCE used as in place of TFE. [l]4 equiv of carboxylic acid and 2 equiv of $NaHCO_3$ employed.

- Modification without racemizing→ 46~48
- Applicable to drug compound, but resulted in low to moderate yield.

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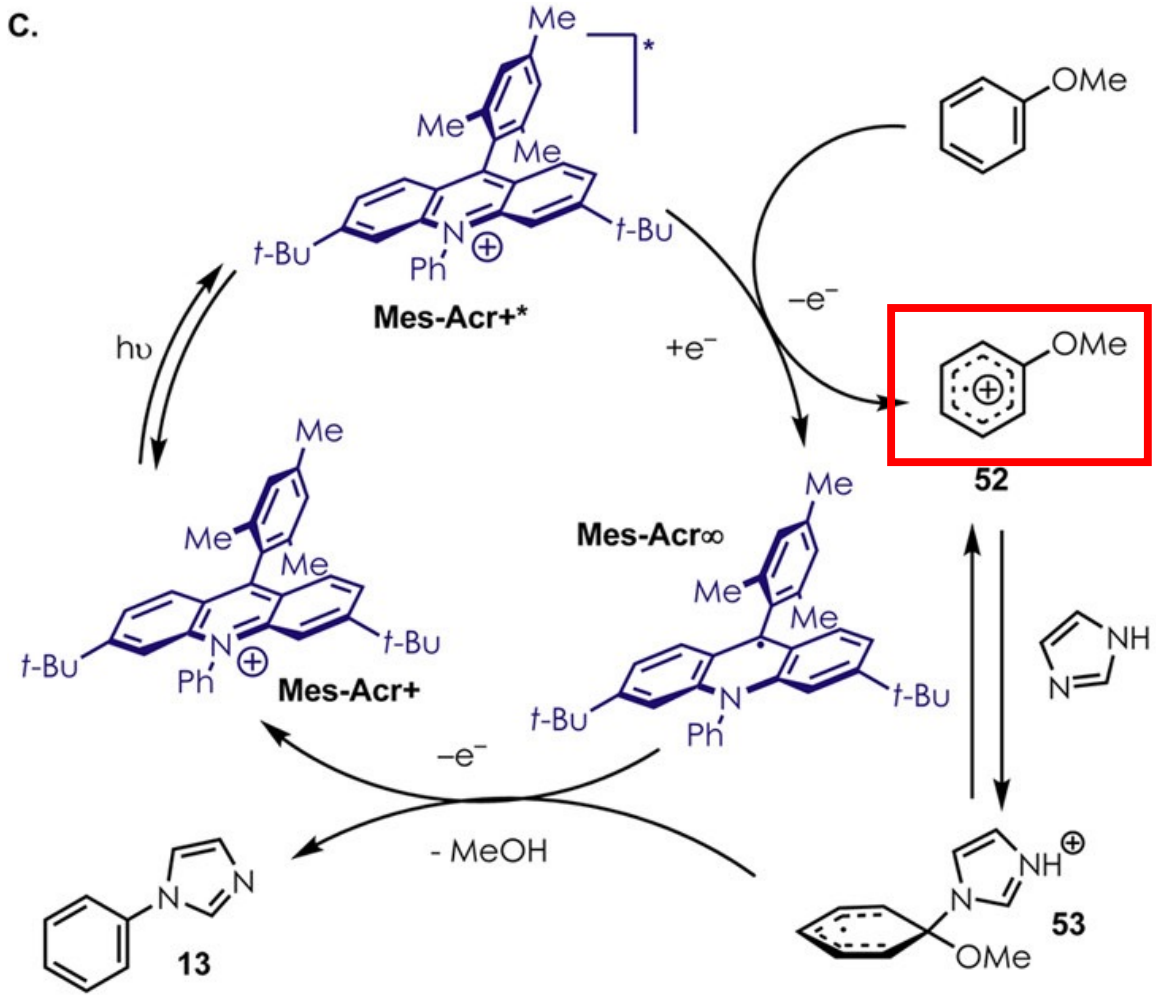
Proposed Mechanism

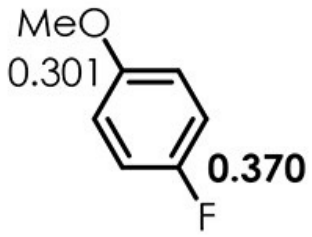


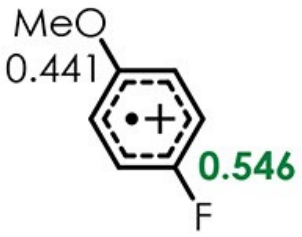
J. Am. Chem. Soc. **2017**, *139*, 16100–16104

Rational for regioselectivity

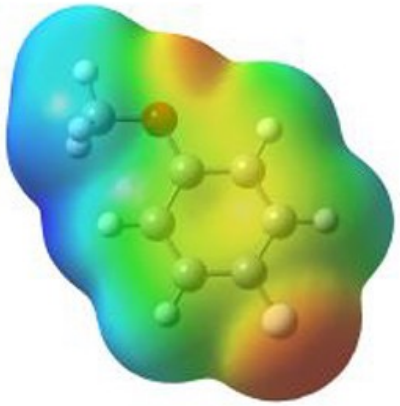
A. Computed Electron Density of 4-fluoroanisole (ground state and cation radical)

