A facile synthesis of alkylated nitrogen heterocycles catalysed by 3D mesoporous aluminosilicates with cage type pores in aqueous medium[†]

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Friedel–Crafts alkylation of nitrogen heterocycles such as indoles and pyrroles with epoxides has been efficiently carried out using cage-type mesoporous aluminosilicates as recyclable catalysts in water under environmentally benign and mild conditions.

Alkylated nitrogen heterocycles such as indoles and pyrroles have been receiving much attention in modern pharmaceutical, biological and synthetic chemistry because of their antibiotic and anticancer activities.^{1,2} The alkylated nitrogen heterocycles are generally prepared by the ring opening of various epoxides with nitrogen heterocycles using highly corrosive acidic or basic catalysts.³ Lewis acids such as lanthanide triflates⁴ and indium salts have also been used as catalysts for the ring opening of epoxides with nitrogen heterocycles.⁵ Recently, highly enantioselective addition of indoles with aromatic epoxides has been carried out using chromium salen complexes as catalysts.⁶ Although the catalysts are highly efficient, they cannot be recovered and reused, which may create a large amount of environmentally hazardous and toxic wastes.

Environmental and economic considerations have recently raised a strong interest in redesigning commercially important processes so that the use of harmful substances and the generation of toxic waste can be avoided.7 In this respect, heterogeneous catalytic processes are more favorable over their homogeneous counterparts in the production of fine chemicals, owing to their ease of handling, simple workup procedures and, most importantly, their reusability. Heterogeneous catalysts such as nanocrystalline titanium(IV) oxide,8 fluoroboric acid adsorbed on silica gel9 and sulfated zirconia10 have been widely used in the alkylation of nitrogen heterocycles with epoxides. Very recently, Kantam et al. have reported the ionic liquid [bmim][OTf] as an efficient promoter for the Friedel-Crafts alkylation of indoles and pyrrole derivatives.11 Friedel-Crafts alkylation of indole and pyrrole derivatives has been reported with carbonyl compounds and nitroalkenes in water.¹² Unfortunately, however, these heterogeneous catalysts suffer from poor textural characteristics and a disordered porous structure which limit the efficiency of these catalysts in the above transformation.

Ordered mesoporous materials with tunable pore size in the range of 2-50 nm have attracted a great deal of attention owing to their unique structures with organized porosity, high surface area and pore volume, and potential applications, mainly in the field of catalysis, adsorption, separation, sensors, and fuel cells. Among the porous materials, mesoporous silica materials consisting of an interconnected large-pore cage-type mesoporous system with three-dimensional (3D) porous networks are highly interesting and believed to be more advantageous than porous materials having a hexagonal pore structure with a one-dimensional array of pores. Very recently, Vinu et al. have reported the preparation of 3D mesoporous cage-type aluminosilicate materials (AlKIT-5) with different pore diameters, aluminium contents and morphologies.13 AlKIT-5 materials possess a highly-ordered cage-type mesoporous structure with cubic Fm3m close packed symmetry, a high surface area, narrow pore size distribution, a high specific pore volume and welldistributed tetrahedral aluminium atoms in the silica framework which provide a high acidity.13 It was also reported that the activity of the AlKIT-5 catalysts in the acetylation of veratrole and other organic transformations was superior to zeolites and AlMCM-41 catalysts.13 These exciting catalytic properties of AlKIT-5 materials stimulated us to utilize them in various other acid-catalyzed organic transformations for the production of value-added products.

In this communication, we report, for the first time, the catalytic performance of AlKIT-5 materials in the Friedel–Crafts alkylation of nitrogen heterocycles such as indoles and pyrroles with epoxides, which are important intermediates and building blocks in organic synthesis and are readily decomposed under acidic conditions in water.¹⁴ The reactions were conducted in water at room temperature. The catalyst was found to be highly active, affording the corresponding alkylated derivatives of indoles and pyrroles in good yields (Scheme 1).

