

Regioselective Aliphatic C-H Functionalization using Neutral FRP

**2023.11.09. Literature Seminar
M2 Jaejoong Han**

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1. Introduction

2. Olefin Bisfunctionalization with Neutral FRP

**3. Regioselective Aliphatic C-H Functionalization
using Neutral FRP (Song Lin, 2023)**

4. Summary

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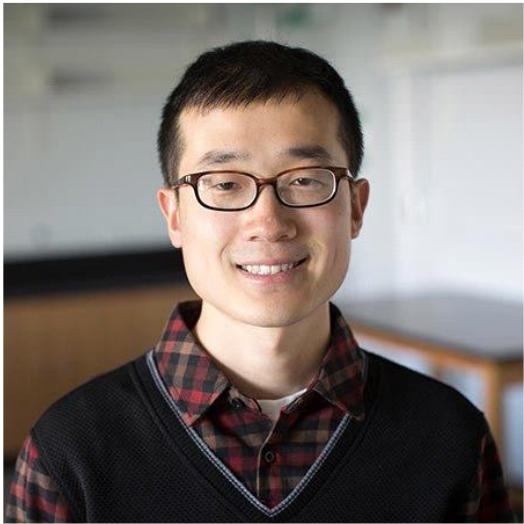
1. Introduction

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**3. Regioselective Aliphatic C-H Functionalization
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Introduction of Prof. Song Lin



Prof. Song Lin

Education and academic career:

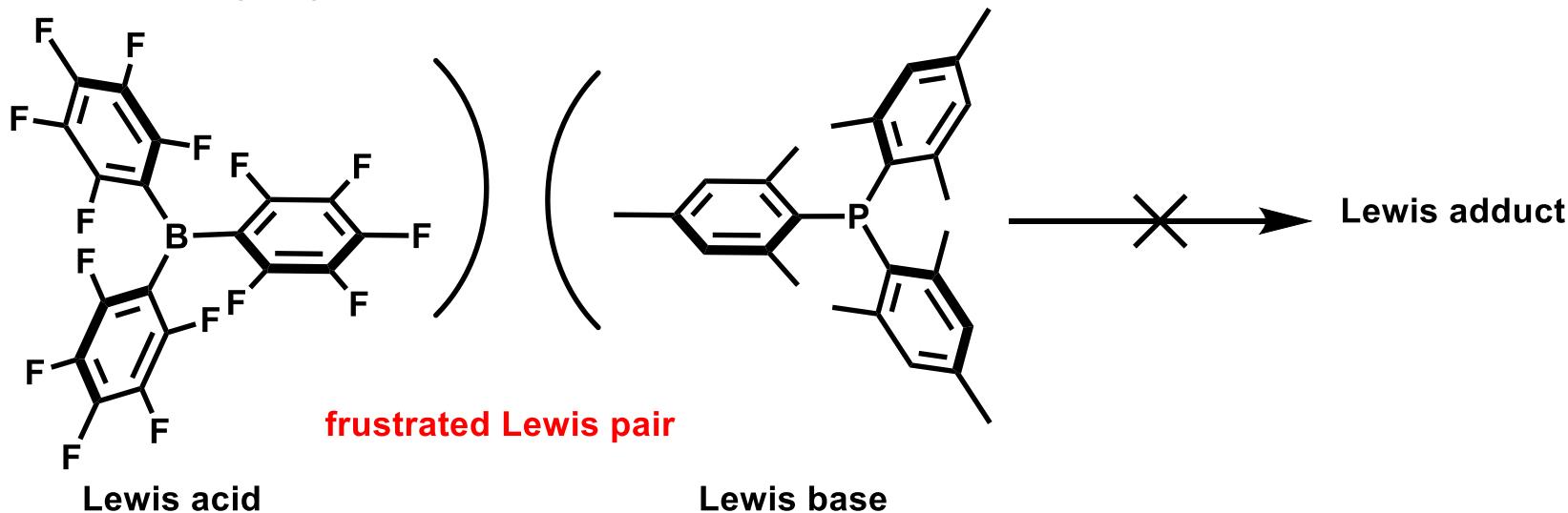
2008 B.S.c @ Peking University (Prof. Zhang-Jie Shi)
2013 Ph. D. @ Harvard University (Prof. Eric N. Jacobsen)
2013-2016 Postdoc @ UC Berkeley (Prof. Christopher J. Chang)
2016- Assistant professor @ Cornell University
2021- Associate professor@ Cornell University
2023- Professor@ Cornell University

Research topics:

- 1. Electrocatalysis**
- 2. Electrophotocatalysis**
- 3. Electroreductive chemistry**
- 4. Radical redox relay chemistry**
- 5. Polymer and materials chemistry**

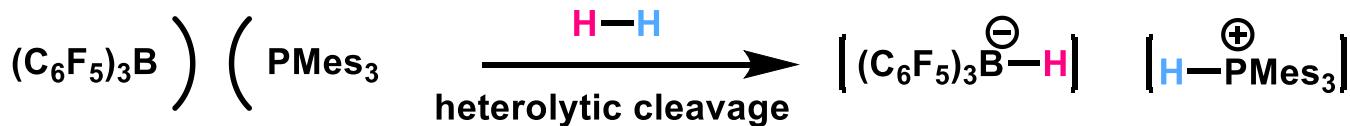
Frustrated Lewis Pair (FLP)

Frustrated Lewis Pair (FLP)



Due to its large steric hinderence or electronic frustration (energetic mismatching between molecular orbitals of the acid and the base), FLP cannot form a Lewis adduct.

Heterolytic cleavage of H₂ by FLP



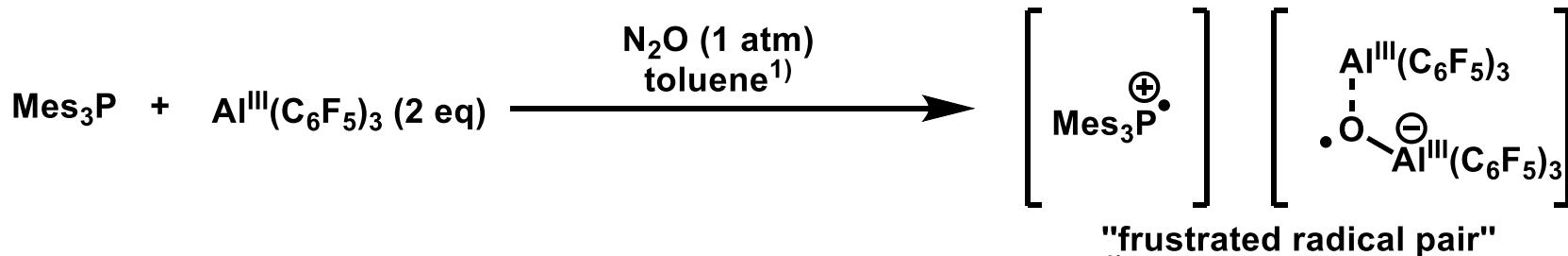
FLPs is kown for the ability of cleaving H-H bond in a heterolytic way¹⁾.

Also, FLPs are applied as a efficient catalyst in many reactions²⁾.

1) Welch, G. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2007**, 129, 1880.

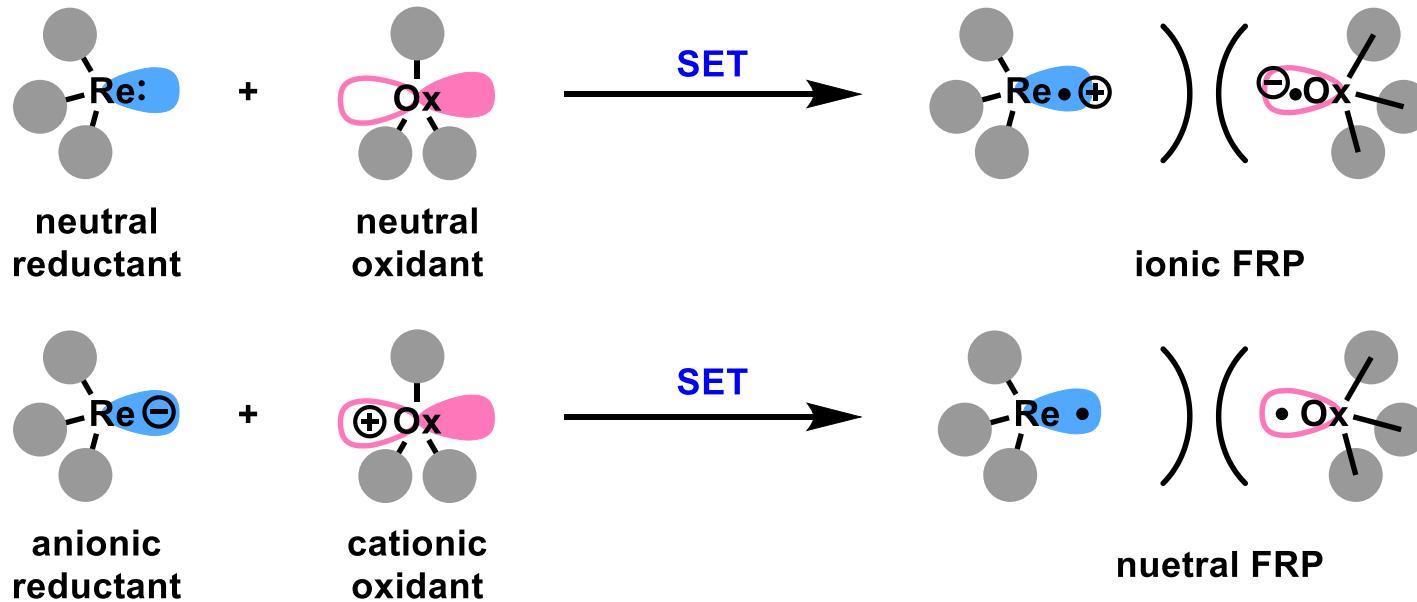
2) See also 150131_LS_Hiroyuki_Mutoh, 230121_LS_Koichi_Hagiwara

Frustrated Radical Pair (FRP)



The term "frustrated radical pair" was first used in 2013 by Stephan^{1).}

Ionic and neutral FRP



These two radicals or radical ion pairs that doesn't recombine or form a very weak adduct that can be readily dissociate under ambient conditions, because of steric or electronic frustration.

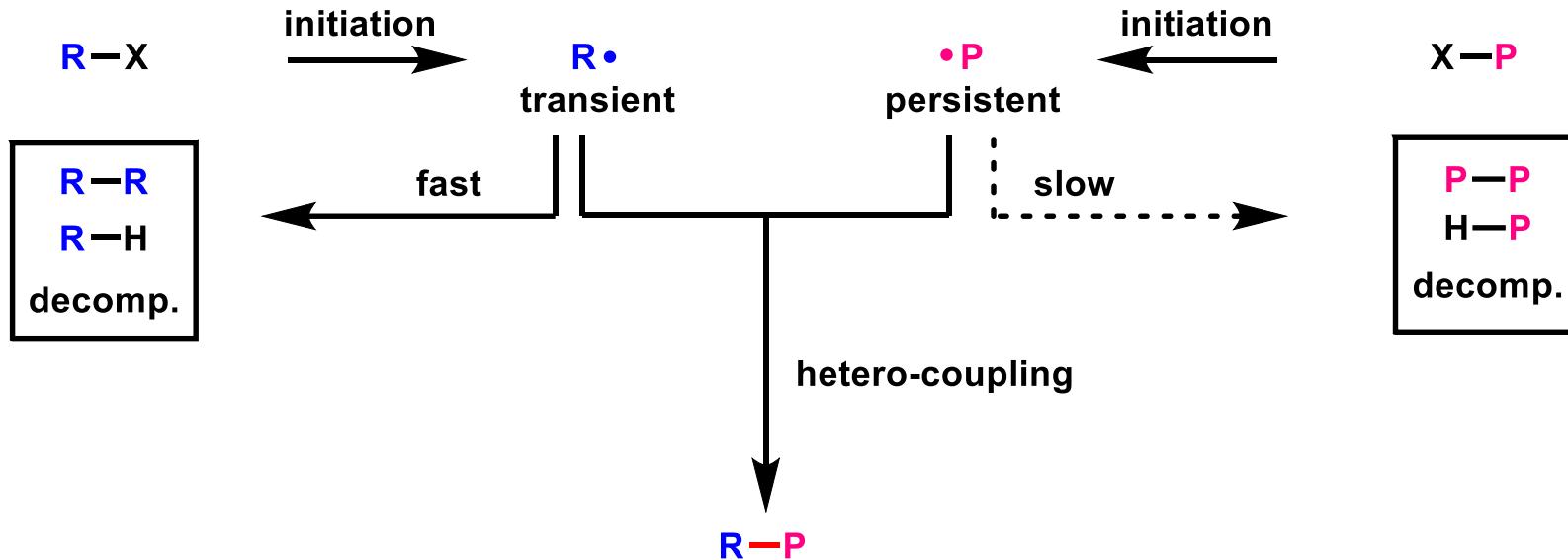
Like FLP, FRP must features two components with distinct chemical properties^{2).}

ex) transient and persistent

1) Stephan, D. W. et al. *J. Am. Chem. Soc.* **2013**, *135*, 6446.

