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Ruthenium-Complex-Catalyzed N-(Cyclo)alkylation of Aromatic Amines with Diols. Selective Synthesis of N-(ω -Hydroxyalkyl)anilines of Type PhNH(CH₂)_nOH and of Some Bioactive Arylpiperazines

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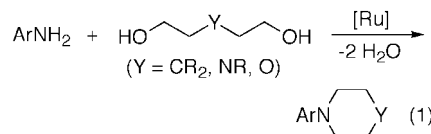
A new class of well-defined neutral mono-, and dicationic ruthenium(II) complexes containing a neutral terdentate donor system [C₅H₃N(CH₂E)₂-2,6] (E = PPh₂ (**PNP**) or NMe₂ (**NN'**N)) has been found effective as catalyst precursor in N-(cyclo)alkylation reactions of aromatic amines with diols Y(CH₂CH₂OH)₂ (Y = CH₂, NR). With these catalysts, N-phenylpiperidine is synthesized from aniline and 1,5-pentanediol in 85% yield (at 180 °C for 24 h in 1,4-dioxane). With neutral RuCl₂(**NN'**N)-(PPh₃) as a catalyst precursor, aniline can be selectively N-monoalkylated with diols of the type HO(CH₂)_nOH (n = 4–6, 10) to give N-(n-hydroxyalkyl)anilines in 40–75% yield. To our knowledge, this represents the first useful catalytic route to this type of compounds. The new catalysts can also be used in the synthesis of arylpiperazines. For example, N-phenyl-N-methylpiperazine is obtained from aniline and MeN(CH₂CH₂OH)₂ in yields up to 34%. N-[m-(Trifluoromethyl)phenyl]-N-methylpiperazine, TFMPMP, is successfully produced from m-(trifluoromethyl)aniline and MeN(CH₂CH₂OH)₂ in 44% yield using monocationic [RuOTf(**NN'**N)(PPh₃)]OTf as the catalyst precursor. A mechanism for the N-(cyclo)alkylation reaction is proposed.

Introduction

The transition-metal-catalyzed N-alkylation reaction of amines with alcohols as alkylating agents is a potentially interesting route for the synthesis of secondary and tertiary amines. The first catalysts reported for this type of reactivity were metallic palladium¹ and complexes of rhodium and iridium.² After ruthenium(II) complexes had been recognized as active catalysts for the hydrogen transfer from alcohols,³ a number of procedures have been developed for ruthenium-catalyzed N-alkylation of amines with primary alcohols.⁴ In this way, indoles⁵ and quinolines^{5c} have been prepared from aromatic amines

and 1,2- and 1,3-dialcohols, respectively. Only very recently was the first example of N-alkylation of heteroaromatic amines with alcohols reported.⁶

From a practical point of view, the reaction of amines with 1,5-dialcohols is interesting since in this way N-substituted saturated heterocyclic products like piperidines, piperazines, or morpholines can be obtained in one step⁷ (eq 1). The synthesis of arylpiperazines is of



particular interest because some of these compounds find applications as antipsychotic pharmaceuticals. A major advantage of this catalytic method over conventional methods lies in the fact that water instead of salts is formed as the only side product. Typically, the reactions are performed by heating the reaction mixture to 150–200 °C for a few hours in a closed pressure reactor.

So far, only a few of the examples reported show synthetic value, and also, the mechanism of this reaction is not yet fully clarified. It is generally thought that the reaction involves dehydrogenation of an alcohol substrate by a ruthenium catalyst as a key step.^{4c–e,7a} The most active ruthenium catalyst found so far, RuCl₂(PPh₃)₃, is known to decarbonylate aldehyde intermediates to give RuHCl(CO)(PPh₃)₃, which is ineffective as a catalyst.^{4e}

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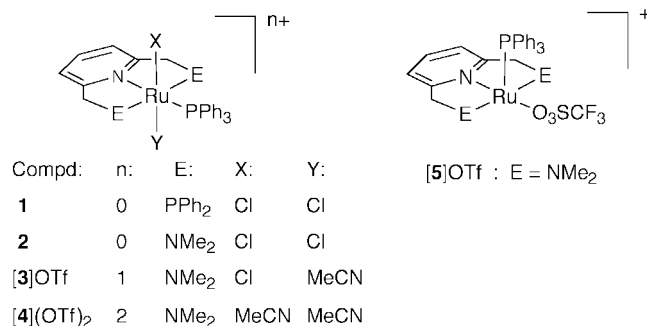
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Moreover, $\text{RuCl}_2(\text{PPh}_3)_3$ itself is not well-defined under catalytic conditions. It shows a tendency to lose phosphine with formation of dimeric species.⁸

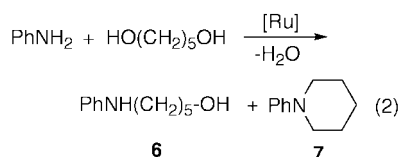
In a parallel project, we are investigating homogeneous transfer-hydrogenation reactions involving well-defined transition-metal catalyst containing monoanionic ligand systems of type $[\text{C}_6\text{H}_3(\text{CH}_2\text{E})_2-2,6]^-$ ($\text{E} = \text{NMe}_2$, $[\text{NCN}]^-$ or PPh_2 , $[\text{PCP}]^-$).⁹ Recently, neutral ruthenium(II) complexes containing these $[\text{ECE}]^-$ ligand systems¹⁰ have proven to be very active catalysts in transfer-hydrogenation reactions of ketones and imines¹¹ and as such would be promising catalysts for the direct alkylation reaction. However, due to the thermal instability of these complexes, they are not applicable in N-cycloalkylation reactions for which relatively high temperatures of 140–180 °C are required. In order to establish the necessity of the presence of a metal-carbon σ -bond in catalytically active complexes, we studied potential ruthenium(II) catalysts containing the neutral analogs of the $[\text{ECE}]^-$ ligand system, i.e., the pyridine-based ligands $[\text{C}_5\text{H}_3\text{N}(\text{CH}_2\text{E})_2-2,6]$ ($\text{E} = \text{NMe}_2$, $[\text{NN}'\text{N}]$ or PPh_2 , $[\text{PNP}]$).¹² We report here on the Ru $[\text{ENE}]$ -catalyzed N-(cyclo)alkylation reaction of aromatic amines with (i) diols of type $\text{HO}(\text{CH}_2)_n\text{OH}$ ($n \geq 4$) and (ii) N-substituted diethanolamines.

