Hydrogen Atom Transfer (HAT) Processes Mediated by Heteroatom Centered Radical

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2022 || Zuo Group

Draft Update time : 2022/8/8

Contents

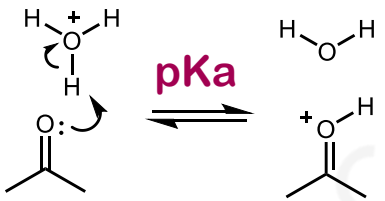
Part I

Basic Introduction

H-Transfer processes in organic reactions

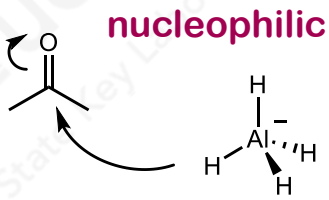
- Elementary steps for functional group activation and transformations

Proton Transfer



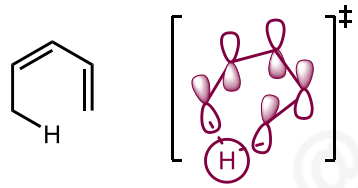
Protonation

Hydride Transfer



Reduction by B-H, M-H etc.

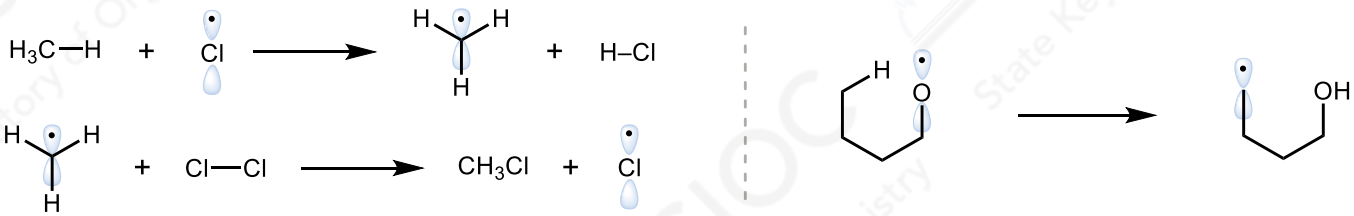
Sigmatropic Shift



[1,n]-Sigmatropic shift
n=4m+1, suprafacial
n=4m-1, antarafacial

Ubiquitous, fundamental, but not trivial steps, well established in organic reactions

Hydrogen Atom Transfer



BDE? **BDFE?** **Polar effect?** **Selectivity?**

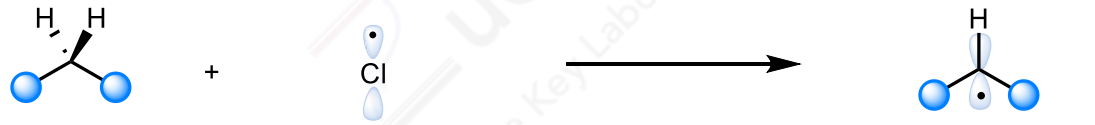
Is HAT equal to radical hydrogen abstraction? What do we know about it ?

Hydrogen Atom Transfer processes in organic reactions

HAT —— Transfer a neutral hydrogen atom or transfer H^+ and e^- concertedly ?

Which of them are actually HAT process on C(sp^3)-H?

A.



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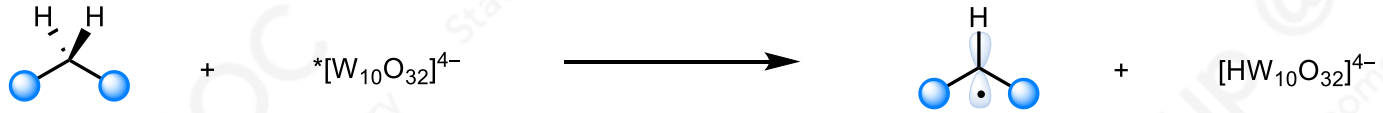
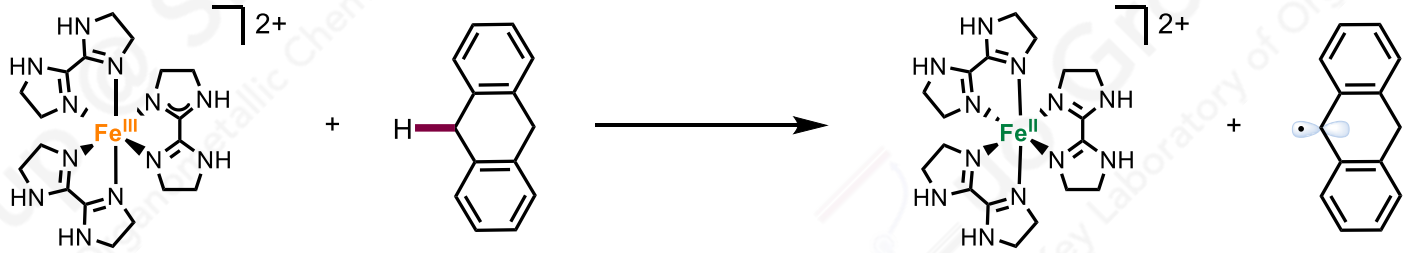
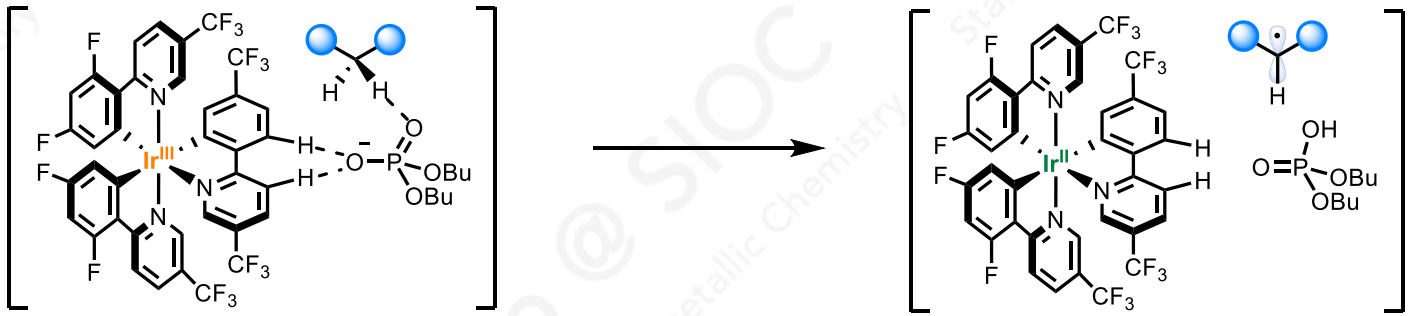


C.

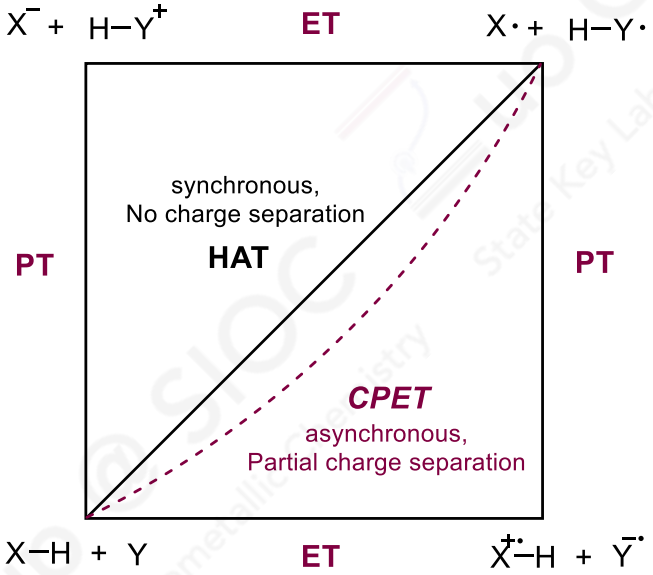


D.

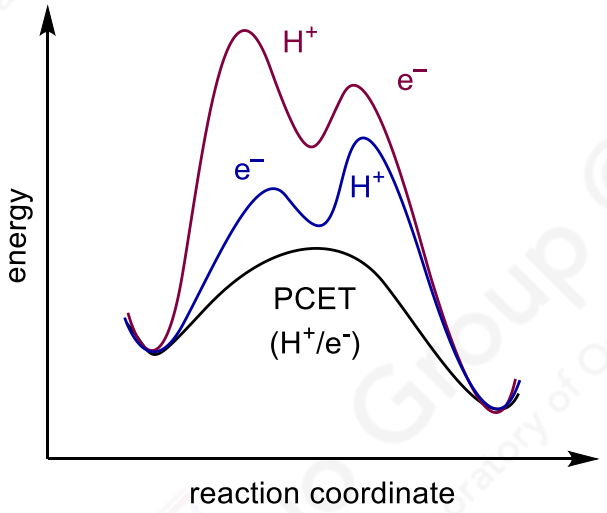


Proton-Coupled Electron Transfer (PCET)

- Concept of PCET, HAT and CPET



More O'Ferrall–Jencks plot



PCET (Proton-Coupled Electron Transfer) : H^+ and e^- transfer concertedly without intermediate

HAT (Hydrogen Atom Transfer) : H^+ and e^- transfer synchronously (diagonal lines)

CPET (Coupled Proton-Electron Transfer) : H^+ and e^- transfer asynchronously (non-diagonal lines)

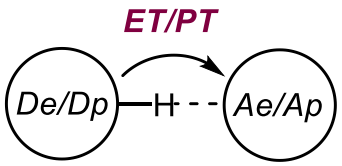
Obviously, HAT reaction is a subclass of the more general reaction of PCET

Mayer J. *et al. Chem. Rev.* **2010**, *110*, 6961–7001.
Hynes J. *et al. Hydrogen-Transfer Reactions*, Wiely, **2006**, 503-562.

Proton-Coupled Electron Transfer (PCET)

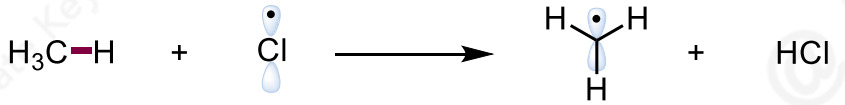
❑ Formal types of PCET reactions

Type A : Hydrogen AtomTransfer



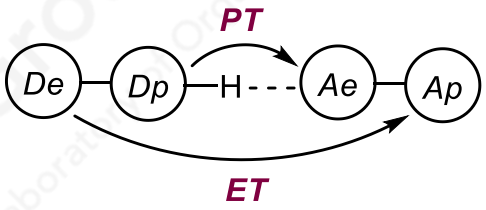
De/Dp = Donor of electron/proton
Ae/Ap = Acceptor of electron/proton

e.g.

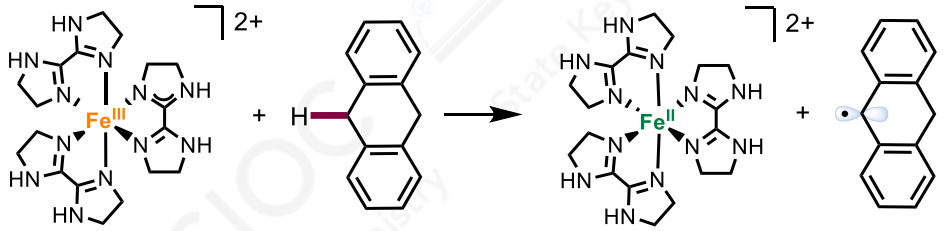


H^+ and e^- transfer to same molecular and same site, mainly synchronous

Type B : Site differentiate PCET



e.g.



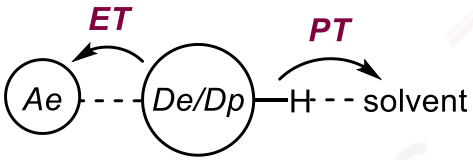
H^+ and e^- transfer to same molecular but different site, mainly asynchronous

Mayer J. *et al. Acc. Chem. Res.* **2011**, *44*, 36–46.

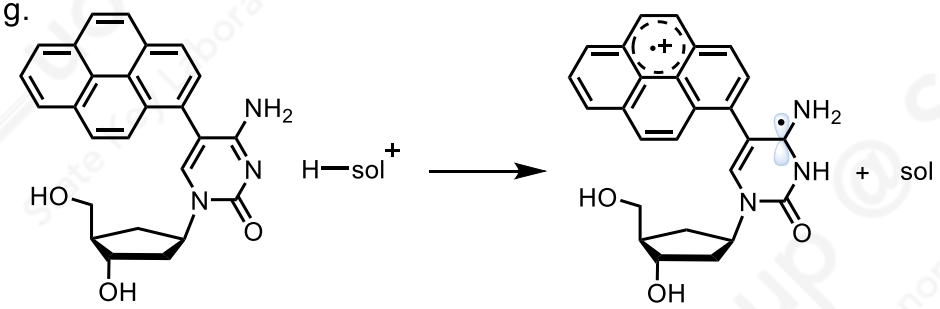
Proton-Coupled Electron Transfer (PCET)

❑ Formal types of PCET reactions

Type C : Non-Specific 3-Point PCET



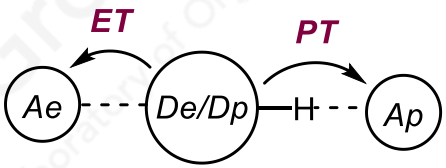
e.g.



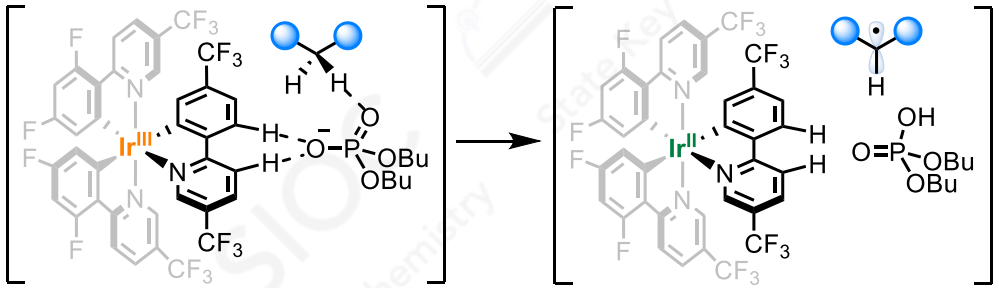
e⁻ transfer to to acceptor and H⁺ transfer to bulk, mainly asynchronous

Fiebig T. *et al. ChemPhysChem.* **2004**, *5*, 706.

Type D : Specific 3-Point PCET



e.g.



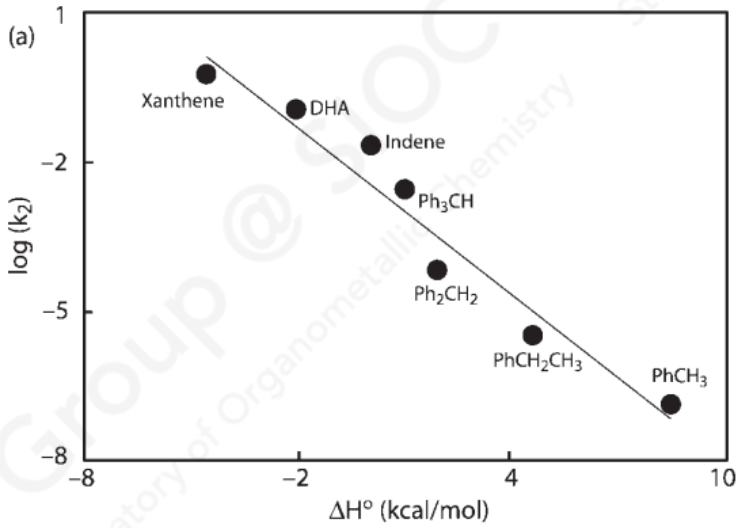
e⁻ transfer to acceptor and H⁺ to another specific acceptor, mainly asynchronous

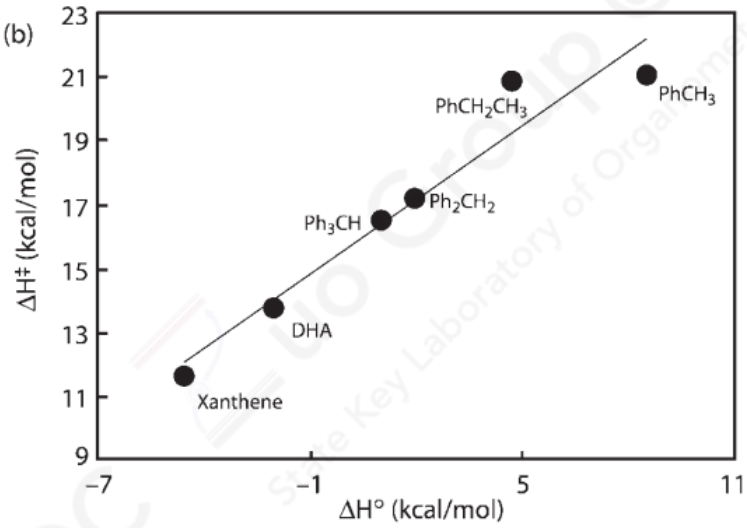
Knowles R. *et al. J. Am. Chem. Soc.* **2019**, *141*, 13253−13260.

Proton-Coupled Electron Transfer (PCET)

- Kinetic explanations on PCET

Evans-Polanyi relation of Mn(VII) mediated C-H oxidation





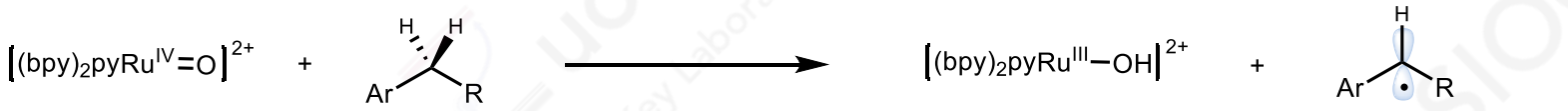
These reactions proceed by a synchronous PCET like process that is mechanistically identical to HAT by an organic radical oxidant

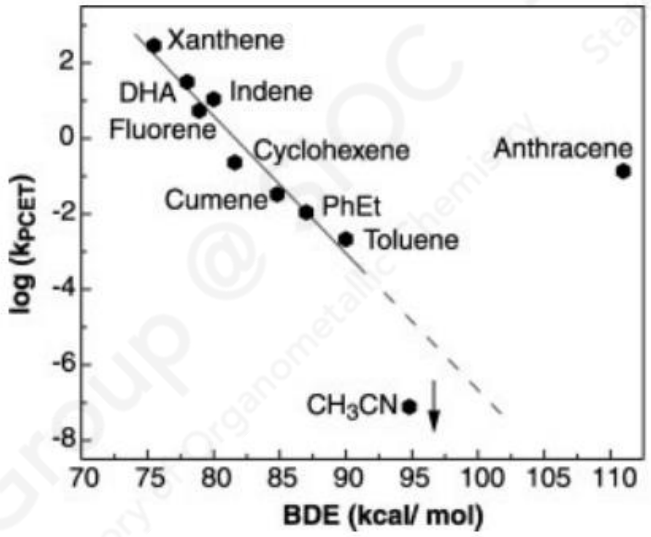
Mayer J. *et al. Inorg. Chem*. **1997**, *36*, 2069.

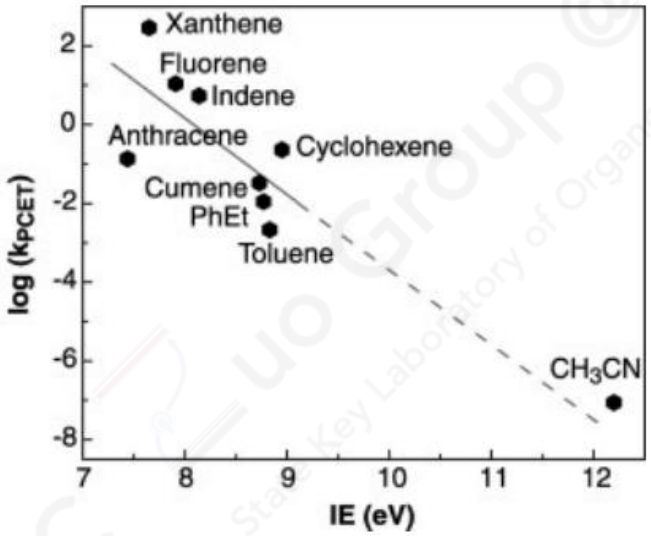
Proton-Coupled Electron Transfer (PCET)

- Kinetic explanations on PCET

Relation between rate constants and BDE/IE on $Ru^{IV}=O^{2+}$ oxidation







Better linear relationship for rate constants and BDE with aliphatic hydrocarbons,

but acetonitrile is included in relationship with IE other than BDE

CPET may favored with polar groups that can stabilize polar transition state

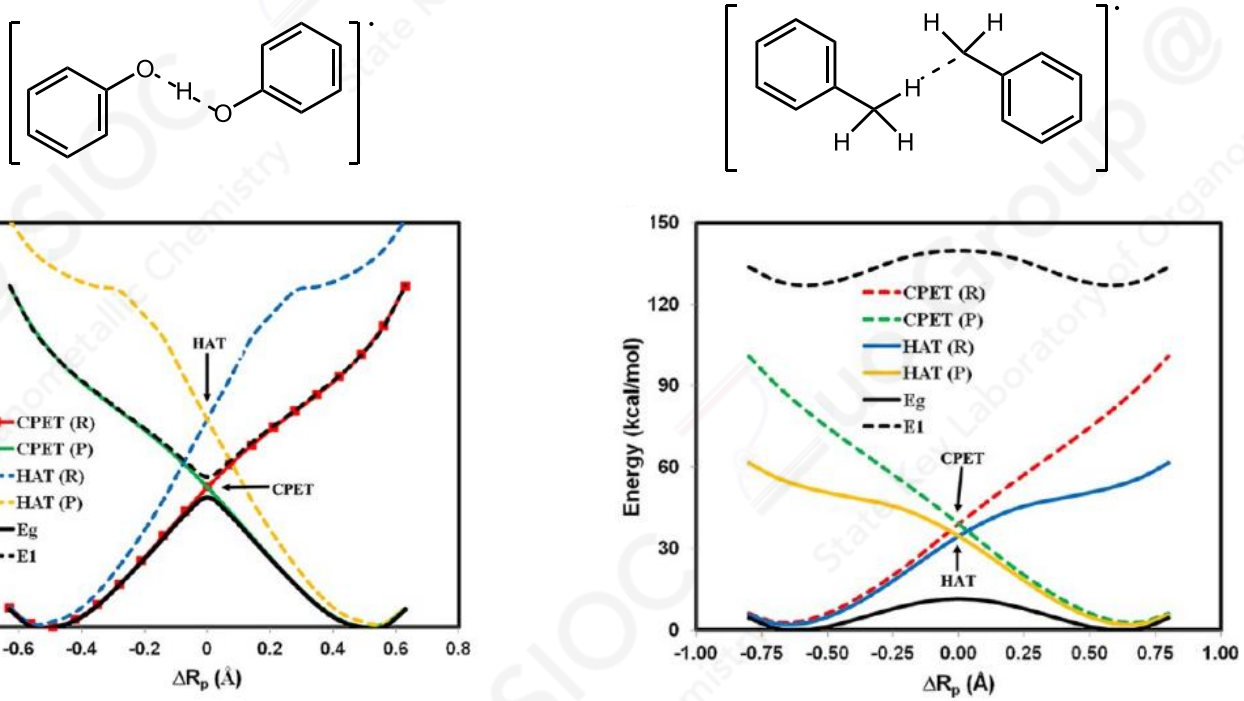
Mayer J. *et al. J. Am. Chem. Soc.* **2003**, *125*, 10351–10361.

Proton-Coupled Electron Transfer (PCET)

- Quantum explanations on PCET

CPET reactions are electronically nonadiabatic; HAT reactions are electronically adiabatic

Calculation on energy of self-exchange in phenoxyl/phenol and benzyl/toluene radical system



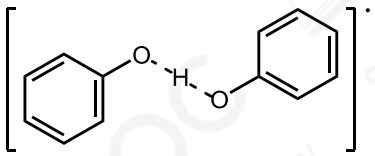
Self-exchange of phenoxyl/phenol radical system is a CPET process under quantum framework

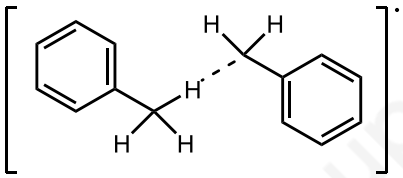
Gao J. *et al. J. Chem. Theory Comput.* **2012**, *8*, 4347−4358.

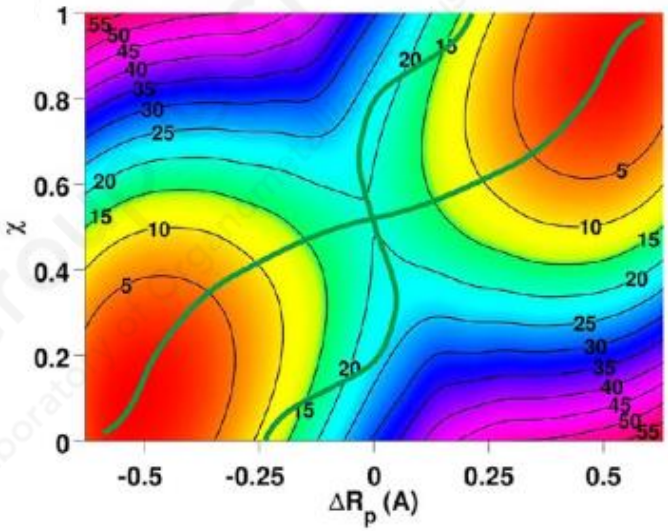
- Quantum explanations on PCET

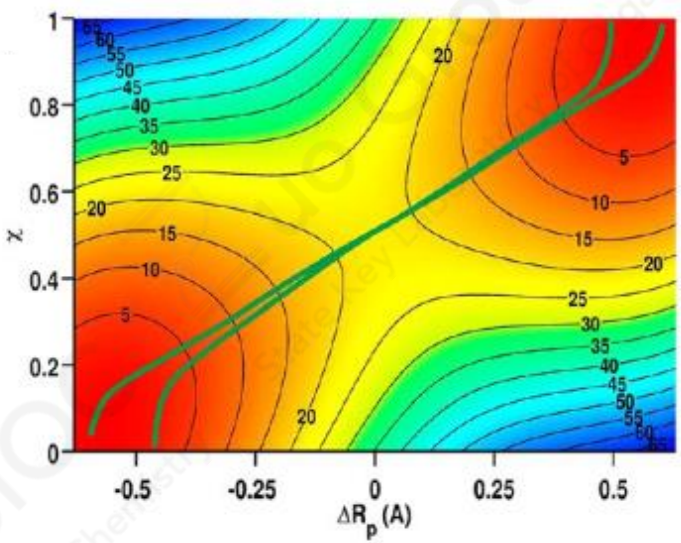
Calculation on potential energy surfaces shows electron properties in PCET

Calculation on potential energy of self-exchange in phenoxyl/phenol and benzyl/toluene radical system









Minimum energy paths of CPET step is non-diagonal lines but diagonal lines for HAT step

Gao J. *et al. J. Chem. Theory Comput.* **2012**, *8*, 4347−4358.

Summary

Neutral Hydrogen Atom Transfer

ET - PT

PT - ET

PCET

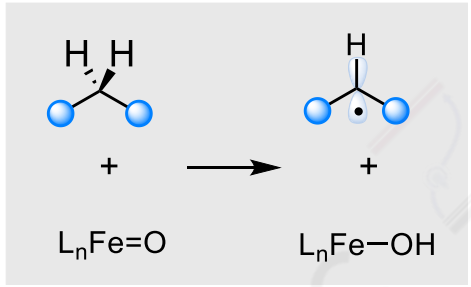
CPET
Nonadiabatic and asynchronous

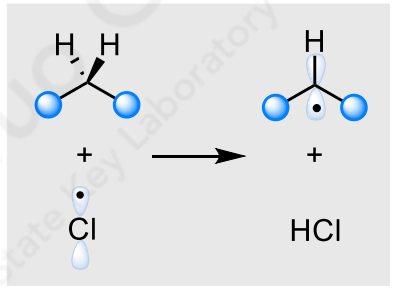
HAT
Adiabatic and synchronous

Normally

Sometimes kinetically identical

Normally



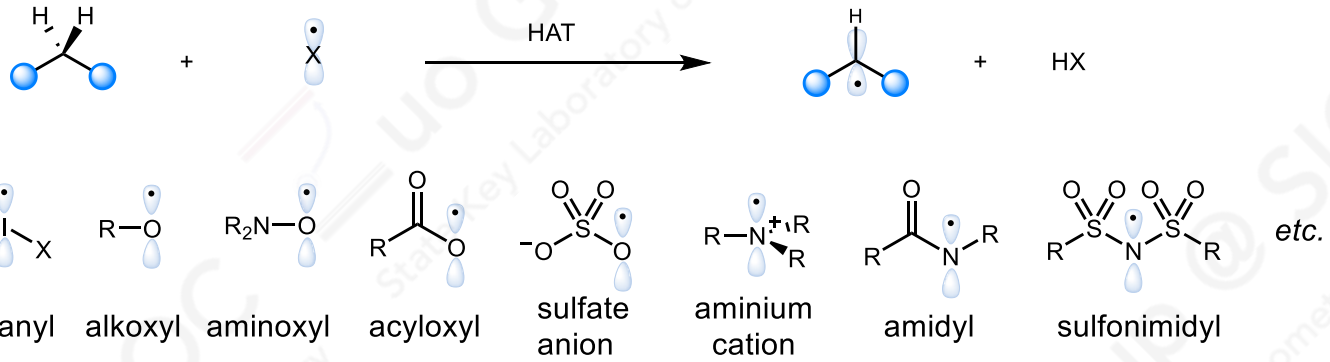


Metal complex mediated hydrogen Atom Transfer

Radical Abstraction

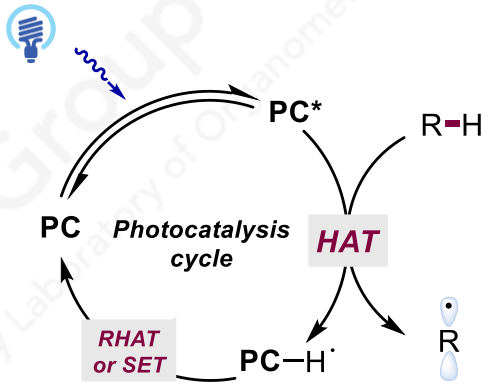
Categories of traditional defined HAT

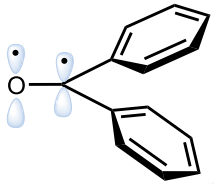
Heteroatom centered radicals



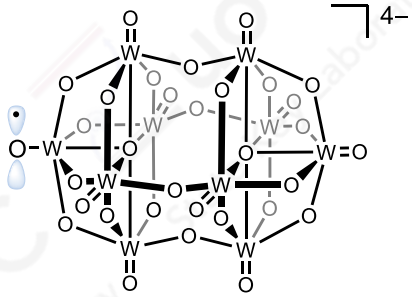
Fagnoni M. *et al. Chem. Rev.* **2022**, *122*, 1875−1924.

Excited molecules

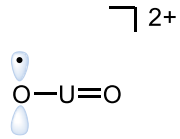




triptet ketone



TBADT



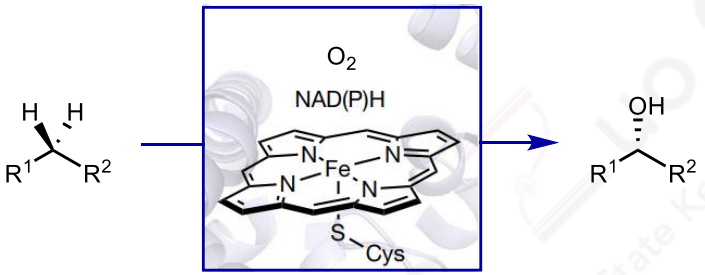
UO_2^{2+}

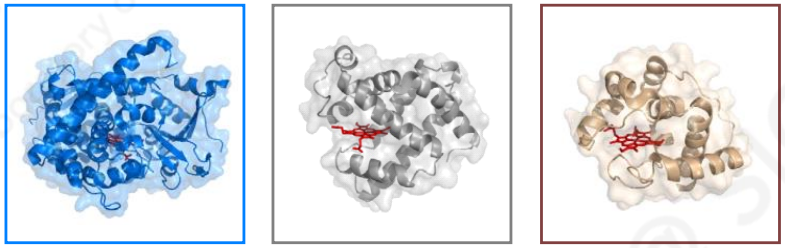
Excitation wavelength **Quantum Yield**

Ravelli D. *et al. Green Chem.* **2020**, *22*, 3376.

Categories of traditional defined HAT

Enzymes





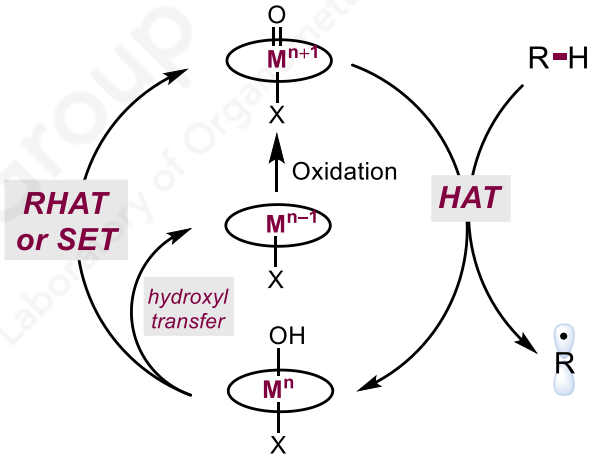
P450 Globin Cyt C

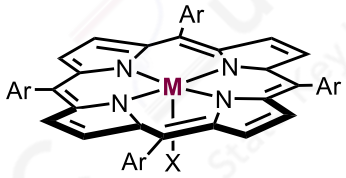
Oxidation in nature

Representive haem protein for HAT

Reetz M. *et al. Chem. Commun.* **2015**, *51*, 2208-2224.

