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Supported CuCl/γ-Al_2O_3 for Friedel–Crafts Acylation with Effective Inhibition of Defluorination

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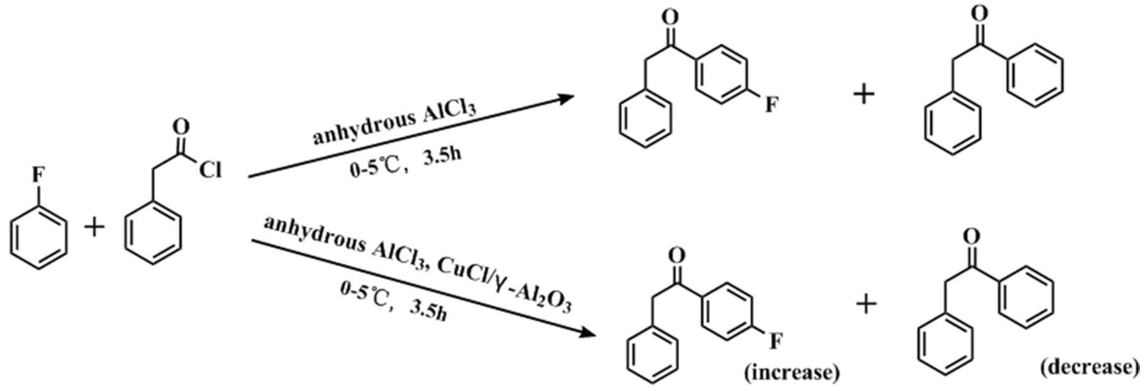
Abstract A series of supported CuCl/γ-Al_2O_3 with different Cu content (2, 6, 10, 13, 16 and 17 wt%) were prepared by the method of wet impregnation and spontaneous monolayer dispersion techniques. These co-catalysts were analyzed by XRD, BET, SEM, XPS and ICP techniques and were found to inhibit the formation of defluorination byproducts during the phenylacetylation of fluorobenzene catalyzed by $AlCl_3$, allowing the using of fluorobenzene as the reaction solvent that could be easily recycled. The best inhibitor was 10 wt% Cu supported CuCl/γ-Al_2O_3, which still had good catalytic performance after being recycled for five times.

Graphical Abstract



Keywords Supported catalysts · CuCl · Al_2O_3 · Friedel–Crafts acylation · Defluorination

1 Introduction

Friedel–Crafts acylation is a common method to synthesize aromatic ketones, which are widely used as intermediates in manufacturing special chemicals such as perfumes, pharmaceutical, dyes and agricultural chemicals [1–4]. However, it has been reported that defluorination would occur during the Friedel–Crafts acylation when fluoroaromatic substrates were used [5]. Although the content of defluorinated by-product is low in many cases, it has

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great impacts on the quality of the final product, especially for those fluorinated pharmaceuticals. For example, M2 (Scheme 1) is the key intermediate for synthesis of atorvastatin calcium-one of the famous lipid-lowering agents used for the prevention of cardiovascular disease——and is usually synthesized by phenylacetylation of fluorobenzene, accompanied by the formation of defluorinated byproduct **1** [6, 7], whose content was required to be lower than 0.2 wt%. In order to achieve high-grade M2, the method of using fluorobenzene as both substrate and reaction solvent is unacceptable because excess fluorobenzene can hardly be recycled for two reasons, one is that the formed benzene cannot be removed from fluorobenzene by simple distillation (the difference of their boiling points is so small), and the other is that benzene is easier to be acylated than fluorobenzene. As a result, other solvents apart from fluorobenzene were used [7–9], and once they are recycled, benzene should be completely removed, which greatly increases the cost of production.

It is consequently worthwhile to develop efficient inhibitors to restrain the occurrence of defluorinated byproduct during the acylation of fluorobenzenes. Herein we describe the using of supported CuCl/γ-Al_2O_3 as inhibitor for phenylacetylation of fluorobenzene. The optimization of the inhibitor was carried out and 10 wt% Cu supported CuCl/γ-Al_2O_3 was found to be the best one. It still kept excellent defluorination inhibiting performance after being recycled for five times.

