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FULL PAPER

Selective Synthesis of Secondary and Tertiary Amines by Reductive *N*-Alkylation of Nitriles and *N*-Alkylation of Amines and Ammonium Formate Catalyzed by Ruthenium Complex

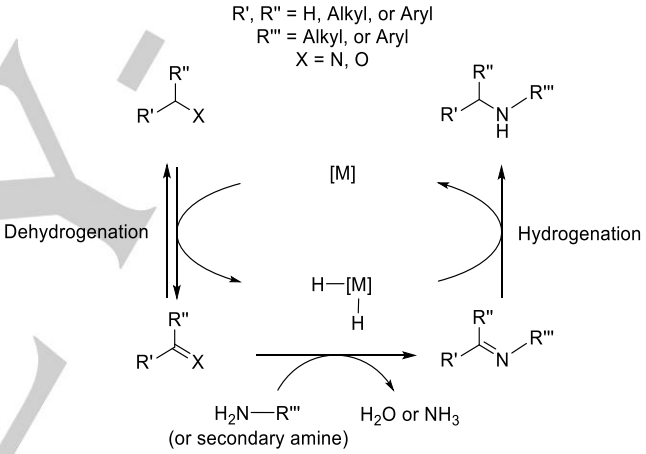
Iryna D. Alshakova[a] and Georgii I. Nikonov*[a]

Dedication to Dr. G. J. Kubas for his outstanding contribution to chemistry

Abstract: A new ruthenium catalytic system for the syntheses of secondary and tertiary amines via reductive *N*-alkylation of nitriles and *N*-alkylation of primary amines is proposed. Isomeric complexes **3** catalyze transfer hydrogenation and *N*-alkylation of nitriles in ethanol to give secondary amines. Unsymmetrical secondary amines can be produced by *N*-alkylation of primary amines with alcohols via the borrowing hydrogen methodology. Aliphatic amines were obtained with excellent yields, while only moderate conversions were observed for anilines. Based on kinetic and mechanistic studies, it is suggested that the rate determining step is the hydrogenation of intermediate imine to amine. Finally, ammonium formate was applied as the amination reagent for alcohols in the presence of ruthenium catalyst **8**. Secondary amines were obtained from primary alcohols within 24 hours at 100°C, and tertiary amines can be produced after prolonged heating. Secondary alcohols can only be converted to secondary amines with moderate yield. Based on mechanistic studies, the process is suggested to proceed through an ammonium alkoxy carbonate intermediate, where carbonate acts as an efficient leaving group.

Introduction

Amines are ubiquitous starting materials for pharmaceutical, agrochemical, fine chemical, and dye industries. There are multiple procedures for the synthesis of secondary and tertiary amines, including the amination of alcohols with pressurized ammonia gas, which is largely employed on industrial scale, reaction of amines with alkyl or aryl halides, reductive amination of carbonyls, etc.[1] The main drawback of these traditional methods is that they produce significant amounts of waste and utilize large quantities of reducing or oxidizing reagents and solvents. An elegant solution to this problem is to use direct *N*-alkylation of amines by alcohols which is very beneficial from the atom-economical point of view, as the only side-products are easily removable light molecules, such as H_2O and/or NH_3 (Scheme 1). These reactions are catalyzed by transition metal catalysts and are an example of the borrowing hydrogen methodology.[2] It is also a much less time-consuming procedure, as it does not require tedious separation or isolation of intermediate products. The key idea behind this strategy is that hydrogen, obtained upon oxidation of a donor molecule, is stored on a catalytic metal species to be later accepted by the intermediate product in the final step.[2b, 3]



Scheme 1. General scheme for the synthesis of amines by means of borrowing hydrogen methodology.

Homogeneous *N*-alkylation of amines with methanol catalyzed by $[RhH(PPh_3)_4]$ was first reported by Grigg *et al.*[4] Secondary and tertiary amines, including saturated *N*-heterocyclic systems, were obtained in the presence of $RuH_2(PPh_3)_3$ by the Murahashi group,[5] while $RuCl_2(PPh_3)_3$ was found to catalyze the reaction between amines and 1,5-diols to produce *N*-substituted piperidines, morpholines, and piperazines.[6] However, these earlier methods were limited by the high load of catalysts, low yields and harsh reaction conditions. An extensive study of transition metal catalysts for this type of transformation was launched nearly a decade ago. A large family of iridium catalysts has been developed for the *N*-alkylation of aromatic and aliphatic amines.[7] Kempe *et al.* reported two iridium complexes, bearing bidentate N,P-ligands for alkylation of anilines with benzyl alcohol or hexanol at 70°C.[8] A half-sandwich iridium complex was studied in the alkylation of primary and secondary amines.[9] In most cases secondary amines were predominantly produced, although double alkylation was observed when simple linear alcohols were used. A cyclometallated iridium complex was

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recently reported as an efficient catalyst (1%, 100 °C) for alkylation of anilines and cyclic amines with benzyl alcohol and, in some cases, methanol.[10]

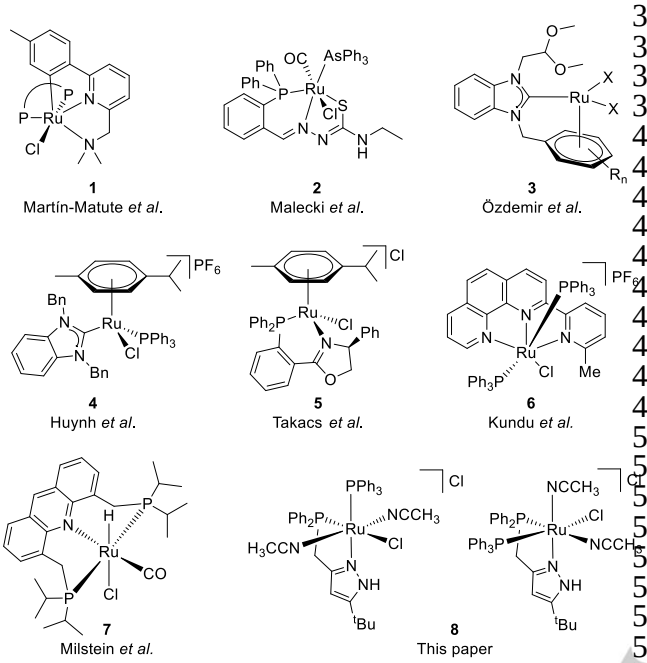

Figure 1. Some ruthenium catalysts for the synthesis of amines by means of borrowing hydrogen methodology.

