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Ruthenium-catalyzed heteroannulation of anilines with alkanolammonium chlorides leading to indoles

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Abstract—Anilines react with alkanolammonium chlorides in an aqueous medium (H_2O–dioxane) at 180°C in the presence of a catalytic amount of a ruthenium catalyst together with $SnCl_2 \cdot 2H_2O$ to afford the corresponding indoles in moderate to good yields. Especially, when triisopropanolammonium chloride is employed to react with anilines, 2-methylindoles are formed regioselectively. The presence of $SnCl_2 \cdot 2H_2O$ is necessary for the effective formation of indoles. A reaction pathway involving alkanol group transfer from alkanolamines to anilines, N-alkylation of anilines by anilinoalkanols and heteroannulation of 1,2-dianilinoalkanes is proposed for this catalytic process.

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1. Introduction

Transition metal-catalyzed heteroannulation processes have been widely introduced for the formation of many heterocyclic compounds which play an important role as a basic skeleton for the design of many pharmacologically and biologically active compounds. In conjunction with this report, for the construction of the structural core of indoles, conventional methods such as the Fischer, Madelung, Bischler, and related syntheses are the most commonly used routes and have been extensively reviewed.[1] However, recently, many homogeneous transition metal-catalyzed synthetic methods have also been attempted and reported for the formation of indoles because of the facility and efficiency of reaction and the versatility of substrate.[2–4] During the course of our continuing studies on homogeneous ruthenium-catalyzed alkyl group transfer reactions from alkylamines to anilines,[5,6] as well as α-carbon of ketones,[7] we recently developed and reported a novel ruthenium-catalyzed synthetic approach for the formation of indoles[5] and quinolines[6] from anilines and alkylamines such as alkanolamines, allylamines, and trialkylamines. It was suggested that all reactions proceed via an initial alkyl group transfer from alkylamines to anilines (amine exchange reaction or amine distribution reaction or amine scrambling reaction).[8] However, a clear-cut example for the synthesis of N-heterocyclic compounds using intermolecular amine exchange reaction seems to be limited to palladium-catalyzed synthesis of pyrimidines and imidazoles[9] and aforementioned ruthenium-catalyzed synthesis of indoles and quinolines.[5,6] Herein, as an another example for the synthesis of N-heterocycles using amine exchange reaction, we report a ruthenium-catalyzed approach for the synthesis of indoles from anilines and alkanolammonium chlorides in an aqueous medium together with some mechanistic considerations.[10]

2. Results and discussion

The several attempted results of the ruthenium-catalyzed heteroannulation between aniline (**1a**) and triethanolammonium chloride (**2**) under various conditions are listed in Table 1. Generally, the reaction was performed under argon atmosphere in the presence of a catalytic amount of a ruthenium catalyst together with $SnCl_2 \cdot 2H_2O$ at 180°C for 20 h to afford indole (**3a**) (Scheme 1). First, we examined the molar ratio of **1a** to **2** and solvent system upon using $RuCl_3 \cdot nH_2O/3PPh_3$ (runs 1–9). The yield of **3a** was considerably affected by the molar ratio of **1a** to **2**, the highest yield of **3a** being obtained at the molar ratio of 10 (runs 1–5). The presence of $SnCl_2 \cdot 2H_2O$ was necessary for the effective formation of **3a** as has been observed in our recent ruthenium-catalyzed synthesis of indoles and quinolines,[5,6] the yield of **3a** being only 32% in the absence of $SnCl_2 \cdot 2H_2O$ (run 6). The use of either dioxane or H_2O and reverse amount of H_2O/dioxane stopped the reaction almost completely (runs 7–9). As a result, the reaction condition of run 1 in Table 1 was eventually revealed to be the best for obtaining **3a**.

Next, the activity of various ruthenium precursors was examined under the aforementioned optimized reaction conditions such as the molar ratio of **1a** to **2** and solvent system (runs 10–15). Among the catalysts examined,

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Keywords: amine exchange reaction; aqueous medium; catalyst; heteroannulation; indoles; ruthenium.

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Table 1. Ruthenium-catalyzed synthesis of **3a** from **1a** and **2** under various conditions (all reactions were carried out with **2** (1 mmol) and $SnCl_2 \cdot 2H_2O$ (1 mmol) at 180°C for 20 h unless otherwise stated)

Run	Molar ratio of **1a/2**	Ruthenium catalysts (mmol)	H_2O/dioxane (mL/mL)	Yield (%)[a]
1	10	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.1)	1/9	63
2	10	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.05)	1/9	37
3	6	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.05)	1/9	11[b]
4	6	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.05)	1/9	26
5	6	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.1)	1/9	39
6	10	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.1)	1/9	32[c]
7	6	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.1)	0/10	1
8	6	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.1)	10/0	0
9	6	$RuCl_3 \cdot nH_2O/3PPh_3$ (0.1)	9/1	1
10	10	$RuCl_3 \cdot nH_2O$/1.5dppm[d] (0.1)	1/9	63
11	10	$RuCl_2(PPh_3)_3$ (0.05)	1/9	77
12	10	$RuH_2(PPh_3)_4$ (0.05)	1/9	92
13	10	$Ru_3(CO)_{12}$ (0.05)	1/9	52
14	10	$Cp^*RuCl_2(CO)$[e] (0.05)	1/9	9
15	10	$Cp^*RuCl_2(PPh_3)$[e] (0.05)	1/9	23

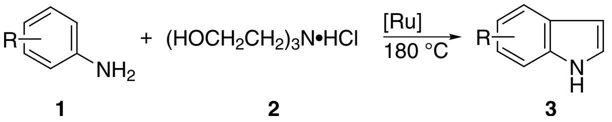
[a] GLC yield based on **2**.

[b] For 6 h.