During the screening process of the catalysts for this reaction, a major emphasis was laid on the zeolites and mesoporous aluminosilicate catalysts due to their characteristic structural and chemical features, which were synthesized by the procedures reported in the literature.¹⁵ In order to find out the best catalytic system suited to the synthesis of alkylated nitrogen heterocycles, the reactions were carried out using various zeolite catalysts such as MOR, BEA, MFI and FAU, and mesoporous catalysts, namely AlSBA-15 and AlMCM-41. Recently, the ringopening reactions of epoxides or aziridines with various types of

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Scheme 1 Alkylation of indole and pyrrole with styrene oxide

nucleophiles have been studied.¹⁶ Several methods with different catalysts employed water as the solvent, and it was believed that water was essential for the success of the reactions.¹⁷ Therefore, water and dichloromethane were used as solvents in the catalyst screening experiments in order to understand the effect of water. Comparatively better results were obtained when water was used as the reaction medium. Finally the reaction results were compared with the AlKIT-5 catalysts which are shown in Table 1. Among the catalysts studied, as can be seen in Table 1, the AlKIT-5 catalysts showed superior performance over the zeolites and other mesoporous catalysts used in this study.

The higher activity of AlKIT-5 catalysts could be mainly attributed to their excellent structural order with 3D pore symmetry and highly dispersed active sites on the uniform pore surface, which are easily accessible for the reactant molecules (Fig. S1, ESI[†]). As the AlKIT-5 catalyst was found to be the best catalyst used in this study, it was selected for use in further studies. It should be pointed out that when the reaction was carried out without any catalyst, no product was formed (Table 1, entry 10) even after prolonged reaction times. The effect of the Al content of the AlKIT-5 catalysts in the alkylation of indoles was also studied. A series of AlKIT-5 catalysts having different $n_{\rm Si}/n_{\rm Al}$ ratios was used in this study. As expected, the activity of the catalyst increases with increasing Al content in the silica framework of AlKIT-5 (Table 1, entries 1-3). Of the AlKIT-5 catalysts studied, AlKIT-5 with $n_{\rm Si}/n_{\rm Al} = 10$ showed the best performance, affording a yield of ca. 88% thanks to

Table 1Screening of different catalysts for the alkylation of indole bystyrene oxide"

Entry	Catalyst	Time/h	Yield (%) ^{<i>b</i>} , <i>c</i>	
1	AlKIT-5(10)	1.5	88, 65	
2	AIKIT-5(28)	1.5	85	
3	AlKIT-5(44)	1.5	80	
4	AlMCM-41	1.5	42	
5	MOR	1.5	35	
6	BEA	1.5	25	
7	MFI	1.5	20	
8	FAU	1.5	20	
9	AlSBA-15	1.5		
10		1.5, 24	0, 2	

^{*a*} Reaction conditions: indole (1.2 mmol, 140 mg), styrene oxide (1.0 mmol, 120 mg), catalyst (50 mg), solvent (2 mL) stirred at room temperature for 1.0 h. ^{*b*} Yields determined by GC. ^{*c*} Yield using dichloromethane as solvent.

Table 2Screening of different solvents for the alkylation of indole with
styrene oxide^a

Entry	Solvent	Time/h	Yield (%) ^b
1	H ₂ O	1.5	88
2	CH ₂ Cl ₂	1.5	65
3	CHCl ₃	1.5	42
4	CH ₃ CN	1.5	42
5	Toluene	1.5	
6	Benzene	1.5	

^{*a*} Reaction conditions: indole (1.2 mmol, 117 mg), styrene oxide (1 mmol, 120 mg), catalyst AlKIT-5(10) (50 mg), solvent (2 mL), stirred at room temperature for 1.5 h. ^{*b*} Isolated yields.

having the highest number of active sites on the surface (Table 1, entry 1).

