Radical-Radical Cross Coupling Reactions

2023.7.15. Literature Seminar

M1 Shintaro Fukaya

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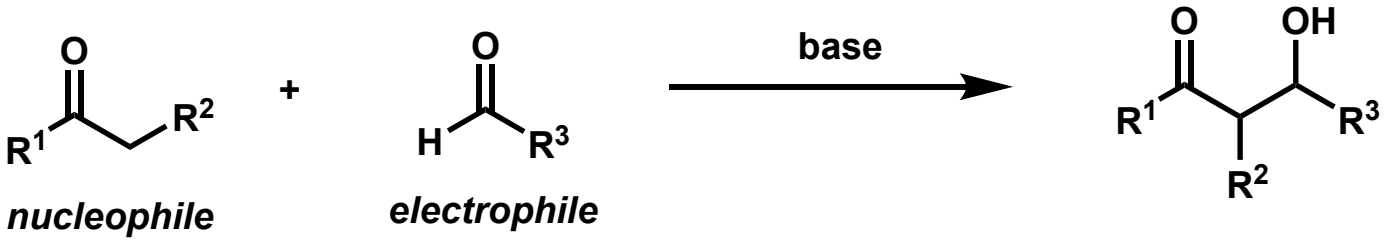
Cross-Coupling Reactions

non-radical / non-radical
ex.) aldol reaction

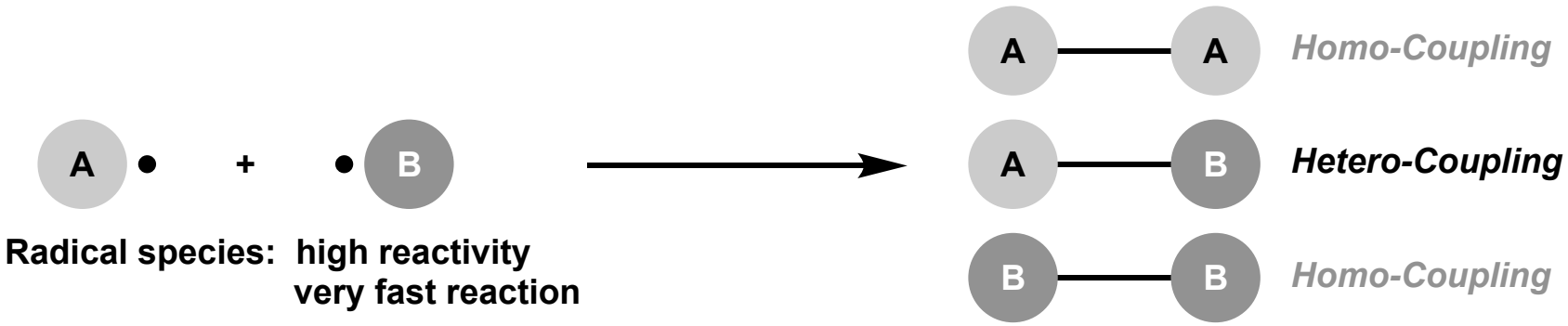


nucleophile *electrophile*

radical / non-radical
ex.) radical addition

donor *acceptor*

Problem in Radical-Radical Cross Coupling



Radical species: high reactivity
very fast reaction

In Statistics…

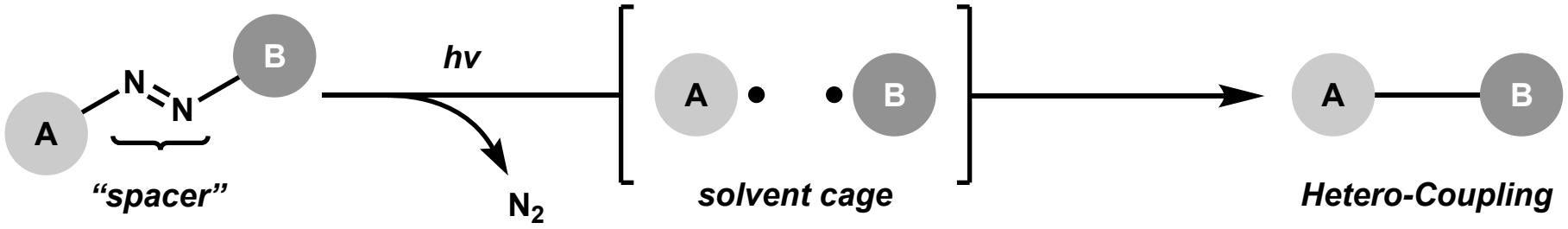
reactivity: A • = • B

A : B	molar ratio AA : AB : BB	maximum yield* AA	AB	BB
1 : 1	1 : 2 : 1	25%	50%	25%
1 : 2	1 : 4 : 4	17%	67%	67%
1 : 3	1 : 6 : 9	13%	75%	113%
.	.		.	
.	.		.	
1 : X	$1 : 2X : X^2$		2X	

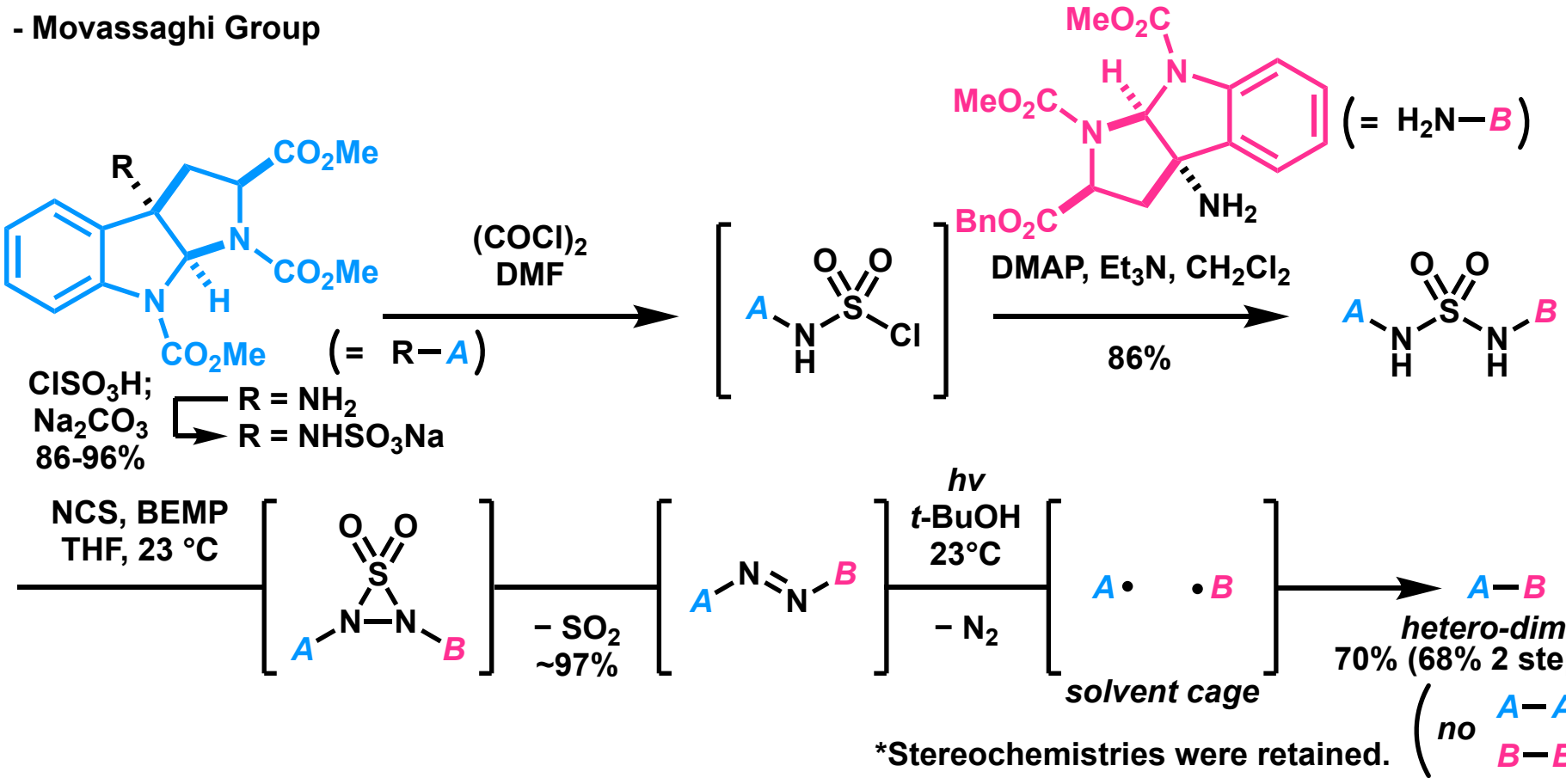
(*relative yields based on heterodimer AB)

$$\frac{2X}{2 \cdot 1 + 2X} = \frac{X}{1+X} \times 100\ [\%]$$ ***statistical limit*** > Yield of AB [%]

Solvent Cage Effect



- Movassaghi Group

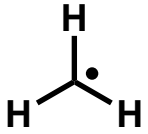


1. Movassaghi, M.; Ahmad, O. K.; Lathrop, S. P. *J. Am. Chem. Soc.* **2011**, *133*, 13002.
2. Braden, D. A.; Parrack, E. E.; Tyler, D. R. *Coord. Chem. Rev.* **2001**, *211*, 279.

Persistent Radical Effect

Half-life time of radicals (298 K, [radical] = 10^{-5} M): $\tau_{1/2}$

ex.)

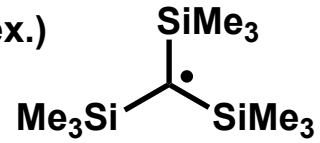


Transient radical

$\tau_{1/2} < 10^{-3}$ s

$\tau_{1/2} \sim 10^{-4.7}$ s

ex.)