Ruthenium catalysts for alkylation of amines via borrowing hydrogen strategy have expanded exponentially since Beller *et al.* reported the activity of $Ru_3(CO)_{12}$ in this type of transformation in 2006.[11] The reaction works even for secondary alcohols and proceeds to full conversion in the presence of 2 mol% catalyst at 110°C, although a five-fold excess of alcohol was required. Later, a different catalytic system based on ruthenium complex $[Ru(p\text{-cymene})Cl_2]_2$ and diphosphine ligand (dppf or DPEphos) was disclosed by the Williams group.[12] Martín-Matute *et al.* proposed the ruthenium pincer catalyst **1** for selective alkylation of anilines and 2-aminopyridines (Figure 1).[13] Ruthenium complex **2**, bearing a phosphine-functionalized hydrazone/ thiosemicarbazone ligand, was applied to *N*-alkylation of 2-aminobenzothiazoles, 2-aminopyrimidines, 2-aminopyridines, anilines, and benzenesulfonamides, although only benzyl alcohols were screened as alkylating agents.[14] Özdemir *et al.* prepared and applied NHC-supported ruthenium complexes **3** in the *N*-alkylation of cyclic amines, pyrrolidine and morpholine, with benzyl alcohols.[15] NHC-supported ruthenium catalyst **4** for the activation of primary alcohols in the borrowing hydrogen methodology was developed by the Huynh group, while the oxazoline-supported ruthenium catalyst **5** was demonstrated by Takacs et al. to activate α-methylated secondary alcohols as well.[16] Although iridium and ruthenium catalysts prevail in *N*-alkylation, catalysts based on other transition metals, such as cobalt, manganese, and iron, have recently also been developed.[17]

Alternatively, secondary and tertiary amines can be obtained as a result of transfer hydrogenation of nitriles in alcohols.[18] Deng *et al.* reported a Ru(II)-catalyzed reductive alkylation of aryl nitriles, using both aromatic and aliphatic alcohols at 150 °C.[19] Recently, the Kundu group applied the ruthenium catalyst **6** (3 mol%) for the synthesis of *N*,*N*-dimethylated amines from nitriles using methanol at 140°C in the presence of one equivalent of base.[20]

Amination of alcohols using ammonia gas or ammonium salts is another approach to the synthesis of amines from alcohols. Classic reductive amination of aldehydes is the most common industrial process for the production of lower alkyl amines.[21] The wide application of this method is supported by the high accessibility of carbonyl compounds and ammonia. However, one of the serious issues of this procedure is the possibility of side reactions due to the high concentration of electrophilic aldehydes. Borrowing hydrogen methodology allows one to circumvent this problem by providing conditions when an aldehyde or ketone is produced *in situ* and is immediately involved in the further reaction without significant accumulation in the reaction mixture. Milstein *et al*. were among the first who investigated the production of primary amines from primary alcohols and ammonia, using their pincer ruthenium complex **7**.[22] Although as low as 0.1 mol% catalyst load was applied, the reaction proceeded at 135°C under 7.5 atm of ammonia. Later, Vogt *et al.* applied $Ru_3(CO)_{12}$ (1 mol%) in combination with pyrrole phosphine ligand to alkylation of ammonia with secondary alcohols at 140°C to obtain primary amines with good to excellent yields.[23] Triphos-supported complex $(P)_3Ru(H)(Cl)CO$ catalyzes amination of n-octanol with NH_3 (6 bar) at low catalyst load (0.2 mol%) and 165°C with 95% selectivity towards primary amine.[24] Ruthenium cluster $Ru_3(CO)_{12}$ in combination with CataCXiumPCy was applied for the alkylation of ammonia by the Beller group.[25] However, sufficient pressure of ammonia (18 atm) was required for chemoselective monoalkylation and high temperature (150°C and higher) is necessary for the full conversion of alcohols. As an alternative to the use of ammonia gas for this reaction and the need of a high-pressure equipment, ammonium salts can be applied as the source of nitrogen. Fujita *et al.* used ammonium tetrafluoroborate and ammonium acetate for the chemoselective synthesis of tertiary or secondary amines in the presence of half-sandwich iridium catalyst $[Cp^*IrCl_2]_2$ at 130-140°C.[26] Up to 5 mol% catalyst load was required to achieve good conversions. A water-soluble half-sandwich iridium catalysts was developed for the amination of a series of primary and secondary alcohols with aqueous ammonia at 140-150°C, resulted in formation of tertiary and secondary amines, respectively.[27]

Herein we report the application of isomeric ruthenium complexes **8**[28] (Figure 1) in the chemoselective synthesis of secondary amines by reductive alkylation of nitriles and alkylation of amines with alcohols via borrowing hydrogen methodology. We also report controlled amination of alcohols with ammonium formate to give secondary and tertiary amines and provide insights into the mechanism of these reactions.

