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An Overview of the Synthesis of Hexafluoroisopropanol and Its Key Intermediates

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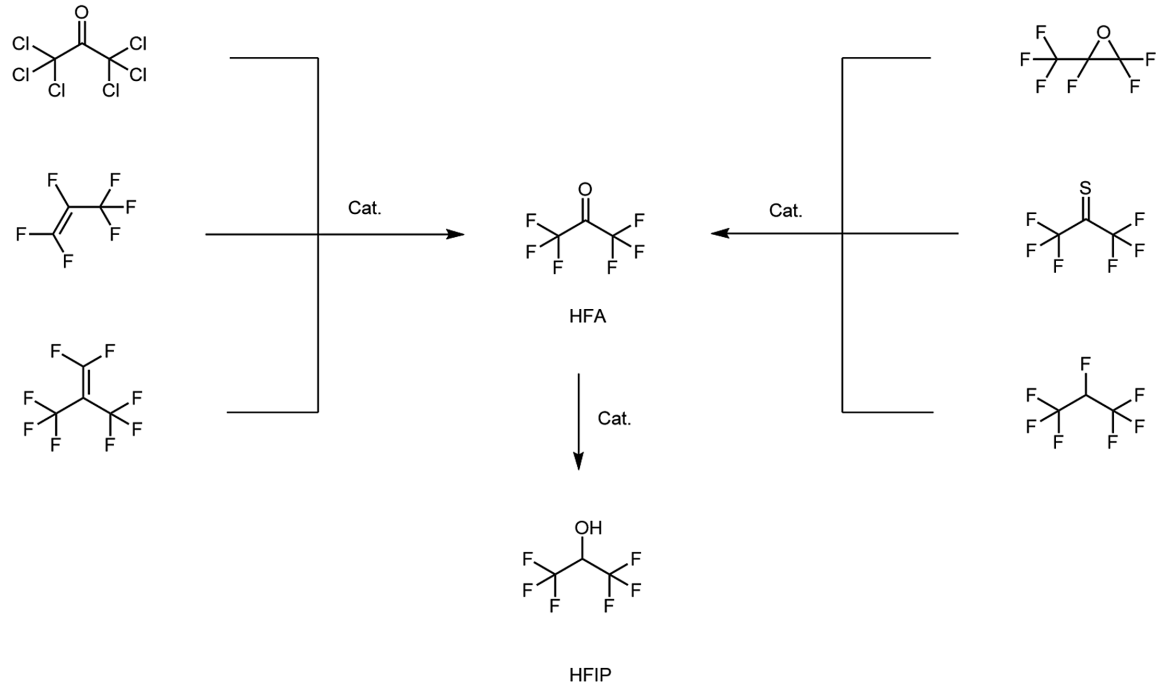

Abstract

Hexafluoroisopropanol (HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol) is a fluorine-containing alcohol, which can be used in the preparation of fluorine-containing fine chemical, pharmaceutical, and pesticide ingredient. It is a widely used solvent in organic reactions that is miscible with water and many organic reagents. Hexafluoroacetone (HFA) is a key intermediate in the synthesis of HFIP. In this work, six methods for synthesizing HFA are discussed based on the different raw materials used. In addition, three methods of synthesizing HFIP, and the applications of HFIP are also reviewed.

