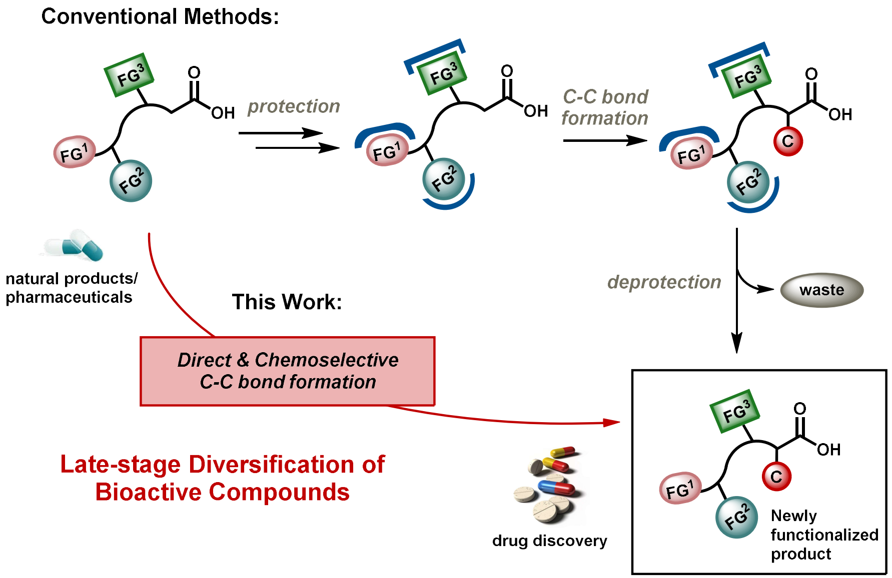
Deconstructive Functionalization via C(sp^3)-C(sp^3) Bond Cleavage

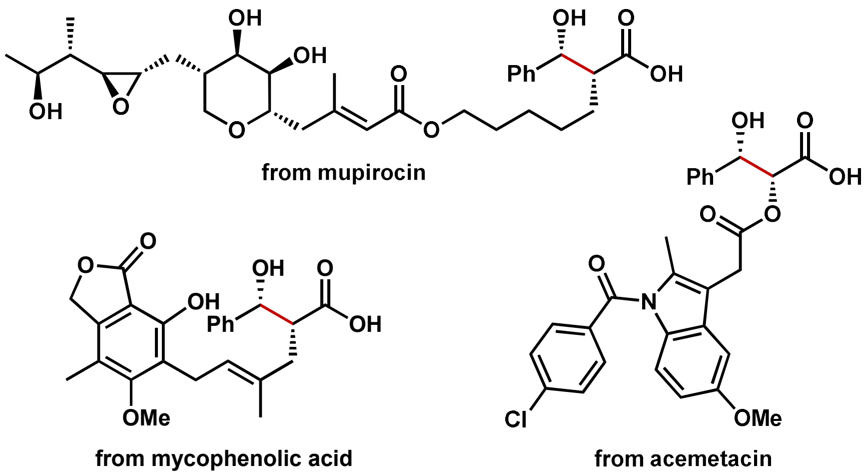
2021/09/30
Literature Seminar
Mina Yamane (M2)

Table of Contents

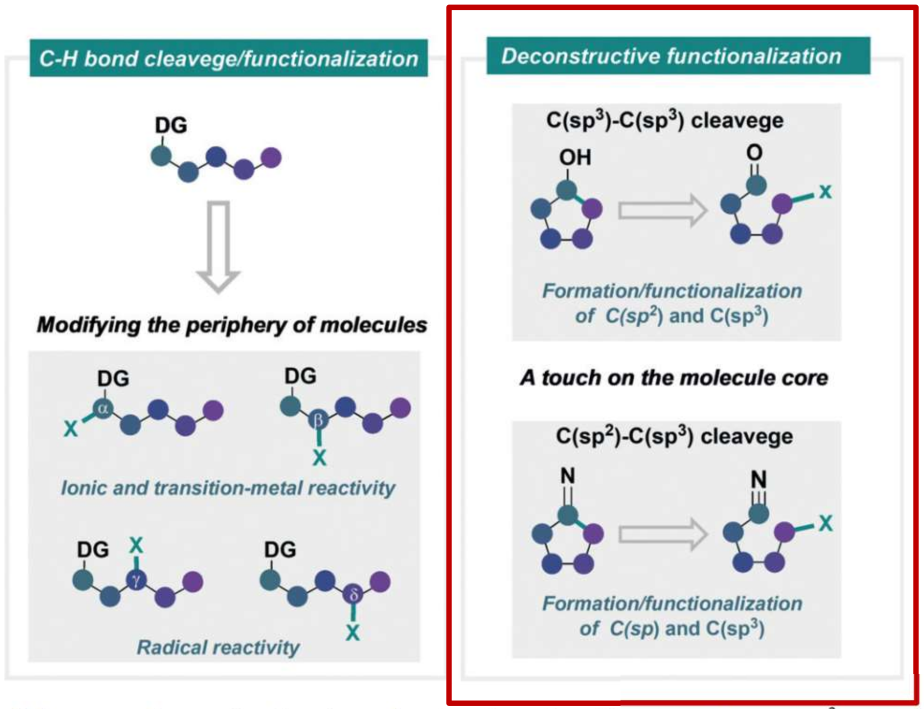
Table of Contents

Introduction





T. Fujita, *et al. Angew. Chem. Int. Ed.* **2021**, *just accepted.*



Scheme 1. Strategies for the selective functionalization of inert sp^3 carbon centers. DG = directing group.

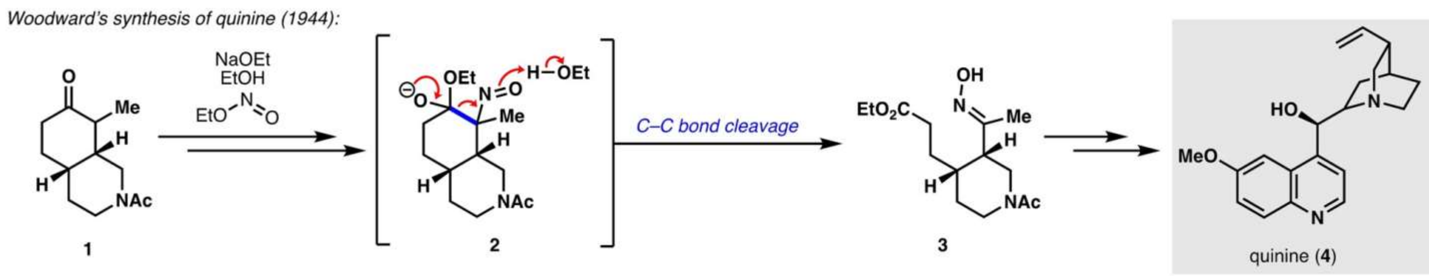
"Fast/efficient exploration of new chemical space for drug discovery"

S. Morcillo, *et al. Angew. Chem. Int. Ed.* **2019**, 58, 14044.

A Brief Introduction to C-C Bond Cleavage

C-C bond cleavage can be encountered in…

- ◆ Steam cracking process of crude oil at high temperature/pressure in the petroleum oil industry
- ◆ Classical reactions (e.g. sigmatropic rearrangements, Beckmann rearrangement, Baeyer-Villiger oxidation, retro-aldol/allylation, etc.)
- ◆ Strategic approaches for total syntheses



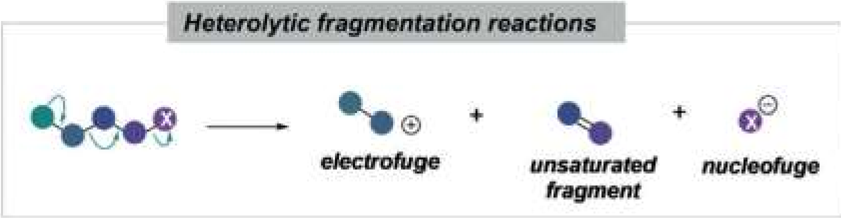
R. Woodward, *et al. J. Am. Chem. Soc.* **1944**, *66*, 849.
(scheme from: R. Sarpong, *et al. Angew. Chem. Int. Ed.* **2020**, *59*, 18898.)

⇒ Remaining Challenge:
Activation of *unbiased* $C(sp^3)$-$C(sp^3)$ bonds in a general/efficient manner

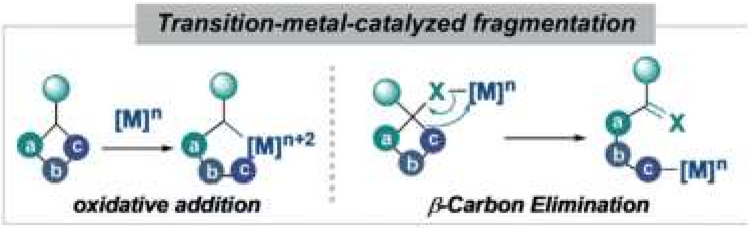
B. Morandi, *et al. Chem. Rev.* **2021**, 121, 300.

Concepts of $C(sp^3)$-$C(sp^3)$ Fragmentation

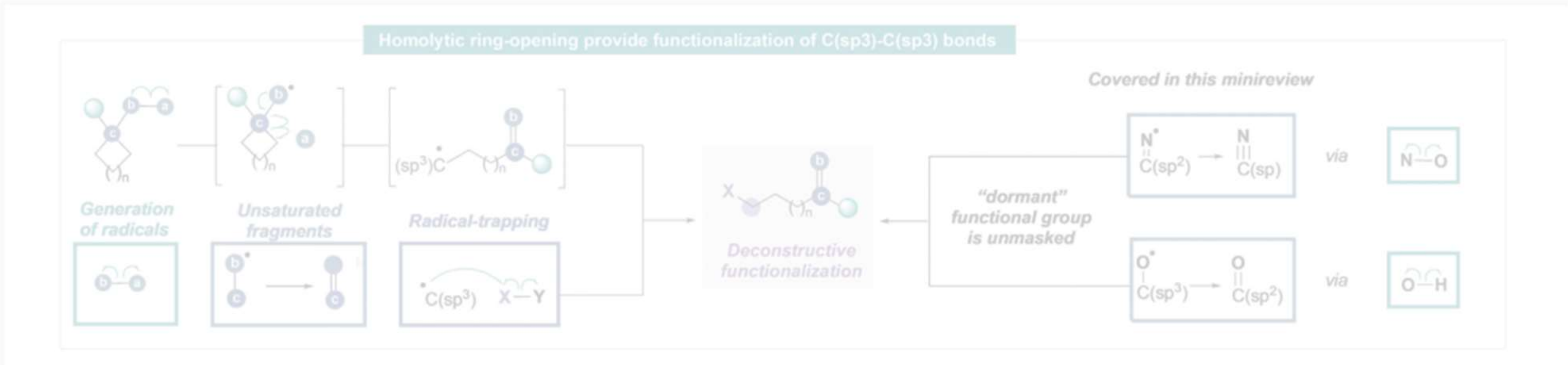
Pioneering Approaches by Eschenmoser (1950s) ⇢ ⇢ Grob



Transition Metal Catalyzed Approaches (over the last 3 decades)



Another Recent Approach



J. Williams, *Angew. Chem. Int. Ed.* **2013**, *52*, 11222.
S. Morcillo, *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 14044.

C(sp^3)-C(sp^3) Bond Activation

Compared to other bonds:
✘ Less polarized

✘ Less favorable orbital directionality for interactions w/ transition metals

✘ Substituents on both ends sterically prevent metal approach

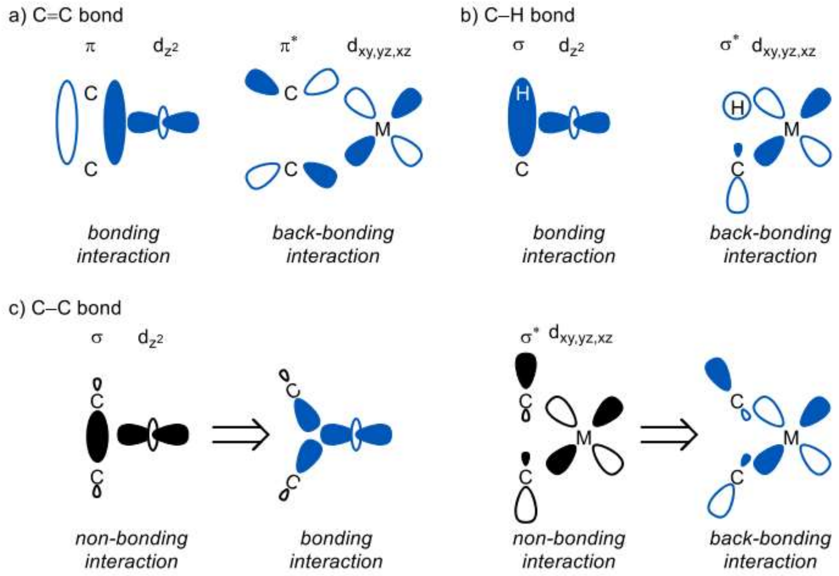
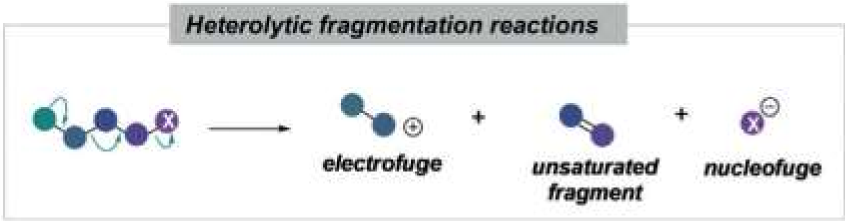


Figure 2. Comparison of the favorable orbital interactions between (a) C=C, (b) C–H, and (c) C–C bonds and transition metals. Symmetry-allowed orbital interactions are indicated in blue and white.