2 Experimental

2.1 Preparation of Supported CuCl/γ-Al_2O_3

The CuCl/γ-Al_2O_3 inhibitors (in the 2–17 wt% Cu range, detected by ICP) were prepared according to the wet impregnation method [10] and spontaneous monolayer dispersion techniques [11–13]. The γ-Al_2O_3 powder was firstly activated in a tube furnace under dry nitrogen atmosphere at 500 °C for about 4 h before being used. Then an exact amount of the activated γ-Al_2O_3 powder was added to a $CuCl_2$ aqueous solution with vigorous stirring. Stoichiometric Na_2SO_3 aqueous solution was subsequently added dropwise to the mixture under stirring. The obtained mixture was stirred for 2 h and then 2 equiv. of H_2SO_3 solution was added. The resulting mixture was centrifuged sufficiently and the supernate was removed. The left wet solids were dried for 4 h at 50 °C in a vacuum oven to avoid air contact. The dried CuCl/γ-Al_2O_3 mixture was finally transferred into a tube furnace and calcinated at 380 °C for 4 h. The obtained CuCl/γ-Al_2O_3 co-catalyst was donated as Cu@Al (X); where X stands for the content of the total Cu in the catalysts.

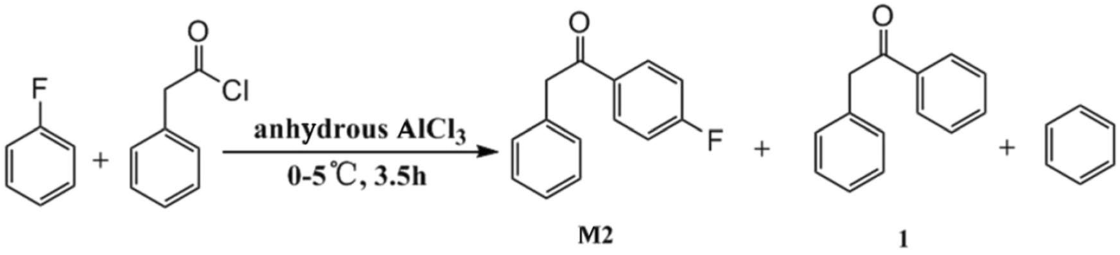
2.2 The Phenylacetylation Reaction of Fluorobenzene

The phenylacetylation reaction of fluorobenzene was then carried out at 0–5 °C with the existence of anhydrous $AlCl_3$ and CuCl/γ-Al_2O_3. Target product **M2** and the by-product **1** were obtained by column chromatography on silica gel. **M2** ^{1}H-NMR (DMSO, 400 MHz, TMS) δ 8.18–8.09 (m, 2H), 7.41–7.20 (m, 7H), 4.39 (s, 2H); EI-TOF MS: m/z calculated for [$C_{14}H_{11}OF$]: 214.0794, found: 214.0793. By product **1** ^{1}H-NMR (DMSO, 400 MHz, TMS) δ 8.09–8.02 (m, 2H), 7.68–7.19 (m, 8H), 4.40 (s, 2H); EI-TOF MS: m/z calculated for [$C_{14}H_{12}O$]: 196.0888, found: 196.0886.

3 Results and Discussion

3.1 The Determination of Using CuCl/γ-Al_2O_3 as Defluorination Inhibitor

The defluorination phenomenon has been commonly found in the synthesis of organic fluorinated compounds such as 1-(4-fluorophenyl)-2-phenyleththanone [5], antidepressant paroxetine hydrochloride [14], ezetimibe [15], double-hexyl-trifluoro-alkyl benzene [16] and so on. It is believed that the formation of defluorination by-product is mainly attributed to the cleavage of C–F bond [15]. There are three main pathways that can cause the cleavage of C–F bond, namely, electron transfer, oxidative addition and nucleophilic pathways, respectively [17, 18]. The electron transfer pathway often involves homolytic splitting of C–F bond via



Scheme 1 Phenylacetylation of fluorobenzene

a single-electron transfer process which is mediated either by electrochemically or low-valent metals. It often proceeds by initial electron transfer from a reductant, followed by scission of the C–F bond to give a fluoride ion and a carbon radical. The oxidative addition pathway means employing transition metals for C–F bond cleavage through oxidative addition of the C–F bond to the transition metal center. The nucleophilic pathway refers to nucleophilic substitution reaction in which fluorine atom is substituted by nucleophile such as OH^-, SH^- and so on.

