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Supported iron catalysts for Michael addition reactions

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ABSTRACT

Heterogeneous catalysts have been widely used for chemical transformations and offer easy product separation in addition to their high activity. Iron is an earth-abundant metal, but it has not been studied thoroughly as heterogeneous catalysts for organic reactions. In this work, supported iron catalysts were synthesized via loading FeCl₃ onto a mesoporous silica SBA-15. These catalysts were highly active for Michael addition reactions, a synthetic pathway for forming C–C bonds that is typically achieved by homogeneous catalysts. Our studies show that for the supported iron catalysts, larger pore sizes of the silica resulting from the loading of iron and the oxidation state of iron being Fe(III) are essential for the high reaction rates. Notably, the catalysts show stability against leaching, regardless the presence or absence of a dendrimer as an additional stabilizing agent. The catalysts could be used for at least three runs without the loss of activity. The successful Michael addition reactions of indole or 2-methylindole and different α , β -unsaturated ketones corroborate the synthetic scope of the catalysts. These results show promises of using supported iron catalysts as inexpensive and effective alternatives for the formation of C–C bonds.

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1. Introduction

The large majority of catalysts consist of metals, specifically precious metals such as Pt, Pd, Au, and Rh [1]. Many of these catalysts have been synthesized in the form of heterogeneous catalysts, which offer many benefits, including easy product separation, recyclability, and efficiency. These metal-containing heterogeneous catalysts can be loaded into porous supports, such as silica [2], in order to achieve heterogeneity. However, precious metals are vulnerable to leaching in organic solutions as sometimes they cannot attach strongly to the silica framework [3–6]. Heavy metals, such as Pt, have been shown to be toxic depending on the dose and type of exposure, acute or chronic [7]. Aside from toxicity, metal leaching reduces the catalytic efficacy of a catalyst over time. Dendrimers have been used to prevent toxic metal leaching and to improve the overall stability and recyclability of metal-containing heterogeneous catalysts [8–10].

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Iron is an inexpensive earth-abundant metal and has been an attractive element for catalysis [11-16]. The synthesis and characterization of Fe salts loaded onto mesoporous silica SBA-15 has been explored by Kuhn et al. [17] and Tilley et al. [18], but the catalytic performances of these materials have yet to be studied in comparison to those containing dendrimers [17-19]. In this study, the hydroxyl-terminated generation-4 polyamidoamine (PAMAM) dendrimer, denoted as G4OH, are investigated as a potential stabilizer of iron, as they are known to encapsulate and stabilize the nanoparticles of noble metals including Pt, Pd, Au, and Rh [9,20-24]. Supported iron catalysts with or without G4OH were synthesized, characterized, and compared in catalytic Michael addition reactions. A Michael addition reaction involving indole and butenone was used as a model reaction to test the ability of supported iron catalysts to catalyze C-C bond formation. C-C bond formation reactions remain one of the most useful but challenging chemical processes for use in synthetic industries [25], among which Michael addition reactions are an important part of the total synthesis for many complex organic compounds [26]. The formation of C-C bonds under mild conditions is necessary for the commercial production especially in the pharmaceutical industry [27,28]. Previously, Pitchumani et al. showed that Michael addition reactions were achieved by an acidified silica under mild conditions with high yields [29]. In this work, the characterization of supported iron catalysts, reaction kinetics studies, metal-leaching tests, and cata-

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lyst recyclability tests were carried out to understand the catalytic properties of supported iron catalysts. Supported iron catalysts show promises in that they are not only highly active but also stable as they bind strongly to the silica support framework.

2. Experimental

2.1. General information

Unless otherwise noted, all commercial materials were used as received without purification. All glassware was dried at $100 \degree$ C for 8 h before use.

