Topic review

Catalysis of Chemical Reactions involving Free Radicals

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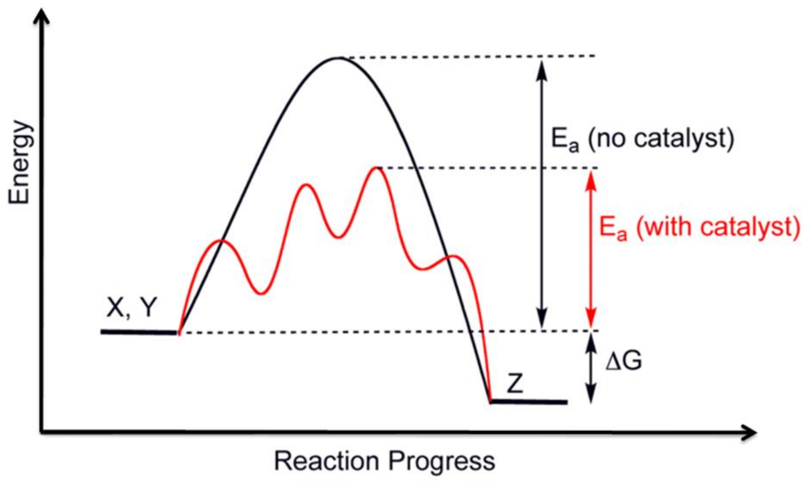
UniBern 2016

Outline

- Generalities
- Catalysis of Initiation
- Catalysis of Chain Reactions
- Redox Catalysis (Chain-reactions)
- Hole Catalysis
- Redox Catalysis (Non-Chain reactions)
- Photoredox Catalysis

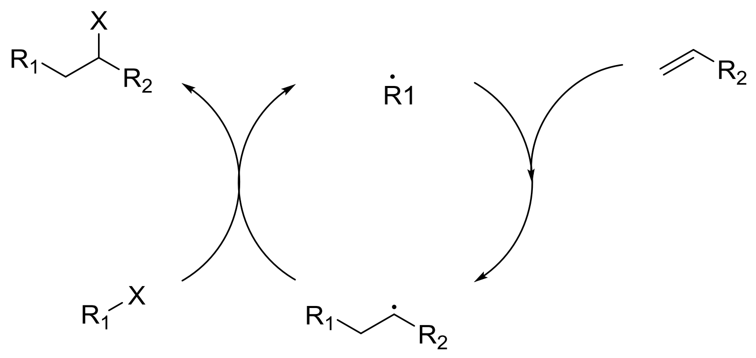
Catalysis of Chemical Reactions involving Free Radicals

Concept of "Catalysis" should be carefully applied to radical reactions



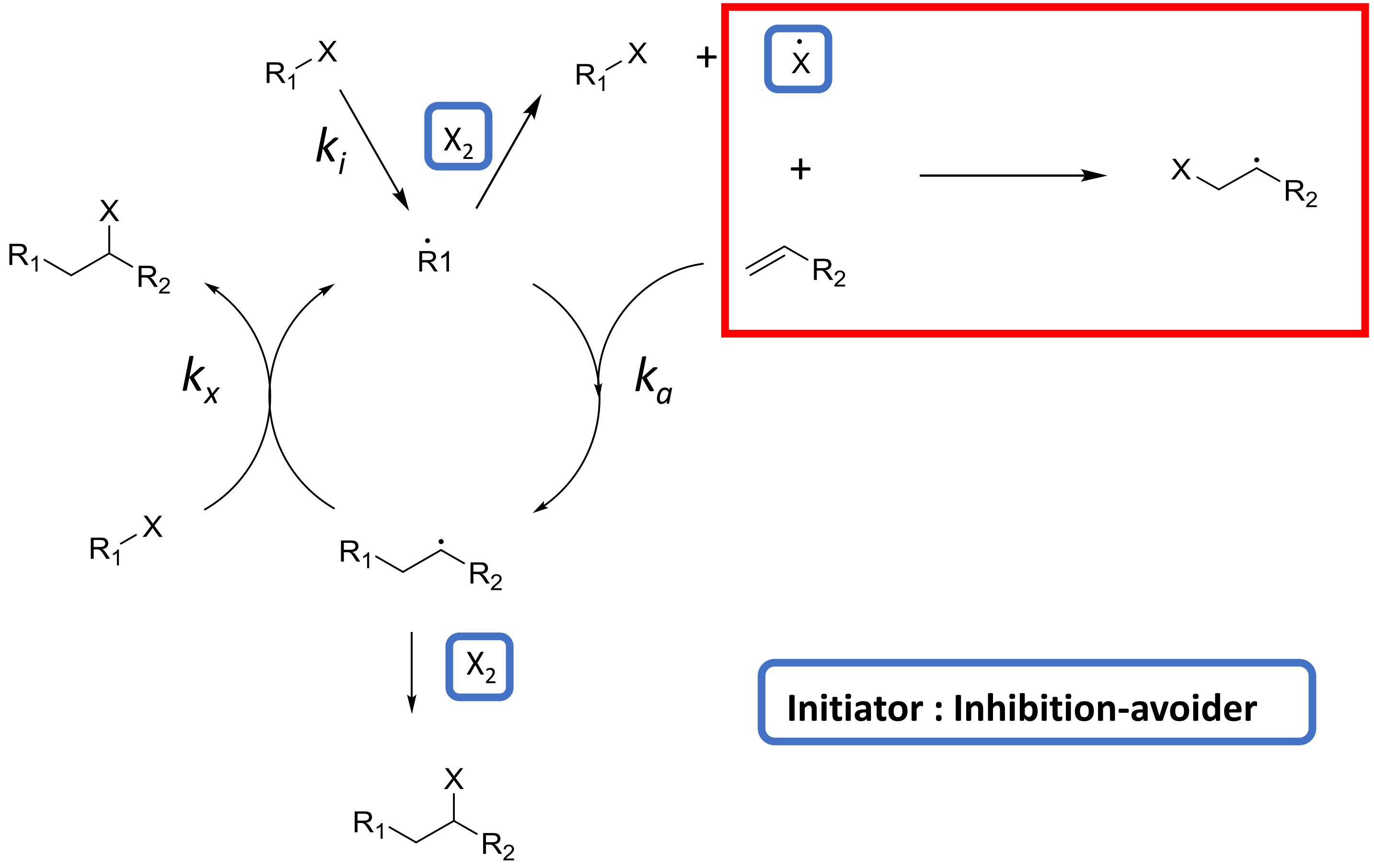
Every catalytic reaction is a cycle
Not every cycle is catalytic

ATRA Reaction
"Innate cycle" "Natural cycle"



Catalytic Reaction?

Catalysis of Chemical Reactions involving Free Radicals



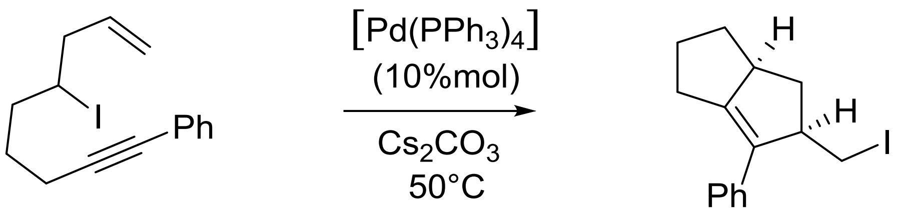
Initiator : Inhibition-avoider

Conditions for good propagation steps:

- All rate constants ≥ 10^5 s^{-1}
- Avoid inhibition

"Catalytic amount" "Substoichometric amount"

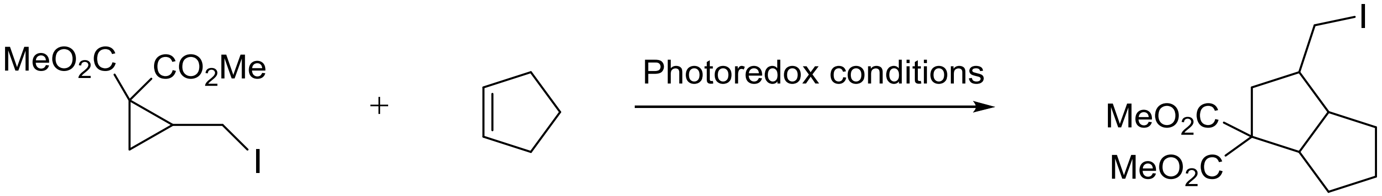
Catalysis of Chemical Reactions involving Free Radicals



B. M. Monks, S. P. Cook, *Angew. Chem. Int. Ed.* **2013**, *52*,14214–14218.

5-*exo-dig, trig* cyclization
2 x 10^5 s^{-1}
Propane-ring-opening
2 x 10^{10} s^{-1}

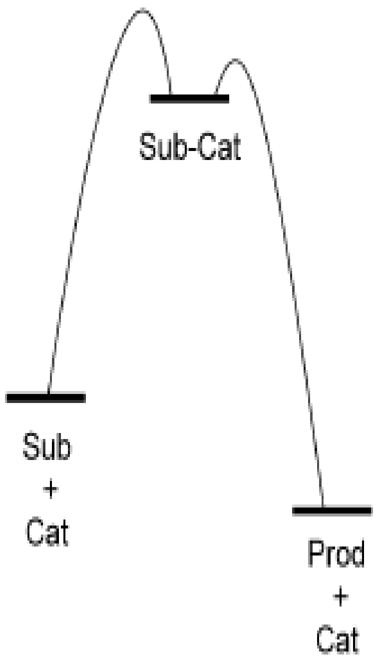
Catalytic reaction or innate chain?



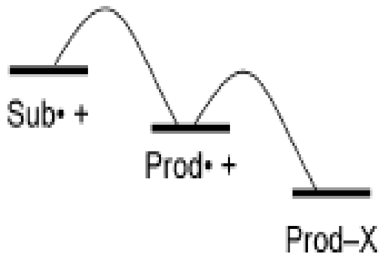
J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *J. Am. Chem. Soc*. **2011**, *133*, 4160–416.

D.C. Nonhebe, *Chem. Soc. Rev*., **1993**, *22*, 347-359

Catalysis of radical reactions drastically differs from closed-shell reactions



Closed-shell reactions Catalysis



Radical reactions Catalysis

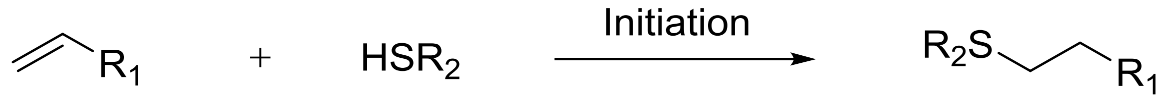
- High-energy species involved
- Remarkable tendency to reduce energy
- Slow, endothermic steps are not tolerated

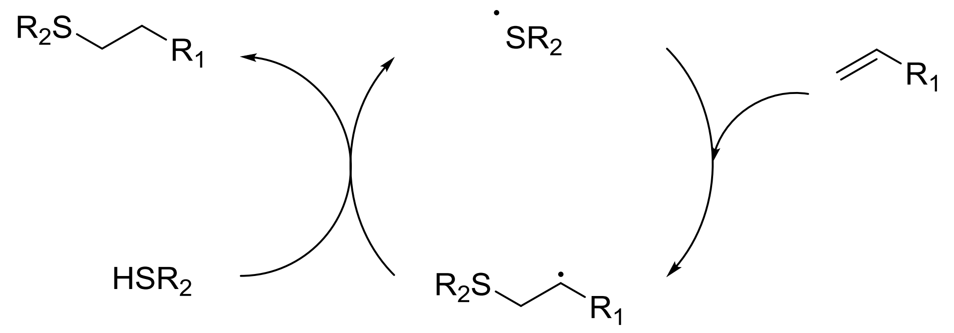
- Endothermic steps are well-tolerated

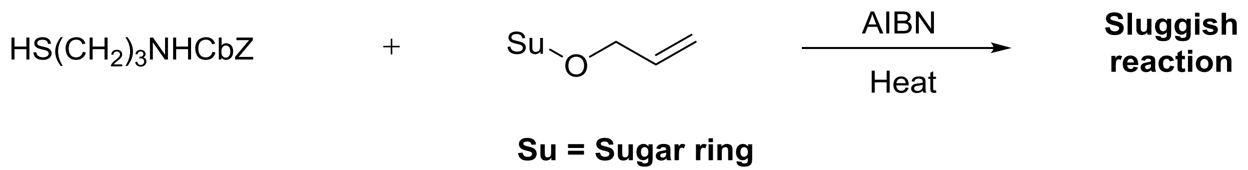
A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

Making efficient an inefficient reaction without "catalysis"

Thio-ene Reactions







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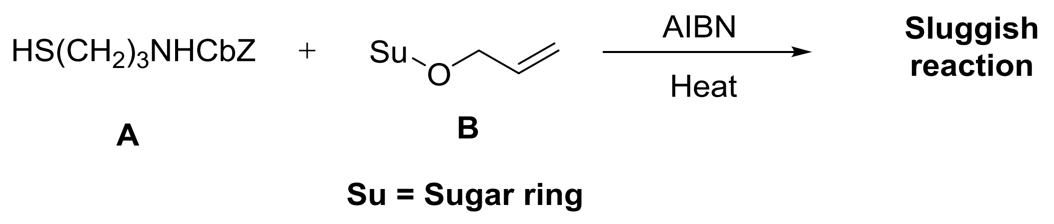
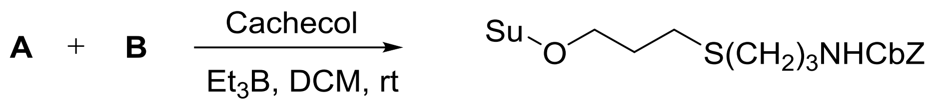
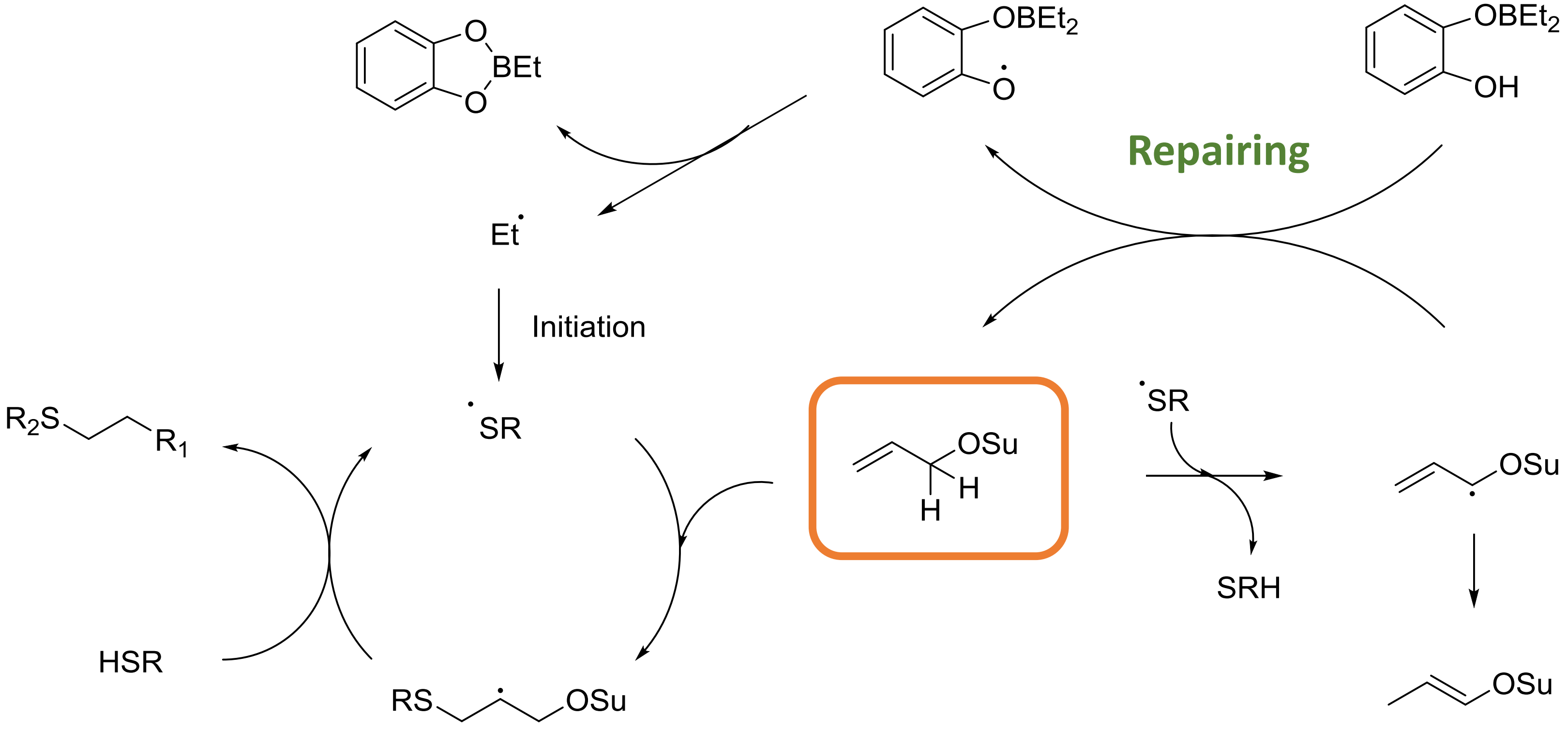
F. Denes, M. Pichowicz, G. Povie, P. Renaud, Chem. Rev. **2014**,*114*, 2587–2693.

Making efficient an inefficient reaction without “catalysis”

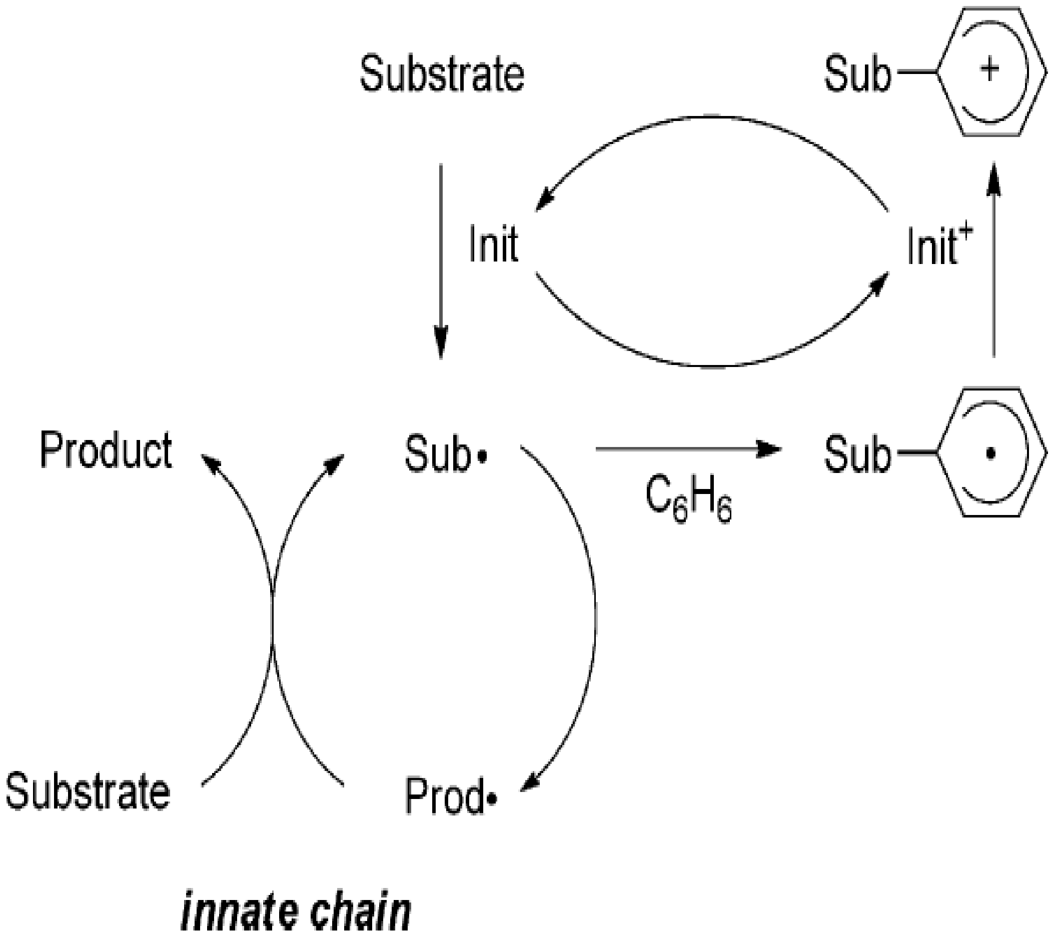






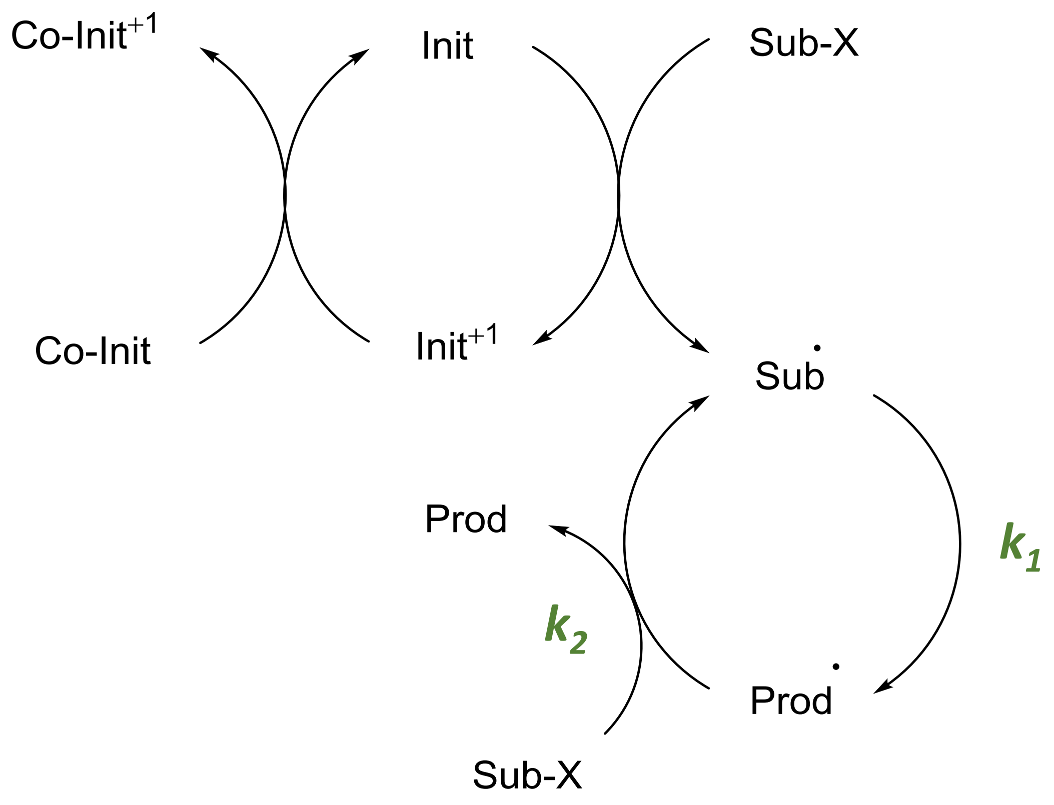
G. Povie, A.-T. Tran, D. Bonnaff, J. Habegger, Z. Hu, C. Le Narvor, P. Renaud, *Angew. Chem. Int. Ed.* **2014**, *53*, 3894 –3898; *Angew. Chem.* **2014**, *126*, 3975–3979

Making efficient an inefficient reaction without “catalysis”



K. U. Ingold, V. W. Bowry, *J. Org. Chem*. **2015**, *80*, 1321–133113

Catalysis of Initiation



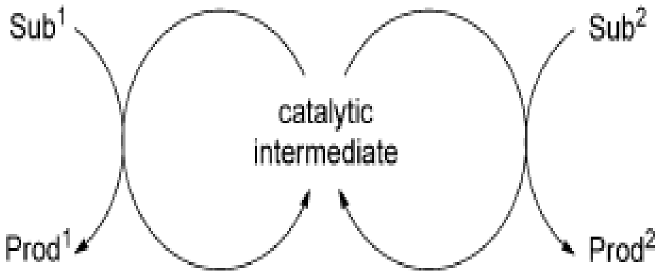
if k_1, k_2 are not high enough, re-initiation could be needed

Co-initiator (Smart initiation)

- Avoiding use of high-energy species (diazenes, peroxides)
- Use of expensive initiators (Substoichometric quantity)
- Improving the performance of short-chain processes
- Overcoming inhibition

A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

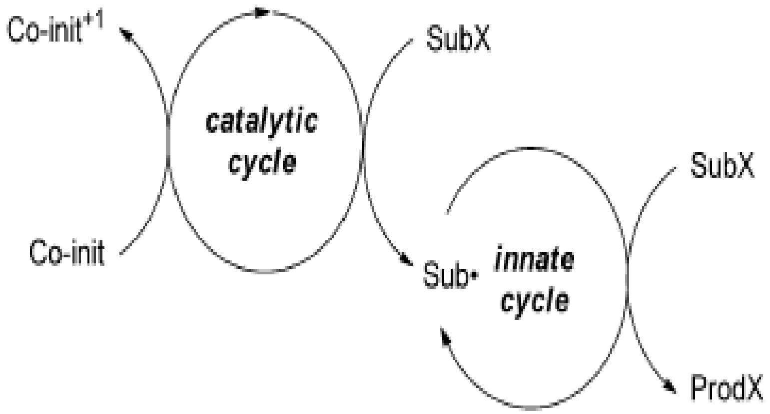
Catalysis of Initiation



Dual Catalysis
(Closed-shell)

"One turn on one cycle
triggers one turn in the other cycle"

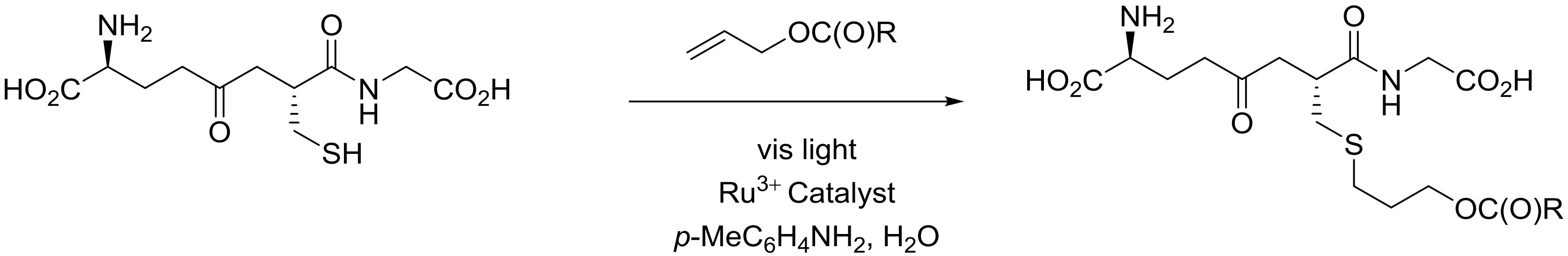
- The innate chain is free to run many times once Initiation takes place
  - Substrate itself helps initiation