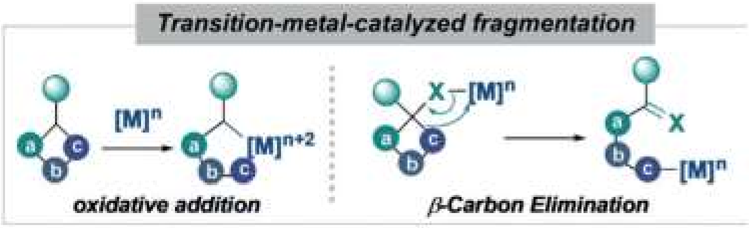
B. Morandi, *et al. Chem. Rev.* **2021**, 121, 300.

Concepts of C(sp3)-C(sp3) Fragmentation

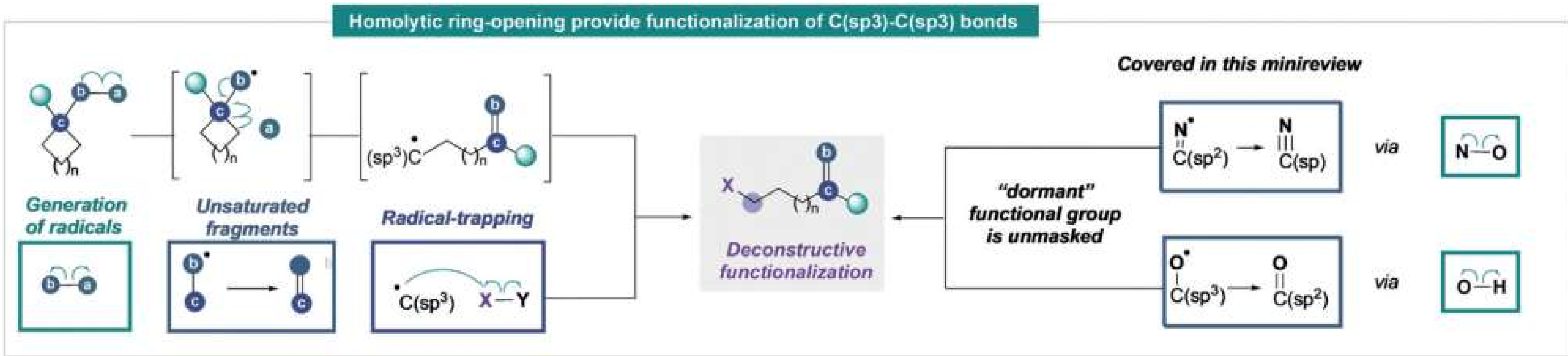
Pioneering Approaches by Eschenmoser (1950s) ⇢ ⇢ Grob



Transition Metal Catalyzed Approaches (over the last 3 decades)



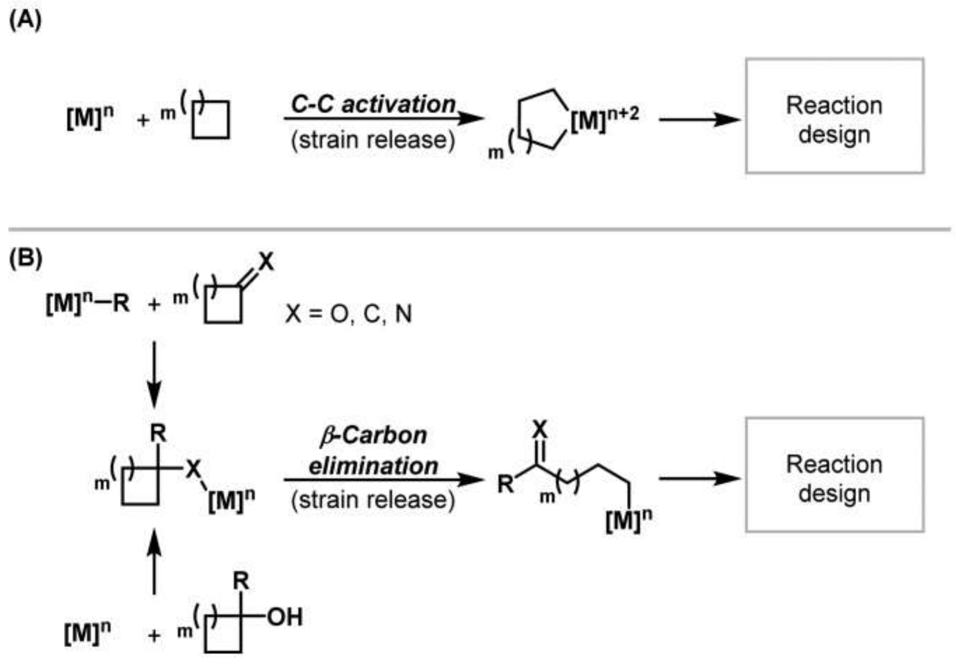
Another Recent Approach



J. Williams, *Angew. Chem. Int. Ed.* **2013**, *52*, 11222.
S. Morcillo, *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 14044.

Point to Note

Scheme 1. C–C Cleavage of Small Rings by (A) C–C Activation and (B) β-Carbon Elimination



Most common tactic: uses strain-release as crucial driving force

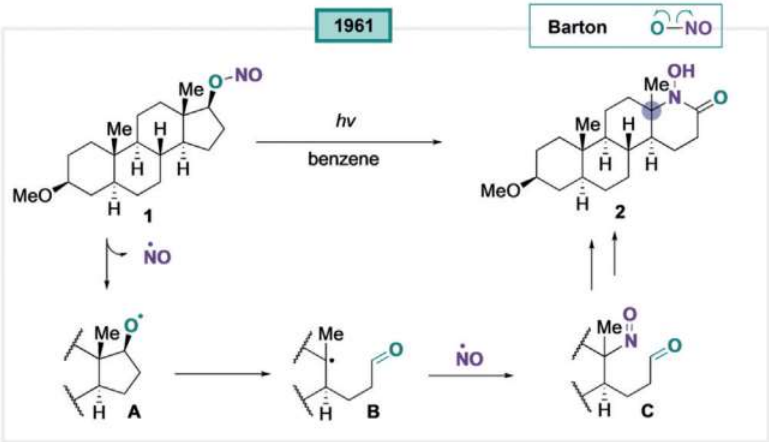
This seminar: covers activation of *unstrained compounds*

J. Bower *et al.* Chem. Rev. **2017**, *117*, 9404.

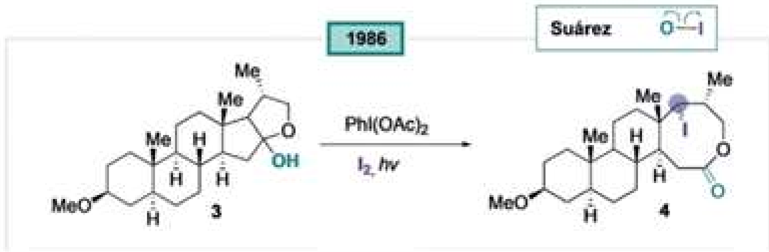
Table of Contents

Deconstructive Functionalization of Cyclic Alcohols

Strategy: Prefunctionalization of alcohols
⇒ BDE(O-H) ≈ 105 kcal/mol >> BDE(O-NO) ≈ 37 kcal/mol



Scheme 3. Deconstructive functionalization by homolysis of O–NO bonds.



✔ **Tandem β-fragmentation/ iodolactonization of steroidal alcohols**

E. Suarez, *et al. J. Org.* **1994**, *59*, 4393.

S. Morcillo, *et al. Angew. Chem. Int. Ed.* **2019**, 58, 14044.

Photocatalyzed Approaches

Photoredox catalyst × Bronsted Base × Thiol H-donor

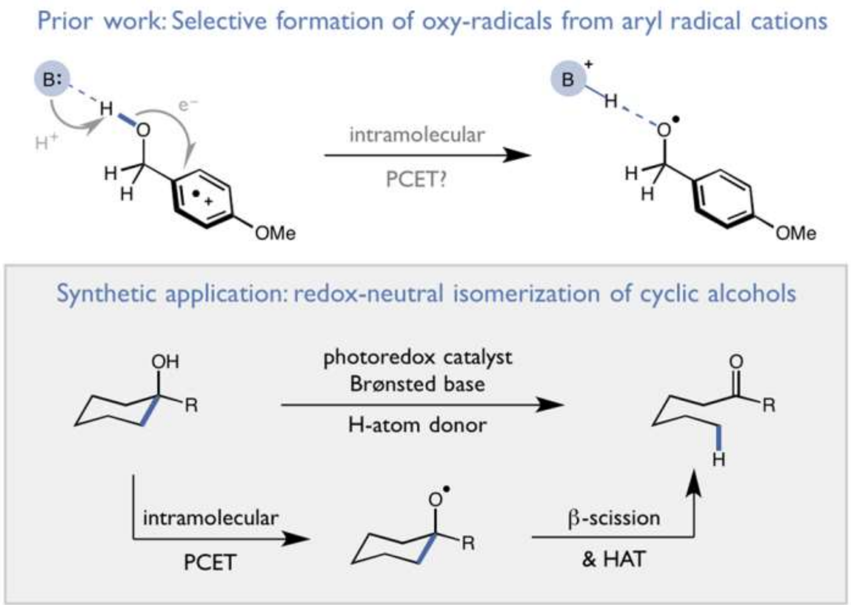


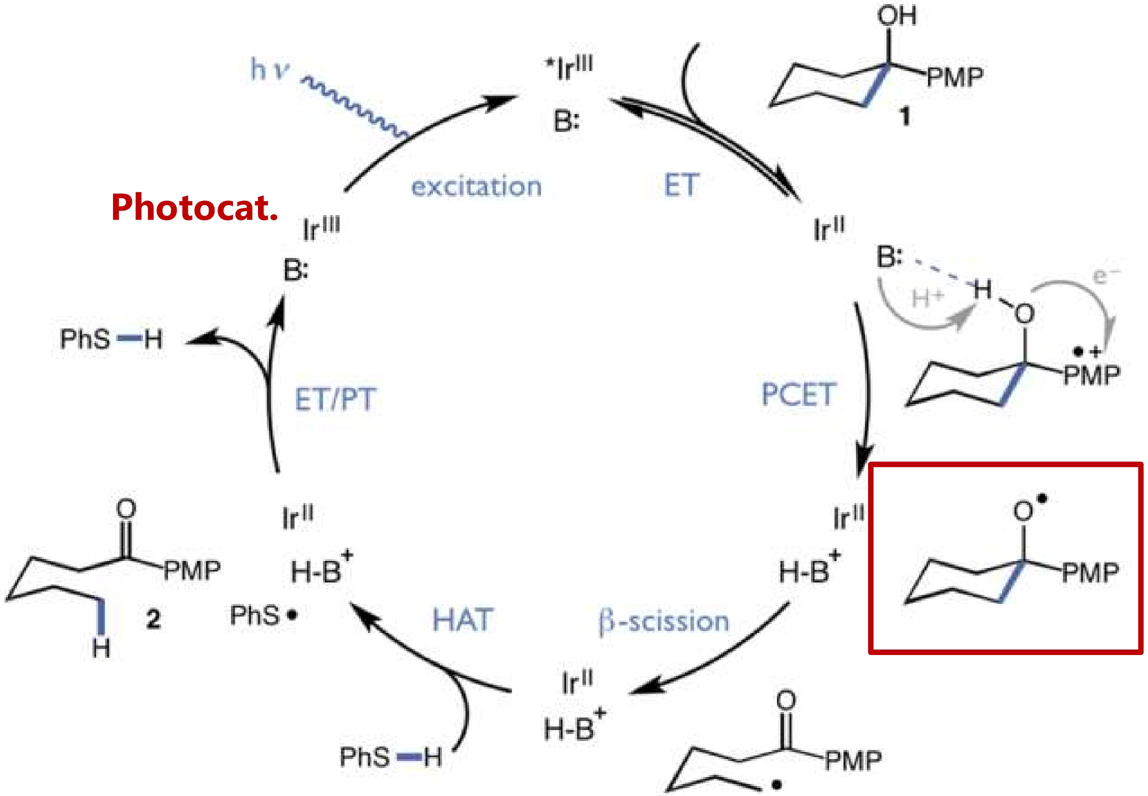
Figure 1. Catalytic ring-opening of cyclic alcohols via PCET.

✔ 1st photocatalyzed activation of unstrained alcohols
✔ Selective cleavage of distal C-C bonds via generation of "spatially removed" alkoxy radicals

R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

Proposed Catalytic Cycle

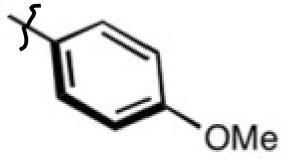
Photoredox catalyst × Bronsted Base × Thiol H-donor



Key alkoxy radical intermediate

Figure 2. Proposed catalytic cycle.