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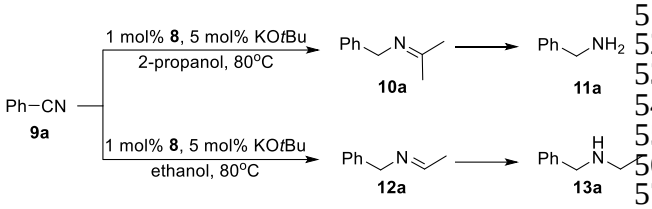
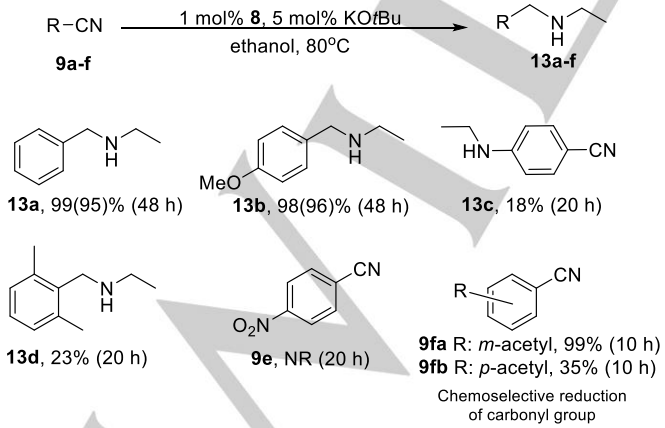
Results and Discussion

Reductive Alkylation of Nitriles. We have previously applied half-sandwich ruthenium complexes to the transfer hydrogenation of nitriles with isopropanol that produces imines as the result of coupling of primary amine products with the acetone co-product.[29] Further reductions of these imines to secondary amines have not been observed, likely because of the steric hindrance near the C=N double bond. Such hydrogenation was, however, observed by Beller *et al.* with $RuCl_2(PPh_3)_3$ which yields secondary amines in the transfer hydrogenation of nitriles.[14] More recently, we have found that transfer hydrogenation of nitriles with 2-propanol catalyzed by the Ru catalyst **8** leads to the formation of ketimine **10a** (Scheme 2),[28] which can be then hydrolyzed to primary amines. However, when ethanol was used as the reaction media, the process resulted in *N*-ethyl benzylamines **13a**.



Scheme 2. Transfer hydrogenation of benzonitrile in 2-propanol and ethanol in the presence of catalyst **8**.

Full conversion to *N*-ethyl benzylamine **13a** was achieved after 48 hours of heating with 1 mol% **8** and 5 mol% KO*t*Bu (Scheme 3). Two equivalents of ethanol are consumed for the reduction of each equivalent of nitrile. Acetaldehyde, the anticipated initial by-product in transfer hydrogenation, was not detected by NMR spectroscopy. Instead, an equivalent of ethyl acetate was formed per each equivalent of the product. Ester is most likely the product of a formal Tishchenko reaction catalyzed by the ruthenium complex. Transition metal-catalyzed Tishchenko reactions, including those mediated by ruthenium, have been previously described.[30] 4-Methoxybenzonitrile **9b** can be reduced and subsequently *N*-alkylated in good yield as well. Unexpectedly, the cyano-group in 4-aminobenzonitrile **9c** was not reduced under these conditions. Instead, the amine function was alkylated to form 4-*N*-ethylaminobezonitrile **13c**, although a small amount of ethyl acetate was also formed. Even though the yield is quite low (18% after 20 hours), the alkylation of amine is certainly preferred over the transfer hydrogenation of nitrile, which is likely inhibited by the strong π-donating effect of the amino group. The production of ethyl acetate in the absence of an obvious reduction process indicates the occurrence of acceptorless dehydrogenation of ethanol.[3] Sterically hindered, ortho-substituted benzonitrile **9d** shows low conversion to the secondary amine **13d**. 4-Nitrobenzonitrile **9e** cannot be reduced under these conditions. Only the carbonyl-group reduction is observed in the case of 3- and 4-cyanobenzophenone **9fa** and **9fb**.



Scheme 3. Transfer hydrogenation of nitriles in ethanol. Reaction conditions: 1 mol% **8**, 5 mol% KO*t*Bu in 2 ml of ethanol at 80°C. Conversions were determined by ^{1}H NMR spectroscopy. Isolated yields are shown in parenthesis.

Alkylation of Amines with Alcohols. The results of transfer hydrogenation of nitrile in ethanol described above, prompted us to study the catalytic efficiency of **8** in *N*-alkylation of amines via the borrowing hydrogen methodology. First, benzylamine was heated in ethanol with 1 mol% **8** and 5 mol% KO*t*Bu at 80°C (Table 1, entry 1). Only 21% conversion was observed in 24 hours. When the temperature was increased to 100°C, 81% of benzylamine could be converted into a secondary amine within 24 hours (Table 1, entry 2), however diethyl benzylamine, the product of double alkylation, started to form at this point and its amount grew under prolonged heating. We were then intrigued to notice that upon reductive alkylation of benzonitrile in ethanol, only a secondary amine was produced and the full conversion was reached in 48 hours (Scheme 3). The only difference between these two reactions is the formation of an equivalent of ethyl acetate, as a product of ethanol oxidation, in the latter case. This factor appears to be crucial to enable the chemoselectivity of alkylation. Indeed, when an equivalent of ester is added to the reaction with amine, 96% conversion to benzylethylamine occurs in 36 hours (Table 1, entry 3).

Table 1. Condition optimization for the synthesis of *N*-ethylbenzylamine by borrowing hydrogen methodology.[a]

Entry	Ethanol, equiv.	Temperature, °C	Yield, %
1	35	80	21
2	35	100	81[b]
3[c]	35	100	96[d]
4[c, e]	0.1	100	-[f]
5[e]	1	100	traces
6[g]	1	100	-[h]
7[g]	3	100	87[i]

[a] Reaction conditions: benzylamine, 1 mol% **8**, 5 mol% KO*t*Bu, in ethanol. Yields of secondary amines after 24 hours were determined by ^{1}H NMR spectroscopy; [b] 4% benzyldiethylamine; [c] an equivalent of ethyl acetate

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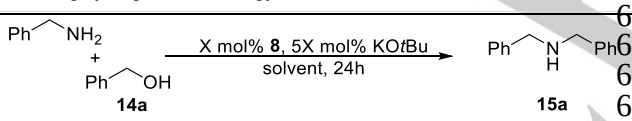
was added; [d] after 36 hours; [e] neat; [f] 20% of *N*-benzylacetamide was observed; [g] in THF; [h] 17% *N*-benzylidene(ethylamine); [i] after 48 hours.