Results

The catalysts used were the neutral, mono-, and dicationic complexes **1–5**,¹² which contain the neutral ligand system **PNP** or **NN'N** as well as one PPh_3 ligand. In these complexes, the **ENE** ligands act as terdentate coordinating ligands. Complexes **1–4** are coordinatively saturated with the **ENE** ligand coordinating meridionally while complex **5** is a coordinatively unsaturated 16-electron complex:



Piperidines from 1,5-Pentanediol and an Arylamine. The activity of complexes **1–5** and of some other ruthenium(II) complexes was determined for a model N-(cyclo)alkylation reaction of aniline with 1,5-pentanediol (eq 2; Table 1). This reaction may give two products, N-(5-hydroxypentyl)aniline, **6**, and N-phenylpiperidine, **7**, resulting from N-mono- and N-cycloalkylation of aniline.



Without a catalyst, no reaction is observed. Also, none of the known complexes $[\text{RuCl}_2(\text{PMe}_3)_4]$, $[\text{RuCl}_2(\text{nbd})]_n$

Table 1. Effect of Catalyst on the Synthesis of Piperidines from 1,5-Pentanediol and Aniline^a

entry	catalyst	convn ^b (%)	yield ^b (%)	
			6	7
1	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}/3 \text{PPh}_3$	100		85
2	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}/3 \text{NN}'\text{N}$			
3 ^c	$\text{RuCl}_2(\text{PPh}_3)_3$	100		85
4 ^d	1	22	19	3
5	2	60	55	5
6	3	74	45	7
7	4	93	47	43
8	5	98	47	22

^a Pressure-reactor ($P_{\text{max}} = 12$ atm), reaction time 5 h, temperature 180 °C, solvent 1,4-dioxane (50 mL), [aniline] = 2.0 M, [diol] = 3.0 M, $[\text{Ru}] = 0.02$ M; **NN'N** = 2,6-bis(dimethylamino)methylpyridine, **PNP** = 2,6-bis(diphenylphosphino)methylpyridine.
^b Conversion based on aniline. ^c See ref 7c. ^d After 24 h.

(nbd = 2,5-norbornadiene), $[\text{RuCl}_2(\text{bpy})_2]$ (bpy = 2,2'-bipyridine), or $[\text{RuCl}_2(\text{terpy})(\text{PPh}_3)]$ (terpy = 2,2,6:2',2'',6'-terpyridine) is catalytically active. Although the mixture $\text{RuCl}_3 \cdot n\text{H}_2\text{O}/3\text{PPh}_3$ effectively catalyzes the reaction of aniline with 1,5-pentanediol to give N-phenylpiperidine in 85% yield (Table 1, entry 1),^{7a} we found the mixture $\text{RuCl}_3 \cdot n\text{H}_2\text{O}/3\text{NN}'\text{N}$ (Table 1, entry 2) to be ineffective. In contrast, all complexes **1–5** showed at least some catalytic activity (Table 1, entries 3–7). Interestingly, the known $\text{RuCl}_2(\text{PPh}_3)_3$ does not give monoalkylated **6** after 5 h at 180 °C (Table 1, entry 1), whereas a considerable amount of this monoalkylated product is formed in the reactions catalyzed by complexes **1–5**. In the case of complex **2**, the yield of **6** is as high as 55% at a conversion of aniline of 60%; this corresponds to a selectivity of 92% (Table 1, entry 5). It is noteworthy that no N,N-bis(5-hydroxypentyl)aniline is formed, which might arise either from an amine-scrambling reaction of the monoalkylation product **6** or from N-dialkylation of aniline. The latter type of ruthenium-catalyzed reactivity is well-studied.¹³ Obviously, in the case of complexes **1–5**, amine exchange of **6** is not competing with N-cycloalkylation to give **7**. Furthermore, no formation of 1,5-dianilinopentane is observed, a product that could result from a double monoamination of 1,5-pentanediol. Also, no products arising from lactonization^{3e,14} of 1,5-pentanediol are detected. It must be noted that all catalytic runs give incomplete mass balances; up to 29% of the aniline starting material could not be detected in the products. These side products, probably arising from polymerization reactions, could not be identified by GCMS. The analogous reaction between more basic benzylamine¹⁵ and 1,5-pentanediol is less effectively catalyzed. With $\text{RuCl}_2(\text{PPh}_3)_3$, full conversion of benzyl-

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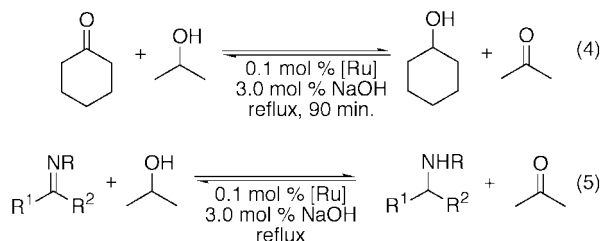
Table 3. Ruthenium-Catalyzed Transfer Hydrogenation of Cyclohexanone and Imines with 2-Propanol^a

entry	substrate	catalyst	yield (%) (time (h))
1 ^b	cyclohexanone	RuCl ₂ (PPh ₃) ₃	87 (5)
2 ^b	cyclohexanone	1	79 (5)
3–6 ^b	cyclohexane	2–5	85–87 (5)
7 ^{c,d}	PhN=CHPh	RuCl ₂ (PPh ₃) ₃	88 (8)
8 ^c	PhN=CHPh	2	88 (7.5)
9 ^{c,d}	PhCH ₂ N=C(Me)Ph	RuCl ₂ (PPh ₃) ₃	48 (18)
10 ^c	PhCH ₂ N=C(Me)Ph	2	41 (7.5)

^a Reaction time 5 h, reflux temperature, solvent 2-propanol (50 mL), [cyclohexanone] or [imine] = 1.0 M, [Ru] = 0.01 M. ^b 1.5 mmol NaOH as cocatalyst. ^c 2.5 mmol K₂CO₃ as cocatalyst. ^d See ref 23b.