Among these three mechanisms, the electron transfer pathway should be the most reasonable way in our work, because that there is no existence of transition metal or nucleophile, while there is free aluminum impurities (which meets the requirement of the presence of low-valent metals in this mechanism) in anhydrous $AlCl_3$ during its industrial manufaction [19, 20]. The side reactions during the acylation can thus be deduced as (1) fluorobenzene was firstly reduced to anion radical by gaining one electron from the trace free Al in $AlCl_3$; (2) the anion radical dissociated as a benzene radical and a F^-; (3) the benzene radical generates benzene by hydrogen abstraction reaction; and (4) the acylation of the formed benzene, which has higher reactivity to be acylated than fluorobenzene, leads to the formation of the by-product 1. In this way, the occurrences of by-product 1 and benzene in Scheme 1 are thus explained.

Then it is hoped that Cu^{2+} or Cu^+ could have defluorination inhibiting effect because of their electron-accepting nature, in the way of being reduced to Cu^+ or Cu by gaining the electron, which would no longer come to fluobenzene again from Al. Before verifying the defluorination inhibiting effect of Cu^{2+}/Cu^+ during the acylation of fluorobenzene, the content of benzene among the starting fluorobenzene was identified as 0.011% by GC measurement. Then phenylacetylation of fluorobenzene under $AlCl_3$ catalyst in the presence of CuCl, CuO, $CuCl_2$ and the blank control were then carried out. The contents of benzene among the first run of the recycled fluorobenzene (C_{ben}) with 1.5 equiv. CuCl, CuO, $CuCl_2$ and blank control were 0.011, 0.032, 0.030 and 0.030%, respectively. It can be seen that CuCl had inhibiting effect for defluorination while CuO and $CuCl_2$ has no effect, indicating that CuCl could be used as the defluorination inhibitor, probably due to its covalent character.

Then different molar ratios of CuCl were then used to evaluate the inhibiting effect. GC results of recycled solvents were shown in Table S1. It was found that the C_{ben} decreased with the addition of CuCl and became the same as that of the starting fluorobenzene when 1.5 equiv. of CuCl was added. Considering that industrial CuCl were nonuniform in size and has small surface area, supported CuCl was supposed to have better defluorination-inhibiting performance for possessing a much larger surface area, and as a result could reduce the amount of inhibitors. Inspired by the fact that a number of suitable supports, such as SiO_2 [21, 22], activated carbons [23, 24], zeolite [25, 26] and γ-Al_2O_3 [27–29], could be used to prepare high efficient immobilized catalysts, and the work of Tang and coworkers, where monolayered CuCl was dispersed on γ-Al_2O_3 [11], a series of γ-Al_2O_3 supported CuCl of different Cu contents (Cu@Al (X), X = 2, 6, 10, 13, 16 and 17%) were prepared to serve as the co-catalysts for inhibiting the defluorination during the phenylacetylation of fluorobenzene.

3.2 The Characterizations of the Supported CuCl/γ-Al_2O_3

3.2.1 XRD

XRD patterns of supported CuCl/γ-Al_2O_3 inhibitors are shown in Fig. 1. The diffraction peaks corresponding to free CuCl could not be observed in Cu@Al (2%), Cu@Al (10%) and Cu@Al (13%), while the increasing reflections corresponding to crystalline CuCl at 2θ = 28.6°, 47.5° and 56.3° were clearly observed in Cu@Al (16%) and Cu@Al (17%). These results indicate that those co-catalysts whose Cu content lower than 16% formed monolayer CuCl on the γ-Al_2O_3 surface, while CuCl began to stack when the Cu content becomes equal to or greater than 16%, this phenomenon is in accordance with the reported result that 0.33 g of CuCl salt was necessary to form a monolayer onto the surface of 1 g γ-Al_2O_3 [30] (Cu content was calculated as 15.9%).

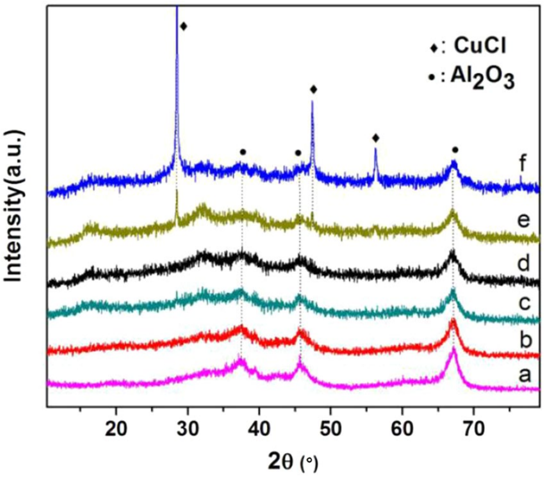


Fig. 1 XRD patterns of γ-Al_2O_3(*a*), Cu@Al (2%) (*b*), Cu@Al (10%) (*c*), Cu@Al(13%) (*d*), Cu@Al(16%) (*e*), and Cu@Al(17%) (*f*)