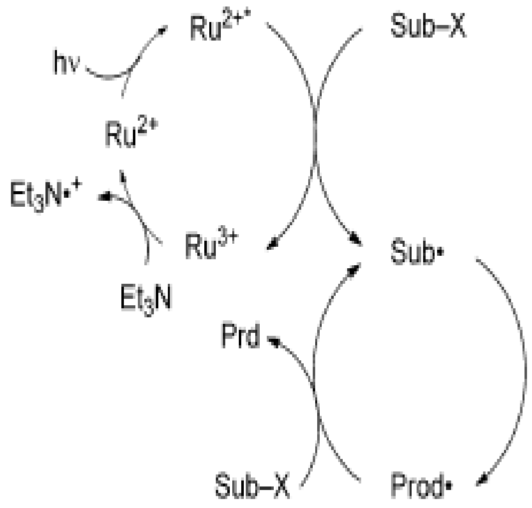


Initiation Catalysis
(Smart initiation)

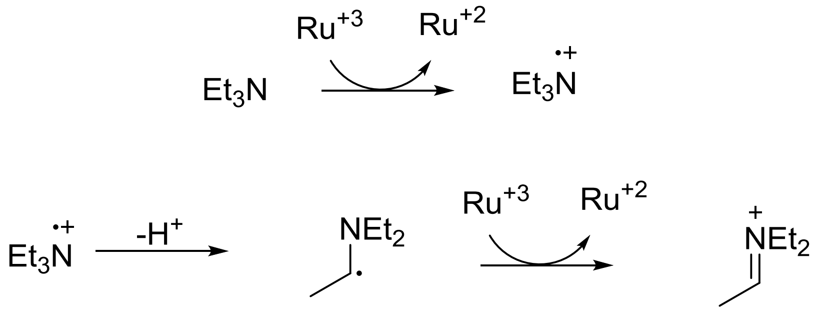
A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

Catalysis of Initiation (Examples)



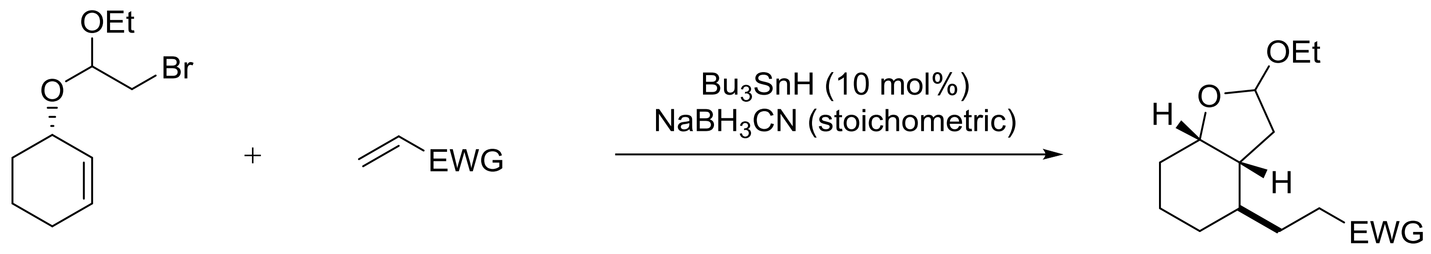


Reduction Steps

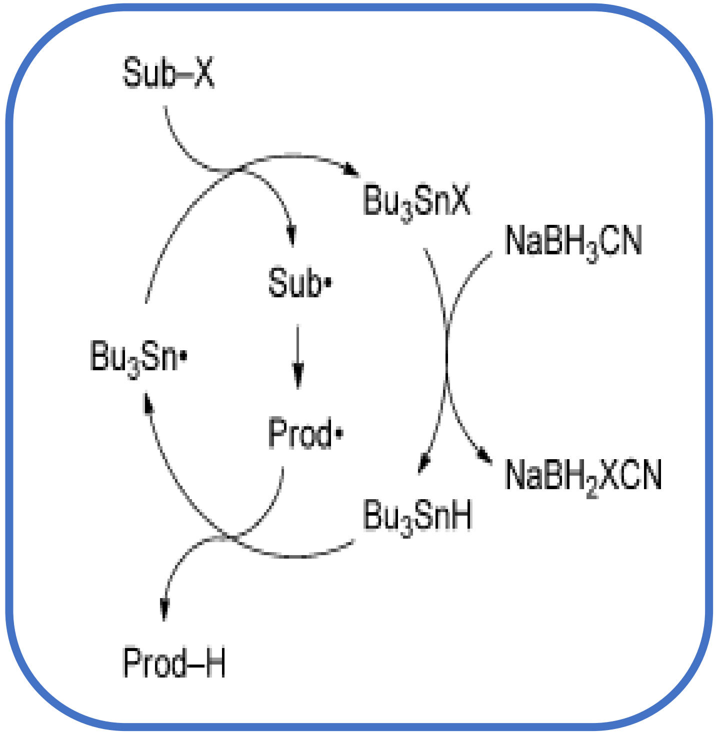


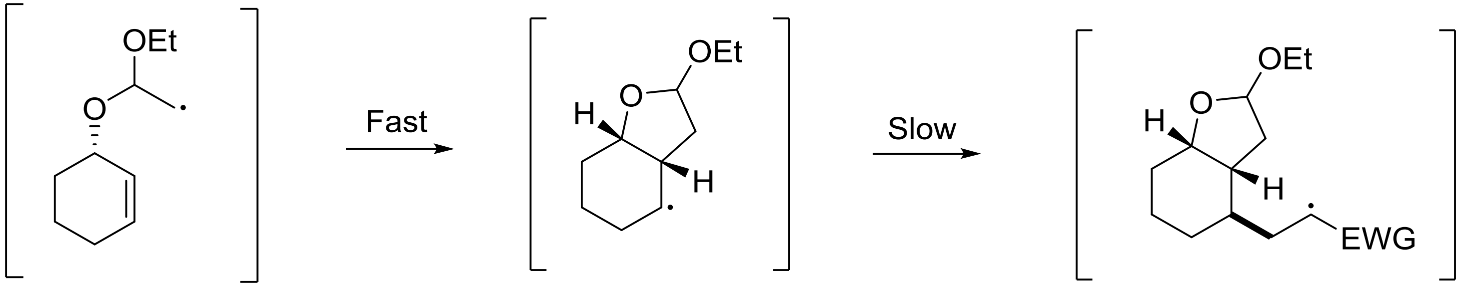
E. L. Tyson, Z. L. Niemeyer, T. P. Yoon, *J. Org. Chem*. **2014**, *79*,1427–1436.

Catalysis of Chain Reactions (Examples)



Avoiding inhibition
Avoiding secondary non-propagating reactions

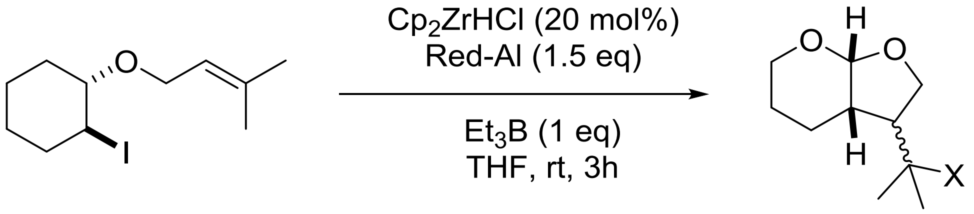




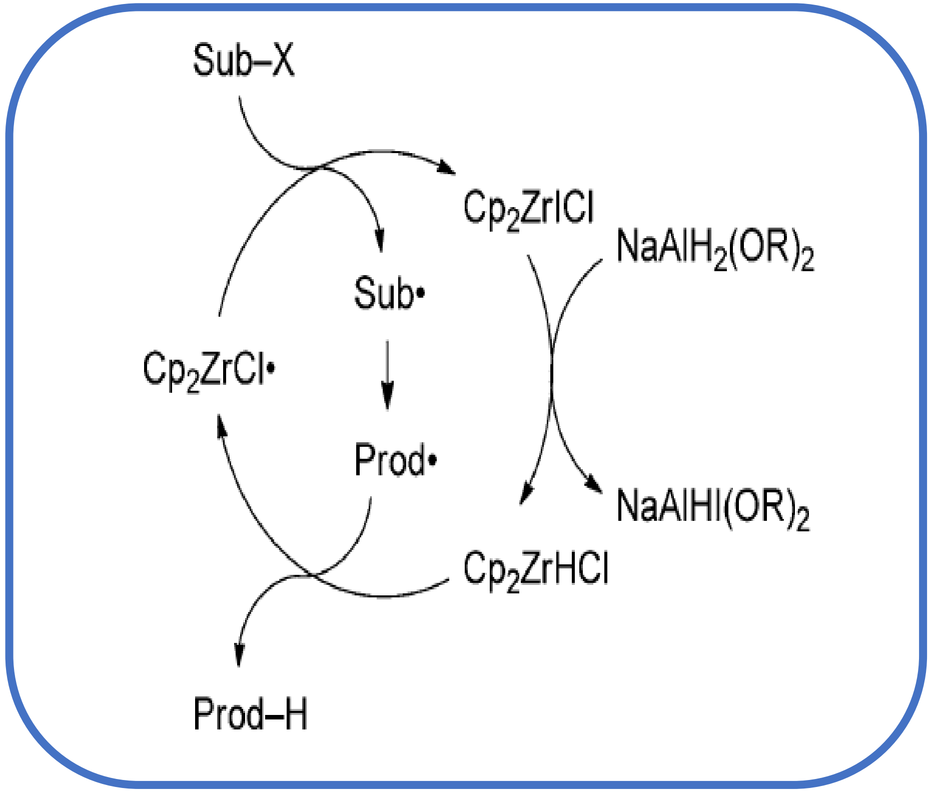
By maintaining low concentration of Bu_3SnH premature H-transfer is avoided

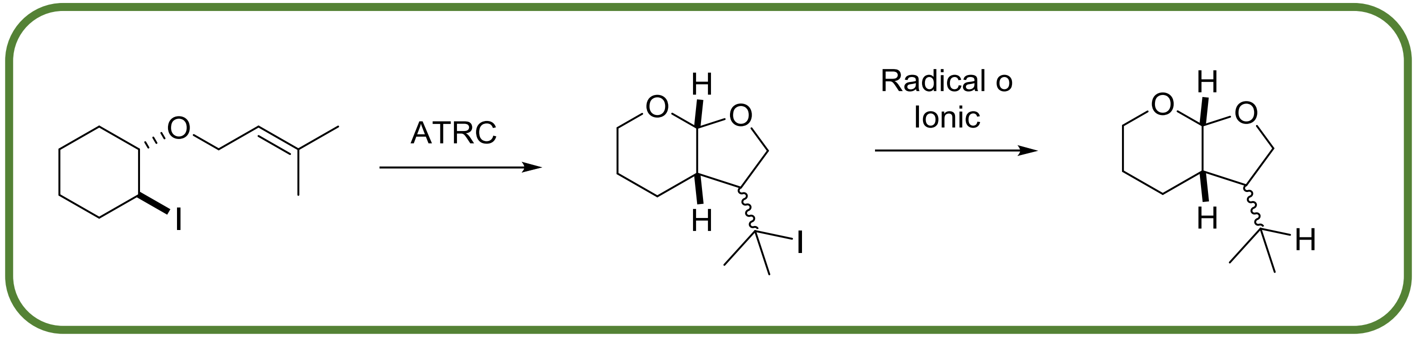
G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1986**, *108*, 303–304.

Catalysis of Chain Reactions (Examples)



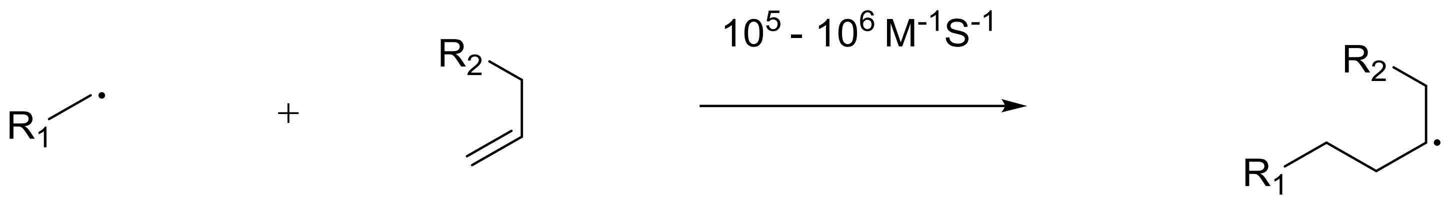
X= H, observed product
(82%, d.r. = 7:3)
X = I, possible intermediate





K. Fujita, T. Nakamura, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 3137–3138.

Lowering the TE-Energy of an innate Chain step (Catalysis approach)



"As faster a reaction, as harder to speed it up"

Maximum reached by using a catalyst: 10^9 – 10^{10} $M^{-1}s^{-1}$ (diffusion control)

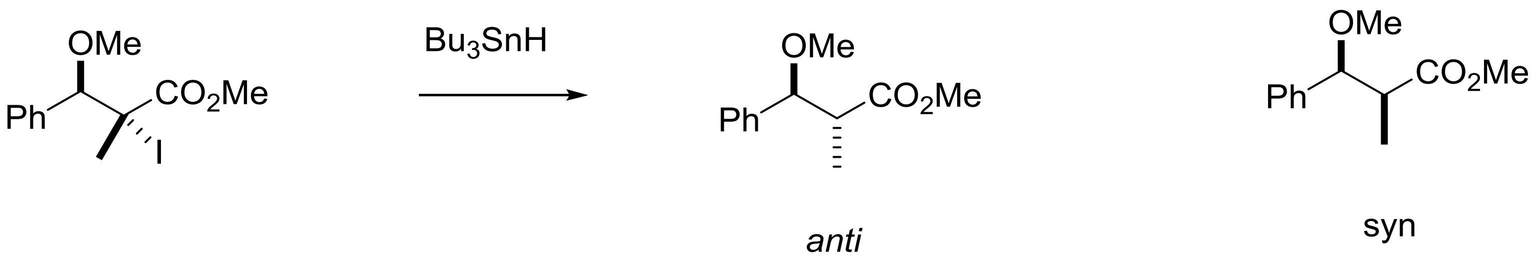
Amount of catalyst	Increasing
Stoichiometric	10000 times
10mol%	1000 times
1mol%	100 times

Usually, large amounts of additive needed

Selectivity improvement rather tan reactivity enhancement

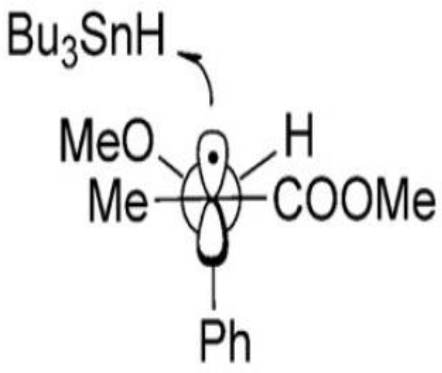
Lowering the TE-Energy of an innate Chain step (Catalysis approach)

Lewis-Acid Catalysis

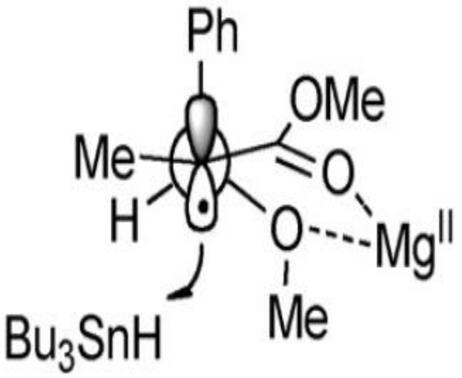


Toluene, -78°C (90%)	**25**	**1**
DCM, MgBr2/OEt2 (25mol%), -50°C (91%)	**1**	**>25**

in absence of catalyst

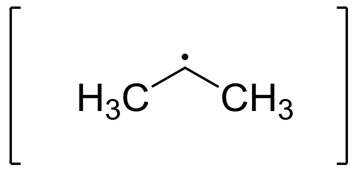


in presence of catalyst

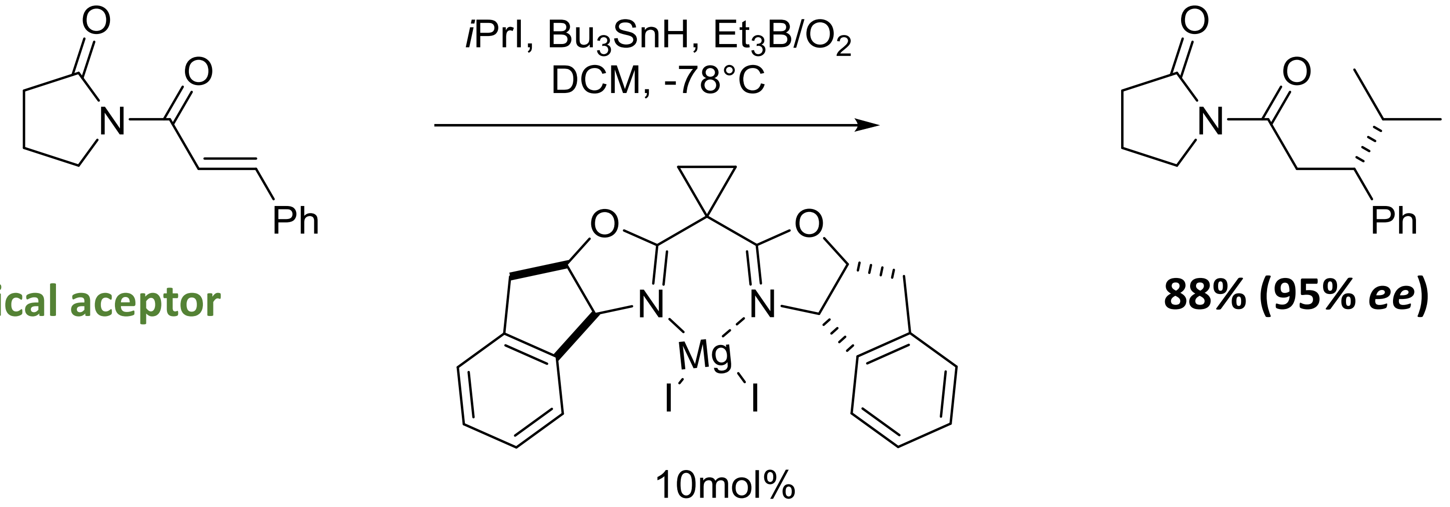


Y. Guindon, J. F. Lavallée, M. Llinas-Brunet, G. Horner, J. Rancourt, *J. Am. Chem. Soc.* **1991**, *113*, 9701–9702.

Lowering the TE-Energy of an innate Chain step (Catalysis approach)



Reactive-nucleophilic radical



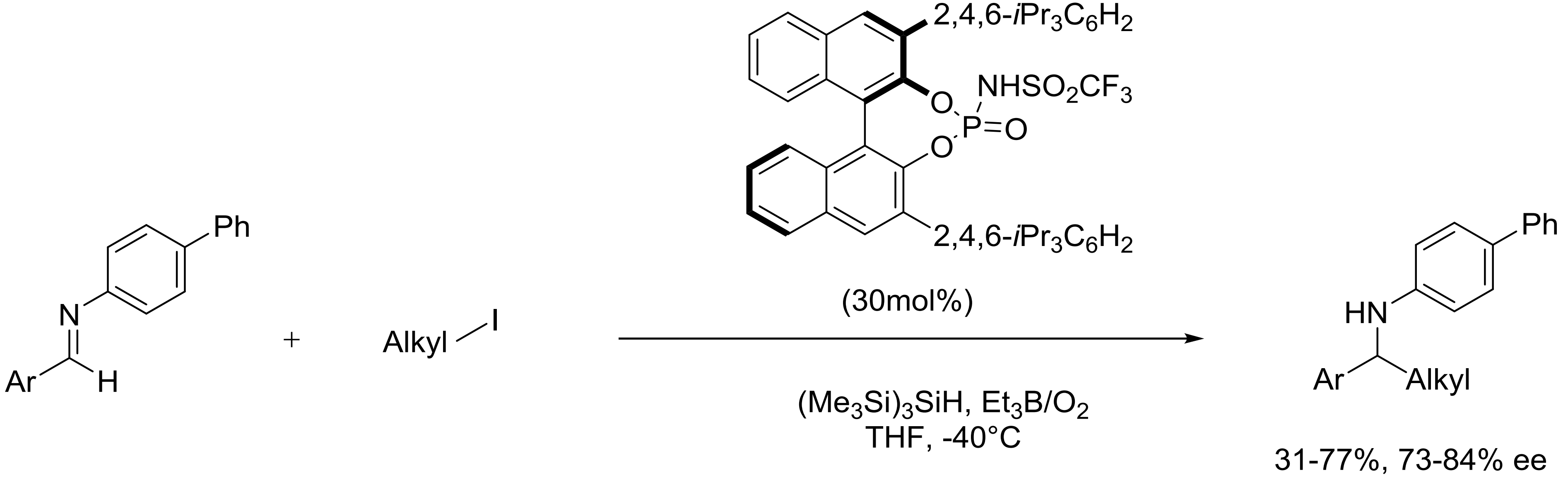
Reactive-electrophilic radical aceptor

Additional (small) activation of the acceptor
Improvement of the stereoselectivity

Y.-H. Yang, M. P. Sibi, in Encyclopedia of Radicals in Chemistry, Biology and Materials, Vol. 2 (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester, 2012, pp. 655–692.

Lowering the TE-Energy of an innate Chain step (Catalysis approach)

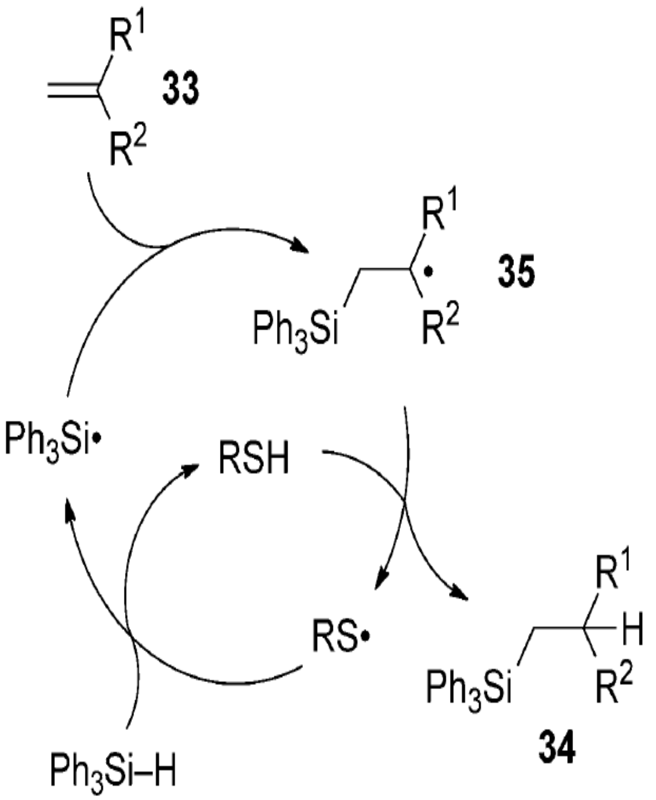
Brønsted Acid Catalysis



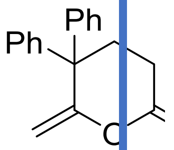
S. Lee, S. Kim, *Tetrahedron Lett*. **2009**, *50*, 3345–3348

Lowering the TE-Energy of an innate Chain step (Catalysis approach)

Brønsted Acid Catalysis



Polarity-Reversal Catalysis



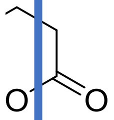
one slow, mis-matched reaction...

$A\bullet^{nuc} + B{-}H^{nuc} \xrightarrow{\text{slow}} A{-}H^{nuc} + B\bullet^{nuc}$

...is replaced by two fast, matched reactions that effect the same outcome

$A\bullet^{nuc} + X{-}H^{elec} \xrightarrow{\text{fast}} R^1{-}H^{nuc} + X\bullet^{elec}$

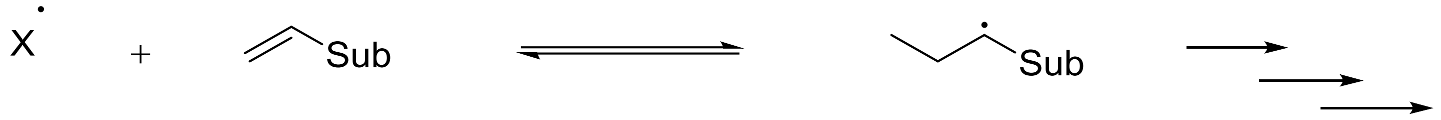
$X\bullet^{elec} + B{-}H^{nuc} \xrightarrow{\text{fast}} X{-}H^{elec} + B\bullet^{nuc}$



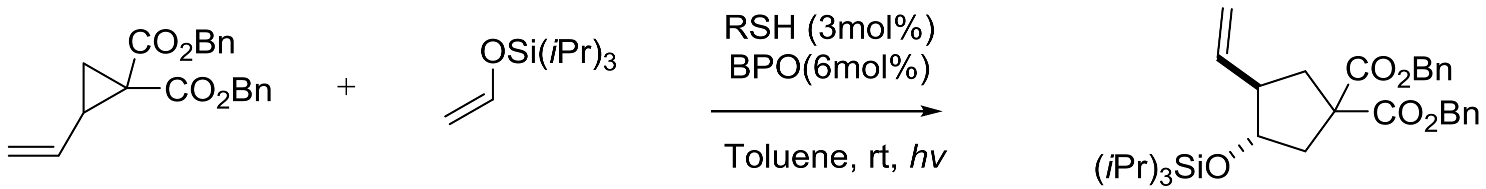
M. B. Haque, B. P. Roberts, *Tetrahedron Lett*. **1996**, *37*, 9123–9126
H.-S. Dang, B. P. Roberts, *Tetrahedron Lett*. **1995**, *36,* 2875–2878
R. P. Allen, B. P. Roberts, C. R. Willis, *J. Chem. Soc. Chem. Commun*. **1989**, 1387–1388;
H. Subramanian, R. Moorthy, M. P. Sibi, *Angew. Chem. Int. Ed*. **2014**, *53*, 13660-13662

Lowering the TE-Energy of an innate Chain step (Catalysis approach)

Addition/Elimination



Disadvantage?