[c] In the absence of $SnCl_2 \cdot 2H_2O$.

[d] dppm=bis(diphenylphosphino)methane.

[e] $Cp^* = \eta^5\text{-}C_5Me_5$.



Scheme 1.

$RuCl_3 \cdot nH_2O$/1.5dppm [bis(diphenylphosphino)methane] exhibited the same catalytic activity as $RuCl_3 \cdot nH_2O/3PPh_3$ (run 10). On the other hand, the reaction proceeded even by the use of 5 mol% of ruthenium catalyst precursors such as $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$ and $RuH_2(PPh_3)_4$, and the yield of **3a** was generally higher than that by the use of 5 mol% of $RuCl_3 \cdot nH_2O/3PPh_3$ (runs 11–13). Other ruthenium precursors such as $Cp^*RuCl_2(CO)$ and $Cp^*RuCl_2(PPh_3)$ were not effective for the formation of **3a** under the employed reaction conditions (runs 14, 15).

Table 2. Ruthenium-catalyzed synthesis of **3** from **1** and **2** (all reactions were carried out with **1** (10 mmol), **2** (1 mmol), and $SnCl_2 \cdot 2H_2O$ (1 mmol) in H_2O/dioxane (=1 mL/9 mL) at 180°C for 20 h)

1 (R=)	**3** (R=)	Yield (%)[a]	
		A	B
H (**1a**)	H (**3a**)	57	85
4-Me (**1b**)	5-Me (**3b**)	48	68
3-Me (**1c**)	4- and 6-Me (**3c**)	98[b]	–
2-Me (**1d**)	7-Me (**3d**)	80	–
4-OMe (**1e**)	5-OMe (**3e**)	43	80
4-Cl (**1f**)	5-Cl (**3f**)	16	31
2-Et (**1g**)	7-Et (**3g**)	87	–
4-*sec*-Bu (**1h**)	5-*sec*-Bu (**3h**)	49	58
2,3-Me (**1i**)	6,7-Me (**3i**)	68[c]	–
2,5-Me (**1j**)	4,7-Me (**3j**)	107[c]	–
3,5-Me (**1k**)	4,6-Me (**3k**)	169[c]	–
2,5-OMe (**1l**)	4,7-OMe (**3l**)	21	35

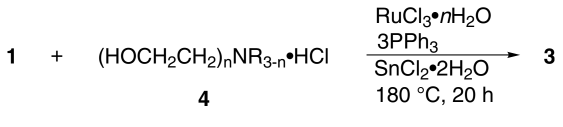
[a] Isolated yield based on **2**. A: $RuCl_3 \cdot nH_2O$ (0.1 mmol)/PPh_3 (0.3 mmol); B: $RuH_2(PPh_3)_4$ (0.05 mmol).

[b] By ^1H NMR (300 MHz): 4-methylindole/6-methylindole=1/1.8.

[c] $RuCl_3 \cdot nH_2O$ (0.05 mmol)/PPh_3 (0.15 mmol).

From the reaction of an array of anilines (**1b–1l**) with **2** the corresponding indoles (**3b–3l**) were also formed in good yields, and several representative results are summarized in Table 2. As shown in Table 2, the employment of $RuH_2(PPh_3)_4$ catalytic system was revealed to be more active towards indole formation than that of $RuCl_3 \cdot nH_2O/3PPh_3$ catalytic system. The indole yield was considerably affected by the electronic nature and the position of the substituent on aniline. With chloroaniline having electron-withdrawing Cl substituent, the product yield was generally lower than that when anilines having electron-donating character were used. With *ortho*- and *meta*-substituted anilines, the indole yield was higher than that when *para*-substituted anilines were used. In the case of *m*-toluidine (**1c**), the corresponding indoles (**3c**) were obtained as a regioisomeric mixture, favoring 6-methyl isomer, which was formed via less sterically hindered position on **1c**. In the cases of two-methyl substituted anilines (**1i–1k**), the reaction proceeded quite well even by the use of 5 mol% of ruthenium catalyst ($RuCl_3 \cdot nH_2O/3PPh_3$) when compared to mono-substituted anilines, as has been observed in our recent report.[5] The formation of >100% yields of indoles indicates that at least two alkanol groups out of three in **2** are available for the C_2-fragment counterpart.

Given these results, several reactions of **1** with mono- and diethanolammonium chlorides **4** in place of **2** were screened using $RuCl_3 \cdot nH_2O/3PPh_3$ catalytic system (Scheme 2). As shown in Table 3, generally, much more indoles **3** were formed with the employment of diethanolammonium chlorides compared to that of monoethanolammonium chlorides. In the reactions with **4d** and **4e**, the product yields were similar to that obtained with **2**.



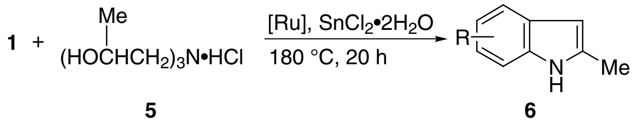
$$\mathbf{1} + \underset{\mathbf{4}}{(HOCH_2CH_2)_nNR_{3-n} \cdot HCl} \xrightarrow[\substack{SnCl_2 \cdot 2H_2O \\ 180\ °C,\ 20\ h}]{\substack{RuCl_3 \cdot nH_2O \\ 3PPh_3}} \mathbf{3}$$

Scheme 2.