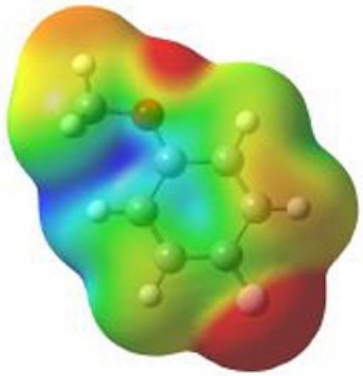
B3LYP/6-31+G(d,p)





Positive charge resides on C-F

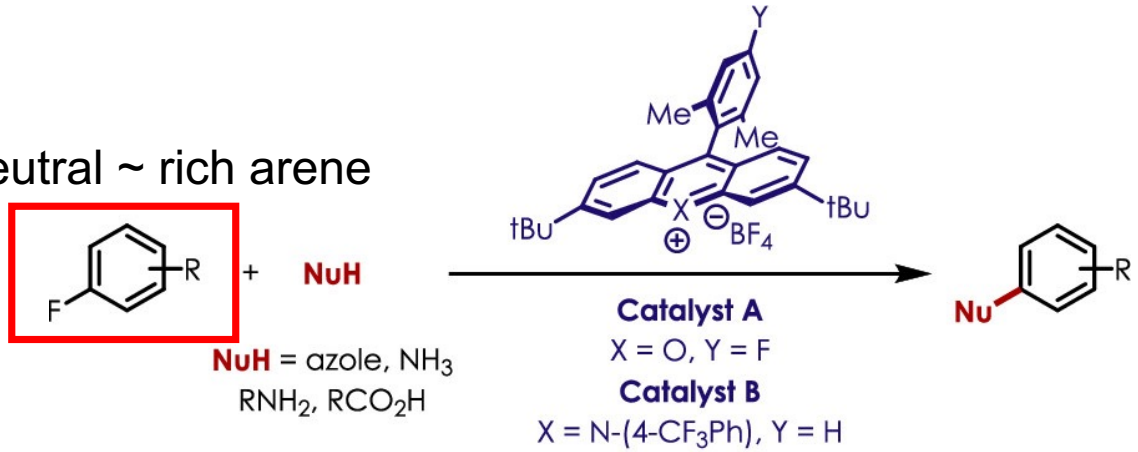




Nicewicz, D. *et al. J. Am. Chem. Soc.* **2020**, *142* , 17187-17194

Short Summary

Electron neutral ~ rich arene



- Reverse the reactivity of electron-rich arene with single-electron oxidation.
- Late-stage functionalization of pharmaceutical compounds

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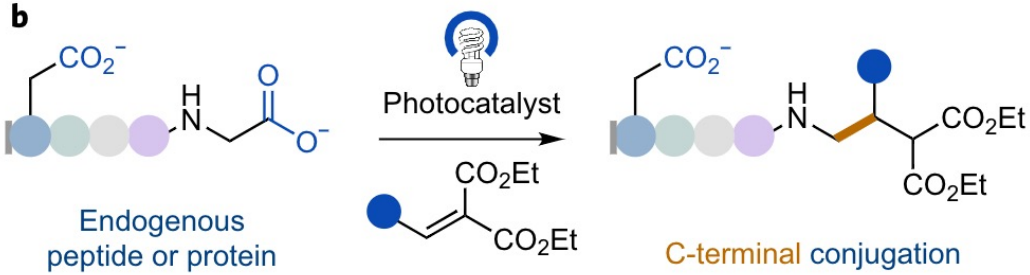
Contents

- Mesolytic Cleavage of Radical Cation
- Oxidative S_NAr Pathway
- Application to Biomolecular
- Summary