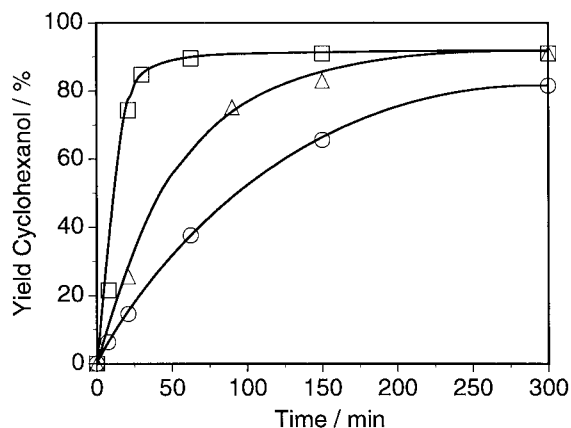
6–10 have not yet been reported in the literature. Only a few reports have been made on selectivity control in the N-mono- and N-dialkylation of amines with alcohols. An example of this is the amination of ethylene glycols.²⁰ Only very recently, N-mono- or N-dialkylation of heteroaromatic amines with primary monoalcohols catalyzed by RuCl₂(PPh₃)₃ was reported.⁶

Activity of Complexes 1–5 in Transfer-Hydrogenation Reactions. To further compare the Ru[NN'N] systems with RuCl₂(PPh₃)₃, we have tested our catalyst precursors in transfer-hydrogenation reactions of propan-2-ol with cyclohexanone²¹ (eq 4) and imines²² (eq 5) (Table 3). These reactions were cocatalyzed by NaOH (in the



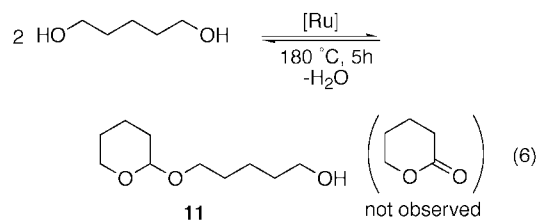
case of cyclohexanone) or K₂CO₃ (in the case of imines) using 30 equiv of base based on [Ru]. The transfer-hydrogenation reaction of imines with propan-2-ol has much in common with the N-alkylation reaction of amines with alcohols: in both cases, it is proposed (vide infra) that after dehydrogenation of the alcohol the hydrogen produced is transferred to an imine to yield an amine. In the case of the N-alkylation reactions, an imine is proposed to result from an intermediate condensation reaction of an amine substrate with the aldehyde formed.

All transfer-hydrogenations of cyclohexanol with propan-2-ol catalyzed by complexes **2–5** (Table 3) gave high yields of cyclohexanol (86–89% after 5 h), corresponding to total turnover (TTO) numbers of 850–870. For RuCl₂(PPh₃)₃, typical turnover numbers of 890/h have been observed.²¹ It must be noted that the total turnover numbers for the Ru[NN'N] complexes are considerably lower than those we recently observed for Ru[ECE] complexes. For example, for the neutral complex [RuOTf(PCP)(PPh₃)], a turnover number as high as 25 000/h was achieved over a period of 12 h.¹¹ During all of the Ru[NN'N]-catalyzed transfer-hydrogenation reactions,

**Figure 3.** Reaction curves of ruthenium-catalyzed transfer hydrogenation of cyclohexanone with propan-2-ol: RuCl₂(PPh₃)₃ (□), RuCl₂(NN'N)(PPh₃) (Δ), RuCl₂(PNP)(PPh₃) (○).

small amounts of aldol condensation products were formed. The complex **1**-catalyzed reaction gave a lower yield of 79% (TTO 790), and more of the aldol condensation products were found. Some of the transfer-hydrogenation reactions of cyclohexanone with propan-2-ol were also monitored by GC (Figure 3). From the curves in Figure 3, it can be seen that the reaction rates for the Ru[NN'N] catalyst precursors are lower than those observed for RuCl₂(PPh₃)₃.

When compared to the ruthenium-catalyzed transfer hydrogenation of ketones, imines react much slower. This may be due to both steric and electronic effects. The results in Table 3 show that our catalyst precursors have a catalytic activity comparable to that of RuCl₂(PPh₃)₃ in transfer-hydrogenation reactions of imines with propan-2-ol. As has already been recognized by other authors,²² aldimines generally react faster than ketimines. The two examples in this work suggest that this is also true for the Ru[NN'N]-catalyzed transfer-hydrogenation reactions. When 1,5-pentanediol is reacted with RuCl₂(PPh₃)₃ or complex **1** or **2**, selective formation of (tetrahydropyranyloxy)-1-pentanol, **11**, in ~35% yield is observed. This complex is the product of a selective oxidative coupling reaction of two molecules of 1,5-pentanediol with exclusion of water. In these reactions, neither δ -valerolactone nor the esterification product 5-(hydroxypentyl)-5-hydroxypentanoate is found (eq 6). These results also show that the catalyst precursors **1** and **2** behave similarly to RuCl₂(PPh₃)₃.



Arylpiperazines from Aromatic Amines and Diethanolamines. Classically, arylpiperazines are obtained by ring closure of suitably substituted anilines and bis(2-chloroethyl)amine hydrochloride in the presence of base.²³ In these reactions, yields of around 40% are obtained after reaction times of 50 h or more.

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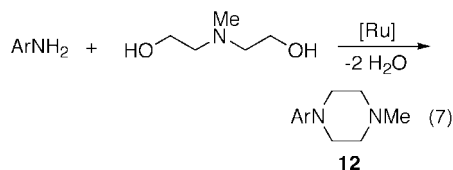
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Table 4. Ruthenium Complex-Catalyzed Synthesis of *N*-Methyl-*N*-phenylpiperazine, **12**, and *N*-[*m*-(Trifluoromethyl)phenyl]-*N*-methylpiperazine, **13**^a

entries	catalyst	yield (%)	
		12	13
1 ^{b,c}	RuCl ₂ (PPh ₃) ₃	32	
2, 3	RuCl ₂ (PPh ₃) ₃	23 (23) ^d	7 (23) ^e
4, 5	2	24	23
6, 7	3	22	25
8, 9	4	32	30
10, 11	5	34	30 (44) ^e

^a Pressure-reactor (P_{\max} = 14 atm), reaction time 5 h, temperature 180 °C, solvent 1,4-dioxane [aniline] = 3.0 M; [N-methyldiethanolamine] = 2.0 M; 2 mol % [Ru] based on aniline. ^b [Ru] = 3 mol % based on aniline. ^c See ref 7a. ^d After 18 h. ^e After 24 h.

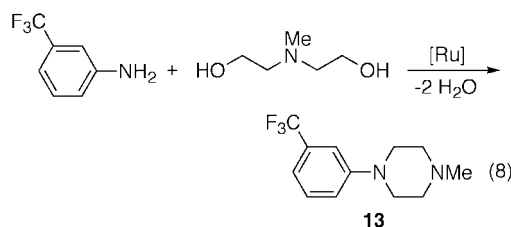
Recently, some new methods for the synthesis of arylpiperazines have been developed that are based on the palladium-catalyzed coupling of aryl halides²⁴ or on the reaction of (η^6 -fluoroarene)tricarbonylchromium complexes with unprotected piperazines.²⁵ However, in these reactions, halogen-containing substrates are still required and salts are formed as a side product. This makes these reactions less interesting from an industrial point of view. In the present study, we have extended the Ru[NNN]-catalyzed N-cycloalkylation reaction of aromatic amines with diols to the synthesis of *N*-phenyl-*N*'-methylpiperazine, **12**, from aniline and *N*-methyldiethanolamine (eq 7 and Table 4). Excess aniline (aniline/diol ratio = 3/2)



