



Free-Radicals: Chemistry and Biology

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<http://iscamap.chem.polimi.it/citterio/education/free-radical-chemistry/>



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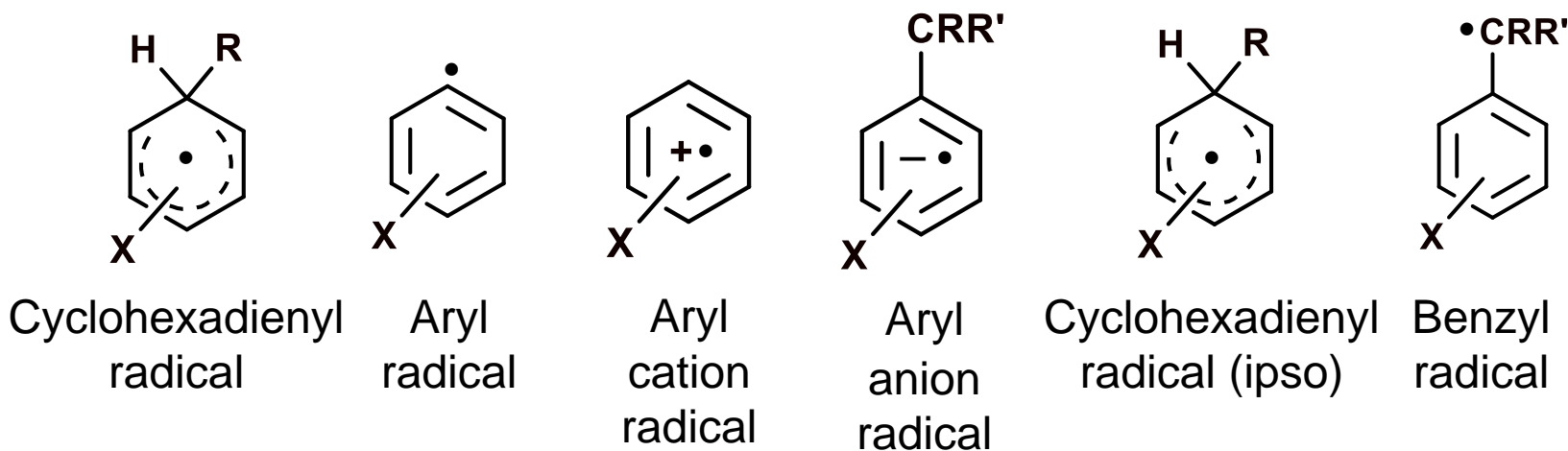
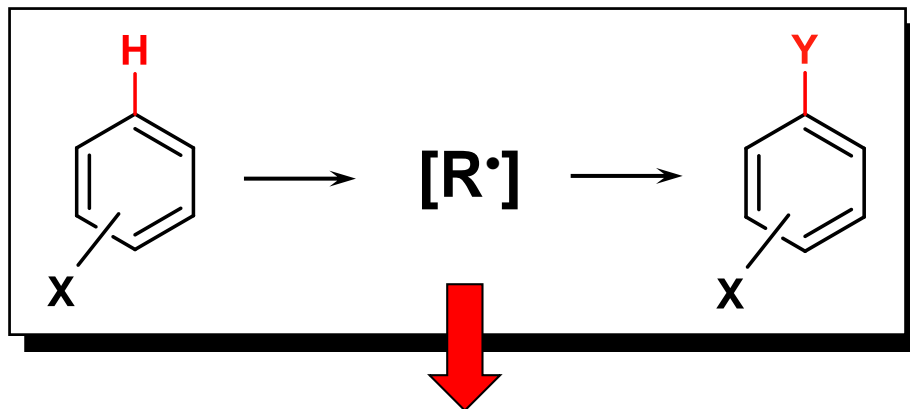


Homolytic Aromatic Substitution

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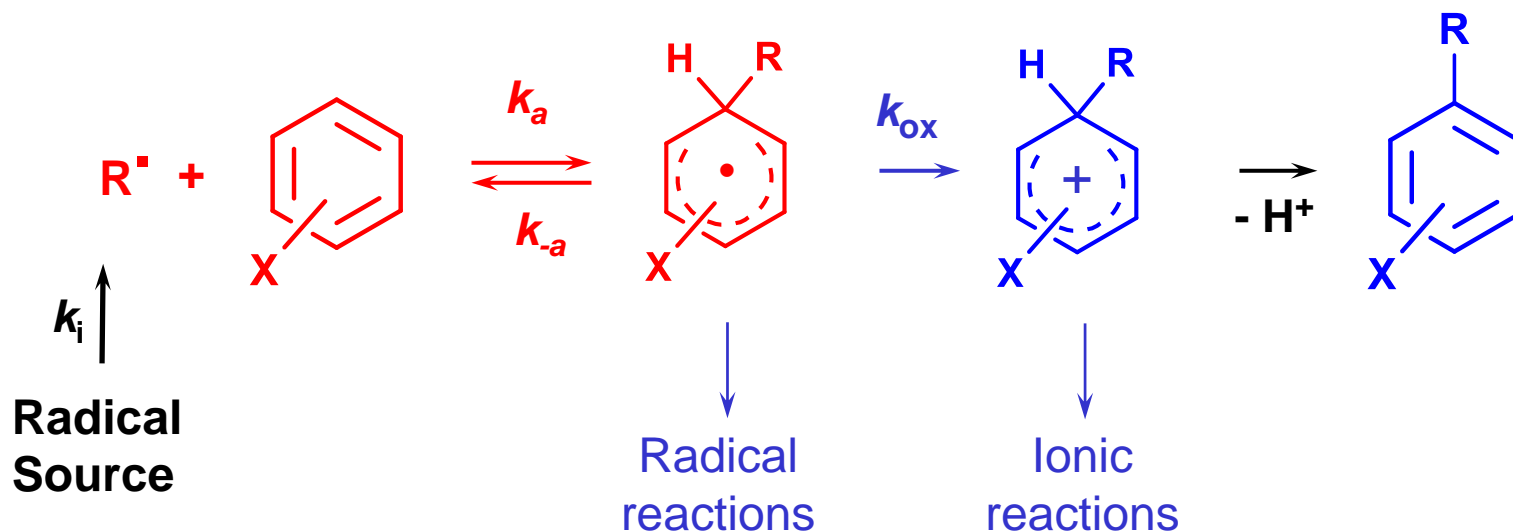


Paramagnetic Intermediates in the Homolytic Aromatic Substitution





Homolytic Aromatic Substitution via Cyclohexadienyl Radicals (Mechanism)



Step A : Reactivity (k_a)
Regioselectivity
Reversibility (k_a/k_{-a})

Step B : Radical Rearrangements
Oxidation/Disproportion
Ionic Reactions

Rate Constants and Substituent Effects in the Radical Addition to Aromatics

Addition Rate Constants of some radicals to **Benzene**

Radical	T(°K)	Source	k_a (M ⁻¹ ·s ⁻¹)
(CH ₃) ₂ NH ⁺	298	R ₂ N-Cl	2.1 × 10 ⁷
HO [•]	298	H ₂ O, e ⁻	3.9 × 10 ⁸
PhCOO [•]	351	(PhCOO) ₂	1.1 × 10 ⁶
CH ₃ COCH ₂ [•]	353	Mn(III)/Ac	5.8 × 10 ⁴
Ph [•]	298	PhN ₂ ⁺ /Ti ³⁺	1.1 × 10 ⁶
CH ₃ [•]	338	(CH ₃ CO ₂) ₂	1.0 × 10 ⁴
5-Hexenyl [•]	333	Perox./Cu ⁺	3.8 × 10 ²
i-Bu [•] , t-Bu [•]	333	Perox./Cu ⁺	< 10

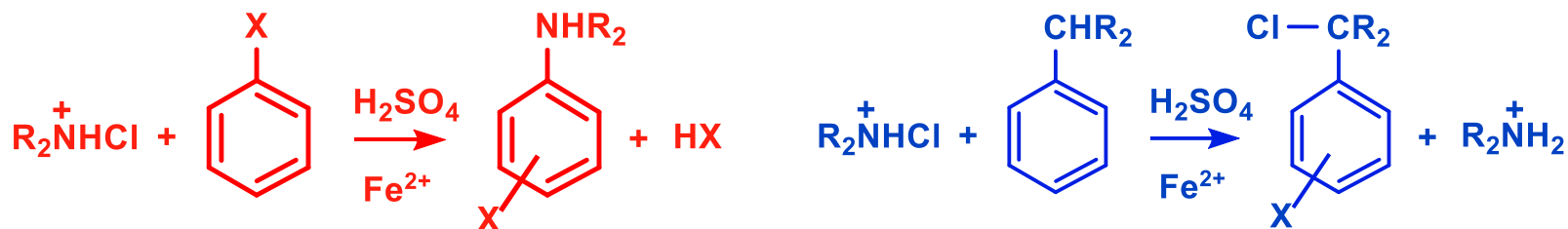
Substituent effects in the addition of some radicals to *para* substituted benzenes

Radical	ρ^+
C ₆ H ₁₁ [•]	+ 1.1
CH ₃ [•]	+ 0.1
Ph [•]	+ 0.1
HO [•]	- 0.3
PhCOO [•]	- 1.6
CH ₃ COCH ₂ [•]	- 1.5
i-C ₃ H ₇ OCO ₂ [•]	- 2.3

- Radicals Ph[•] and OH[•] add easily but show low substrate selectivity
- Electrophilic radicals (R₂NH⁺, RCO₂[•]) add fast with good selectivity
- Nucleophilic carbon radicals add inefficiently with moderate selectivity



Homolytic Aromatic Amination and Benzylic Halogenation with N-Chloramines

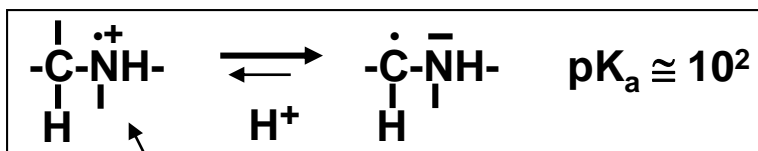
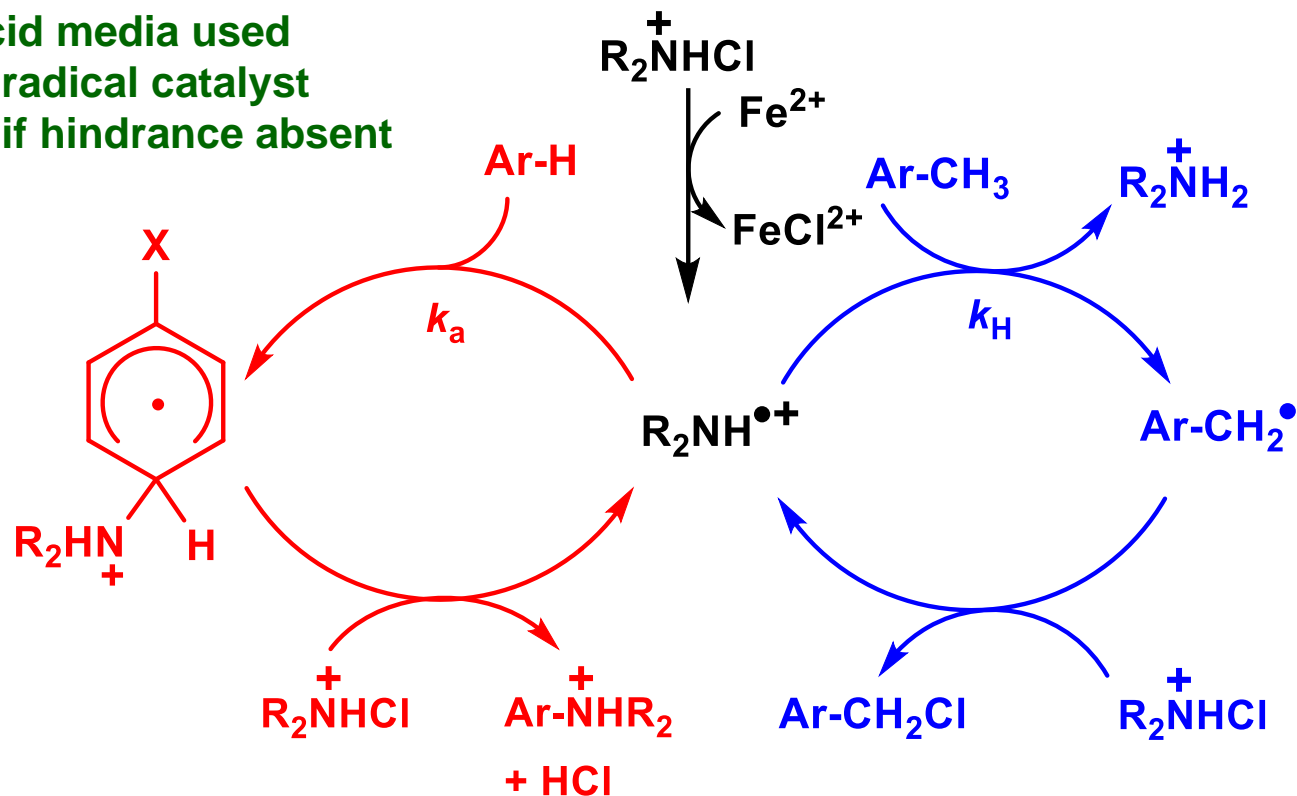