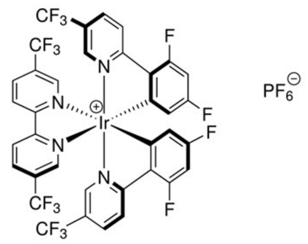
Ring opening:
generation of aryl ketone and distal alkyl radical



PMP (e$^-$ rich arene)

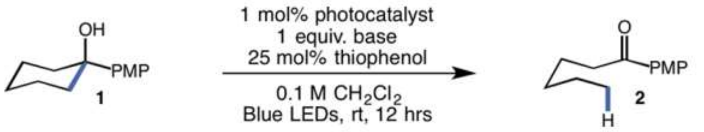
R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

Screening of Reaction Conditions



[Ir(dFCF$_3$ppy)$_2$-(5,5′-dCF$_3$bpy)]PF$_6$

Table 1. Reaction Optimization[a]

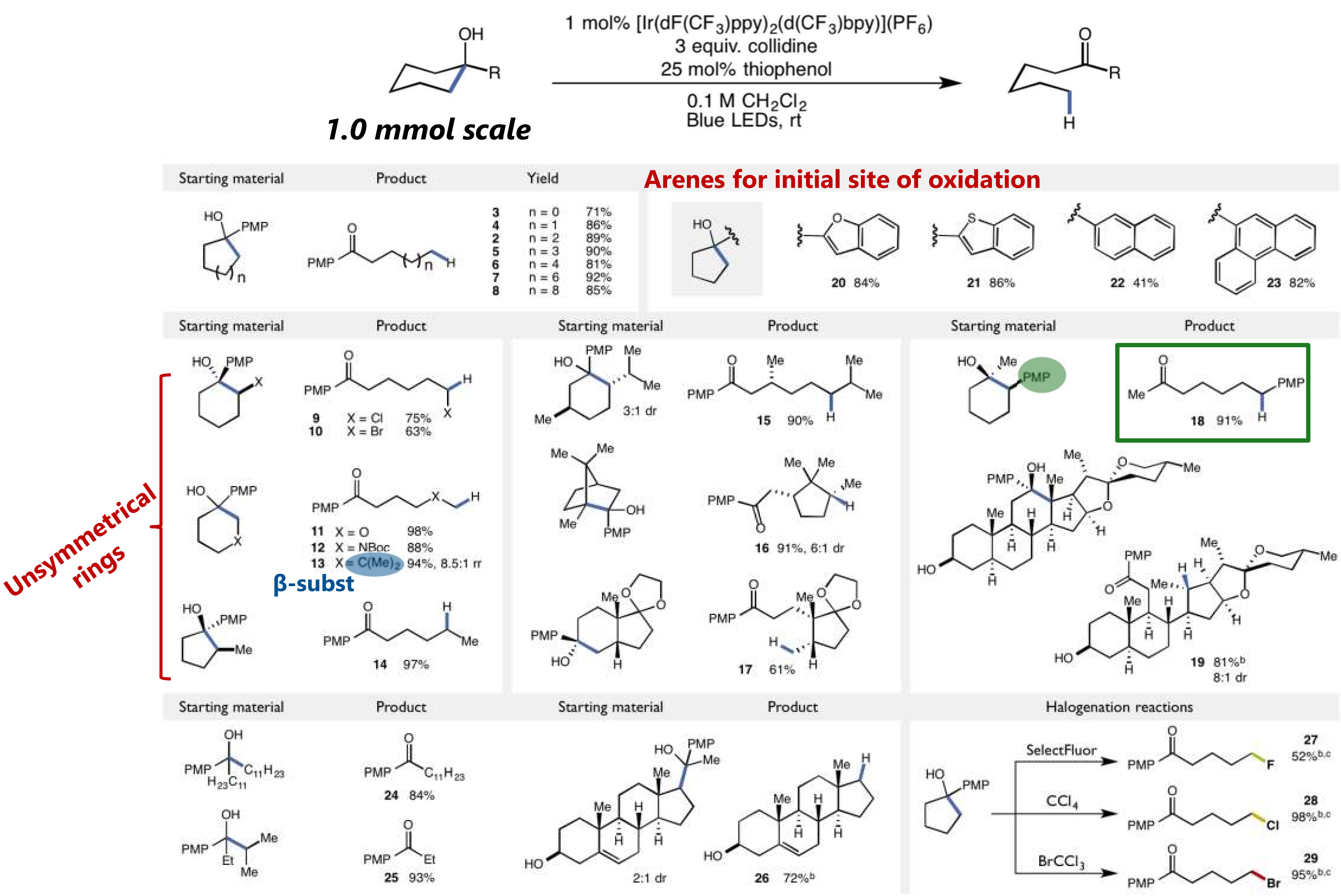


entry	photocatalyst	base	yield (%)
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ (**A**)	collidine	0
2	$[Ir(dF(CF_3)ppy)_2(bpy)](PF_6)$ (**B**)	collidine	9
3	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	collidine	79
4	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	pyridine	6
5	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	TBA^+ $(PhO)_2POO^-$	4
6	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	TBA^+ CF_3COO^-	48
7	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	TBA^+ $PhCOO^-$	8
8	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	collidine (2 equiv)	83
9	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	collidine (3 equiv)	91

[a]Optimization reactions were performed on a 0.05 mmol scale. Yields determined by ^{1}H NMR analysis of the crude reaction mixtures. Structures and potential data for all photocatalysts are included in the SI.

R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

Substrate Scope



[a]Reactions run on 1.0 mmol scale. Reported yields are for isolated and purified material and are the average of two experiments. Diastereomeric ratios were determined by ^{1}H NMR or GC analysis of the crude reaction mixtures. [b]0.5 mmol scale. [c]For experimental details of halogenations, see SI.

R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

Mechanistic Insights

Q. Does the charge transfer between arene radical cation and O-H bond proceed via *stepwise PT/ET* or *concerted PCET* ?

ASSUMPTION: if $d \rightarrow \infty$, then pK_a → ~40 (value for isolated tert-alkanol in MeCN)

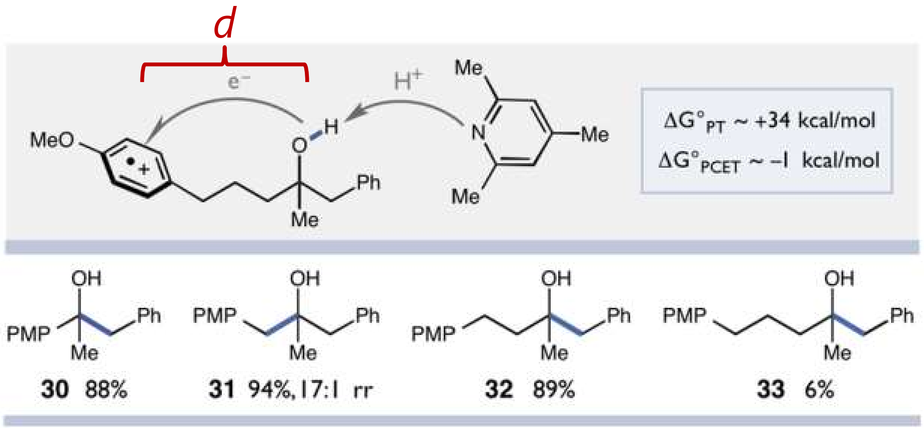


Figure 3. Distal C–C bonds cleaved via long-range PCET.

C-C cleavage was observed w/ up to 4 carbon atoms separating the arene and alcohol.

Deprotonation by collidine (pK_a =15.0 in MeCN) ⇒ **ΔG ≈+34 kcal/mol**

vs

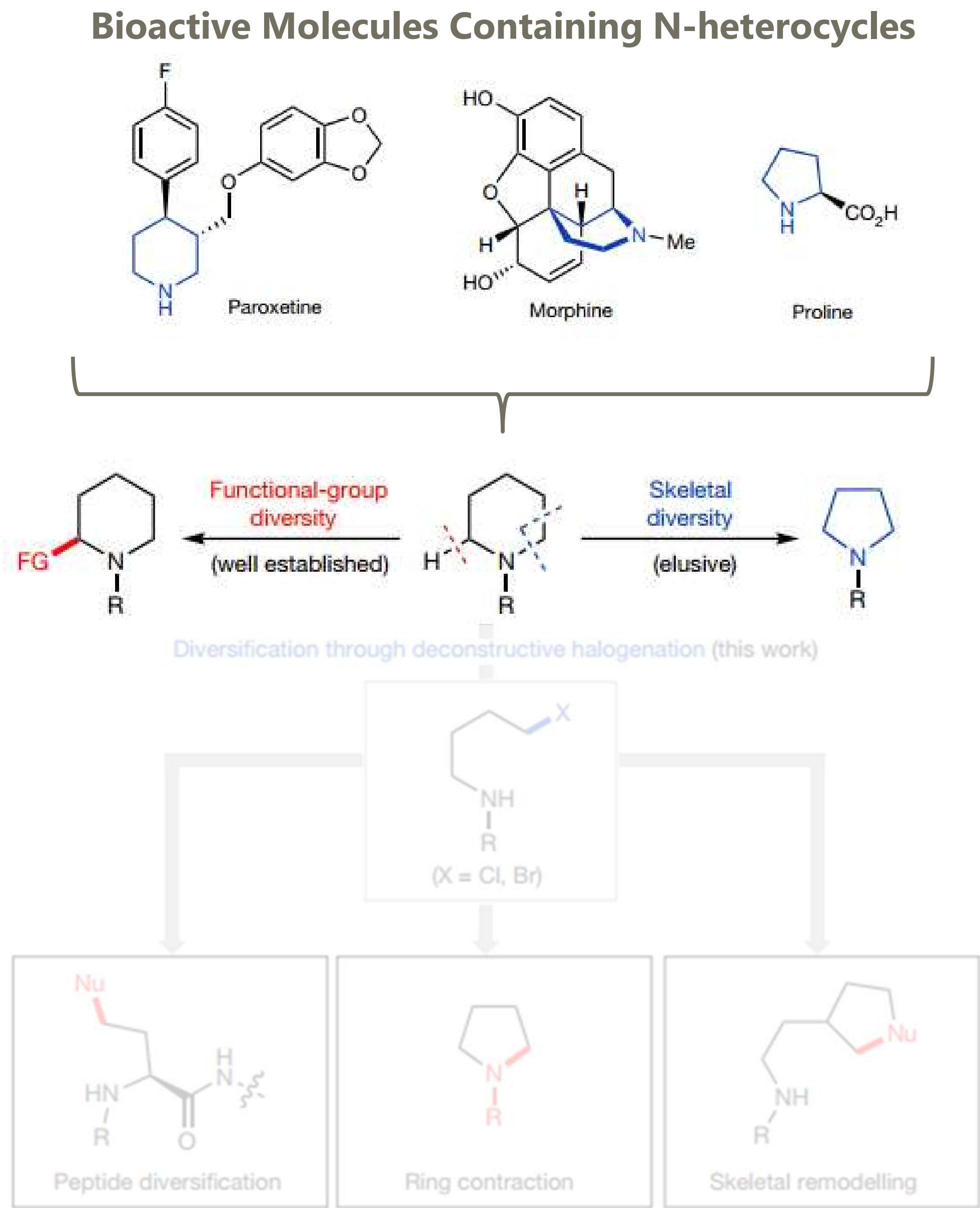
Charge recombination of Ar radical cation w/ reduced photocatalyst ⇒ **ΔG ≈-53 kcal/mol**

Strongly Suggestive of a concerted PCET mechanism

R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

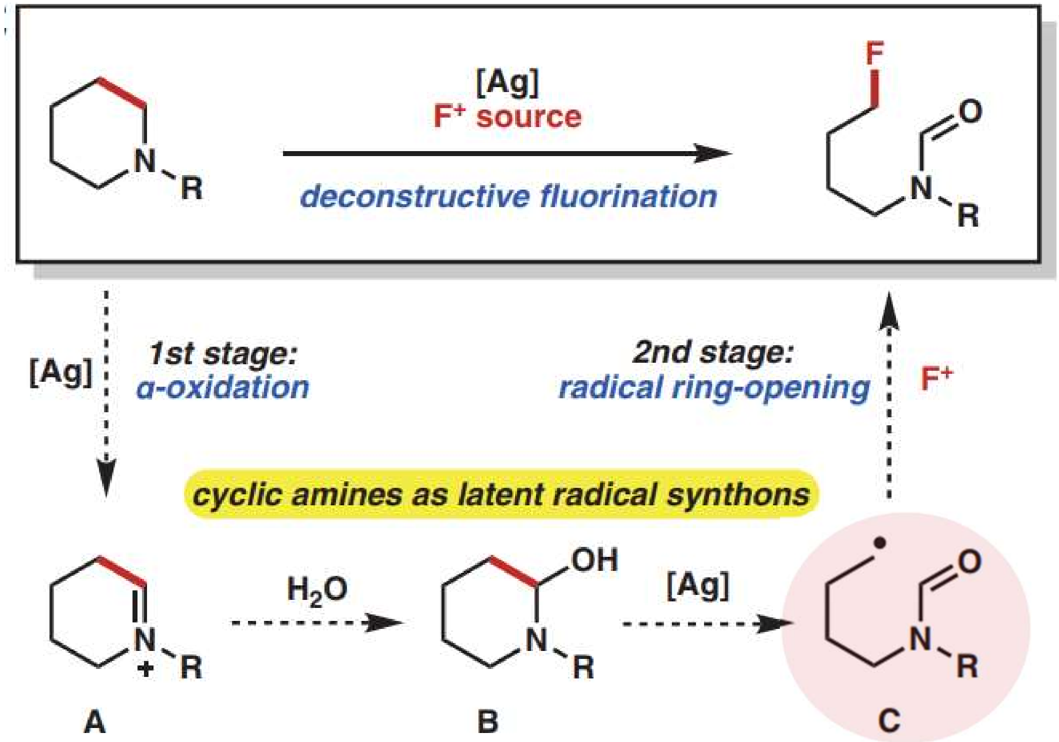
Table of Contents

Deconstructive Functionalization of Cyclic Amines



R. Sarpong, *et al. Nature* **2018**, *564*, 244.

Deconstructive Fluorination



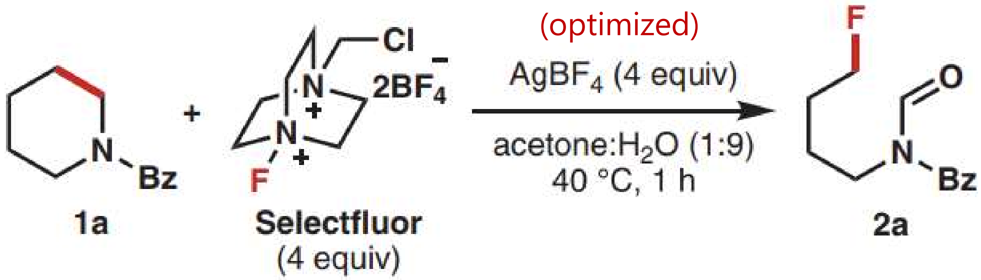
⇒ Cyclic amines as synthons for amino alkyl radicals

Challenges:

1) **Competing over-oxidation to amides (instead of hemiaminals)**
2) **Limited examples of ring-opening fluorination of unstrained cycloalkanols**

R. Sarpong, *et al. Science* **2018**, *361*, 171.

Optimization of Reaction Conditions



entry	variation from the standard conditions	yield (%)*
1	none	81†
2	$AgNO_3$ instead of $AgBF_4$	42
3	no [Ag]	0
4	NFSI instead of Selectfluor	0
5	MeCN instead of acetone	51
6	$AgBF_4$ (50 mol%)	52

*Yield by ^1H NMR integration using Ph_3CH as an internal standard.
† Isolated yield.