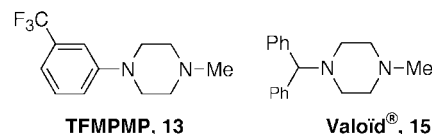
was used as it is known that in reactions of aromatic amines with *N*-substituted diethanolamines no piperazines are obtained when excess *N*-methyldiethanolamine is used.^{7a} This is in contrast to the arylpiperidine syntheses, where an excess of 1,5-pentanediol (aniline/diol ratio = 2/3) is favored. The arylpiperazine syntheses are known^{7a} to give only low yields. Interestingly, our new catalyst precursors give comparable or higher yields than RuCl₂(PPh₃)₃ (entries 2, 3–10, 11). For example, **5** improves the yield of *N*-methyl-*N*-phenylpiperazine to 34% (entry 10). During these reactions, no formation of 4-methylmorpholin-2-one from lactonization of *N*-methyldiethanolamine is observed, a product that has been reported to be formed under the influence of RuH₂-(PPh₃)₄.¹⁴

We have also applied our catalysts to the synthesis of some bioactive arylpiperazines. First, we tried to synthesize *N*-(2-methoxyphenyl)-*N*-methylpiperazine, a compound that has recently been recognized²⁶ as biologically active, from *o*-anisidine and *N*-methyldiethanolamine. In the presence of either RuCl₂(PPh₃)₃ or complex **2**, no reaction was observed under standard conditions (the analogous reaction of *o*-anisidine with 1,5-pentanediol has been reported to give *N*-(2-methoxyphenyl)piperidine

in 84% yield^{7a}). Interestingly, when complexes **4** and **5** were used, *N*-(2-methoxyphenyl)-*N*-methylpiperazine was formed, albeit in low yield (ca. 10%). These low yields are probably caused by steric effects, the basicity of *o*-anisidine being comparable to that of aniline.¹⁵ Also, *N*-[*m*-(trifluoromethyl)phenyl]-*N*'-methylpiperazine (TFMPMP, **13**),²⁷ a potent serotonin agonist, has been synthesized from *m*-(trifluoromethyl)aniline and *N*-methyldiethanolamine (eq 8 and Table 4).



The results in Table 4 show that in this particular reaction the NN'N-containing ruthenium(II) catalyst precursors are more active than RuCl₂(PPh₃)₃. With complex **5**, **13** was obtained in 44% yield (Table 4, entry 11). Recently, an alternative synthesis of this product



was reported, which involves the reaction of *m*-(trifluoromethyl)aniline with bis(2-bromoethyl)amine over a solid alumina support (70% yield).²⁸ To synthesize the *N*-benzyl-substituted analog of **13**, a reaction of *m*-(trifluoromethyl)aniline with *N*-benzyldiethanolamine was carried out; this gave the desired *N*-benzylated product **14** in 29% yield using **5** as a catalyst. The *N*-benzyl-substituted piperazine **14** is of particular interest, as a benzyl group can be easily removed by a simple hydrogenation step, giving the unprotected piperazine. A problem is that this N-cycloalkylation suffers from a competing amine-scrambling reaction, giving substantial amounts of dibenzylamine. Finally, we applied our method to the synthesis of *N*-methyl-*N*-benzhydrylpiperazine (Valoid, Cyclizine, **15**), a drug against travel sickness.²⁹ However, using our catalytic systems **1**–**5**, only low yields (<10%) of the desired product were obtained. It must be noted that in none of the arylpiperazine syntheses reported here could unreacted aniline starting materials be recovered. Also, we have been unable to isolate or identify any side products.

Discussion

Effect of the Nature of the Catalyst Precursor.

The nature of the catalyst precursor has a critical influence on the N-alkylation reaction. Early catalysts⁴ that have been used for N-(cyclo)alkylation reactions are neutral ruthenium(II) complexes with monodentate phosphine ligands as well as chloride anions. Ruthenium(II) complexes containing bidentate nitrogen or phosphorus

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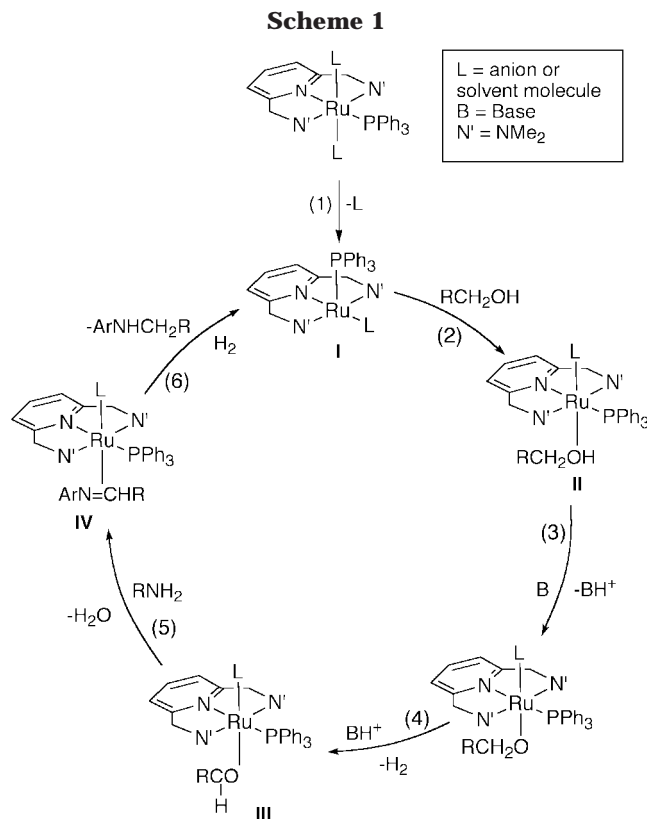
ligands, or mixed nitrogen-phosphorus donor ligands (e.g., $\text{RuCl}_2(\text{bpy})_2$, $\text{RuCl}_2(\text{dppe})_2$ (dppe = 1,2-bis(diphenylphosphino)ethane) or $\text{RuCl}_2(\text{PN})_2$ (PN = 2-(diphenylphosphino)-*N,N*-dimethylaniline) are ineffective in the reaction of alkylamines with long-chain alcohols.^{4e} However, upon replacement of terpy by **PNP** (complex **1**), some catalytic activity is found (Table 1, entry 4). Replacement of the PPh_2 groups in **PNP** by purely σ -donating NMe_2 groups to give **NN'N** then drastically increases the catalytic activity, cf. complex **2** (Table 1, entry 5). Obviously, the combination of one sp^2 - and two sp^3 -hybridized nitrogens (as in **NN'N**) gives rise to active catalysts. As had been recognized earlier, ruthenium catalyst precursors containing basic phosphines like PMe_3 are inactive in the *N*-(cyclo)alkylation of aromatic amines.^{7a} When the chloride ligands in $[\text{RuCl}_2(\text{NN'N})(\text{PPh}_3)]$, **2**, are replaced by acetonitrile ligands, the resulting mono- and dicationic complexes **3** and **4**, respectively, show an increase in conversion of aniline (Table 1, entries 6 and 7), although the selectivity of the reaction for **6** and **7** is slightly reduced. This is the first successful application of cationic ruthenium(II) complexes in *N*-alkylation reactions. The high activity of the cationic complexes **3** and **4** suggests that in solution free coordination sites are made available by $\text{Ru}-\text{MeCN}$ bond dissociation. The coordinatively unsaturated complex **5** contains a weakly coordinating triflate ligand. The high activity of this complex may similarly be explained by facile dissociation of the η^1 -bonded OTf ligand.³⁰ During the reactions, no loss of **PNP** or **NN'N** is observed, which indicates that the catalytically active species indeed contains a $\text{Ru}[\text{ENE}]$ -moiety.

