



Short Communication

Magnetic nano Fe₃O₄ and CuFe₂O₄ 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 Fe₃O₄ and CuFe₂O₄ 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.

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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 Fe₃O₄ and CuFe₂O₄ 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 ¹³C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer (using CDCl₃ with TMS as the standard). PXRD, HRTEM and HPLC data sets were recorded on Rigaku Ultima IV diffractometer, JEOL JEM 2100 Instrument and Shimadzu HPLC system, respectively. The copies of ¹H and ¹³C 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 Fe₃O₄-catalyzed reaction of indoles/pyrroles with epoxides

A RB flask containing a mixture of styrene oxide (**2a**, 1 mmol), indole (**1a**, 1 mmol) and magnetic nano Fe₃O₄ (< 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 Fe₃O₄ 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 Fe₃O₄ 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 Fe₃O₄-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-NO₂ and 5-CN were smoothly furnished the respective products **3o–s**.

Table 1
Magnetic nano Fe₃O₄-catalyzed alkylation of **1a**.

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Yield (%) ^a
a	Nil	Neat	rt	<5
b	Nil	Neat	70–75	<5
c	Nano Fe ₃ O ₄ (15)	Hexane	Reflux	30
d	Nano Fe ₃ O ₄ (15)	Toluene	Reflux	34
e	Nano Fe ₃ O ₄ (15)	THF	Reflux	35
f	Nano Fe ₃ O ₄ (15)	DMF	Reflux	15
g	Nano Fe ₃ O ₄ (15)	MeOH	Reflux	36
h	Nano Fe ₃ O ₄ (15)	EtOH	Reflux	38
i	Nano Fe ₃ O ₄ (15)	1,4-Dioxane	Reflux	37
j	Nano Fe ₃ O ₄ (15)	MeCN	Reflux	65 (45) ^b
k	Nano Fe ₃ O ₄ (15)	DCM	Reflux	57 (40) ^b
l	Nano Fe ₃ O ₄ (15)	1,2-DCE	Reflux	64 (45) ^b
m	Nano Fe ₃ O ₄ (5)	Neat	rt	66
n	Nano Fe ₃ O ₄ (8)	Neat	rt	68
o	Nano Fe ₃ O ₄ (10)	Neat	rt	76 (75) ^c (71) ^d
p	Powder Fe ₃ O ₄ (10)	Neat	rt	50 (47) ^c (43) ^d
q	Powder Fe ₃ O ₄ (10)	Neat	70–75	50
r	Nano Fe ₂ O ₃ (10)	Neat	rt	(20) ^c (22) ^e
s	Powder Fe ₂ O ₃ (10)	Neat	rt	(20) ^c (21) ^e
t	Nano CuFe ₂ O ₄ (10)	MeCN	Reflux	59
u	Nano CuFe ₂ O ₄ (10)	Hexane	rt	34
v	Nano CuFe ₂ O ₄ (5)	Neat	rt	54
w	Nano CuFe ₂ O 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 Fe₃O₄-catalyzed reaction of indoles with epoxides.

