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RUTHENIUM-CATALYZED HYDROXYETHYLATION OF CYCLIC AMINES WITH ETHYLENE GLYCOL

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Abstract – It was found that a catalyst system $RuCl_2(PPh_3)_3$/Xantphos is effective to install hydroxyethyl groups to the nitrogen atom of cyclic amines. Thus, the reactions of cyclic amines with ethylene glycol were performed in the presence of the $RuCl_2(PPh_3)_3$/Xantphos catalyst in toluene at 120 °C for 22 h to provide the corresponding β-amino alcohols in up to 92% yield.

INTRODUCTION

Heterocyclic compounds having the *N*-(2-hydroxy)ethyl group and their derivatives are often found in approved drugs and drug candidates (Figure 1). These structures are generally constructed by the nucleophilic substitution of cyclic amines with 2-haloethanol.[1] However, using harmful halogenated reactant with a stoichiometric amount of bases and the discharge of the stoichiometric or more waste are not preferred from the view point of green chemistry.[2]

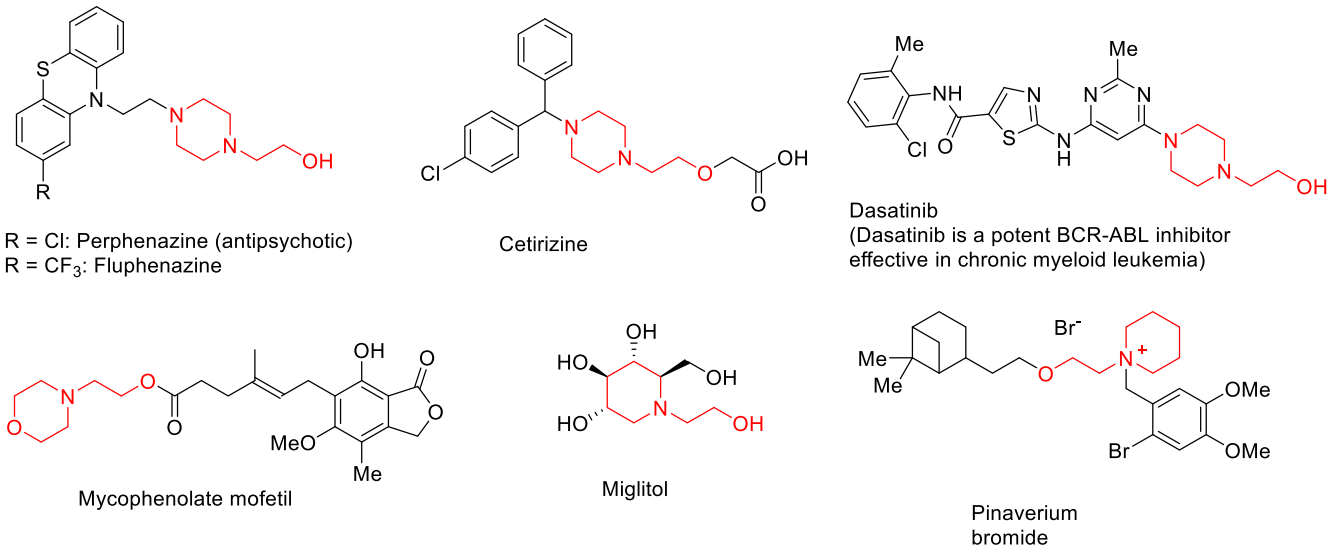


Figure 1. Examples of in approved drugs including *N*-(hydroxyethyl)heterocycles

An alternative method for constructing these structures is the reaction of cyclic amines with flammable and carcinogenic ethylene oxide,[3] though the reaction proceeds with perfect atom-economy. It is considered that the use of ethylene glycol instead of these reactants is safer; therefore, several researchers have attempted to synthesize the *N*-hydroxyethylation of cyclic amines with ethylene glycol based on the "borrowing hydrogen" strategy in which the alcohol is directly used as an alkylating reagent.[4]

The pioneering study on the hydroxyethylation of cyclic amines by the metal-catalyzed reaction of amines with ethylene glycol is Marsella's work reported in 1987.[5] The author found that secondary amines were transformed to the corresponding hydroxyethylated amines in the presence of the $RuCl_2(PPh_3)_3$ or $RuCl_3{\cdot}nH_2O/xPPh_3$ catalyst by using ethylene glycol as a solvent and that the phosphine ligand played a very important role in the selective formation of β-amino alcohols. Although the $RuCl_3{\cdot}nH_2O/11PPh_3$ catalyst showed extremely high β-amino alcohol selectivity (>99:0) on the reaction of morpholine with ethylene glycol, only limited amines such as morpholine and pyrrolidine were discussed. The author mentioned that this catalyst system required an induction period of a variable length from 1 to 5 h, which hindered further investigations including further scope of amine substrates and utility.[5] Afterwards, Leonard et al. checked the catalytic activity of $RuCl_2(PPh_3)_3$ on the reaction of 1-methylpiperazine with ethylene glycol in their research on the synthetic process of their potent SRC kinase inhibitor AZ-1 in 2015.[6] Their key intermediate, 1-hydroxyehtyl-4-methylpiperazine, was obtained selectively similar to Marsella's conditions,[5] but they conclude this method was not suitable for their process due to the accompanying formation of the undesired diamine. An iridium pincer catalyst has been reported by Börner, where the reaction proceeded with almost perfect selectivity but the use of excess amine was required; nevertheless, ethylene glycol is usually less expensive than amine substrates.[7] A heterogeneous catalyst using Pd/C and an excess amount of ZnO has been developed, but only the hydroxyethylation of tetrahydroquinoline was examined, and only 50% yield of amino alcohol product was obtained because of the formation of undesired tricyclic by-product.[8] Over the course of studies on our ruthenium-catalyzed borrowing hydrogen reactions using ethylene glycol for the construction of amino alcohols[9] and cyclic compounds,[10] we found that the $RuCl_2(PPh_3)_3$/Xantphos catalyst is effective for the representative and highly selective formation of β-amino alcohols by the reaction of cyclic amines and ethylene glycol. We report here the Ru-catalyzed hydroxyethylation of cyclic amines and survey the reaction pathways based on the several experiments.