Different solvents were used for the alkylation of indole with styrene oxide. It was found that AlKIT-5 is very efficient in water, affording an excellent yield of the corresponding product in a shorter reaction time (Table 2, entry 1) compared to other, organic solvents such as dichloromethane, chloroform, acetonitrile, toluene and benzene (Table 2, entries 2–6). The reaction was also carried out under solvent-free conditions but the catalyst was not effective in the absence of any solvent. This observation can be accounted for by the co-ordinating nature of water as a solvent which may act as a tool for facile ring opening of epoxides to form the corresponding products. The tendency of epoxides to decompose under acidic water conditions also provides an added advantage for the completion of the reaction in shorter times.^{14,18}

The reaction was also carried out using a wide variety of structurally-diverse indoles and pyrroles, with several epoxides, to form the corresponding alkylated products using AlKIT-5(10) in water. The differences in the yields of the corresponding alkylated products formed depend on the intrinsic properties of the substituted indoles and pyrroles used.

It was evident from the NMR spectral data that the aryl epoxides underwent cleavage at the benzylic position in the case of indoles to selectively give the primary alcohol product. No trace of the secondary alcohol product was detected. Moreover, in the case of all the substituted indoles used, it was found that the 3-alkylated indole products are formed selectively; no traces of the 2-alkylated products were detected in the reaction mixture. In all cases, the reactions proved to be faster than most of those reported earlier in the literature, ^{58,9,10} and the yields of the products were also found to be comparable. The regioselectivities of the resulting products are in complete agreement with the earlier reports.^{89,11}

The general trend noticed in case of these reactions is that the indoles bearing electron-donating groups afforded the corresponding alkylated products in good yields (Table 3, entries 3 & 4). On the other hand, electron withdrawing groups being present on the indole moiety drastically decreases the rate of the reaction and the yield of the product formed is also very low, even after prolonged reaction times (Table 3, entries 8 & 9) when 5-nitroindole was used in the reaction. It was observed that in the case of 1-methylindole, the reaction proceeds in a significantly more facile manner to afford the corresponding

Entry	Nucleophile	Epoxide	Product	Time/h	Yield (%) ^b
1			Ph OH N	1.5	88, 85 ^c
2	N Me		Ph OH Ne	1.5	85
3	Me N N H		Me Ph OH	1.0	88
4	MeO		MeO Ph OH	1.0	88
5	Me H		Ph OH Ne	1.0	90
6	N H	CI CI	H Cl OH	1.0	80
7	Br		Br Ph N	2.5	78
8	NC NC		NC Ph NC OH	24	18
9	O ₂ N		O ₂ N OH	24	10
10			ОН	1.5	78
11		O	No reaction	24	_
12		O	No reaction	24	_

 Table 3
 Alkylation of indoles and pyrroles with epoxides over AlKIT-5(10)^a

 Table 3 (Contd.)

Entry	Nucleophile	Epoxide	Product	Time/h	Yield (%) ^b
13	N H		ЛОН	2.5	65, 15 ^d
14	N Me		Me Ph OH	2.5	60, 13 ^{<i>d</i>}

^{*a*} Reaction conditions: indole/pyrrole (1.2 mmol), epoxide (1 mmol), AlKIT-5(10) (50 mg), water (2 mL) stirred at room temperature for an appropriate time. ^{*b*} Isolated yield of the product. ^{*c*} Yield after five cycles. ^{*d*} Isolated yields of 2-alkyl and 3-alkyl pyrroles, respectively.

product in greater yield than in the reaction of unsubstituted indole.

In contrast, in the case of pyrroles, the alkylation reaction results in the corresponding product mixture of 2-alkylated and 3-alkylated pyrroles, in which the 2-alkylated pyrrole is the major one.¹¹

It was observed from the spectroscopic data that the epoxide ring opens by the attack of the nucleophile at the benzylic position, to afford the primary alcohol. In this case, the preferred site for electrophilic attack being the 2-position of the pyrrole ring, the reaction proceeds to yield mostly the 2-alkylated product (Table 3, entry 10). This reveals that the reaction was highly regioselective, affording only primary alcohols.