Table 3. Ruthenium-catalyzed synthesis of **3** from **1** and **4** (all reactions were carried out with **1** (10 mmol), **4** (1 mmol), $RuCl_3 \cdot nH_2O$ (0.1 mmol), PPh_3 (0.3 mmol), and $SnCl_2 \cdot 2H_2O$ (1 mmol) in H_2O/dioxane (=1 mL/9 mL) at 180°C for 20 h)

1	4		3	Yield (%)[a]
	n=	R=		
1a	1	Et (**4a**)	**3a**	8
1a	1	Bu (**4b**)	**3a**	17
1a	1	Me, Bn (**4c**)	**3a**	15
1a	2	H (**4d**)	**3a**	58
1a	2	Me (**4e**)	**3a**	60
1a	2	Ph (**4f**)	**3a**	35
1a	2	Bn (**4g**)	**3a**	48
1k	1	H (**4h**)	**3k**	46

[a] GLC yield based on **4**.



Scheme 3.

We then examined similar cyclization between anilines **1** and triisopropanolammonium chloride (**5**) as another C_2-fragment (Scheme 3). Treatment of **1** with **5** under either $RuCl_3 \cdot nH_2O/3PPh_3$ or $RuH_2(PPh_3)_4$ catalytic system afforded almost exclusively 2-methyl substituted regioisomers **6**. Representative results are shown in Table 4. As is the case for the reaction with **2**, the use of $RuH_2(PPh_3)_4$ worked well for the formation of indoles **6** without the loss of selectivity. The regioselectivity was retained even when decreasing the amount of catalyst employed (runs 1, 2 and 4, 5). However, the regioselectivity was affected according to the structural nature of anilines. For example, in the reaction with several *ortho*-substituted anilines such as 2-methylaniline, 2-ethylaniline and 2,3-dimethylaniline the products were obtained as regioisomeric mixtures, which also favors 2-methyl isomers (runs 4, 5, 8 and 9). We recently reported that anilines reacted with triisopropanolamine in organic medium under similar ruthenium catalytic systems to give 2- and 3-methylindoles, favoring 2-methylindoles.[5] However, the selectivity of 2-isomer to 3-isomer varied, ranging from 4 to 5. Considering this result, the present aqueous reaction is the best option for the selective formation of 2-methylindoles. On the other hand, the reaction of **1a** with 2-amino-1-propanol hydrochloride (**7**) which has methyl substituent on α-carbon did not proceed toward indole (Scheme 4).

Table 4. Ruthenium-catalyzed synthesis of **6** from **1** and **5** (all reactions were carried out with **1** (10 mmol), **5** (1 mmol), and $SnCl_2 \cdot 2H_2O$ (1 mmol) in H_2O/dioxane (=1 mL/9 mL) at 180°C for 20 h)

Run	1	6 (R=)	Yield (%)[a]	
			A	B
1	**1a**	H (**6a**)	118	–
2	**1a**	H (**6a**)	64[b]	–
3	**1b**	5-Me (**6b**)	107	117
4	**1d**	**6d**[c]	97[d]	–
5	**1d**	**6d**[c]	30[b,d]	–
6	**1e**	5-OMe (**6e**)	–	37
7	**1f**	5-Cl (**6f**)	26	107
8	**1g**	**6g**[e]	28[f]	71[f]
9	**1i**	**6i**[g]	91[h]	–
10	**1j**	4,7-Me (**6j**)	50	121
11	**1k**	4,6-Me (**6k**)	44	78
12	**1l**	4,7-Me (**6l**)	50	–

[a] Isolated yield based on **5**. A: $RuCl_3 \cdot nH_2O$ (0.1 mmol)/PPh_3 (0.3 mmol); B: $RuH_2(PPh_3)_4$ (0.05 mmol).

[b] $RuCl_3 \cdot nH_2O$ (0.05 mmol).

[c] 2,7- and 3,7-Dimethylindole.

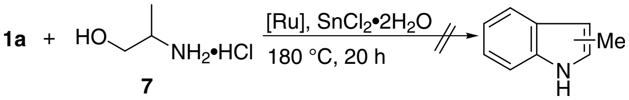
[d] By ^1H NMR (300 MHz): 2,7-dimethylindole/3,7-dimethylindole=2/1.

[e] 7-Ethyl-2-methylindole and 7-ethyl-3-methylindole.

[f] By ^1H NMR (300 MHz): 7-ethyl-2-methylindole/7-ethyl-3-methylindole=5/1.

[g] 2,6,7- and 3,6,7-Trimethylindole.

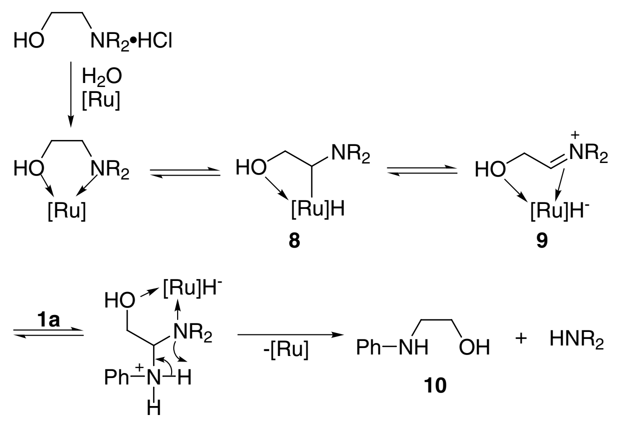
[h] By ^1H NMR (300 MHz): 2,6,7-trimethylindole/3,6,7-trimethylindole=3/1.