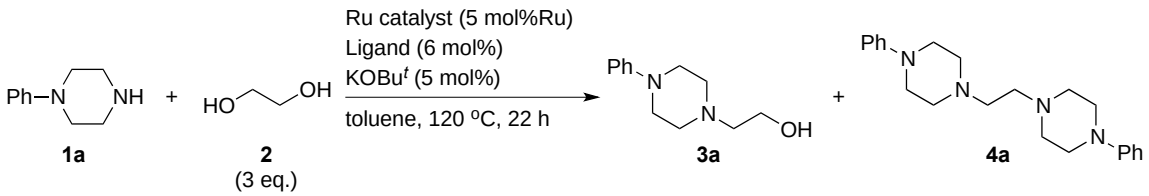
RESULTS AND DISCUSSION

The reaction conditions were initially optimized using 1-phenylpiperazine (**1a**) and ethylene glycol (**2**) as the test substrates, and the results are summarized in Table 1. When the reaction was performed with $[RuCl_2(p\text{-cymene})]_2$ as a catalyst in the presence of 5 mol% of KOBu^t at 120 °C, the desired amino

alcohol **3a** was obtained in 20% yield accompanied with the formation of diamine **4a** in 80% yield (entry 1). The reaction by using $RuCl_2(PPh_3)_3$ as a catalyst gave **3a** in 25% yield accompanied with **4a** in 30% yield, apparently lower selectivity than the reported results[5-6] (entry 2). This difference in the results may be due to the difference in the amounts of ethylene glycol and by using solvent. Ruthenium complexes with the Cp* ring were not effective for the present reaction (entries 3 and 4). Next, effects of ligands were investigated using various diphosphine ligands having a wide range of bite angles[11] and $[RuCl_2(p\text{-cymene})]_2$, which showed the highest conversion among the ruthenium complexes we tested. When 1,1-bis(diphenylphosphino)methane (Dppm) having the smallest bite angle (73º) was used as a ligand, the desired **3a** was obtained in spite of low conversion (entry 5). We assumed that Dppm worked as a monodentate ligand[12] and lowered the catalytic efficiency. The catalyst with 1,2-bis(diphenylphosphino)benzene (DppBenzene), which is a promising bidentate ligand, afforded **3a** in 14% yield and high conversion (84% conversion, entry 6). Chemical yields of **3a** were improved as bite angle of the ligands were widened (entries 7-14), and **3a** was selectively formed in 65% yield when 2,2'-bis(diphenylphosphino)diphenyl ether (DPEphos) having wide bite angle (104º) was used (entry 11). 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) having a rigid back bone and the widest bite angle (108°) among the ligands we tested showed lower selectivity than DPEphos to give **3a** in 43% yield (entry 12). We hypothesized that the rigidness of xanthene backbone and the bulkiness slowed the coordination to the ruthenium center and the reaction proceeded under ligand-free conditions at the early stage of the reaction. Therefore, Xantpshos was treated with $[RuCl_2(p\text{-cymene})]_2$ and $KOBu^t$ in toluene for 30 min before the reaction, then the reaction was performed in the resulting solution. As a result, **3a** was obtained in 82% yield with quantitative conversion (entry 13). Since it is known that the complexation of Xantphos and $RuCl_2(PPh_3)_3$ proceeds nicely to afford the Xantphos-Ru complex,[13] we tested the combination catalyst of Xantphos and $RuCl_2(PPh_3)_3$. We finally found that this catalysis afforded **3a** in almost quantitative yield (entry 14). Almost no reaction took place when DPEphos was used instead of Xantphos under the reaction conditions in entry 14, presumably due to the insolubility of the catalytically active species generated by the treatment of $RuCl_2(PPh_3)_3$ with DPEphos and $KOBu^t$ (entry 15).

The reactions of various cyclic amines **1a-p** with ethylene glycol (**2**) were investigated under the optimized reaction conditions, and the results are summarized in Table 2. The *N*-hydroxyethylation of six-membered aliphatic cyclic amines, such as piperazine **1a**, piperidine (**1b**), and morpholine (**1c**) proceeded effectively to afford the corresponding amino alcohols **3a-c** in 92, 83, and 86% isolated yields, respectively. Thiomorpholine (**1d**) was successfully reacted with **2** under the optimized reaction conditions to afford the hydroxyethylation product **3d** in 80% isolated yield, suggesting that sulfide moiety can be tolerated to the present catalytic reaction. The cyclic acetal protecting groups can be tolerated; thus, the reaction of cyclic amine bearing dioxolane moiety **3e** with **2** afforded the amino

Table 1. Optimization of reaction conditions[a]