2.2. Chemicals

Iron (III) chloride (\geq 99.99%), iron(II) sulfate heptahydrate (\geq 99.0%), indole (98%), 2-methylindole (98%), butenone (99%), 2-cyclopenten-1-one (98%), 2-cyclohexen-1-one (\geq 95%), 4-phenyl-3-buten-2-one (99%), and 1,3-diphenyl-2-propenone (\geq 98.0%) were purchased from Sigma-Aldrich. All PAMAM dendrimers, G4OH, G4NH₂, and G4SA were purchased from Dendritech Inc. as water solutions. Deuterated solvents (chloroform, toluene, benzene, water, methanol, and acetonitrile) were purchased from Cambridge Isotope Laboratories, Inc.

2.3. Instruments

The catalyst loading was analyzed by Optima 7000 DV Inductively coupled plasma optical emission spectroscopy (ICP-OES). The transmission electron microscopy (TEM) images were taken with an FEI Tecnai TEM at an accelerating voltage of 200 kV. All NMR spectra were obtained at ambient temperature on Bruker AVB-400 and AVQ-400 spectrometers. Centrifugation was performed on a Thermo Scientific IEC Centra[®] CL2. Physisorption experiments were recorded on Micromeritics 3Flex with Ultra-high-purity grade N₂ (Praxair, 99.999% purity). A liquid nitrogen bath was used for the measurements at 77 K. Powder X-ray diffraction (PXRD) patterns were recorded using a Rigaku Miniflex 600 (Bragg-Brentano geometry, Cu K α radiation λ = 1.54 Å) diffractometer. X-ray photoelectron spectrometric (XPS) experiments were performed on a Perkin-Elmer PHI 5300 XPS spectrometer with a position-sensitive detector and a hemispherical energy analyzer in an ion-pumped chamber (evacuated to 2×10^{-9} Torr). The Mg K α (*hv* = 1253.7 eV) X-ray source of the XPS spectrometer was operated at 350 W with 15 kV acceleration voltage.

2.4. Synthesis of the support

The procedure established by Zhao et al. was followed for the synthesis of the support SBA-15 [30]. Briefly, 8 g of Pluronic 123 was dissolved in 60 g of deionized H_2O and 240 g of 2 M HCl with stirring at 35 °C for 1 h. Then, 17 g of tetraethyl orthosilicate was added and allowed to stir for an additional 20 h. Next, the mixture was aged at 80 °C for 24 h overnight without stirring. The resulting solid was collected by filtration and washed with water and ethanol, and then finally dried at 100 °C. The solid was then heated to 500 °C in 8 h and held at 500 °C for 6 h and then allowed to cool. The resulting solid, SBA-15, was grinded using mortar and pestle and stored before usage.

2.5. Synthesis of catalysts

For the synthesis of the supported iron catalyst Fe/SBA-15, approximately 0.06 mmol of FeCl₃ (9.73 mg), 1 g of SBA-15, and 60 mL of H_2O was mixed for 24 h at room temperature with stirring. Care was taken to quickly weigh FeCl₃ as it is extremely

Table 1

Loading amount	of iror	ı in	catalysts.
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catalyst	Fe concentration (mmol/g) ^a	percent loaded (%) ^a
Fe/G4OH/SBA-15 Fe/G4OH/SBA-15(10×) Fe/SBA-15	$\begin{array}{c} 4.49 \times 10^{-2} \\ 1.97 \times 10^{-1} \\ 4.54 \times 10^{-2} \end{array}$	74.9 65.7 75.7
$Fe/SBA-15(10\times)$	2.13×10^{-1}	71.0

^a Approximately 10 mg of each catalyst was used in ICP-OES analyses. Samples were prepared by digesting approximately 10 mg of a solid catalyst in a centrifuge tube with 0.2 mL HF, 0.2 mL HNO₃, and 0.6 mL HCl, and then diluted to 10 mL with deionized water. The total amount of iron in the sample was calculated accordingly, which was divided by that amount of iron used in the synthesis process to calculate the loading percentage.