Application to Biomolecular

- Previous reports

  - Decarboxylative C term modification



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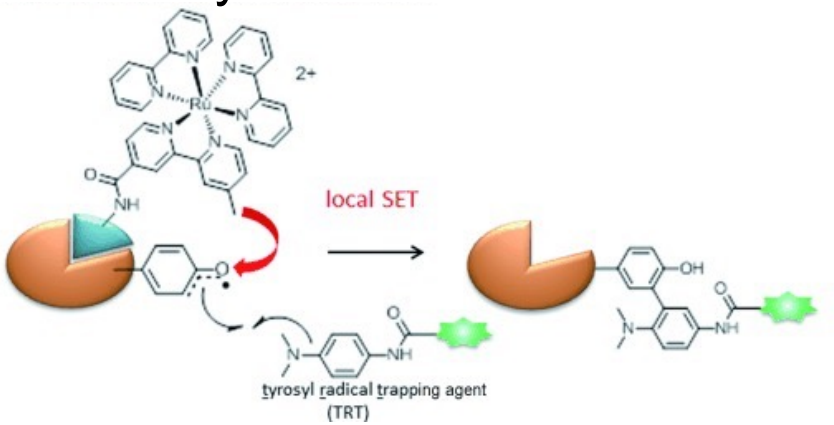
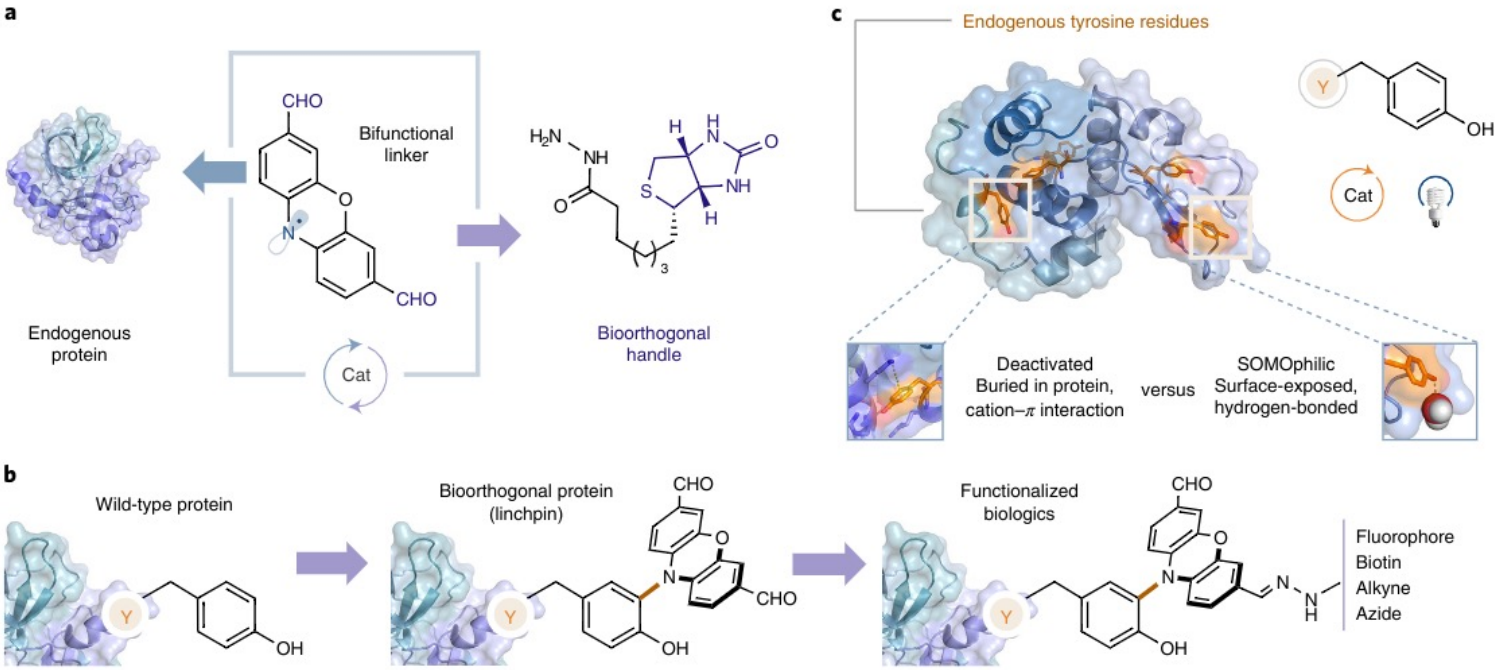
  - Ligand directed Tyr modification



Sato, S., & Nakamura, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 8681-8684

Site-selective Tyr Modification



- Tyrosine selective modification
- Further functionalization with versatile handle

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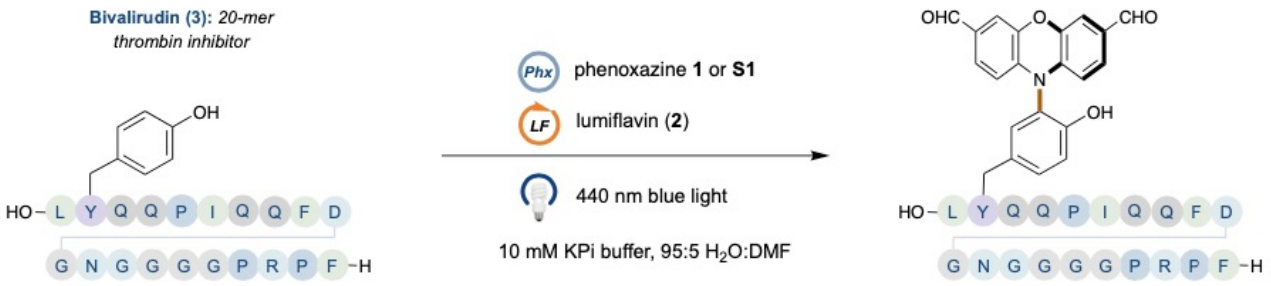
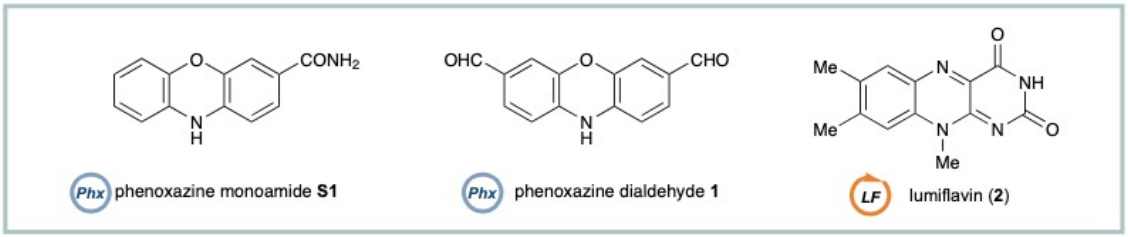
Optimization

II. Reaction optimization with bivalirudin (3)





entry	phenoxazine (equiv.)	lumiflavin	reaction time	conversion
1	phenoxazine monoamide **S1** (10 equiv.)	1 equiv.	3 hours	65%
2	phenoxazine dialdehyde **1** (10 equiv.)	3 equiv.	3 hours	46%
3	phenoxazine dialdehyde **1** (10 equiv.)	3 equiv.	5 hours	74%
4	phenoxazine dialdehyde **1** (100 equiv.)	3 equiv.	5 hours	95%
5	phenoxazine dialdehyde **1** (100 equiv.)	0 equiv.	5 hours	0% (sm recovered)
6	phenoxazine dialdehyde **1** (100 equiv.)	3 equiv.	5 hours (dark)	0% (sm recovered)

