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A novel vapor-phase catalytic synthetic approach for industrial production of 1,1,1,3,3,3-hexafluoroisopropyl methylether

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Graphical Abstract



Highlights

- A novel synthetic method based on vapor-phase catalytic methylation was presented
- Environmental friendly 1,1,1,3,3,3-hexafluoroisopropylmethyl ether was synthesized

- The synthetic process is continuous and pollution-free
- The reaction is catalyzed by alkaline earth metal fluorides, with MgF2 most active
- A mechanism for the catalytic methylation was proposed

ABSTRACT. 1,1,1,3,3,3-Hexafluoroisopropylmethyl ether (**HFE-356mmz**) is an important substitute for chlorofluorocarbons and hydrochlorofluorocarbons due to its zero ozone depletion potential and low global warming potential. However, mass production of **HFE-356mmz** remains a long-standing challenge. Herein, we applied metal fluorides as catalysts in the methylation of 1,1,1,3,3,3-hexafluoroisopropanol to produce **HFE-356mmz** for the first time. The catalyst not only improves the synthetic efficiency, but also makes the reaction solvent-free. The pollution-free, recyclable, and continuous synthetic process enables industrial production of **HFE-356mmz**. To optimize the synthetic efficiency, a series of metal fluorides (AlF₃, MgF₂, CaF₂, SrF₂, and BaF₂) was used, among which MgF₂ exhibited the highest activity. Through careful examination of each metal fluoride, it was found that the activity of the catalyst was determined by co-operative action of the surface acid–base properties and the total amount of surface acid sites. Based on these results, a rational mechanism for the vapor-phase methylation was proposed.

KEYWORDS: 1,1,1,3,3,3-hexafluoroisopropylmethyl ether, vapor-phase catalytic methylation, metal fluoride, Lewis acidity, Lewis basicity.

1. Introduction

Owing to the implementation of the Montreal Protocol, the chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), which show high ozone depletion potentials (ODP) and high global warming potentials (GWP), were banned from using [1]. Thereafter, hydrofluoroethers

(HFEs) were considered as potential substitutes for CFCs and HCFCs due to their zero ODP and relatively short atmospheric lifetimes [2-4]. Among the various HFEs, 1,1,1,3,3,3-hexafluoroisopropylmethyl ether (**HFE-356mmz**) has attracted particular attention because it exhibits an ODP of zero, an atmospheric lifetime of 62 days, a GWP₁₀₀ value of 6, weak flammability, high chemical stability, and low toxicity [3-6]. These advantageous properties enable huge application potentials of **HFE-356mmz** in coolants, solvents, cleaners, and the like. As a result, mass production of **HFE-356mmz** with excellent synthetic efficiency is highly desired.

Up to now, a number of synthetic strategies for **HFE-356mmz** from different starting materials have been reported (Scheme 1). One of the most popular methods is the liquid-phase *O*methylation of 1,1,1,3,3,3-hexafluoroisopropanol (**HFiP**) using (CH₃)₂SO₄ [7], dimethyl carbonate (**DMC**) [8], or CH₃X (X = Cl, Br, I) [9] as the methylating reagent. However, (CH₃)₂SO₄ is highly toxic and the reaction using **DMC** needs to be carried out in an autoclave under a harsh condition. In addition, strong bases are required as catalysts in all these reactions, leading to cumbersome post-processing problems. All the other methods employ high-cost starting materials such as 1,1,3,3,3-pentafluoro-2-meth-oxyprop-1-ene [10], methyl-3,3,3trifluoro-2-hydroxy-2-(trifluoromethyl) propanoate [10], 2-methoxymalo-nonitrile [11], 1,1,1,3,3,3-hexafluoro-2-(trichlorometh-oxy) propane [12], and sevoflurane [13]. Moreover, most of these methods are based on liquid-phase reactions which are of intermittent operation and high pollution due to the production of a large amount of unrecyclable solvents and base.

Therefore, there is still no suitable method for mass production of HFE-356mmz so far.