2) Ju, M.; Lu, Z.; Novaes, L. F. T.; Alvarado, J. I. M.; Lin, S. *J. Am. Chem. Soc.* **2023**, *145*, 19478.

Persistent Radical Effect



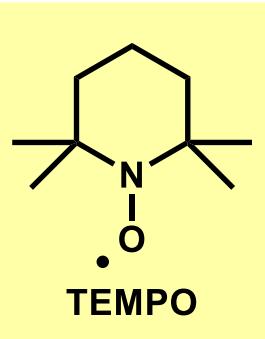
In steady state $[R\cdot] \ll [P\cdot]$, so transient radical is efficiently trapped by persistent radical. Thus, combining transient and persistent radical selectively occurs, leading to hetero-coupling product.

The concept of PRE is essential for designing a new reaction using FRP.

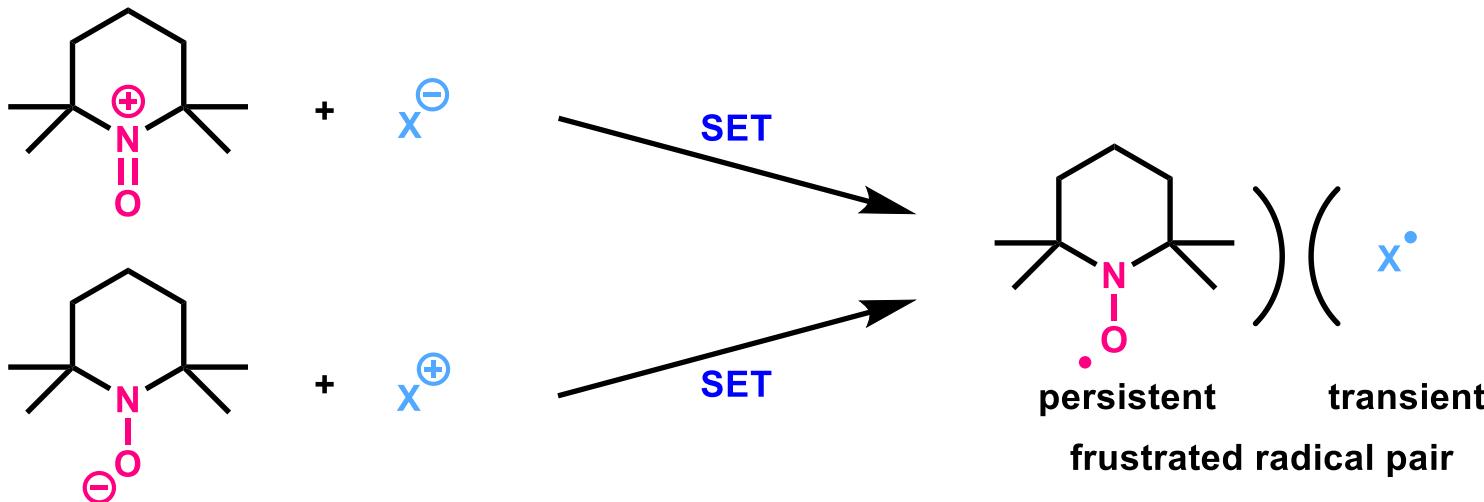
1) Fischer, H. *Chem. Rev.* 2001, 101, 3581.

2) See also 230715_LS_Shintaro_Fukaya, 150523_LS_Haruka_Fujino

TEMPO as Persistent Radical



Due to its steric hinderence and absence of hydrogen atom that could be easily extracted, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) is one of the most common persistent radicals.
It is widely used as radical scavenger.



1. SET between TEMPO^+ and X^\bullet or TEMPO^- and X^\bullet give TEMPO and X^\bullet
 2. TEMPO and X^\bullet could not be combined due to steric hinderence or weak bond association
 3. X^\bullet is transient radical that could be react with various substrates
- If these three demands were met, that nuetral FRP could pave the way for new synthetic strategies.

Contents

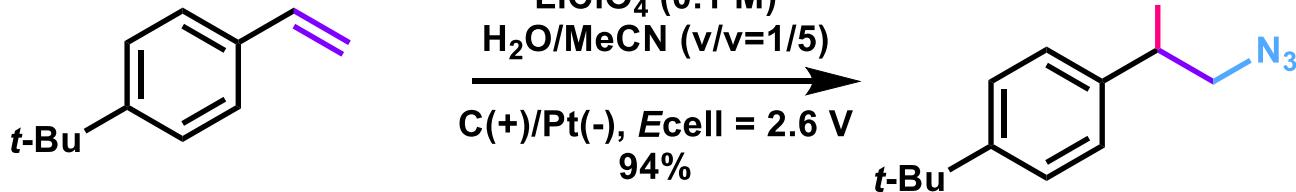
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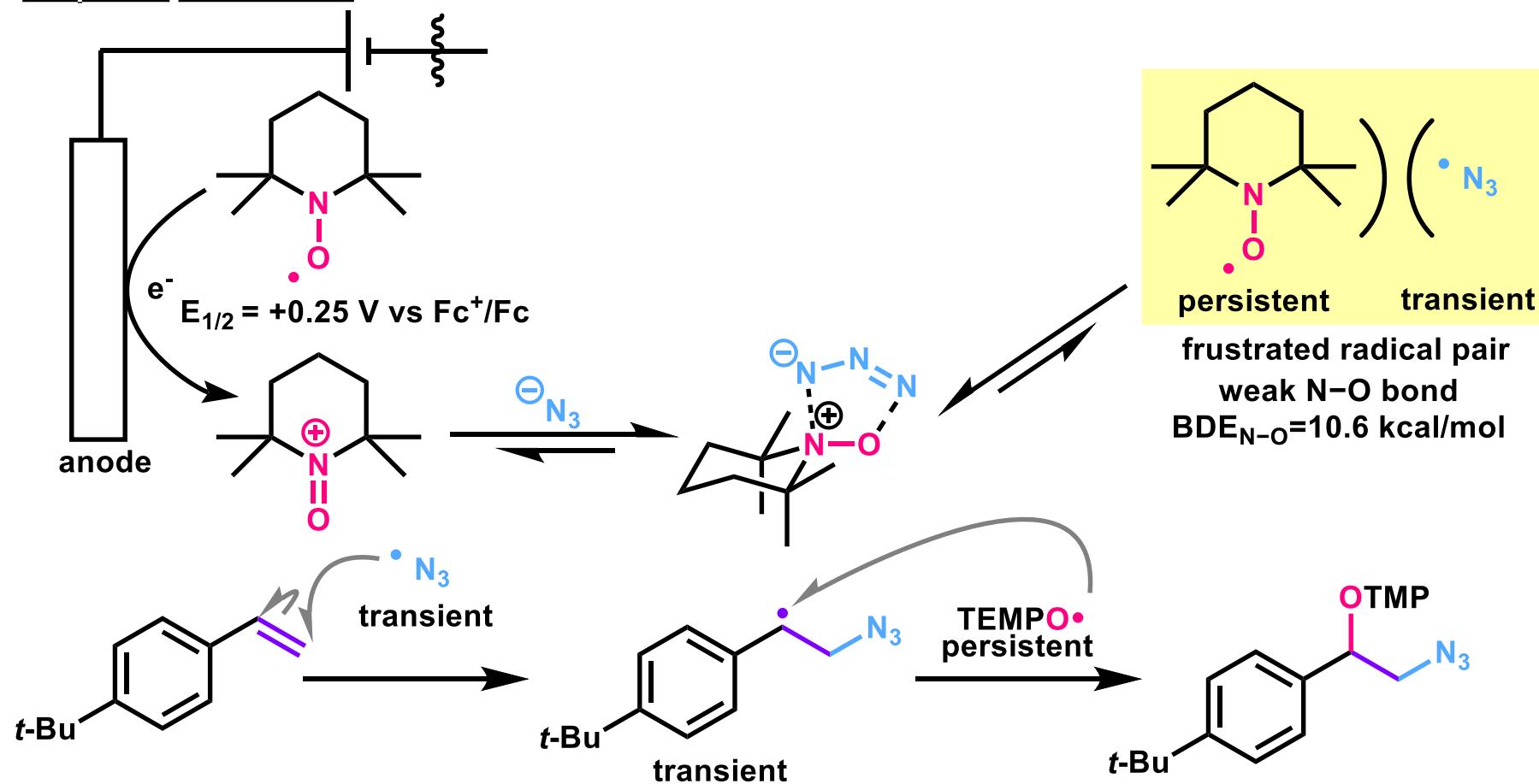
**3. Regioselective Aliphatic C-H Functionalization
using Neutral FRP (Song Lin, 2023)**