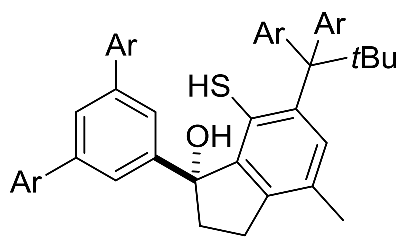


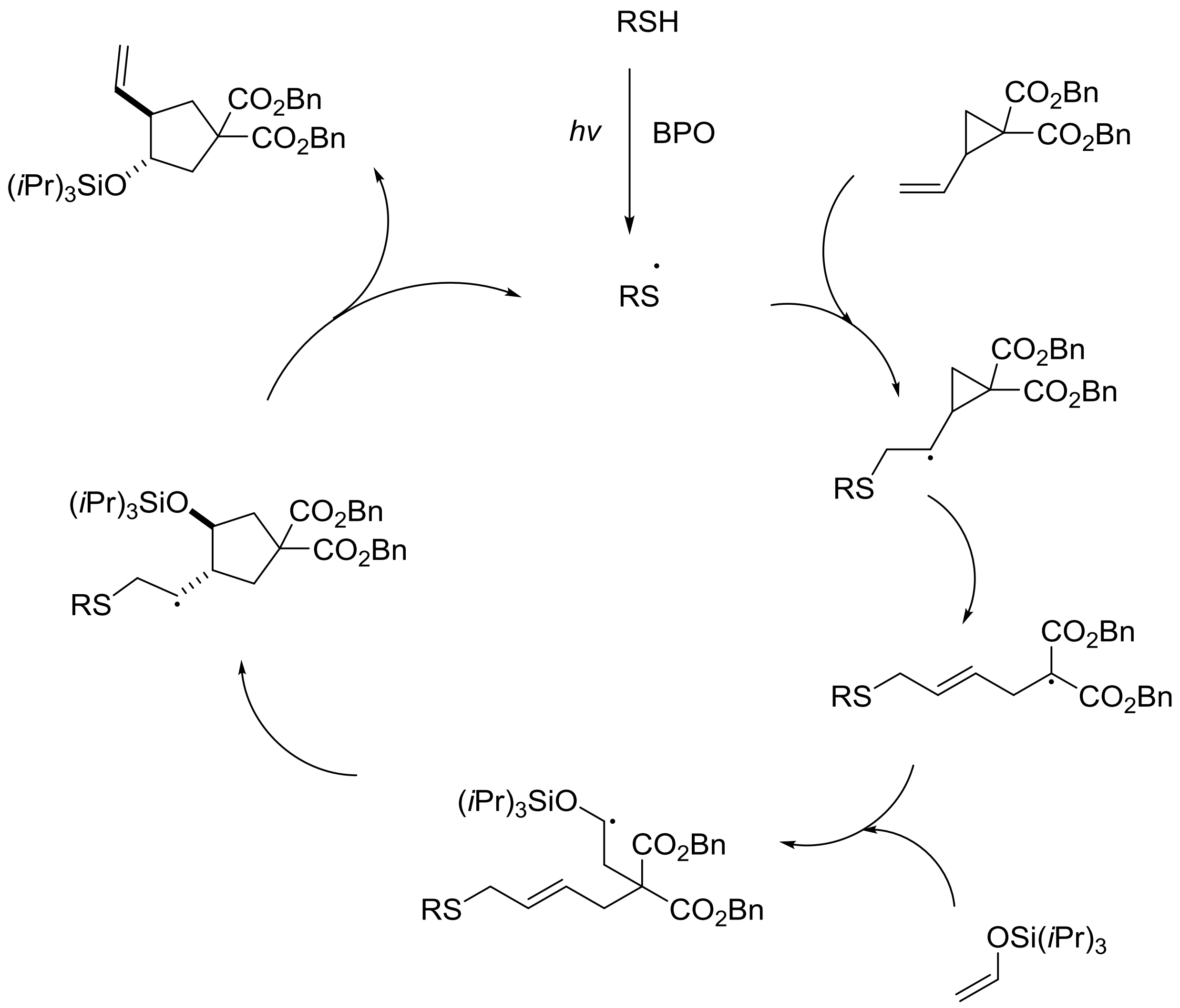
90%, d.r. > 95:5, 90% *ee*

T. Hashimoto, Y. Kawamata, K. Maruoka, *Nat. Chem*. **2014**, *6*, 702 –705

Lowering the TE-Energy of an innate Chain step (Catalysis approach)

Addition/Elimination



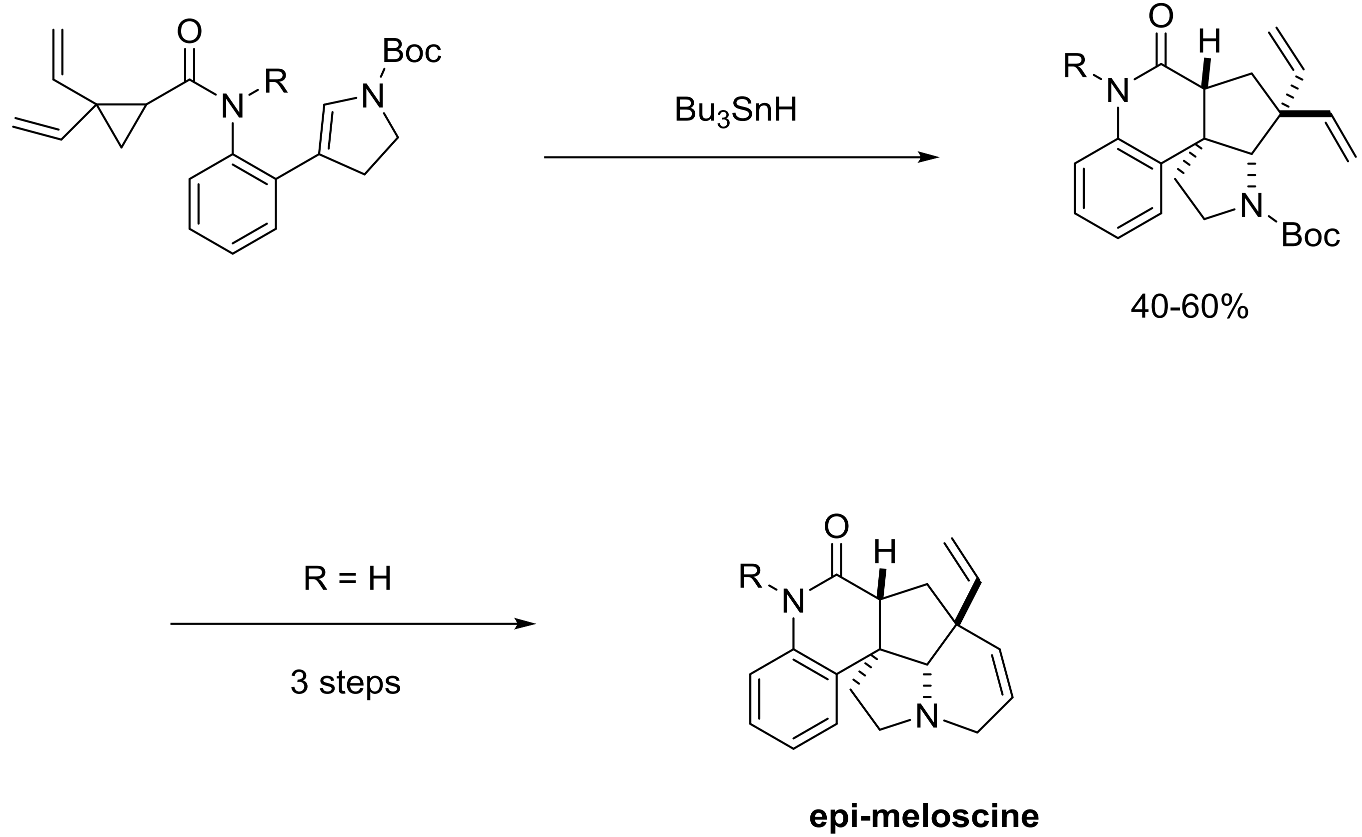


T. Hashimoto, Y. Kawamata, K. Maruoka, *Nat. Chem*. **2014**, *6*, 702 –705

Lowering the TE-Energy of an innate Chain step (Catalysis approach)

Addition/Elimination

Application in the total synthesis
Of natural products



H. Zhang, D. P. Curran, *J. Am. Chem. Soc.* **2011**, *133*, 10376 –10378

Redox Catalysis (Chain-reactions)

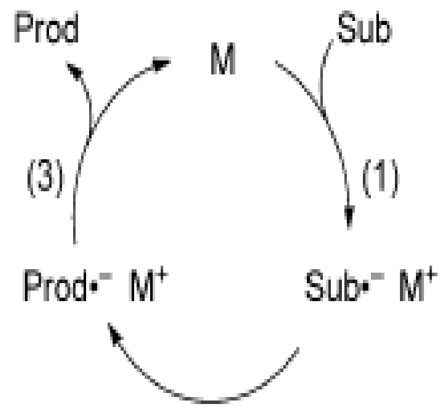
Redox Catalysis

Electron Catalysis

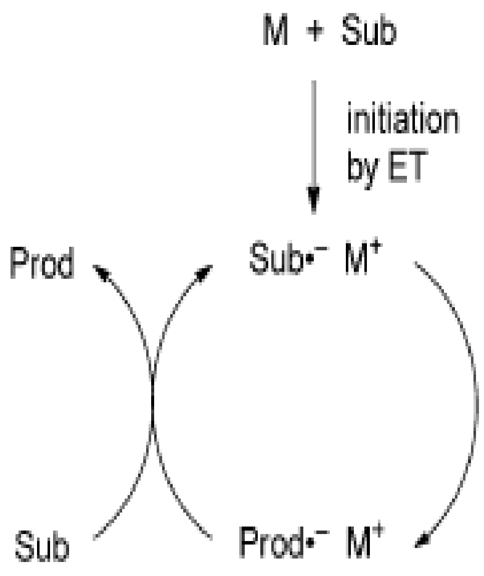
Hole Catalysis

Sub $\xrightarrow{ET}$ [Radical / Radical ion] $\longrightarrow$ Prod

Are metals in redox processes true catalyst?



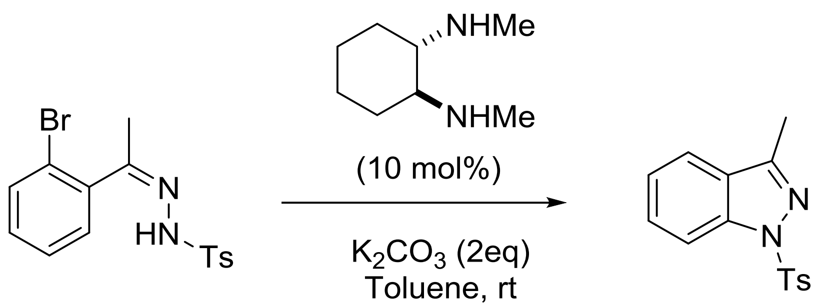
Metal involved acts as a catalyst

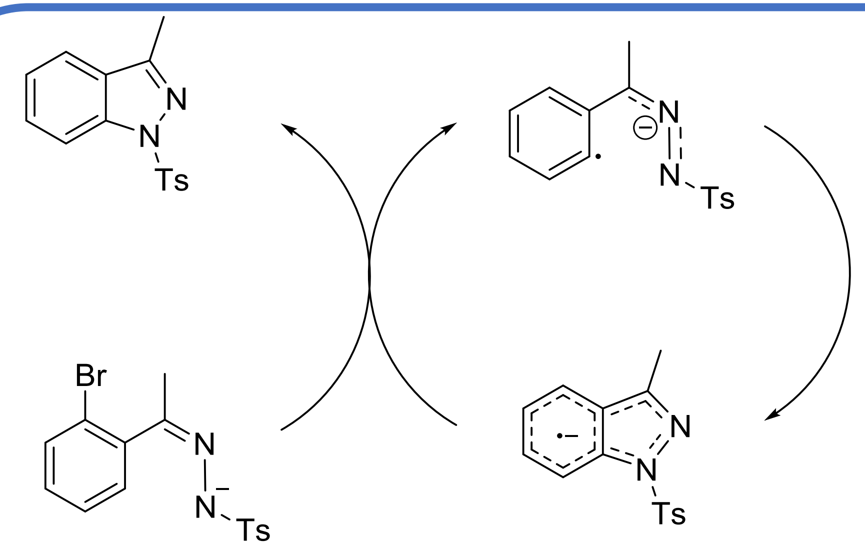


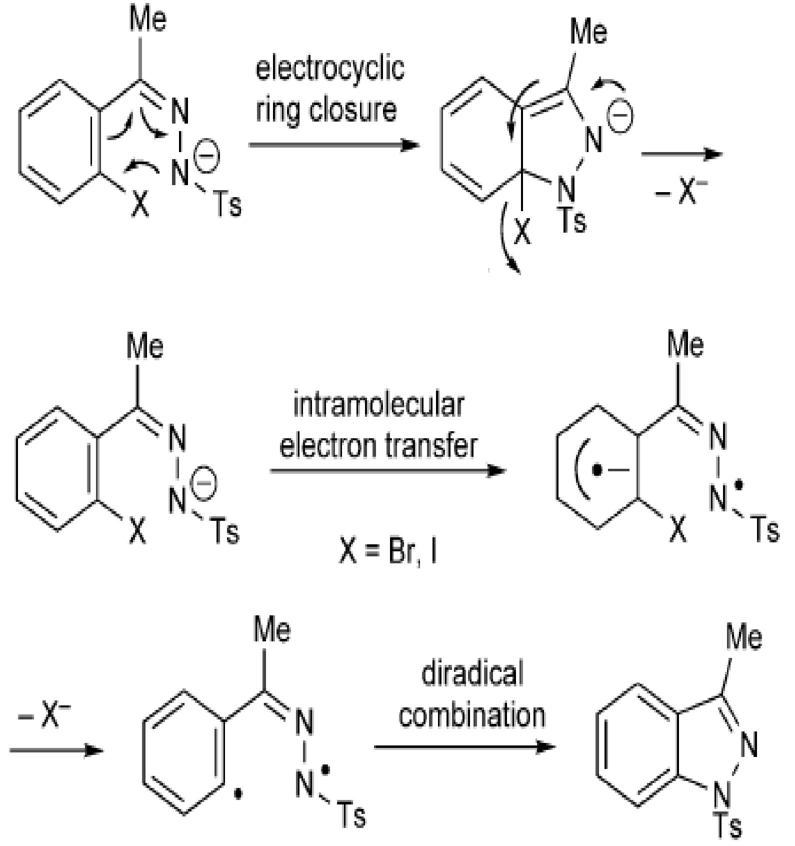
Metal involved is
An initiator
A single electron is the
True catalyst

A. Studer, D. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58 – 102

Redox Catalysis (Chain-reactions, electron catalysis)

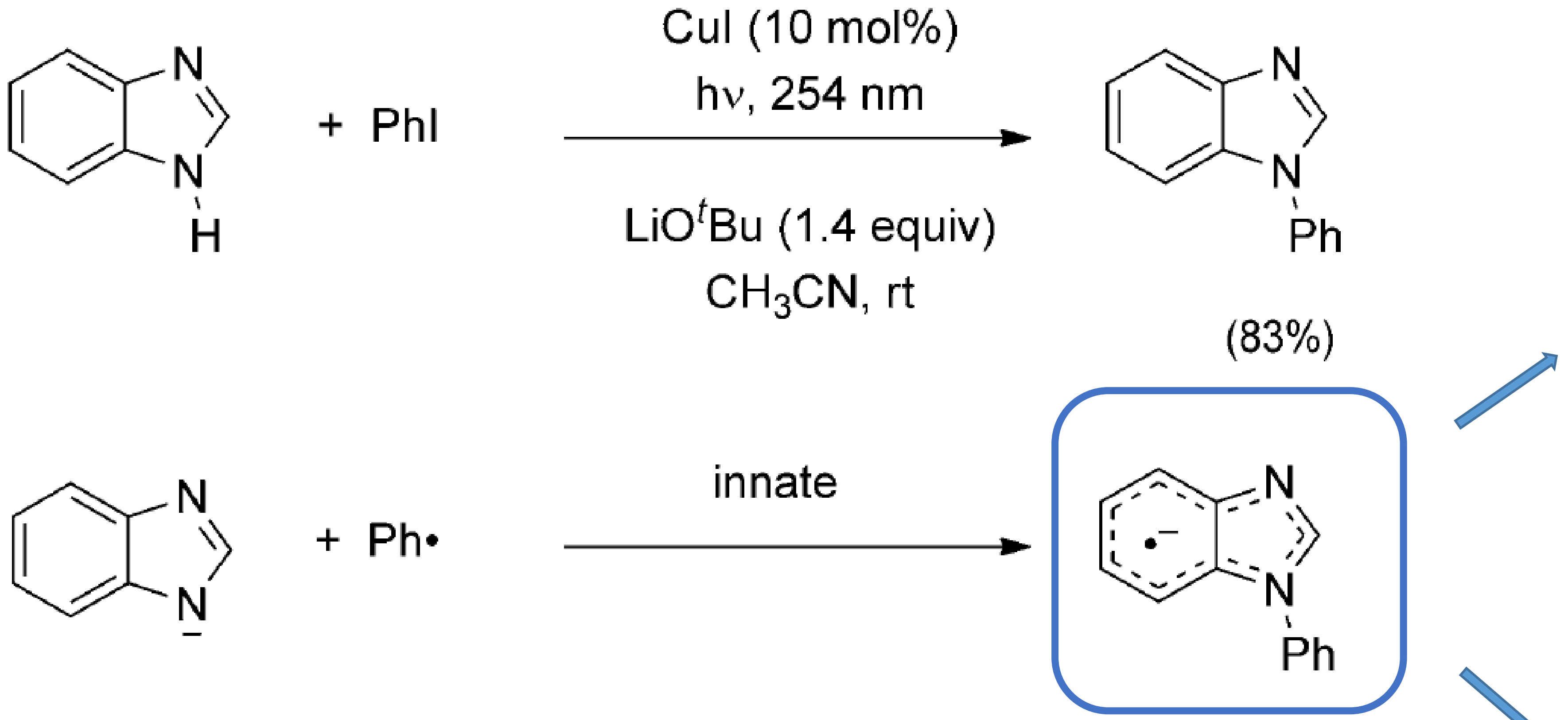






I. Thomé, C. Besson, T. Kleine, C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 7509–7513; *Angew. Chem.* **2013**, *125*, 7657–7661

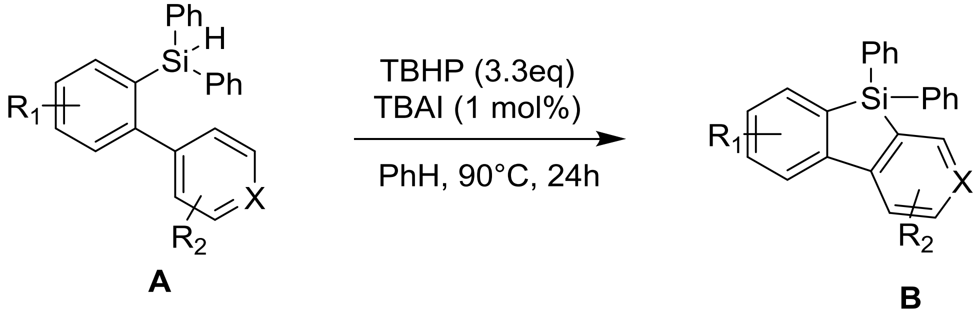
Redox Catalysis (Chain-reactions)

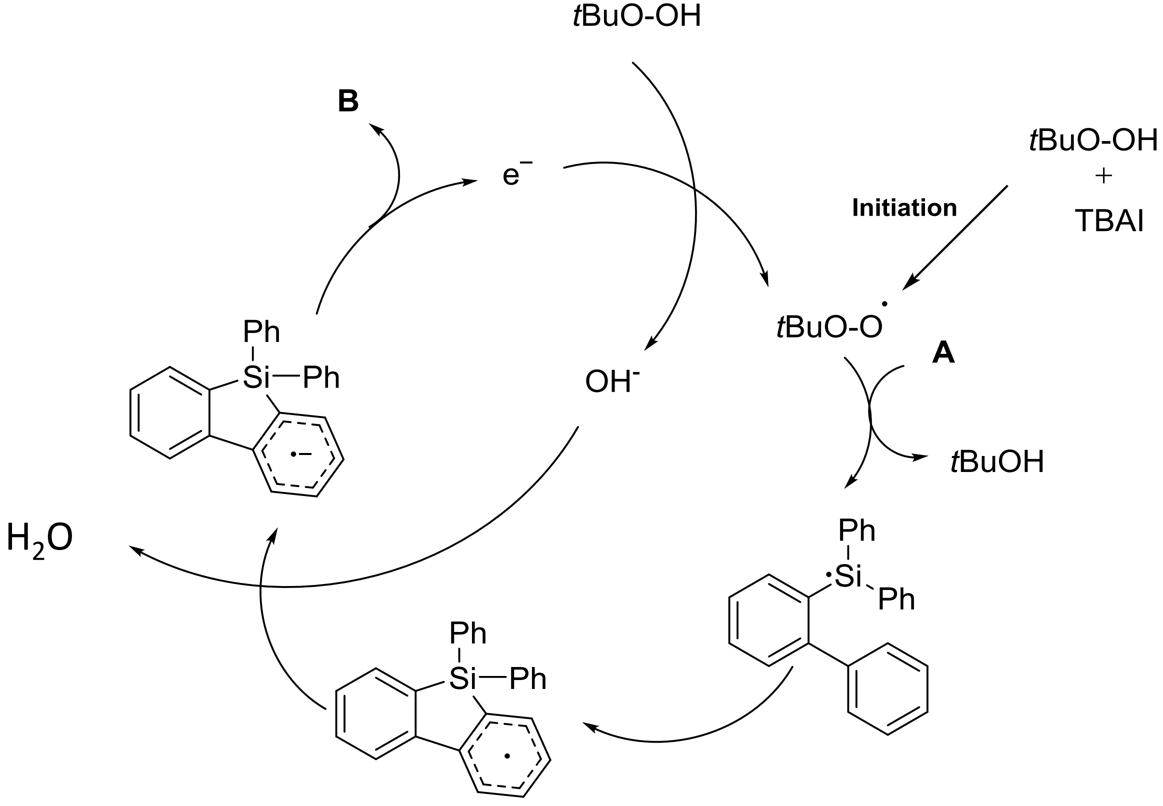


Electron-transfer to PhI (metal-initiated, Electron-catalyzed)

Electron-transfer to Cu (Redox-catalyzed, Metal-catalyzed)

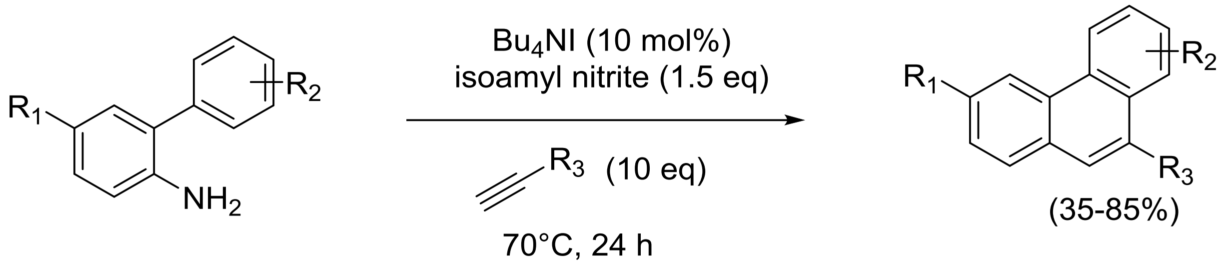
Redox Catalysis (Chain-reactions, electron catalysis)

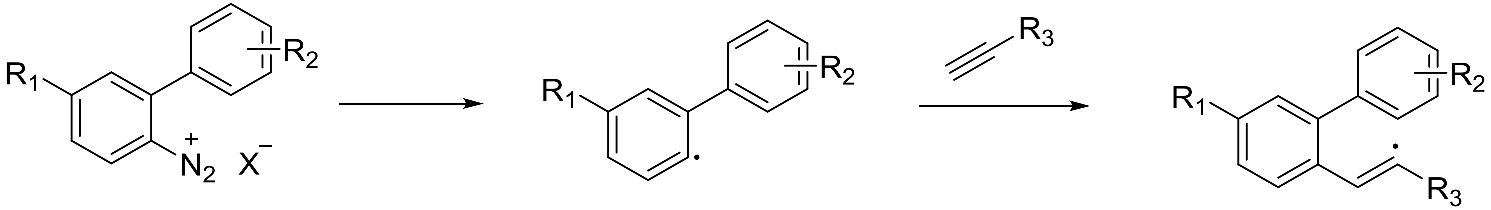




D. Leifert, A. Studer, *Org. Lett.* **2015**, *17*, 386–389

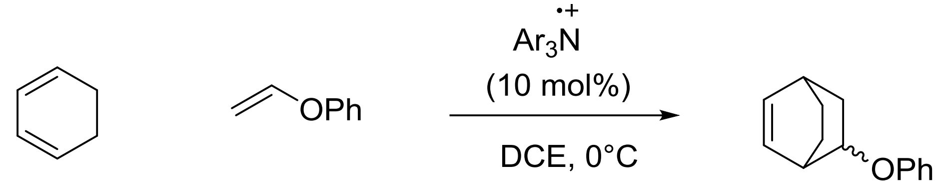
Redox Catalysis (Chain-reactions, Chain-reactions, electron catalysis)