3.2.2 BET

The surface area of samples was calculated by using BET method; the pore volume distributions were calculated by BJH method, the results were listed in Table 1. It can be seen that the BET surface area and pore volume of γ-Al_2O_3 were correspondingly 178.2 $m^2\ g^{-1}$ and 0.253 $cm^3\ g^{-1}$, and they decreased gradually to 69.4 $m^2\ g^{-1}$ and 0.137 $cm^3\ g^{-1}$ respectively with the increasing contents of Cu from 2 to 17%. This is no doubt because that the increasing loading of CuCl onto the supporter would reduce the specific surface area and the pore volume.

3.2.3 XPS

The obtained XPS spectra were dealt with XPS Peak Fitting Program, which made it possible to calculate the ratio of Cu^+:CuO:Cu^{2+}. The peak fitting results are shown in Fig. 2. The ratios of Cu^+:CuO:Cu^{2+} in Cu@Al (2%), Cu@Al (6%),Cu@Al (10%), Cu@Al (13%), Cu@Al (16%) and Cu@Al (17%) were 1.2:2.1:1.0, 1.2:1.0:1.0, 1.4:1.0:1.0, 1.6:1.1:1.0, 1.7:1.2:1.0 and 1.8:1.2:1.0, respectively. Taking into account that Cu^{2+} and CuO has no contributions for defluoronation, the percentages of Cu^+ among the total copper in these inhibitors would reflect their inhibiting activities. The Cu^+ contents were then calculated as 27.9, 37.5, 41.2, 43.2, 43.6 and 45.0%, respectively. It can be found that the percentage of Cu^+ among the total copper (Cu^+/Cu%) in these co-catalysts increased sharply before the Cu content reaches 10%, while it grown little when Cu^+/Cu% exceed 10%.

Table 1 BET data of the co-catalysts and the respective GC data of recycled fluorobenzene

Entry	Samples	BET surface area ($m^2\ g^{-1}$)	Pore volume ($cm^3\ g^{-1}$)	Recycled fluorobenzene	
				Fluorobenzene (%)	C_{ben} (%)
1	Al_2O_3	178.2	0.253	–	–
2	Cu@Al (2%)	157.4	0.238	99.80	0.013
3	Cu@Al (6%)	120.3	0.198	99.98	0.011
4	Cu@Al (10%)	98.5	0.160	99.96	0.008
5	Cu@Al (13%)	81.8	0.142	99.72	0.009
6	Cu@Al (16%)	72.7	0.138	99.85	0.008
7	Cu@Al (17%)	69.4	0.137	99.90	0.009

3.3 The Defluorination-Inhibiting Performance of the CuCl/γ-Al_2O_3

The defluorination-inhibiting performance experiments using the Cu@Al(X) were then carried out and the GC results are listed in Table 1. It can be found that the using of CuCl/γ-Al_2O_3 indeed restrained the defluorination because all the C_{ben}s were lower than that of the blank control (0.030%). The C_{ben} became equal to that of the starting fluorobenzene (0.011%) when the content of X reached to 6%, then it came to a lower content of 0.008% when X is 10%, and finally kept nearly unchanged in spite of X came to 17%.

It should be pointed out that the removal of the CuCl/γ-Al_2O_3 by filtration using filter paper was still facile when $X \leq 10\%$ but became quite difficult when X reached to 13%. The SEM images of CuCl/γ-Al_2O_3 might offer the reason, as illustrated in Fig. 3. It can be seen that the loading of CuCl caused the collapse of Al_2O_3 particles. The morphology of γ-Al_2O_3 was regular with an average particle diameter of ~50 μm, and became less regular with a size distribution from ~20 to 50 μm when X = 10%, with a size distribution from ~10 μm to 40 μm when X = 13%, and finally with a size distribution from several micrometers to 20 μm when X = 16%. The bad filterability should be attributed to the decreasing size of the co-catalyst with the increasing X.

