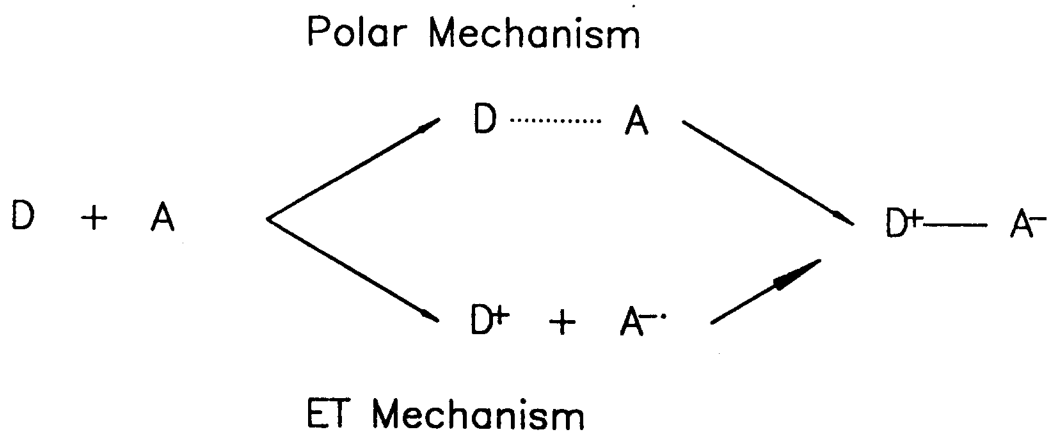
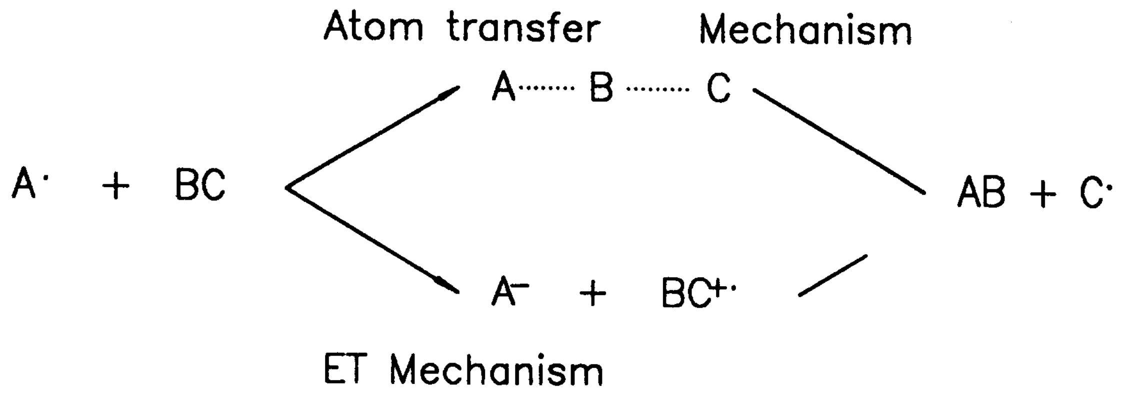
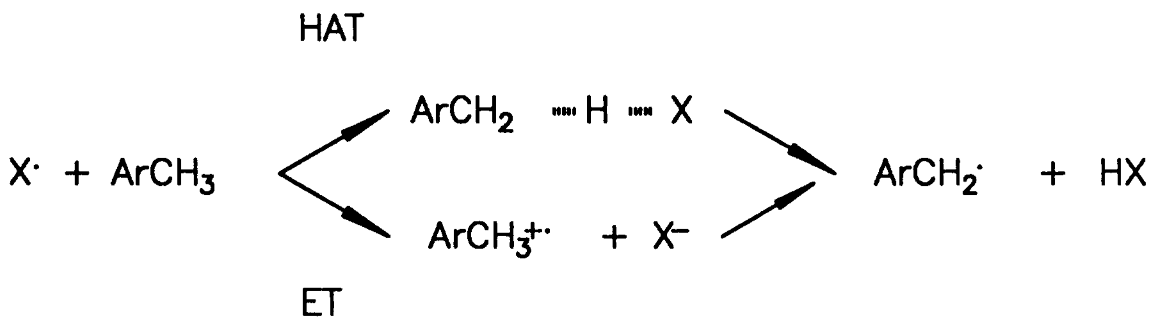






HAT = Hydrogen Atom Transfer

ET = Electron Transfer

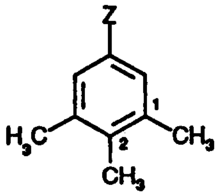
DISTINCTION OF HAT AND ET MECHANISMS

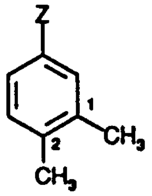
Direct approach: **EPR, CIDNP, Laser flash photolysis, Pulse radiolysis**

Indirect approach: **Reaction selectivity and products studies (Kinetic investigations)**

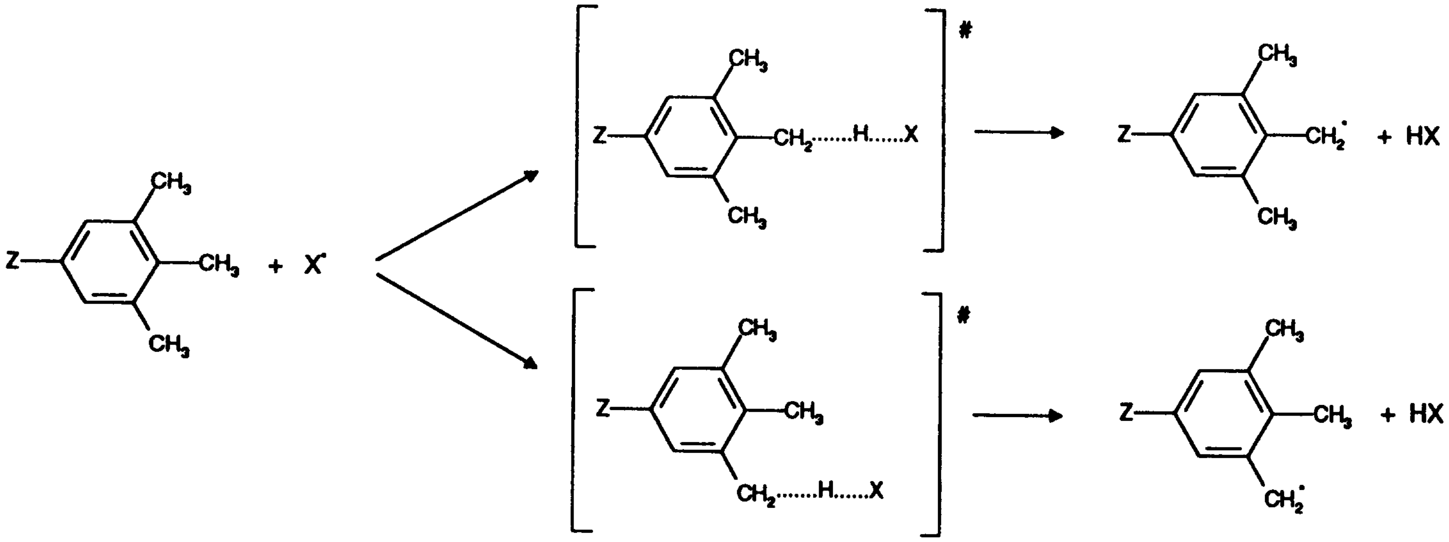
POSITIONAL SELECTIVITY

Relative reactivity of methyl groups located in nonequivalent positions of the aromatic ring.

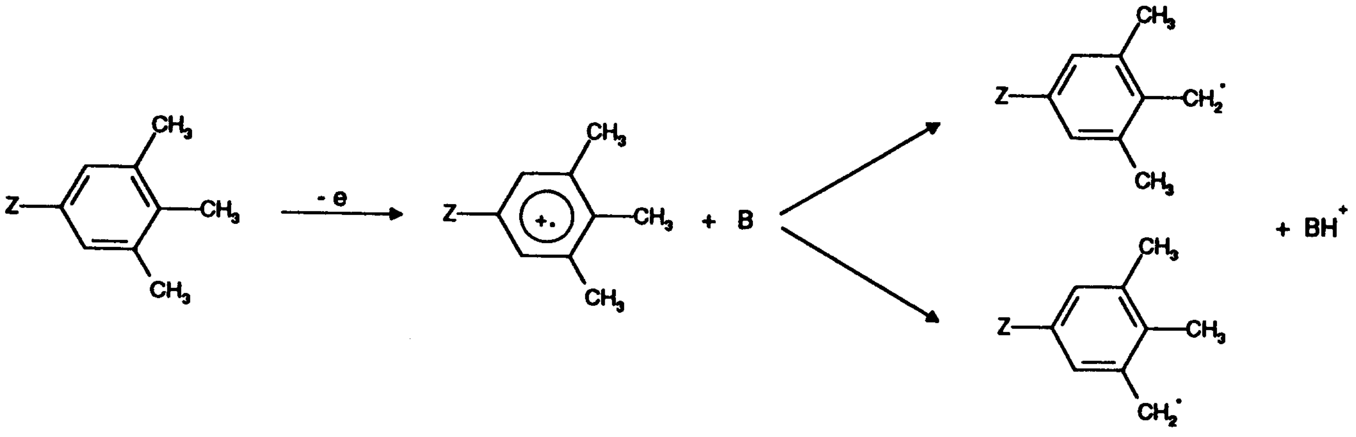




Question: should we espect that positional selectivity is different in HAT and ET reactions?