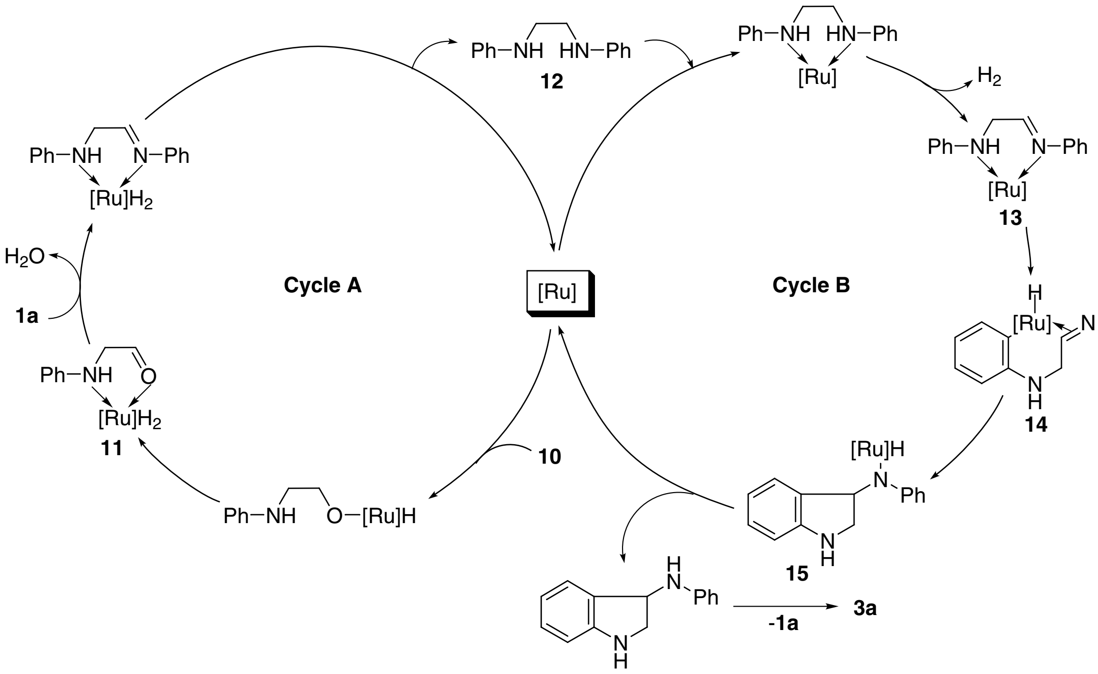
Scheme 4.

Although the present reaction mechanism including the role of $SnCl_2 \cdot 2H_2O$ is not yet fully understood, a plausible pathway is shown in Schemes 5 and 6.[11] The initial formation of 2-anilinoethanols by an alkanol group transfer from alkanolammonium chlorides to anilines (amine exchange reaction) seems to be a key step, as has been observed in our recent ruthenium-catalyzed synthesis of indoles and quinolines from anilines and functionalized aliphatic amines.[5,6] It is well-known that the intermolecular alkyl group transfer between alkylamines proceeds through an imine or iminium ion complex under transition metals.[8] Thus, the transfer of alkanol moiety from alkanolammonium chlorides to **1a** is explicable by Scheme 5. Quaternary alkanolammonium salt seems to be converted into an alkanolamine.[12] The initial coordination of alkanolamine to ruthenium followed by oxidative insertion of ruthenium into the adjacent C–H bond forms an alkylruthenium complex **8**, which rapidly equilibrates with an iminium complex **9**. Nucleophilic attack of **1a** to **9** gives 2-anilinoethanol (**10**) along with regeneration of ruthenium catalyst.

Subsequent steps seem to proceed via N-alkylation and ruthenium-mediated heteroannulation shown in Cycle A and Cycle B in Scheme 6. In Cycle A, **1a** can be N-alkylated



Scheme 5.

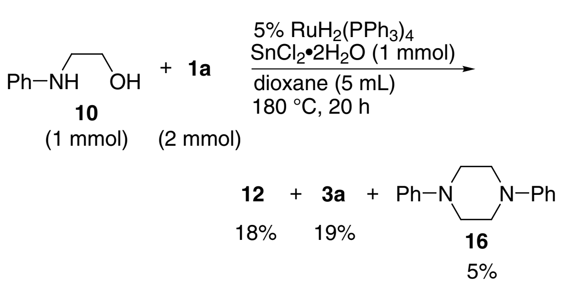


Scheme 6.

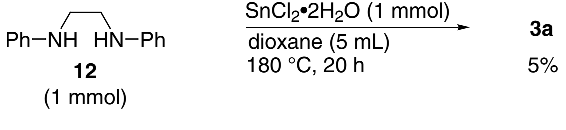
with 2-anilinoethanol (**10**) to afford 1,2-dianilinoethane (**12**). Oxidative addition of ruthenium to O–H bond of **10** followed by β-hydride elimination gives α-aminoaldehydic ruthenium complex **11**. The precedents of such an oxidative addition of O–H bond to ruthenium has been well documented in several hydrogen transfer reactions.[13] Intermediate **11** is condensed with **1a** and then reduced to give **12**. It is well known that amines react with primary alcohols in the presence of a ruthenium catalyst to give N-alkylated amines via a sequence involving oxidation, condensation, and reduction.[14,15] In the subsequent heteroannulation stage, **12** seems to be cyclized by Cycle B shown in Scheme 6. Oxidative addition of the *ortho* C–H bond of iminoruthenium complex **13** (orthometallation[16]) gives arylruthenium intermediate **14**. This is followed by insertion of C=N double bond into Ru–C bond of **14** via *exo*-5-cyclization mode[17] to form amidoruthenium complex **15**.[14h] Reductive elimination and deamination afford **3a** and regenerate active ruthenium catalyst. A similar catalytic cycle has already been proposed in ruthenium-catalyzed synthesis of quinolines from anilines and allylammonium chlorides in an aqueous medium by us.[6d]

