SELECTIVE REDUCTIVE DEHALOGENATION – A CONSISE ROUTE FROM BASE TO DIFFICULTLY ACCESSIBLE POLYFLOROARENES AND BENZO AZAHETEROCYCLES ON THEIR BASIS

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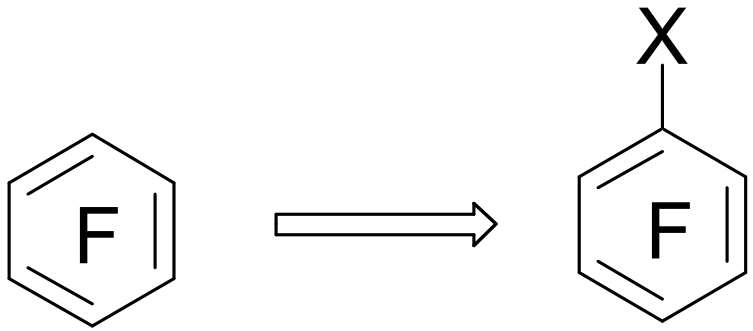
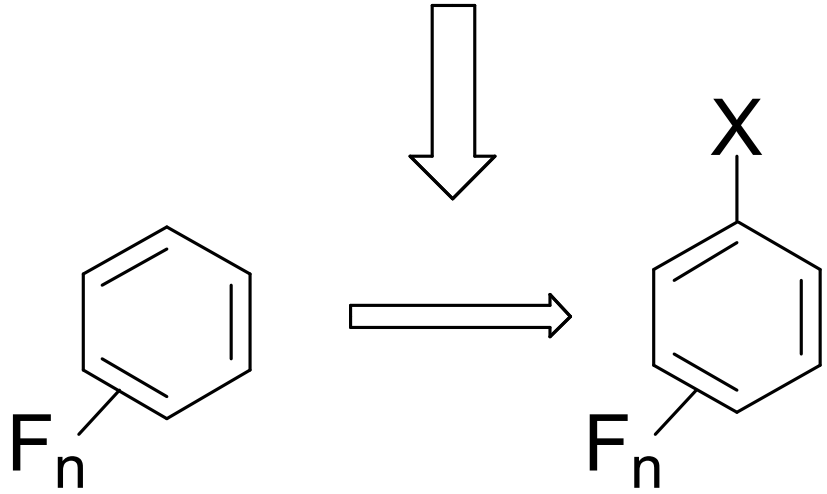


easily accessible base compounds



n = 3, 4

inaccessible base compounds

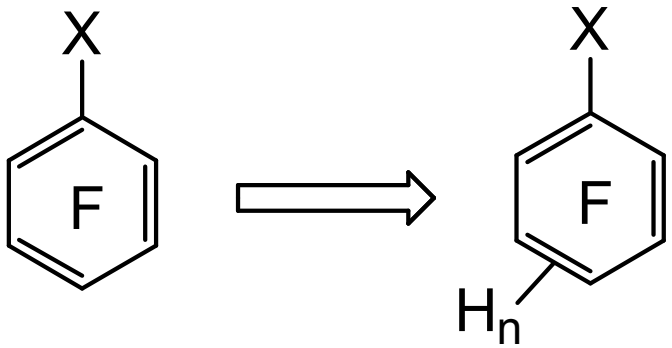
PARTIALLY FLUORINATED ARENES

- versatile valuable starting materials for the synthesis of fluorine containing compounds suitable for diverse application;
- less accessible than perfluoro- and perfluorochloroarenes;

⇩

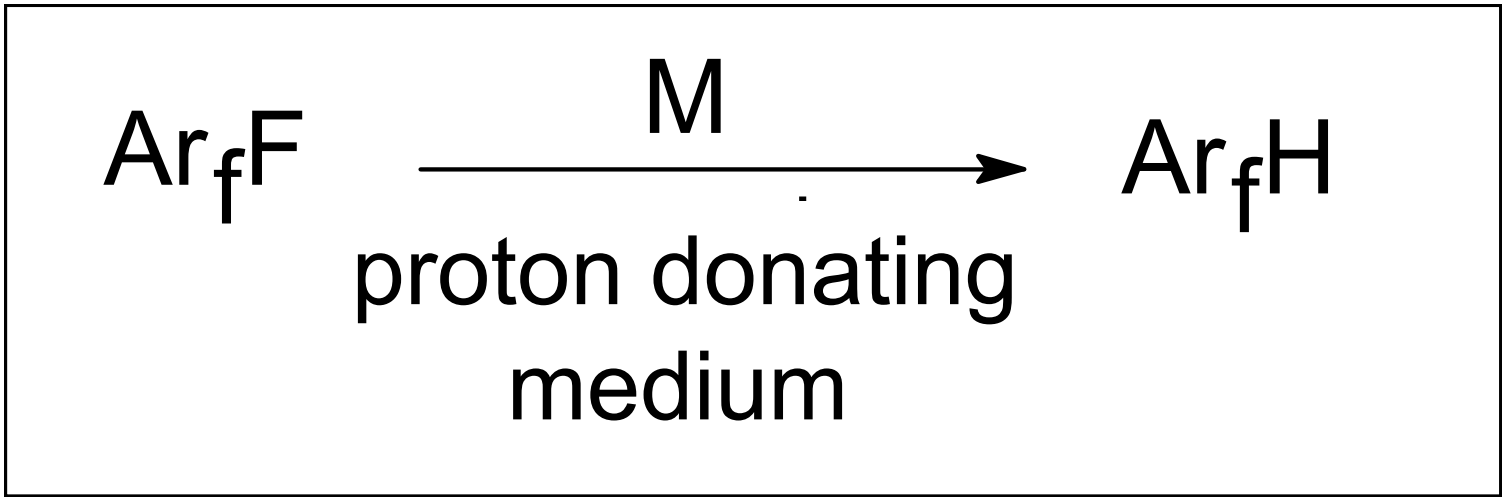
CHALLENGING PROBLEM

to develop a concise and highly selective synthesis of partially fluorinated arenes by using perfluoro- and perfluorchloroarenes as precursors

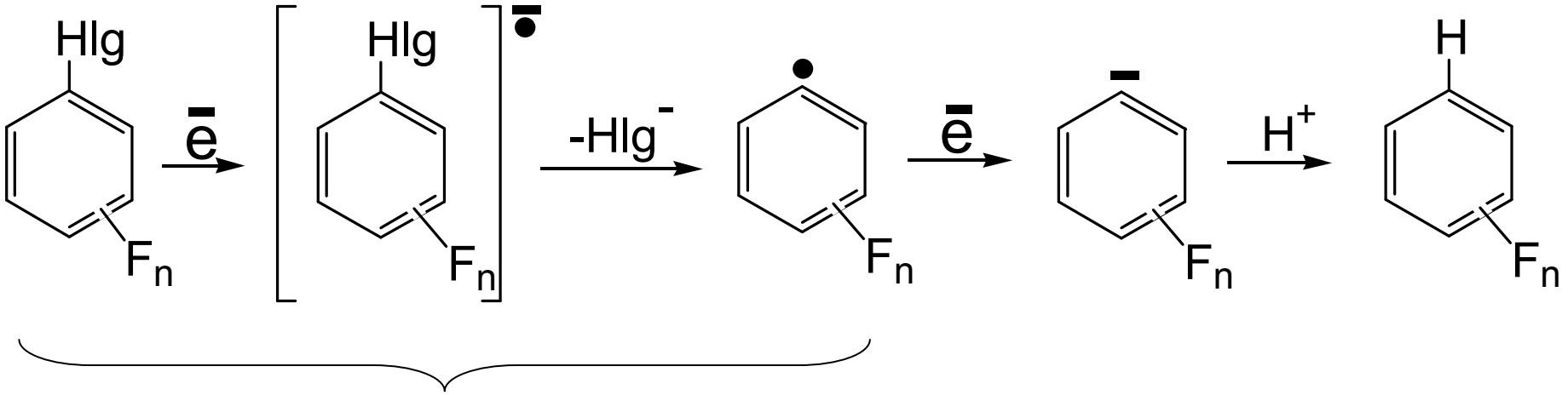


n = 2, 3

Selective hydrodehalogenation of perfluoro- and perfluorochloroarenes – the shortest pathway to partially fluorinated arenes



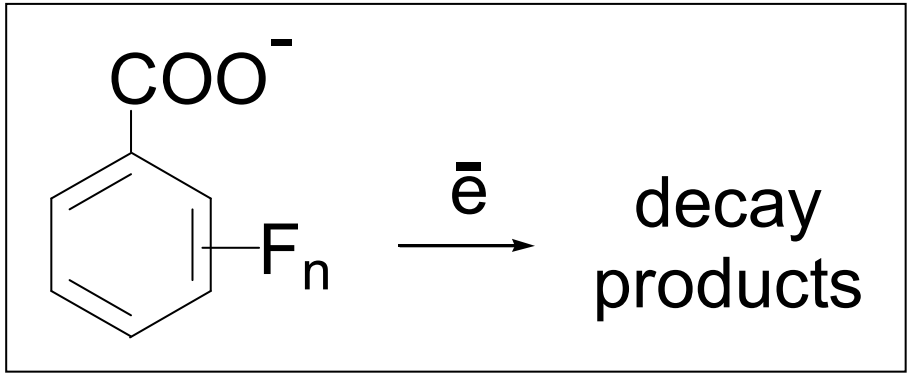
Mechanistic background:



key steps – the formation and further fragmentation of the polyfluoroarene radical anion

Influence of fluorine accumulation on the decay rate of polyfluoro benzoate radical anions

Method: photoinjection of electrons from a mercury cathode into aqueous electrolyte solution



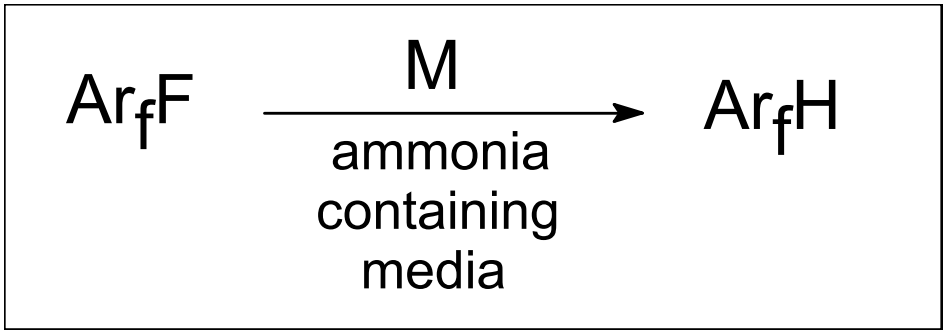
arene radical anion decay is dramatically accelerating with fluorine accumulation

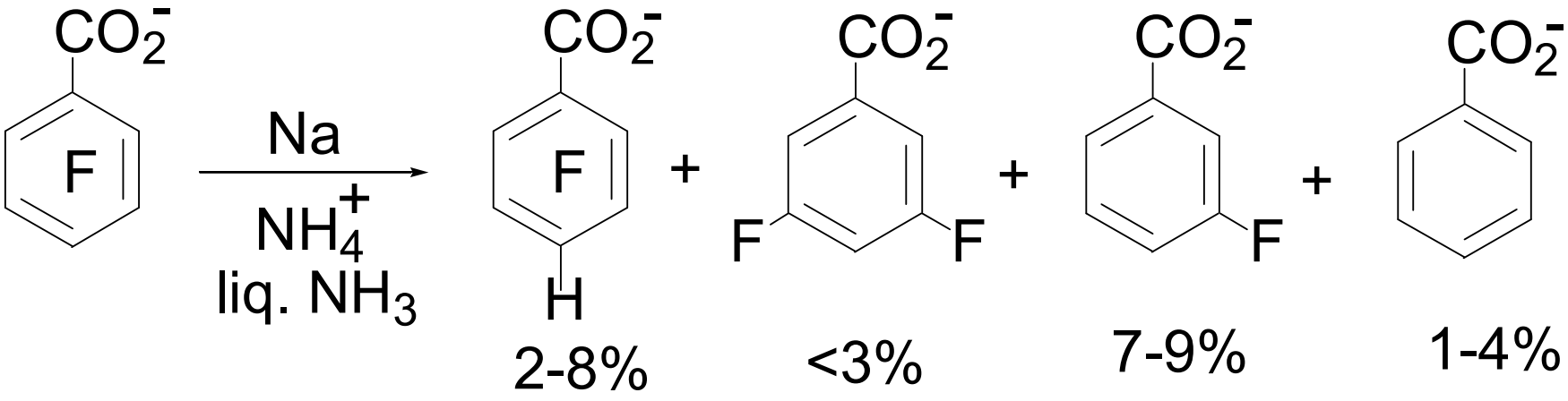
near-by location of substituents is favorable

$k_p > k_o > k_m$

compound	k_{fr} (s^{-1})
2-F-$C_6H_4CO_2^-$	$(1.5\pm0.8) \times 10^4$
3-F-$C_6H_4CO_2^-$	$\geq 3 \times 10^3$
4-F-$C_6H_4CO_2^-$	$(5\pm2) \times 10^5$
2,3-F_2-$C_6H_3CO_2^-$	$(1.6\pm0.8) \times 10^7$
2,4-F_2-$C_6H_3CO_2^-$	$(1.5\pm0.7) \times 10^7$
2,5-F_2-$C_6H_3CO_2^-$	$(1.4\pm0.6) \times 10^5$
2,6-F_2-$C_6H_3CO_2^-$	$(1.9\pm0.8) \times 10^6$
3,4-F_2-$C_6H_3CO_2^-$	$(7\pm3) \times 10^7$
3,5-F_2-$C_6H_3CO_2^-$	$(1\pm0.8) \times 10^4$
2,3,5-F_3-$C_6H_2CO_2^-$	$(6.5\pm2.5) \times 10^5$
2,3,6-F_3-$C_6H_2CO_2^-$	$(1.1\pm0.5) \times 10^8$
2,4,5-F_3-$C_6H_2CO_2^-$	$(1.1\pm0.5) \times 10^8$
2,4,6-F_3-$C_6H_2CO_2^-$	$(6.5\pm2.5) \times 10^7$
3,4,5-F_3-$C_6H_2CO_2^-$	$(3.2\pm1.5) \times 10^8$
2-H-$C_6F_4CO_2^-$	$(1.7\pm0.6) \times 10^8$
3-H-$C_6F_4CO_2^-$	$(1.2\pm0.8) \times 10^9$
4-H-$C_6F_4CO_2^-$	$(2.1\pm0.8) \times 10^7$
$C_6F_5CO_2^-$	$(1.2\pm0.8) \times 10^9$

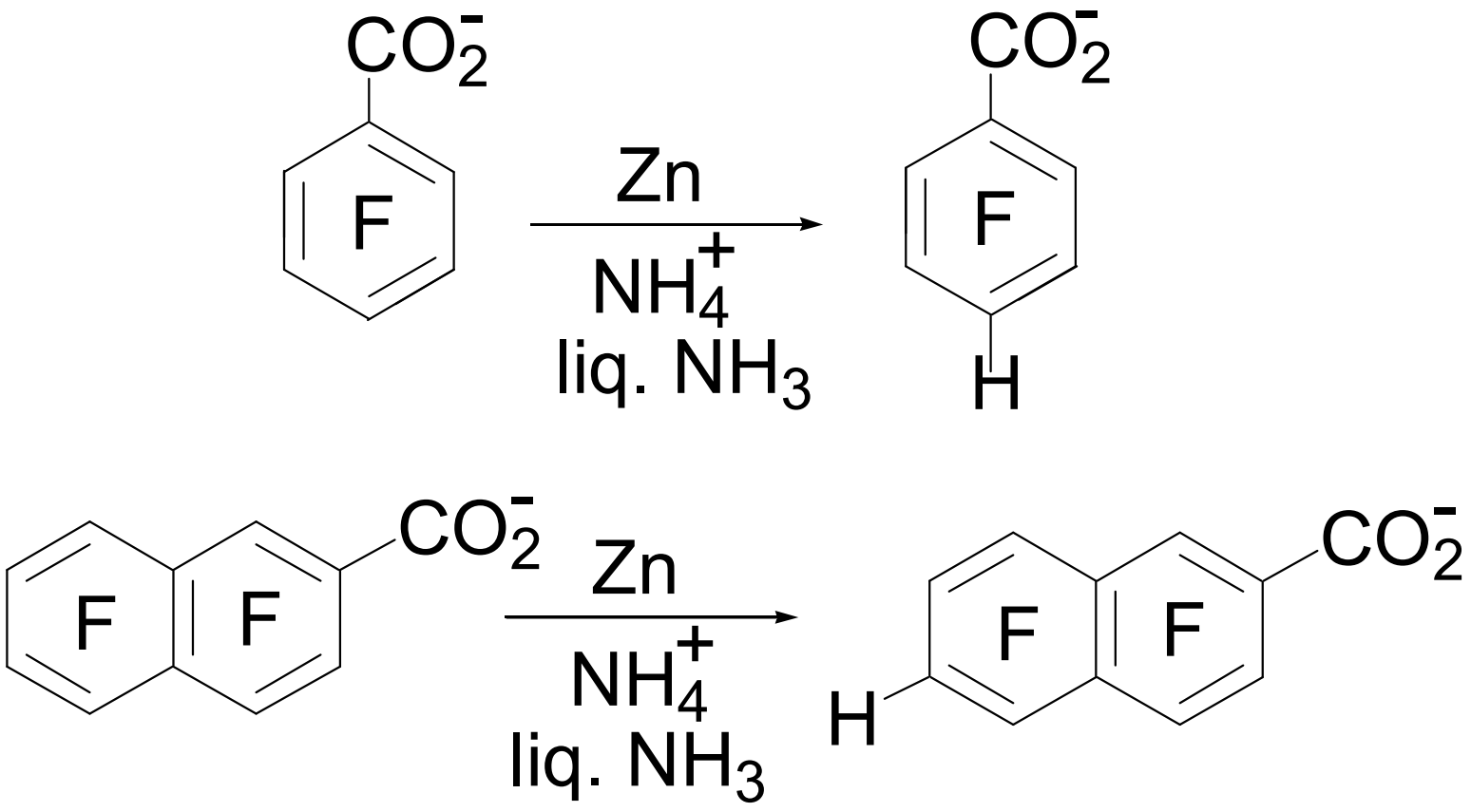
Preparative hydrodehalogenation of polyfluoroarenes