Taking into account the inhibiting performance, the ease of filtration and XPS result, Cu@Al (10%) was deemed to be the best inhibitor and the optimal amount of Cu@Al (10%) was then investigated, as illustrated in Table S2. The defluorination-inhibiting performance continued to improve until the amount of co-catalyst reached to 0.5 equiv. (based on Cu), and then remained at this level even 0.8 equiv. of Cu@Al (10%) was added. The using of 0.5 equiv. amount of the inhibitor was consequently adopted for the next recycling experiments.

3.4 The Recycling of Cu@Al (10%) Inhibitor

The recycling experiments using 0.5 equiv. of Cu@Al (10%), along with the blank controls were carried out and the corresponding GC results of recycled fluorobenzene and HPLC data of obtained M2 are listed in Tables 2 and 3. It can be seen that Cu@Al (10%) still had good defluorination-inhibiting performance after being used for five times. The C_{ben}s were restrained lower than that of the starting fluorobenzene; the contents of defluorinated **1** in M2 were kept at a satisfactory level of lower than 0.05%; and the yields of M2 were the same level as the blank controls.

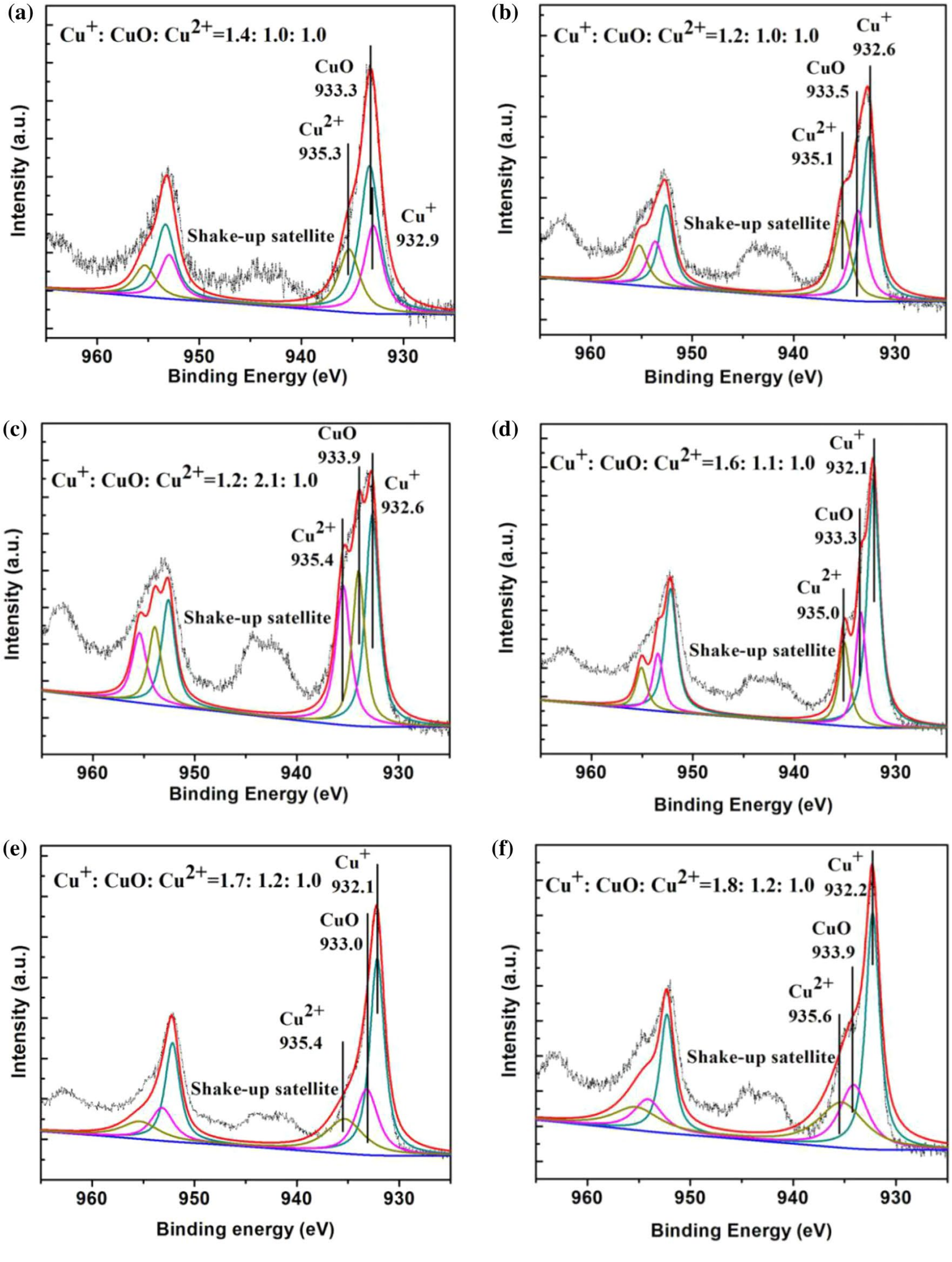


Fig. 2 XPS spectra and the fitting Cu^+:CuO:Cu^{2+} ratios of Cu@Al (2%) (**a**), Cu@Al (6%) (**b**), Cu@Al (10%) (**c**), Cu@Al (13%) (**d**), Cu@Al (16%) (**e**) and Cu@Al (17%) (**f**)

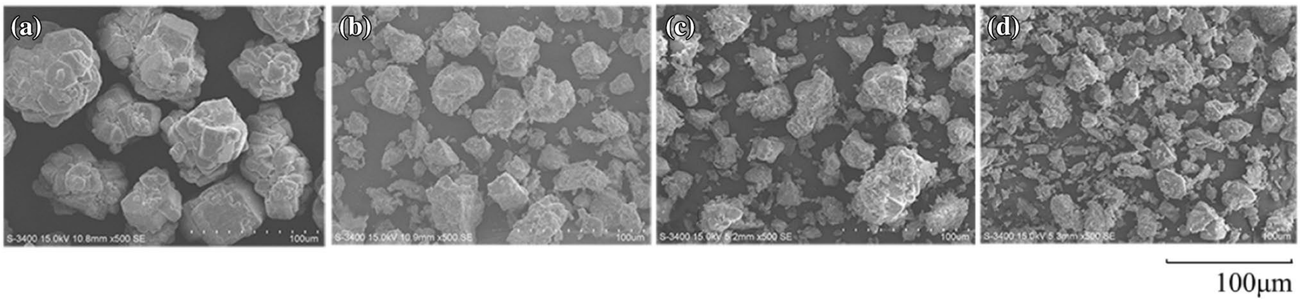


Fig. 3 The SEM images of γ-Al_2O_3 (**a**), Cu@Al (10%) (**b**), Cu@Al (13%) (**c**) and Cu@Al (16%) (**d**)

Table 2 GC data of recycled fluorobenzene and HPLC results of M2 products among the recycling experiments with 0.5 equiv. amount Cu@Al (10%) co-catalyst

Entry	Recycled fluorobenzene		Products		Yield (%)
