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Short Communication

Magnetic nano Fe_3O_4 and $CuFe_2O_4$ as heterogeneous catalysts: A green method for the stereo- and regioselective reactions of epoxides with indoles/pyrroles

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ABSTRACT

In this paper, we report a new solvent-free catalytic method using the magnetic nano Fe_3O_4 and $CuFe_2O_4$ as competent heterogeneous catalysts for the stereo- and regioselective reactions of epoxides with indoles/pyrroles, which gave the C-alkylated indoles/pyrroles. Chiral epoxides gave the alkylated indoles with a complete inversion of stereochemistry.

1. Introduction

The development of efficient catalytic methods, facile recovery of the catalyst from the reaction medium and recyclability of the catalyst are very important tasks in modern synthetic chemistry. Indole and pyrrole motifs are the core unit in various natural products and biologically active molecules. Especially, the alkylated indoles/pyrroles are potential synthetic intermediates as their synthesis has been the subject of various studies [1–4]. The ring opening of epoxides with N-, O- and S-based nucleophiles is well studied; however, the reactions of epoxides with carbon nucleophiles (e.g. indole) are relatively less explored [5]. The synthesis of alkylated indoles/pyrroles from the reaction of epoxides with indoles/pyrroles is an atom economic conversion. Generally this conversion has been carried out using strong acidic/basic catalysts [6–8] or Lewis acids [9–12] or heterogeneous catalysts [13–17]; notably, in this regard there exist only limited reports based on eco-friendly conditions and heterogeneous catalysts [16]. Further, there exist few reports [6,7,10] on the stereoselective reactions of chiral epoxides with indoles/pyrroles [18,19].

Many of the reported methods are efficient; however, in some methods the catalyst recovery/reuse is not possible and halogenated solvent (DCM) or relatively expensive catalysts or high temperature/pressure were employed [5–19]. Generally, indoles/pyrroles have relatively low nucleophilicity for the direct attack at epoxides. Hence a mild activation of the C-O bond of an epoxide is preferred as the strongly acidic catalysts may cause isomerization of epoxides.

In recent years, the magnetic nanoparticles-based catalysts have been widely used as heterogeneous catalysts for achieving various important chemical transformations [20,21]. Because of the magnetic properties, a complete recovery of the catalyst from the reaction medium is highly possible.

To the best of our knowledge, the reaction of epoxides with indoles/pyrroles has not been reported using iron-based nanoparticles/catalysts. We herein report the magnetic nano Fe_3O_4 and $CuFe_2O_4$ as proficient heterogeneous catalysts for the stereo- and regioselective reaction of epoxides with indoles/pyrroles.

2. Experimental

2.1. General

Solvents were purified by conventional methods. All reagents/catalysts were purchased from Aldrich. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer (using $CDCl_3$ with TMS as the standard). PXRD, HRTEM and HPLC data sets were recorded on Rigaku Ultimia IV diffractometer, JEOL JEM 2100 Instrument and Shimadzu HPLC system, respectively. The copies of ^1H and ^{13}C NMR spectra of all the (known and new) products obtained in this work have been given in the supplementary file.

2.2. General procedure for the magnetic nano Fe_3O_4-catalyzed reaction of indoels/pyrroles with expoxides

A RB flask containing a mixture of styrene oxide (**2a**, 1 mmol), indole (**1a**, 1 mmol) and magnetic nano Fe_3O_4 (< 50 nm, 10 mol%) was

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stirred at rt for 24 h. The purification of the compound **3a** and catalyst recovery were carried out as stated in the work-up method ‘A’ (for the other work-up methods see the supplementary file).

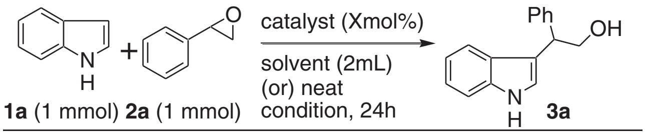
Work-up method ‘A’: Step 1. After the reaction period, EtOAc (1–2 mL) was added to the reaction flask containing the crude reaction mixture and stirred for 1–2 min. Step 2. A magnet was externally appended to the RB flask and the magnetic nano Fe_3O_4 catalyst was accumulated at the walls of the flask; the resulting clear solution was transferred in to a fresh RB flask using a dropper. Next, Steps 1 and 2 were repeated thrice. Then, the catalyst containing flask was dried in an oven (at 100–110 °C, overnight) and recycled. The combined organic layers were concentrated in vacuum and purification of the resulting reaction mixture by column chromatography furnished the product **3a**.

3. Results and discussion

At the outset, we performed the optimization reactions, which revealed that 10 mol% of the magnetic nano Fe_3O_4 and solvent-free condition as the best operative experimental conditions for the reaction of indole with styrene oxide (Table 1).