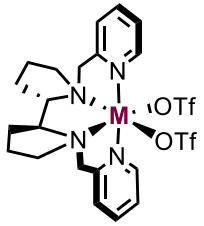
Metal oxo complexes





M(pro-Ar)X

M = Fe, Mn, Co, Ru, etc.



M(pdp)$(OTf)_2$

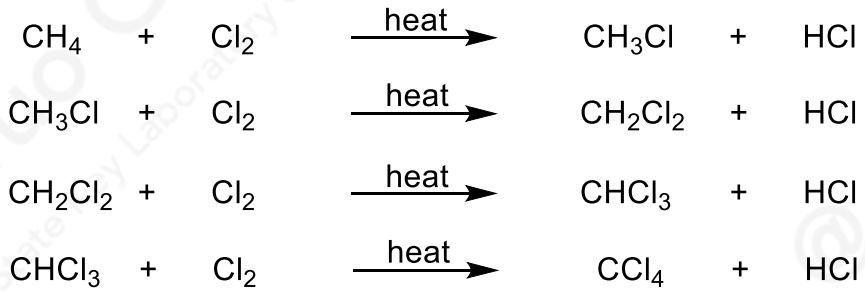
M = Fe, Mn, etc.

Che C. *et al. Chem. Soc. Rev.* **2011**, *40*, 1950-1975.

Early discovery on heteroatom radical HAT

Chlorination of methane (Discovered in 1840)

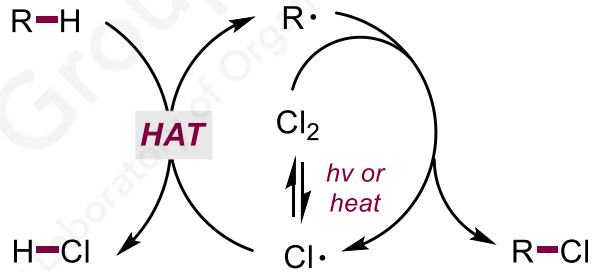
Jean-Baptiste Dumas



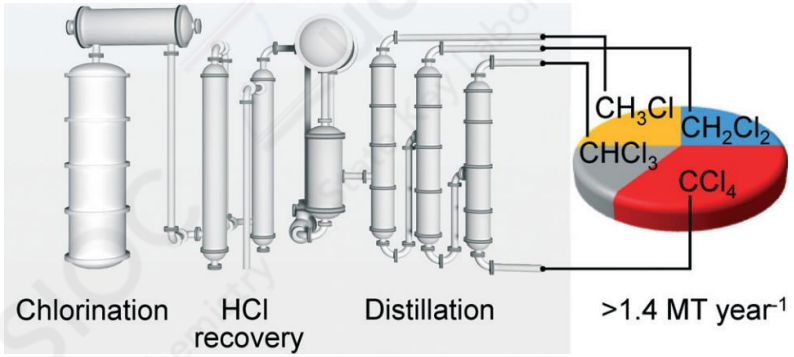
Gas-phase chlorination of marsh gas

Pérez-Ramírez J. *et al. Chem. Rev.* **2017**, *117*, 4182–4247.

Industrial production of alkane chlorides (Date back to 1920s)



Chain Mechanism of radical chlorination

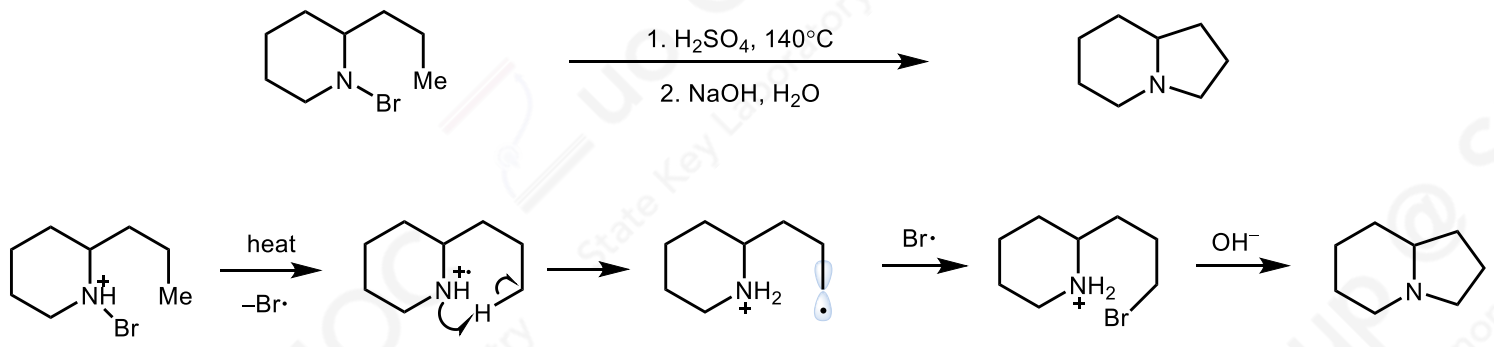


Industrial production of methane chlorides in 1923

Paunović V. *et al. Catal. Sci. Technol.* **2019**, *9*, 4515–4530.

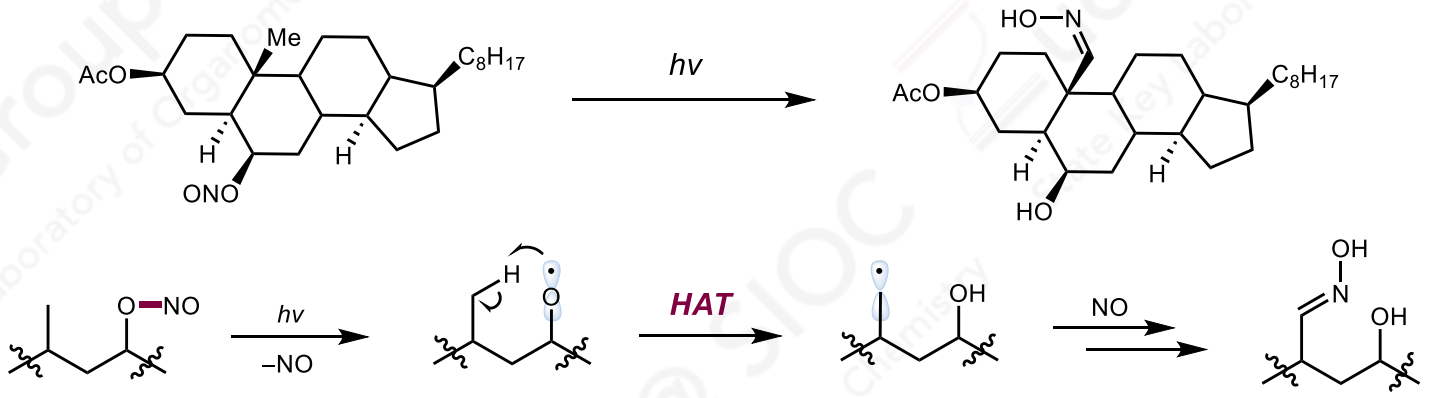
Early discovery on heteroatom radical HAT

Hoffmann-Loffler Reaction (Established in 1883)



Hofmann A. *et al. Ber.* **1883**, *16*, 558.

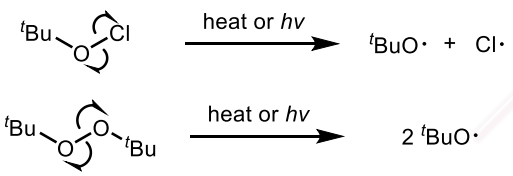
Barton Reaction (Established in 1961)



Barton D. *J. Am. Chem. Soc.* **1961**, *83*, 4076.

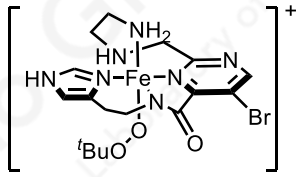
Development of heteroatom radical HAT —— alkoxyl radical as an example

1940s



heat or hv direct initiation

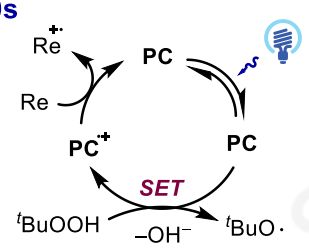
1990s



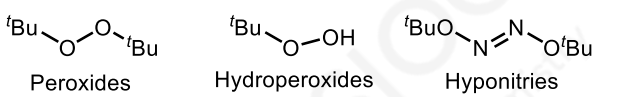
$Fe^{III}(PMA)OO^tBu$

Metal-catalyzed decompositon

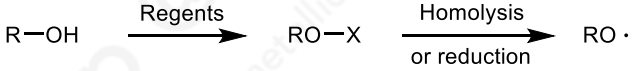
2010s



Photoredox catalysis

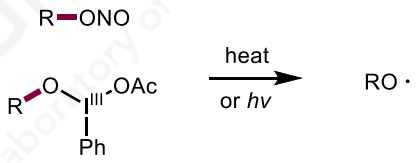


Specific alkoxyl radical for intermolecular HAT



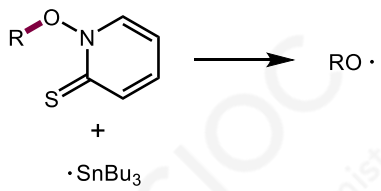
Various alkoxyl radical mainly for intramolecular HAT

1960s



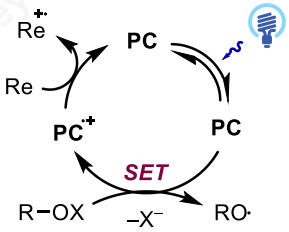
heat or hv induced homolysis

1980s



Radical induced homolysis

2010s

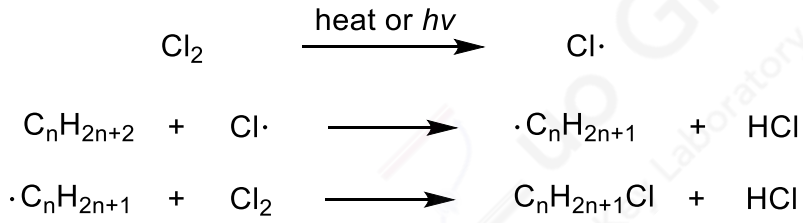


Photoredox catalysis

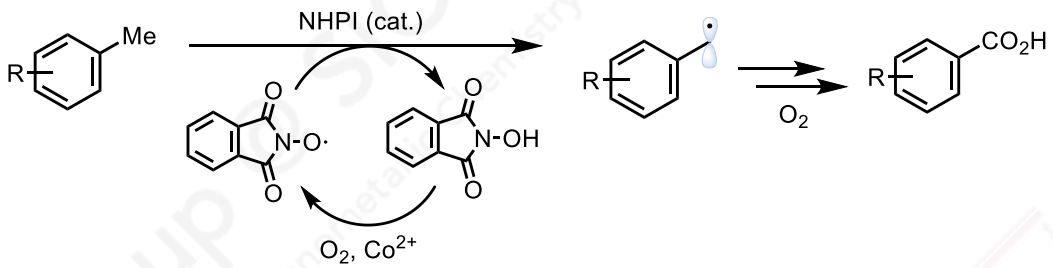
Future prospect : direct generation of alkoxyl radicals from all kinds of alcohols

Industrial Application of heteroatom radical HAT

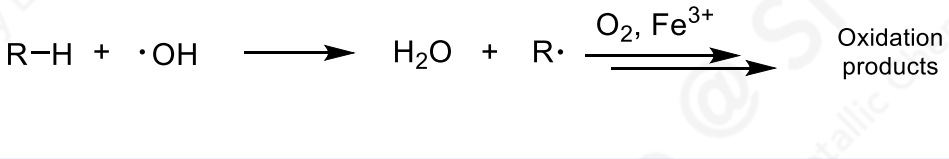
Chlorination of alkanes



NHPI-mediated liquid phase oxidation of toluene



Fenton onxidation in sewage treatment

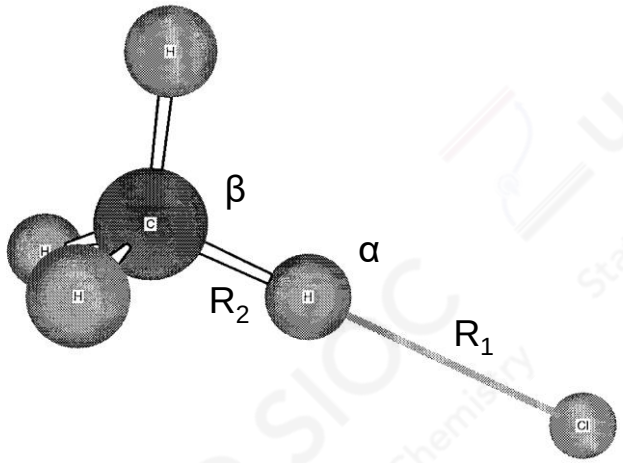


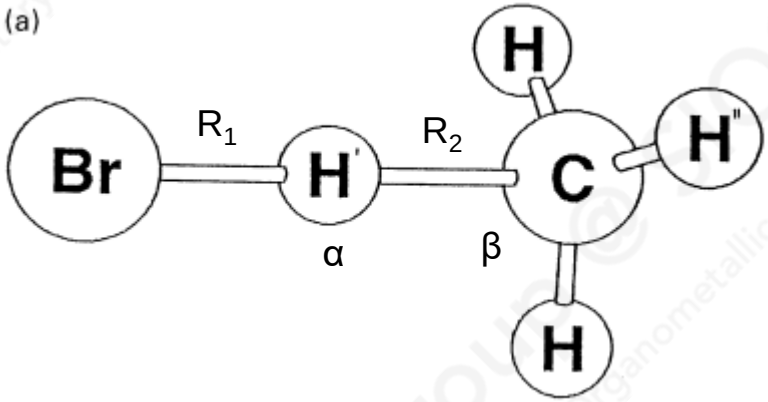
Part II

Effects on Reactivity and Selectivity of HAT Steps

Calculation of transition state

Calculation of transition state of hydrogen abstraction by chlorine and bromine radical





Method [a]	R_1/A	R_2/A	α/°	β/°
HF/3-21G** [b]	1.4896	1.3505	–	102.37
AM1	1.540	1.264	–	104.4
SRP13	1.410	1.411	–	100.4
DFT/6-311G(d,p)	1.431	1.433	–	100.6
MP2-SAC	1.431	1.388	–	100.2
(U)MP2/6-31G* [c]	1.435	1.418	180.0	107.3

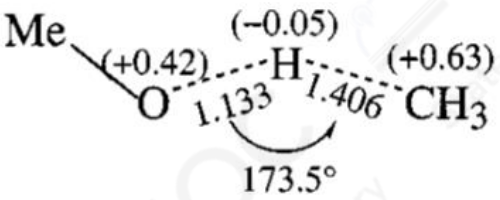
[a] Truhlar D. *et al. J. Phys. Chem. A* **1998**, *102*, 4568-4578.
[b] Truong T. *et al. J. Phys. Chem.* **1989**, *90*, 7137.
[c] CHF_3+Cl• Tschuikow-Roux. E. et *al. J. Phys. Chem.* **1993**, *97*, 3742.

Method [a]	R_1/A	R_2/A	α/°	β/°
QCISD/6-31G(d,p)	1.508	1.599	180.0	99.5
QCISD/6-311G(d,p)	1.509	1.612	180.0	99.1
QCISD/6-311G(2d,2p)	1.510	1.617	180.0	98.9
QCISD/6-311G(2df,2p)	1.511	1.621	180.0	98.5
(U)MP2/6-31G* [b,c]	1.528	1.575	179.3	107.4
(U)MP2/6-31G* [b,d]	1.513	1.592	180.0	107.0

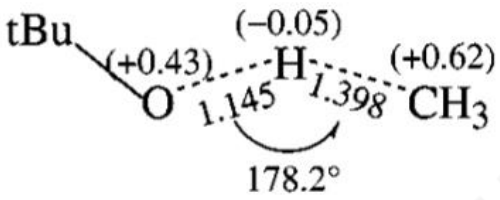
[a] Francisco. *et al.* , *J. S. J. Mol. Struct. (THEOCHEM).* **2001**, 573, 171-180.
[b] Tschuikow-Roux *et al. J. Phys. Chem.* ***1993***, 97, 3742.
[c] CH_2F_2+Br• [d]CHF_3+Br•

Calculation of transition state

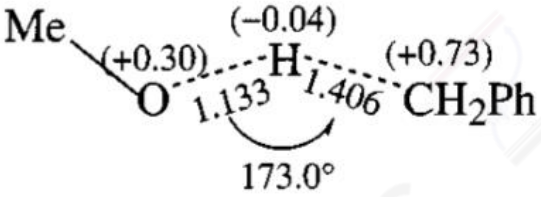
Calculation of transition state of hydrogen abstraction by alkoxyl radicals



$^2TS_{MeO}$



$^2TS_{tBuO}$



$^2TS_{Tol}$

Shaik S. *et al. Eur. J. Inorg. Chem.* **2000**, 2455-2458.

Rate Constants

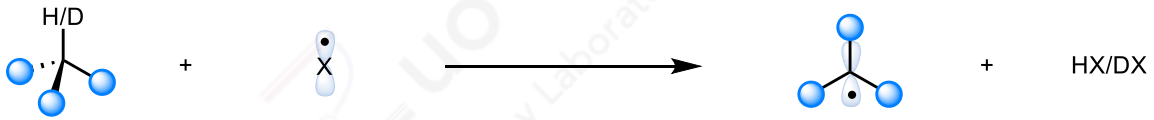
Rate constants of hydrogen abstraction from selected substrates by radicals

Substrate	C–H BDE /kcal·mol^{-1}	Cl· [a] /M^{-1}s^{-1}	Br· [b] /M^{-1}s^{-1}	Substrate	C–H BDE /kcal·mol^{-1}	^{t}BuO· [c] /M^{-1}s^{-1}	RS· [d] /M^{-1}s^{-1}
CH_4	105	1.5×10^{7}	8.3×10^{-3}	cyclohexane	97.6	8.1×10^{5}	
butane	97.9 (2°)	6.0×10^{9}	1.9×10^{3}	n-dodecane	99.1 (2°)		2.4×10^{4}
tert-butane	95.3 (3°)	6.3×10^{9}	1.0×10^{6}	t-butylbenzene	98.6	3.9×10^{4}	
propylene	87.9	4.6×10^{9}	2.5×10^{6}	toluene	89.4	1.9×10^{5}	3.4×10^{5}
toluene	89.4	1.2×10^{10}	3.4×10^{6}	MeOH	95.9	5.2×10^{4}	
EtCl	96.8	2.8×10^{8}	6.0×10^{2}	diphenylmethanol	78	6.9×10^{6}	
EtOH	95.5	1.4×10^{9}	2.7×10^{6}	Et_2O	92.6	3.9×10^{6}	
Me_2O	95.7	2.0×10^{10}	1.5×10^{5}	PhOMe	92		6.0×10^{4}
acetone	95.5	2.3×10^{8}		BnOMe	85.8		2.7×10^{7}
MeCN	96.6	2.4×10^{6}		THF	95.7	7.4×10^{6}	
CH_2Cl_2	95.4	1.1×10^{8}	56	1,4-dioxane	97	1.5×10^{6}	
CHF_3	106	3.0×10^{5}	5.5×10^{-7}	NEt_3	90.7	9.7×10^{7}	

[a] Gas phase at T=298K, Poutsma M. *et al. J. Phys. Chem. A,* **2013**, *117*, 6433-6449.
[b] Solution phase at T=298~350K, CHF_3 at T=646~738K, Poutsma M. *et al. J. Phys. Chem. A,* **2016**, *120*, 183-190.
[c] Solution phase at T=300K, Malatesta V. *et al J. Org. Chem.* **1982**, *47*, 1455-1459.
[d] Solution phase at T=353K, RS$^{\bullet}$ = cyclohexanethiyl radical, Pryor W. *et al. J. Org. Chem.* **1978**, *43*, 793-800.

Kinetic Isotope Effects

Kinetic isotope effects of hydrogen abstraction by selected radicals



radical	Cl·	Br·	^{t}BuO·
k_H/k_D (cal.)	12.8 (CH_4/CD_4) 1.42 (CH_4/CH_3D)		6.46 (methane)[a]
k_H/k_D (exp.)	12.2 (CH_4/CD_4) 1.51 (CH_4/CH_3D) 3.1 (ethane)[aa a] 1.4 (n-butane) 1.2 (cyclohexane)	3.05 (methane)[b] 5.33 (cyclohexane) 4.30 (cyclohexane)[c]	4.9 (cyclohexane)[a]
k_{C12}/k_{C13} (cal.)	1.021 ($^{12}CH_4/^{13}CH_4$)		
k_{C12}/k_{C13} (exp.)	1.066 ($^{12}CH_4/^{13}CH_4$)		

AM1-SRP4[MP2]-IC Level of Calculation at T=296~300K, Truhlar D. *et al.* *J. Phys. Chem. A* **1998**, *102*, 4568–4578.

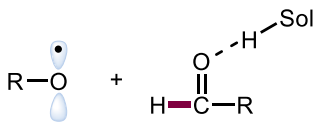
[a] Quoated from Fokin A. *et al. Chem. Rev.* **2002**, *102*, 1551-1593.

[b] T=562K, Timmons R. *et al.* Int *J Chem Kinet.* **1970**, 325-334.

[c] In Freon 113 solution.

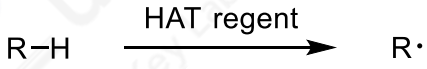
❑ Basic Effects influencing HAT steps

Solvent Effect



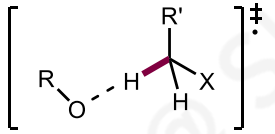
Solvent Polarity
Hydrogen bond

Hydrogen Atom Transfer



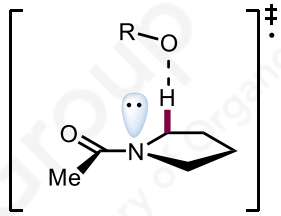
Effects on
Reactivity amd Selectivity

Polar Effect



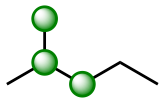
X = EDG, C-H activated
X = EWG, C-H deactivated

Stereoelectronic Effect

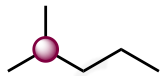


Activation by long pair

Bond Dissociation Energy



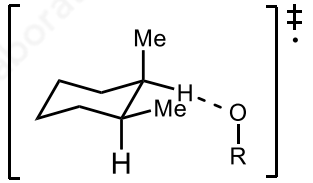
Cl• activation



Br• activation

More reactive HAT regent for
stronger C-H bond activation

Strain Effect



Strain released TS

Bond Dissociation Energy and Bond Dissociation Free Energy

❑ Difference between BDE and BDFE

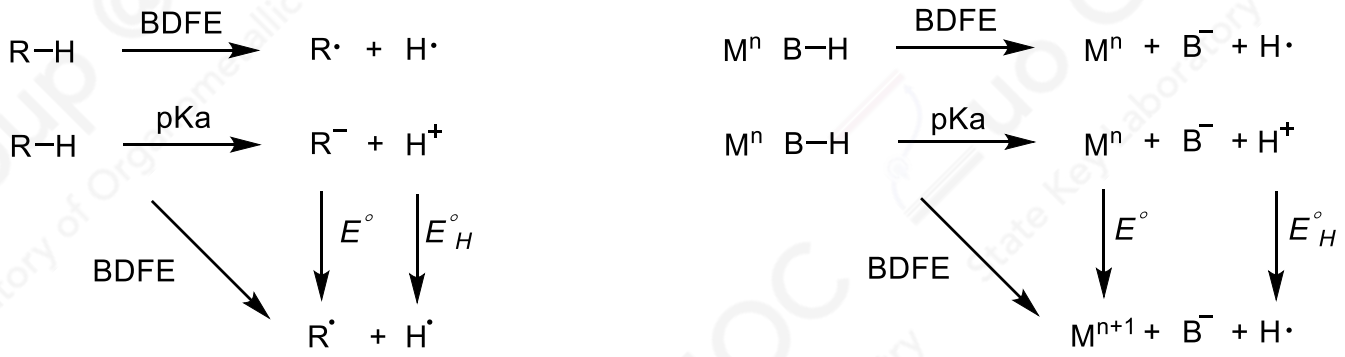
Bond dissociation Energy (BDE): The enthalpy change in bond dissociation

Bond dissociation Free Energy (BDFE): The free energy change in bond dissociation

$$BDE = \Delta H^{\circ}$$

$$BDFE = \Delta G^{\circ}$$

Measurement of BDFE



$$BDFE\ (kcal/mol) = 1.37\ pKa\ (B\text{-}H) + 23.06E^{\circ}(M^{n}/M^{n+1}) + 23.06E^{\circ}(H^{+}/H^{\bullet})$$

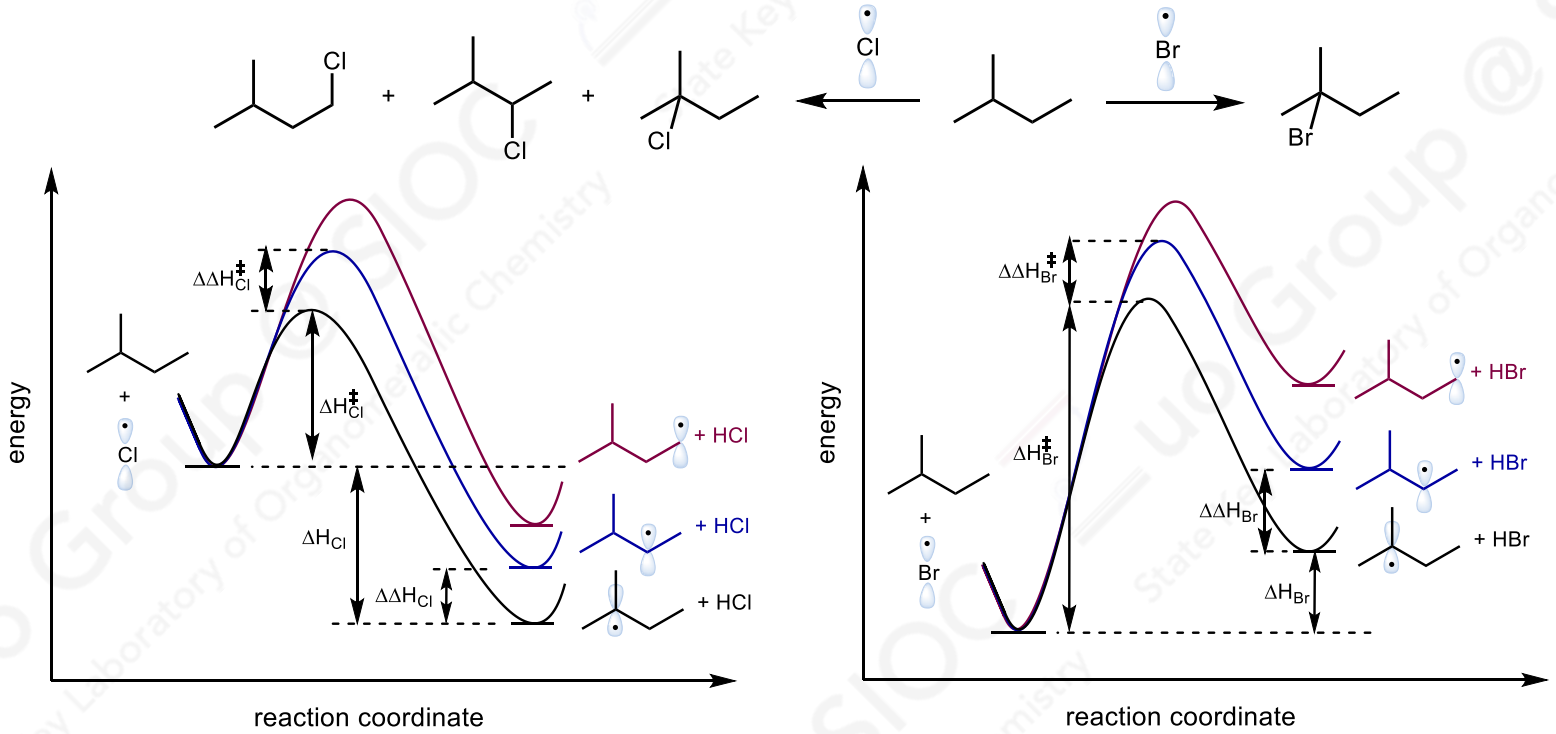
Mayer J. *et al. Chem. Rev.* **2022**, *122*, 1, 1–49.

Evans-Polanyi Principle

❑ Evans-Polanyi Principle and BDE

Evans-Polanyi Principle : A linear relationship between the activation energy and enthalpy

In a series of related reactions, more exothermic reactions give smaller activation energy



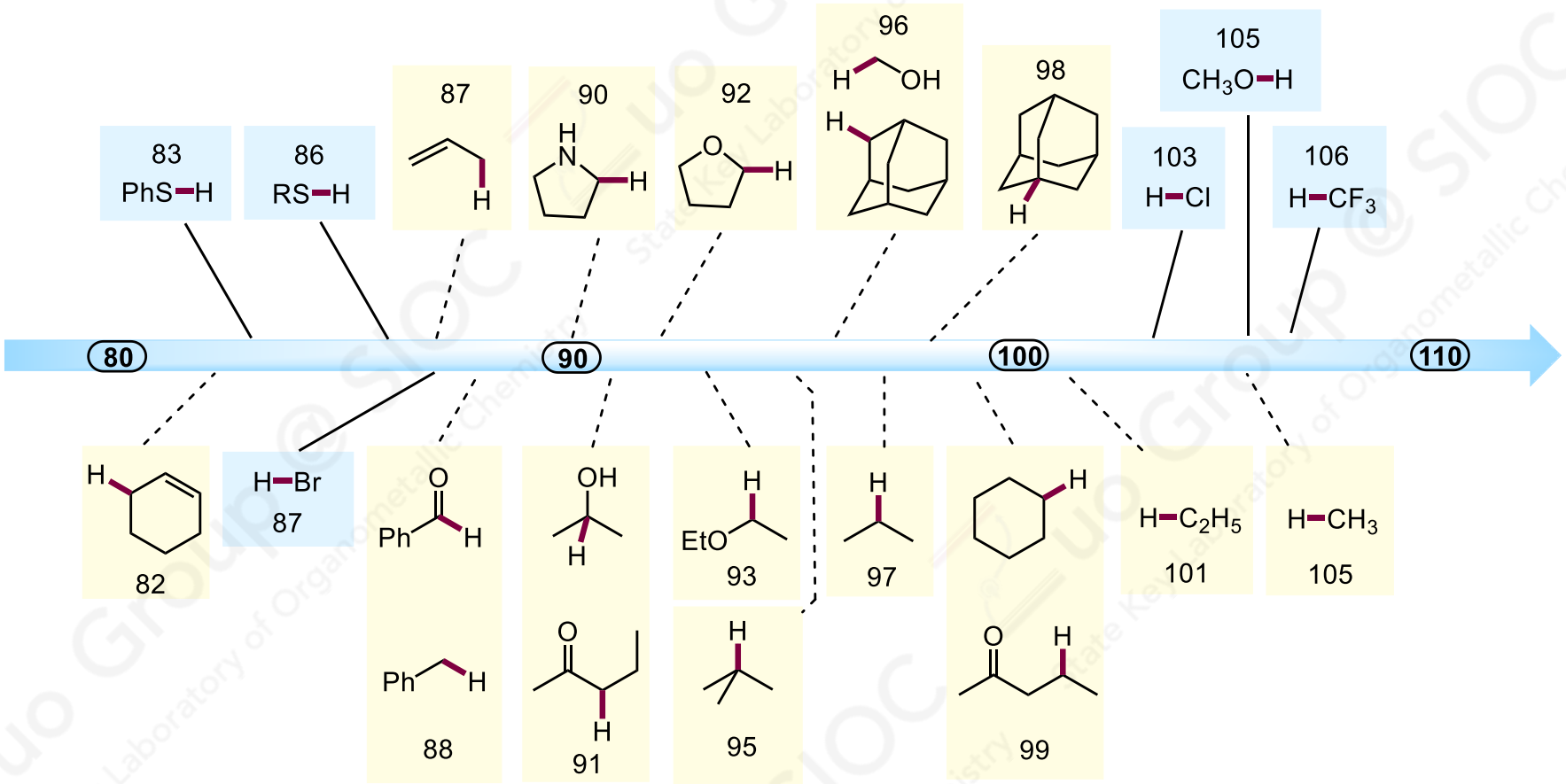
Normally, Cl• with higher BDE has lower Ea while Br• with smaller BDE has higher Ea

Thus, Cl• gives high-energy radical intermediate or high reactivity but poor selectivity

Bruckner R.. *Advanced Organic Chemistry: Reaction Mechanisms*, Academic Press. **2001**.

Bond Dissociation Energy

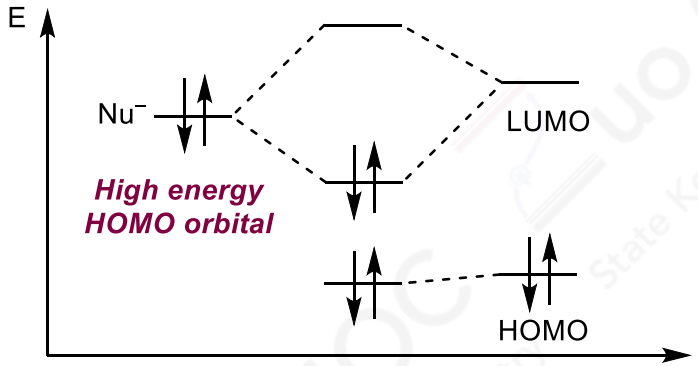
Bond Dissociation Energy Spectrum



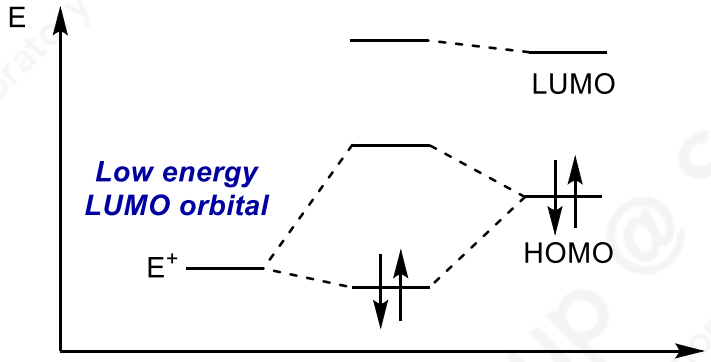
Most data are quoted from Fagnoni M. *et al. Chem. Rev.* **2022**, *122*, 1875-1924.
For data not covered, see:
Luo Y. R. *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, **2007**.
Kruppa G. H. and Beauchamp J. *et al. J. Am. Chem. Soc.* **1986**, *108*, 2162-2169.

