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An efficient Friedel–Crafts alkylation of nitrogen heterocycles catalyzed by antimony trichloride/montmorillonite K-10

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ABSTRACT

It has been found that $SbCl_3$ supported on montmorillonite K-10 is an efficient and reusable catalyst for Friedel–Crafts alkylation of nitrogen heterocycles such as indoles and pyrroles with epoxides. The reaction gives the corresponding C-alkylated derivatives in good to excellent yields with a high regioselectivity.

Indole and pyrrole derivatives are important heterocyclic compounds and have wide application in medicinal chemistry.[1–4] In particular, 3-alkylindole derivatives have significant biological and pharmacological importance.[5] Due to the nucleophilic nature of indolyl and pyrrolyl compounds, various methods have been developed for the alkylation of indoles and pyrroles.[6–8,10] From the synthetic point of view, the direct catalytic alkylation of indoles and pyrroles with epoxides is an attractive reaction due to the fact that this reaction is atom economic. Thus, some methodologies for opening of epoxides with indoles or pyrroles have been developed. This ring-opening reaction can be carried out in the presence of Lewis acids such as $LiClO_4$,[9] $InBr_3$,[10] $Ln(OTf)_3$,[11] $RuCl_3{\cdot}nH_2O$,[12] and $InCl_3$,[13] and heterogeneous catalysts such as HBF_4–SiO_2,[14] silica gel,[15] and nanocrystalline titanium(IV) oxide.[16] Bis(cyclopentadienyl)zirconium dichloride[17] and chromium salen complexes[18] have been used in alkylation of heteroaromatics with epoxides. This reaction can also be performed under high pressure[19] or in ionic liquids.[20] However, these procedures are associated with one or more disadvantages such as long reaction times,[11] high temperature,[9,11] and high pressure,[15,19] and special efforts are needed to prepare the catalyst,[17] and the protocol for the Friedel–Crafts alkylation reaction of nitrogen heterocycles with epoxides is still actively pursued.

In recent years, antimony trichloride has been used as a catalyst for various types of organic transformations in organic synthesis because this compound is not only commercially available and inexpensive, but is also easier to handle than other metal halides such as $InCl_3$, $GdCl_3$, and $TiCl_4$.[21,22] Clay-supported reagents have been widely applied in organic synthesis mainly because of the ease of separation of the products, simple work-up, mild reaction conditions, high yield and selectivity, much improved reaction rates, and recyclability of the catalyst.[23] In continuation of our work on the development of new synthetic methodologies,[24] we herein wish to report a simple, practical, and efficient method for regioselective ring opening of aliphatic and aryl epoxides with nitrogen heterocycle compounds using $SbCl_3$/montmorillonite K-10 as catalyst at room temperature under solvent-free conditions (Scheme 1).[25]

Initially, we examined the Friedel–Crafts alkylation of indole with the less-reactive glycidyl phenyl ether (Table 1, entry **m**). There was no reaction in the presence of literature-reported catalyst HBF_4–SiO_2,[14] or in ionic liquid [bmin][OTf].[20] It was reported that this reaction was carried out in refluxing acetonitrile in the presence of $Yb(OTf)_3$ for 9 days to give the product in less than 20% yield.[11] This reaction could also be catalyzed by SiO_2 under high pressure for 3 days with poor yield (16–29%).[15] To our delight, the corresponding product 1-(1*H*-indol-3-yl)-3-phenoxypropan-2-ol was obtained in 58% yield when the reaction was performed in the presence of $SbCl_3$/montmoril-