To develop a green, pollution-free, and continuous process for the synthesis of **HFE356mmz**, we came up with the idea of using a Lewis acid catalyst, namely, metal fluoride,

because Lewis acid catalysts (eg. FeCl₃, AlCl₃, and zeolites) [14, 15] and Lewis base catalysts (eg, K_2CO_3 , CsF/α -Al₂O₃, and MgO) [16, 17] were reported to be constructive in the methylation reaction. The metal fluoride was selected because it can resist the corrosive HF, which might be produced from the decomposition of HFiP at high temperatures. In addition, metal fluorides, in many cases, are powerful catalysts to help achieve green gas-phase reactions such as dehydrohalogenation reaction [18], Cl/F exchange reaction [19] and isomerisation reaction [20]. To our best knowledge, the metal fluoride has not been disclosed in any open literature as a catalyst in the methylation reaction. Herein, we achieved a green vapor-phase synthetic approach for **HFE-356mmz** for the first time by utilizing metal fluoride as the catalyst. As shown in Scheme 2, the methylation of HFiP using DMC gave rise to HFE-356mmz and a series of volatile by-products. To achieve high synthetic efficiency, a number of metal fluorides with an order of decreasing Lewis acidity (AlF₃, MgF₂, CaF₂, SrF₂, and BaF₂) were prepared and tested. MgF₂ with moderate Lewis acidity and moderate Lewis basicity exhibited the highest activity. Through systematic investigation of all these metal fluorides, their catalytic activity was found to depend on the combination of the surface acidity and basicity, as well as the total amount of surface Lewis acid sites. In addition, the MgF₂ showed high stability over 1000 hours and HFE-**356mmz** in 50 kg scale could be prepared, suggesting great potential of the synthetic route for industrial production of **HFE-356mmz**. Accordingly, a rational mechanism of the vapor-phase methylation was proposed at the end. Our study not only paves the way for industrial production of HFE-356mmz, but also expands the application of metal fluorides.



Scheme 1. Reported synthetic routes for HFE-356mmz.



Scheme 2. Synthesis of HFE-356mmz through metal fruoride catalysed methylation of HFiP using DMC.

2. Experimental Section

2.1. Preparation of the catalysts

Metal fluorides (AlF₃, MgF₂, CaF₂, SrF₂, and BaF₂) were prepared by fluorination of the corresponding metal oxides (Al₂O₃, MgO, CaO, SrO, and BaO) [21, 22], in which MgO and Al₂O₃ were obtained by a precipitation method. The typical process for synthesizing MgF₂ was as follows: Mg(NO₃)₂ (148 g, 1.0 mol) was dissolved in distilled water (400 mL) and stirred for 1 h, then ammonium hydroxide (5%) was slowly added to the solution at room temperature until pH = 8.5 was reached. The precipitate formed was filtered off and washed with distilled water to

remove nitrate ions. After drying at 120 °C for 4 h and calcining at 500 °C for 12 h in a muffle furnace, the solid was ground and pelletized. The MgO pellets prepared above were packed on monel alloy reactor and fluorinated by a mixture of N₂ (100 ml min^{D1}) and HF (100 mL min^{D1}) at 200 °C for 2 h. Then pure HF (100 mL min^{D1}) passes through the reactor at 200 °C and 250 °C for 2 h each. Finally, the remaining HF on the catalyst was blown away by N₂ (100 ml min^{D1}) for 12 h. AlF₃ was prepared from Al(NO₃)₃ in a procedure similar to that of MgF₂. CaF₂, SrF₂, and BaF₂ were prepared by fluorination of commercially available CaO (Aladdin, 99.9%), SrO (Aladdin, AR), and BaO (Aladdin, AR), respectively, in a procedure similar to the preparation of MgF₂ from MgO.

2.2. Characterization of the catalysts

Unless otherwise mentioned, characterization of all the catalysts was done after being used in the methylation reaction for over 4 h.

The structures of the catalysts were determined by X-ray diffraction (XRD) in the range of $2\theta = 10-90\Box$, using a Bruker D8 Advance diffractometer and Ni-filtered Cu K α radiation ($\lambda = 1.540$ Å).

The surface areas of the catalysts were determined by N_2 physisorption in a Quanta-chrome Autosorb-iQ-C equipment. All the samples were degassed for 3 h at 250 °C prior to the N_2 physisorption. The surface areas were calculated according to the Brunauer–Emmett–Teller (BET) equation.