Keywords
- hexafluoroisopropanol
- hexafluoroacetone
- synthetic route

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Introduction

Hexafluoroisopropanol (HFIP) can be used to prepare a wide range of chemicals such as fluorinated surfactants, fluorinated emulsifiers, fluorinated pharmaceuticals, etc.[1] The presence of two tri-fluoroalkyl groups in HFIP is thought to significantly alter the course of chemical reactions and plays a huge role in traditional organic synthesis,[2] electrocatalysis,[3] photocatalysis,[4] biological research,[5] and even environmental science.[6] HFIP is also a very popular solvent and additive for the activation of hydrogen peroxide,[7] organic functionality,[8] hypervalent iodine reagents,[9] metal-free C–H,[10] etc., due to its strong polarity, recyclability, hydrogen bond donor nature, as well as its low nucleophilicity, high acidity, cationic stabilizing ability, easy intermiscibility with water and many organic reagents,[11,12] heat resistance, and allowance for the passage of ultraviolet (UV) light. The solvent together with trifluoroethanol provides an excellent reaction system for many of the classical organic transformations and can be used to achieve catalyst-free systems.[13] HFIP is mainly synthesized from hexafluoroacetone (HFA) or its hydrates and prepared by liquid-phase or gas-phase methods. HFA is an efficient site-selective reagent in organic synthesis first prepared by Fukuhara and Bigelow using direct fluorination of acetone, and subsequently by Henne, Shepherd, and Young by oxidizing chlorofluoroolefin $(CF_3)_2C=CC1_2$.[14–17] The preparation methods of HFA mainly include hexachloroacetone gas-phase exchange (►**Fig. 1i**), catalytic oxidation of hexafluoropropylene (►**Fig. 1ii**), oxidation of octafluoroisobutene (►**Fig. 1iii**), catalytic isomerization of hexafluoropropylene oxide (►**Fig. 1iv**), dipolythiohexafluoroacetone-catalyzed oxidation (►**Fig. 1v**) and oxidation of 2-hydroheptafluoropropane (►**Fig. 1vi**), and the research progress of which has been discussed in this work.

HFIP is obtained from HFA by catalytic hydrogenation reduction via gas-phase and liquid-phase methods. The gas-phase method generally adopts a fixed-bed reactor, in which hydrogen and HFA gas pass through the catalyst bed and react within a few seconds of contact. The advantages of this method include high conversion and selectivity, a short reaction time, a low-pressure requirement, the ability to react at an atmospheric pressure, and continuous operation. However, it needs to pass excessive hydrogen, the reaction temperature is relatively high, and it is easy to have side reactions. The liquid-phase method employs noble metals such as Pd and Pt or their oxides as catalysts, and the reaction is performed with hydrogen to produce HFIP. The reaction temperature is low, the reaction is easy for operation and product purification, but the reaction pressure is high, making it difficult to achieve continuous operation. In this article, the research progress in the preparation of HFA and HFIP is highlighted.

Research Progress on the Preparation of HFA

Fluorination of Hexachloroacetone

Hexachloroacetone fluorination is based on Cr-, Ni-, and Al-based catalysts, usually using HF as the fluorine source for the fluorination of the catalyst. In 1972, Ramanadin prepared chromium oxide and nickel oxide catalysts from one or more organochromium and nickel salts prepared by thermal decomposition under vacuum or in an inert gas atmosphere followed by fluorination with anhydrous HF at 100 to 500°C for 1 to 12 hours.[18] This method has a high catalyst fluorination rate of over 90% and a high catalyst lifetime, with a 2.2% reduction in catalyst activity for 1,000 hours of reaction at 290°C. In 1976, Knaak used hexagonal-CrOOH as the catalyst, it is mainly prepared from γ-CrOOH, and the inert carrier used is calcium fluoride, which can prolong the catalyst life of 750 hours at a reaction temperature of 375°C.[19] The catalyst needs to be preactivated by heating in an inert gas environment before use, and after the activation is completed, the reaction is performed at a low temperature. In 1982, Foulletier used a sol-gel method to prepare chromium oxide microspheres as the catalyst and heated the microspheres at 200 to 500°C to increase their activity, with the reaction temperature at 300°C.[20] The yield of HFA was 75%. The catalyst is not easily crystallized and is suitable in fluidized bed reactors at this reaction temperature. Foulletier's method of preparing this catalyst significantly reduces losses due to particle size screening of the catalyst. In 2020, Zhao et al