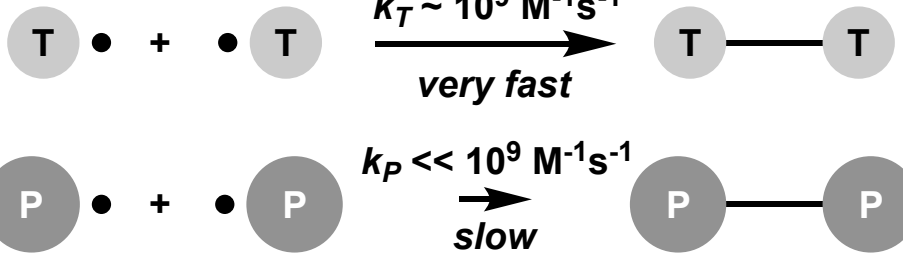


Persistent radical

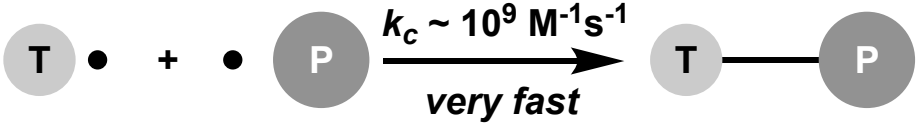
$\tau_{1/2} > 10^{-3}$ s

$\tau_{1/2} \sim 10^{5.3}$ s

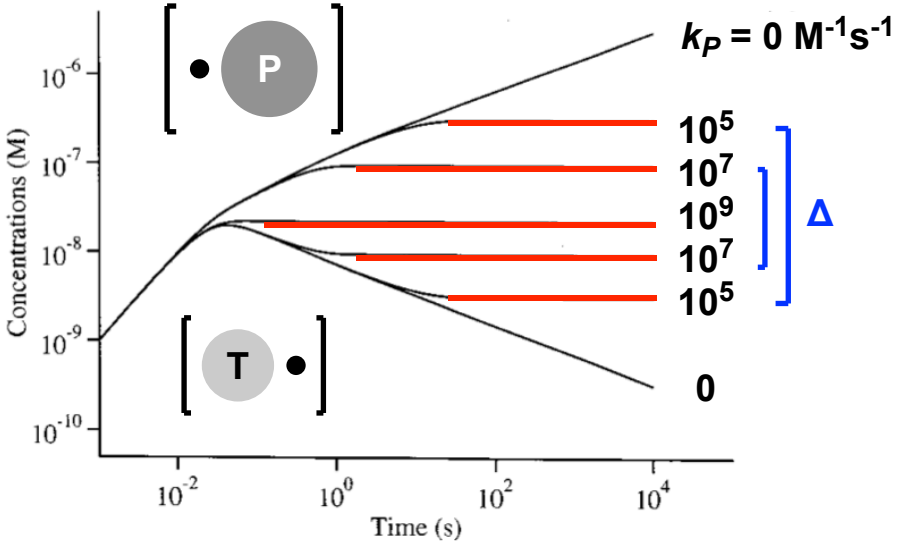
Homo-Coupling



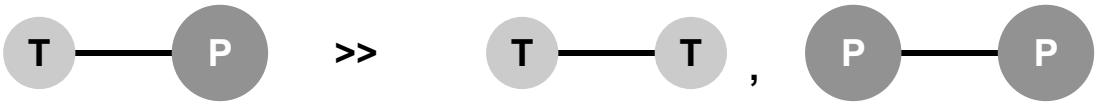
Hetero-Coupling



when $r_T = r_P$, $k_T = k_c$ …

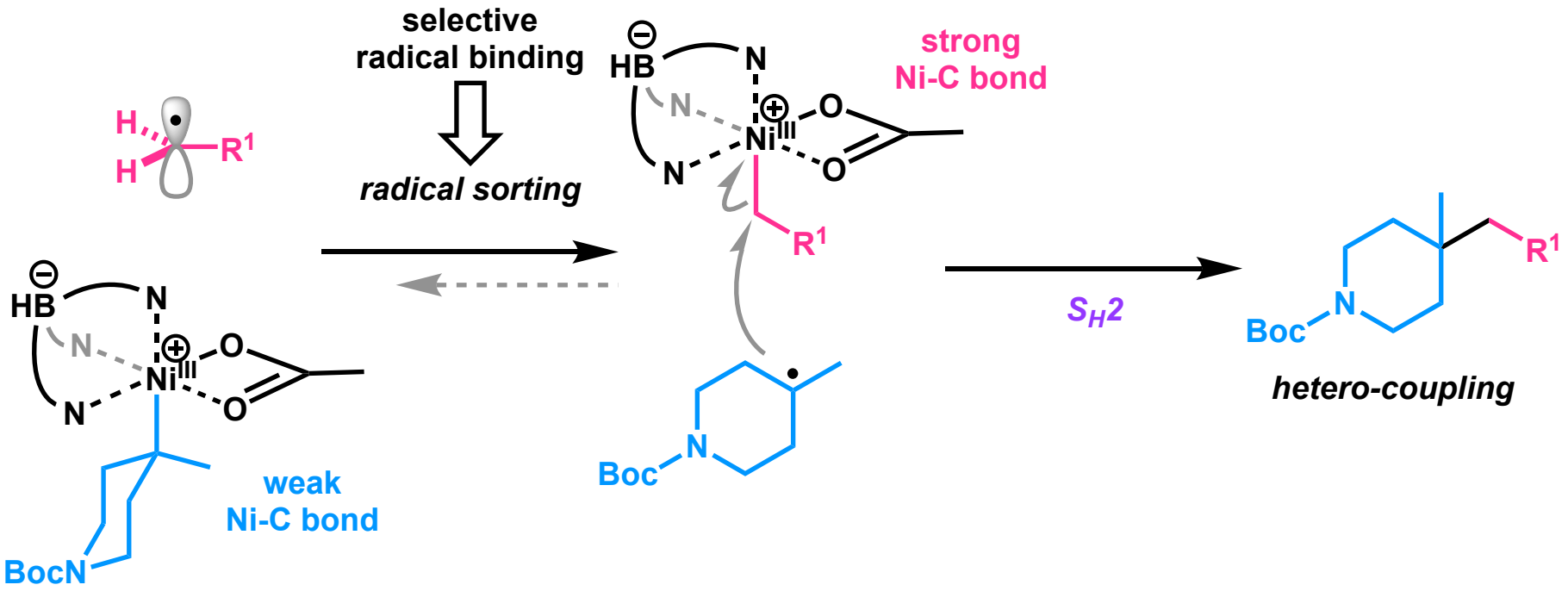


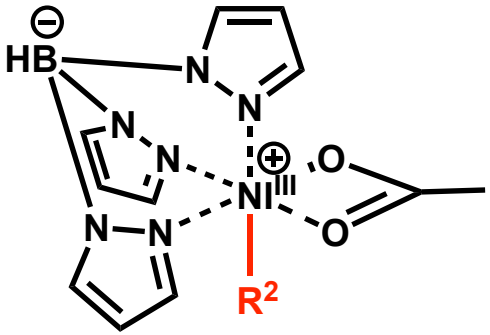
In steady-state, [P] >> [T] → Hetero-coupling product is highly favored.



1. 150523_LS_Haruka_Fujino_Radical_radical_crosscoupliung
2. Fischer, H. *Chem. Rev.* **2001**, *101*, 3581.

Radical Sorting Effect





R^2	Ni-R^2 BDFE
Me	9.5 kcal/mol
Et	1.1 kcal/mol
i-Pr	−1.9 kcal/mol
t-Bu	−9.8 kcal/mol

only methyl and 1° alkyl bind to the nickel complex

radical sorting

(BDFE = bond dissociation free energies)

1. Tsymbal, A. T.; Bizzini, L. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 21278.

Contents

Introduction of Prof. Ohmiya

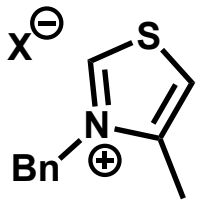
Prof. Hirohisa Ohmiya

Research topic:
Organic synthesis by designing catalyst and chemical reaction as well as molucule

2002 B.S., @ Kyoto Pharmaceutical University
2004 M.S., @ Kyoto Pharmaceutical University (Prof. Uenishi, J.)
2007 Ph.D. @ Kyoto University (Prof. Oshima, K.)
2007 Postdoctoral fellow @ Massachusetts Institute of Technology (Prof. Jamison, T. F.)
2008 Assistant Professor @ Hokkaido University (Prof. Sawamura, M.)
2010 Associate Professor @ Hokkaido University (Prof. Sawamura, M.)
2017 Professor @ Kanazawa University
2019- JST PRESTO Researcher
2022- Professor @ Kyoto University

Breslow Intermediate

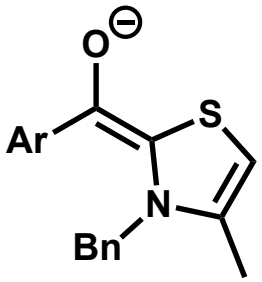
- Fukuzumi Group: Studies of the Breslow intermediate



1a

ArCHO

DBU



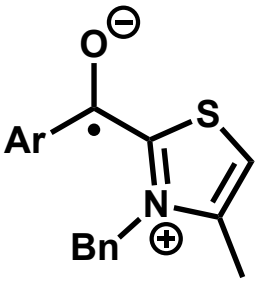
2a

enolate form of Breslow intermediate

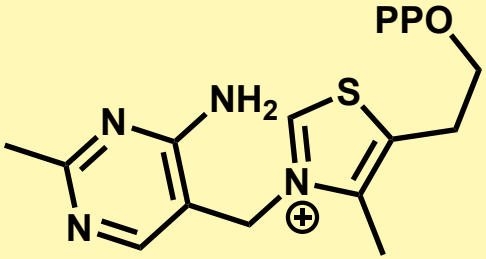
−0.97 V vs SCE

− e⁻

SET

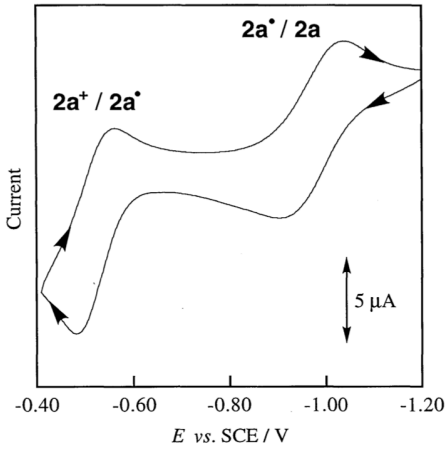


3a

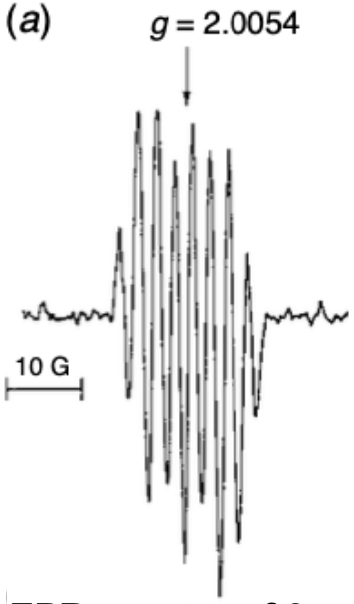


thiamine diphosphate (ThDP)

Ar =



cyclic voltammogram of 2a



EPR spectra of 3a

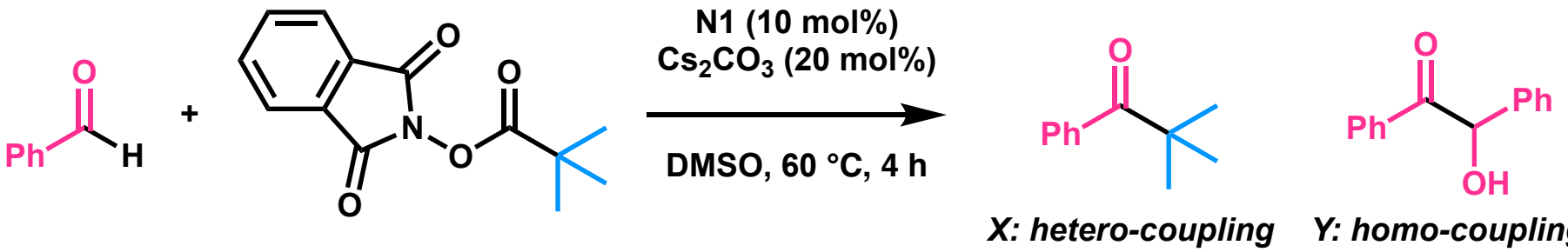
The spectra of radical species 3a was persistent for several hours.

↓

3a: *persistent radical*

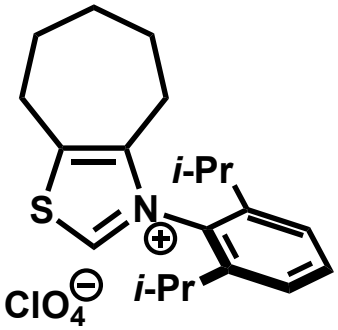
1. Nakanishi, I.; Itoh, S.; Suenobu, T.; Inoue, H.; Fukuzumi, S. *Chem. Lett.* **1997**, *26*, 707.
2. Nakanishi, I.; Itoh, S.; Suenobu, T.; Fukuzumi, S. *Chem. Commun.* **1997**, 1927.

Screening Results of Cross-Coupling

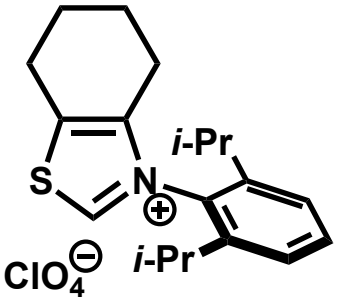


X: hetero-coupling *Y: homo-coupling*

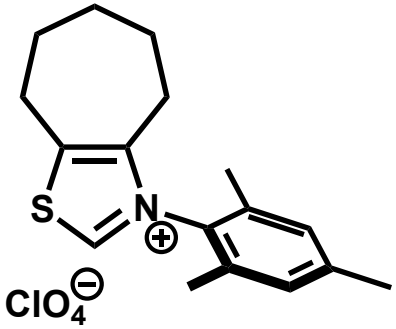
entry	change from standard conditions	yield of *X*	yield of *Y*
1	none	99%	0%
2	N2 instead of N1	31%	0%
3	N3 instead of N1	11%	4%
4	N4 instead of N1	0%	0%
5	$LiCO_3$ instaed of Cs_2CO_3	7%	3%
6	K_2CO_3 instead of Cs_2CO_3	74%	0%
7	*i*-Pr_2NEt instead of Cs_2CO_3	4%	8%



