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A REVIEW ARTICLE

CATALYTIC HYDROGENOLYSIS OF CARBON-FLUORINE BONDS: π BOND PARTICIPATION MECHANISM

M. HUDLICKY

Department of Chemistry, Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061 (U.S.A.)

SUMMARY

A new mechanism with the participation of π bonds is proposed to account for a relatively easy hydrogenolysis of carbon-fluorine bonds in catalytic hydrogenation of allylic, vinylic, benzylic and aromatic fluorides. This cyclic mechanism can also underlie some unusual results of hydrogenation of other halogen compounds.

Replacement of halogen by hydrogen in catalytic hydrogenation - catalytic hydrogenolysis of carbon-halogen bond - is very scarce in saturated halides [1-4] but occurs frequently in allylic, vinylic, benzylic and aromatic halides [2-8]. Bromine is replaced more readily than chlorine, and this in turn more readily than fluorine [5-8]. Hydrogenolysis of allylic chlorine precedes the saturation of the double bond [4]. Hydrogenolysis of vinylic bromine [9] or chlorine [10] can be accomplished without the hydrogenation of the double bond.

$$CH_3CBr = C(CH_3)CO_2C_2H_5 \xrightarrow[Et_3N, RT, 1\ atm]{H_2/Pd(BaSO_4)} \underset{71\%}{CH_3CH = C(CH_3)CO_2C_2H_5} \quad [9]$$

$$CClF = CF_2 \xrightarrow[130\text{-}135^\circ,\ 10\ sec]{H_2/5\%\ Pd(C)} \underset{85\%}{CHF = CF_2} + \underset{15\%}{CH_2FCHF_2} \quad [10]$$

Conspicuously easy hydrogenolysis in allylic and vinylic systems suggests that some cooperation of the double bond at the surface of a catalyst may be

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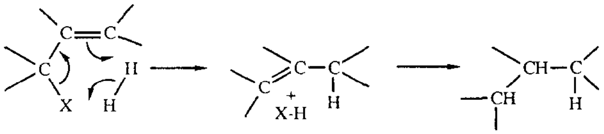
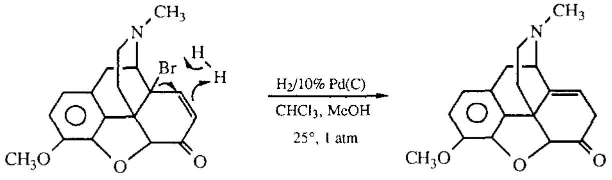
responsible for the ready replacement of halogens by hydrogen. Horner et al. [2] and Conroy [11] hinted at "a multicenter process" but did not elaborate on this idea any further.

A direct proof of a π bond participation according to the following scheme is not easy since the double bond is very readily hydrogenated. However, a few examples in support of such a mechanism can be quoted.



In the hydrogenation of 14-bromocodeinone, bromine was replaced, under very gentle conditions, by hydrogen with the simultaneous shift of the allylic double bond from α,β- to β,γ-position to the carbonyl [11]. Such a thermodynamically unfavorable shift can hardly be understood without assuming a six-center transition state in which the double bond participates.

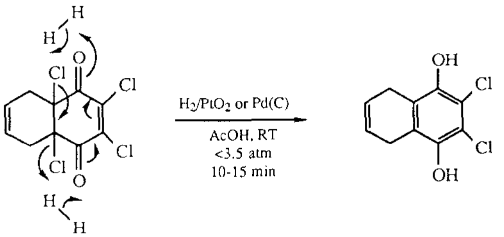


14-Bromocodeinone

Neopinone 81%

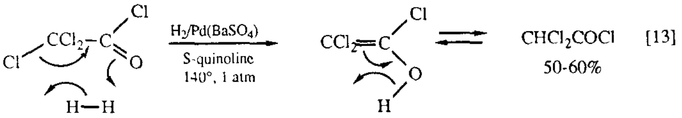
[11]

Similar participation of a π system can be visualized in a surprisingly easy hydrogenolysis of two bridgehead chlorine atoms in the adduct of chloranil and 1,3-butadiene [12].