The following experimental observations are worth noting as evidence for the reaction mechanism proposed above. Although no intermediates were detected in the reaction of the employed anilines (**1a**–**1l**) with **2**,[18] we confirmed the evidence for the formation and pathway for intermediates **10** and **12**. In a separate experiment, when intermediate **10** was employed to react with **1a** under similar reaction conditions, intermediate **12** and **3a** were formed in 18 and 19% yields, respectively, together with 1,4-diphenylpiperazine (**16**, 3%) on GLC analysis (Scheme 7). Further, although the yield is low, intermediate **12** was cyclized to give **3a** under the ruthenium catalyst system (Scheme 8). These results indicate that the catalytic cycles shown in Schemes 5 and 6 might be a reliable candidate. On the other hand, Watanabe and Tsuji reported that 2-anilinoalkanol and 1,2-dianilinoalkane were key intermediates in the ruthenium-catalyzed synthesis of indoles from anilines and ethylene glycols.[15d,e]

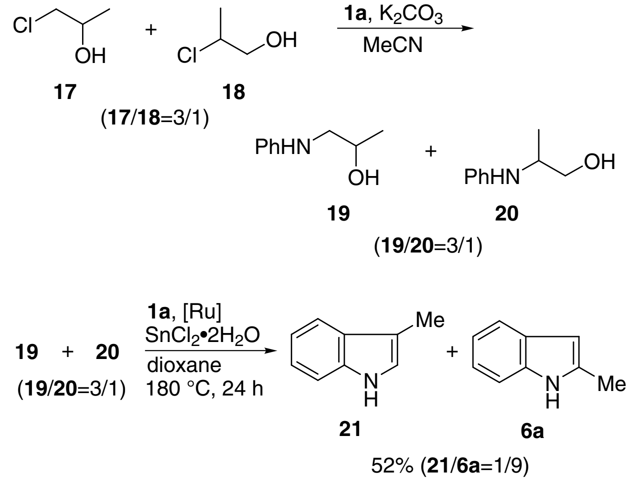
On the other hand, selective formation of 2-methylindoles in the reaction from anilines and triisopropanolammonium chloride seems to be explained on the basis of Cycle B in Scheme 6. In a separate experiment, a mixture of 1-anilino-2-propanol (**19**) and 2-anilino-1-propanol (**20**) (**19**/**20**=3/1), which was synthesized from **1a** and a commercial chloropropanol (1-chloro-2-propanol (**17**)/2-chloro-1-propanol (**18**)=3/1), reacted with nine-fold excess of **1a** under similar reaction conditions to afford 3-methylindole (**21**) and 2-methylindole (**6a**) in 52% yield (**21**/**6a**=1/9) (Scheme 9). Considering the reaction pathway shown in Cycle B in Scheme 6, it is quite natural to suppose that **21** and **6a** were



Scheme 7.

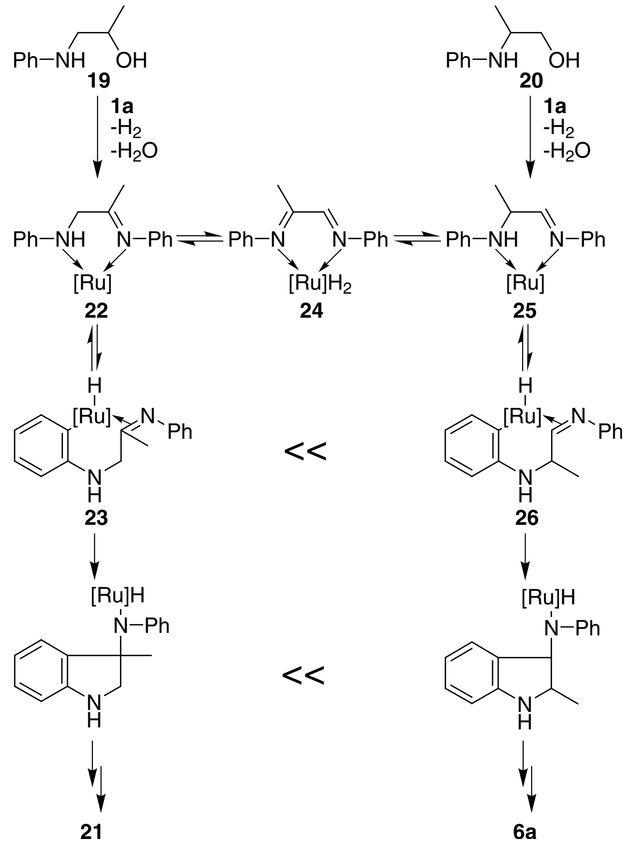


Scheme 8.



Scheme 9.

formed from **19** and **20**, respectively. However, theoretically, the product molar ratio (**21**/**6a**=1/9) does not correspond to the starting molar ratio (**19**/**20**=3/1). Although anilinopropanol **20** was completely reacted with **1a** to give only **6a**, its yield does not exceed practically obtained yield. This result indicates that a putative isomerization of intermediates had occurred during the course of reaction. A plausible isomerization pathway is shown in Scheme 10. As depicted in Cycle B in Scheme 6, arylruthenium intermediates **23** and **26** seem to be formed via iminoruthenium intermediates **22** and **25** from anilinopropanols **19** and **20**, respectively. Intermediates **23** and **26** in turn undergo a sequence involving insertion of C=N double bonds into Ru–C bonds, reductive elimination, and dehydroamination to give methylindoles **21** and **6a**, respectively. Taking account of the selective formation of 2-methyl isomer, the insertion of C=N double bond into Ru–C bond of **23** seems to be more difficult than that into Ru–C bond of **26**, since **23** bears methyl substituent which affects initial coordination to ruthenium. Thus, the isomerization of **22** into **25** seems to be occurring via a diiminoruthenium intermediate **24**. It is generally known that the hydrogenation reactivity of olefins parallels their coordination ability to dihydridometals.[19]



Scheme 10.

$$\mathbf{1a} + \mathbf{19} \xrightarrow[\text{dioxane, } 180\ ^\circ\text{C, 24 h}]{10\%\ \text{RuCl}_3\bullet n\text{H}_2\text{O/3PPh}_3,\ \text{SnCl}_2\bullet 2\text{H}_2\text{O}} \mathbf{21} + \mathbf{6a}$$

67% (**21**/**6a**=1/9

Scheme 11.

