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Fluoroboric acid adsorbed on silica gel catalyzed regioselective ring opening of epoxides with nitrogen heterocycles

B. P. Bandgar* and Abasaheb V. Patil

Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded 431 606, Maharashtra, India

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Abstract—Aryl epoxides can be opened in a regioselective and efficient manner with nitrogen heterocycles such as indoles, pyrroles and imidazoles in the presence of a catalytic amount of HBF_4–SiO_2 under mild conditions to afford the corresponding C-alkylated derivatives in good yields and with a high regioselectivity.

Aromatic epoxides are an ideal source for diversity because they can easily be opened with nucleophiles furnishing functionally diverse compounds. They are well-known carbon electrophiles and their ability to undergo regioselective ring opening reactions contributes to their synthetic value.[1] The epoxide opening reaction with nucleophiles is generally performed with acidic or basic catalysis, and in the absence of such catalysts, the reaction is moderately slow.[2] Indole is a key structural motif in many pharmacologically and biologically active compounds[3] as well as in many natural products.[4] While pyrrole derivatives are also important intermediates, not only for the synthesis of drugs, pigments and pharmaceuticals, but also for the development of functional organic materials.[5]

In the literature, the ring opening of epoxides with indoles and pyrroles have been described either by acid catalysis[6] or under high pressure conditions.[7] In recent years, lanthanide triflate[8] and Lewis acid[9] catalysts have been reported. However, acid catalyzed alkylation reactions of pyrrole are limited and require careful control of the acidity to prevent side reactions.[5] It is therefore necessary to perform epoxide-based alkylation of pyrroles under carefully controlled conditions.[6] Furthermore, there are only a limited number of reports on the alkylation of pyrroles and indoles under acidic conditions, leaving scope for further synthetic studies to develop a convenient and efficient protocol for the regioselective ring opening of epoxides with indoles and pyrroles.

Here, we report HBF_4–SiO_2 as a supported catalyst for the regioselective ring opening of oxiranes with indoles and pyrroles at room temperature. Initially, a study was carried out to evaluate HBF_4–SiO_2 as a catalyst for the reaction of styrene oxide with indole in various solvents (Table 1).

The reaction was slow in the absence of a catalyst (Table 1, entry 1) and inferior results were obtained in the presence of solvents such as THF, CH_3CN and $CHCl_3$ (Table 1, entries 2–5). With respect to the amount of catalyst, the yield depended on the catalyst loading. We optimized the quantity of the catalyst at room

Table 1. Reactions of styrene oxide with indole under various conditions

Entry	Solvent	HBF_4–SiO_2 (mol %)	Time (h)	Yield (%)
1	Neat	—	20	10
2	THF	2	4	45
3	CH_3CN	2	4	55
4	$CHCl_3$	2	4	60
5	CH_2Cl_2	0.5	3.5	55
6	CH_2Cl_2	1.0	3.5	62
7	CH_2Cl_2	1.5	3.5	70
8	CH_2Cl_2	2	2.5	80
9	CH_2Cl_2	2.5	2.5	80
10	CH_2Cl_2	3.3	2.5	78

Keywords: Aryl epoxides; Nitrogen heterocycles; HBF_4–SiO_2; Regioselectivity.
* Corresponding author. Fax: +91 2462 229245; e-mail: bandgar_bp@yahoo.com

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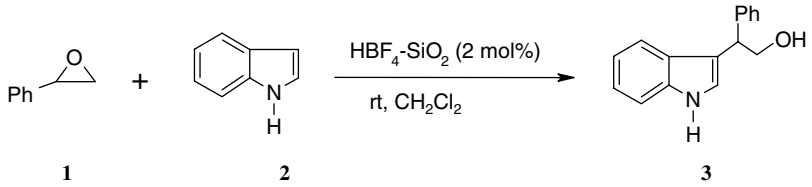
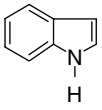
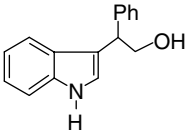
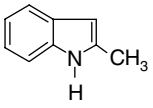
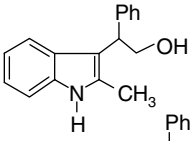
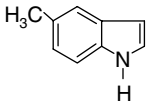
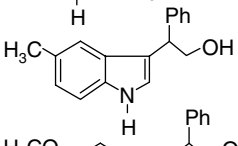
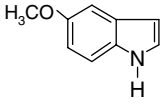
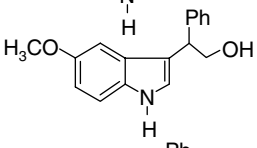
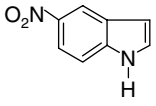
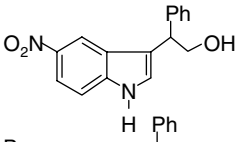
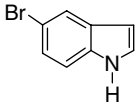
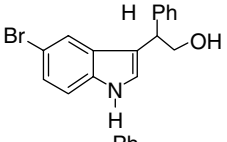
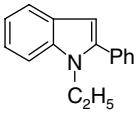
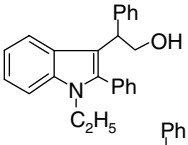
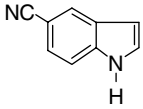
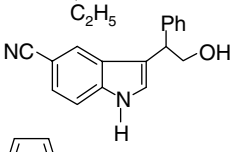
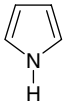
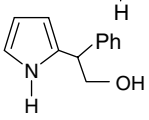
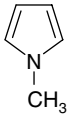
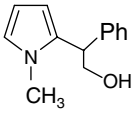
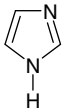
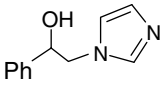
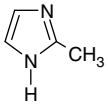
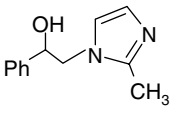