hygroscopic. The mixture was centrifuged at 4000 rpm for 5 min, the supernatant was discarded and the resulting solid was dried at 100 °C for 20 h. In addition, a version was synthesized with the G4OH dendrimer, and the resulting catalyst was called Fe/G4OH/SBA-15. The synthesis of Fe/G4OH/SBA-15 is similar to that of Fe/SBA-15. First, 1g of SBA-15, 1.5 µmol of G4OH dendrimer, and 30 mL of deionized H₂O were allowed to stir for three hours at room temperature. Then the solution was centrifuged for 5 min at 4000 rpm, and the supernatant was discarded. Next, 0.06 mmol of FeCl₃ was added and allowed to mixed for 24 h at room temperature with stirring. The mixture was centrifuged at 4000 rpm for 5 min, the supernatant was discarded and the resulting solid was dried at 100 °C for 20 h. Two other catalysts were also synthesized using 0.6 mmol of FeCl₃ without or with $15 \,\mu$ mol of G4OH in the same way, which are denoted as Fe/SBA-15($10 \times$) and Fe/G4OH/SBA-15($10 \times$), respectively.

2.6. Representative procedure for catalytic reactions

To a dry 2 mL reaction vial equipped with a stir bar, were added 0.05 mmol of butenone, 0.06 mmol of indole, 0.2 mL CDCl_3 , and a catalyst. The reaction mixture was heated with stirring at the desired temperature for 22 h. The mixture was then cooled to room temperature, and the solid catalyst filtered using a polytetrafluoroethylene syringe filter. The filtrate was transferred to a NMR tube for analysis.

3. Results and discussions

Inductively coupled plasma optical emission spectroscopy (ICP-OES) was used to determine iron concentrations of the supported iron catalysts, and the results are summarized in Table 1. 75.7% and 74.9% of iron used in the synthesis were found to be loaded into Fe/SBA-15 and Fe/G4OH/SBA-15, respectively (Table 1). While the Fe/SBA-15($10\times$) catalyst had 4.7% lower loading percent compared to Fe/SBA-15, the Fe/G4OH/SBA-15($10\times$) catalyst had a decrease of 9.2% in loading compared to Fe/G4OH/SBA-15. The dendrimer decreases the loading percent of iron, which is more significant at higher concentrations of iron.

 N_2 physisorption isotherms show that the addition of iron increased the pore size of the SBA-15, which is likely due to the restructuring of the pores during the loading process, while the G4OH dendrimer decreased the pore size because of their steric bulk (Fig. 1A). The physisorption isotherms for all four samples are Type IV isotherms which are indicative of multilayer adsorption [31]. The supported iron catalysts retain their mesoporous structure after the synthetic process, as expected. In the case of Fe/G4OH/SBA-15(10×), the non-negligible amount of G4OH greatly decreased the pore size, which outweighed the effect of the iron on the SBA-15. In addition, the lower S_{BET} of Fe/G4OH/SBA-15(10×) shows that surface areas decrease with the addition of dendrimers (Table 2). Similarly, the V_{micro} was reduced for samples contain-



Fig. 1. (A) N₂ physisorption isotherms of solid materials at 77 K with adsorption and desorption points represented by closed and open symbols, respectively. (B) PXRD patterns of Fe/SBA-15 and Fe/G4OH/SBA-15 catalysts. (C-F) TEM images of (C) Fe/G4OH/SBA-15, (D) SBA-15 (E) Fe/G4OH/SBA-15(10 ×), (F) Fe/SBA-15(10 ×). The scale bar is 10 nm.

Table 2

Physisorption characterizations of the solid materials.

Catalyst	$S_{\rm BET} (m^2 g^{-1})^{\rm a}$	D _{pore} (nm) ^b	$V_{\rm BJH}~({ m cm}^3~{ m g}^{-1})^{ m c}$	$V_{ m micro}~(m cm^3~g^{-1})^{ m d}$
Fe/G4OH/SBA-15	710	5.96	0.75	0.064
Fe/G4OH/SBA-15(10×)	571	5.84	0.63	0.040
$Fe/SBA-15(10\times)$	789	5.70	0.74	0.100
SBA-15	731	5.48	0.63	0.093

^a S_{BET}: the BET surface area.

^b *D*_{pore}: average pore diameter.

^c BJH adsorption cumulative volumes of pores between 0.85 nm and 150.00 nm radium.