4. Summary

Azidooxygenation of Olefin

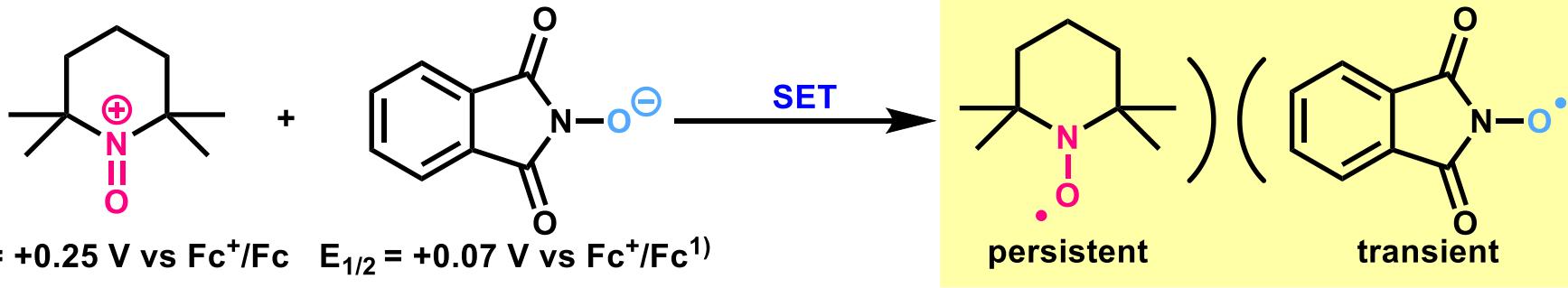


Proposed mechanism

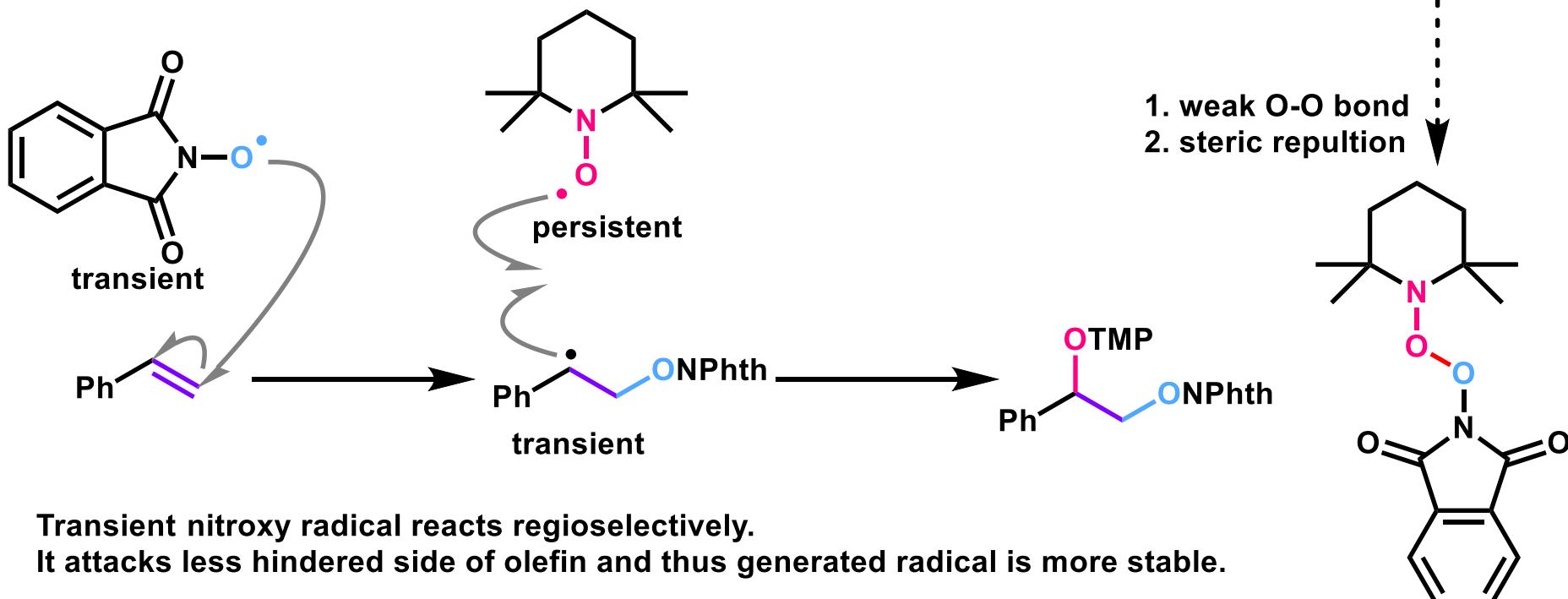


Dioxygenation of Olefin

Formation of FRP



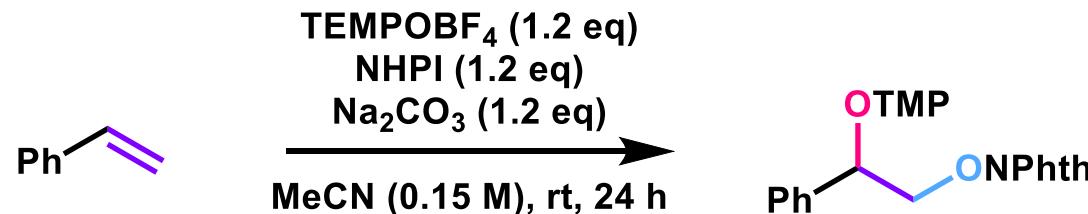
Assumed mechanism for olefin bisfunctionalization



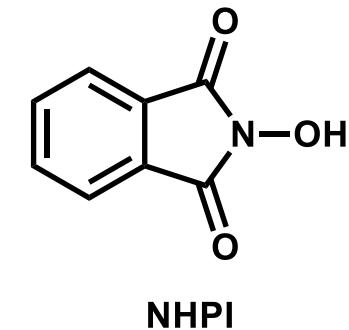
1) Stephenson, C. R. J. et al. *J. Am. Chem. Soc.* **2021**, 143, 10324.

2) Zheng, Y.; Yang, Q. Y.; Wu, L. Y.; Zhu, X. Y.; Ge, M. J.; Yang, H.; Liu, S. Y.; Chen, F. *Org. Lett.* **2021**, 23, 8533.

Optimization of Reaction Conditions

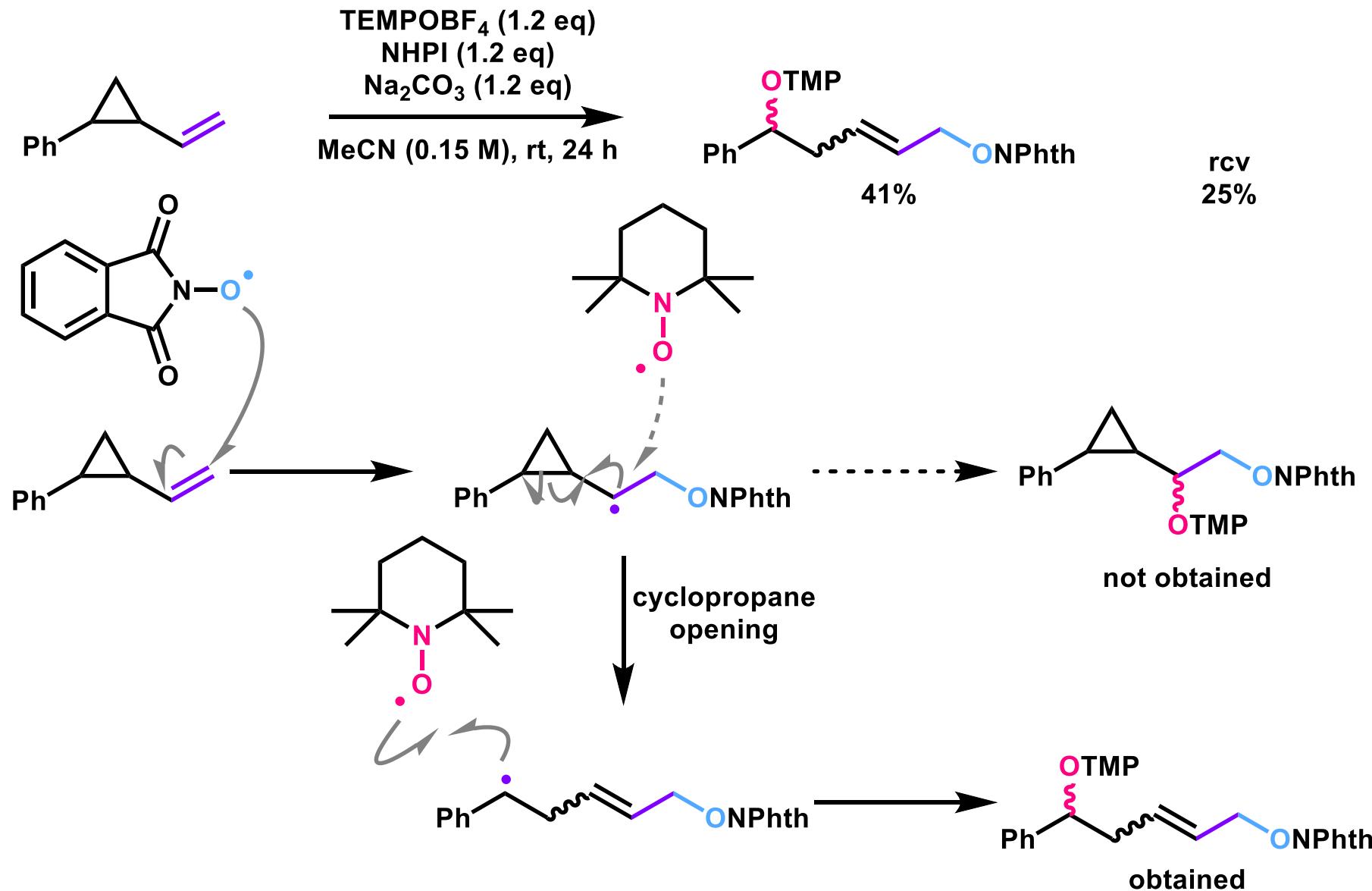


entry	deviation from above	yield
1	none	82%
2	no Na_2CO_3 , 1,1 eq of TEMPOBF ₄ , NHPI	27%
3	under air atmosphere	80%
4	Cs_2CO_3 instead of Na_2CO_3	57%
5	DMSO or acetone instead of MeCN	0%

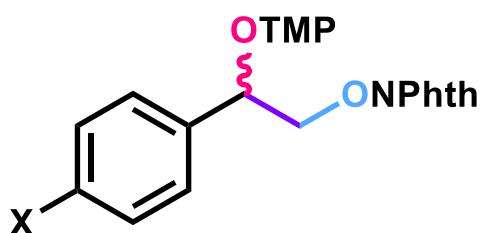
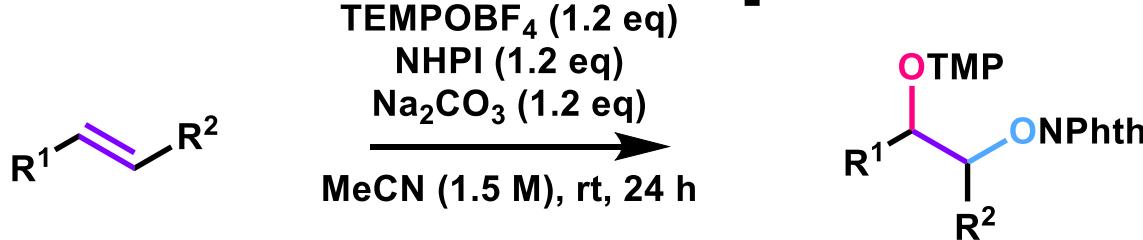


All reactions were conducted on 0.3 mmol scale.

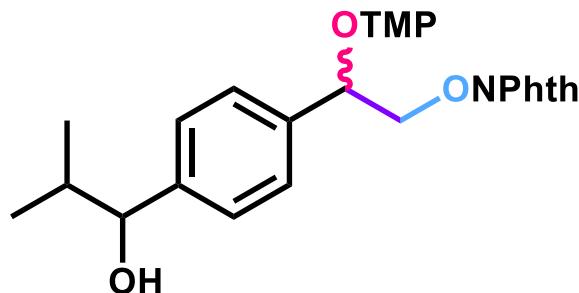
Mechanistic Study



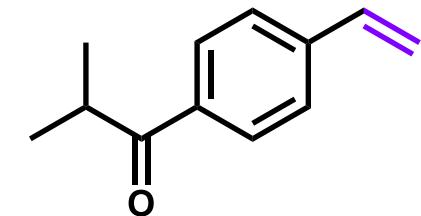
Substrate Scope



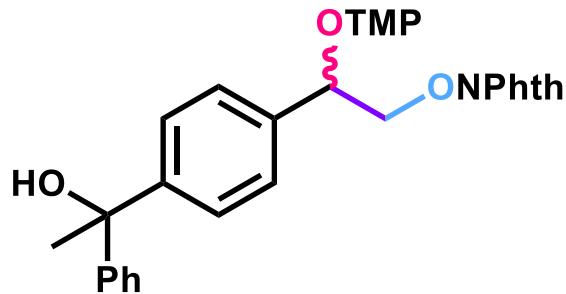
X = OCOMe : 81%
 X = F : 83%
 X = Cl : 84%
 X = Br : 84%
 X = CF_3 : 77%