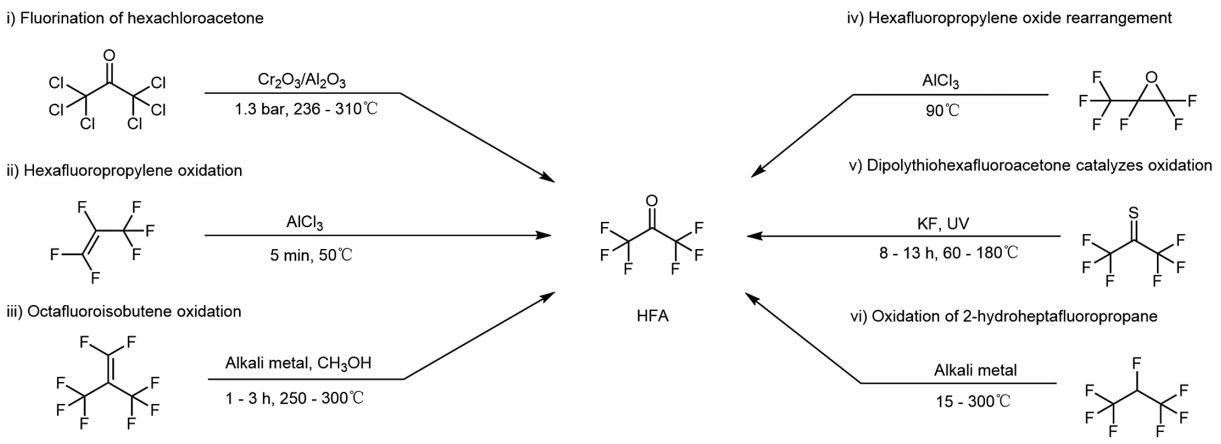

Fig. 1 HFA preparation methods. HFA, hexafluoroacetone.

improved the reactor by using a three-layer reactor (3.56 cm inner diameter and 1.5 m length),[21] with each layer filled with an appropriate amount of chromium oxide and aluminum oxide. The reaction was performed at temperatures of 236°C, 265°C, and 310°C and a pressure of 1.3 bar, giving a 96.8% yield of HFA. HFA was prepared from impurities (hexachloroacetone and hydrogen fluoride). The advantages of this device are that it saves production costs, requires little effort in purification process, and can be used to prepare HFIP, but it is more complicated to use.

This process is an early method for industrial production of HFA. The disadvantages of this process are that the reaction temperature is high, the by-products are easily produced due to the incomplete exchange of fluorine and chlorine, and the products contain HCl, HF, and various congeners that are not completely replaced, which increases the difficulty of the subsequent separation process, and the boiling point of HFA is very high, which makes it not easy to be gasified.

Hexafluoropropylene Oxidation Method

The oxidation of hexafluoropropylene is based on the availability of raw materials and mild reaction conditions, often using aluminum oxide, iron oxide, or rare metals as catalysts and oxygen as oxidizing agents. In 1977, Tozuka and Ohsaka used fluorinated alumina as a catalyst to prepare HFA at atmospheric pressure, while the stability of the catalyst and the selectivity of the product could be improved when an appropriate amount of water was present in the system and the yield could be increased by increasing the pressure appropriately, achieving 71.6% yield of the target product.[22] Subsequently, Igumnov et al[23,24] and Kurosaki and Okazaki[25] loaded fluorine compounds of metals on activated carbon as catalysts and used SF_4, SF_6, and HF as fluorination reagents, at a reaction temperature of 130 to 170°C, and reassuringly, the selectivity of more than 96% was achieved, but the conversion is not high, only 55%, with highly toxic fluorinated reagent being used. Wang et al improved this method by using one or both of $AlCl_3$, $CrCl_3$, AgI, KF, AlF_3,, or Cr_2O_3 as catalysts and reacting in a circulating circuit reactor with 1 to 5 minutes of reaction time.[26] HFA yields and selectivities were greater than 95%, yet, catalyst preparation is complicated.

The difficulties of this method are the preparation of suitable catalysts and the separation of the by-products, hexafluoropropylene, and HFA, which have similar boiling points and are difficult to separate, thus affecting the downstream process. If a suitable catalyst system is developed to reduce the generation of by-products, this method would be the most desirable industrialized process for the production of HFA.

