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Solvent-free, ruthenium-catalyzed, regioselective ring-opening of epoxides, an efficient route to various 3-alkylated indoles

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Abstract

Ruthenium-catalyzed regioselective ring-opening of aliphatic and aryl epoxides under solvent-free conditions is reported. It was found that $RuCl_3{\cdot}nH_2O$ catalyzes the Friedel–Crafts alkylation of indoles, providing 3-alkylated derivatives in good yields under mild reaction conditions.

Keywords: Ruthenium; Ring-opening; Epoxides; Indoles

1. Introduction

Homogeneous transition metal catalysis is a gentle art.[1] Many organic transformations which involve organometallic ruthenium species as catalyst are known and well documented.[2–4] Ru^{III} salts are also known to catalyze a variety of organic transformations,[5–10] and the investigation of the chemistry of ruthenium continues to be an active area of organometallic chemistry. On the other hand, indole derivatives occur in many pharmacologically and biologically active compounds.[11–13] In particular, 3-alkylindole derivatives have significant medical importance,[14–16] and can be prepared by ring-opening of epoxides using indoles. In the literature, this type of reaction has been reported using different methods such as acid catalysis,[17] high pressure conditions,[18] lanthanide triflates,[19] nanocrystalline titanium(IV) oxide[20] and HBF_4–SiO_2.[21] The drawbacks of these methods are long reaction times, high temperatures, a large excess of reagents, high pressure and unsatisfactory yields, especially, with regard to aliphatic epoxides. In continuation of our recent work on indole derivatives and the catalytic reactivity of ruthenium,[22–24] we now describe our study of the Friedel–Crafts alkylation reaction of indoles using various epoxides.

2. Results and discussion

Whilst the majority of synthetic methods for ring-opening of epoxides using indoles have been focused on aryl epoxides, little attention has been paid to the use of aliphatic analogues because of the lower reactivity of these compounds. The ring-opening of phenyl glycidyl ether with indole in a low yield under harsh reaction conditions has been reported.[18] We decided to evaluate the catalytic activity of Ru^{III} as a mild Lewis acid in this reaction and during the optimization process, we noticed that $RuCl_3{\cdot}nH_2O$ freely dissolves in most epoxides (both aliphatic and aryl epoxides), resulting in a homogeneous solvent-free process. The optimized conditions are outlined in Scheme 1.

Typical results for the ruthenium-catalyzed ring-opening of glycidyl and aryl epoxides with an array of substituted indoles are shown in Table 1, indicating the generality and scope of the reaction. Treatment of indole (1 mmol) with 2,3-epoxypropyl phenyl ether (0.5 mL, 3.7 mmol) in the presence of the $RuCl_3{\cdot}nH_2O$ catalyst (5 mol %) at rt for 6 h gave 1-(3-indolyl)-3-phenoxy-2-propanol in a 67%