R	X	Yield %	Regoselectivity			side-chain funct.
			<i>o</i>	<i>m</i>	<i>p</i>	
H	H	82	-	-	-	-
Me	H	95	-	-	-	-
Me	Me	82	9.6	54.2	36.2	5
Me	Bu ^t	72	1	22.8	77.2	-
Me	OMe	65	8.9	1	91.1	-
Me, Bu ^t	Me	50	10	50	40	30
<i>c</i> -C ₆ H ₁₁	Me	-	-	-	-	98
<i>c</i> -C ₆ H ₁₁	<i>m</i> -diMe	-	-	-	-	96

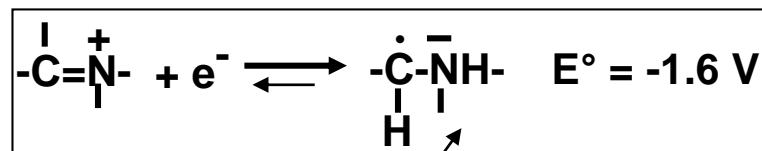


Amination/Halogenation with N-Chloramines

- Very acid media used
- Cation radical catalyst
- $k_a > k_H$ if hindrance absent



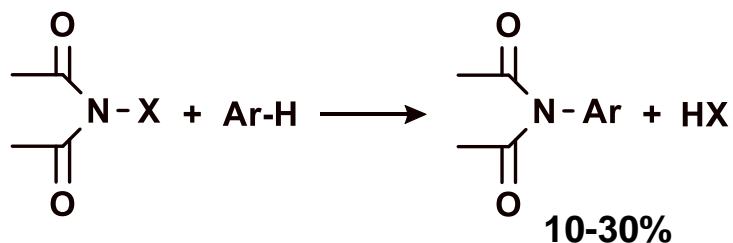
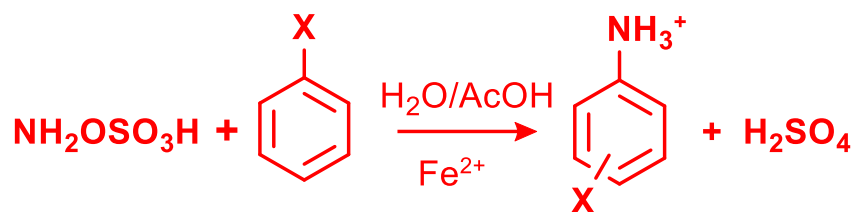
Sensitive to deprotonation



Sensitive to oxidation

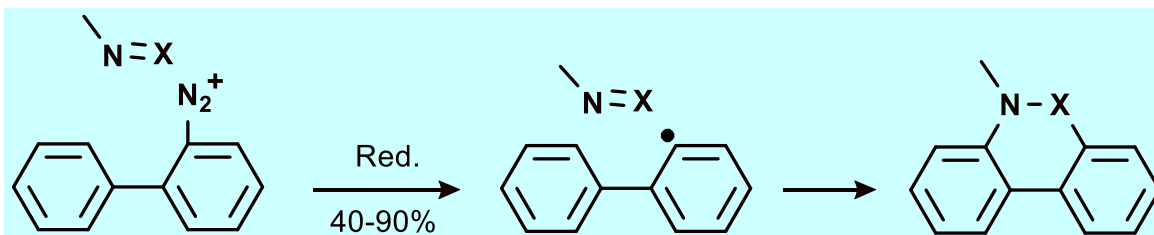
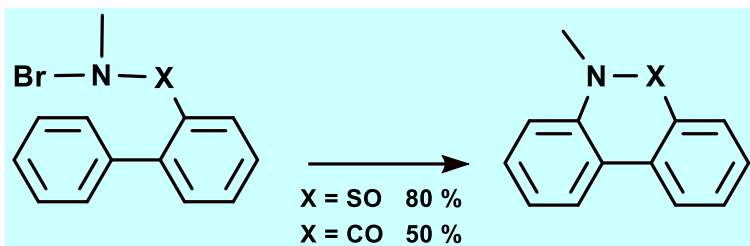


Inter- and Intramolecular Amination (Examples)



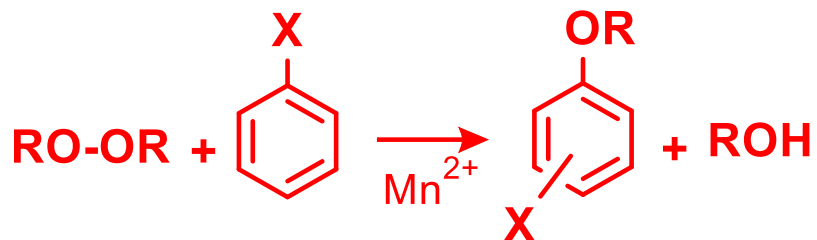
X	Yield %	Selectivity		
		o	m	p
H	65	-	-	-
OCH ₃	60	28.5	1.7	69.8
Me	53	35.7	22.7	41.6
Bu ^t	58	3.7	43.6	52.7
Cl	24	20.7	20.6	58.7
CO ₂ Et	21	23.0	45.6	31.4
CN	7	9.8	51.6	38.6

(for N-Br see benzylic/allylic halogenation)



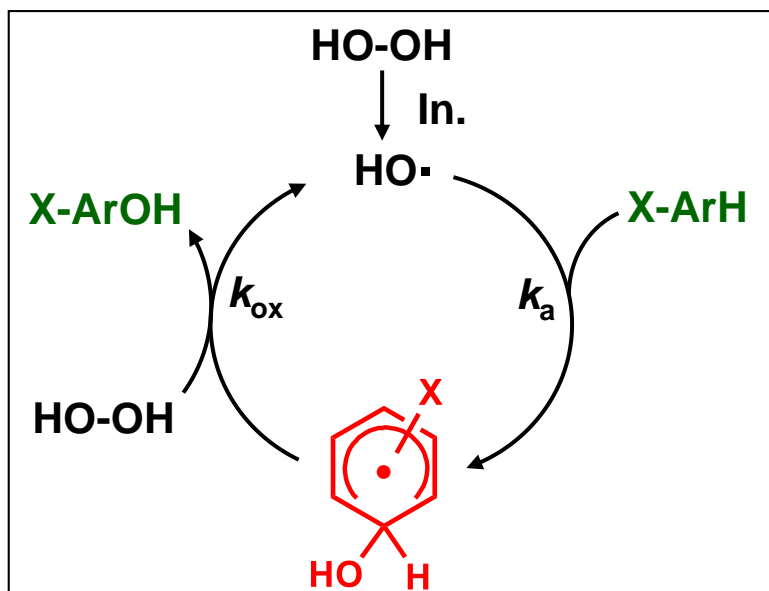


Homolytic Aromatic Hydroxylation

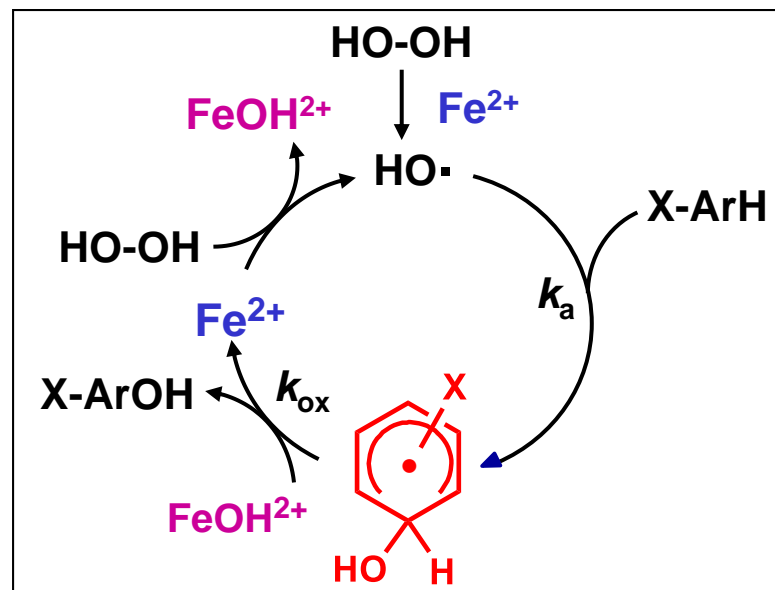


$\left\{ \begin{array}{l} \text{R} = \text{H}; \text{M}^{n+} = \text{Fe}^{2+}, \text{Ti}^{3+} \text{ [Fenton]} \\ \text{R} = \text{OCOAr}; \text{M} = \text{Cu}^+ \text{ (only Ar because} \\ \text{the decarboxylation of aryloxy} \\ \text{radical is slow } k_{300\text{K}} = 10^6 \text{ s}^{-1}) \end{array} \right.$

Direct Redox Chain Process



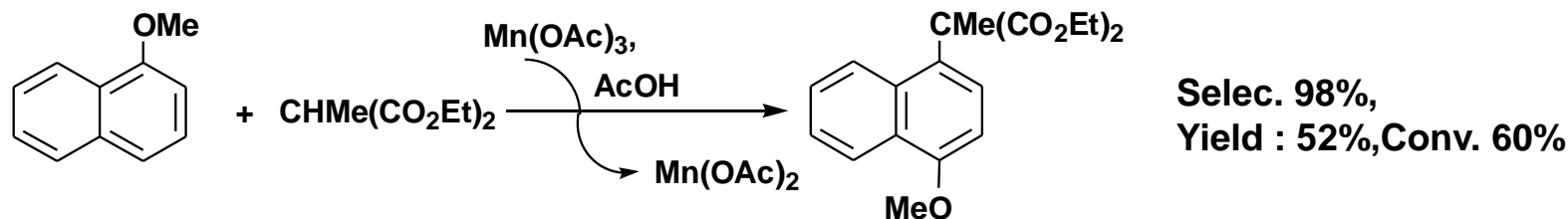
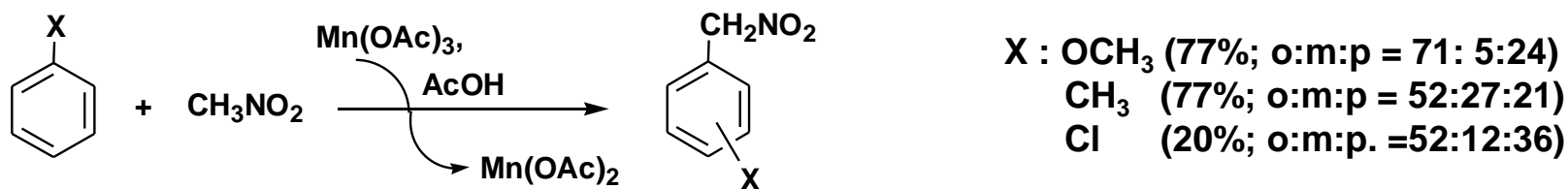
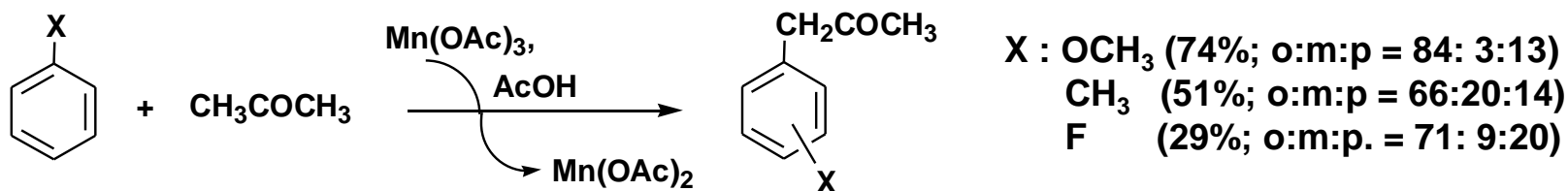
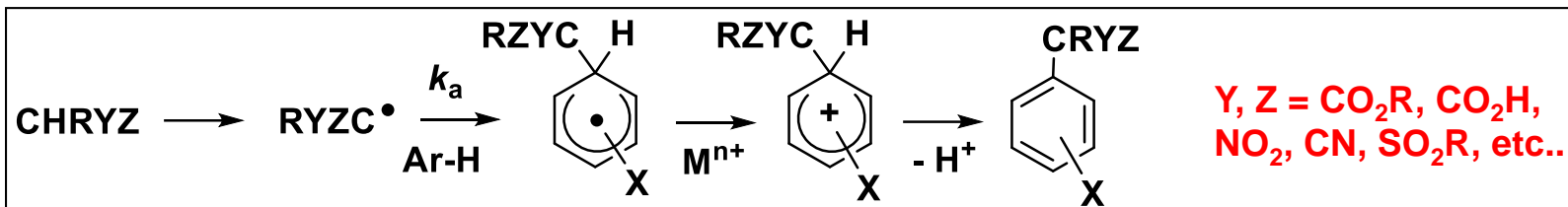
Catalyzed Redox Chain Process