→ 2nd best Ag source (entry 2)

→ substoichiometric Ag, modest yield (entry 6)

✔ cheap / commercially available $AgBF_4$
✔ mild reaction conditions

R. Sarpong, *et al. Science* **2018**, *361*, 171.

Deconstructive Fluorination: Substrate Scope

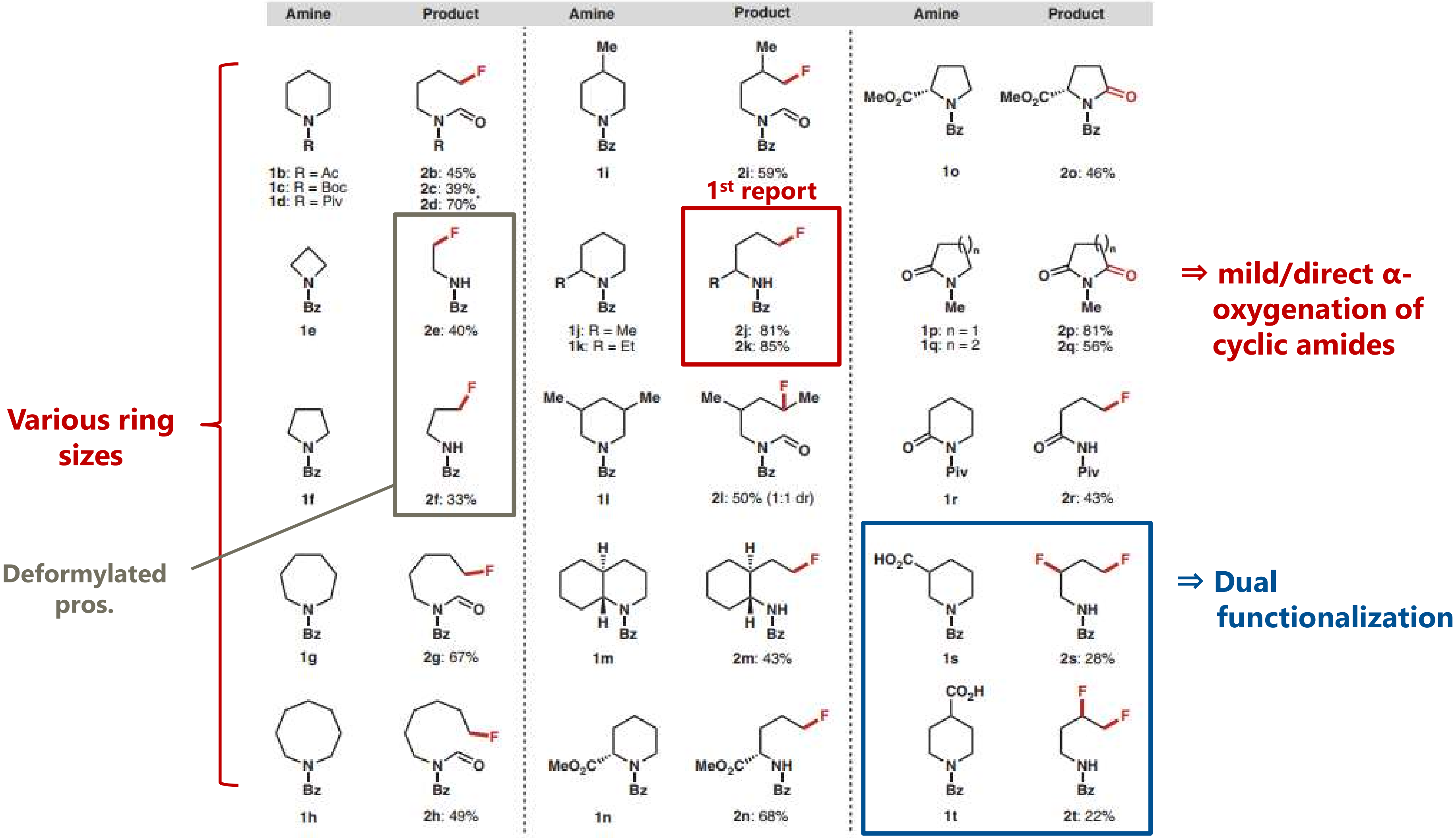


Fig. 2. Deconstructive fluorination: cyclic amine scope. Only isolated yields are shown. Reaction conditions: **1** (0.1 mmol), $AgBF_4$ (4 equivalents), Selectfluor (4 equivalents), acetone:H_2O (1:9), 40°C, 1 hour. *Deformylated product obtained. dr, diastereomeric ratio.

R. Sarpong, *et al. Science* **2018**, *361*, 171.

Decarboxylative Fluorination: Previous Studies

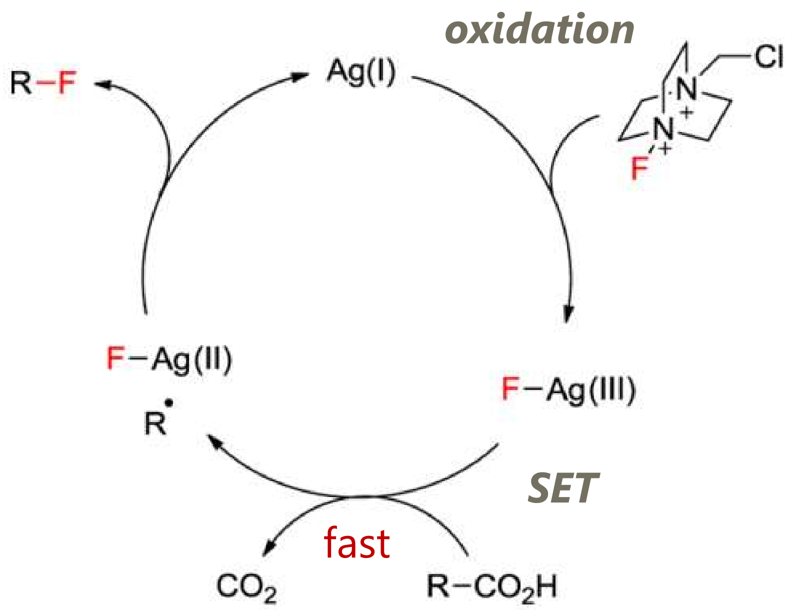
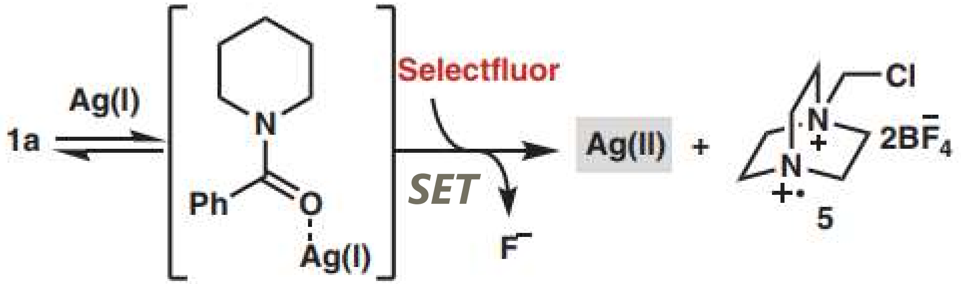


Figure 1. Proposed Mechanism of Silver-Catalyzed Decarboxylative Fluorination.

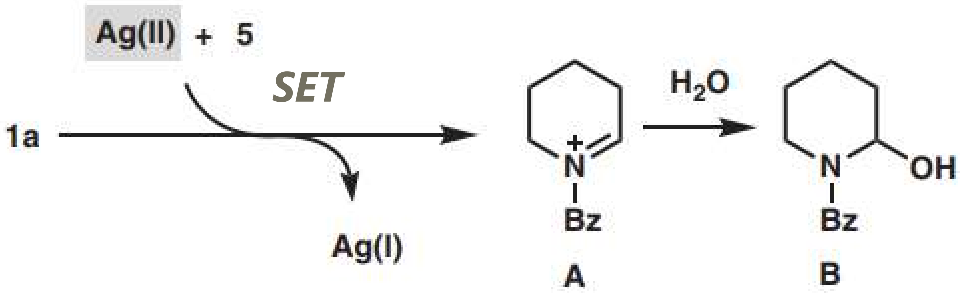
※Detailed mechanism is still unclear...??

C. Li, *et al. J. Am. Chem. Soc.* **2012**, *134*, 4258.

Proposed Mechanism: This Study



(1)



(2)

※ An alternative pathway (reversed order of events) cannot be ruled out

NMR EXPERIMENTS:

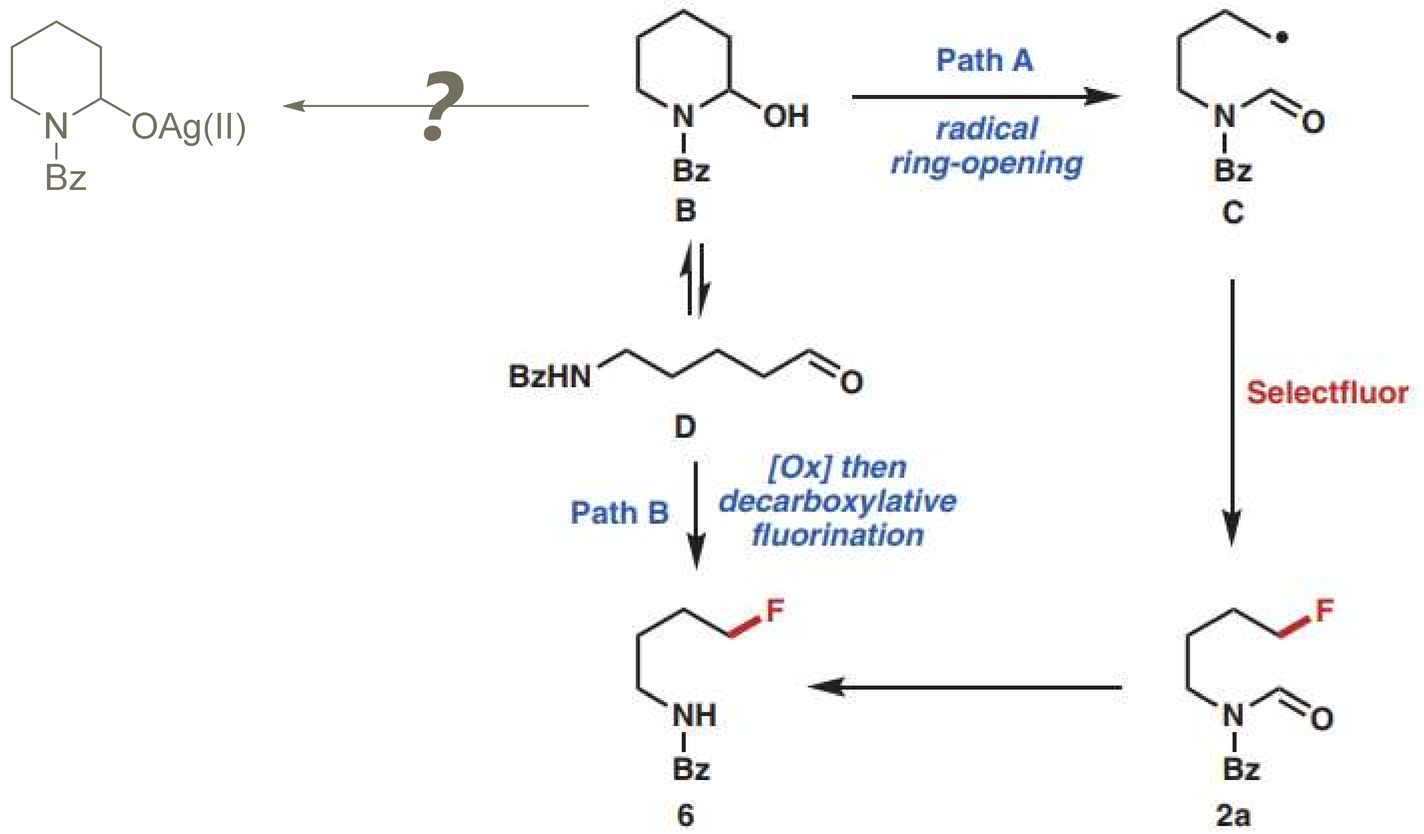
1) Consumption of Selectfluor was observed only under the presence of cyclic amine (according to ^{19}F NMR)

2) Broadening of 1H NMR spectrum ⇒ formation of paramagnetic Ag(II)

3) Downfield shifts of cyclic amine 1a upon addition of $AgBF_4$ ⇒ binding of Ag(I) to amide moiety