^d *t*-plot micropore volume.

ing the dendrimer. The size of micropores is close to the sizes of small molecule reactants and products, so the pore size is related to the diffusion of reactants and products; larger pores correlate with faster reaction rates especially when bulkier reactant species are used. On the other hand, Fe/SBA-15(10×) had a larger S_{BET} and V_{micro} , attributable to the high amount of iron in this sample.

The powder X-ray diffraction (PXRD) patterns of Fe/SBA-15 and Fe/G4OH/SBA-15 show only a peak for amorphous silica, but no peak for iron species is visible (Fig. 1B), indicating that the iron is not forming detectable nanoparticles. In addition, no particle is observed from transmission electron microscopy (TEM) images of the samples (Fig. 1 C-F). In fact, attempts were made to reduce Fe(III) using strong reducing agents such as NaBH₄ but these attempts did not lead to the formation of iron nanoparticles. From these observations, either the nanoparticles are below the detection limit, i.e., smaller than ~0.5 nm, or the iron is staying in the form of Fe(III) or Fe(II) as isolated single ions. According to the negative standard reduction potential of Fe²⁺/Fe relative to the standard hydrogen electrode, the formation of Fe(0) nanoparticles is thermodynamically unfavorable under our reduction conditions. Also based on the

results discussed below, the iron probably exists as isolated single ions in the supported iron catalysts.

3.1. Michael addition and kinetics

Since nanoparticle formation was not observed, the catalytically active species was thought to be iron ions. The Michael addition in Fig. 2A was studied to determine the catalytic properties of supported iron catalysts. Comparing unsupported Fe(III) and Fe(II) ions, Fe(III) is more active in the reaction than iron (II), as 3.07 μ mol of FeCl₃ and 3.55 μ mol of FeSO₄ were found to catalyze the Michael addition reaction to 100% and 27.0%, respectively, at 50 °C; no conversion is observed without catalysts. Because the reaction can be acid catalyzed [29], the higher activity of Fe(III) is expected because Fe(III) is a stronger Lewis acid than Fe(II).

X-ray photoelectron spectroscopy (XPS) was utilized in an attempt to determine the oxidation state of iron in these catalysts. However, no iron signal was detected even for the concentrated samples, probably because the iron has a small weight percentage [$\sim 1 \text{ wt\%}$ for the Fe/SBA-15(10 ×)] and is distributed evenly in the



Fig. 2. (A) Schematic of the catalytic Michael addition reaction. (B) Rates of the Michael addition reaction catalyzed by iron catalysts and SBA-15. Reactions were carried out with 0.05 mmol of butenone, 0.06 mmol of indole, 1.0 mL CDCl₃ at 50 °C, with 10 mg Fe/SBA-15, Fe/G40H/SBA-15, and SBA-15, and 0.449 µmol of FeCl₃ (equimolar of Fe for all catalysts). (C) Arrhenius Plots for the Michael addition of indole and butenone. Reactions were carried out with 0.05 mmol of butenone, 0.06 mmol of indole, 0.2 mL CDCl₃ for 1.5 h with 10 mg of catalysts.

solid, which leads to a surface concentration of iron too low to be detected by XPS.

In addition to the identification of Fe(III) as the catalytic species, the reaction rates with different catalysts were compared. The support SBA-15 displays very little catalytic activity, thanks to its very small number of acid sites, but its activity is not comparable to that of catalysts containing iron (Fig. 2B). The percent yield is approximately 90% after 20 h of reaction for the three iron-containing catalysts. Diffusion rates are not an obstacle for these catalysts. The activation energy was 108 kJ/mol and 94 kJ/mol, based on the Arrhenius plot (Fig. 2C) for Fe/SBA-15 and Fe/G4OH/SBA-15, respectively.