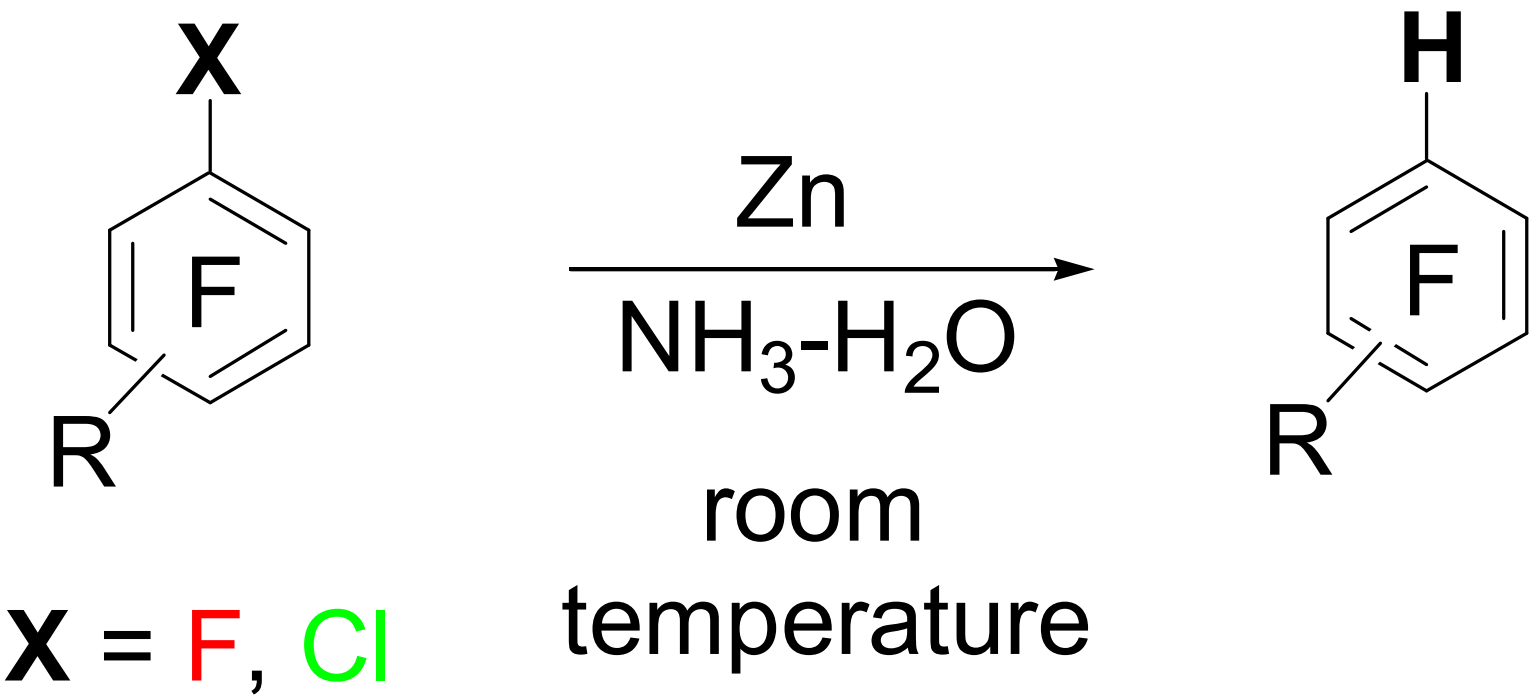


no more than 40% conversion regardless of the sequence of reagent mixing

Zinc in ammonia containing media – the reagent for selective monohydrodehalogenation of polyfluorinated aromatic ring

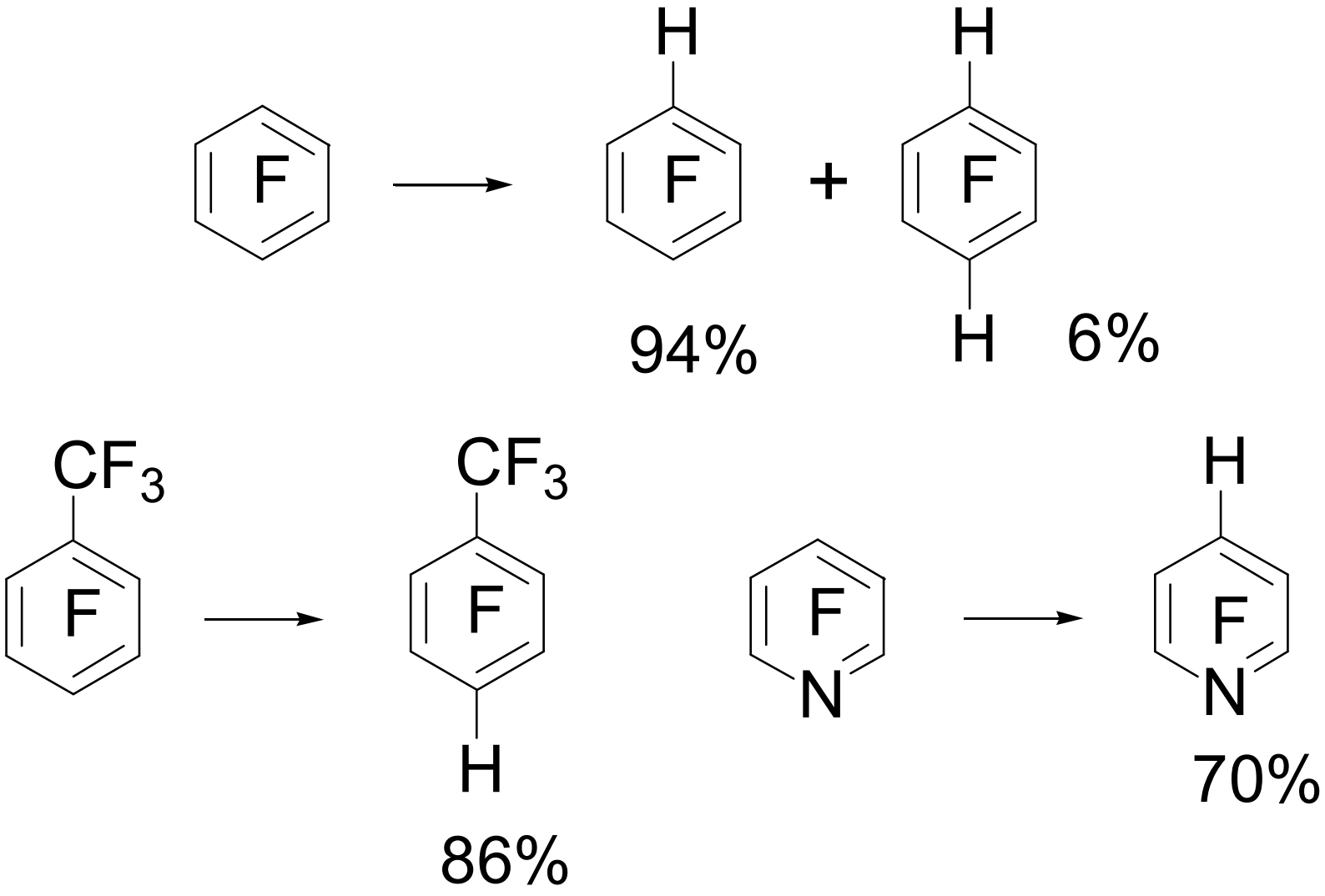


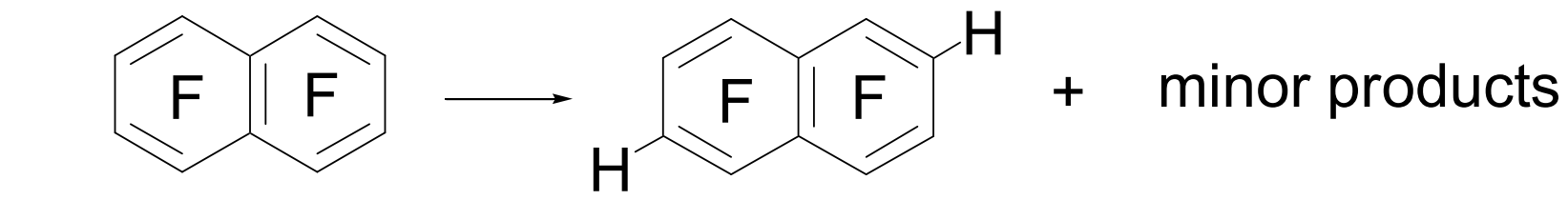
Zinc in aqueous ammonia – the simplest reductive system for hydrodehalogenation of polyfluoroarenes