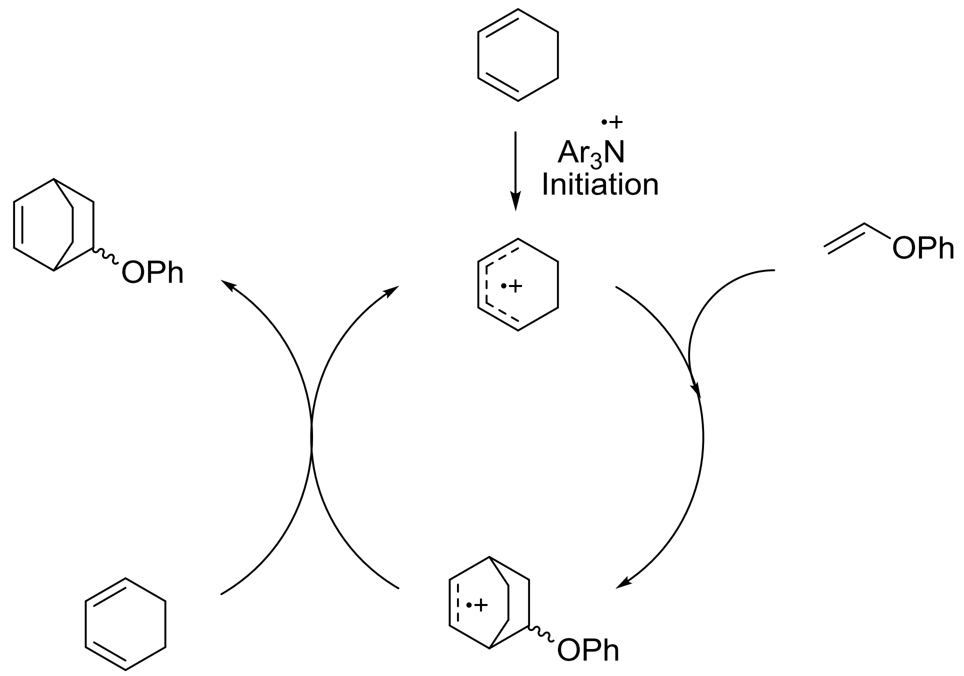


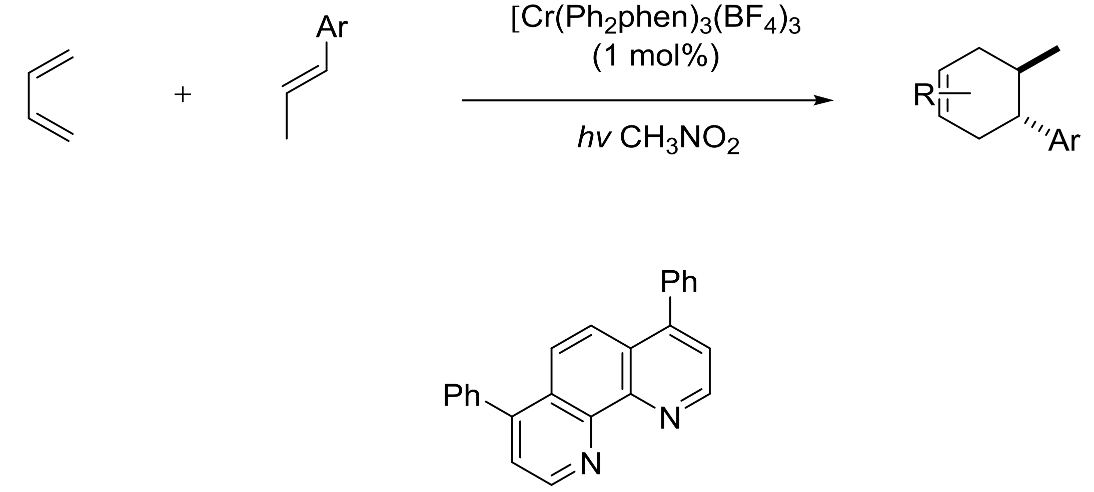


M. Hartmann, C. G. Daniliuc, A. Studer, *Chem. Commun.* **2015**, *51*, 3121–3123

Hole Catalysis





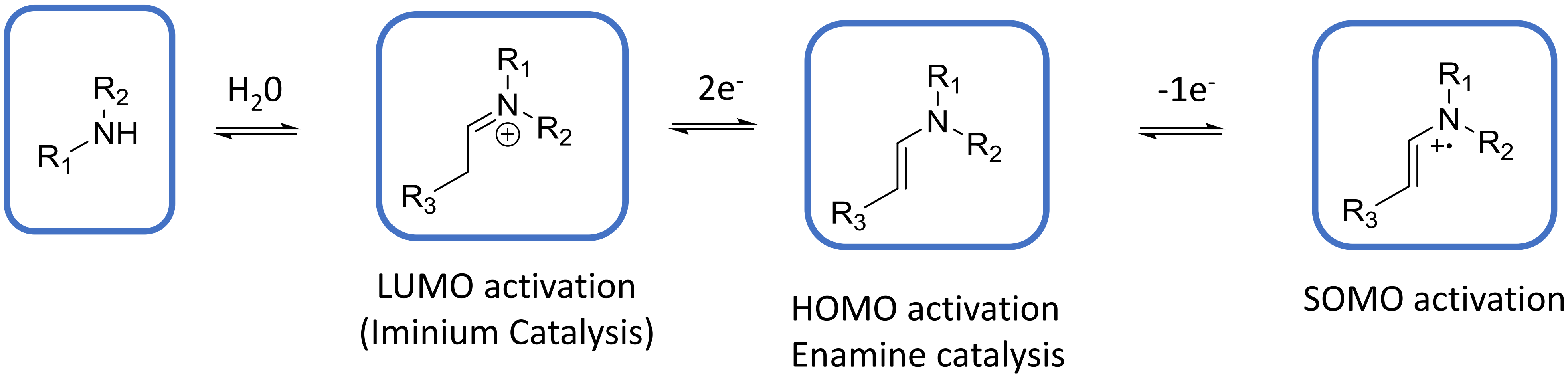


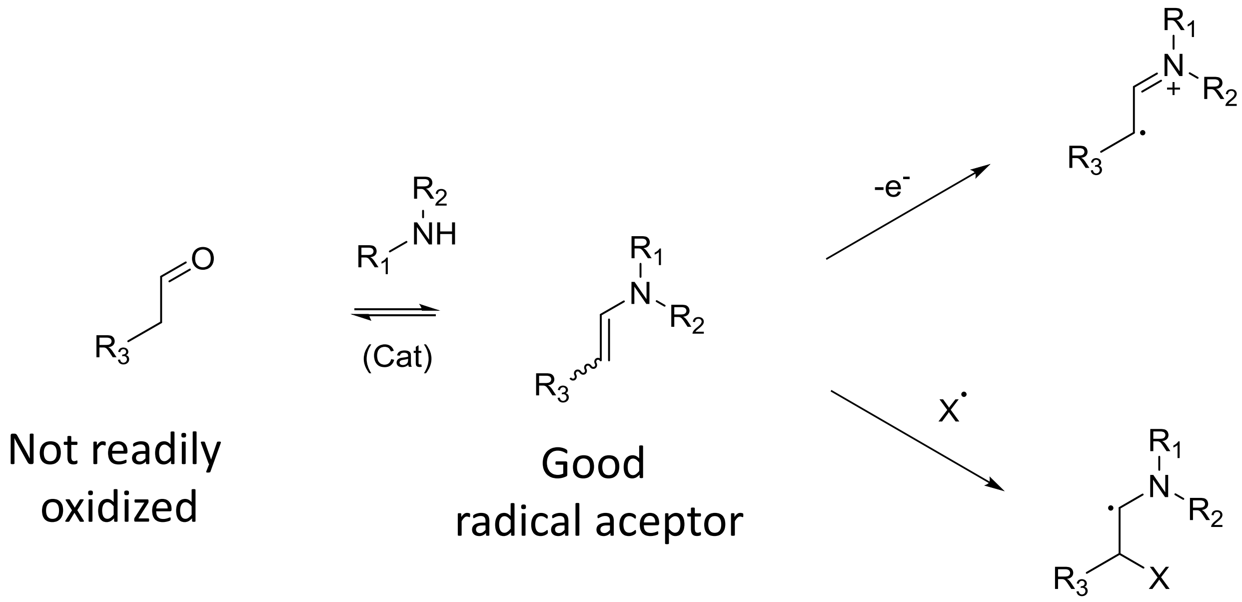
N. L. Bauld, in Advances in Electron Transfer Chemistry, Vol. 2 (Ed.: P. S. Mariano), Jai Press, Greenwich, CT, 1992,pp. 1–66

N. L. Bauld, *Tetrahedron* **1989**, *45*, 5307–5363

S. M. Stevenson, M. P. Shores, E. M. Ferreira, *Angew. Chem. Int. Ed*. **2015**, *54*, 6506–6510; *Angew. Chem*. **2015**, *127*, 6606 –6610.

Amine Catalysis (Innate chains involving enamines)

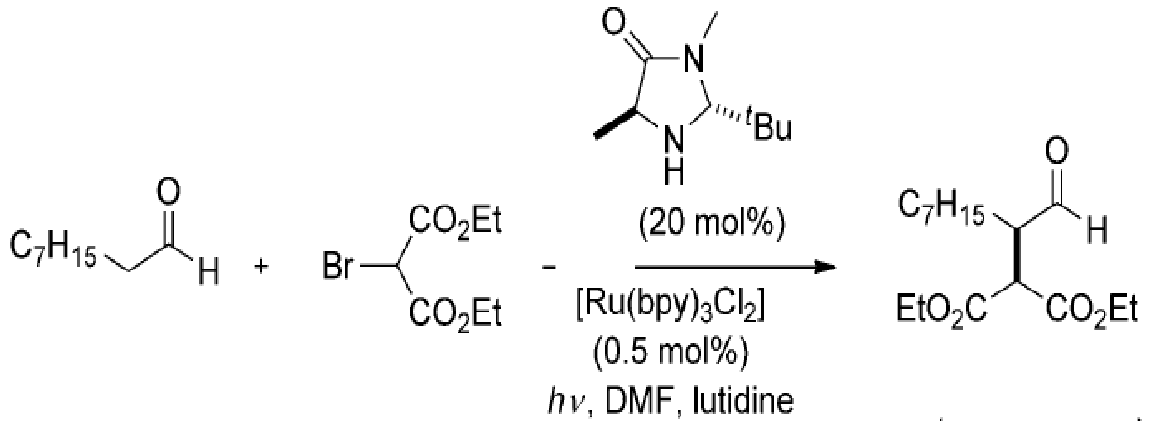


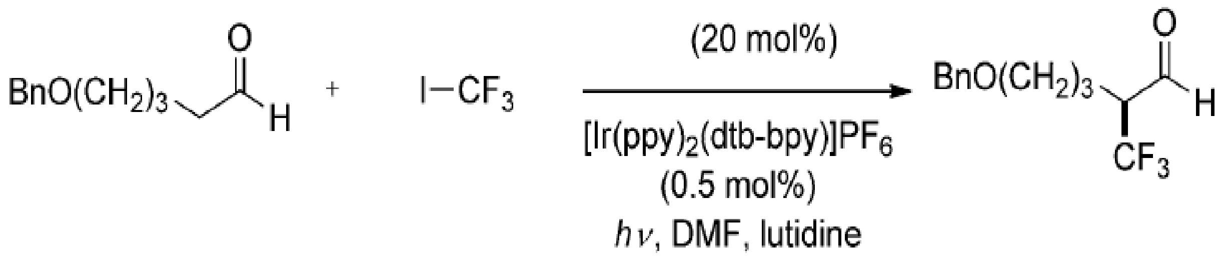


SOMO Activation
Innate Chain?

A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

Amine Catalysis (Innate chains involving enamines)





D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77– 80.

D. A. Nagib, M. E. Scott, D. W. C. MacMillan*, J. Am. Chem.Soc*. **2009**, *131*, 10875–10877..

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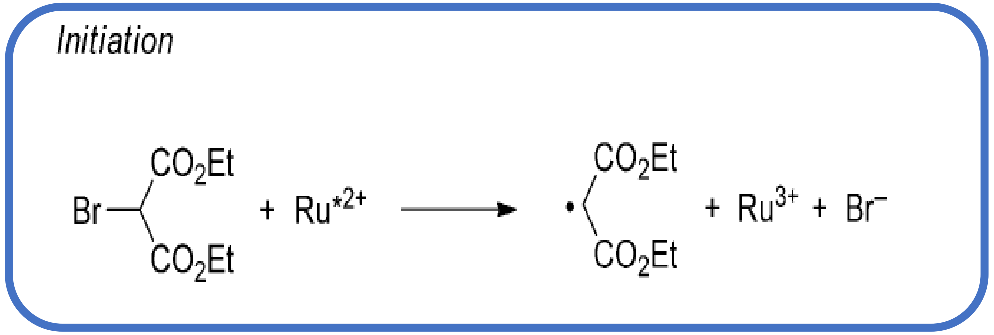
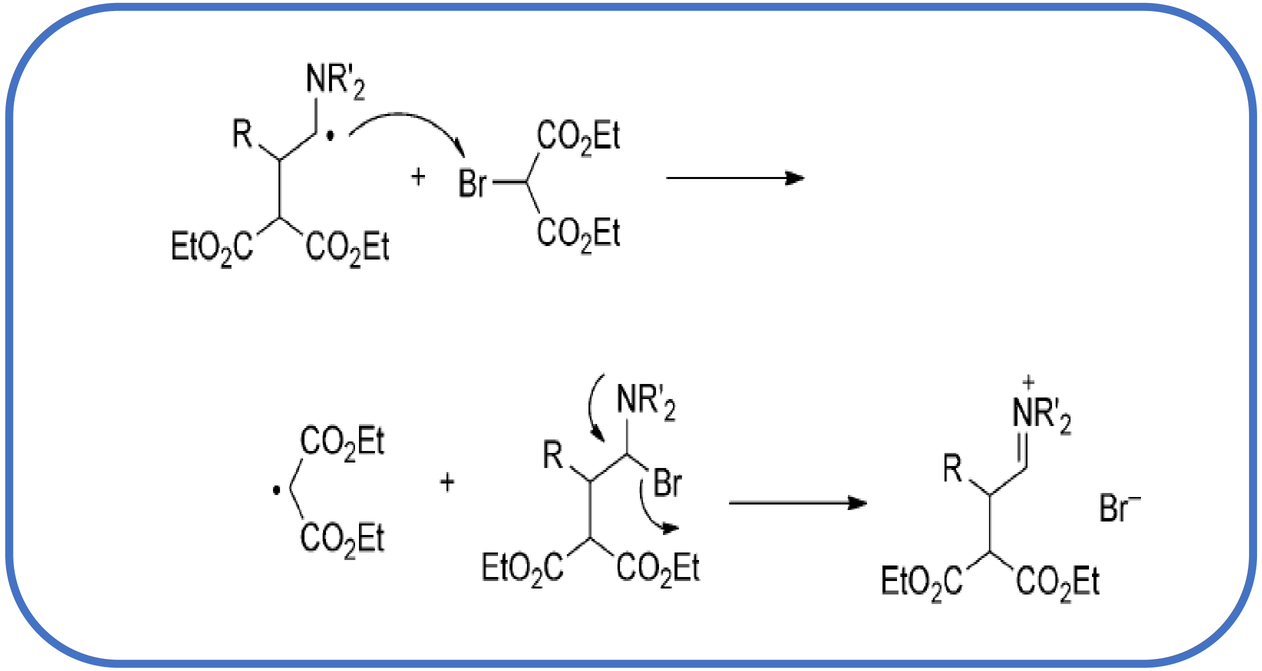
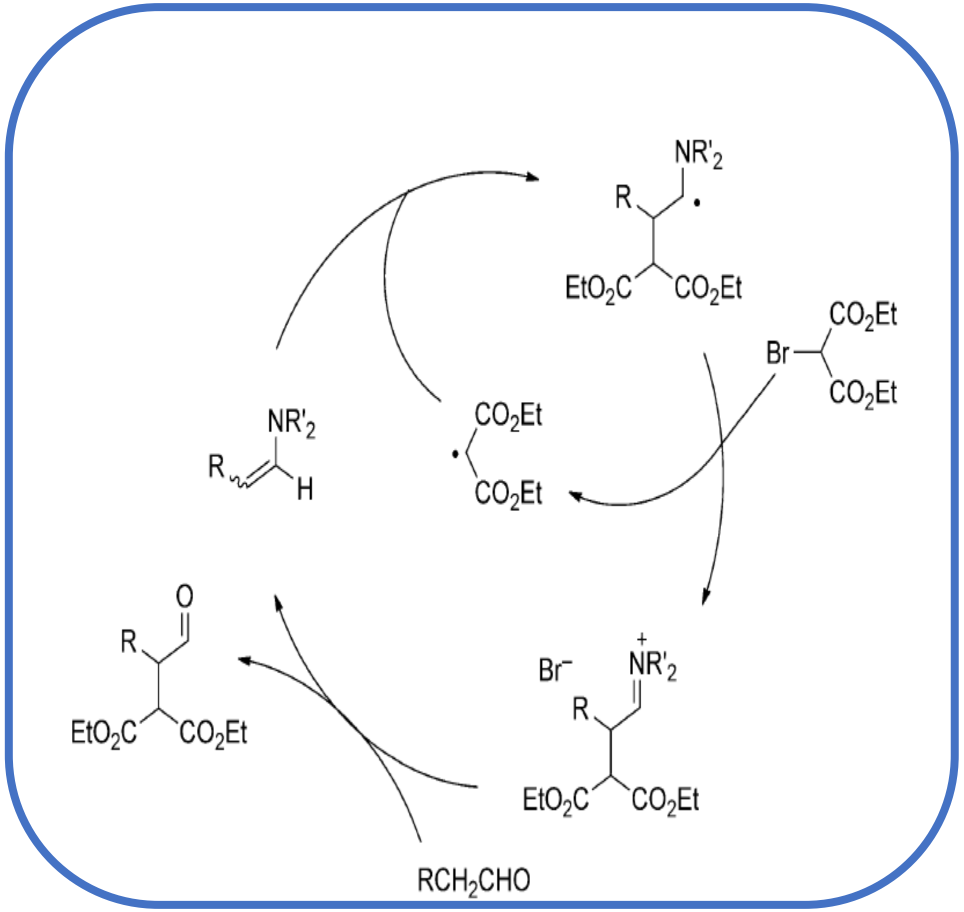




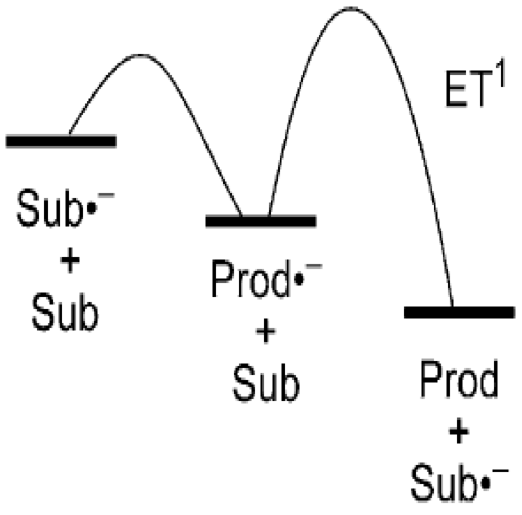


D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77– 80.
D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem.Soc*. **2009**, *131*, 10875–10877.

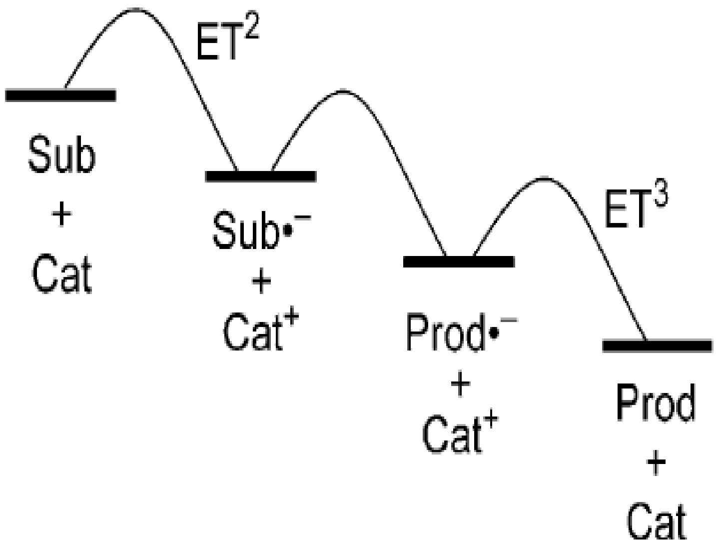
Redox Catalysis (Non-Chain reactions)

Electron-transfer or Atom-transfer reactions

Reaction coordinate of electron catalysis with an exothermic ET step that is too slow to support the chain

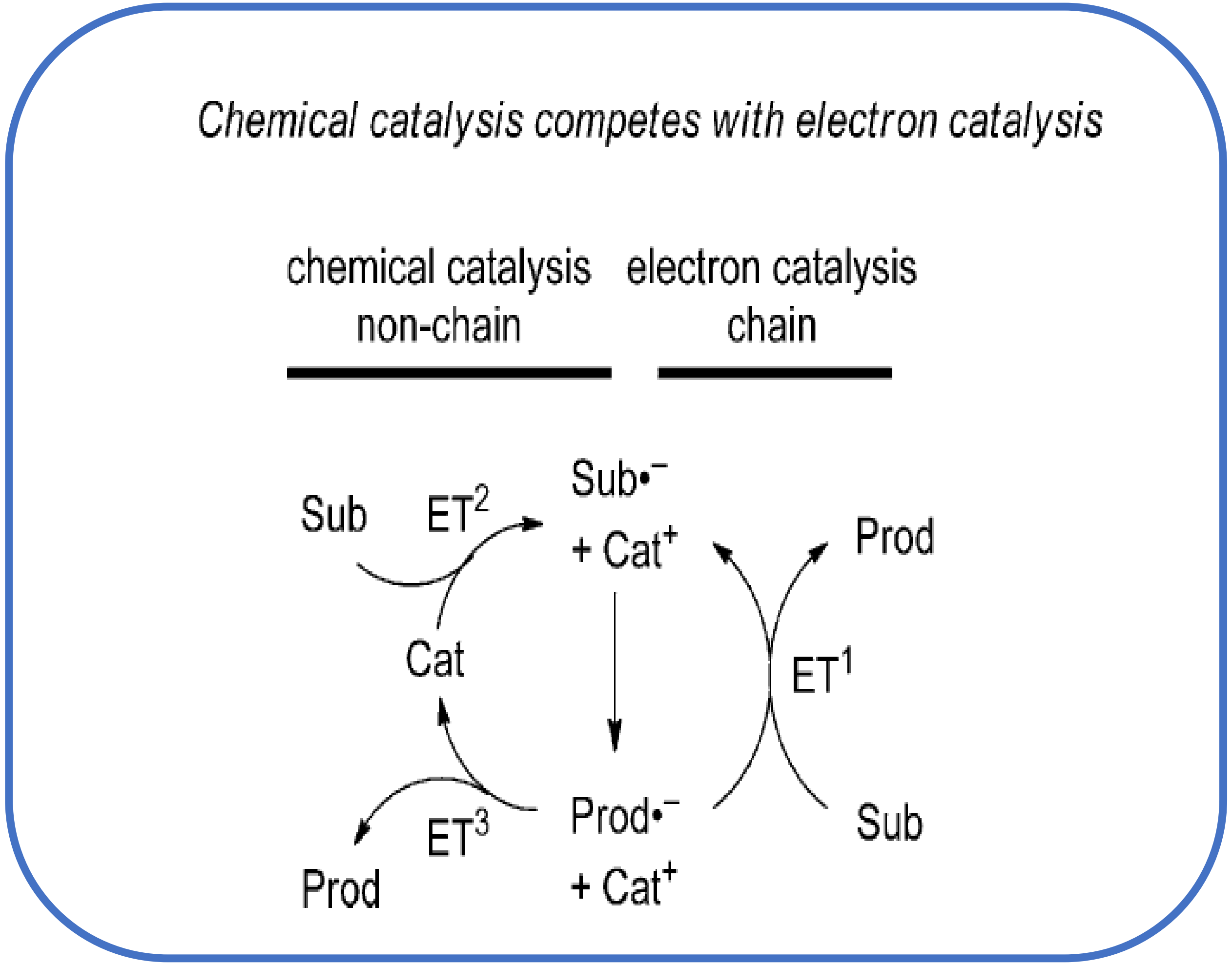


Reaction coordinate diagram of redox catalysis cycle in which two fast steps replace the slow step



