

**VIETNAM NATIONAL UNIVERSITY – HO CHI MINH CITY  
HO CHI MINH UNIVERSITY OF TECHNOLOGY**

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NGUYỄN VĂN TÚ

**INTRODUCING FLUORINE AND TRIFLUOROMETHYL  
GROUP INTO ORGANIC COMPOUNDS UNDER  
HETEROGENEOUS TRANSITION METAL CATALYSIS**

Major: Chemical Engineering

Major Code: 62.52.03.01

**PhD THESIS SUMMARY**

HO CHI MINH CITY, 2018

The thesis was accomplished in Ho Chi Minh University of Technology - Vietnam National University - Ho Chi Minh City

Advisors:           1) Prof. Dr. Phan Thanh Son Nam  
                          2) Dr. Trương Vũ Thanh

Independent Reviewer No.1:

Independent Reviewer No.2:

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Reviewer No.3:

The thesis was defended before the scientific committee at the Faculty of Chemical Engineering, Ho Chi Minh University of Technology, Vietnam National University - Ho Chi Minh City

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## LIST OF PUBLICATIONS

1. Tu V. Nguyen, Toan D. Ong, Anh H.M. Lam, Vu. T. Pham, Nam T.S. Phan, Thanh Truong, *Nucleophilic trifluormethylation of aryl boronic acid under heterogeneous Cu(INA)<sub>2</sub> catalysis at room temperature: The catalytic copper-based protocol*. Molecular Catalysis, 2017. **436**: p. 60-66. (DOI: 10.016/j.mcat.2017.04.010) (**IF = 4.0**)
2. Tu V. Nguyen, Vu T. Pham, Tin V.T. Nguyen, Nam T.S. Phan, Thanh Truong, *Decarboxylative fluorination of aliphatic carboxylic acids under heterogeneous delafossite AgFeO<sub>2</sub> nanoparticle catalysis: the utilization of bimetallic cooperativity*. Journal of Catalysis, 2018. **360**: p. 270–276. (DOI: 10.1016/j.jcat.2018.02.018) (**IF = 7.0**)

## INTRODUCTION

The organofluoride compounds are the least common natural ones compared to the other organohalides. Most organofluorides found in the earth are insoluble, averting the uptake of bioorganisms. However, the fluorine containing groups are of precious characteristics in pharmaceuticals, agrochemicals and materials due to their enhanced electronegativity, lipophilicity, metabolic stability and bioavailability. Besides,  $^{18}\text{F}$ -radiotracers used for Positron Emission Tomography (PET) are remarkably applied to both diagnosis and pharmaceutical development. Not until 1970 had fluorinated drugs been prevalent in medicinal chemistry. Since then, there has been a significant growth in fluorine chemistry, especially over the last 20 years. Until 2002, more than 150 fluorine containing drugs have come to market, estimably contributed to ca. 20-25% of all pharmaceuticals, and even higher in agrochemicals with ca. 28% in market. Of 31 new drugs licensed in USA in 2002, nine contained fluorine in their scaffolds. In 2006, Lipitor® (atorvastatin calcium, which contains one fluorine) and Advair® (a mixture of fluticasone propionate and salmeterol, which contains three fluorine atoms) are orderly the best- and the second-best-selling pharmaceuticals over the world.

In spite of the importance of fluorinated frameworks in actual areas, the number of these compounds in nature is rare. Therefore, the investigations to figure out novel strategies to synthesize fluorinated products are needed. Of strategies, the developments of simple handling, facile and inexpensive methods have been attracting a great deal of attention.

Almost previous studies employed homogeneous catalysts that could not be recovered and reused after reactions. Most of protocols proceeded under harsh

or costly conditions owing to the usage of the reagents susceptible to benchtop setup or the expensive reagents, respectively, or both. Additionally, the substrate scope and functional group tolerance still remain challenging. Further studies, therefore, are required to ameliorate the disadvantages in the former works. From above observations, we propose the thesis: **“Introducing fluorine and trifluoromethyl group into organic compounds under heterogeneous transition metal catalysis”**.

The purpose of the thesis is to develop the novel and more effective strategies to furnish fluorine containing compounds employing readily, inexpensive and effective methods under heterogeneous transition metal catalysts. Moreover, the wide scope and functional group tolerance are also under our consideration. From our knowledge, there has been no work utilizing the heterogeneous catalysts to introduce fluorine into organic molecules so far. This is an important factor to publish our accomplished studies in ISI ranked magazines with high IF factor.

The inexpensive transition metal such as copper, iron, manganese, cobalt, silver under nanoparticles and metal organic frameworks (MOFs) are applied to discover the reactivity in model reactions. Additionally, numerous feedstocks ranging from aromatics, heteroaromatics, alkynes, alkenes to aliphatic compounds bearing various functional groups are used to develop the novel strategies under readily, effective conditions. Moreover, the consideration to pick the inexpensive fluorine and fluorine containing group transfer reagents is also our priority in the studies.

