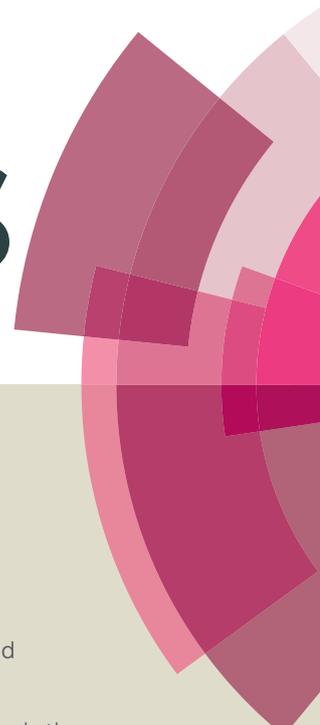


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Facile *O*-Glycosylation of Glycals Using Glu-Fe₃O₄-SO₃H, a Magnetic Solid Acid Catalyst

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A new glucose derived magnetic solid acid catalyst (Glu-Fe₃O₄-SO₃H) was synthesized in a convenient and ecofriendly manner and well characterized using FTIR, PXRD, EDAX, SEM, and XPS which showed the presence of Fe₃O₄ embedded on the surface of the catalyst along with -SO₃H, -OH and -COOH functional groups. This new heterogeneous catalyst was studied for synthesis of 2-deoxy galactosides/glucosides with good yields and selectivity. Moreover, the catalyst can be easily separated from the reaction with an external magnetic force and reused minimum four times without any significant decrease in yields of the products after every recycle.

Keywords: glycosylation, glycals, magnetic, sulfonated, recycled

1. Introduction

2-deoxy-*O*-glycosides are found widely in number of natural products.¹⁻² 2-deoxy-*O*-glycoside component in any natural product plays an important role as it is responsible for the bioactivity of a drug. For chemical synthesis of these natural products large quantities of 2-deoxy-*O*-glycosides are required. Hence, attention has been extensively paid for synthesis of these glycosides. Till date, number of homogeneous catalyst have been reported for the synthesis of 2-deoxy-*O*-glycosides by direct addition of alcohols to glycals using protic acids or Lewis acids.³⁻⁸ They suffer from drawback of corrosion, contamination and needs neutralization after the reaction and hence the workup is tedious. Such catalysts are difficult

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to separate from the reaction and they cannot be reused. Also one main disadvantage in these direct glycosylations is the possibility of the Ferrier reaction. Heterogeneous catalysts have advantages over homogeneous catalyst that they are inexpensive, more efficient, stable, easily separable and reusable. Hence there is a need to develop mild and efficient catalyst for glycosylation reactions to overcome the above mentioned problems. Balmond et. al⁹ in 2012,

reported selective synthesis of 2-deoxy-*O*-galactoside using thiourea as a catalyst. Das et. al¹⁰ in 2015, reported selective synthesis of 2-deoxy-*O*-glycosides using electron deficient pyridinium salts. Our continuous interest in this field prompted us to synthesize glucose derived magnetic solid acid catalyst.¹¹ Herein, we report the synthesis of new Glu-Fe₃O₄-SO₃H catalyst and showed its application for tetrahydropyran protection of alcohols and glycosylation of protected glycols in the synthesis of 2-deoxy-*O*-glycosides (Figure 1).

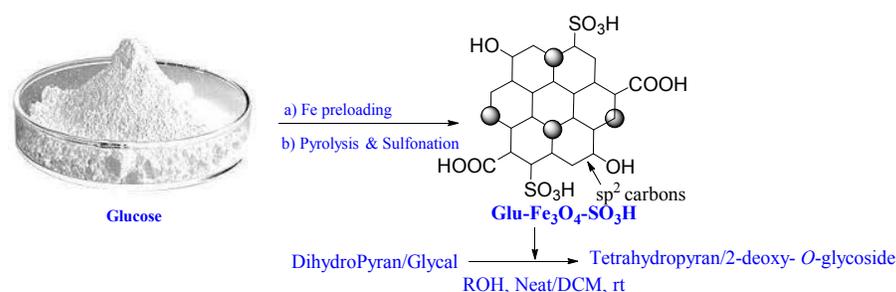


Figure 1. Schematic representation for synthesis of Glu-Fe₃O₄-SO₃H catalyst and its application for THP protection of alcohol and 2-deoxy-*O*-glycoside synthesis.