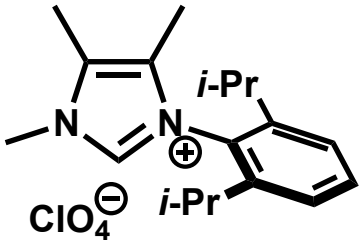
N1



N2



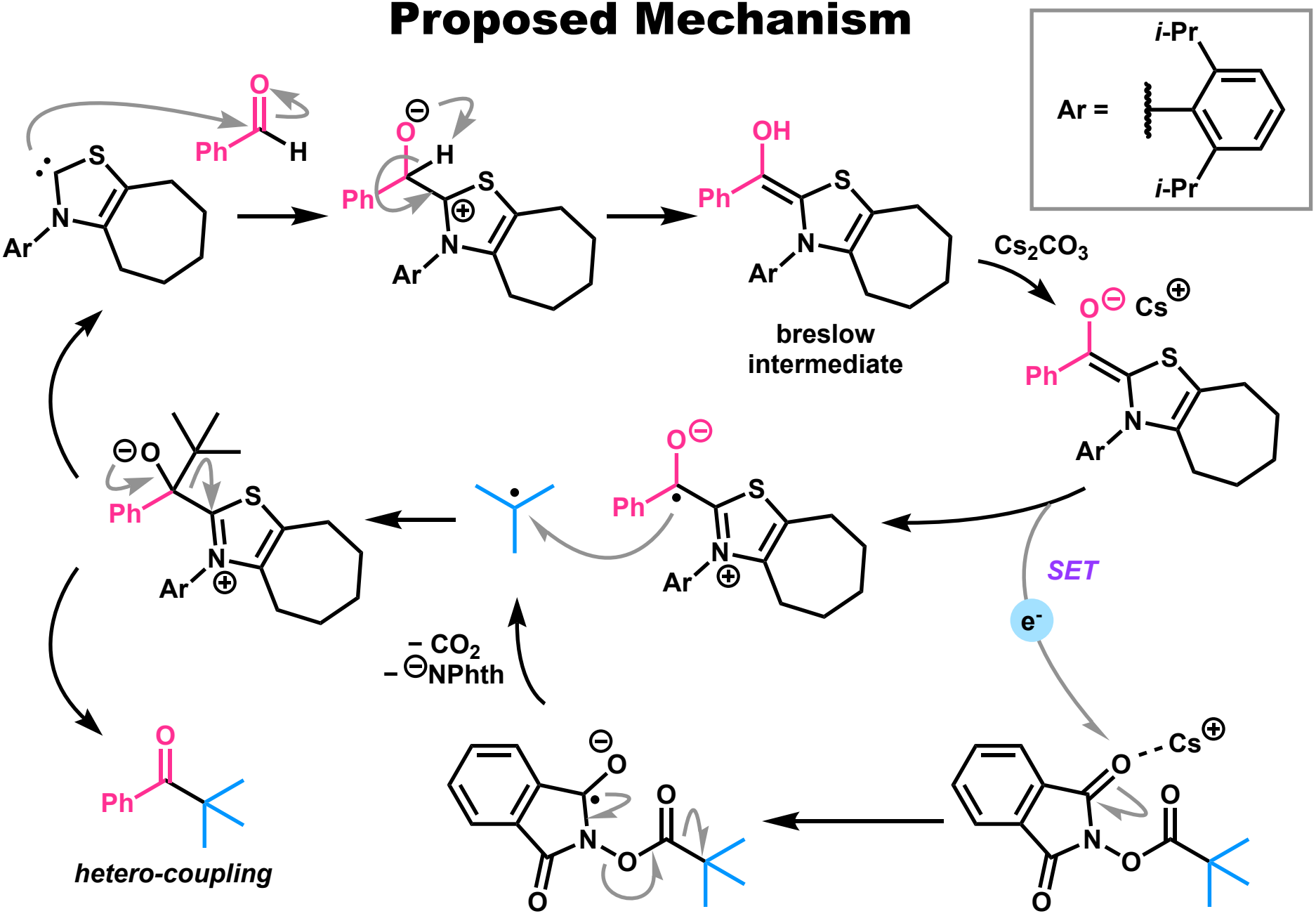
N3



N4

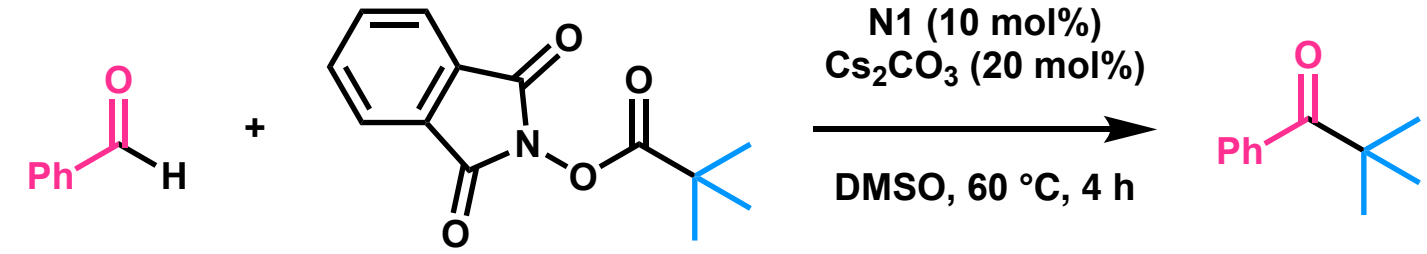
1. Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. *J. Am.Chem. Soc.* **2019**, *141*, 3854.

Proposed Mechanism

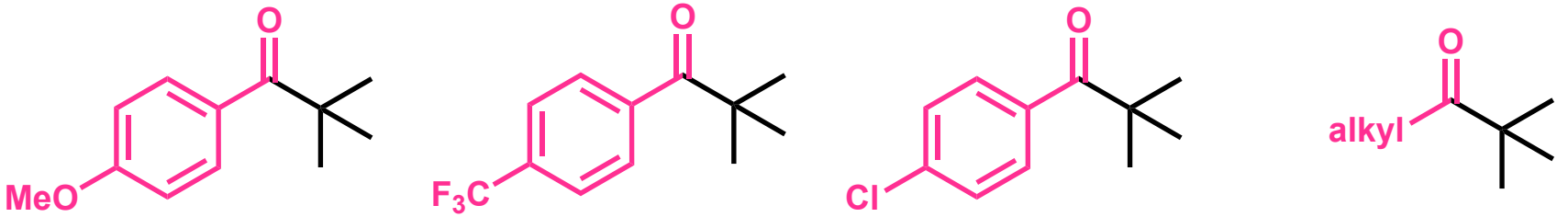


1. Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. *J. Am.Chem. Soc.* **2019**, *141*, 3854.

Substrate Scope



(1.5 equiv.) (1 equiv.)



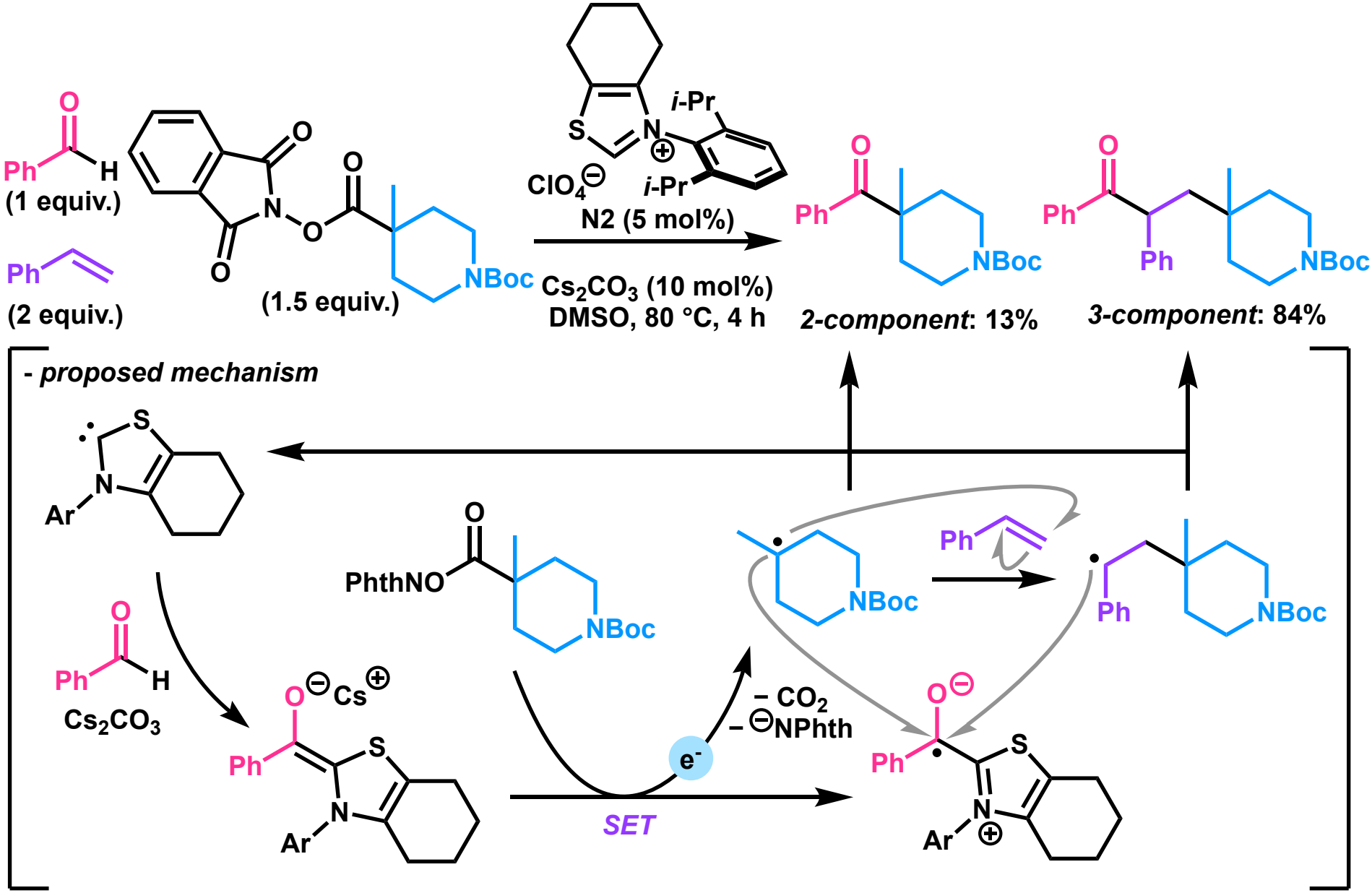
72% 78% 80% not successful

76% 32% 83% racemic, 56% (DBU instead of Cs_2CO_3)

statistical limit: 60%

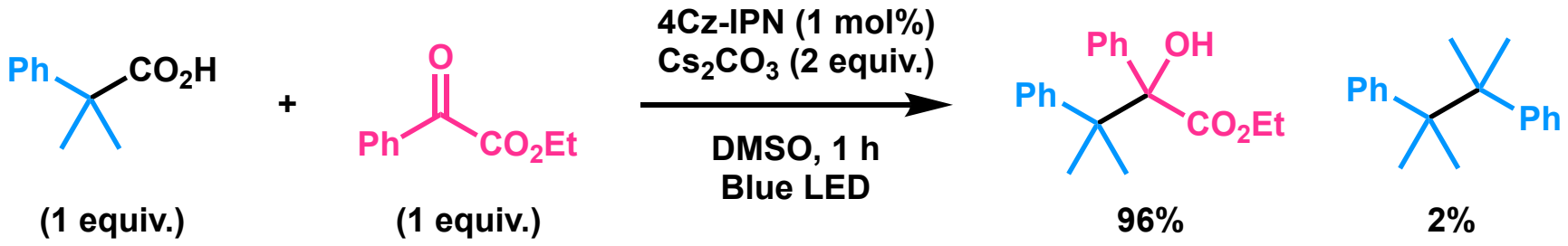
1. Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. *J. Am.Chem. Soc.* **2019**, *141*, 3854.