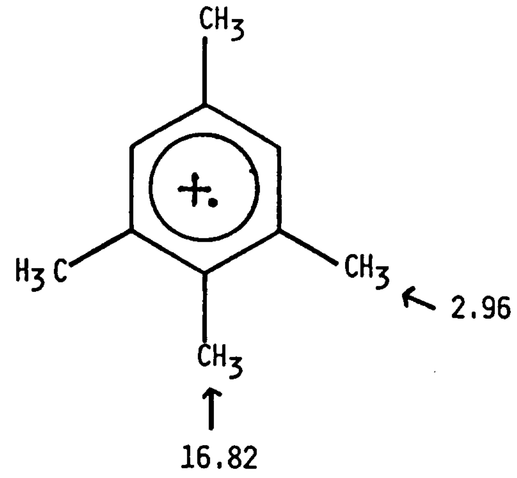


Z
CH3
X·
#
CH2......H......X
HX



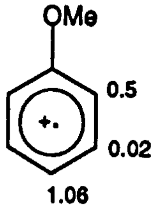
Z
CH3
- e
+·
B
CH2·
BH+

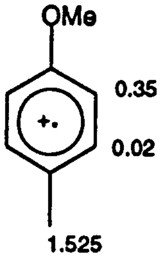
Hyperfine Coupling Constants



R.M. Dessau et al., J.Am.Chem.Soc., (1970)

Coupling Constants (mT).





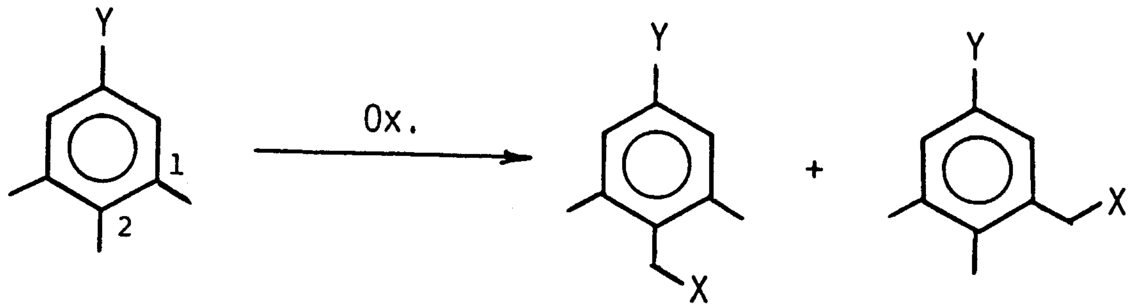
Bonafide ET and HAT Reactions

ET $$ArCH_3 \xrightarrow[AcOH]{ox} ArCH_2OAc$$

ox = $(NH_4)_2Ce(NO_3)_6$ (CAN) or anodic oxidation

HAT $$ArCH_3 + NBS \longrightarrow ArCH_2Br$$

NBS = N-bromosuccinimide

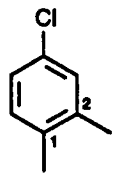
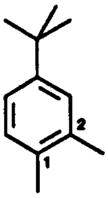
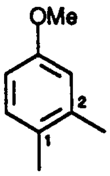


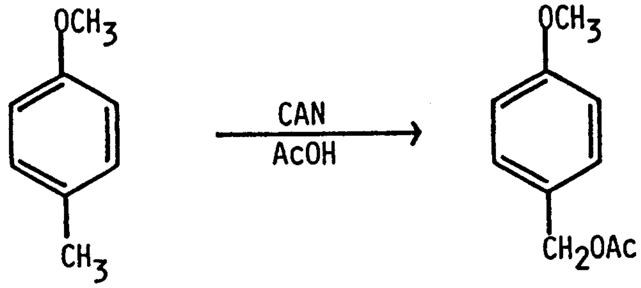
		k_2/k_1[a]						
	Y=	CO_2Me	H	t-Bu	Br	Me	OAc	OMe
Anod.Ox.	AcOH, BF_4^-[b]	1.5	3.0	16	31	37	59	
	AcOH, AcO^-[b]		2.1	7.5		16	41	>200
NBS, CCl_4, AIBN[c]		4.6	3.1	6.3	4.6	5.4	8.2	11

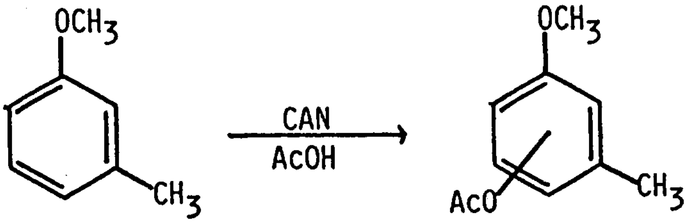
a. From the isomeric distribution (statistically corrected); b. X = OAc; c. NBS = N-bromosuccinimide. AIBN = azobisisobutyronitrile. X = Br.

Work in collaboration with Prof. L.Eberson

Positional selectivity (k_1 / k_2) in the side-chain reactions of 4-substituted-1,2-dimethylbenzenes with CAN and NBS.