The generality, scope and limitations of the magnetic nano Fe_3O_4-catalyzed reaction of epoxides with indoles are shown in Table 2. A variety of substituted indoles were reacted with various epoxides, which afforded the regioselective products **3b-v** in very good yields. Indoles containing electron-withdrawing substituents e.g. 5-NO_2 and 5-CN were smoothly furnished the respective products **3o-s**.

Table 1
Magnetic nano Fe_3O_4-catalyzed alkylation of **1a**.

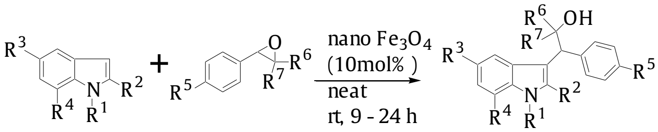


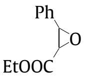
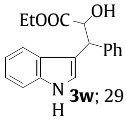
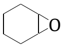
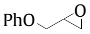
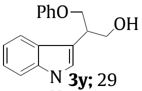
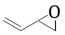
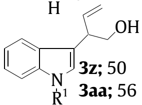
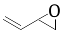
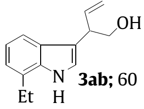
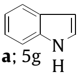
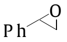
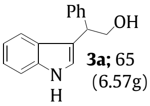
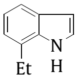
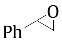
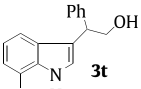
1a (1 mmol) **2a** (1 mmol) **3a**

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Yield (%)[a]
a	Nil	Neat	rt	<5
b	Nil	Neat	70–75	<5
c	Nano Fe_3O_4 (15)	Hexane	Reflux	30
d	Nano Fe_3O_4 (15)	Toluene	Reflux	34
e	Nano Fe_3O_4 (15)	THF	Reflux	35
f	Nano Fe_3O_4 (15)	DMF	Reflux	15
g	Nano Fe_3O_4 (15)	MeOH	Reflux	36
h	Nano Fe_3O_4 (15)	EtOH	Reflux	38
i	Nano Fe_3O_4 (15)	1,4-Dioxane	Reflux	37
j	Nano Fe_3O_4 (15)	MeCN	Reflux	65 (45)[b]
k	Nano Fe3O4 (15)	DCM	Reflux	57 (40)[b]
l	Nano Fe_3O_4 (15)	1,2-DCE	Reflux	64 (45)[b]
m	Nano Fe_3O_4 (5)	Neat	rt	66
n	Nano Fe_3O_4 (8)	Neat	rt	68
o	Nano Fe_3O_4 (10)	Neat	rt	76 (75)[c] (71)[d]
p	Powder Fe_3O_4 (10)	Neat	rt	50 (47)[c] (43)[d]
q	Powder Fe_3O_4 (10)	Neat	70–75	50
r	Nano Fe_2O_3 (10)	Neat	rt	(20)[c] (22)[e]
s	Powder Fe_2O_3 (10)	Neat	rt	(20)[c] (21)[e]
t	Nano $CuFe_2O_4$ (10)	MeCN	Reflux	59
u	Nano $CuFe_2O_4$ (10)	Hexane	rt	34
v	Nano $CuFe_2O_4$ (5)	Neat	rt	54
w	Nano $CuFe_2O_4$ (10)	Neat	rt	70

[a] Work up was carried out as given in method ‘A’ (see experimental Section 2.2 and supplementary file) unless otherwise stated.
[b] The reaction was carried out at rt and the corresponding yield is given in the parenthesis.
[c] Work up was carried out as given in method ‘B’ (see the supplementary file).
[d] Work up was carried out as given in method ‘C’ (see the supplementary file).
[e] Work up was carried out as given in method ‘D’ (see the supplementary file).

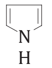
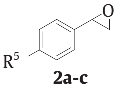
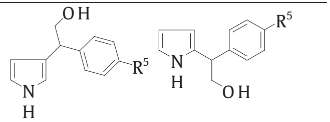
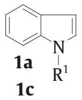
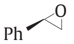
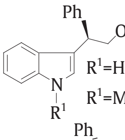
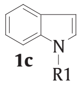
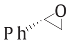
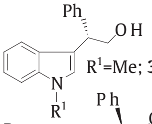
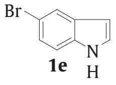
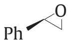
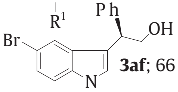
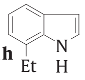
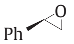
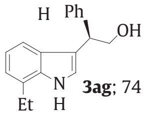
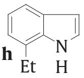
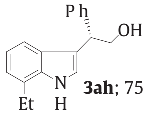
Table 2
Magnetic nano Fe_3O_4-catalyzed reaction of indoles with epoxides.