In the sphere of our thesis, the investigations are conducted over a variety of organic scaffolds delivered by prestigious providers such as Sigma Aldrich,

Across Organics and Merck, using nanoparticles and MOFs of transition metals as catalysts in the presence of inexpensive fluorinated reagents.

Our studies will contribute to current knowledge of fluorine chemistry the novel methods employing heterogeneous catalysts to introduce fluorine and fluorine containing groups into organomolecules which have not yet been developed ever before. Our investigations are also carried out to ameliorate drawbacks in previous studies so far, proving the importance and the practice of our work. Furthermore, we establish the new methods for the usage of heterogeneous catalysts in fluorine chemistry that can be restored and recycled many times after reactions, making the methods more inexpensive.

Our studies are the first investigations in using heterogeneous transition metal catalysts for introduction of fluorine and fluorine containing groups into organic scaffolds. The first time Cu(INA)<sub>2</sub> MOFs is employed in the trifluoromethylation of boronic acids, and the first time AgFeO<sub>2</sub> nanoparticles is used in the fluorination of aliphatic acids. Thus, they make up vitally practical approaches to synthesize the fluorinated products that are necessary in pharmaceuticals, agrochemicals and materials due to unique effects of fluorine and fluorine containing groups on organomolecules. Our results may make a turning point in the application of methods using heterogeneous catalysts in fluorine chemistry.



## CHAPTER 1. LITERATURE REVIEW

Fluorine and fluorinated groups have the strong effects on the properties of organic compounds due to their enhancement of lipophilicity, metabolic stability, bioactivity and binding selectivity. Therefore, more and more fluorinated compounds have been used in medicinal chemistry, even higher in agrochemicals. Several fluorinated products have come to the market and have been also the top-selling products over years.

Though the necessity of fluorine containing compounds in pharmaceuticals, agrochemicals, materials and PET, and fluorine is the 13<sup>rd</sup> most abundant element in the earth's crust, the available natural fluorinated compounds are rare. As a result, a great number of studies have been done to elicit numerous methods for introduction of fluorine and fluorine containing groups into organic frameworks, especially after 1970s. Different substrates, reagents, additives, promoters and catalysts have been employed to develop various approaches in the syntheses of fluorine containing scaffolds. Of reported works, the attachment of fluorine and trifluoromethyl groups is most prevalent and has attracted increasing attention from researchers over the world. Generally, more and more effective, inexpensive works have been conducted to ameliorate the drawbacks of the previous ones. However, the regioselectivity, substrate scope and functional group tolerance still remain problematic so far.

In this thesis, we summarize the previous works corresponding to the mechanism, focusing on two major fields that have attracted an increasing attention from the scientific community. These are the fluorination and the trifluoromethylation of organic scaffolds. We herein describe the methods in

general, analyze the pros and cons of developed methods basing upon the transformational, economical efficiency and environmental green.

## 1.1 Introduction of fluorine into organic scaffolds

Previous studies showed different methods to introduce fluorine into organic molecules using various fluorinating reagents as the fluorine transfer sources. In general, there are three ultimate mechanisms of fluorination reactions including electrophilic fluorination, nucleophilic fluorination and radical fluorination.

The early developments using strongly fluorine transfer reagents, namely fluorine gas, fluorine solution, hypofluorites, fluoroxysulfates and perchloryl fluoride coped with their high reactivity resulting in the difficulty of C-F bond formation due to the generation of a number of isomers. Xenon fluoride then exhibited the more stable reactivity than above reagents, but its high oxidizing potential restricted the substrate scope with limited functional group tolerance. Fortunately, the successful syntheses of N-fluoro reagent classes made a watershed in the fluorine chemistry, and certainly they are still used in fluorine synthesis to date. N-fluoro reagents such as N-fluorobis(phenyl)sulfonimide (NFSI) and related analogs, N-fluoropyridinium salts, and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate) (Selectfluor®, F-TEDA-BF<sub>4</sub>) have gone dominant compared to the early reagents due to their air-setup stability, regioselectivity and functional group tolerance. This is demonstrated by that they have been used in the multitude of investigations from the beginning time so far.

Generally, the subsequent developments have been of a lot of advantages over the previous ones, such as the lower reaction temperature, high chemoselectivity and regioselectivity, easy manipulation, wide substrate scope

and variously functional group tolerance. However, such investigations are rare and the more developments are needed to ameliorate either most or all of drawbacks existing in previous studies.

The fluorination of aliphatic acids has just been explored recent years, and it has prodded a number of groups over the world. The single electron transfer and radical pathways are the main ones for this transformation. However, the low substrate scope and the expensive procedure are the disadvantages of this approach.