[12]

Also an unexpected outcome of a Rosenmund reduction of trichloroacetyl chloride which gives, instead of chloral, dichloroacetyl chloride, can be best accounted for by a six-center transition state with the participation of the carbonyl bond [13].



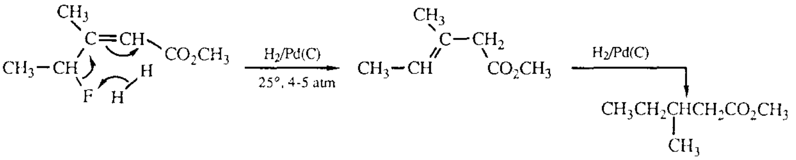
Catalytic hydrogenolysis of carbon-fluorine bond is much more difficult to accomplish than that of carbon and other halogens [5-8]. A list of replacements of fluorine by hydrogen in catalytic hydrogenations is not very long and covers only some two scores of compounds [14,15]. The vast majority of them contain allylic, benzylic, vinylic or aromatic fluorine. Only a very few examples of the catalytic hydrogenolysis of sp^3 carbon-fluorine bonds are known. In unsaturated fluorides, the hydrogenolysis of carbon-fluorine bond does not take place without the saturation of the double bond. This is a striking difference from the behavior of other halogen compounds.

A short glance at the thermochemistry of hydrogenation will clarify such a difference. While carbon-chlorine bond dissociation energy is 60-84 kcal/mol depending on the structure of the chlorine-containing compounds (60 for allylic, 68 for benzylic, 84 for vinylic, 86 for aromatic, and 79-84 for saturated chlorides), carbon-fluorine bond rupture requires 107-116 kcal/mol [16]. Because of this, in hydrogenations of chlorofluoro compounds chlorine is frequently replaced by hydrogen, while fluorine remains unaffected [10,17-24]. The bond dissociation energy of a π bond estimated at 75 kcal/mol [25] is not far from that of carbon-chlorine bond but much lower than that of carbon-fluorine bond. This explains why the replacement of fluorine by hydrogen in unsaturated fluorides is almost always accompanied by the saturation of the double bond.

Catalytic hydrogenolysis of sp^3 carbon-fluorine bond requires very drastic conditions [26,27]. Methyl and ethyl fluoride were converted to methane and ethane, respectively, over palladium on charcoal only in 10% yields at 240° and atmospheric pressure [27]. Propyl fluoride was completely hydrogenolyzed only at 190° [27]. Hydrogenolysis of isopropyl fluoride at 110° took place to the extent of only 5-10%, and was complete only at temperatures higher than 155° [27]. Reduction of methyl β-6-fluoro-6-deoxyglucoside to methyl β-glucoside required hydrogenation over Raney nickel at 100° and 120 atm [28].

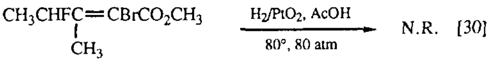
It comes, therefore, as a suprise that catalytic hydrogenolysis of allylic, vinylic, benzylic and aromatic fluorine atoms takes place at very mild conditions, frequently even at room temperature and atmospheric pressure [14,15,29-32]. Also fluorine bound to a cyclopropane ring was replaced by hydrogen relatively easily, but most probably only after the ring has been cleaved to give a fluorinated alkene [33]. Since all the above examples contain π bonds, it can be easily deduced that this bond plays an important role in the hydrogenolysis of carbon-fluorine bonds. In the following survey examples will be shown of putative mechanisms of catalytic carbon-fluorine hydrogenolyses.

Allylic fluorine is replaced by hydrogen fairly readily. Hydrogenation of methyl 4-fluoro-3-methyl-2-pentenoate gave always a mixture of two products, one resulting from the saturation of the double bond, and the other from both, saturation of the double bond and replacement of fluorine by hydrogen. The following mechanism accounts well for the hydrogenolysis [30].



