Ruthenium-Catalyzed Synthesis of Quinolines from Anilines and Tris(3-hydroxypropyl)amine *via* Amine Exchange Reaction

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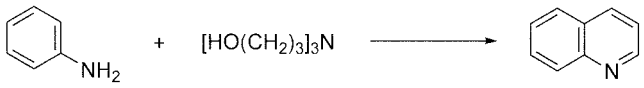
It is known that transition metal-catalyzed alkyl group transfer between alkylamines (amine exchange reaction or amine scrambling reaction) has been used for the synthesis of unsymmetrical amines and N-heterocycles and for the study of the metabolism of amines.[1] During the course of our ongoing studies on homogeneous ruthenium catalysis,[2-6] we have directed our attention to the alkyl group transfer from α-hydrogen containing amines to the N-atom of anilines, which eventually leads to indoles[2] and quinolines.[3] However, except for our findings, cyclization reaction using such an alkyl group transfer as yet seems to be limited to only palladium-catalyzed synthesis of hydropyrimidines, imidazolidines and imidazoles.[7] In relation to our ruthenium-catalyzed quinoline synthesis, several amines such as triallylamine,[3a] trialkylamines,[3b,3c] and 3-amino-1-propanols[3d,3e] as well as alkylammonium halides[3f,3g] were used as alkyl group donors. Herein, as an another example for the synthesis of N-heterocycles using such an intrinsic alkyl group transfer, we report a ruthenium-catalyzed quinoline formation *via* C_3-fragment transfer from tris(3-hydroxypropyl)amine[8] to nitrogen atom of anilines.

Based on our previous reports for ruthenium-catalyzed synthesis of indoles and quinolines *via* an amine exchange reaction,[2,3] some results for the ruthenium-catalyzed reaction between aniline (**1a**) and tris(3-hydroxypropyl)amine (**2**) under various conditions are listed in Table 1. Treatment of **1a** with **2** in the presence of a catalytic amount of $RuCl_3 \cdot nH_2O$ (5 mol%)/PPh_3 (15 mol%) along with $SnCl_2 \cdot 2H_2O$ and acetone at 180 °C for 24 h afforded quinoline (**3a**) in 60% yield (based on **2**) (entry 1). The yield of **3a** was considerably affected by the molar ratio of [**1a**]/[**2**]. The best result was accomplished by the molar ratio of [**1a**]/[**2**] = 4.0. The addition of $SnCl_2 \cdot 2H_2O$ was essential for the formation of **3a**. When the reaction was carried out in the absence of $SnCl_2 \cdot 2H_2O$, **3a** was produced in only 5% yield (entry 2). Furthermore, the addition of a suitable hydrogen acceptor was necessary for the effective formation of **3a**. Performing the reaction in the absence of hydrogen acceptor resulted in a lower yield of **3a** when compared to the reaction in the presence of hydrogen acceptor (entries 1 and 3). Several hydrogen acceptors such as acetophenone and dodec-1-ene could be alternatively used, but the yield of **3a** was lower than that when acetone was used (entries 4 and 5). However, performing the reaction in the presence of oct-1-yne was ineffective and GLC analysis of crude reaction mixture showed very complicated products, which may be attributed to dimerization and trimerization of oct-1-yne under ruthenium catalyst system (entry 6).[9] Among various ruthenium precursors we examined, $RuCl_3 \cdot nH_2O/3PPh_3$ revealed to be the catalyst of choice (entries 7-11). As a result, the reaction condition of entry 1 in Table 1 was revealed to be optimal for obtaining **3a**.

Table 1. Optimization of conditions for the reaction of **1a** with **2**[a]



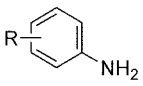
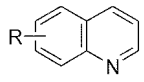
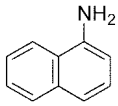
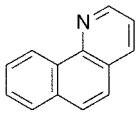
1a **2** **3a**