3.2. Dendrimer effects

As dendrimers could provide additional activity and stability to the precious metal nanoparticle catalysts, to check whether the same is true for the iron species, three different dendrimers were mixed with FeCl₃ in order to understand how iron interacts with different dendrimers. The mixing process involved sonication of 6 µmol of dendrimer and 45 µmol of FeCl₃ in 1 mL of deionized H₂O for an hour, and then aging for 24 h to allow the complexation between the iron and the dendrimer. G4OH and succinamic acidterminated generation four polyamidoamine (G4SA) dendrimers both complexed with iron as observed from the transition from a cloudy to clear orange appearance, which occurred within three minutes. The activity of iron was not hampered by the coordination with these dendrimers. 10 µL of aged FeCl₃/G4OH and FeCl₃/G4SA solutions were used to carry out the Michael addition reaction in methanol for 1.5 h at 20 °C, and the yields were 17.4% and 22.5%, respectively, comparable to free FeCl₃. However, mixing FeCl₃ with the primary amine-terminated fourth-generation polyamidoamine (G4NH₂) led to a precipitation, which could be attributed to a high

pH of the solution resulting from the amine groups. This study focused on the investigation of G4OH, so its effects on catalysis could be compared to earlier works in our group that involved G4OH dendrimers [9,32].

In order to further study the effects of the G4OH dendrimer on iron, hot filtration tests were performed to examine the potential leaching of iron from Fe/SBA-15 and Fe/G4OH/SBA-15. A hot filtration was performed for a run after two hours of reaction, and the filtrate was heated under the same condition before the filtration till 4 h of total reaction time. The yield of such a run remains the same after the hot filtration, but a run of 4 h without the filtration gives a higher yield (Fig. 3A). Since free Fe(III) is catalytically active, it is expected that if leaching does occur, the yield will increase even after the filtration of the solid catalyst. Thus, Fig. 3A suggests that neither Fe/SBA-15 nor Fe/G4OH/SBA-15 showed iron leaching into the solvent, as the yield did not increase after the filtration in either case. To further ensure the validity of the hot filtration test, the concentrated catalysts Fe/SBA-15(10×) and Fe/G4OH/SBA- $15(10 \times)$ were also examined in the same manner (Fig. 3B) to rule out the possibility that the concentrations of the potential leached iron were so small that the increased yield is not detectable. A higher concentration of iron could also increase the chance for leaching, so the stability of the catalysts could be more rigorously examined. Interestingly, no leaching was seen from either of the concentrated catalysts (Fig. 3B). This is quite surprising as even under high concentrations the iron stays attached to the silica support with or without dendrimer. Iron does not need a dendrimer to attach to the silica framework, which could be explained by the strong interaction between iron ions and the oxygen in the silica. The test with the concentrated catalysts also spotlights the effects of the dendrimer on the catalytic activity, as the yield of Fe/SBA- $15(10 \times)$ greatly exceeded that of Fe/G4OH/SBA- $15(10 \times)$ (Fig. 3B), partially because of the larger amount of iron in the same mass of



Fig. 3. (A) and (B) Hot filtration tests of (A) Fe/SBA-15 and Fe/G4OH/SBA-15, and (B) Fe/SBA-15(10×) and Fe/G4OH/SBA-15(10×). Reactions were carried out with 0.05 mmol of butenone, 0.06 mmol of indole, 1.0 mL CDCl₃ at 50 °C, with 10 mg of a catalyst. (C) Recycling tests of Fe/SBA-15(10×) and Fe/G4OH/SBA-15(10×). Reactions were carried out with 0.20 mmol of butenone, 0.24 mmol of indole, 0.10 mmol of CHCl₂CHCl₂ as the internal standard, 1.0 mL CDCl₃ at 50 °C, with 50 mg catalysts for 23 h. Upon the end of each 23 h cycle, the liquid was removed after centrifugation, the catalysts were dried under rotary evaporation, a new stock solution of the solvent and reactants was added, and the next cycle started.



Fig. 4. Solvent screening. Reactions were carried out with 0.05 mmol of butenone, 0.06 mmol of indole, 0.2 mL solvent at 20 °C, with 10 mg Fe/SBA-15 (0.4 mol% Fe) for 22 h.

