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Ruthenium-catalyzed regioselective synthesis of 2-substituted indoles via ring-opening of epoxides by anilines

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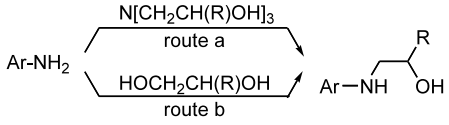
Abstract—Anilines react with epoxides in dioxane at 180°C in the presence of a catalytic amount of a ruthenium catalyst along with tin(II) chloride to afford 2-substituted indoles in moderate to good yields.

Indoles have been known as pharmacologically and biologically active compounds. Thus, many conventional named and transition metal-catalyzed synthetic methods have been developed and documented for the indole framework formation.[1] In connection with this report, during the course of our ongoing studies on homogeneous ruthenium catalysis,[2–5] we have also reported on the formation of indoles via a ruthenium-catalyzed C_2-fragment transfer from alkanolamines to N-atom of anilines (amine exchange reaction).[2,6] Furthermore, though not yet clear, it was suggested that such an amine exchange reaction produces a 2-anilinoalkanol as an initial intermediate (Scheme 1, route a). Watanabe et al. also proposed the formation of the 2-anilinoalkanol as an intermediate on ruthenium-catalyzed synthesis of indoles from anilines and ethylene glycols (Scheme 1, route b).[7] Actually, in separate experiments made by both groups, it was confirmed that these 2-anilinoalkanols react with anilines to form indoles under their ruthenium catalyst systems. On the other hand, although it is known that epoxides are introduced for the indole synthesis over heterogeneous catalysts,[8] the version is of little synthetic use since the reaction is carried out under severe conditions and gives low regioselectivity. In these regards, we have directed our attention to transition metal-catalyzed in situ formation route of 2-anilinoalkanols for eventual indole framework construction. Herein we disclose a regioselective synthesis of 2-substituted indoles via ruthenium- and $SnCl_2$-catalyzed ring-opening of epoxides by anilines.



Scheme 1.

Table 1 shows optimization of the conditions for the ring-opening and heteroannulation between aniline (**1a**) and propylene oxide (**2a**) leading to 2-methylindole (**3a**) and 3-methylindole (**4a**). Under these circumstances, the reaction selectively gives rise to **3a** in preference to **4a** in the range of 7.3–16.5 selectivities. The product yield was considerably affected by the molar ratio of **1a**/**2a**, increasing with the increase of the molar ratio up to **1a**/**2a** = 10 without significant change of the product selectivity (entries 1–4). The addition of $SnCl_2$ was essential for the effective formation of **3a** and **4a** (entry 5).[9] When the reaction was carried out in the absence of $SnCl_2$, **3a** and **4a** were produced in only 12% yield with similar selectivity of **3a**/**4a**. However, the use of a catalytic amount of $SnCl_2$ (0.1 mmol) under the condition of entry 5 in Table 1 afforded **3a** and **4a** in 29% yield (**3a**/**4a** = 8.6). Among the activity of various ruthenium precursors examined $RuCl_3 \cdot nH_2O/3PPh_3$ and $RuCl_2(PPh_3)_3$ in terms of overall yield revealed to be the catalysts of choice (entries 4 and 6). However, performing the reaction under $RuCl_2(PPh_3)_3$ was accompanied by many by-products which gives difficulty in separation comparing with that under $RuCl_3 \cdot nH_2O/3PPh_3$. Other ruthenium complexes such as $RuH_2(PPh_3)_4$ and $Ru_3(CO)_{12}$ were moderately effective for the formation of **3a** and **4a** (entries 7 and 8).

Keywords: anilines; epoxides; indoles; ring-opening; ruthenium catalyst.

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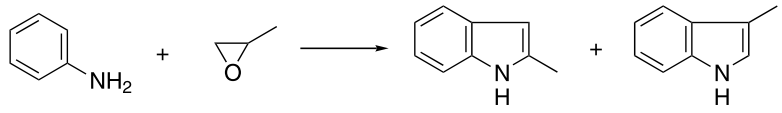
Table 1. Ruthenium-catalyzed reaction of **1a** with **2a** under several conditions[a]



1a **2a** **3a** **4a**

Entry	Molar ratio (**1a**/**2a**)	Ruthenium catalyst	Yield (%)[b] of **3a**+**4a**	**3a**/**4a**
1	4	$RuCl_3{\cdot}nH_2O$-3PPh_3	52	9.0
2	6	$RuCl_3{\cdot}nH_2O$-3PPh_3	58	9.3
3	8	$RuCl_3{\cdot}nH_2O$-3PPh_3	68	8.8
4	10	$RuCl_3{\cdot}nH_2O$-3PPh_3	72	8.2
5[c]	10	$RuCl_3{\cdot}nH_2O$-3PPh_3	12	9.3
6	10	$RuCl_2(PPh_3)_3$	77	8.6
7	10	$RuH_2(PPh_3)_4$	59	8.2
8	10	$Ru_3(CO)_{12}$	61	7.3
9	10	Cp*$RuCl_2$(CO)[d]	23	16.5
10	10	$RuCl_2(=CHPh)(PCy_3)_2$	28	9.5

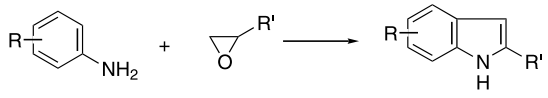
[a] Reaction conditions: **2a** (1 mmol), ruthenium catalyst (5 mol% based on **2a**), $SnCl_2$ (1 mmol), dioxane (10 ml), 180 °C, for 20 h, under argon.
[b] GLC yield based on **2a**.
[c] In the absence of $SnCl_2$.
[d] Cp* = η^5-C_5Me_5.