Octafluoroisobutene Oxidation Method

Oxidation of octafluoroisobutene was one of the early methods for the preparation of HFA. Perfluoropropene and elemental sulfur can be used to prepare HFA in the presence of KF, but its toxicity limits its use in industry. To reduce its toxicity, in 2009, Ying et al dissolved octafluoroisobutene in alcohol and reacted it with tertiary amines to prepare tetraalkylammonium salts of hexafluoroisobutene alcohol, then mixed alkali metal or alkaline earth metal nitrites with tetraalkylammonium salts of hexafluoroisobutene alcohol to prepare HFA oxime, and finally reacted it with inorganic acids to produce HFA.[27] The present synthetic route involves oxidation of nitrogen oxides and acid digestion of oximes; it also involves the purification of oximes. The complexity of the process, especially the danger of oxidation of nitrogen oxides and the corrosion protection of the equipment by the high-temperature acid digestion reaction, results in a high investment and operating costs of the equipment. Heptafluoroisobutylene methyl ether can be obtained by treating octafluoroisobutylene methanol absorbent, and HFA can be prepared from heptafluoroisobutylene methyl ether by oxidizing it with hydrogen peroxide under UV light.[28] This route is simple in terms of raw materials and methods, but the main equipment is an expensive high-power UV generator and a special reactor capable of transmitting UV light, and it needs to be resistant to hydrofluoric acid corrosion, so the investment in equipment and research costs are very high. The ozone oxidation method is relatively simple in terms of raw materials and process, requiring only one step of oxidation and the tail gas (containing gaseous HFA) is water absorption, but the yield is not high.[29] In 2013, He et al improved the catalyst by using alkali metals or their oxides after fluorination with HF as catalysts, resulting in a conversion of more than 98%.[30] The method is complex, with low yields and high toxicity, and has not been applied on a large scale in industry.

Hexafluoropropylene Oxide Rearrangement Method

Hexafluoropropylene oxide is rearranged in the presence of a catalyst to give HFA, the catalyst used is generally a Lewis acid catalyst, and the reaction is generally performed in a fixed bed. In 1965, both Morin and Squire used SbF_5 as a catalyst, which requires high corrosion resistance of the carrier, as well as harsher and more toxic reaction conditions.[31,32] In 1995, Petrov and Smart used aluminum chlorofluoride Lewis acid catalysts, thereby reducing the temperature and pressure required for the reaction.[33] In 2003, Ohtsuka and Yamamoto used titanium oxide and fluorinated titanium oxide as catalysts to produce high-purity HFA, and the prepared hydrates were almost acid-free.[34] Since the isomerization reaction is exothermic, the temperature of the catalyst bed will continue to rise as the reaction proceeds, thus accelerating the deactivation of the catalyst. To solve this problem, Xu et al[35] and Jiang et al[36] explore the catalyst by mixing Cr_2O_3, $A1F_3$, TiO_2, and graphite powder in a certain ratio, enabling the reaction performed at atmospheric pressure with a selectivity of more than 90%. The method improved the stability and thermal conductivity of the catalyst without the generation of acyl fluoride byproducts, but the catalyst composition is complex and the preparation process is tedious. In 2020, Chen et al developed a simpler catalyst, a fluorinated ZSM-5 molecular sieve with a silica-to-aluminum ratio of 50.[37] In the same year, He and Pei provide a sample method to prepare