## **1.2 Introduction of trifluoromethyl group into organic scaffolds**

Similar to the introduction of fluorine into organic compounds, that of trifluoromethyl group into organic compounds has attracted much attention from the research groups. Previous studies set forth various approaches to introduce the trifluoromethyl group into organomolecules. Like methods for fluorination, the developed tools for trifluoromethylation of organic molecules employed numerous reagents to attach  $\text{CF}_3$  group to different substrates. The problems of group tolerance and the selectivity still remain in these reactions. Herein, we categorize the developed methods into three major groups according to the corresponding mechanism inclusive of electrophilic, nucleophilic and radical trifluoromethylation.

A number of researches have been conducted since the early investigation disclosed by Swarts in 1892, especially from exploration of fluoroalkylcopper intermediate discovered by McLoughlin and Thrower in 1968. However, like the fluorination, the trifluoromethylation of organic frameworks has coped with some drawbacks inclusive of harsh conditions, expensive reagents and inputs or limited substrate scope and functional group tolerance or both. Moreover, all of

methods conducted used the homogeneous reactions wherein the transition metals acted as the promoters or mediators for the generation of intermediacy and they are employed under the stoichiometric equivalents in the reaction mixtures.

For the novel methods in the trifluoromethylation, we are willing to investigate the simply facile, efficient approaches using transition metals as catalysts in the heterogeneous mixture, which has not yet to be developed before.

Boronic acids has emerged as the air-stable, commercially available and easily handling reactants in the trifluoromethylation reaction. In the trifluoromethylation of boronic acids, trifluoromethyl copper has been the common intermediate in a number of investigations. With respect to the previous studies, we turn our attention into the reaction of boronic acids under the catalysis of copper in the heterogeneous system.

### **1.3 Aim and objectives of the study**

From our observations, we turn our attention to the novel methods that can ameliorate some drawbacks of previous studies. The choice of inexpensive fluorine transfer reagents is the first priority in our experiments. Moreover, we develop the readily, effective methods which are easily handling using the commercially available agents. The temperature is lowered for product transformation. More importantly, we priorly explore the approaches that have not yet to be found ever before.

Transition metal catalysts are employed in our investigations as the potential catalysts in the organic chemistry due to the compatible reactivity and

selectivity in the C-F formation. Transition metal under nanoparticles and MOFs will be the objectives in the heterogeneous catalyses for our approaches.

No previous studies employed the heterogeneous catalysts in fluorine chemistry. Our studies are the first methods to introduce fluorine and fluorine containing groups into organic scaffolds under heterogeneous catalysts. This is the advantage of our developments to be published in ISI ranked magazines.

A number of substrates ranging from aromatics, heteroaromatics, alkenes, alkynes to aliphatic molecules are employed to discover the novel methods under heterogeneous transition metal catalysts such as iron, copper, silver, cobalt, etc under MOFs or nanoparticles. The experiments are conducted under various conditions to choose the best ones that are mild, effective and selective. Additionally, the numerous functional groups in feedstocks are investigated to expand the application of the methods to various compounds.

## CHAPTER 2. EXPERIMENTAL

### 2.1 Preparation of MOFs Cu(INA)<sub>2</sub> and nanoparticles AgFeO<sub>2</sub>

The MOFs Cu(INA)<sub>2</sub> was synthesized by solvothermal methods with the yield of 53% of blue fine-crystalline solid (calculated based upon the molar ratio of isonicotinic acid HINA)

Nanoparticles AgFeO<sub>2</sub> was prepared by the co-precipitation/hydrothermal of Fe<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> and AgNO<sub>3</sub>. The dark brown powder was obtained in 62% yield (calculated based upon the molar ratio of Fe<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>).

The solids were then characterized by numerous techniques inclusive of X-ray diffraction measurements (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), Fourier transform infrared (FT-IR), Inductively coupled plasma (ICP), and nitrogen physisorption measurements, X-ray fluorescence (XRF).

### 2.2 The fluorination of boronic acids and trifluoromethylation of boronic acids using two type of materials as catalysts

The Cu(INA)<sub>2</sub> and AgFeO<sub>2</sub> catalysts were then used to synthesize the fluorinated products through the trifluoromethylation of boronic acids and fluorination of aliphatic acids, respectively, under the mild, facile and efficient conditions in the heterogeneous systems.

In a typical experiment of the trifluoromethylation of boronic acids, a vial contained a magnetic stir bar was added with cesium fluoride (304 mg, 2.0 mmol, 2.0 equiv.) which was activated under vacuum at 200°C, 1,10-phenanthroline (59.5 mg, 0.33 mmol, 1.1 equiv.) and Cu(INA)<sub>2</sub> (0.3 mmol, 30