3-Component Coupling

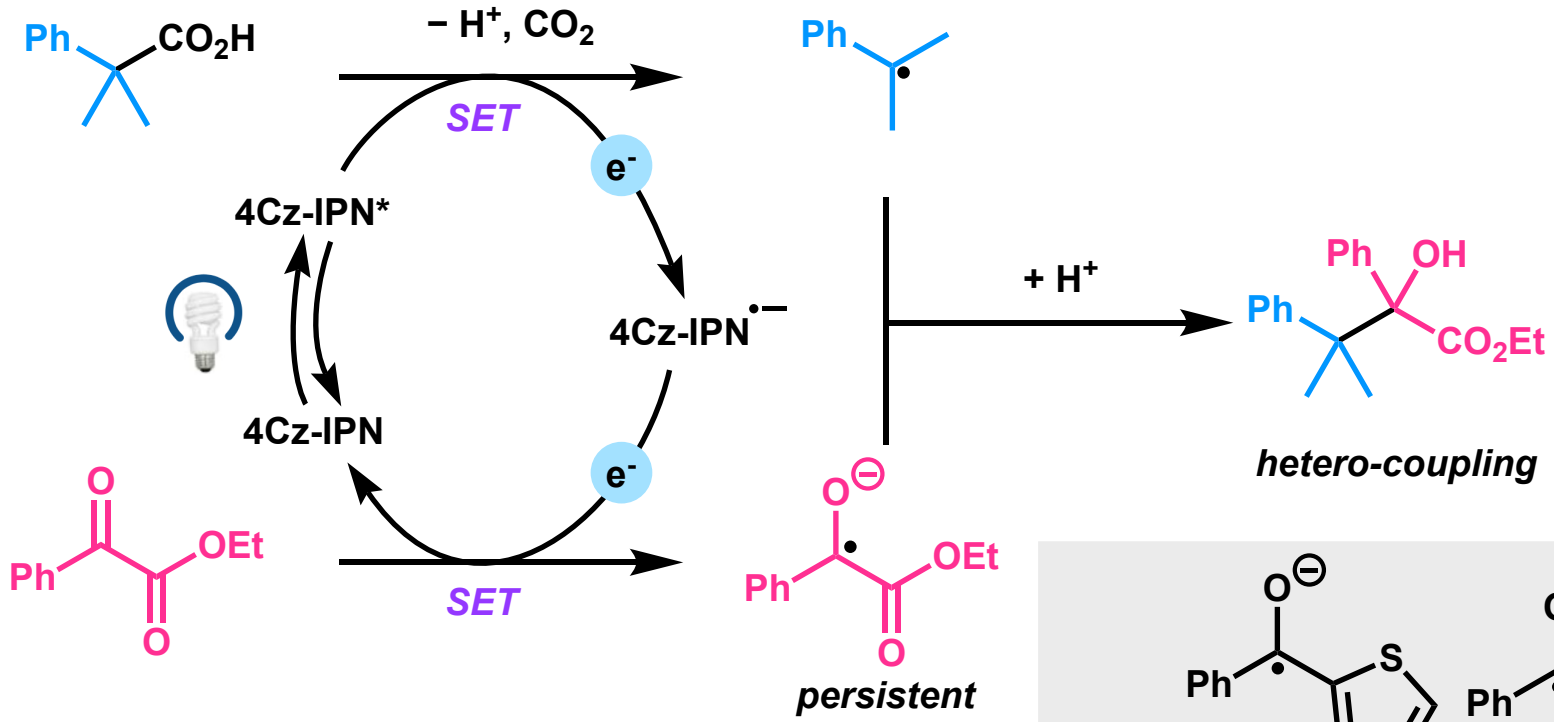


1. Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H. *J. Am.Chem. Soc.* **2019**, *141*, 14073.

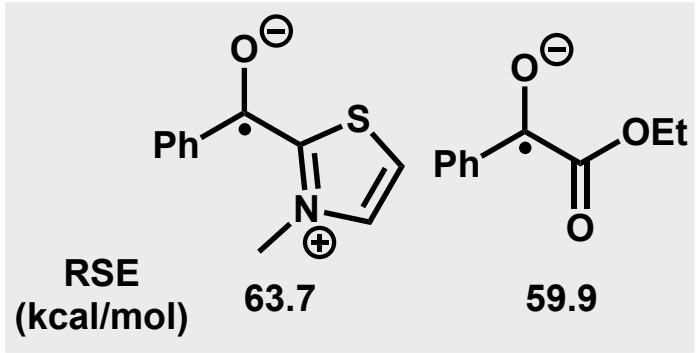
Synthesis of Sterically Hindered Alcohol



- *proposed mechansim*



*RSE = radical stabilization energy
RSE = BDE (CH_4) − BDE (CHX_3), RSE > 0: stabilized radical



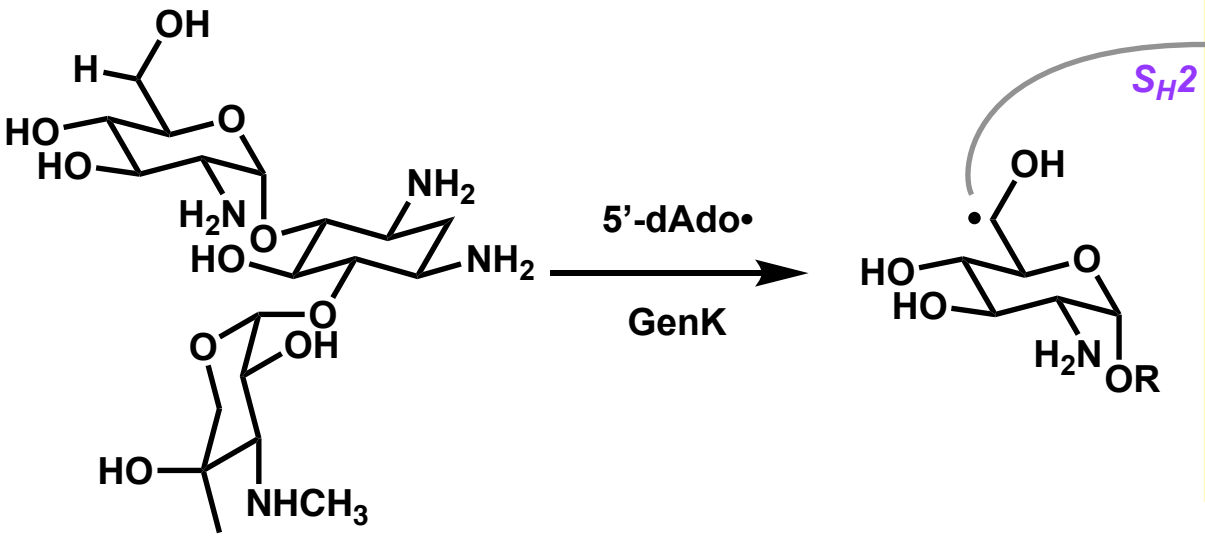
1. Ota, K.; Nagao, K.; Ohmiya, H. *Org. Lett.* **2021**, *23*, 4420.

Contents

Biological Methylation

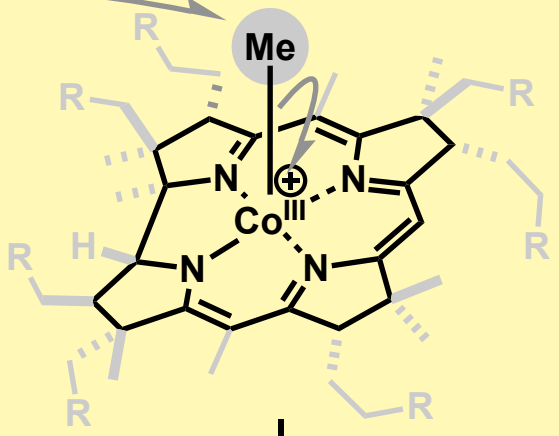
In biosynthesis of Gentamicin…

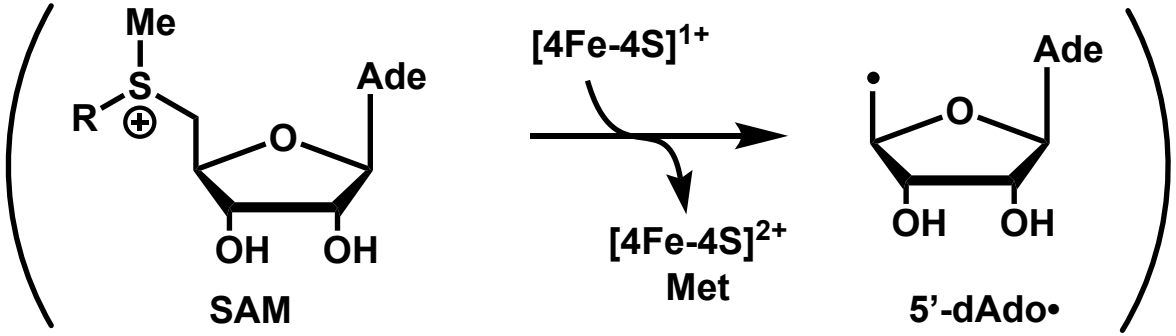
GenK: one of the Cobalamin (Cbl)-dependent radical S-adenosylmethionine (SAM) methyltransferases

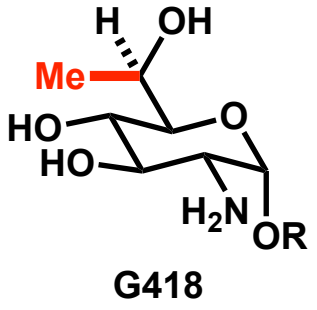


Gentamicin X_2

Methylcobalamin
nature's free radical carrier
a form of vitamin B12



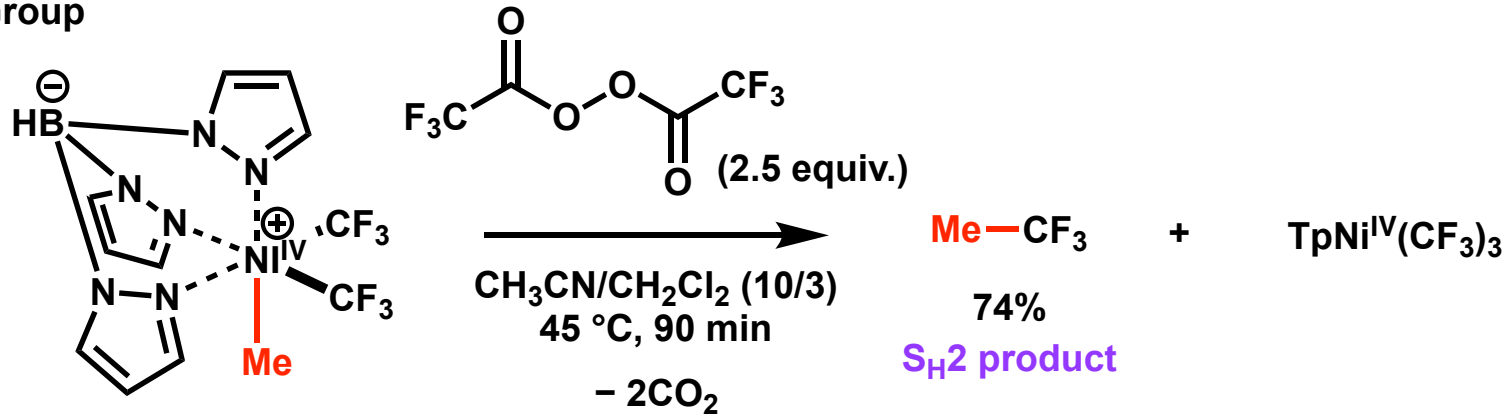




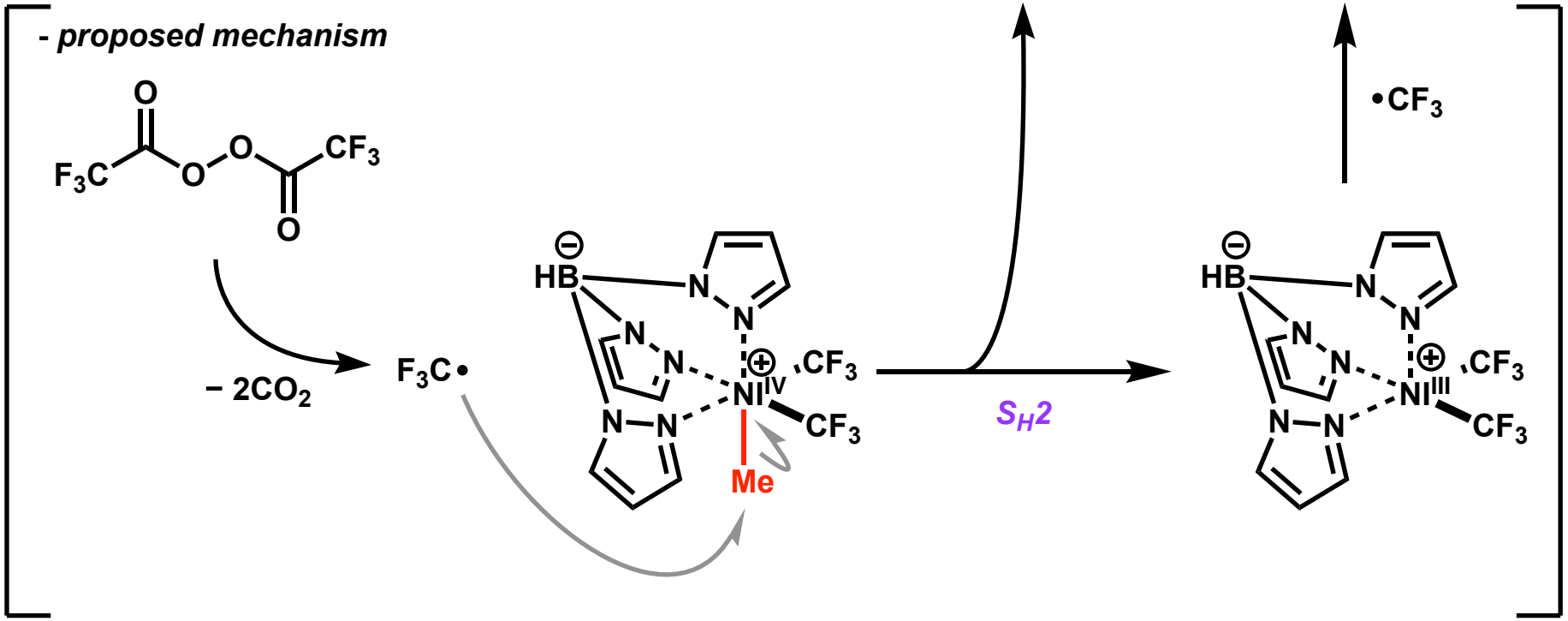
1. Wang, Y.; Begley, T. P. *J. Am. Chem. Soc.* **2020**, *142*, 9944.
2. Wang, S. C. *Nat. Prd. Rep.*, **2018**, *35*, 707.