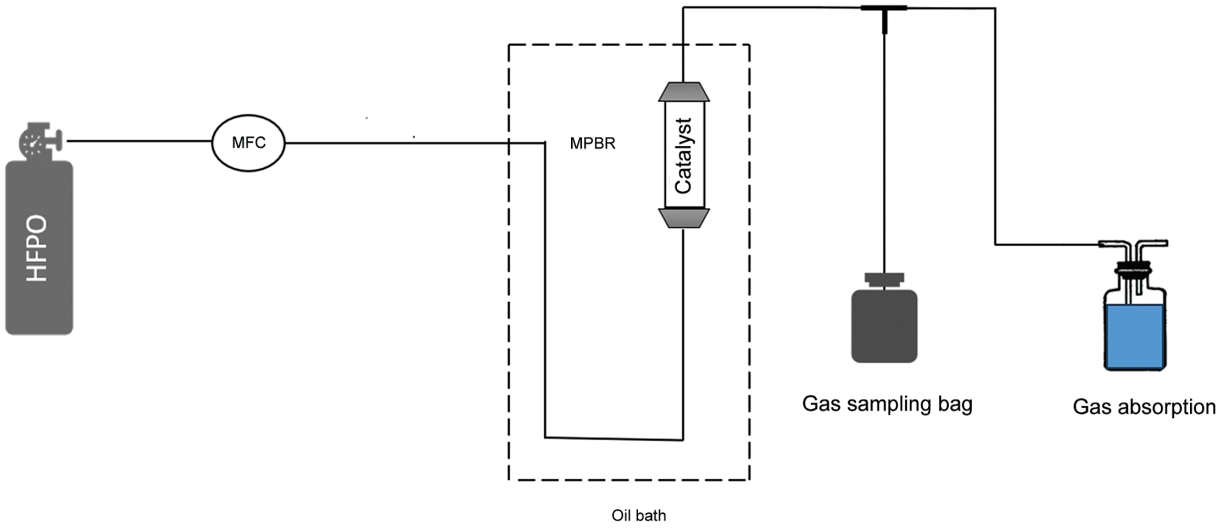

Fig. 2 Hexafluoropropylene oxide continuous flow synthesis system.

substituted phenols loaded onto Merrifield resins, which are used as catalysts to achieve 95% yields of target product under mild conditions.[38] However, the preparation of HFA by the method involves a liquid-phase reaction, which needs to be purified by distillation fraction, and is complicated to operate. In 2022, Li et al used a three-stage reactor filled with a catalyst, a Cr-based composite metal oxide, at each of the three positions,[39] thereby enabling the catalytic reaction to be operated stably at low temperatures (20–40°C) and improving the conversion and selectivity of the reaction, but with a more complex reaction unit.

In recent years, continuous flow synthesis has become increasingly popular in chemical synthesis,[40–42] offering a safer reaction process, more accurate control of reaction parameters, and the ability to effectively suppress side reactions.[43–45] In 2023, Qi et al used $AlCl_3$ as a catalyst and filled the catalyst in a micro-packed-bed reactor with a continuous flow reactor (►**Fig. 2**).[46] At the same time, they used a global multi-objective optimization machine learning model to quickly find the optimal response conditions, finding a compromise between high conversion rates and low energy costs within an acceptable number of experiments. Under reaction conditions of 25.1°C, atmospheric pressure, and a gas hour space velocity (hourly airspeed of gas) of 931.5 h^{-1}, the conversion was 98.6%, the selectivity was 99.9%, and the energy cost was 0.121 kWh/kg. It increases the yield, and the reaction can be performed at room temperature. This method allows the use of mixed metal oxides as catalysts, with more options and long catalyst life, high yields, and mild reaction conditions, but its feedstock costs are higher.

Dipolythiohexafluoroacetone Catalyzes the Oxidation

The reaction is mainly performed in nonprotonic solvents, commonly used are dimethyl sulfoxide and dimethyl formamide, etc. The catalyst used is a mixture of halogenated alkali metal salts and oxidants. The oxidizing agent can be either a metal oxidant or a gas.[47,48] Gaseous oxidants are generally chosen as oxygen due to their low cost.[49] Alkali metal salts such as KF, NaF, etc. are used. Metal oxidants are used for mild reaction conditions and high yields of target products, but they have a high water content of the reactants, which generally does not exceed 0.05%. In 2012, Peng et al found that the introduction of UVG into the reaction system could effectively reduce the side reactions.[49] The yield of HFA reached 89.8%, but the reaction time is longer, it takes more than 8 hours, and the side reaction will be increased if the temperature is increased to speed up the reaction rate.

The advantages of method are the simple process, the use of conventional equipment, easy operation, cheap and easy-to-obtain raw materials, as well as high yield of the product. However, there are also disadvantages including producing a large amount of solid waste, which is difficult to recycle and causes environmental pollution, and inadvertently raising the production cost.