Entry	(1) Nucleophile					(2) Epoxide				t(h)	Isolated Yield (%)[a]
		R^1	R^2	R^3	R^4		R^5	R^6	R^7		
a	**1a**	H	H	H	H	**2b**	Cl	H	H	12	**3b**; 70
b	**1a**	H	H	H	H	**2c**	Br	H	H	9	**3c**; 70
c	**1b**	H	Me	H	H	**2a**	H	H	H	24	**3d**; 75
d	**1b**	H	Me	H	H	**2b**	Cl	H	H	16	**3e**; 77
e	**1b**	H	Me	H	H	**2c**	Br	H	H	18	**3f**; 70
f	**1b**	H	Me	H	H	**2d**	F	H	H	24	**3g**; 63
g	**1c**	Me	H	H	H	**2a**	H	H	H	24	**3h**; 71 (55)[b]
h	**1c**	Me	H	H	H	**2b**	Cl	H	H	24	**3i**; 71
i	**1c**	Me	H	H	H	**2c**	Br	H	H	24	**3j**; 74
j	**1c**	Me	H	H	H	**2d**	F	H	H	24	**3k**; 70
k	**1d**	H	H	OMe	H	**2a**	H	H	H	24	**3l**; 71
l	**1d**	H	H	OMe	H	**2b**	Cl	H	H	24	**3m**; 75
m	**1d**	H	H	OMe	H	**2c**	Br	H	H	24	**3n**; 74
n	**1e**	H	H	Br	H	**2a**	H	H	H	15	**3o**; 65
o	**1e**	H	H	Br	H	**2b**	Cl	H	H	18	**3p**; 70
p	**1e**	H	H	Br	H	**2c**	Br	H	H	24	**3q**; 65
q	**1f**	H	H	CN	H	**2a**	H	H	H	12	**3r**; 67[c]
r	**1g**	H	H	NO_2	H	**2a**	H	H	H	24	**3s**; 63[c]
s	**1h**	H	H	H	Et	**2a**	H	H	H	24	**3t**; 80 (74)[b] (45)[d] (75)[e]
t	**1h**	H	H	H	Et	**2b**	Cl	H	H	24	**3u**; 74
u	**1h**	H	H	H	Et	**2c**	Br	H	H	16	**3v**; 74
v	**1a**	H	H	H	H	**2e**	 Ph O EtOOC			24	 EtOOC OH Ph N H **3w**; 29
w	**1a**	H	H	H	H	**2f**	 O			24	**3x**; N.D
x[f]	**1a**	H	H	H	H	**2g**	 PhO O			24	 PhO OH N H **3y;** 29
y[g]	**1a**	H	H	H	H	**2h**	 O			24	 OH N R^1 **3z;** 50
z[g]	**1c**	Me	H	H	H	**2h**				24	**3aa;** 56
za[g]	**1h**	H	H	H	Et	**2h**	 O			24	 OH N Et H **3ab;** 60
zb	 N H **1a**; 5g					 Ph O **2a**; 6.15g					 Ph OH N H **3a;** 65 (6.57g)
zc[h]	**1h**  N Et H					 Ph O **2a**					 Ph OH N Et H **3t** I recyclization = 75 II recyclization = 74

[a] All the reactions were done using 1 mmol of **1/2** unless otherwise stated and work up was carried out as given in method 'A'.
[b] Nano $CuFe_2O_4$ was used instead of nano Fe_3O_4.
[c] 2 mmol of **2** was used.
[d] Powder Fe_3O_4 was used and the work up was carried out as given in method 'C' (see the supplementary file).
[e] Nano Fe_3O_4 was used as a catalyst and the work up was carried out as given in method 'C' (see the supplementary file).
[f] The reaction was done in MeCN at 80 °C.
[g] 2.2 mmol of **2h** was used as **2h** has a low Bp.
[h] The catalyst was recycled twice.

Table 3
Magnetic nano Fe_3O_4-catalyzed alkylation of pyrrole and stereoselective reactions of *R*-(**2i**) and *S*-(**2j**) with indoles.

Entry	(**1**) Nucleophile	(**2**) Epoxide	t (h)	Isolated Yield (%)
	 **1i**	 **2a-c**		
a			24	R^5=Cl; **4a** (14%) R^5=Cl; **5a** (43%)
b			24	R^5=Br; **4b** (14%) R^5=Br; **5b** (42%)
c			24	R^5=F; **4c** (23%) R^5=F; **5c** (32%)
d			24	R^5=H; **4d** (23%) R^5=H; **5d** (35%)
e	 **1a**	 **2i**; (*R*)	24	 R^1=H; **3ac**; 72 (99%ee)
f	**1c**	**2i**; (*R*)	24	R^1=Me; **3ad**; 71 (99%ee)
g	 **1c**	 **2j**; (*S*)	2	 R^1=Me; **3ae**; 72 (99%ee)
h	 **1e**	 **2i**; (*R*)	24	 **3af**; 66 (99%ee)
i	 **1h**	 **2i**; (*R*)	24	 **3ag**; 74 (99%ee)
j	 **1h**	 **2j**; (S)	24	 **3ah**; 75 (99%ee)

[a] All the reactions were done using **1** (1 mmol), **2** (1 mmol) and Fe_3O_4 (10 mol%).