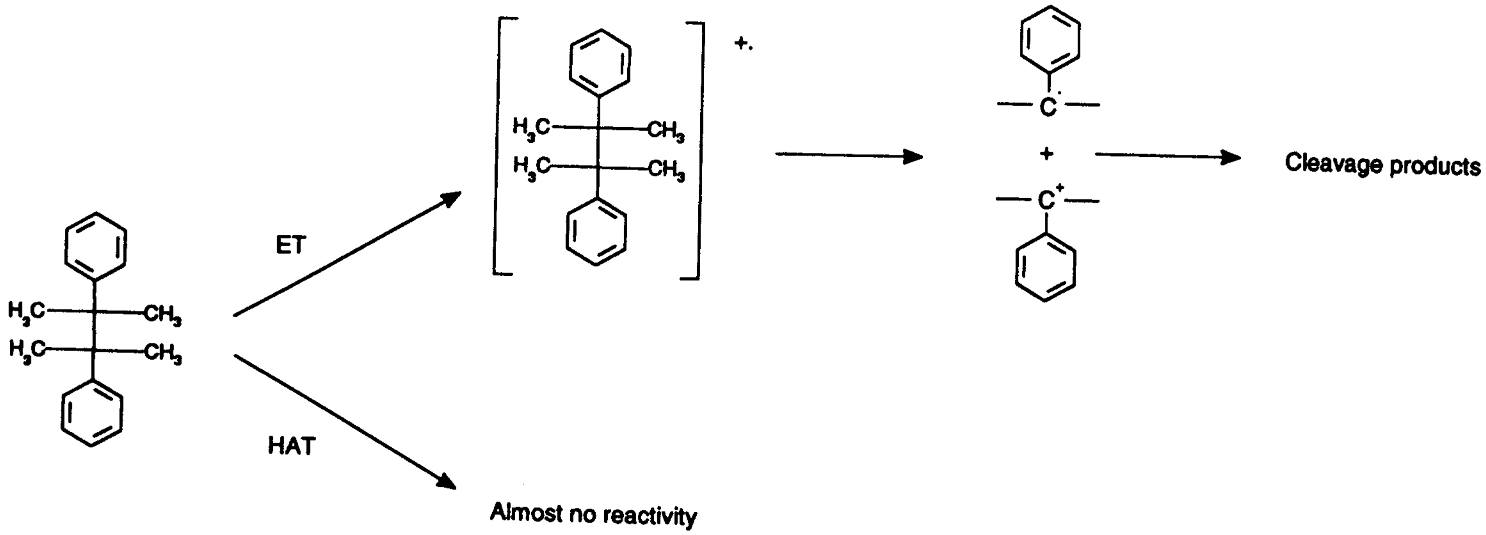
			
With CAN (ET)	6.0	13.0	>100
With NBS (HAT)	1.6	3.0	8

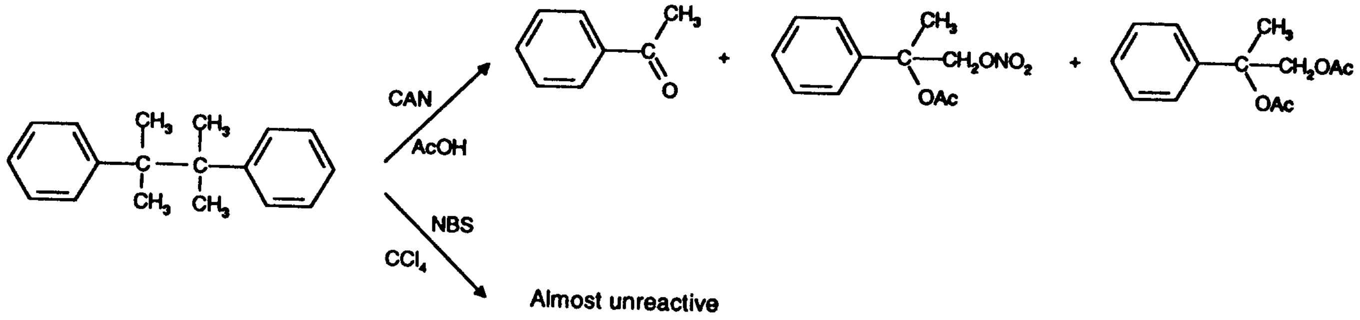




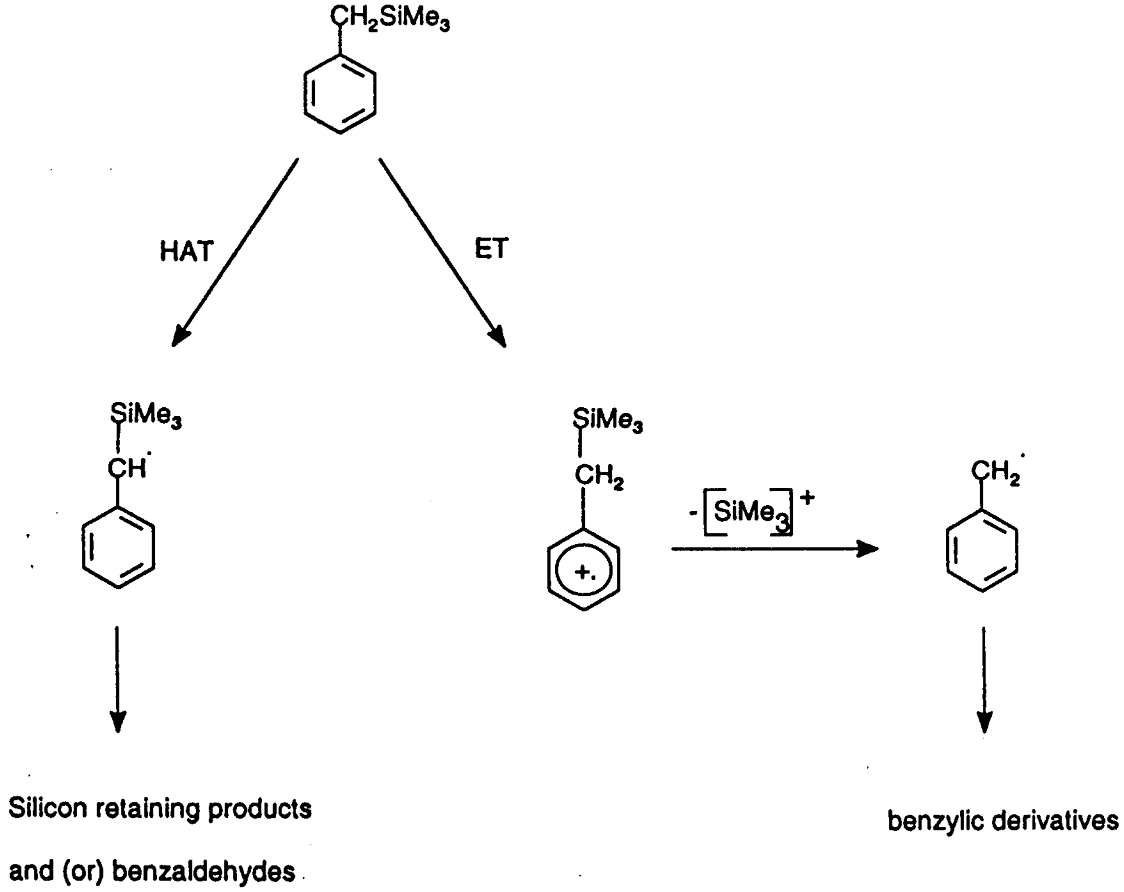
(mixture of 3 isomers)

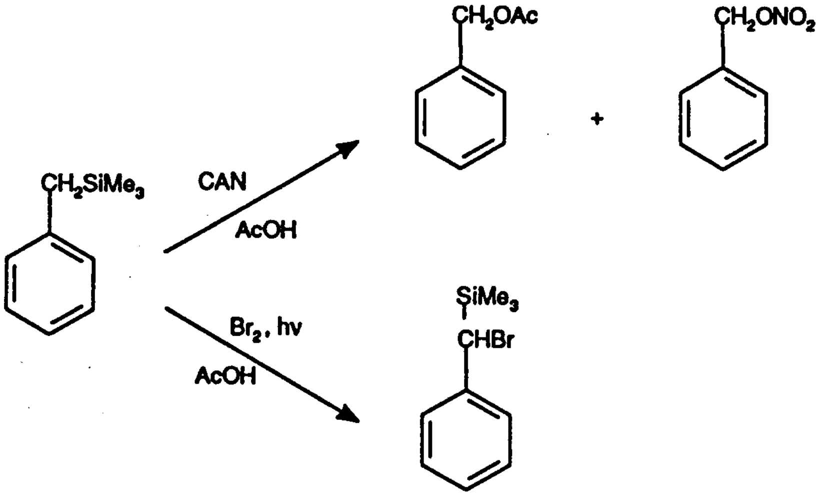
C-H vs C-C Bond Cleavage





C-H vs C-Si BOND CLEAVAGE





Criteria for the Differentiation of HAT and ET Mechanisms in One Electron Side-chain Oxidations of Alkylaromatic Compounds.

1. **The positional selectivity of a reaction occurring by the ET mechanism is generally significantly higher than that of a reaction occurring by the HAT mechanism. The difference is particularly remarkable for substituents like CH_3, Br and OR.**

2. **ET reactions lead to cleavage products with bicumyl systems. HAT reactions practically do not occur or are very slow.**

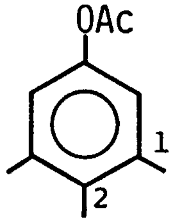
3. **With benzylsilanes, ET reactions form benzylic derivatives. HAT reactions lead to silicon retaining products. When silicon is lost benzaldehydes and not benzylic derivatives are formed.**

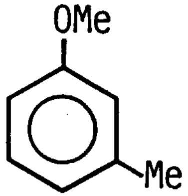
The Reaction of $NO3^{\bullet}$ with alkylaromatics

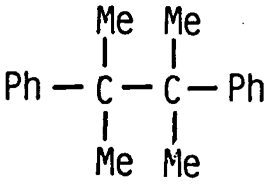
$$\mathrm{Ce(IV)ONO_2} \xrightarrow[\mathrm{MeCN}]{h\nu} \mathrm{Ce(III)ONO_2} + \mathrm{NO_3^{\bullet}}$$