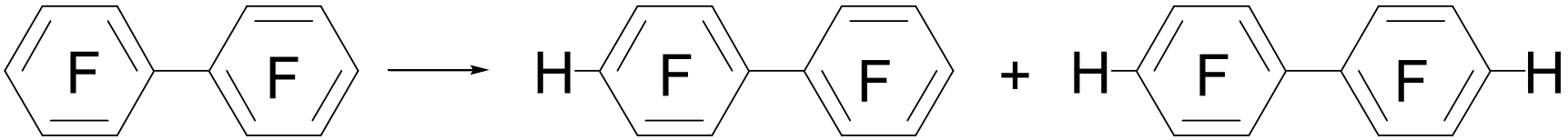
X = F, Cl

Per(poly)fluoroarene selective hydrodefluorination by zinc in aqueous ammonia

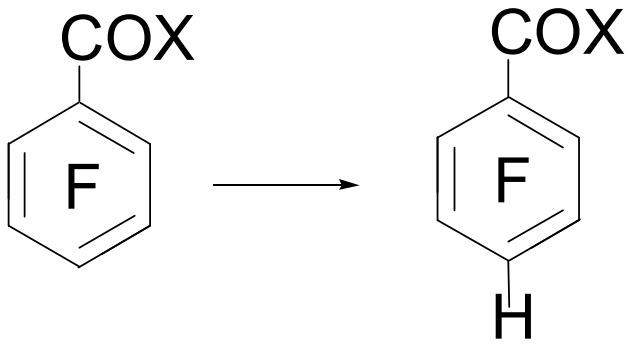




isolated
yield 45%

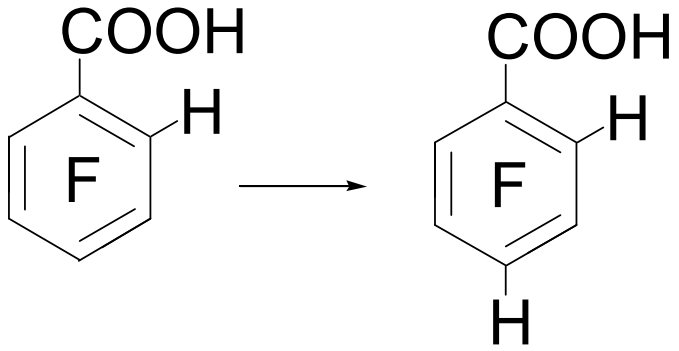


isolated
yield 27%

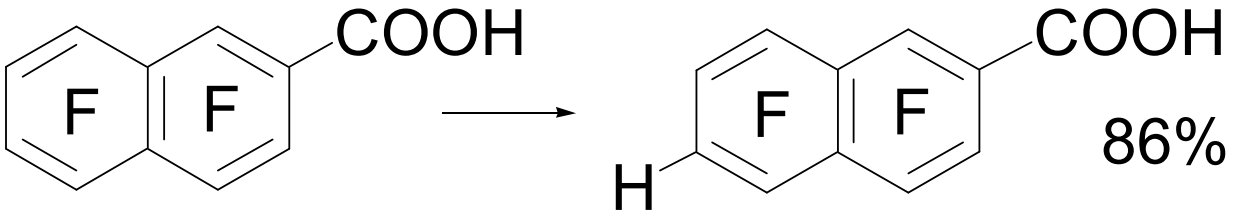


X = OH 93%

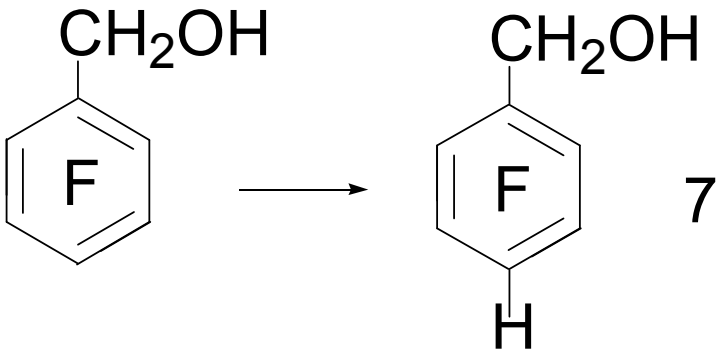
X = NH_2 92%



80%

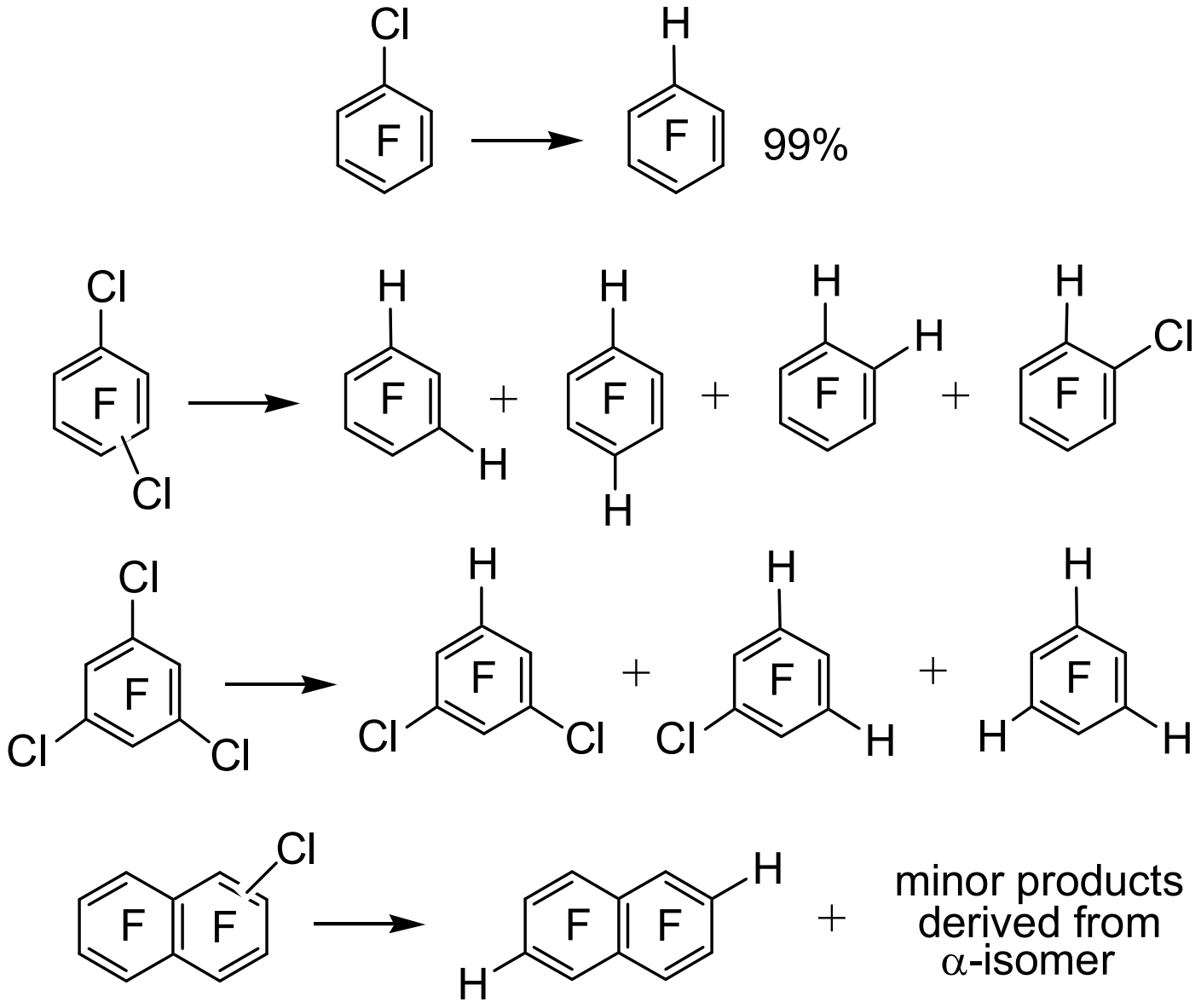


86%

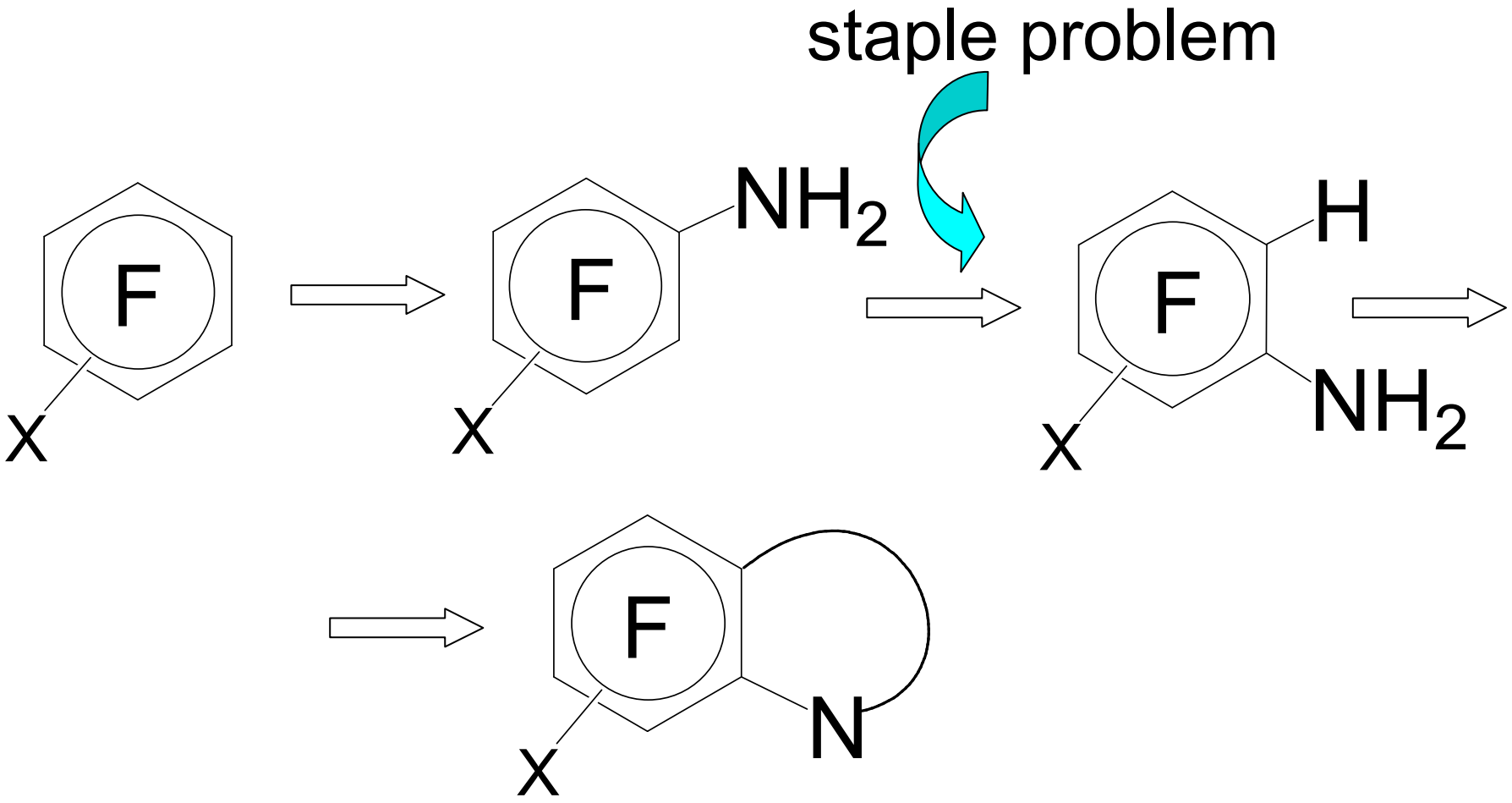


72%

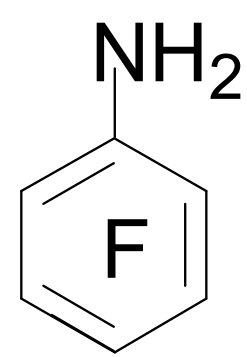
Polyfluorochloroarene selective hydrodechlorination

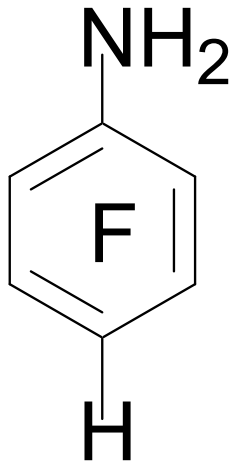


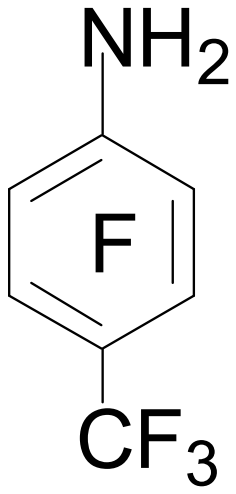
Selective *ortho*-hydrodefluorination of polyfluoroarylamines – the chalenging task to open a concise route to polyfluorobenzo nitrogen heterocycles

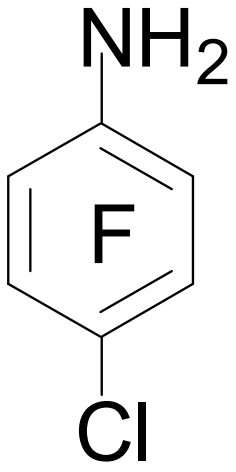


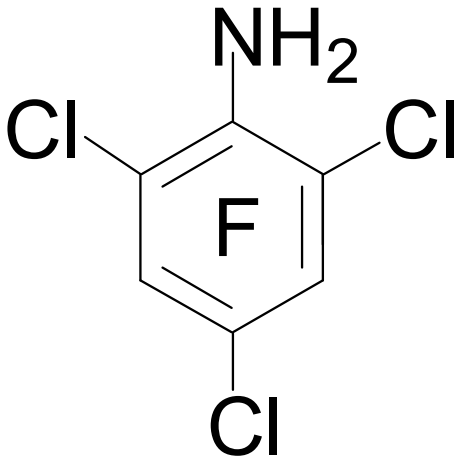
Polyfluoroarylamines available via direct ammonolysis of base polyfluoroarenes:

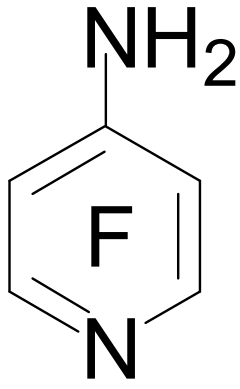


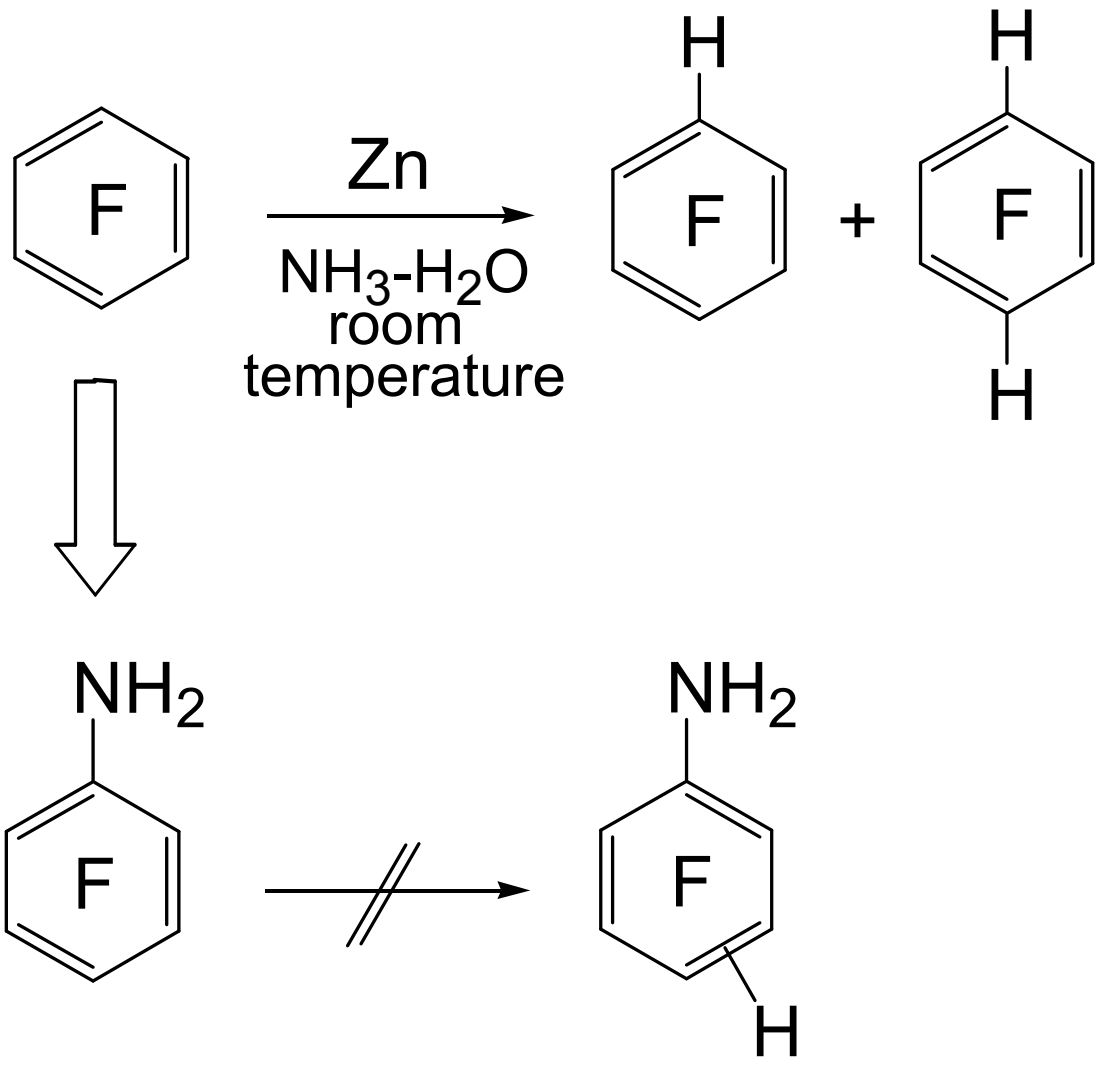






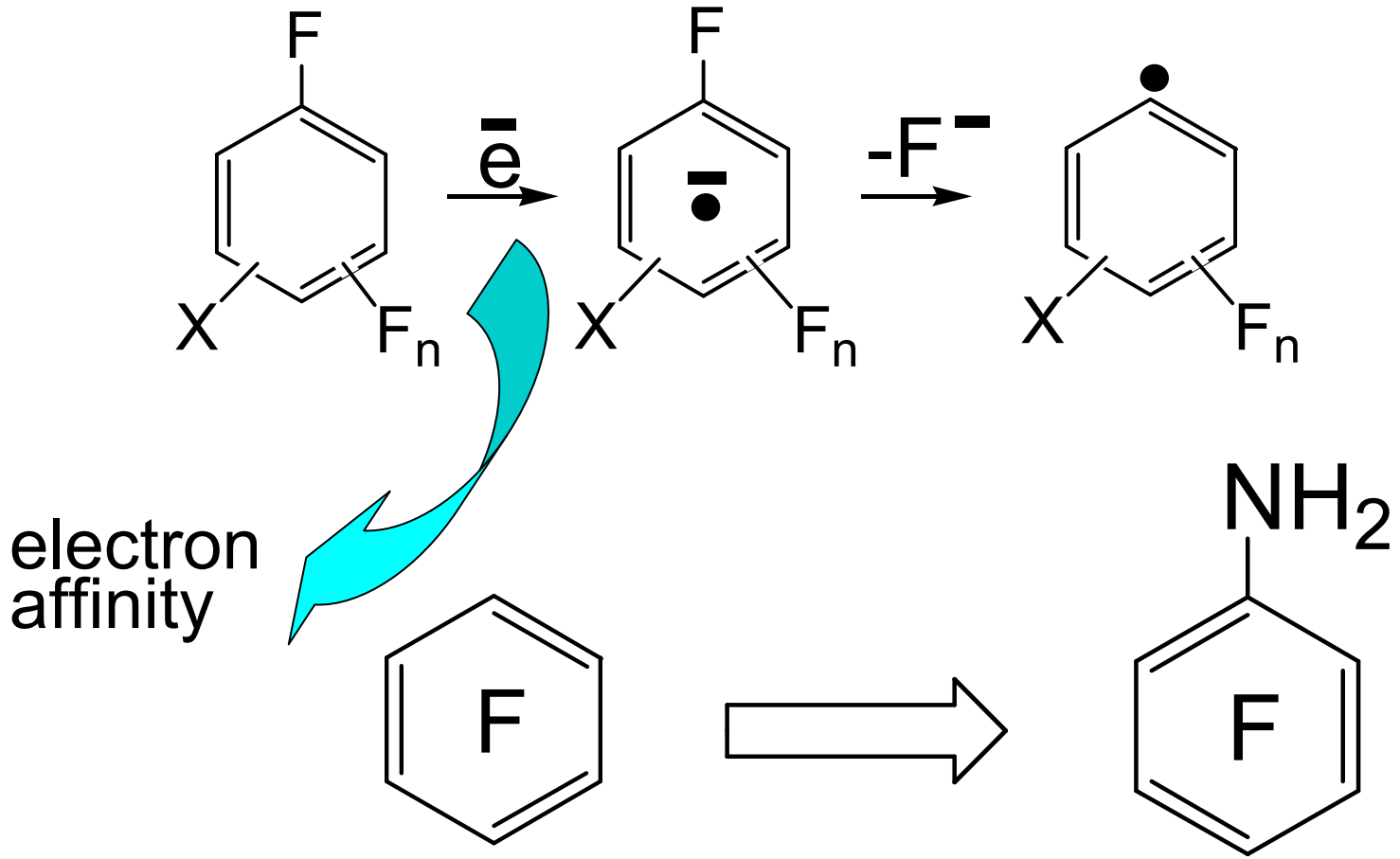




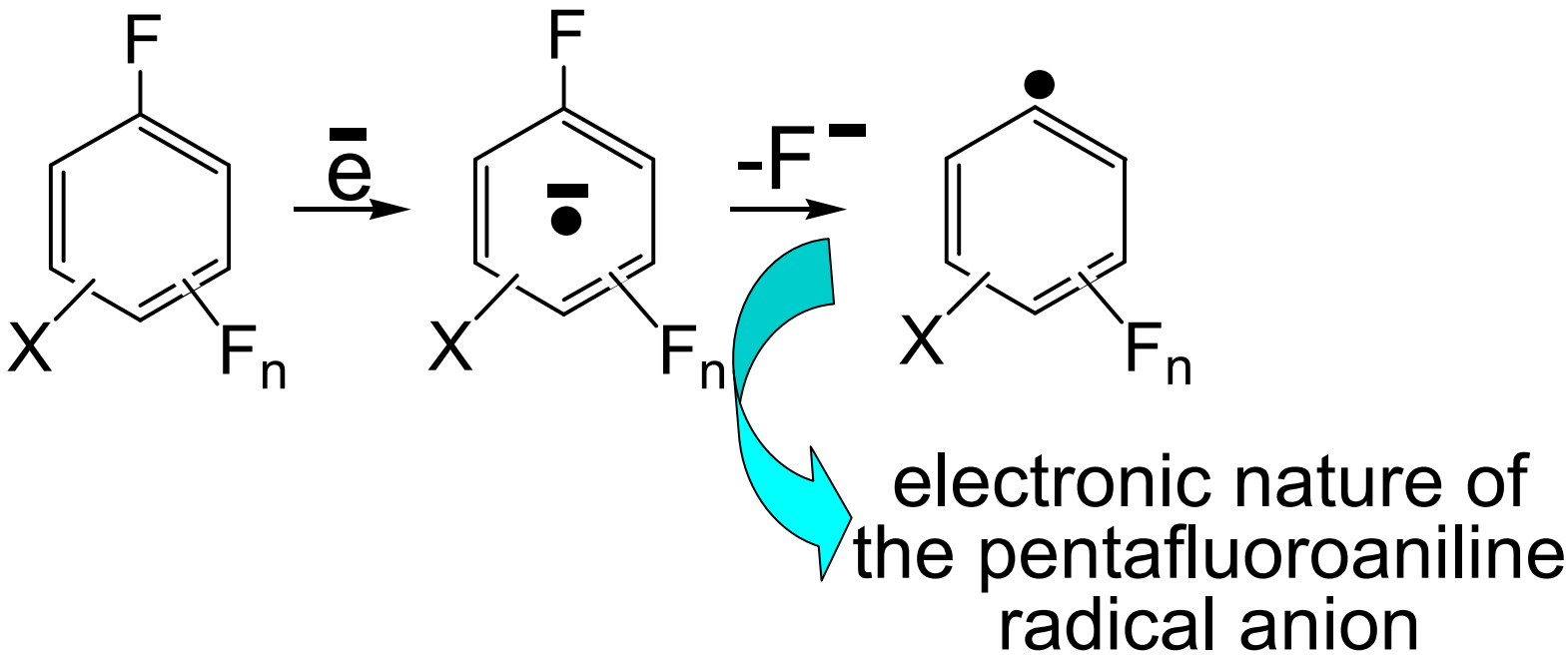


implantation of the amino group blocks hydrodefluorination

Likely origins of the amino group blocking effect:



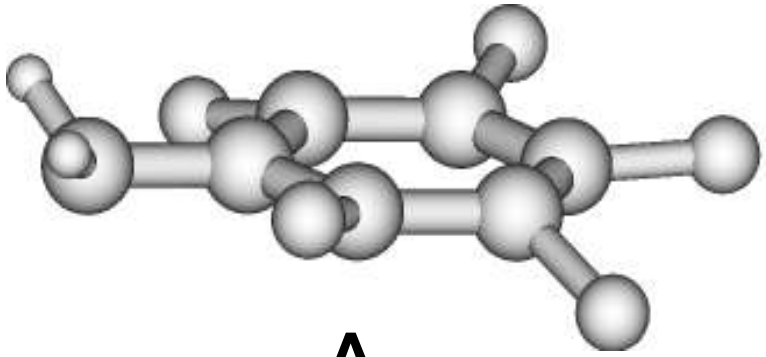
experimental	0.5-0.8 eV	-
calculated (ROB3LYP/6-31+G*)	0.60 eV	0.13 eV



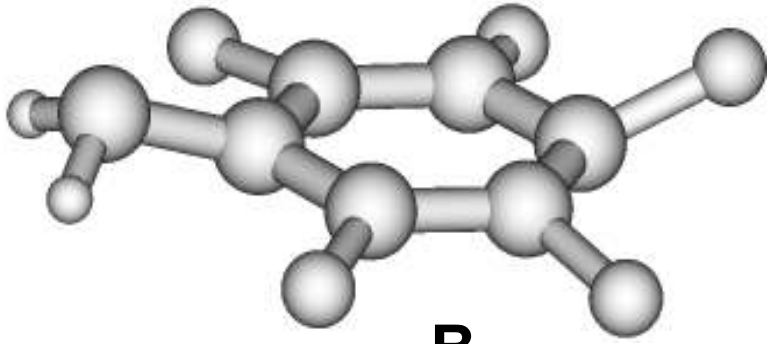
Stationary PES structures of $C_6F_5NH_2^{-\cdot}$			
Structure	E_{tot}	E_{rel}	EA^{ad}
A (π)	-783.454080 (minimum)	0	0.13
B (π)	-783.452660 (minimum)	0.89	0.10
(σ)	-783.452575 (saddle)	0.94	0.09

E_{tot} - a.u., E_{rel} - kcal/mol, EA - eV

PES minima of $C_6F_5NH_2^{-\cdot}$:



A



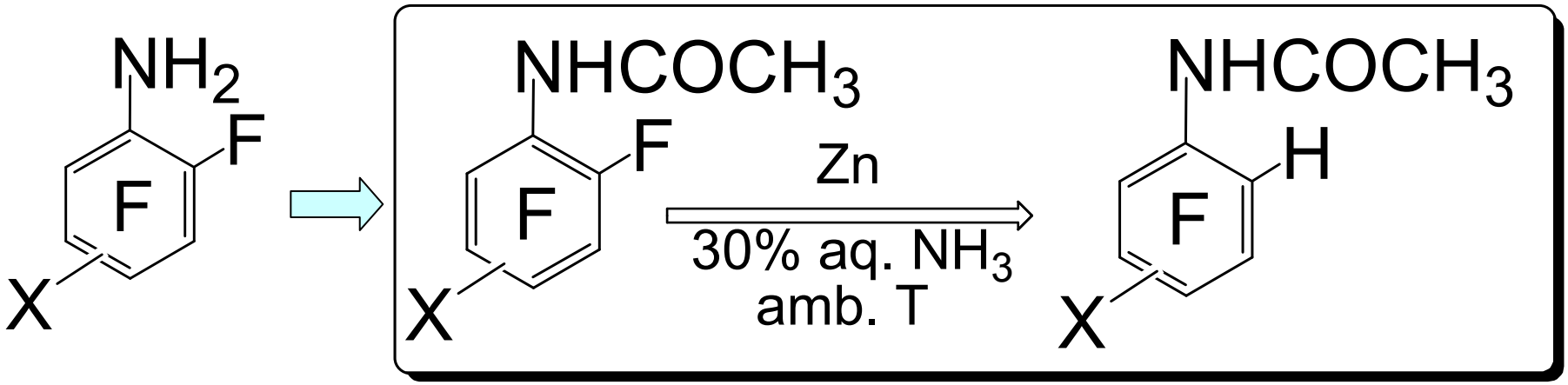
B

determines EA^{adiab}

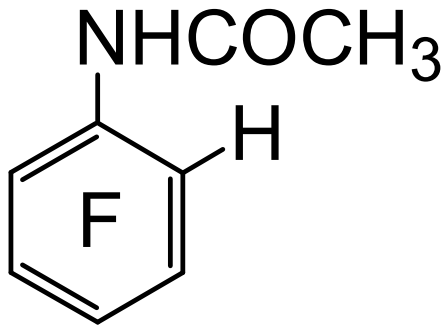
energy difference - no more than ~1 kcal/mol; energy barrier - negligibly small

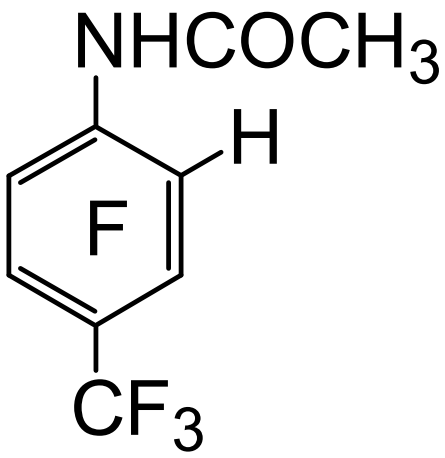
The general conclusion:

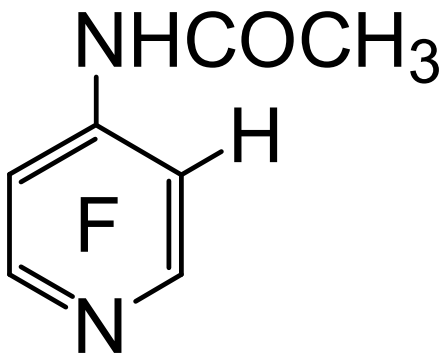
most likely reason of the amino group blocking effect – diminishing electron affinity



acetylation of the amino group deblocks hydrodefluorination

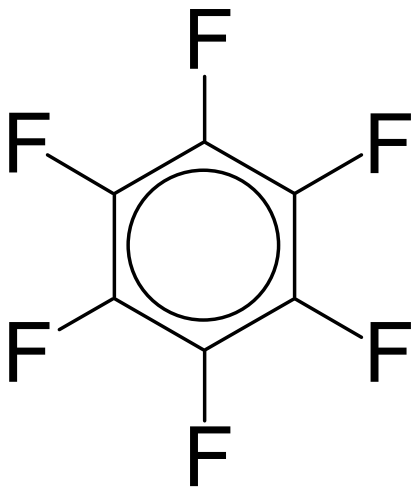




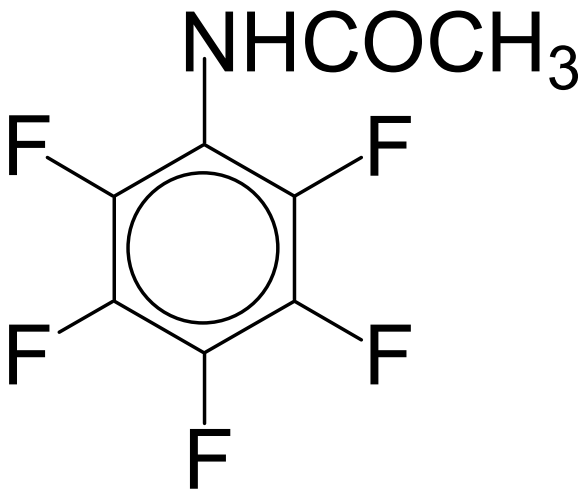


yields 40-70%

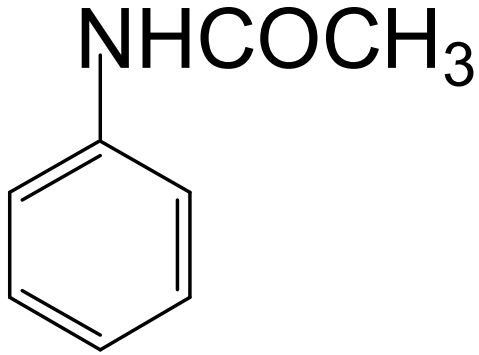
Electrochemical reduction potentials (CVA, DMF, Pt electrode, (n-Bu)$_4$NBF$_4$)



-2.10 V

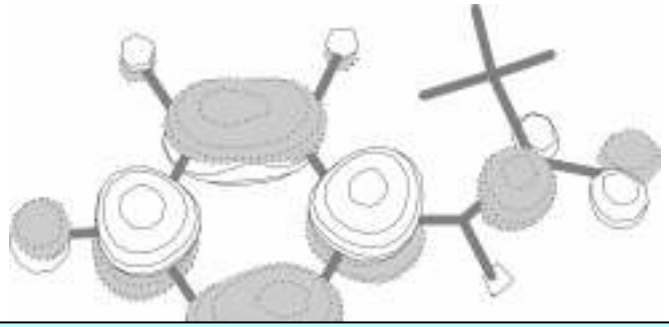


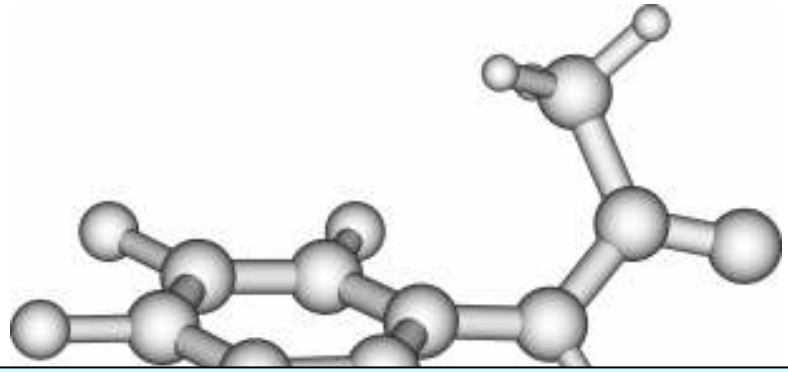
-1.64 V



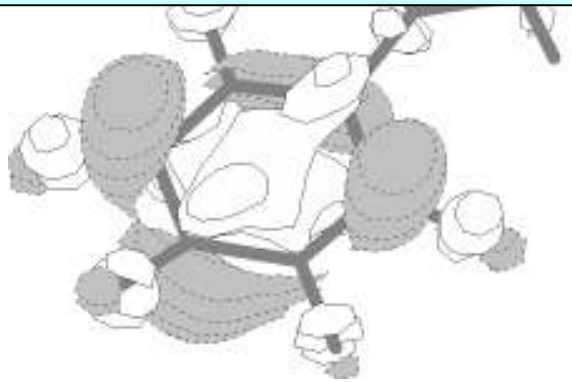
-(>2.6) V

PBE/6-31+G* calculation

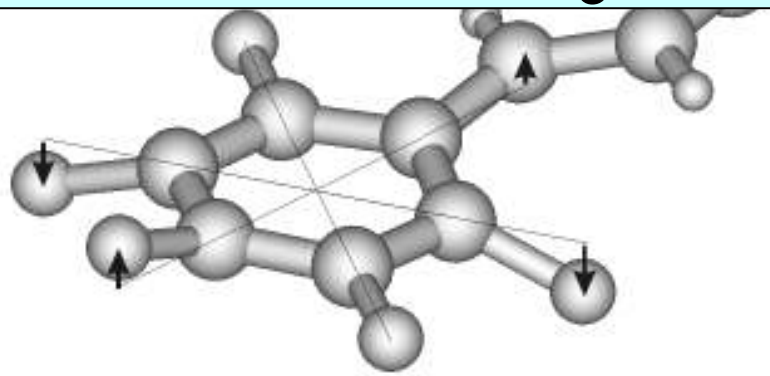




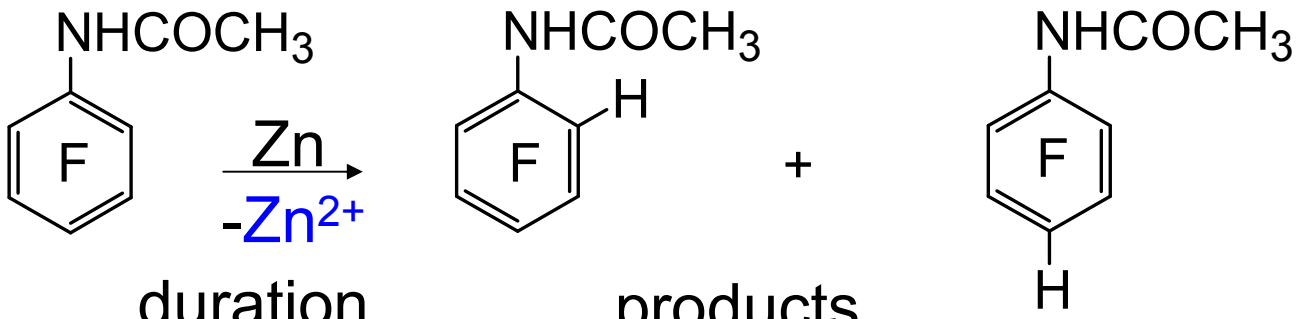
the likely origins of the N-acetylation deblocking effect: electronic influence of the $COCH_3$ group + sterically induced out-of-plane deviation of the $NHCOCH_3$ group