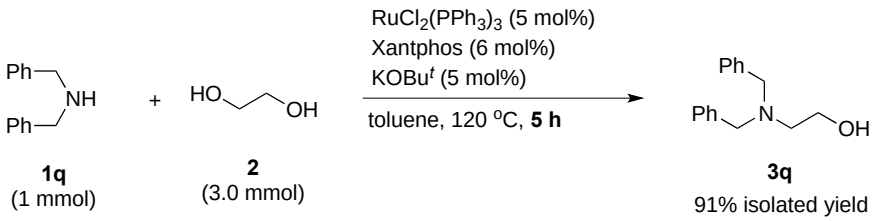


Entry	Ru catalyst	Ligand (bite angle)	Yield (%)[b]	
			3a	**4a**
1	$[RuCl_2(p\text{-cymene})]_2$	-	20	80
2	$RuCl_2(PPh_3)_3$	-	25	30
3	$Cp^*RuCl(PPh_3)_2$	-	9	27
4	$Cp^*RuCl_2(PPh_3)$	-	trace	5
5	$[RuCl_2(p\text{-cymene})]_2$	Dppm[c] (73)	8	21
6	$[RuCl_2(p\text{-cymene})]_2$	DppBenzene[d] (83)	14	70
7	$[RuCl_2(p\text{-cymene})]_2$	Dppe[e] (86)	26	52
8	$[RuCl_2(p\text{-cymene})]_2$	Dppb[f] (94)	30	48
9	$[RuCl_2(p\text{-cymene})]_2$	(*R*)-BINAP[g] (93)	39	46
10	$[RuCl_2(p\text{-cymene})]_2$	Dppf[h] (99)	46	59
11	$[RuCl_2(p\text{-cymene})]_2$	DPEphos[i] (104)	65	27
12	$[RuCl_2(p\text{-cymene})]_2$	Xantphos (108)	43	49
13[k]	$[RuCl_2(p\text{-cymene})]_2$	Xantphos (108)	82	20
14[k]	$RuCl_2(PPh_3)_3$	Xantphos (108)	>99 (92)	0
15[k]	$RuCl_2(PPh_3)_3$	DPEphos[i] (104)	trace	trace

[a]Reaction conditions: Ru catalyst (0.05 mmolRu), ligand (0.06 mmol), KOBu^t (0.05 mmol), 1-phenylpiperazine (**1a**) (1 mmol), ethylene glycol (3 mmol), and toluene (1 mL) at 120 °C for 22 h. [b]Yields were determined by ^{1}H NMR. Isolated yield is in parentheses. [c]1,1-Bis(diphenylphosphino)methane. [d]1,2-Bis(diphenylphosphino)benzene. [e]1,2-Bis(diphenylphosphino)ethane. [f]1,4-Bis(diphenylphosphino)butane. [g](*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl. [h]1,1'-Bis(diphenylphosphino)ferrocene. [i]2,2'-Bis(diphenylphosphino)diphenyl ether. [j]4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [k]Ru complexes were preliminary treated with ligand and KOBu^t in toluene at room temperature for 30 min.

alcohol **3e** in 88% yield. Fused cyclic amine, decahydroquinoline (**1f**) also gave the corresponding amino alcohol **3f** in 91% yield. The present hydroxyethylation of azepane (**1g**) also provided **3g** in 65% isolated yield. On the other hand, five-membered cyclic amines required the modification of the reaction conditions. Thus, the reaction of pyrrolidine (**1h**) with **2** under the above optimized condition afforded a 35% yield of **3h**, where undesired diamine **4d** was frequently detected. To avoid the diamine formation, the reaction was performed under lower concentration to improve the reaction efficiency to afford **3h** in

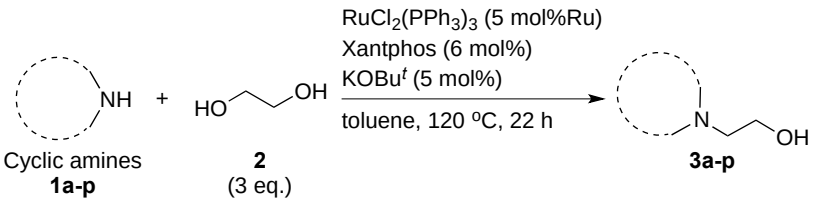
82% NMR yield, though the isolated yield was not good due to the difficulty in its isolation (57% isolated yield). L-Proline *t*-butyl ester (**1i**) obtained a moderate yield of amino alcohol **3i**, but the chemical yield improved by lowering the concentration and increasing the catalyst loadings to afford **3i** in 72% isolated yield. In this case, partial racemization unfortunately occurred to give **3i** with 54% ee. Low yield (11% isolated yield) of amino alcohol **3j** was obtained when indoline (**1j**) was used as a cyclic amine substrate, which was not due to the formation of undesired diamine by-product but to the formation of several by-products having indole frameworks. The transformation into the undesired indole ring systems was suppressed by using 2-methylindoline (**1k**) to afford excellent yield (91%) of the amino alcohol **3k**. A complex mixture was obtained when isoindoline (**1l**) was used as a substrate presumably due to the reason similar to the case of indoline. On the other hand, tetrahydroquinolines and isoquinolines **1m-p** were reacted with **2** under the standard reaction conditions to provide the corresponding amino alcohols in 62-87% yields. Successful result in **3n** suggested the bromoarene moiety, which could be used as a substrate for the various cross coupling reactions, was tolerated to the present hydroxyethylation. A successful example of a non-cyclic amine substrate was shown in Scheme 1. Thus, dibenzylamine (**1q**) was treated with **2** under the optimized reaction conditions to afford 2-dibenzylaminoethanol (**3q**) in 96% NMR yield (91% isolated yield), where the undesired diamine **4q** was not detected.

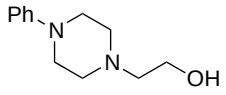


Scheme 1. Hydroxyethylation of dibenzylamine (**1q**)

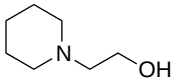
The plausible reaction mechanism is illustrated in Scheme 2. The reaction started from the dehydrogenation of ethylene glycol to give the hydroxy aldehyde intermediate **I**, which was reacted with cyclic amine to afford the corresponding iminium ion intermediate **II**. Hydrogenation of this intermediate **II** led to forming the desired amino alcohol **3**. Another pathway is deprotonation of intermediate **II**, affording the enamine form **III** and its tautomer **IV**. Intermediate **III** or **IV** would also be hydrogenated by the Ru-H species to give **3**. On the other hand, the nucleophilic attack of the next amine onto intermediate **III** or **IV** afford the corresponding tautomeric intermediates **V** and **VI**, which were subjected to hydrogenation with Ru-H species to afford diamine **4**. It is considered that an alternative pathway to **4** is the dehydrogenation of **3**, followed by the reaction with the next amine then the hydrogenation of resulting intermediate **V** or **VI**.