Oxidation of 2-Hydroheptafluoropropane

In this method, fluorinated alkali metals are loaded onto activated carbon as a catalyst. In 2000, Igumnov et al disclosed a method for the preparation of HFA[50]: 2-hydroheptafluoropropane and oxygen are reacted at 15 to 300°C, using alkali metal fluorides and activated carbon as catalysts. The content of alkali metal was approximately 60% and the yield of HFA was 77 to 83%. The reaction is simple, and the catalyst is cheap and readily available.

Other

In 1991, Clark and Lagow mixed acetone and sodium fluoride powder and dispersed the raw material mixture evenly on copper chips in the reactor cavity, cooled the reactor to −50°C, filled it with helium and left it overnight, then continued cooling to −100°C, passed HF for fluorination to produce the product.[51] In 1997, Thenappan prepared HFA from 1,1,1,3,3,3-hexafluoropropane by reacting it with fluorine gas in a fluid bed reactor filled with alumina in the 180 to 220 mesh size range.[52] The reaction temperature was between

50 and 300°C and the reaction time was 2 to 100 seconds. In 2013, Zhang prepared HFA from 1,1,3,3-tetrafluoro-1,3-dichloroacetone gas by reaction with HFA gas in a complex salt of chromium salt and LaF_3 as a catalyst.[53] However, the reaction temperature is high (230–380°C), which requires the use of a distillation column to separate the products. In 2020, Zhang put trifluoroacetic anhydride, metal fluoride, and tetrahydrofuran into the reactor. The reaction was conducted at 20 to 50°C for 1 to 3 hours to obtain trifluoroacetyl fluoride, then added alkaline salt and trifluoroacetate and raised the temperature to 70 to 120°C for 2 to 10 hours, and the coupling reaction between trifluoroacetate and trifluoroacetyl fluoride generated HFA with a yield above 95%.[54] In 2022, Wang et al prepared HFA by reacting trifluoromethyl magnesium chloride Grignard reagent with trifluoro acetonitrile in ether solvent with one or more of potassium fluoride, sodium fluoride, and cesium fluoride; the reaction temperature was −30 to 0°C and the reaction time was 3 to 6 hours.[55] The reaction was performed at −30 to 0°C and magnesium trifluoromethyl chloride at a concentration of 1.0 to 0.3 mol/L was added dropwise, the reaction was performed at 70 to 20°C for 2 to 12 hours, the product was collected, and purification gave 92% or more yield of the product.

In summary, the rearrangement method has become the most commonly used method for HFA preparation in industry due to its advantages such as long catalyst life and simple operation, etc.

Synthesis of HFIP

Vapor Phase Method

The gas-phase method generally uses a fixed bed reactor where hydrogen and HFA gas pass through the catalyst bed and allow for reaction in a few seconds of contact. In 1963, Hollander and Woolf chose copper and chromium oxides as catalysts to obtain HFIP with approximately 40% yield,[56] the ratio of copper to chromium metal by mass was between 1:1 and 5:1, the reaction temperature was 250 to 375°C, and the reaction time was 14 seconds. In 1970, Swamer improved the yield by using Pd/Al_2O_3 as the catalyst and the reaction temperature was 120 to 160°C.[57] The product in the condenser was collected after 4 hours of continuous reaction to give a 100% yield of HFIP. When the same process was used but the reaction temperature was lowered to 100 to 140°C, the yield was 98%. In 1981 Kawai et al used nickel as the catalyst and diatomaceous earth and high-quality gypsum as the catalyst carrier, setting the reaction temperature at 70°C and the contact time of 4 seconds.[58] The feedstock ratio was HFA:hydrogen = 1:3, the feedstock conversion was 97.5%, and the product selectivity was 100%, but the catalyst cannot be recycled. In 2020, Chen et al instead used a completely new catalyst, the hydrogen storage material $LaNi_5$ or $La_{0.67}Mg_{0.33}Ni_{3.0}$, and the metal borides Co-B, Ni-B, or Pd-B alloys.[59] The reaction condition was: a reaction temperature of 150 to 350°C, a reaction time of 1 to 3 hours, and hydrogen to HFA molar ratios of 3 to 20:1, achieving a conversion of over 96% and selectivities of over 99%. The advantages of this method are that the required pressure is low, it can be reached at atmospheric pressure, and it can be operated continuously with a short reaction time. However, it is necessary to introduce excessive hydrogen, the reaction temperature is high, and side reactions are likely to occur.