unpaired electron MO of $C_6F_5NHCOCH_3^{\bullet}$



spatial structure of $C_6F_5NHCOCH_3^{\bullet}$



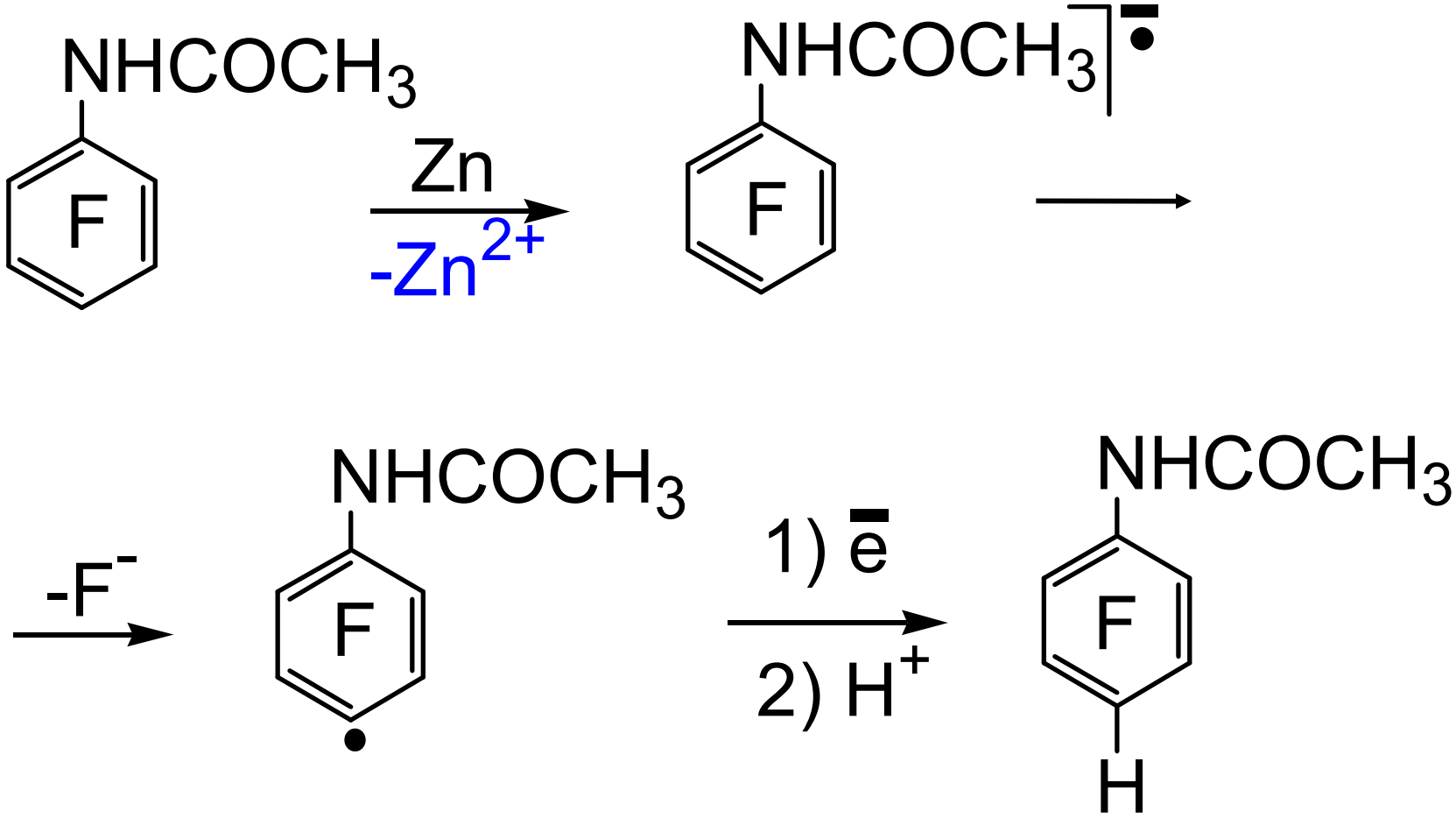
	duration, h	products, %	
first phase	1.2	6	**9**
	3	12	12
second phase	5	**20**	15
	13	**51**	16
with $ZnCl_2$ additive	1.2	**21**	3
	13	**72**	11
	22	**78**	13

40% isolated yield

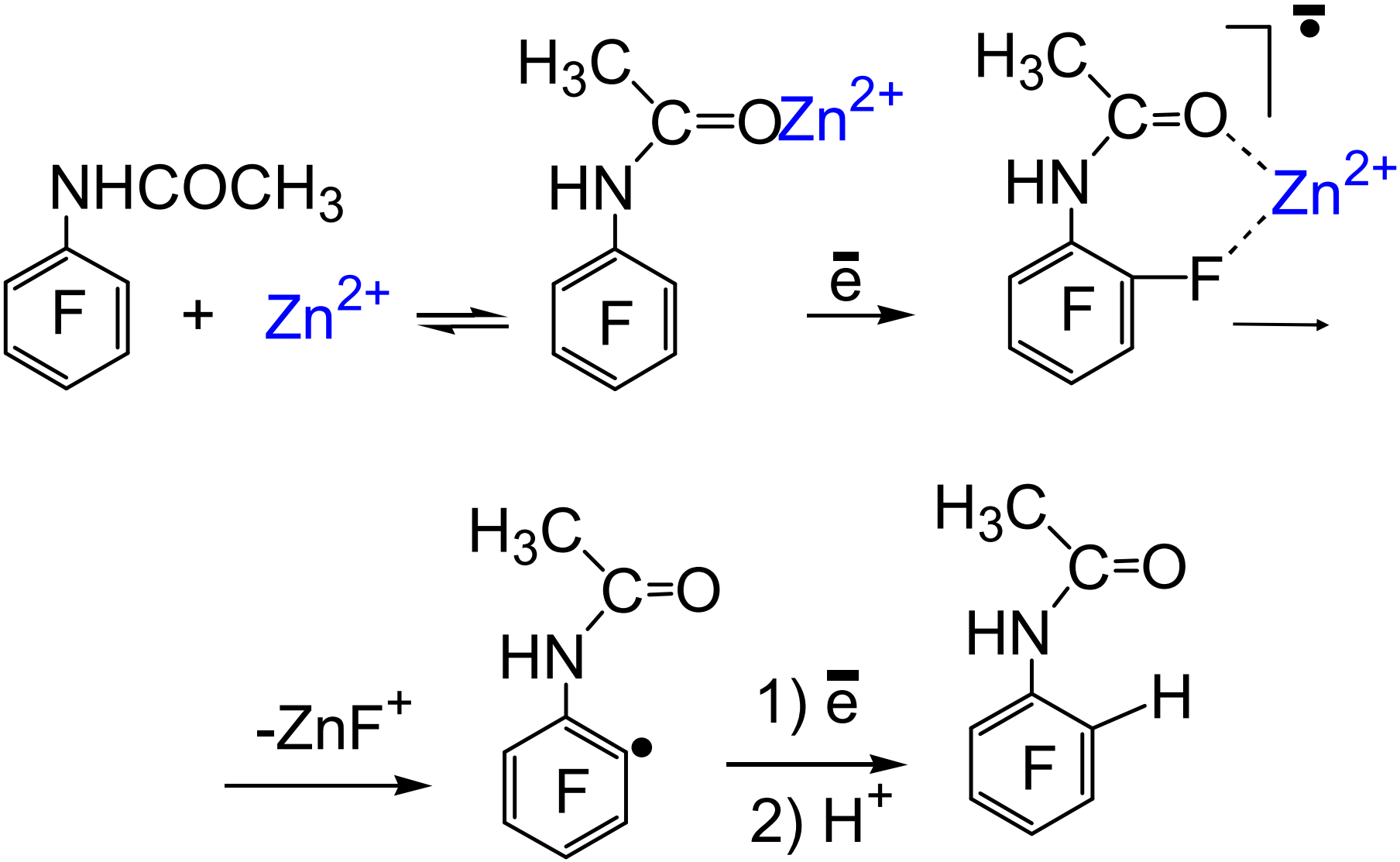
Zn^{2+} selectively induces *ortho*-hydrodefluorination

Suggested mechanism

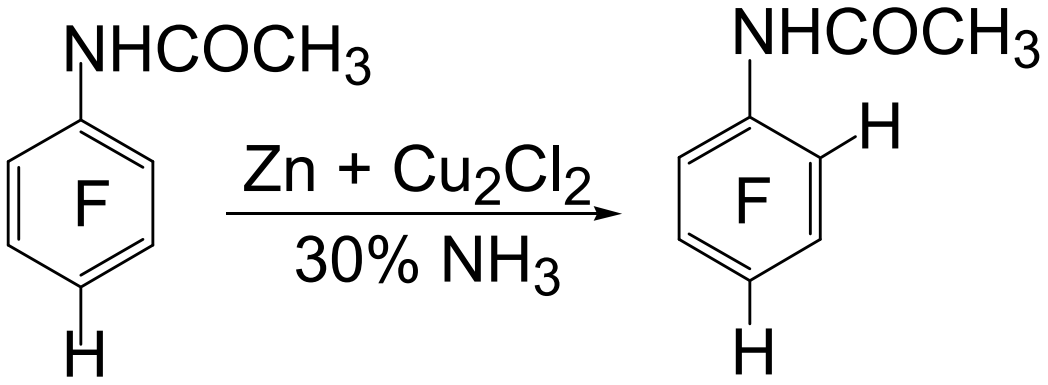
first phase

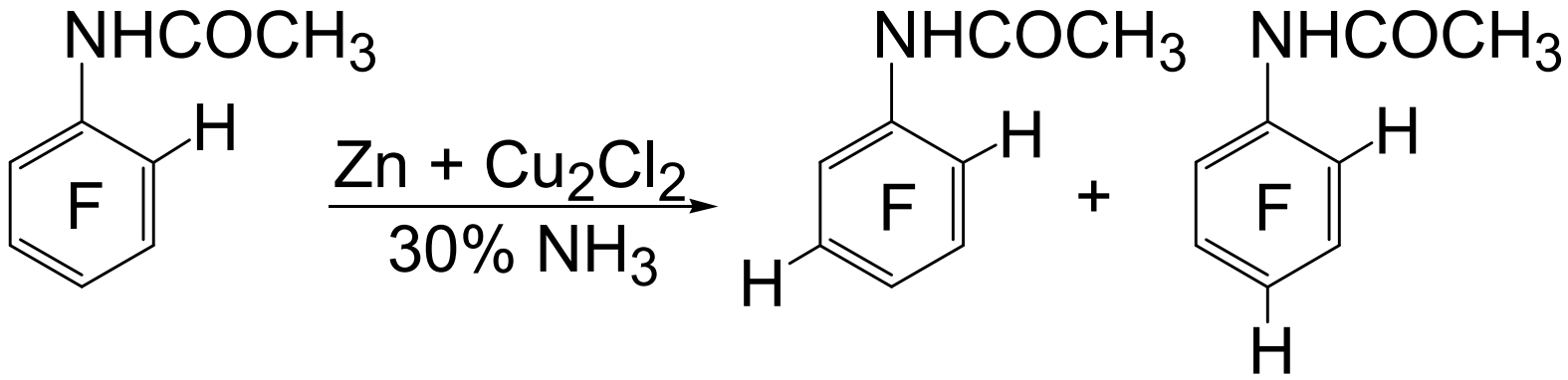


second phase

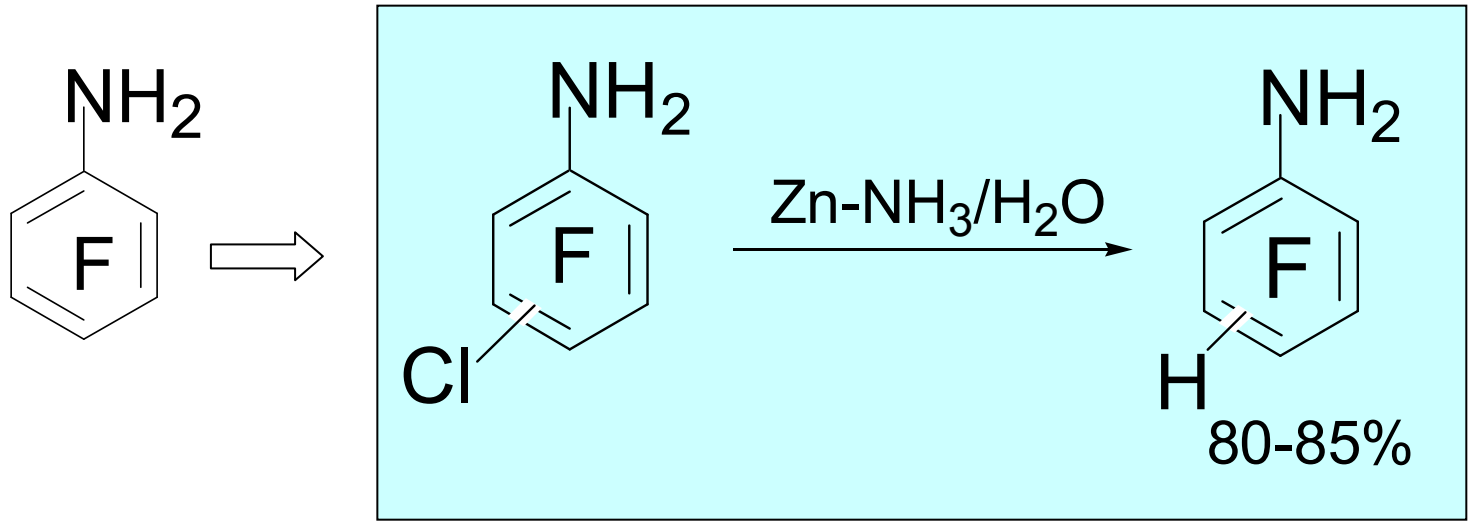


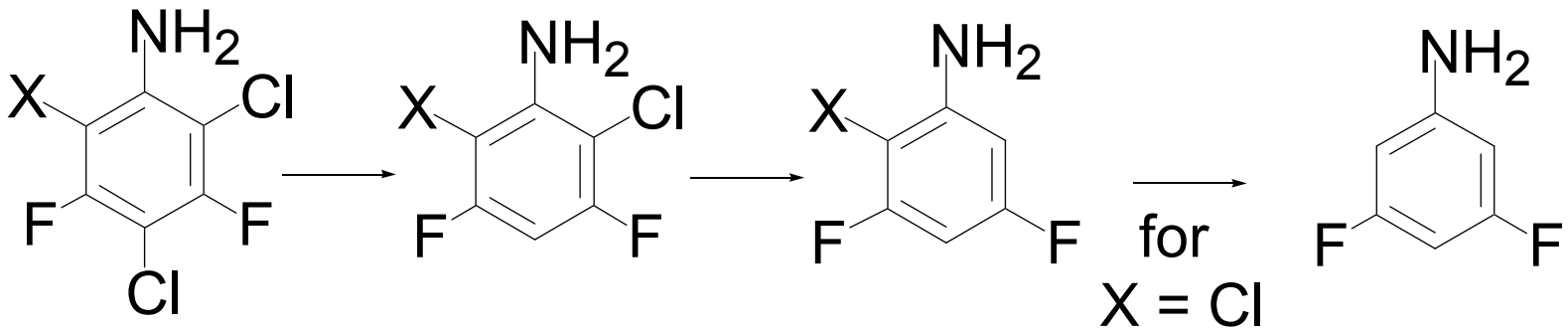
Reaction acceleration by the cupruous salt additive