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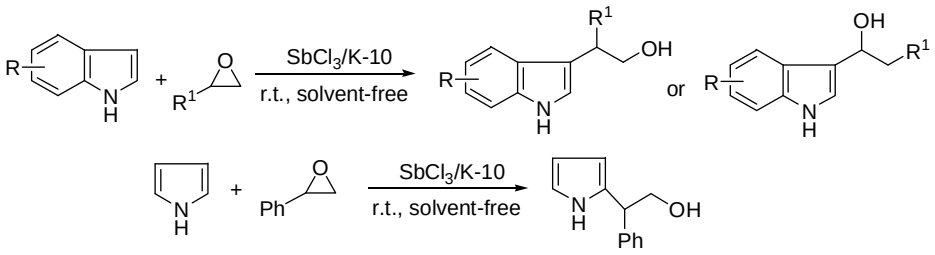
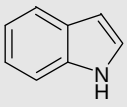
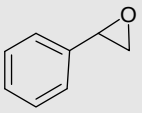
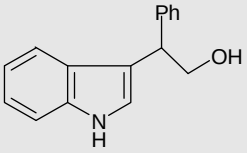
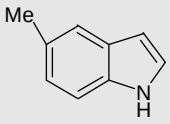
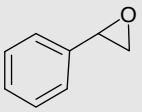
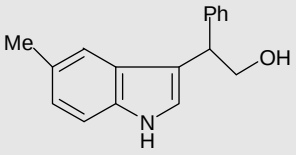
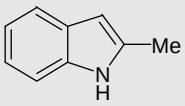
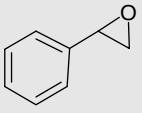
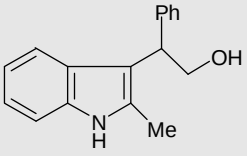
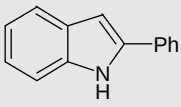
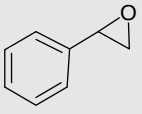
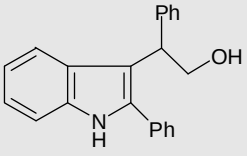
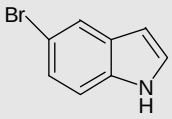
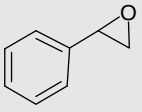
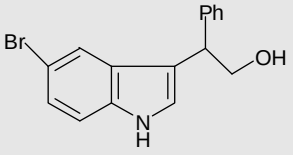
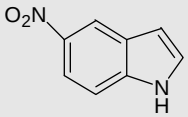
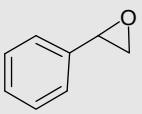
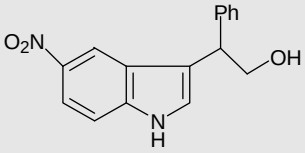
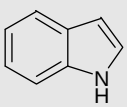
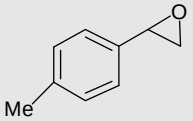
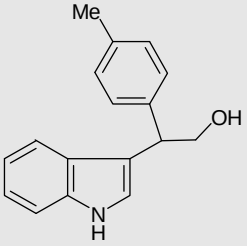


Scheme 1.

Table 1
$SbCl_3$/K-10 catalyzed Friedel–Crafts alkylation of nitrogen heterocycles with epoxides

Entry	Indole	Epoxide	Product	Time (h)	Yield[a] (%)
a				0.25	90
b				0.70	70
c				0.40	80
d				0.50	70
e				0.80	85
f				3.5	50
g				0.50	75

(*continued on next page*)

Table 1 (*continued*)