1 2 3

Scheme 1.

Table 2. HBF_4–SiO_2 catalyzed ring opening of aryl epoxides with nitrogen heterocycles

Entry	Reactant	Substrate	Product	Time (h)	Yield (%)
a				2.5	80[7b]
b				2.5	75[7b]
c				3.0	70[7a]
d				3.0	78[7a]
e				3.0	52[9a]
f				2.5	60[9a]
g				3.0	52
h				2.5	50[9a]
i				3.5	75:15[a,7a]
j				3.5	50:15[a,7a]
k				3.0	70[7a]
l				3.0	63[7a]

[a] Ratio of products **5**:**6**.

temperature in CH_2Cl_2 as solvent and it was observed that the use of just 2 mol % (Table 1, entry 8) was sufficient to produce an excellent yield of the product. Further studies showed that increasing the amount of catalyst did not produce significantly better yields (Table 1, entries 9–10).

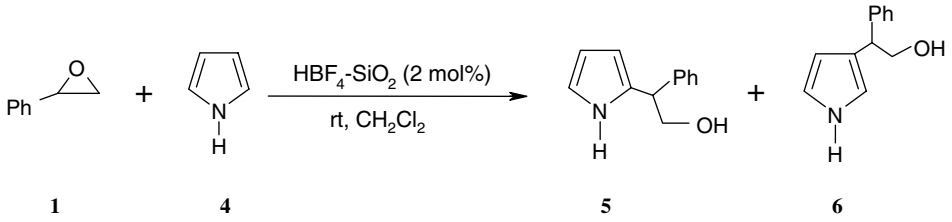
Indole on treatment with styrene oxide in the presence of HBF_4–SiO_2 (2 mol %), afforded 2-(3-indolyl)-2-phenylethanol in a 80% yield[10] with preferential attack at the benzylic position (Scheme 1).

The structure was confirmed by ^1H and ^{13}C NMR spectroscopy. The methylene protons occurred at 4.18 ppm in the ^1H NMR spectra and the methylene carbon appeared at 66.38 ppm in the ^{13}C NMR spectra which indicated that indole reacted at the benzylic position of styrene oxide resulting in the 3-substituted indole derivative **3**. Encouraged by these results, various substituted indoles were treated with styrene oxide. A single regioisomer **3** was formed in each reaction, consistent with the 3-position of indole being the preferred site for the electrophilic substitution (Table 2, entries a–h). The structures of all the products were confirmed by IR, ^1H NMR, ^{13}C NMR and mass spectroscopic data.

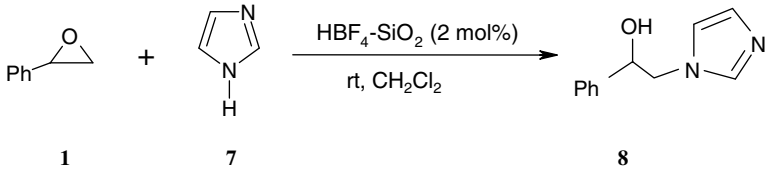
We then treated styrene oxide with pyrrole in the presence of HBF_4–SiO_2 (Scheme 2). The reaction was highly regioselective affording the corresponding product **5** as the major isomer along with a minor amount of **6** (Table 2, entries i–j).