$$\mathrm{ArCH_3} \xrightarrow{\mathrm{NO_3^{\bullet}}} \mathrm{ArCH_2ONO_2}$$

Selectivity in Reactions of $NO_3^{\cdot}$ in MeCN







$$Ph-\overset{Me}{\underset{Me}{C}}-\overset{Me}{\underset{Me}{C}}-Ph$$

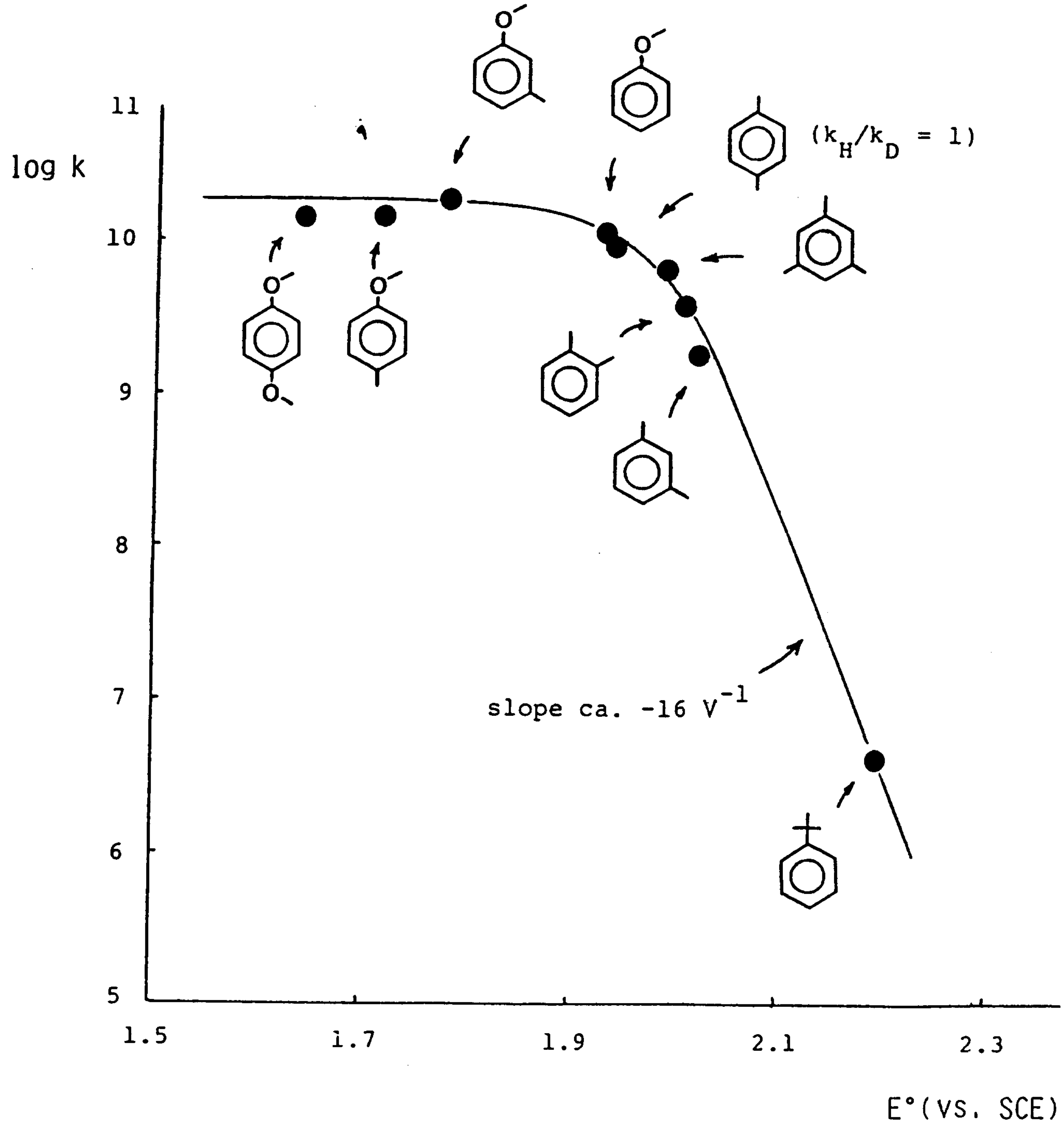
$k_2/k_1 > 200$

No side-chain reaction

Extensive C-C bond cleavage

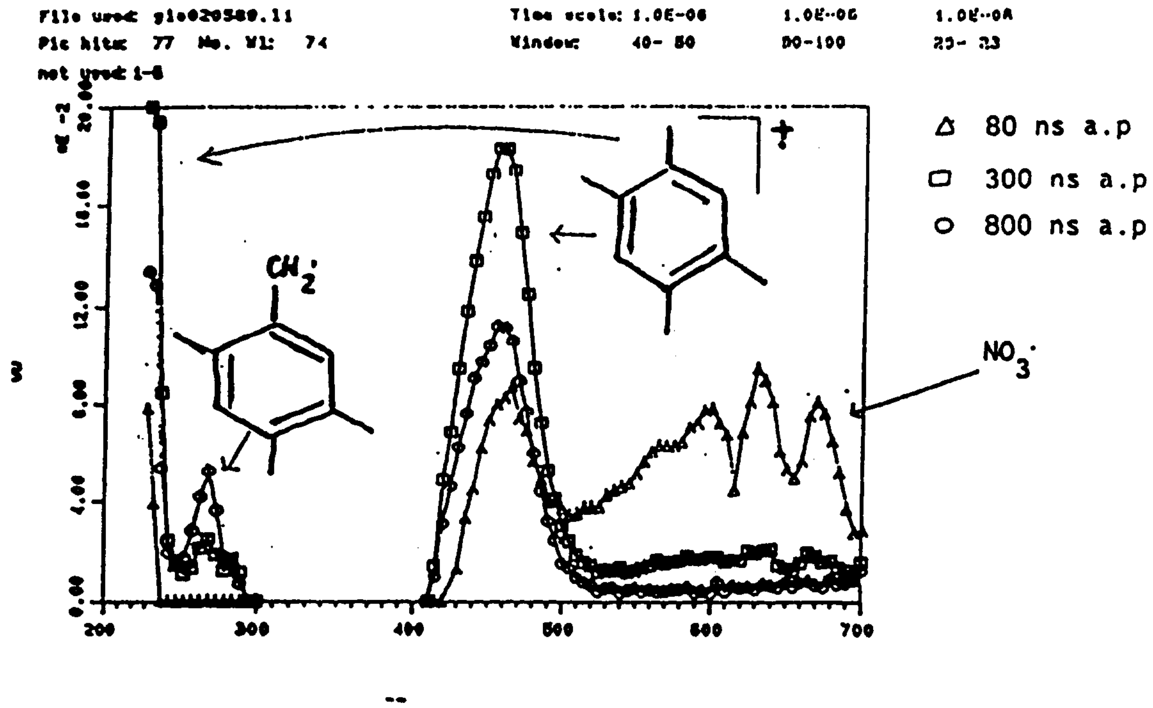
⇓

Electron transfer mechanism



$$ArCH_3 + NO_3^{\cdot} \rightleftharpoons (ArCH_3 \ldots NO_3^{\cdot}) \rightleftharpoons (ArCH_3^{+\cdot} \ldots NO_3^{-}) \rightleftharpoons ArCH_3^{+\cdot} + NO_3^{-}$$

$$\Delta G^{\neq} = \frac{\Delta G^{\circ\prime}}{2} + \left[\left(\frac{\Delta G^{\circ\prime}}{2}\right)^2 + \left(\frac{\lambda}{4}\right)^2\right]^{1/2}$$ Rehm and Weller

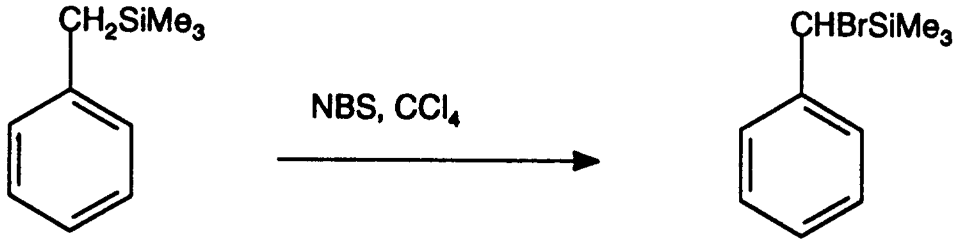


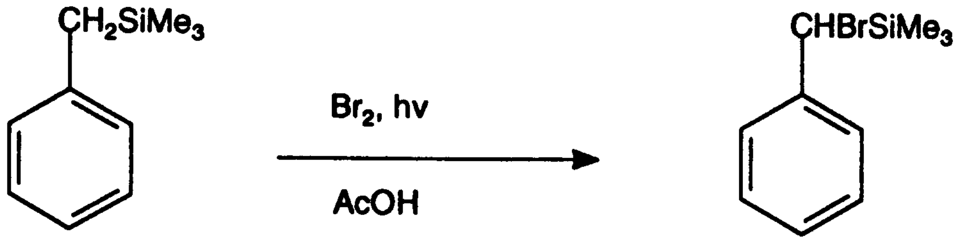
$$Ce(IV)ONO_2 \xrightarrow{h\nu} Ce(III) + NO_3\cdot$$

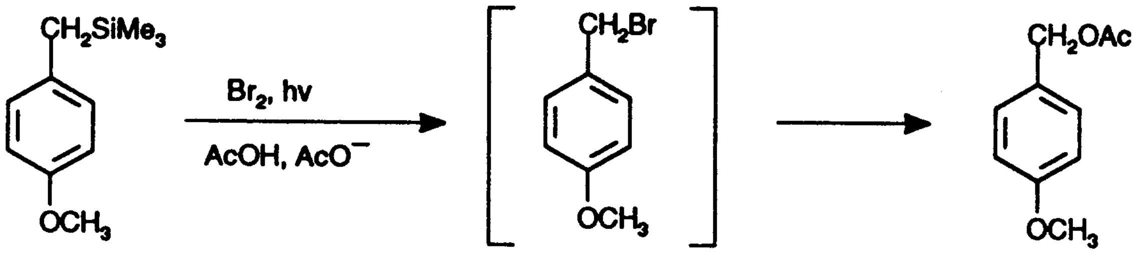
$$ArCH_3 + NO_3\cdot \longrightarrow ArCH_3^{\cdot+} + NO_3^-$$

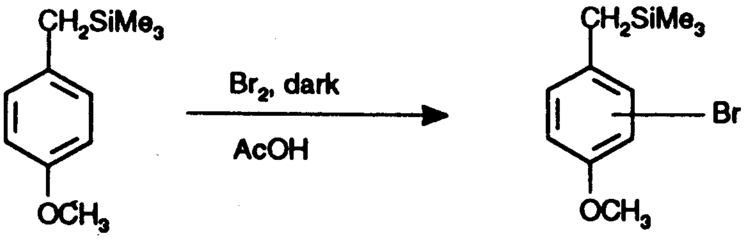
$$ArCH_3^{\cdot+} + NO_3^- \longrightarrow ArCH_2\cdot + HNO_3$$