For further confirmation of the isomerization described above, we carried out the reaction of **1a** with isomerically pure 1-anilino-2-propanol (**19**) under similar reaction conditions.[20] The product indole was formed in 67% yield as an isomeric mixture (**21**/**6a**=1/9) along with intermediate 1,2-dianilinopropane (23%). If the isomerization had not occurred during the reaction course depicted in Scheme 10, 3-methyl isomer **21** should be formed as sole product from the reaction between **1a** and **19**. Taking account of this result, it is quite proper that the isomerization occurred during the course of reaction (Scheme 11).

In summary, we have demonstrated that indoles can be synthesized from anilines and alkanolammonium chlorides in the presence of a ruthenium catalyst and $SnCl_2\cdot 2H_2O$ in an aqueous medium in moderate to good yields. Interestingly, 2-methylindoles were formed regioselectively in the reaction between anilines and triisopropanolammonium chloride. The present aqueous heteroannulation is a novel synthetic approach leading to indoles via an alkanol group transfer from alkanolammonium chlorides to anilines. Although several reports are known for the synthesis of N-heterocyclic compounds using amine exchange reactions in organic media, the present aqueous process is a first synthetic approach for indoles using amine exchange reactions. We believe that this aqueous process combined with a mechanistic amine exchange reaction will be successfully applied for the synthesis of other N-heterocycles.

3. Experimental

NMR spectra were recorded on a Varian Unity Plus 300 spectrometer (300 MHz for ^1H NMR; 75 MHz for ^{13}C NMR) and a Bruker Avance Digital 400 spectrometer (400 MHz for ^1H NMR; 100 MHz for ^{13}C NMR) using TMS as an internal standard. Chemical shifts are reported in δ units downfield from TMS. Mass spectra were obtained on a Shimadzu QP-1000 spectrometer. GLC analyses were carried out with Shimadzu GC-17A equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm×25 m, 0.25 mm film thickness) using N_2 as carrier gas. Melting points were determined on a Thomas Scientific

Capillary Melting Point Apparatus and are uncorrected. The isolation of pure products was carried out with column chromatography (silica gel 60, 70–230 mesh, Merck). $RuH_2(PPh_3)_4$,[21] $RuCl_2(PPh_3)_3$,[22] $Ru_3(CO)_{12}$,[23] $Cp^*RuCl_2(CO)$[24] and $Cp^*RuCl_2(PPh_3)$[25] were prepared by the reported methods.

3.1. Typical procedure for ruthenium-catalyzed synthesis of indoles from anilines and alkanolammonium chlorides

A mixture of aniline (0.931 g, 10 mmol), triethanolammonium chloride (0.186 g, 1 mmol), $RuCl_3{\cdot}nH_2O$ (n=3, 0.026 g, 0.1 mmol), PPh_3 (0.079 g, 0.3 mmol) and $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in H_2O/dioxane (1 mL/9 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 20 h. The reaction mixture was poured into an aqueous 5% HCl solution to remove excess aniline, extracted with chloroform, and dried over Na_2SO_4. Removal of the solvent left an oil which was separated by column chromatography (ethyl acetate–hexane mixture) to give indole (0.067 g, 57%). The products prepared by the above procedure were characterized spectroscopically as shown below.

3.1.1. 5-Methylindole (3b). White solid (hexane–ethyl acetate); mp 59–60°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.46 (s, 1H), 7.01 (d, J=8.3 Hz, 1H), 7.12 (s, 1H), 7.25 (d, J=8.3 Hz, 1H), 7.42 (s, 1H), 7.95 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 102.1, 110.6, 120.3, 123.6, 124.2, 128.1, 129.0, 134.1; MS m/z (relative intensity) 131 (M^+, 100).

3.1.2. 4- and 6-Methylindole (3c). These compounds were isolated as a mixture and the molar ratio was determined from the peak areas of the clearly separated methyl protons in the ^{1}H NMR spectrum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 3/3H, 4-Me), 2.84 (s, 6/3H, 6-Me).

3.1.3. 7-Methylindole (3d). White solid (hexane–ethyl acetate); mp 80–82°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.53–6.54 (m, 1H), 6.97–7.10 (m, 3H), 7.50 (d, J=7.5 Hz, 1H), 7.89 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 103.3, 118.8, 120.4, 120.7, 122.8, 124.4, 127.7, 135.7; MS m/z (relative intensity) 131 (M^+, 95), 130 (100).

3.1.4. 5-Methoxyindole (3e). White solid (hexane–ethyl acetate); mp 53–54°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.43 (s, 1H), 6.85 (d, J=8.5 Hz, 1H), 7.01 (s, 1H), 7.09 (s, 1H), 7.13 (d, J=8.5 Hz, 1H), 7.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 102.1, 102.3, 111.8, 112.2, 125.0, 128.2, 131.0, 154.1; MS m/z (relative intensity) 147 (M^+, 100).

3.1.5. 5-Chloroindole (3f). White solid (hexane–ethyl acetate); mp 65–67°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38–6.40 (m, 1H), 7.13 (dd, J=8.5, 2.0 Hz, 1H), 7.17 (t, J=2.5 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 7.60 (d, J=2.0 Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.3, 112.0, 120.1, 122.3, 125.4, 125.6, 128.9, 134.1; MS m/z (relative intensity) 153 ($M^+ + 2$, 30), 151 (M^+, 100).