Limited use of S_H2 Reactions in Cross-Coupling

- Sanford Group

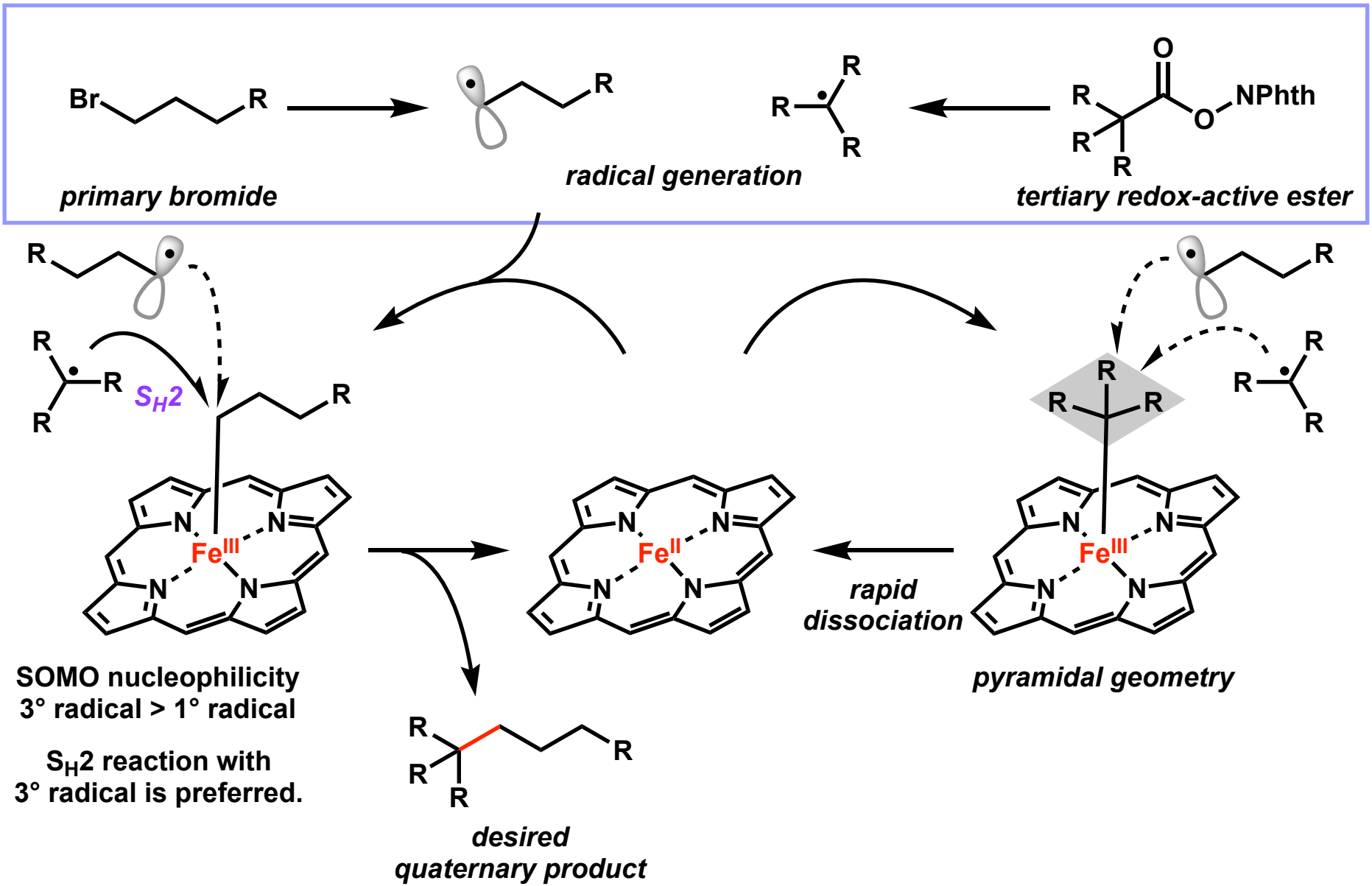


- *proposed mechanism*



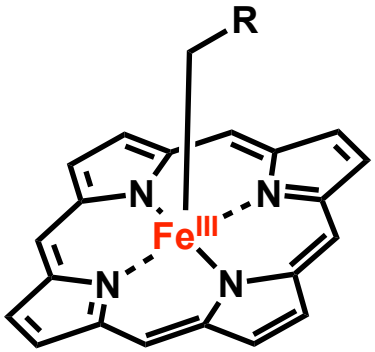
1. Bour, J. R.; Ferguson, D. M.; McClain, E. J.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2019**, *141*, 8914.

Reaction design



1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

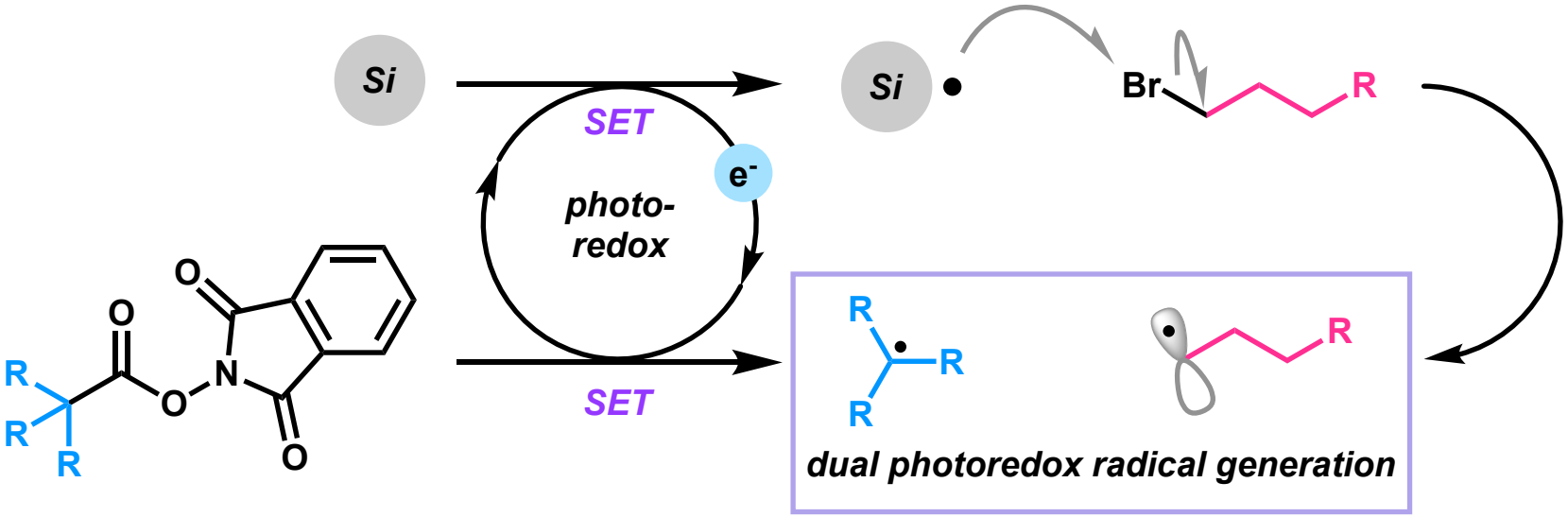
Radical Generation



sensitive to heat, O_2
→Mild conditions are required in the radical generation step.

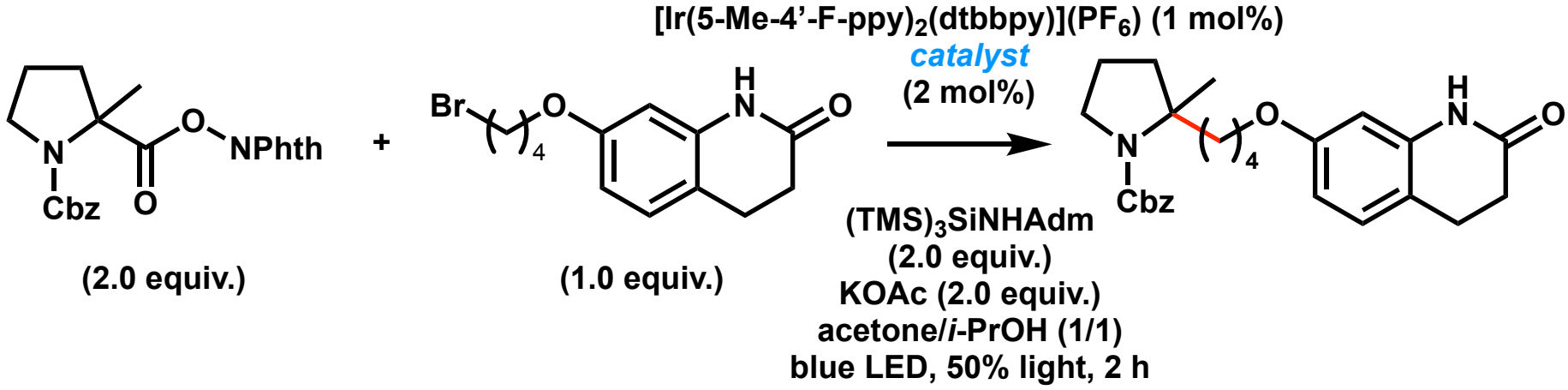
MacMillan's strategy

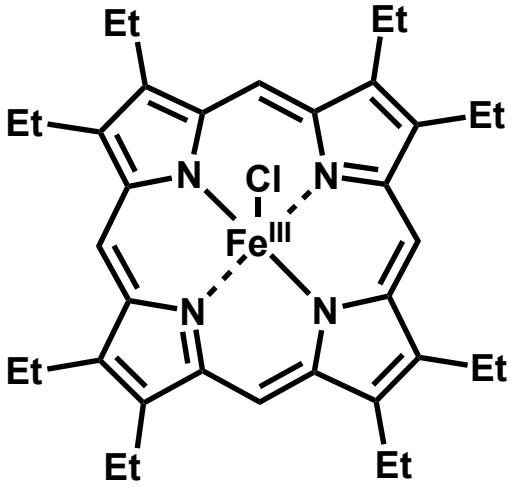
- Silyl radical-mediated halogen abstraction-radical capture (HARC) strategy
- Photoredox-neutral pathway



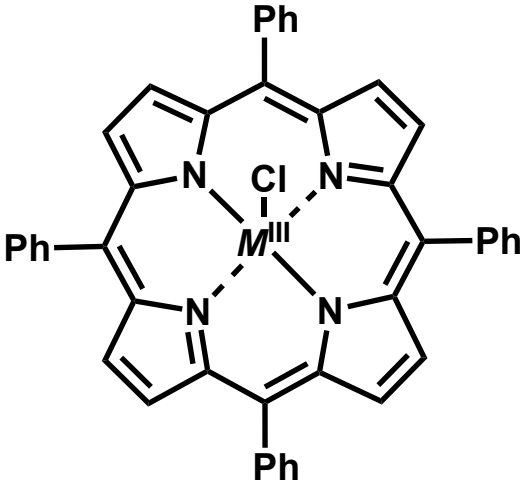
1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.
2. Lexa, D.; Mispelter, J.; Saveant, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 6806.