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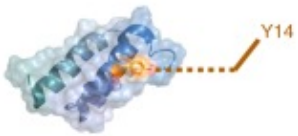
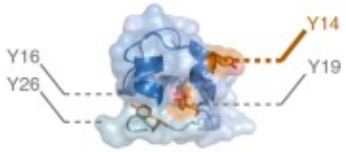
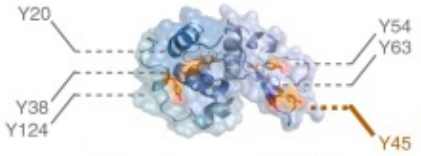
Substrate Scope of Peptide or Protein



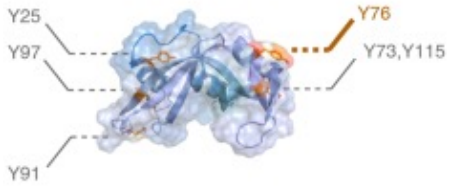
4, ZVar affibody (8.1 kDa)
1 tyrosine
76%[a]
Y14 single product



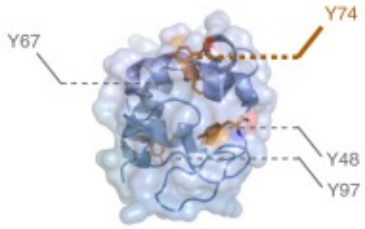
5, Human insulin (5.8 kDa)
4 tyrosines
100%[a]
Y14/Y19, 6:1



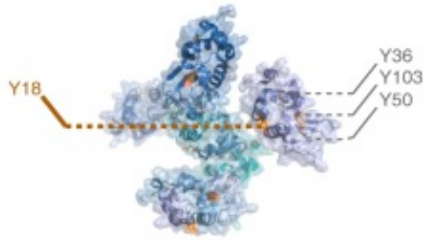
6, Human lysozyme (14.4 kDa)
6 tyrosines
65%[a]
Y45 single product



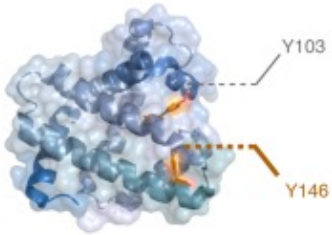
7, Ribonuclease A (13.7 kDa)
6 tyrosines
49%[a]
Y76 single product



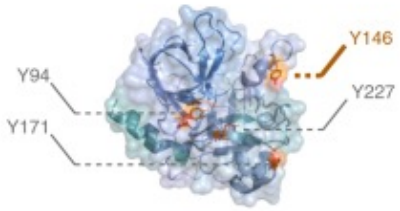
8, Cytochrome C (12.4 kDa)
4 tyrosines
64%
Y74/(Y48,Y97), 20:1



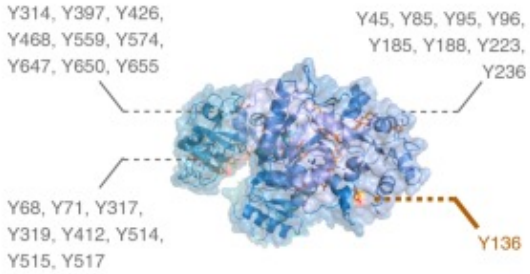
9,
4 tyrosines
89%[a]
Y18/Y103, 30:1



10, Myoglobin (13.7 kDa)
2 tyrosines
72%
Y146 single product



11, Chymotrypsinogen A (25.7 kDa)
4 tyrosines
76%[a]
Y146/Y171, 10:1



12, Serotransferrin (77.0 kDa)
26 tyrosines
55%
Y136 single product

- Site-selective Tyr modification was achieved

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Rational for Site-selectivity