3.1.6. 7-Ethylindole (3g). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.5 Hz, 3H), 2.68 (q, J=7.5 Hz, 2H), 6.48–6.50 (m, 1H), 6.89–6.91 (m, 1H), 6.99 (d, J=7.0 Hz, 1H), 7.06 (t, J=7.5 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.67 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 23.9, 102.7, 118.4, 120.0, 120.3, 123.9, 126.5, 127.5, 134.5.

3.1.7. 5-*sec*-Butylindole (3h). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J=7.3 Hz, 3H), 1.28 (d, J=6.5 Hz, 3H), 1.61–1.66 (m, 2H), 2.63–2.72 (m, 1H), 6.48 (d, J=2.5 Hz, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.08–7.10 (m, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.44 (s, 1H), 7.95 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 22.6, 31.7, 41.8, 102.3, 110.7, 118.4, 121.6, 124.2, 127.9, 134.4, 139.2; MS m/z (relative intensity) 173 (M^+, 47), 144 (100).

3.1.8. 6,7-Dimethylindole (3i). White solid (hexane–ethyl acetate); mp 66–67°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.35 (s, 3H), 6.42–6.44 (m, 1H), 6.85–6.87 (m, 1H), 6.93 (d, J=8.3 Hz, 1H), 7.36 (d, J=8.3 Hz, 1H), 7.53 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 19.2, 102.6, 117.6, 117.9, 122.5, 123.5, 125.6, 129.0, 135.9; MS m/z (relative intensity) 145 (M^+, 68), 144 (100).

3.1.9. 4,7-Dimethylindole (3j). White solid (hexane–ethyl acetate); mp 96–98°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.53 (s, 3H), 6.55–6.57 (m, 1H), 6.83 (d, J=7.8 Hz, 1H), 6.90 (d, J=7.8 Hz, 1H), 7.11–7.13 (m, 1H), 7.94 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 18.5, 101.4, 117.6, 119.9, 122.4, 123.3, 127.2, 127.7, 134.9; MS m/z (relative intensity) 145 (M^+, 63), 144 (100).

3.1.10. 4,6-Dimethylindole (3k). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.48 (s, 3H), 6.44 (d, J=3.3 Hz, 1H), 6.74 (s, 1H), 6.78 (s, 1H), 6.85–6.88 (m, 1H), 7.47 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 21.5, 100.4, 108.6, 121.7, 122.9, 125.4, 129.6, 131.6, 135.8; MS m/z (relative intensity) 145 (M^+, 69), 144 (100).

3.1.11. 4,7-Dimethoxylindole (3l). White solid (hexane–ethyl acetate); mp 120–122°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.92 (s, 3H), 6.38 (d, J=8.0 Hz, 1H), 6.51 (d, J=8.0 Hz, 1H), 6.62 (t, J=2.7 Hz, 1H), 7.08–7.10 (m, 1H), 8.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7 (×2), 98.8, 100.3, 101.5, 120.0, 122.5, 127.6, 141.1, 147.8; MS m/z (relative intensity) 177 (M^+, 65), 162 (100).

3.1.12. 2-Methylindole (6a). White solid (hexane–ethyl acetate); mp 56–58°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.12 (d, J=0.9 Hz, 1H), 6.95–7.04 (m, 2H), 7.14 (dd, J=7.8, 0.9 Hz, 1H), 7.43 (d, J=7.2 Hz, 1H), 7.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 100.2, 110.2, 119.5 (×2), 120.8, 129.0, 135.1, 136.0.

3.1.13. 2,5-Dimethylindole (6b). White solid (hexane–ethyl acetate); mp 110–111°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.32 (s, 3H), 6.00 (s, 1H), 6.82 (d, J=8.1 Hz, 1H), 6.94 (d, J=8.1 Hz, 1H), 7.19 (s, 1H), 7.33 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 21.4, 99.7, 109.9, 119.3, 122.3, 128.6, 129.2, 134.3, 135.2.

3.1.14. 2,7- and 3,7-Dimethylindole (6d). The isomeric molar ratio was determined from the peak areas of the clearly separated protons. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J*=8.0 Hz, 2/3H, 4-C*H*, 2-methyl isomer), 7.43 (d, *J*=8.0 Hz, 1/3H, 4-C*H*, 3-methyl isomer).

3.1.15. 5-Methoxy-2-methylindole (6e). White solid (hexane–ethyl acetate); mp 83–85°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.81 (s, 3H), 6.12 (s, 1H), 6.75 (dd, *J*=8.5, 2.0 Hz, 1H), 6.99 (d, *J*=2.0 Hz, 1H), 7.08 (d, *J*=8.5 Hz, 1H), 7.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 55.9, 100.2, 101.9, 110.6, 110.9, 129.5, 131.2, 136.0, 154.0.

3.1.16. 5-Chloro-2-methylindole (6f). White solid (hexane–ethyl acetate); mp 108–111°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 6.11 (s, 1H), 7.01–7.08 (m, 2H), 7.44 (d, *J*=1.5 Hz, 1H), 7.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 100.1, 111.1, 118.9, 120.9, 125.0, 130.1, 134.3, 136.7.

3.1.17. 7-Ethyl-2-methyl- and 7-ethyl-3-methylindole (6g). The isomeric molar ratio was determined from the peak areas of the clearly separated protons. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3/6H, 3-C*H*$_3$, 3-methyl isomer), 2.32 (s, 15/6H, 2-C*H*$_3$, 2-methyl isomer), 6.17 (s, 5/6H, 3-C*H*, 2-methyl isomer), 6.71 (s, 1/6H, 2-C*H*, 3-methyl isomer), 7.35 (d, *J*=8.0 Hz, 5/6H, 4-CH, 2-methyl isomer), 7.40 (d, *J*=8.0 Hz, 1/6H, 4-CH, 3-methyl isomer).