Acidity of the catalysts was determined by temperature programmed desorption of NH_3 (NH_3 -TPD) (Quantachrome Autosorb-iQ-C, USA). All the samples (100 mg) were treated in He (30 cm³ min^{D1}) at 250 °C for 1 h and then exposed to a 5% NH_3 /He stream for 60 min at 100 °C. The weakly adsorbed NH_3 was removed by flushing with He at 100 °C for 6 h. The temperature

was then increased to 500 °C at a rate of 10 °C min^{\Box 1}, and the liberated NH₃ was detected by an on-line gas chromatograph with a thermal conductivity detector. Basicity of the catalysts was determined by temperature programmed desorption of CO₂ (CO₂-TPD) measurements which was performed in a manner similar to the NH₃-TPD measurements, except that CO₂ was injected instead of NH₃.

The nature of surface acid sites was determined by fourier-transform infrared spectroscopy (FTIR) using pyridine as a probe molecule and a Thermo scientific (Nicolet 380) spectrophotometer. Sample wafer was formed by pressing 20–40 mg of a catalyst at 5 tons cm¹², which was transferred to a sample holder made of quartz. All the samples were initially degassed at 200 °C for 5 h and then a background spectrum was recorded after cooling the sample to room temperature. The spectra were recorded at room temperature before the adsorption of pyridine and after the evacuation of pyridine (absorbed at 40 °C) at 250 °C, respectively.

2.3. Test of catalyst and analysis of product

The vapor-phase methylation of **HFiP** (Sinochem, Lantian, >99%) with **DMC** (Aladdin, > 99%) was carried out in a down flow reactor at 250 °C under 101.1 kPa. The catalysts (particles with 0.8-1.2 mm diameter, 20 g) were treated *in situ* at 250 °C under N₂ flow for 4 h before the reaction. A mixture of **HFiP** and **DMC** with a 1:2 molar ratio was fed using a syringe pump. Standard catalytic tests were conducted at a contact time of 11.4 s. The outlet reaction mixture was analysed by gas chromatography (GC) using an GC-2014C (Shimadzu) equipped with a DB-VRX capillary column (30 m \Box 0.45 mm \Box 0.25 µm), the temperature of which was set as follows: 50 °C for 5 min, heating to 200 °C at a rate of 10 °C min^{D1}, and then holding at 200 °C for 8 min. The temperature of the injection port and the hydrogen flame ionization detector were

maintained at 200 °C and the He carrier gas was introduced at a rate of 10 mL min^{\Box 1}. Besides, the stability of MgF₂ was evaluated using the same reaction condition for 1000 h.

The conversion of **HFiP** (X_H) was calculated as: $X_H = \Sigma Y_i/(\Sigma Y_i + Y_P)$, where ΣY_i is the molar fraction of products formed from **HFiP** and Y_P is the outlet molar fraction of **HFiP**. In order to calculate the X_H, the GC relative response factor of **HFiP** to **HFE-356mmz** was measured preliminarily. **HFiP** (1 mmol) and **HFE-356mmz** (1 mmol) were mixed and warmed in a sample bag approximately 1 L in volume. The mixture was then carried to the GC by a carrier gas (He) under warm atmosphere and their relative GC areas were measured. Finally, the GC relative response factor was obtained and a ratio of f(**HFiP**):f(**HFE-356mmz**) = 1:1.49 was used to calculate the X_H.

The selectivity of product (S_i) was determined as: $S_i = Y_i / \Sigma Y_i$, where Y_i is the amount of product and ΣY_i is the amount of **HFiP** reacted.