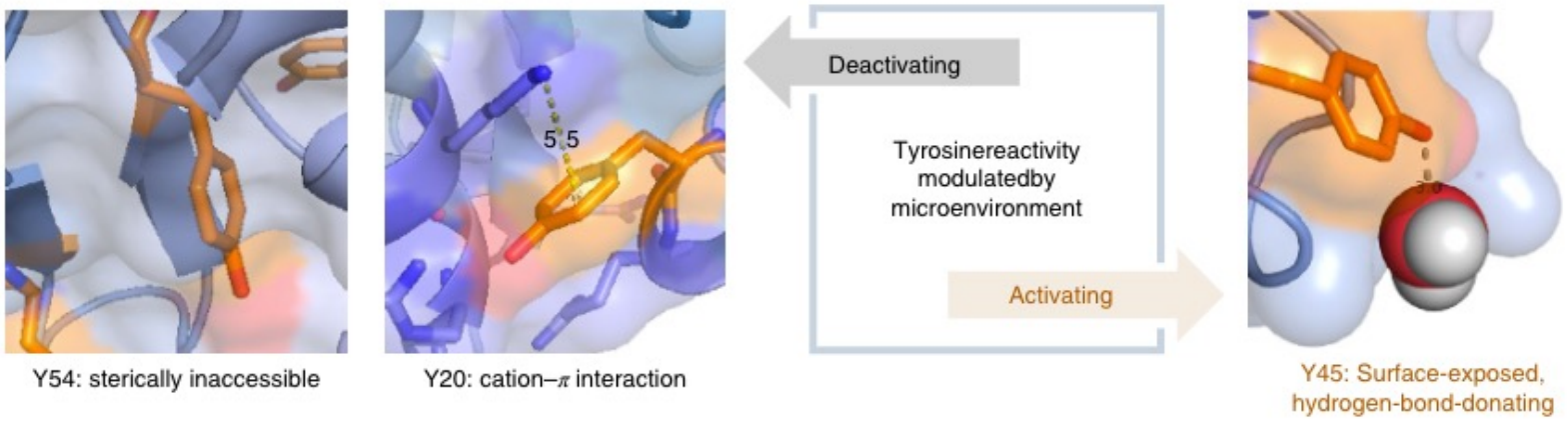

Fig. 2 | Tyrosine microenvironments. Representative tyrosines from human lysozyme (**6**) in their respective microenvironments. Y20 and Y54 are not reactive due to steric constraints or deactivating cation–π interactions, whereas Y45 is labelled with high efficiency because it is surface-exposed and hydrogen-bond-donating to surrounding aqueous media.

- A residue surface-exposed and activated is modified.
- Sterically hindered or deactivated Tyr did not react.
- Cation-π interaction reduces π electron density.

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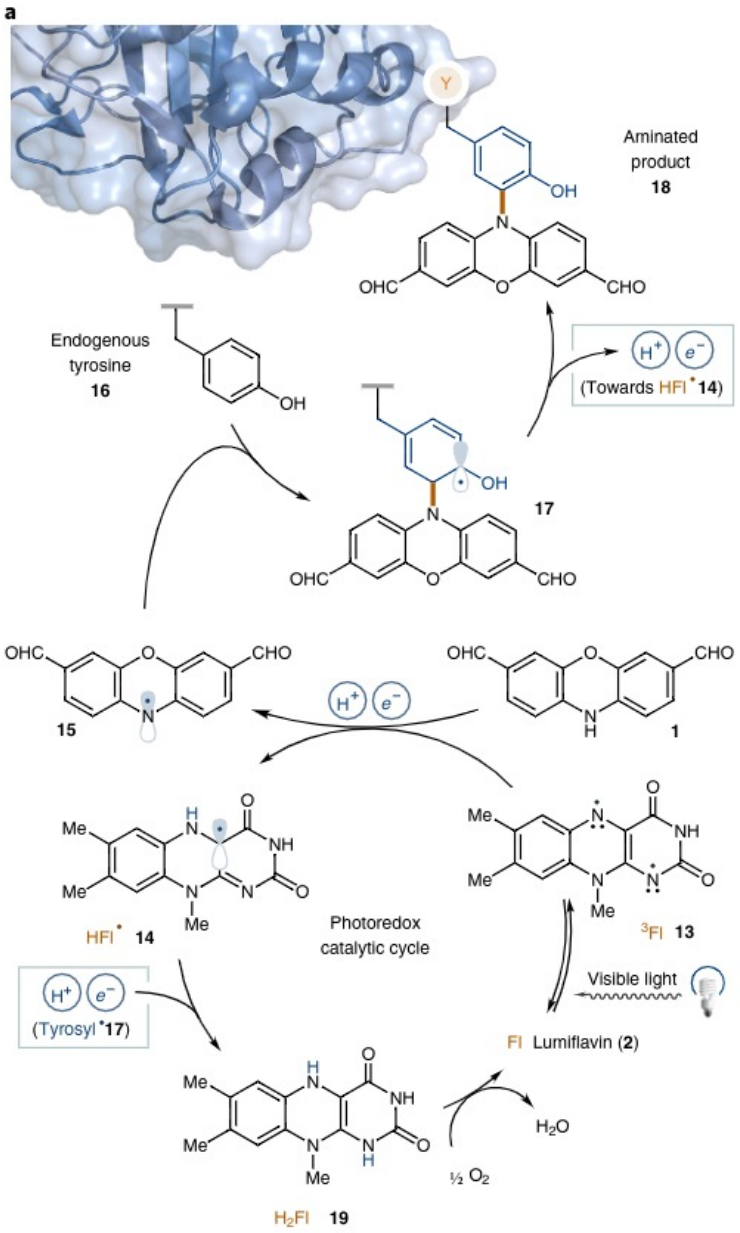
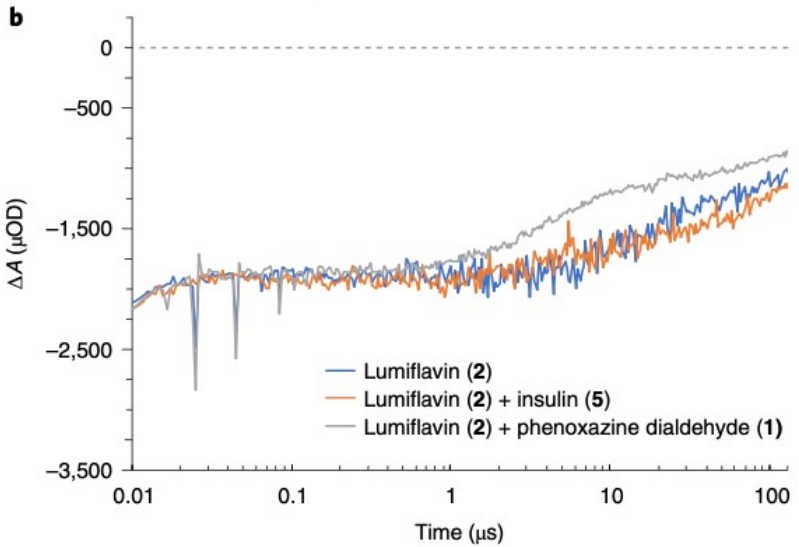
Proposed Mechanism