mol%). Anhydrous dichloroethane (DCE, 5 mL) were then added to the reaction vial, which was then stirred vigorously for 5 min.  $\text{TMSCF}_3$  (0.6 mL, 4.0 mmol, 4.0 equiv) and 4-methoxyphenylboronic acid (152 mg, 1 mmol, 1 equiv.) was quickly added to the reaction vessel, before purging the vial with oxygen gas. The reaction yield was monitored by withdrawing aliquots from the reaction mixture at different time intervals, diluting with ethylacetate (2.0 mL), quenching with an aqueous KOH solution (1%, 1.0 mL), and then drying over anhydrous  $\text{Na}_2\text{SO}_4$  before analyzing by GC with dodecane used as internal standard, and further confirming product identity by GC-MS and NMR. To investigate the recyclability of  $\text{Cu}(\text{INA})_2$ , the catalyst was filtered from the reaction mixture after experiment, washed with copious amounts of DCE, ethylacetate, water and THF, dried at  $140^\circ\text{C}$  in 6 h, and reused. For the leaching test, a catalytic reaction was stopped at 15 min, analyzed by GC, and filtered to remove the solid catalyst. The reaction solution was then stirred for a further 105 min. Reaction progress, if any, was monitored by GC as previously described.

Additionally, in a typical experiment of the fluorination of aliphatic acids, 3,3-diphenylpropionic acid (0.0452 g, 0.2 mmol), SelectFluor (0.178 g, 0.5 mmol), silver ferrite nanoparticles catalyst  $\text{AgFeO}_2$  (0.0098 g, 25 mol%) were added to a 8 mL vial containing magnetic stir bar. The mixture solvent of acetone/water (1:1 v/v) (1.0 mL) was the added to the vial. The reaction mixture was then purged with Argon and sealed with a Teflon cap before putting on magnetic heater for reaction occurrence at room temperature. The reaction yield was monitored by withdrawing aliquots from the reaction mixture at different time intervals, diluting with ethylacetate (2.0 mL), quenching with an aqueous solution (1%, 1.0 mL), and the drying over anhydrous  $\text{Na}_2\text{SO}_4$  before analyzing by GC with 1,2-dichlorobenzene used as internal standard, and further confirming product identity by GC-MS and NMR. To investigate the reusability of  $\text{AgFeO}_2$ , the catalyst was filtered from the reaction mixture after experiment,

washed with copious amounts of ethylacetate, acetone, water and ethanol, dried at 140°C in 8 h under vacuum, and reused. For the leaching test, a catalytic reaction was stopped at 15 min, analyzed by GC, and filtered to remove the solid catalyst. The filtrate was then stirred for a further 165 min. Reaction progress, if any, was monitored by GC as described above.



## CHAPTER 3. RESULTS AND DISCUSSION

### 3.1 Catalyst characterization

The results from the characterization validated the successful preparation of two above type of materials.

The XRD spectra revealed the succesful formation of crystalline structures of MOFs  $\text{Cu}(\text{INA})_2$  and nanoparticles  $\text{AgFeO}_2$  with the similar peaks on the pattern.

The TGA curves of synthetic  $\text{Cu}(\text{INA})_2$  and  $\text{AgFeO}_2$  demonstrated the stability of the materials around the temperature below  $300^\circ\text{C}$  and  $400^\circ\text{C}$ , respectively. The loss of complement parts was in combination with the calculation.

The surface area of the MOFs and nanoparticles were determined by the nitrogen physisorption measurement, which were akin to that observed in the previous studies, as following:

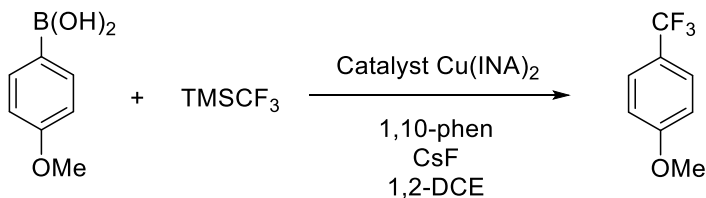
| Catalyst                  | Surface area, $\text{m}^2/\text{g}$ |
|---------------------------|-------------------------------------|
| $\text{Cu}(\text{INA})_2$ | 121                                 |
| $\text{AgFeO}_2$          | 22.3                                |

ICP result of  $\text{Cu}(\text{INA})_2$  revealed the copper loading of 19.32% in the structure of MOFs. That is quite close to the calculated value of 20.01% in the  $\text{Cu}(\text{INA})_2$  framework. In addition, the X-ray fluorescence (XRF) result provided the molar ratio of Ag/Fe in the  $\text{AgFeO}_2$  nanoparticles was approximately 1/1.04, which was akin to that in the theoretical formula of  $\text{AgFeO}_2$ .

## 3.2 Catalytic studies

The  $\text{Cu}(\text{INA})_2$  and  $\text{AgFeO}_2$  were then used to synthesize the fluorinated products through the trifluoromethylation of boronic acids and the fluorination of aliphatic acids, respectively.