3. Results and Discussion

3.1. Synthesis of HFE-356mmz

The **HFE-356mmz** was synthesized through methylation reaction of **HFiP** using **DMC** as the methylation reagent over different metal fluorides (AlF₃, MgF₂, CaF₂, SrF₂, or BaF₂) at 250 °C under 101.1 kPa. According to the GC analysis results of the outlet reaction mixture, methanol (CH₃OH) and methyl ether (CH₃OCH₃) were produced in addition to the product **HFE-356mmz** and the unreacted raw materials (**DMC** and **HFiP**). CH₃OH was probably formed by the methylation reaction of **DMC** while CH₃OCH₃ might be generated through the condensation reaction of CH₃OH [23]. Therefore, all the by-products are volatile under the reaction condition, making the reaction solvent-free. Since no by-product from **HFiP** was detected in the outlet

reaction mixture, the selectivity of **HFE-356mmz** was considered to be 100%. Such a highly efficient vapor-phase synthetic approach is applicable for industrial production of **HFE-356mmz** because the synthetic process is pollution-free and continuous and all the starting materials are recyclable.

Catalyst	$\mathbf{X}_{\mathbf{H}^{\mathbf{b}}}\left(\% ight)$	Total activity ^c (mmol $h^{\Box 1} m^{\Box 2}$)
AlF ₃	2.6	0.04
MgF ₂	94.3	2.01
CaF ₂	84.9	1.61
SrF_2	53.3	1.34
BaF_2	3.7	0.25

Table 1. Conversion of HFiP (X_H) over various catalysts^a

^aReaction condition: temperature = 250 °C; pressure = 101.1 kPa; contact time = 11.4 s; injection rate of **HFiP** = 139.8 mmol $h^{\Box 1}$; running time = 4 h. ^bX_H was determined by GC versus a calibrated internal standard. ^cTotal activity (mmol $h^{\Box 1}$ m^{$\Box 2$}) was determined by the molar reaction rate of **HFiP** and the specific surface area of the catalysts.

Notably, even under the same reaction condition, the conversion of **HFiP** (X_H) is different using different metal fluorides, which follows an order of MgF₂ (94.3%) > CaF₂ (84.9%) > SrF₂ $(53.3\%) > BaF_2 (3.7\%) > AlF_3 (2.6\%)$ (Table 1). Such a difference should be originated from the different catalytic activity of each catalyst. To explore the reasons of the different catalytic activity, all the catalysts were carefully characterized after being used in the methylation reaction.

3.2. Characterization of the catalysts

3.2.1. Structure



Fig. 1 XRD profiles of the catalysts used after the methylation reaction: a) AlF₃ (PDF: 801007), b) MgF₂ (PDF: 72-2231), c) CaF₂ (PDF: 75-0097), d) SrF₂ (PDF: 86-2418), and e) BaF₂ (PDF: 85-1341).

The structure of all the catalysts were analysed by XRD and the results were summarized in

Fig. 1. As shown in Fig. 1a, the XRD profile of AlF₃ displays diffraction peaks at $2\theta = 25\Box$, $42.4\Box$,

51.6□, and 57.8□, respectively, indicating a hexagonal crystalline structure (ICCD, PDF:80-1007).

All the other alkaline earth metal fluorides (MgF₂, CaF₂, SrF₂, and BaF₂) show broad reflexes

(Fig. 1a-d). The maxima of their diffractograms are in good agreement with those of the

corresponding crystal fluorides published previously [18]. Therefore, all of the metal fluorides are of crystalline structures.

3.2.2. Surface area

Catalyst	Surface Area $(m^2 g^{\Box 1})$	Pore Volume $(cm^3 g^{\Box 1})$	Average Pore Size (nm)
AlF ₃	100.1	0.138	5.5
MgF_2	65.6	0.176	10.7
CaF ₂	73.6	0.249	13.5
SrF ₂	55.6	0.161	11.5
BaF ₂	20.9	0.168	30.6

Table 2. Surface properties of the investigated catalysts

The surface properties of all the catalysts were summarized in Table 2, according to which AlF₃ exhibits the largest surface area (100.1 m² g^{□1}) whereas BaF₂ possesses the smallest one (20.9 m² g^{□1}). All the other alkaline earth metal fluorides (MgF₂, CaF₂, and SrF₂) show analogous surface areas, which falls in the range of 55.6–73.6 m² g^{□1}. In addition, the pore volumes and the average pore sizes of MgF₂, CaF₂, and SrF₂, which are within the ranges of 0.161–0.249 cm³ g^{□1} and 10.7–13.5 nm, respectively, are not significantly different. Based on the surface area of the catalysts (Table 2) and the X_H of **HFiP** in the methylation

reaction (Table 1), the total activity of the metal fluorides was calculated (Table 1). All the catalysts were active for the reaction. In spite of the medium surface area of MgF₂, it exhibits the highest activity (2.01 mmol $h^{\Box 1} m^{\Box 2}$). In sharp contrast, the AlF₃ possessing the largest surface

area shows the lowest activity (0.04 mmol $h^{\Box 1} m^{\Box 2}$). Therefore, the activity of these catalysts should not be dominated by their surface properties **3.2.3.** Acidity