2. Experimental

2.1 Catalyst Preparation

5.0 g of glucose and 276 mL of FeCl₃ solution with a concentration of 100 mmol/L were mixed in a flask and stirred for 5 h at rt. Then, the water in the mixture was evaporated, and the solid residue was dried at 378 K overnight and sieved again to collect the particles with a size smaller than 120 mesh to obtain the Fe preloaded glucose. Fe preloaded glucose was then stirred with *p*-TSA (5 eq) at 140 °C for 24 h under argon atmosphere. The mixture was then cooled to rt, and then slowly added to a beaker containing 500 mL deionised water. The suspension mixture was then filtered off and washed repeatedly with deionised water to remove all the sulfate ions (SO₄²⁻). The solid was further washed with absolute ethanol to remove the water, and then dried at 353 K overnight to get a black magnetic material (Glu-Fe₃O₄-SO₃H).

2.2 General procedure for THP protection of alcohols using Glu-Fe₃O₄-SO₃H under neat conditions

Dihydropyran (0.30 mmol), alcohol (0.9 mmol) and catalyst Glu-Fe₃O₄-SO₃H (1 wt %) were stirred together in a screw-capped vial under argon atmosphere. The mixture was stirred neat at rt for 2-5 min. The reaction was monitored by TLC analysis. After completion of the reaction, DCM was added and the catalyst was separated from the reaction mixture by applying external magnetic field. DCM layer was decanted and then evaporated to obtain the product.

2.3 General procedure for glycosylation of protected glycols using Glu-Fe₃O₄-SO₃H.

Glycol (1.2 mmol), alcohol (1.4 mmol) and catalyst Glu-Fe₃O₄-SO₃H (5 wt %) were stirred together in a screw-capped vial under argon atmosphere neat or in DCM (DCM was used when the glycol and alcohol both are solids). The mixture was stirred for required temperatures and required time. The reaction was monitored by TLC. After completion of the reaction the catalyst was separated from the reaction mixture by applying external magnetic field (In neat conditions, DCM was added after completion of the reaction). DCM layer was then decanted and evaporated to obtain the product. The anomeric ratio's were determined from the ¹H NMR of the products.

3. Results and Discussion

3.1 Characterization of the catalyst

Due to our continuous interest in this field, we have synthesized a magnetic carbonaceous solid acid catalyst Glu-Fe₃O₄-SO₃H. For preparation of this catalyst, we choose readily available D-glucose as a carbon precursor, Fe was preloaded on glucose using FeCl₃ and *p*-TSA was used as a sulphonating agent to create active acidic sites. Initially Fe was preloaded on glucose using FeCl₃. The free -OH groups in glucose easily coordinated with adsorbed Fe (III) ions and then evaporation of solvent and drying gave black Fe (III) based complex. This

complex was then pyrolysed and sulfonated simultaneously using *p*-TSA at 140 °C under nitrogen. The Fe preloaded on glucose was partly hydrolysed to FeO(OH) during drying. FeO(OH) was further reduced to Fe₃O₄ by reducing components like H₂, CO₂ and CO which are formed during carbonation process.¹² Pyrolysis and sulfonation in-situ leads to formation of a polycyclic aromatic structure embedded with active Fe₃O₄, -SO₃H, -COOH and -OH sites.