Catalysts for the Piperazine Syntheses. In contrast to the piperidine syntheses, in the synthesis of piperazines our catalyst precursors **1–5** are more active than conventional $\text{RuCl}_2(\text{PPh}_3)_3$, although the overall yields are still not satisfactory. The low activity of $\text{RuCl}_2(\text{PPh}_3)_3$ may be due to deactivation of the catalyst by interaction of the basic nitrogen function in the *N*-substituted diethanolamines with ruthenium. Such interactions are less likely in our $\text{Ru}[\text{NN'N}]$ complexes in which the terdentate-bonded **NN'N** ligand is unlikely to be replaced by *N*-methyldiethanolamine. This is corroborated by reactions of complex **2** with *N*-methyldiethanolamine in which no dissociation of the **NN'N** ligand was observed. Also, at room temperature, no interaction between the ruthenium complexes **1–5** and aniline, 1,5-pentanediol, or *N*-methyldiethanolamine could be detected by ^1H and ^{31}P NMR and UV/vis spectroscopy.

Other authors have observed a relation between the basicity of the amine substrate and the basicity of the phosphine ligands³¹ in ruthenium catalysts, i.e., more basic alkylamines require ruthenium complexes containing more basic alkylphosphines.^{7a} The ineffectiveness of complex **5** for the synthesis of *N*-methyl-*N*-benzhydrylpiperazine **15** is in accord with this qualitative relationship.

Mechanistic Considerations. The results obtained with the $\text{Ru}[\text{NN'N}]$ catalysts allow a detailed mechanism for the *N*-alkylation of amines with alcohols to be proposed (Scheme 1). The different steps in this mechanism will be discussed.

(i) Fate of the Catalyst Precursor. The fate of the complex $\text{RuCl}_2(\text{PNP})(\text{PPh}_3)$, **1**, during the catalysis was



monitored by ^{31}P NMR spectroscopy. **1** itself shows a characteristic pair of one-doublet and one-triplet resonances due to the presence of a MX_2Y system. During a model *N*-cycloalkylation reaction of aniline with 1,5-pentanediol using catalyst precursor **1**, samples were taken from the reaction mixture and their ^{31}P NMR spectra were recorded (see the Supporting Information). In none of the spectra was free **PNP** observed, but during the reaction a new set of a doublet and a triplet appears at 48.6 and 57.9 ppm with a coupling constant of 30 Hz. Such a pattern is characteristic for a complex containing two equivalent P nuclei coupled to a third phosphorus atom as in the $[\text{Ru}(\text{PNP})(\text{PPh}_3)]$ moiety. During the reaction, an increasing amount of free triphenylphosphine ($\delta = -5$ ppm) is observed. After prolonged reaction times (>24 h), the intensities of all of the resonances in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum decrease in intensity and gradually disappear completely. Along with this, a precipitate is formed, and the catalytic activity goes back to zero. Apparently, the catalyst decomposes.

(ii) Effect of Phosphine Ligands on Catalytic Activity. The presence of phosphine ligands is regarded to be essential for any catalytic activity.^{4c-e,7a} Even in the case of our $\text{Ru}[\text{NN'N}]$ complexes, the presence of a triphenylphosphine ligand seems to be essential for catalytic activity, cf. the ineffectiveness of the combination of $\text{RuCl}_3 \cdot x\text{H}_2\text{O}/\text{NN'N}$. Indeed, in the *N*-cycloalkylation of aniline with 1,5-pentanediol catalyzed by $\text{RuCl}_2(\text{NN'N})(\text{PPh}_3)$, **2**, a 36% increase in reactivity was found when 3 equiv of triphenylphosphine was added to the reaction mixture. Roundhill et al.^{4e} reported a comparable increase in catalytic activity for the $\text{RuCl}_2(\text{PPh}_3)_3$ -catalyzed *N*-alkylation of $\text{C}_{16}\text{H}_{33}\text{OH}$ with diisopropyl-

(31) Basicity of phosphines:³² PPh_3 , $\text{p}K_a = 2.73$; P^iBu_3 , $\text{p}K_a = 8.43$.

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amine (*i*-Pr)₂NH upon addition of 4 equiv of triphenylphosphine. They suggested that triphenylphosphine may displace the complexed aldehyde to facilitate its reaction in solution with amine^{4c} or that it may accelerate the catalytic hydrogenation of imine to tertiary amine (compare the N-alkylation of 2-aminopyridine with ethanol catalyzed by (η^4 -1,5-cyclooctadiene)(η^6 -1,3,5-cyclooctatriene)ruthenium (Ru(cod)(cot)), which is also positively affected by the addition of phosphine ligands⁶).

(iii) Step 1: Activation of Coordinatively Saturated Ru[NN'N] Complexes. We have observed that RuCl₂(NN'N)(PPh₃), **2**, easily loses chloride ions in MeCN at 55 °C to form a monocationic complex that can be formulated as [mer-RuCl(NN'N)(PPh₃)-(MeCN)]Cl.¹² Therefore, we propose that the first step in the catalytic cycle consists of dissociation of one of the axial ligands. This may give either a five-coordinate 16-electron ruthenium(II) complex with a square pyramidal geometry, cf. the structure of complex **5**, or a six-coordinate 18-electron complex. In the 16-electron complex, both in the solid state and in solution, the triphenylphosphine occupies the apical position of a square pyramid¹² (see Scheme 1). This can be converted into a structure **I** analogous to **5** via a Berry-pseudo rotation. In the six-coordinate complex, the sixth coordination site is occupied by the substrate (aniline or the dialcohol), cf. intermediate **II** in Scheme 1, which was identified separately by an X-ray determination.¹² As stated earlier, whereas the presence of excess diol is required in the synthesis of piperidines, the syntheses of piperazines do not proceed when an excess of diethanolamine is used. Watanabe et al.^{4c} have shown that for the N-monoalkylation of aromatic amines with primary alcohols the reaction is zero order in alcohol concentration, and they suggested that this is also the case for the N,N-dialkylation and N-cycloalkylation reactions. However, the piperazine syntheses are obviously not zero order in diethanolamine concentration. Although this implies differences in the mechanistic details, it is difficult to evaluate them.