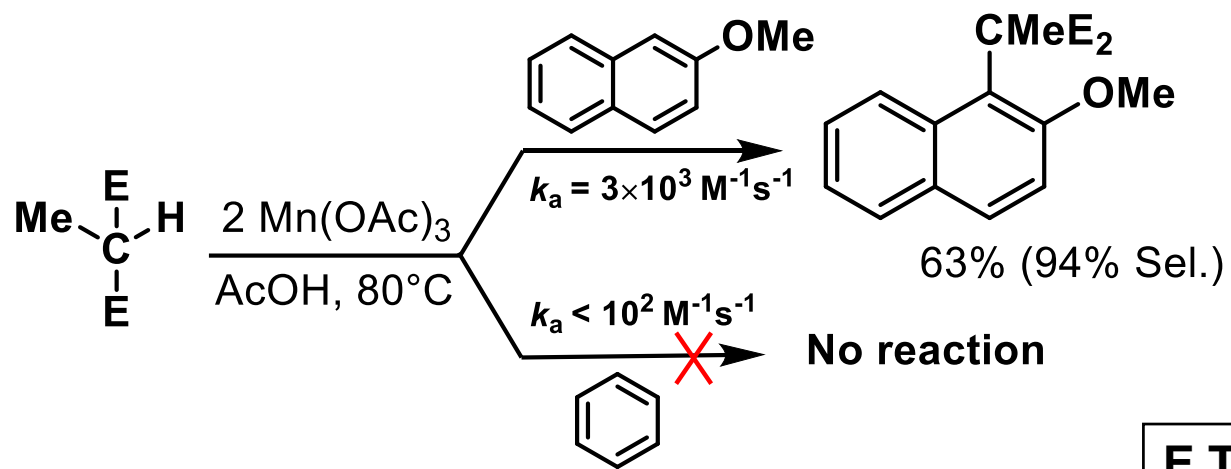


Homolytic Aromatic Alkylation

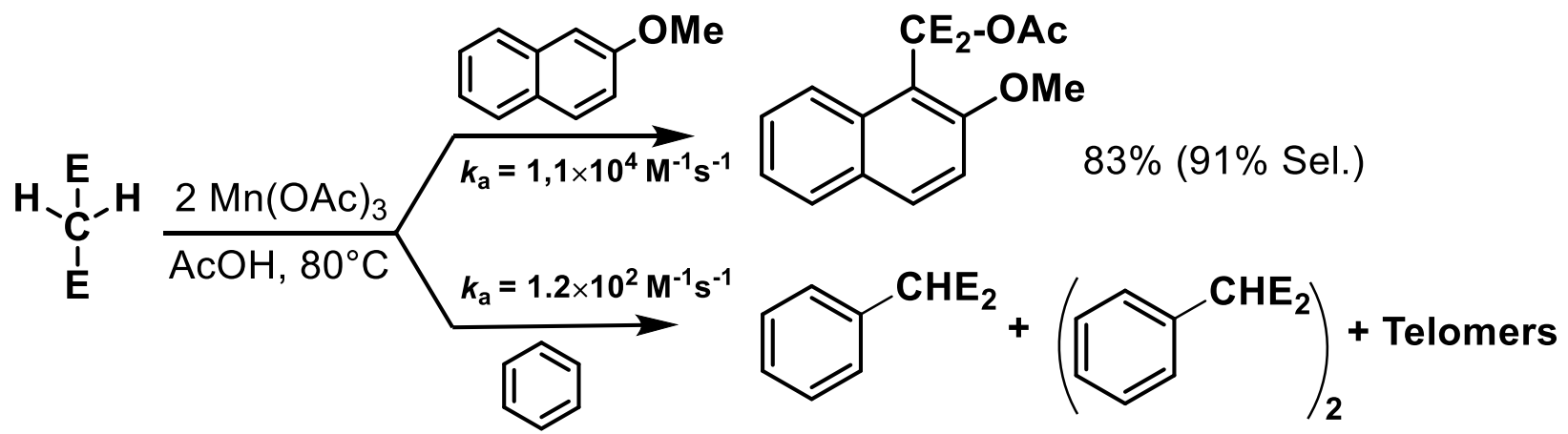
Oxidative addition of **electrophilic radicals** (stoichiometric redox)



Competition Reaction in the Homolytic Aromatic Alkylation

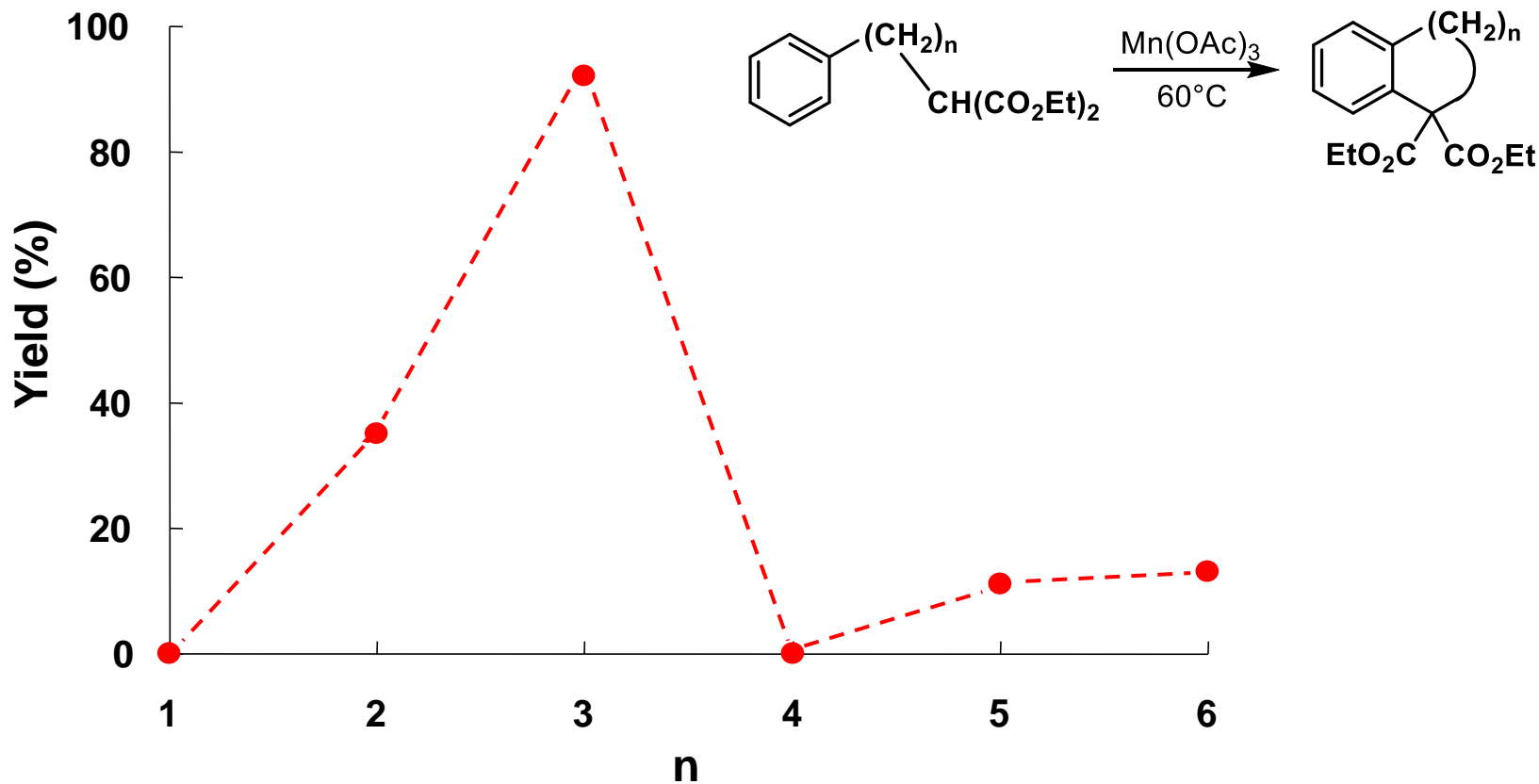


E.T. per $\text{IP}_{\text{ArH}} < 7.2 \text{ eV}$



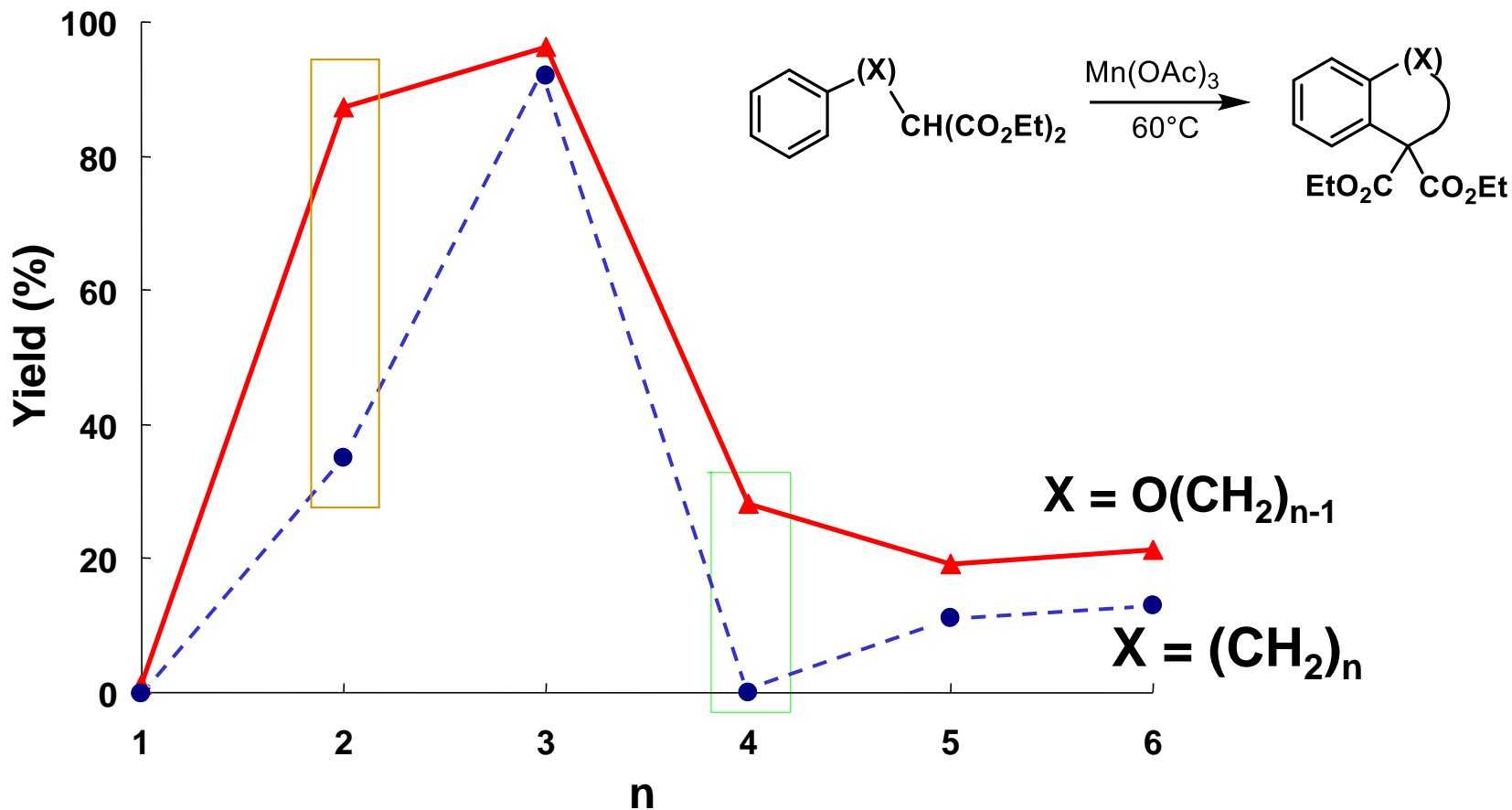
Intramolecular Aromatic Substitution by Malonyl Radicals

Source: oxidation of ω -arylalkylmalonates by Mn(III) and Fe(III) salts



A. Citterio et al., *J. Org. Chem.* 54, 2713 (1989).

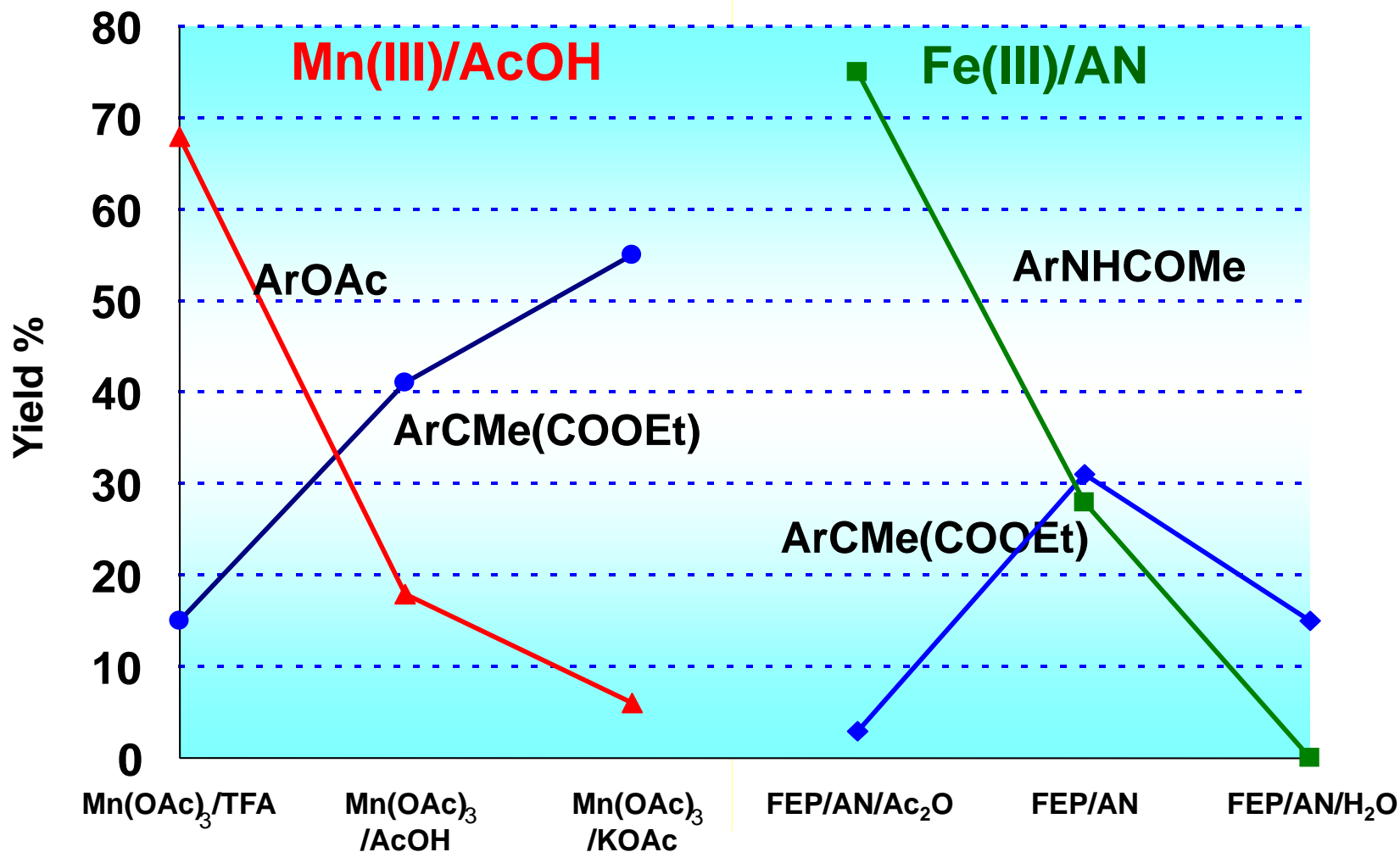
Intramolecular Aromatic Substitution by Malonyl Radicals