The catalyst thus obtained was characterized with FT-IR (Spectrum 400), PXRD (Panalytical X'Pert Pro), Elemental analysis from EDAX (Nova Nano SEM 450), SEM (Quanta™ Scanning Electron Microscope), XPS (Prevac Ambient Pressure Photo Electron Spectroscopy) and BET surface area (Quantachrome ASiQwin). The acid densities were measured by acid base titration.¹³ FT-IR spectrum (Figure 2a) showed characteristic peaks at 1012 cm⁻¹ and 1040 cm⁻¹ which are attributed to O=S=O stretching vibrations in -SO₃H groups and peak at 1127 cm⁻¹ for SO₃H stretching. This indicates that the sulfonic acid groups have been successively incorporated on the catalyst surface. Peaks at 1645 cm⁻¹ attributed for C=C stretching vibrations in aromatic carbons and peak at 1670 cm⁻¹ attributed for C=O stretching. Peak at 1714 cm⁻¹ attributed to presence of C=O stretching vibration of -COOH group. Bands at 2925 cm⁻¹ attributed for C-H stretching band. Bands due to O-H stretching were observed at 3410 cm⁻¹. The PXRD (Figure 2b) showed a weak but broad peak of 2θ at 15-30°, indicating formation of amorphous carbon having aromatic carbon sheets oriented in a random fashion. The sharp peaks seen indicates the formation of Fe₃O₄ crystallite in the pyrolysis process. The energy dispersive X-ray analysis (Figure 2c) confirms that the catalyst surfaces are composed mainly of C, O, Fe and S. Composition of S and Fe is found to be 7.4% and 7.7% respectively from EDAX. The elemental analysis showed composition of C to be 50%, H to be 4% and S to be 9%. SEM (Figure 2d) image shows formation of porous nature of the catalyst. The surface composition of Glu-

Fe₃O₄-SO₃H was analysed by XPS (Figure 2e). The C 1s spectrum includes six peaks with different binding energy values. The peaks could be assigned to the carbon atoms in the forms of C-S (283.5 eV), C-C (284 and 284.5 eV), C-O (285 eV), C=O (285.5 eV), O=C-O (286 eV). The S 2p spectrum showed three different peaks that can be assigned to S-C (186.5), S-O (169 eV) and S=O (169.5 eV). O 1s spectrum shows peaks in the range 530-535 eV indicating the presence of Fe-O and C-O-Fe groups suggesting the linkage of Fe₃O₄ with