Table 2. Scope of cyclic amines for Ru-catalyzed hydroxyethylation with ethylene glycol[a]

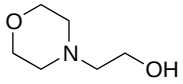




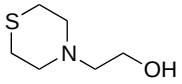
3a
>99% (92%)



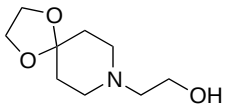
3b
98% (83%)



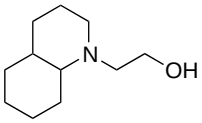
3c
95% (86%)



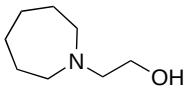
3d
87% (80%)



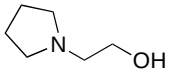
3e
>99% (88%)



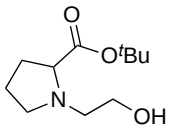
3f
94% (91%)[c]



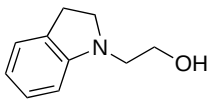
3g
78% (65%)



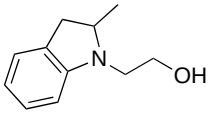
3h
1. 35%
2. 82% (57%)[d]



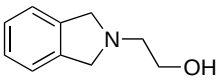
3i
1. 47%
2. 92% (72%), 54% ee[e]



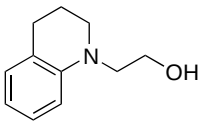
3j
25% (11%)



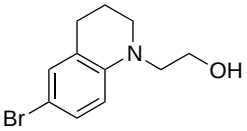
3k
96% (91%)



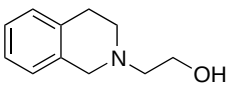
3l
N.d.



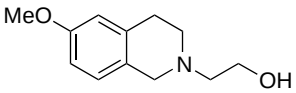
3m
80% (62%)



3n
95% (66%)

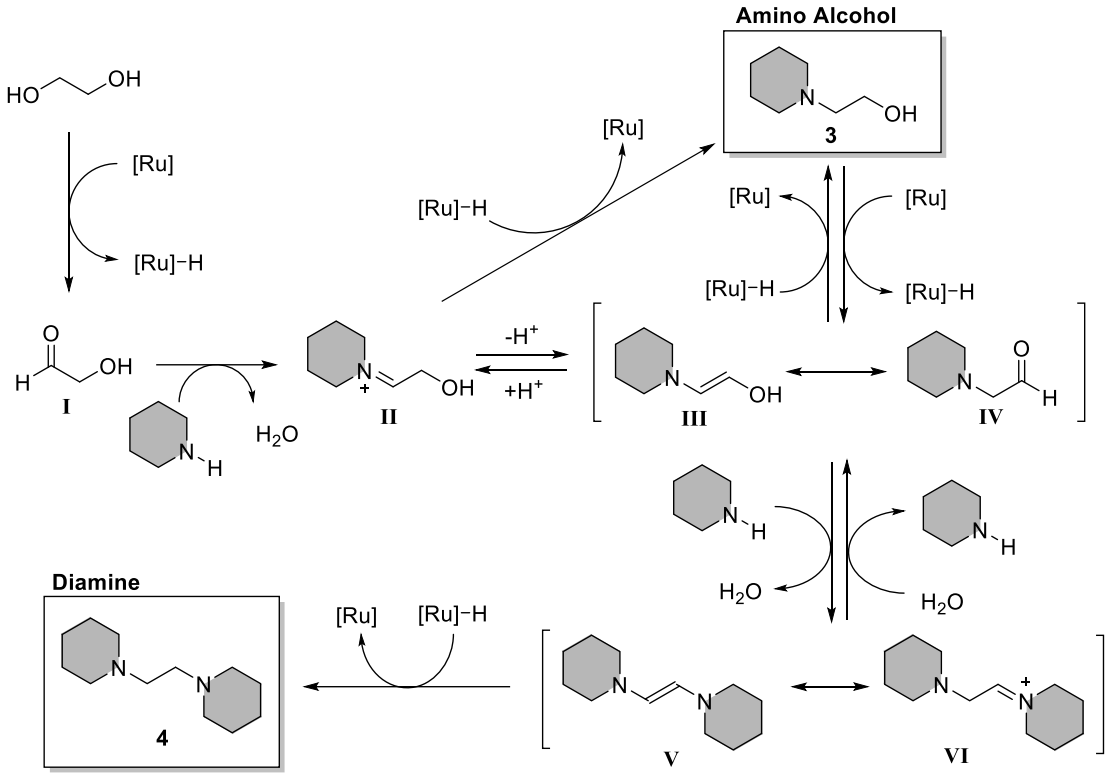


3o
90% (87%)



3p
80% (63%)

[a]Reaction conditions: $RuCl_2(PPh_3)_3$ (0.05 mmolRu), Xantphos (0.06 mmol), $KOBu^t$ (0.05 mmol), cyclic amine (1 mmol), ethylene glycol (3 mmol) and toluene (1 mL), at 120 °C for 22 h. Ru complexes were preliminary treated with ligand and $KOBu^t$ in toluene at room temperature for 30 min. [b]Yields were determined by ^1H NMR using internal standard method. The value in parentheses is isolated yield. [c]*trans*-**1f** as a substrate was used. [d]Toluene (5 mL) was used. [e]Catalyst (10 mol%) and toluene (5 mL) were used. The enantiomeric excess was determined by HPLC with Daicel Chiralpak AD-H.