A. Citterio et al., *J. Org. Chem.* 54, 2713 (1989).

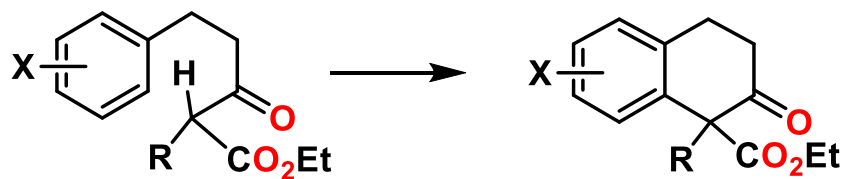


Ligand/Metal Effect in the Oxidation of Ethyl Methylmalonate in the Presence of 2-Methoxynaphthalene



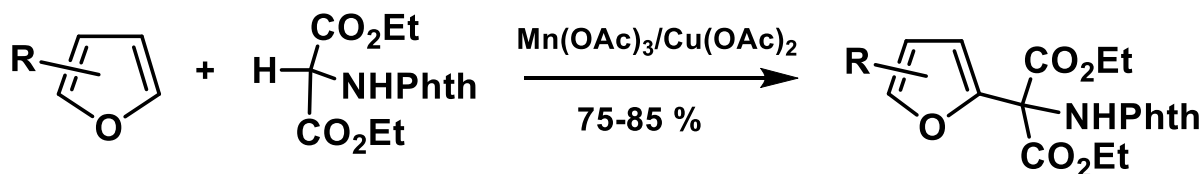
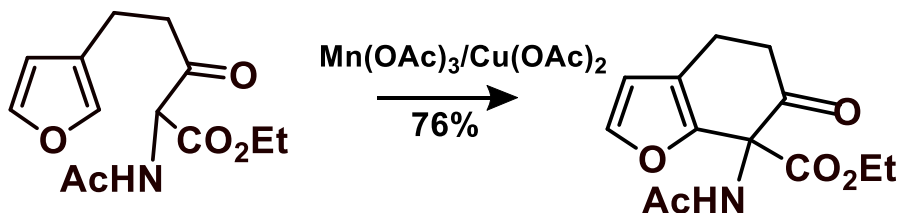


α -Amido- and α -OxyAlkyl Radical Cyclization



R = CO₂Et, 80-90%; Me, 25-60 %
R = NHAc, OMe, OAc, 0%

Moreover, with more electron-rich aromatics:

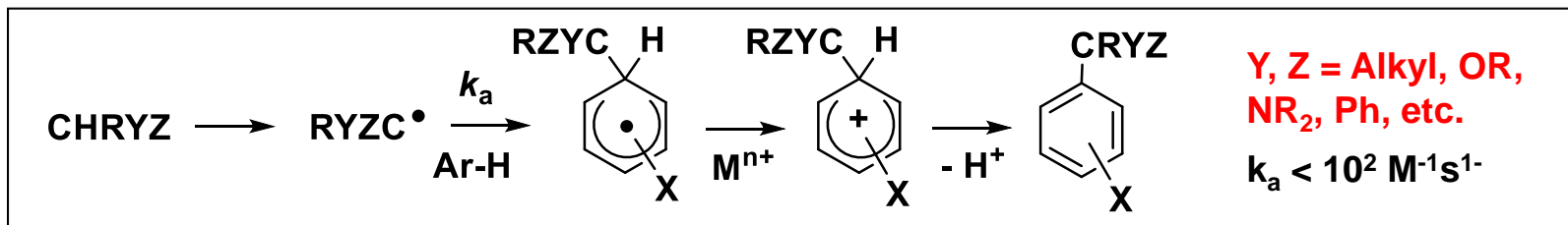


A. Citterio et al. *Tetr. Lett.* 1993 , 7981

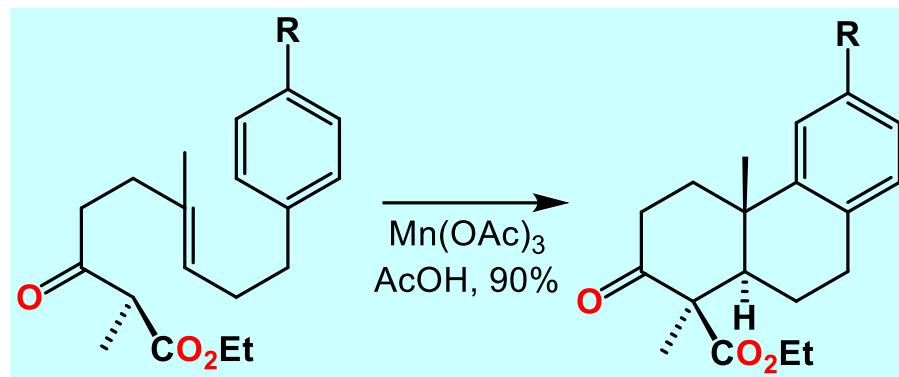
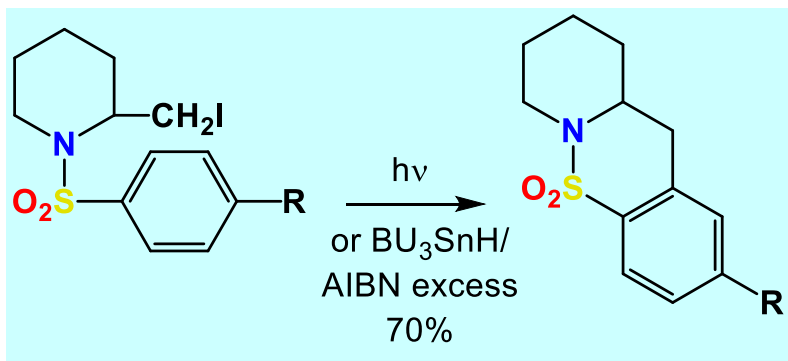


Homolytic Aromatic Alkylation (2)

The intermolecular oxidative addition of **nucleophilic radicals** is quite slow!

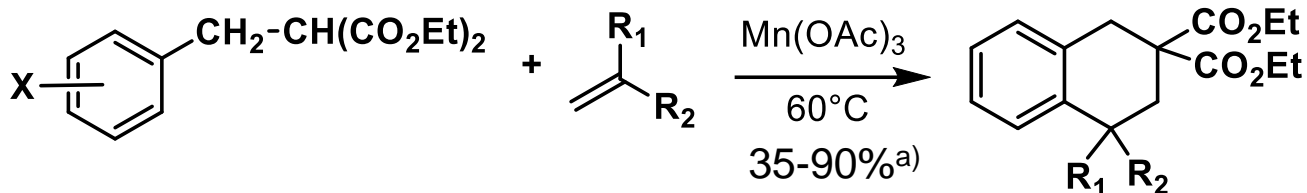


However, intramolecular additions are possible ($k_a = 10^3\text{-}10^5 \text{ M}^{-1}\text{s}^{-1}$)





Addition-Cyclization of Benzylmalonates to Olefins



Addition rate constants of diethylbenzyl malonic radicals to alkenes^{b)}

Olefin	k_a (mol ⁻¹ s ⁻¹)
CH ₂ =CH-Ph	8.0×10^6
CH ₂ =CH-CN	7.1×10^4
CH ₂ =CH-COOMe	5.7×10^4
CH ₂ =CH-SiMe ₃	3.9×10^4
CH ₂ =CH-n-C ₆ H ₁₃	9.8×10^4
CH ₂ =C(Me)-i-Pr	4.4×10^5

Cyclization rate constants at 333 °K in AcOH

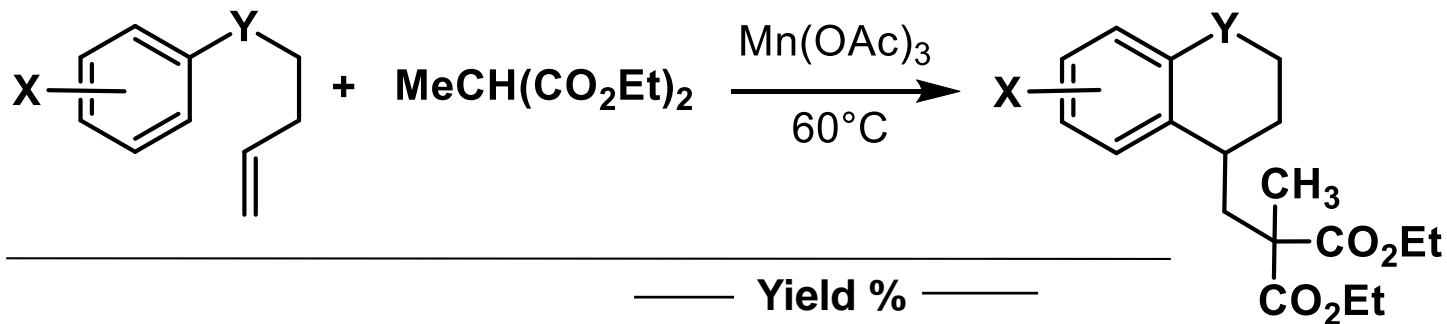
X-Ar	R ₁	R ₂	k_a (s ⁻¹) ^{a)}
Phenyl	H	Ph	$\sim 2.0 \times 10^1$
Phenyl	H	SiMe ₃	4.2×10^3
Phenyl	H	n-C ₆ H ₁₃	5.6×10^3
3-Piridyl	H	n-C ₆ H ₁₃	4.2×10^5
Phenyl	Me	i-Pr	3.2×10^2
3-Piridyl	Me	i-Pr	1.2×10^6

a) A. Citterio et. al. *J. Org. Chem.* 56, 5328 (1991)

b) A. Citterio et. al. *J. Org. Chem.* 57, 4250 (1992)



1,6-Cyclizations of 3-Butenylarylethers and Amides



	Yield %	
1 ; X = H, Y = O	65	38
2 ; X = 3,5-COOEt, Y = O	94	88
3 ; X = 3,5-Me, Y = O	31	10
4 ; X = 3-F, Y = O	77 (R = 0.8)	40 (R = 1.0)
5 ; X = 3-CN, Y = O	78 (R = 0.5)	35 (R = 0.7)
6 ; 3-piridyl, Y = O	86 (R = 1.0)	69 (R = 1.4)
7 ; 2-piridyl, Y = O	40	13
8 ; 4-piridyl, Y = O	51	23
9 ; X = H, Y = NCOMe	58	38
10 ; X = 3,5-COOEt, Y = NCOMe	90	71
11 ; 3-piridyl, Y = NCOMe	71 (R = 2.1)	70 (R = 2.9)

R = orto/para ratio to X

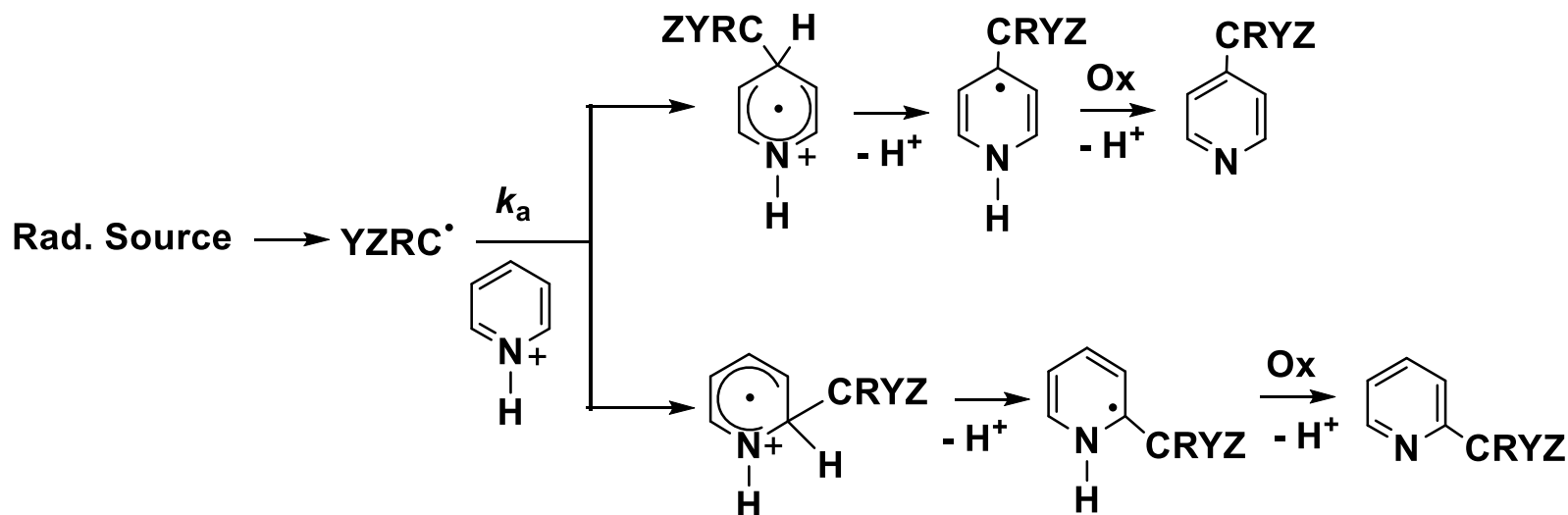
Electrochemical (Mn(III) = 0.01 M)

Chemical (Mn(III) = 0.2 M)



Homolytic Eteroaromatic Alkylation (H⁺)

The intermolecular oxidative addition of **nucleophilic radicals** is quite fast



Y, Z = Alkyl, OR,
NR₂, Ph, Acyl.