Polar Effect

- Energy of FMO determines philicity of Nu^- or E^+

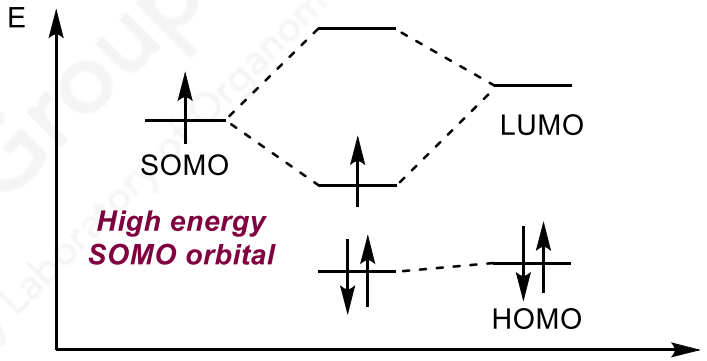


Typical nucleophilic regents
Interaction with vacant LUMO and donate electrons

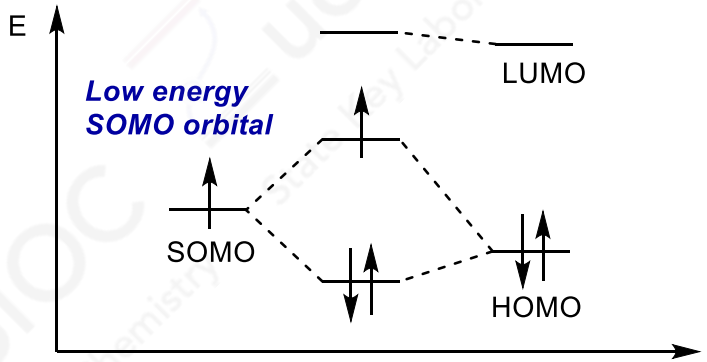


Typical electrophilic regents
Interaction with filled orbital and accept electrons

- What about radicals?



High energy SOMO with interaction with LUMO
— Nucleophilic radical

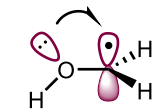


Low energy SOMO with interaction with HOMO
— Electrophilic radical

Ian Fleming. *Molecular Orbitals and Organic Chemical Reactions, Reference Edition*, John Wiley & Sons, Ltd. **2010**, pp 369-372 .

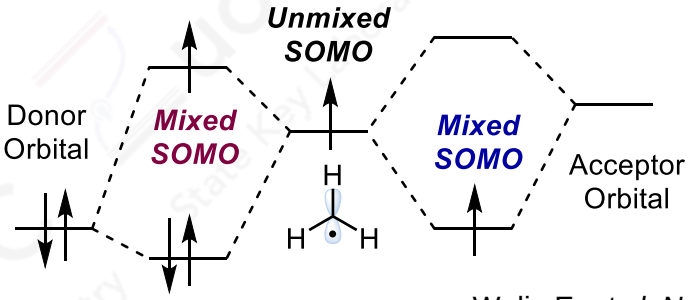
❑ Factors influencing SOMO energy of radicals

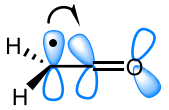
Carbon radicals : Orbital interactions



$n_O \rightarrow p_{SOMO}$

Electron-rich nuclephilic radical





$p_{SOMO} \rightarrow \pi^*_{C=O}$

Electron-poor electrophilic radical

Welin E. *et al. Nat. Rev. Chem*, **2021**, *5*, 486-499.

Heteroatom radicals : Inherent electronegativity

Top : Pauling Electronegativity χ_P

Buttom : Mulliken Electronegativity $\chi_M = \frac{IE + EA}{2}$

	B					**O**	**Cl**	
	2.04					3.44	3.16	
	4.29					7.53	8.30	
Si		**Sn**	⟵	**C**	⟶	**N**	**S**	**Br**
1.74		1.96		2.55		3.04	2.96	2.58
4.76		4.30		6.27		7.27	6.22	7.59

Less electronegative
tend to donate electrons
Typically nucleophilic

More electronegative
tend to accept electrons
Typically electrophilic

Putz M. *et al. Theor. Chem. Acc.* **2005**, *114*, 38–45.

Polar Effect

❑ Quantitative measurement of philicity

Mulliken Electronegativity

Mulliken Electronegativity $\chi = \dfrac{IE + EA}{2}$

For polar effect in HAT, $\Delta E_a \sim -\Delta\chi^2$

Roberts B. *et al. J. Chem. Soc. Perkin Trans. 2*, **1994**, 2155.

Electrophilicity and Nucleophilicity Index

Electrophilicity Index : *a measurement of stabilization when charge transfer from environment to system*

$$\omega = \frac{\mu^2}{2\eta}$$

$$\mu = -\chi = -\frac{IE + EA}{2} \qquad \eta = IE - EA$$

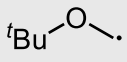
Nucleophilicity Index : *a relative measurement of nucleophic scale to a chosen electrophilic system*

$$\omega^- = \frac{(\mu_A - \mu_B)^2}{2(\eta_A + \eta_B)^2}\eta_A$$

Parr R. *et al. J. Am. Chem. Soc.* **1999**, *121*, 1922-1924.
Jaramillo P. *et al. J. Phys. Chem. A.* **2006**, *110*, 8181-8187.

- Quantitative measurement of philicity

Mulliken Electronegativity **χ**, Global Electrophilicity Index **ω,** and Nucleophilicity Index **ω⁻** for selected organic radicals

Nuclephilic Radicals					Electrophilic Radicals				
Radical	BDE/kcal·mol^{-1}	χ /eV	ω /eV[a]	ω^- /eV[a]	Radical	BDE/kcal·mol^{-1}	χ /eV	ω /eV[a]	ω^- /eV[a]
	92	3.28	–	–	·CF_3	106	5.53	1.672	0.271
	93	3.28	–	–	PhS·	83	5.55	2.358	0.254
^{t}Bu·	95	3.32	0.651	0.505	·NH_2	107	6.07	–	–
·CH_2OH	96	3.59	0.717	0.486	MeO·	104	6.76	–	–
$PhCH_2$·	88	4.05	1.239	0.388	^{t}BuO·	106	6.91	–	–
Me·	105	4.96	1.209	0.364	Br·	87	7.60	3.614	0.066
	92	5.33	–	–	Cl·	103	8.32	3.772	0.042

[a] ω and ω^- calcluated by B3LYP/6-311+g(d,p), ω^- reletive to fluorine

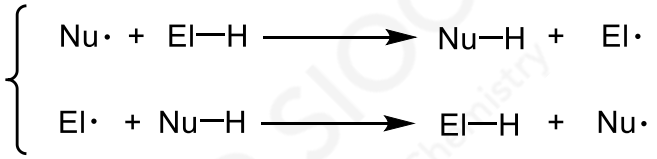
Roberts B. *et al. J. Chem. Soc. Perkin Trans. 2*, **1994**, 2155.
Proft F. *et al. Org. Lett.* **2007**, *9*, 2721–2724.

Polar Effect

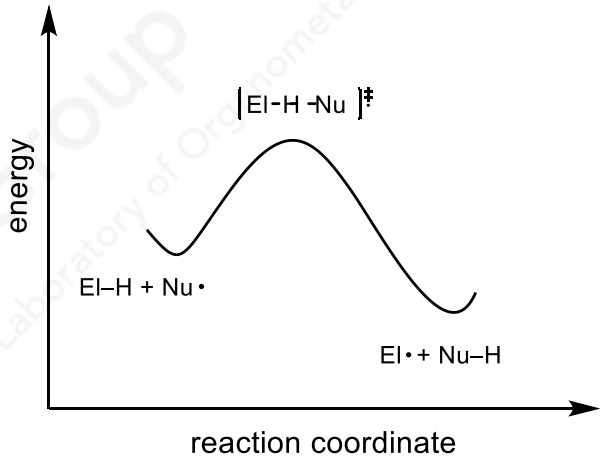
❑ Polarity Matching

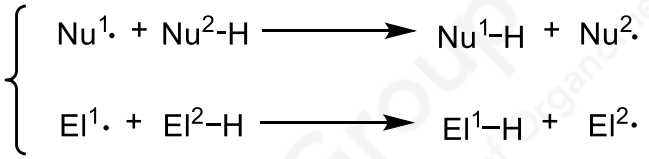
Mulliken Electronegativity $\chi = \frac{IE + EA}{2}$

For polar effect in HAT, $\Delta E_a \sim -\Delta\chi^2$

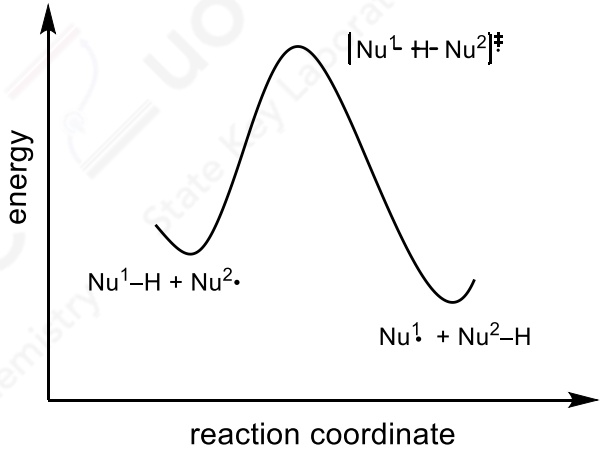


Polarity matched





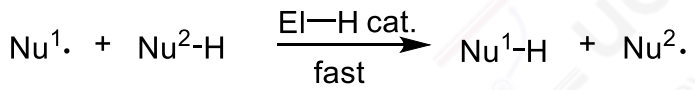
Polarity mismatched



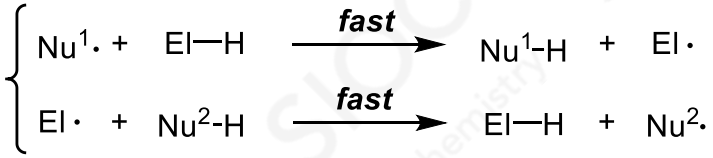
Roberts B. *et al. Chem. Soc. Rev.* **1999**, *28*, 25–35.

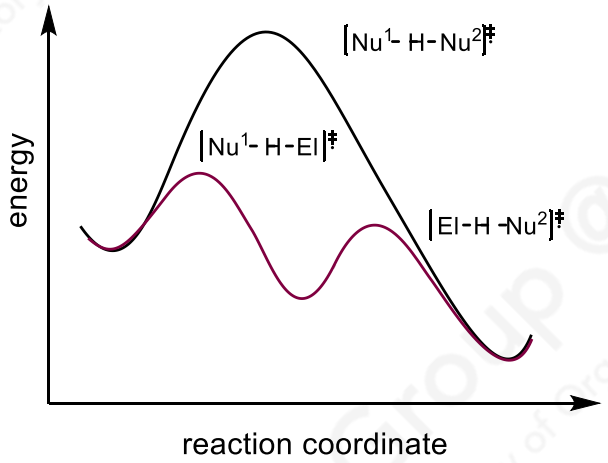
❑ Polarity Reversal Catalysis

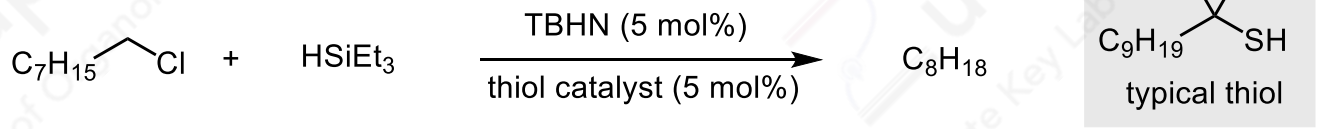
Overall reaction

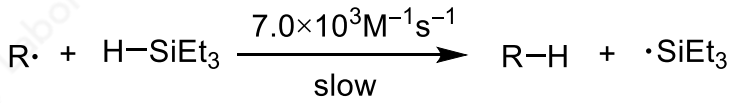


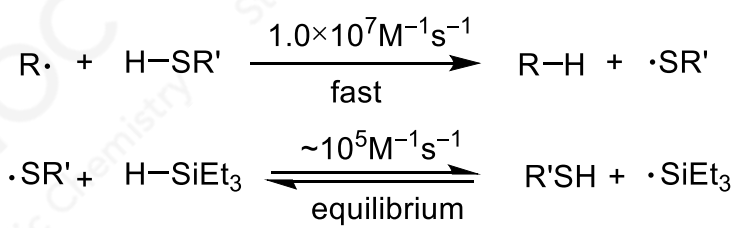
Polarity reversal cycle







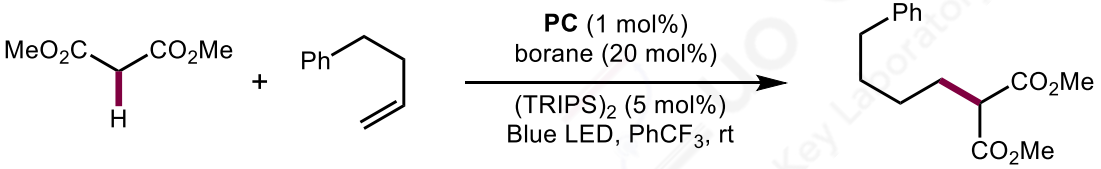


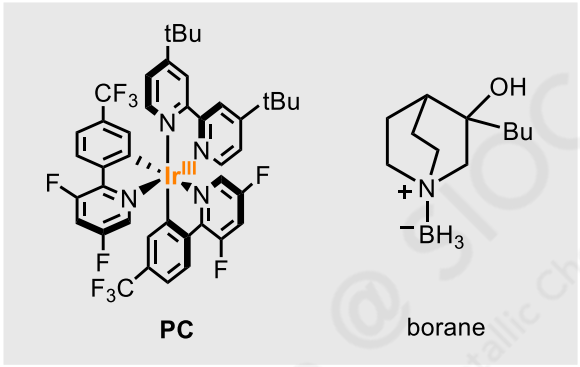


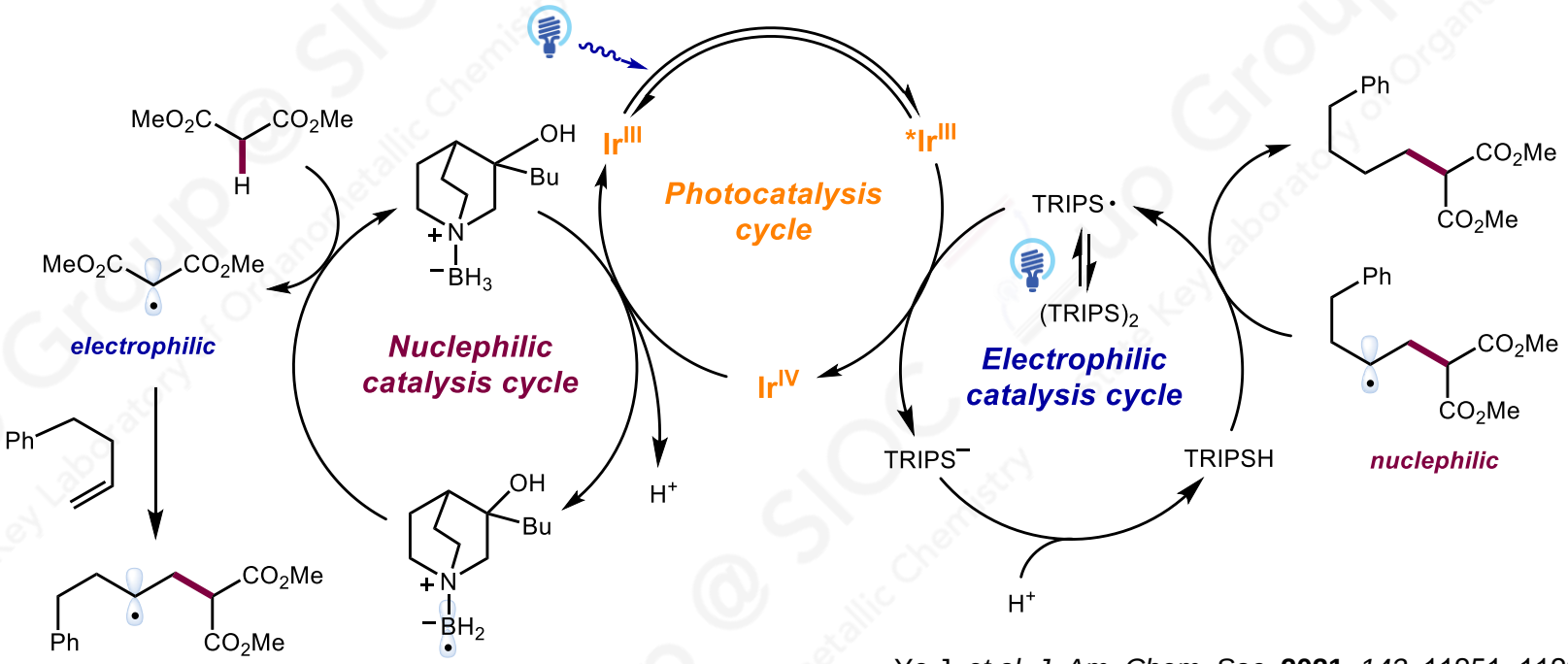
Willis C. *et al. J. Chem. Soc. Perkin Trans. 1*, **1991**, 103-112.

Polar Effect

❑ Polarity Matching in photocatalysis



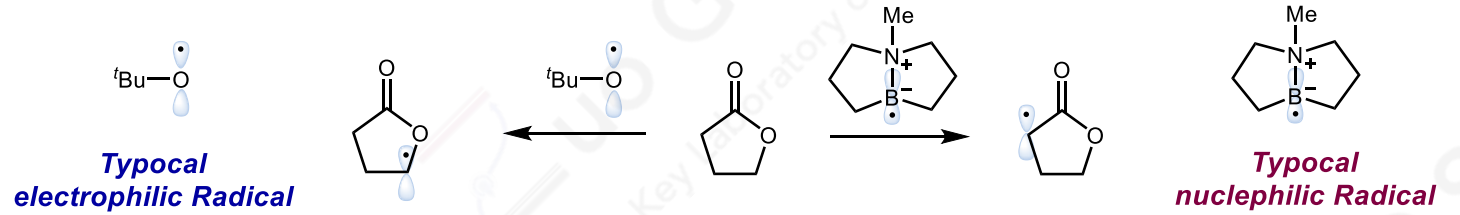




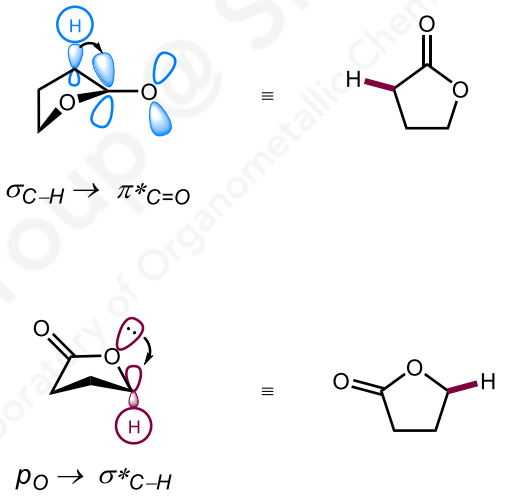
Ye J. *et al. J. Am. Chem. Soc.* **2021**, *143*, 11251−11261.

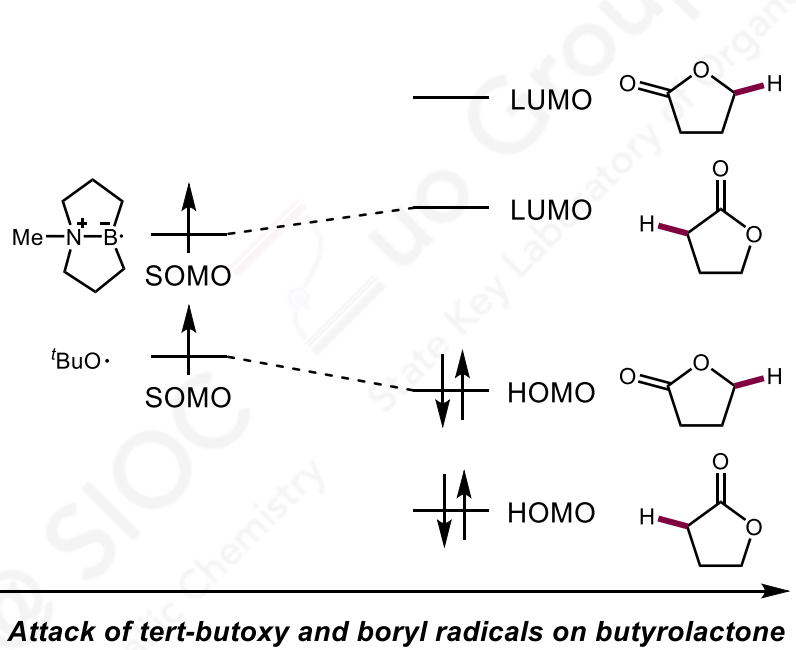
Polar Effect

- Polar Effect influence on site selectivity in HAT steps



Electrophilic and nuclephilic radicals give different site selectivity





Attack of tert-butoxy and boryl radicals on butyrolactone

Willis C. *et al. J. Chem. Soc. Perkin Trans. 2*, **1989**, 1953-1961.

Polar Effect

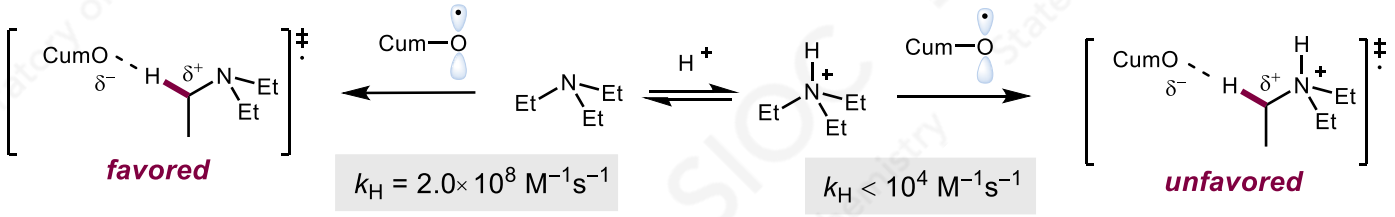
❑ Polar Effect influence on rate constant in HAT steps

X group	α-H BDE /kcal mol^{-1}	K_H/M^{-1}s^{-1} [a]	k_{rel} (propane)
Cl	~97	1.84×10^5	0.59
H	98	3.1×10^5	1.0
Ph	86	7.9×10^5	2.54
OH	93.5	1.36×10^6	4.7
NH_2	92.3	1.55×10^7	50

[a] Measured in argon-saturated acetonitrile solution at T = 25 °C employing 355 nm LFP

Electron rich substituent activate HAT on α-position by electrophilic radical

Bietti M. *et al. J. Org. Chem.* **2017**, *82*, 13542-13549.



$k_H = 2.0\times10^8$ M^{-1}s^{-1}

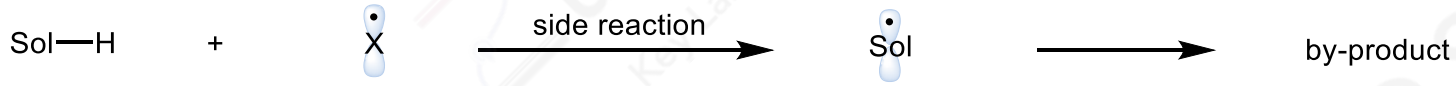
$k_H < 10^4$ M^{-1}s^{-1}

Protonation reverse electronic properties of N-**α carbon radical**

Bietti M. *et al. Chem. Sci.* **2013**, *4*, 3255-3262.

❑ Solvent engaged HAT process

Solvent properties and C-H bond energy of common organic solvents

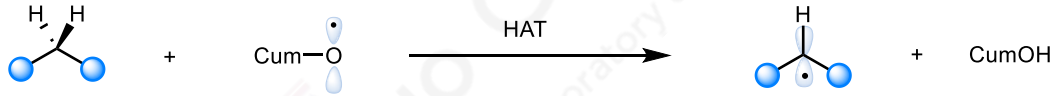


Solvent	C–H BDE /kcal mol^{-1}	Dipole moment /D	Dielectric constant ε	Relative polarity index	Solvent	C–H BDE /kcal mol^{-1}	Dipole moment /D	Dielectric constant ε	Relative polarity index
cyclohexane	97.6	0	2.0	0.006	PhCN	-	4.1	26	0.333
hexane	99.1	0	1.9	0.009	acetone	95.5	2.85	21	0.355
toluene	89.4	0.36	2.4	0.099	DMF	81.7 (CO-H) 105 (N-α)	3.8	37	0.386
benzene	112.4	0	2.3	0.111	$PhNH_2$	89.4(N–H)	1.6	6.8	0.420
Et_2O	92.6	1.25	4.3	0.117	DMSO	93.6	3.9	46.7	0.444
THF	95.7	1.63	7.5	0.207	MeCN	96.6	3.5	37.5	0.460
AcOEt	96.1 (C=O-α) 94.4 (O-α)	1.78	6.0	0.228	acetic acid	94.9	1.68	6.2	0.648
$CHCl_3$	93.5	1.0	4.8	0.259	EtOH	95.5	1.7	24	0.654
pyridine	105~112	2.2	13	0.302	MeOH	95.7	1.6	33	0.762
CH_2Cl_2	95.4	1.6	9.0	0.309	H_2O	118(O–H)	1.85	80.1	1.000

Solvent properties are quoted from Christian Reichardt, *Solvents and Solvent Effects in Organic Chemistry,* Wiley-VCH Publishers, 3rd ed. **2003**
Bond energy are quoted from iBond database, Tsinghua University and Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, **2007.**

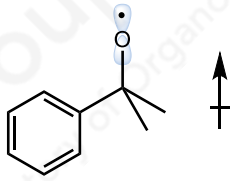
Solvent Effect

- Effects of solvent polarity on rate constant in HAT steps

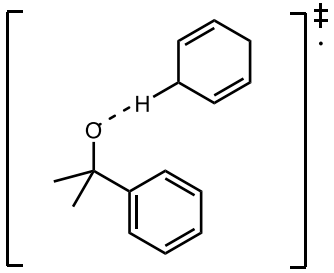


Solvent	$k_H/10^7\ M^{-1}s^{-1}$ [a]			
				
AcOEt	2.4	5.5	1.8	2.3
AcOEt/MeCN =1:1	2.0	4.3	1.4	1.9
MeCN	1.8	3.6	1.2	1.5

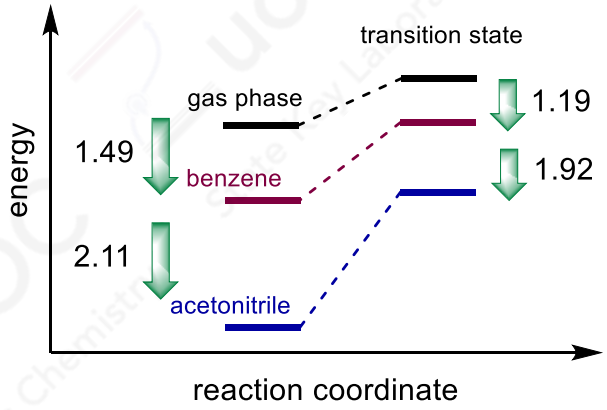
[a] Rate constants mesured by fluorescence quenching at 295K



Big dipole moment
more *stable in polar solvent*



TS with small dipole moment
less *stable in polar solvent*

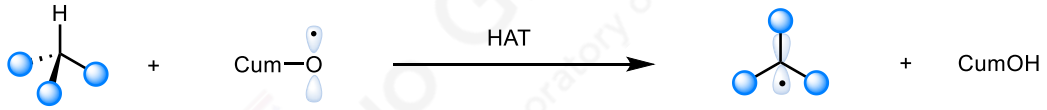


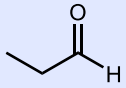
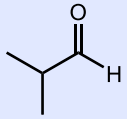
Polar solvents result in a selective stabilization of the reactants, giving lower rate constants

Nau W. *et al. Org. Lett.* **2011**, *13*, 2694–2697.

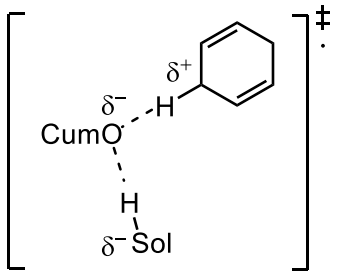
Solvent Effect

- Effects of solvent hydrogen-bond on rate constant in HAT steps

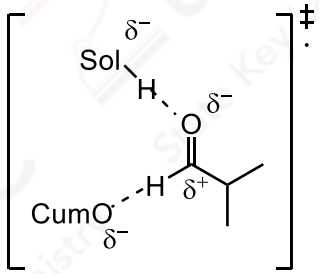


Solvent	$k_H/10^7\ M^{-1}s^{-1}$ [a]			
				NEt_3
benzene	***6.79***	4.27	5.0	28
MeCN	***6.56***	2.23	2.33	21.9
MeOH	***8.25***	0.95	1.7	3.8
TFE[b]	***18.9***	0.93	1.04	-

[a] Measured by the decay of the CumO• visible absorption band at 490~515 nm at T = 25 °C employing 355 nm LFP. [b] 266mm LFP



*TS **more** stabilized than reactant by hydrogen bond*



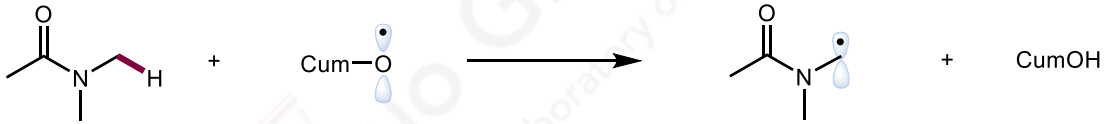
*TS **less** stabilized than reactant by hydrogen bond*

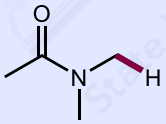
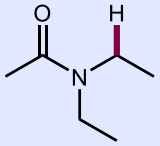
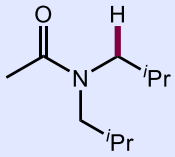
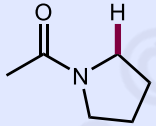
Hydrogen bond can work reversely in stabilizing reactants and TS of various substrates

Bietti M. *et al. J. Org. Chem.* **2011**, *76*, 4645–4651.

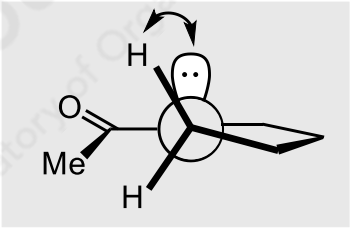
Stereoelectronic Effect

- Stereoelectronic effect on reactivity in HAT steps

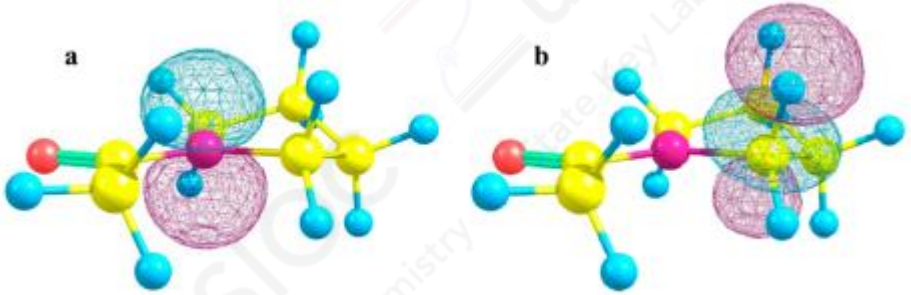


k_H (CumO·)				
k_H (obv.)[a] /$M^{-1}s^{-1}$	1.2×10^6	6.6×10^5	3.1×10^5	***9.0×10^6***
k_H (per H)/$M^{-1}s^{-1}$	2.0×10^5	1.7×10^5	7.8×10^4	***2.3×10^6***
rel. (DMF per H)	1.0	0.85	0.39	***11.5***

[a] Measured by the decay of the CumO• visible absorption band at 485nm at T = 25 °C employing 266 nm LFP.



Conformation of N-acetylpyrrolidine



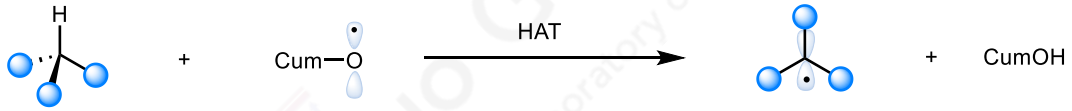
a Nitrogen p-type orbital **b** C−H antibonding orbital

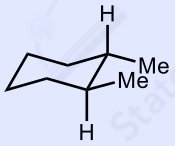
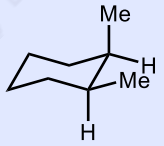
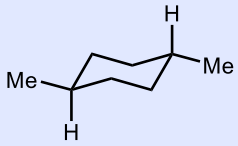
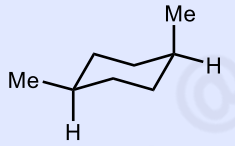
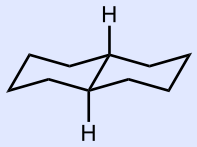
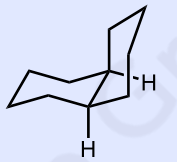
Overlap between C−H antibond **and the amide π**-obital lead to higher reactivity

Bietti M. *et al. J. Org. Chem.* **2014**, *79*, 7179–7184.