### 3.2.1 Copper-catalyzed trifluoromethylation of aryl boronic acids using MOFs $\text{Cu}(\text{INA})_2$ as catalyst



Scheme 0.1. The trifluoromethylation of 4-methoxyphenylboronic acid with  $\text{TMSCF}_3$  to produce 4-trifluoromethylanisole using MOF  $\text{Cu}(\text{INA})_2$

The beginning study focused on the influence of catalyst loading on reaction yield. The oxidative trifluoromethylation of 4-methoxyphenylboronic acid was carried out at RT in anhydrous dichloroethane for 120 min, using 4 equivalents of  $\text{TMSCF}_3$ , 2 equivalents of  $\text{CsF}$  and 30 mol% of 1,10-phenanthroline as ligand under the  $\text{O}_2$  atmosphere as the oxidant, in the presence of 10 mol%, 20 mol%, 30 mol%, and 40 mol% catalyst, respectively. It was found that no yield of 4-trifluoromethylanisole was detected after 120 min without catalyst, which revealed the necessity of using catalyst of  $\text{Cu}(\text{INA})_2$  in this transformation, and that the catalyst loading of 30 mol% gave the highest yield of desired product in 79%. Increasing or decreasing the catalyst concentration did not lead to the higher efficiency.

The fluorine anion source was vital in the reaction, which was reported in the literature. Therefore, the effect of fluorine anion source on reaction yield was

then investigated by the use of different fluorine anion sources inclusive of cesium fluoride (CsF), potassium fluoride (KF), tetrabutyl ammonium fluoride (TBAF) and silver fluoride (AgF) in the trifluoromethylation of 4-methoxyphenylboronic acid to form 4-trifluoromethylanisole. The results from this test proved the overwhelming role of CsF in the trifluoromethylation, with 79% yield of 4-trifluoromethylanisole being observed after 120 min.

The effect of temperature on reaction yield was then tested with conducting the reaction at different temperature of 5°C, room temperature, 50°C and 70°C, respectively. The experimental results showed RT was the compatible temperature with the transformation, which afforded 79% yield of 4-trifluoromethylanisole after 120 min. Meanwhile, reactions carried out at lower or higher temperature than room temperature did not enhance the reaction yields.

It was found that, the reactant molar ratio strongly affected the reaction yield. The use of 4.0 equivalents of trifluoromethyltrimethylsilane  $\text{TMSCF}_3$  yielded the desired product of 4-trifluoromethylanisole in 79%, whereas increasing or decreasing the reactant molar ratio did not give higher efficiency.

In the precedent, the ligand was used to stabilize the copper complex and increase electron density. In this transformation, the 1,10-phenanthroline was used as the ligand, and the investigation of the effect of ligand proved its importance. The results from the experiment witnessed the highest yield of 4-trifluoromethylanisole in 79% yield with the presence of 30 mol% of 1,10-phenanthroline. The use of lower or higher concentration of 1,10-phenanthroline did not show the better formation of desired product.

Different solvents were used to select the suitable one for the trifluoromethylation of 4-methoxyphenylboronic acid. It was revealed that the presence of trace amount of water in the solvent retarded the formation of 4-trifluoromethylanisole due to the acceleration of homocoupling reaction. The use of anhydrous 1,2-DCE in this transformation gave the competitive yield of the expected product compared to other various solvents.

The reaction environment and oxidant were the vital factors influencing the reaction yields. Different oxidants were tested in the progress of the reaction and it was observed that only silver carbonate  $\text{Ag}_2\text{CO}_3$  gave the competitive yield of the desired product in 80% yield, nearly close to the use of oxygen as the oxidant. However, the use of oxygen which was purged into the reaction system was more advantageous. Moreover, reactions were retarded under inert atmosphere and without added oxidant, confirming the necessity of  $\text{O}_2$  oxidant in this transformation.

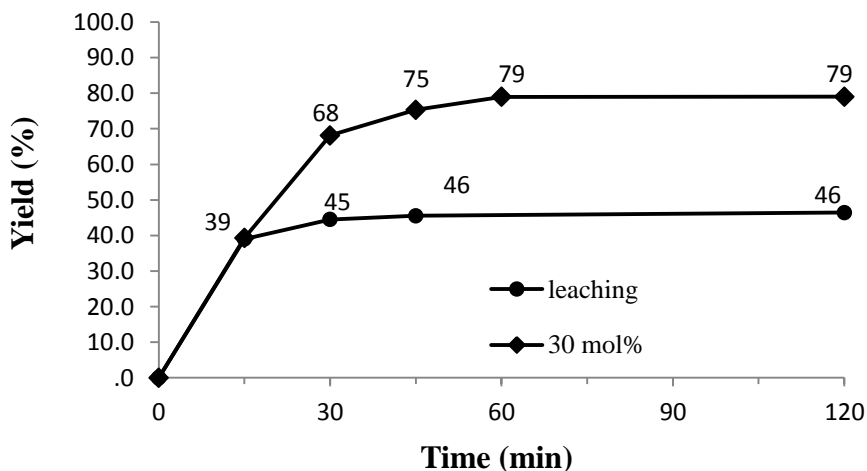


Figure 0.1. Leaching Test

In order to define the role of catalyst in the transformation and whether the leached copper species removed from the solid catalyst were active in the reaction mixture, the leaching test was conducted. Under the observation of tested experiments, no further remarkable conversion was detected in the reaction mixture after the  $\text{Cu}(\text{INA})_2$  catalyst was separated from the reaction mixture (Figure 3.13). In addition, ICP-MS revealed  $<0.5$  ppm of copper in the filtrate from reaction mixture. Therefore, it is likely that reactions could only proceed in the presence of the solid  $\text{Cu}(\text{INA})_2$  catalyst, and there should be no contribution from leached active copper species in the liquid phase.