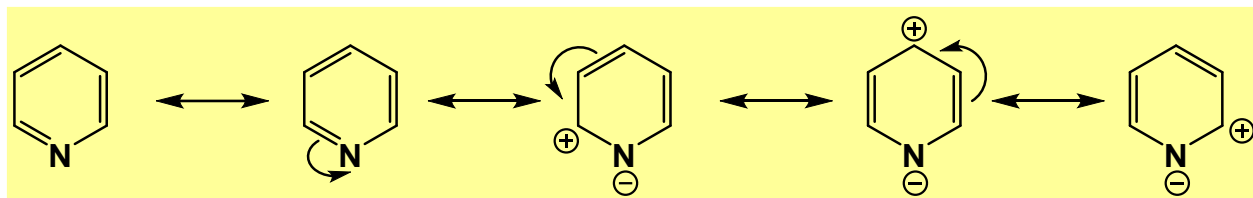
$k_a > 10^4 \text{ M}^{-1}\text{s}^{-1}$

Rad. = C ₂ H ₅	56(p) 44(o)	Source: RCOOH/K ₂ S ₂ O ₈ /Ag ⁺
Rad. = c-C ₆ H ₁₁	63(p) 37(o)	
Rad. = Bu ^t	68(p) 32(o)	
Rad. = HOCH ₂	72(p) 28(o)	
Rad. = CH ₃ CO	70(p) 30(o)	

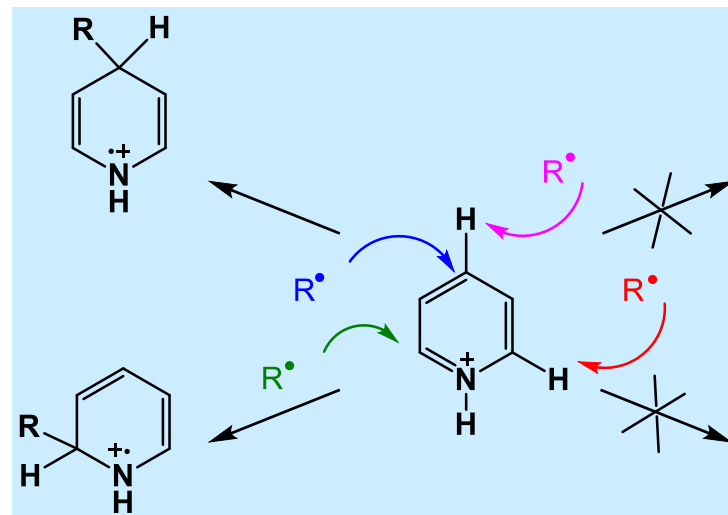
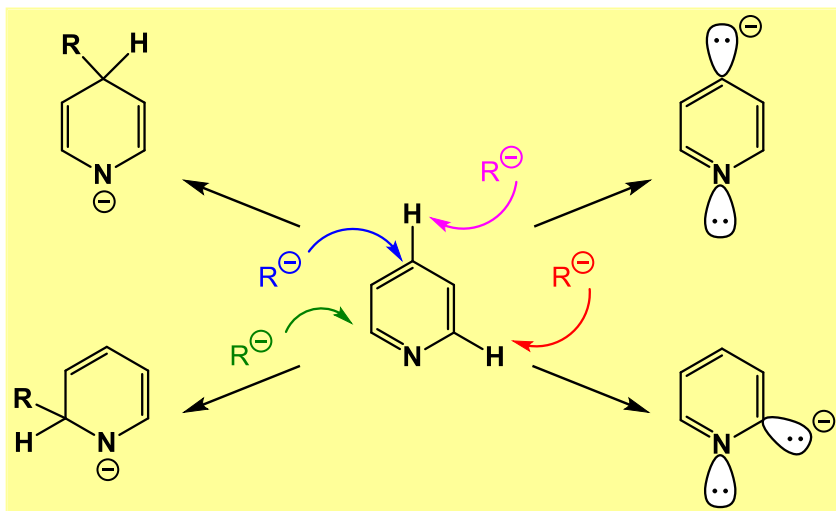
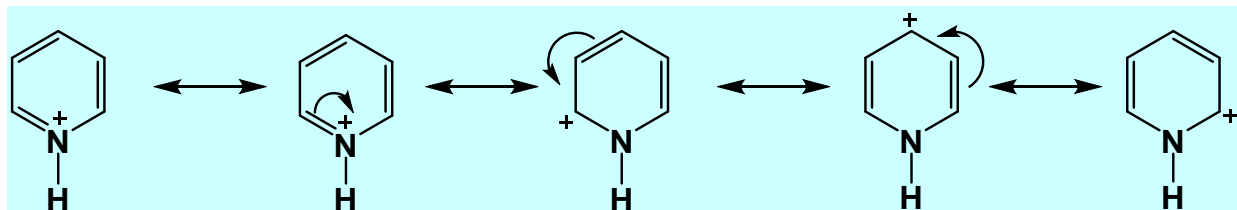


Nucleophiles and Nucleophilic Radicals add Preferentially to Electron-poor C atoms.

pyridine

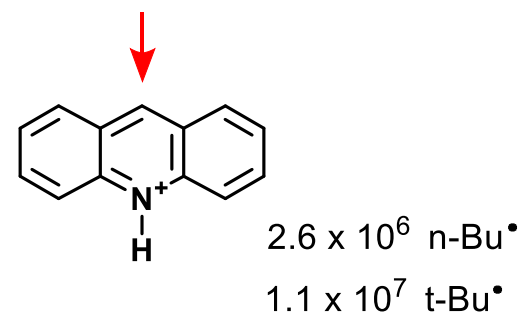
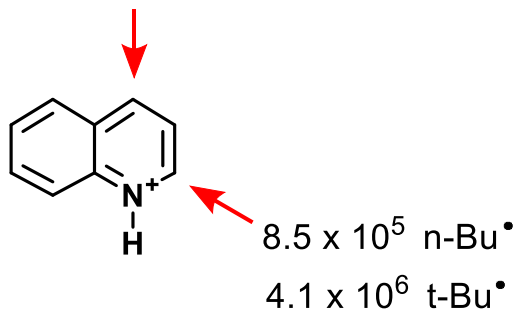
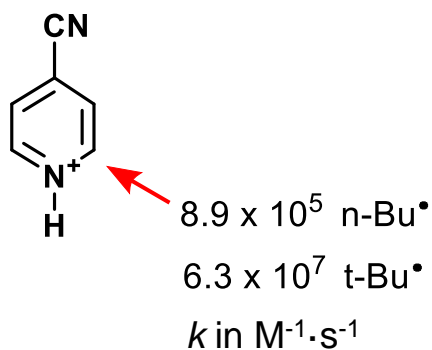


Pyridinium cation

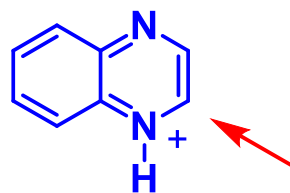
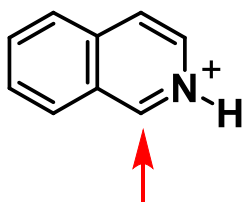
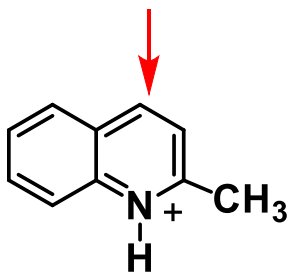




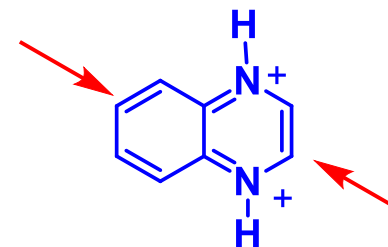
Absolute Rate Constants of Homolytic Alkylation of Substituted Pyridinium Cations



The high reactivity is associated to an high positional selectivity for aromatic carbon with low electron density conjugated with the positive nitrogen.



pH = 4-0

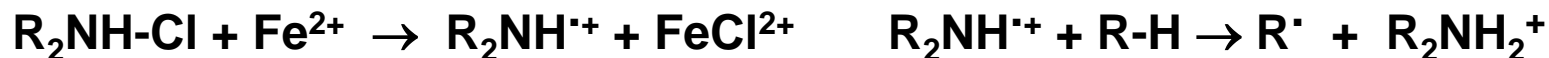


H $^{\circ}$ = -(3-5)

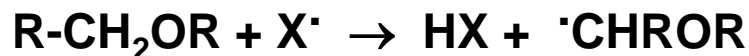


Radical Sources Useful in the Heteroaromatic Homolytic Alkylation and Acylation

1) N-Chloramines and hydrocarbons



2) Alcohols and ethers with electrophilic radical sources (N, O)

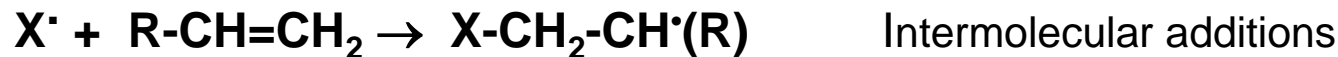


$\text{H}_2\text{O}_2/\text{M}^{n+}$, $\text{Bu}^t\text{-OOH}/\text{M}^{n+}$, $\text{NH}_2\text{SO}_3\text{H}/\text{M}^{n+}$, $\text{S}_2\text{O}_8^{2-}/\text{M}^{n+}$ ($\text{M}^{n+} = \text{Fe}^{2+}$, Ti^{3+})
 $^+\text{NH}_3\text{OH}/\text{Ti}^{3+}$, thermal decomposition of peroxides, radiolysis

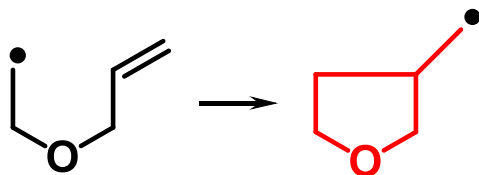
3) Alkyl iodides and peroxides



4) Addition to alkenes



$\text{X} = \text{N}_3^{\cdot}$ ($\text{H}_2\text{O}_2/\text{M}^{n+}$, N_3^-), $\cdot\text{CH}_2\text{COCH}_3$ ($\text{Ag}^+/\text{S}_2\text{O}_8^{2-}/\text{Acetone}$), PhCO_2^{\cdot} ($(\text{PhCO}_2)_2$)