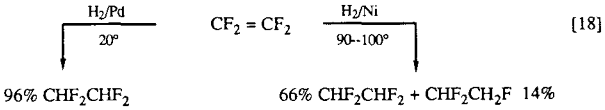
[30]

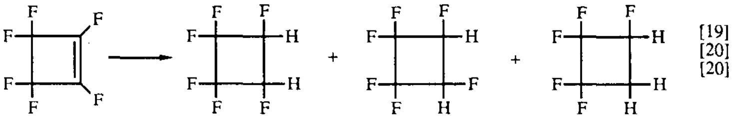
When the double bond is inaccessible, as in methyl 2-bromo-4-fluoro-3-methylpentenoate, no hydrogenation nor hydrogenolysis took place even under very energetic conditions [30].



$$CH_3CHFC(CH_3){=}CBrCO_2CH_3 \xrightarrow[80°,\ 80\ atm]{H_2/PtO_2,\ AcOH} N.R. \quad [30]$$

Replacement of **vinylic fluorine** by hydrogen occurs frequently during the hydrogenation of polyfluoroalkenes. Clear-cut addition of hydrogen is rare and occurs under gentle conditions [14,15,17-20,34]. Usually, both saturation of the double bond and hydrogenolysis of fluorine take place next to each other, affording mixtures of fluoroalkanes with the same or smaller numbers of fluorines [14,15,17-20].

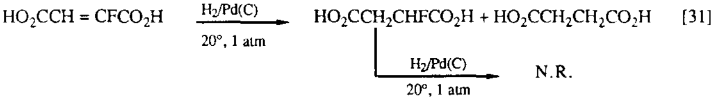




Pd/Al$_2$O$_3$, 60°, 1 atm	93%	7%		[19]
10% Pd/pumice, 45°	70%	4%	26%	[20]
10% Ni/pumice, 25°	66.8%	1.4%	21.5%	[20]

Conspicuously easy is hydrogenolysis of carbon-fluorine bond in some fluorinated unsaturated amino acids [29] and dicarboxylic acids [31,32] where fluorine is replaced by hydrogen under very mild conditions.

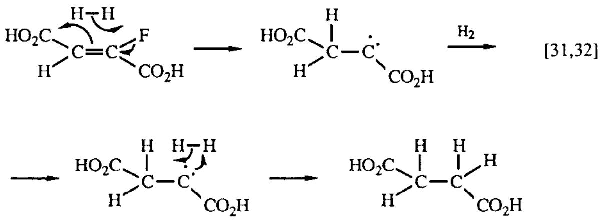
$$H_2NCH_2CH = CFCO_2H \xrightarrow[R.T.,\ 1\ atm]{H_2/PtO_2} H_2NCH_2CH_2CH_2CO_2H \quad [29]$$



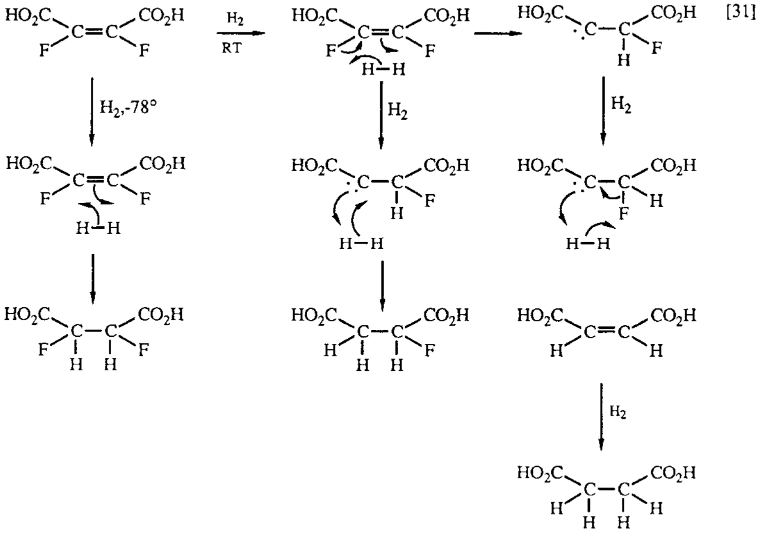
$$HO_2CCH = CFCO_2H \xrightarrow[20°,\ 1\ atm]{H_2/Pd(C)} HO_2CCH_2CHFCO_2H + HO_2CCH_2CH_2CO_2H \quad [31]$$