Catalyst Evaluation

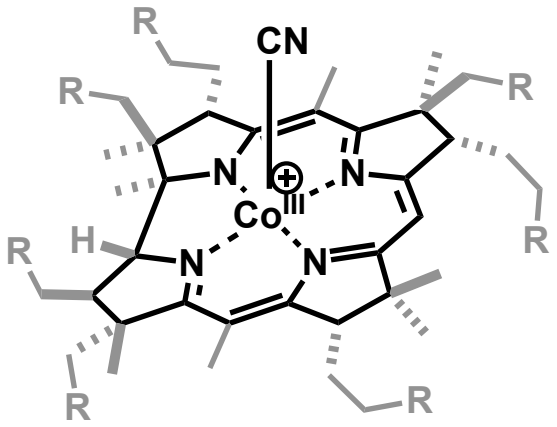




Fe(OEP)Cl
86%



M(TPP)Cl
M = Fe: 6%, *M* = Co: 3%



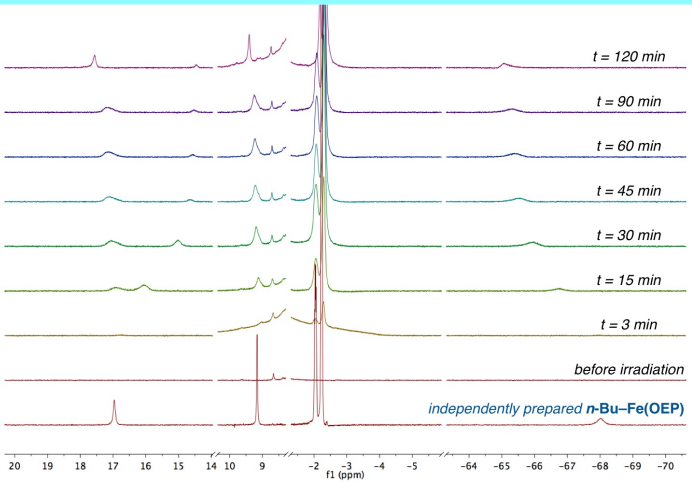
Vitamin B12*
7%

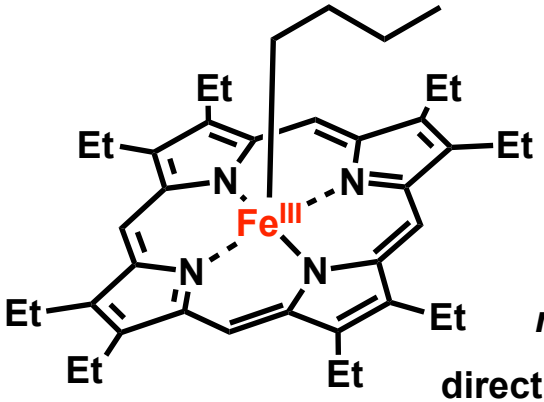
*exact structure: see appendix

1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

Mechanistic Studies (1)

Photo-NMR experiment to direct observe n-Bu-Fe(OEP) complex in situ

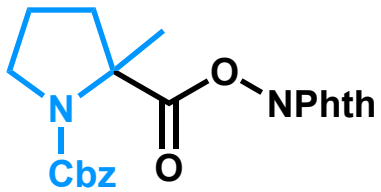




***n*-Bu-Fe(OEP)**

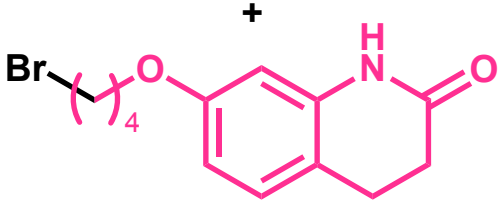
directly observed in *situ*

Direct use of n-Bu-Fe(OEP) complex as precatalyst

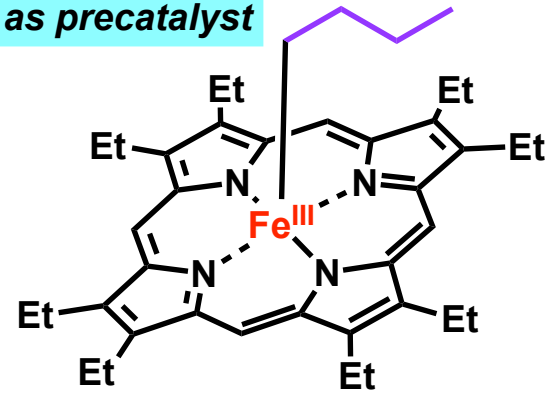


(2.0 equiv.)

+

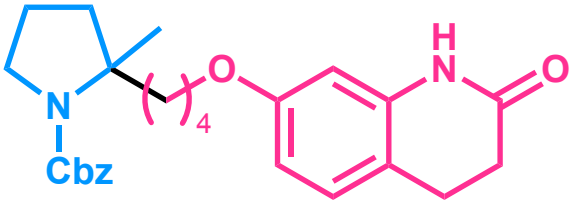


(1.0 equiv.)

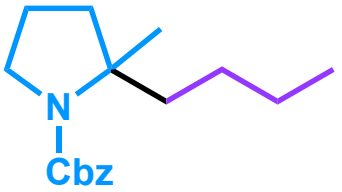


(10 mol%)

[Ir(5-Me-4'-F-ppy)$_2$(dtbbpy)](PF$_6$) (2 mol%)
(TMS)$_3$SiNHAdm (1.5 equiv.)
KOAc (2.0 equiv.)
acetone/*i*-PrOH (1/1)
blue LED, 2 h



64% (±3)

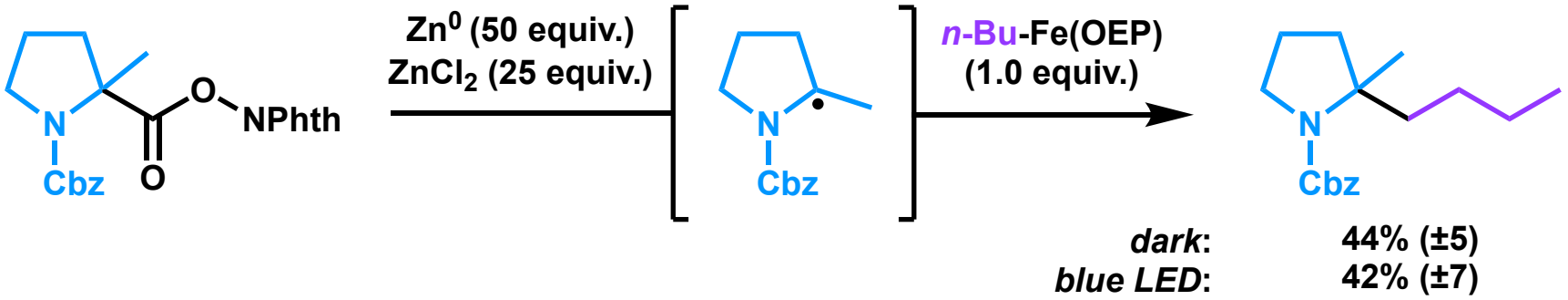


7% (±1)

1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

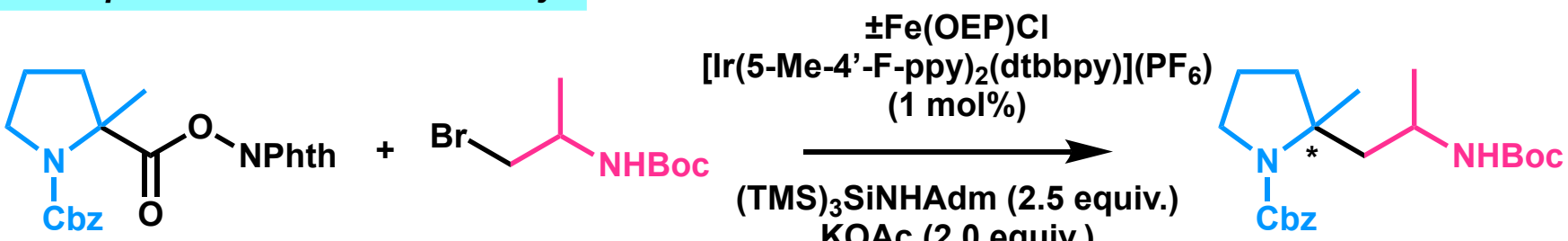
Mechanistic Studies (2)

Light-Free Radical Generation Studies



Light is not required for C-C bond formation.

Iron-dependent diastereoselectivity



redox-active ester **(2.0 equiv.)**

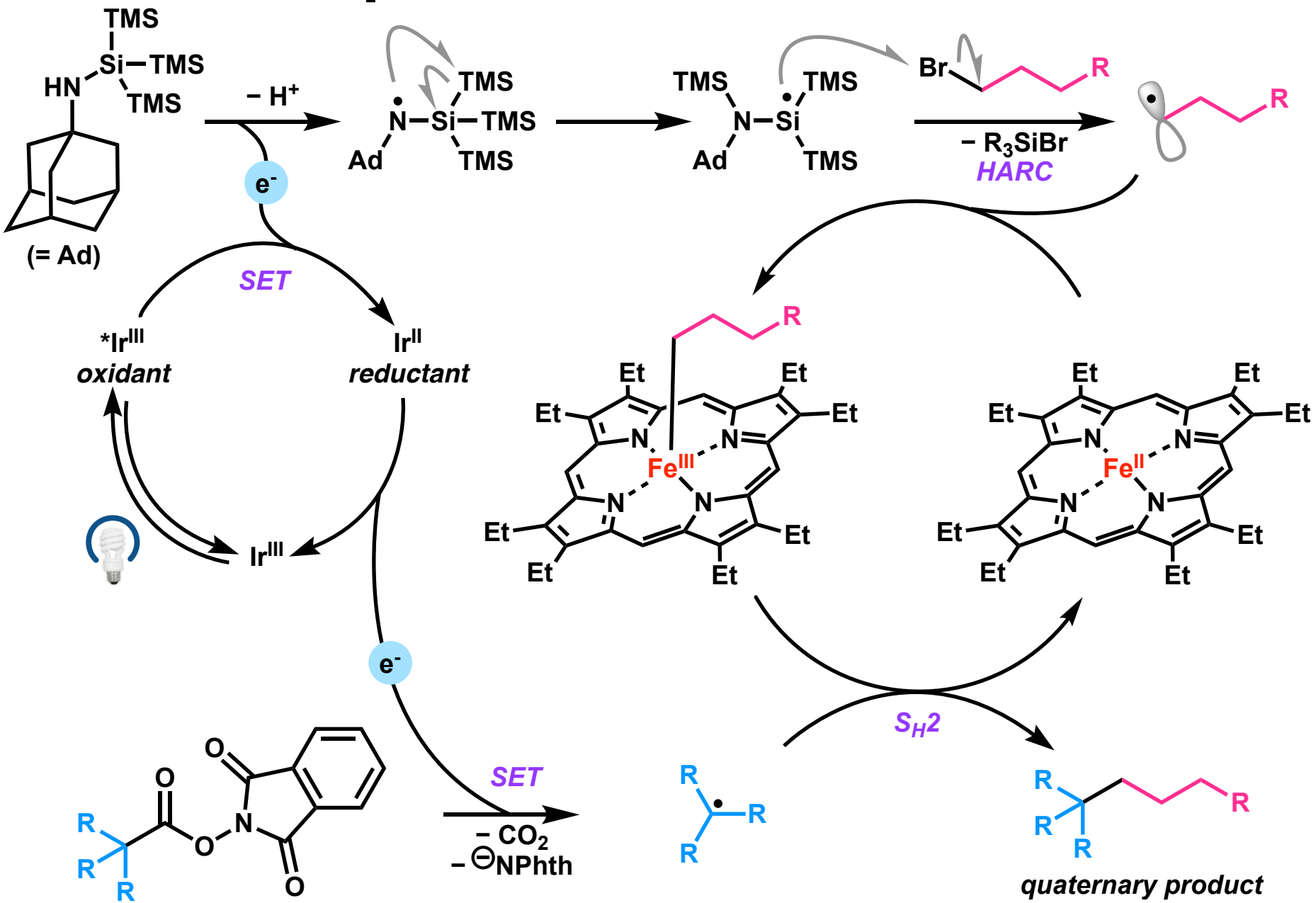
1° alkyl bromide **(1.0 equiv.)**

0 mol% [Fe]	**15% yield, *dr. 1.1 : 1**
10 mol% [Fe]	**56% yield, *dr. 3.2 : 1**

Reaction proceeds via SH2 mechanism, not free-radical/radical coupling.