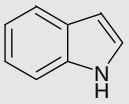
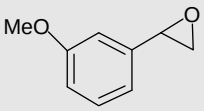
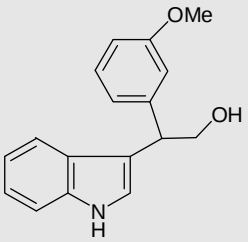
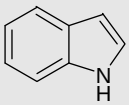
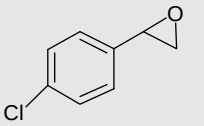
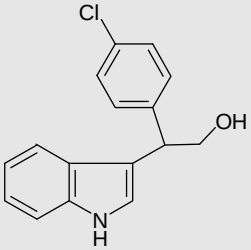
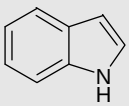
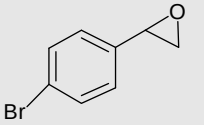
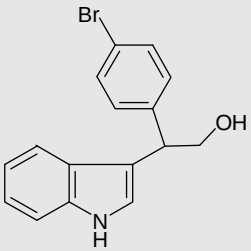
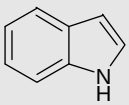
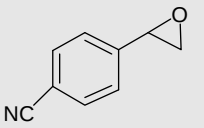
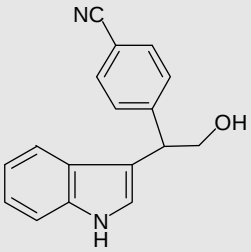
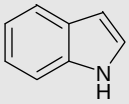
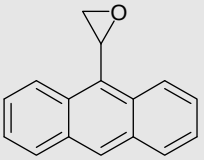
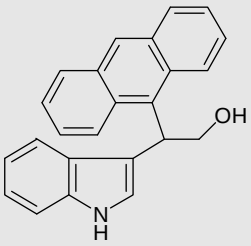
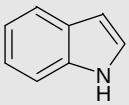
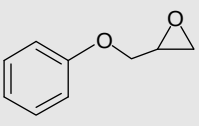
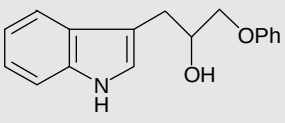
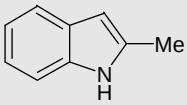
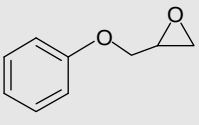
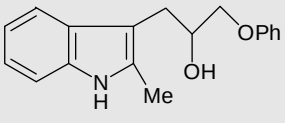
Entry	Indole	Epoxide	Product	Time (h)	Yield[a] (%)
h				0.50	85
i				0.65	90
j				0.65	80
k				0.65	75
l				0.35	90
m				1.0	58
n				1.0	40

Table 1 (*continued*)

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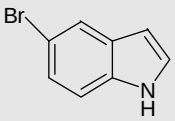
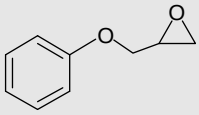
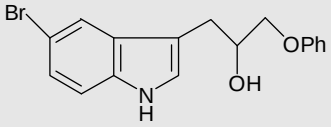
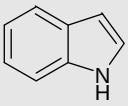
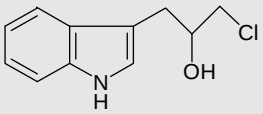
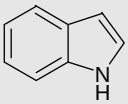
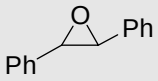
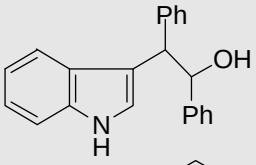
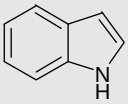
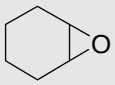
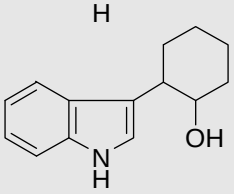
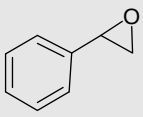
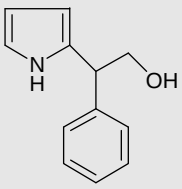
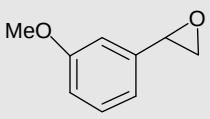
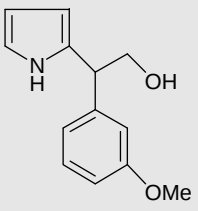
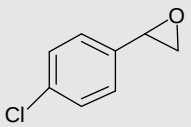
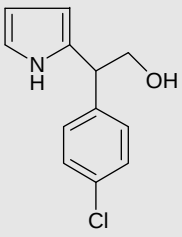
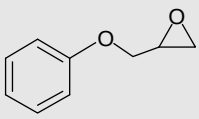
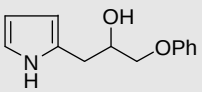
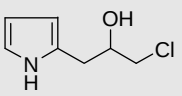
o				2.0	30
p				0.80	70
q				1.5	86
r				1.5	72
s				0.50	88
t				0.50	85
u				0.25	90
v				2.0	45
w				2.0	51

[a] Isolated yield.

lonite K-10[26] at room temperature at solvent-free conditions. Further studies showed that the catalyst loading of 10 mol % was substantially efficient for this reaction (1 h, 58% yield). Higher amount (20 mol %) of the catalyst did not improve the result.