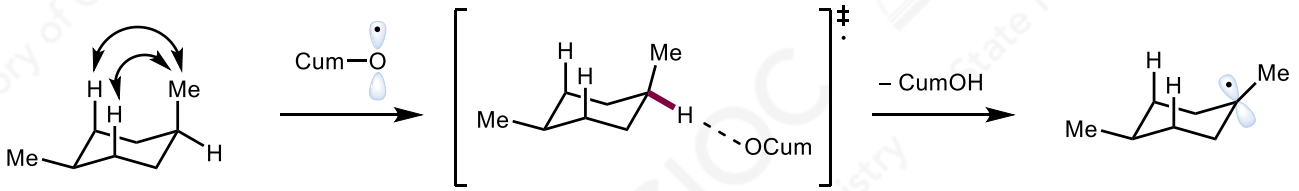
Strain Effect

❑ Strain effect on rate constants



Substrates				
Rate constant[a] / $M^{-1}s^{-1}$	1.03×10^6	2.34×10^6	1.10×10^6	2.05×10^6
Substrates				
Rate constant / $M^{-1}s^{-1}$	1.58×10^6	2.85×10^6		

[a] Rate constants mesured in Argon-saturated acetonitrile solution, T = 25°C, 355 nm LFP



Strain released TS

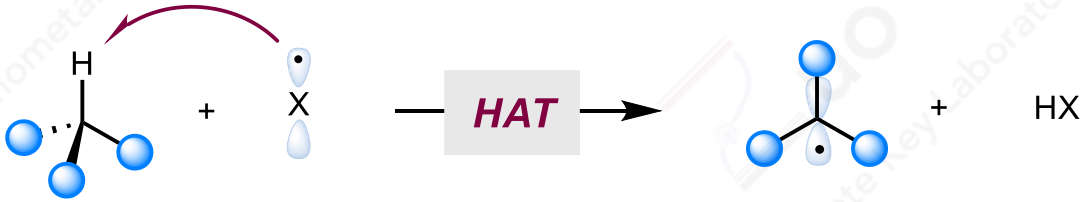
Decrease in torsional strain in the HAT transition state accounts for C−H bond activation

Bietti M. *et al. J. Org. Chem.* **2015**, *80*, 4710-4715.

Part III

Reactivity and Selectivity of Typical HAT Regents

3.1 Halogen radical



X = Cl, Br or I(III)

Early Discovery of Chlorine Radical Mediated HAT

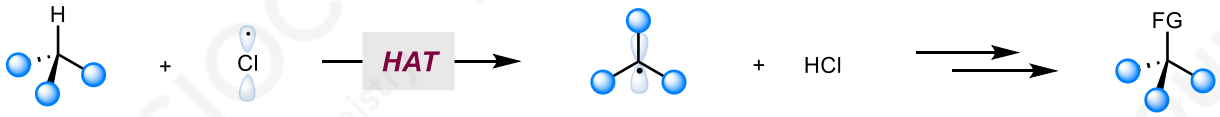
❑ Selectivity and Isotope effects of early reactions

*"It shows a ratio of about **60 percent 2-chloro propane** to **40 percent 1-chloropropane**"*

*"Hydrogen atoms are always substituted at rates that are in the order **primary < secondary < tertiary**"*

"At increasing temperatures, these relative rates approach 1:1:1."

H. B. Hass, 1935



Regents	Selectivity			k_H / k_D
	Primary	Secondary	Tertiary	
Cl_2	1	2.8	3.6	1.4[a]
ClNO[b]	1	3.8	9.2	1.2
SO_2Cl_2[c]	1	-	4.5	-
PCl_5[d]	1	2.2	2.8	-
$ClSO_2NCO$[e]	1	4.3	94	1.7
$CuCl_2$[f]	1	-	3.6	-

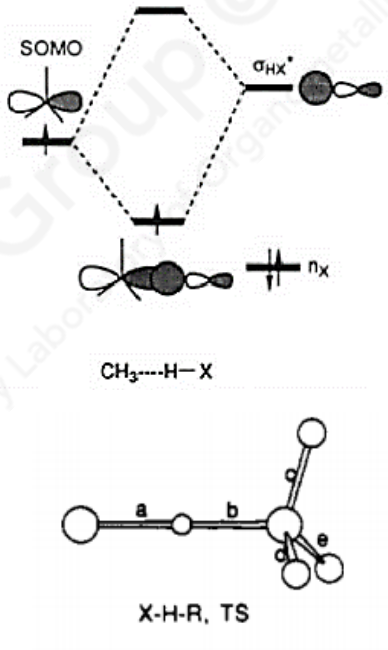
[a] Wiberg. K. *et al. Chem. Rev.* **1955**, *55*, 713. [b] Mosher M. *et al. Can. J. Chem*. **1971**, *49*, 28-34.
[c] Brown H. *et al. J. Am. Chem. Soc.* **1955**, *77*, 4031-4035. [d] Olah. G. *et al.J. Org. Chem.* **1974**, *39*, 3472-3478.
[e] Mosher M. *et al.* . *J. Org. Chem.* **1982**, *47*, 1875-1879. [f] Kochi J. *et al. J. Am. Chem. Soc.* **1962**, *84*, 2121-2127.

Calculation on Chlorine Radical Mediated HAT

- Transition state of chlorine radical mediated HAT

Calculated Transition-state Parameters of HAT by Cl•

Parameter	Me-H	Et-H	^{i}Pr-H	^{t}Bu-H
$r_{C\text{-}H}$	1.397	1.381	1.365	1.348
$r_{H\text{-}Cl}$	1.475	1.489	1.505	1.522
$n_{C\text{-}H}$	0.352	0.374	0.396	0.422
$n_{H\text{-}Cl}$	0.500	0.477	0.452	0.427
$\Delta E^{\neq}$	18.0	12.7	8.0	4.2



Tschuikow-Roux E. *et al. J. Phys. Chem.* **1993**, *97*, 3742–3749.

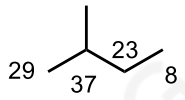
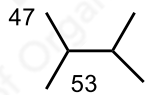
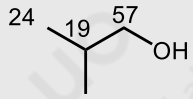
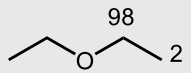
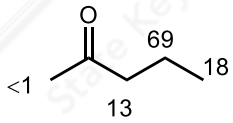
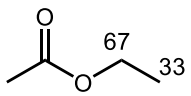
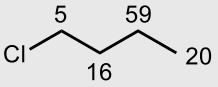
Calculation on Chlorine Radical Mediated HAT

❑ Rate constant of chlorine radical mediated HAT

Rate Constants for HAT by Cl•

Compound	$k_H/10^7 M^{-1}s^{-1}$	$\Delta_r H$
CHF_3	0.03	3.6
CH_4	1.5	1.8
EtCl	28	–2.0
EtOH	144	–2.3
butane	602	–2.1
$COEt_2$	960	–9.7
toluene	1170	–13.3
Me_2O	1960	–6.5

Calculated selectivity by Rate Constants

Selected substrates	
	
	
	
	

Poutsma M. *et al.* *J. Phys. Chem. A* **2013**, *117*, 687-703.

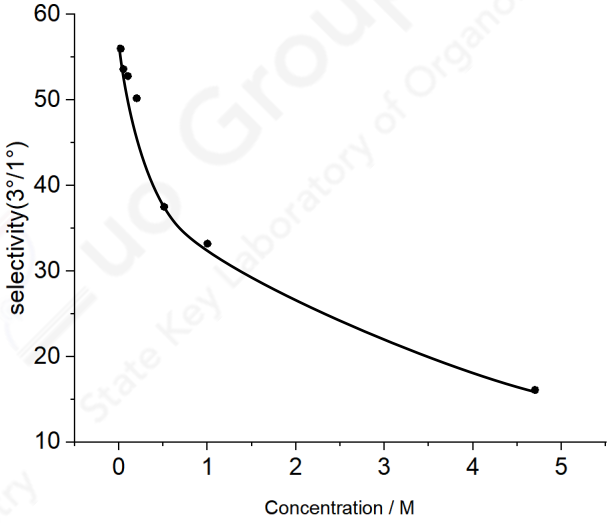
Special Solvent Effects of Chlorine Radical Mediated HAT

❑ Special solvent effects of chlorine radical

Photochlorination of 2,3-dimethylbutane in solvents at 55℃

Solvent	selectivity (3°/1°)
neat	3.7
CCl_4	3.5
$PhNO_2$	4.7
PhCl	6.4
benzene	**14**
^{t}Butylbenzene	**24**
1-Chloronahthalene	**37**

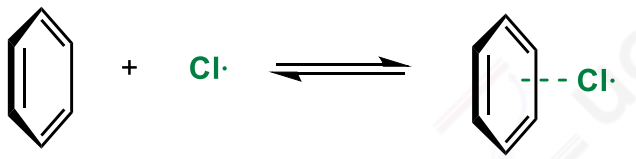
Photochlorination of 2,3-dimethylbutane in benzene at 20℃



Russell G. *et al. J. Am. Chem. Soc.* **1957**, *79*, 2977.
Skell. P. *et al. J. Am. Chem. Soc.* **1983**, *105*, 120-121.

Special Solvent Effects of Chlorine Radical Mediated HAT

- Generation of chlorine-benzene complex



Russell predicted this complex in 1957, and finally Ingold confirmed this complex by UV-spectrum in 1990s.

Ingold K. *et al. Acc. Chem. Res.* **1990**, 23, 219-225.

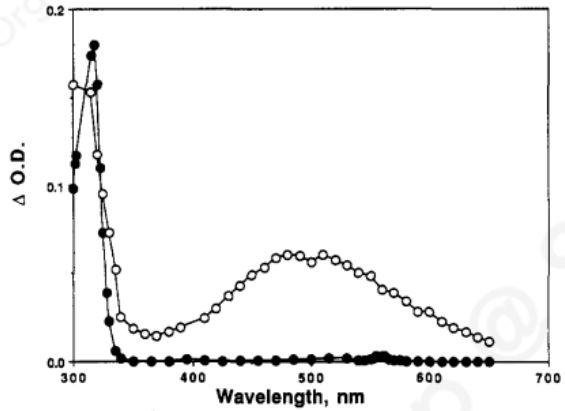


Figure 1. Transient spectra obtained by 308-nm excitation of solutions of di-*tert*-butyl peroxide (0.27 M) in HCl-saturated benzene (○) and 0.27 M di-*tert*-butyl peroxide in benzene containing 1.0 M 1,4-cyclohexadiene (●).

Selectivity of chlorine radical in chlorinated and brominated solvents

Solvent	selectivity (2°/1°)	selectivity (3°/1°)
CCl_4	1.81	3.0
$CHCl_3$	1.94	3.3
CH_2Cl_2	2.13	3.6
^{n}PrCl	3.32	6.8
EtCl	3.56	7.8
^{t}BuCl	3.91	8.9
EtBr	**8.81**	**38.0**

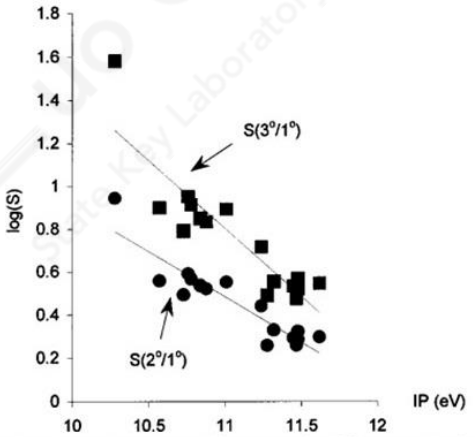
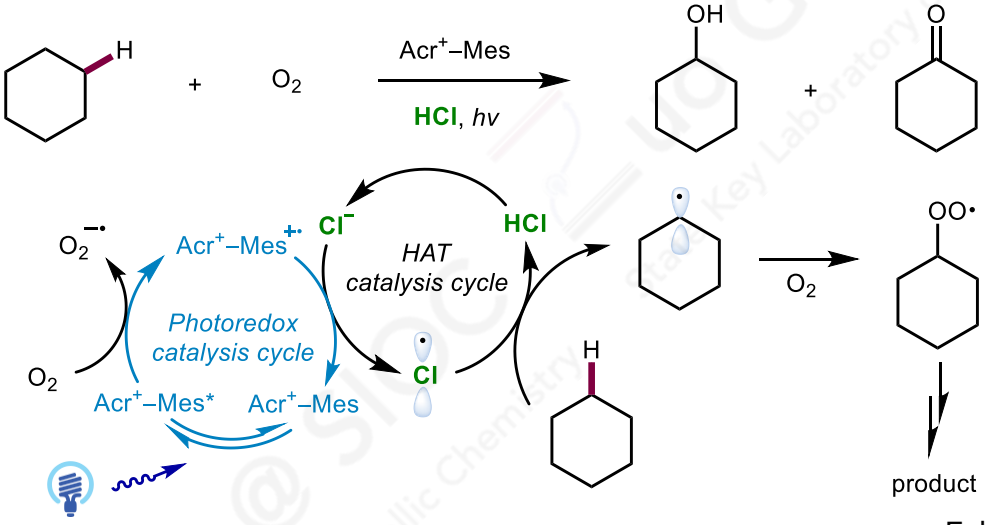


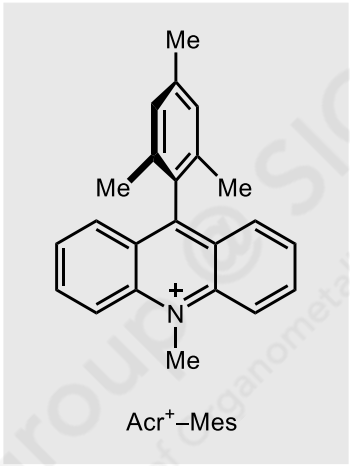
Figure 1. Variations in selectivity for chlorination of alkanes in haloalkane solvents as a function of the ionization potential of the solvent.

Tanko J. *et al. J. Org. Chem.* **1998**, *63*, 8860-8864.

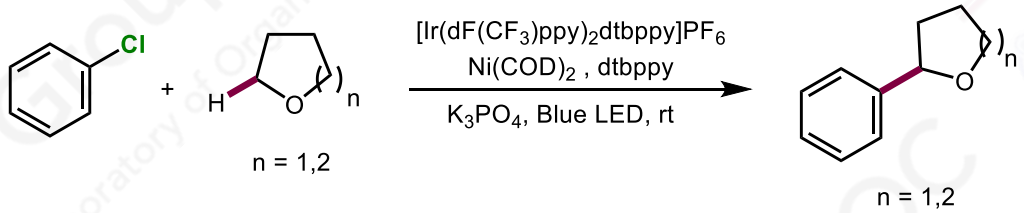
Catalysis Generation of Chlorine Radical

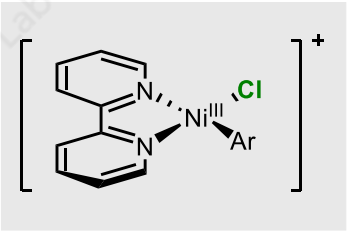
- Early catalysis generation of chlorine radical

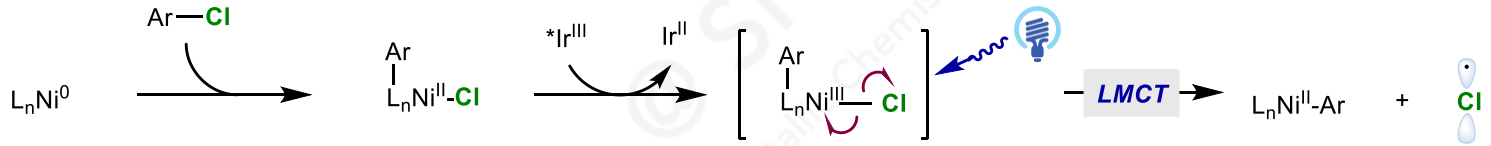




Fukuzumi S. *et al. Chem. Commun.* **2011**, *47*, 8515.



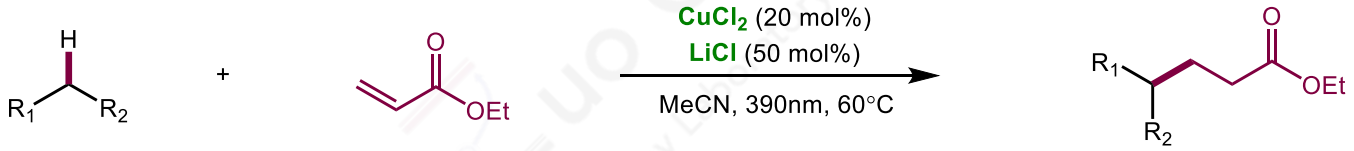


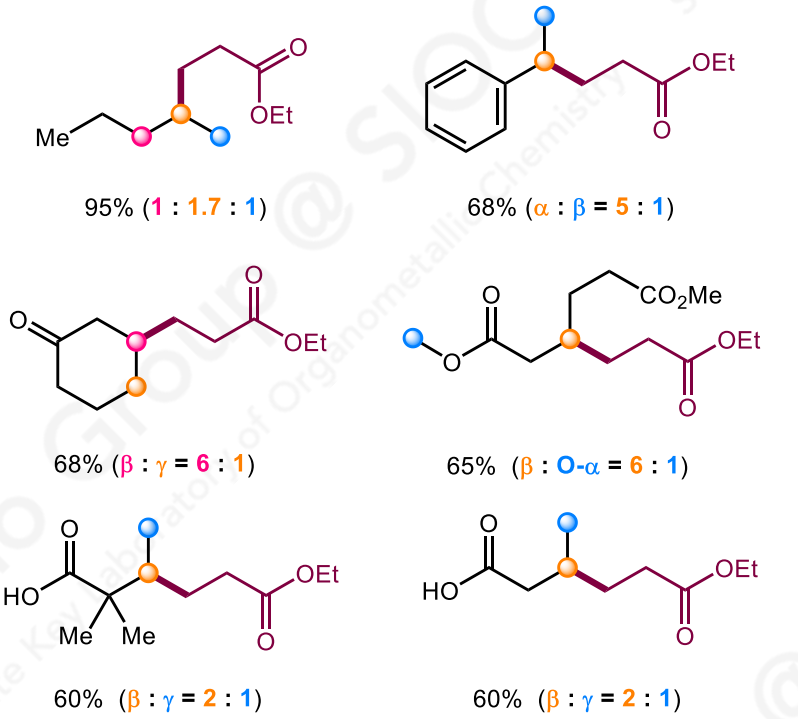


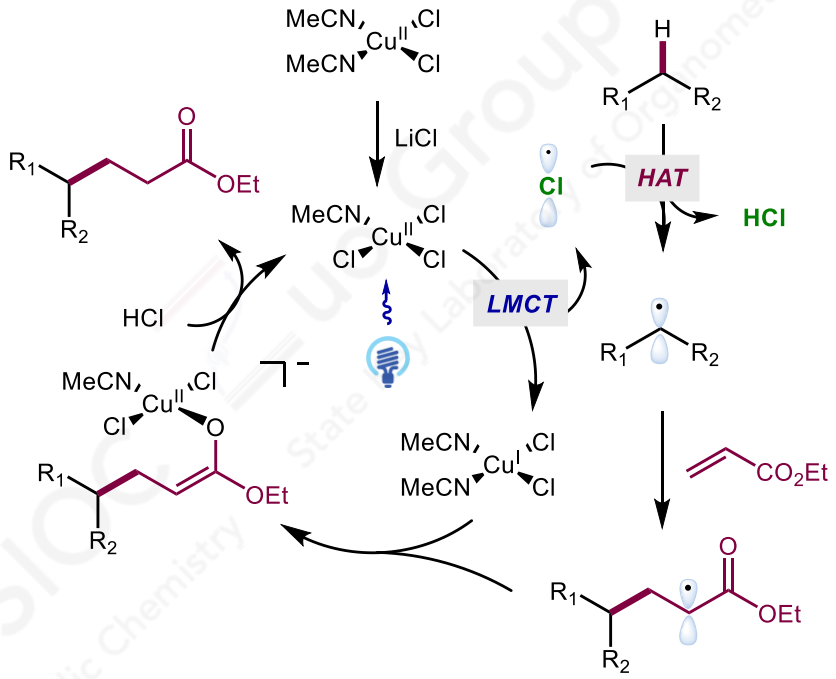
Doyle A. *et al. J. Am. Chem. Soc.* **2016**, *138*, 12719-12722.

Reactivity and Selectivity of HAT by Chlorine Radical

- Selected example of C(sp^3)-H functionalization mediated by chlorine radical



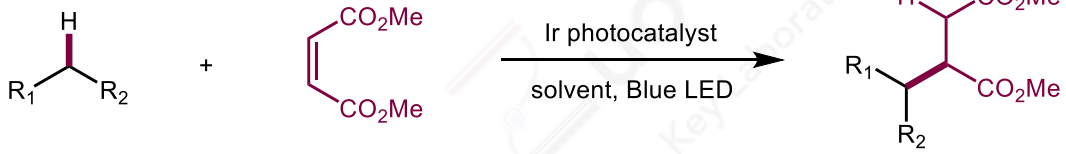


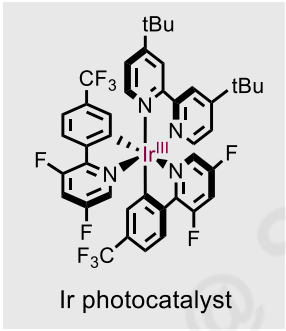


Rovis T. *et al. J. Am. Chem. Soc.* **2021**, *143*, 2729-2735.

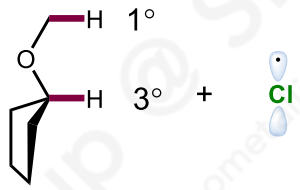
Reactivity and Selectivity of HAT by Chlorine Radical

❑ Improved selectivity by radical-solvent complex

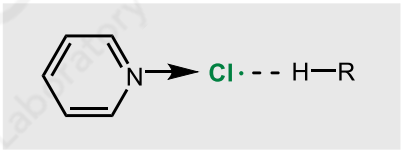




Ir photocatalyst



Site selectivity



Possible radical complex

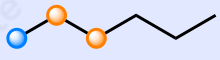
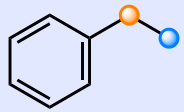
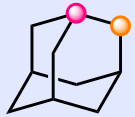
Improved selectivity by solvent and concentration

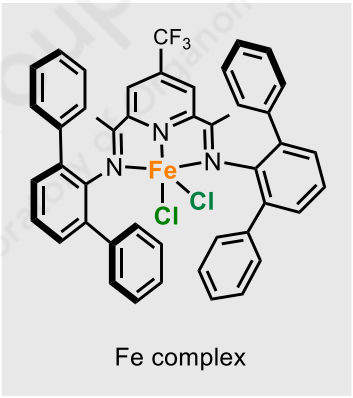
Solvent	[M]	yield	3°/1°
benzene	0.5	66	3.6
benzene	0.05	64	4.4
toluene	0.5	70	3.9
PhCOMe	0.5	64	4.0
$PhCF_3$	0.5	57	4.1
pyridine	**0.5**	**72**	**9.1**
pyridine	**0.05**	**64**	**10.0**

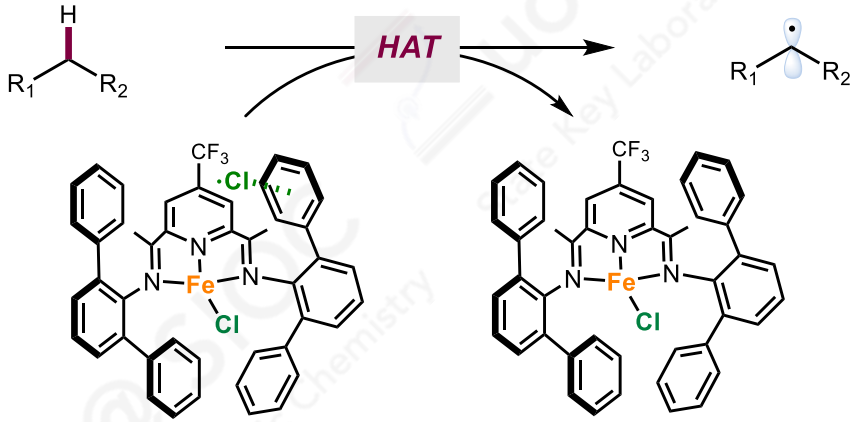
Barriault L. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 15664-15669.

Reactivity and Selectivity of HAT by Chlorine Radical

- Improved selectivity by steric effect

Regents				
Fe complex	1 : 31	1.5 : 1	1 : 10	3 : 1
$FeCl_3$	2.8 : 1	2.7 : 1	4.3 : 1	1.6 : 1

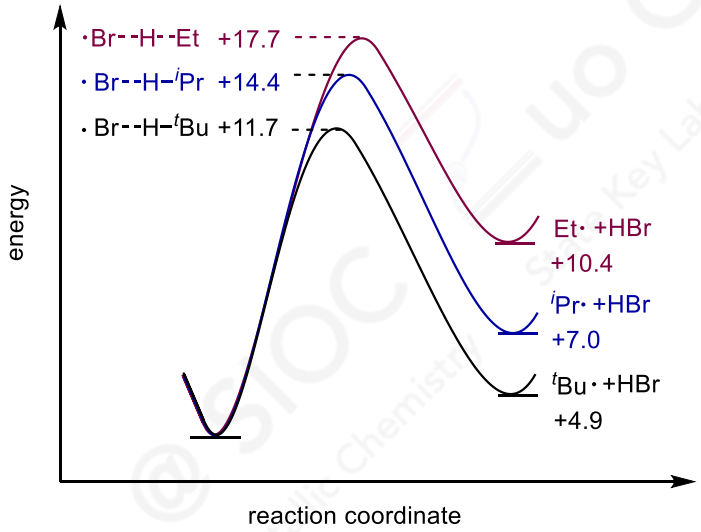


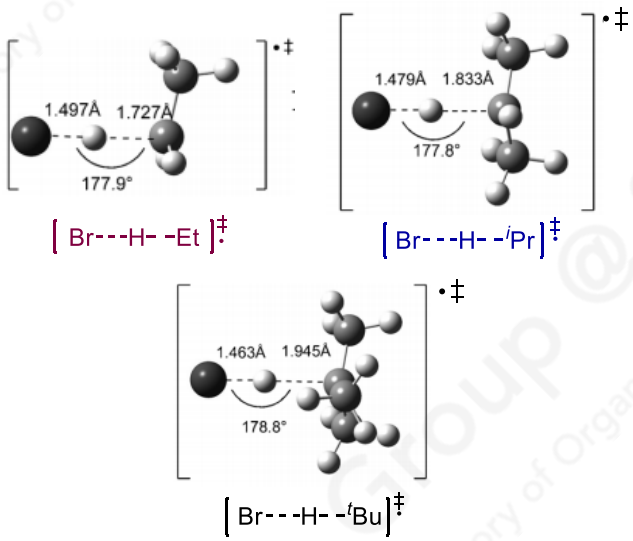


Nocera D. *et al. J. Am. Chem. Soc.* **2022**, *144*, 1464-1472.

Reactivity and Selectivity of HAT by Bromine Radical

- Rate constant and transition state of HAT by bromine radical





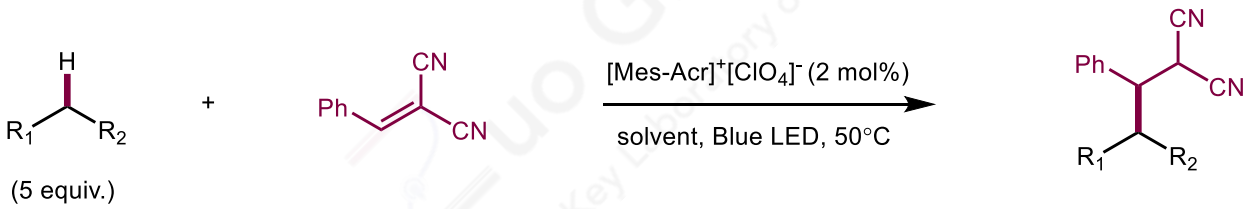
Rate constants for hydrogen abstraction by Br•

Compound	k_H/M^{-1}s^{-1}	$\Delta_r H$	Compound	k_H/M^{-1}s^{-1}	$\Delta_r H$
$COMe_2$	5.5×10^{-7}	19.1	EtOH	4.4×10^{3}	8.5
CH_4	8.3×10^{-3}	17.3	Me_2O	1.6×10^{5}	9.5
EtCl	2.04	12.1	toluene	3.4×10^{6}	2.2
CHF_3	4.57	8.9	$CH_3CH{=}CH_2$	2.5×10^{6}	0.55

Ryu I. *et al. Chem. Eur. J.* **2014**, *20*, 12750.

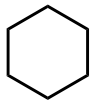
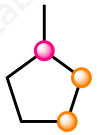
Reactivity and Selectivity of HAT by Bromine Radical

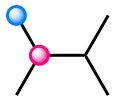
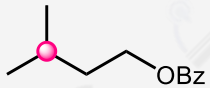
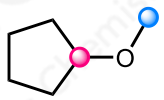
❑ Comparison on reactivity and selectivity of HAT by chlorine and bromine radical



Comdition **Cl**: **HCl** (5 mol%), CH_3CN/DCE (7:1, 0.1M)

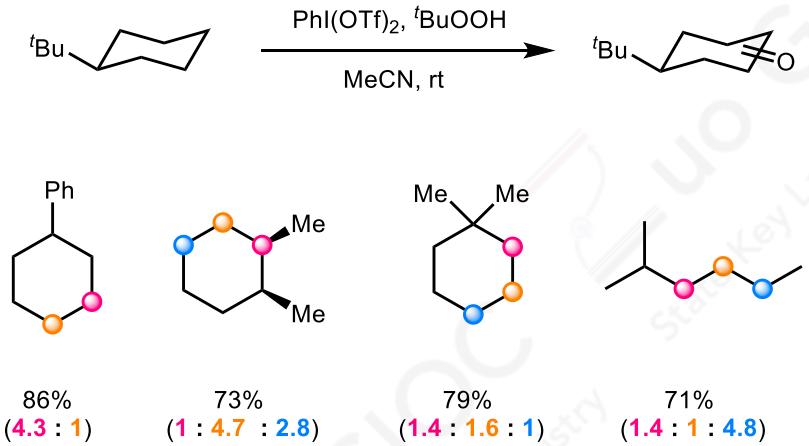
Condition **Br**: **CH_2Br_2** (0.2M)

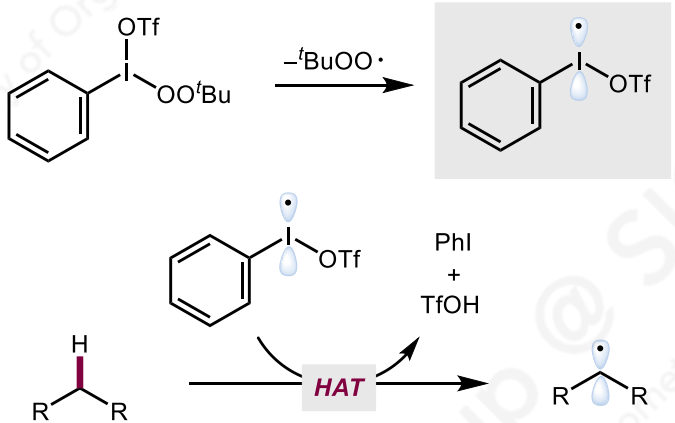
Substrates	condition	yield	selectivity
 (2 equiv.)	**Cl**	98	-
(10 equiv.)	**Br**	35	-
	**Cl**	85	**1.5 : 3 : 1**
	Br	59	**1 : 2 : 0**
	**Cl**	43	**4 : 3**
	Br	80	**36 : 1**

Substrates	condition	yield	selectivity
	**Cl**	43	**6 : 1**
	Br	63	**> 60 : 1**
	**Cl**	8	-
	Br	64	**> 20 : 1**
	**Cl**	60	**3 : 1**
	Br	89	**9 : 1**

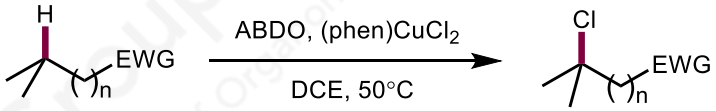
Wu J. *et al. Chem*, **2020**, *6*, 1766.