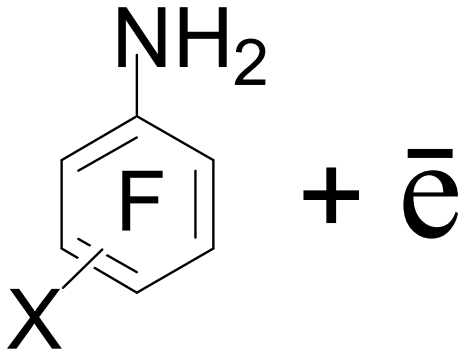


30 : 1


NH2
F
NH2
F
Cl
Zn-NH3/H2O
NH2
F
H
80-85%


NH2
X
Cl
F
F
Cl
NH2
X
Cl
F
F
NH2
X
F
F
for
X = Cl
NH2
F
F

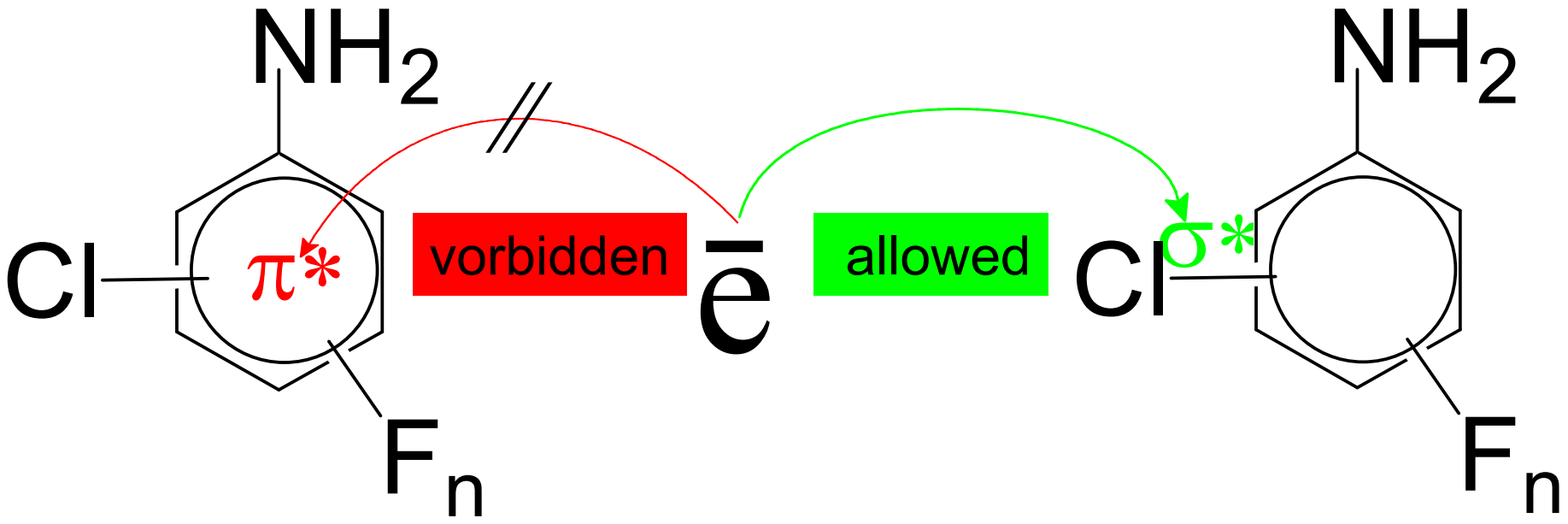
X = F, Cl



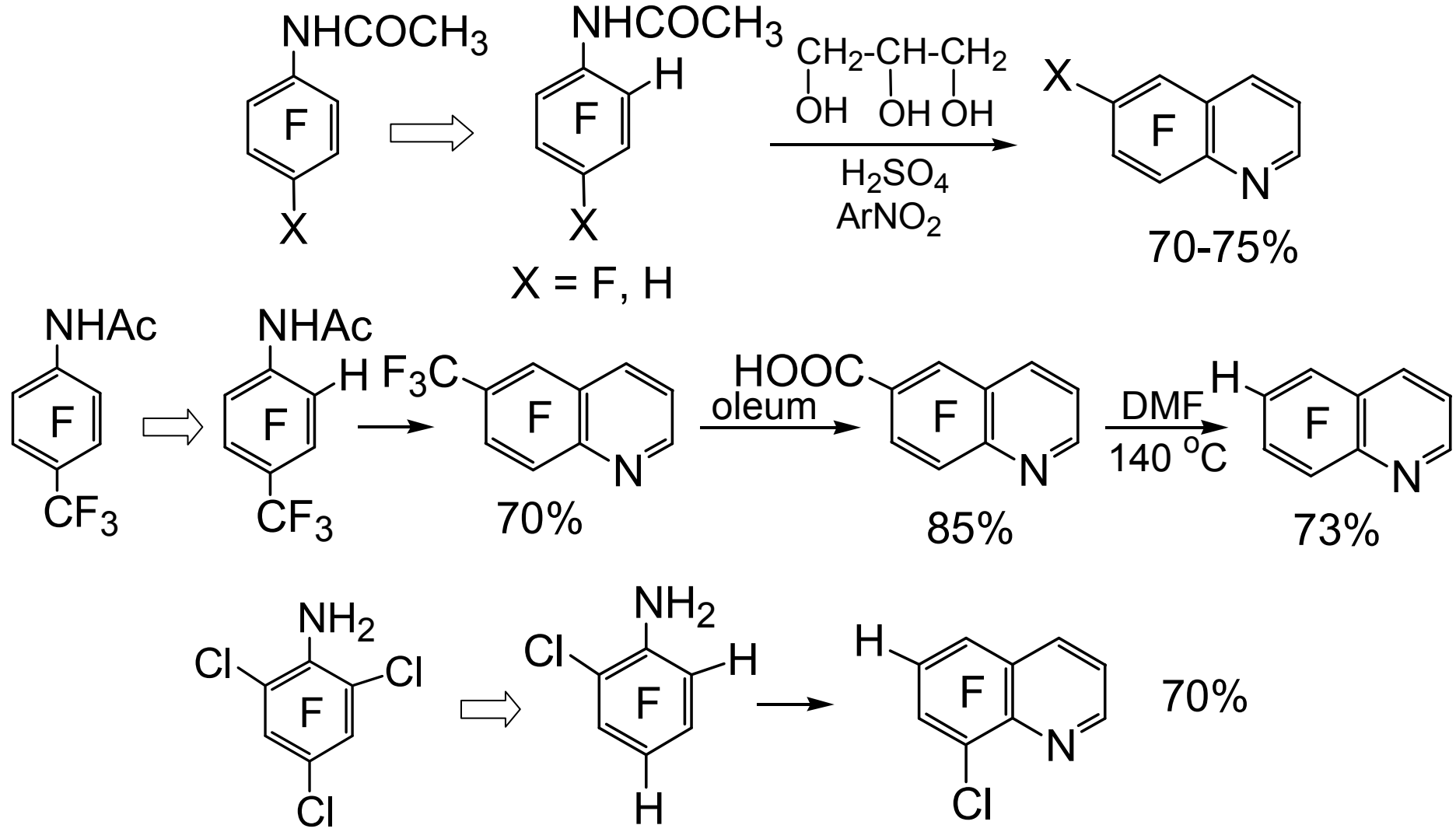
+ $\bar{e}$

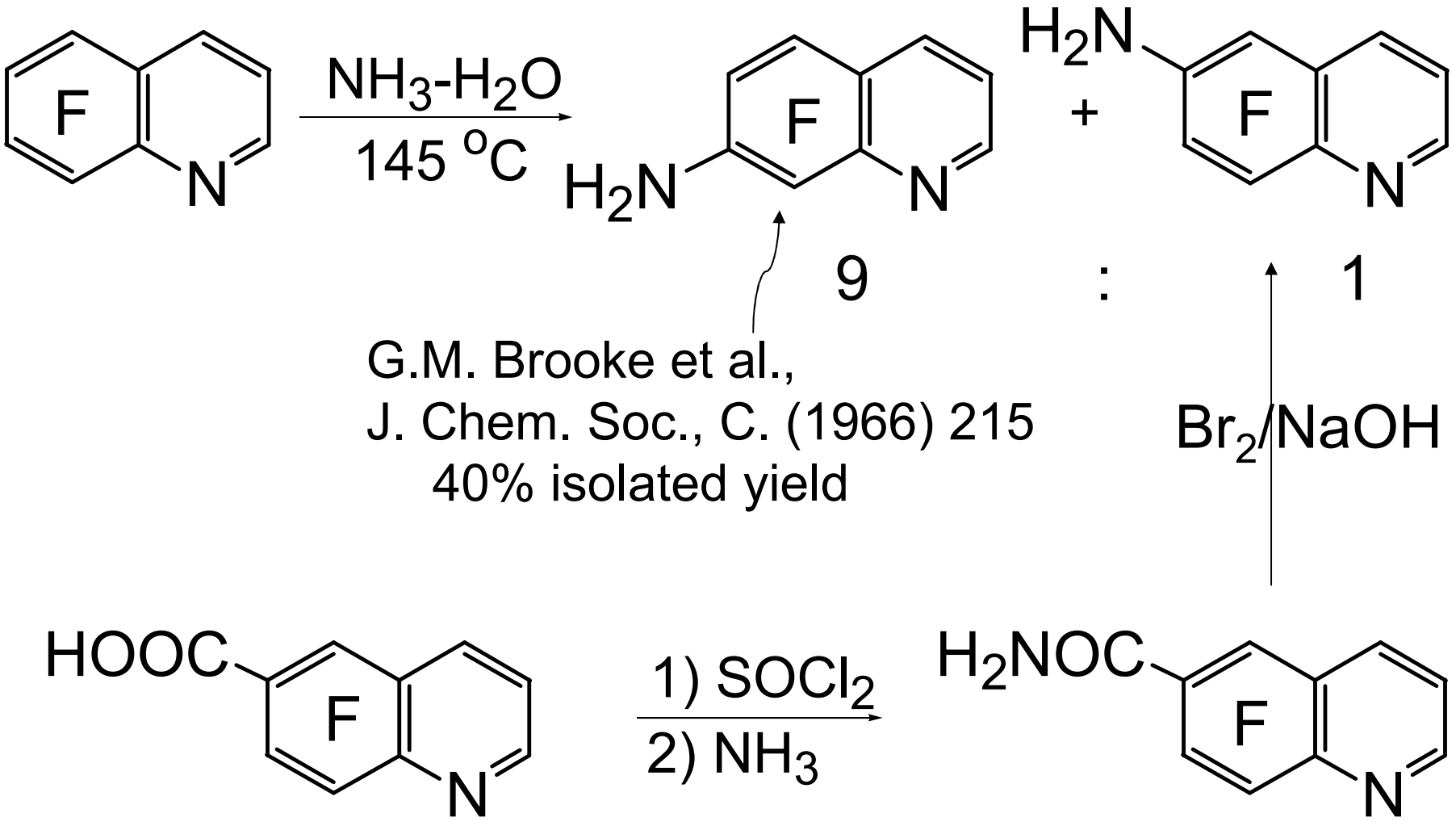
X = F ⟹ X = Cl

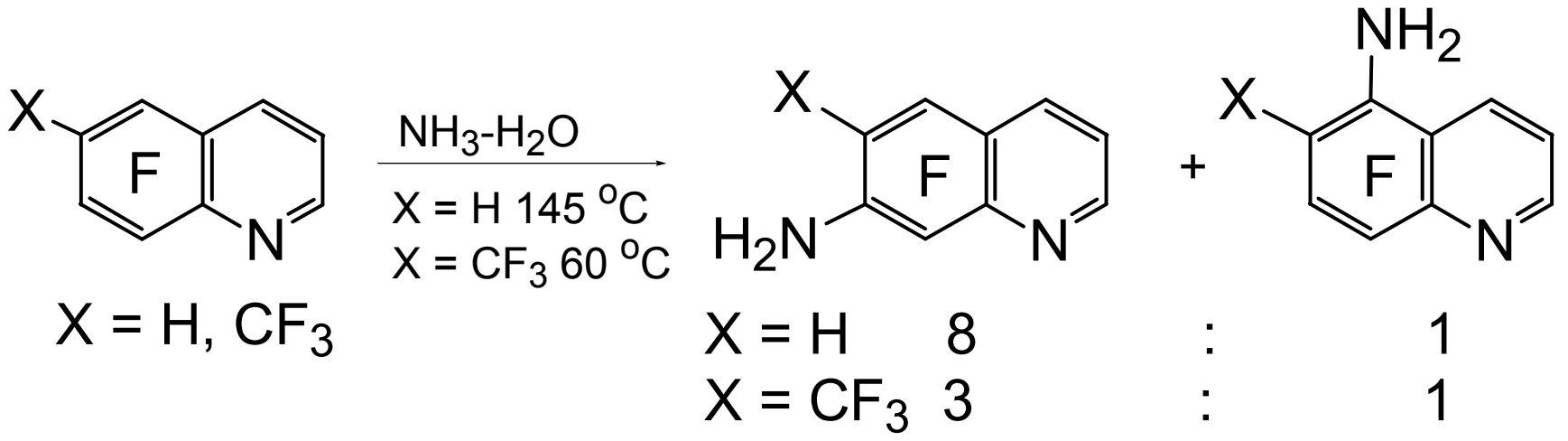
change of the nature of the MO
accepting an electron

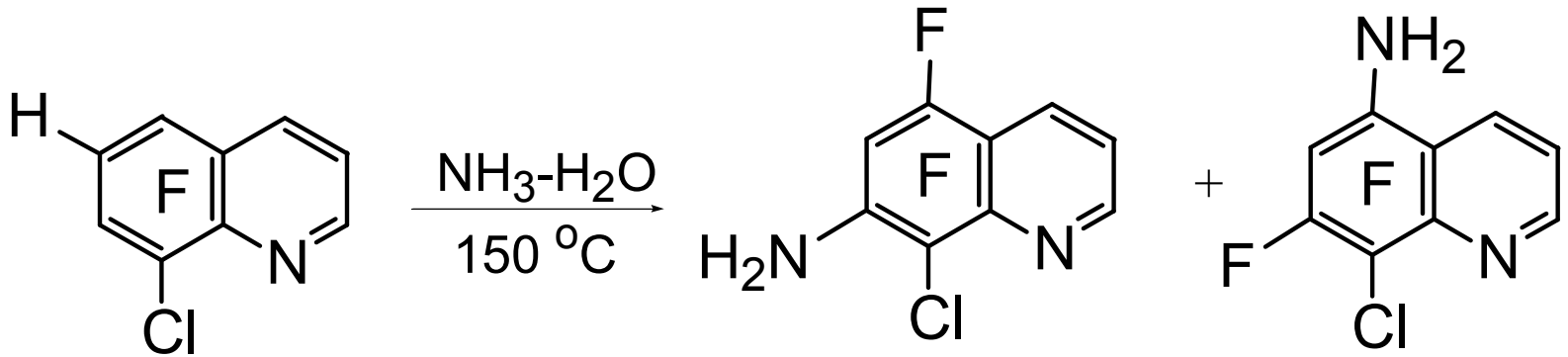


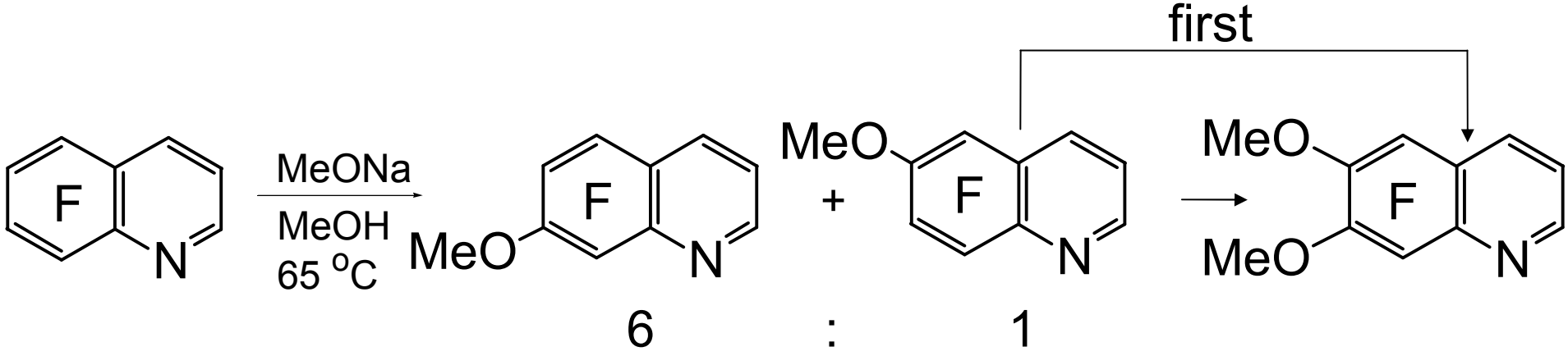
Selective *ortho*-hydrodehalogenation of polyfluoroarylamines – unprecedentedly concise route to polyfluorobenzo azaheterocycles