Lower catalyst loading (5 mol %) could be used with only a marginal drop in reaction rate. Reaction in organic solvents such as CH_3CN, CH_2Cl_2, THF, DMF, and ethyl acetate gave very low yield of the desired product after prolonged reaction time.

The above experiment was carried out with 10 mol % of $SbCl_3$ alone, and it was found that only 20% yield of product was obtained after 2 h. There was no reaction in the presence of montmorillonite K-10 alone, and the starting materials remained intact. Meanwhile, the catalyst could be recycled five times for the reaction between glycidyl phenyl ether and indole and gave the corresponding product in 58%, 56%, 53%, 50%, and 49% yields.

To evaluate the scope of catalyst's application, various structurally divergent epoxides were tested with substituted indoles under the optimized conditions and the results are presented in Table 1. The reactions proceeded smoothly to afford the corresponding products in good yields with high regioselectivity. The regioselectivity was determined by ^{1}H NMR and also by comparison with known samples.[9,12,14] Aryl epoxides (Table 1, entries **a**–**k**) underwent cleavage by indoles with preferential attack at the benzylic position, resulting in the formation of primary alcohols. On the other hand, in the case of aliphatic oxiranes (Table 1, entries **m**–**p**), the reaction likely occurred through an attack by the indole on the less-substituted carbon atom. Since the 3-position of indole is the preferred site for electrophilic substitution reactions, 3-alkyl indole derivatives were formed exclusively in all cases. In general, unsubstituted indole and electron-donating substituted indoles gave high to excellent yields with short reaction time. The indole containing weakly electron-withdrawing group such as 5-bromoindole furnished the desired product in good yield (85%, entry **e**), whereas a 50% yield for 5-nitroindole was obtained due to a strongly withdrawing group in aromatic ring (entry **f**). 2-Anthracen-9-yl-oxirane reacted with indole also to give an excellent yield (entry **l**). The aliphatic epoxides (entries **m**–**p**) were converted into alkylated products in mediocre yields. Likewise, 1,2-disubstituted epoxides such as *trans*-stilbene oxide and cyclohexene oxide (entries **q** and **r**) also reacted with indole under the same experimental conditions and provided the corresponding products in good yields.

Having successfully developed an efficient C3-alkylation of indoles with epoxides, we finally checked the possibility of applying this method to the synthesis of alkylated pyrroles. Thus, the reaction of pyrrole with aromatic epoxides, under $SbCl_3$/montmorillonite K-10 catalysis, afforded the corresponding pyrrole derivatives in high yields (Table 1, entries **s**–**u**). Since the 2-position of pyrrole is the preferred site for electrophilic substitution reactions, 2-alkyl pyrrole derivatives were obtained in all reactions. We have also observed that the presence of an electron-withdrawing group in the epoxide reacted rapidly and gave higher yields (Table 1, entry **s**). Furthermore, aliphatic epoxides such as glycidyl phenyl ether and 2-chlorooxirane (Table 1, entries **v** and **w**) reacted with pyrrole to give the expected products in satisfactory yields.

In summary, we have demonstrated that $SbCl_3$/montmorillonite K-10 could efficiently promote Friedel–Crafts alkylation of nitrogen heterocycles with epoxides at room temperature under solvent-free conditions. The present procedure is endowed with some merits, such as mild reaction conditions, relative short reaction times, wide applicability, and recyclability of catalyst. Further study on $SbCl_3$-catalyzed reaction is currently underway in our laboratory.