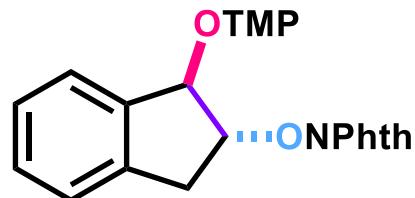
63% (25% with ketone X)



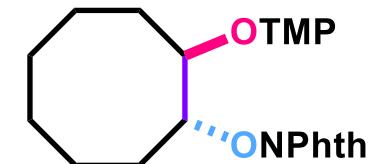
X



90%

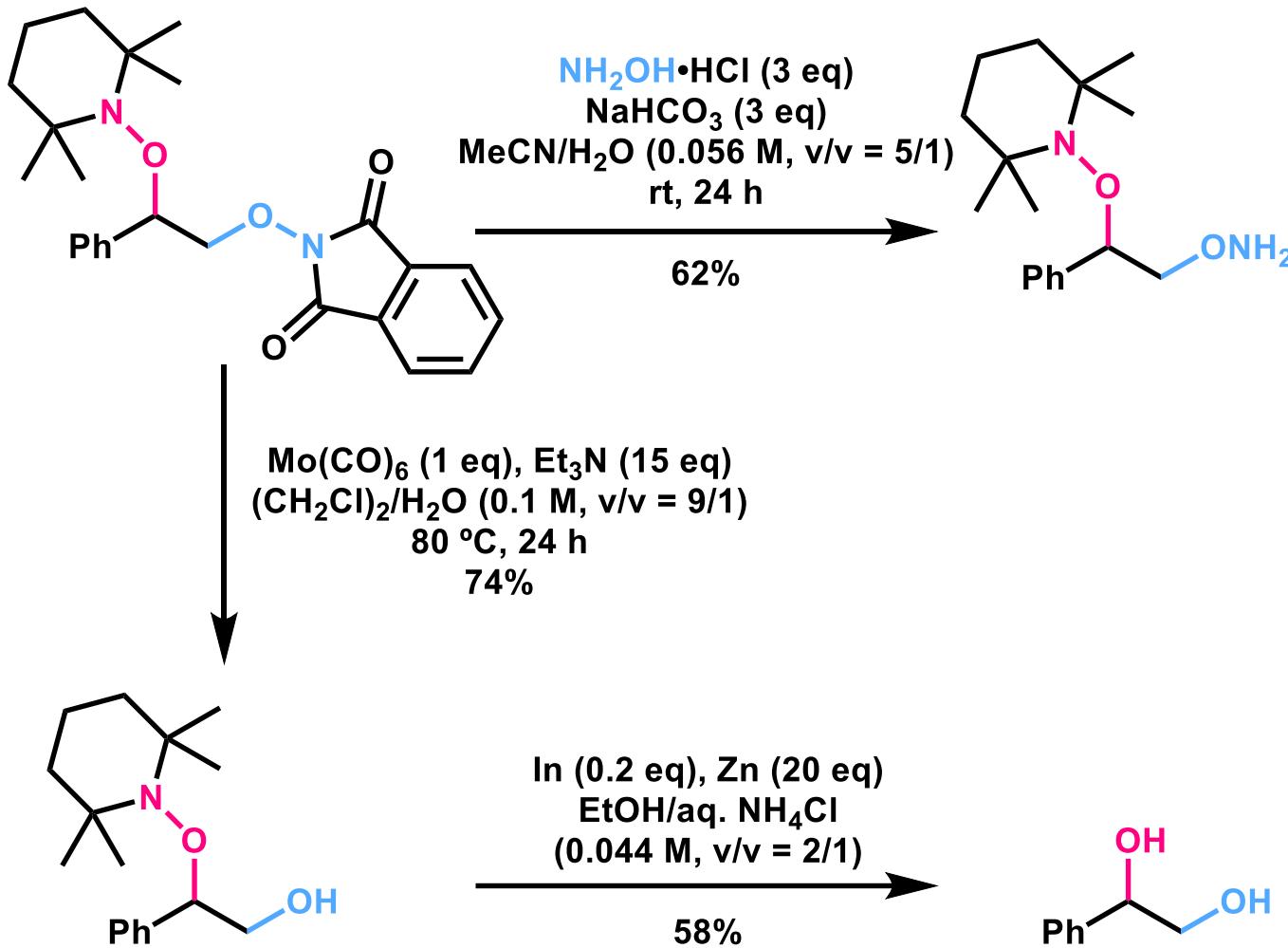


68% (dr = 2.3:1)



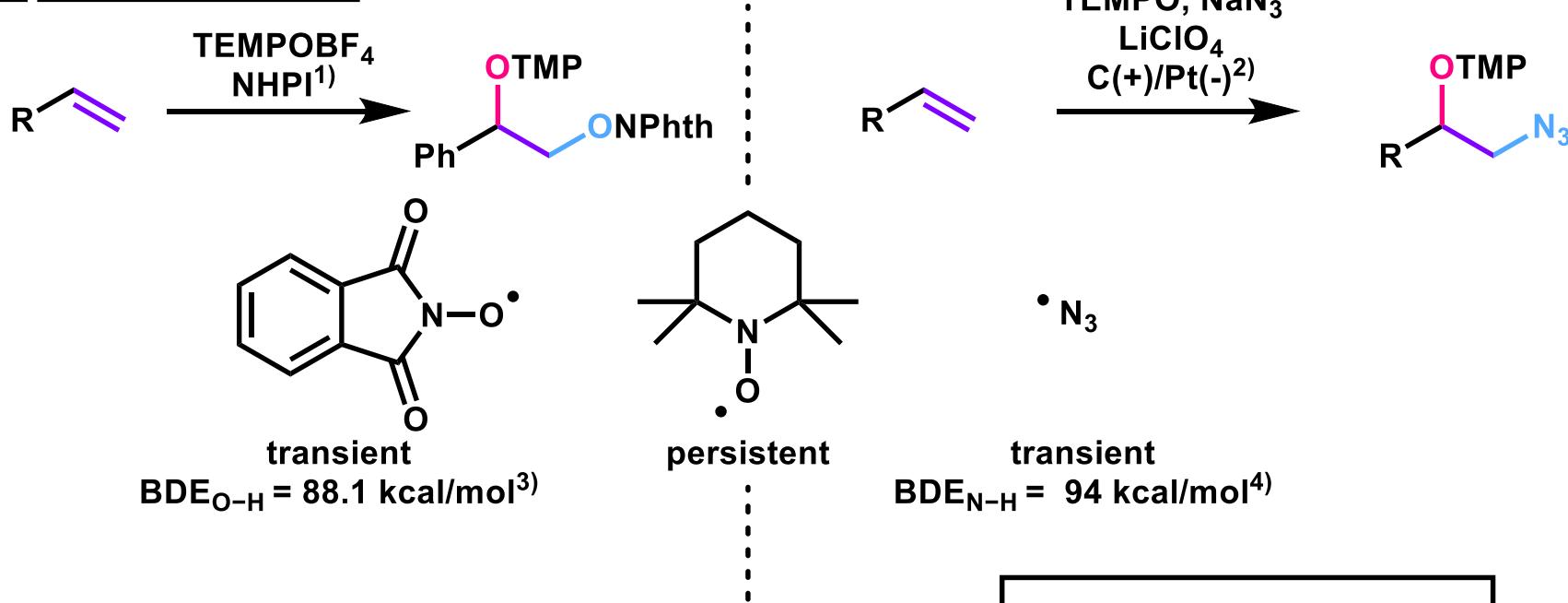
52% (dr = 2:1)

Selective N-O Bond Cleavage



Neutral FRP for C-H Functionalization

Olefin bisfunctionalization



Is it applicable to aliphatic C-H functionalization...?



If X[⊖] meets these two demands, then that could be the perfect candidate for FRP precursor for C-H functionalization.

1. X[⊖] could be easily oxidized by TMEPO[⊕] and form FRP
2. BDE of X-H is stronger than that of N₃

BDE of each C-H bond

H ₃ C—H	103 kcal/mol
—CH ₂ —H	98 kcal/mol
—CH=CH—H	85 kcal/mol
—C ₅ H ₉ —H	92 kcal/mol

1) Chen, F. et al. *Org. Lett.* **2021**, 23, 8533. 2) Lin, S. et al. *J. Am. Chem. Soc.* **2018**, 140, 125.

3) Stephenson, C. R. J. et al. *Nat Rev Chem*, **2023**, 7, 653.

4) Ju, M.; Lu, Z.; Novaes, L. F. T.; Alvarado, J. I. M.; Lin, S. *J. Am. Chem. Soc.* **2023**, 145, 19478.

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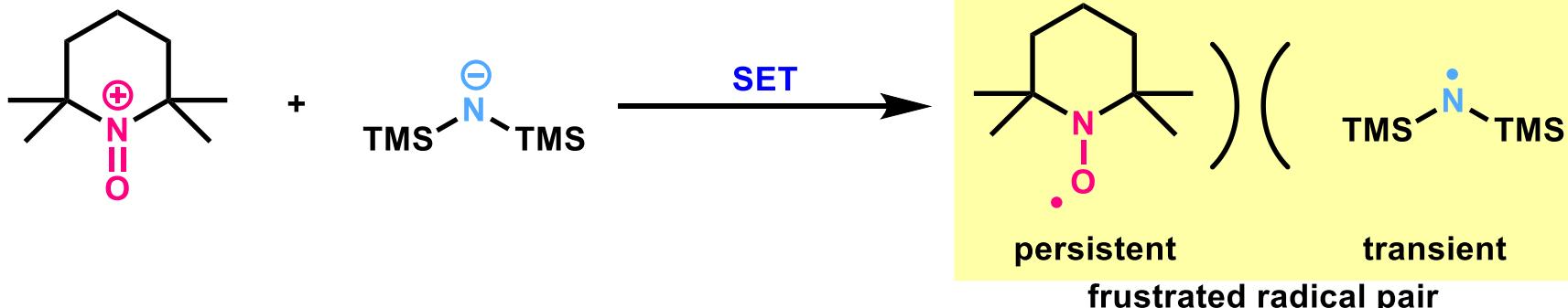
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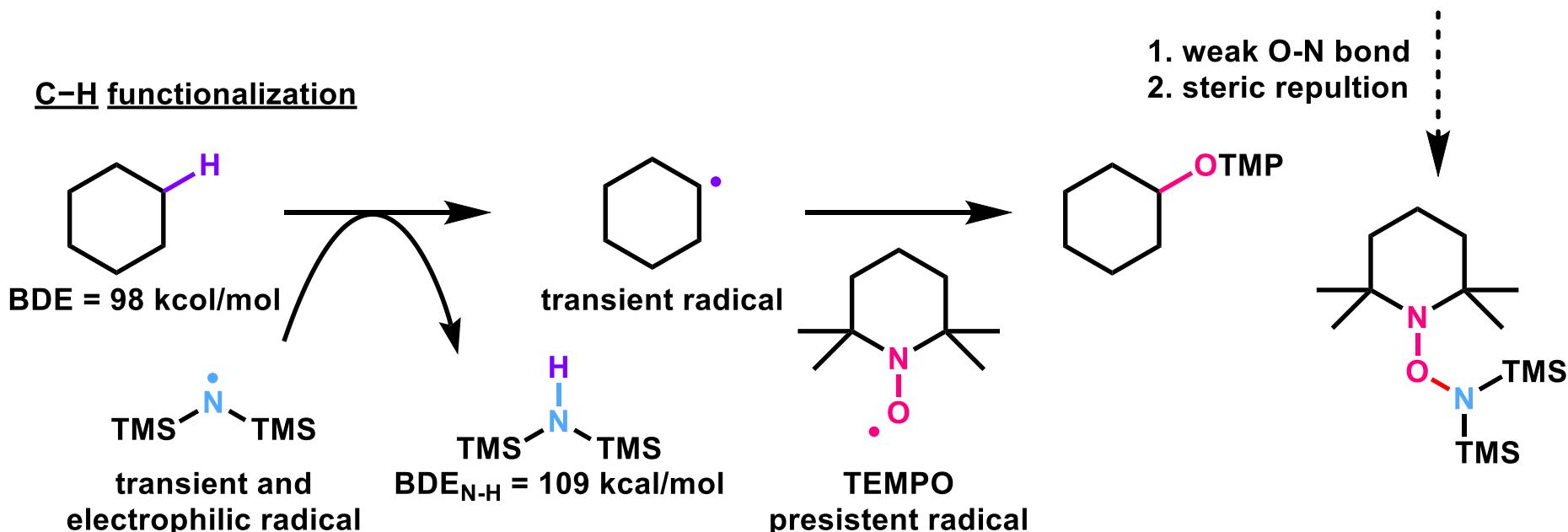
4. Summary

Reaction Design

Formation of FRP



C-H functionalization



Strong BDE of N-H and highly electrophilic property of disilylaminyl radical (due to hyperconjugation of low energy C-Si σ^* orbital) makes $\text{•N}(\text{TMS})_2$ a good hydrogen atom acceptor (HAA).