A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

Redox Catalysis (Non-Chain reactions) / Intertwined mechanisms



A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

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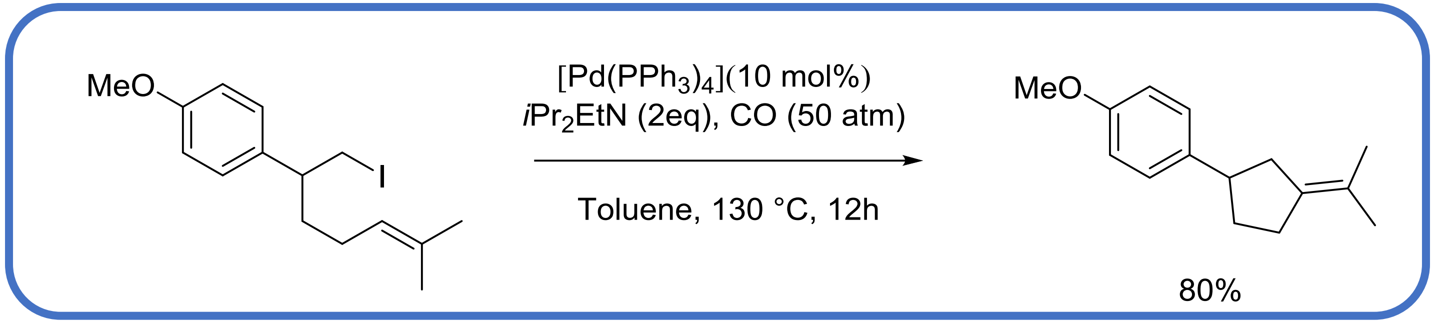
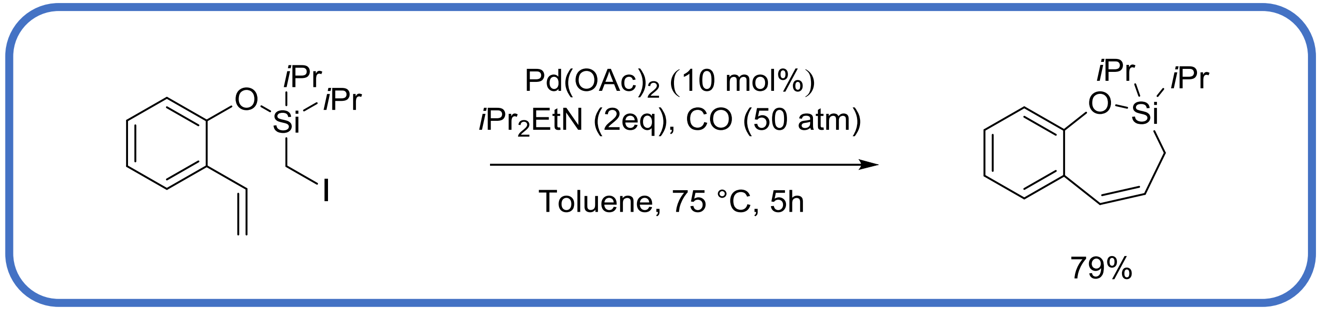
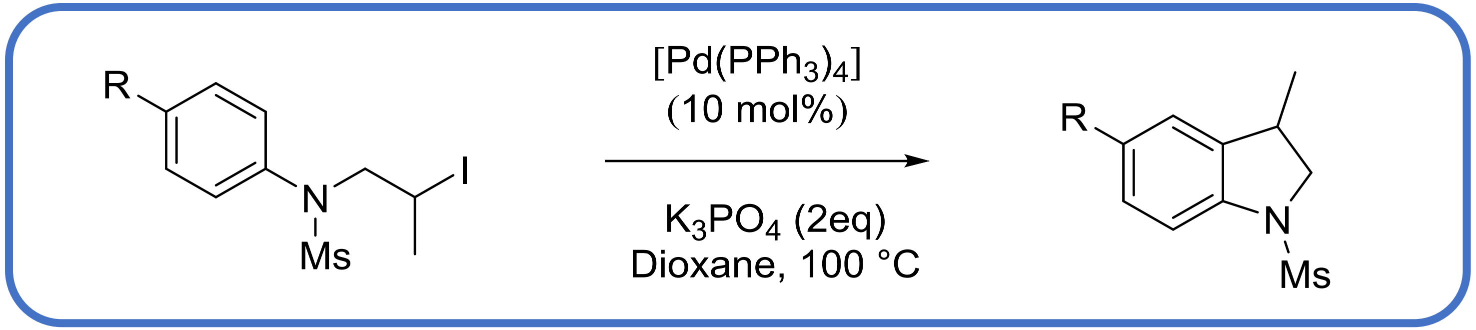
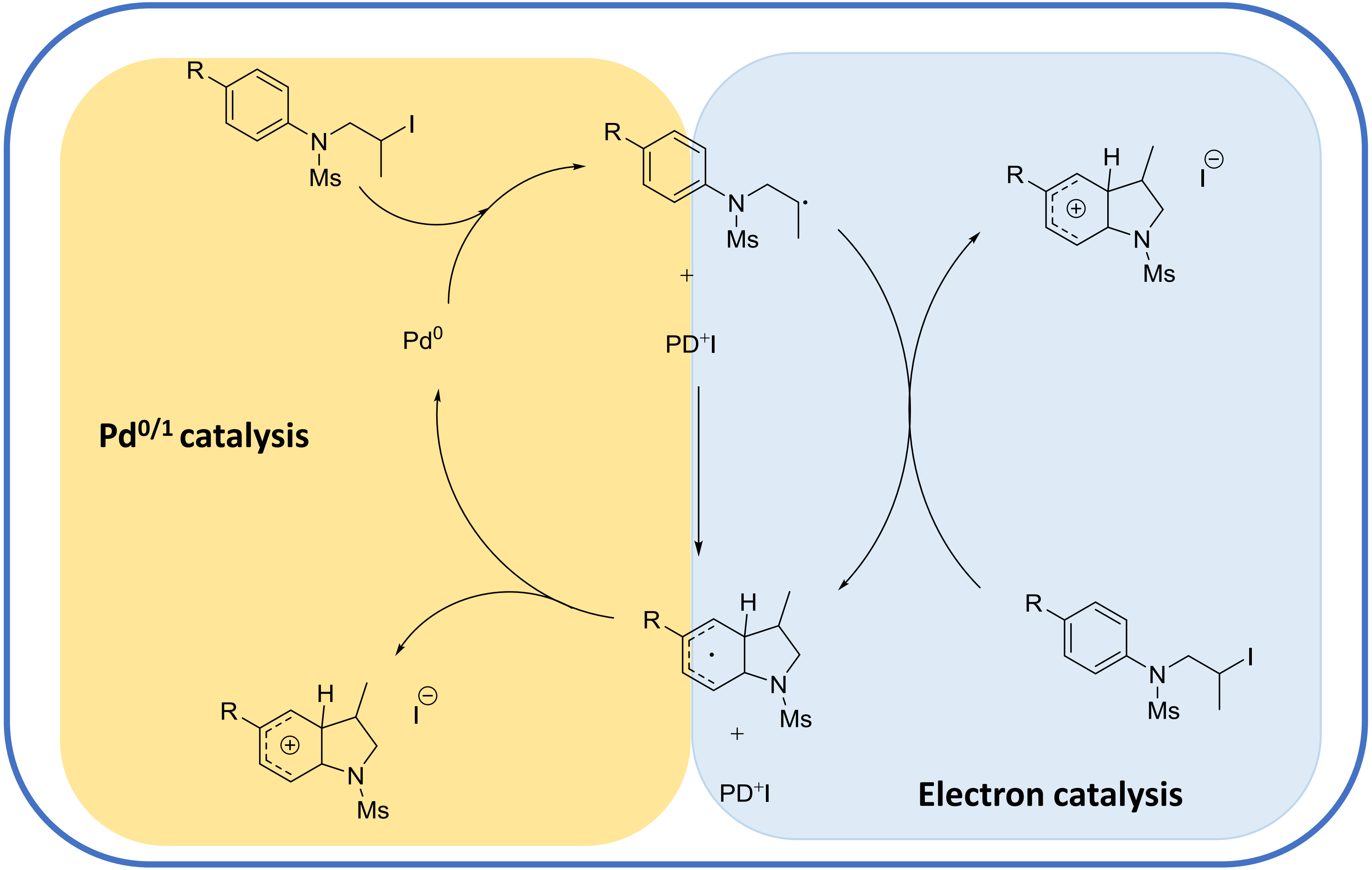






K. S. Bloome, R. L. McMahen, E. J. Alexanian, *J. Am. Chem. Soc*. **2011**, *133*, 20146–20148.
M. Parasram, V. O. Iaroshenko, V. Gevorgyan, *J. Am. Chem. Soc*. **2014**, *136*, 17926–17929.
A. R. O. Venning, P. T. Bohan, E. J. Alexanian, *J. Am. Chem.Soc*. **2015**, *137*, 3731–3734

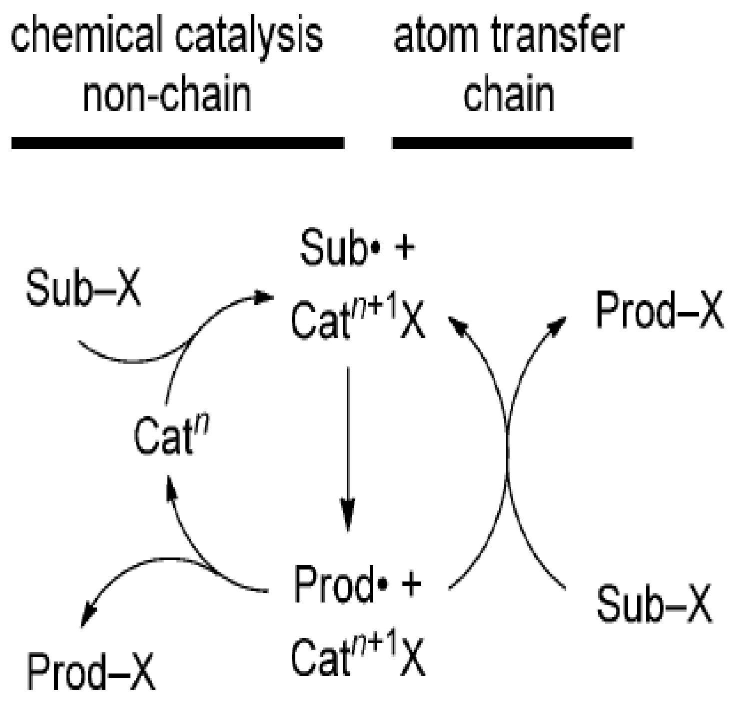
Redox Catalysis (Non-Chain reactions)



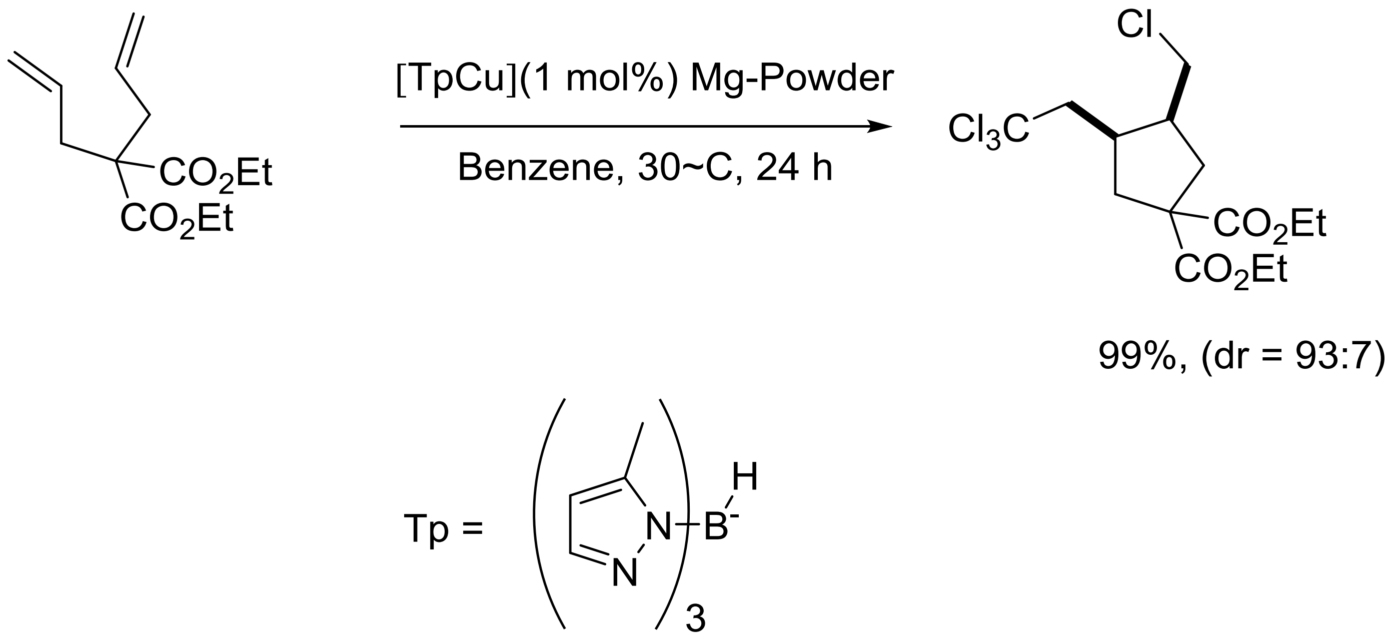
Redox Catalysis (Non-Chain reactions) / Atom-transfer reactions

Net Reaction

$$\text{Sub-X} \xrightarrow[\text{Catalyst}]{\text{Redox}} \text{Prod-X}$$

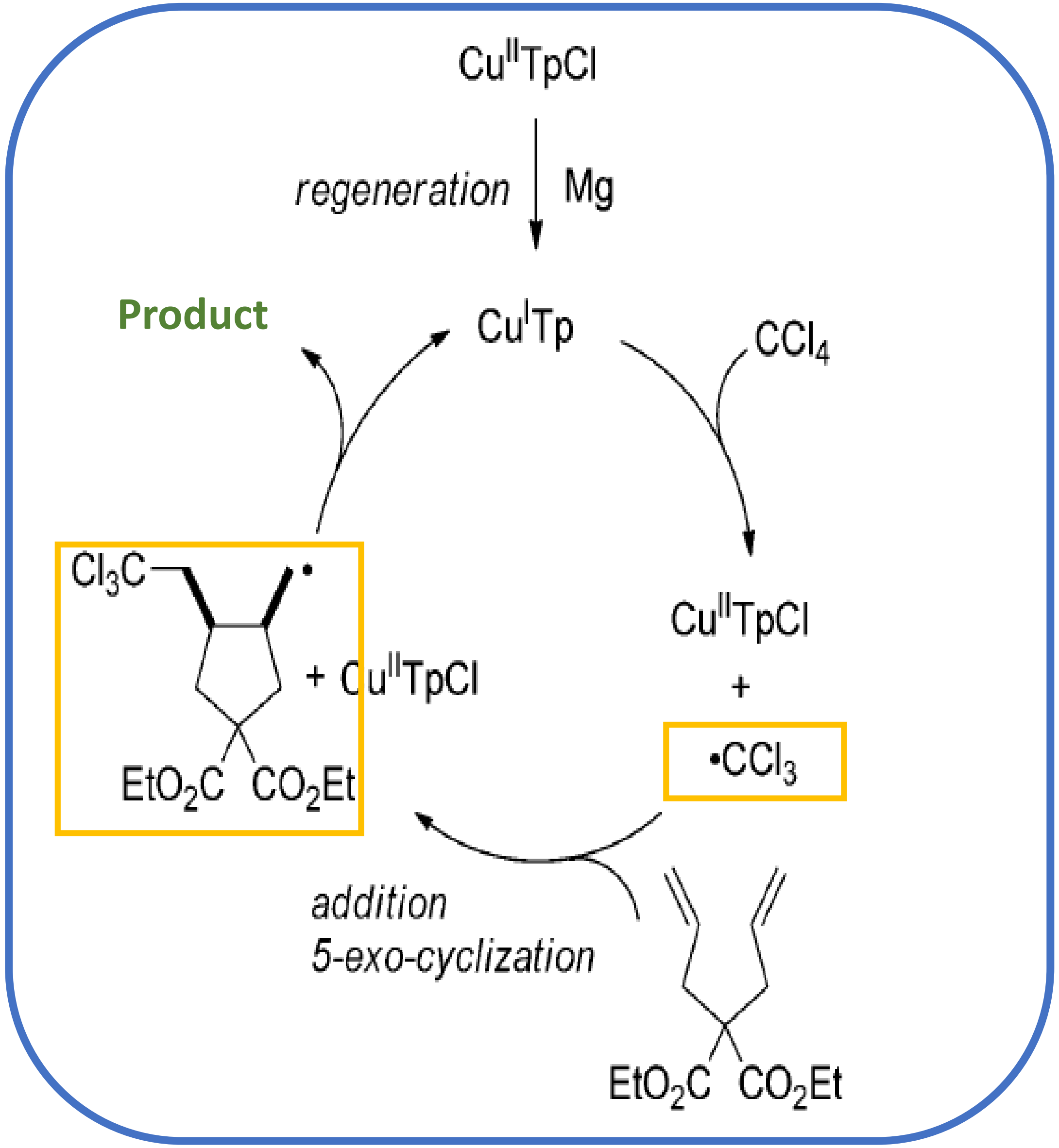


Redox Catalysis (Non-Chain reactions) / Atom-transfer reactions



W. T. Eckenhoff, S. T. Garrity, T. Pintauer, *Eur. J. Inorg. Chem*. **2008**, 563–571

Redox Catalysis (Non-Chain reactions) / Atom-transfer reactions

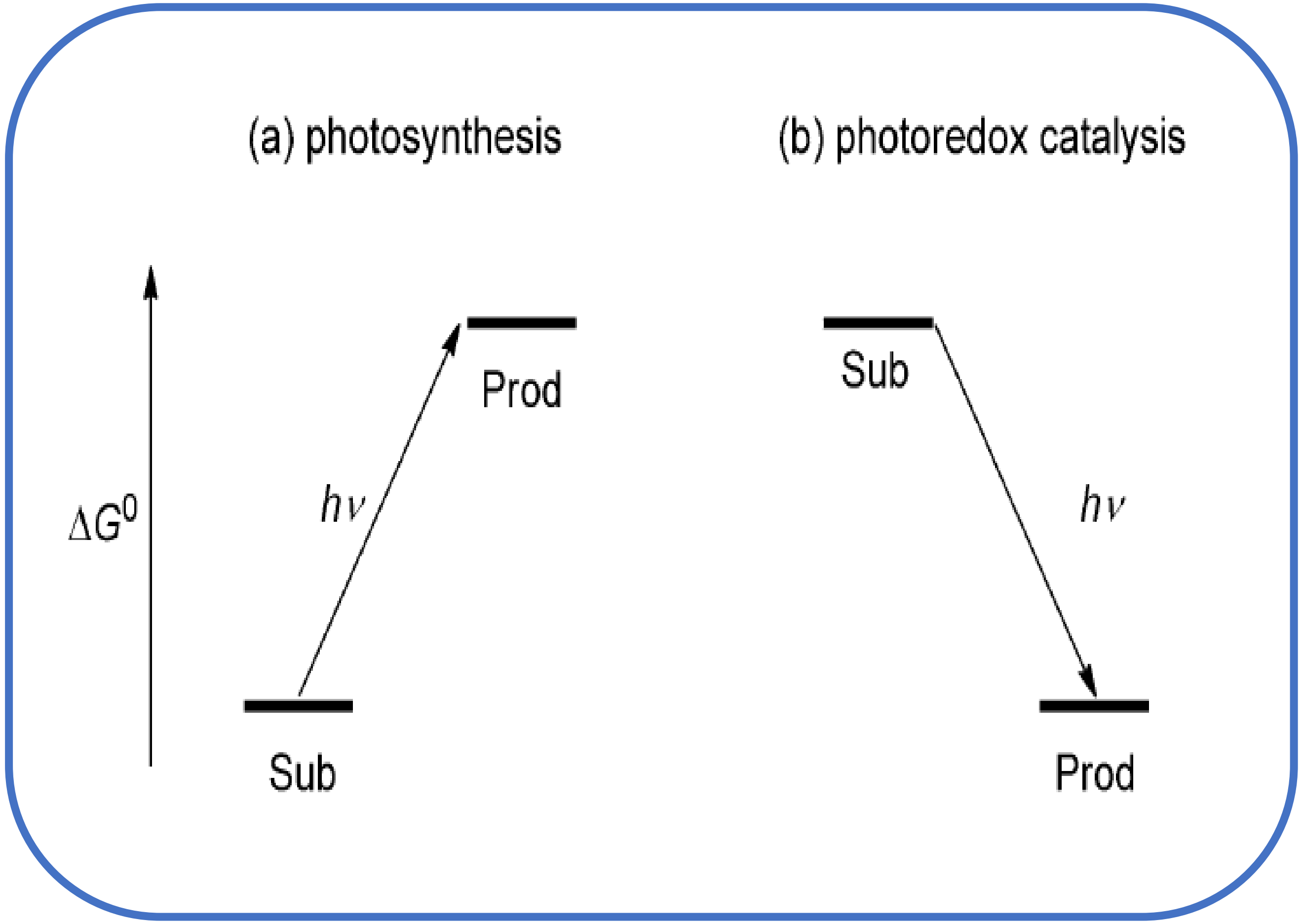


Transient radicals can dimerize

Accumulation of Cu^{2}TpCl
The chain breaks

Photoredox Catalysis (Non-Chain reactions)

Photoredox is not photosynthesis…



Redox-cat: exothermic process

The coupled reaction is usually an innate chain

Catalysis or Activation?

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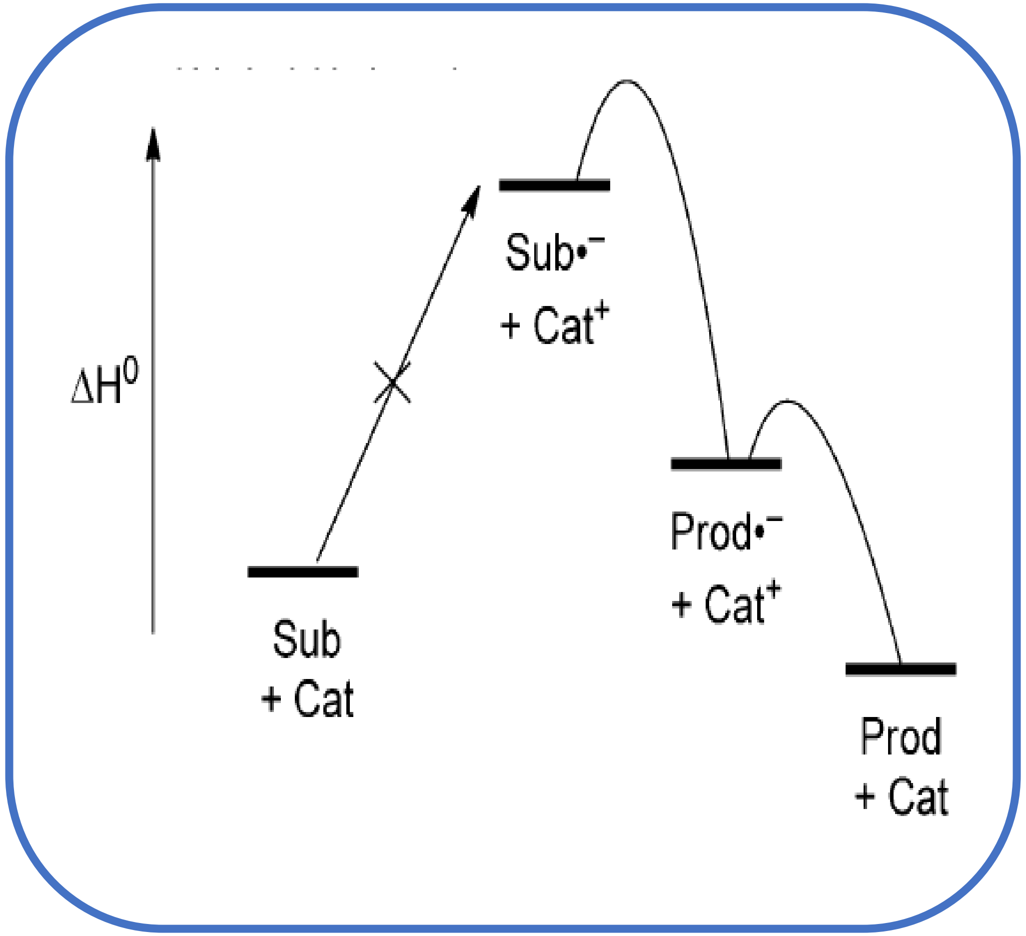
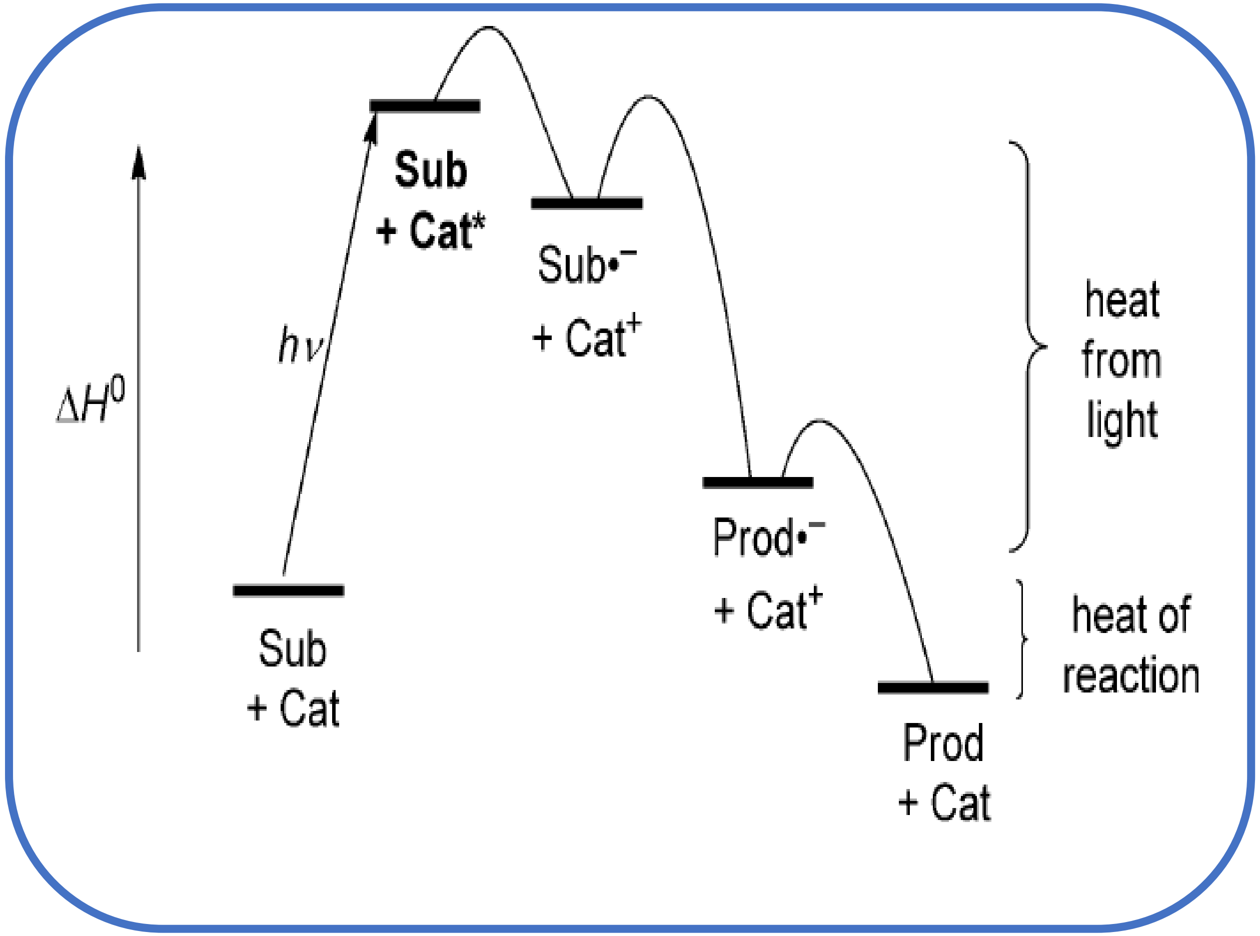
Photoredox Catalysis (Non-Chain reactions)

Thermal redox catalysis fails.



Photoinduced formation of a new reactive intermediate.



A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

Photoinitiation or Photocatalysis?