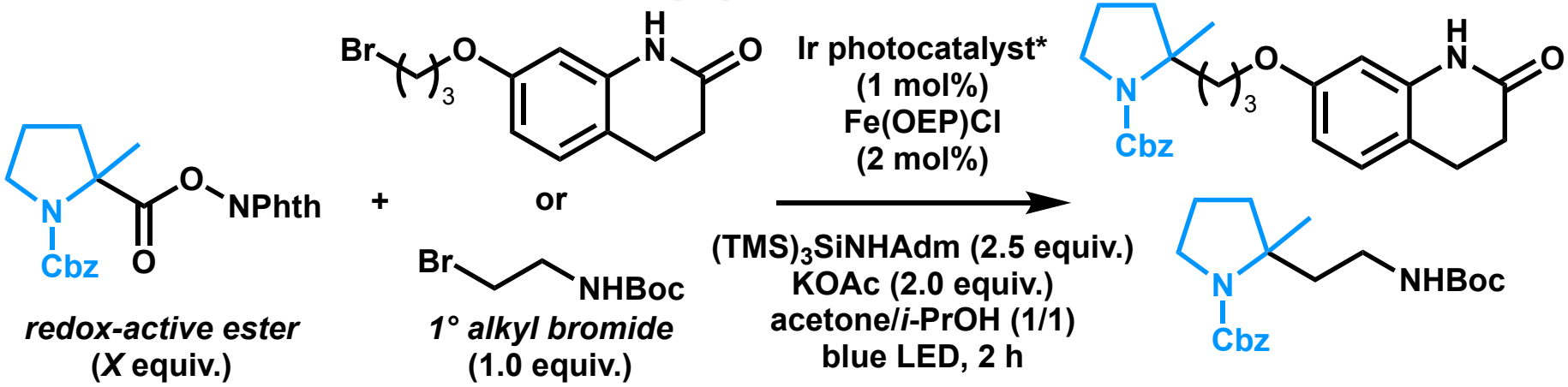
1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

Proposed Reaction Mechanism

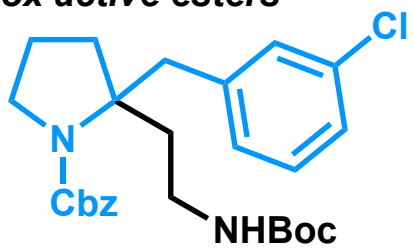


1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

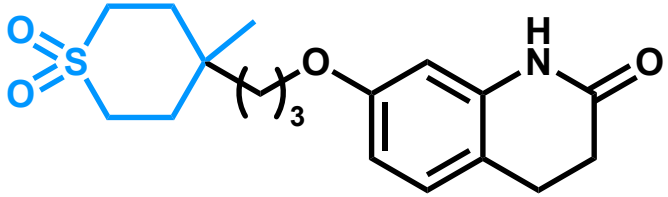
Substrate Scope (1): Redox Active Esters



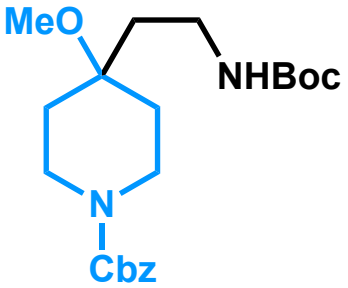
- *redox active esters*



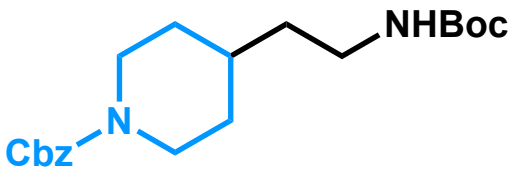
X = 1.5, (±), 80%



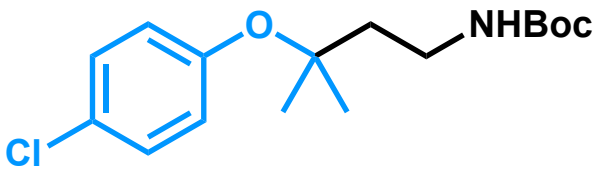
X = 2.0, 60%



X = 1.5, 68%

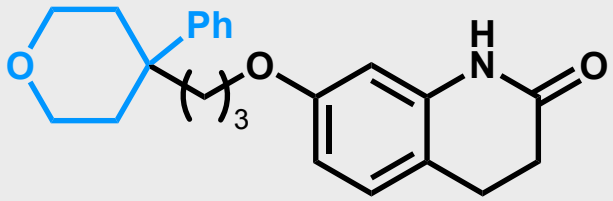


X = 2.0, 65%



X = 2.0, 50%

- *Limitation*



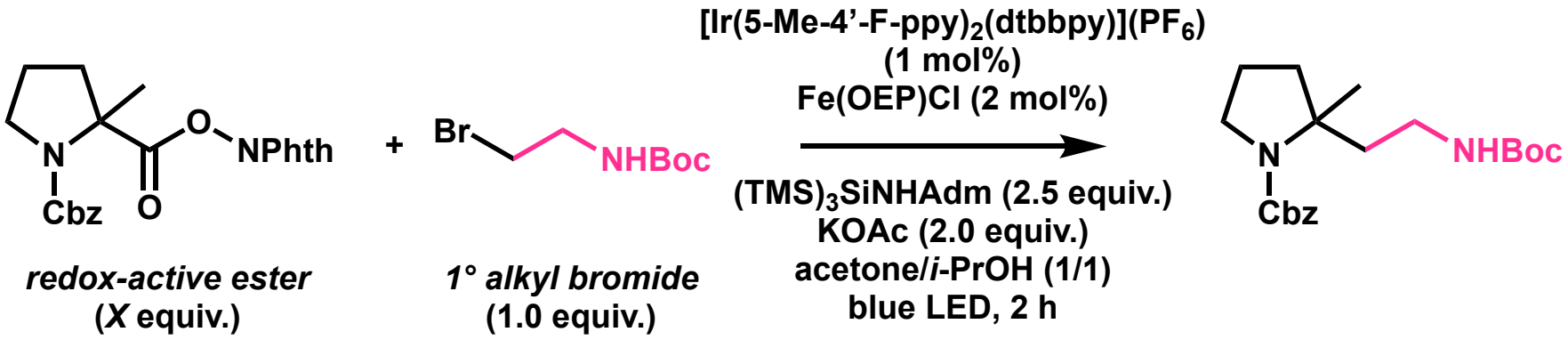
22%

*Ir photocatalyst = $[Ir(5\text{-Me-}4'\text{-F-ppy})_2(dtbbpy)](PF_6)$

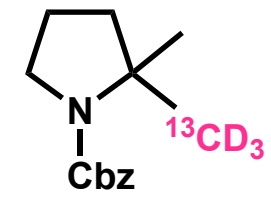
statistical limit: *X* = 1.5 → 60%
X = 2.0 → 67%

1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

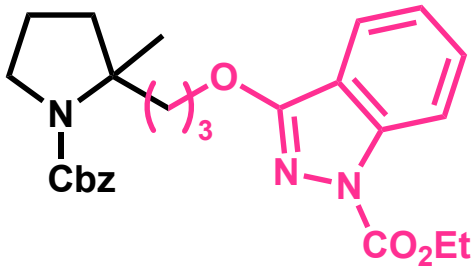
Substrate Scope (2): 1° Alkyl Bromide



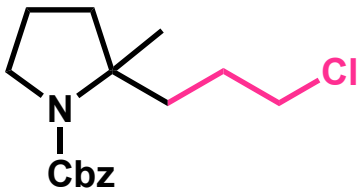
- *1° alkyl bromide*



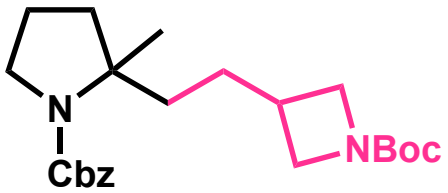
X = 1.5, (±), 75%



X = 2.0, (±), 63%



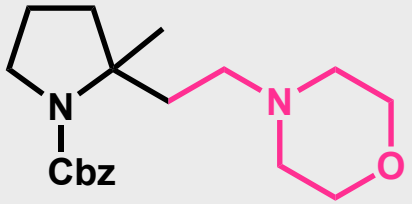
X = 1.5, (±), 75%



X = 2.0, (±), 65%

- *Limitation*

R = H, (±), 30%
R = Ac, (±), 72%



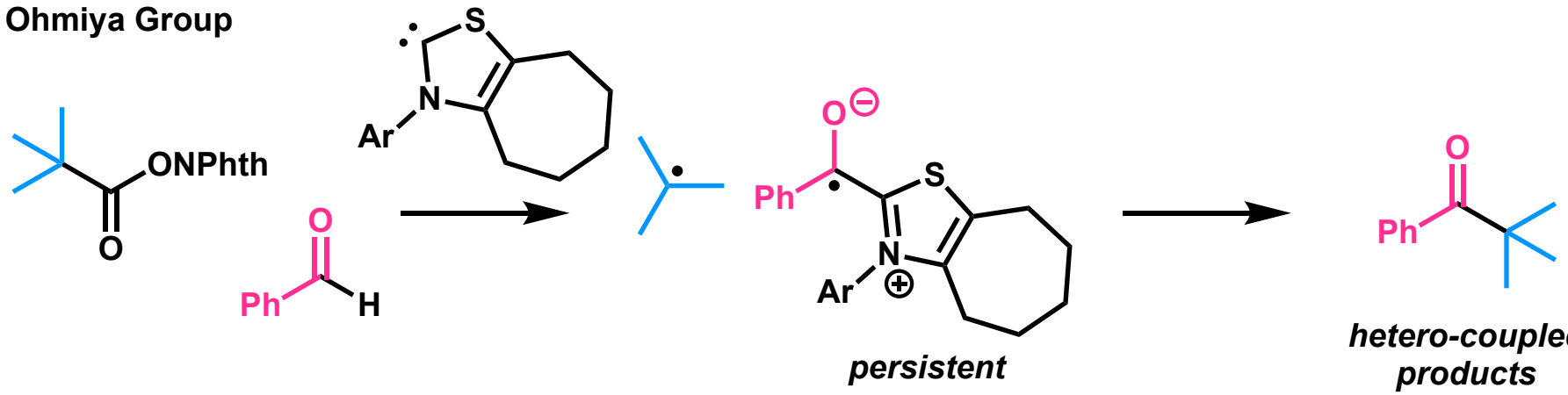
<5%

statistical limit: *X* = 1.5 → 60%
X = 2.0 → 67%

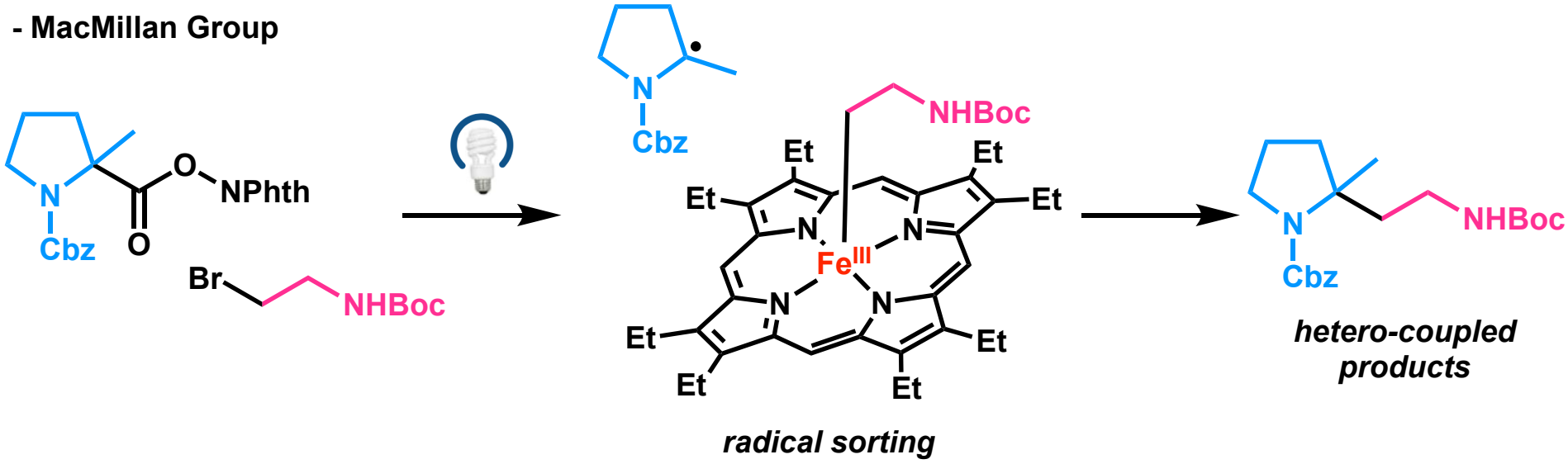
1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