$$ArCH_2\cdot + Ce(IV)ONO_2 \longrightarrow ArCH_2ONO_2 + Ce(III)$$


CH2SiMe3
NBS, CCl4
CHBrSiMe3


CH2SiMe3
Br2, hv
AcOH
CHBrSiMe3

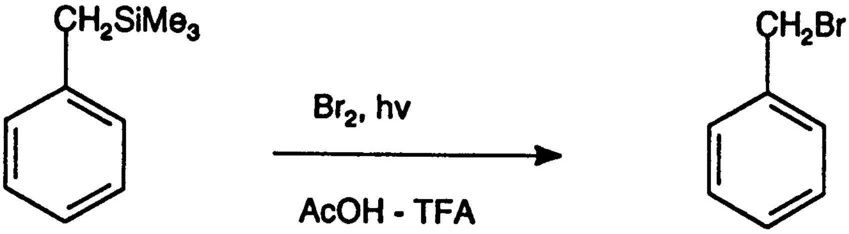

CH2SiMe3
OCH3
Br2, hv
AcOH, AcO−
CH2Br
OCH3
CH2OAc
OCH3


CH2SiMe3
OCH3
Br2, dark
AcOH
CH2SiMe3
Br
OCH3

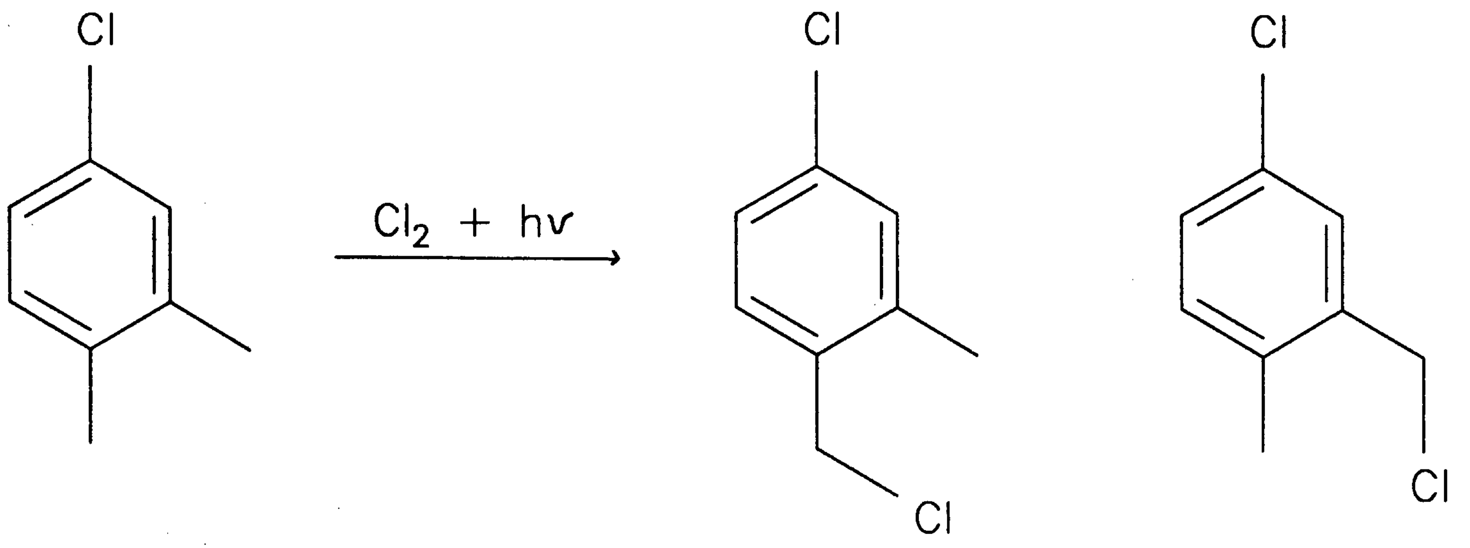
$$ArCH_3 + Br^{\bullet} \longrightarrow ArCH_3^{\bullet +} + Br^{-}$$

$$ArCH_3^{\bullet +} + Br^{-} \longrightarrow ArCH_2^{\bullet} + HBr$$

$$ArCH_2^{\bullet} + Br_2 \longrightarrow ArCH_2Br + Br^{\bullet}$$



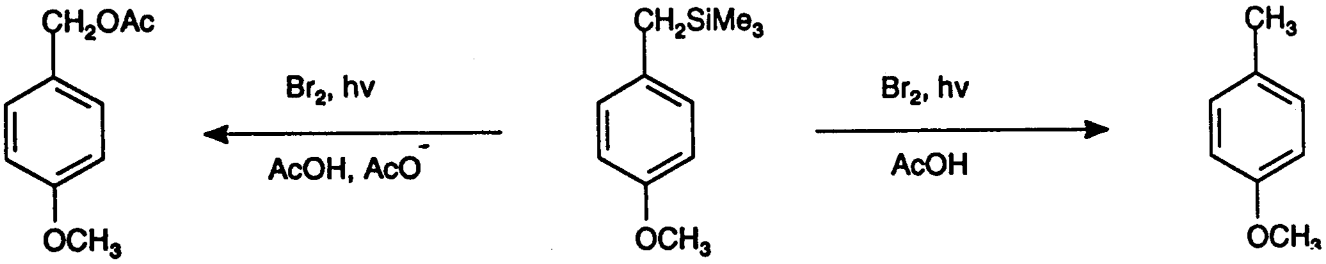
$E^{o}_{Br^{\cdot}/Br^{-}}$ in AcOH - TFA is probably larger than in AcOH