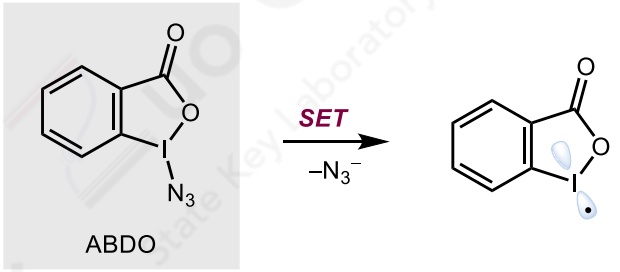
Reactivity of Hypervalent Iodine Radical

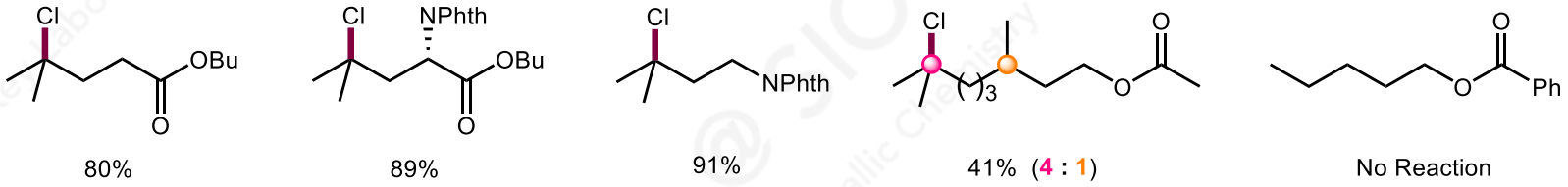




K. Maruoka *et al. Angew. Chem., Int. Ed.* **2013**, 52, 8657.



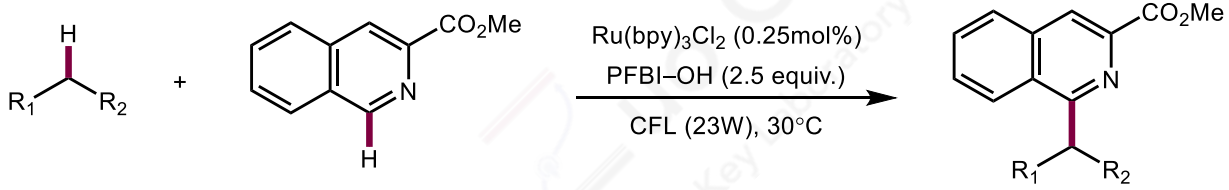


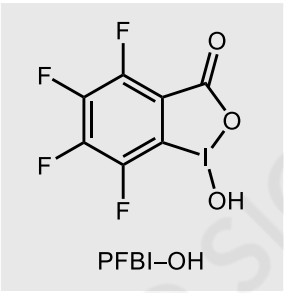


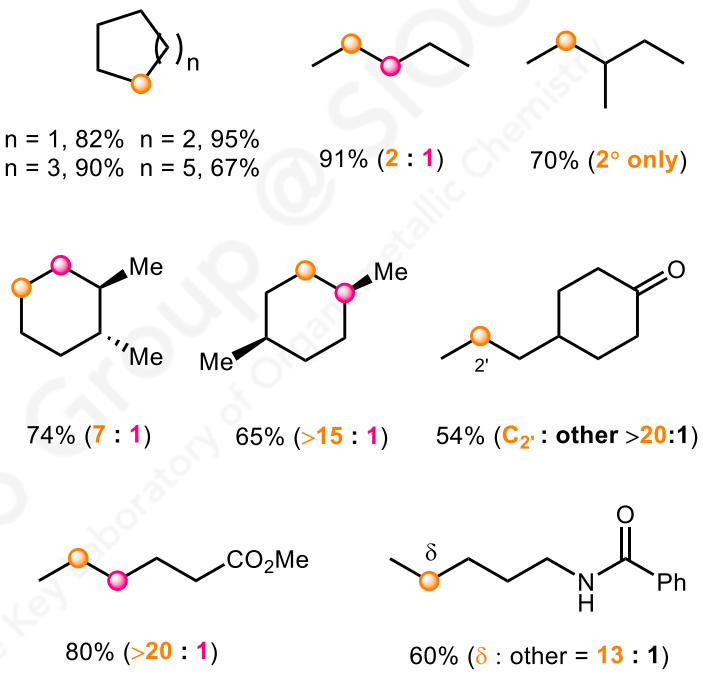
Hartwig J. *et al. Angew. Chem., Int. Ed.* **2021**, *60*, 8276–8283.

Reactivity of Hypervalent Iodine Radical

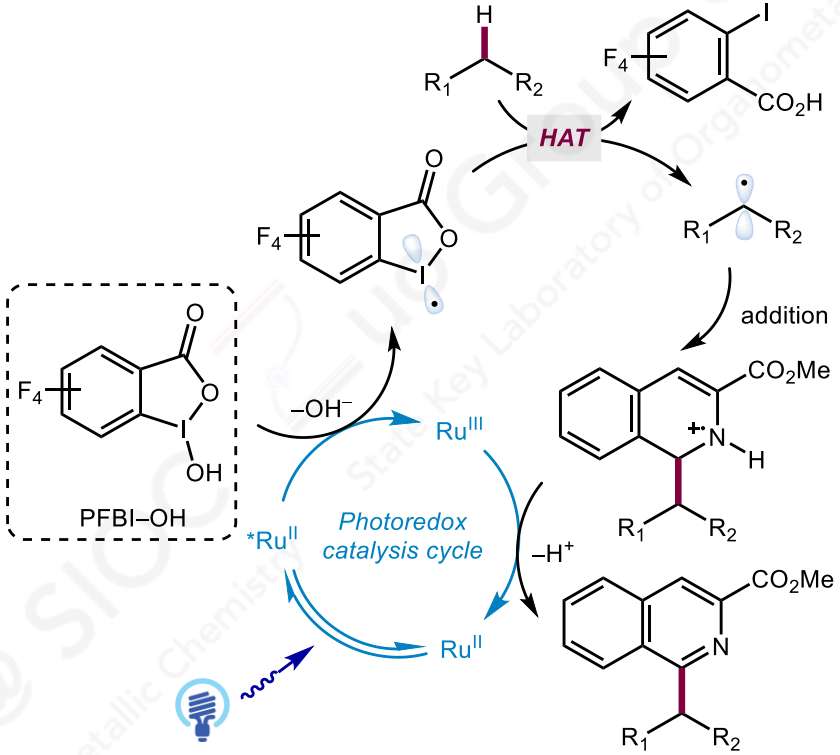
❑ Catalysis reaction of hypervalent Iodine radical



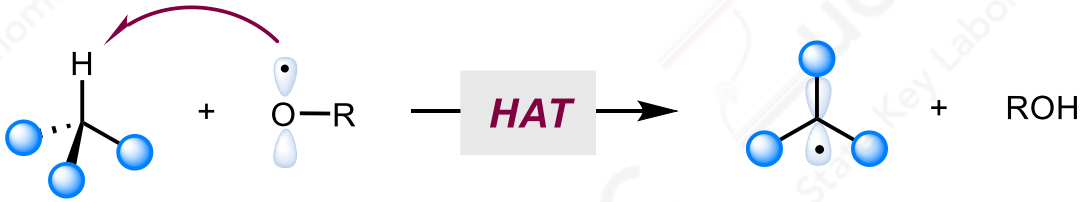




Chen G. *et al. ACS Catal.* **2018**, *8*, 11847-11853.

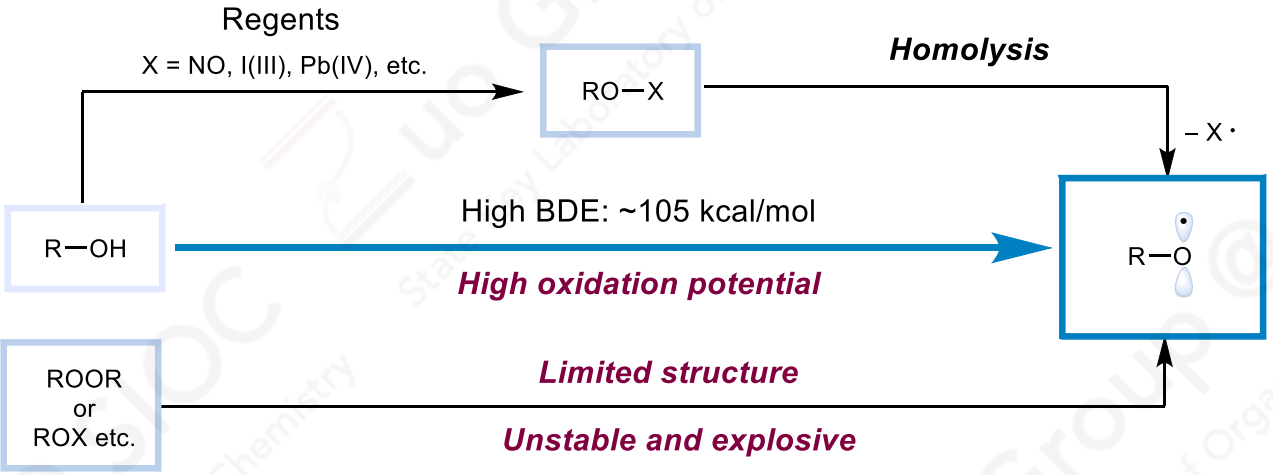


3.2 Oxygen centered radical



Generation of Alkoxyl Radical

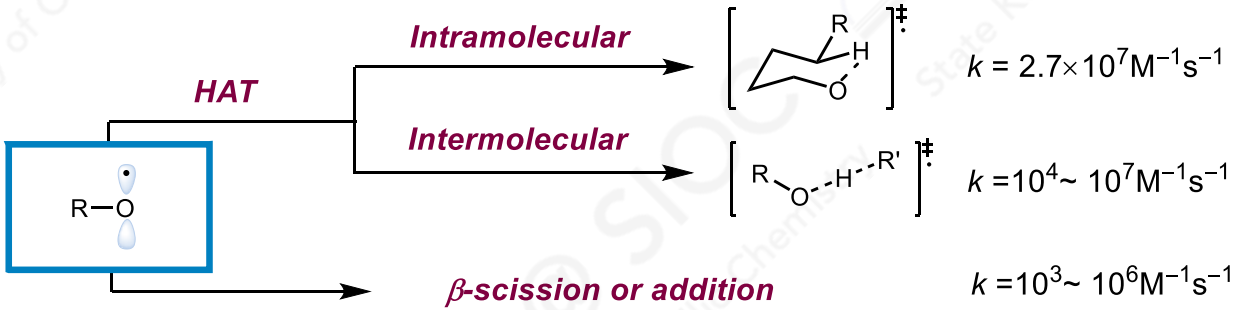
- Generation of alkoxyl radical from alcohol



Stucture of RO· is limited as intermolecular HAT regent

Direct and economy ways to generate RO· from alcohol is necessary!

- Reactions of alkoxyl radicals



HAT process is normally a fast process and intramolecular HAT is more favored

Rate Constant and Transition State of HAT by Alkoxyl Radical

- Rate constant and transition state of HAT by alkoxyl radical

Calculated rate constants for hydrogen abstraction by $^{t}BuO^{\bullet}$

Compound	$k_H/M^{-1}s^{-1}$	E_a /kcal mol^{-1}	C–H BDE /kcal mol^{-1}
t-butylbenzene	4.0×10^5	6.14	101
MeOH	5.2×10^5	5.30	98
^{t}BuOMe	9.8×10^5	5.2	96
cyclohexane	8.1×10^6	4.42	98.7
toluene	1.9×10^6	3.46	90
1,3-dioxolane	7.9×10^7	3.00	93
THF	7.4×10^7	2.5	94
diphenylmethane	3.4×10^7	2.42	84
triphenylmethane	2.0×10^7	1.86	81

Tanko J. *et al.* J. Am. Chem. Soc. 2004, 126, 7578-7584.

Selectivity of Alkoxyl Radical

❑ Selectivity of alkoxyl radical

Averaged selectivity of hydrogen abstraction by $^{t}BuO^{\bullet}$

Compound	Selectivity		
	Primary	Secondary	Tertiary
Paraffinic	1.0	12.2	44
Benzylic	10	32	69
Allylic	20	61	176

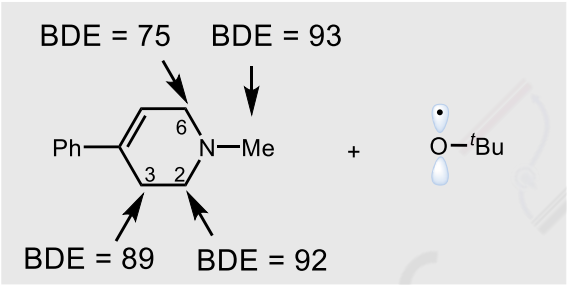
Solvent effect on selectivity of hydrogen abstraction by $^{t}BuO^{\bullet}$

Solvent	k_{tert}/k_{pri}		$\Delta E_{pri} - \Delta E_{tert}$
	70°C	0°C	
benzene	55(40°C)	89	1.99
$PhOCH_3$	45	106	2.25
PhCl	35	94	3.85
acetone	30	128	3.77
CH_3CN	17	47(25°C)	4.57

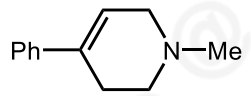
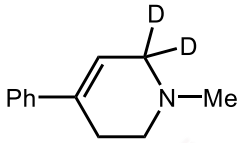
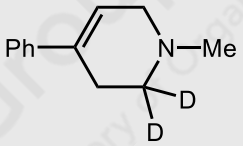
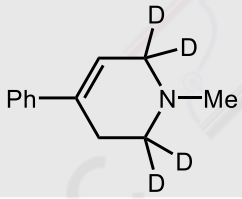
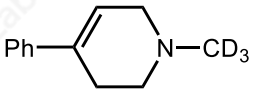
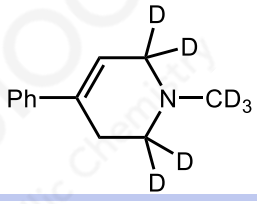
Walling C.*et al.* J. Am. Chem. Soc. 1961, 83, 3877-3884.

Selectivity of Alkoxyl Radical

❑ Selectivity of alkoxyl radical



Position	selectivity	k_H/k_D
N-Me	< 6	4.7
2-H	21	4.5
3-H	< 10	–
6-H	73	1.84

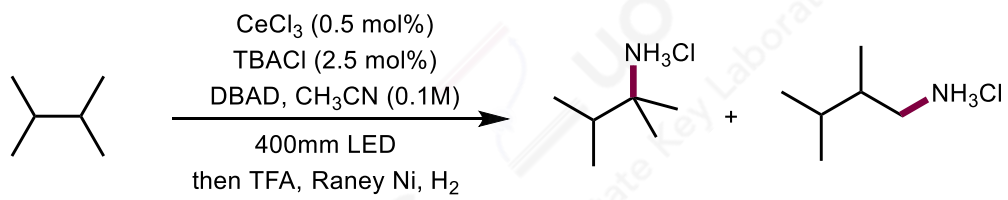
Coupound	k_H/ $10^8M^{-1}s^{-1}$	k_H/k_D	Coupound	k_H/ $10^8M^{-1}s^{-1}$	k_H/k_D
	2.27	–		1.60	1.41
	2.02	1.13		1.21	1.30[a]
	2.30	0.98		1.07	1.13[b]

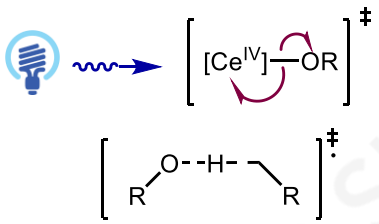
[a] 6,6-2d-MPTP *vs* 2,2,6,6-4d-MPTP. *b* 2,2,6,6-4d-MPTP *vs* 7d-MPTP

Suleman N. *et al. Bioorg. Med. Chem.* **2008**, *16*, 8557-8562.

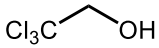
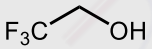
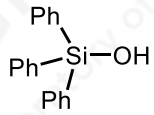
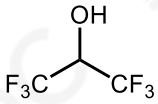
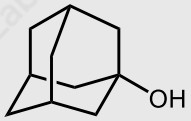
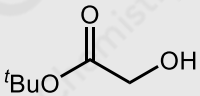
Selectivity of Alkoxyl Radical

❑ Selectivity of alkoxyl radical





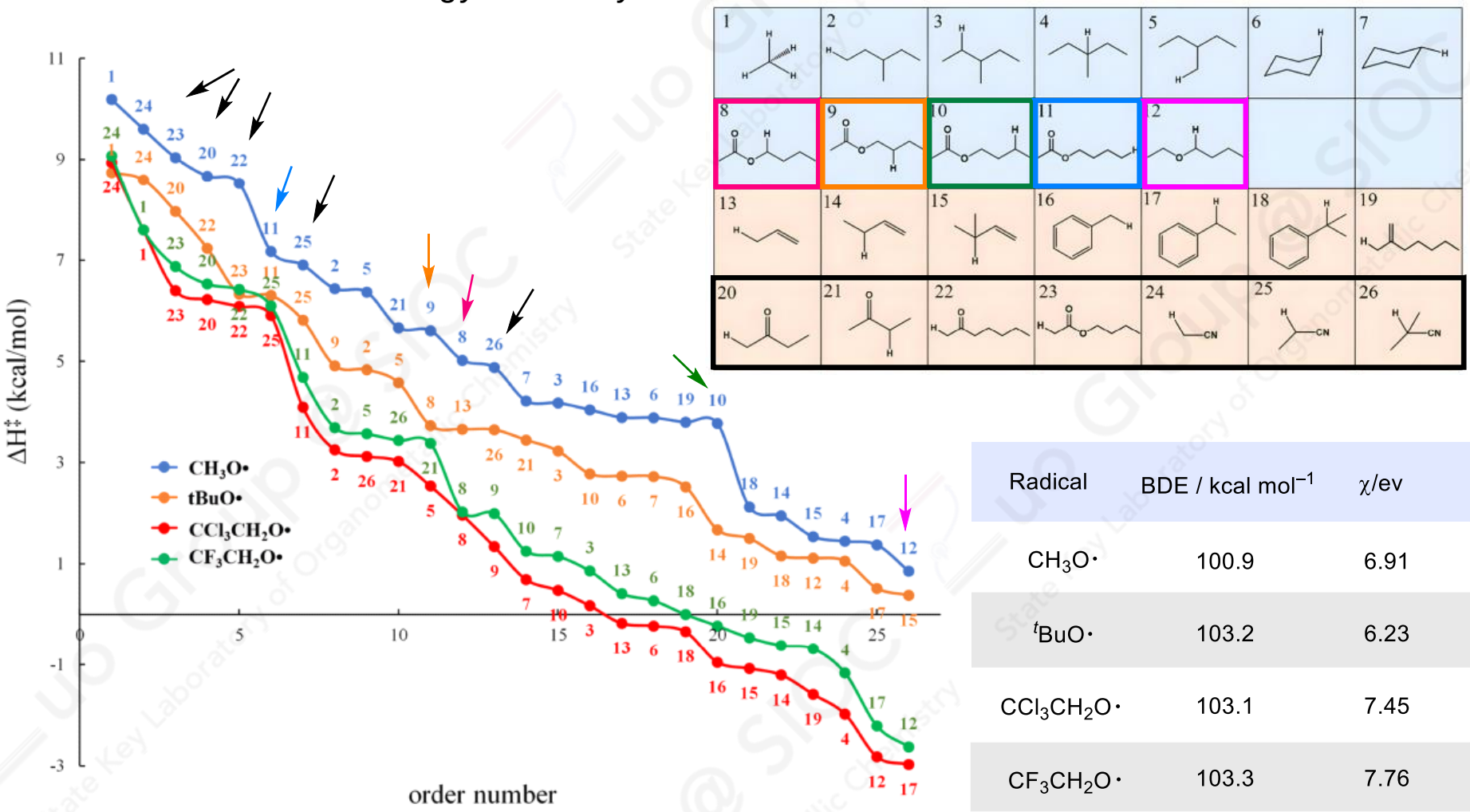
Mild generation
Diverse structures

Alcohol (50 mol%)	O–H BDE	3° : 1° selectivity	Alcohol (50 mol%)	O–H BDE	3° : 1° selectivity
MeOH	105.2	97 : 3		~106.8	44 : 56
EtOH	105.4	92 : 8		107.0	49 : 51
	>110	53 : 47		-	46 : 54
	-	70 : 30		-	46 : 54

Zuo Z. *et al. J. Am. Chem. Soc.* **2020**, *142*, 6216−6226.

Selectivity of Alkoxyl Radical

- Transition state energy of alkoxyl radical mediated HAT

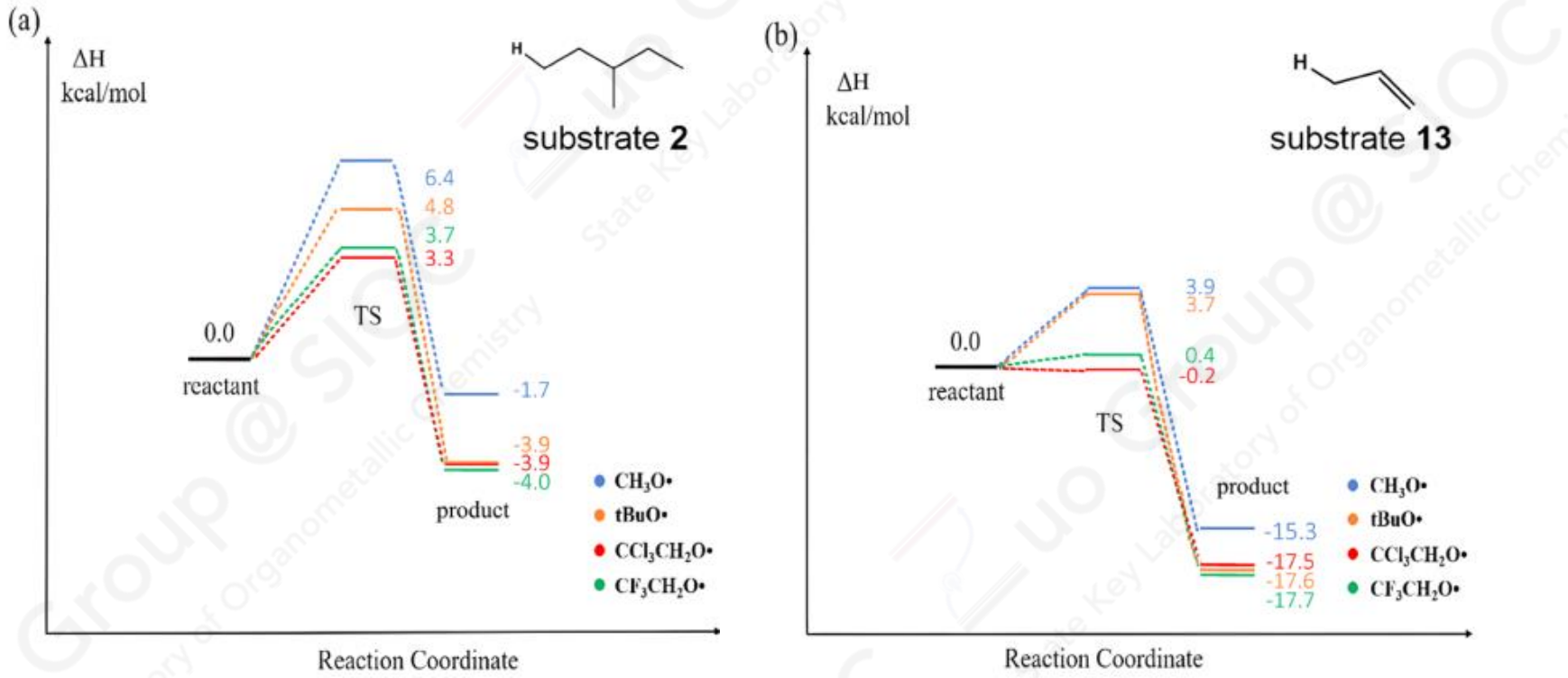


Radical	BDE / kcal mol^{-1}	χ/ev
$CH_3O\cdot$	100.9	6.91
$^{t}BuO\cdot$	103.2	6.23
$CCl_3CH_2O\cdot$	103.1	7.45
$CF_3CH_2O\cdot$	103.3	7.76

Houk K. *et al. J. Am. Chem. Soc.* **2022**, *144*, 6802−6812.

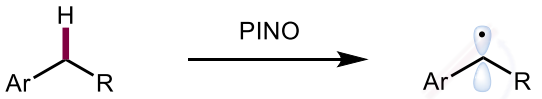
Selectivity of Alkoxyl Radical

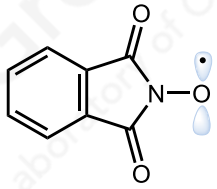
- Transition state energy of alkoxyl radical mediated HAT



- C-H BDE and O-H BDE influence the **Δ**H of the HAT step
- **Larger −Δ**H lead to lower TS energy (Evans-Polanyi Principle discussed above)
- TS energy can be further influenced by polar effects (CCl/F_3CH_2O• on right side)

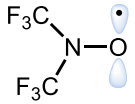
Reactivity and selectivity of N-Hydroxy radical





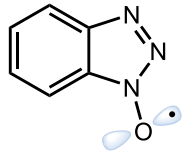
PINO

88.1 kcal mol^{-1}



$(CF_3)_2NO^{\bullet}$

84 kcal mol^{-1}



BTNO

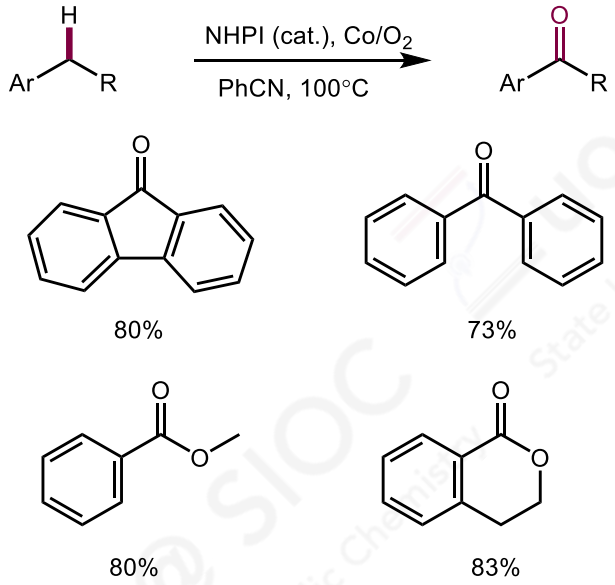
~88 kcal mol^{-1}

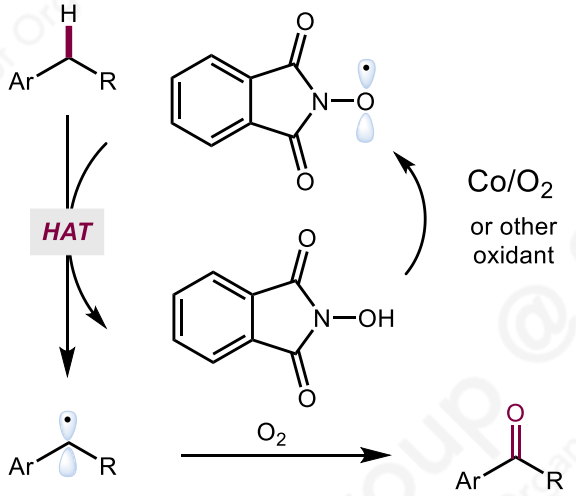
Rate constants for hydrogen abstraction by hydroxylamide radicals at 25 ℃

R–H	BDE / kcal mol^{-1}	$k_{H,}$ PINO / $M^{-1}s^{-1}$	$k_{H,}$ $(CF_3)_2NO^{\bullet}$ / $M^{-1}s^{-1}$	$k_{H,}$ BTNO / $M^{-1}s^{-1}$
p-OMe-C_6H_4-CH_2OH	79	45	-	6.2
Ph_2CHOH	79	58	-	3.2
$PhCH_2OH$	80	12	-	1.9
fluorene	82	40	-	3.8
Ph_2CH_2	84	13	0.48	0.72
PhEt	85	5.4	0.3	0.7
toluene	89	0.62	8.8×10^{-3}	0.27
THF	92	-	0.35	-

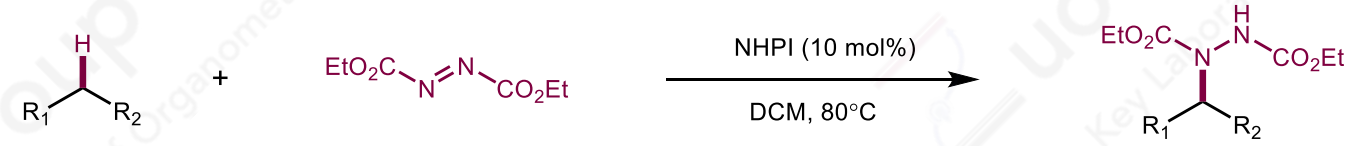
Galli C.*et al*. *Angew. Chem. Int. Ed.* **2008**, *47*, 4790 – 4796.

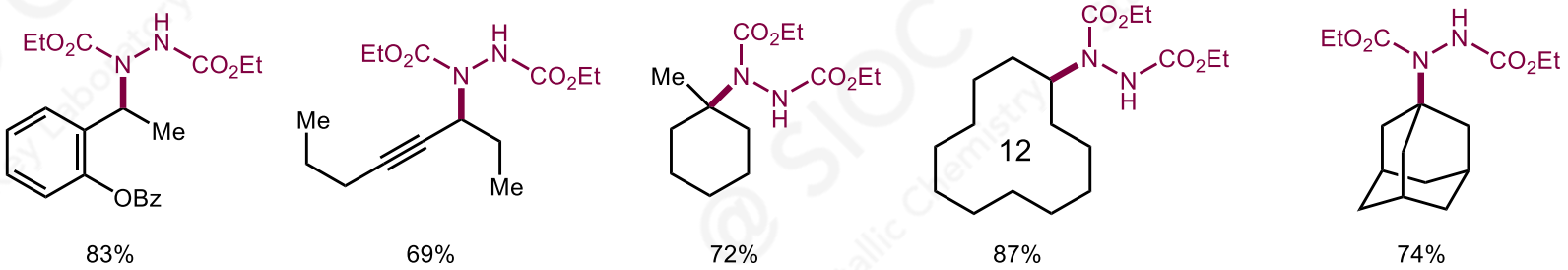
Reactivity and selectivity of N-Hydroxy radical





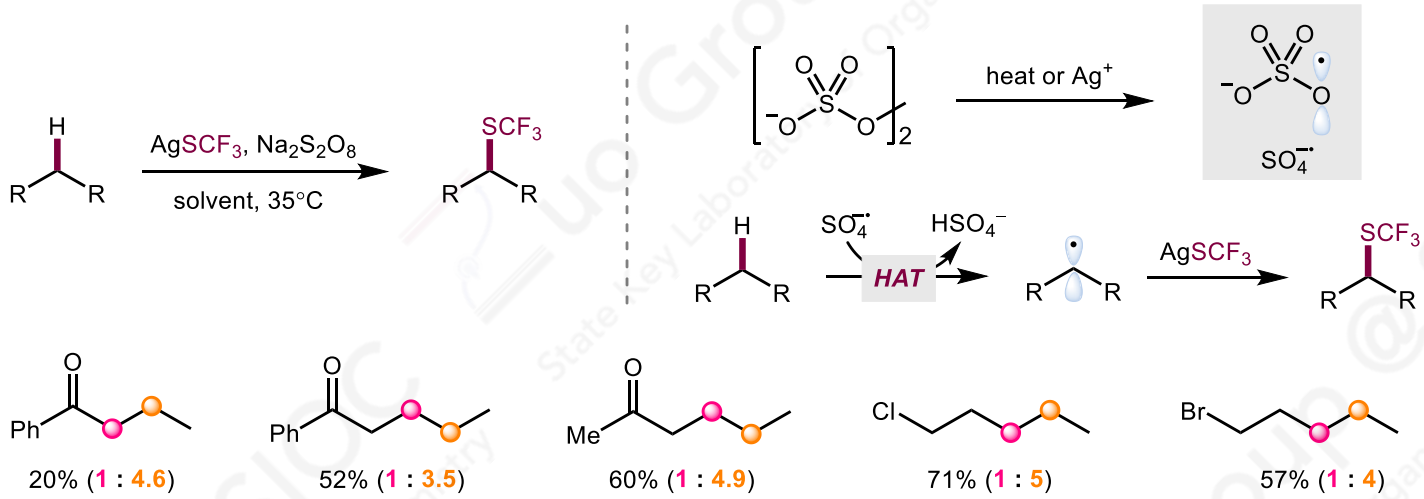
Ishii Y. *et al. J. Org. Chem.* **1995**, *60*, 3934-3935.



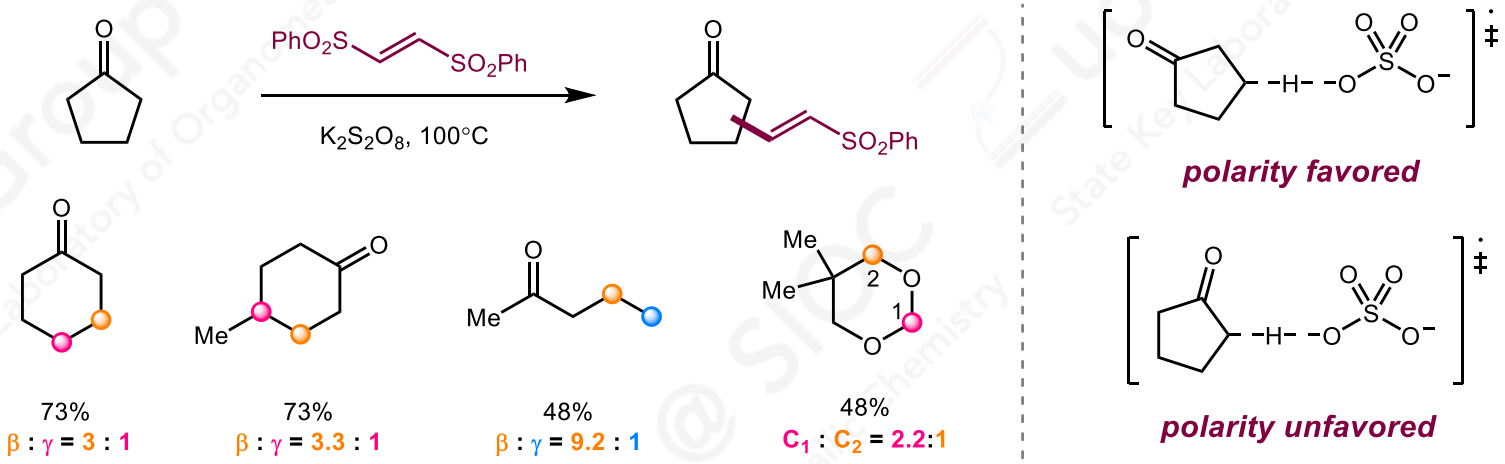


Inoue M. *et al. J. Org. Chem.* **2012**, *77*, 9959−9969.