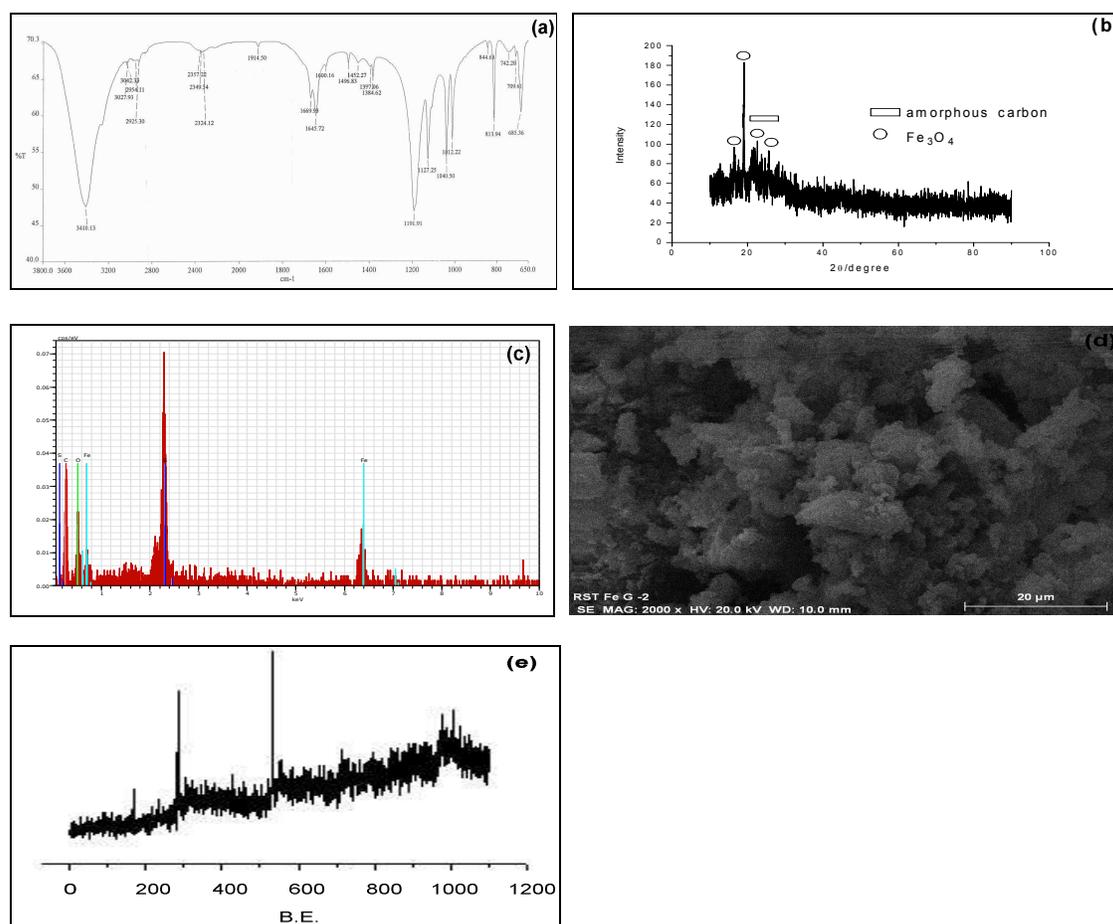


Figure 2. a) FT-IR of Glu-Fe₃O₄-SO₃H. b) PXRD of Glu-Fe₃O₄-SO₃H. c) EDAX of Glu-Fe₃O₄-SO₃H. d) SEM image of Glu-Fe₃O₄-SO₃H. e) XPS of Glu-Fe₃O₄-SO₃H

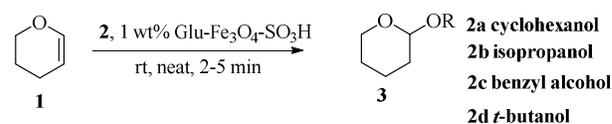
porous carbon. BET surface area, pore size and pore volume was calculated using the standard Brunauer-Emmett-Teller (BET) equation and was found to be 3.38 m²/g, 9.53 Å^o and 6.07 m³/g respectively. The total acid density and the sulphonic acid density of Glu-

Fe₃O₄-SO₃H based on acid base titration was found to be 2.87 mmol/g and 1.46 mmol/g respectively.

3.2 Effect of catalyst on tetrahydropyran protection of alcohols

Initially we focused our attention on the tetrahydropyranyl (THP) protection of alcohols. As a first set of experiments, we studied the THP protection of various primary, secondary and tertiary alcohols like cyclohexanol **2a**, isopropanol **2b**, benzyl alcohol **2c** and *t*-butanol **2d** with dihydropyran **1** (Table 1).

Table 1. Tetrahydropyran protection of alcohols using Glu-Fe₃O₄-SO₃H catalyst under solvent free conditions at room temperature



Entry	Alcohol	Product	Yield ^a (%)
1.	2a		99
2.	2b		89
3.	2c		96
4.	2d		80

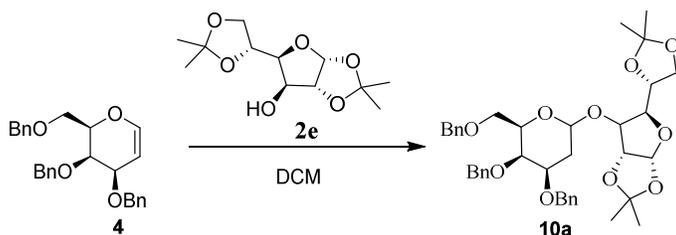
[a] Isolated yields

To our delight, the Glu-Fe₃O₄-SO₃H catalyst efficiently catalyzed this reaction under neat reaction conditions at rt within 2-5 minutes to obtain THP-protected products **3a-3d** using 1 wt% loading of catalyst to give full conversion and high yields. The reaction when performed without using Glu-Fe₃O₄-SO₃H catalyst, no formation of THP protected product was observed.

3.3 Effect of catalyst on glycosylation of protected glycals

After successful establishment of the THP protection of various alcohols, we turned our attention towards the more challenging glycosylation reaction of different glycols using various acceptors as alcohols. For this study the required glycol components 3,4,6-tri-*O*-benzyl, 3,4,6-tri-*O*-silyl and 3,4,6-tri-*O*-acetyl galactals (**4-6**) as well as 3,4,6-tri-*O*-benzyl, 3,4,6-tri-*O*-silyl and 3,4,6-tri-*O*-acetyl glucals (**7-9**) were synthesized by known procedure.¹⁰ Glycosyl acceptors chosen for the study were bisacetone-D-glucose **2e**, (-) menthol **2f**, cholesterol **2g**, octanol **2h**, propargyl alcohol **2i** and methanol **2j**.