Optimization of Reaction Conditions



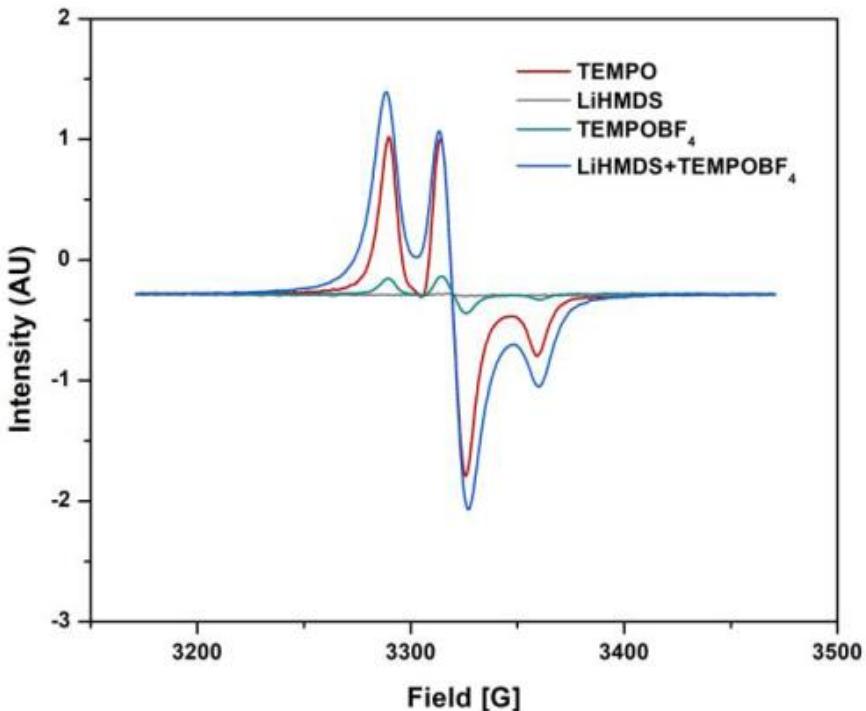
entry	deviation from above	yield ^b
1	none	67%
2	1 eq of SM	35%
3	no LiN(TMS) ₂	0%
4	rapid addition of Li(TMS) ₂	51%
5	ClO ₄ [−] , PF ₆ [−] , OTf instead of BF ₄	22-57%
6	0.2 eq of TEMPO additive	74%

^aLiN(TMS)₂ was added dropwise over 5 min

^bYield was determined using TEMPOBF₄ as limiting reagent.

Mechanistic Study (1)

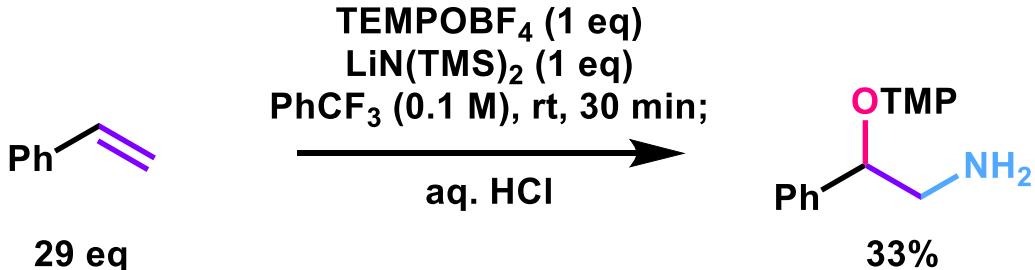
1. EPR (Electron Paramagnetic Resonance) signal



1. LiN(TMS)₂ is EPR silent
2. A weak signal with only TEMPOBF₄
→ trace amount of TEMPO exists
3. A strong peak with LiN(TMS)₂+TEMPOBF₄

Considering 1-3, LiN(TMS)₂ seems to have supported the formation of TEMPO radical. Although only persistent TEMPO was detected, SET between LiN(TMS)₂ and TEMPO⁺ must have given a radical pair.

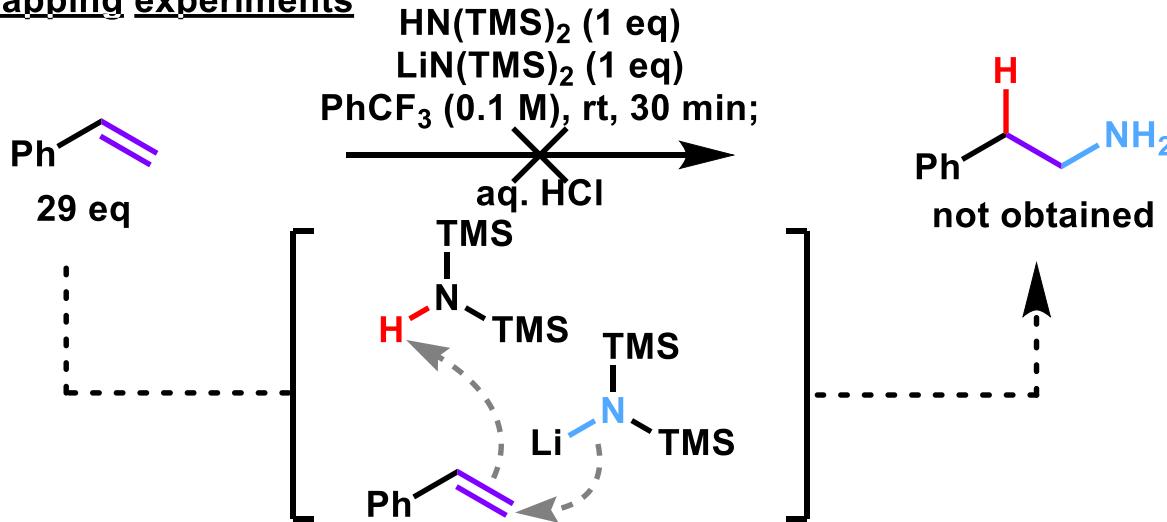
2. Radical trapping experiments



This reaction pathway could be either radical pathway or anionic addition of LiN(TMS)₂ pathway. In order to rule out the latter path, a control experiment was conducted.

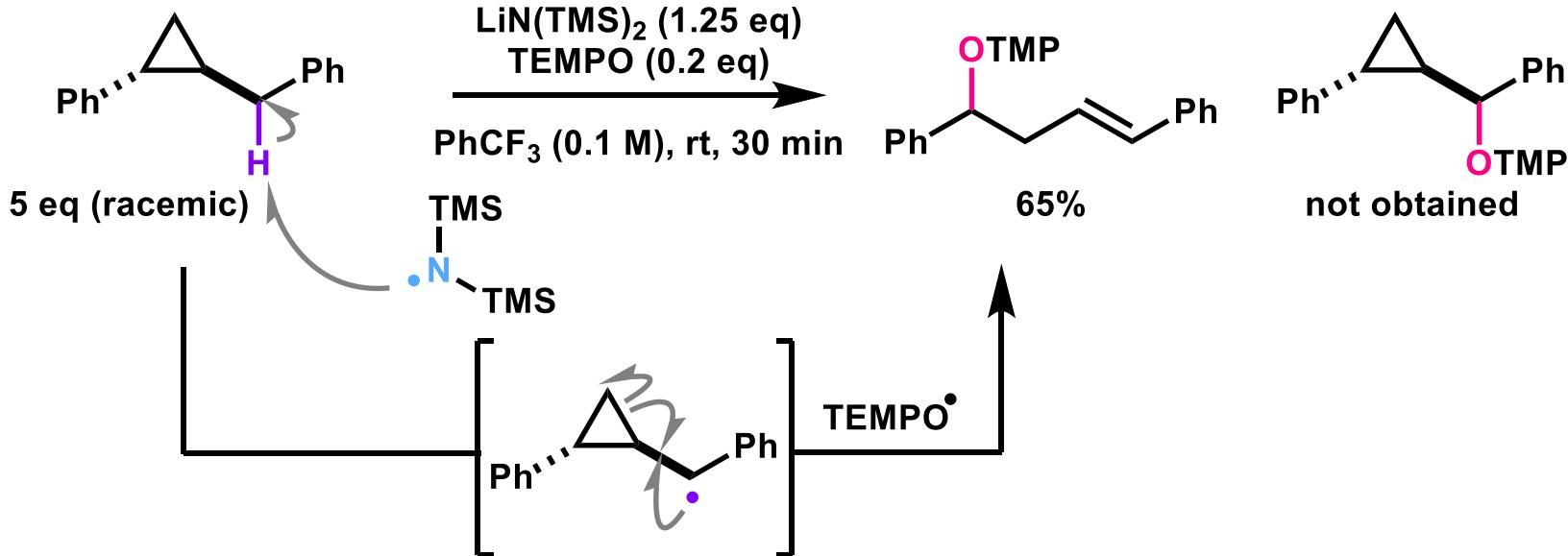
Mechanistic Study (2)