To elucidate the role of ethyl acetate, a set of experiments was performed to investigate whether the ester could be the source of ethyl group in amine alkylation. First of all, benzylamine was heated in THF with 0.1 equivalent of ethanol and an equivalent of ethyl ester in the presence of the catalyst (Table 1, entry 4). After 20 hours 20% of ester reacted with amine to give *N*-benzylacetamide. Subsequent addition of excess ethanol (3 equivalents) drives the reaction to alkylation of the unreacted amine, while *N*-benzylacetamide remains in the solution as it is. Moreover, if benzylamine is alkylated in the presence of ethyl propionate, *N*-ethylated product forms exclusively. Thus, the ester group does not act as the alkyl source. Meanwhile, some amount of ester, although less than an equivalent, is consumed during the reaction because of hydrolysis. The acetic acid produced likely forms benzylethylammonium acetate, which is less prone to further alkylation, resulting in chemoselective synthesis of a secondary amine.

On the other hand, the overalkylation, which is most likely promoted by large excess of an alkylating agent, can be in principle avoided if stoichiometric amounts of alcohol are used. However, when a benzylamine/ethanol mixture (1:1) was heated with the ruthenium catalyst, only traces of *N*-alkylated product were obtained (Table 1, entry 5). When the reaction was performed in THF media, *N*-benzylidene(ethylamine) formed (Table 1, entry 6), which is the product of isomerization of intermediate *N*-ethylidene(benzylamine), driven by the formation of a more favorable π-conjugated system. Increasing the amount of ethanol to 3 equivalents resulted in 63% conversion after 24 hours and 87% after 48 hours (Table 1, entry 7).

Table 2. Condition optimization for the synthesis of dibenzylamine via borrowing hydrogen methodology.



14a **15a**

Entry	Catalyst load	**14 a**, equiv.	Solvent	Temp.	Yield, %[a]
1	1 mol%	20	neat	100ºC	96[b]
2	1 mol%	1	THF	100ºC	-
3	1 mol%	1	toluene	120°C	traces[c]
4	1 mol%	1	methanol	100ºC	-[d]
5	1 mol%	1	*tert*-amyl alcohol	100ºC	-[e]
6	1 mol%	1	*tert*-amyl alcohol	120ºC	49
7	2 mol%	1	*tert*-amyl alcohol	120ºC	52
8	1 mol%	2	*tert*-amyl alcohol	120ºC	98[f]

[a] Yield of secondary amine after 24 hours was determined by ^{1}H NMR spectroscopy; [b] after 48 hours; 4% benzyldiethylamine; [c] 19% *N*-benzylidene(benzyl)amine; [d] 36% benzylmethylamine; [e] 13% *N*-benzylidene(benzyl)amine; [f] isolated yield.

Further, benzyl alcohol as an alkylating agent was studied. Complete alkylation of benzylamine with excess benzyl alcohol was achieved after 48 hours of heating at 100°C (Table 2, entry 1). When stoichiometric amounts of benzylamine and benzyl alcohol in THF solution were heated, no reaction was observed even after prolonged heating (Table 2, entry 2). The reaction in toluene resulted in 19% formation of imine but only in a trace amount of **15a** after heating for 24 hours at 120°C (Table 2, entry 3). Based on the consideration that protic media may be more beneficial for the reaction, it was performed in methanol (Table 2, entry 4). Surprisingly, low conversion to *N*-methylated amine was observed but no dibenzylamine formed. This result was unexpected, as dehydrogenation of methanol was considered to be much more challenging than benzyl alcohol, because dehydrogenation of the latter results in the formation of a π-conjugated system. This observation led to the conclusion that a tertiary alcohol, uncapable of dehydrogenation, had to be used as a solvent. The simplest tertiary alcohols are *tert*-butanol and *tert*-amyl alcohol, so the latter was chosen due to its low melting point, which makes it easier in operating. However, heating benzylamine and benzyl alcohol in *tert*-amyl alcohol at 100°C resulted in the formation of *N*-benzylidene(benzyl)amine (Table 2, entry 5). Reaction can be forced by increasing the temperature to 120°C, when 49% conversion to a secondary amine is observed in 24 hours with no further change (Table 2, entry 6). Assuming that the moderate yield was due to the catalyst decomposition, the reaction was performed with 2 mol% **8** and 10 mol% KO*t*Bu, however again only half of the amine was alkylated (Table 2, entry 7). Finally, it was found that at least a 2-fold excess of the alkylating agent is required to achieve full conversion to the secondary amine within 24 hours in the presence of 1 mol% **8** and 5 mol% KO*t*Bu at 120°C (Table 2, entry 8).

A number of alcohols and amines were involved in the reaction under the optimized conditions (Table 3). Thus, alkylbenzylamines can be obtained with excellent yields regardless of the reagent combination: benzyl alcohol/alkylamine (entries 1 and 2) or aliphatic alcohol/benzylamine (entry 3). Unsymmetrical aliphatic secondary amines can be produced with high efficiency as well (entries 4 and 5). In contrast, a secondary amine, morpholine, was found to be totally inactive under the proposed conditions (Table 3, entry 6).