Initially, we optimized the reaction conditions for glycosylation of 3,4,6-tri-*O*-benzyl *D*-galactal¹⁰ **4** using bisacetone-D-glucose **2e** using Glu-Fe₃O₄-SO₃H catalyst (Table 2). Since both reagents are solid, DCM was used as a solvent for glycosylation reaction. The reaction was studied at various temperatures such as -20 °C, 0 °C, rt and 40 °C using 10 wt% of catalyst loading. It was observed that the reaction did not proceed at all at -20 °C in DCM even after 24 h. At 0 °C, in DCM after 12 h, the reaction did not proceed to completion thus giving 45% yield of the glycoside **10a** in 1:1 α : β anomeric ratio. At rt in DCM, glycosylation was found to be complete giving 94% yield of the glycoside **10a** in 83:17 α : β anomeric ratio. When the glycosylation was carried out at 40 °C in DCM, only 32% of the glycosylated product **10a** was obtained along with the Ferrier rearranged product. Hence the optimum temperature for the reaction was found to be room temperature. The catalyst loading was further studied and it was found out that glycosylation of **4** with 5 wt% catalyst in DCM at rt gave quantitative yield of the glycoside with 83:17 α : β selectivity. When the catalyst loading was further decreased to 1 wt% at rt, it was observed that the reaction was incomplete. Hence 5 wt% catalyst loading was optimized for further glycosylation reactions that were carried out. It was also observed that the isopropylidene groups were stable under these catalytic conditions.

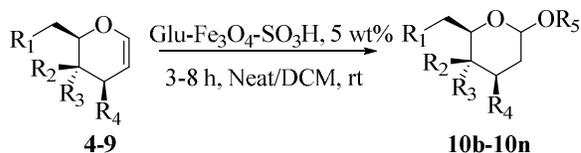
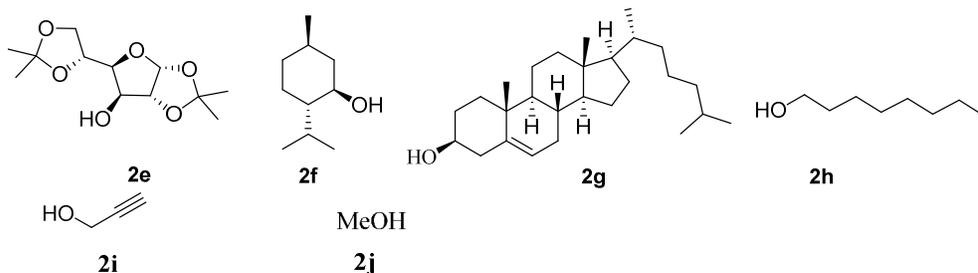
Table 2. Optimisation of reaction conditions in glycosylation of 3,4,6-tri-*O*-benzyl-*D*-galactal **4** and alcohol **2e** in presence of Glu-Fe₃O₄-SO₃H catalyst^a

Entry	Catalyst loading (wt %)	Temp (°C)	Time (h)	Yield ^b (%)	α : β ratio ^c
1	10	-20	24	-	-
2	10	0	12	45	50:50
3	10	rt	3	94	83:17
4	10	40	4	32	50:50
5	5	rt	3	97	83:17

[a] All reactions performed in screw-capped vial on 100 mg scale of **4** and **2e** in 2 mL DCM. [b] Isolated yields [c] Ratio determined from ¹H NMR.