Entry	Ruthenium catalyst	Hydrogen acceptor	Yield (%)[b]
1	$RuCl_3 n \cdot H_2O/3PPh_3$	acetone	60
2[c]	$RuCl_3 n \cdot H_2O/3PPh_3$	acetone	5
3	$RuCl_3 n \cdot H_2O/3PPh_3$	-	35
4	$RuCl_3 n \cdot H_2O/3PPh_3$	acetophenone	49
5	$RuCl_3 n \cdot H_2O/3PPh_3$	dodec-1-ene	45
6	$RuCl_3 n \cdot H_2O/3PPh_3$	oct-1-yne	26
7	$RuCl_2(PPh_3)_3$	acetone	33
8	$RuCl_2(=CHPh)(PCy_3)_2$	acetone	21
9	$Ru_3(CO)_{12}$	acetone	45
10	$RuH_2(PPh_3)_4$	acetone	9
11	$Cp^*RuCl_2(CO)$[d]	acetone	18

[a]Reaction conditions: **1a** (4 mmol), **2** (1 mmol), hydrogen acceptor (10 mmol), ruthenium catalyst (0.05 mmol), $SnCl_2 \cdot 2H_2O$ (1 mmol), dioxane (10 mL), 180 °C, for 24 h, under argon. [b]GLC yield based on **2**. [c]In the absence of $SnCl_2 \cdot 2H_2O$. [d]$Cp^* = \eta^5$-C_5Me_5.

Having established optimal reaction conditions, the reactions of various anilines (**1b**-**1m**) with **2** were screened to investigate the scope of the present method (Table 2). The quinoline yield was considerably affected by the position and electronic nature of the substituent on **1**. With *ortho*-substituted anilines, the quinoline yield was lower than that when *meta*- and *para*-substituted anilines were used (entries 2-4). Especially, the reaction with *o*-anisidine (**1e**) scarcely afforded product **3e** (entry 5). It is reported by Watanabe *et al*. that this may be due to deactivation of ruthenium catalyst by coordination of two adjacent methoxy and amino substituent of **1e** to ruthenium.[10] In the case of *m*-toluidine (**1c**), the corresponding quinolines (**3c**) were obtained as a

Table 2. Ruthenium-catalyzed synthesis of quinolines **3**[a]

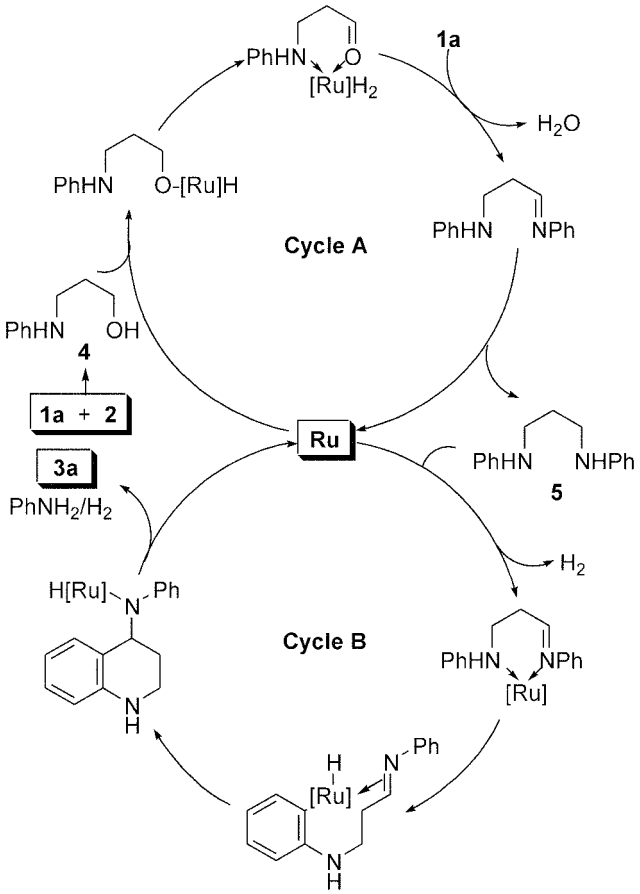
Entry	Anilines **1**	Quinolines **3**	Yield (%)[b]
			