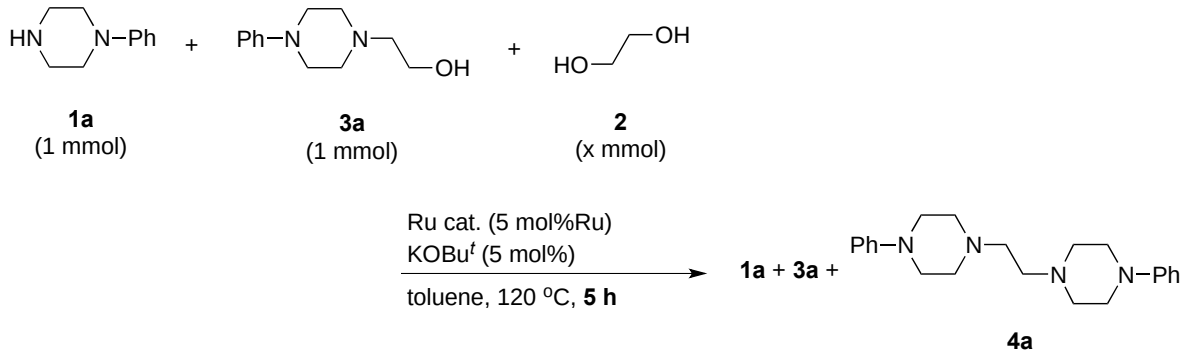
Scheme 2. Plausible reaction pathways

To confirm these reaction pathways, several reactions were performed (Table 3). Reaction of amino alcohol **3a** with amine **1a** was performed in toluene at 120 °C for 5 h in the presence of $[RuCl_2(p\text{-cymene})]_2$ catalyst (entry 1), and it was found that **3a** was recovered in 91%, and only 2% of **4a** was obtained. Apparent increase in the chemical yield of **4a** was observed when ethylene glycol (**2**) was added to this reaction conditions, and **4a** was afforded in 16% yield in spite of the almost quantitative recovery of **3a** (entry 2). It seemed that the direct formation of **4a** would be faster than the indirect formation through **3a**. However, the amino alcohol **3a** was obtained in moderate yield (8%) when the reaction was performed without using **3a**, meaning that the indirect formation of **4a** through **3a** would be possible with the $[RuCl_2(p\text{-cymene})]_2$ catalyst. Therefore, the $[RuCl_2(p\text{-cymene})]_2$ catalyst afforded diamine **4a** selectively. Next, reactions of **3a** with **1a** using the $RuCl_2(PPh_3)_3$/Xantphos catalyst were performed with or without ethylene glycol (**2**) (entries 4 and 5). Almost no reaction took place when **3a** was treated with **1a** in the absence of ethylene glycol (entry 4). On the other hand, treatment of **3a** with **1a** in the presence of **2** afforded **4a** in 108% yield (entry 5). In this case, no **4a** was obtained. These results revealed that indirect formation of **4a** through **3a** did not occur with the $RuCl_2(PPh_3)_3$/Xantphos catalyst in contrast to the case with the $[(RuCl_2(p\text{-cymene})]_2$ catalyst. The selective formation of **3a** was achieved by the faster hydrogenation of the corresponding iminium ion **II**, enamine **III**, or β-amino aldehyde **IV** intermediates than the nucleophilic attack of the next amine substrate to these intermediate. Therefore,

pyrrolidine derivatives having higher nucleophilicity than the six-membered cyclic amines led to the difficulty in adjusting the reaction conditions to obtain good selectivity.[14]

In conclusion, we developed the $RuCl_2(PPh_3)_3$/Xantphos catalyst system for the selective formation of *N*-(hydroxyethyl)heterocycles from cyclic amines with ethylene glycol and discussed the scope and limitation of the present reaction.

Table 3. Treatment of amino alcohol **3a** under catalytic conditions[a]



entry	**2** (x mmol)	Ru cat.	amount (mmol)[b]		
			1a	**3a**	**4a**
1	0.0	[(*p*-cymene)$RuCl_2$]$_2$	0.99	0.91	0.02
2	1.0	[(*p*-cymene)$RuCl_2$]$_2$	0.73	0.97	0.16
3[c]	1.0	[(*p*-cymene)$RuCl_2$]$_2$	0.65	0.08	0.14
4	0.0	$RuCl_2(PPh_3)_3$/Xantphos	>0.99	0.95	Trace
5	1.0	$RuCl_2(PPh_3)_3$/Xantphos	0.88	1.08	0

[a]Reaction conditions: **1a** (1 mmol), **3a** (1 mmol), and **2** (x mmol) were treated with Ru catalyst (0.05 mmol Ru) and KOBu^t (0.05 mmol) in toluene at 120 °C for 5 h. [b]Determined by ^{1}H NMR. [c]No amino alcohol **3a** was added.

EXPERIMENTAL

General information

NMR spectra were recorded with Bruker Ascend 400 spectrometer (400 MHz) spectrometers by using TMS (δ = 0 ppm) as an internal standard for ^{1}H NMR and $CDCl_3$ (δ = 77 ppm) for ^{13}C NMR spectroscopy. High-resolution mass spectra (FAB) were recorded using a JEOL JMS-700 instrument with *meta*-nitrobenzyl alcohol and glycerol as the matrix and PEG-200 as the calibration standard. Chiral HPLC analysis was performed on a Shimadzu LC-20AD with Daicel Chiralpak AD-H at 40 °C. Melting points were measured by use of Yanako. Unless noted otherwise, all reagents and solvents were purchased from commercial suppliers. Reagents obtained from commercial sources were used without

purification. The $[RuCl_2(p\text{-cymene})]_2$,[15] $RuCl_2(PPh_3)_3$,[16] $CpRuCl(PPh_3)_2$[17] and $Cp^*RuCl_2(PPh_3)$[18] were synthesized according to literature protocols.