Additions of various alcohols **2e-2j** on different glycals **4-9** using Glu-Fe₃O₄-SO₃H catalyst are reported in Table 3. It was observed that addition of alcohols **2f**, **2g** and **2h** with 3,4,6-tri-*O*-benzyl-*D*-galactal **4**, afforded exclusively the α -galactoside with excellent yields and selectivity (Table 3, entries 1-3). Addition of alcohol **2i** gave formation of galactoside in α : β 71:29 ratio (Table 3, entry 4). When methanol **2j** was used, selectively α -galactoside was formed in good yield (Table 3, entry 5). Both primary and secondary alcohols reacted smoothly to provide the glycoside product. 3,4,6-tri-*O*-silyl-*D*-galactal **5** with alcohol **2e** afforded the glycoside in 91:9 α : β ratio with excellent yield (Table 3, entry 6). 3,4,6-tri-*O*-acetyl-*D*-galactal **6** did not undergo addition of alcohol **2e** even on prolonged time (Table 3, entry 7). The deactivating effect of acetyl protection in glycosylation has been reported earlier.¹⁴

Table 3. Addition of alcohols to the glycals **4-9** in the presence magnetic Glu-Fe₃O₄-SO₃H catalyst

**4:** R₁=R₂=R₄=OBn, R₃=H**7:** R₁=R₃=R₄=OBn, R₂=H**5:** R₁=R₂=R₄=OTBS, R₃=H**8:** R₁=R₃=R₄=OTBS, R₂=H**6:** R₁=R₂=R₄=OAc, R₃=H**9:** R₁=R₃=R₄=OAc, R₂=H

Entry	Glycal	Alcohol	Time (h)	Product	Yield ^a (%)	α:β ratio ^b
1	4	2f	8	10b	82	α
2	4	2g	6	10c	89	α
3 ^c	4	2h	4	10d	91	α
4 ^c	4	2i	3	10e	96	71:29
5 ^c	4	2j	3	10f	94	α
6	5	2e	3	10g	88	91:9
7	6	2e	5	-	no reaction	-
8	7	2e	3	10h	84	77:23
9	7	2f	6	10i	80	83:17
10	7	2g	6	10j	83	77:23
11 ^c	7	2h	4	10k	80	91: 9 ^d , 50:50 ^e , 90:10 ^f
12 ^c	7	2i	3	10l	93	90: 10 ^d , 50:50 ^e , 83:27 ^f
13 ^c	7	2j	3.5	10m	94	69: 31 ^d , 38:62 ^e , 91:9
14	8	2e	3	10n	81	91:9
15	9	2e	6	-	no reaction	-

[a] Isolated yields [b] Ratio's determined from ¹H NMR spectroscopy [c] 3 equiv of alcohols were used [d] α:β ratio of 2-deoxy-*O*-glycoside [e] Ratio of the Ferrier product and 2-deoxy-*O*-glycoside [f] α:β ratio of the Ferrier product.

We next turned our attention to glucals **7-9** for glycosylation. 3,4,6-tri-*O*-benzyl-*D*-glucal **7**, reacted smoothly with alcohol **2e**, **2f** and **2g** giving $\alpha:\beta$ glycoside in 77:23, 83:17 and 77:23 ratio respectively (Table 3, entries 8-10). In case of addition of alcohol **2h** to 3,4,6-tri-*O*-benzyl-*D*-glucal **7**, 2-deoxy-*O*-glycoside and Ferrier product were formed in a ratio of 50:50, of which 2-deoxy-*O*-glycoside was formed in a $\alpha:\beta$ ratio of 91:9, whereas Ferrier product was formed in a $\alpha:\beta$ ratio of 90:10 (Table 3, entry 11). Similarly in case of addition of alcohols **2i** and **2j** to 3,4,6-tri-*O*-benzyl-*D*-glucal **7** gave mixture of 2-deoxy-*O*-glycoside and Ferrier products (Table 3, entries 12 and 13). 3,4,6-tri-*O*-silyl-*D*-glucal **8** on addition of alcohol **2e** gave **91:9** $\alpha:\beta$ mixture of the glucoside (Table 3, entry 14). 3,4,6-tri-*O*-acetyl-*D*-glucal **9** did not show formation of any product (Table 3, entry 15) due to deactivating effect of acetyl group.