(iv) Steps 2–4. Coordination and Dehydrogenation of Alcohol Substrate: Reductive Elimination of Dihydrogen. In mechanisms proposed so far for the N-alkylation reaction catalyzed by RuCl₂(PPh₃)₃, dehydrogenation of alcohol into aldehyde is a key step.^{4c–e,7a} For the N-alkylation of secondary amines with alcohols, Roundhill et al.^{4c,d} proposed the alcohol to add oxidatively to a [RuCl₂(PPh₃)₂] intermediate (resulting from dissociation of triphenylphosphine from RuCl₂(PPh₃)₃) to give [Ru^{IV}HCl₂CH₂R](PPh₃)₂, which subsequently reductively eliminates HCl and produces [Ru^{II}Cl(OCH₂CH₂R)P₂L] (L = phosphine or amine). Formation of HCl is well known in reactions of RuCl₂(PPh₃)₃ with alcohols.³³ Some authors^{4c,7a} have pointed out that the presence of a chloride anion is a prerequisite for catalytic activity in N-alkylation reactions. However, this does not apply to our catalytic systems, as our mono- and dicationic complexes [RuOTf(NN'N)(PPh₃)OTf], **2**, and [Ru(NN'N)-(MeCN)₂(PPh₃)OTf]₂, **4**, which both lack chloride anions, are more active than the neutral analog [RuCl₂(NN'N)(PPh₃)]. An alcohol substrate can coordinate directly to coordinatively unsaturated ruthenium intermediate **I** to give **II** (see Scheme 1); on the other hand, formation of **II** could also occur directly from the starting material RuCl₂(NN'N)(PPh₃) via direct solvent or anion replace-

ment. According to the transfer-hydrogenation mechanism,³⁴ **II** can then be converted into an alkoxyruthenium species that undergoes subsequent β -elimination to provide a ruthenium(aldehyde)(hydride) intermediate. Reaction of the protonated base with the latter ruthenium(aldehyde)(hydride) results in formation of dihydrogen.^{3b,35–37} Indeed, after each catalytic run, we found a substantial amount of hydrogen gas (2–5 atm) in the pressure reactor. Moreover, from a separate experiment in which the reaction between aniline and 1,5-pentanediol was performed under 10 atm of hydrogen pressure, we found that the activity decreases drastically: after 5 h under standard conditions, only trace amounts of *N*-phenylpiperidine and monoalkylated *N*-(5-hydroxypentyl)aniline were formed. This suggests that molecular hydrogen is present during the reaction and acts as a competing ligand blocking the catalytic activity. Therefore, we propose an equilibrium between a Ru(alkoxide)(hydride) and a Ru(aldehyde) complex **III**.

(v) Step 5. Condensation of Aldehyde and Amine in the Ruthenium Coordination Sphere. We propose that in a next step the aldehyde condenses with the amine to an imine intermediate and 1 equiv of water.^{4c,7a} During the reaction, no imine intermediates could be detected by GCMS analysis. This suggests that such intermediates are rapidly hydrogenated to the alkylated products. Despite the comparable activity of RuCl₂(PPh₃)₃ and our Ru[NN'N] complexes in transfer-hydrogenation reactions (see Table 3), the latter were found to be far less active in the N-cycloalkylation of aniline with 1,5-pentanediol. Therefore, the proposed condensation reaction between aldehyde and amine (giving imine) must be the rate-limiting step. This is also suggested by other authors.^{4c,7a} Furthermore, the rate differences in catalytic activity of the Ru[NN'N] complexes indicate that the condensation reaction takes place *in the coordination sphere* of the ruthenium center, a feature that has also been postulated.^{4c,7a} Supporting evidence is the observation that during the N-cycloalkylation reactions no lactonization products are formed (vide supra). This suggests that the stronger coordination of amine substrates in comparison with alcohols inhibits bidentate coordination of the dialcohol substrates and thus prevents a ring-closure reaction. A similar effect has been found in the oxidative transformation of dialcohols catalyzed by RuH₂(PPh₃)₄.¹⁴ For example, in the absence of the strong donor acetonitrile, 1,5-pentanediol is converted in δ -valerolactone, whereas in the presence of acetonitrile it is converted into 5-hydroxypentyl-5-hydroxypentanoate.

The water that is formed in the condensation reaction does not effect the N-alkylation reaction. In a separate experiment in which 50 mmol of water was added to the reaction mixture of aniline with 1,5-pentanediol using complex RuCl₂(NN'N)(PPh₃), **2**, as a catalyst, no differences in the product distribution or reaction rate were found.

(vi) Step 6. Product Formation by Hydrogenation of the Unsaturated Intermediate. In a final step, the imine intermediate was hydrogenated, releasing the monoalkylated secondary amine product. This product can re-enter the catalytic cycle and can be intramo-

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lecularly cyclized into a tertiary cyclic amine. As has been stated before, this cycloalkylation of the monoalkylated products proceeds slower with Ru[NN'N]-based catalysts than with RuCl₂(PPh₃)₃. The only important difference between the first alkylation step and the second is that the condensation reaction between secondary amine and aldehyde in the latter case should give an iminium intermediate instead of an imine. Several authors have proposed the second cycle to proceed via a Ru(iminium) complex.^{4c,7a} However, a positively charged iminium ion is unlikely to coordinate to a cationic ruthenium center. Therefore, we propose the reaction to proceed via a ruthenium(ene-amine) intermediate. On the basis of a series of catalyzed and uncatalyzed reactions of valeraldehyde with diethylamine, Roundhill et al. have also postulated an ene-imine instead of an iminium intermediate.^{4d,e}

(vii) Deactivation of Ruthenium[NN'N]-Catalysts. After some of the catalytic runs, light-brown ruthenium-containing deposits were recovered from the reaction mixtures. Infrared spectra of these residues show a strong absorption in the $\nu(\text{CO}_{\text{stretch}})$ area at 1944 cm⁻¹, pointing to the formation of ruthenium-carbonyl complexes during the reaction. Decomposition of ruthenium-aldehyde intermediates has been reported to occur during N-alkylation reactions of long-chain aliphatic amines with primary alcohols catalyzed by RuCl₂(PPh₃)₃.^{4e} In these reactions, decarbonylation leads to the formation of RuHCl(CO)(PPh₃)₃, which is inactive as a catalyst. Obviously, the carbonyl complexes formed during our Ru[NN'N]-catalyzed reactions are not active anymore. Attempts to characterize them failed because of their insolubility. In separate experiments, we have isolated a number of Ru[NN'N] carbonyl complexes.¹²