R. Sarpong, *et al. Science* **2018**, *361*, 171.

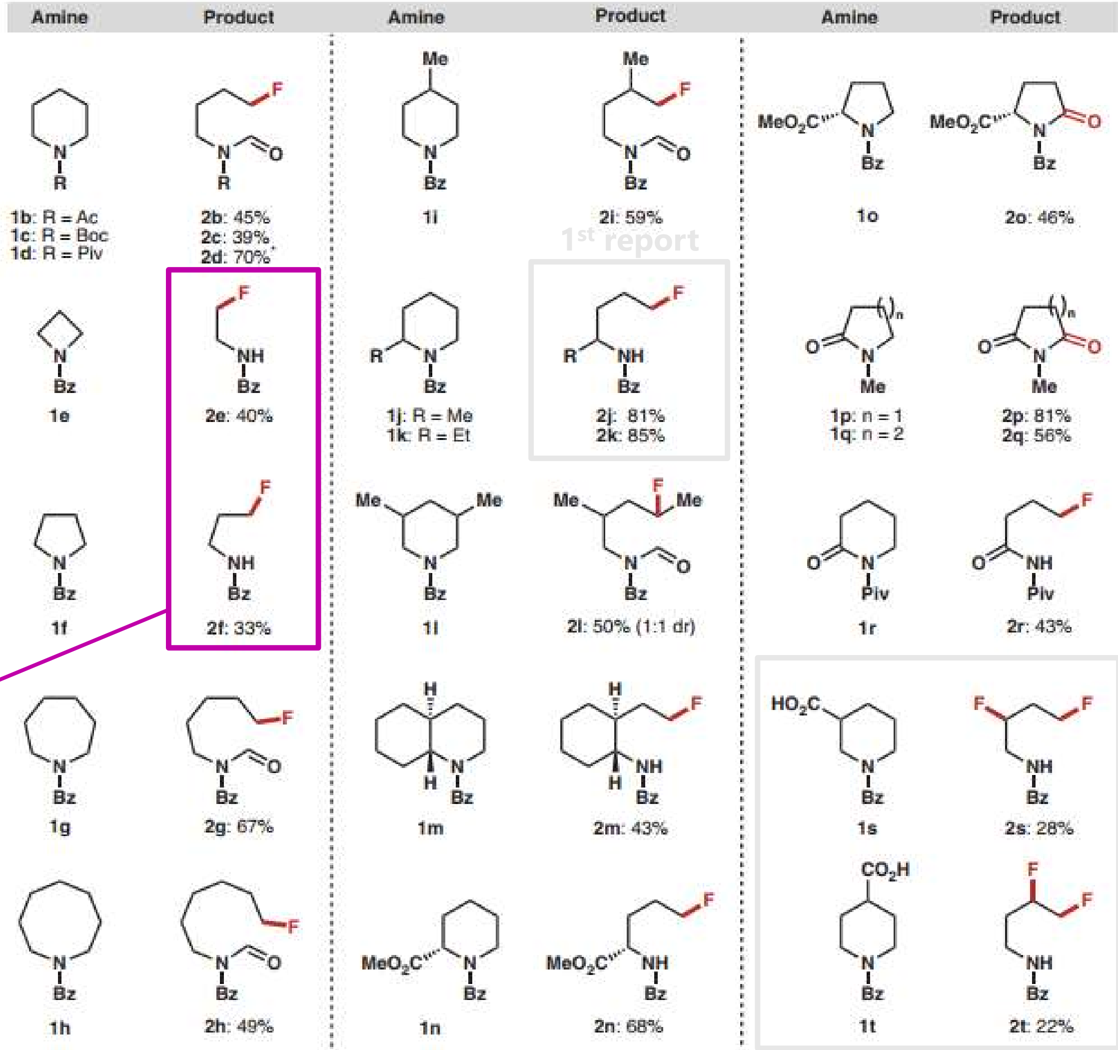
Possible Mechanisms for Fluorination



R. Sarpong, *et al. Science* **2018**, *361*, 171.

Deconstructive Fluorination: Substrate Scope

Various ring sizes



Deformylated pros.

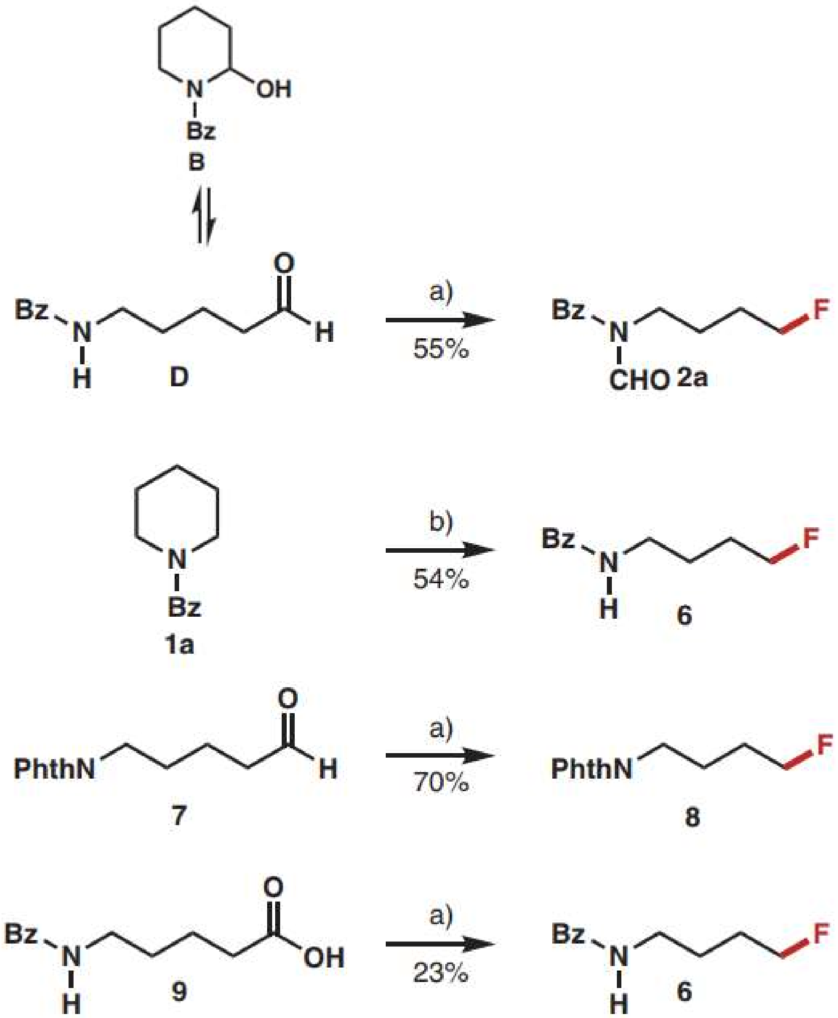
⇒ mild/direct α-oxygenation of cyclic amides

⇒ Dual functionalization

Fig. 2. Deconstructive fluorination: cyclic amine scope. Only isolated yields are shown. Reaction conditions: **1** (0.1 mmol), $AgBF_4$ (4 equivalents), Selectfluor (4 equivalents), acetone:H_2O (1:9), 40°C, 1 hour. *Deformylated product obtained. dr, diastereomeric ratio.

R. Sarpong, *et al. Science* **2018**, *361*, 171.

Possible Mechanisms for Fluorination (continued)



Red → in favor of path A
Blue → in favor of path B

Start from aldehyde:
⇒ Pro. Accessible by path A only

Prolonged rxn time:
⇒ Deformylated pros. were major

No equilibrium with hemiaminal:
⇒ Fluorination proceeded from aldehyde

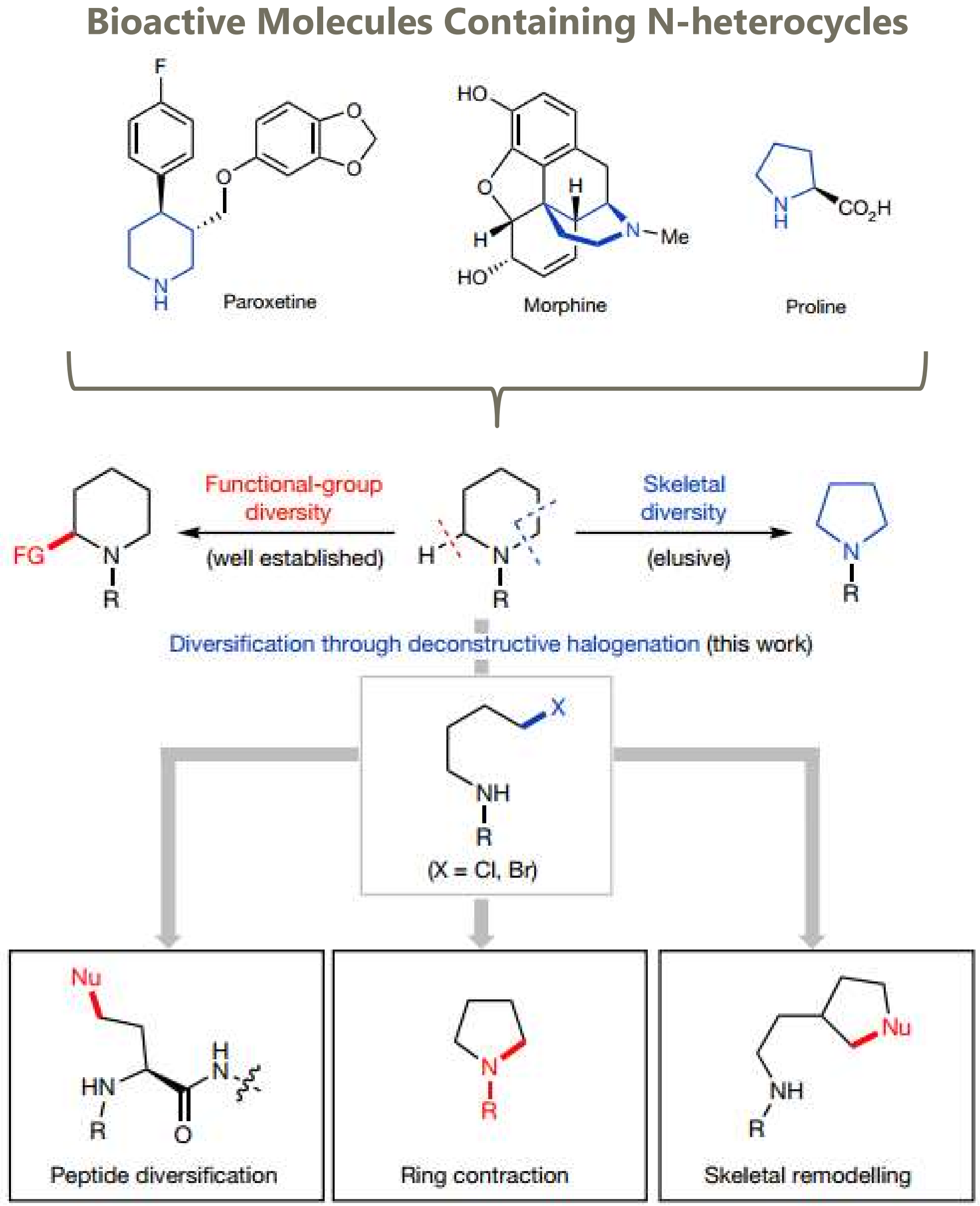
Start from carboxylic acid:
⇒ Decarboxylation proceeded

Fig. 4. Mechanistic studies. (**A**) Proposed mechanism for **1a** oxidation. (**B**) Possible mechanisms for fluorination of **B**. (**C**) Mechanistic studies. Reaction conditions: (a) starting material (0.1 mmol), $AgBF_4$ (4 equivalents), Selectflu (0.5 mmol), $AgBF_4$ (4 equivalents) 16 hours. (**D**) Mechanistically driven gem-fluorination of enamide **10**. Reaction conditions: **10** (0.1 mmol), $AgBF_4$ (0.25 equivalents), Selectfluor (4 equivalents), acetone:H_2O (1:1), room temperature, 15 hours. Phth, phthaloyl.

Neither path could be ruled out...

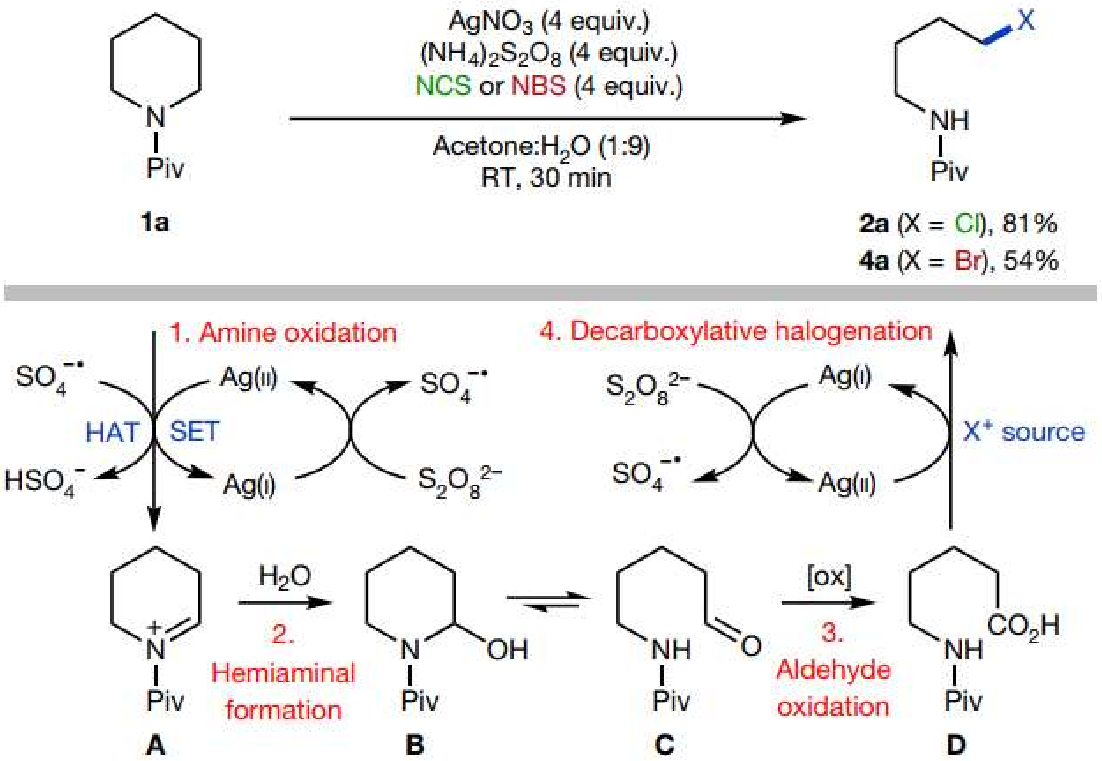
R. Sarpong, *et al. Science* **2018**, *361*, 171.