	Fluorobenzene (%)	C_{ben}s (%)	M2 (%)	**1** (%)	
Run1	99.96	0.008	98.93	0.044	76
Run2	99.91	0.008	97.77	0.030	74
Run3	99.94	0.009	99.43	0.026	78
Run4	99.89	0.010	99.21	0.028	76
Run5	99.82	0.009	99.63	0.031	75
Run6	99.98	0.007	99.29	0.039	78

Table 3 GC data of the recycled fluorobenzene and HPLC results of M2 products in the recycling experiments of blank control

Entry	Recycled fluorobenzene		Products		Yield(%)
	Fluorobenzene (%)	C_{ben}s (%)	M2 (%)	**1** (%)	
Run1	99.95	0.030	98.79	0.152	76
Run2	99.95	0.041	98.70	0.341	77
Run3	99.88	0.062	98.70	0.465	76

By comparison in those blank controls (Table 3), C_{ben} kept increasing to over 0.06% with the increasing runs of recycling, and the content of **1** in M2 began to exceed the required 0.2% at the second run and kept increasing to 0.46% after three times of recycling.

4 Conclusions

In this work, supported CuCl/γ-Al_2O_3 with 2–17% mass contents of Cu were prepared by using wet impregnation method and spontaneous monolayer dispersion techniques. These Cu@Al (X)s were characterized by XRD, BET, SEM, XPS and ICP techniques. CuCl could be dispersed in the form of monolayer onto γ-Al_2O_3 when mass content of Cu was lower than 16%. These CuCl/γ-Al_2O_3 all exhibited good defluorination-inhibiting nature during the phenylacetylation of fluorobenzene. The best inhibitor was Cu@Al (10%) and the optimal amount added was 0.5 equiv. basing on immobilized Cu. The Cu@Al (10%) inhibitor kept its good performance after being reused for at least five times and could be recycled through simple filtration, making the using of fluorobenzene as both substrate and reaction solvent possible during the acylation.

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