General procedure for hydroxyethylation

To an argon-purged reaction tube equipped with J-Young stop valve was added $RuCl_2(PPh_3)_3$ (0.05 mmol), Xantphos (0.06 mmol), $KOBu^t$ (0.05 mmol), and anhydrous toluene (1 mL). The mixture was stirred at rt for 30 min. Cyclic amine (1 mmol) and ethylene glycol (**2**) (3 mmol) were added to the reaction mixture. The mixture was degassed using FPT cycles then purged with argon again. The reaction mixture was stirred at 120 °C for 22 h. After the reaction, the yield was determined by ^{1}H NMR using an internal standard.

2-(4-Phenylpiperazin-1-yl)ethan-1-ol (3a)

3a was obtained as a white solid by purification (Silica gel column chromatography, $CHCl_3 \rightarrow CHCl_3$:MeOH = 20:3) after the catalytic reaction. Mp 82-85 °C. ^{1}H NMR ($CDCl_3$): δ = 2.61 (t, J = 5.2 Hz, 2H, -C*H*$_2$CH$_2$OH), 2.68 (t, J = 4.8 Hz, 4H, -C*H*$_2$NCH$_2$-), 3.21 (t, J = 5.2 Hz, 4H, -C*H*$_2$NPh), 3.66 (t, J = 5.2 Hz, 2H, -C*H*$_2$OH), 6.86 (t, J = 6.4 Hz, 1H, Ar-*H*), 6.94 (d, J = 8.0 Hz, 2H, Ar-*H*), 7.24-7.30 (m, 2H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 49.3, 52.9, 57.8, 59.3, 116.1, 119.8, 129.1, 151.2 ppm. HRMS: Calcd. for C12H19ON2 ([M+H]+) 207.1497; found 207.1503.

1,2-Bis(4-phenylpiperazin-1-yl)ethane (4a)

4a was obtained as a white solid by purification (Silica gel column chromatography, $CHCl_3$) after the catalytic reaction. Mp 176-180 °C. ^{1}H NMR ($CDCl_3$): δ = 2.63 (s, 4H, -NC*H*$_2$C*H*$_2$NCH$_2$-), 2.68 (t, J = 4.8 Hz, 8H, -NC*H*$_2$CH$_2$NPh), 3.21 (t, J = 5.2 Hz, 8H, -C*H*$_2$NPh), 6.86 (t, J = 6.4 Hz, 2H, Ar-*H*), 6.93 (d, J = 8.0 Hz, 4H, Ar-*H*), 7.23-7.29 (m, 4H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 49.2, 53.8, 56.0, 116.1, 119.7, 129.1, 151.3 ppm. HRMS: Calcd. for C22H31N4 ([M+H]+) 351.2548; found 351.2541.

2-(Piperidin-1-yl)ethan-1-ol (3b)

3b was obtained as a colorless oil by purification (Silica gel column chromatography, EtOAc → EtOAc:MeOH = 20:3) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 1.39-1.50 (br-m, 2H, -C*H*$_2$CH$_2$CH$_2$N-), 1.58 (quin, J = 5.6 Hz, 4H, -CH$_2$C*H*$_2$CH$_2$N-), 2.43 (br-s, 4H, -CH$_2$CH$_2$C*H*$_2$N-), 2.48 (t, J = 5.6 Hz, 2H, -C*H*$_2$CH$_2$OH), 3.59 (t, J = 5.6 Hz, 2H, -C*H*$_2$OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.3, 26.0, 54.4, 57.8, 60.0 ppm. HRMS: Calcd. for C7H16ON ([M+H]+) 130.1232; found 130.1234.

2-(Morpholin-1-yl)ethan-1-ol (3c)

3c was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3 \rightarrow CHCl_3$:MeOH = 20:3) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 2.51 (t, J = 4.4 Hz, 4H, -C*H*$_2$NCH$_2$CH$_2$OH), 2.55 (t, J = 5.2 Hz, 2H, -C*H*$_2$CH$_2$OH), 3.63 (t, J = 5.2 Hz, 2H, -C*H*$_2$OH), 3.73 (t, J = 4.8 Hz, 4H, -C*H*$_2$O-) ppm. ^{13}C NMR ($CDCl_3$): δ = 53.3, 57.5, 59.8, 67.0 ppm. HRMS: Calcd. for $C_6H_{14}O_2N$ ([M+H]+) 132.1024; found 132.1024.

2-(Thiomorpholin-1-yl)ethan-1-ol (3d)

3d was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3$:MeOH = 20:1) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 2.56 (t, J = 5.2 Hz, 2H, -C*H*$_2$CH$_2$OH), 2.62 (br-s, 1H, -O*H*), 2.68 (t, J = 4.0 Hz, 4H, -C*H*$_2$NCH$_2$CH$_2$OH), 2.78 (t, J = 5.2 Hz, 4H, -C*H*$_2$S-), 3.59 (t, J = 5.2 Hz, 2H, -C*H*$_2$OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.1, 54.9, 57.5, 59.9 ppm. HRMS: Calcd. for $C_6H_{14}NOS$ ([M+H]+) 148.0796; found 148.0799.