1	**1a** R=H	**3a** R=H	54
2	**1b** R=2-Me	**3b** R=8-Me	29
3	**1c** R=3-Me	**3c** R=5- and 7-Me	71[c]
4	**1d** R=4-Me	**3d** R=6-Me	58
5	**1e** R=2-OMe	**3e** R=8-OMe	0
6	**1f** R=4-OMe	**3f** R=6-OMe	62
7	**1g** R=4-acetyl	**3g** R=6-acetyl	40
8	**1h** R=4-Bu	**3h** R=6-Bu	82
9	**1i** R=4-*s*-Bu	**3i** R=6-*s*-Bu	65
10	**1j** R=2,3=Me_2	**3j** R=7,8=Me_2	72
11	**1k** R=2,5=Me_2	**3k** R=5,8=Me_2	49
12	**1l** R=3,5=Me_2	**3l** R=5,7=Me_2	94
13	 **1m**	 **3m**	36

[a]Reaction conditions: **1** (4 mmol), **2** (1 mmol), acetone (10 mmol), $RuCl_3 \cdot nH_2O$ (0.05 mmol), PPh_3 (0.15 mmol), $SnCl_2 \cdot 2H_2O$ (1 mmol), dioxane (10 mL), 180 °C, for 24 h, under argon. [b]Isolated yield based on **2**. [c]Regioisomeric distribution was determined by ^1H NMR (400 MHz): 7-Me/5-Me = 5/1.

regioisomeric mixture, favoring the 7-methyl isomer which was formed *via* less sterically hindered position on **1c** (entry 3). With **1g** having electron-withdrawing acetyl substituent, the product yield was lower than that when anilines having electron-donating substituents such as alkyl and methoxy were employed (entry 7). The reaction proceeds likewise with two-methyl substituted anilines (**1j**-**1l**) to give the corresponding quinolines (**3j**-**3l**) in good yields (entries 10-12). The cyclization also took place with 1-aminonaphthalene (**1m**) to afford 7,8-benzoquinoline (**3m**) in 36% yield (entry 13).

As to the reaction pathway, although the exact role of $SnCl_2 \cdot 2H_2O$ is not yet understood and no intermediates were detected at present stage,[11] this seems to proceed *via* a sequence involving initial propanol group transfer from **2** to N-atom of **1a** (amine exchange reaction) to form 3-anilino-1-propanol (**4**),[1] N-alkylation of **1a** with **4** to form 1,3-dianilinopropane (**5**) (Cycle A in Scheme 1)[12,13] and hetero-annulation of **5** *via* orthometallation (Cycle B in Scheme 1).[14] Watanabe and Tsuji proposed the formation of **4** and **5** as intermediates on ruthenium-catalyzed synthesis of quinolines from anilines and 1,3-diols.[10] They also confirmed in a separate experiment that **4** reacted with **1a** in the presence of a ruthenium catalyst to give **3a** and **5** was intramolecularly cyclized to give **3a**.[10]

In summary, we have shown that anilines react with tris(3-hydroxypropyl)amine in the presence of a ruthenium catalyst along with $SnCl_2 \cdot 2H_2O$ and acetone to give quinolines in moderate to good yields. The present reaction is an another approach for the synthesis of N-heterocycles using transition metal-catalyzed amine exchange reaction.



Scheme 1

Experimental Section

General procedure for ruthenium-catalyzed reactions between 1a and 2 for 3a (for GLC analysis). A mixture of **1a** (0.373 g, 4 mmol), **2** (0.191 g, 1 mmol), ruthenium catalyst (0.05 mmol), $SnCl_2 \cdot 2H_2O$ (0-1 mmol) and hydrogen acceptor (0-10 mmol) in dioxane (10 mL) was charged in a 50 mL stainless steel autoclave. After the system was flushed with argon, the resulting mixture was stirred at 180 °C for 24 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture) to eliminate inorganic salts. To the extract was added appropriate amount of internal standard and analyzed by GLC.

General procedure for ruthenium-catalyzed synthesis of 3 from 1 and 2 (for isolation). A mixture of **1** (4 mmol), **2** (0.191 g, 1 mmol), $RuCl_3 \cdot nH_2O$ (0.013 g, 0.05 mmol), PPh_3 (0.039 g, 0.15 mmol), $SnCl_2 \cdot 2H_2O$ (0.226 g, 1 mmol) and acetone (0.730 mL, 10 mmol) in dioxane (10 mL) was charged in a 50 mL stainless steel autoclave. After the system was flushed with argon, the reaction mixture was allowed to react at 180 °C for 24 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture) to remove inorganic compounds and

concentrated under reduced pressure. The residual mixture was separated by TLC to give the product quinoline. All products prepared by the above procedure are known.

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