can be oxidized by O_2. **b**, Time-resolved transient absorption spectroscopy (pump/probe, 370 nm/433 nm) indicates that under reaction conditions (10 mM KPi buffer, pH 7, 95:5 H_2O/dimethylformamide), the lumiflavin excited state is quenched by **1** and not by insulin (**5**). This offers support for the formation of **15** versus protein oxidation. ΔA, change in absorbance; μOD, optical density units. See Supplementary Section 7 for additional experimental details.

- From excited state absorption, flavin oxidates phenoxiazine not Tyr.

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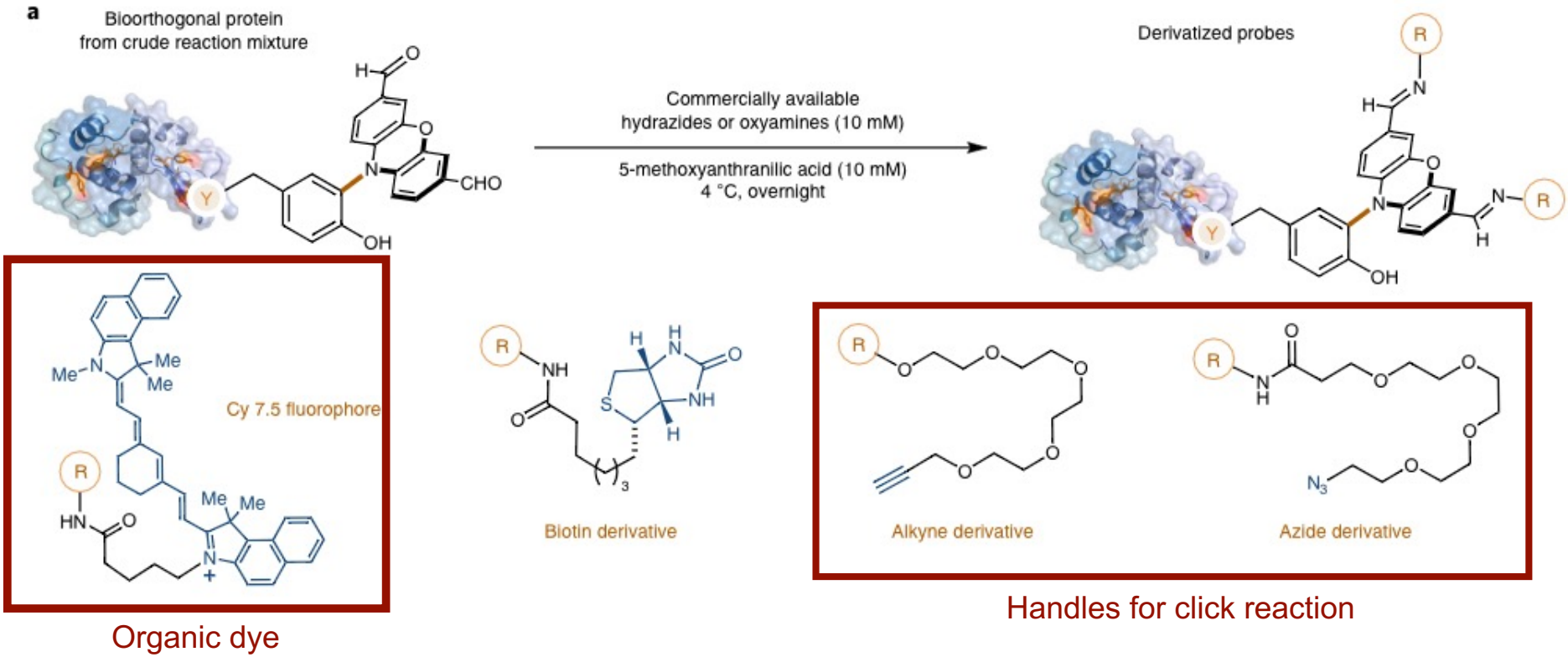
Further Functionalization