The catalytic activity of the  $\text{Cu}(\text{INA})_2$  was compared with numerous homogeneous and heterogeneous catalysts to confirm its exceptionally catalytic activity for the trifluoromethylation of 4-methoxyphenylboronic acid to form 4-trifluoromethylanisole under the mild conditions. The experimental results proved that the highest yield of the desired product was obtained in the presence of  $\text{Cu}(\text{INA})_2$ , whereas the employment of several homogeneous and heterogeneous catalysts for this reaction gave the much lower yield of the expected product in less than 38% yield.

To confirm the reusability and stability of the  $\text{Cu}(\text{INA})_2$  used for the the trifluoromethylation of boronic acids to afford the corresponding products, the catalyst recycling study was conducted. The tested results showed the  $\text{Cu}(\text{INA})_2$  was possibly reused in 6 consecutive runs without a significant degradation in catalytic activity. Indeed, the expected product was still obtained in 76% yield in the 6<sup>th</sup> run.

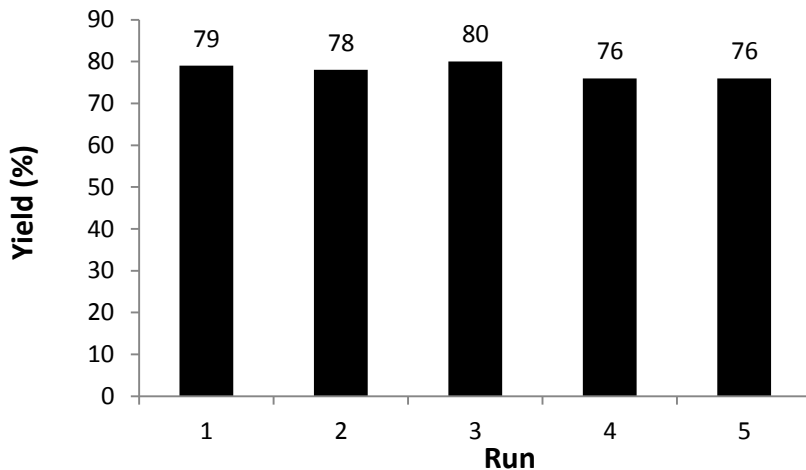


Figure 0.2. Catalyst recycling studies

The characterization of reused catalyst by FT-IR and XRD proved the consistence of the crystallinity of the  $\text{Cu}(\text{INA})_2$  after the reactions.

Then, the generality of optimal conditions using the heterogeneous  $\text{Cu}(\text{INA})_2$  catalyst on other derivatives of coupling components was investigated. In general, lightly lower yields of the trifluoromethylated adducts were observed with the substrate bearing the electron-withdrawing groups such as formyl, fluoro, and acetyl groups than that of compounds bearing the electron-donating groups such as methoxy, ethyl, methyl. Gratifyingly, hetero-aryl and vinyl boronic acid derivatives were also active and desired products were achieved in reasonable yields, wherein the trifluoromethylation reaction of benzo[d]thiazol-2-ylboronic acid afforded 2-(trifluoromethyl)benzo[d]thiazole in 52% isolated yield and that of styrylboronic acid formed (3,3,3-trifluoroprop-1-en-1-yl)benzene in 71% isolated yield.

### 3.2.2 Silver-catalyzed fluorination of aliphatic acids using $\text{AgFeO}_2$ nanoparticles as catalyst

In this reaction, the fluorination of aliphatic acids was carried out at RT, using 2.5 equivalents of SelectFluor as the fluorine transfer reagent and 25 mol% of  $\text{AgFeO}_2$  nanoparticles as catalyst in the solvent of acetone/water (1/2 v/v). 3,3-diphenylpropionic acid was used as the pattern in choosing the best conditions for the fluorination reaction.



Scheme 0.2. The fluorination of 3,3-diphenylpropionic acid with SelectFluor to afford (2-fluoroethane-1,1-diyl)dibenzene using  $\text{AgFeO}_2$  nanoparticles as catalyst

The first parameter tested was the equivalent of SelectFluor as the fluorine transfer reagent. The amount of 2.5 equivalents of SelectFluor exhibited the highest activity with the highest yield of product compared to the other amount.

Various catalyst loadings were then used for this transformation. The results showed the best activity of catalyst was obtained with using 25 mol% catalyst in the reaction mixture. The lower or higher catalyst concentration did not exhibit the better yield of the desired product. More importantly, no yield of product was detected without using  $\text{AgFeO}_2$  as catalyst. This confirmed the necessity of the  $\text{AgFeO}_2$  in the fluorination reaction.