Liquid-Phase Method

Liquid-phase catalytic hydrogenation is generally performed in an autoclave, using raw materials such as hydrates of HFA and generally using precious metals such as Pd, Pt, or their oxides as catalysts (►**Fig. 3**). In 2012, Liu and Xie used large-particle metal catalysts such as Pd, Pt, and Rh, and the reaction took place in an autoclave at a reaction pressure of 1 to 5 bar with a yield of 45.5% of the target product and a conversion of 97.5%.[60] In 1971, Lee found that the reaction temperature could be reduced when a small amount of HFIP was present in the reaction system.[61] In 2017, Morino et al distilled HFA to make HCFC-123 content (less than 120 ppm) and added acid acceptors (bases) to the reaction system to increase the reaction conversion.[62] In 1985, Katsuhara and Nakamichi added 0.1 to 0.5% aluminum hydroxide to HFA hydrate to inhibit the formation of fluoride ions and thus improve the life of the catalyst.[63] In 2023, Su's group prepared HFIP by continuous flow hydrogenation of $HFA•3H_2O$ in a micropacked-bed reactor using Pd/C as the catalyst (►**Fig. 4**),[64] with operating conditions of temperature between 363 and 393 K, hydrogen pressure of 10 bar, and catalyst loading of 0.1 to 0.5 g. Both the selectivity and conversion were more than 99%, and a space–time yield was approximately nine times that of the batch reactor.

The liquid-phase method uses precious metals such as Pd and Pt or their oxides as catalysts and reacts with hydrogen to obtain HFIP, the reaction temperature is low, the operation is simple, and the product is easy to purify, but the reaction pressure is high and is difficult to achieve a continuous operation.

MPV Method

The Meerwein–Ponndorf–Verley (MPV) reaction can be used to prepare HFIP (►**Fig. 5**).[65,66] The reaction is suitable for preparing the corresponding alcohols by reducing carbonyl groups containing unsaturated double bonds and benzene rings. It has good selectivity and can avoid the by-products caused by the catalytic reduction method. However, the conversion rate of this method is not high.

In 2003, Lermontov et al found that HFA was readily reduced to HFIP by secondary alcohols at high temperatures without any catalyst, and the molar ratio of HFA to secondary alcohols was 1:10. The reaction was performed at 240°C in an autoclave, achieving 96% yield of HFIP.[67]

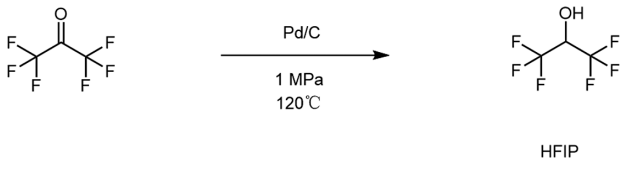

Fig. 3 HFIP synthesis. HFIP, hexafluoroisopropanol.