Cp*$RuCl_2$(CO) and $RuCl_2(=CHPh)(PCy)_3$ were not effective for the present reaction, however, the selectivity of **3a**/**4a** was significantly increased under Cp*$RuCl_2$(CO) (entries 9 and 10).

Having established suitable reaction conditions, a series of anilines **1** and epoxides **2** were screened in order to investigate the reaction scope, and several representative results are summarized in Table 2. The reactions of **1a** with several epoxides (**2b–d**) also proceed to give the corresponding indoles (**3b–d**) with exclusive regioselectivity.[10] This result indicates that the bulkiness of substituent on epoxides dominates the regioselectivity. In the case of styrene oxide (**2d**), although **2d** was completely disappeared after the reaction, we obtained 2-phenylindole (**3d**) in only 27% yield and could not find other detectable products. On the other hand, with cyclohexene oxide the reaction resulted in complicated mixture on GLC and TLC analyses. Various anilines (**1b–k**) were also reacted with (2,3-epoxypropyl)benzene (**2c**) to give the corresponding 2-benzylindoles (**3e–n**) in the range of 22-98% yields. Here again, exclusive regioselectivity in favor of 2-substituted isomer was observed. The indole yield was not significantly affected by the position and electronic nature of the substituent on aromatic ring of **1** except for 2-anisidine (**1f**), which gave lower yield than that of other anilines. It is known that catalyst ruthenium is deactivated by coordination of two adjacent methoxy and amino substituents of **1f** to ruthenium.[7b] With anilines having two-methyl substituents (**1j** and **1k**), the product yield was higher than that when anilines having mono-substituents were employed (**1b–i**).

As to the reaction pathway, although it is not yet fully understood, this seems to proceed via a sequence such as ring-opening of 1,2-epoxyhexane (**2b**) by **1a** to form 2-anilinoalkanol **5**,[11] N-alkylation of **1a** with **5** to produce 1,2-dianilinoalkane **6**,[12] and heteroannulation to give **3b** (Scheme 2).[2c,7b] A variety of catalysts are known to catalyze a nucleophilic ring-opening of epoxides.[13] It appears that ruthenium halides and $SnCl_2$ as Lewis acids facilitate the initial opening of **2b** in the present

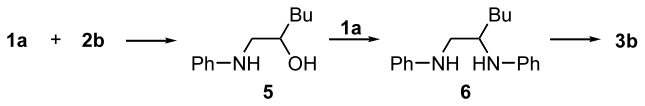
Table 2. Ruthenium-catalyzed synthesis of 2-substituted indoles[a]



1 **2** **3**

Anilines **1**	Epoxides **2**	Indoles **3**	Yield (%)[b]
1a R = H	**2a** R′ = Me	**3a** R = H	62[c]
1a	**2b** R′ = Bu	**3b** R = H	49
1a	**2c** R′ = benzyl	**3c** R = H	75
1a	**2d** R′ = Ph	**3d** R = H	27
1b R = 4-Me	**2c**	**3e** R = 5-Me	60
1c R = 3-Me	**2c**	**3f** R = 4- and 6-Me	62[d]
1d R = 2-Me	**2c**	**3g** R = 7-Me	59
1e R = 4-OMe	**2c**	**3h** R = 5-OMe	41
1f R = 2-OMe	**2c**	**3i** R = 7-OMe	22
1g R = 4-Cl	**2c**	**3j** R = 5-Cl	54
1h R = 4-Bu	**2c**	**3k** R = 5-Bu	61
1i R = 4-*s*-Bu	**2c**	**3l** R = 5-*s*-Bu	62
1j R = 2,5-Me_2	**2c**	**3m** R = 4,7-Me_2	98
1k R = 3,5-Me_2	**2c**	**3n** R = 4,6-Me_2	72

[a] Reaction conditions: **1** (10 mmol), **2** (1 mmol), $RuCl_3{\cdot}nH_2O$ (0.05 mmol), PPh_3 (0.15 mmol), $SnCl_2$ (1 mmol), dioxane (10 ml), 180 °C, for 20 h, under argon.
[b] Isolated yield based on **2**.
[c] Regioisomeric mixture of 2- and 3-methylindoles noted in Table 1.
[d] Regioisomeric distribution was determined by ^{1}H NMR (400 MHz): 4-Me/6-Me = 0.7/1.



Scheme 2.

reaction. In a careful separate experiment, we isolated intermediate **6** in 22% yield, whereas intermediate **5** was not found.[14]

General experimental procedure: a mixture of aniline (10 mmol), epoxide (1 mmol), $RuCl_3 \cdot nH_2O$ (0.05 mmol), PPh_3 (0.15 mmol), and $SnCl_2$ (1 mmol) in dioxane (10 ml) was placed in a 50 ml stainless steel autoclave. After the system was flushed with argon, the mixture was allowed to react at 180°C for 20 h. The reaction mixture was filtered through a short silica gel column using ethyl acetate–chloroform as an eluent to eliminate inorganic salts and the filtrate was concentrated. To the residual oily material was added 30 ml of $CHCl_3$ and washed with 50 ml of aq. 5% HCl solution to remove excess aniline. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give indoles.

In summary, we have shown that anilines react with epoxides in the presence of a ruthenium catalyst and $SnCl_2$ to afford 2-substituted indoles regioselectively in moderate to good yields. The present reaction is a novel regioselective strategy for the synthesis of 2-substituted indoles from readily available anilines and epoxides. The exact regioselective mechanism and reductive cyclization of nitroarenes with epoxide for indoles are currently under investigation.

Acknowledgements

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14. The reaction was carried out with the conditions described in Table 2. **1,2-Dianilinohexane (6):** MS m/z (relative intensity) 268 (M^+, 13), 162 (100).