Several solvents were investigated to select the apt solvent for the fluorination. Both polar and non-polar ones were used in the presence of 25 mol% of  $\text{AgFeO}_2$ . The experimental entries witnessed the exceptional compatibility of the mixed solvent of acetone/water with the transformation of aliphatic acid to

corresponding adduct. The use of the mixed solvent of acetone/water (1/1 v/v) gave the highest yield of product in 50% yield. Interestingly, other solvent chosen in our tests only gave the desired product in trace amount.

The volume ratio of acetone to water in the solvent mixture was then taken into account. In this experiment, the ratio of acetone/water at 1/2 gave the higher yield of product than other choices.

In the heterogeneous catalysis, the concentration of reactants greatly affected the reaction yield due to the possibility of collision and diffusion rate. Therefore, the concentration of reactants in this fluorination reaction was changed to various concentrations by changing the volume of solvent in the reaction mixture containing invariable amount of reactants. The experimental results witnessed the considerable increase in product yield to the excellent yield with the use of 1.0mL of the mixed solvent of acetone/water (1/2 v/v) for the reaction containing 2.5 equivalents of SelectFlour. The increase of the solvent volume resulted in the decrease in the yield of the expected adduct.

The influence of temperature on reaction yield was then investigated. The reaction seemed to be pleased with the low temperature surrounding room temperature. The similar product yield was obtained as performing reaction at the temperature from 25°C to 60°C. However, the reaction conducted at RT afforded the slightly higher yield than that at other temperature.

To confirm the structure stability in the reaction mixture and test whether the leached silver species removed from the solid catalyst was active in the reaction, the leaching test was conducted. The catalyst was removed from the reaction after 15 min of progress by the centrifugation. The filtrate was



transferred into another chamber and was performed at the same conditions as before. The results showed that no further increase in product yield was detected after removing the catalyst from the reaction mixture, which confirmed the necessity of the  $\text{AgFeO}_2$  catalyst in the transformation. The ICP-MS of the filtrate revealed trace amount of silver and iron was detected in the filtrate after reaction. This proved no contribution of the leached silver species to the generation of the desired product in the chosen conditions.

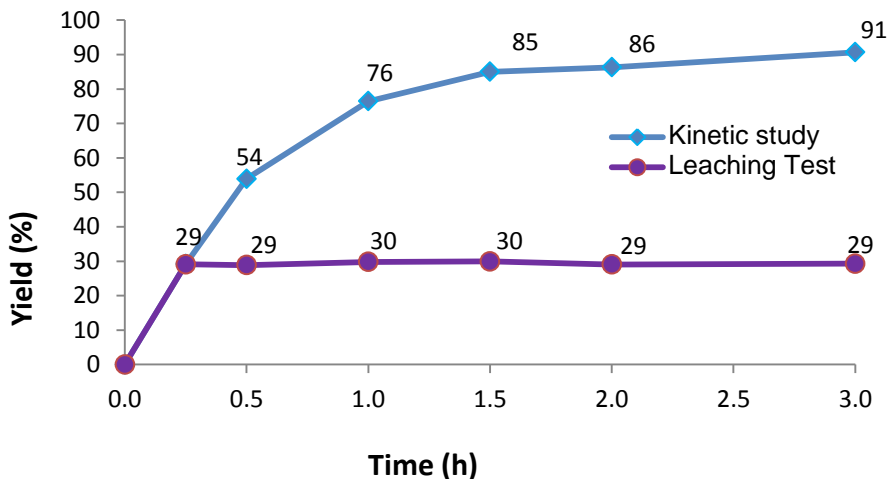


Figure 0.3. Leaching Test

The catalytic activity of nanoparticles  $\text{AgFeO}_2$  was then compared with other both homogeneous and heterogeneous catalyst in this transformation. Only  $\text{AgNO}_3$  as the homogeneous catalyst and  $\text{Ag}_2\text{O}$  nanoparticles as the heterogeneous one exhibited the moderate to high yields in 63% and 81%, which was lower than the yield obtained by using  $\text{AgFeO}_2$  affording the product yield in 91%. Other choices of various catalysts were not suitable to the fluorination reaction. This proved the exceptionally catalytic activity of  $\text{AgFeO}_2$  nanoparticles in this transformation under the heterogeneous catalyst, which has yet to be reported never before.

The reusability of the  $\text{AgFeO}_2$  in this type of reaction was then tested to prove the efficiency of this approach. In fact, the  $\text{AgFeO}_2$  catalyst was recovered and reused for seven consecutive reactions without any significant degradation in catalytic reactivity. Indeed, the yield of 82% was obtained in the 7<sup>th</sup> run, proving the stability in catalytic reactivity of the used catalyst. Moreover, the XRD spectra of the recovered  $\text{AgFeO}_2$  revealed that the crystallinity was intact with negligible difference compared to the fresh sample.