2. Radical trapping experiments



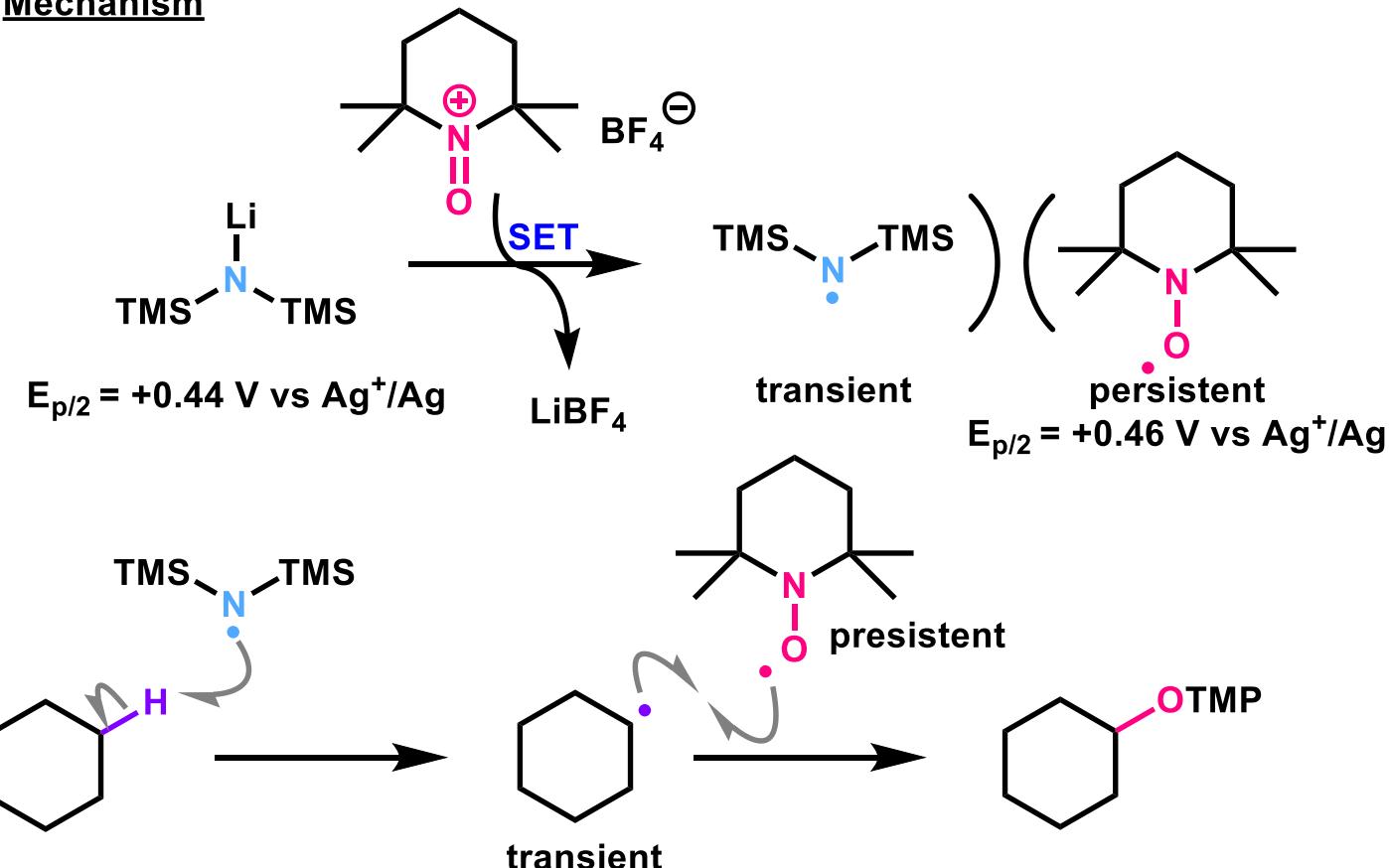
As addition of amine didn't occur at all without TEMPOBF₄, radical path seems to be correct.

3. Radical clock experiment

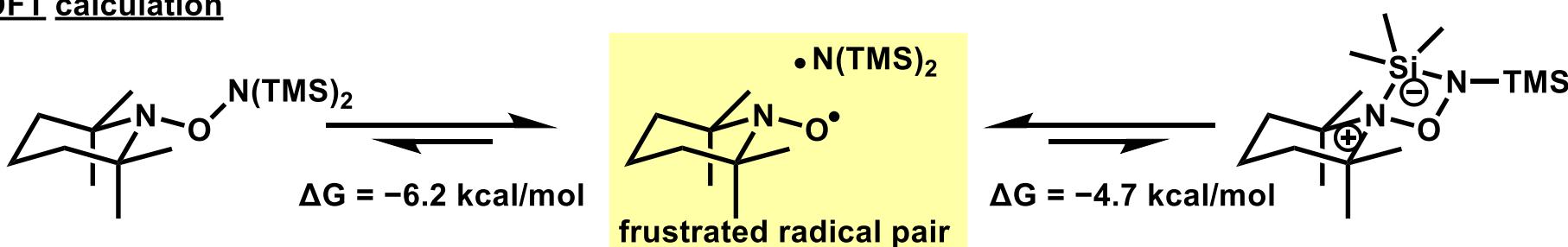


Proposed Mechanism

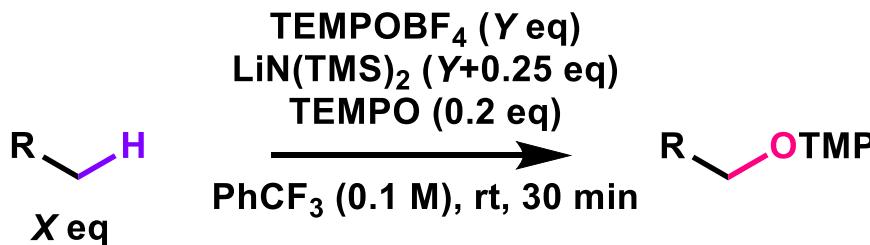
Reaction Mechanism



DFT calculation



Substrate Scope



conditions A

$X = 5, Y = 1$

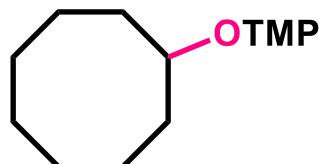
limiting reagent: TEMPOBF_4

conditions B

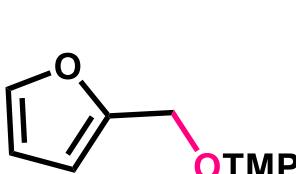
$X = 1, Y = 2$

limiting reagent: SM

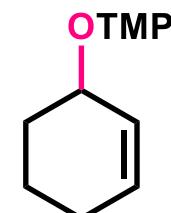
^aconditions A, ^bconditions B



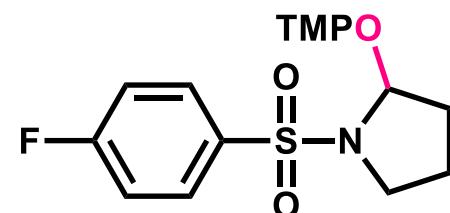
62%^a



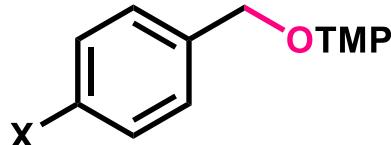
49%^a



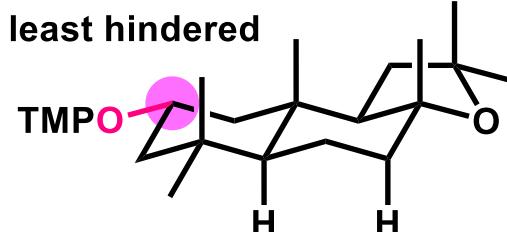
68%^a, 55%^b



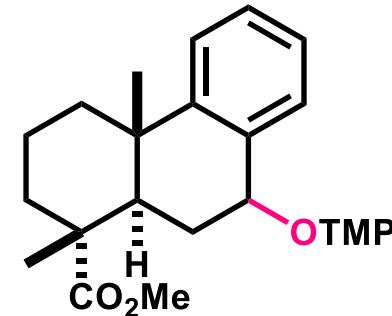
55%^a



$X = \text{Cl} : 71\%^{\text{a}}$
 $X = \text{Br} : 68\%^{\text{a}}$
 $X = \text{I} : 69\%^{\text{a}}$
 $X = \text{CN} : 63\%^{\text{a}}$
 $X = \text{CF}_3 : 62\%^{\text{a}}$
 $X = \text{Bpin} : 64\%^{\text{a}}$



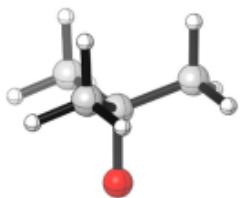
42%^b, dr = 5.7:1



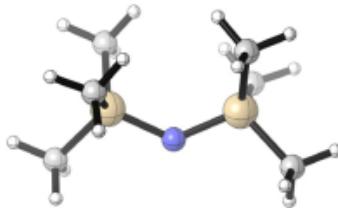
87%^b, dr = 1:1

Several HAAs with Different Bulkiness

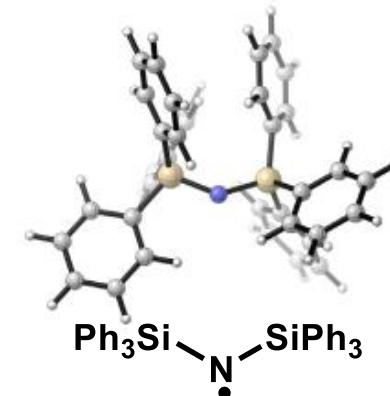
DFT calculation and redox potential of each HAAs



t-BuO[•]



TMS-N(TMS)[•]



Ph₃Si-N(SiPh₃)[•]

%V _{Bur} ^{a,b}	35.3
BDE _{X-H} ^b	105.2 kcal/mol
E _{p/2} vs Ag ⁺ /Ag	+0.70 V

51.7
109.4 kcal/mol
+0.44 V

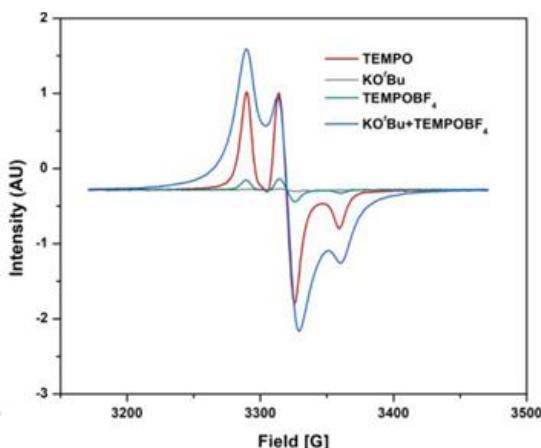
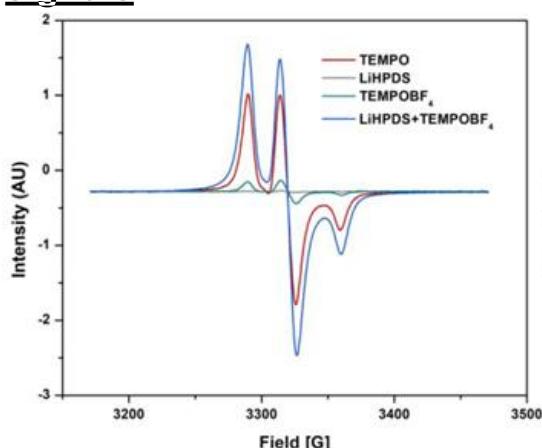
65.7
109.0 kcal/mol
+0.44 V

^aHydrogen atom was used as the center atom.

^bDFT calculation was carried out using (U)M06-2X and 6-31+G(d,p) E_{p/2} = +0.46 V vs Ag⁺/Ag

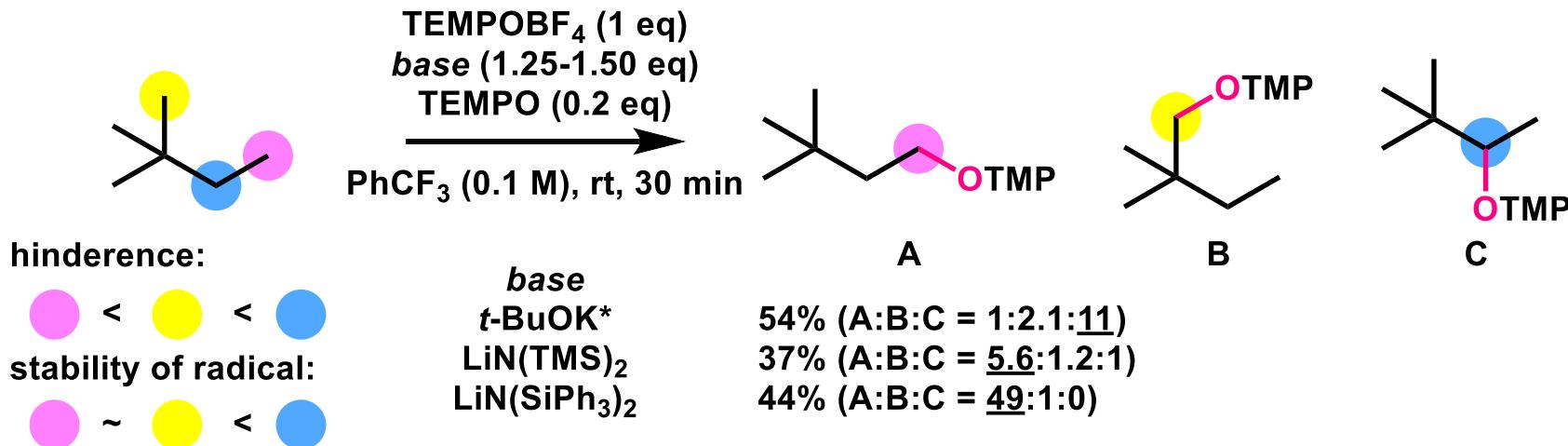
Oxidation of *t*-BuO[•] is uphill, though irreversible H abstraction and following TEMPO⁺ trap might facilitate SET between *t*-BuO[•] and TEMPO⁺.