Table 3. N-Alkylation of amines via borrowing hydrogen methodology.[a]

Entry	Amine	Alcohol	Yield, %
1	Benzylamine	1-Hexanol	99(96)
2	Benzylamine	1-Butanol	99(95)
3	Hexylamine	Benzyl alcohol	98(93)
4	Hexylamine	1-Butanol	98(91)
5	Butylamine	1-Hexanol	99(92)
6	Morpholine	1-Hexanol	-

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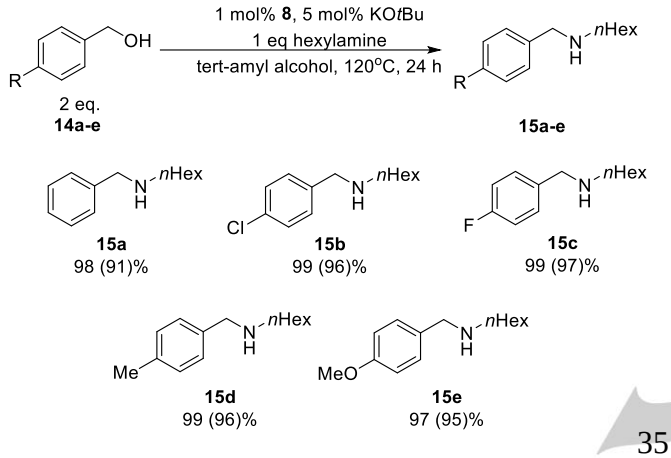
[a] Reaction conditions: 1 mol% **8**, 5 mol% KO*t*Bu, in 1 mL *tert*-amyl alcohol. Conversions after 24 hours were determined by ^{1}H NMR spectroscopy. Isolated yields of corresponding ammonium salts are in parentheses.

Benzyl alcohols with different substituents in the *para*-position were screened then in the alkylation of hexylamine under the optimized conditions (Scheme 4). Thus, the reaction tolerates the ether group and halogens. All screened benzyl alcohols can alkylate hexylamine within 24 hours, however, the reaction rate depends linearly on the electronic properties of the alkylating reagent.



Scheme 4. N-Alkylation of hexylamine with different benzyl alcohols. Reaction conditions: 1 mol% **8**, 5 mol% KO*t*Bu, 1 eq. hexylamine and 2 eq. alcohol in 1 ml *tert*-amyl alcohol. Conversions after 24 hours were determined by ^{1}H NMR spectroscopy. Isolated yields of corresponding ammonium salts are in parentheses.

The Hammett plot, i.e. the dependence of the reaction rate on the substituent constant σ_p, was built for the reaction of hexylamine with different benzyl alcohols (Figure 2). The slope of the plot is positive and larger than one, suggesting that the reaction is slowed in the case of alcohols with electron-donating group and faster in the case of alcohols with electron-withdrawing groups. This implies the building up of a negative charge on the reaction center in the rate determining step, which is likely the transfer of a hydride to imine.[31]

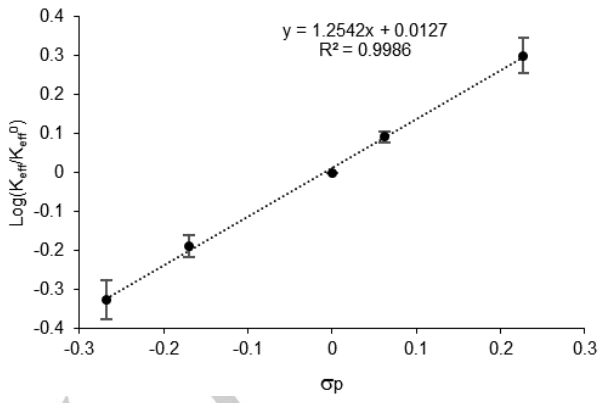
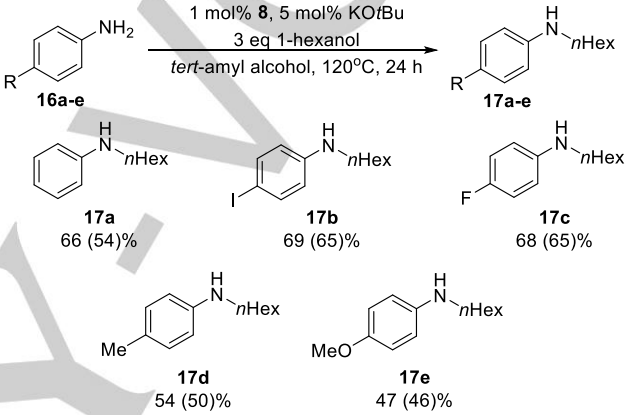


Figure 2. The Hammett plot for the *N*-alkylation of hexylamine with benzyl alcohols, containing different substituents in the *para*-position of the benzene ring relative to the reaction with unsubstituted benzyl alcohol.

Further, anilines containing different substituents in the *para*-position were involved in the reaction with 1-hexanol in the presence of catalyst **8**. Anilines can be alkylated under the proposed conditions with moderate yields, if 3 equivalents of alcohol are used (Scheme 5). However, slightly higher yields for substrates with electron-withdrawing groups (**16b** and **16c**) and slightly lower yields for substrates with electro-donating groups (**16d** and **16e**) can be observed.



Scheme 5. *N*-Alkylation of different anilines with 1-hexanol. Reaction conditions: 1 mol% **8**, 5 mol% KO*t*Bu, 1 eq. aniline and 3 eq. 1-hexanol in 1 ml *tert*-amyl alcohol. Conversions after 24 hours were determined by ^{1}H NMR spectroscopy. Isolated yields of corresponding ammonium salts are in parentheses.

The Hammett plot was also built for the *N*-alkylation of anilines with different *para*-substituents (Figure 3). Although the slope of the plot is considerably less than one, and thus the process is not much sensitive to the electronic properties of the substrates, a tendency of rate acceleration for the substrates bearing electron-withdrawing substituents can be observed, while the presence of electron-donating groups results in rate suppression. Again, this is consistent with the building up of a negative charge on the imine center upon hydride transfer in the rate determining step, which is stabilized by the presence of electron-withdrawing groups. However, the remoteness of substituents in anilines results in a weaker impact on the reaction rate, as compared to the case of benzyl alcohols.