Reactivity and selectivity of sulfate radical

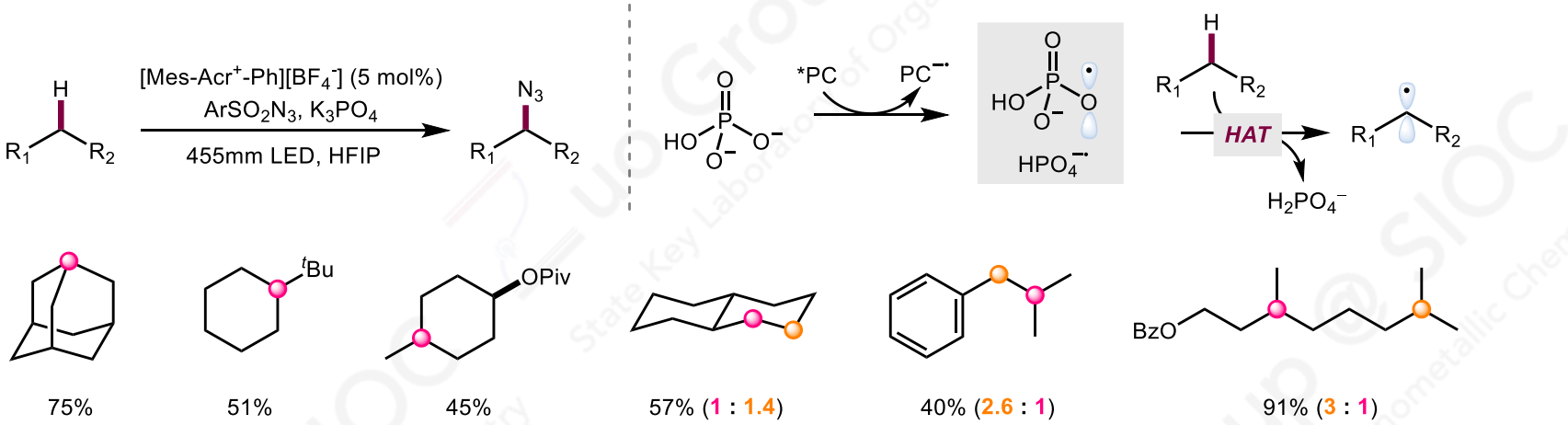


Tang P. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 4065 –4069.

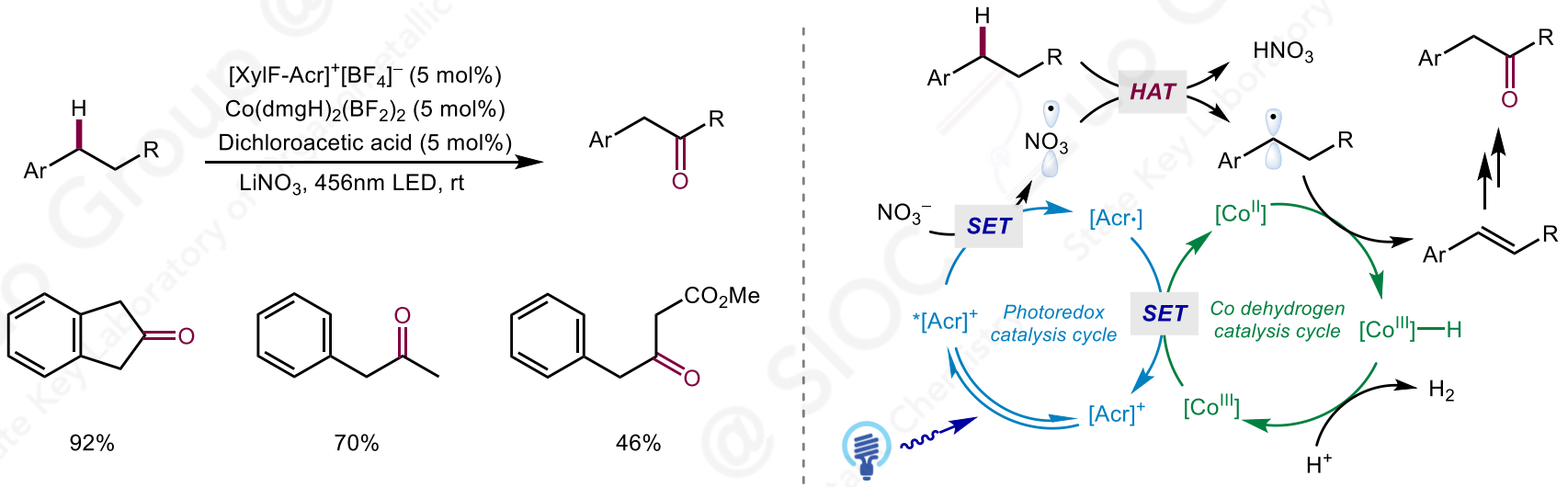


Ryu I. *et al. Angew. Chem. Int. Ed.* **2021**, *60*, 3545 –3550.

Other Types of oxygen-centered radical

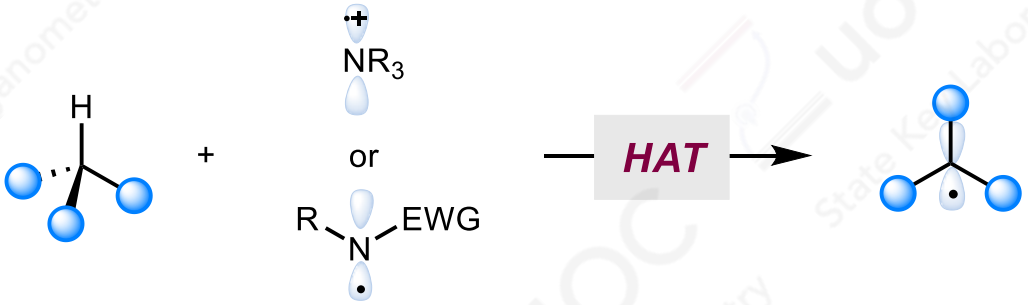


Alexanian E. *et al. J. Am. Chem. Soc.* **2018**, *140*, 4213–4217.

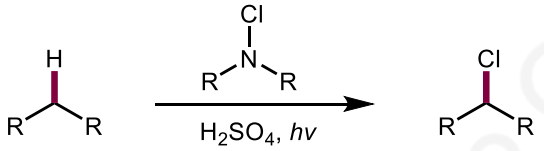


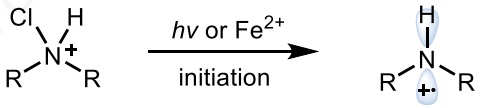
Nicewicz D. *et al. J. Am. Chem. Soc.* **2020**, *142*, 10325–10330.

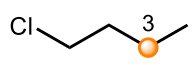
3.3 Nitrogen centered radical



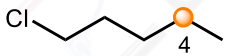
Selectivity of Amine Radical Cation



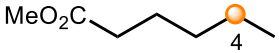




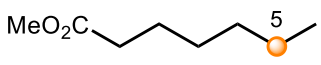
C_3 : other = 6.8 : 1



C_4 : other = 3.4 : 1

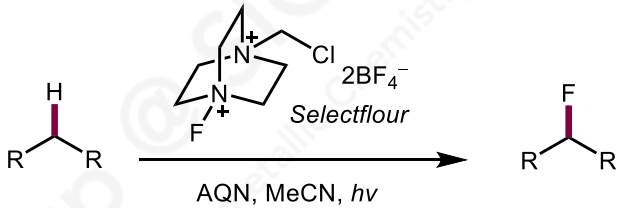


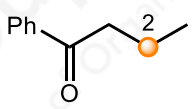
C_4 : other = 3.5 : 1



C_5 : other = 2.5 : 1

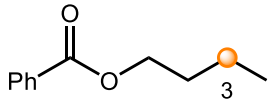
Tedder. J. *et al. Synthesis.* **1973**, 1-24.





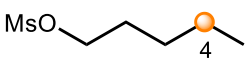
68%

C_2 : other = >20 : 1



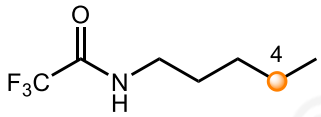
39%

C_3 : other = 2.3 : 1



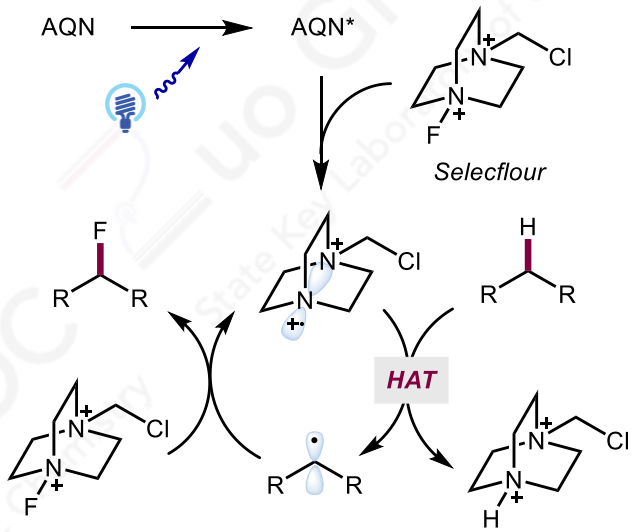
60%

C_4 : other = 5 : 1



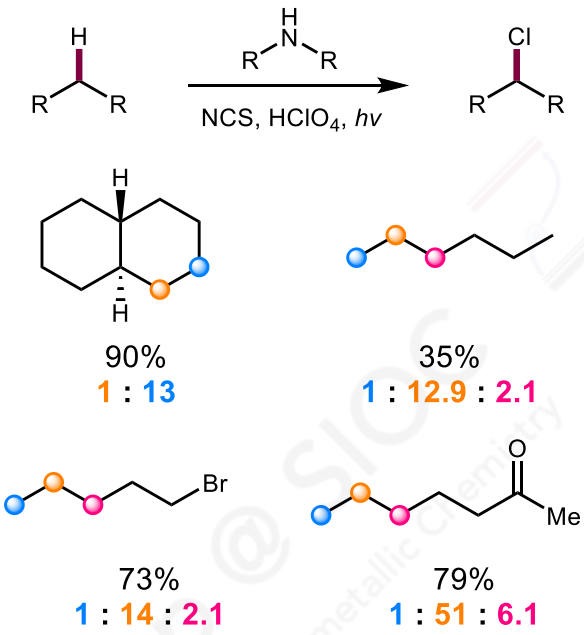
40%

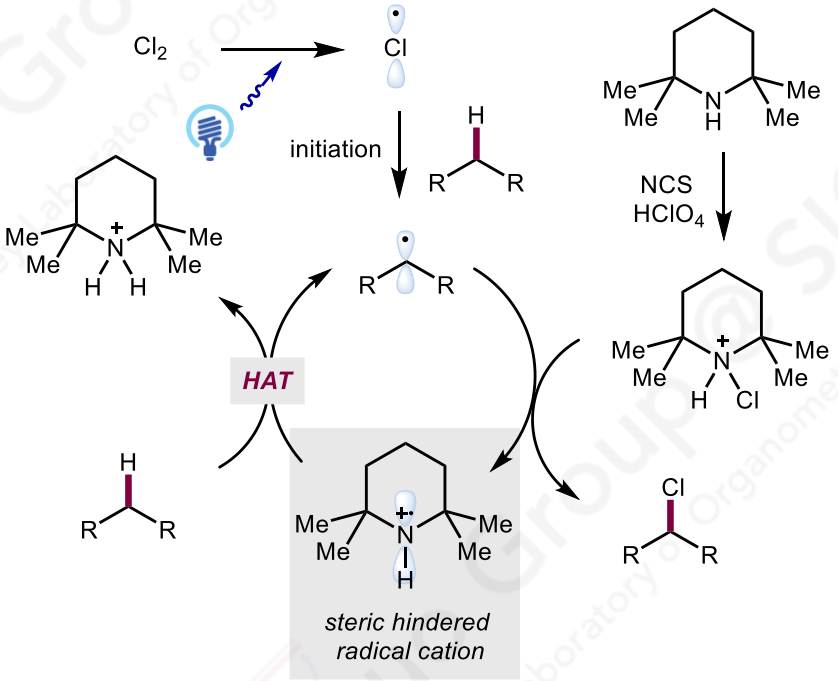
C_4 : other = 3.2 : 1

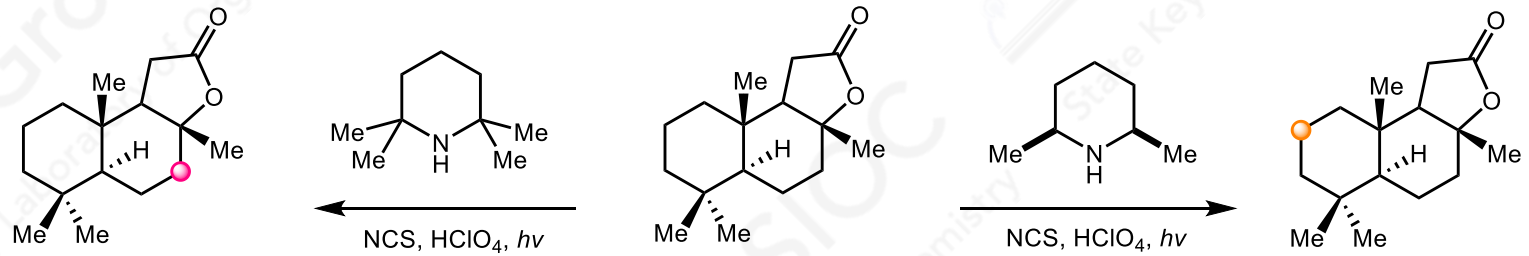


Tan C. *et al. Chem. Commun.* **2014**, *50*, 8211-8214.

Improved Selectivity of Amine Radical Cation

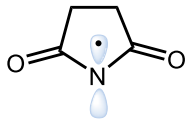
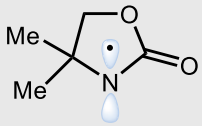
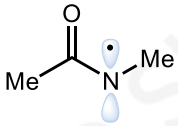




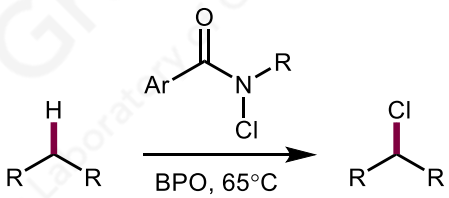


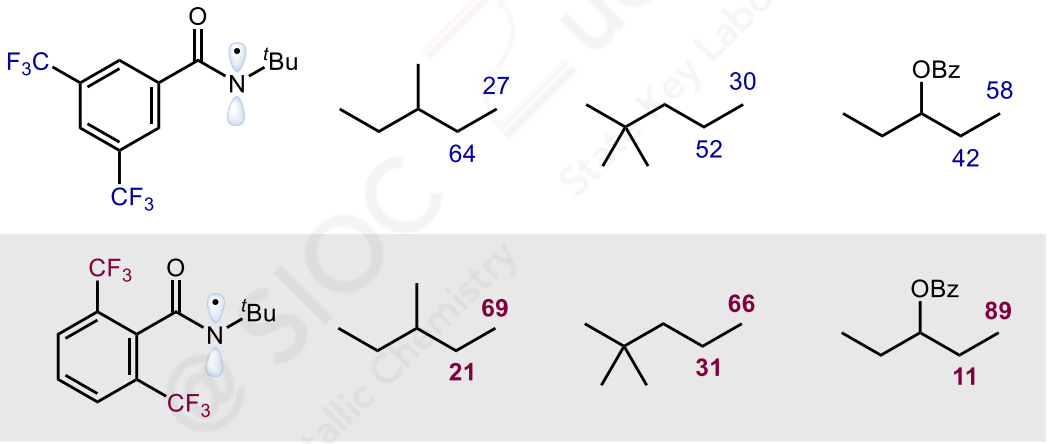
Leonori D. *et al. Angew. Chem. Int. Ed.* **2021**, *60*, 7132-7139.

Selectivity of Amide Radical

Radical	BDE / kcal mol^{-1}	Temp./°C	1°C–H	2°C–H	3°C–H
	92.5	80	1	4	11
	~106	80	1	8	70
	103.9	25	1	–	95

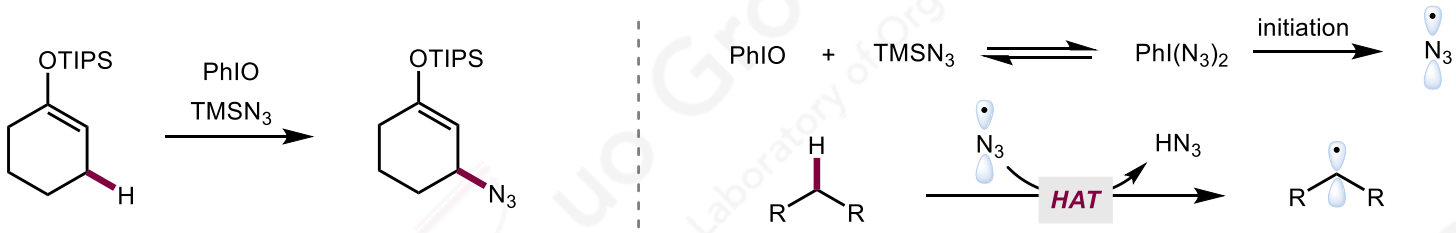
Migita T. *et al. Bull. Chem. Soc. Jpn.* **1981**, *54*, 822-827.



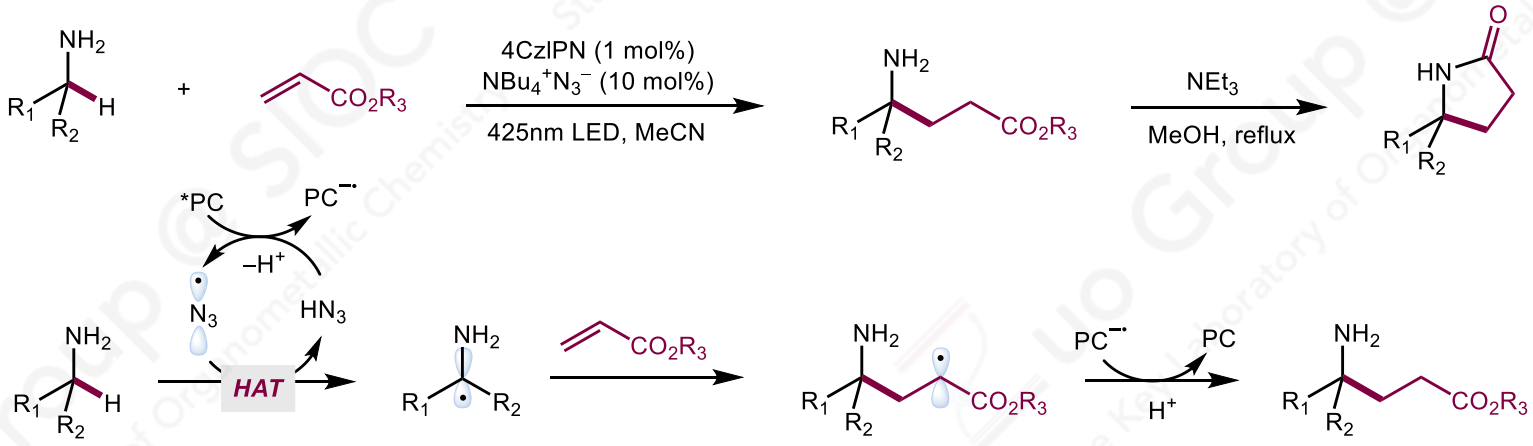


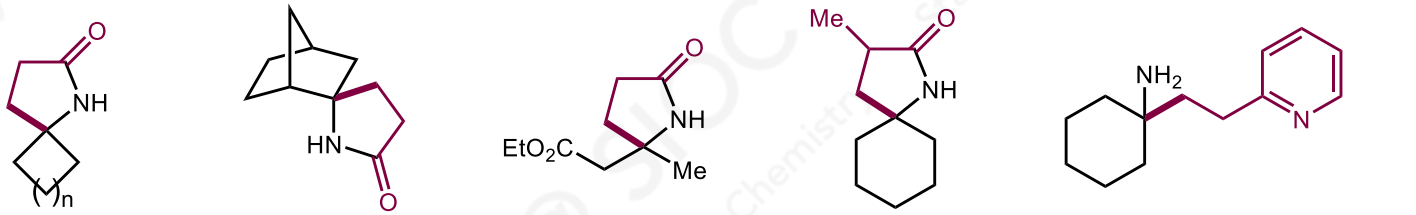
Alexanian E. *et al. Chem. Sci.* **2018**, *9*, 5360-5365.

Selectivity of Azide Radical



P. Magnus *et al. J. Am. Chem. Soc.* **1992**, 114 , 767-769.





n = 1, 49%; n = 2, 65%
n = 3, 68%; n = 4, 60%

64%

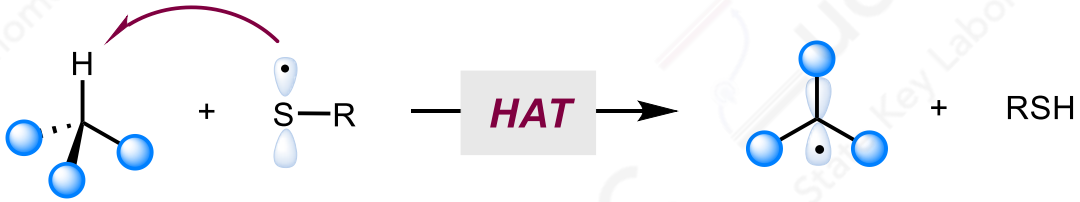
73%

78%

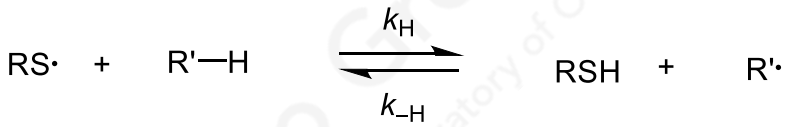
59%

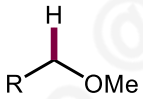
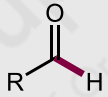
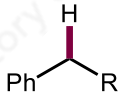
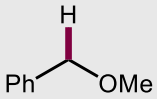
Cresswell A. *et al. Angew. Chem., Int. Ed*. **2020**, *59*, 14986–14991.

3.4 Thiol centered radical



Rate Constant of HAT Mediated by Sulfate Radical



R–H	thiol	k_H/$M^{-1}s^{-1}$	k_{-H}/$M^{-1}s^{-1}$	ΔH/kcalmol^{-1}
	^{t}BuSH		8×10^6 (298K)	**13**
	RCH_2SH PhSH	2×10^4 (353K)	4×10^6 (303K) 1.4×10^6 (298K)	**8** **12**
	RCH_2SH		2×10^7 (298K)	**4**
	RCH_2SH		7×10^6 (353K)	**1**
	RCH_2SH	1×10^6 (353K)	7×10^2 (353K)	**–2**
	RCH_2SH	2×10^7 (353K)		**–2**

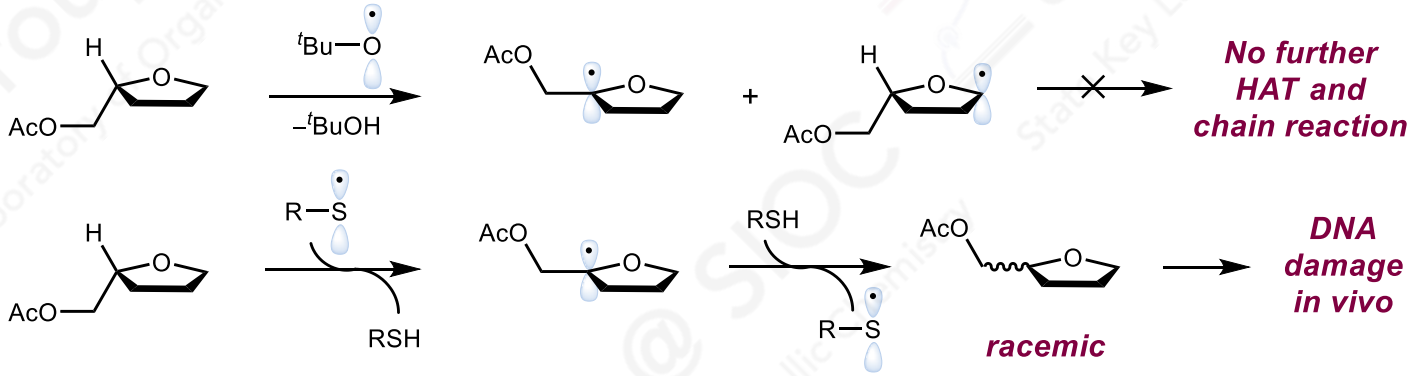
Denes F. *et al. Chem. Rev.* **2014**, *114*, 2587-2693.

Reactivity of HAT Mediated by Thiol Radical

- Reactivity of thiol radical

Roberts B. *et al. Tetrahedron Lett.* **1999**, *40*, 8929-8933.

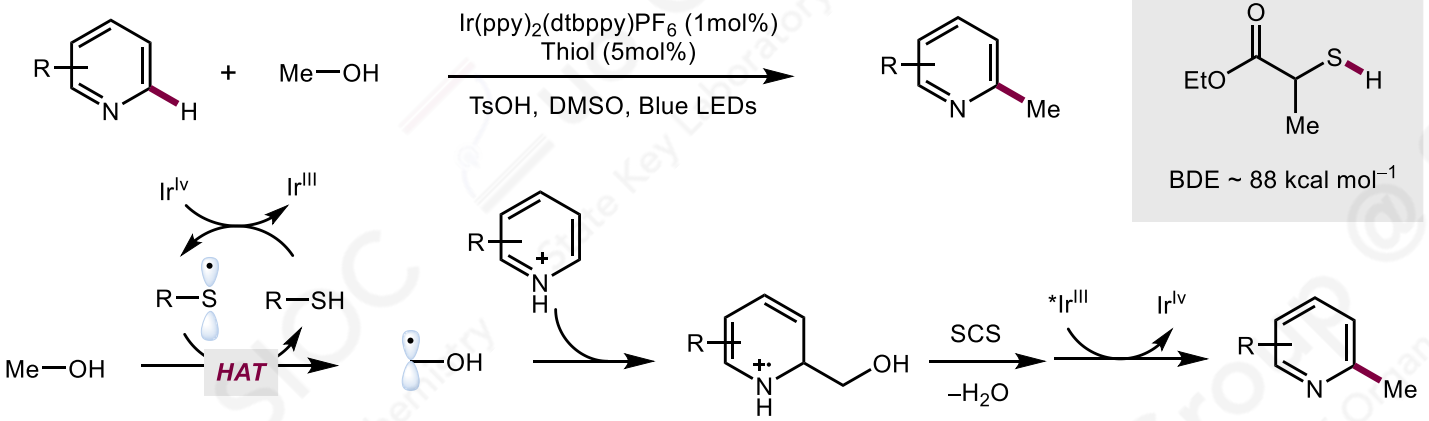
- Difference on reactivity of alkoxyl radical and thiol radical



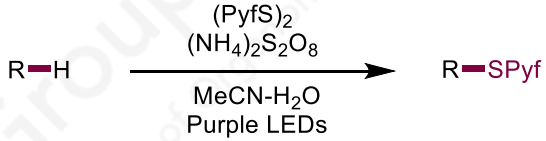
Roberts B. *et al. Chem. Commun.* **1998**, 1145.

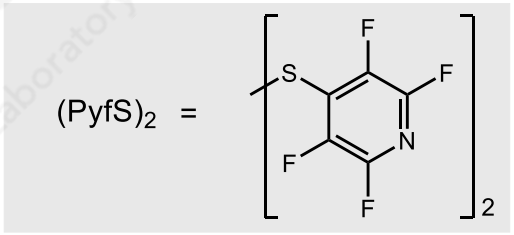
Improved reactivity of HAT Mediated by Thiol Radical

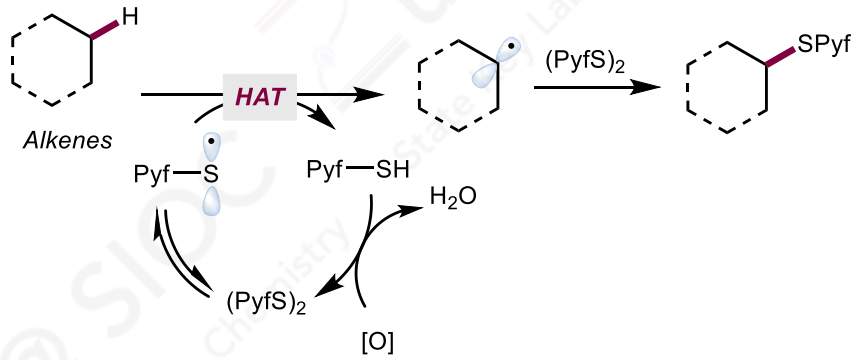
- Improved reactivity of thiol radical



MacMillan D. *et al. Nature*, **2015**, 87-90.

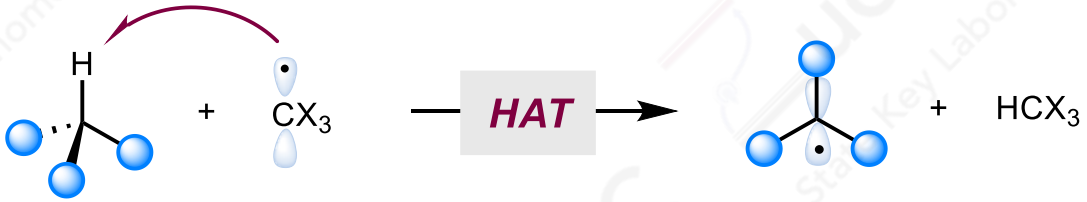






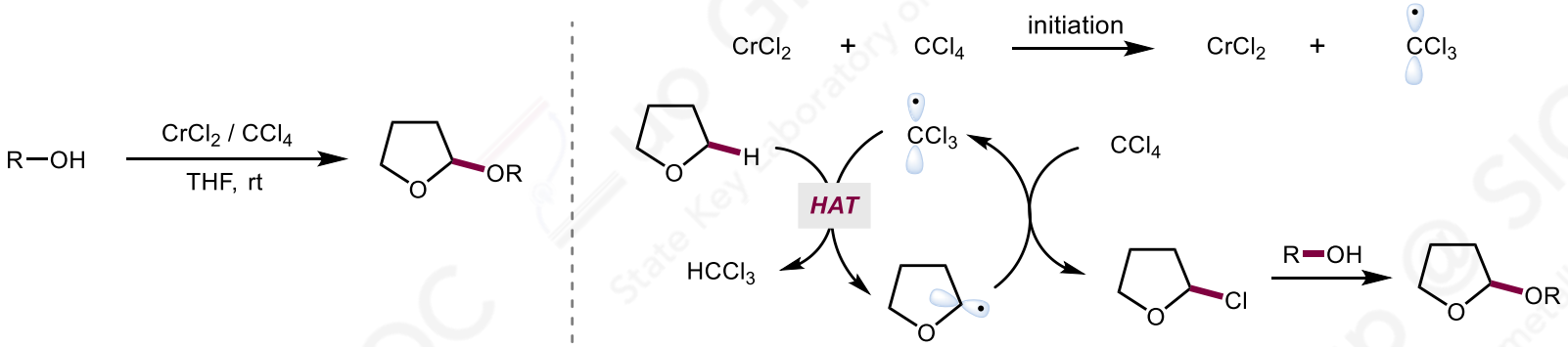
Dilman. A. *et al. Angew. Chem. Int. Ed.* **2021**, *60*, 2849-2854.

3.5 Carbon centered radical

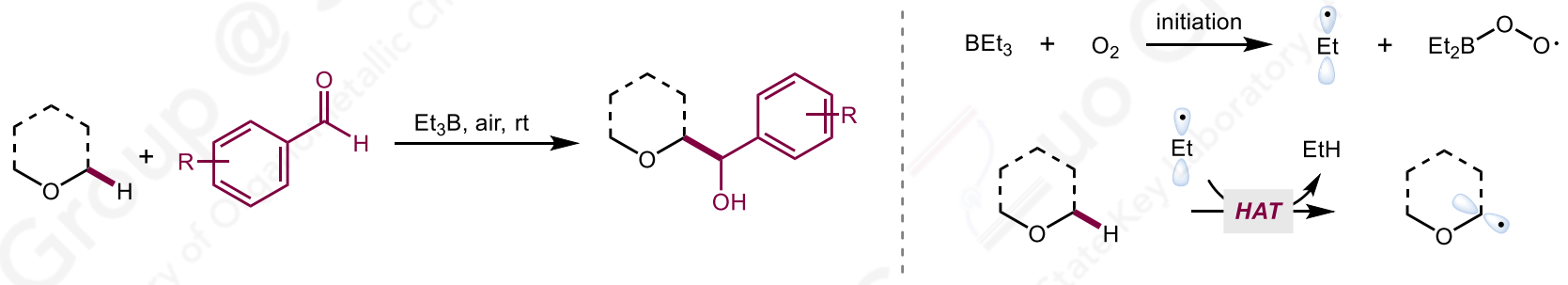


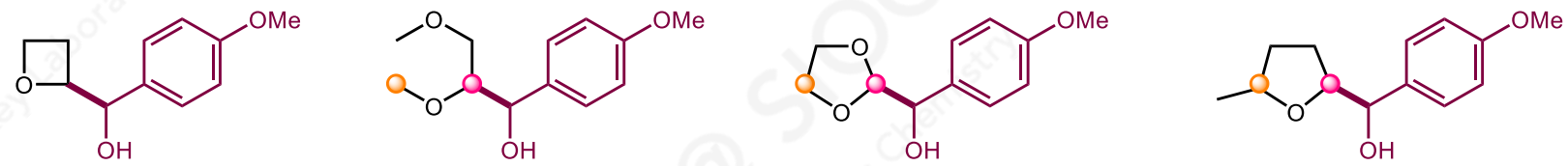
Reactivity of HAT Mediated by Carbon Centered Radical

❑ Reactivity of alkyl radical



Falck J. *et al. Org. Lett.* **2000**, *2*, 485–487.