Deconstructive Halogenation of Cyclic Amines

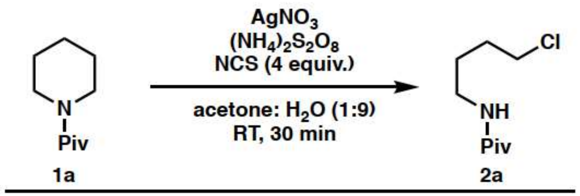


R. Sarpong, *et al. Nature* **2018**, *564*, 244.

Proposed Mechanism for Ag-mediated Deconstructive Halogenation



Optimization of Reaction Conditions



$AgNO_3$ (equiv.)	$(NH_4)_2S_2O_8$ (equiv.)	yield (%)*
0	4	0
4	0	0
1	4	26
2	4	41
4	4	81†

*Yield by ^1H NMR integration using Ph_3CH as an internal standard.
†Isolated yield

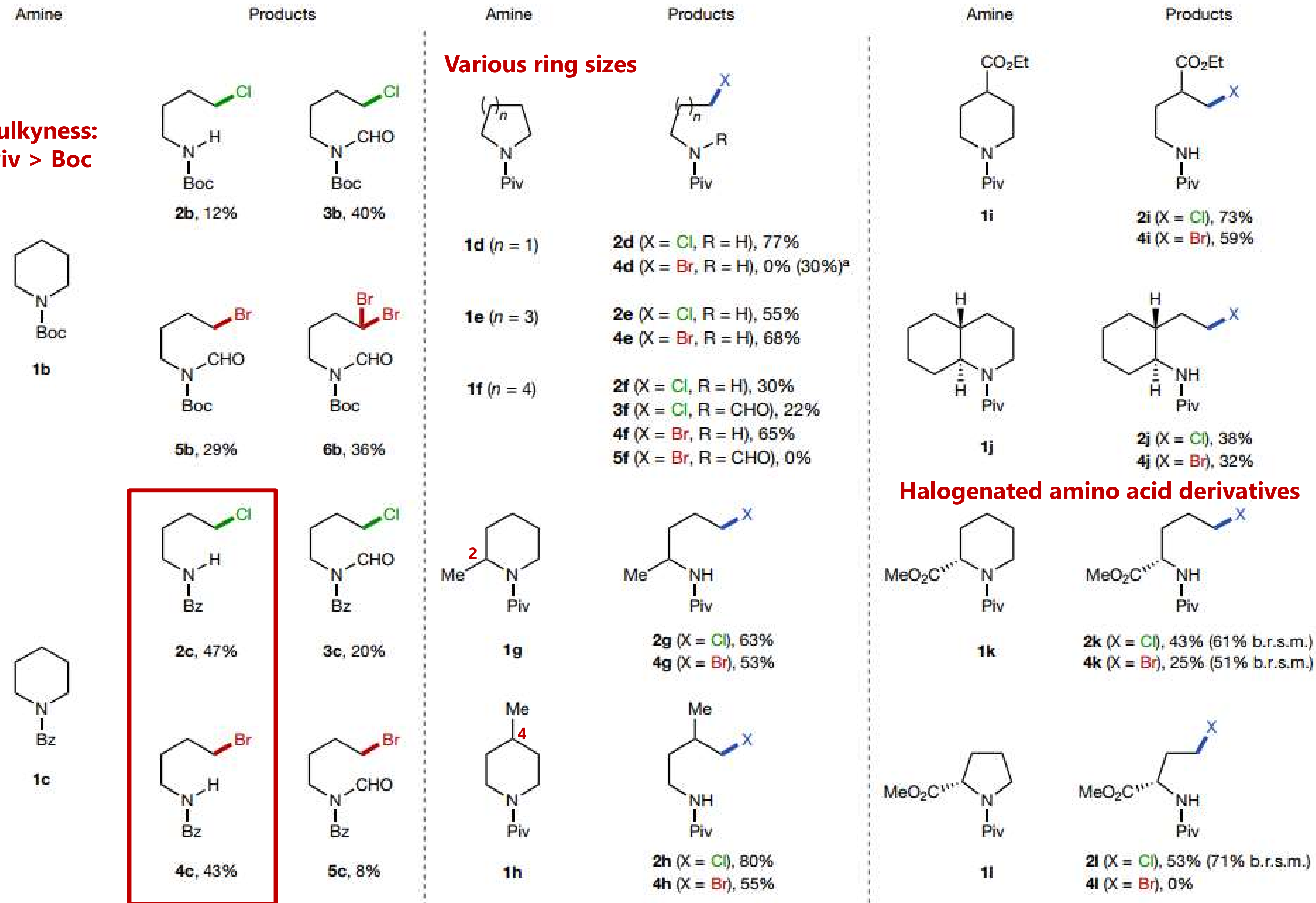
※ Screening was conducted on Ag salts, halogenating reagents, and solvent combinations (see Science, 2018).

✔ **Electrophile is independent of initial redox cycle**
✔ **Can be performed w/out strict exclusion of air**
✔ **Choice of halogenating reagent leads to divergence of products**

R. Sarpong, *et al. Nature* **2018**, *564*, 244.

Deconstructive Halogenation: Substrate Scope

bulkyness:
Piv > Boc



2° amides
(major)

⇒ int. for unnatural amino acids

R. Sarpong, *et al.* *Nature* **2018**, *564*, 244.

Application of Deconstructive Halogenation

※ showcases C-N bond cleavage only…

Ring Contraction: piperidine → pyrrolidine

Choice of halogenating reagent led to product divergence.

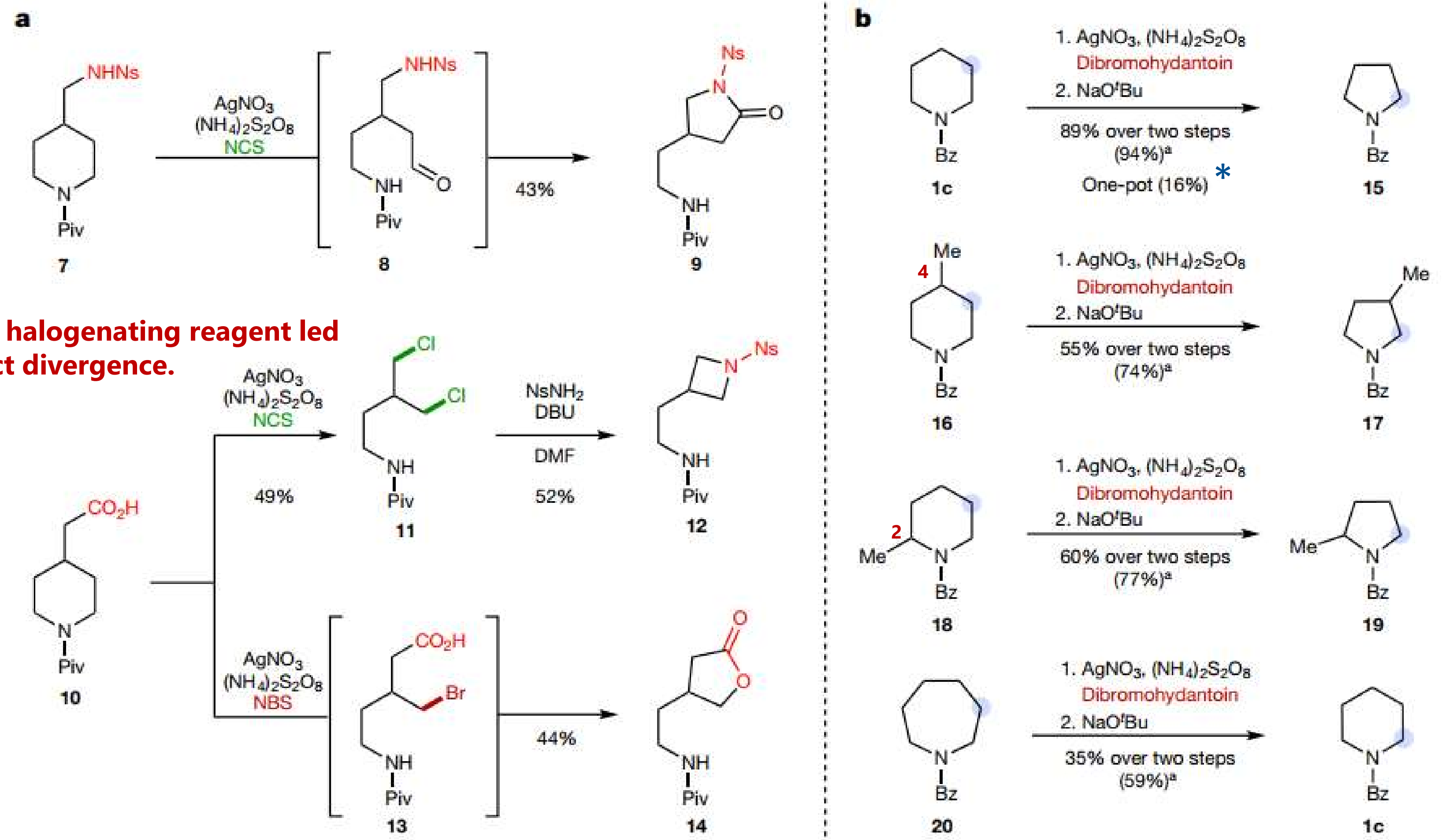
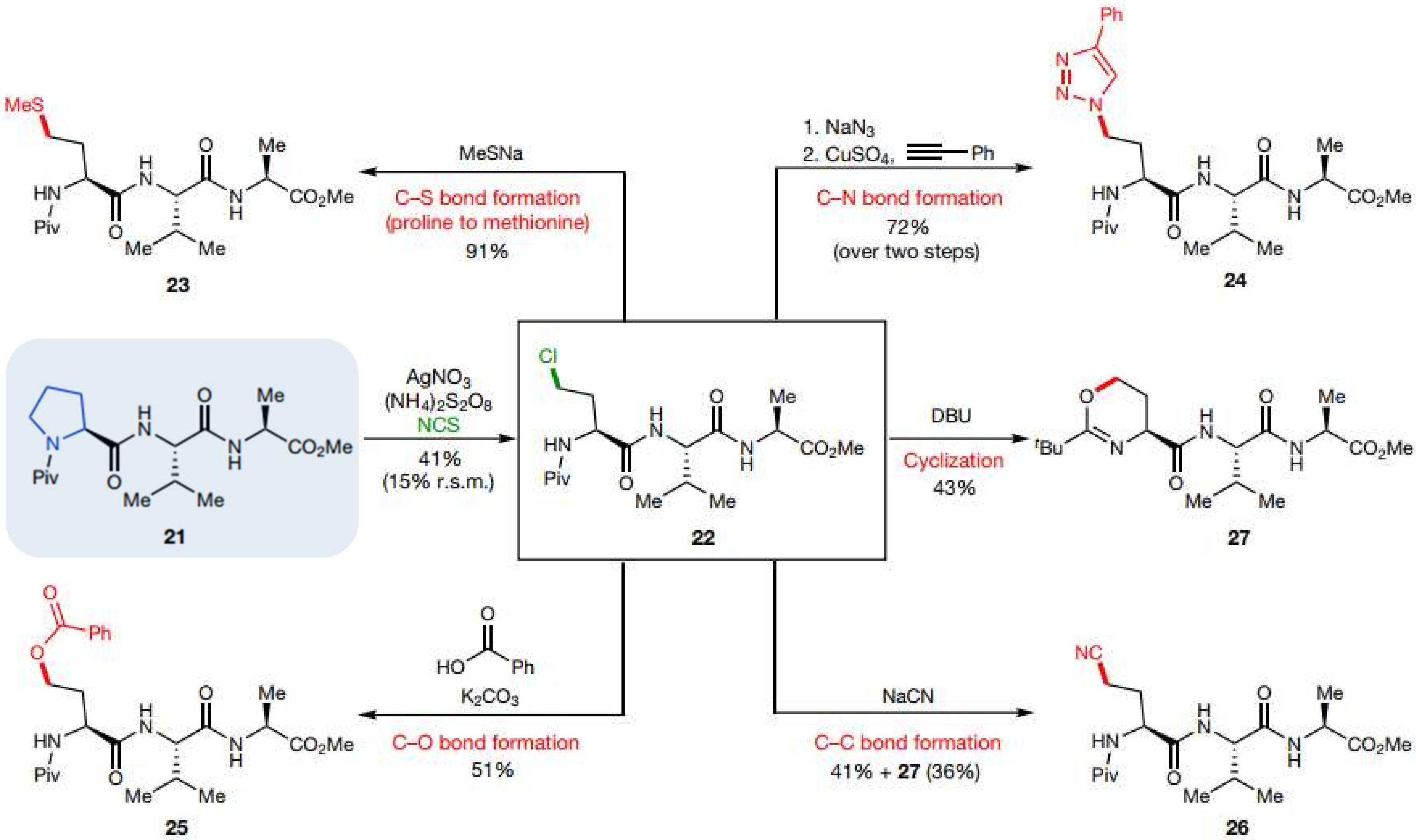


Fig. 3 | Applications of deconstructive halogenation. a, Skeletal remodelling of cyclic amines. **b**, Dehomologation of cyclic amines. [a]Yields in bracket represent the average yield per step.