$$HO_2CCH_2CHFCO_2H \xrightarrow[20°,\ 1\ atm]{H_2/Pd(C)} N.R.$$

The proposed mechanism or conjugate hydrogenolysis will be illustrated on the hydrogenation of fluorofumaric and difluoromaleic acids [31,32]. Hydrogenation of fluorofumaric acid over palladium on activated charcoal at room temperture and atmospheric pressure gave fluorosuccinic and succinic acid in varying ratios [31]. Since fluorosuccinic acid does not suffer hydrogenolysis of fluorine under the same conditions [31], it must be assumed that succinic acid was formed directly from fluorofumaric acid by a mechanism involving the participation of the double bond:

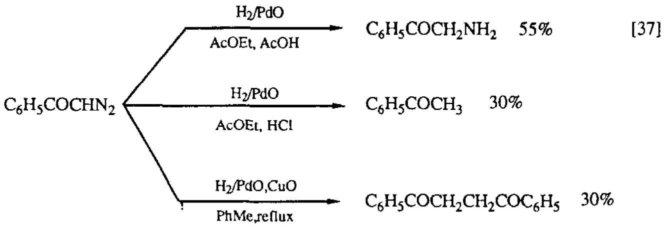

[31,32]

Elimination of hydrogen fluoride gives a carbene or a carbene-like intermediate which inserts into another molecule of hydrogen to form succinic acid. Similar sequence of reactions can be visualized in the hydrogenation of difluoromaleic acid which gives, in addition to a regular addition product, α,α'-difluorosuccinic acid, fluorosuccinic and succinic acid [31].


[31]

Experiments aimed at the support of the carbene mechanism by using mixtures of hydrogen and deuterium in catalytic hydrogenations of fluoro- and difluorobutenoic acids and their esters did not fulfill the expectations, as ^1H and ^1D spectra overlapped and did not give conclusive results [32].

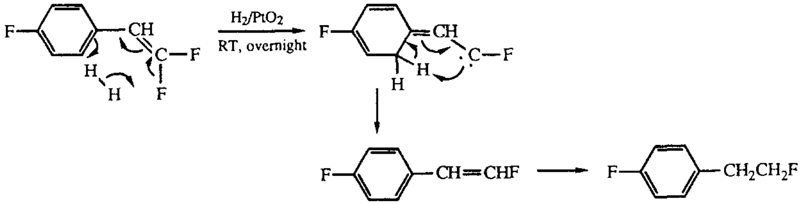
The carbenoid, the intermediate assumed in the two above examples, is not easy to intercept since it is very reactive and is expected to undergo fast hydrogenation prior to other reactions. Such a behavior of a carbene has been observed during catalytic hydrogenation of some diazo compounds [35-37]. The most extensive study by Birkofer [37] shows that, whereas hydrogenation over palladium or platinum oxide alone gave hydrazones or amines, hydrogenation over palladium oxide in the presence of hydrochloric acid or of cupric oxide took place with elimination of elemental nitrogen.