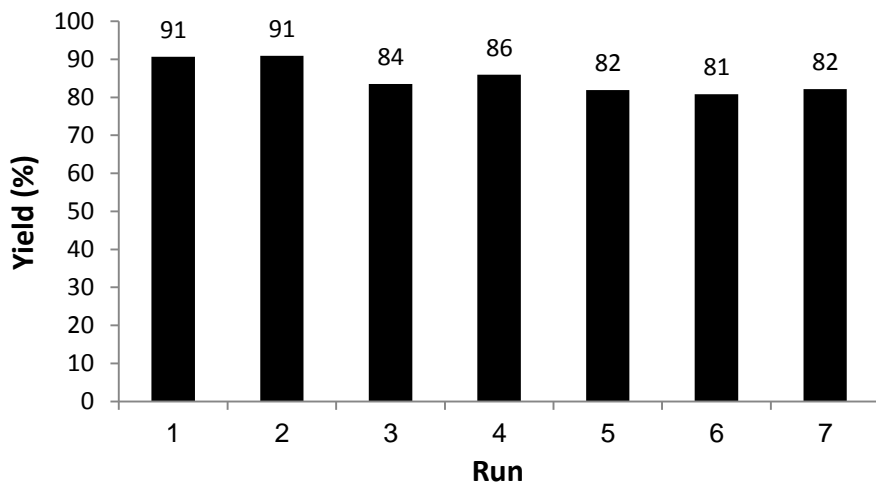


Figure 0.4. Catalyst recycling studies

The scope of the research was then expanded to the fluorodecarboxylative reactions of different aliphatic acids with SelectFluor to produce corresponding fluorinated derivatives. The application of the optimal conditions to other derivatives of aliphatic acids gave the satisfactory results, wherein both electron-donating and electron-withdrawing groups exhibited the compatibility with the chosen conditions. The fluorinated products of different substrates were afforded in high to excellent yields, which repeatedly proved the exceptionally catalytic activity of  $\text{AgFeO}_2$  nanoparticles for the decarboxylative fluorination of aliphatic acids.

Initial study to find the pathway of this transformation was tested. The reaction with the presence of the radical scavenger TEMPO did not generate the fluorinated product in combination with the undefined peaks on the GC spectra. These results suggested us the possibility of radical pathway for the fluorodecarboxylative reaction of the aliphatic acids and SelectFluor, which was also described in the previous studies using the homogeneous catalysts and photocatalysts in the literature precedent.

## CONCLUSION

1. The first heterogeneous trifluoromethylation of boronic acids and the first heterogeneous fluorination of aliphatic acids were described. Both facile reactions were conducted under the mild conditions and the high to excellent yields of the desired products were obtained, which proved the highly catalytic reactivity of the selected catalysts.
2. The characterization of the catalysts of the MOFs - Cu(INA)<sub>2</sub> and AgFeO<sub>2</sub> nanoparticles confirmed the successful syntheses. Their catalytic reactivity and heterogeneity were also investigated by the recovered reactions and leaching tests, wherein the catalysts were recovered and reused several times without any significant degradation in the yields of the desired product. Moreover, the chosen heterogeneous catalysts showed the unexpected compatibility with the fluorination and trifluoromethylation mentioned above, wherein the product yields obtained from using these catalysts were even higher than that from using other both analogously heterogeneous and homogeneous catalysts.
3. The best conditions for the trifluoromethylation of boronic acids involved the use of the nucleophilic TMSF<sub>3</sub> reagent, 1,10-phenanthroline ligand in DCE solvent at room temperature for 2 h under oxygen atmosphere with the presence of the heterogeneous catalyst of MOFs - Cu(INA)<sub>2</sub>. Those for the fluorination of aliphatic acids are inclusive of using SelectFluor reagent in the solvent of acetone/H<sub>2</sub>O at room temperature for 3 h under the Argon atmosphere with the presence of the heterogeneous catalyst of AgFeO<sub>2</sub> nanoparticles.
4. The best reaction conditions were compatible with a variety of substrates. Compounds either bearing electron-withdrawing or - donating groups gave the moderate to excellent yields under the conditions.
5. Drawbacks remained in the previous studies using the homogeneous catalysts were eradicated. The harsh conditions, expensive transition metal catalysts and reagents, complicated handling procedures and using the synthetically fluorinated complex were not repeated in our studies. Our developments proposed the facile, efficient reactions under the mild conditions using the

recoverable and reusable heterogeneous catalysts without any reduced yields compared to the aforementioned studies.

6. Our future works are expanding the substrate scopes of the reactions described above. Even though a number of studies conducted to introduce fluorine containing groups into organic compounds and though our initial success for fluorinating boronic acids and aliphatic acids was gained, the experiments using various heterogeneous catalysts still need developed. We will strive to carry out other fluorinated reactions using different catalysts that have not yet used ever before or stoichiometrically used in former studies.