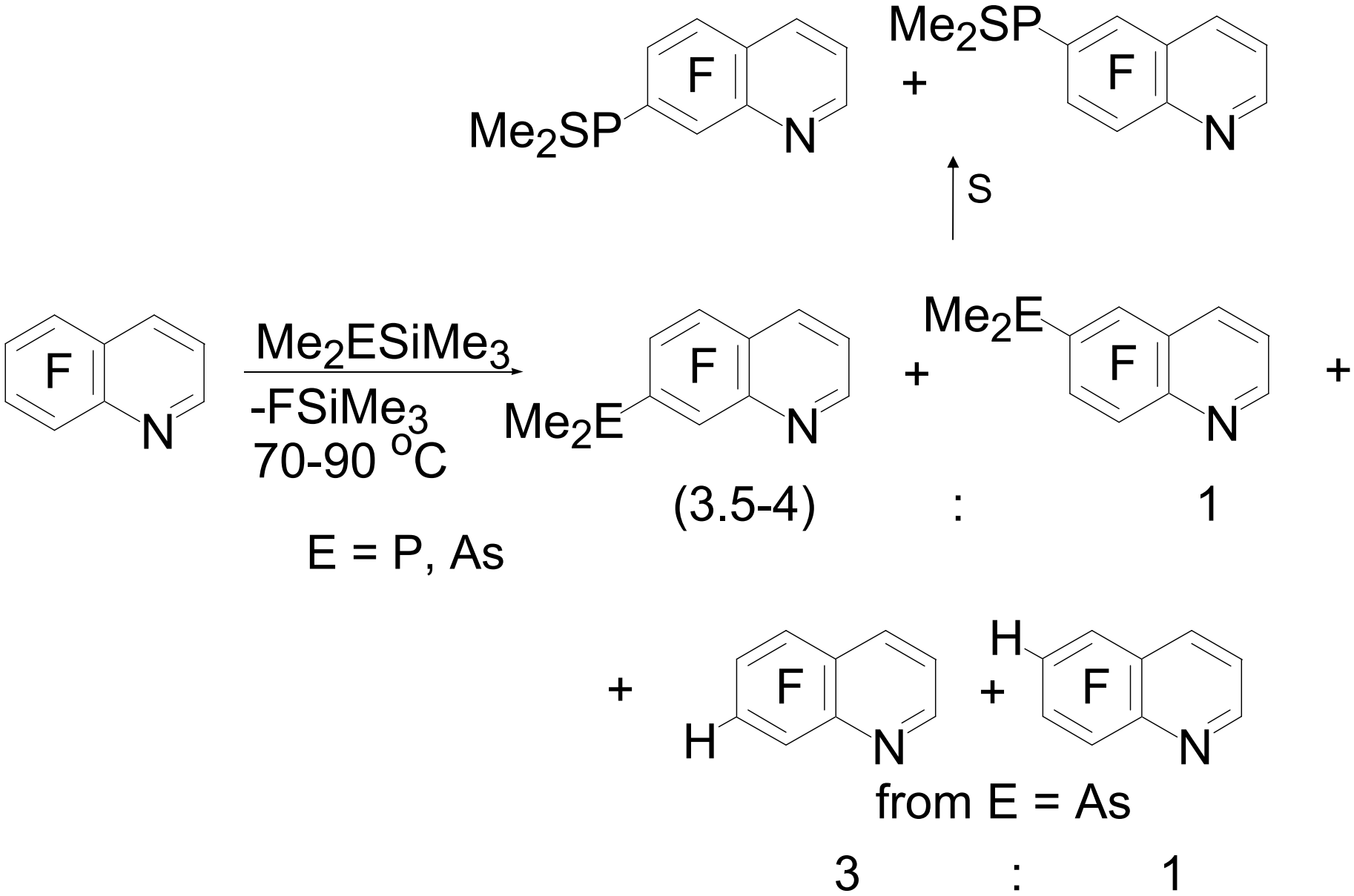


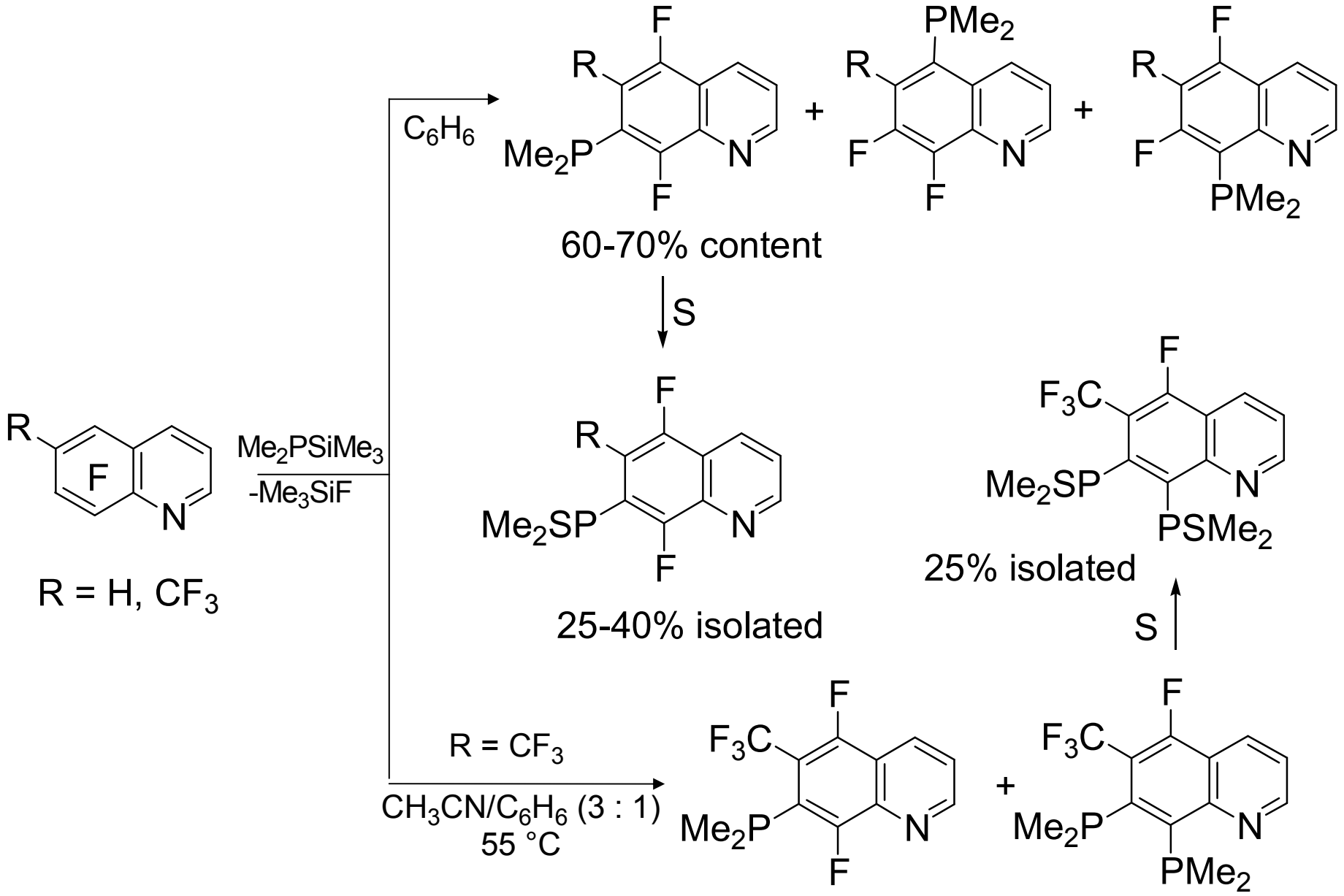

F
N
NH3-H2O
145 oC
H2N
F
N
H2N
+
F
N
9
:
1
G.M. Brooke et al.,
J. Chem. Soc., C. (1966) 215
40% isolated yield
Br2/NaOH
HOOC
F
N
1) SOCl2
2) NH3
H2NOC
F
N

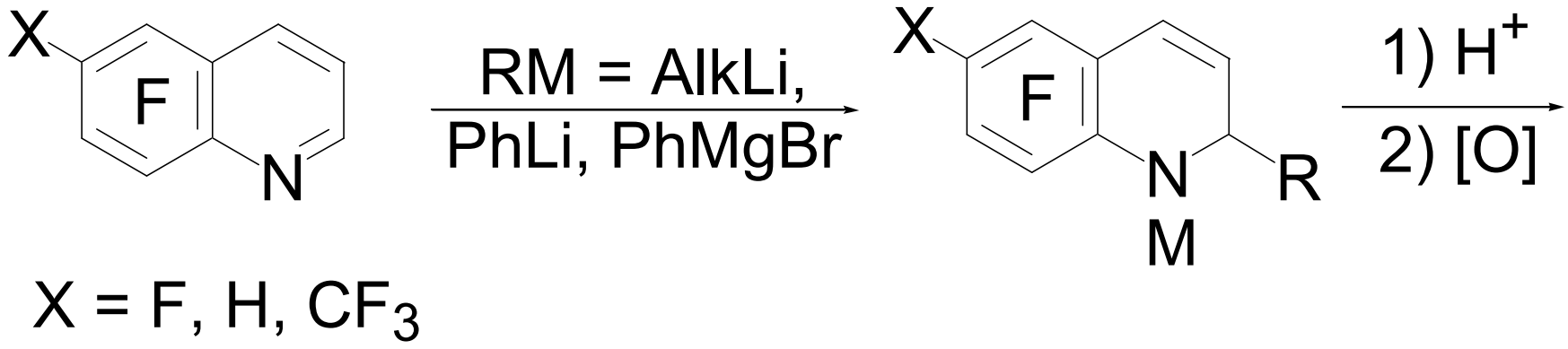

X
F
N
NH3-H2O
X = H 145 °C
X = CF3 60 °C
X = H, CF3
H2N
NH2
+
X = H 8 : 1
X = CF3 3 : 1


H
F
N
Cl
NH3-H2O
150 °C
H2N
NH2
+


first
F
N
MeONa
MeOH
65 °C
MeO
+
6 : 1


Me2SP
F
N
+
Me2SP
F
N
S
F
N
Me2ESiMe3
-FSiMe3
70-90 °C
Me2E
F
N
(3.5-4)
:
1
+
Me2E
F
N
+
E = P, As
+
H
F
N
+
H
F
N
from E = As
3
:
1


R
F
N
R = H, CF3
Me2PSiMe3
-Me3SiF
C6H6
60-70% content
S
25-40% isolated
25% isolated
R = CF3
CH3CN/C6H6 (3 : 1)
55 °C


X
F
N
RM = AlkLi,
PhLi, PhMgBr
X
F
N
M
R
1) H+
2) [O]
X = F, H, CF3
X
F
N
R

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chemistry

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quantum chemical calculations

N.V. Vasil'eva

electrochemistry

Yu.D. Tsvetkov
V.V. Konovalov
Institute of Chemical Kinetics and Combustion (Novosibirsk)

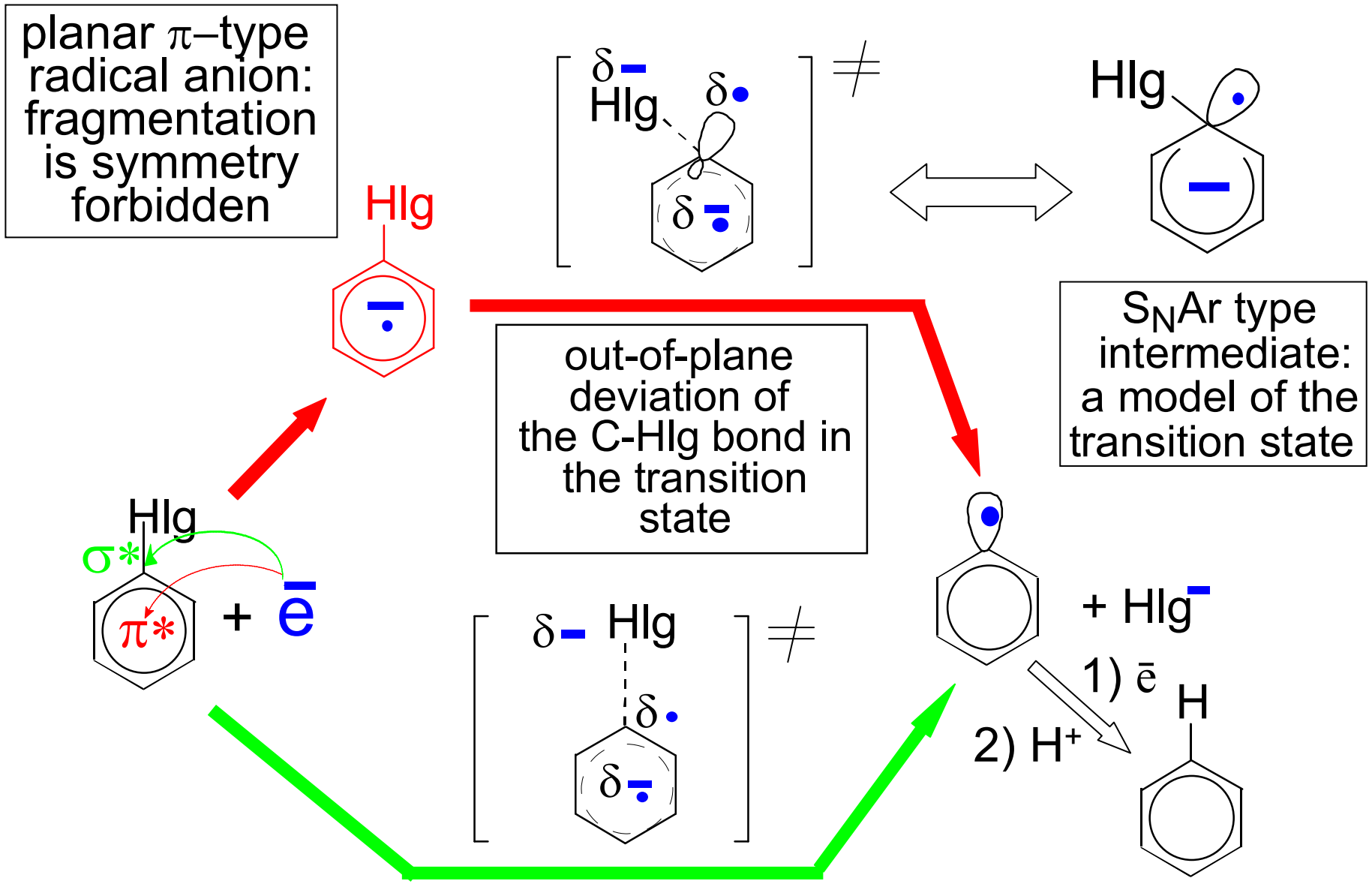
radical anion fragmentation rate measurements by the electron photoinjection method

Prof. Dr. Joseph Grobe

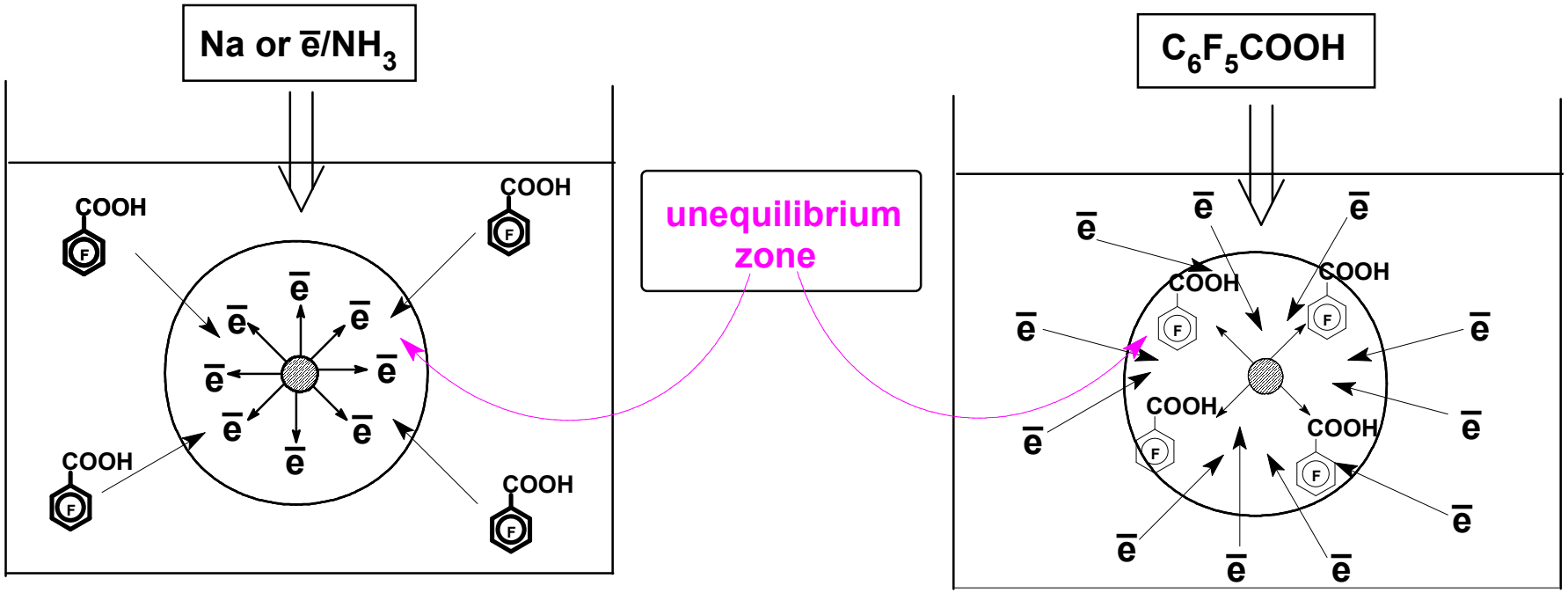
Institut für Anorganische und Analytische Chemie, Westfälische Wilhelms-Universität, Münster, Germany

reactions of polyfluoroquinolines with Me_2ESiMe_3 reagents

Stiftung Volkswagenwerk (BRD) for financial support of the Cooperation Project between this Institute and the N.N.Vorozhtsov Institute of Organic Chemistry


planar π–type radical anion: fragmentation is symmetry forbidden
Hlg
δ−
Hlg
δ•
δ−
≠
Hlg
SNAr type intermediate: a model of the transition state
out-of-plane deviation of the C-Hlg bond in the transition state
Hlg
σ*
π*
+ e
δ−
Hlg
δ•
δ−
≠
+ Hlg−
1) ē
2) H+
H

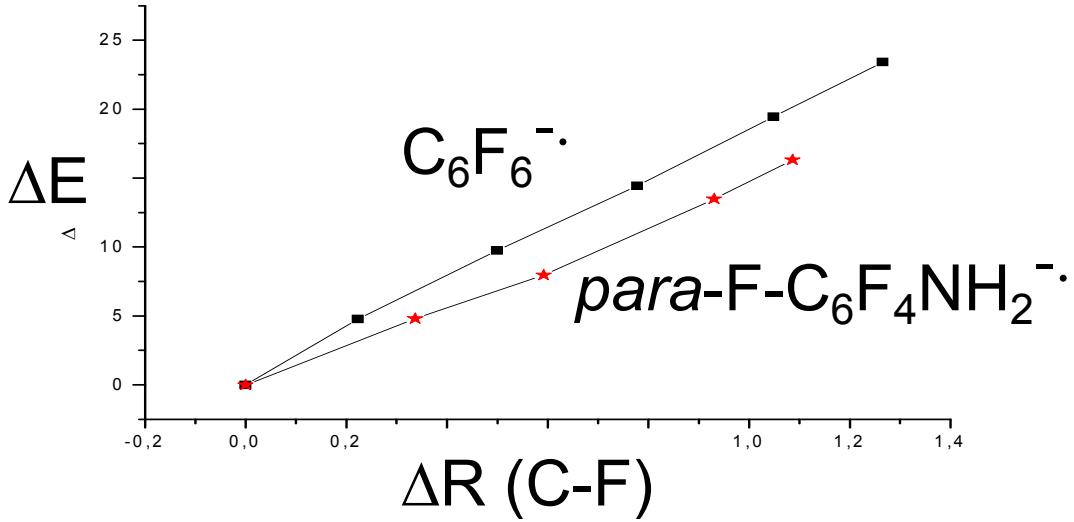
the likely reason of nonselectivity of the reduction in liquid ammonia: the electron diffusion is much faster than the molecule diffusion