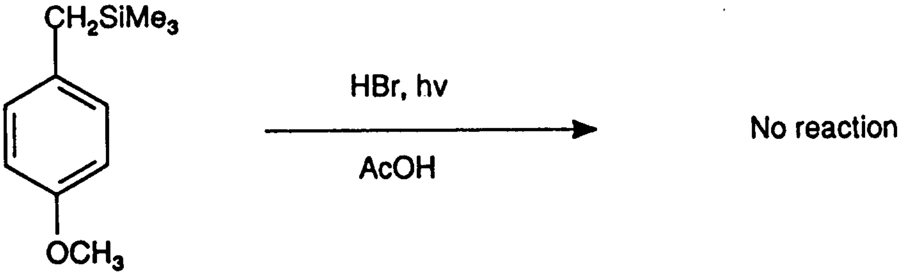


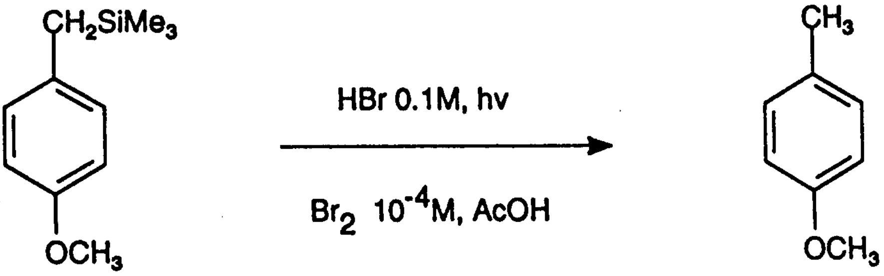
I

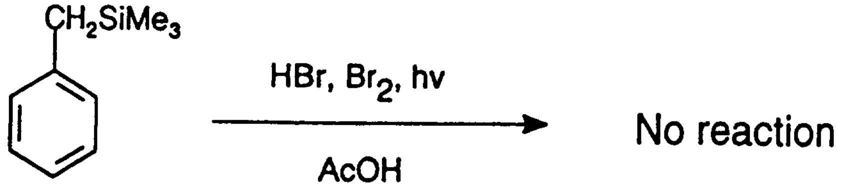
II

	CCl_4	AcOH	AcOH/TFA
I/II	2·0	3·2	11


CH2OAc
Br2, hv
AcOH, AcO⁻
CH2SiMe3
Br2, hv
AcOH
CH3
OCH3
OCH3
OCH3


CH2SiMe3
HBr, hv
AcOH
No reaction
OCH3

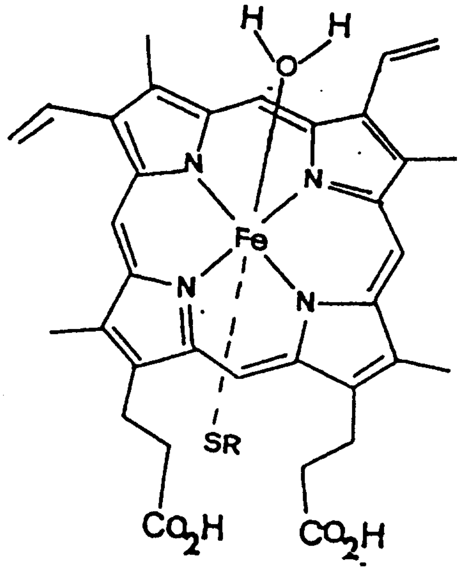

CH2SiMe3
HBr 0.1M, hv
Br2 10⁻⁴M, AcOH
CH3
OCH3
OCH3



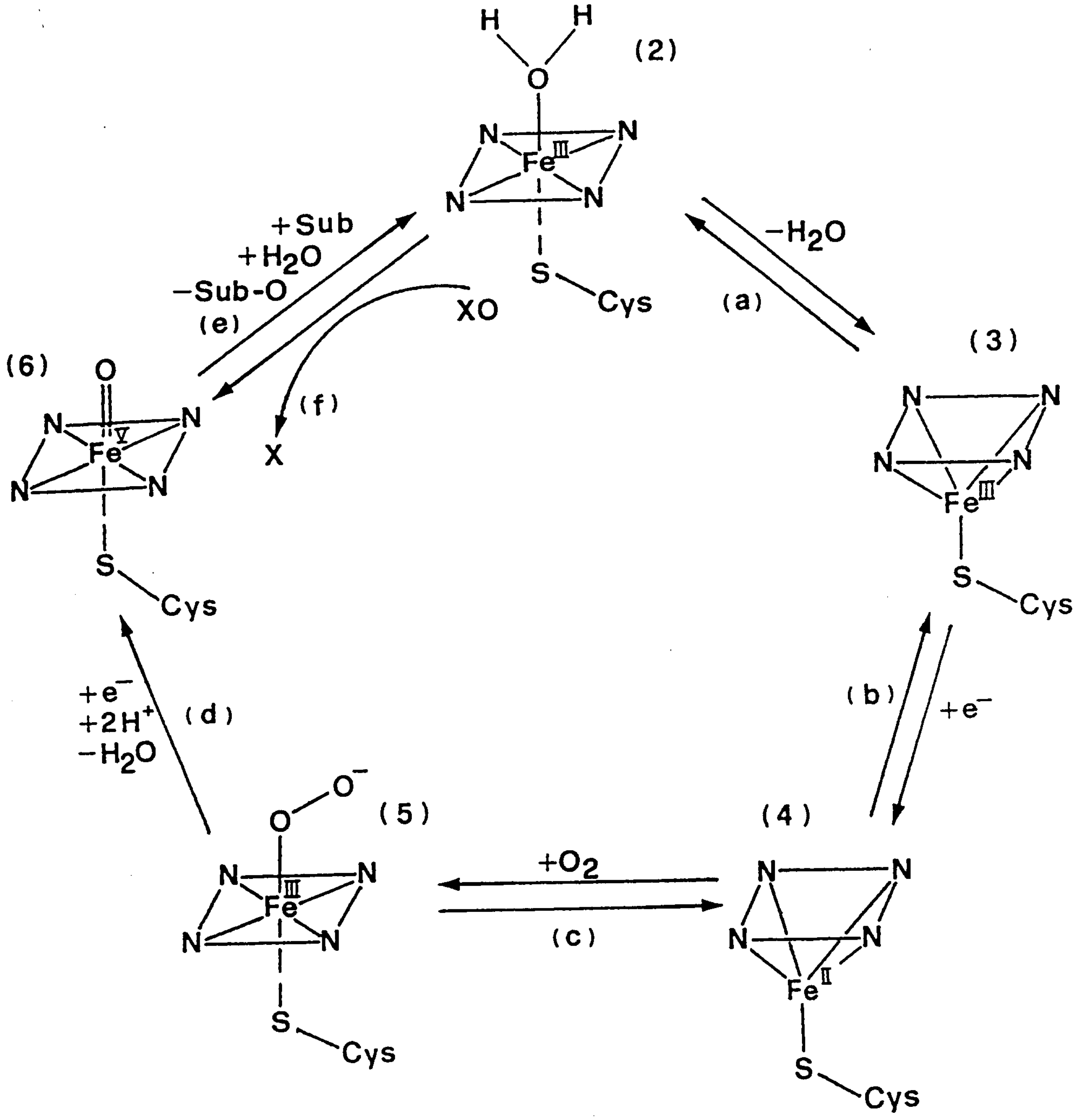
$$\mathrm{Br}^{\bullet} + \mathrm{ArCH_2SiMe_3} \rightleftharpoons \mathrm{ArCH_2SiMe_3}^{+\bullet} + \mathrm{Br}^{-}$$

$$\mathrm{ArCH_2SiMe_3}^{+\bullet} + \mathrm{AcOH} \longrightarrow \mathrm{ArCH_2}^{\bullet} + \mathrm{Me_3SiOAc} + \mathrm{H}^{+}$$

$$\mathrm{ArCH_2}^{\bullet} + \mathrm{HBr} \longrightarrow \mathrm{ArCH_3} + \mathrm{Br}^{\bullet}$$

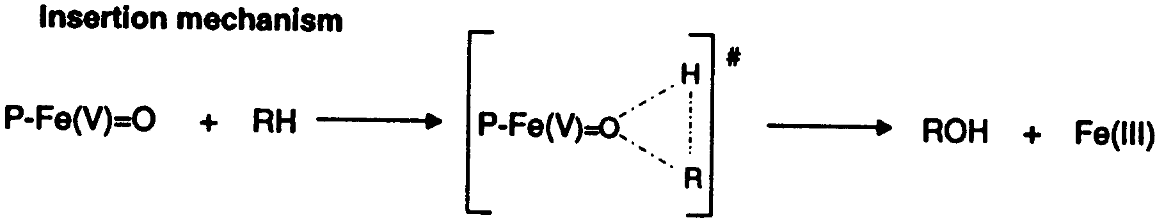


(1)

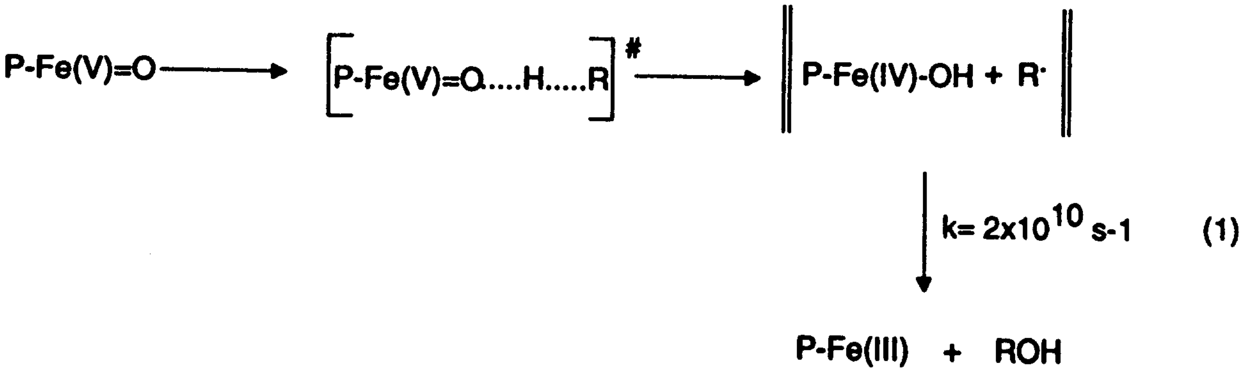

(2)
H
H
O
N
N
N
N
Fe^{III}
S
Cys
$-H_2O$
(a)
(3)
Fe^{III}
S
Cys
(b)
$+e^-$
(4)
Fe^{II}
S
Cys
$+O_2$
(c)
(5)
O
O^-
Fe^{III}
S
Cys
$+e^-$
$+2H^+$
$-H_2O$
(d)
(6)
O
Fe^{V}
S
Cys
+Sub
$+H_2O$
−Sub-O
(e)
XO
(f)
X

Possible mechanisms for the hydroxylation reaction catalyzed by cytochrome P-450.