Experimental Section

All boiling points are uncorrected. ¹H and ¹³C NMR spectra were recorded on 200 or 300 MHz spectrometers. Elemental analyses were performed by Dornis und Kolbe, Mikroanalytisches Laboratorium, Mulheim a.d. Ruhr, Germany. GC analyses were performed using a DB-17 capillary column in combination with a flame ionization detector. Conversions and yields were determined by the internal standard method according to calibration curves obtained for each product in separate experiments. MS analyses were made on a Unicam Automass System 2. *N*-Phenylpyrrolidine,³⁸ *N*-phenylpiperidine,³⁹ *N*-benzylpiperidine,⁴⁰ *N*-(4-hydroxybutyl)aniline,¹⁸ *N*-(5-hydroxypentyl)aniline,¹⁸ *N*-phenyl-*N*-methylpiperazine,⁴¹ and *N*-[*m*-(trifluoromethyl)phenyl]-*N*-methylpiperazine²⁷ are known compounds. ¹H and ¹³C NMR data for these compounds are cited below. Aniline, alkanediols, *N*-substituted diethanolamines, and solvents were commercial materials and were purified by distillation under a dry nitrogen atmosphere before use. *N*-Benzyl-diethanolamine,⁴² [RuCl₂(nbd)]_n,⁴³ RuCl₂(PMe₃)₄,⁴⁴ RuCl₂(PPh₃)₃,⁴⁵ RuCl₂(bpy)₂,⁴⁶ RuCl₂(terpy)(PPh₃),⁴⁷ and the complexes **1–5**¹² were prepared according to published procedures.

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General Procedure for the N-(Cyclo)alkylation Reactions. A typical reaction of aniline with 1,5-pentanediol will be described here. A stainless steel reactor (300 mL, Parr 4600 minireactor) was charged (under a nitrogen stream) with dioxane (25 mL), aniline (9.32 g, 100 mmol), 1,5-pentanediol (15.62 g, 150 mmol), and **1** (0.63 g, 1 mmol). After the reactor was sealed, a nitrogen purge was performed by three pressurization–depressurization sequences. Subsequently, the reactor was heated to 180 °C in 15 min in a mantle heater and kept at this temperature for 5 h with stirring. The reaction was terminated by rapid cooling, and the reactor was discharged.

Transfer-Hydrogenation Reactions. All hydrogen-transfer experiments were carried out under a nitrogen atmosphere in refluxing propan-2-ol with magnetic stirring. To solid **1** (40.2 mg, 0.0641 mmol), after evacuation and purging with nitrogen (3×), was added propan-2-ol (32.0 mL), and this mixture was heated at 82 °C for 10 min. Cyclohexanone (6.28 g, 64.0 mmol) dissolved in propan-2-ol (16.5 mL) was added dropwise to the refluxing mixture. The resulting reddish brown mixture was stirred for 10 min, and then a solution of NaOH (77.0 mg, 1.925 mmol) in propan-2-ol (15.6 mL) was added dropwise. The reaction mixture rapidly turned into a clear dark-red colored solution after addition of the base. Hexanol was used as an internal standard during the GC analyses of the reaction mixtures.

N-(5-Hydroxypentyl)aniline (6). The reaction mixture was extracted with water (100 mL) to remove remaining diol. Column chromatography of the evaporated reaction mixture on silica gel (Merck, 60–230 mesh) with a hexane/ethyl acetate mixture as eluent (gradient from 98:2 to 2:1 in volume) gave *N*-(5-hydroxypentyl)aniline. The product was purified by further Kugelrohr distillation and was obtained as a colorless oil: pot temperature 105 °C (0.01 mmHg); ¹H NMR (300 MHz) (CDCl₃) δ 7.23 (t, 2H), 6.75 (t, 1H), 6.65 (d, 2H), 3.63 (t, 2H), 3.13 (t, 2H), 1.68–1.60 (m, 4H), 1.50–1.48 (m, 2H), OH and NH not observed; ¹³C (75.47 MHz) (CDCl₃) δ 148.57, 129.30, 117.28, 112.93, 62.50, 44.00, 32.46, 29.3, 23.45. MS *m/z* 179 (M⁺). Anal. Calcd for C₁₁H₁₇NO: C, 73.70; H, 9.50; N, 7.88. Found: C, 73.61; H, 9.56; N, 7.81.

N-Phenylpiperidine (7). Pure product was obtained by distillation of the evaporated reaction mixture as a colorless oil: bp 86 °C (1 mmHg); ¹H NMR (300 MHz, CDCl₃) δ 7.47 (t, 2H), 7.15 (d, 2H), 7.05 (t, 1H), 3.36 (t, 4H), 2.00–1.82 (m, 4H), 1.82, 1.75 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 152.54, 129.21, 119.37, 116.76, 50.87, 26.19, 24.66; MS *m/z* 161 (M⁺).

N-Benzylpiperidine (8). Pure product was obtained by distillation of the evaporated reaction mixture as a colorless oil: bp 66 °C (0.5 mmHg); ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.21 (m, 5H), 3.49 (s, 2H), 2.42–2.38 (m, 4H), 1.62–1.57 (m, 4H), 1.46–1.44 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 138.74, 129.90, 128.09, 126.80, 63.92, 54.54, 26.05, 24.45; MS *m/z* 175 (M⁺). Anal. Calcd for C₁₂H₁₇N: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.11; H, 9.69; N, 8.06.

N-(4-Hydroxybutyl)aniline (9a). The reaction mixture was extracted with water (100 mL) to remove remaining diol. Column chromatography of the concentrated reaction mixture on silica gel (Merck, 60–230 mesh) with a hexane/ethyl acetate mixture as a eluent (gradient from 98:2 to 2:1 in volume) gave *N*-(4-hydroxybutyl)aniline. The pure product was obtained by further Kugelrohr distillation as a colorless oil: pot temperature 122 °C (0.01 mmHg); ¹H NMR (300 MHz) (CDCl₃) δ 7.20 (t, 2H), 6.75 (t, 1H), 6.64 (d, 2H), 3.66 (t, 2H), 3.15 (t, 2H), 1.72–1.67 (4H₂), OH and NH not observed; ¹³C NMR (75.47 MHz) (CDCl₃) δ 148.40, 129.28, 117.46, 113.01, 62.51, 43.93, 30.35, 26.09; MS *m/z* 165 (M⁺). Anal. Calcd for C₁₀H₁₅NO: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.52; H, 8.94; N, 8.58.