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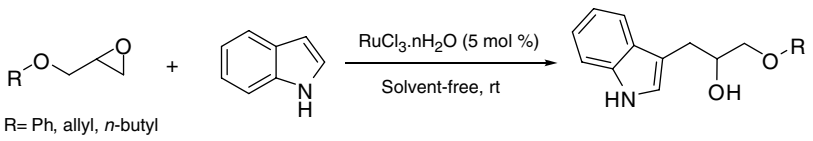
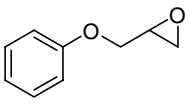
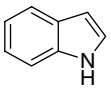
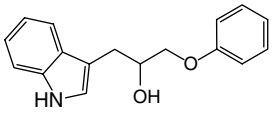
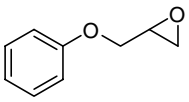
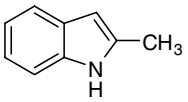
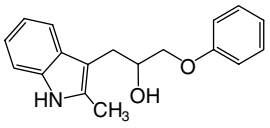
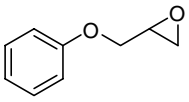
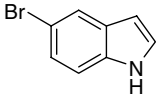
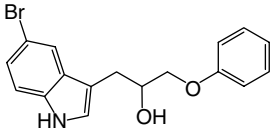
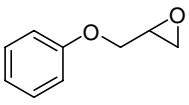
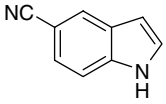
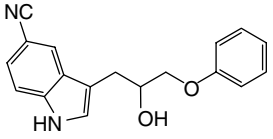
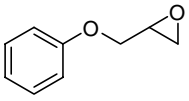
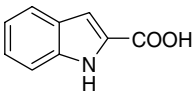
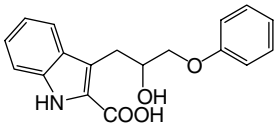
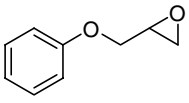
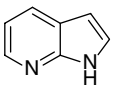
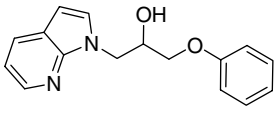
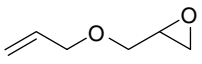
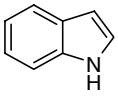
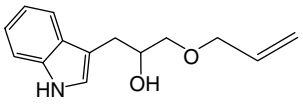
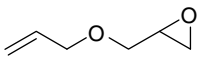
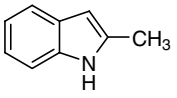
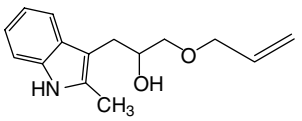
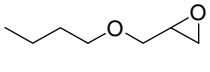
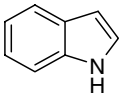
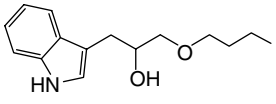
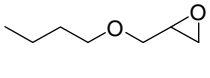
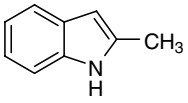
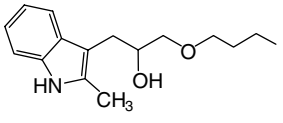
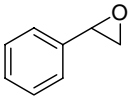
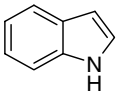
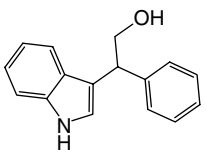


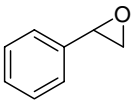
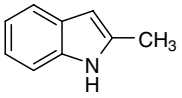
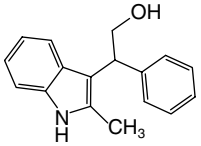
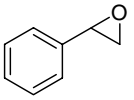
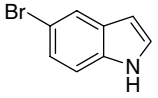
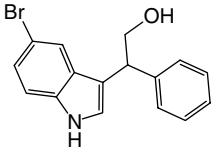
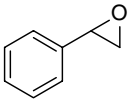
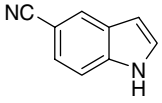
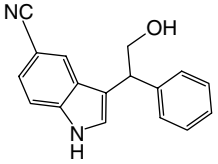
Scheme 1. Ru^{III}-catalyzed Friedel–Crafts alkylation of indole using glycidyl ethers.

Table 1
Ru^{III}-catalyzed alkylation of indoles with epoxides

Entry[a]	Epoxide	Indole	Product	Time (h)	Yield[b] (%)
1				6	67[c]
2				4	73
3				6	60
4				8	56
5				8	52
6				4	98
7				6	57[d]
8				6	61
9				6	52[d]
10				6	59
11				3	82[c]

(*continued on next page*)

Table 1 (*continued*)