Fig. 2 NH₃-TPD profiles of catalysts used in this study.

Since the acid sites on the surface of a catalyst are closely related with its catalytic activity, the surface acidity of all the catalysts was analysed by NH₃-TPD. According to the acid strength measurement by Narayanan [24], the desorption temperature of NH₃ at the range of 80–150 °C, 150–300 °C, and 300–450 °C represent weak, medium, and strong acid strength, respectively. As shown in Fig. 2, the NH₃-TPD profile of AlF₃ displays two desorption bands (180°C and 320 °C) and a shoulder (\Box 430 °C), which can be ascribed to the NH₃ adsorbed on medium and strong acid sites of the catalyst, respectively. In contrast, the NH₃-TPD profile of BaF₂ displays a weak band at 140 °C, reflecting the existence of weak acid sites only. For MgF₂ showing the desorption peaks at 100 °C and 275 °C and CaF₂ with the desorption peaks at 130 °C and 240 °C, weak and medium acid sites coexist. Desorption of NH₃ from SrF₂ gives rise to a weak band at about 160 °C, indicating medium acid strength of the catalyst.



Fig. 3. FTIR spectra recorded after pyridine adsorption on different catalysts at 40 °C, followed by evacuation of pyridine at 250 °C: a) AlF₃, b) MgF₂, c) CaF₂, d) SrF₂, and e) BaF₂. **Table 3.** Acid-base properties of the catalysts used in this study

Catalyst	Acidity ^a	Paciaity	Amount of Acid ^c (mol $g^{\Box 1}$)	
		Dasicity	Brønsted Acid	Lewis Acid
AlF ₃	strong	weak	12.7	290.5
MgF_2	medium	medium	5.5	66.1
CaF ₂	medium	medium	1.2	19.5
SrF ₂	medium	medium, strong	0.5	12.1
BaF_2	weak	strong	0.1	0.3

^aDetermined by NH₃-TPD. Temperature range: 100–500 °C. ^bDetermined

by CO₂-TPD. Temperature range: 100–500 °C. °Calculated by

integrating the characteristic FTIR bands (1450 cm^{D1}, 1490 cm^{D1}, and

1600 cm^{\Box 1}) of all catalysts recorded after the adsorption of pyridine at 40

°C and subsequent evacuation at 250 °C.

To further identify the nature of the surface acid sites, FTIR spectra of all the catalysts were recorded after the adsorption of pyridine at 40 °C and subsequent evacuation of pyridine at 250 °C. Only the bending and stretching frequency ranges were shown (Fig. 3). The absence of the characteristic bands of Brønsted acid sites at 1640 and 1540 cm^{□1} suggests negligible Brønsted

acid site in all of the catalysts [25]. On the contrary, the stretching vibrations of pyridine coordinatively bonded to Lewis acid sites of AlF₃, MgF₂, CaF₂, and SrF₂, which are located at 1440–1450 cm^{D1}, 1480–1500 cm^{D1}, and 1600 cm^{D1}, are observed. No Lewis acid site is detected on the surface of BaF₂ due to its weak acid strength, which agrees well with the NH₃TPD profile of BaF₂ presented in Fig. 2. Notably, the wavenumber of the band (\Box 1600 cm^{D1}) increases gradually from 1598 cm^{D1} (SrF₂, Fig. 3d) to 1600 cm^{D1} (CaF₂, Fig. 3c) to 1608 cm^{D1} (MgF₂, Fig. 3b) and to 1626 cm⁻¹ (AlF₃, Fig. 3a). This is because the 1600 cm^{D1} band is very sensitive to the strength of acidity, which shifts to higher frequencies with stronger acidities [26, 27, 28]. Therefore, the acidity of the four catalysts SrF₂, CaF₂, MgF₂, and AlF₃ increases in sequence. In addition, the total amount of the absorbed pyridine, namely, the total Lewis acid amount of all the catalysts, was estimated by integrating the bands around 1450 cm⁻¹, 1490 cm⁻¹, and 1600 cm⁻¹, which decreases in the following order: AlF₃ (290.5 mmol g^{D1}) > MgF₂ (66.1 mmol g^{D1}) > CaF₂ (19.5 mmol g^{D1}) > SrF₂ (12.1 mmol g^{D1}) > BaF₂ (0.3 mmol g^{D1}) (Table 3).

