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Salt-Free Synthesis of Tertiary Amines by Ruthenium-Catalyzed Amination of Alcohols

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The amination of secondary alcohols to give tertiary amines in the presence of different in situ generated ruthenium catalysts has been investigated in detail. By applying a combination of $[Ru_3(CO)_{12}]$ and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole as the catalyst, cyclic amines can be alkylated with different alcohols in high yield, whereas aliphatic amines gave transalkylation side products.

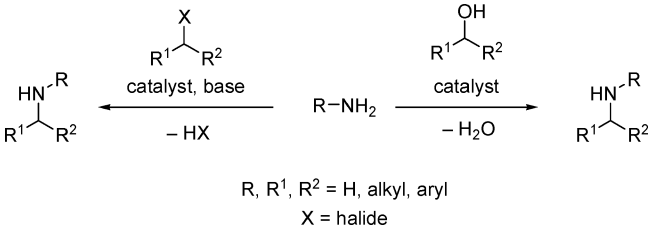
Introduction

A variety of amines is of significant importance for the bulk- and fine-chemical industry as building blocks for polymers and dyes, but also for the synthesis of pharmaceuticals and agrochemicals.[1] In addition, a plethora of naturally bioactive compounds such as alkaloids, amino acids, and nucleotides contain amino groups. Despite numerous known procedures, the development of improved methods for the synthesis of amines continues to be a challenging and actual area of research.[2] In the last decade especially catalytic aminations, such as palladium-, copper-, and nickel-catalyzed aminations of aryl halides,[3] hydroaminations,[4,5] as well as hydroaminomethylations[6] of olefins or alkynes have received significant attention. Compared to the well-known classic *N*-alkylations of amines by using alkyl halides as starting materials[7] and reductive aminations with carbonyl compounds,[8] an atom economical[9] and environmentally attractive method is the amination of primary and secondary alcohols (Scheme 1).

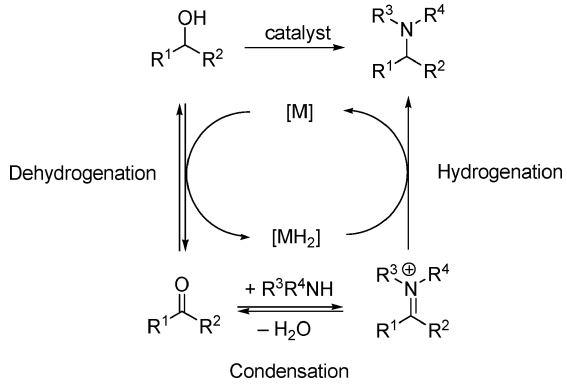
Although formally a nucleophilic substitution takes place, this reaction is based on the in situ dehydrogenation of the alcohol to give the corresponding aldehyde or ketone. Then, the carbonyl intermediate reacts with an amine to give the corresponding imine or iminium species. Depending on the substituents, an enamine intermediate might also be involved, for example, $R^1 = RCH_2$ (R = H, alkyl, aryl). Finally, reduction with the initially produced hydrogen produces the *N*-alkylated amine (Scheme 2).

As no additional hydrogen is needed, this reaction sequence has been coined by Williams and coworkers as the "borrowing hydrogen" mechanism.[10] Notably, the same type of dehydrogenation–functionalization–hydrogenation sequence has recently been used in alkane metathesis,[11] β-alkylation of alcohols,[12] and C–C bond-formation processes such as the Wittig or Knoevenagel reactions.[13–15]

Advantages of the catalytic amination of alcohols are the availability of substrates and the high atom efficiency of the reaction sequence, which forms water as the only sideprod-



Scheme 1. Catalytic *N*-alkylation of amines with alcohols or alkyl halides.



Scheme 2. Catalytic hydrogen transfer in the *N*-alkylation of secondary amines with secondary alcohols.

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uct. Moreover, compared to typical reductive aminations, it is possible to run these reactions in the absence of additional hydrogen. Hence, the reaction can be performed at ambient pressure in typical glassware.