EPR signals

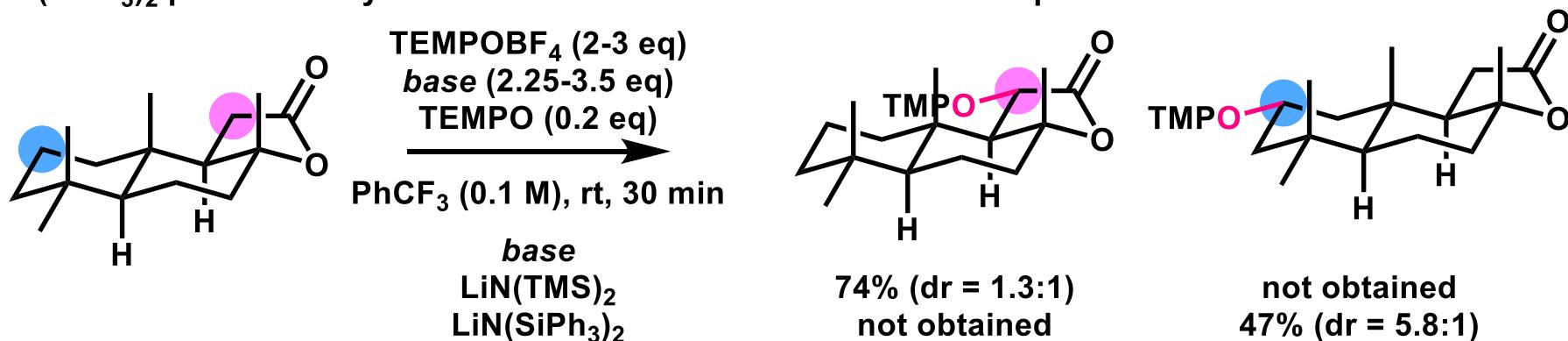


Regioselectivity of Each HAA

Other bases such as $\text{LiN}(\text{SiPh}_3)_2$ or $t\text{-BuOK}$ can be also applied to this procedure.
Regioselectivity changes as the base is changed to the other one.



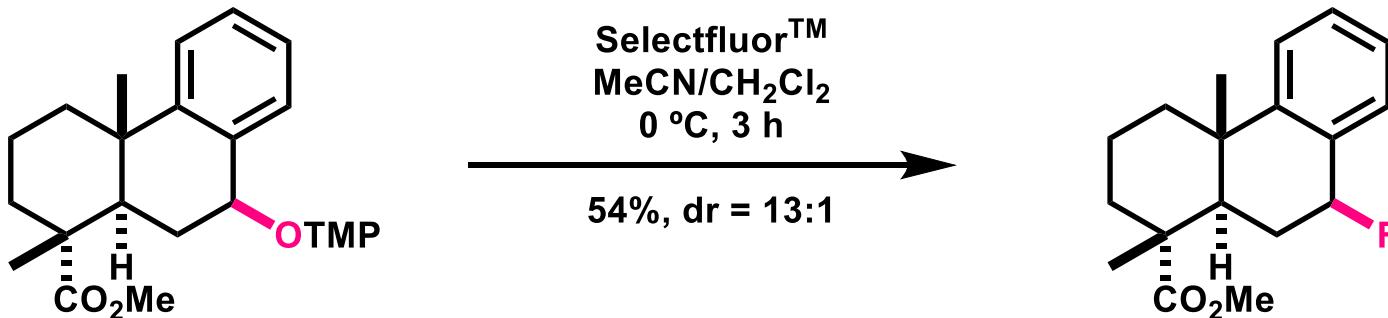
* $t\text{-BuOH}$ and KH are added in order to generate $t\text{-BuOK}$ in situ. Also TEMPOPF_6 is used.
 $t\text{-BuO}\cdot$ preferentially abstracts H atom from the position that resulting radical is most stable.
• $\text{N}(\text{SiPh}_3)_2$ preferentially abstracts H atom from the least hindered position.



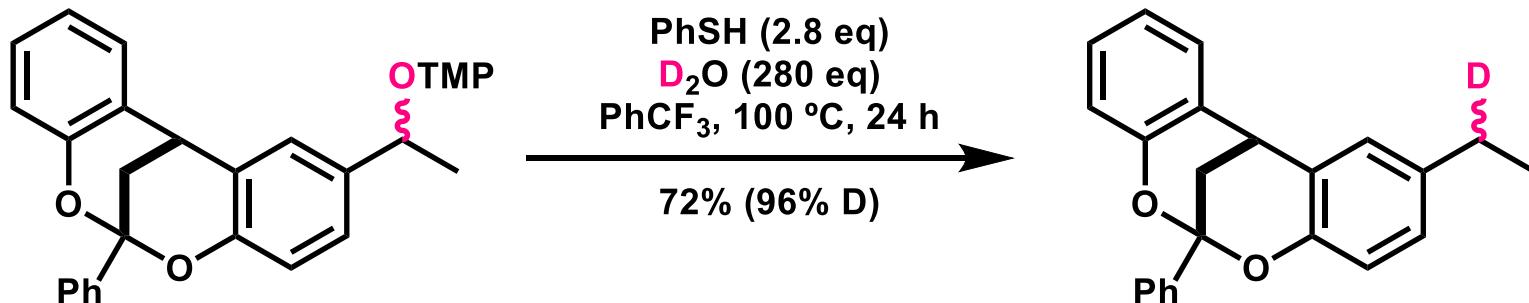
With using $\text{LiN}(\text{TMS})_2$, deprotonation of acidic ketone α -position might have occurred first.
This can be suppressed with using bulkier $\text{LiN}(\text{SiPh}_3)_2$ as a base.

Synthetic Diversification (1)

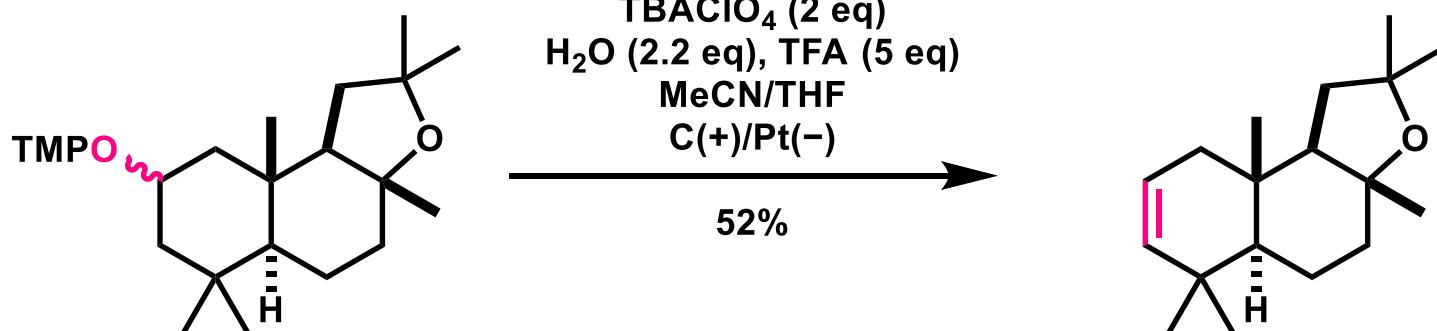
1. Halogenation



2. Deuteration



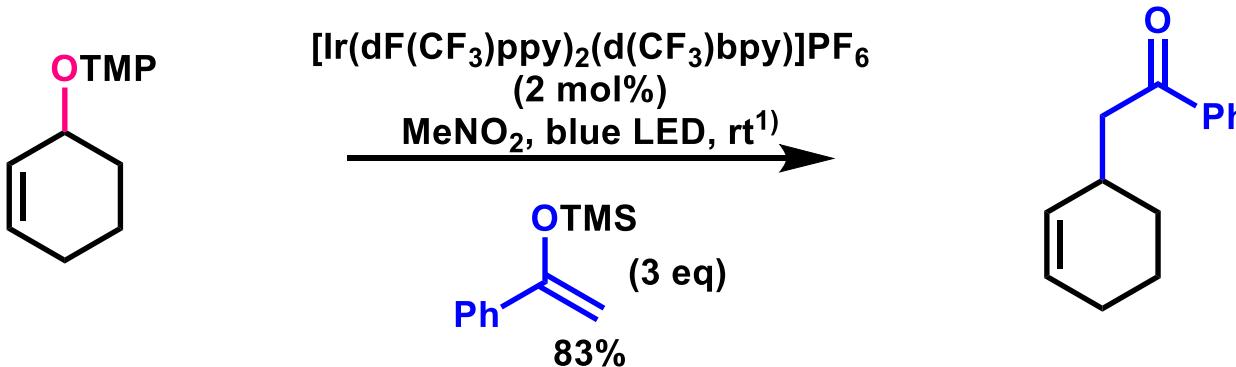
3. Electrochemical elimination



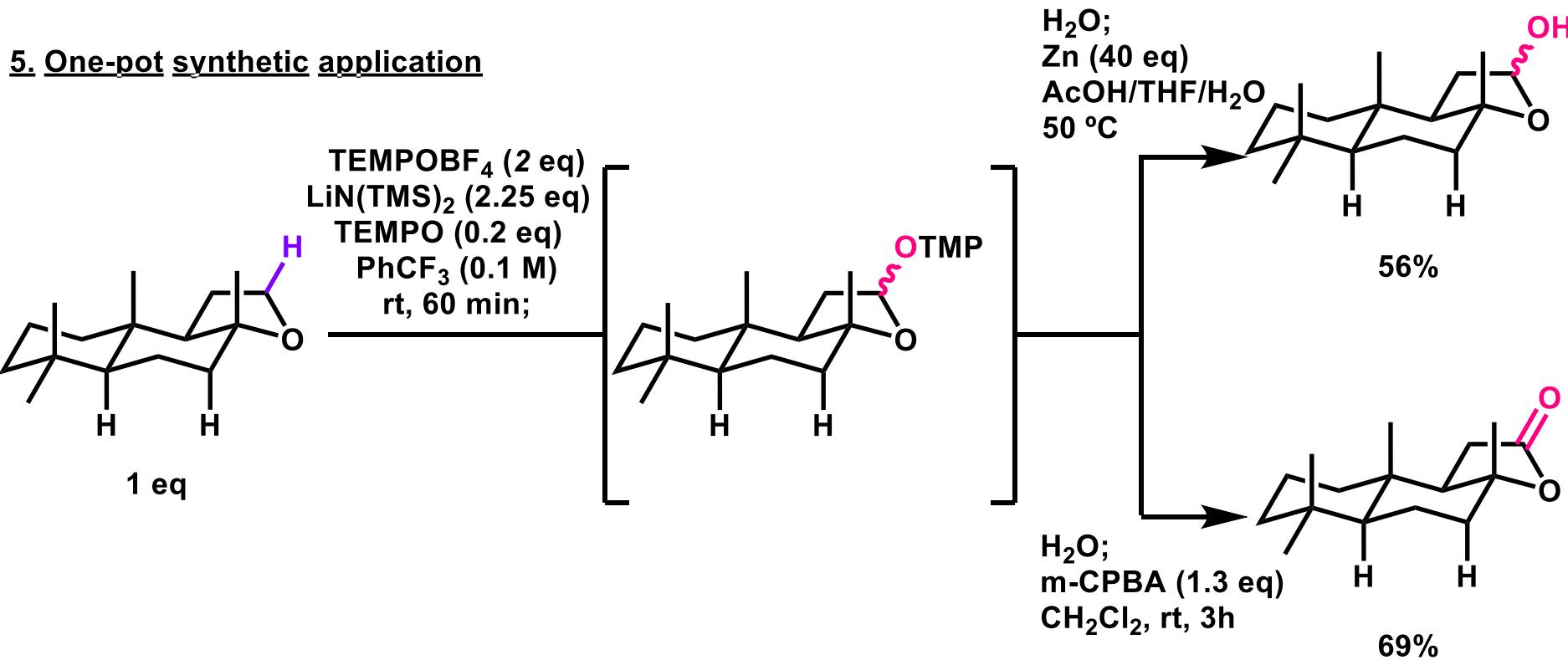
*All starting materials were synthesized using general procedure of this paper.