Sub-X $\xrightarrow[\text{Catalyst}]{h\nu}$ Prod-X

Sub-X $\xrightarrow{h\nu}$ Sub-X* $\longrightarrow$ Innate chain **Photoinduced reaction**

Common misunderstandings:

Sub-X $\longrightarrow$ Prod-X

Photocatalyzed reactions stops

- Light-driven (endothermic reaction)
- Light-activated (exothermic reactions)

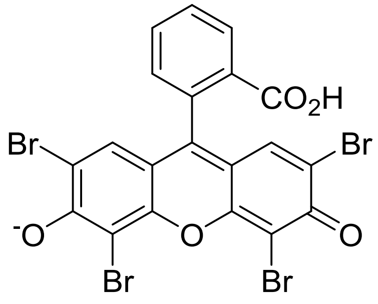
"light-promoted
light-induced
light-mediated"

Photoinduced reactions succeeds

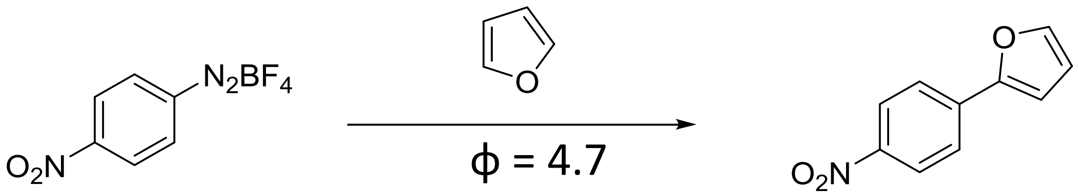
Light-initiated (chain reactions)

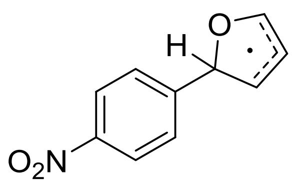
Photoinitiation or Photocatalysis? (Quantum yield)

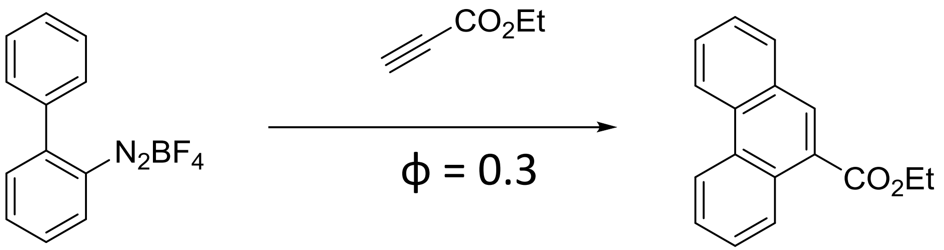
Quantum yield (ϕ) = number of substrates consumed / photon absorbed

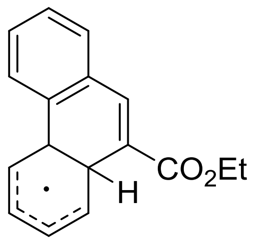


Eosyn Y



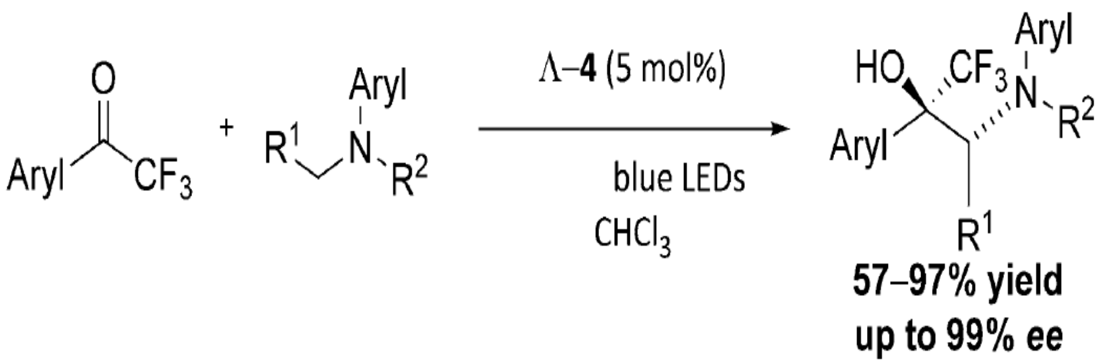


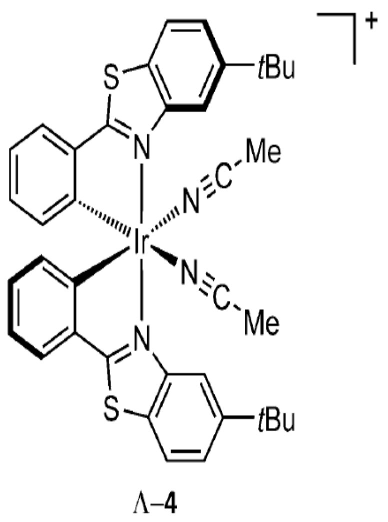




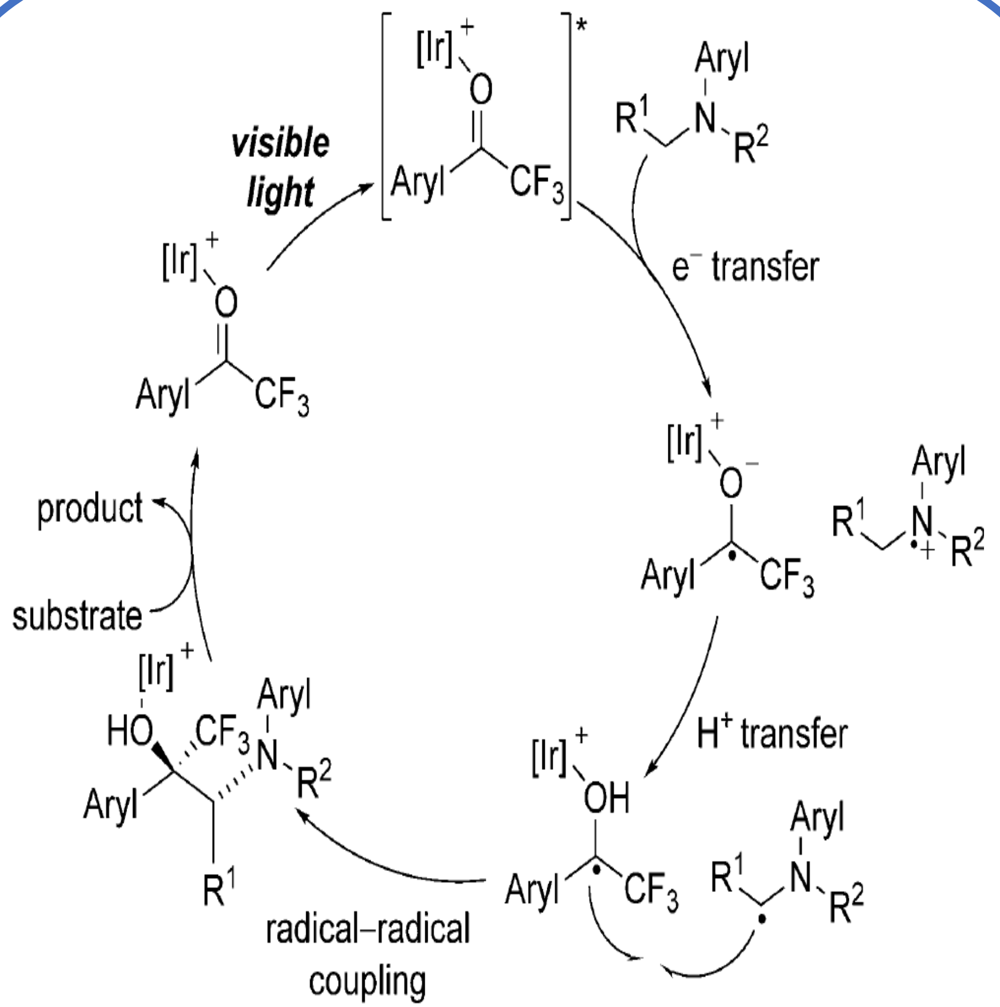
M. Majek, F. Filace, A. J. von Wangelin, *Beilstein J. Org. Chem.* **2014**, *10*, 981 –989

Selected examples



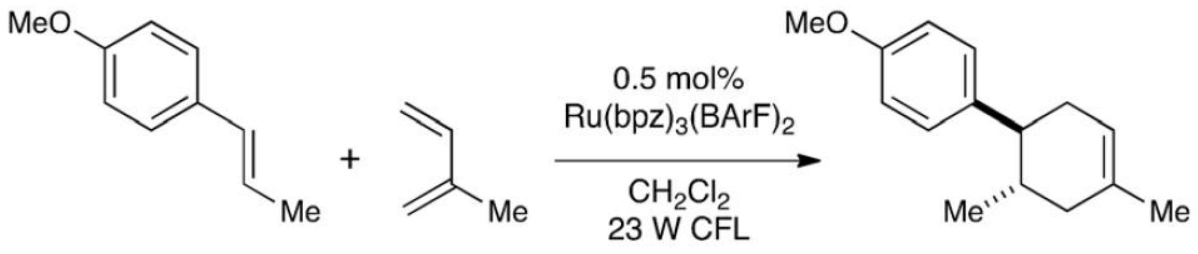


Quantum yield
Not calculated

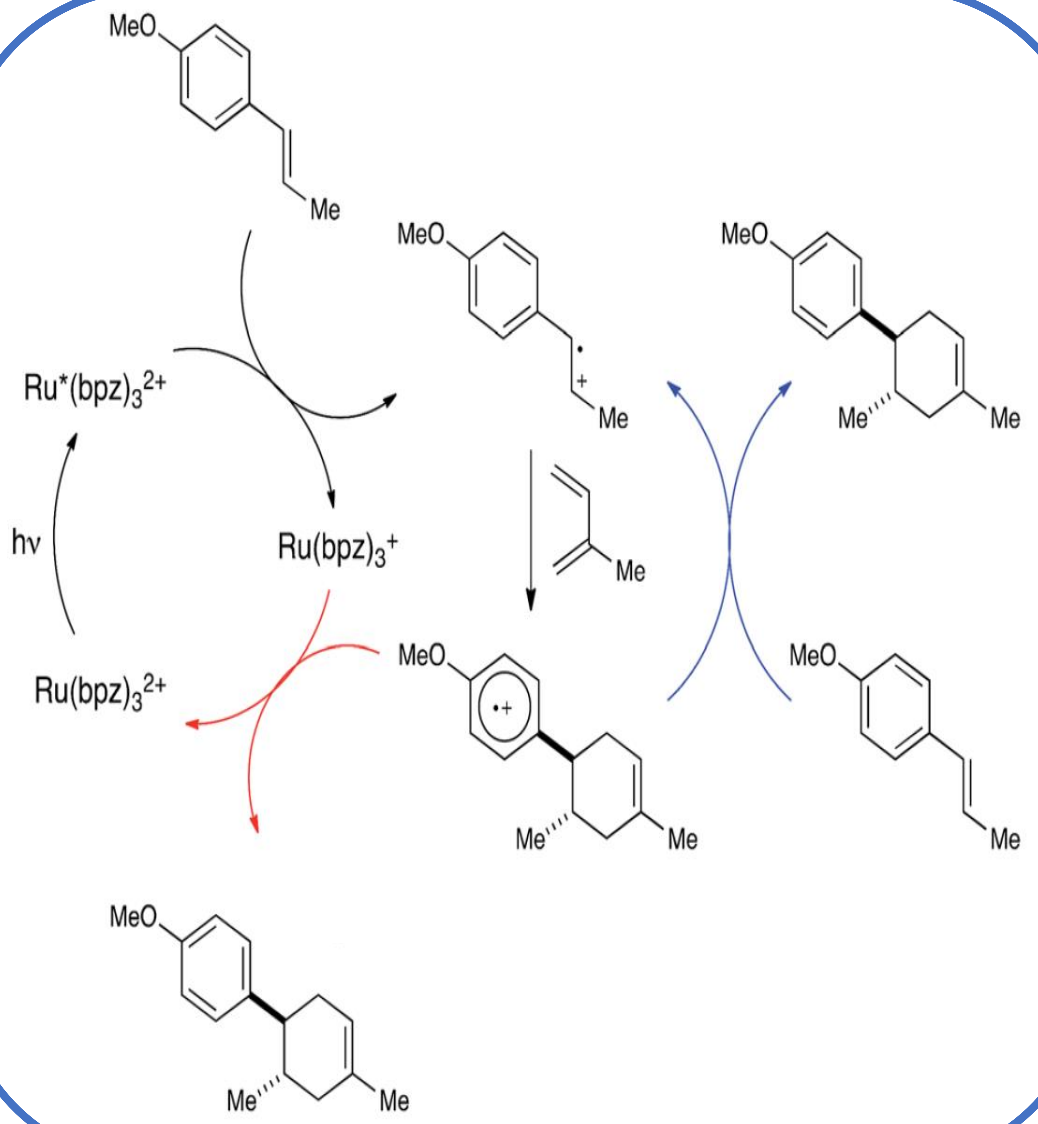


A. G. Amador, T. P. Yoon, *Angew. Chem. Int. Ed*. **2016**, *55*, 2304 – 2306

Selected examples

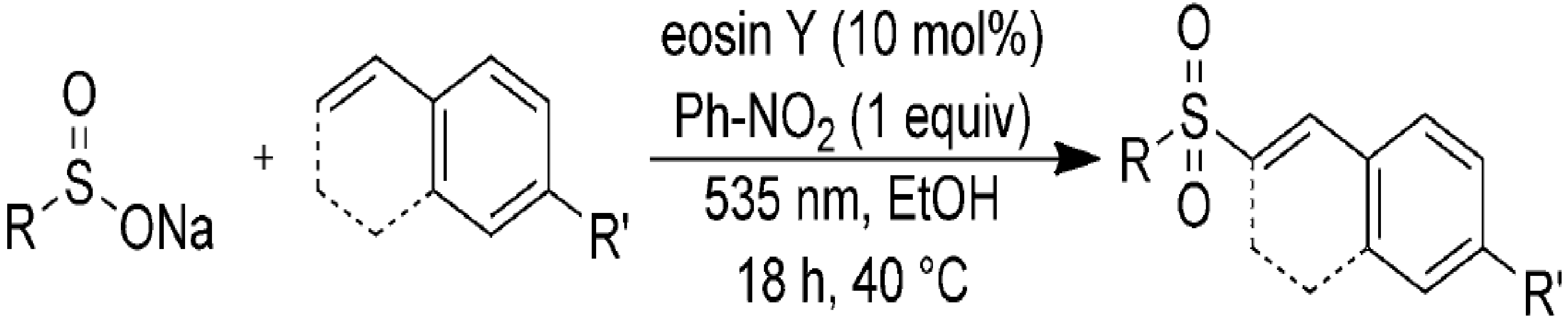


ϕ = 44



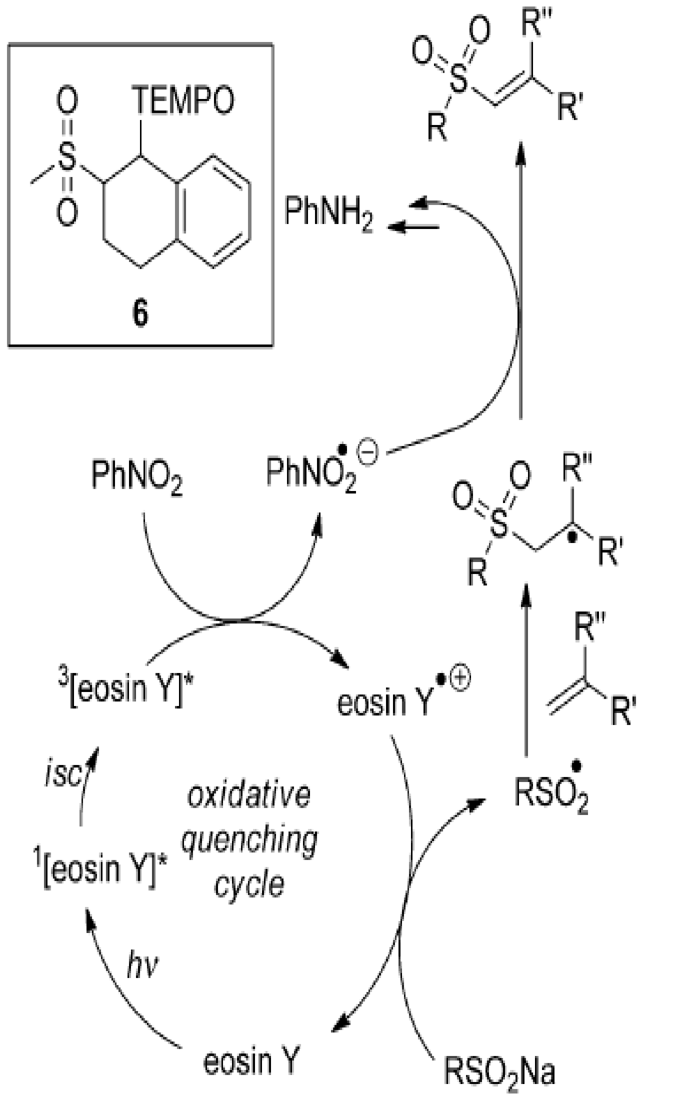
Megan A. Cismesia and Tehshik P. Yoon, *Chem. Sci.*, **2015**, *6*, 5426

Selected examples



A.U. Meyer, K. Strakov, T. Slanina, B. Kçnig, *Chem. Eur. J*. **2016**, *22*, 1 – 7

Selected examples



ϕ = 1.3 ± 0.4 %.

Photoiniciated or photocatalyzed?

A.U. Meyer, K. Strakov, T. Slanina, B. Kçnig, *Chem. Eur. J.* **2016**, *22*, 1 – 7

Conclusions

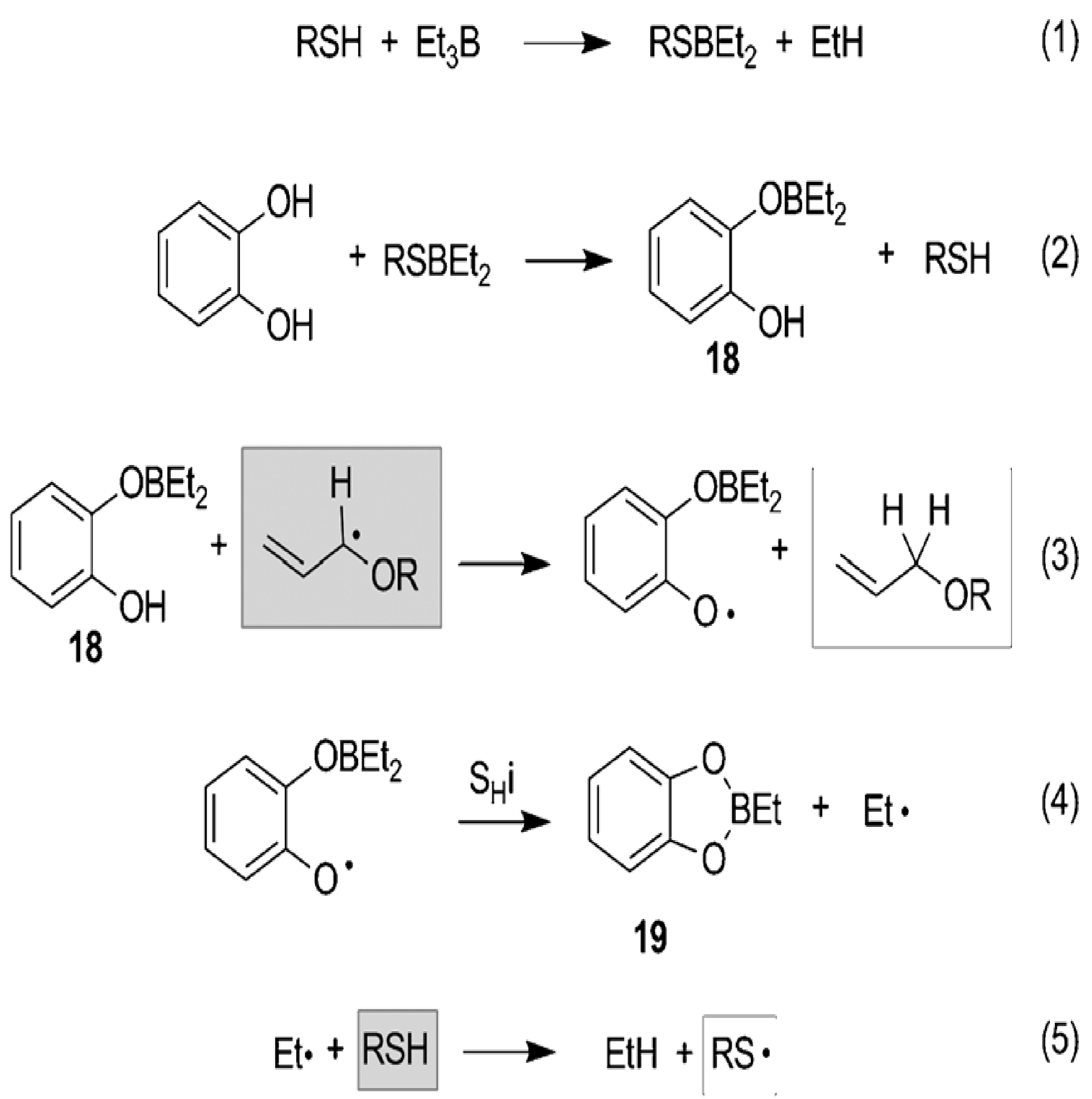
Chain reactions are innate cycles that can occur without a catalyst

The catalytic cycles in radical chemistry commonly have one or several innate reactions (“catalyst-free" intermediates -Free radicals- in the cycle)

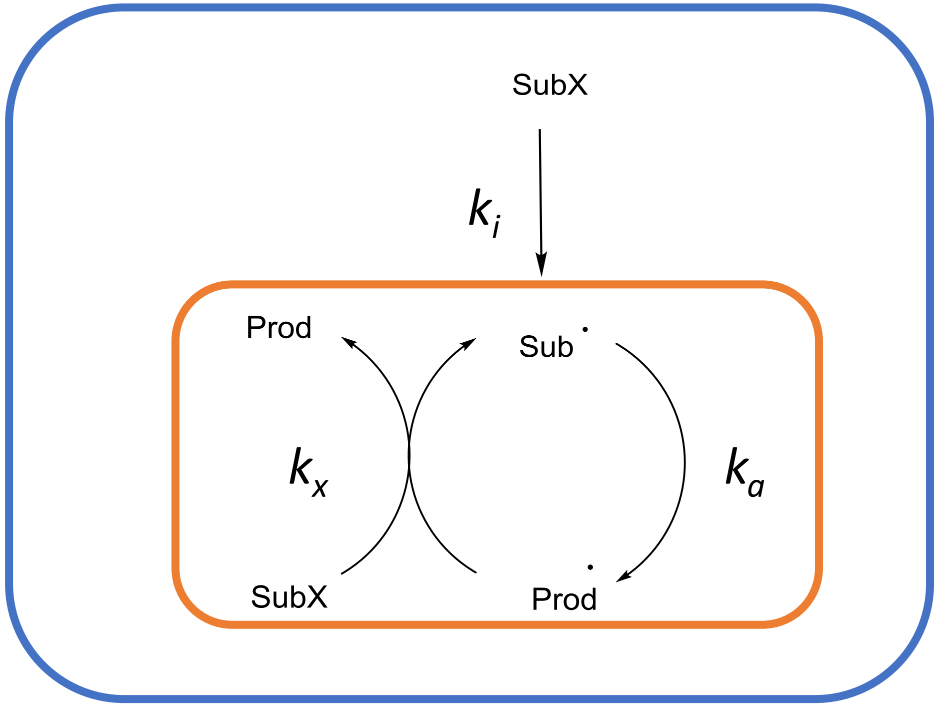
Smart initiation and redox (or photoredox) catalysis are in competition in various kinds of reactions.

It may not be easy to develop a mechanism for such transformations with standard kinds of control experiments

THANK YOU FOR YOUR ATTENTION


RSH + Et3B → RSBEt2 + EtH (1)
OH
OH
+ RSBEt2
OBEt2
OH
18
+ RSH (2)
OBEt2
OH
18
+
H
OR
OBEt2
O
+
H H
OR
(3)
OBEt2
O
SHi
O
BEt
O
19
+ Et (4)
Et + RSH → EtH + RS (5)

Redox Processes

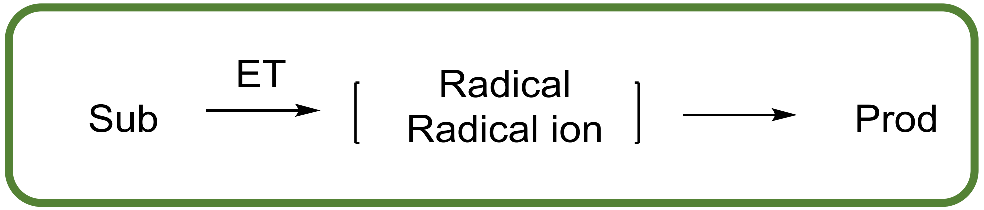


Conditions for good propagation steps "Innate chain":

- All rate constants ≥ 10^5 s^{-1}
- Inhibition avoided

$$k_{cat} > k_x, k_a$$

Redox Processes

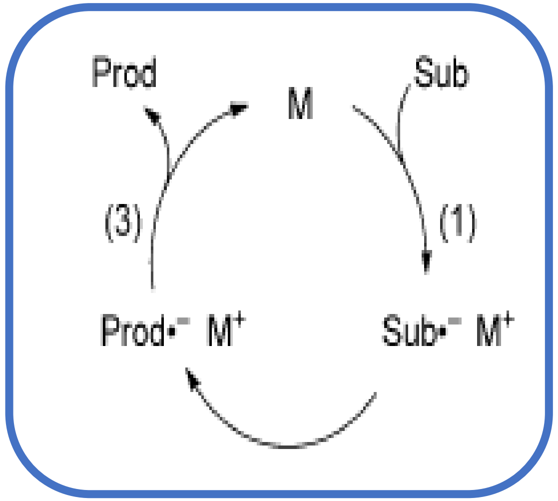


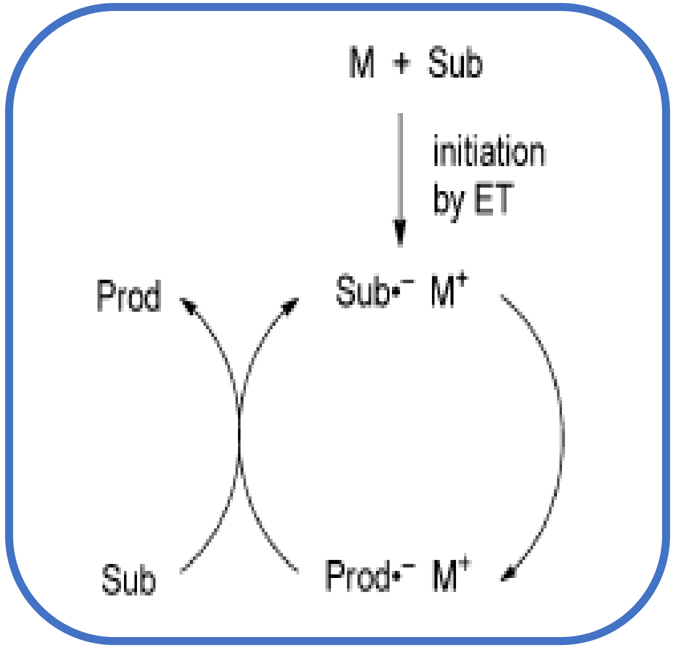
Electron Transfer ET

“Hole” transfer

Metals as Initiators

Metals as catalyst



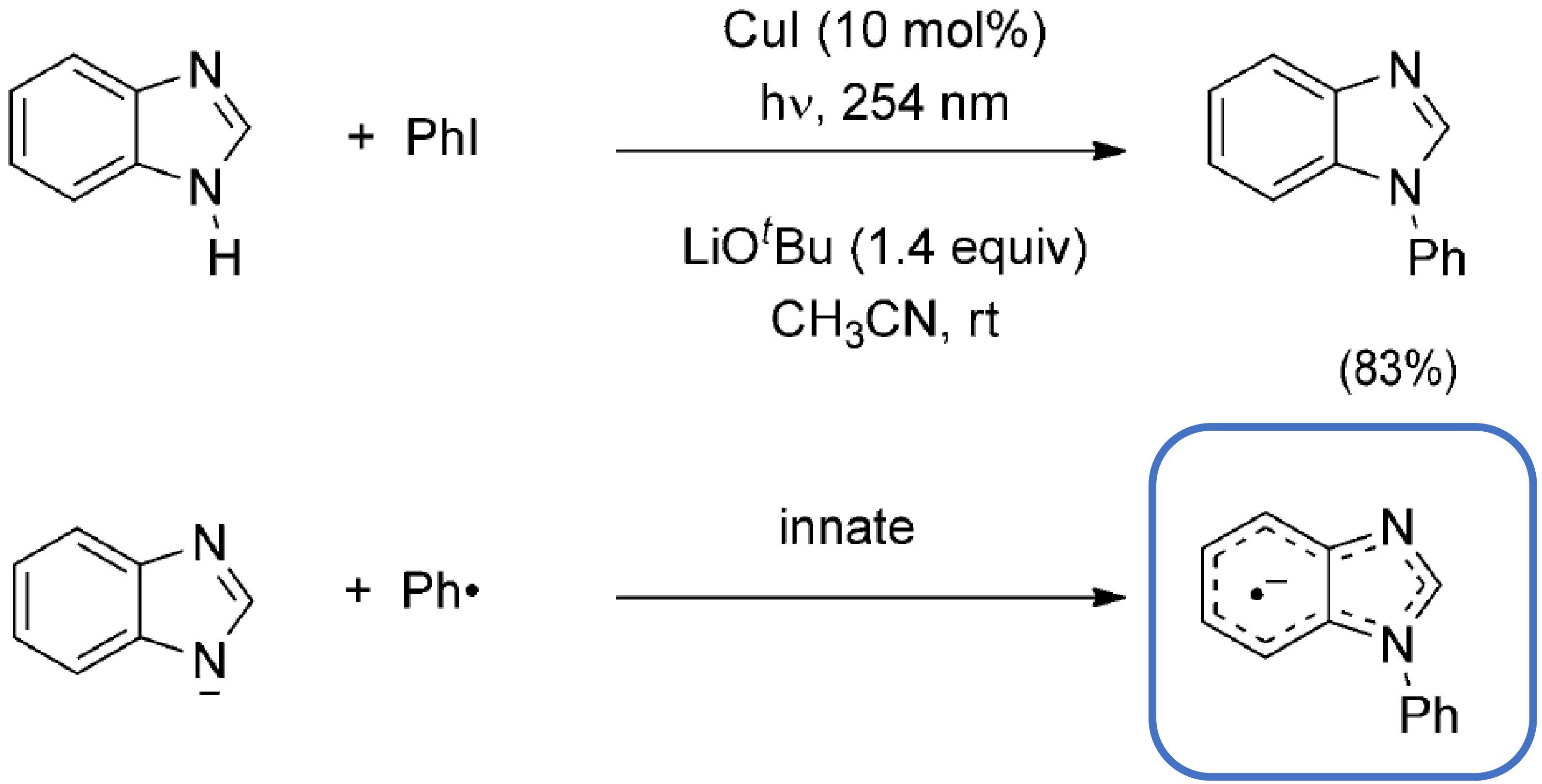


...What is the true catalyst?