Acknowledgments

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25. *General procedure for Friedel–Crafts alkylation of nitrogen heterocycles with epoxides*: To a mixture of indole (1.0 mmol) and styrene oxide (1.2 mmol), $SbCl_3$/montmorillonite K-10 (0.3 g, 10 mol % corresponding to the amount of $SbCl_3$) was added, and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration and the filtrate was diluted with ethyl acetate (3×10 mL), dried ($MgSO_4$), and evaporated to give the crude product. Further purification was achieved by silica gel chromatography using ethyl acetate/cyclohexane as eluent to afford pure product. *1-(4-Cyanophenyl)-2-(1H-indol-3-yl)ethanol* (Table 1, entry **k**): IR (KBr): ν = 3411, 2937, 2227, 1606, 1458, 1400, 1384, 1340, 1222, 1047, 835, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (br s, 1H), 4.13–4.26 (m, 2H), 4.51 (t, J = 6.0 Hz, 1H), 7.04–7.09 (m, 2H), 7.18–7.22 (m, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 8.34 (br s, 1H). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.76; H, 5.46; N, 10.75. *2-(3-Methoxyphenyl)-2-(1H-pyrrol-2-yl)ethanol* (Table 1, entry **r**): IR (KBr): ν = 3421, 2943, 1600, 1583, 1490, 1400, 1257, 1151, 1047, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (br s, 1H), 3.78 (s, 3H), 4.02 (dd, J = 10.4, 5.6 Hz, 1H), 4.07–4.17 (m, 2H), 6.01 (dd, J = 5.6, 3.2 Hz, 1H), 6.17 (dd, J = 5.6, 2.8 Hz, 1H), 6.69 (dd, J = 4.0, 2.4 Hz, 1H), 6.78–6.83 (m, 3H), 7.23–7.27 (m, 1H), 8.44 (br s, 1H). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.78; H, 7.05; N, 6.53. *1-Phenoxy-3-(1H-pyrrol-2-yl)propan-2-ol* (Table 1, entry **t**): IR (KBr): ν = 3385,

2922, 2852, 1568, 1429, 1298, 1118, 1091, 885, 794, 725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.22 (br s, 1H), 2.79 (d, J = 6.3 Hz, 2H), 3.53 (dd, J = 10.8, 6.3 Hz, 1H), 3.63 (dd, J = 10.8, 4.5 Hz, 1H), 3.95–4.02 (m, 1H), 6.12 (dd, J = 3.9, 2.4 Hz, 1H), 6.68 (dd, J = 4.8, 3.9 Hz, 1H), 6.76 (dd, J = 4.8, 2.4 Hz, 1H), 8.17 (br s, 1H). Anal. Calcd for $C_7H_{10}ClNO$: C, 52.67; H, 6.31; N, 8.78. Found: C, 52.80; H, 6.08; N, 8.96. *1-Chloro-3-(1H-pyrrol-2-yl)propan-2-ol* (Table 1, entry **u**): IR (KBr): ν = 3413, 2956, 2871, 1618, 1598, 1458, 1400, 1292, 1244, 1076, 887, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.39 (br s, 1H), 3.91 (dd, J = 9.3, 6.6 Hz, 1H), 3.98 (dd, J = 9.3, 3.9 Hz, 1H), 4.14–4.22 (m, 1H), 6.11 (dd, J = 3.9, 2.1 Hz, 1H), 6.64 (dd, J = 4.8, 3.9 Hz, 1H), 6.72 (dd, J = 4.8, 2.1 Hz, 1H), 6.89-6.96 (m, 3H), 7.22–7.29 (m, 2H), 8.21 (br s, 1H). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.65; H, 7.10; N, 6.68.

26. *Preparation of $SbCl_3$/montmorillonite K-10 catalyst*: Antimony trichloride (2.28 g, 10 mmol) was added to a suspension of montmorillonite K-10 (27.8 g) in ethanol (50.0 mL). The mixture was stirred at room temperature for 1 h. The solvent was removed with rotary evaporator, and the residue was heated at 100 °C under vacuum for 5 h to furnish $SbCl_3$/montmorillonite K-10 as a free flowing powder.