The first homogeneous catalysts for *N*-alkylation of amines with alcohols were introduced by Grigg et al.[16] and Watanabe et al.[17] in 1981. Thereafter, ruthenium,[18,19] rhodium,[19] platinum,[20] and iridium complexes[19,21] have been described as homogeneous transition-metal catalysts for such reactions. Recently, we developed a general protocol for the synthesis of secondary aliphatic amines starting from primary amines and secondary alcohols in the presence of ruthenium carbonyl {$[Ru_3(CO)_{12}]$} and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole (cataCXium® PCy) (**I**) as catalyst system.[22] Moreover, we discovered a related synthesis of secondary aromatic amines starting from aliphatic amines and anilines by using the so-called Shvo catalyst.[23]

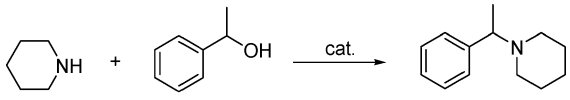
On the basis of this work, we became interested in the synthesis of tertiary amines by *N*-alkylation of secondary amines. Clearly, a variety of tertiary amines are of pharmaceutical interest,[24] especially piperazine derivatives.[25] However, so far only few examples are known for catalytic *N*-alkylations of secondary amines.[16,18g,19] For example, Williams et al. reported recently the Ru-catalyzed synthesis of tertiary amines from primary alcohols and secondary amines.[18a] Earlier, Fujita et al.[21c] reported the *N*-alkylation of secondary amines, for example, *N*-methylaniline, *N*-(1-phenethyl)aniline, and pyrrolidine, with cyclohexanol as the secondary alcohol in the presence of $[Cp^*IrCl_2]_2$. However, to the best of our knowledge, there is no general ruthenium-catalyzed synthesis of tertiary amines from secondary alcohols known.

Results and Discussion

Recently, we reported the advantageous use of ruthenium carbonyl $[Ru_3(CO)_{12}]$ and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole[22] for the synthesis of secondary amines. Hence, we started our investigations with this in situ generated catalyst system. Initially, the reaction of 1-phenylethanol with piperidine was investigated as a model system. Preliminary results are shown in Table 1. By using an excess amount of alcohol, only moderate yields and no complete conversions were observed (Table 1, Entries 1–4).

Increasing the reaction temperature to 140 °C led to an improved product yield of 71% (Table 1, Entries 2–4). Surprisingly, in the presence of *tert*-amyl alcohol (2-methylbutan-2-ol) as solvent, full conversion and excellent yield (98%) of the desired product were obtained (Table 1, Entry 6). Notably, under the same conditions without ligand only 41% yield was observed (Table 1, Entry 5). Upon further optimization (Table 1, Entries 7–20), the ratio of amine to alcohol could be reduced without decreasing the yield (Table 1, Entry 11).

Table 1. Catalytic *N*-alkylation of piperidine with 1-phenylethanol.[a]