electron catalysis and well-established Brønsted acid catalysis. The electron behaves as a catalyst in radical cascades in a way that is loosely similar to a proton acting as a catalyst in ionic transformations. We posited that diverse radical cascade

A. Studer, D. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58 – 102

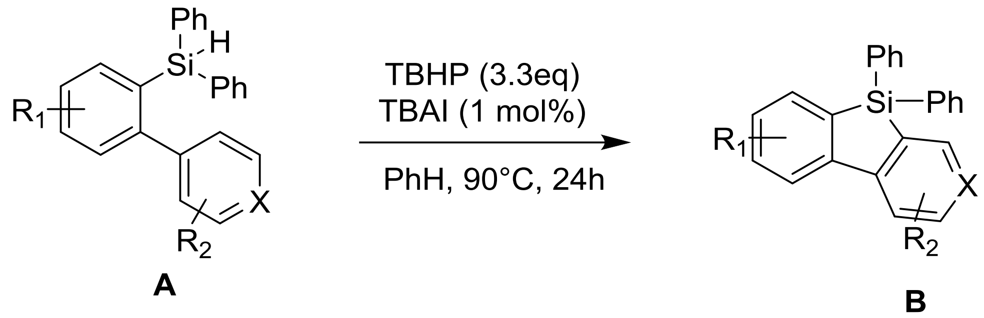
Redox Processes

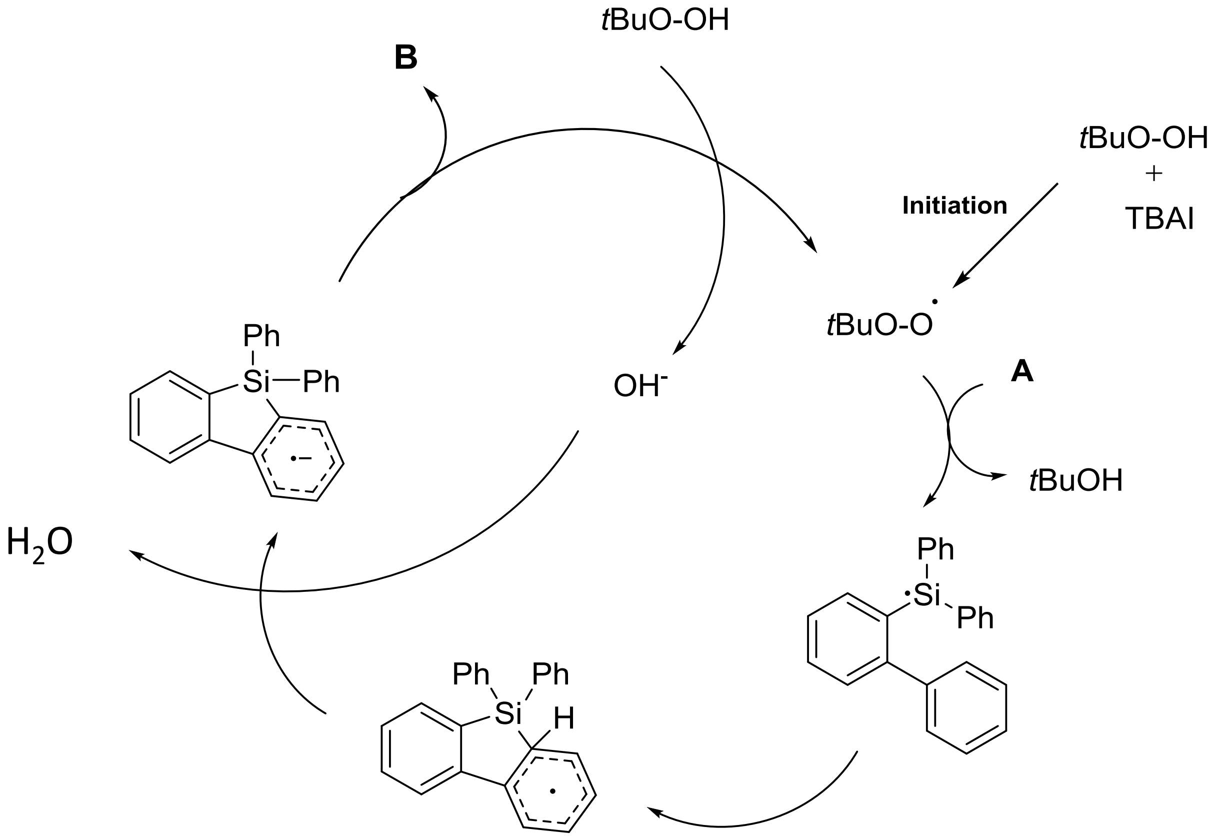


Electron-transfer to PhI (metal-initiated, Electron-catalyzed)

Electron-transfer to Cu (Redox-catalyzed, Metal-catalyzed)

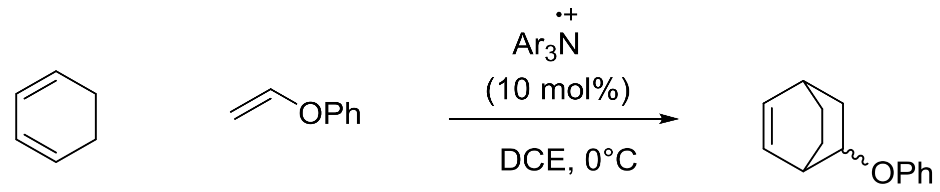
Redox Processes

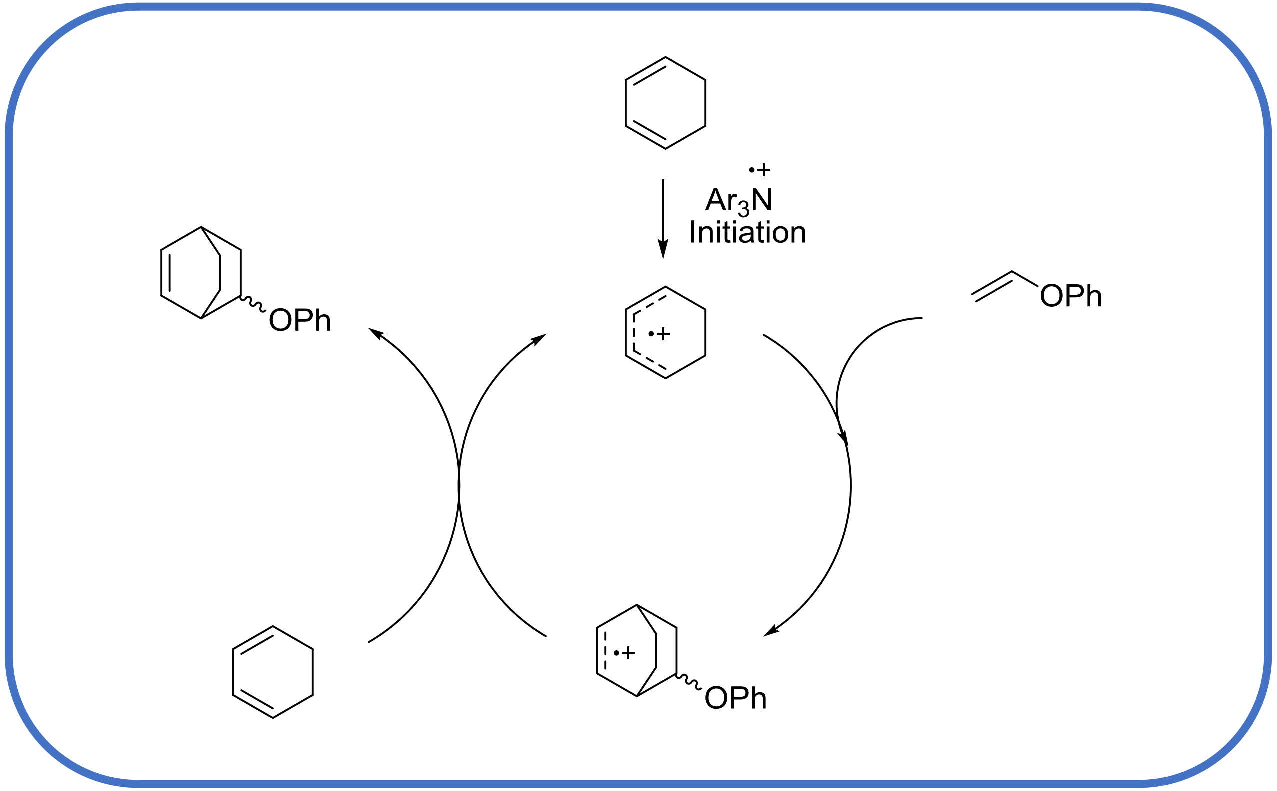




D. Leifert, A. Studer, *Org. Lett.* **2015**, *17*, 386–389

Redox Processes





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Amine-initiated?

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S. M. Stevenson, M. P. Shores, E. M. Ferreira, *Angew. Chem. Int. Ed*. **2015**, *54*, 6506–6510; *Angew. Chem*. **2015**, *127*, 6606 –6610.

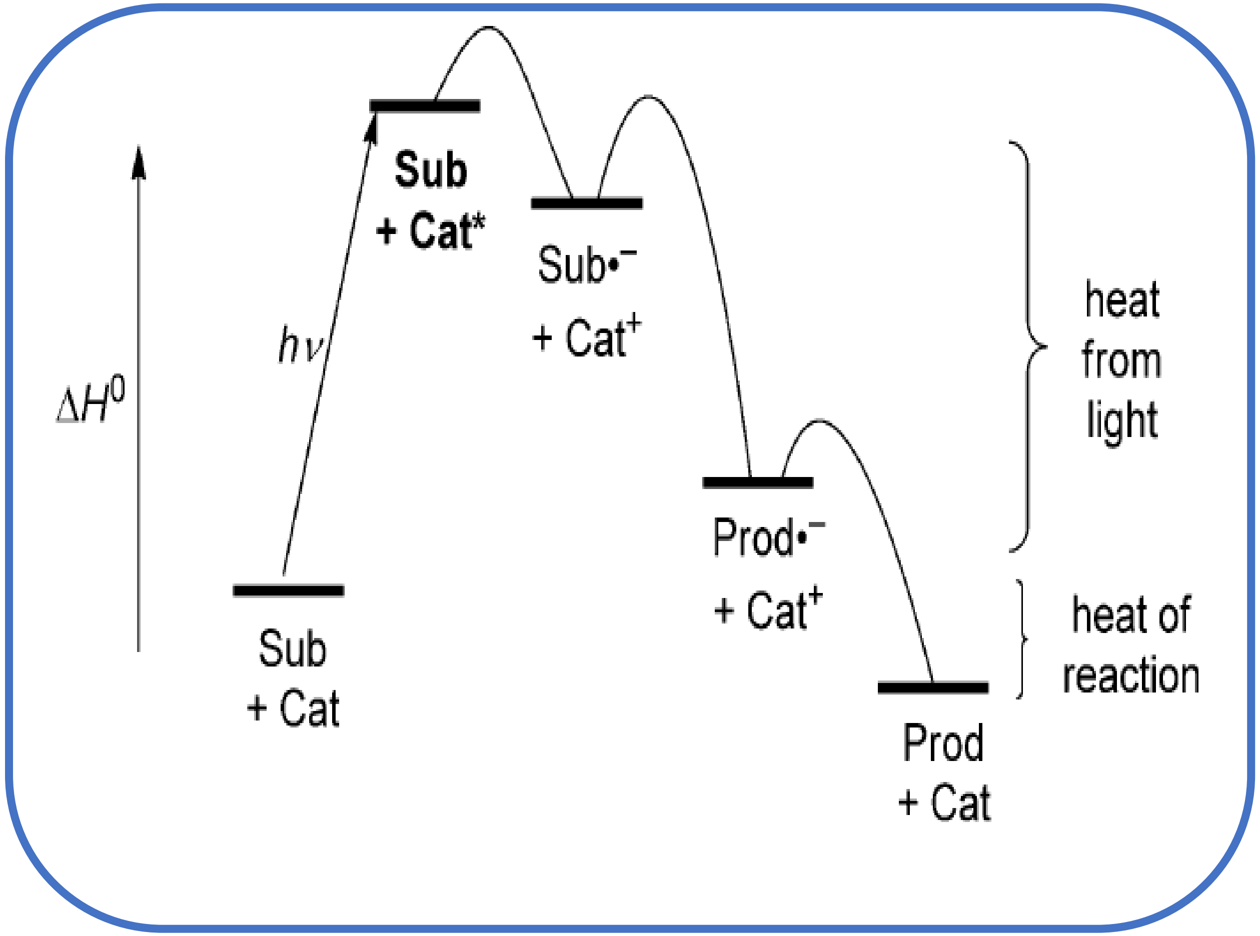
Photoredox

Photoinduced formation of a new reactive intermediate.

Redox-cat: exothermic process

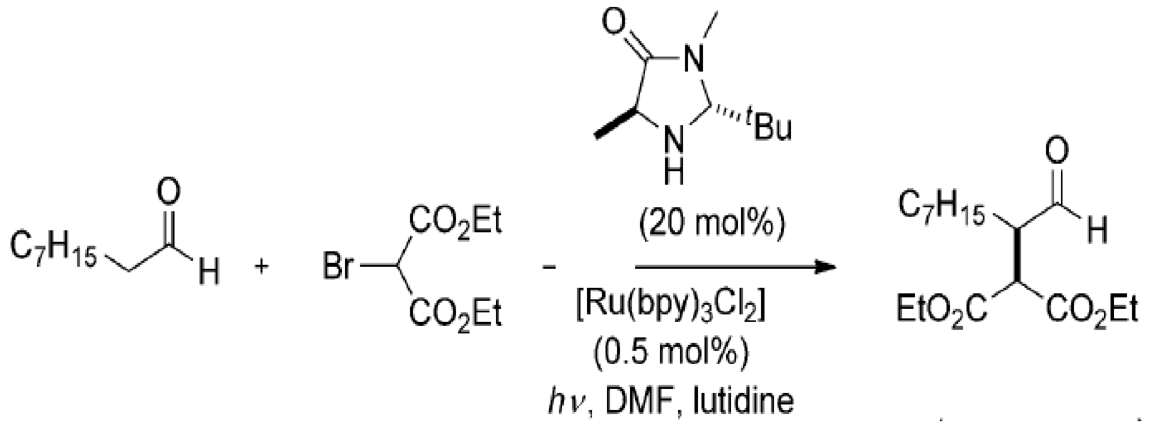
The coupled reaction is usually an innate chain

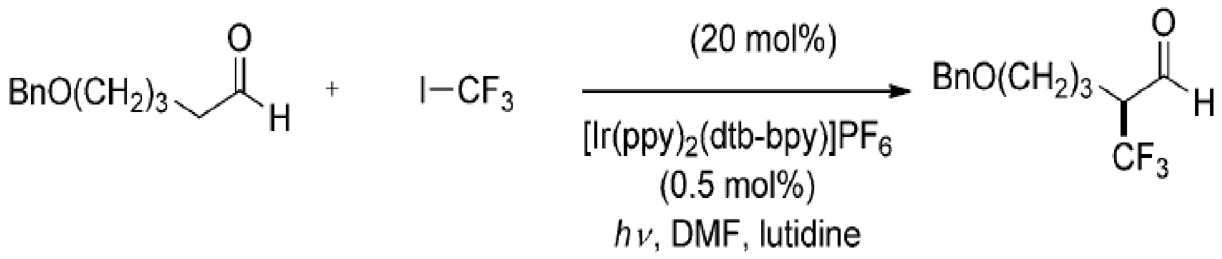
Catalysis or Activation?



A. Studer, D. Curran, *Angew. Chem. Int. Ed*. **2016**, *55*, 58 – 102

Photoredox





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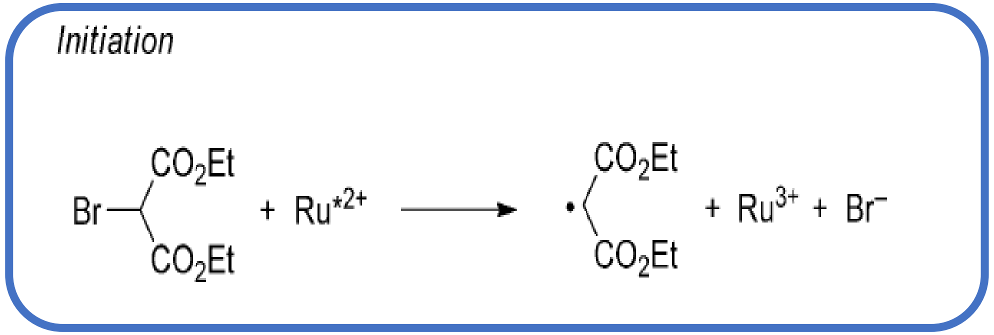
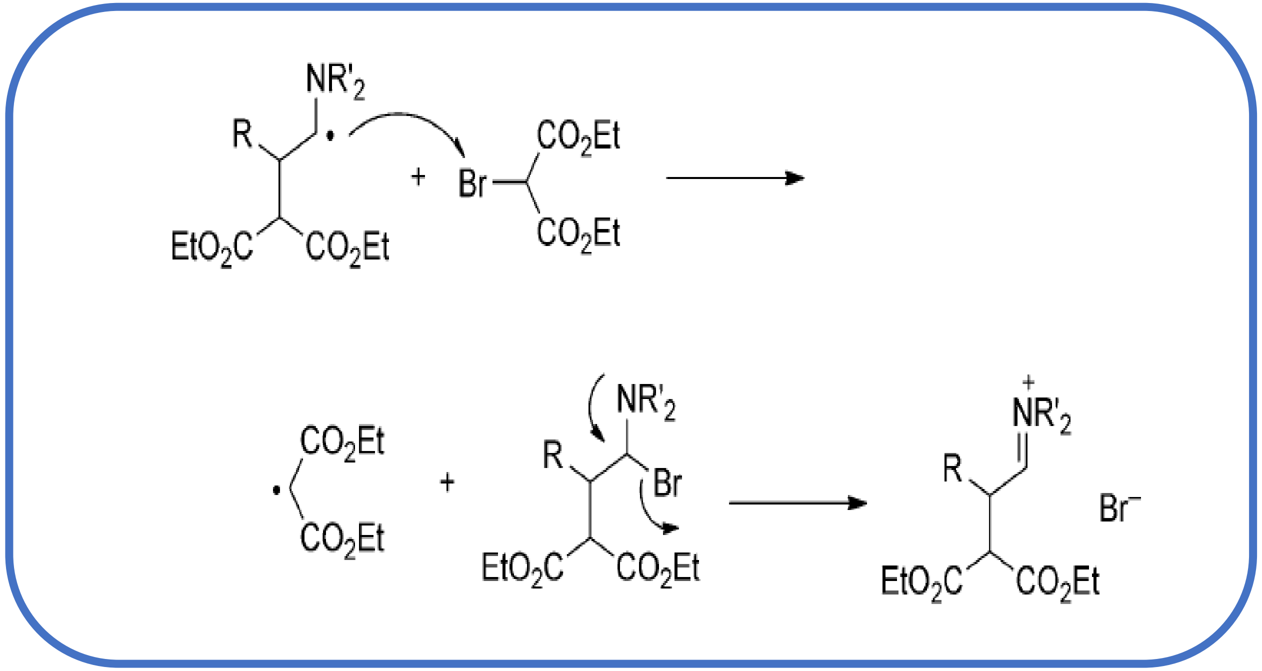
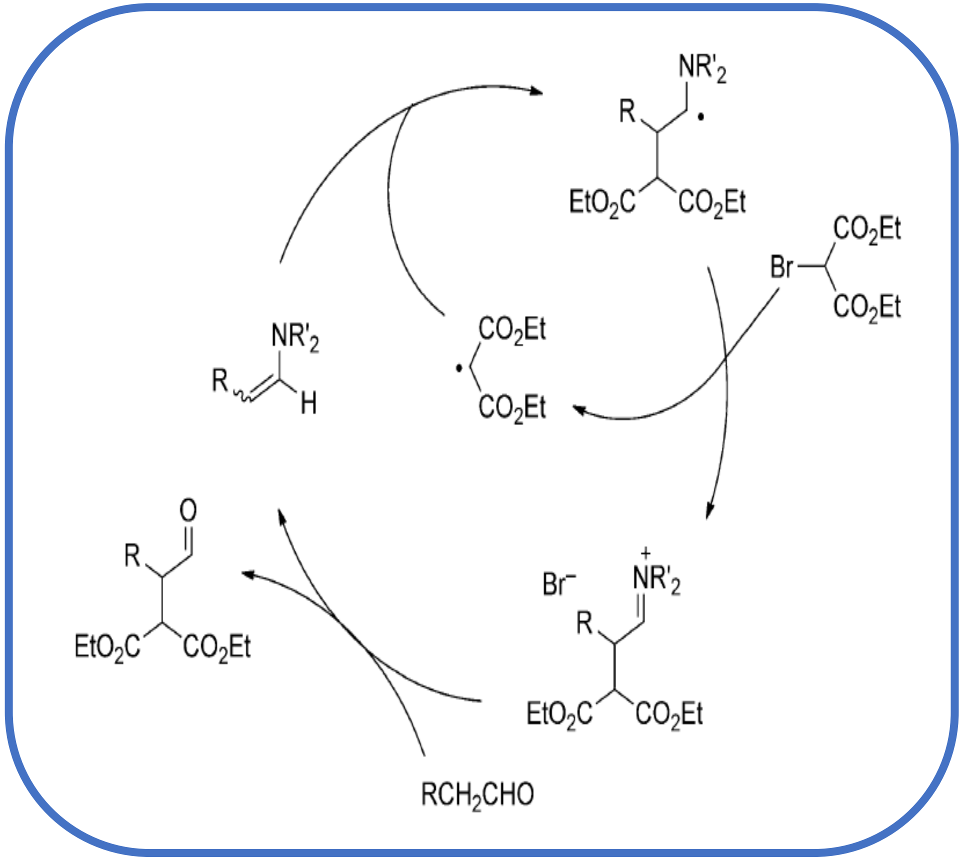
Photoredox