N-(6-Hydroxyhexyl)aniline (9b). The reaction mixture was extracted with water (100 mL) to remove remaining diol. Column chromatography of the evaporated reaction mixture on silica gel (Merck, 60–230 mesh) with a hexane/ethyl acetate

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mixture as an eluent (gradient from 98:2 to 2:1 in volume) gave 6-*N*-(6-hydroxyhexyl)aniline. The pure product was obtained by crystallization from benzene/pentane: white crystals; mp 43 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.19 (t, 2H), 6.71 (t, 1H), 6.62 (d, 2H), 3.64 (t, 2H), 3.12 (t, 2H), 1.67–1.56, and 1.42–1.44 (m, 4H), OH and NH not observed; ^{13}C NMR (75.47 MHz, CDCl_3) δ 148.54, 129.25, 117.28, 112.79, 62.67, 43.95, 32.69, 29.56, 27.00, 25.64; MS m/z 193 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.38; H, 9.86; N, 7.22.

***N*-(10-Hydroxydecyl)aniline (9c).** The reaction mixture was extracted with water (100 mL) to remove remaining diol. Column chromatography of the evaporated reaction mixture on silica gel (Merck, 60–230 mesh) with a hexane/ethyl acetate mixture as an eluent (gradient from 98:2 to 2:1 in volume) gave *N*-(10-hydroxydecyl)aniline. The pure product was obtained by crystallization from benzene/pentane: white crystals; mp 39 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.20 (t, 2H), 6.72 (t, 1H), 6.63 (d, 2H), 3.63 (t, 2H), 3.12 (t, 2H), 1.67–1.50 (m, 4H), 1.49–1.30 (m, 12H), OH and NH not observed; ^{13}C NMR (75.47 MHz, CDCl_3) δ 148.60, 129.23, 117.13, 112.79, 62.93, 44.06, 32.81, 29.61, 29.57, 29.47, 27.10, 25.80; MS m/z 249 (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{27}\text{NO}$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.22; H, 10.84; N, 5.75.

***N*-Phenylpyrrolidine (10a).** Pure product was obtained by distillation of the evaporated reaction mixture as a colorless oil: bp 81 °C (0.5 mmHg); ^1H NMR (300 MHz, CDCl_3) δ 7.33 (t, 2H), 7.76 (t, 1H), 6.66 (d, 2H), 3.37 (t, 4H), 2.08 (q, 4H); ^{13}C NMR (300 MHz, CDCl_3) δ 148.09, 129.21, 115.47, 111.75, 47.65, 25.56; MS m/z 149 (M^+).

***N*-Phenylhexahydroazepine (10b).** Pure product was obtained by distillation of the evaporated reaction mixture as a colorless oil: bp 117 °C (2.5 mmHg); ^1H NMR (300 MHz, CDCl_3) δ 7.42 (t, 2H), 6.90 (d, 2H), 6.85 (t, 1H), 3.64 (t, 4H), 2.00–1.97 (m, 4H), 1.77–1.73 (m, 4H); ^{13}C NMR (300 MHz, CDCl_3) δ 149.10, 129.46, 115.42, 111.4, 49.30, 28.04, 27.40; MS m/z 175 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.06; H, 9.82; N, 8.06.

(Tetrahydropyranyloxy)-1-pentanol (11). The crude reaction mixture was flash-distilled to remove ruthenium complexes and subsequently dissolved in water (100 mL). Extraction with Et_2O (50 mL, 5 \times) and removal of the solvent under reduced pressure afforded the pure product as a colorless oil: bp 92 °C, 0.1 mmHg; ^1H NMR (300 MHz, CDCl_3) δ 4.51 (t, 1H), 3.81–3.30 (m, 6H), 2.36 (s, 1H), 1.80–1.34 (m,

12H); ^{13}C NMR (300 MHz, CDCl_3) δ 98.84, 67.50, 62.50, 62.29, 32.44, 30.68, 29.40, 25.41, 22.45, 19.59. Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{O}_2$: C, 63.80; H, 10.71. Found: C, 63.68; H, 10.65.

***N*-Phenyl-*N*-methylpiperazine (12).** Pure product was obtained by vacuum distillation of the evaporated reaction mixture as a colorless oil: bp 105 °C (0.4 mmHg); ^1H NMR (300 MHz, CDCl_3) δ 7.28 (t, 2H), 6.94 (d, 2H), 6.66 (t, 1H), 3.22 (t, 4H), 2.58 (t, 4H), 2.36 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 151.30, 129.14, 119.10, 116.06, 55.20, 49.12, 46.23; MS m/z 176 (M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.88; H, 9.26; N, 16.04.

***N*-[*m*-(Trifluoromethyl)phenyl]-*N'*-methylpiperazine (13).** Column chromatography of the concentrated reaction mixture on silica gel (Merck, 60–230 mesh) with a hexane/ethyl acetate mixture as an eluent (gradient from 98:2 to 2:1 in volume) gave the crude product as a light yellow oil. The pure product was obtained by further Kugelrohr distillation as a colorless oil: pot temperature 75 °C (0.45 mmHg); ^1H NMR (300 MHz, CDCl_3) δ 7.32 (t, 1H), 7.11 (s, 1H), 7.07–7.03 (m, 2H), 3.24 (t, 4H), 2.55 (t, 4H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 151.37, 131.42 (q, $^2J_{\text{CF}} = 32$ Hz), 129.51, 124.35 (q, $^1J_{\text{CF}} = 272$ Hz), 118.59, 115.70, 112.04, 54.90, 48.56, 46.07; MS m/z 244 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{F}_3$: C, 59.01; H, 6.19; N, 11.47. Found: C, 58.85; H, 6.25; N, 11.56.

***N*-Benzyl-*N*-[*m*-(trifluoromethyl)phenyl]piperazine (14).** Low-boiling impurities were removed by Kugelrohr distillation. Flash distillation gave the pure product as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 7.37–7.30 (m, 6H), 7.12 (s, 1H), 7.07 (t, 2H), 3.59 (s, 2H), 3.26 (t, 4H), 2.63 (t, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.49, 137.92, 131.43 (q, $^2J_{\text{CF}} = 32$ Hz), 124.37 (q, $^1J_{\text{CF}} = 272$ Hz), 129.51, 129.15, 128.32, 127.21, 118.64, 115.68, 112.10, 62.99, 52.88, 48.69; MS m/z 320 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{F}_3$: C, 67.49; H, 5.98; N, 8.74. Found: C, 67.42; H, 6.04; N, 8.71.

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