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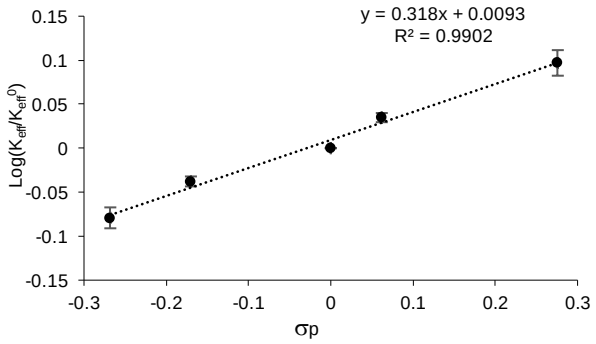


Figure 3. The Hammett plot for the *N*-alkylation by 1-hexanol of anilines with different substituents in the *para*-position of the benzene ring relative to the reaction with unsubstituted aniline.

Further, the kinetic profile of the *N*-alkylation of hexylamine with benzyl alcohol was analyzed (Figure 4). A small amount of imine intermediate (~10%) accumulated in the system quite fast, and then slowly decreased over the time of the reaction. One can also observe an induction period in the formation of *N*-hexylbenzylamine, as the maximum reaction rate is reached only after a sufficient amount of imine is produced. This pattern is reproduced for every substrate, and no signals of an aldehyde or any other intermediate could be determined. Altogether, these data indicate that the rate determining step is the conversion of an imine to amine.

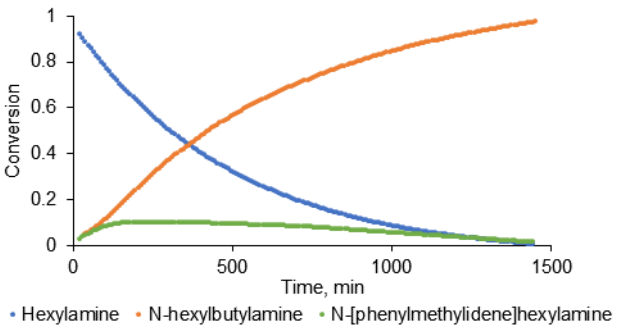
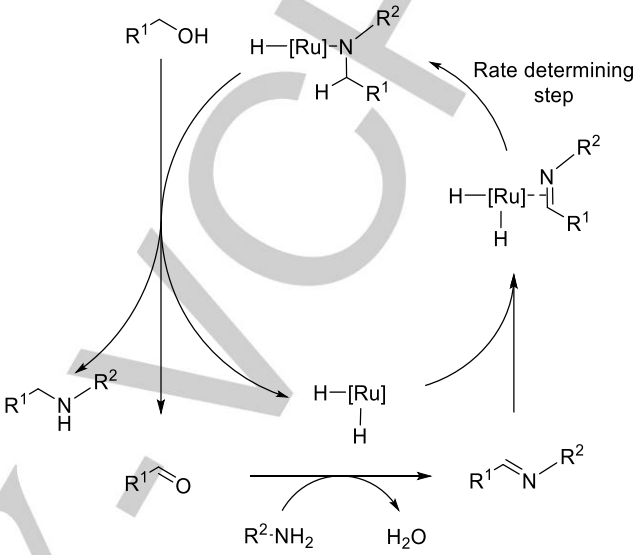


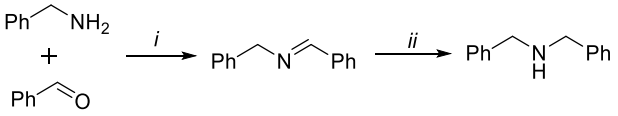
Figure 4. The kinetic profile of the N-alkylation of hexylamine with benzyl alcohol in the presence of 1 mol% **8**.

The generally proposed mechanism for *N*-alkylation via borrowing hydrogen strategy involves three main steps: (1) dehydrogenation of alcohol to form an aldehyde or ketone; (2) coupling reaction of the carbonyl compound and an amine; (3) hydrogenation of the produced imine (Scheme 6).[3] Primary alcohols undergo acceptorless dehydrogenation much less readily than secondary due to their higher oxidation potential, and often disproportionate to give esters under basic conditions. However, a primary amine can intercept the aldehyde almost instantly with the formation of an imine, thus driving the reaction of dehydrogenation. Considering that an imine intermediate can be observed during the reaction and taking into account the influence of substituents in the *para*-position of benzyl alcohol on the reaction rate, we suggest that the rate determining step in the process is the reduction of imine.



Scheme 6. Proposed mechanism of amine alkylation in the presence of **8**.

To confirm the proposed mechanism, benzylamine was treated with benzaldehyde first in the absence of a ruthenium catalyst, albeit with addition of a base (Scheme 7). Full conversion to *N*-(benzylidene)benzylamine was reached after 1 hour of heating at 80°C. Subsequent addition of 1 mol% **8** yielded 92% conversion to dibenzylamine in 24 hours when 2-propanol was used as the hydrogen source.



Scheme 7. One-pot synthesis of dibenzylamine by the coupling of benzylamine and benzaldehyde and subsequent hydrogenation of *N*-(benzylidene)benzylamine. Reaction conditions: *i*) 5 mol% KO*t*Bu, 80°C, 1 h, 2-propanol; *ii*) 1 mol% **8**, 5 mol% KO*t*Bu, 120°C, 24 h, 2-propanol.

Moreover, when *N*-(benzylidene)benzylamine obtained by the coupling of benzylamine and benzaldehyde in benzyl alcohol was heated in the presence 1 mol% **8** and 5 mol% base at 100°C for 24 h, a slow reduction of imine occurred within 24 hours (73% conversion). The reaction was slower than alkylation of benzylamine under the analogous conditions (Table 2, entry 1). Benzaldehyde as well as benzyl benzoate were detected in the reaction mixture by NMR spectroscopy as byproducts of benzyl alcohol dehydrogenation.