Summary

- Ohmiya Group

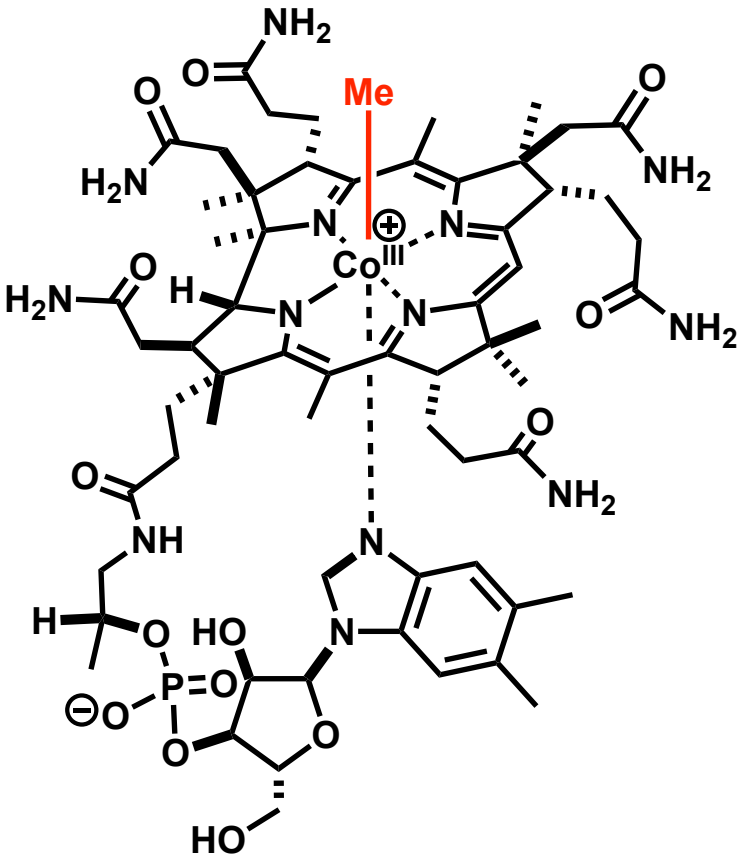


- MacMillan Group

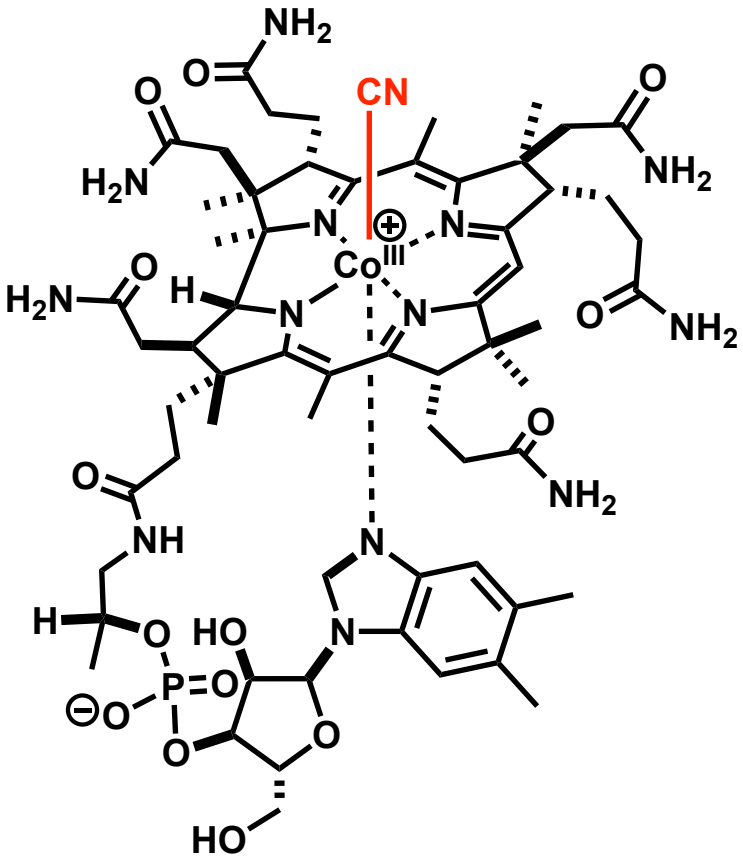


Appendix

Structures



Methylcobalamin



Vitamin B12

SOMO Orbital

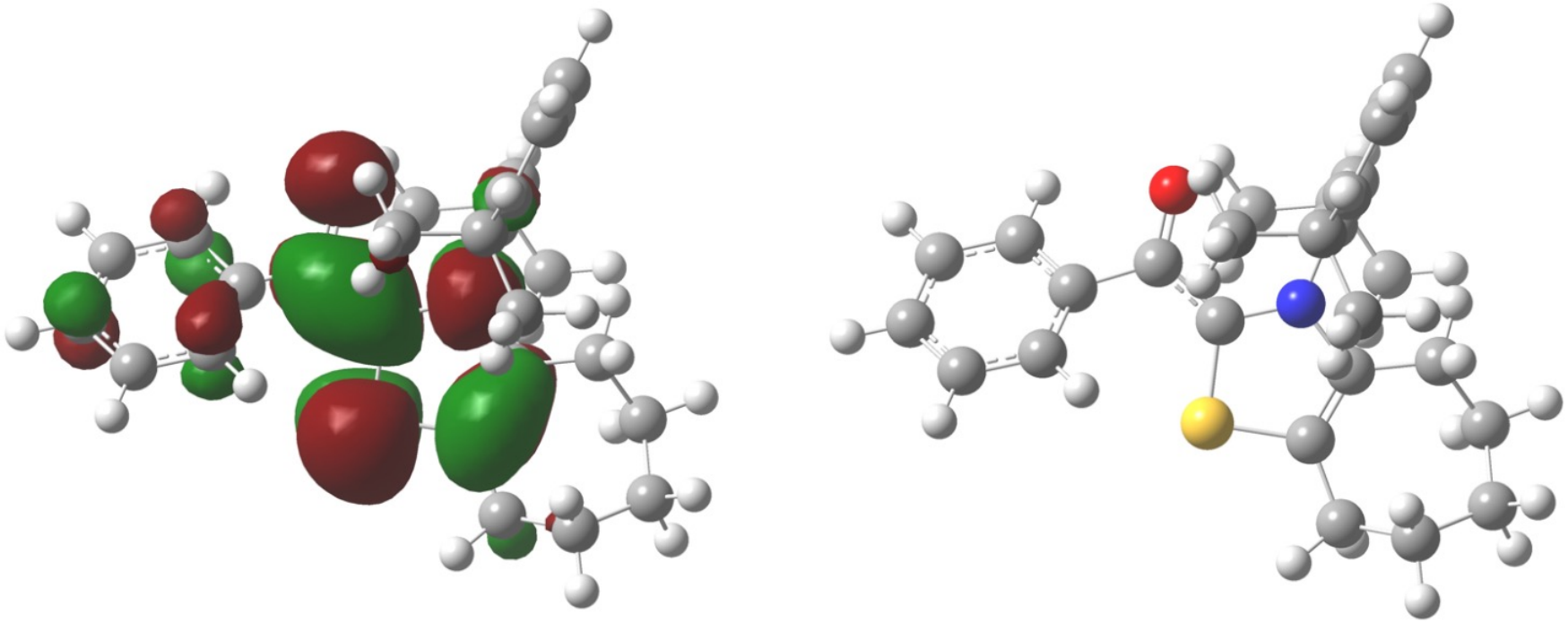
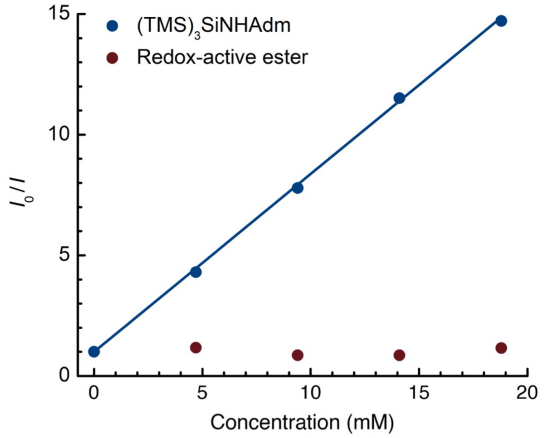


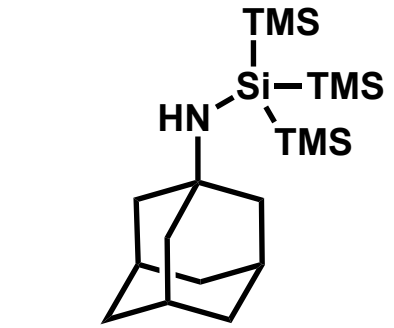
Figure S1. SOMO orbital of the enolate radical of the Breslow intermediate

Mechanistic studies

Fluorescene quenching studies



Stern-Volmer relationship for quenching of Ir photocatalyst by aminosilane or redox-active ester.

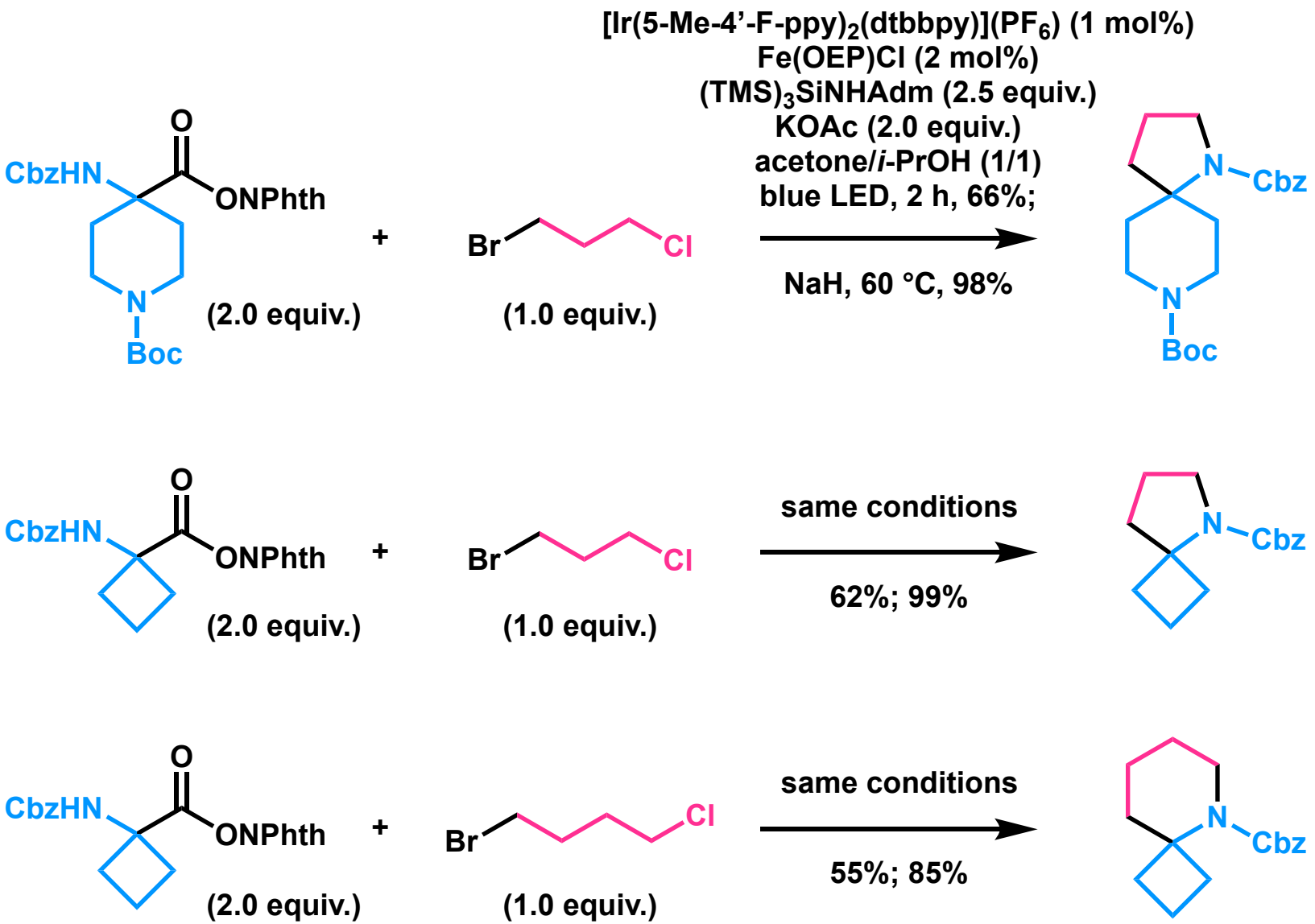


$*Ir^{III} \rightarrow Ir^{II}$

$k = 6.7 \times 10^8\ M^{-1}s^{-1}$

reductive quenching by aminosilane at a near diffusion-controlled rate

Further Scope: Synthesis of Spirocycles



1. Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcazar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.