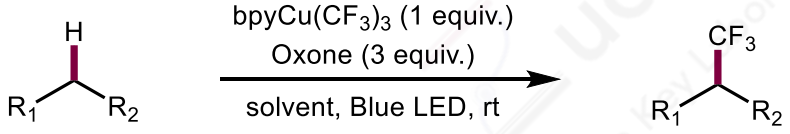


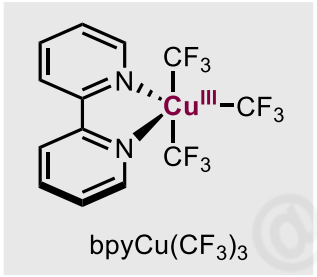


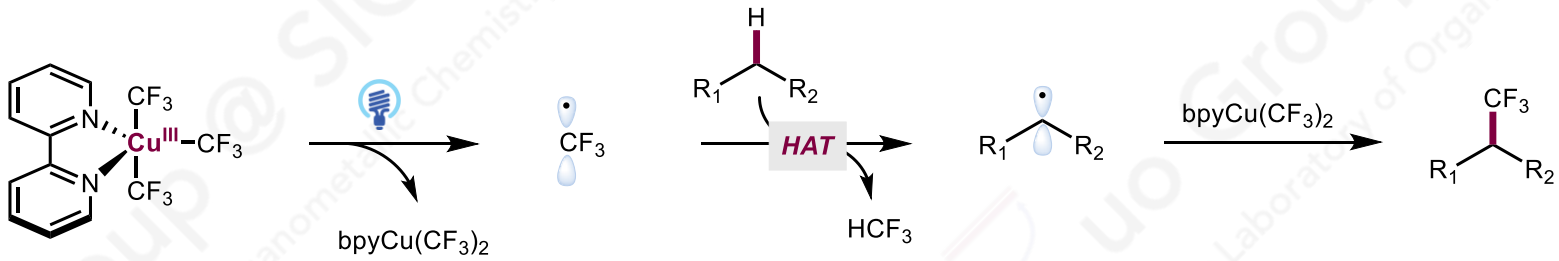
Nagaoka H. *et al. J. Org. Chem.* **2005**, *70*, 2342–2435.

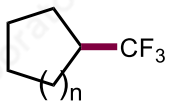
Reactivity of HAT Mediated by Carbon Centered Radical

❑ Reactivity and Selectivity of trifluoromethyl radical

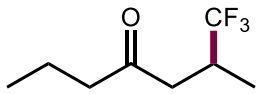




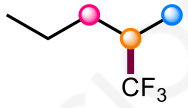




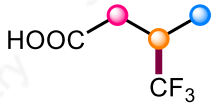
n = 1, 96%; n = 2, 82%
n = 3, 84%; n = 4, 57%



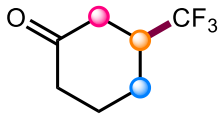
88%



76% (**6.8** : **7.2** : **1**)



62% (**1.5** : **5** : **1**)



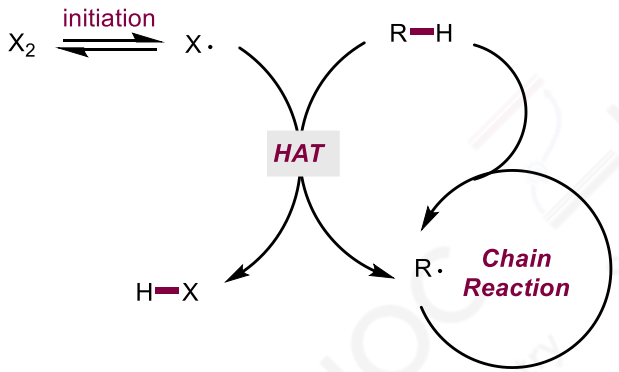
80% (**1** : **8** : **2**)

Hong S. *et al. Angew.Chem. Int. Ed.* **2021**, *60*, 5467–5474.

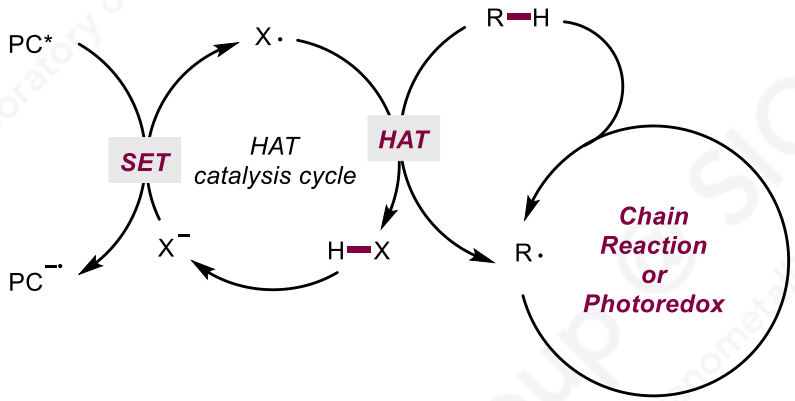
3.6 Photocatalyst and metal complex induced direct HAT

Photocatalyst Induced Direct HAT

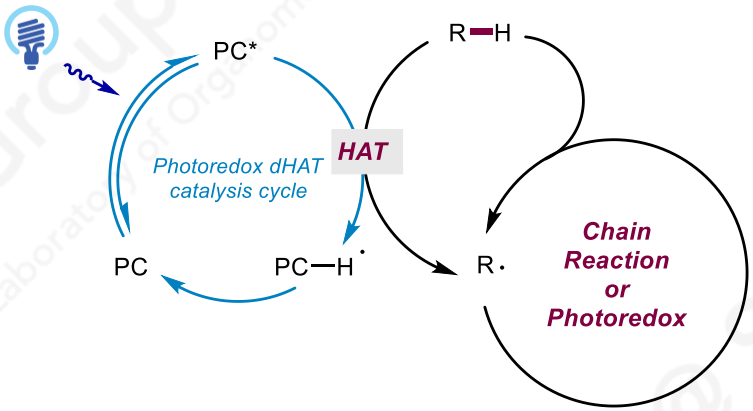
Traditional HAT

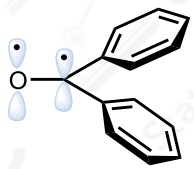


Photocatalyzed Indirect HAT

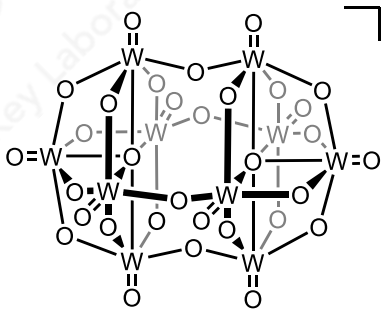


Photohcatalyzed Direct HAT





triptet ketone

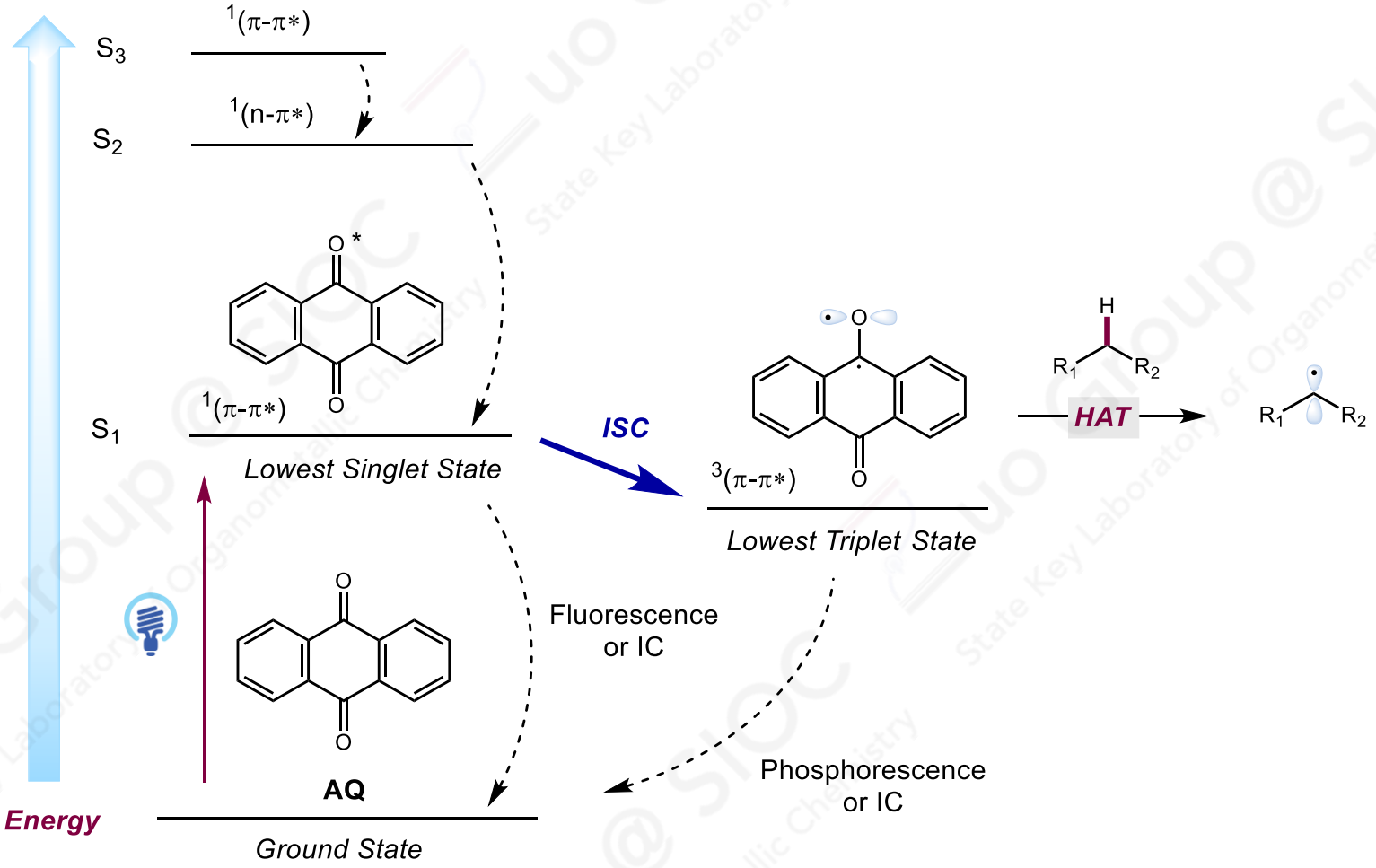


$[W_{10}O_{32}]^{4-}$

Typical dHAT Reagents

Reactivity and Selectivity of Triplet Ketone

- Jablonski diagram of the photochemical process of ketones

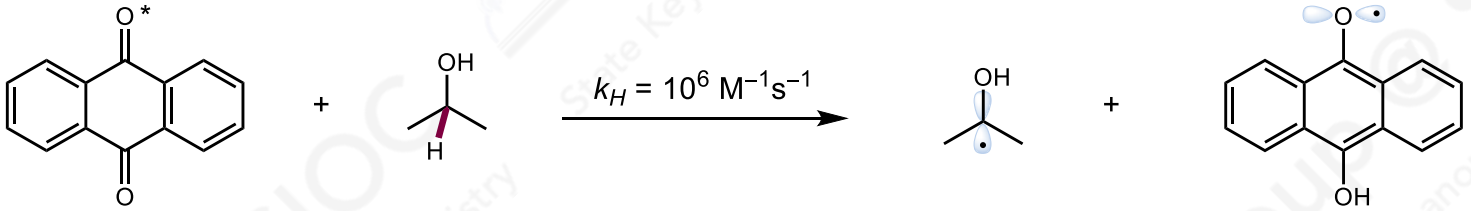


Lagunas-Rivera S. *et al. ChemCatChem.* **2020**, *12*, 3811–3827.

Reactivity and Selectivity of Triplet Ketone

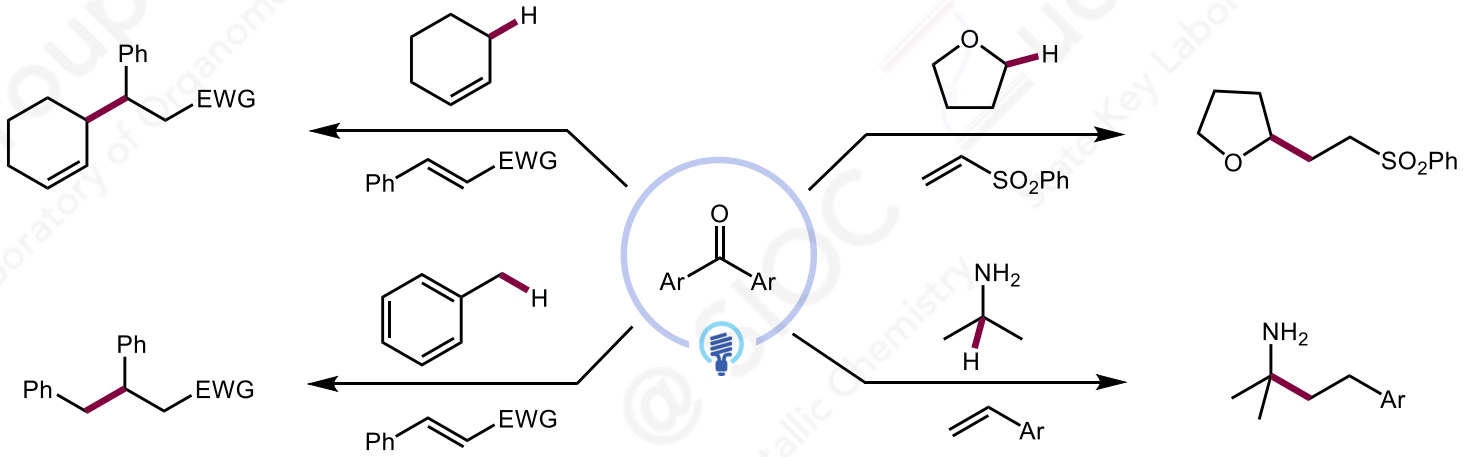
Early Reactions of Ketone

Yang N. C. *J. Am. Chem. Soc.* **1958**, *80*, 2913–2914.



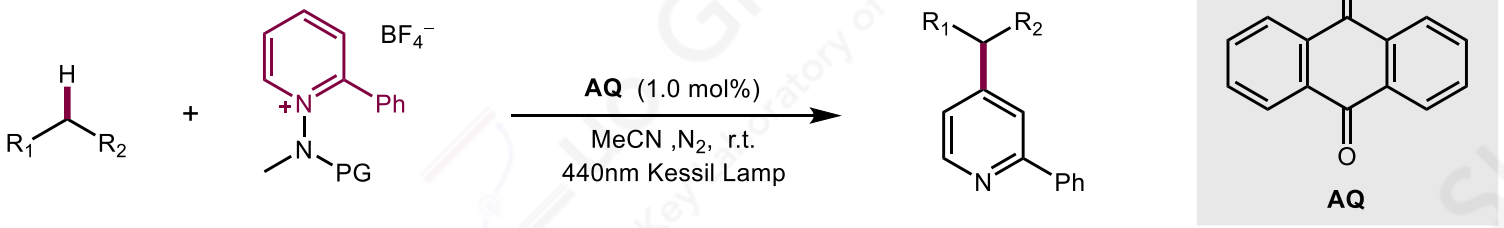
Lindquist L. *Arkiu. Kimi.* **1960**, *16*, 79.

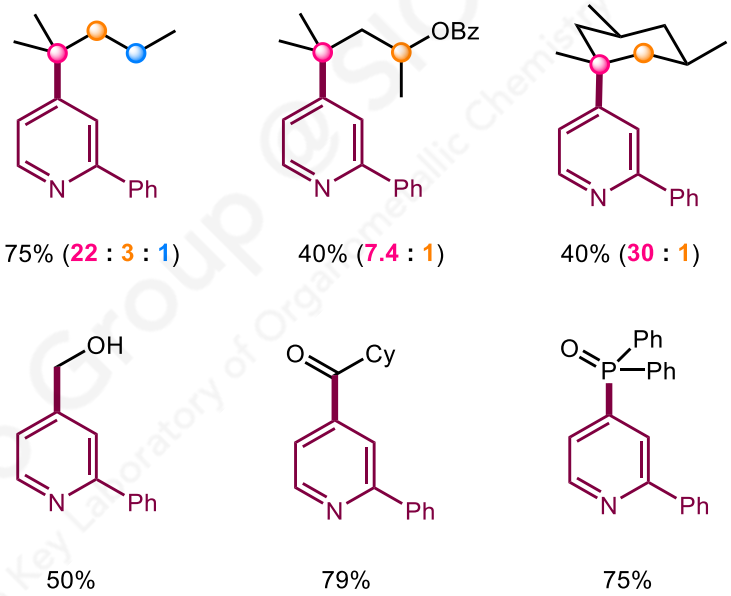
❑ Catalysis C-H functionalization reactions mediated by ketones

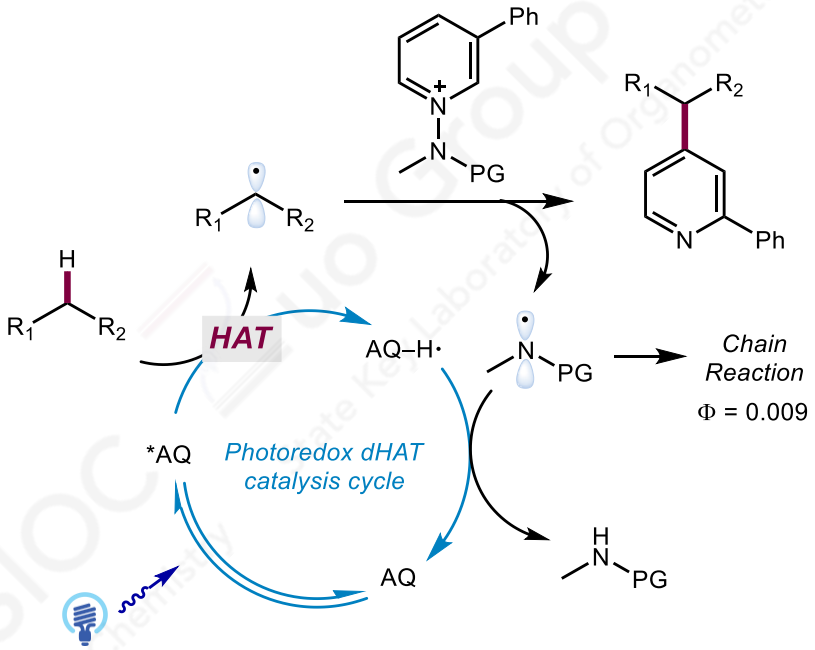


Fagnoni M. *et al. Chem. Rev.* **2022**, *122*, 1875−1924.

Reactivity and Selectivity of Triplet Ketone

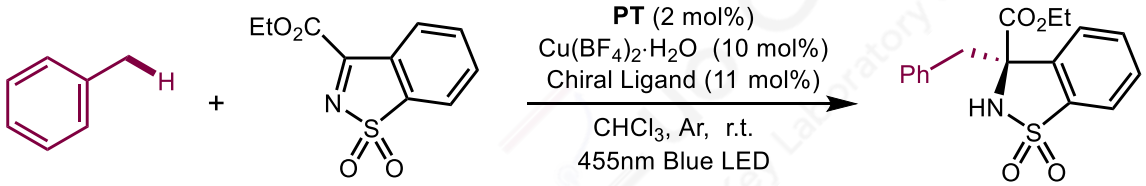


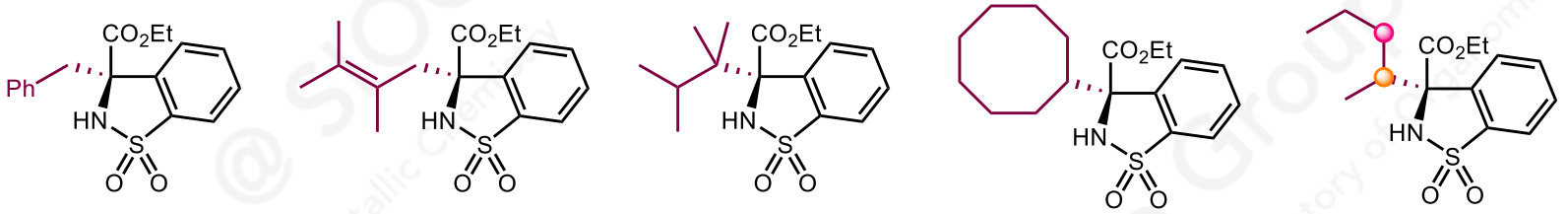




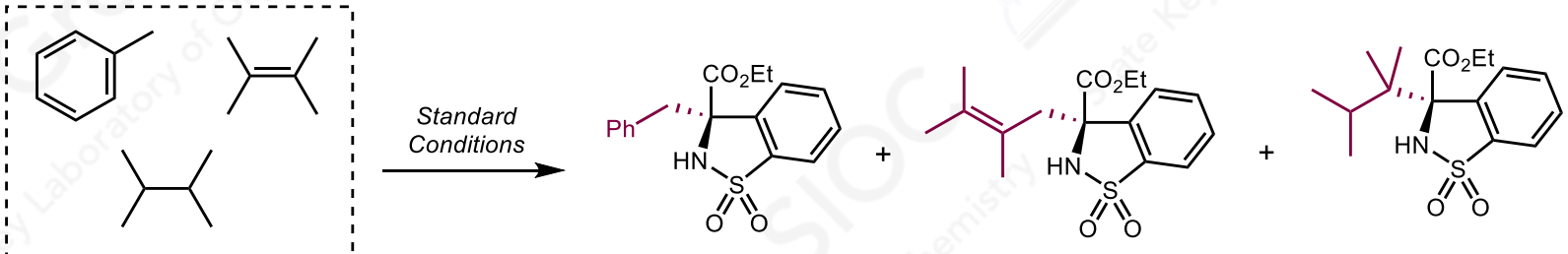
Hong S. *et al. J. Am. Chem. Soc.* **2021**, *143*, 3003−3012.

Reactivity and Selectivity of Triplet Ketone





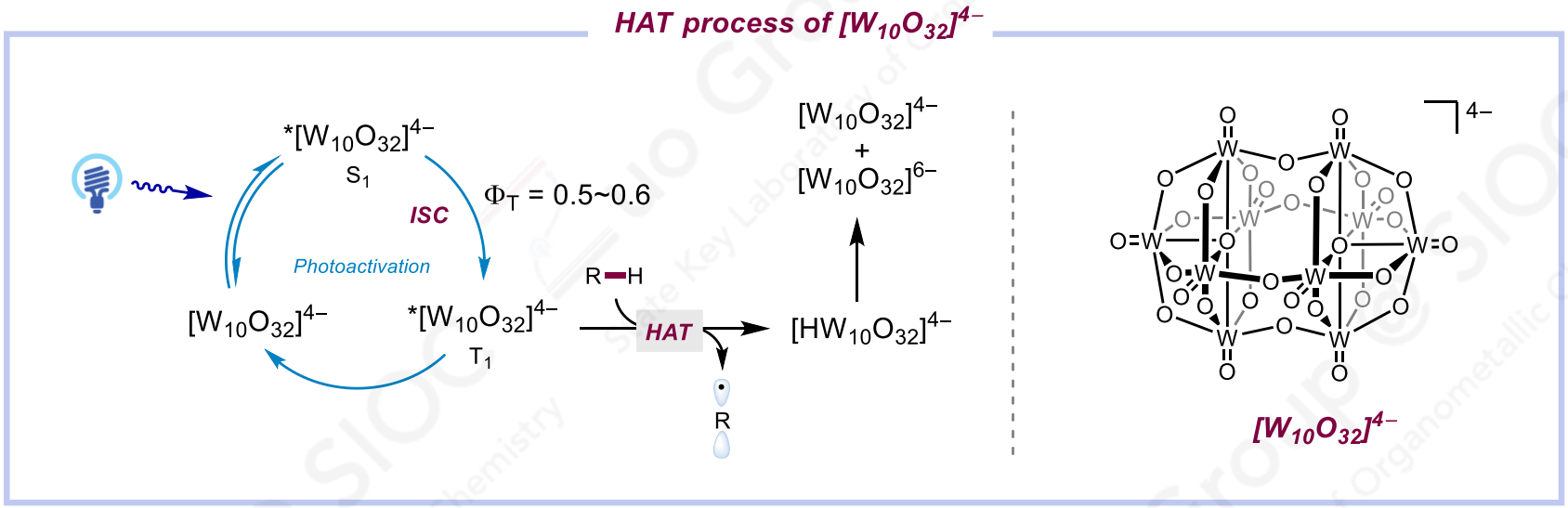
93% / 93% e.e. | 82% / 90% e.e. | 60% / 97% e.e. | 81% / 69% e.e. | 18% (2 : 1)

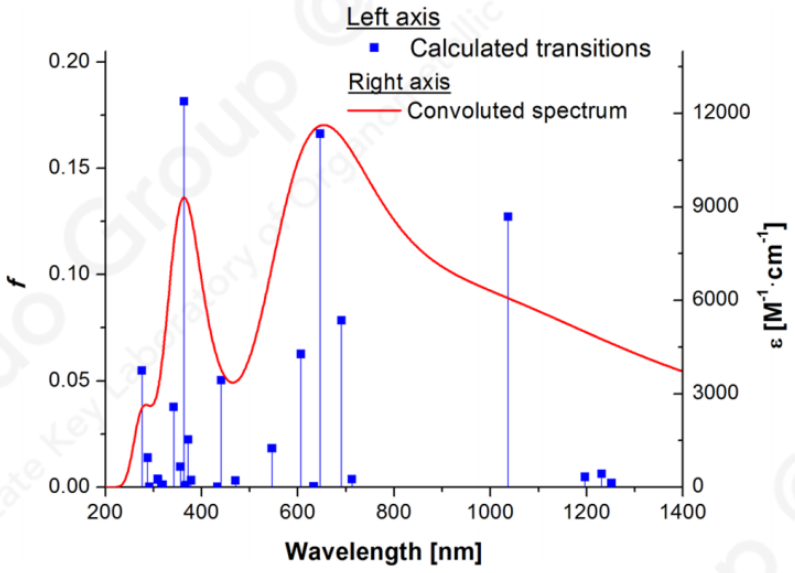


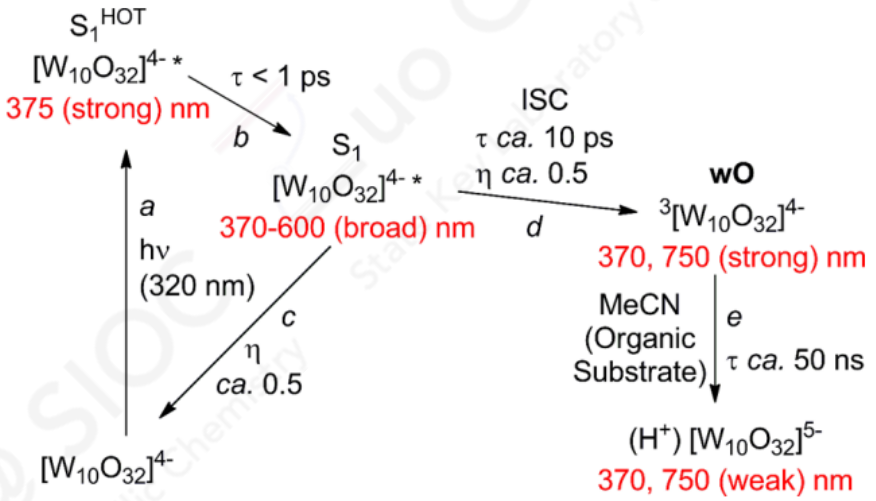
17% / 93% e.e. | 78% / 90% e.e. | no product

Gong L. *et al. Nat. Catal.* **2019**, *2*, 1016-1026.

Polyoxotungstates Mediated Direct HAT



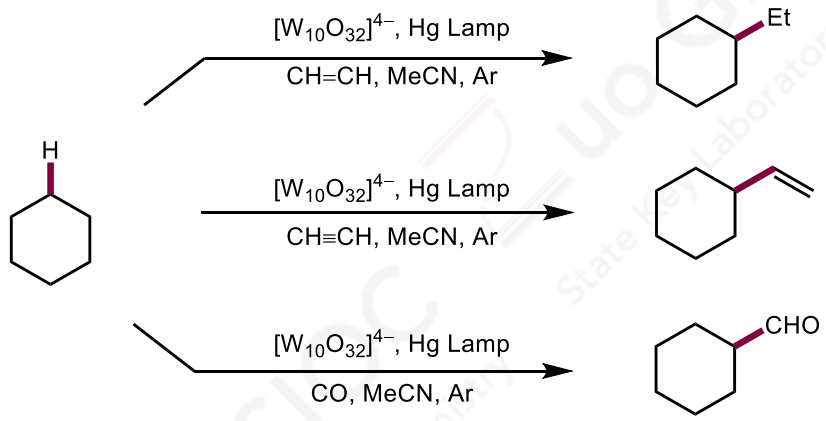


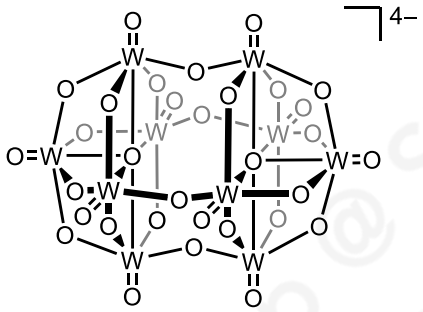


Ravelli D. *et al. ACS Catal.* **2016**, *6*, 7174−7182.

Polyoxotungstates Mediated Direct HAT

Early Reactions of $[W_{10}O_{32}]^{4-}$

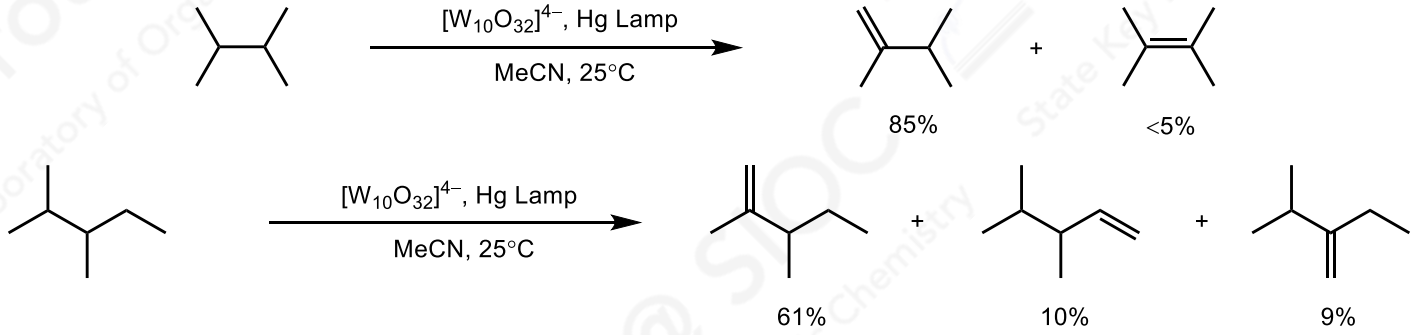




$[W_{10}O_{32}]^{4-}$

Hill C. *et al. J. Am. Chem. Soc.* **1993**, *115*, 12212−12213.

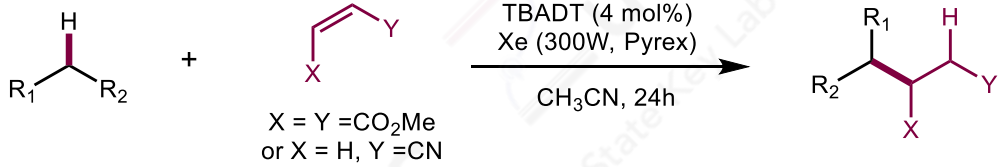
Early Study on selectivity of $[W_{10}O_{32}]^{4-}$

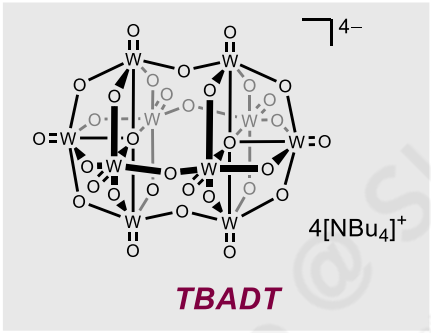


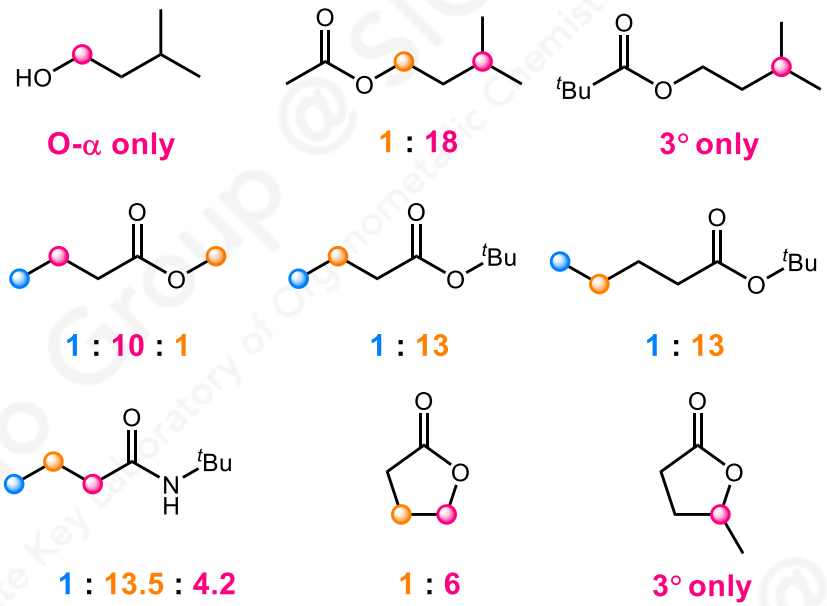
Hill C. *et al. J. Am. Chem. Soc.* **1990**, *112*, 6585−6594.