Insertion mechanism

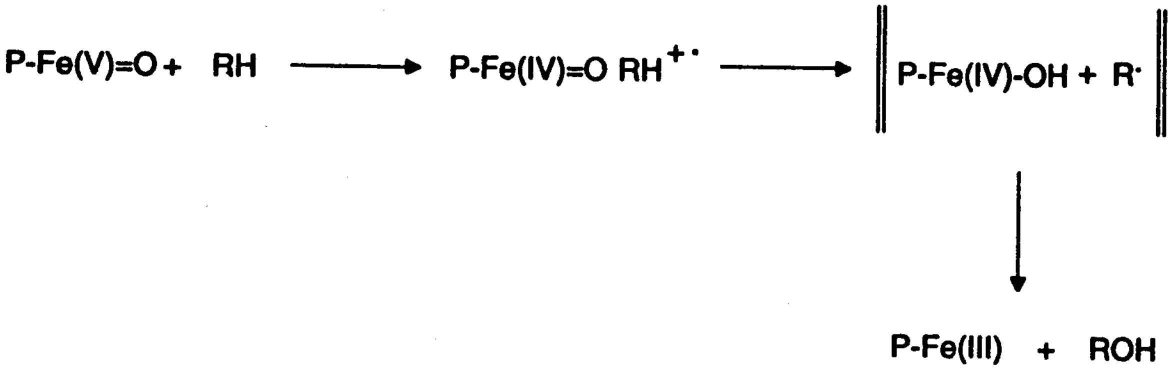


HAT mechanism

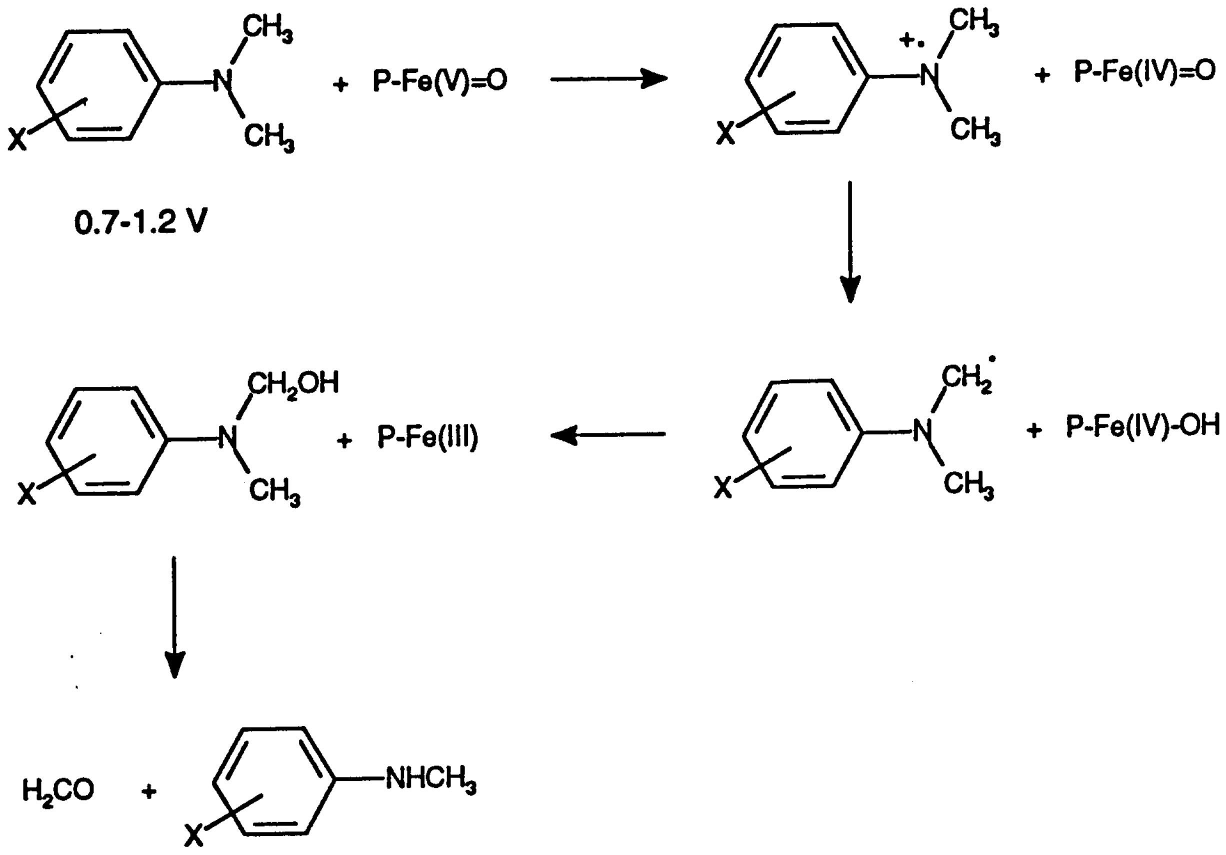


(1) W. Bowry, K. U. Ingold, *JACS* 1991, *113*, 5699.

ET mechanism for the hydroxylation reaction catalyzed by cytochrome P-450.

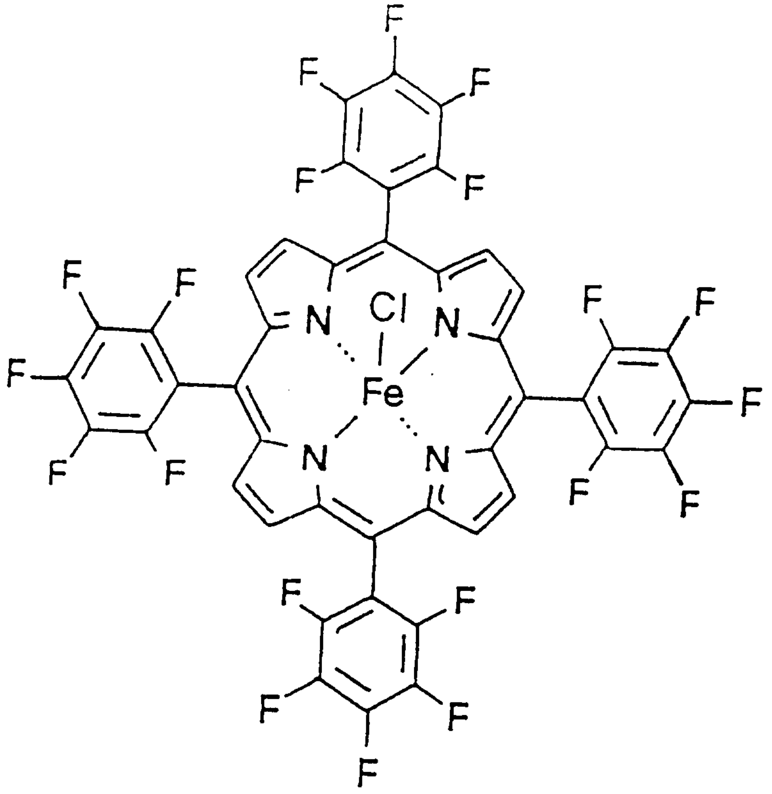


N-demethylation by Cytochrome P-450.

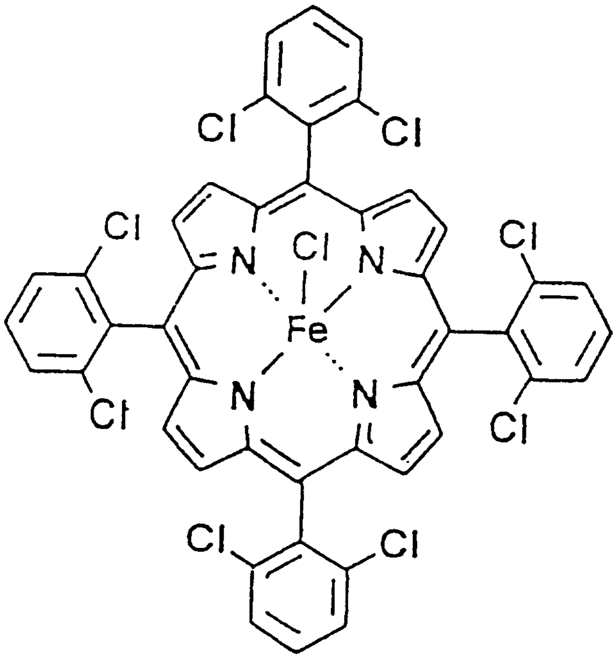


$$E^0{}_{Fe(V)=O/Fe(IV)=O} \cong 1.8 - 2.0\ V\ (\text{vs SCE})$$

T. McDonald, W. Gutheim, R. B. Martin, F. P. Guengerich, *Biochem.* 1989, *28*, 2071.

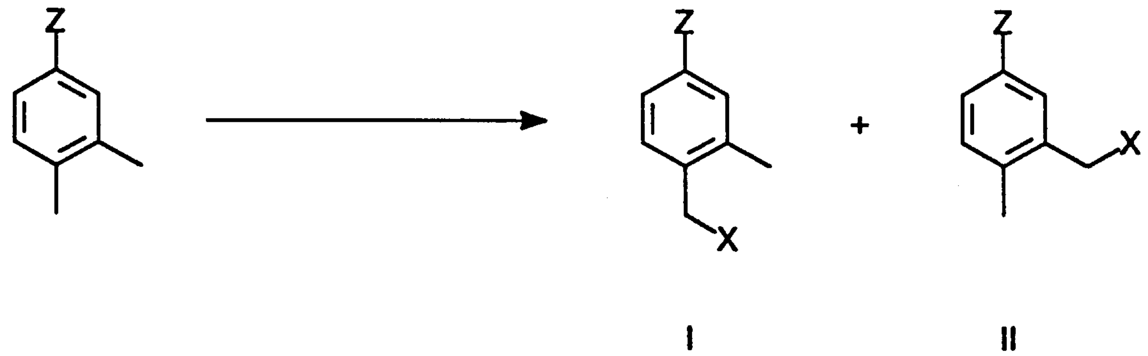


(18) TFPPFe(Ⅲ)Cl



(19) TDCPPFe(Ⅲ)Cl

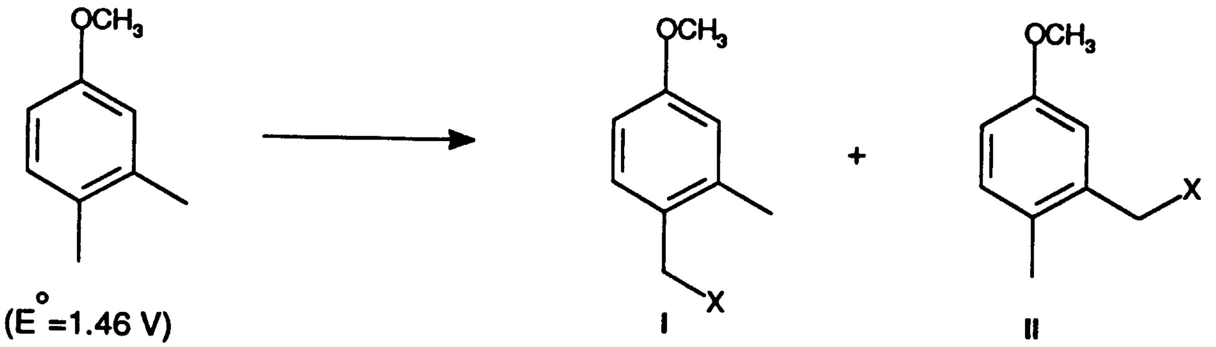
I / II Values in the Side-Chain Oxidation of 4-Z-1,2-dimethylbenzenes



	FeTFPPCl / PhIO in CH_2Cl_2 (X=OH)	FeTFPPCl / PhIO in CH_2Cl_2 / MeOH / H_2O (X=OH)	Microsomal Oxidation	NBS in CCl_4 (X=Br)	CAN in AcOH (X=OAc, ONO_2)
Z = t-Bu (E˚ = 1.9 V)	1.8	2.0	1.6	1.6	6.0
Z = Cl	2.2	2.2	1.4	3.0	13.0

FeTFPPCl = Iron(III) tetrakis(pentafluorophenyl)porphyrin chloride

Side-Chain Oxidation of 4-Methoxy-1,2-dimethylbenzene.