Intramolecular additions

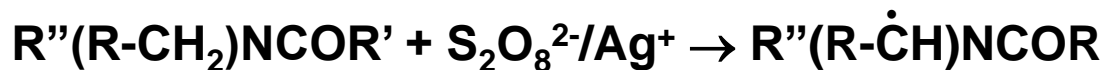


Radical Sources Useful in the Heteroaromatic Homolytic Alkylation and Acylation

5) Oxidation of carboxylic acids

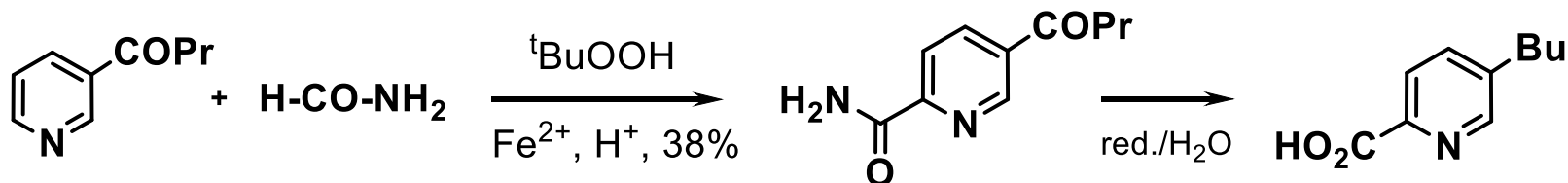
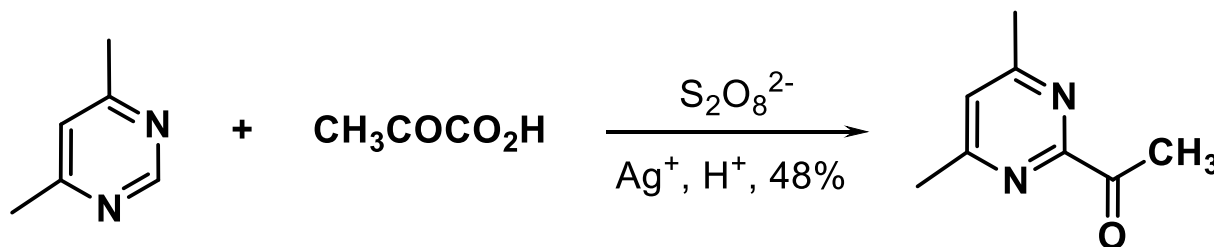
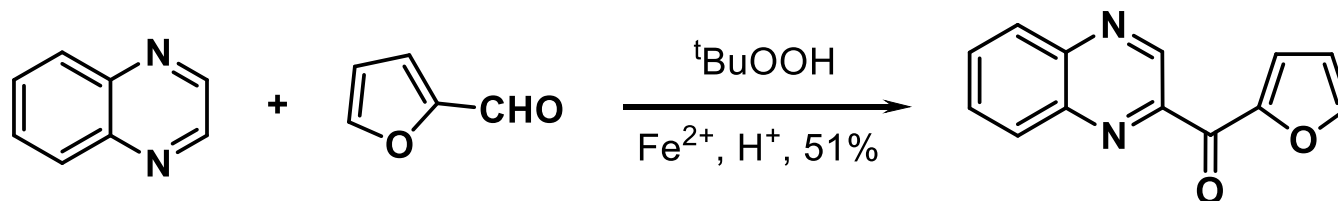


6) Oxidation of amides



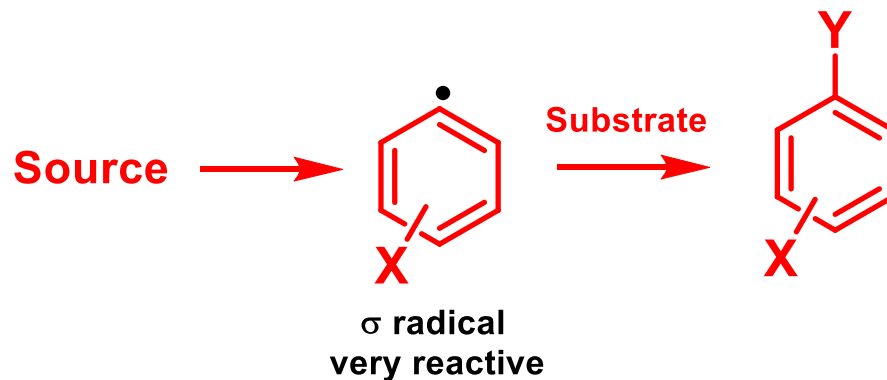
(via N-cation radical or H-abstraction)

1') Acylation

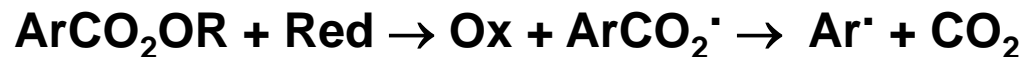
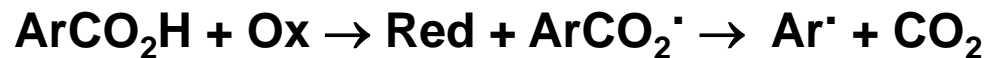
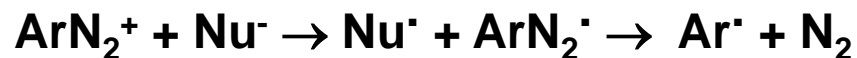
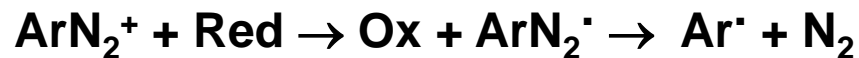




Homolytic Aromatic Substitution via Aryl Radicals



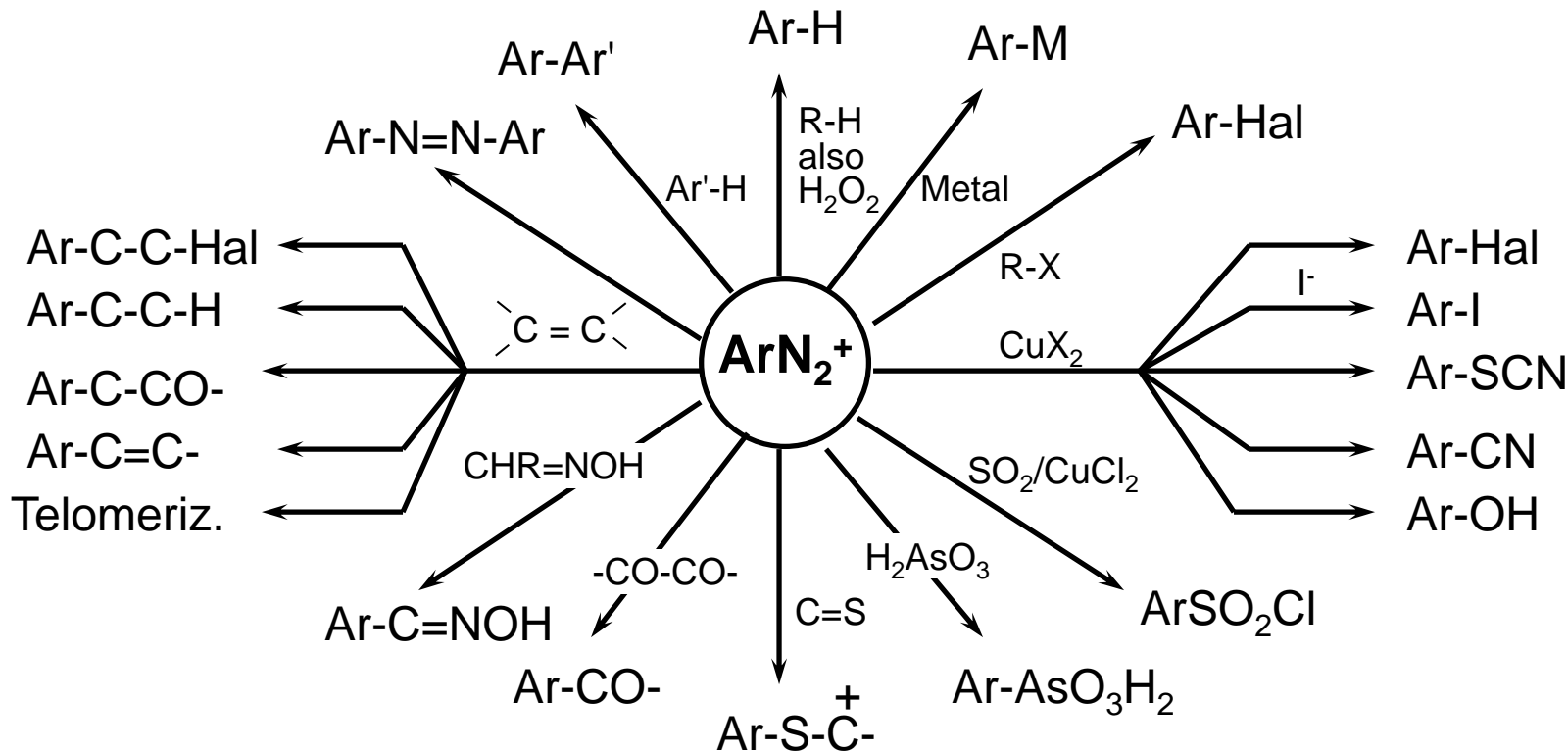
Sources:





Homolytic Reactivity of Diazonium Salts

Displacement and addition processes by aryl radicals



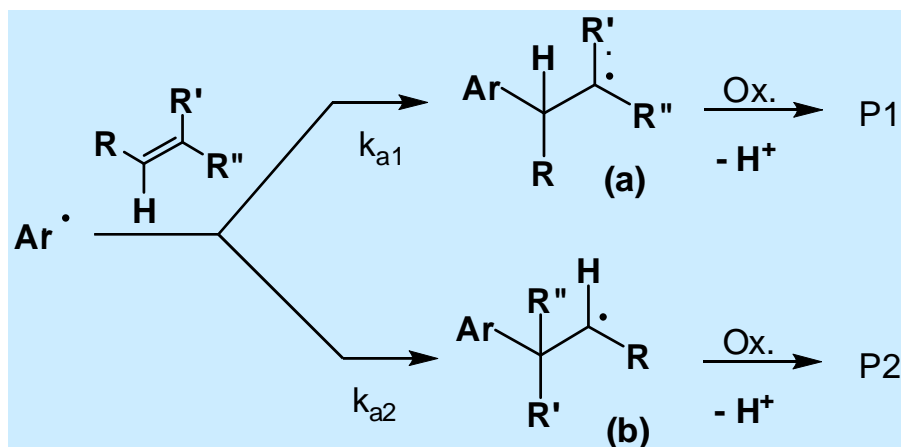
Zollinger, *Angew. Chem I.E.*, 1978, 17, 141
Rondeveldt, *Org. React.* 1976, 24, 225; 1960, 11, 189

C. Galli, *Chem. Rev.*, 1988, 88, 765
A. Citterio, *J. Org. Chem.*, 1982, 47, 81; *Org. Synth.* 62, 67



Homolytic Arylation of Olefins

(Rate and regioselectivity – Steric and electronic Effects)



Regioselectivity

R	R'	R''	α (%)	β (%)
H	H	COMe	< 4	> 96
Me	H	COMe	23	77
i-Pr	H	COMe	47	53
t-Bu	H	COMe	80	20
Ph	H	COMe	76	24
Me	Me	COMe	84	16

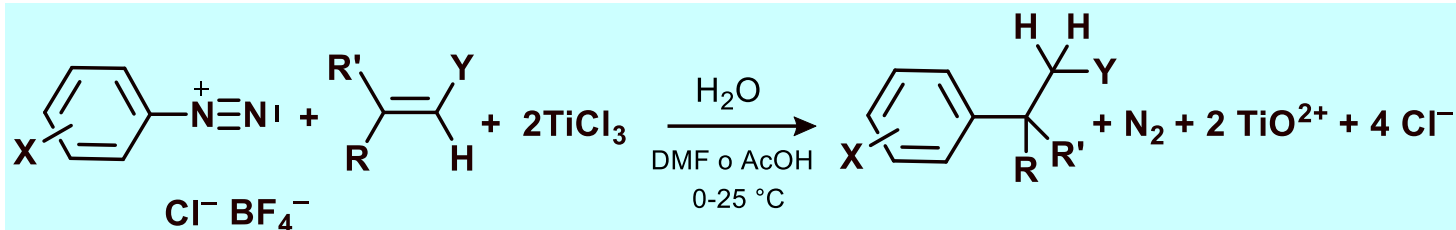
Reactivity

R	R'	R''	k_a ($\text{M}^{-1}\cdot\text{s}^{-1}$)
H	H	H	5.1×10^6
H	H	Ph	1.1×10^8
H	H	COMe	8.1×10^7
H	H	C_6H_{13}	8.6×10^6
H	H	OMe	1.0×10^7
H	Me	COOMe	9.2×10^7

A. Citterio, *J. Org. Chem.*, 1982, 42, 81

J.C. Scaiano, *J. Am. Chem. Soc.*, 1983, 105, 3609

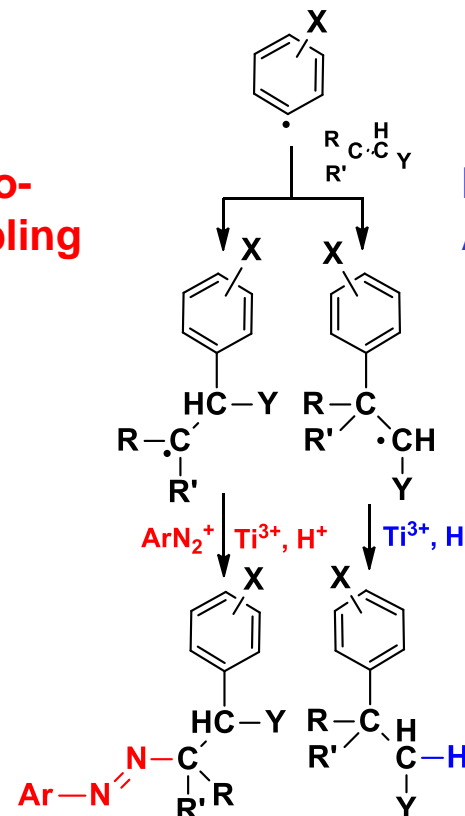
Reductive Arylation of Electron-deficient Olefins