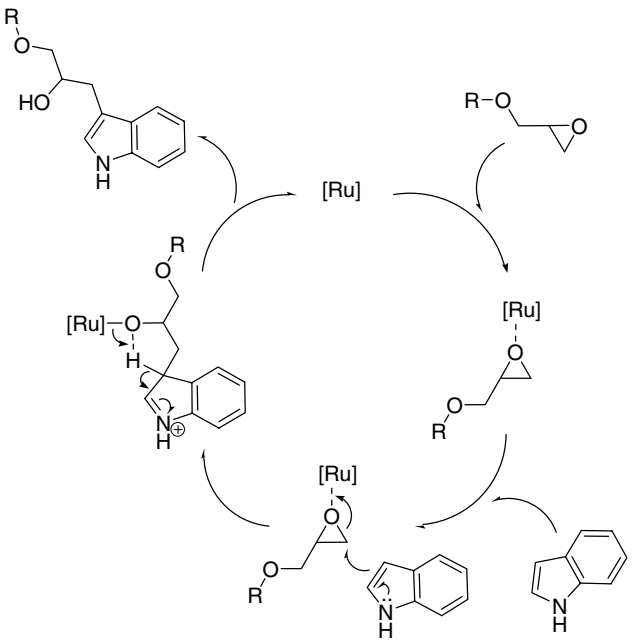
Entry[a]	Epoxide	Indole	Product	Time (h)	Yield[b] (%)
12				3	83[c]
13				4	72[c]
14				4	60[c]

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR and IR data.
[b] Isolated yields.
[c] Identified by comparison with authentic samples.[18,19]
[d] 10 μL of CF_3COOH was added as co-catalyst.

yield (entry 1). From the NMR spectral data, it was evident that the reaction occurred exclusively at the less hindered carbon of the epoxide ring. The reaction can be used for substituted indoles with either electron-donating or electron-withdrawing groups (Table 1, entries 2–5), and the same regioselectivity was observed in each case. Electron-rich indoles, however, gave better yields and proceeded with shorter reaction times. When 7-azaindole was treated with 2,3-epoxypropyl phenyl ether, the reaction furnished an excellent yield of the N-alkylation product, which was insoluble in the reaction media. In this case, the white solid precipitate was filtered and washed with methanol to provide a completely pure product (entry 6).

With regard to the epoxide moiety, the present protocol is noteworthy because styrene epoxide as well as allyl- and butyl-2,3-epoxypropyl ethers underwent ring-opening with indoles. These results are also included in Table 1 and indicate the scope of reaction. Electron-rich substituents on the glycidyl ether, however, decreased the yield and rate of the reaction, and in the case of entries 7 and 9, the reaction was only promoted in the presence of CF_3COOH as a co-catalyst. Using styrene epoxide, however, better results in terms of yield and reaction time were obtained in comparison with previous reports. With regard to regioselectivity, preferential attack at the benzylic position of styrene epoxide gave primary alcohols (entries 11–14). It should be noted that cyclohexene oxide resulted in no isolated product even in the presence of CF_3COOH at elevated temperatures. Although the precise mechanism of the reaction awaits further studies, a possible mechanistic pathway for the ring-opening of glycidyl ethers, which rationalizes the formation of products, is presented in Scheme 2.

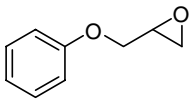
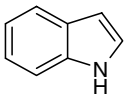
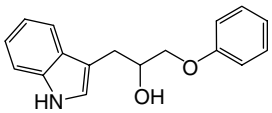
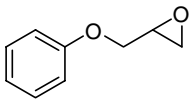
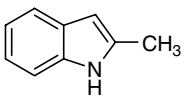
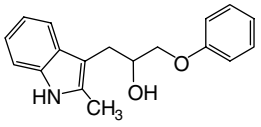
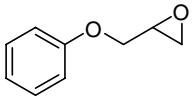
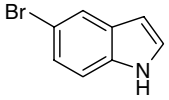
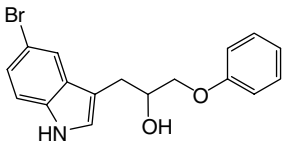
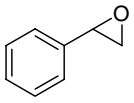
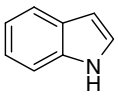
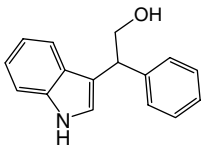
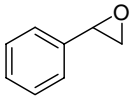
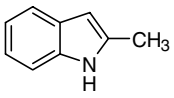
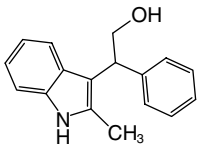
Encouraged by these results, we decided to overcome the problem of prolonged reaction times using microwave irradiation. A mixture of indole (1 mmol), epoxide (0.5 mL) and 5 mol % of catalyst was irradiated in a 450 W microwave oven in an open vessel at 50 °C for the time specified in Table 2, and the progress of the reaction was checked by TLC.