Organic dye

Handles for click reaction

- Aldehyde selective and one-pot transformation

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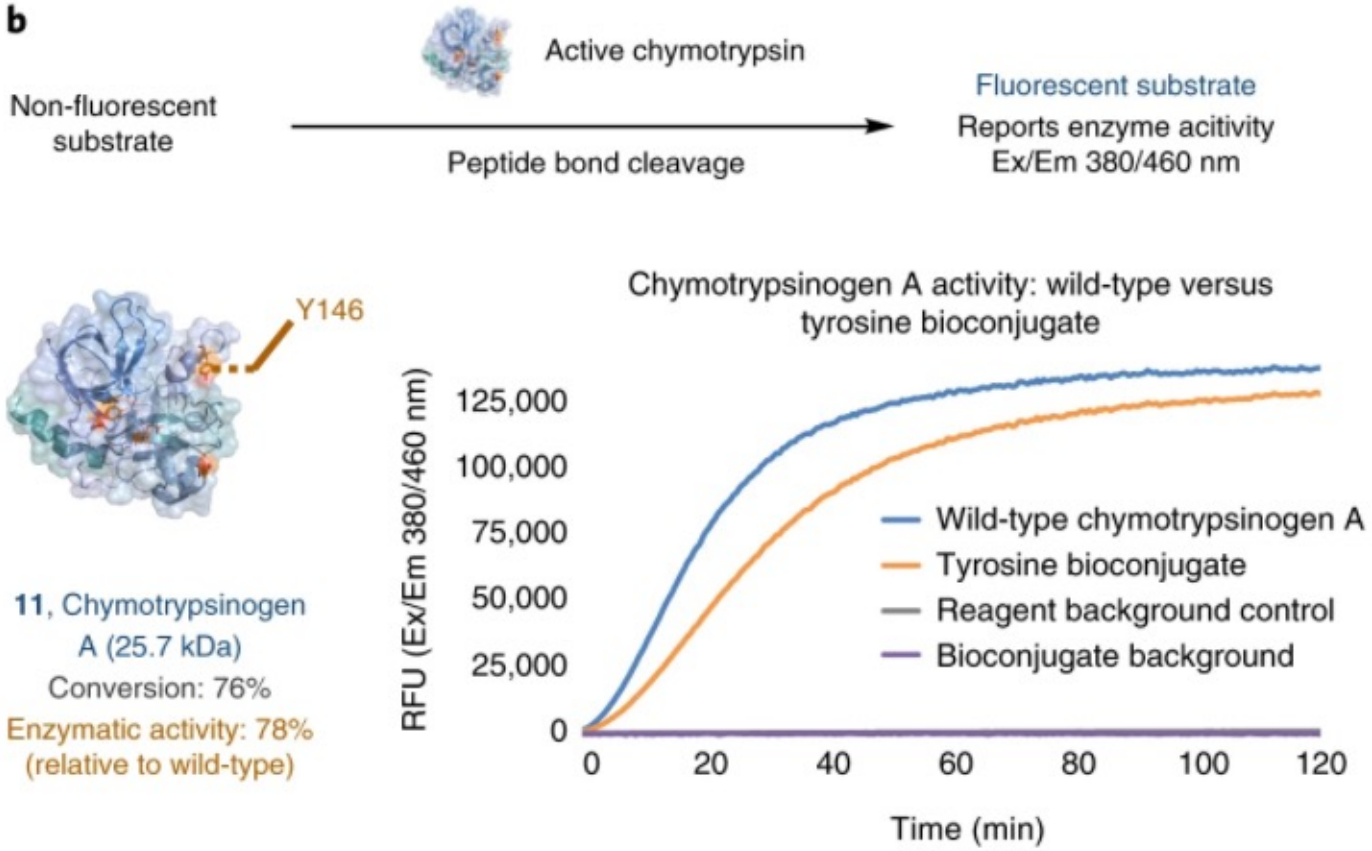
Influence on Protein Structure



- 78% of the native activity was retained.

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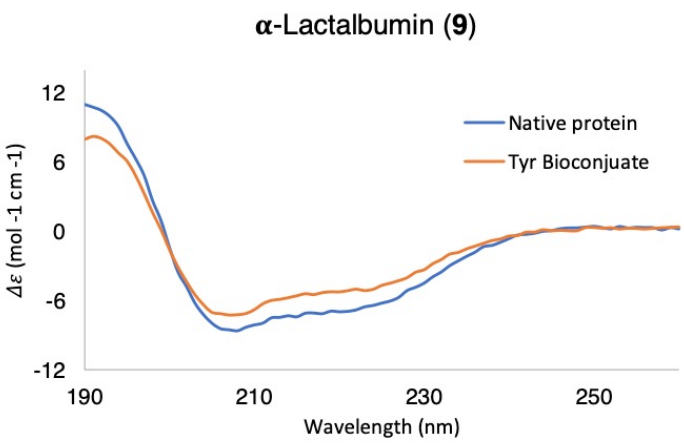
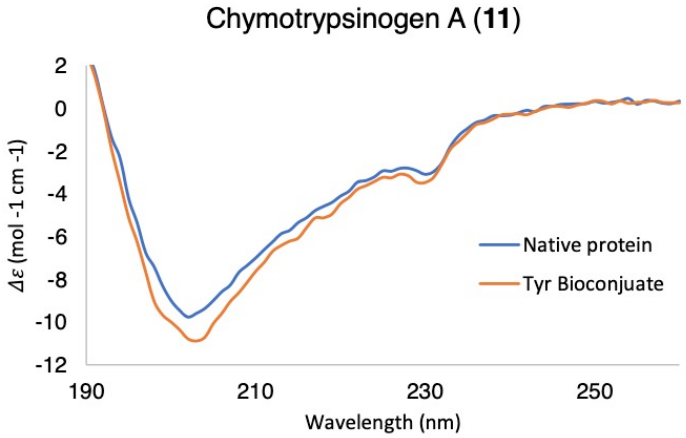
Influence on Protein Structure