Entry	(1) Nucleophile	(2) Epoxide	t(h)	Isolated Yield (%) ^a
a	1a (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2b (R ⁵ : Cl, R ⁶ : H, R ⁷ : H)	12	3b ; 70
b	1a (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2c (R ⁵ : Br, R ⁶ : H, R ⁷ : H)	9	3c ; 70
c	1b (R ¹ : H, R ² : Me, R ³ : H, R ⁴ : H)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	24	3d ; 75
d	1b (R ¹ : H, R ² : Me, R ³ : H, R ⁴ : H)	2b (R ⁵ : Cl, R ⁶ : H, R ⁷ : H)	16	3e ; 77
e	1b (R ¹ : H, R ² : Me, R ³ : H, R ⁴ : H)	2c (R ⁵ : Br, R ⁶ : H, R ⁷ : H)	18	3f ; 70
f	1b (R ¹ : H, R ² : Me, R ³ : H, R ⁴ : H)	2d (R ⁵ : F, R ⁶ : H, R ⁷ : H)	24	3g ; 63
g	1c (R ¹ : Me, R ² : H, R ³ : H, R ⁴ : H)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	24	3h ; 71 (55) ^b
h	1c (R ¹ : Me, R ² : H, R ³ : H, R ⁴ : H)	2b (R ⁵ : Cl, R ⁶ : H, R ⁷ : H)	24	3i ; 71
i	1c (R ¹ : Me, R ² : H, R ³ : H, R ⁴ : H)	2c (R ⁵ : Br, R ⁶ : H, R ⁷ : H)	24	3j ; 74
j	1c (R ¹ : Me, R ² : H, R ³ : H, R ⁴ : H)	2d (R ⁵ : F, R ⁶ : H, R ⁷ : H)	24	3k ; 70
k	1d (R ¹ : H, R ² : H, R ³ : OMe, R ⁴ : H)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	24	3l ; 71
l	1d (R ¹ : H, R ² : H, R ³ : OMe, R ⁴ : H)	2b (R ⁵ : Cl, R ⁶ : H, R ⁷ : H)	24	3m ; 75
m	1d (R ¹ : H, R ² : H, R ³ : OMe, R ⁴ : H)	2c (R ⁵ : Br, R ⁶ : H, R ⁷ : H)	24	3n ; 74
n	1e (R ¹ : H, R ² : H, R ³ : Br, R ⁴ : H)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	15	3o ; 65
o	1e (R ¹ : H, R ² : H, R ³ : Br, R ⁴ : H)	2b (R ⁵ : Cl, R ⁶ : H, R ⁷ : H)	18	3p ; 70
p	1e (R ¹ : H, R ² : H, R ³ : Br, R ⁴ : H)	2c (R ⁵ : Br, R ⁶ : H, R ⁷ : H)	24	3q ; 65
q	1f (R ¹ : H, R ² : H, R ³ : CN, R ⁴ : H)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	12	3r ; 67 ^c
r	1g (R ¹ : H, R ² : H, R ³ : NO ₂ , R ⁴ : H)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	24	3s ; 63 ^c
s	1h (R ¹ : H, R ² : H, R ³ : H, R ⁴ : Et)	2a (R ⁵ : H, R ⁶ : H, R ⁷ : H)	24	3t ; 80 (74) ^b (45) ^d (75) ^e
t	1h (R ¹ : H, R ² : H, R ³ : H, R ⁴ : Et)	2b (R ⁵ : Cl, R ⁶ : H, R ⁷ : H)	24	3u ; 74
u	1h (R ¹ : H, R ² : H, R ³ : H, R ⁴ : Et)	2c (R ⁵ : Br, R ⁶ : H, R ⁷ : H)	16	3v ; 74
v	1a (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2e (Ph, EtOOC)	24	3w ; 29
w	1a (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2f (Cyclohexane)	24	3x ; N.D
x ^f	1a (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2g (PhO)	24	3y ; 29
y ^g	1a (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2h (Allyl)	24	3z ; 50
z ^g	1c (R ¹ : Me, R ² : H, R ³ : H, R ⁴ : H)	2h (Allyl)	24	3aa ; 56
za ^g	1h (R ¹ : H, R ² : H, R ³ : H, R ⁴ : Et)	2h (Allyl)	24	3ab ; 60
zb	1a ; 5g (R ¹ : H, R ² : H, R ³ : H, R ⁴ : H)	2a ; 6.15g (R ⁵ : Ph, R ⁶ : H, R ⁷ : H)		3a ; 65 (6.57g)
zc ^h	1h (R ¹ : H, R ² : H, R ³ : H, R ⁴ : Et)	2a (R ⁵ : Ph, R ⁶ : H, R ⁷ : 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 CuFe₂O₄ was used instead of nano Fe₃O₄.

^c 2 mmol of **2** was used.

^d Powder Fe₃O₄ was used and the work up was carried out as given in method 'C' (see the supplementary file).

^e Nano Fe₃O₄ 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.

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