3.1.18. 2,6,7- and 3,6,7-Trimethylindole (6i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J*=7.8 Hz, 3/4H, 5-C*H*, 2-methyl isomer), 6.94 (d, *J*=7.8 Hz, 1/4H, 5-C*H*, 3-methyl isomer), 7.24 (d, *J*=7.8 Hz, 3/4H, 4-C*H*, 2-methyl isomer), 7.31 (d, *J*=7.8 Hz, 1/4H, 4-C*H*, 3-methyl isomer).

3.1.19. 2,4,7-Trimethylindole (6j). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.41 (s, 3H), 2.47 (s, 3H), 6.22 (s, 1H), 6.77–6.82 (m, 2H), 7.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 16.4, 18.5, 99.4, 116.8, 119.9, 121.6, 126.7, 128.3, 134.0, 135.1.

3.1.20. 2,4,6-Trimethylindole (6k). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.31 (s, 3H), 2.36 (s, 3H), 6.04 (s, 1H), 6.62 (s, 1H), 6.66 (s, 1H), 7.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 18.6, 21.6, 98.5, 108.0, 121.5, 126.4, 128.6, 130.5, 133.6, 136.1.

3.1.21. 4,7-Dimethoxy-2-methylindole (6l). White solid (hexane–ethyl acetate); mp 100–101°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.88 (s, 6H), 6.27 (s, 1H), 6.34 (d, *J*=8.4 Hz, 1H), 6.44 (d, *J*=8.4 Hz, 1H), 8.20 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 55.6, 55.7, 97.9, 98.8, 100.7, 120.7, 127.3, 133.4, 140.5, 147.0.

3.1.22. Ruthenium-catalyzed reaction between aniline (1a) and 2-anilinoethanol (10). A mixture of **1a** (0.186 g, 2 mmol), **10** (0.137 g, 1 mmol), $RuH_2(PPh_3)_4$ (0.058 g, 0.05 mmol) and $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in dioxane (5 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 20 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–$CHCl_3$), poured into brine, extracted with $CHCl_3$ and dried over Na_2SO_4. GLC analysis revealed the presence of **3a** (19%), **12** (18%) and **16** (3%).

3.1.23. Ruthenium-catalyzed heteroannulation of 1,2-dianilinoethane (12). A mixture of **12** (0.212 g, 1 mmol), $RuH_2(PPh_3)_4$ (0.058 g, 0.05 mmol) and $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in dioxane (5 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 20 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–$CHCl_3$), poured into an aqueous 5% HCl solution, extracted with $CHCl_3$ and dried over Na_2SO_4. GLC analysis revealed the presence of indole (5%).

3.1.24. Ruthenium-catalyzed heteroannulation of a mixture of 1-anilino-2-propanol (19) and 2-anilino-1-propanol (20) with aniline (1a). A mixture of **1a** (0.838 g, 9 mmol), **19** and **20** (**19**/**20**=3/1, 0.151 g, 1 mmol), $RuCl_3{\cdot}nH_2O$ (*n*=3, 0.026 g, 0.1 mmol), PPh_3 (0.079 g, 0.3 mmol), and $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in dioxane (10 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 24 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–$CHCl_3$), poured into an aqueous 5% HCl solution, extracted with $CHCl_3$ and dried over Na_2SO_4. Removal of the solvent left an oil which was separated by column chromatography (ethyl acetate–hexane mixture) to give a mixture of **6a** and **21** (**6a**/**21**=9/1, 0.068 g, 52%).

3.1.25. Ruthenium-catalyzed heteroannulation of 1-anilino-2-propanol (19) with aniline (1a). A mixture of **1a** (0.838 g, 9 mmol), **19** (0.151 g, 1 mmol), $RuCl_3{\cdot}nH_2O$ (*n*=3, 0.026 g, 0.1 mmol), PPh_3 (0.079 g, 0.3 mmol), and $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in dioxane (10 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 24 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–$CHCl_3$), poured into brine, extracted with $CHCl_3$ and dried over Na_2SO_4. Removal of the solvent left an oil which was separated by column chromatography (ethyl acetate–hexane mixture) to give a mixture of **6a** and **21** (**6a**/**21**=9/1, 0.088 g, 67%) and 1,2-dianilinopropane (0.053 g, 23%).

3.1.26. 1,2-Dianilinopropane. Viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J*=6.3 Hz, 3H), 2.99 (dd, *J*=7.4, 12.3 Hz, 1H), 3.19 (dd, *J*=4.6, 12.3 Hz, 1H), 3.58 (br s, 2H), 3.61–3.70 (m, 1H), 6.53 (d, *J*=7.2 Hz, 2H), 6.55 (d, *J*=7.2 Hz, 2H), 6.63 (t, *J*=7.2 Hz, 1H), 6.64 (t, *J*=7.2 Hz, 1H), 7.09 (t, *J*=7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 48.5, 49.6, 113.0, 113.6, 117.6, 117.8, 129.2, 129.3, 147.3, 148.2.

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20. **19** was synthesized from **1a** and **17** in the presence of $NaHCO_3$ in MeCN at 100°C for 24 h in 16% isolated yield, and **17** was quantitatively prepared by the reduction of chloroacetone with $NaBH_4$ in MeOH at rt for 24 h. **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J=6.3 Hz, 3H), 2.80 (dd, J=8.2, 12.8 Hz, 1H), 3.02 (dd, J=3.3, 12.8 Hz, 1H), 3.41 (br s, 2H), 3.79–3.85 (m, 1H), 6.49 (d, J=8.4 Hz, 2H), 6.61 (t, J=7.5 Hz, 1H), 7.05 (t, J=7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 50.3, 65.0, 112.0, 116.6, 128.1, 147.0.
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