Amination of alcohols with ammonium formate. Alcohols are readily available substrates for the synthesis of amines using simple ammonia sources, such as ammonia gas or aqueous ammonia.[22-23, 25, 27a] In our further study we wanted to optimize the reaction conditions, so that it would not require pressurized ammonia gas, and thus could be performed, using a general laboratory equipment. The most tempting solution is to use aqueous ammonia. However, complexes **8** have very low solubility in water and would require degassed solutions, as an active species formed *in situ* is very sensitive to oxygen. Thus, the reaction was performed with a 0.5 M solution of ammonia in dioxane, where ethanol was in 10-fold excess with respect to the ammonia content. After 24 hours of heating at 100°C, 25% conversion to diethylamine was observed (Table 4, entry 1).

Table 4. Alcohol amination via borrowing hydrogen methodology.[a]

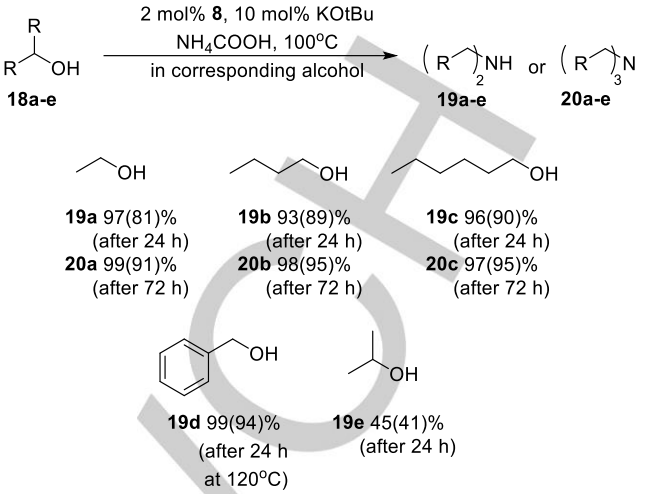
Entry	Aminating agent	Alcohol	Yield, %
1	NH_3 (0.5 M in dioxane)	Ethanol	25
2	NH_3 (0.5 M in dioxane)	1-Hexanol	-
3	NH_3 (0.5 M in dioxane)	Benzyl alcohol	-
4	NH_4COOH	Ethanol	97 (81)
5	NH_4COOCH_3	Ethanol	-

[a] Reaction conditions: 1.58 mmol ammonia equivalent, 2 mol% **8**, 5 mol% KO*t*Bu, in 1 mL of corresponding alcohol. Conversions after 24 hours were determined by ^{1}H NMR spectroscopy. Isolated yields of corresponding dialkylammonium salts are in parentheses.

However, neither 1-hexanol nor benzyl alcohol gave any products of amination (Table 4, entry 2 and 3). Then ammonium formate was tested as the nitrogen source for this type of transformation. High yield of diethylamine along with traces of triethylamine were observed for ethanol after heating at 100°C for 24 hours (Table 4, entry 4). The tertiary amine, however, can be produced after more prolonged heating. When ammonium acetate was used as the nitrogen source, the only product was ethyl acetate, without any amination product (Table 4, entry 5).

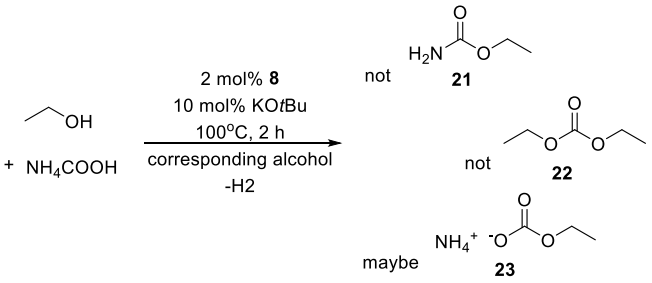
Next, a number of primary alcohols were screened under the optimized conditions (Scheme 8). 1-Butanol (**18b**) and 1-hexanol (**18c**) were converted to the corresponding secondary amines after 24 hours at 100°C. Tertiary amines were obtained when the reaction was heated for 72 hours. Benzyl alcohol (**18d**) also gave a secondary amine, albeit 120°C was required to obtain high conversion in 24 hours. Tribenzylamine cannot be produced under these conditions even after prolonged heating. 2-Propanol (**18e**) was converted to a secondary amine with a significantly lower yield (45%) under the same catalytic conditions.

The mechanism of alcohol amination under the proposed catalytic conditions turned out to be not so straightforward as expected. Initially, ammonia was suggested to be released to the reaction by decomposition of ammonium formate, and it was supposed to be alkylated according to the general hydrogen borrowing mechanism, i.e. by dehydrogenation of alcohol to aldehyde



Scheme 8. Amination of alcohols with ammonium formate. Reaction conditions: 100 mg NH_4COOH, 2 mol% **8**, 10 mol% KO*t*Bu in 1 mL of corresponding alcohol at 100°C. Conversions, in respect to ammonium formate, were determined by ^{1}H NMR spectroscopy. Isolated yields are shown in parentheses.

followed by condensation with ammonia and reduction. However, monitoring the reaction by ^{1}H NMR spectroscopy revealed fast consumption (within 2 hours) of formate and simultaneous formation of free hydrogen gas and an intermediate with an alkoxide signal shifted downfield in respect to alcohol signal (Figure S4). Further heating led to the conversion of the intermediate into a secondary amine. Comparison to authentic spectra revealed that the intermediate was neither the alkyl carbamate **21** nor the dialkyl carbonate **22** (Scheme 9). Meanwhile, the proton and carbon signals of the alkoxide group (^{1}H NMR δ = 3.83 ppm and ^{13}C NMR δ = 60.8 ppm) were very close to the latter compound. Based on these data, we suggest that the intermediate is likely the ammonium alkyl carbonate **23**. Although the intermediate product can be isolated by filtration, it shows poor solubility in THF, benzene, DCM, and chloroform.



Scheme 9. Formation of an intermediate product under the conditions of alcohol amination.