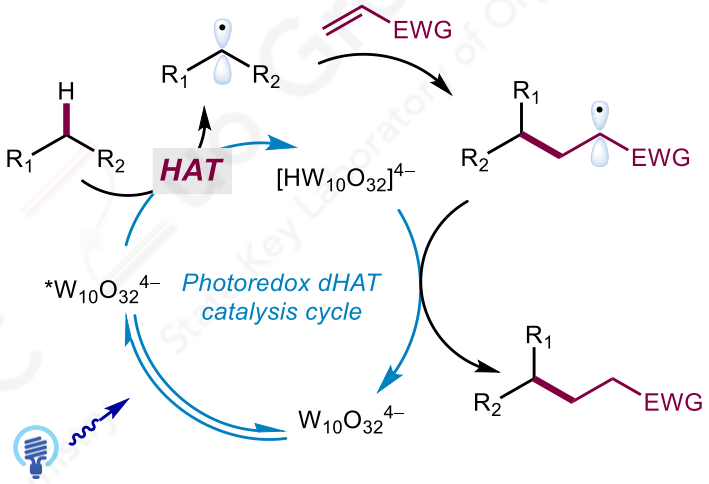
Selectivity of Polyoxotungstates induced direct HAT

❑ Selectivity of Polyoxotungstates Induced HAT





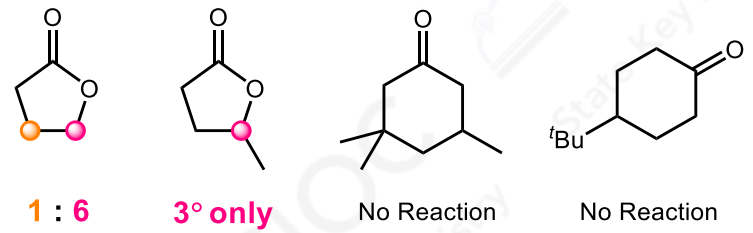




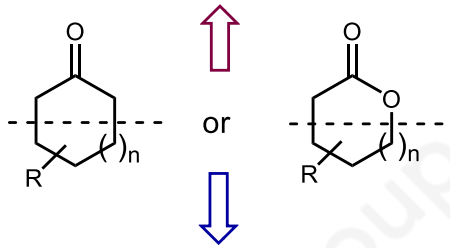
Ryu I. *et al. Chem. Eur. J.* **2017**, *23*, 8615 – 8618.

❑ Selectivity of Polyoxotungstates induced HAT

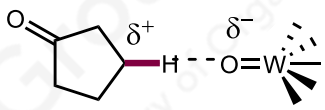
Regioselectivity of TBADT



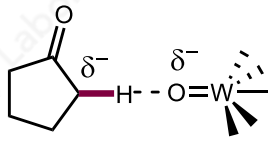
Selectivity controlled by polar effect



Selectivity controlled by steric effect



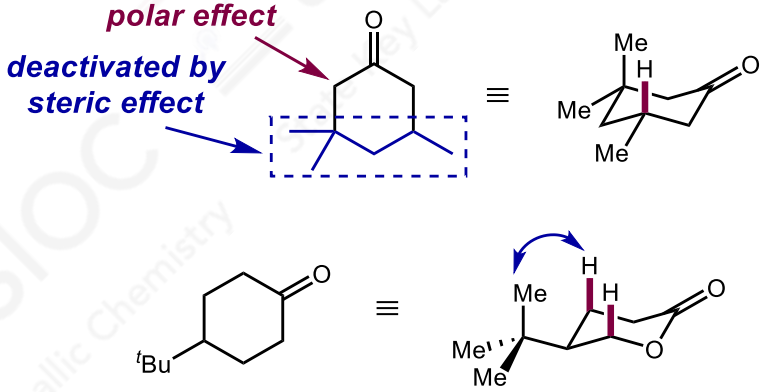
Polarity matched
Major product



Polarity mismatched
Minor product

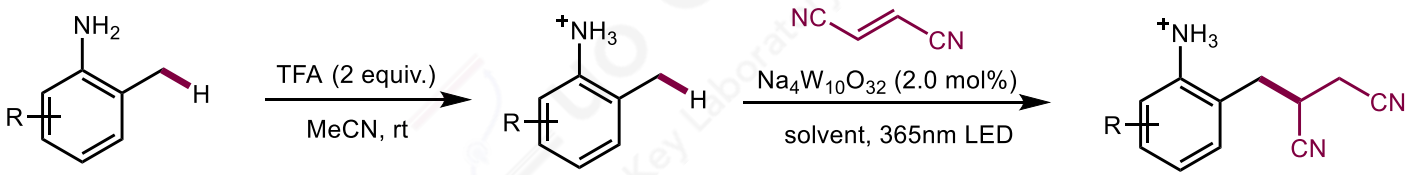
deactivated by polar effect

deactivated by steric effect

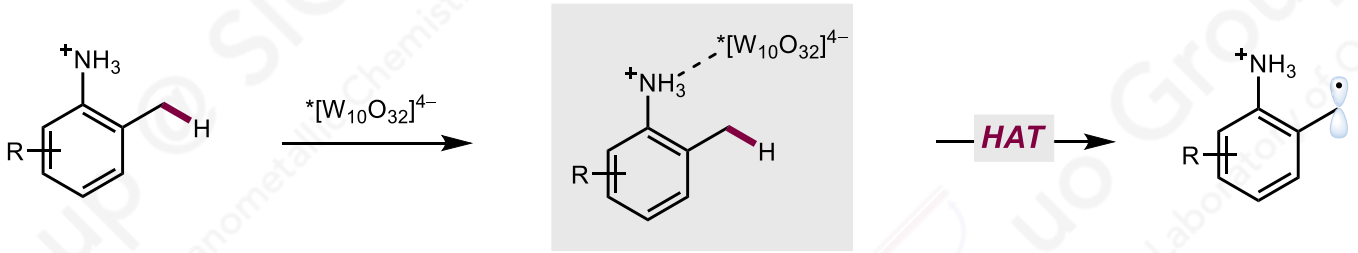


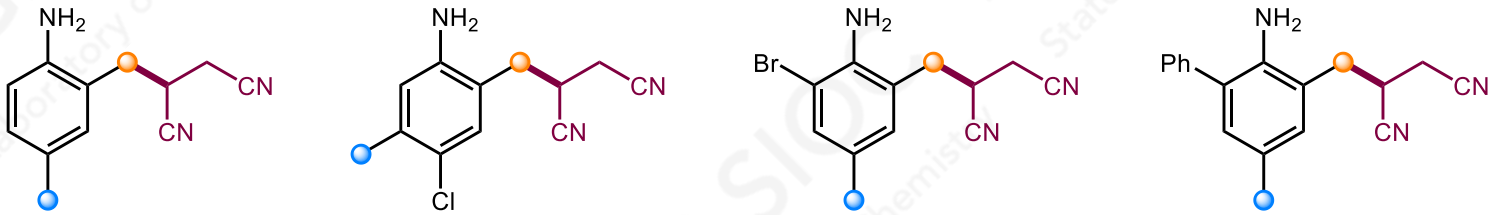
Improved reactivity of TBADT Mediated by Thiol Radical

❑ Improved selectivity of Polyoxotungstates



Control of Regioselectivity

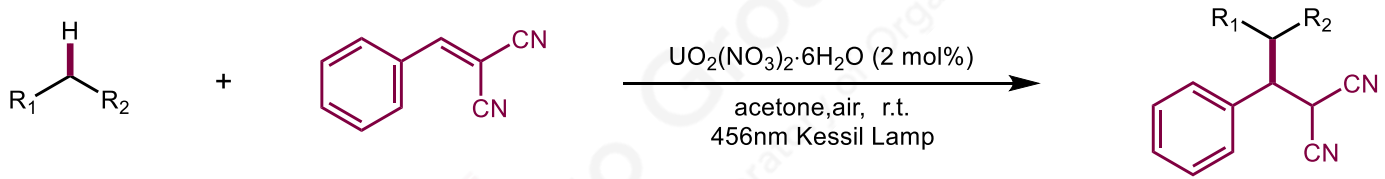


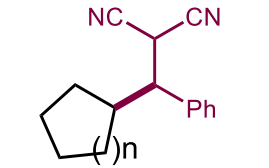


74% (98 : 2) 81% (98 : 2) 63% (93 : 7) 61% (94 : 6)

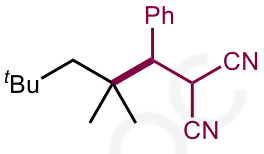
Kuninobu Y. *et al. ACS Catal.* **2022**, *12*, 3058−3062.

Reactivity of dioxouranium

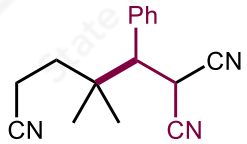




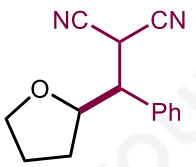
n = 1, 67%; n = 2, 96%
n = 3, 76%; n = 4, 78%



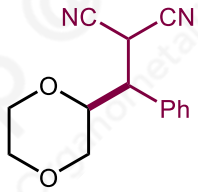
68%



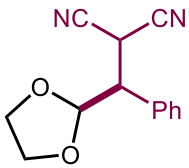
68%



60%



70%



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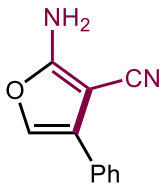
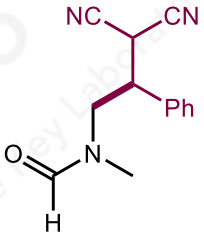
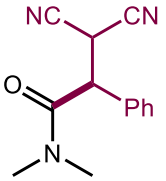


75%



quant.



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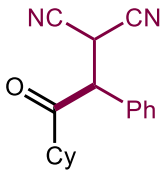
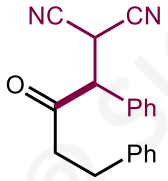


93%



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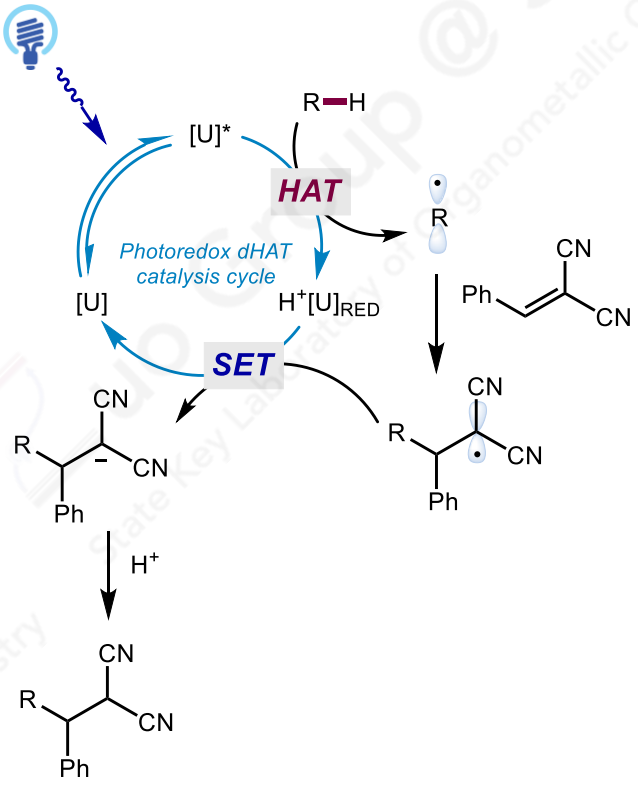
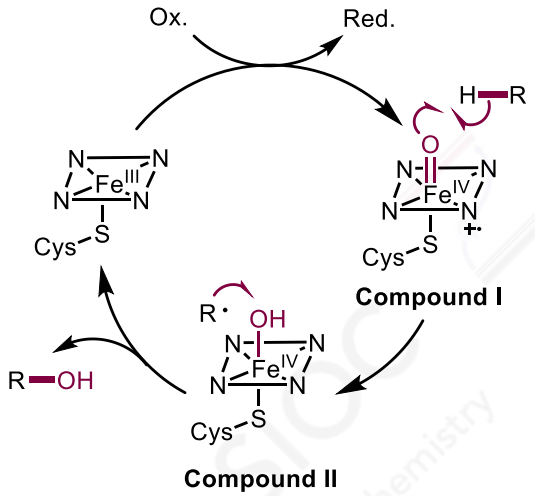
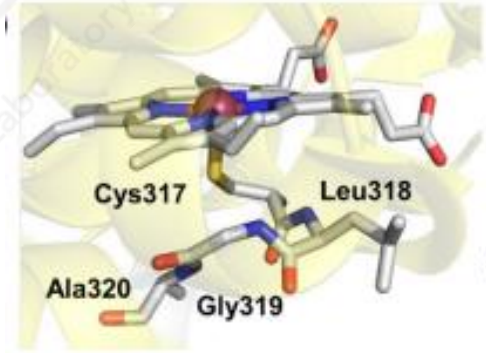


Ravelli D. *et al. ACS Catal.* **2019**, 9, 3054−3058.

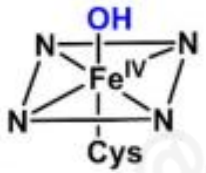
Reactivity of enzyme and metal complex

Metal oxo catalysis cycle





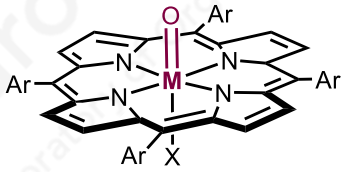
P450 (CYP119)



pK_a (cpd II) = 12.0

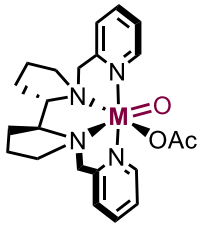
Groves J. *et al. J. Bio. Inorg. Chem.* **2017**, *22*, 185–207.

Metal complexes



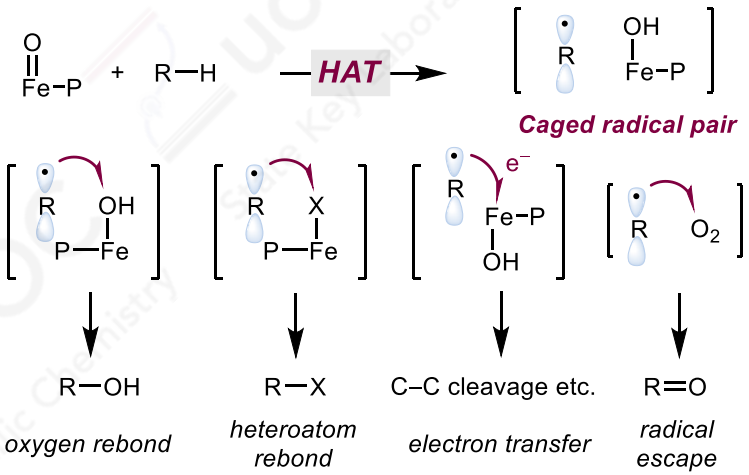
M=O(pro-Ar)X

M = Fe, Mn, Co, Ru, etc.

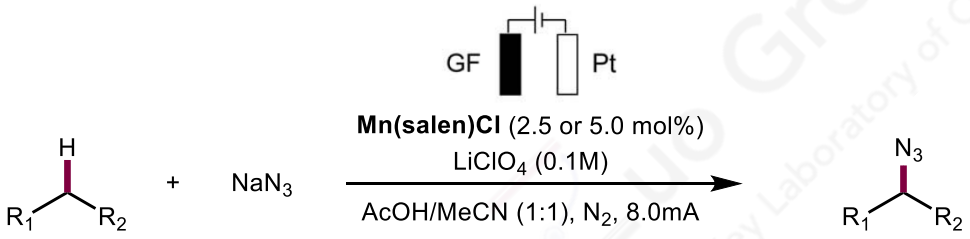


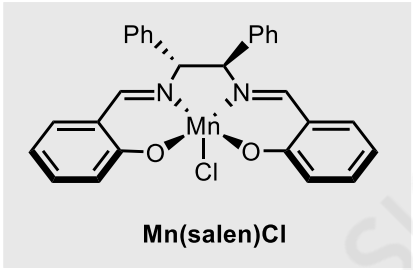
M=O(pdp)(OAc)

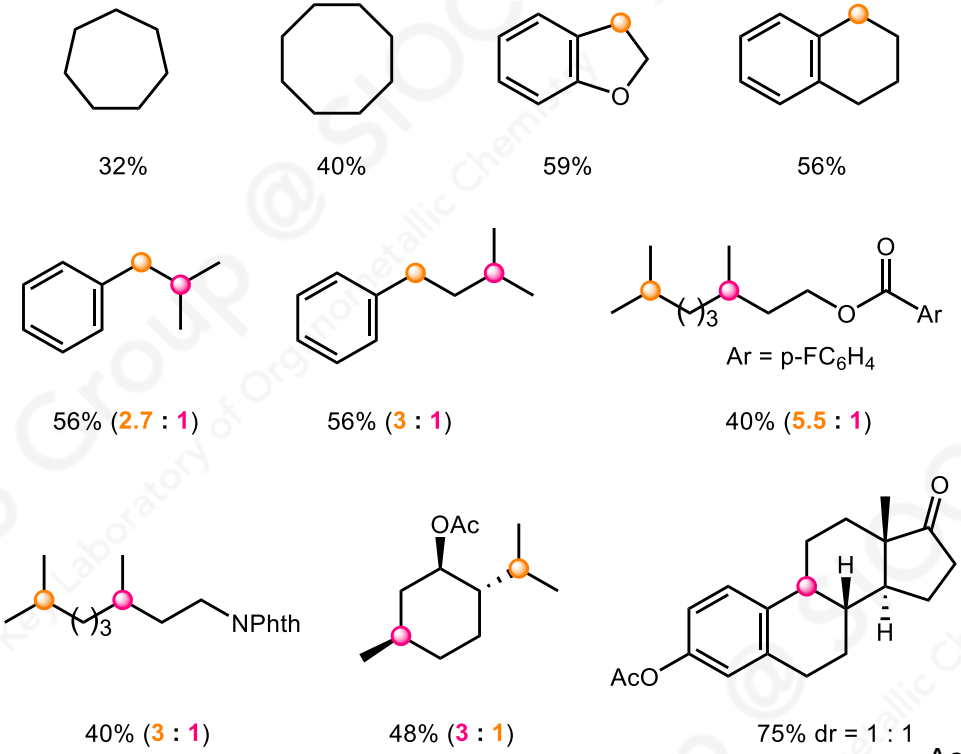
M = Fe, Mn, etc.

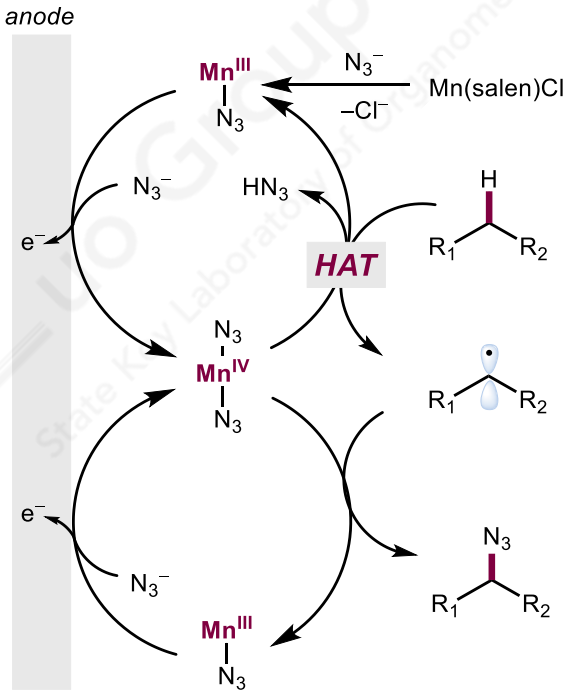


Reactivity and Selectivity of Metal Complex



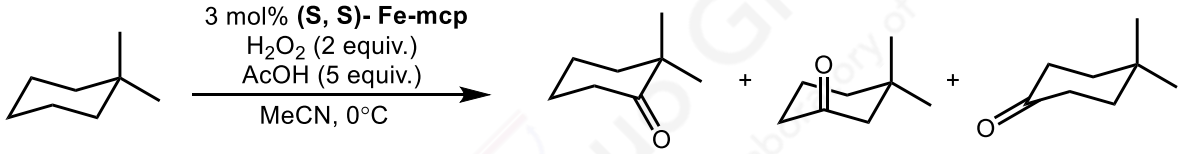


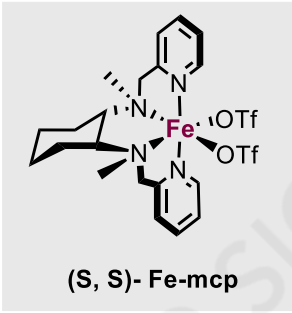




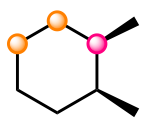
Ackermann L. *et al. Chem. Sci.* **2021**,*12*, 2890-2897.

Reactivity and Selectivity of Metal Complex

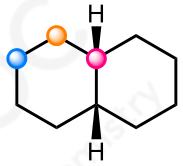




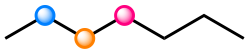
(S, S)- Fe-mcp



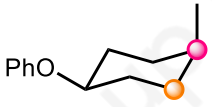
83% (1 : 8.5)



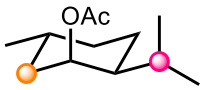
86% (8 : 2 : 1)



50% (1 : 2 : 3)

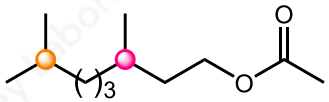


57% (5 : 1)

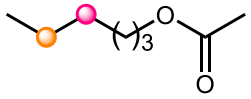


47% (2 : 1)

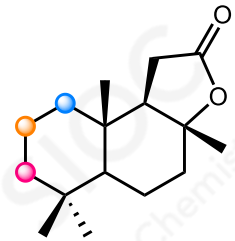
63% (4.5 : 1)



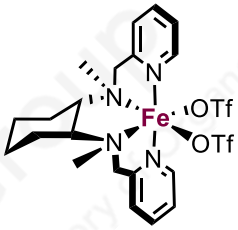
45% (1 : 5)

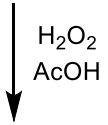


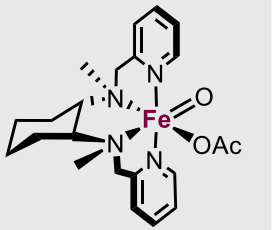
37% (3 : 1)



64% (1 : 3 : 8)



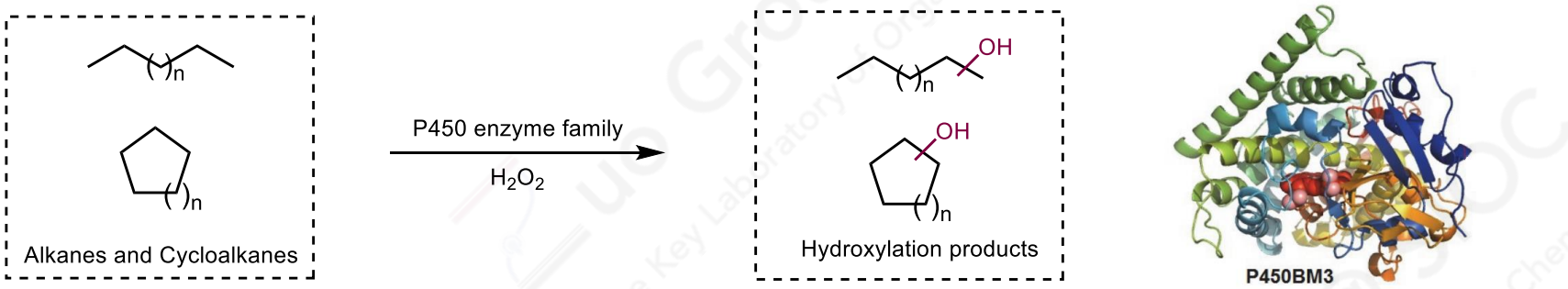




Possible Intermediate

Costas M. *et al. Adv. Synth. Catal.* **2014**, *356*, 818–830.

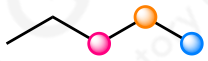
Reactivity and Selectivity of P450 enzyme



Cong Z. *et al. Acta Chim. Sinica* **2020**, *78*, 490-503.

Summary

- Summary on selectivity of various HAT regents



3 : 2.7 : 1 [1]

13.8 : 12 : 1 [2][a]

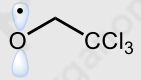
3 : 2.5 : 1 [4]

1 : 1 [6]

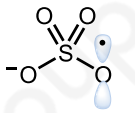
4.8 : 6.3 : 1 [27]

1 : 1.5 [9]

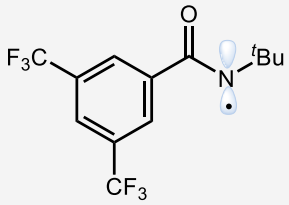
12.4 : 13.7 : 1 [11]



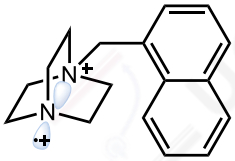
3 : 2.8 : 1 [11]



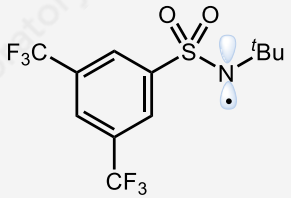
1 : 1.5 [10]



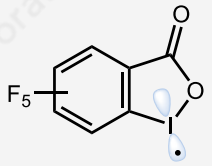
9.6 : 13.1 : 1 [16]



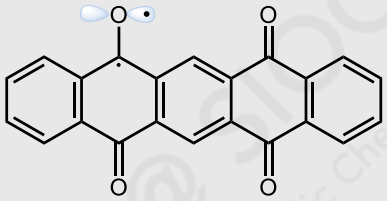
1 : 6 : 2.2 [17]



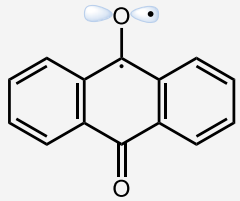
1.5 : 1 [18]



1 : 2 [7]



1 : 1 [21]

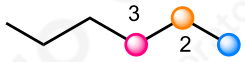


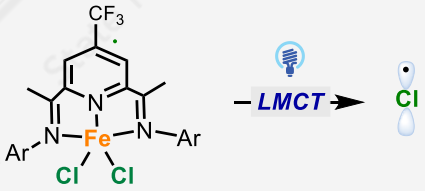
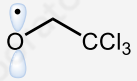
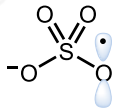
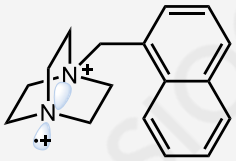
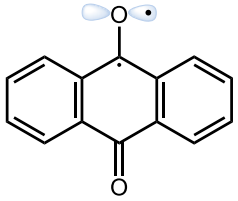
1.7 : 1 [22]

[a] benzene as solvent.

Summary

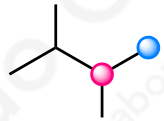
- Summary on selectivity of various HAT regents

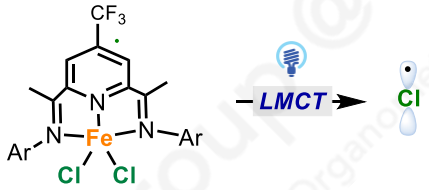
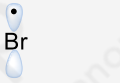
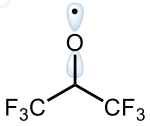
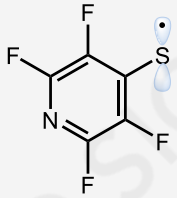
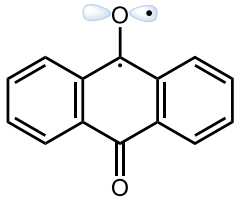


 2.7 : 2.6 : 1 [1]	 1.5 (2 + 3) : 1 [3]	 5.4 : 5.8 : 1 [27]
 1 : 2.6 [9]	 14.2 : 14.5 : 1 [11]	 2.7 : 2.7 : 1 [11]
 1 : 1.7 [10]	 6.3 : 12.9 : 1 [17]	 1.7 : 1 [22]

Summary

- Summary on selectivity of various HAT regents

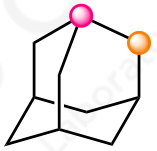


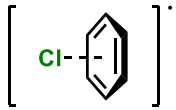
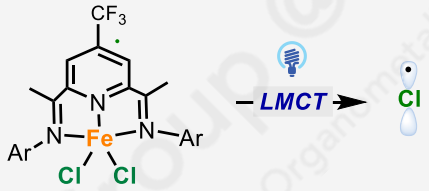
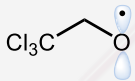
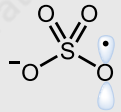
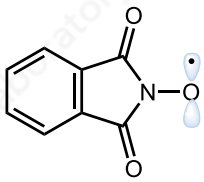
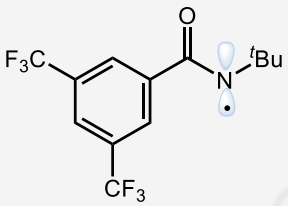
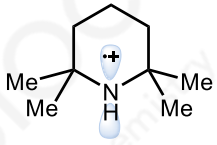
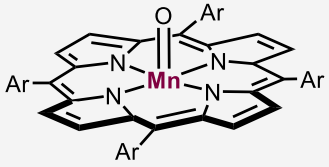
 5 : 1 [1]	 21 : 1 [2][a]	 31 : 1 [3]
 >20 : 1 [6]	 >100 : 1 [11]	 10 : 1 [11]
 5.1 : 1 [11]	 3° only [13]	 3° only [22]

[a] benzene as solvent

Summary

- Summary on selectivity of various HAT regents

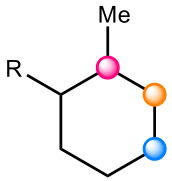


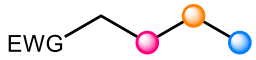
 2.1 : 1 [1]	 2.3 : 1 [2][a]	 4.9 : 1 [5]	 12 : 1 [3]
 10.6 : 1 [11]	 6.6 : 1 [9]	 2 : 1 [11]	 >20 : 1 [14]
 3° only [12]	 100 : 1 [16]	 3° only [20]	 2.2 : 1 [26]

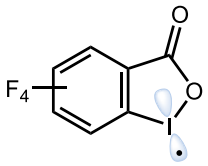
[a] benzene as solvent

Summary

❑ Summary on selectivity of various HAT regents

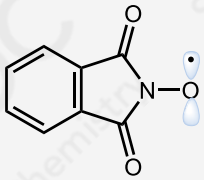






R = Me, *trans*

β and γ [7]



R = H

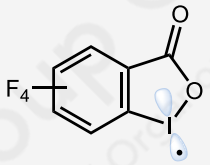
3° only [12]

EWG = CO_2Ph

1 : 4.2 : 1 [2]

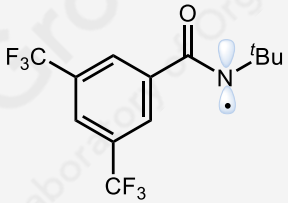
EWG = COMe

3.1 : 8.1 : 1 [2]



EWG = CO_2Me

>20 : 1 [7]

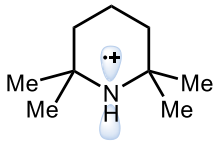


R = Me, *cis*

3 : 1 (β + γ) [16]

R = Me, *trans*

>20 : 1 (β + γ) [16]

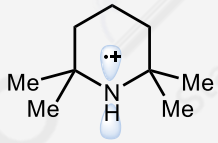


R = Me, *cis*

1 : 9.4 [20]

R = Me, *trans*

1 : 18 [20]

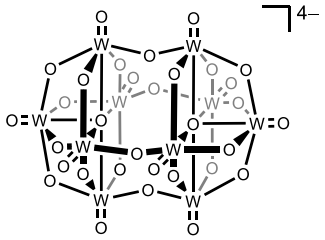


EWG = Br

1.2 : 10.6 : 1 [20]

EWG = CO_2Me

2.5 : 12 : 1 [20]

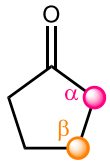


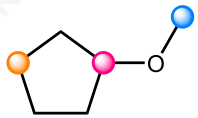
EWG = $CO_2{}^tBu$

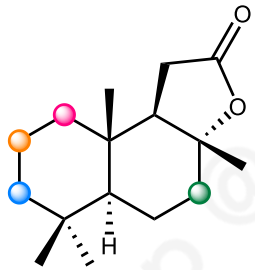
4.2 : 14 : 1 [23]

Summary

- Summary on selectivity of various HAT regents

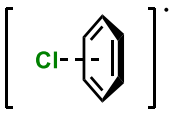






1 : 3.2 [1]

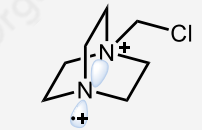
1 : 3.8 [27]



9 : 1 [5]

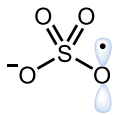
9 : 1 [6]

1 : 6 : 3.1 [2]

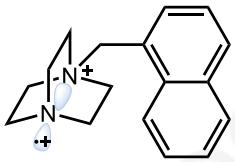


3.3 : 1 [19]

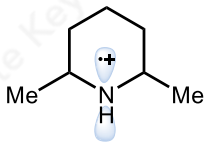
β only [2]



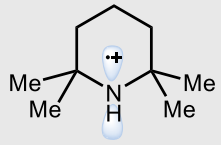
β only [15]



2 : 1 : 6 [17]



β only [20]



O–β only [20]

Summary

❑ Summary on selectivity of various HAT regents

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