Both, hydrochloric acid and cupric oxide are known to catalyze decomposition of diazo ketones to carbenes or carbenoids $RCOCHN_2 \rightarrow RCOCH:$ (called "freie Radikale" at that time) [37]. The carbene can insert into the molecule of hydrogen to give a methyl ketone, or else dimerize to an α,β-unsaturated γ-diketone [38] which readily undergoes saturation of the double bond [39]. Depending on the stability of the carbene, different yields of methyl ketones and γ-diketones result from different diazo ketones [37].

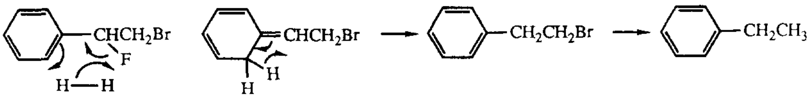
$$(CH_3)_2CHCOCHN_2 \xrightarrow[C_6H_6,\text{reflux}]{H_2/PdO,CuO} \underset{5\%}{(CH_3)_2CHCOCH_3} + \underset{90\%}{[(CH_3)_2CHCOCH_2]_2} \quad [37]$$

The carbene mechanism can be also operating in the hydrogenolysis of carbon-fluorine bond in *p*,β,β-trifluorostyrene [40]. Here not only the double bond but also the aromatic ring may participate:



[40]

Participation of the π system of the aromatic ring accounts for easy hydrogenolysis of **benzylic fluorine** [41-44].



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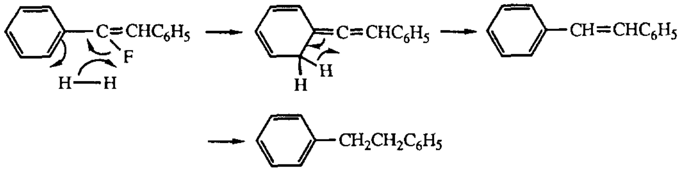

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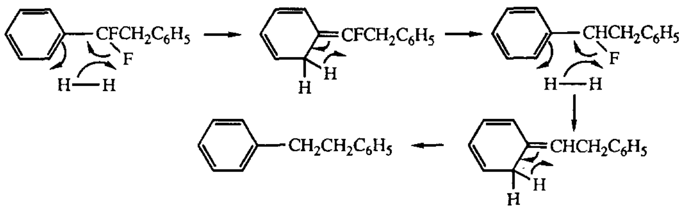
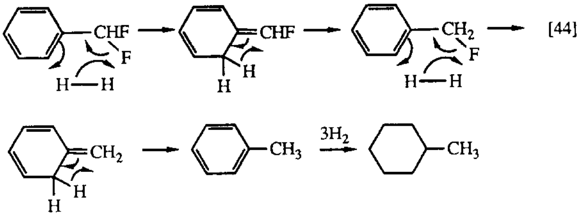
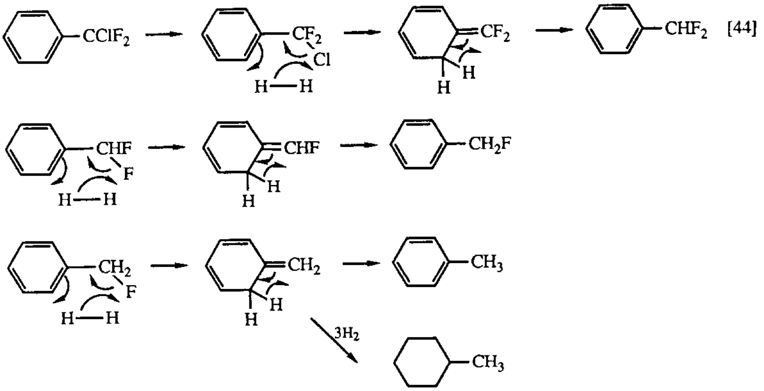


[43]

The participation of the π bond in the benzene ring may facilitate the concomitant complete hydrogenation of the benzene ring in the case of benzylidene fluoride [44] which gives, in addition to toluene, a small amount

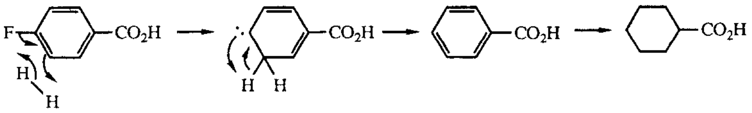


of methylcyclohexane, and in the case of α-chloro-α,α-difluorotoluene which gives benzylidene fluoride, toluene and methylcyclohexane [44].