The reaction of indole with ethyl 3-phenylglycidate (**2e**, mixture of *trans* and *cis*) afforded the product **3w** in 29% yield. The reaction of cyclohexene oxide with indole failed to give any product. The reaction of indole and 2-(phenoxymethyl)oxirane (**2 g**) in MeCN at refluxing temperature gave the product **3y** in 29% yield. These limitations are because, generally, the aliphatic epoxides are less reactive than aryl epoxides [16]. Notably, the reaction of indoles **1a,c,h** with aliphatic epoxide 2-vinyloxirane successfully gave the respective homoallylic alcohols **3z**, **3aa** and **3ab**. To demonstrate the recyclability of the magnetic nano Fe_3O_4, the reaction of **1h** and **2a** was performed using the recovered magnetic nano Fe_3O_4, which gave the product **3t** in 75% (I recyclization) and 74% (II recyclization) yields, respectively.

The FT-IR spectra and XRD patterns revealed the absence of any characteristic peaks of organic impurities in the used magnetic nano Fe_3O_4. Evaluation of the HRTEM images of the used magnetic nano Fe_3O_4 revealed that the morphology of the used magnetic nano Fe_3O_4 is considered to be stable (See the supplementary file for FT-IR, PXRD and HRTEM data).

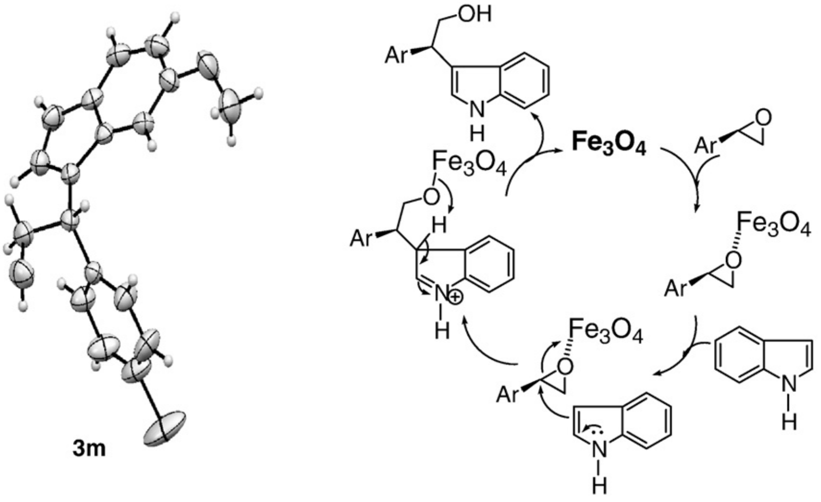
Then, the reaction of pyrrole with styrene oxides (**2a-d**) in the presence of the magnetic nano Fe_3O_4 (10 mol%) furnished the respective regioisomeric C-alkylated products **4a-d** and **5a-d** (Table 3). Finally, we performed the stereoselective reactions of (*R*)-styrene oxide and (*S*)-styrene oxide with various indoles using the magnetic nano Fe_3O_4 (10 mol%, Table 3).

Interestingly, the chiral epoxides gave the alkylated indoles in very good yields with a complete inversion of stereochemistry, which indicated the operation of a S_N2-type mechanism and based on the X-ray structure of a representative product **3m** [22], a plausible mechanistic pathway for the magnetic nano Fe_3O_4-catalyzed reaction of epoxides with indoles is proposed (Scheme 1).

All the reactions are clean, highly regio- and stereoselective as the epoxide **2** underwent cleavage by indoles with preferential attachment at the benzylic position and selectively furnished the primary alcohols. Since the 3-position of indole is the preferred site for electrophilic substitution reactions, C3-alkylated indole derivatives were exclusively obtained in all of the above reactions.

4. Conclusion

In summary, we have shown that the magnetic nano Fe_3O_4- and $CuFe_2O_4$ as competent heterogeneous catalysts for the highly stereo- and regioselective reaction of epoxides with indoles/pyrroles. In the case of chiral epoxides, the alkylated indoles were obtained with a complete inversion of stereochemistry. This is an eco-friendly heterogeneous catalytic method in which no need of any solvent and high temperature/pressure.



Scheme 1. Ortep diagram of **3m** and plausible mechanism.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.09.030.

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[22] Crystallographic data of X-ray crystal structure of the compound 3m, reported in this work has been deposited with the Cambridge Crystallographic Data Centre under the following deposition number: CCDC 856690.