The structures of **5** and **6** were confirmed by ^1H NMR and ^{13}C NMR spectroscopy. For compound **5**, the protons on the pyrrole ring at 6.0 (dd, 1H, $J = 5.3$ and 3.7 Hz), 6.16 (dd, 1H, $J = 5.3$ and 2.4 Hz) and 6.69 (dd, 1H, $J = 3.7$ and 2.4 Hz) ppm and the carbons of the pyrrole ring at 105.7, 108.1, 117.1 and 131.8 ppm were indicative of the formation of the 2-substituted pyrrole derivative. However, pyrrole ring protons of compound **6** at 6.10 (dd, 1H, $J = 3.7$ and 2.5 Hz), 6.60 (dd, 1H, $J = 3.7$ and 2.0 Hz) and 6.74 (dd, 1H, $J = 2.5$ and 2.0 Hz) ppm and the carbons of the pyrrole ring at 108, 115.9, 118.3 and 123.6 ppm indicated the formation of the 3-substituted isomer. This clearly indicates that pyrrole attacks styrene oxide at the benzylic position with the expected regioselectivity.

These results with indoles and pyrroles prompted us to extend the generality of the protocol to imidazole, which reacted with styrene oxide efficiently at room temperature under mild conditions (Scheme 3). Ring opening occurred exclusively at the less hindered carbon of the epoxide. This is consistent with S_N2-type attack by the imidazole nitrogen. The structure of the product was confirmed from its ^1H NMR and ^{13}C NMR spectral data. The characteristics signals of the aliphatic protons in the ^1H NMR at 4.11 ppm (d, 2H, $J = 5.7$ Hz for CH_2N) and at 4.89 ppm (t, 1H, $J = 5.7$ Hz for CH(OH))



Scheme 2.



Scheme 3.

Table 3. Comparative study of HBF_4–SiO_2 with recently reported literature methods for the ring opening reactions of aryl epoxides by nitrogen heterocycles

Entry	Catalyst	Catalyst loading (mol %)	Yield (%)	Reaction conditions
1	High pressure technique	—	13–90	10 K bar, 42 °C, 24 h
2	$Yb(OTf)_3$	5	19–66	42 h to 9 d, reflux
3	High pressure-silica gel	500 mg	19–88	10 K bar, 42 °C, 24 h to 7 d
4	$InCl_3$	10	70–85	2.5–5.5 h, rt
5	$InBr_3$	10	24–84	2–5 h, rt
6	HBF_4–SiO_2	2	50–80	2.5–3.5 h, rt

and signals in the ^{13}C NMR at 52.1 ppm (CH_2N) and at 70.3 ppm ($CHOH$) are in agreement with structure **8**.

All of the reactions proceeded efficiently at an ambient temperature with a high regioselectivity. No anhydrous solvents or harsh reaction conditions were required. All the reactions were clean and regioselective giving good yields of products in short reaction times. The results shown in Table 2 clearly indicate the scope and generality of this protocol. A comparison of the results obtained using HBF_4–SiO_2 with other recently reported methods indicated the superiority of the present protocol in terms of yield, catalyst loading (2 mol %) and reaction conditions (Table 3). It is important to note that no trace of the product was observed in the case of aliphatic epoxides (e.g., epichlorohydrin) even after stirring for a longer time (24 h) with various nitrogen heterocycles. In each case the reactants were recovered in almost quantitative amounts.

In conclusion, this paper describes a simple and convenient procedure for the alkylation of nitrogen heterocycles with aryl epoxides using a supported catalyst.

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10. General experimental procedure: To a stirred mixture of indole (1 mmol) and styrene oxide (1 mmol) in CH_2Cl_2 (1 ml), HBF_4–SiO_2 (40 mg, 2 mol %) was added with continuous stirring at room temperature. After completion of the reaction (TLC), the reaction mixture was diluted with diethyl ether (15 ml). The catalyst was separated by filtration. The filtrate was dried over anhydrous Na_2SO_4 and then evaporated under vacuum to afford the crude product which on further purification by column chromatography, gave 2-(1*H*-3-indolyl)-2-phenylethanol in a 80% yield.
    Spectral data for new compound **3g**: 2-(1-Ethyl-2-phenyl-3-indolyl)-2-phenylethanol (**3g**): White solid; mp 122 °C; IR (KBr): 3549, 3400, 3060, 3030, 1610, 1600, 1470, 1360, 1335, 1020, 910, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.50 (t, $J = 6.8$ Hz, 3H), 1.58 (br s, 1H), 3.78 (m, 2H), 4.16–4.25 (m, 2H), 4.50 (t, $J = 6.8$ Hz, 1H), 6.98–7.05 (s, 5H), 7.10–7.45 (m, 9H); EIMS: *m/z* 341 (M^+); Anal Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.78; N, 4.10. Found: C, 84.51; H, 6.60; N, 4.28.