Table 4. Effect of catalyst on addition of alcohol to 3,4,6-tri-*O*-benzyl-*D*-galactal **4**

Entry	Catalyst	Alcohol	Yield (%)	$\alpha:\beta$ ratio of 2-deoxy- <i>O</i> -glycoside
1	TMSONO ₂	Cholesterol	68	81:19 ¹⁵
2	<i>p</i> TSA/[bmim]BF ₄	MeOH	91	4:1 ¹⁶
3	Ceric ammonium nitrate	MeOH	78	32:1 ¹⁷
4	Y zeolites	BnOH	80	Only Ferrier product ¹⁸
5	SiO ₂ .H ₂ SO ₄	MeOH	81	Only Ferrier product ¹⁹
6	Glu-Fe ₃ O ₄ -SO ₃ H	MeOH	94	Only α

Comparison of some known catalyst vs. Glu-Fe₃O₄-SO₃H has been shown in Table 4 for addition of alcohols to 3,4,6-tri-*O*-benzyl-*D*-galactal **4**. Addition of cholesterol to *D*-galactal **4** in presence of trimethylsilylnitrate gave 81:19 $\alpha:\beta$ ratio of 2-deoxy-*O*-glycoside (Table 4, entry 1). Whereas addition of methanol to *D*-galactal **4** in presence of *p*-TSA/[bmim]BF₄ and CAN gave 4:1 and 32:1 $\alpha:\beta$ ratio of 2-deoxy-*O*-glycoside respectively (Table 4, entries 2 and 3). Heterogeneous catalyst such as Y zeolites and SiO₂.H₂SO₄ gave no formation of 2-deoxy-*O*-glycoside instead gave only Ferrier rearranged product formation

(Table 4, entries 4 and 5). Whereas, Glu-Fe₃O₄-SO₃H gave addition of methanol to *D*-galactal 4 selectively forming α -2-deoxy-*O*-glycoside which indicates good efficiency of the catalyst for selective formation of 2-deoxy-*O*-glycoside (Table 4, entry 6).

It was observed that addition reaction of alcohols to galactals displayed high α -stereoselectivity, which is consistent with the anomeric effect. While, addition reaction of alcohols to glucals generally gave a low α : β ratio along with the Ferrier rearranged products in some cases. This phenomenon can be explained by the steric hindrance of the bulky benzyloxy/silyl group at C-4 position of galactals which prevents the attack of acceptors from the top face of the sugar ring, thus promoting the formation of major α -anomer.

3.4 Reusability of the catalyst

Reusability and isolation of the catalysts are important factors for any practical application. It is very convenient to recover Glu-Fe₃O₄-SO₃H catalyst in the end of the reaction by separating it using external magnetic field (Figure 3).



Figure 3. Separation of catalyst Glu-Fe₃O₄-SO₃H using external magnetic field.

The solid catalyst thus separated could be readily reused for the next runs without any prior activation. It was observed that reuse of Glu-Fe₃O₄-SO₃H catalyst gave no significant decrease in yield of products in case of THP protection as well as glycosylation of glycols after four recycles (Table 5).

Table 5: Reusability of Glu-Fe₃O₄-SO₃H catalyst in THP protection and 2-deoxy-*O*-glycoside synthesis

Entry	Reuse	THP protection ^a (%)	Glycosylation ^b (%)
1	1 st recycle	99	94
2	2 nd recycle	99	92
3	3 rd recycle	98	91
4	4 th recycle	96	86

[a] Reaction performed between **1** and **2a**. [b] Reaction performed between **4** and **2e**

4. Conclusion

In conclusion, a new porous magnetic carbonaceous solid acid catalyst Glu-Fe₃O₄-SO₃H was efficiently prepared and was found to show excellent catalytic activity for THP protection of alcohols and synthesis of 2-deoxy-*O*-glycoside under mild reaction conditions giving high yields and selectivity. The catalyst could also be recovered by external magnetic force and reused several times without any loss of activity. This catalytic system is environmentally green and can be used as an ideal method for glycosylation reactions.

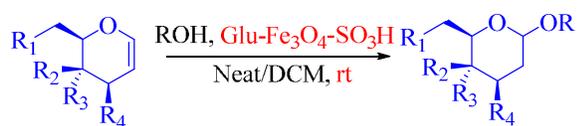
Acknowledgements

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4: R₁=R₂=R₄=OBn, R₃=H

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6: R₁=R₂=R₄=OAc, R₃=H

7: R₁=R₃=R₄=OBn, R₂=H

8: R₁=R₃=R₄=OTBS, R₂=H

9: R₁=R₃=R₄=OAc, R₂=H

Short reaction time

100% conversion

Yields: 80-99%

Mainly α selective