Moreover, the alkoxy group undergoes fast exchange even at room temperature when the volatiles are removed under reduced pressure and a different alcohol is added. A control experiment with sodium formate resulted in a compound giving rise to the

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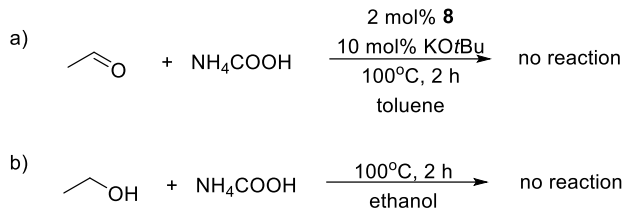
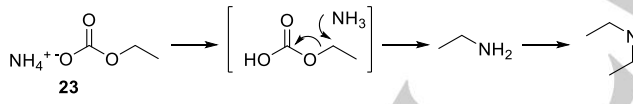
same pattern in the ^{1}H and ^{13}C NMR spectra as for the intermediate discussed above. We then investigated the origin of hydrogen gas. In principle, it may be formed during alcohol dehydrogenation. However, this is likely not the case because the product of alcohol dehydrogenation, acetaldehyde, does not react with ammonium formate (Scheme 10a). Furthermore, there was no reaction between alcohol and ammonium formate in the absence of catalyst **8** (Scheme 10b). Based on these observations, we conclude that the hydrogen gas is likely produced by a Ru-mediated dehydrogenative coupling between the formate and alcohol.



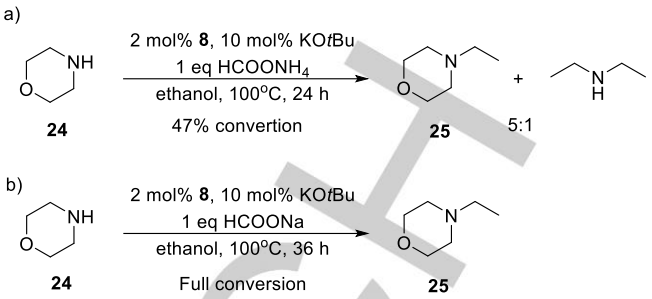
Scheme 10. a) No reaction occurs between aldehyde and ammonium formate under the proposed catalytic conditions; b) No reaction between alcohol and ammonium formate is observed in the absence of catalyst **8**.

Although the intermediate product is consumed during the reaction and no other by-products are seen by NMR, there is no evidence that amination occurs directly with free alcohol. Alternatively, the reaction may proceed via protonation of the alkoxy carbonate by ammonium, followed by nucleophilic substitution at the alkoxy group, with the bicarbonate acting as an efficient leaving group (Scheme 11). Secondary amination takes place when the intermediate **23** reacts with the ethylamine product.



Scheme 11. Alternative route of alcohol amination under the proposed catalytic conditions.

Considering the formation of tertiary amines under the conditions described above, alkylation of morpholine in ethanol with the addition of an equivalent of ammonium formate was studied (Scheme 12a). In contrast to the result of Table 3 (entry 6), 47% of morpholine was alkylated in 24 hours at 100°C, accompanied by the formation of diethylamine (the *N*-ethylmorpholine to diethylamine ratio is 5:1). However, the alkylated morpholine was formed exclusively when ammonium formate was replaced with sodium formate, which can form a similar intermediate (Scheme 12b). Full alkylation occurred within 36 hours at 100°C.



Scheme 12. Alkylation of morpholine in the presence of an equivalent of a) ammonium formate and b) sodium formate.

Conclusions

A new ruthenium catalytic system for the synthesis of secondary and tertiary amines via different strategies was developed. It was found that nitriles undergo reductive *N*-alkylation to secondary amines in primary alcohols by means of borrowing hydrogen process. This transformation is possible due to the lower steric hindrance caused by primary alcohol near the C=N double bond of an intermediate imine, as compared to secondary alcohols, such as 2-propanol, which can only affect the reduction of nitriles but not alkylation. Unsymmetrical secondary amines can be also produced by *N*-alkylation of primary amines with alcohols. Aliphatic amines were obtained with excellent yields, whereas only moderate conversions were observed for anilines. Based on kinetic and mechanistic studies, the rate determining step was suggested to be the transfer hydrogenation of imines. Different sources of nitrogen were also explored for amination of alcohols. Ammonium formate was found to be a good amination reagent for alcohols in the presence of 2 mol% **8** and 10 mol% KO*t*Bu. Secondary amines were obtained from primary alcohols within 24 hours at 100°C, and tertiary amines can be produced after prolonged heating. Secondary alcohols can only be converted to secondary amines with moderate yields. Mechanistic studies revealed fast formation of hydrogen gas and an alkoxy intermediate, which was suggested to be a transient ammonium alkyl carbonate formed by dehydrogenative coupling of formate with alcohol. It was suggested that the success of amination with formate was due to the carbonate group acting as an efficient leaving group. Finally, formate salts can be used to promote alkylation of a secondary amine, morpholine.

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Keywords: ruthenium • borrowing hydrogen strategy • amines • catalysis • ammonium formate

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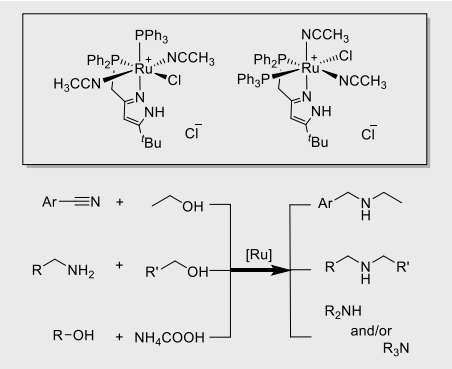
Entry for the Table of Contents

FULL PAPER

A new ruthenium catalytic system for the syntheses of secondary amines via reductive alkylation of nitriles in ethanol, *N*-alkylation of amines with alcohols and amination of alcohols with ammonium formate is reported.



*Iryna D. Alshakova and Georgii I. Nikonov**

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Selective Synthesis of Secondary and Tertiary Amines by Reductive *N*-Alkylation of Nitriles and *N*-Alkylation of Amines and Ammonium Formate Catalyzed by Ruthenium Complex.

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