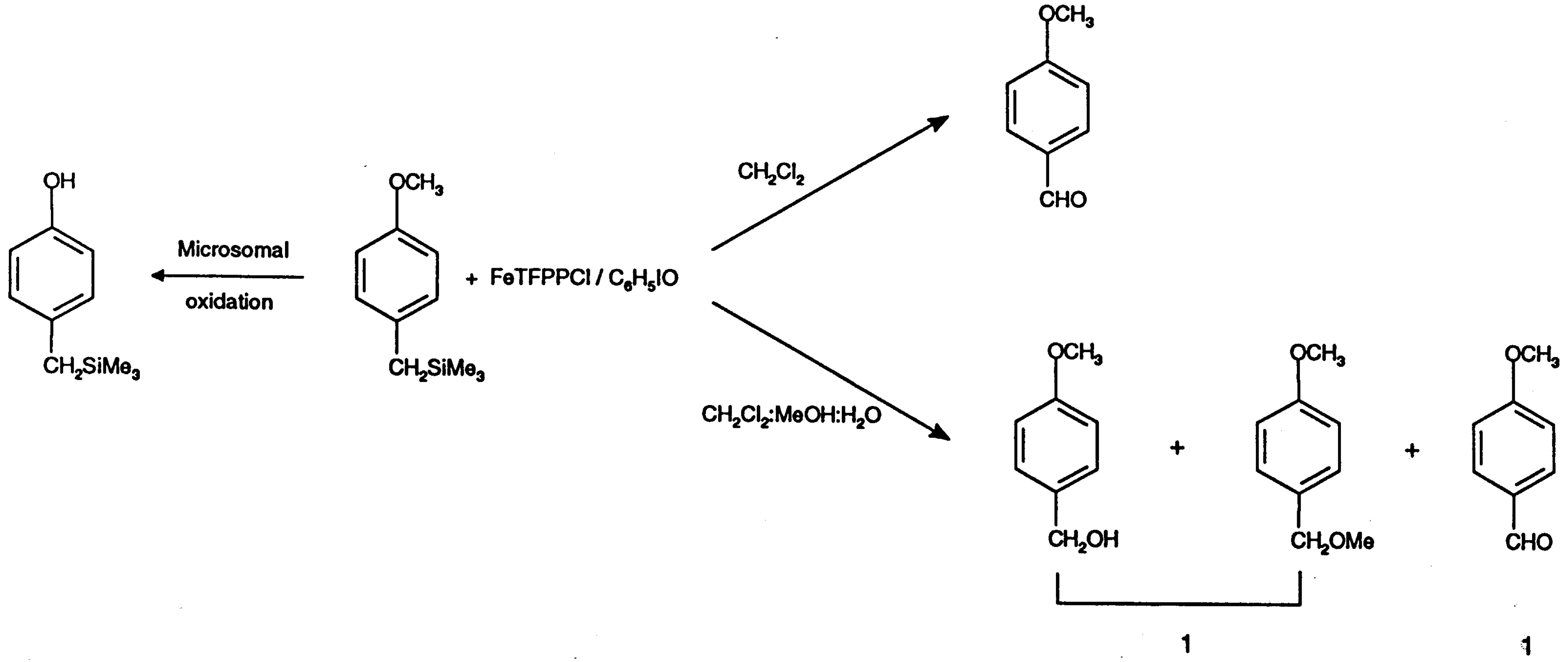
(E° =1.46 V)

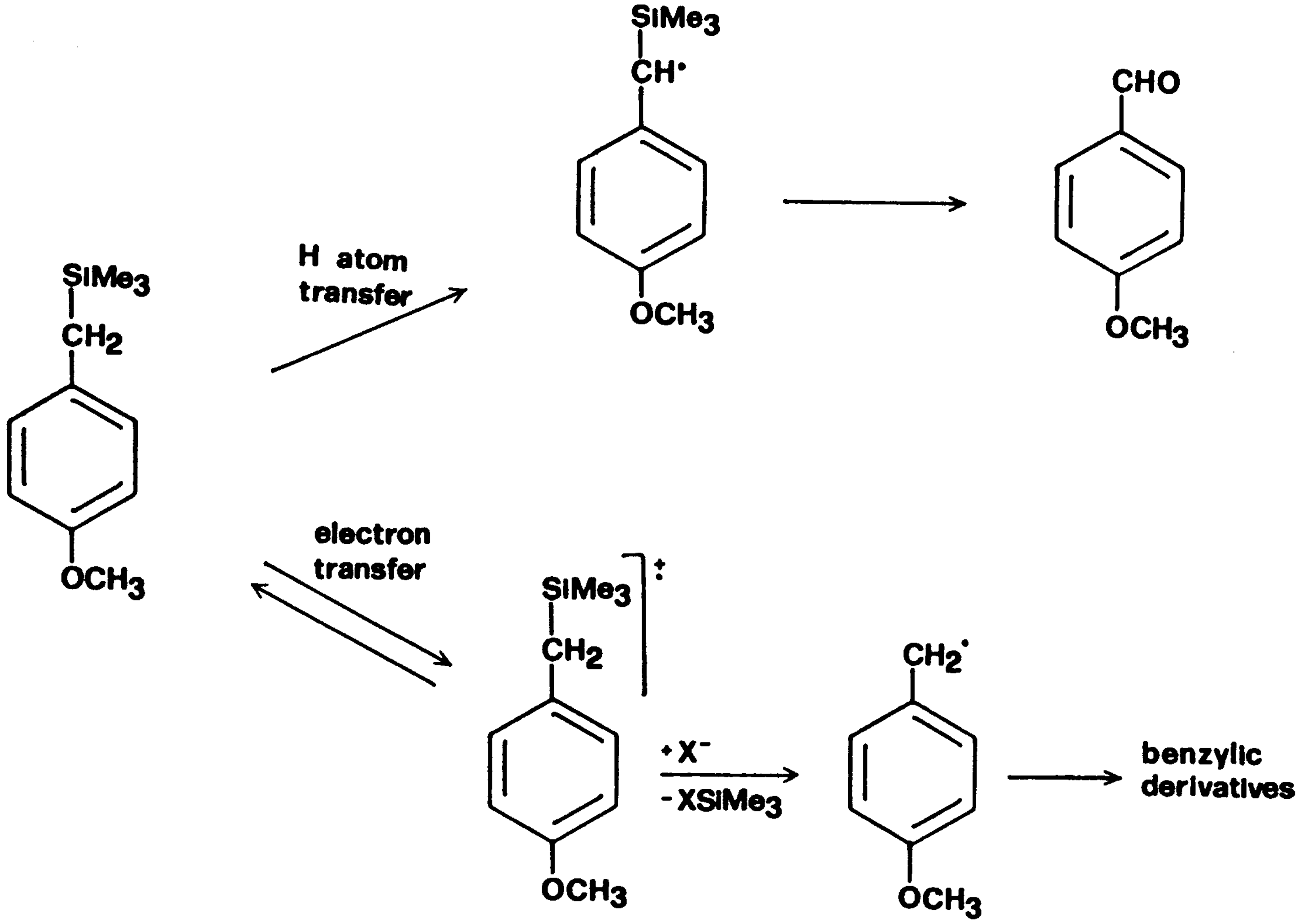
I

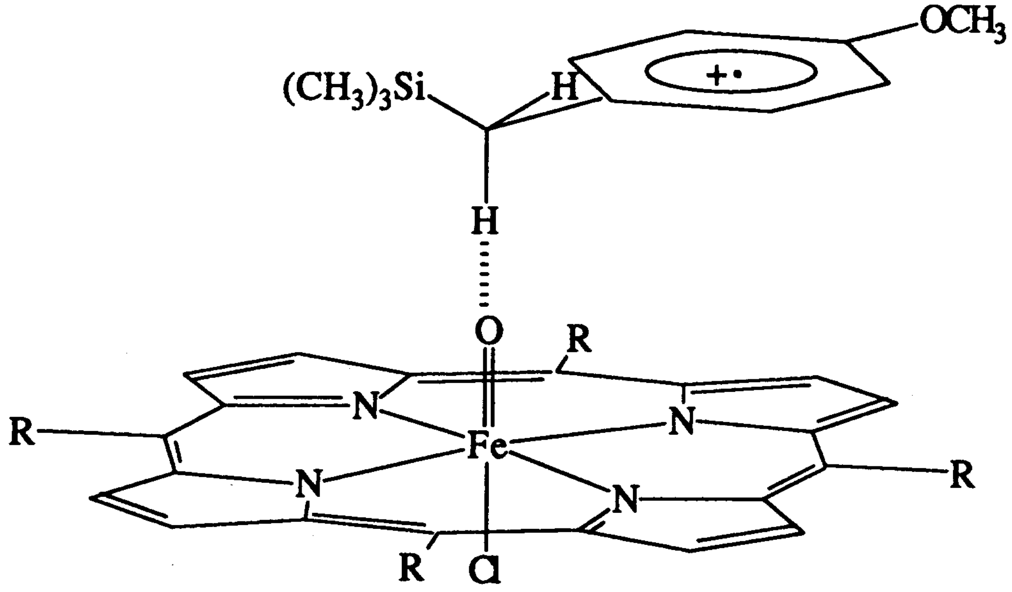
II

Oxidizing System	I / II
FeTFPPCl / C_6H_5IO / CH_2Cl_2	> 50 (X=OH)
Microsomal oxidation	3.2 (X=OH)
NBS / CCl_4	8 (X=Br)
CAN / AcOH	> 100 (X=OAc, ONO_2)

Reaction of 4-methoxybenzyltrimethylsilane with iron porphyrins.




SiMe3
CH2
OCH3
H atom transfer
SiMe3
CH•
OCH3
CHO
OCH3
electron transfer
SiMe3
CH2
+•
OCH3
+X−
-XSiMe3
CH2•
OCH3
benzylic derivatives


OCH3
(CH3)3Si
H
+•
H
O
R
N
N
Fe
N
N
R
R
R
Cl