X	R	R'	Y	Yield %
4-OMe	H	H	COCH ₃	65
H	H	H	COCH ₃	75
4-Br	H	H	COCH ₃	68
4.COMe	H	H	COCH ₃	72
4-Cl	H	H	COCH ₃	63
4-Cl	Me	H	COCH ₃	44
4-Cl 4-Cl	Pr ⁱ	H	COCH ₃	28
4-Cl	Bu ^t	H	COCH ₃	14
4-Cl	Me	Me	COCH ₃	12
4-Cl	Ph	H	COCH ₃	18
4-Cl	H	H	CN	25 ^b
4-Cl	H	H	COOH	33 ^b
4-Cl	H	H	COOEt	32 ^b
4-Cl	H	H	CHO	63

Diazo-coupling

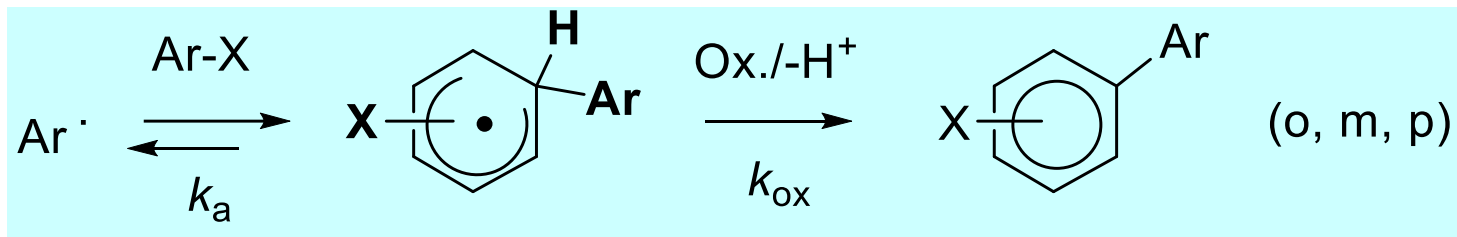
Reductive Arylation



A. Citterio, *Org. Synth.*, 1984, 62, 67.



Homolytic Aromatic Substitution by Aryl Radical Addition



Ph·

4-NO₂-Ph·

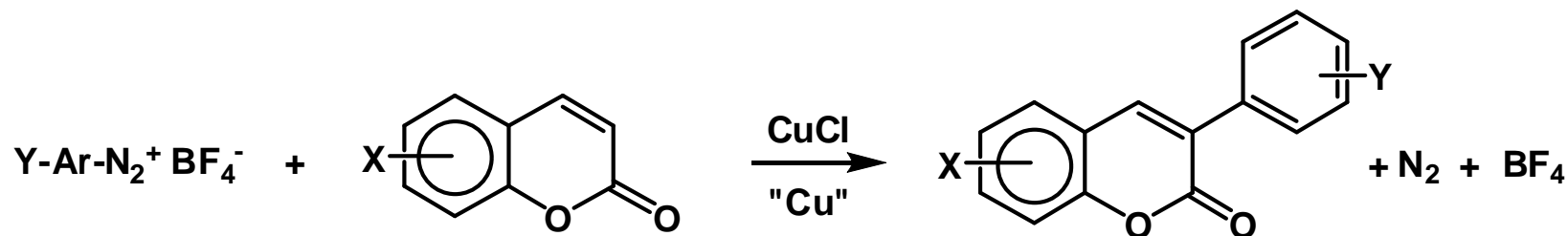
X	<i>k_r</i>	o	m	p	<i>k_r</i>	o	m	p
OMe	1.71	69	18	13	2.39	72	12	16
NO₂	5.02	62	8	30	0.68	45	17	38
Me	1.68	66	22	12	1.80	61	25	14
Cl	1.61	64	21	15	0.89	57	24	19

$$k_a = 4.8 \times 10^5 \text{ M}^{-1} \cdot \text{s}^{-1} \text{ (298 } ^\circ\text{K)}$$

R. Ito, *Tetrahedron*, 1965, 21, 955



Homolytic Aromatic Substitution of Coumarin



Y	X	R'	Diazonium (mol. Ratio)	Yield (%)	Select.
H	H	H	1	12 (8)	> 95
4-F	H	H	1	16	> 95
4-F	H	H	2	23	92
4-F	7-OMe	H	1	51	100
4-F	7-OMe	H	2	58	>98
4-F	7-OMe	H	3	65	>95
4-NO ₂	H	H	1	21	>95
4-NO ₂	7-OMe	H	1	63	100
H	H	OH	1	32	100

Experimental Conditions :

diazonium BF_4^-

solvent : acetone

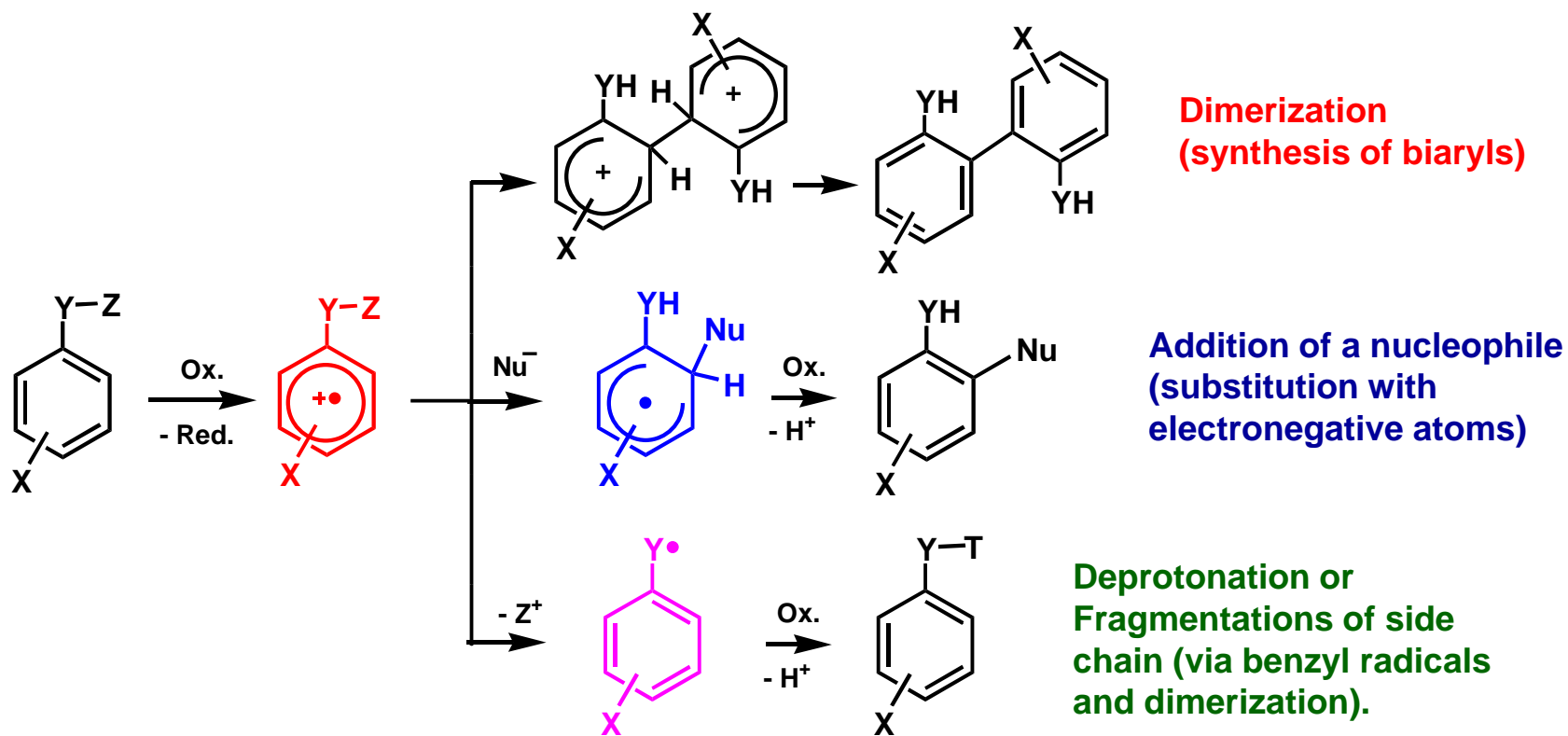
T = 290-300°K

Catalyst : CuCl (8%)



Substitution via Aromatic Cation Radicals

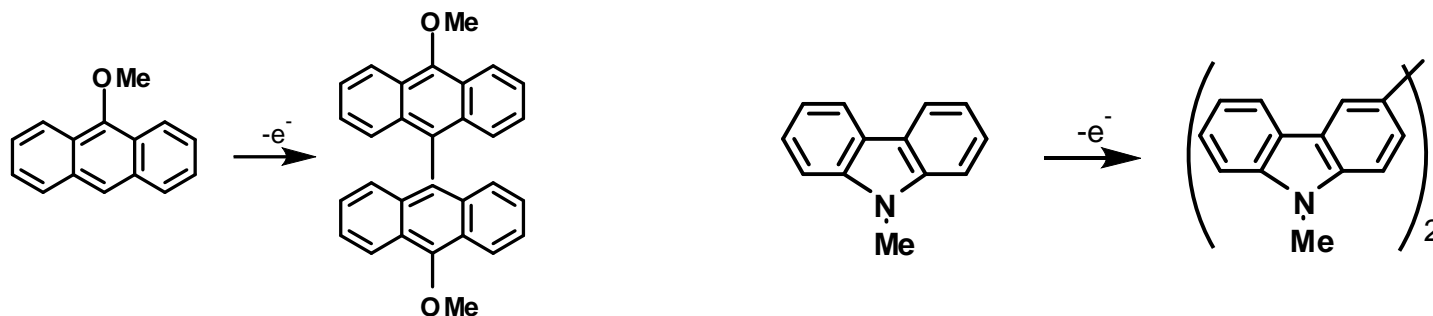
- The oxidation of aromatic substrates by strong oxidants can involve the aromatic pi-system with formation of cation radicals. These intermediate, depending on the aromatic substitution, can evolve following three main routes :





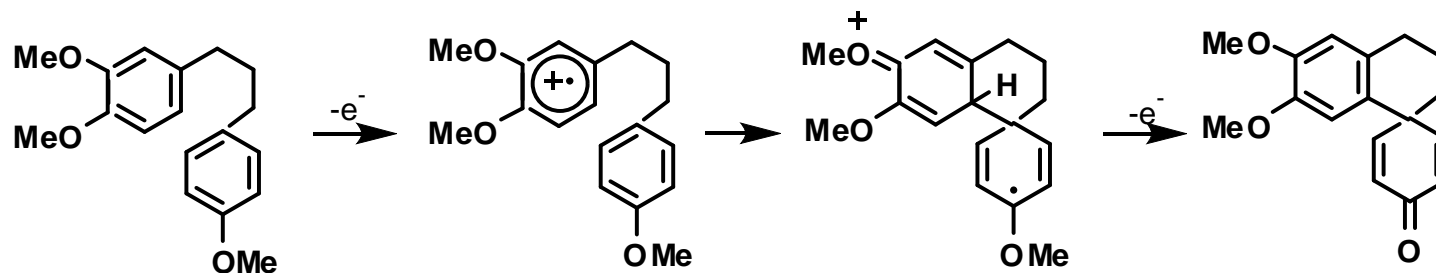
Dimerization Via Cation Radicals

1) Intermolecular Processes



S. Torii *Electro-organic Synthesis, Oxidations*, VCH 1985

2) Intramolecular Processes

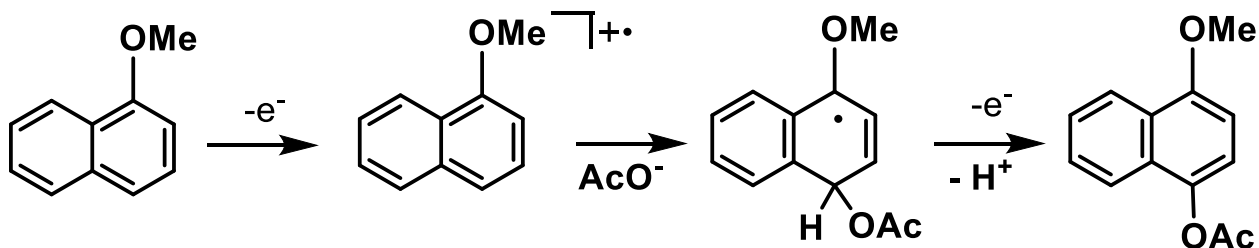


E. Kotani et al. *JCS Chem. Comm.*, 1973, 550; TELE, 1986, 95

L.L. Miller, et al. *J. Am. Chem. Soc.*, 1971, 93, 5941

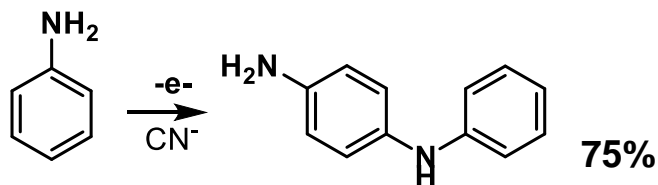
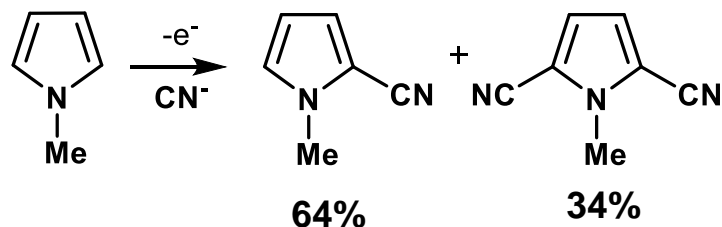


Nucleophilic Substitution via Cation Radicals

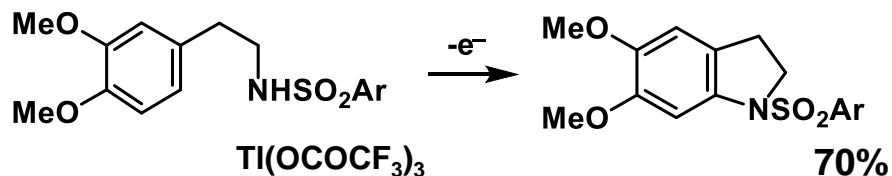


Acetoxylation of aromatics can be obtained by electrochemical oxidation or by high valent metal salts (M = Ce(IV), Co(III), Fe(III), Mn(III), etc.)