2-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-ol (3e)

3e was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3$:MeOH = 10:1) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 1.75 (t, J = 5.6 Hz, 2H, -CC*H*$_2$CH$_2$N-), 2.56 (t, J = 5.2 Hz, 2H, -C*H*$_2$CH$_2$OH), 2.59 (br-t, J = 4.8 Hz, 4H, -CCH$_2$C*H*$_2$N-), 3.59 (t, J = 5.2 Hz, 2H, -C*H*$_2$OH), 3.96 (s, 4H, -OC*H*$_2$C*H*$_2$O-) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.9, 51.1, 57.9, 58.7, 64.3, 107.1 ppm. HRMS: Calcd. for $C_9H_{18}NO_3$ ([M+H]+) 188.1286; found 188.1282.

***trans*-2-(Octahydroquinolin-1(2H)-yl)ethan-1-ol (3f)**

3f was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3 \rightarrow CHCl_3$:MeOH = 20:3$\rightarrow$$CHCl_3$:MeOH = 10:3) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 0.94-1.10 (m, 3H), 1.14-1.33 (m, 3H), 1.52-1.67 (m, 5H), 1.75-1.87 (m, 2H), 2.03-2.23 (m, 3H, -C*H*NC*H*$_2$CH$_2$CH$_2$-), 2.97-3.13 (m, 2H, -C*H*$_2$CH$_2$OH), 3.46-3.53 (m, 1H, -C*H*HOH), 3.58-3.66 (m, 1H, -CH*H*OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6, 25.7, 25.9, 30.8, 32.5, 33.2, 42.2, 53.0, 54.1, 58.6, 67.1 ppm. HRMS: Calcd. for $C_{11}H_{22}ON$ ([M+H]+) 184.1701; found 184.1696.

2-(Azepan-1-yl)ethan-1-ol (3g)

3g was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3 \rightarrow CHCl_3$:MeOH = 20:7) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 1.54-1.70 (br-m, 9H, -C*H*$_2$C*H*$_2$CH$_2$N-, -O*H*), 2.62-2.71 (m, 6H, -C*H*$_2$NC*H*$_2$CH$_2$OH), 3.53 (t, J = 5.6 Hz, 2H, -C*H*$_2$OH) ppm.

^{13}C NMR ($CDCl_3$): δ = 26.9, 28.6, 55.3, 58.3, 58.9 ppm. HRMS: Calcd. for $C_8H_{18}ON$ ([M+H]+) 144.1388; found 144.1391.

2-(Pyrrolidin-1-yl)ethan-1-ol (3h)

3h was obtained as a colorless oil by purification (Silica gel column chromatography, EtOAc→ EtOAc:MeOH = 20:3) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 1.78 (quin, *J* = 3.6 Hz, 4H, -$CH_2CH_2CH_2$N-), 2.54-2.59 (m, 4H, -$CH_2CH_2CH_2$N-), 2.66 (t, *J* = 5.6 Hz, 2H, -CH_2CH_2OH), 3.64 (t, *J* = 5.6 Hz, 2H, -CH_2OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.5, 53.8, 57.6, 59.9 ppm. HRMS: Calcd. for $C_6H_{14}NO$ ([M+H]+) 116.1075; found 116.1075.

1-(2-Hydroxyethyl)pyrrolidine-2-carboxylic acid *tert*-butyl ester (3i)

3i was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3$:MeOH = 20:3) after the catalytic reaction (54% ee). ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9H, *tert*-butyl), 1.74-1.95 (m, 3H, -CHHCH-, -CH_2CH_2CH-), 2.07-2.19 (m, 1H, -CHHCH-), 2.41-2.49 (m, 1H, -CHHNCH_2CH_2OH), 2.73-2.78 (m, 2H, -CHHNCHHCH_2OH), 3.14 (dd, *J* = 9.2 Hz, *J* = 5.2 Hz, 1H, -CHHCH_2OH), 3.17-3.23 (m, 1H, -CHN-), 3.46-3.54 (m, 1H, -CHHOH), 3.57-3.64 (m, 1H, -CHHOH) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.7, 28.0, 29.9, 53.9, 56.8, 59.8, 66.2, 81.1, 174.4 ppm. HRMS: Calcd. for $C_{11}H_{22}NO_3$ ([M+H]+) 216.1599; found 216.1597. HPLC (Daicel chiralpak AD-H, UV: 222 nm, Flow rate: 1.0 mL/min, hexane/EtOH = 90/10 + 0.1%TFA): tR_1 = 3.55 min (major), tR_2 = 4.55 min (minor).

2-(Indolin-1-yl)ethan-1-ol (3j)

3j was obtained as a colorless oil by purification (Silica gel column chromatography, EtOAc:Hexane = 1:1) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 2.07 (t, *J* = 5.6 Hz, 1H, -OH), 2.99 (t, *J* = 8.4 Hz, 2H, -CCH_2CH_2N-), 3.25 (t, *J* = 5.2 Hz, 2H, -CCH_2CH_2N-), 3.39 (t, *J* = 8.4 Hz, 2H, -CH_2CH_2OH), 3.81 (t, *J* = 5.2 Hz, 2H, -CH_2OH), 6.57 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.71 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.05-7.13 (m, 2H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.7, 52.6, 54.0, 60.2, 107.4, 118.4, 124.6, 127.4, 130.1, 152.8 ppm. HRMS: Calcd. for $C_{10}H_{13}NO$ ([M+H]+) 163.0997; found 163.0996.

2-(2-Methylindolin-1-yl)ethan-1-ol (3k)

3k was obtained as a pale yellow oil by purification (Silica gel column chromatography, $CHCl_3$→ $CHCl_3$:MeOH = 20:1) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 1.32 (d, *J* = 6.0 Hz, 3H, -Me), 2.00 (t, *J* = 6.0 Hz, 1H, -CHCH_3), 2.62 (dd, *J* = 15.6 Hz, *J* = 9.6 Hz, 1H, -CHHCHCH_3), 3.09-3.21 (m, 2H, -CHHCHCH_3, -CHHN-), 3.27-3.36 (m, 1H, -CHHN-), 3.60-3.86 (m, 2H, -CH_2OH), 6.51 (d, *J* = 7.6 Hz,

1H, Ar-*H*), 6.68 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.02-7.09 (m, 2H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9, 37.4, 50.7, 61.1, 61.9, 106.8, 118.1, 124.2, 127.4, 129.0, 152.9 ppm. HRMS: Calcd. for $C_{11}H_{15}ON$ (M+) 177.1154; found 177.1154.