Scheme 2. Proposed mechanism for the Ru^{III}-catalyzed ring-opening of epoxides.

These results reveal the potential of microwave irradiation for promotion of the reaction. Generally, the products were limited to 3-alkylated indoles; however, in some cases lower yields were obtained.

Table 2
Ru^{III}-catalyzed ring-opening of epoxides under microwave irradiation

Entry[a]	Epoxide	Indole	Product	Time (min)	Yield[b] (%)
1				5	65[c]
2				5	75
3				6	57
4				3	80[c]
5				3	85[c]

[a] All products were characterized by ^1H NMR, ^{13}C NMR and IR data.
[b] Isolated yields.
[c] Identified by comparison with authentic samples.[18,19]

In conclusion, we have developed a convenient method for the Friedel–Crafts alkylation of indoles with aryl- and glycidyl epoxides. To the best of our knowledge, this is the first report on the ring-opening of epoxides using Ru^{III} as a catalyst. The advantages of the present protocol are the ease of work-up, the small amount of waste, the solvent-free conditions and the regioselectivity.

3. General procedure for solvent-free ruthenium-catalyzed ring-opening of glycidyl and aryl epoxides with indoles

A 3 mL screw-capped vial equipped with a magnetic stirring bar was charged with indole (1 mmol) and 2,3-epoxypropyl phenyl ether (0.5 mL, 3.7 mmol). $RuCl_3{\cdot}nH_2O$ (10.7 mg, 0.05 mmol) was added and the reaction mixture was stirred at rt. After 6 h, the reaction mixture was purified by preparative TLC (*n*-hexane/ethyl acetate 10/3), providing the product (179 mg, 67%). For microwave reactions, irradiation was conducted in an open vessel at 50 °C in a 450 W microwave oven.

3.1. 1-(1H-Indol-3-yl)-3-phenoxypropan-2-ol (Table 1, entry 1)

Solid, mp 82–84 °C, IR (KBr): ν (cm^{-1}); 690, 752, 814, 1037, 1083, 1172, 1244, 1296, 1338, 1427, 1456, 1494, 1595, 2877, 2926, 3056, 3326, 3416, 3545. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 2.23$ (1H, br), 3.15 (1H, dd, $J = 14.5$, 7.0 Hz), 3.20 (1H, dd, $J = 14.5$, 6.2 Hz), 4.01 (1H, dd, $J = 9.3$, 6.4 Hz), 4.07 (1H, dd, $J = 9.3$, 3.9 Hz), 4.41 (1H, m), 6.96 (2H, d, $J = 8.3$ Hz), 7.02 (1H, t, $J = 7.3$ Hz), 7.15 (1H, s), 7.18 (1H, t, $J = 7.8$ Hz), 7.27 (1H, t, $J = 7.6$ Hz), 7.31–7.36 (2H, m), 7.42 (1H, d, $J = 8.2$ Hz), 7.70 (1H, d, $J = 7.9$ Hz), 8.11 (1H, br) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 29.86$, 70.57, 71.59, 111.66, 111.84, 115.06, 119.30, 120.06, 121.50, 122.69, 123.35, 128.03, 129.94, 136.77, 159.09 ppm. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.40; H, 6.45; N, 5.23.

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