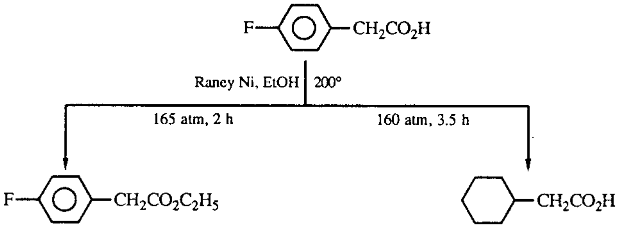


On the other hand, benzotrifluoride was hydrogenated to trifluoromethylcyclohexane without the loss of fluorine [44].

Hydrogenolysis also occurs when the **fluorine is linked to the aromatic ring** [44-48]. *p*-Fluorobenzoic acid gave benzoic and ultimately cyclohexanecarboxylic acid in hydrogenation over platinum black [44], *p*-fluorophenylacetic acid gave ethyl cyclohexylphenylacetate in hydrogenation over Raney nickel in ethanol, at 180-200° and 160-180 atm [48], and *p*-fluoroacetophenone afforded ultimately 1-phenylethanol on heating with Raney alloys, hydrogen adsorbed at the surface of Raney nickel or Raney copper being probably responsible for the hydrogenolysis [45].



[44]



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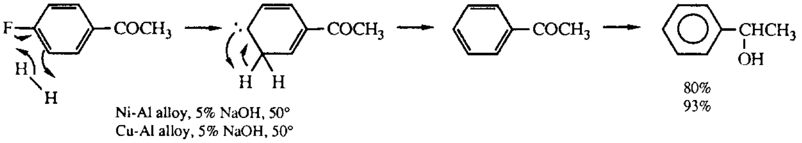
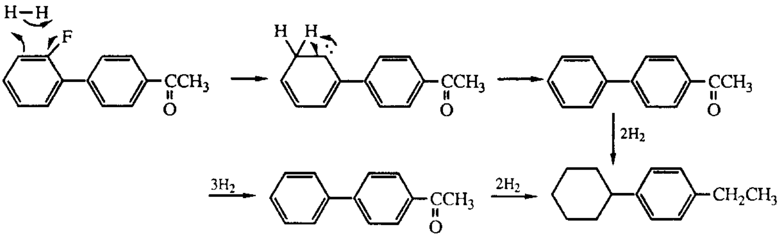


[45]

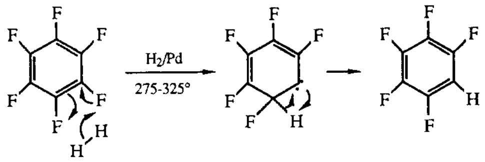
In the case of 2-fluoro-4'-acetylbiphenyl, only the ring containing fluorine was saturated after hydrogenolysis of fluorine. This result points to the participation of the benzene ring in the hydrogenolysis of carbon-fluorine bond [47].



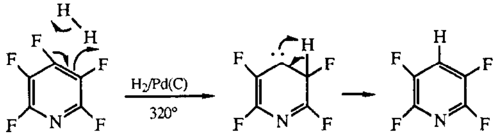
[47]

Similar replacement of single aromatic fluorine atoms was also achieved by catalytic hydrogenation of fluoronitroaromatics [49], o-fluorobenzenephosphonic acid [50], and of 5-fluorouracil [51].

Even fluorine in poly- and perfluoroaromatics is replaced by hydrogen, although usually only at high temperatures (280-320°C) [52-54].