According to the study of the acidity mentioned above, the catalysts can be classified into three categories based on the scale of their Lewis acidity: the catalyst with strong Lewis acid centers (AlF₃), the catalysts with medium strength of Lewis acid centers (MgF₂, CaF₂ and SrF₂), and the catalyst with weak Lewis acid centers (BaF₂) (Table 3). **3.2.4. Basicity**



Fig. 4 CO₂-TPD profiles of catalysts used in this study.

The basicity of the catalysts was evaluated by CO₂-TPD, the profiles of which were indicative of the presence of basic sites with different strengths (Fig. 4). As reported previously, the bands at temperatures of $\Box 100$ °C, $\Box 200$ °C, and > 300 °C are attributed to desorption of CO₂ interacted with sites having weak, medium, and strong basic strength, respectively [29, 30]. The CO₂-TPD profile of BaF₂ displays a broad band at about 410 °C, evidencing the presence of strong basic sites. Whereas both medium and strong basic sites coexist on the surface of SrF₂, as indicated by its two broad desorption bands at about 210 °C and 330 °C. For MgF₂ and CaF₂, medium basic sites are predominant because desorption of CO₂ completed at 250 °C. For AlF₃, desorption of CO₂ gives rise to a weak desorption band at about 140 °C, suggesting the existence of weak basic sites only. Based on these results, the catalysts can be divided into three types: the catalysts with strong Lewis base centers (BaF₂ and SrF₂), the catalysts with medium strength of Lewis base centers (MgF₂ and CaF₂), and the catalyst with weak Lewis base centers (AlF₃) (Table 3).

Based on the characterization of the acidity and basicity of the metal fluorides mentioned above, the Lewis acidity decreases from AlF₃ to MgF₂ to CaF₂ to SrF₂ to BaF₂, while the Lewis basicity increases. With this behaviour, the predominance of the acid–base pair in these catalysts changes from acid site (AlF₃) to basic site (SrF₂ and BaF₂), while MgF₂ and CaF₂ exhibit medium acidity and basicity. Since MgF₂ and CaF₂ show the highest activity and largest X_H in the methylation reaction among all the catalysts, catalyst with medium surface acidity and basicity should be more favourable for the methylation reaction of **HFiP**.

In addition, the lifetime of MgF₂ was evaluated. As shown in Fig. 5, the selectivity of **HFE356mmz** remained unchanged in 1000 hours, and the conversion of **HFiP** decreased slowly from 94.8% to 85.1%, suggesting good stability and high activity of MgF₂.



Fig. 5 The conversion of **HFiP** (red dots) and selectivity of **HFE-356mmz** (black squares) over 1000 hours. Reaction conditions: temperature = 250 °C; contact time = 11.4 s.



Scheme 3. Plausible mechanisms for methylation of HFiP with DMC over the catalysts.