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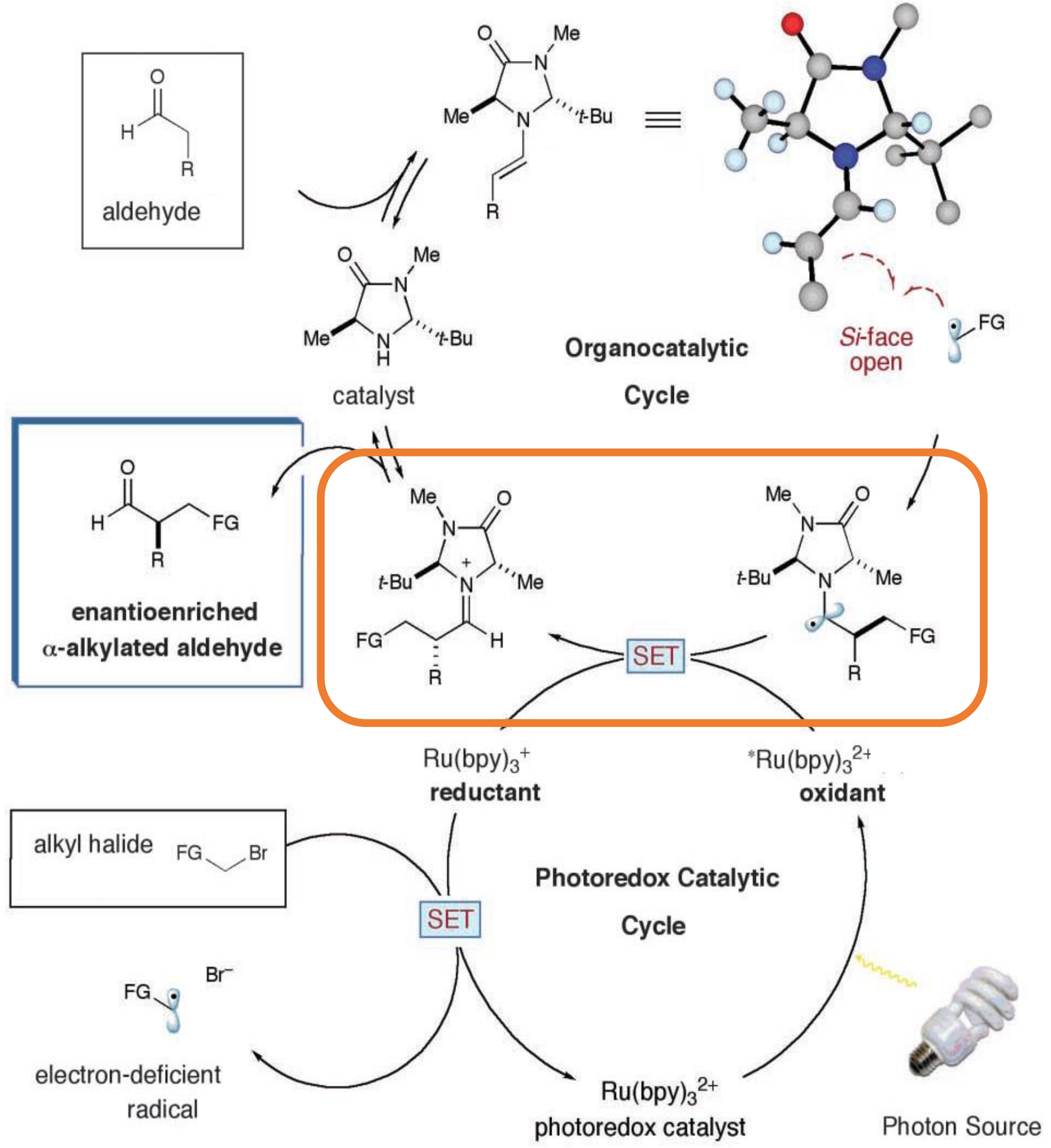
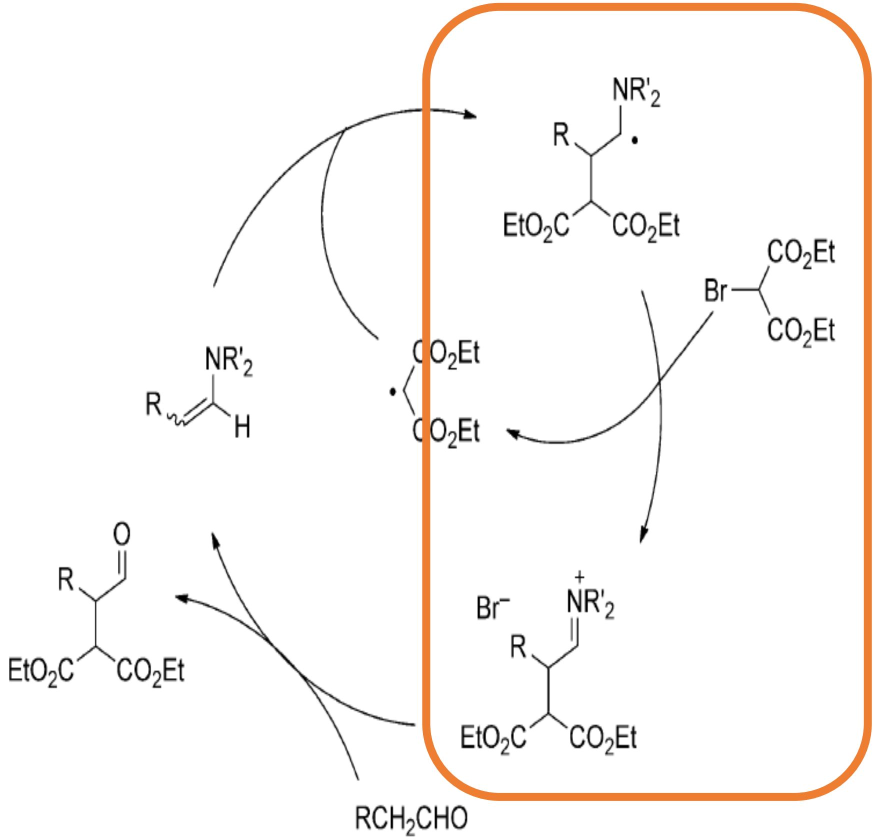
Photoredox





“One photon is needed”

“Continuous irradiation is needed”

Photoinitiation or Photocatalysis?

Sub-X $\xrightarrow[\text{Catalyst}]{h\nu}$ Prod-X

Sub-X $\xrightarrow{h\nu}$ Sub-X* $\longrightarrow$ Innate chain

Photoinduced reaction

Common misunderstandings:

Sub-X $\longrightarrow$ Prod-X

Photocatalyzed reactions stops

- Light-driven
- Light-activated

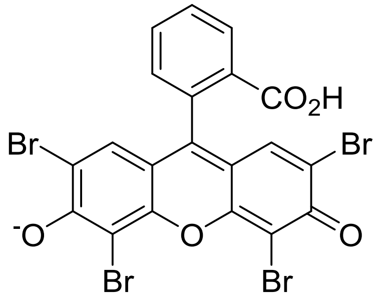
"light-promoted light-induced light-mediated"

Photoinduced reactions succeeds

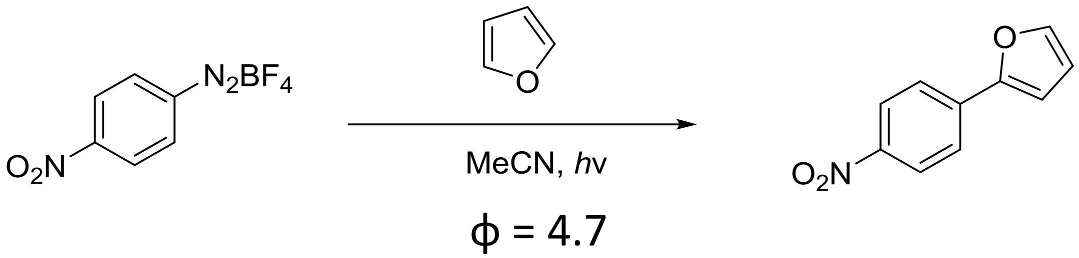
Light-initiated (chain reactions)

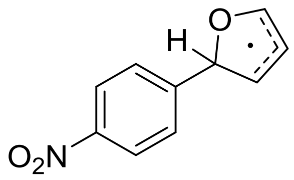
Photoinitiation or Photocatalysis? (Quantum yield)

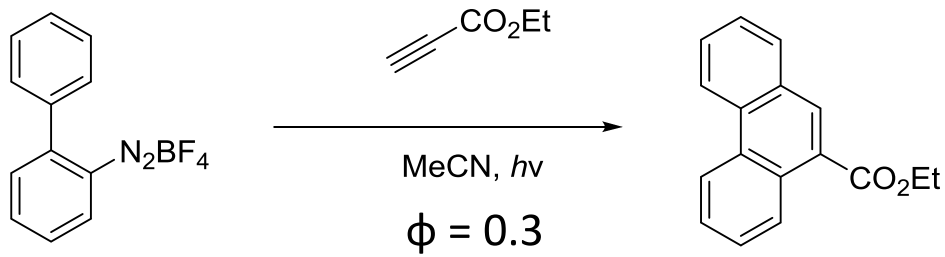
Quantum yield (ϕ) = number of substrates consumed / photon absorbed

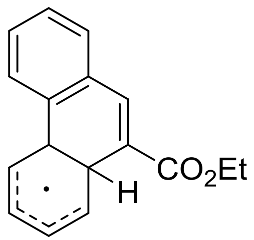


Eosyn Y









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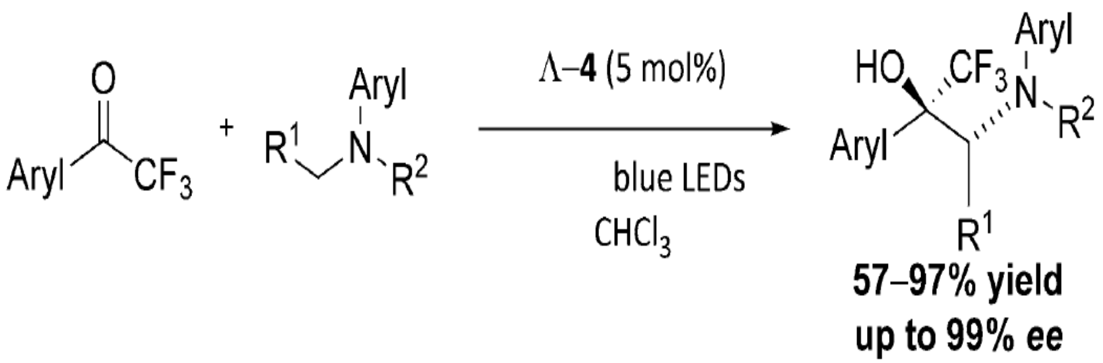
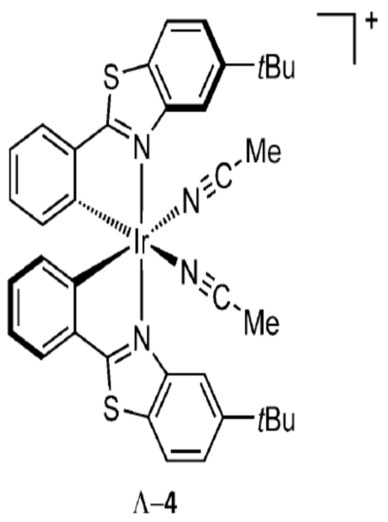
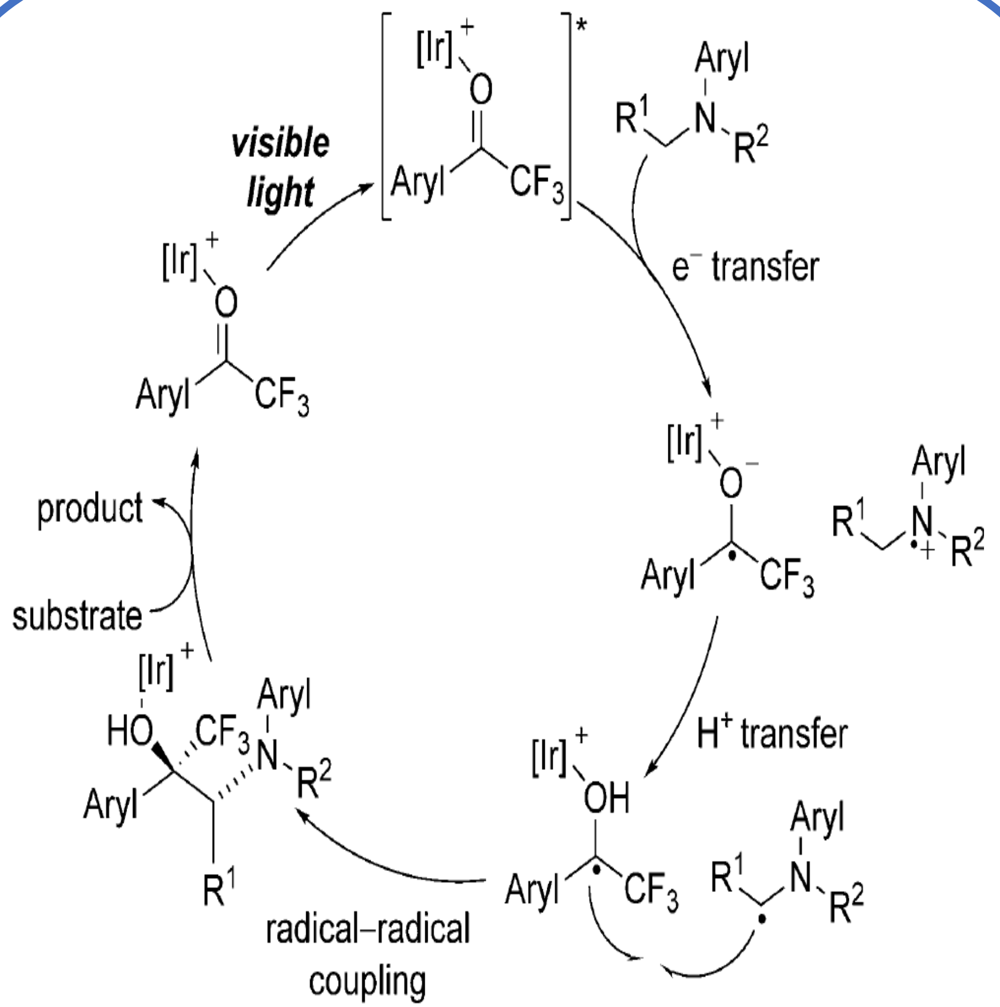
Selected examples





Quantum yield
Not calculated



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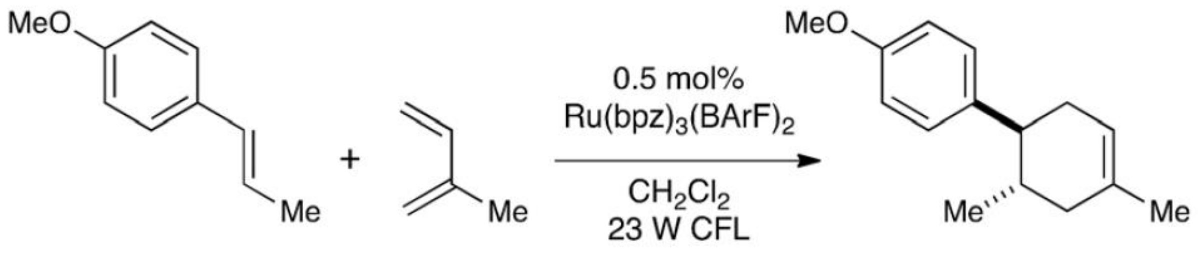
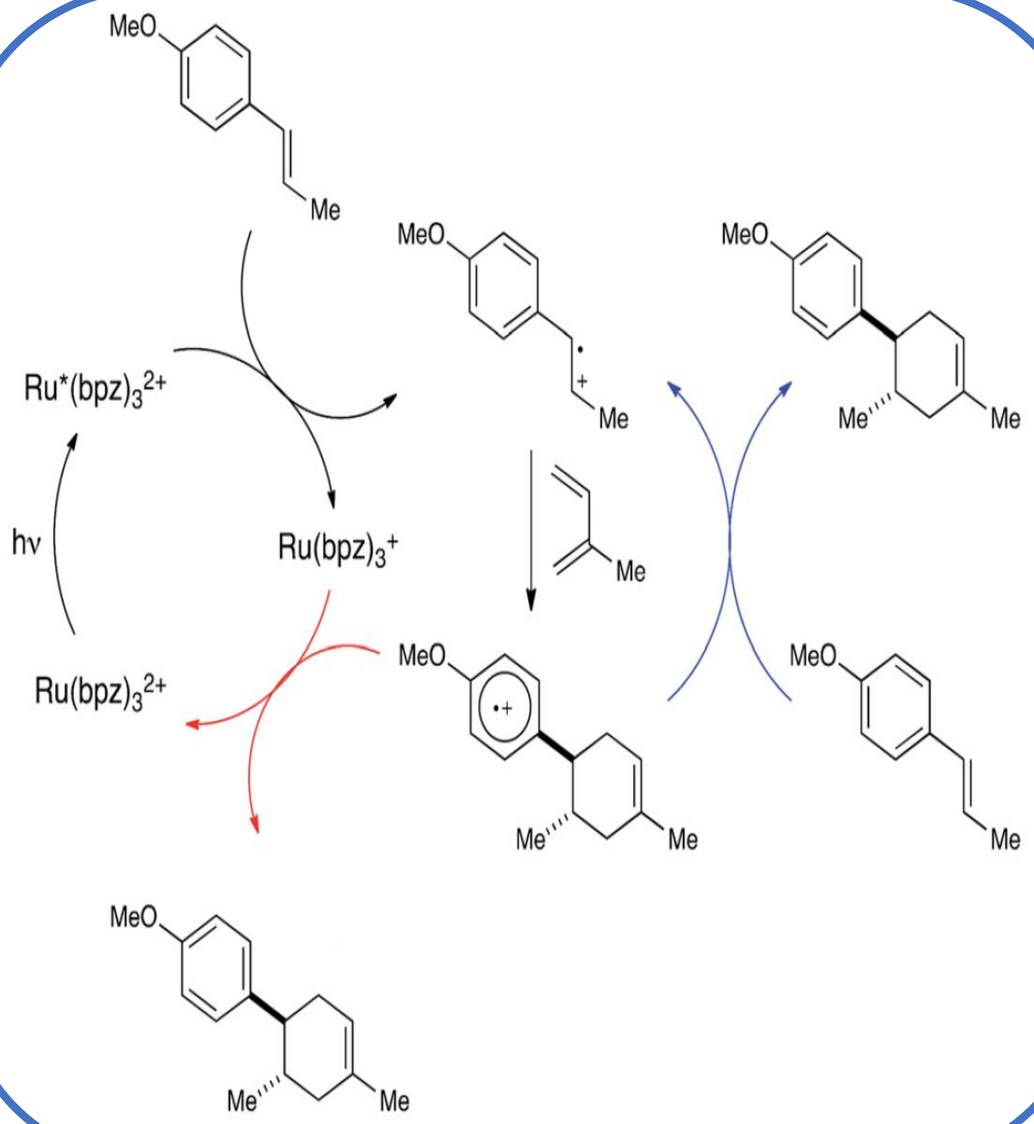
Selected examples



ϕ = 44



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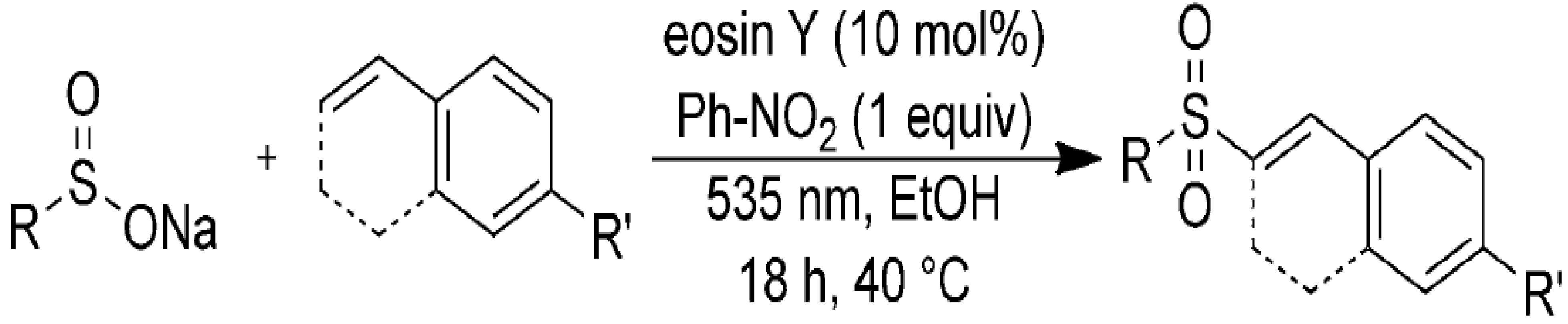
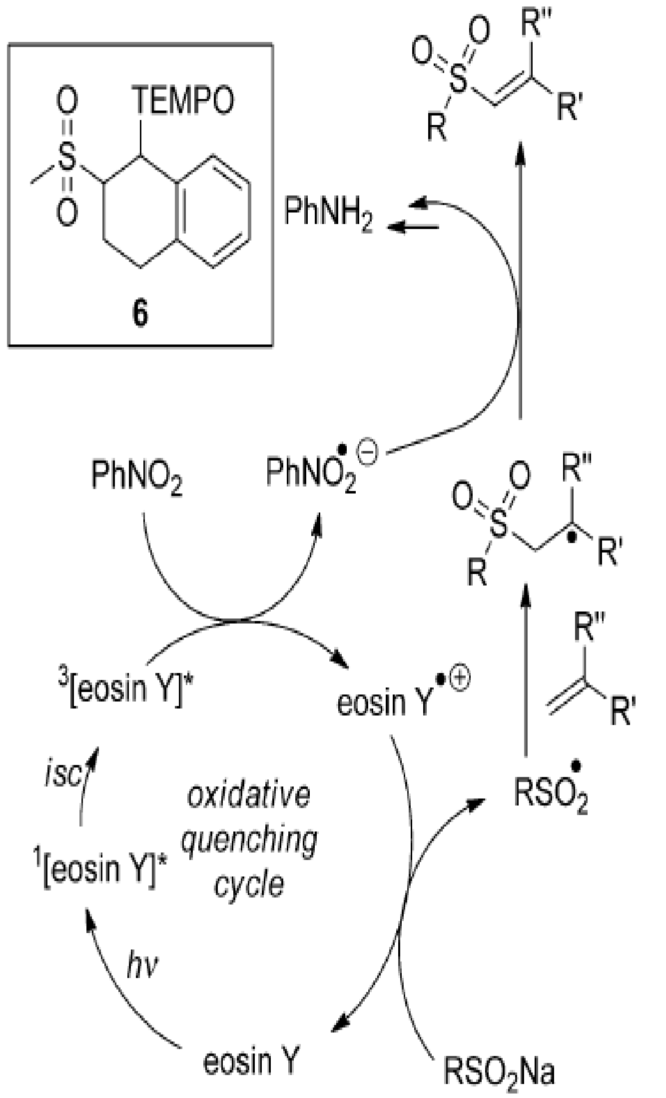
Selected examples



A.U. Meyer, K. Strakov, T. Slanina, B. Kçnig, *Chem. Eur. J*. **2016**, *22*, 1 – 7

Selected examples



ϕ = 1.3 ± 0.4 %.

Photoiniciated or photocatalyzed?

A.U. Meyer, K. Strakov, T. Slanina, B. Kçnig, *Chem. Eur. J.* **2016**, *22*, 1 – 7

Conclusions

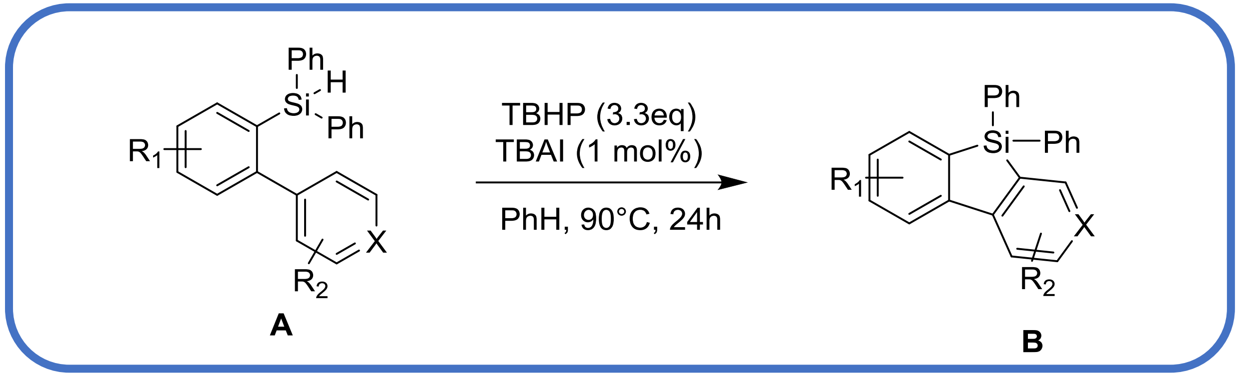
Chain reactions are innate cycles that can occur without a catalyst

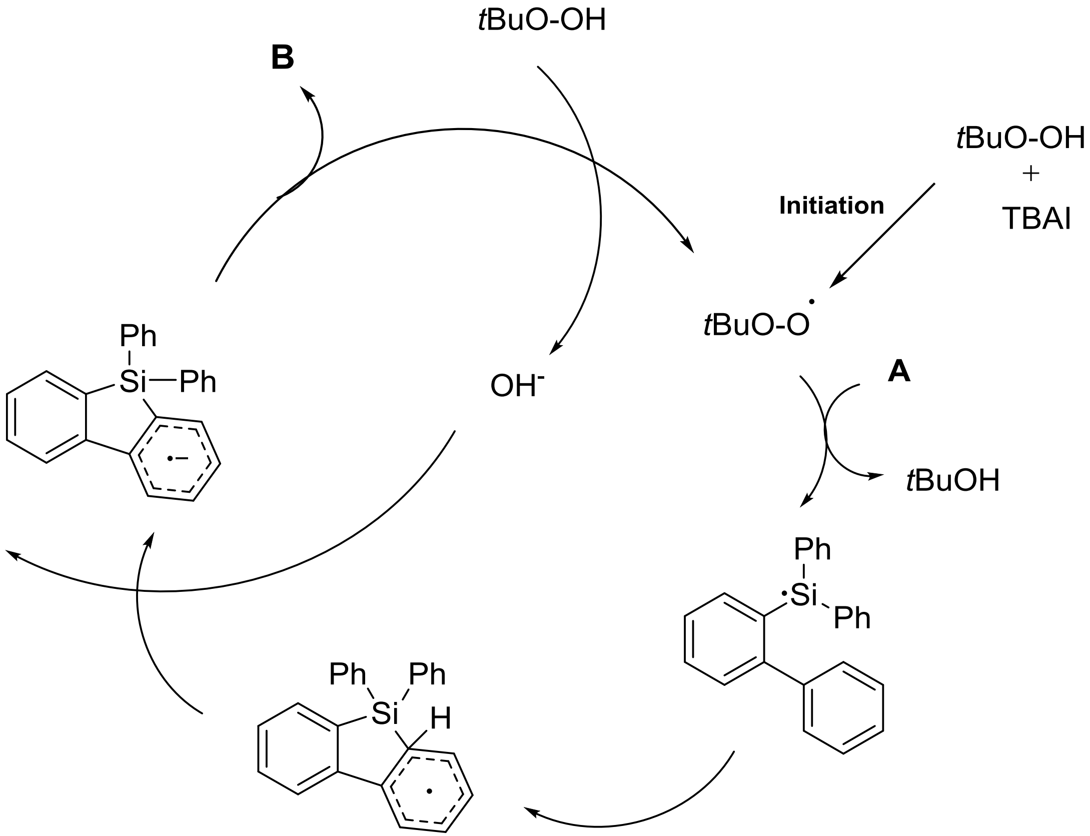
The catalytic cycles in radical chemistry commonly have one or several innate reactions (“catalyst-free" intermediates -Free radicals- in the cycle)

Smart initiation and redox (or photoredox) catalysis are in competition in various kinds of reactions.

It may not be easy to develop a mechanism for such transformations with standard kinds of control experiments


X
R_1 R_2
$\dot{R}1$
R_2
R_1 X
R_1 R_2
THANK YOU FOR YOUR ATTENTION





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