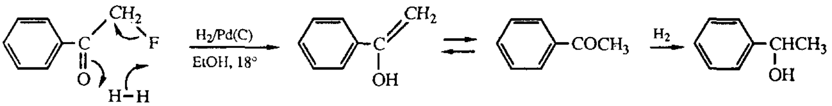
40-60% [52]



30% [54]

On the other hand, perfluorotoluene suffered hydrogenolysis of carbon-fluorine bond only partly, and at very energetic conditions (450°, 100 atm) [55].

The cyclic mechanism also explains the relatively easy hydrogenolysis of fluorine in **α-fluoroketones** [56,57] and **α-fluoronitro compounds** [58]. In these cases, the π bonds between carbon and oxygen and between nitrogen and oxygen, respectively, participate in the mechanism.



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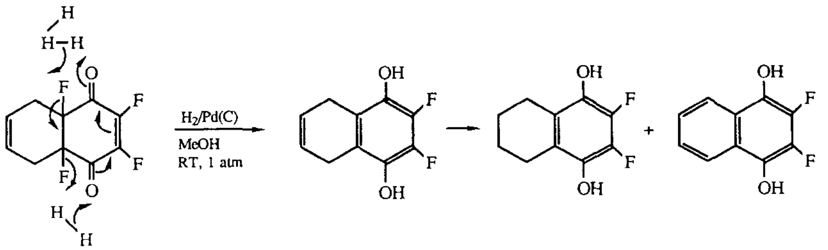

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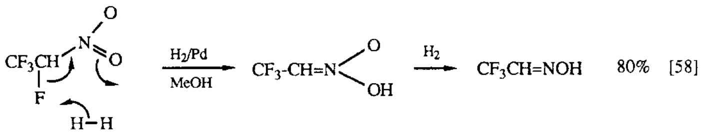
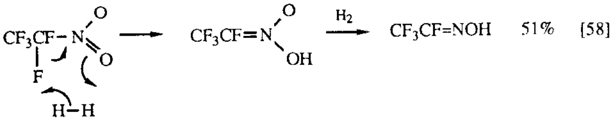
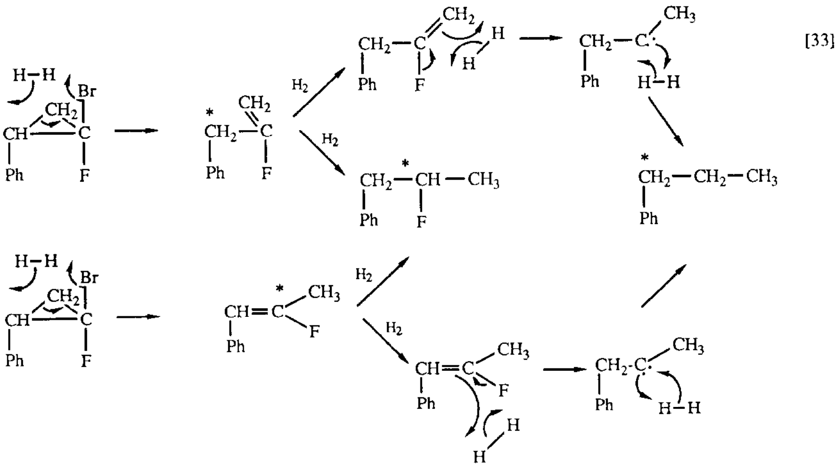




Finally, an interesting case of replacement of fluorine during the hydrogenation of two isomeric 2-bromo-2-fluoro-1-phenylcyclopropanes can be explained using cyclic transitions states between the molecules of hydrogen and the intermediate 2-fluoro-1-phenylpropene and 2-fluoro-3-phenylpropene, formed by hydrogenolytic opening of the cyclopropane ring [33].



All four asterisked products were isolated. The hydrogenation took place over palladium oxide in methanol, at much lower temperatures than those necessary for hydrogenolysis of a non-substituted cyclopropane ring.

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