- CD spectra of native and modified protein

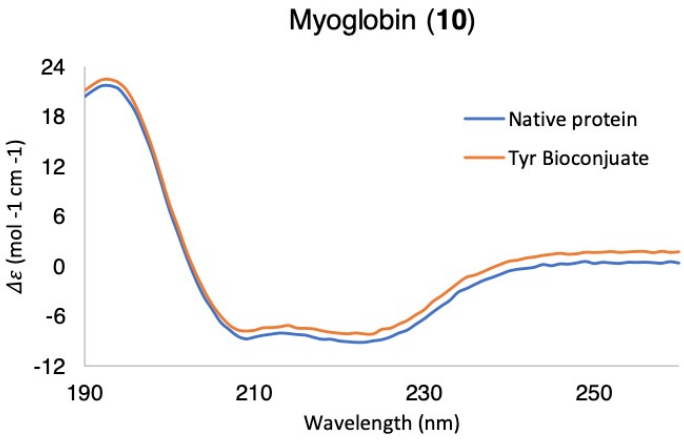
f. α-Lactalbumin (9)



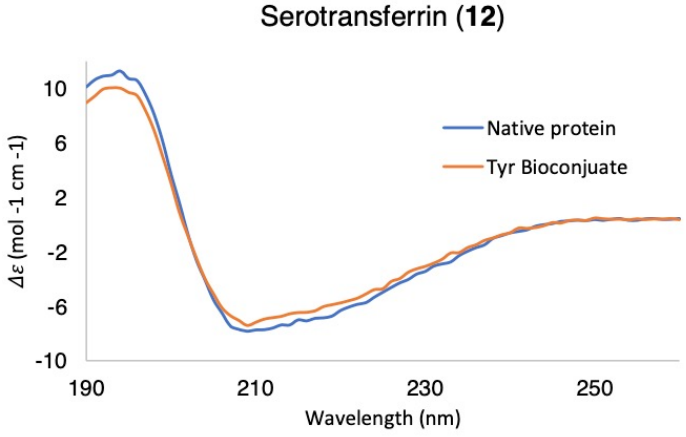
h. Chymotrypsinogen A (11)



g. Myoglobin (10)



i. Serotransferrin (12)



➢ Secondary structures were generally retained

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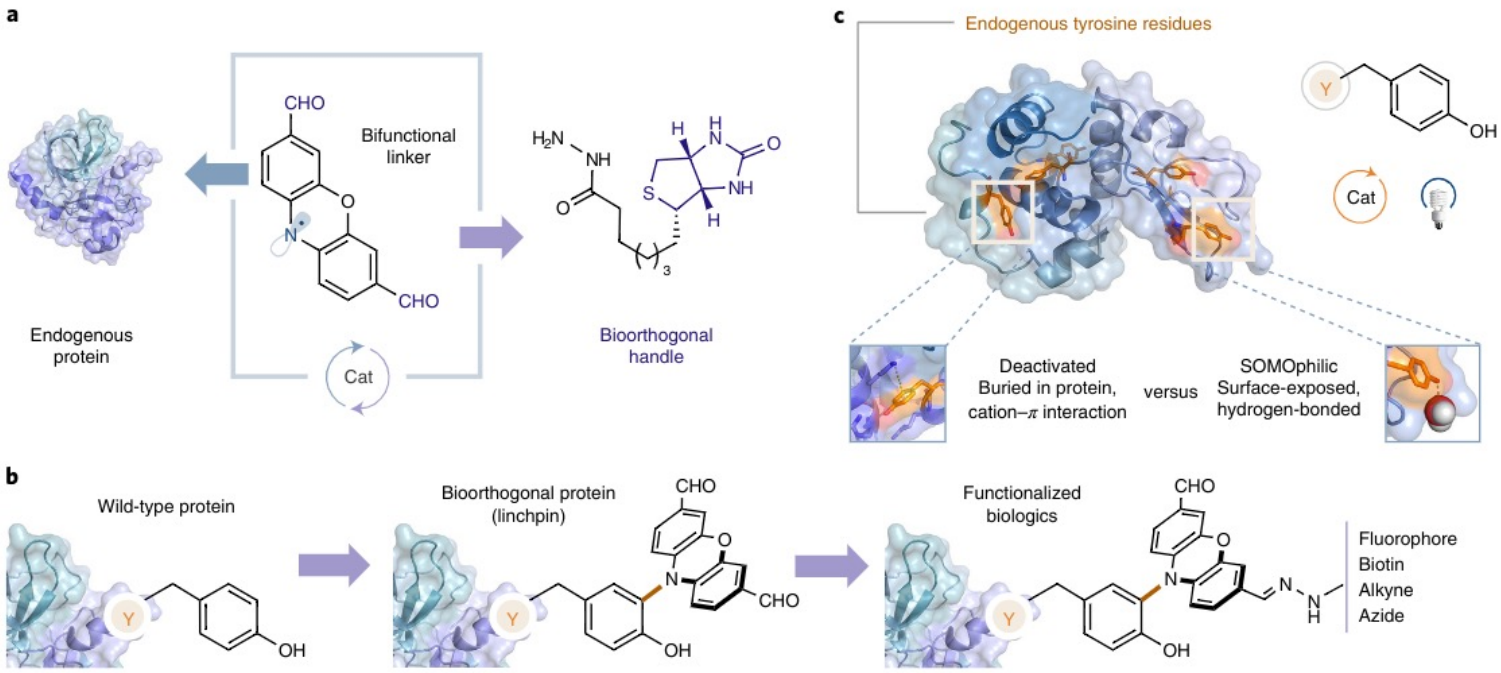
Short Summary



- Reactive Tyr residue is functionalized selectively.
- Further functionalization with various biorthogonal moieties
- Retaining 3D structure or enzymatic activities

Summary

- Reaction proceeds generally under mild condition
- Reversing reactivity of the substrates unreactive in conventional pathways
- Applicable to biomolecular modification