The importance of acidity and basicity of the catalyst in promoting the vapor-phase methylation reaction of HFiP can be further rationalized by the reaction mechanism using DMC as the methylation reagent. Beutel [31] proposed a mechanism based on *in situ* spectroscopic studies of the alkylation of phenol using **DMC**, where **DMC** was activated by the Lewis acid sites of the zeolite NaX catalyst through complexation of its ester oxygen or carbonyl oxygen atoms with the Na⁺ ions while phenol was activated by Lewis base site of the catalyst via hydrogen bonding. Jyothi et al. [32] proposed a similar mechanism for the vapor-phase methylation reaction of **DMC** making use of both the acid and the basic sites on the surface of the catalysts. Inspired by these studies, we proposed a reasonable mechanism for the vapor-phase methylation reaction of **HFiP** using **DMC** as the methylation reagent (scheme 3). The first step was the adsorption of **DMC** and **HFiP** on the Lewis acid and basic sites of the surface of the metal fluoride catalyst, respectively. Specifically, **DMC** was adsorbed through coordination of its carbonyl oxygen to the unsaturated metal center of the catalyst and HFiP was adsorbed via hydrogen bonding to the basic fluoride atoms of metal fluoride. Then, the nucleophilic oxygen atom of **HFiP** attacked the carbon atom of the methyl group in **DMC**. Finally, the product HFE356mmz, together with the by-products (CO₂ and CH₃OH), was produced and the catalyst

was regenerated. In addition, CH₃OCH₃, detectable in the outlet mixture, was also produced via condensation of CH₃OH.

According to the reaction mechanism, the vapor-phase methylation of **HFiP** with **DMC** obeys a co-operative action of acid-base pairs of the metal fluoride catalysts. The catalysts with medium Lewis acidity and medium Lewis basicity (eg. MgF₂ and CaF₂) promote not only the adsorption of **DMC** and **HFiP** but also the desorption of the products, and thus exhibit the highest activity. In the case of a catalyst with very strong Lewis acidity (eg. AlF₃), its adsorption to the carbonyl oxygen of **DMC** would be too strong, which would "poison" its activity [33]. On the contrary, if the basicity of the catalyst was strong (eg. BaF₂ and SrF₂), the catalyst would also be "poisoned" by the hardly reversible adsorption of acid molecules like CO₂ or even **HFiP** itself [34].

Notably, although both MgF₂ and CaF₂ show medium Lewis acidity and medium Lewis basicity, they exhibit different catalytic activity (Table 1). The higher activity of MgF₂ (2.01 mmol $h^{\Box 1} m^{\Box 2}$) than CaF₂ (1.61 mmol $h^{\Box 1} m^{\Box 2}$) is probably due to the larger total amount of Lewis acid sites of MgF₂ (66.1 mmol $g^{\Box 1}$) than CaF₂ (19.5 mmol $g^{\Box 1}$) (Table 3). Since Lewis acid sites play an important role in absorbing the **DMC** molecules and promoting the methylation reaction, it's easy to understand that a larger amount of medium Lewis acid sites represents higher activity of the catalyst

4. Conclusions

A novel and efficient vapor-phase synthetic approach to prepare **HFE-356mmz** was demonstrated by utilizing metal fluorides as the catalysts in the methylation reaction of HFiP for the first time. The catalysts enabled 100% selectivity of **HFE-356mmz** since no by-product from

HFiP was produced. All the other by-products from the methylation reagent (DMC) are volatile, making the reaction solvent-free. Through systematic investigation of a series of metal fluorides (AlF₃, MgF₂, CaF₂, SrF₂, and BaF₂), it was found that the activity of the catalyst was influenced by the strength of both Lewis acidity and Lewis basicity of the surface of the catalyst. This is because the two reactants, **HFiP** and **DMC**, were activated by the Lewis base sites and Lewis acid sites of the catalysts, respectively. As a result, MgF₂ with medium Lewis acidity and medium Lewis basicity, as well as a large amount of Lewis acid sites, exhibits the highest activity, which allows a very high conversion of HFiP (94.3%) in the methylation reaction. In addition, MgF₂ exhibits excellent stability and activity in 1000 hours. The significance of this study is four-fold. First, it provides a novel strategy for the synthesis of HFE-356mmz, the mechanism of which was clearly elucidated. Second, it paves the way for industrial production of HFE-356mmz because the synthetic process is solvent-free, pollution-free, and continuous. Third, it demonstrates a successful attempt of utilizing metal fluoride as catalyst in the methylation reaction, which expands the application of metal fluorides. Fourth, the synthetic strategy may be extended to other methylation reactions in future.

Declaration of Competing Interest

The authors declare no competing financial interest.

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