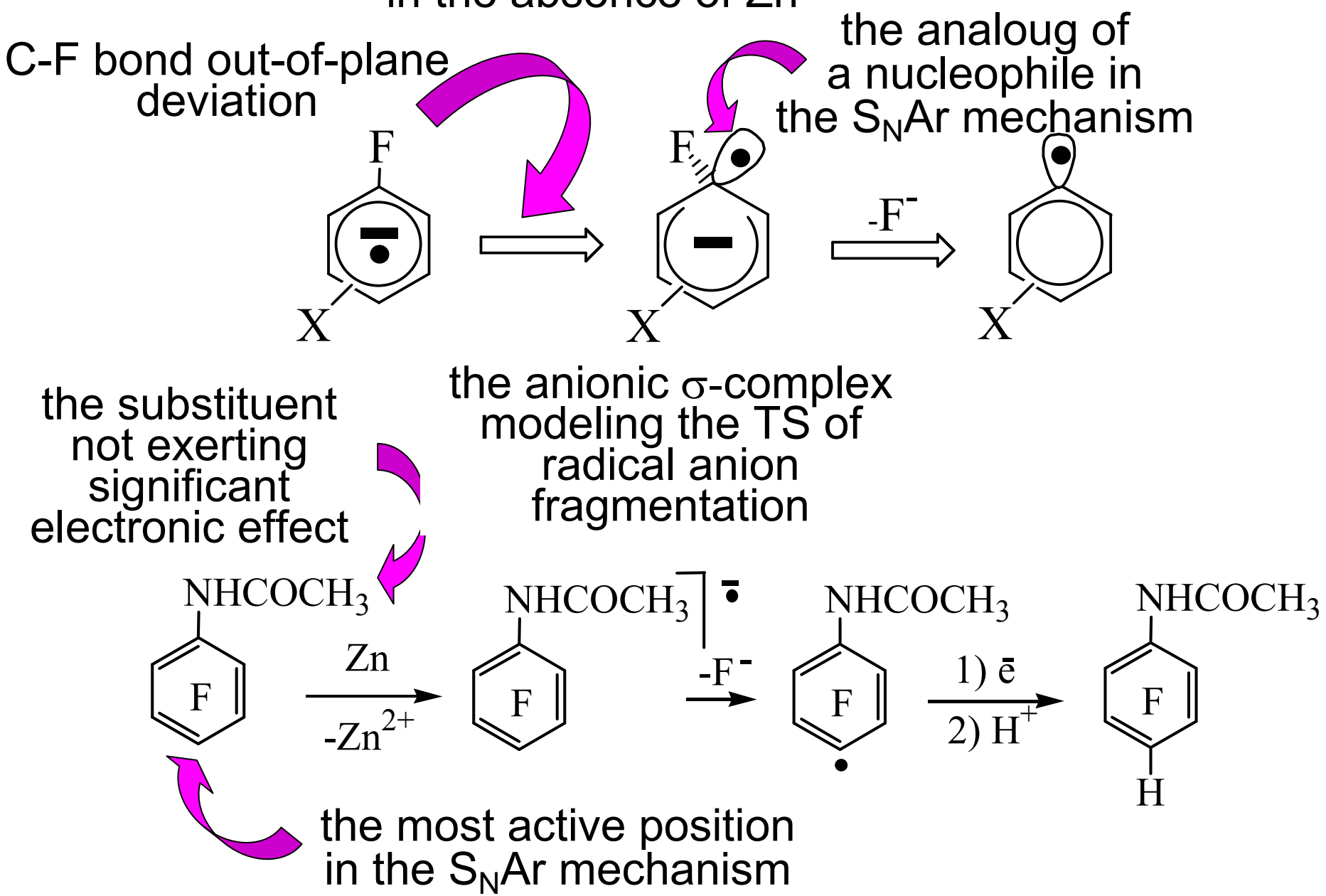
full (a.u.) and relative (kcal/mol) energies of isomeric radicals $NH_2C_6F_5\bullet$

isomer	E_{tot}	E_{rel}
para	-683.561263	0.
ortho	-683.560692	0.36
meta	-683.558827	1.53

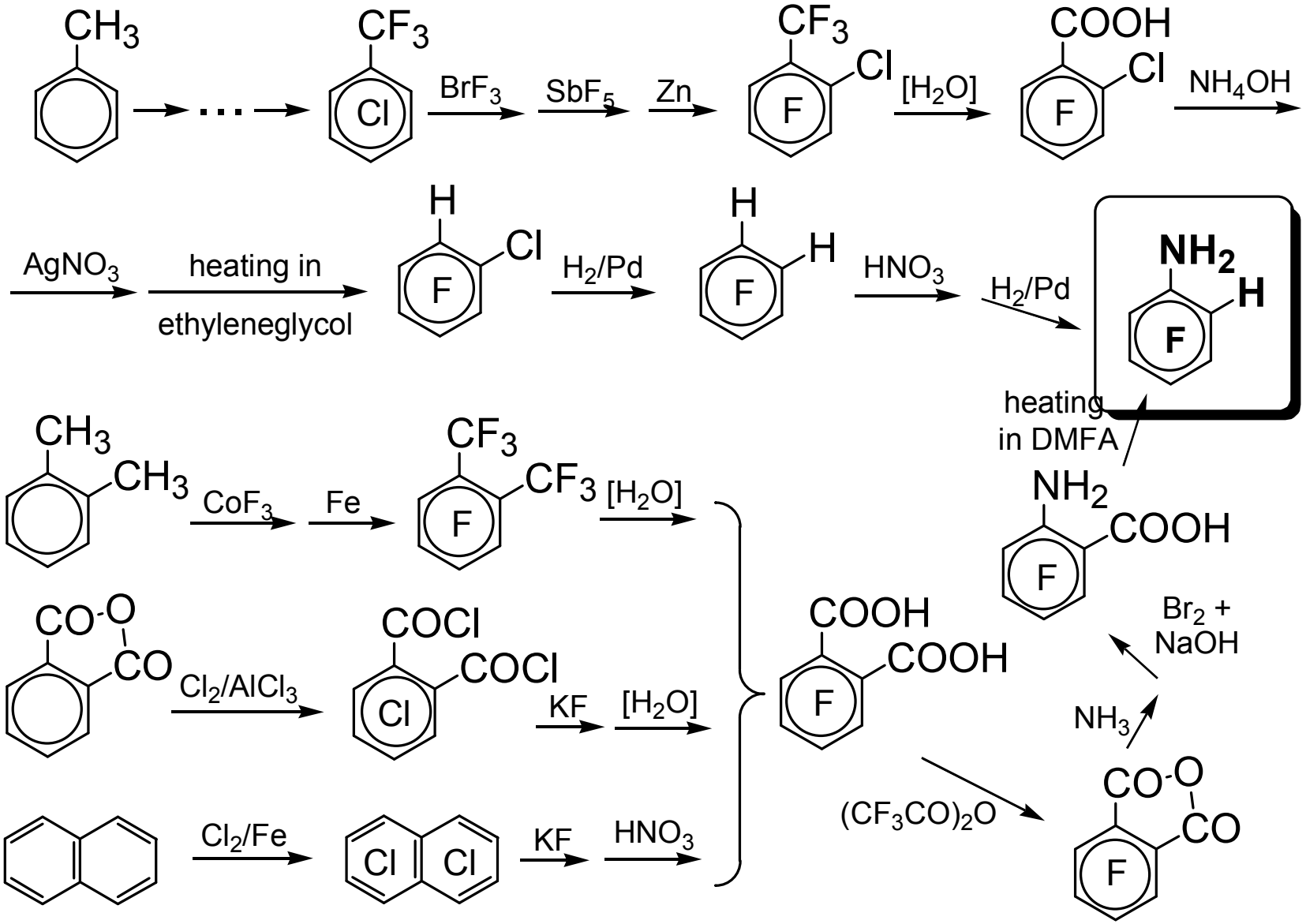
- *para*-fragmentation of $C_6F_4NH_2^{-}\cdot$ occurs easier than for $C_6F_6^{-}\cdot$



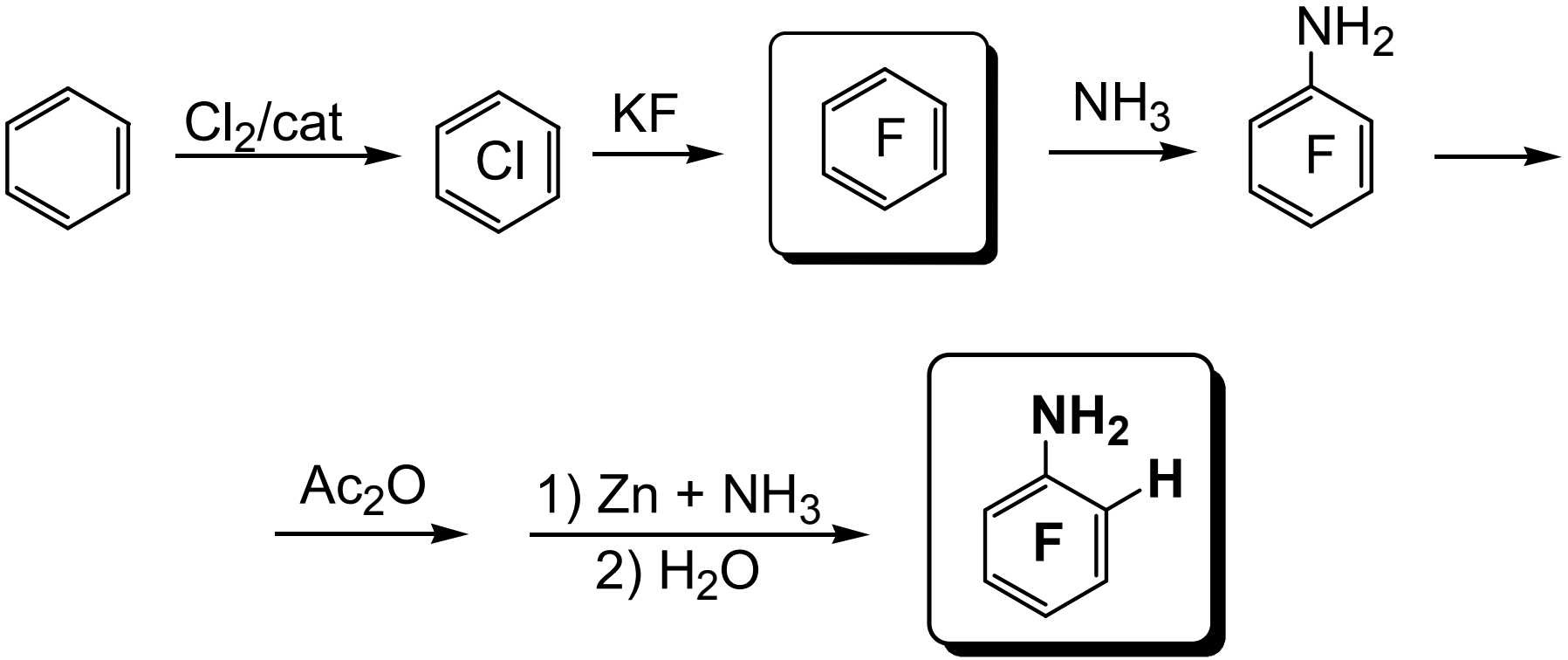
Orientation of pentafluoroacetanilide hydrodefluorination in the absence of Zn^{2+}



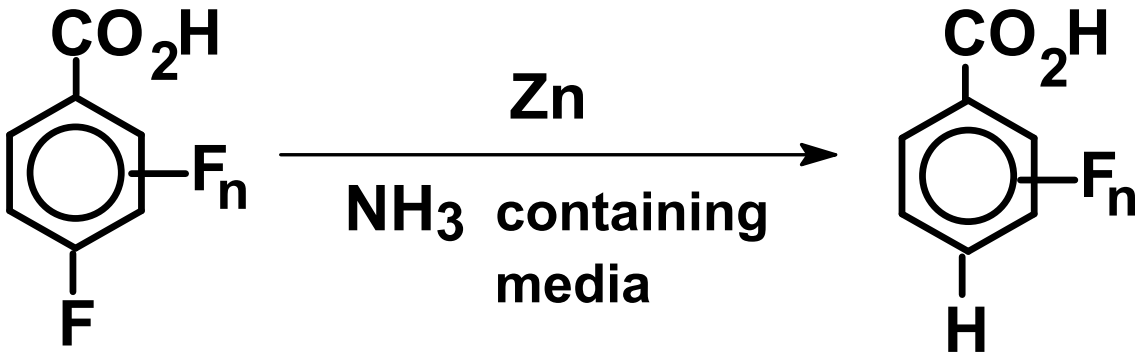
Literature data on the synthesis of 2,3,4,5-tetrafluoroaniline



Present approach

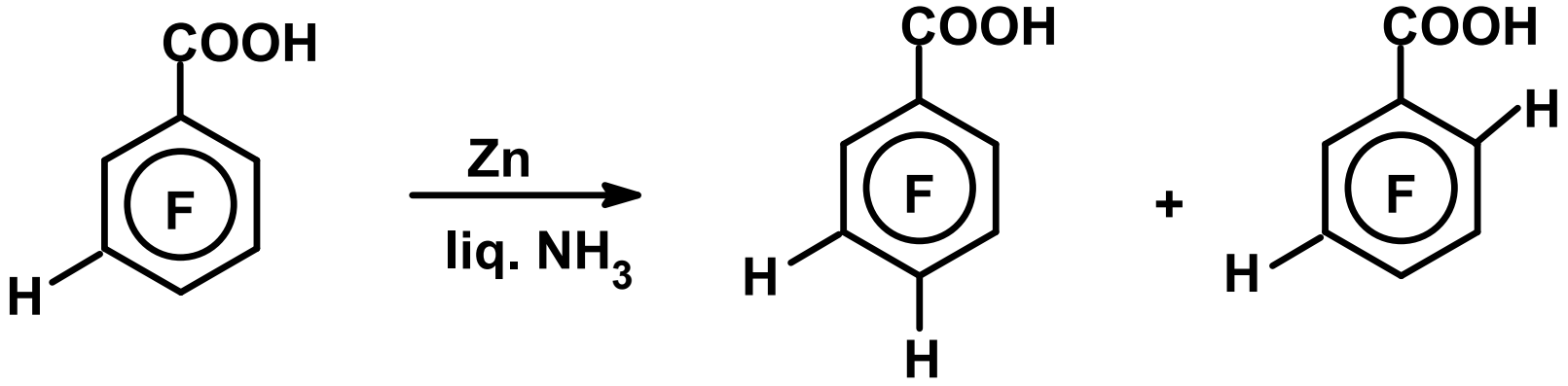


Regioselectivity



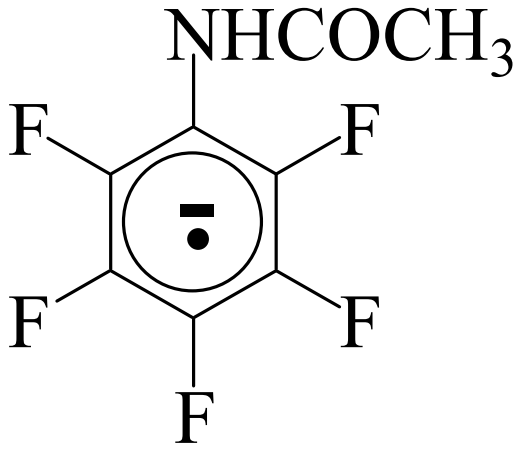
$k_p > k_o > k_m$

$F_n = F_4$, 2,3,5-F_3 , 3,5-F_2



1 : 1

Выводы:



- рецептором электрона в пентафторацетанилиде скорее всего является пентафторфенильное кольцо;

- повышение сродства к электрону при переходе от пентафторанилина к его N-ацетильному производному обусловлено подавлением π-электронодонорного эффекта заместителя как электронным влиянием карбонильной группы, так и выводом заместителя $NHCOCH_3$ из плоскости бензольного кольца.

the likely origins of the N-acetylation deblocking effect: electronic influence of the $COCH_3$ group + sterically induced out-of-plane deviation of the $NHCOCH_3$ group

MO symmetry correlation