*lower yield due to imide bp from halogenating reagent

R. Sarpong, *et al. Nature* **2018**, *564*, 244.

Late-Stage Diversification of L-Proline-Containing Tripeptide



R. Sarpong, *et al. Nature* **2018**, *564*, 244.

Late-Stage Diversification of Other *n*-peptides

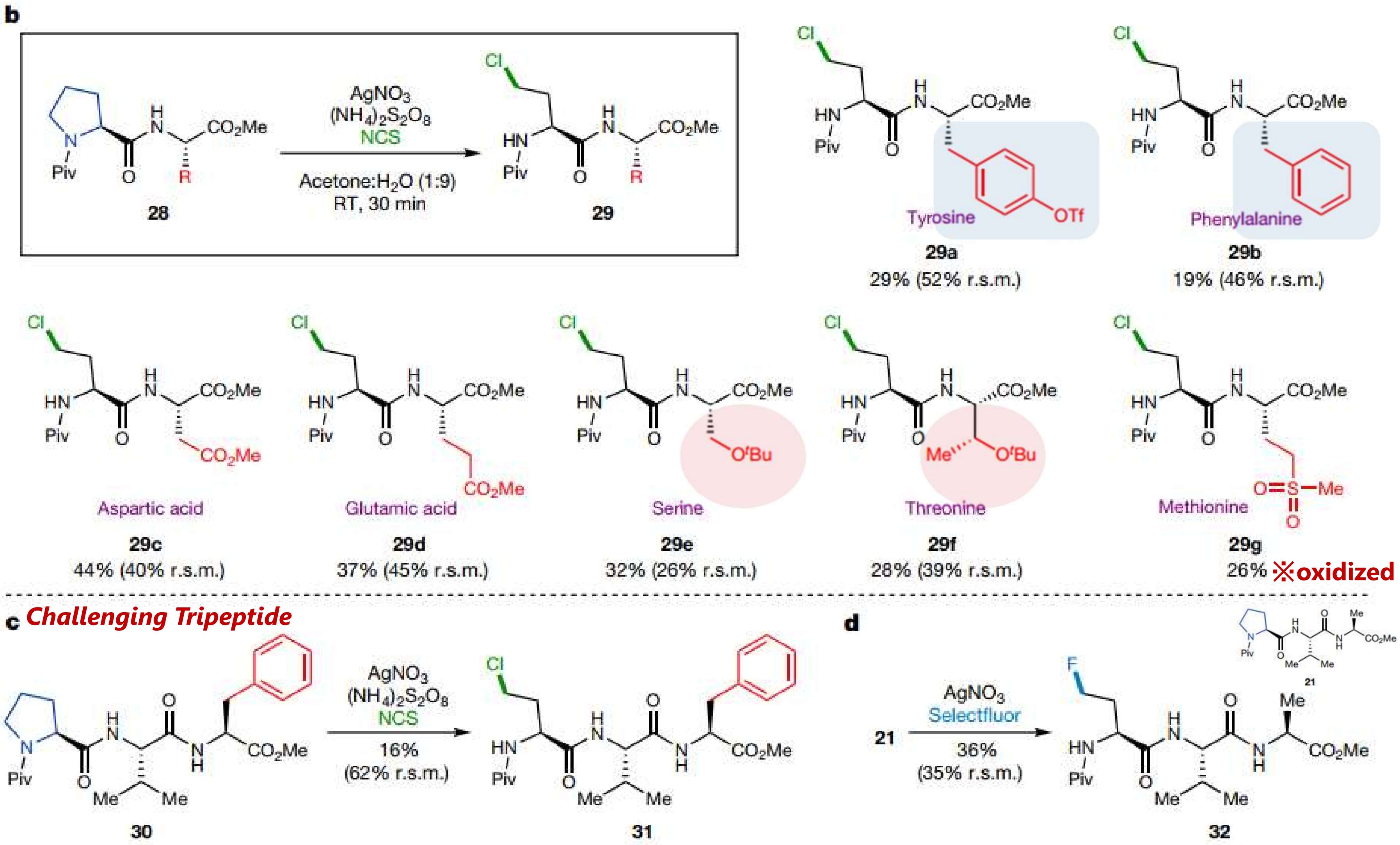


Fig. 4 | Deconstructive chlorination of l-proline-containing peptides. **a**, Deconstructive diversification of tripeptide **21**. **b**, The tolerance for oxidizable amino acid residues. **c**, Deconstructive chlorination of L-phenylalanine-containing tripeptide **30**. **d**, Deconstructive fluorination of tripeptide **21**. r.s.m., recovered starting material; Tf, trifluoromethanesulfonyl.

R. Sarpong, *et al. Nature* **2018**, *564*, 244.

Table of Contents

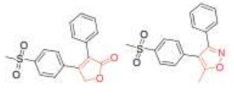
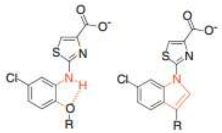
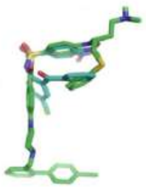
Scaffold Hopping (omake)

…"scaffold-hopping", that is, identification of isofunctional molecular structures with significantly different molecular backbones…

G. Schneider, *et al. Angew. Chem. Int. Ed.* **1999**, *38*, 19, 2894.

TABLE 1

The four types of scaffold-hopping methods, their pros and cons, and frequently used software for each method

Category	Definition	Pros and cons	Software [Refs]
1°	 Heterocycle replacement	Pros: (1) High success rate (2) Immediate design Cons: (1) IP position (2) Limited changes in properties	MORPH [45] and Recore [48]
2°	 Ring opening closure	Pros: (1) Improve binding (2) Improve stability Cons: (1) Reduce solubility (2) Flatten molecule (3) Synthetic feasibility	CSD [67]
3°	 Pseudopeptide peptidomimetic	Pros: Ready templates from bioactive peptides or protein–protein interactions Cons: Metabolic stability is a concern, especially for pseudopeptides	Recore [48], CAVEAT [87] and pharmacophore modeling tools from CCG [100], Accelrys [101] and Schrodinger [102]
4°	 Topology-based hopping	Pros: Significantly different scaffold, implying novel properties Cons: Lower success rate	CSD [67], ROCS [108] and SHOP [112,124]

H. Sun, *et al. Drug Discovery Today.* **2012**, *17*, 310.

Table of Contents

Summary

- Deconstructive functionalization of C(sp^3)-C(sp^3) provides access to unprecedented structures

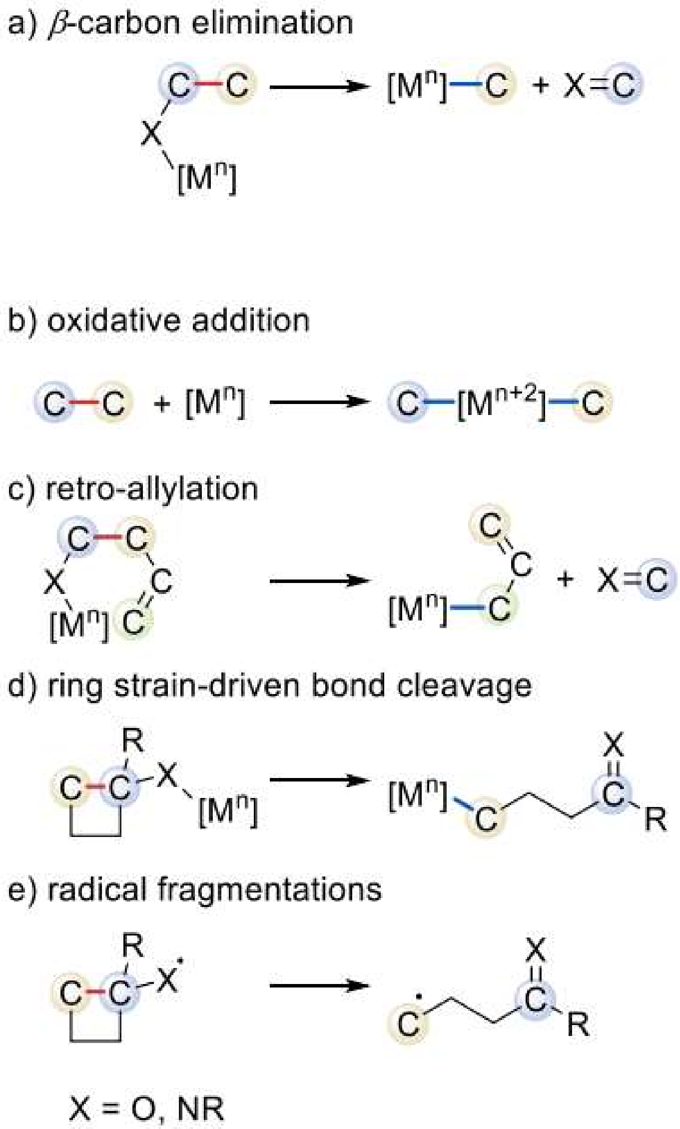
- And seems to be a good strategy for “scaffold hopping”

- Leading to efficient exploration of new chemical space for drug discovery…!

Thank you for your attention.

Appendix

General Strategies for Inert C-C Bond Cleavages



B. Morandi, *et al. Chem. Rev.* **2021**, 121, 300.

C-C vs C-H Bonds

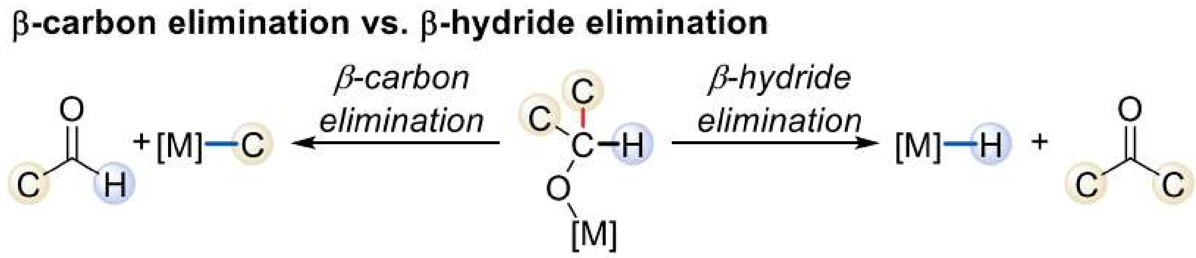


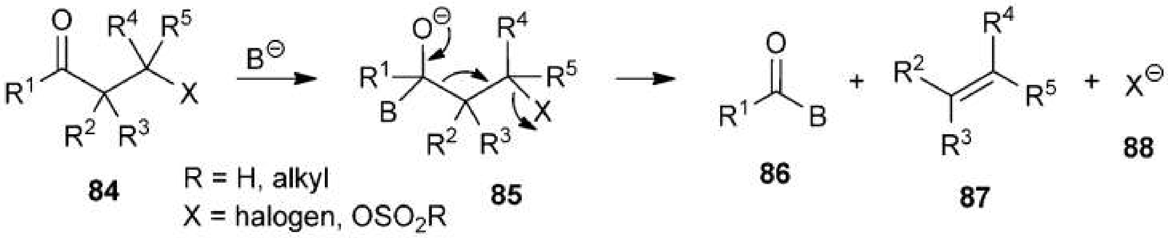
Figure 3. Competition between activation of adjacent C−C and C−H bonds in the *β*-position.

β-hydride elimination > β-carbon elimination
⇒ selective activation of a C-C bond within a substrate bearing β-hydrogen atoms (i.e., 1° and 2° alcohols) is still a challenge

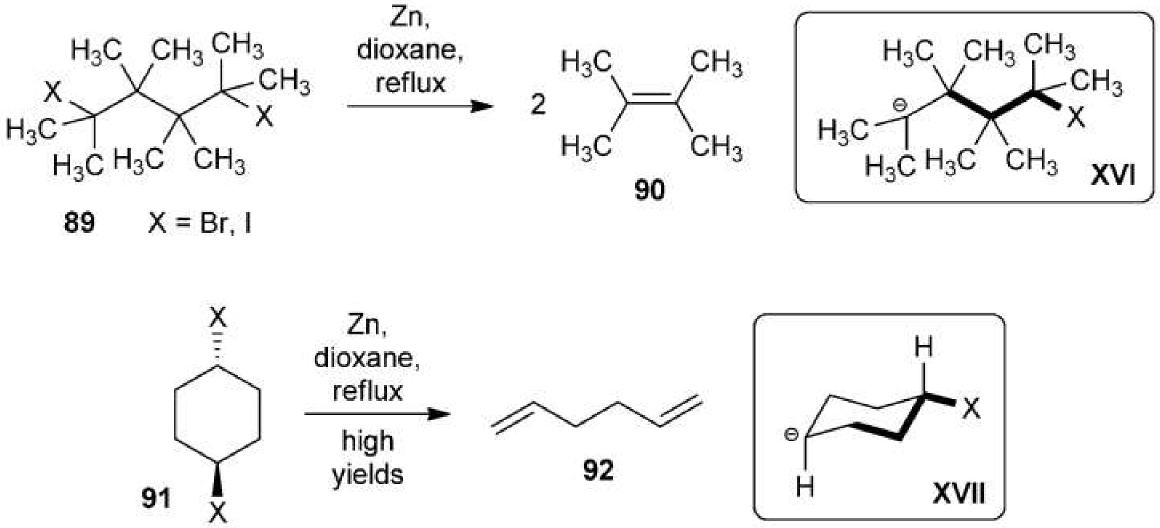
BDE(C-H) ≈ 100-110 kcal/mol > BDE(C-C) ≈ 90-105 kcal/mol
⇒ C-H bond is thermodynamically more stable than a C-C bond

B. Morandi, *et al*. *Chem. Rev.* **2021**, 121, 300.

Heterolytic C-C Bond Cleavages



Scheme 18. The original C–C fragmentation mechanistic framework by Eschenmoser (1952).[1]



Scheme 19. Grob's 1,4-eliminations and diene synthesis (1955).[71]

J. Williams, *Angew. Chem. Int. Ed.* **2013**, *52*, 11222.

Stern-Volmer Studies

Constant [collidine], varied alcohol substrate [SM]

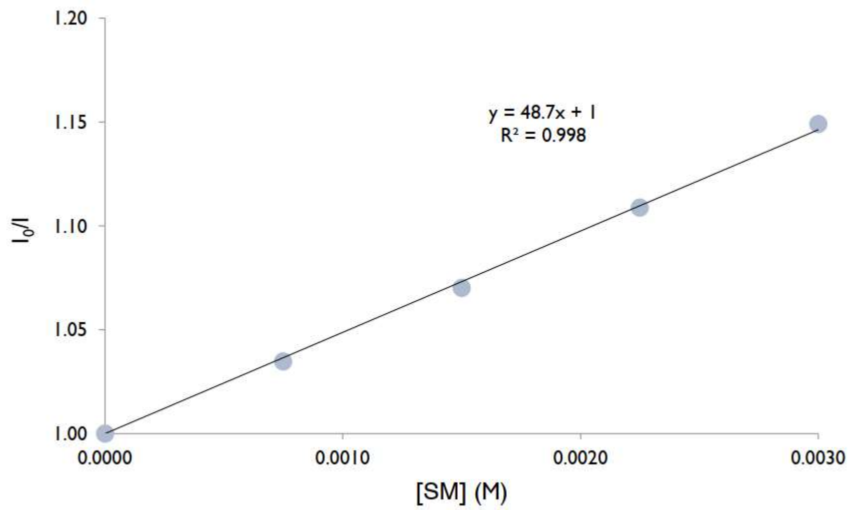


Figure S1. Stern-Volmer plot of $[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (244 μM) with varied [SM] in the presence of a constant concentration of collidine (7.22 mM) in CH_2Cl_2 at 23 °C.