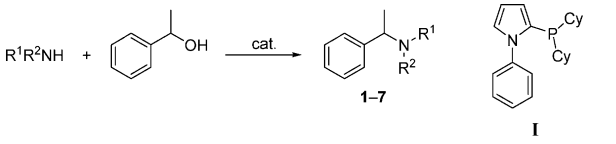
1

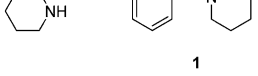
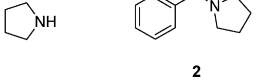
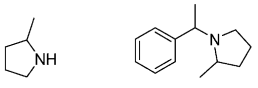
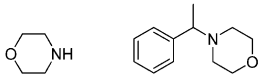
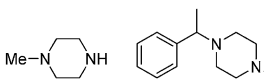
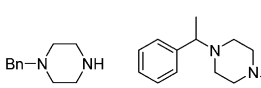
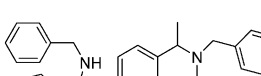
Entry	Ligand	Solvent (mL)	*T* [°C]	Amine/Alcohol	Conv.[b] [%]	Yield[b] [%]
1	–	–	130	1:5	72	32
2	cataCXium® PCy[c]	–	130	1:5	80	50
3	cataCXium® PCy[c]	–	140	1:5	87	71
4	cataCXium® PCy[c]	–	150	1:5	84	70
5	–	*tert*-amyl alcohol (0.5)	140	1:3	51	41
6	cataCXium® PCy[c]	*tert*-amyl alcohol (0.5)	140	1:3	100	98
7	cataCXium® PCy[c]	*tert*-amyl alcohol (0.5)	140	1:2	100	88
8	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:2	100	94
9	cataCXium® PCy[c]	*tert*-amyl alcohol (0.5)	140	1:1.1	87	78
10	cataCXium® PCy[c]	*tert*-amyl alcohol (0.2)	140	1:1.1	94	88
11	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:1.5	100	97 (92)
12	cataCXium® PCy[c]	*tert*-amyl alcohol (0.4)	140	1:1.5	100	93
13	cataCXium® PCy[c]	*tert*-amyl alcohol (0.2)	140	1:1.5	100	84
14	cataCXium® PCy[c]	toluene (0.3)	140	1:1.5	99	86
15	cataCXium® PCy[c]	dioxane (0.3)	140	1:1.5	97	84
16[d]	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:1.5	83	64
17[e]	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:1.5	88	77
18	2-(dicyclohexylphosphanyl)biphenyl	*tert*-amyl alcohol (0.3)	140	1:1.5	80	68
19	(*o*-tolyl)$_3$P[f]	*tert*-amyl alcohol (0.3)	140	1:1.5	69	49
20	cataCXium® A[g]	*tert*-amyl alcohol (0.3)	140	1:1.5	78	74

[a] Reaction conditions: pyridine (1.0 mmol), 1-phenylethanol (1.1–5.0 mmol), $[Ru_3(CO)_{12}]$ (2.0 mol-%), ligand (6.0 mol-%), without or with solvent (0.20–0.50 mL), 130–150 °C, 8–24 h. [b] Conversions and yields were determined by GC analysis with hexadecane as internal standard, isolated yields are given in parenthesis. [c] CataCXium® PCy = *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole. [d] Catalyst (1.0 mol-%). [e] Reaction time: 8 h. [f] Tri-*o*-tolylphosphane. [g] CataCXium® A = *n*-butyldi-1-adamantylphosphane.[26]

Next, the amination of 1-phenylethanol with different secondary amines was explored. Unfortunately, it turned out that all of the substrates performed in their own way. Hence, each reaction needed its own set of optimized conditions, which are shown in Table 2. Pyrrolidine gave the best results (88% yield) without any stabilizing phosphane ligand present (Table 2, Entry 2).

Table 2. Catalytic *N*-alkylation of different secondary amines with 1-phenylethanol in the presence of $[Ru_3(CO)_{12}]$ and cataCXium® PCy (**I**).[a]

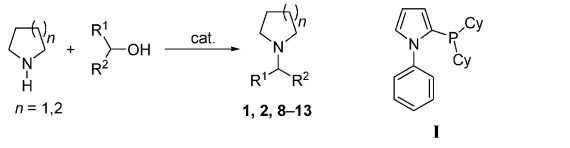


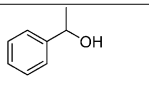
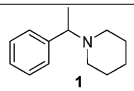
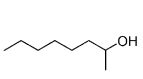
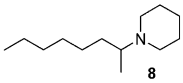
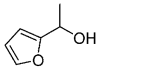
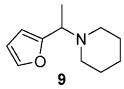
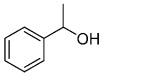
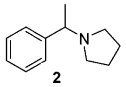
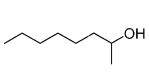
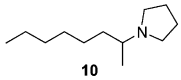
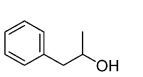
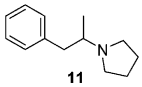
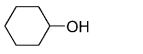
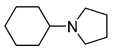
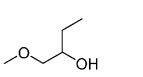
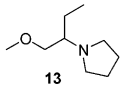
Entry	Amine	Product	Solvent (mL)	Amine/ Alcohol	Yield[b] [%]
1		**1**	*tert*-amyl alcohol (0.3)	1:1.5	97 (92)
2[c,d]		**2**	*tert*-amyl alcohol (0.2)	1:1.5	88 (83)
3[e]		**3**	*tert*-amyl alcohol (0.25)	1:1.5	81 (69)
4[f]		**4**	*tert*-amyl alcohol (0.5)	1:3	47 (37)
5[g]					34
6[c]		**5**	–	1:5	90 (69)
7[c]		**6**	–	1:5	97 (79)
8[c,h]		**7**	–	1:5	<5