Fe/SBA-15($10\times$) compared to Fe/G4OH/SBA-15($10\times$) (Table 1). The steric effect of the dendrimer might further lower the turnover rate of Fe/G4OH/SBA-15($10\times$).

In addition to the hot filtration test, recyclability tests were performed on the Fe/SBA-15(10×) and Fe/G4OH/SBA-15(10×) catalysts. It was initially thought that the dendrimer would offer the advantage of recyclability based on the cases of Au, Pt, and Rh. However, both catalysts maintained 100% yield after each cycle, for at least three cycles under the test conditions (Fig. 3C). Treatments to reactivate the catalysts by heating them in the air at 100 or 150 °C for 2 h after each cycle were performed in case of the loss of catalyst activity between cycles, but catalysts after these treatments also showed 100% conversion in each cycle.

3.3. Reaction optimization and synthetic scope

The reaction was carried out in six solvents in order to optimize the yield and see how solvents affect the catalysts. Fe/SBA-15 performed optimally in chloroform. Toluene and benzene both provided high yields as well. Furthermore, the catalysts provided mediocre yields in acetonitrile, methanol, or water (Fig. 4). The partial insolubility of the reactants (indole and butenone) in methanol or water may account for the low yields in these solvents. Aside from the solvent screening, the synthetic scope of the reaction was also explored in CDCl₃ at 50 °C and C_6D_6 at 80 °C (Table 3). In these tests, the reaction time was chosen to be 23 h to compare the reaction rates of various reactants at different conditions. With higher catalysts loadings or longer reaction times, all these reactions can reach a full conversion, demonstrating the scope of applicability of the supported iron catalysts. Notably, among the substitution of butenone for α , β -unsaturated ketones tested so far, butenone showed the highest reaction rate, presumably due to the least steric effect it experienced as a terminal alkene. In general, 2-methylindole reacts faster than indole, attributable to the higher nucleophilicity due to the electron donation from the methyl group.

4. Conclusions

The Fe/SBA-15 catalyst is at least equally active compared to its dendrimer counterpart, and almost as active as free Fe(III) in a solution. The Fe/SBA-15 catalyst has the advantage of being a stable catalyst, in comparison to other metal catalysts loaded in silica, as it experiences no toxic metal leaching even without the dendrimer, resulting in a more cost-effective application. On the

Table 3 Reaction scope tests.

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ketone +	-R4 mol % Fe/SBA-15(10x)	A product	x: R = H		
0.05 mmol 0.06 mmol	CHCl ₂ CHCl ₂ (internal standar 23 h, solvent	d) B	∃: R = Me		
ketone	nucleophile	product	solvent	temperature (°C)	yield (%)
o N	A B	O HN R	CDCl ₃ CDCl ₃	50 50	100 100
	A A B B	HN-R	$\begin{array}{c} CDCl_3\\ C_6D_6\\ CDCl_3\\ C_6D_6\end{array}$	50 80 50 80	33 53 51 56
0	A A B B		$\begin{array}{c} CDCl_3\\ C_6D_6\\ CDCl_3\\ C_6D_6\end{array}$	50 80 50 80	33 66 80 87
Ph Me	A A B B	HN R Ph	$\begin{array}{c} \text{CDCl}_3\\ \text{C}_6\text{D}_6\\ \text{CDCl}_3\\ \text{C}_6\text{D}_6 \end{array}$	50 80 50 80	17 44 42 74
Ph Ph	A A B B	HN R Ph O	$CDCl_3 \\ C_6D_6 \\ CDCl_3 \\ C_6D_6$	50 80 50 80	11 41 52 73

other hand, Fe/SBA-15 also has larger pores than Fe/G4OH/SBA-15, allowing for higher diffusion rates. The catalyst can also catalyze the C—C bond formation with several different reactants under a variety of solvents with high yields. As a heterogeneous catalyst consists of an earth-abundant metal and a mesoporous silica support, Fe/SBA-15 provides a promising starting point for stable and recyclable catalysts that do not need extra stabilizers. These catalysts are highly active, recyclable, cost-effective, and prove greatly useful for synthetic reactions involving C—C bond formation under mild conditions.

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