Constant [SM], varied [collidine]

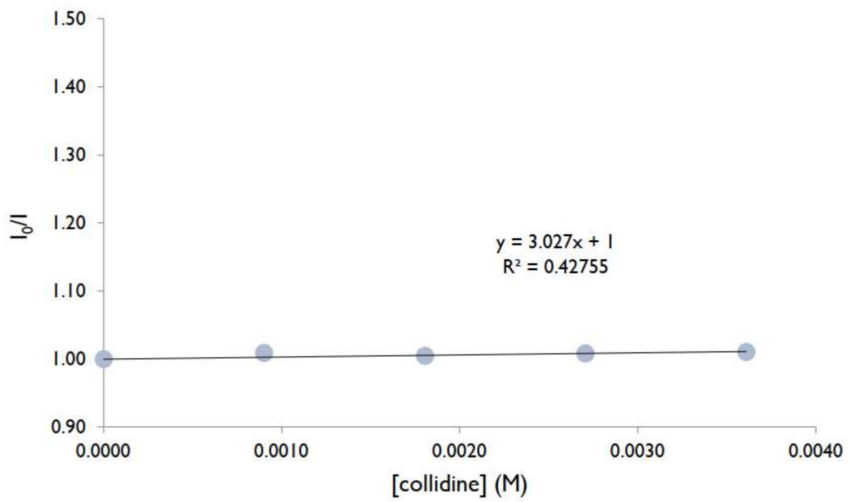


Figure S2. Stern-Volmer plot of $[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (244 μM) with varied [collidine] in the presence of a constant concentration of SM (15.0 mM) in CH_2Cl_2 at 23 °C.

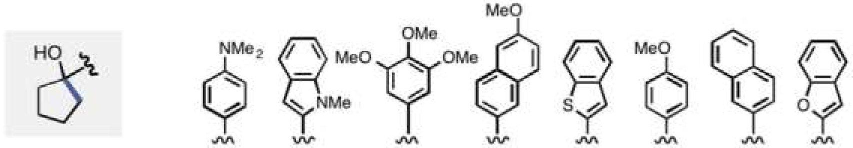
1st order dependence on alcohol conc.
0 order dependence on collidine conc.
⇒ Direct Ar oxidation is suggested, rather than O-H PCET

R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

Mechanistic Insights II

Purpose: Examine the relationship between effective BDFEs and reaction outcomes.

oxidation potential



Base	$E_{p/2}$ (V)	0.39	0.69	0.92	0.96	1.18	1.22	1.24	1.27
2-MeO-pyridine pK_a = 9.9	'BDFE'	77	84	90	91	96	97	97	98
	Yield (%)	0	0	0	0	0	0	<5	8
pyridine pK_a = 12.5	'BDFE'	81	88	93	94	99	100	101	101
	Yield (%)	0	0	0	<5	6	16	5	19
CF_3COO^- pK_a = 12.5	'BDFE'	81	88	93	94	99	100	101	101
	Yield (%)	0	0	0	0	23	87	97	18
collidine pK_a =15	'BDFE'	84	91	97	98	103	104	104	105
	Yield (%)	0	0	<5	7	86	86	41	84

basicity

effective BDFE = $23.06\,E_{1/2}(Ar^{0/\bullet+}) + 1.37\,pK_a(\text{base}) + 54.9$ (rt in MeCN)

Figure 4. Effective BDFE correlations with reactivity.

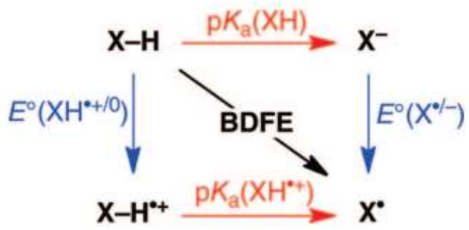
Forecast the feasibility of PCET process.

- BDFE ≥ O-H BDFE ≈ 102 kcal/mol ⇒ rxn proceeded
- BDFE < ~98 kcal/mol ⇒ rxn did NOT proceed

J. Mayer, *et al. Chem. Rev.* **2010**, *110*, 6961.
R. Knowles, *et al. J. Am. Chem. Soc.* **2016**, *138*, 10794.

PCET and BDFE

Scheme 4. Thermochemical Square Scheme for a PCET Reagent



The capacity of any given oxidant/base pair to function as a formal H$^{\cdot}$ acceptor can be quantified as an effective bond strength (BDFE).

$$\mathrm{BDFE_{sol}(X\text{-}H)} = 1.37\mathrm{p}K_a + 23.06E^{\circ} + C_{G,sol}$$

Table 1. Summary of Constants C_G and C_H in Common Solvents[a]

solvent	C_G	$T(\Delta S°)_{solv}$[b]	C_H	electrochemical reference
acetonitrile	54.9	4.62	59.4	$Cp_2Fe^{+/0}$
DMSO	71.1	4.60	75.7	$Cp_2Fe^{+/0}$
DMF	69.7	4.56	74.3	$Cp_2Fe^{+/0}$
methanol	65.3	3.81	69.1	$Cp_2Fe^{+/0}$
water	57.6	−1.80	55.8	normal hydrogen

[a] Values in kcal mol^{-1} at 298 K from references.[39,51] [b] $T(\Delta S°)_{solv} = T(S°(H^{\bullet})_g + \Delta S_{solvation}°(H_2)_{solv})$.

J. Mayer, *et al. Chem. Rev.* **2010**, *110*, 6961.

Ag Catalyzed Decarboxylative Chlorination

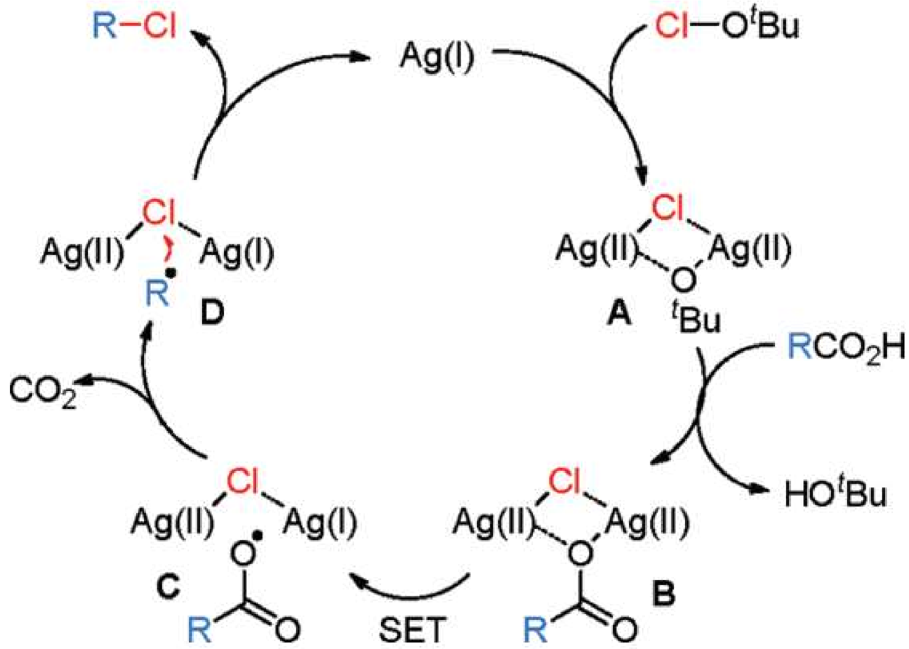
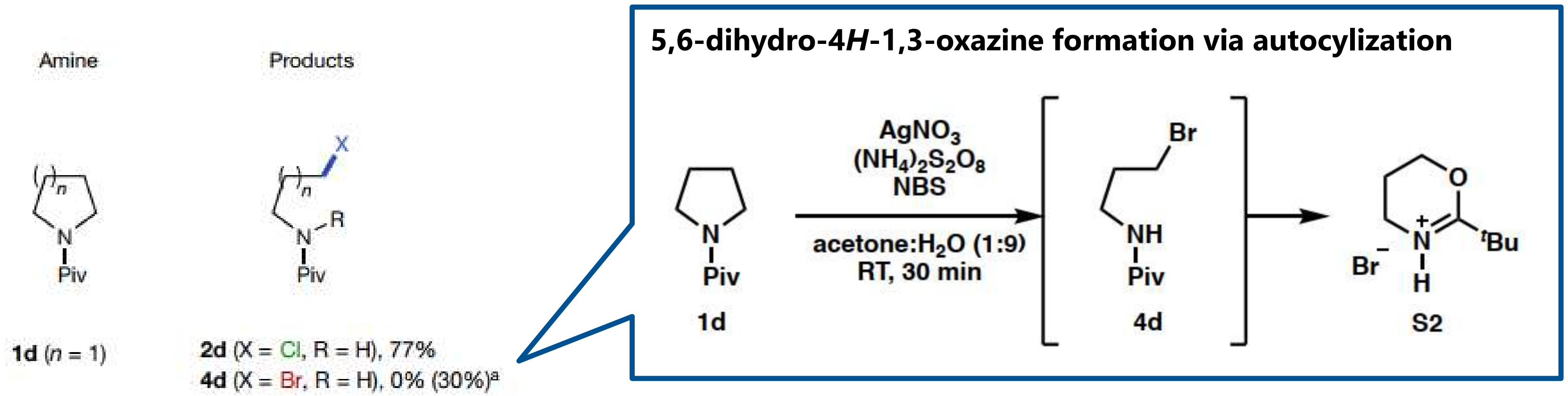


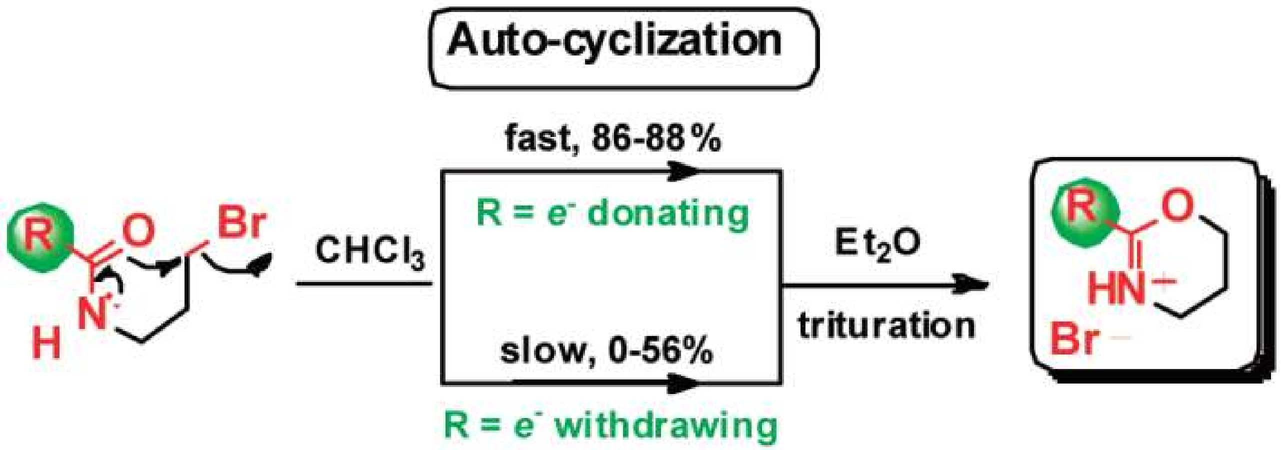
Figure 2. Proposed mechanism for Ag(I)-catalyzed decarboxylative chlorination.

C. Li, *et al. Chem. Rev.* **2012**, *134*, 4258.

Oxazine Formation via Autocyclization



R. Sarpong, *et al. Nature* **2018**, *564*, 244.



E. Prabharakan, *et al. J. Org. Chem* **2011**, *76*, 680.

Oxidation with Peroxydisulfate Ion

※1st step: unimolecular homolytic scission of peroxydisulfate ion

$$SO_4\cdot^- + CH_3CH_2OH \xrightarrow{k_{2a}} HSO_4^- + CH_3\dot{C}HOH$$

$$SO_4\cdot^- + CH_3CHO \longrightarrow HSO_4^- + CH_3\dot{C}O$$

$$CH_3\dot{C}HOH + S_2O_8^{2-} \xrightarrow{k_{3a}} CH_3CHO + HSO_4^- + SO_4\cdot^-$$

$$2CH_3\dot{C}HOH \xrightarrow{k_{4a}} CH_3CHO + CH_3CH_2OH$$

$$H_2O + CH_3CHO \rightleftharpoons CH_3CH(OH)_2$$ rapid hydration

$$SO_4\cdot^- + CH_3CH(OH)_2 \xrightarrow{k_{2b}} HSO_4^- + CH_3\dot{C}(OH)_2$$

$$CH_3\dot{C}(OH)_2 + S_2O_8^{2-} \xrightarrow{k_{3b}} CH_3CO_2H + HSO_4^- + SO_4\cdot^-$$

$$CH_3\dot{C}(OH)_2 + CH_3\dot{C}HOH \xrightarrow{k_{4b}} \text{termination products}$$

J. Edwards, *et al. J. Org. Chem.* **1971**, *36*, 4089.