2-(3,4-Dihydroquinolin-1(*2H*)-yl)ethan-1-ol (3m)

3m was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3$→ $CHCl_3$:MeOH = 20:1) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 1.71 (t, *J* = 6.0 Hz, 1H, -O*H*), 1.96 (quin, *J* = 6.0 Hz, 2H, -$CH_2CH_2CH_2$N-), 2.78 (t, *J* = 6.4 Hz, 2H, -$CH_2CH_2CH_2$N-), 3.32 (t, *J* = 5.6 Hz, 2H, -$CH_2CH_2CH_2$N-), 3.44 (t, *J* = 5.6 Hz, 2H, -CH_2CH_2OH), 3.82 (qurt, *J* = 5.6 Hz, 2H, -CH_2OH), 6.61 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.68 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.96 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.05 (t, *J* = 8.0 Hz, 1H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.2, 28.1, 50.4, 54.2, 59.9, 111.4, 116.4, 122.9, 127.1, 129.4, 145.9 ppm. HRMS: Calcd. for $C_{11}H_{15}NO$ (M+) 177.1154; found 177.1150.

2-(6-Bromo-3,4-dihydroquinolin-1(*2H*)-yl)ethan-1-ol (3n)

3n was obtained as a white solid by purification (Silica gel column chromatography, EtOAc:Hexane= 1:2) after the catalytic reaction. Mp 67-68 °C. ^{1}H NMR ($CDCl_3$): δ = 1.67 (t, *J* = 5.6 Hz, 1H, -O*H*), 1.94 (quin, *J* = 6.0 Hz, 2H, -$CH_2CH_2CH_2$N-), 2.74 (t, *J* = 6.4 Hz, 2H, -$CH_2CH_2CH_2$N-), 3.31 (t, *J* = 5.6 Hz, 2H, -$CH_2CH_2CH_2$N-), 3.41 (t, *J* = 5.6 Hz, 2H, -CH_2CH_2OH), 3.80 (qurt, *J* = 5.6 Hz, 2H, -CH_2OH), 6.53 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.04-7.06 (br-m, 1H, Ar-*H*), 7.10 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.9, 27.9, 50.2, 54.1, 59.8, 107.9, 112.8, 124.9, 129.6, 131.6, 144.8 ppm. HRMS: Calcd. for $C_{11}H_{14}NOBr$ (M+) 255.0259; found 255.0266.

2-(3,4-Dihydroisoquinolin-2(*1H*)-yl)ethan-1-ol (3o)

3o was obtained as a colorless oil by purification (Silica gel column chromatography, $CHCl_3$:MeOH = 20:3) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 2.70 (t, *J* = 5.2 Hz, 2H, -CH_2CH_2OH), 2.79 (t, *J* = 6.0 Hz, 2H, -CCH_2CH_2N-), 2.89 (t, *J* = 5.6 Hz, 2H, -CCH_2CH_2N-), 3.64 (s, 2H, -CCH_2N-), 3.69 (t, *J* = 5.6H, -CH_2OH), 3.78 (s, 3H, -OMe), 6.65 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.71 (dd, *J* = 8.4 Hz, *J* = 2.8 Hz, 1H, Ar-*H*), 6.94 (d, *J* = 8.4 Hz, 1H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.1 50.7, 55.8, 58.1, 59.2, 125.7, 126.3, 126.6, 128.7, 134.2, 134.5 ppm. HRMS: Calcd. for $C_{11}H_{16}ON$ ([M+H]+) 178.1232; found 178.1233.

2-(6-Methoxy-3,4-dihydroisoquinolin-2(*1H*)-yl)ethan-1-ol (3p)

3p was obtained as a colorless oil by purification (Silica gel column chromatography, EtOAc:MeOH = 20:3) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 2.70 (t, J = 5.2 Hz, 2H, -CH_2CH$_2$OH), 2.80 (t, J = 6.0 Hz, 2H, -CCH$_2$CH_2N-), 2.91 (t, J = 5.6 Hz, 2H, -CCH_2CH$_2$N-), 3.67-3.72 (m, 4H, -CH_2OH, -CCH_2N-), 6.99-7.04 (m, 1H, Ar-*H*), 7.08-7.17 (m, 3H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.4, 50.6, 55.2, 55.3, 58.0, 59.1, 112.2, 113.3, 126.7, 127.5, 135.4, 158.1 ppm. HRMS: Calcd. for $C_{12}H_{18}NO_2$ ([M+H]+) 208.1337; found 208.1333.

2-Dibenzylaminoethanol (3q)[19]

3q was obtained as a light yellow oil by purification (Silica gel column chromatography, EtOAc:Hexane = 1:4) after the catalytic reaction. ^{1}H NMR ($CDCl_3$): δ = 2.55 (br-s, 1H, -O*H*), 2.66 (t, J = 5.2 Hz, 2H, -CH_2CH$_2$OH), 3.58 (t, J = 5.2 Hz, 2H, -CH$_2$CH_2OH), 3.62 (s, 4H, -NCH_2Ph), 7.22-7.36 (m, 5H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 54.8, 58.2, 58.5, 127.2, 128.4, 128.9, 138.7 ppm. FAB-MS: ([M+H]+) 242.1. CAS Registry No. 101-06-4.

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