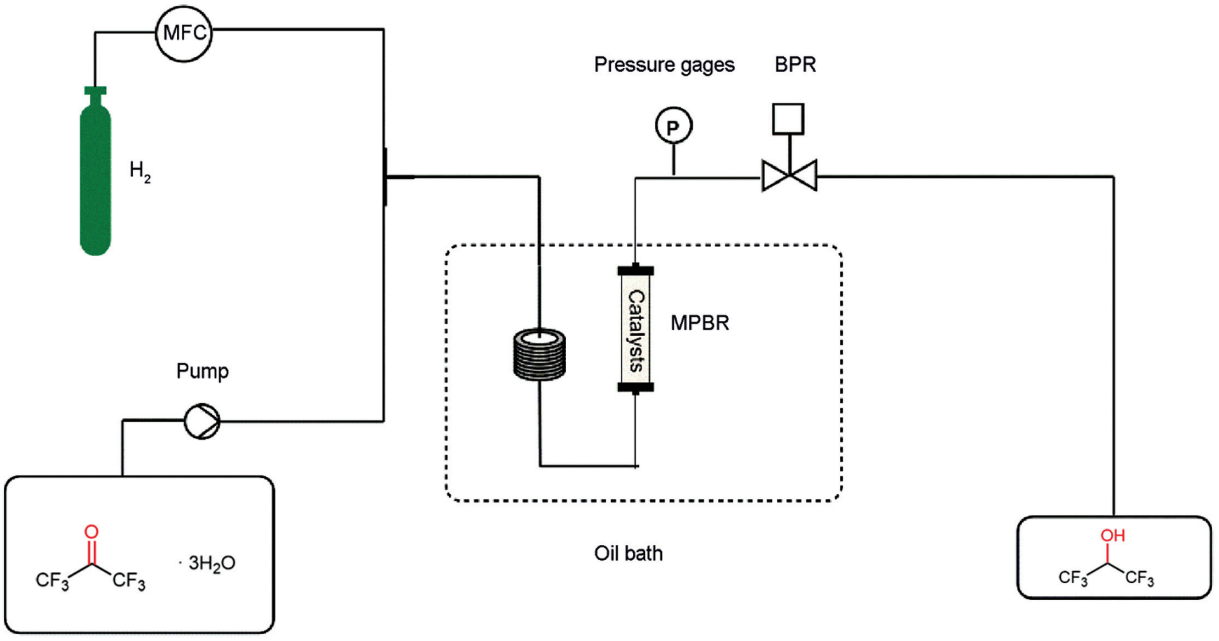

Fig. 4 Schematic overview of the flow system for hydrogenation based on the micro packed bed reaction.

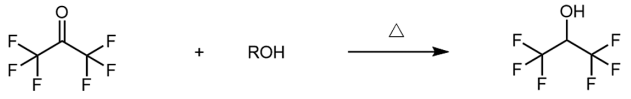

Fig. 5 MPV method. MPV, Meerwein–Ponndorf–Verley.

Of the three methods mentioned above for the synthesis of HFIP, the liquid-phase method is the most commonly used because the gas-phase method requires the use of more toxic HFA gas, and the MPV method is suitable for the preparation of small quantities in the laboratory, which is not suitable for industrial production.

Applications of HFIP

HFIP can be used in the preparation of anesthetics, refrigerants, and other fluorinated fine chemicals. Matsukawa et al prepared hydrofluoric ethers using Pd^0 as a catalyst and HFIP as a raw material.[68] Borrero et al use a one-pot method to prepare the lithium salt of fluoroalkyl trifluoroborate by the reaction of HFIP and anhydrous lithium hydroxide.[69] Kudzma et al used HFIP as a raw material for the multistep synthesis of sevoflurane.[70] HFIP can be served as a good solvent with high polarity and thermal stability. It can dissolve amino acids, and is also popular in the synthesis of insecticides, fungicides, and surfactants.

Conclusion

The synthesis of HFA by gas-phase exchange and oxidation methods suffers from harsh reaction conditions, complicated catalyst preparation, and many side reactions, while catalytic isomerization is considered an ideal method for the industrial preparation of HFA due to its mild reaction conditions and high yield.

The main methods for the synthesis of HFIP from HFA are liquid-phase, gas-phase, and MPV methods. The MPV method has a low conversion rate and is suitable for the preparation of small amounts of HFIP in the laboratory. The liquid phase method is optimized for low toxicity and low reaction temperatures, but it is more difficult to achieve continuous operation and has higher reaction pressures. The gas-phase method can operate continuously and has higher conversion and selectivity but has the disadvantage that it requires excess hydrogen and the contact area between feedstock and catalyst is difficult to control. Also, when using a micro packed-bed reactor flow system compared with a conventional intermittent reactor, the contact between feedstock and catalyst is more adequate, achieving higher throughput per unit time and unit volume. HFIP is an important fluorinated fine chemical, and in this work, we discussed the progress of its synthesis method, which may inspire the development of the related research fields in organic synthesis.

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Conflict of Interest
None declared.

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