The aryl epoxides having an electron-withdrawing substituent underwent the reaction comparatively faster (Table 3, entry 6) than the unsubstituted ones. Later, the reaction was carried out on a gram scale to test its effectiveness on a larger scale. In this reaction, 1 g of styrene oxide was reacted with 1.2 g of indole in the presence of AlKIT-5 in water. Interestingly, even in this case, the reaction proceeds smoothly to give 85% yield of the product. All the reactions proceeded smoothly at ambient temperature and pressure in water with high regioselectivity to afford good yields of the products in short periods. It should be pointed out that N-alkylation of the indoles and pyrroles does not take place under the optimized mild reaction conditions.

The use of water as a solvent is not only advantageous in being the most 'green' solvent available but also allows a simple, efficient and robust system for the recycling of the catalyst. In fact, after the completion of the reaction, the aqueous solution containing the catalyst and the products was extracted with ethyl acetate. To the remaining aqueous solution containing the dispersed AlKIT-5 catalyst, fresh substrates were added and the process was repeated for five cycles. The catalyst was found to be highly stable and the activity of the catalyst was not much changed even after repeated cycles (Table 3, entry 1).

In order to understand the influence of the aqueous media and the reactants on the structural order of AlKIT-5, the catalyst was dried, calcined at 540 °C, and subjected to nitrogen physisorption and X-ray diffraction (XRD) analysis after the fifth cycle (Fig. S2 and S3, ESI[†]). Although the shape of the nitrogen adsorption isotherm, the XRD pattern, and the pore size of the AlKIT-5(10) catalyst used are similar to that of the fresh catalyst, a slight reduction in the surface area and pore volume was observed. This could be due to a slight deterioration of the structure of the catalyst after the reaction and the activation of the catalyst at higher temperature.

In summary, a simple and an efficient protocol for a highly regio- and chemoselective alkylation of indoles and pyrroles with epoxides has been described. The reaction occurs in aqueous media and requires only a catalytic amount of AlKIT-5 catalyst. No other promoters or additives are required to obtain a good yield of the product. The catalyst AlKIT-5 dispersed in water forms a robust and recyclable catalytic system, which can be reused several times without any regeneration, thus reducing the amount of disposed waste considerably. Further, the recycling of the heterogeneous catalyst makes the process of separation simpler and cheaper. The reaction has also been extended to the gram scale to prove its industrial usefulness, which could pave the way to replace the existing toxic, corrosive and expensive homogenous catalysts currently used in the industry.

Experimental section

AlKIT-5 catalysts with different n_{Si}/n_{Al} ratios were synthesized using the procedure reported in the literature.¹³ The various zeolites used were also synthesized using reported procedures.¹³

A typical experimental procedure

To a stirred solution of indole (1.2 mmol, 140 mg) and styrene oxide (1 mmol, 120 mg) in water (2 mL), AlKIT-5 (50 mg) was added. The reaction mixture was stirred at room temperature for an appropriate time (Table 3). After completion of the reaction, as monitored by TLC, the aqueous phase containing the catalyst was recovered quantitatively via simple extraction of the product with ethyl acetate $(3 \times 10 \text{ mL})$. The organic extracts were then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting product was then purified by column chromatography on silica gel (100-200 mesh) with ethyl acetate-n-hexane (1:4) as eluent to afford pure 2-(3-indolyl)-2phenylethanol (Table 3, entry 1). 1H NMR (300 MHz, CDCl₃): $\delta = 1.60$ (br, 1 H), 4.18–4.23 (m, 2 H), 4.50 (t, J = 6.7 Hz, 1 H), 7.01–7.45 (m, 10 H), 8.11 (br, 1 H) ppm. MS (EI): m/z = 237(25), 206 (100), 178 (30), 128 (15), 102 (10), 77 (15), 63 (5), 51 (11).

Other known products were identified by comparison with the data in the literature. 5,9,11

The aqueous phase containing the catalyst was recycled by the addition of fresh substrates and by continuing the reaction for appropriate times.

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