Synthetic Diversification (2)

4. Nucleophilic substitution



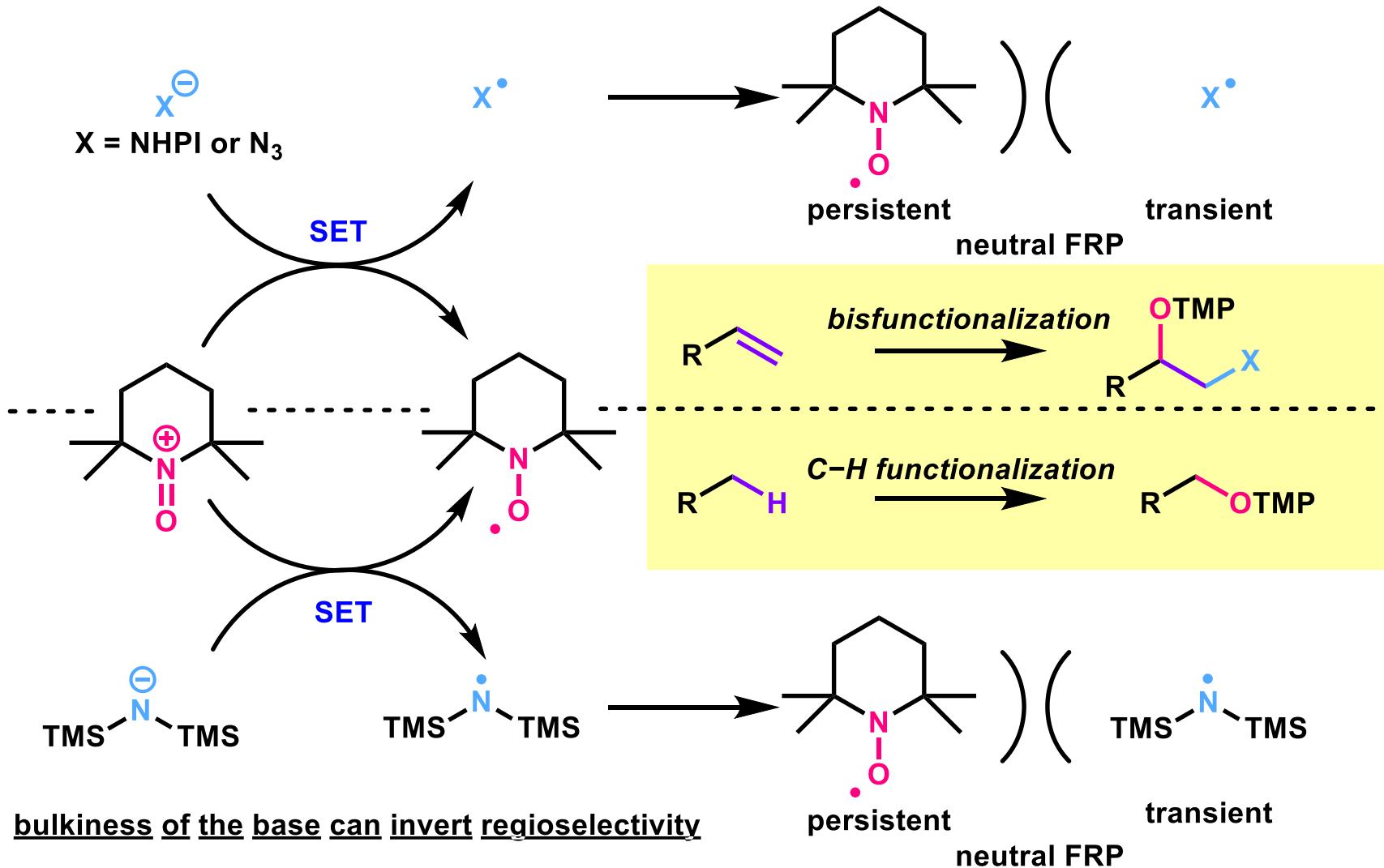
5. One-pot synthetic application



1) Knowles, R. R. et al. *Angew. Chem. Int. Edn.* **2016**, *55*, 9969.

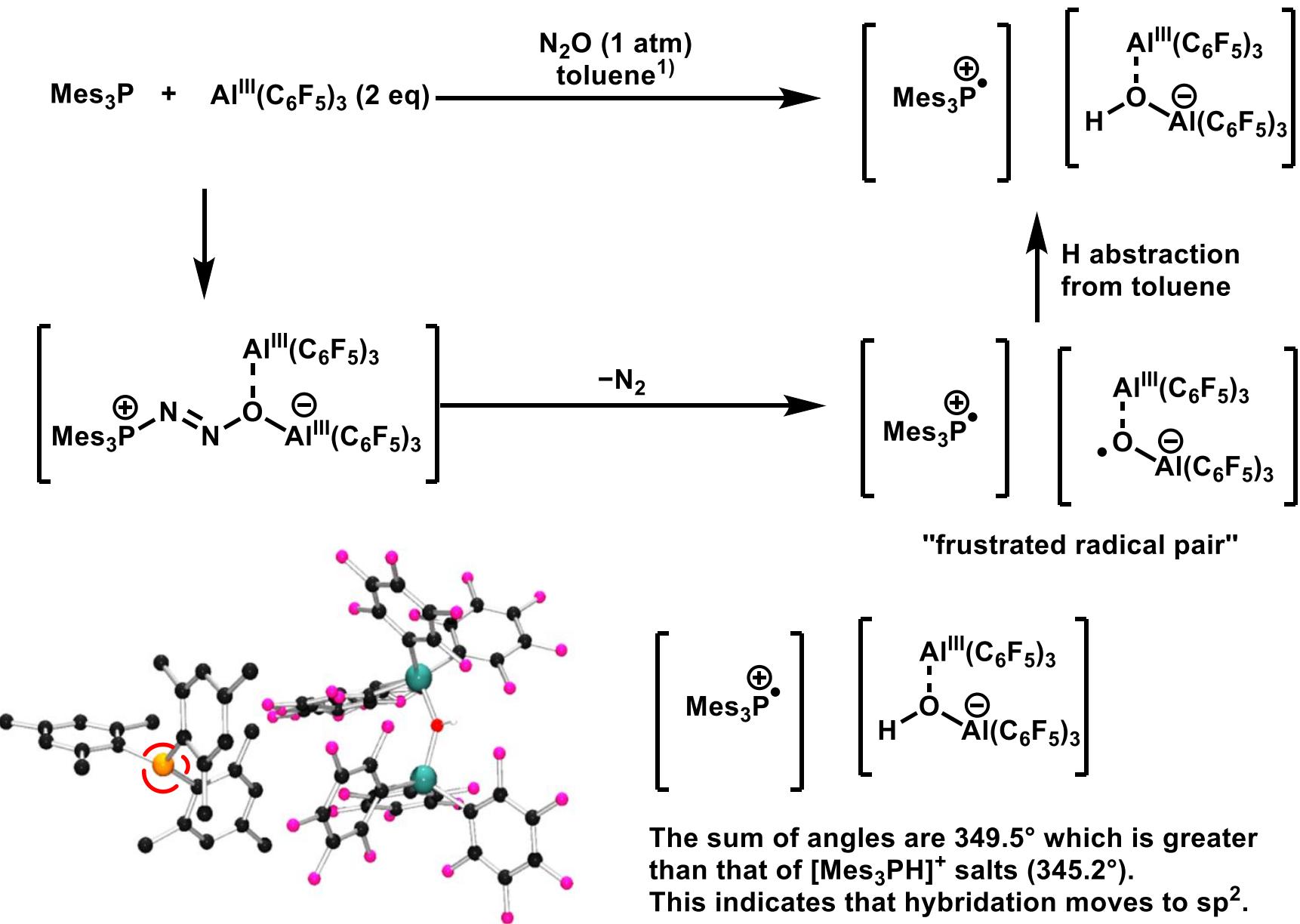
2) Lin, S. et al. *Nature*. **2023**, *619*, 514.

Summary

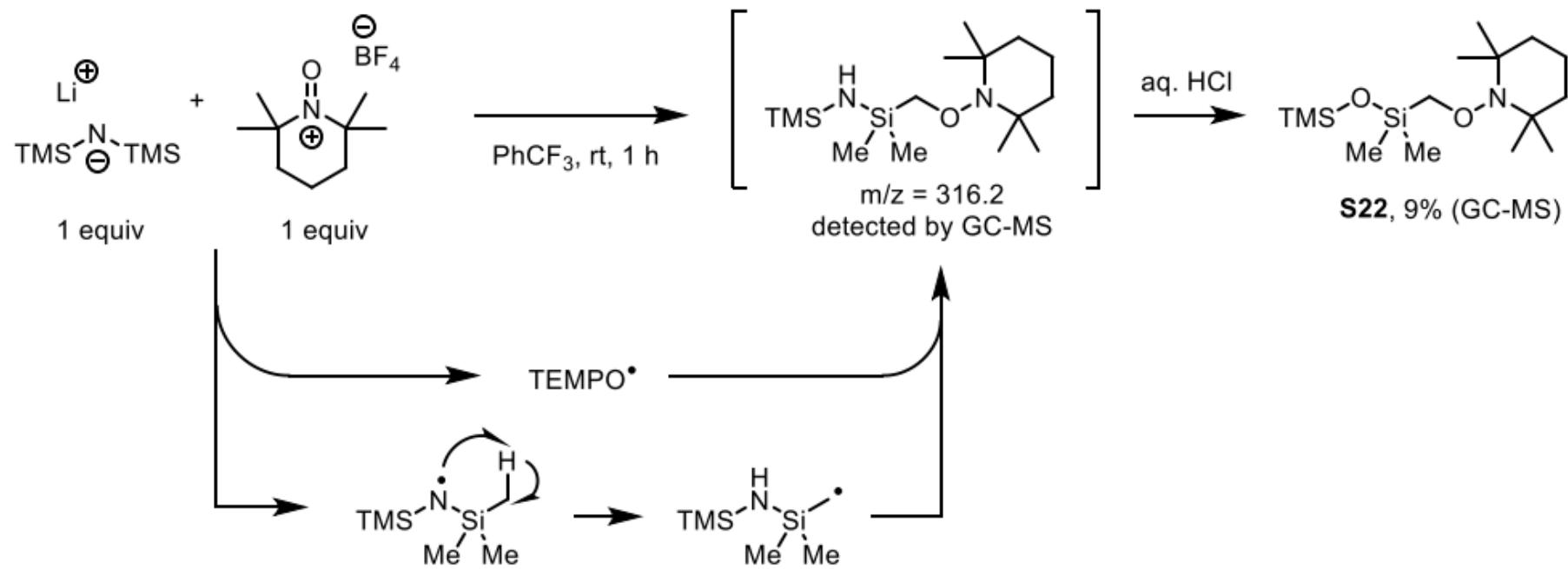


Appendix

FRP



Decomposition of Radical (1)



Decomposition of Radical (2)