Nucleophilic anions to oxygen, nitrogen, carbon (CN⁻), and halides (both as ligand of the metal oxidant or as anions in the medium (i.e. in electrochemical reactions)) can be used. The same substitution can be obtained also by photochemical activation.

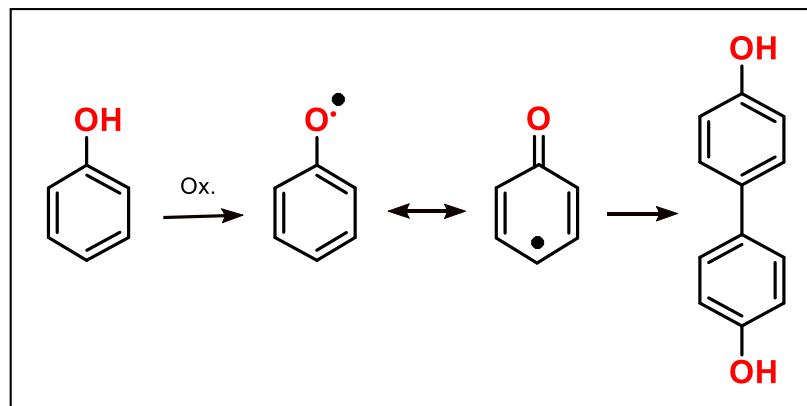
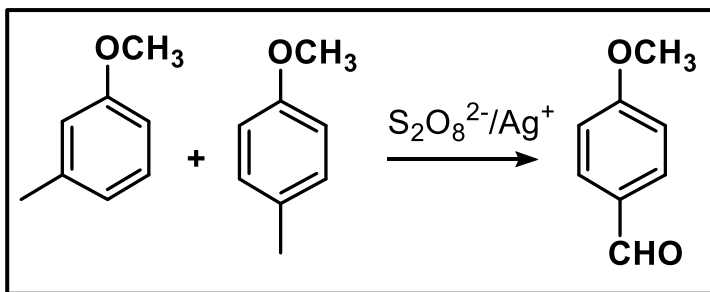
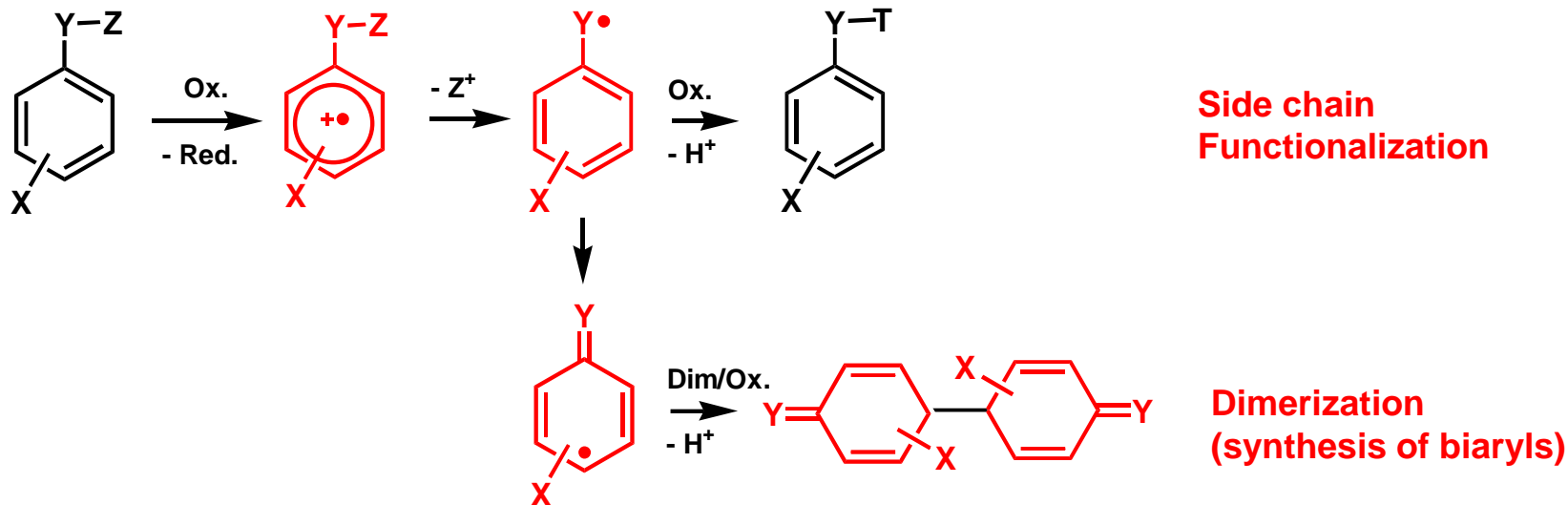


Intramolecular processes





Side-chain Fragmentation via Cation Radicals





Radical Generated by SET Process

Kornblum and Russell firstly provided details of the Single Electron Transfer (SET) pathway as early as 1966.

Mechanistic Pathway:

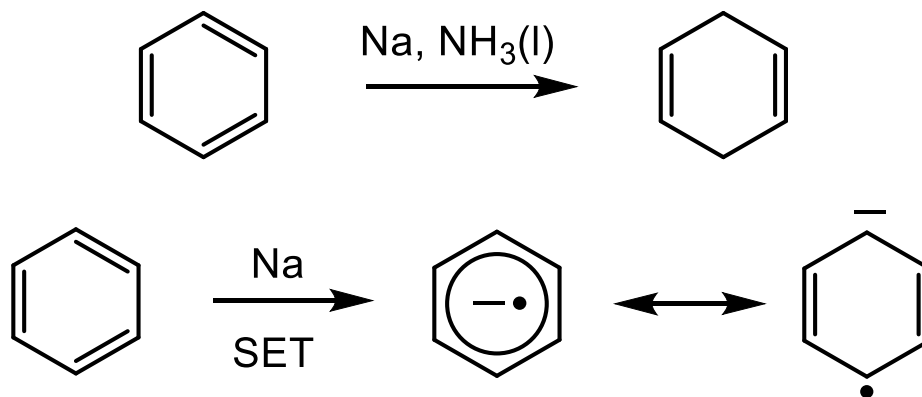


The reaction was then indicated as $\text{S}_{\text{RN}}1$ being a Radicals Nucleophilic Substitution in which the rate determining step is the unimolecular (1th order) decomposition of anion radical $\text{RX}^{\bullet-}$.

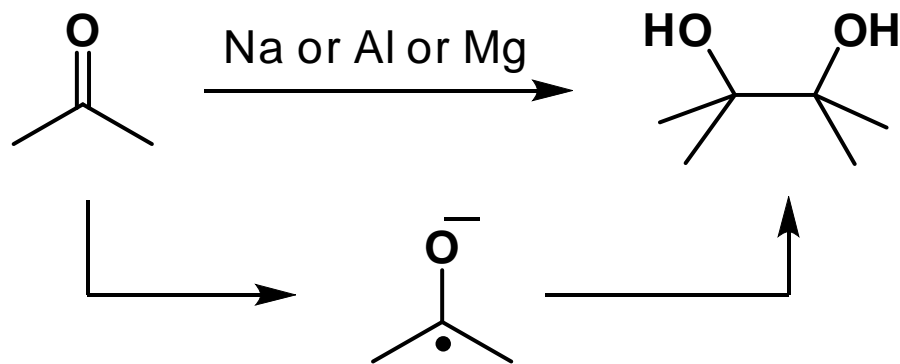


Some Examples of SET Processes

Birch Reduction



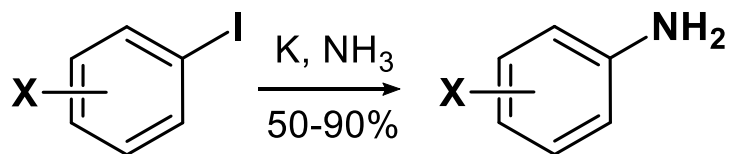
Pinacol-Coupling Reaction



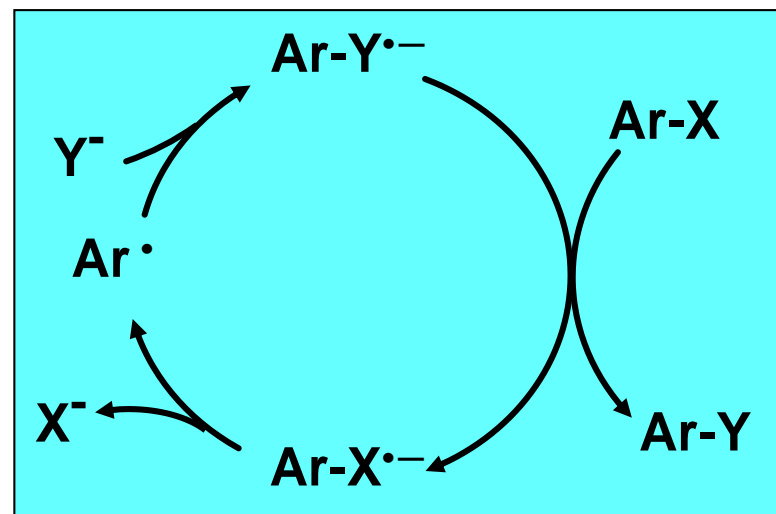


$S_{RN}1$ - Aromatic Substitution via Anion Radicals

$S_{RN}1$ Reaction



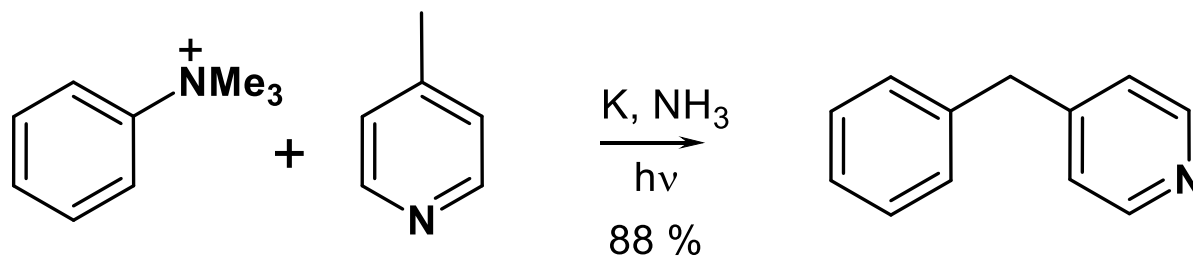
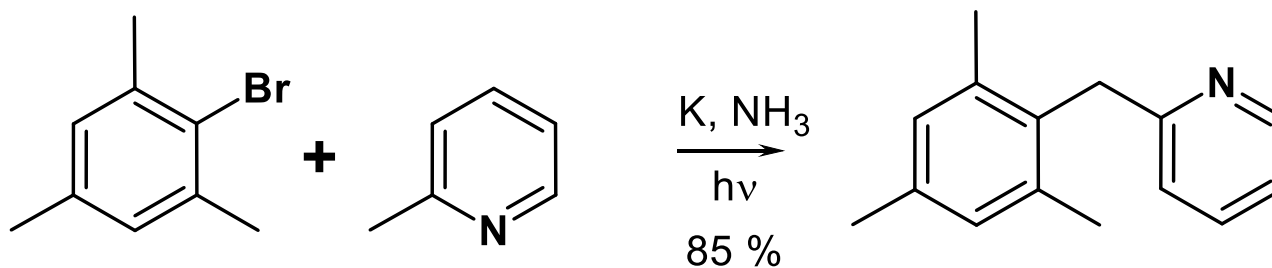
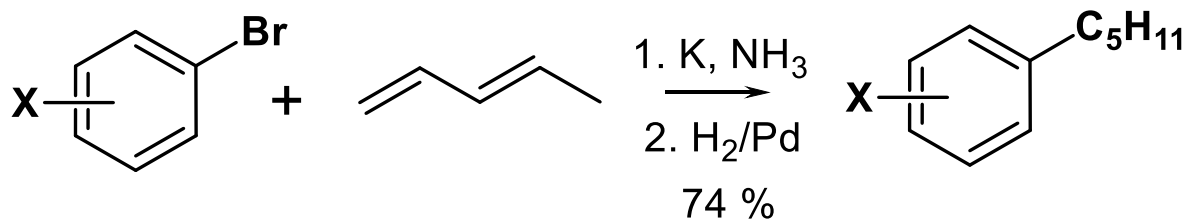
X = 2,3,5-trimethyl



- High regioselectivity
- Can be photo-stimulated
- Sensitive to inhibition
- Traces amount of Ar-H Products



S_{RN}1 - Substitutions by Conjugated Hydrocarbons





S_{RN}1 - Substitutions by Ketones