[a] Reaction conditions: amine (1.0 mmol), 1-phenylethanol (1.5–5.0 mmol), $[Ru_3(CO)_{12}]$ (2.0 mol-%), cataCXium® PCy (6.0 mol-%), without or with *tert*-amyl alcohol (0.20–0.50 mL), 140 °C, 24 h. [b] Yields were determined by GC analysis with hexadecane as internal standard; isolated yields are given in parenthesis. [c] Reaction without ligand. [d] 120 °C. [e] 130 °C. [f] 62% conversion. [g] Without ligand, 49% conversion. [h] 90% conversion; main reaction is the transalkylation to tribenzylamine and benzyl(1-phenylethyl)-amine. In the presence of ligand, the conversion was <10%.

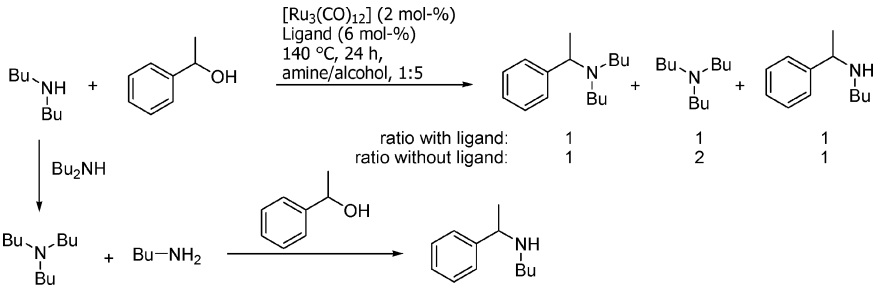
N-Methylpiperazine and *N*-benzylpiperazine led to the corresponding tertiary amines in high yield (90–97%) without any solvent (Table 2, Entries 6 and 7). By using morpholine only moderate conversion and yield (47%) were obtained (Table 2, Entries 4 and 5). In addition to *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole, 11 different ligands were tested for this reaction. However, no improved yield was obtained [e.g., tri-*o*-tolylphosphane: 42% conv., 28% yield; tricyclohexylphosphane: 19% conv., 18% yield; *n*-butyldi-1-adamantylphosphane: 55% conv., 42% yield; 2-(dicyclohexylphosphanyl)biphenyl: 48% conv., 34% yield; and *N*-(2-trimethylsilylphenyl)-2-(dicyclohexylphosphanyl)pyrrole: 52% conv., 45% yield]. Because 2-methylpyrrolidine was used as a racemic mixture, the corresponding tertiary amine was obtained as a mixture of diastereomers in a ratio of 1:1

Table 3. Catalytic *N*-alkylation of piperidine and pyrrolidine with different alcohols in presence of $[Ru_3(CO)_{12}]$ and cataCXium® PCy (**I**).[a]



Entry	Alcohol	Product	Solvent (mL)	Amine/ Alcohol	Yield[b] [%]
1		 **1**	*tert*-amyl alcohol (0.3)	1:1.5	97 (92)
2		 **8**	*tert*-amyl alcohol (0.25)	1:1.5	91 (79)
3[c]		 **9**	–	1:5	75 (52)
4[d]		 **2**	*tert*-amyl alcohol (0.2)	1:1.5	88 (83)
5		 **10**	*tert*-amyl alcohol (0.4)	1:3	89 (54)
6		 **11**	*tert*-amyl alcohol (0.4)	1:3	85 (72)
7		 **12**	*tert*-amyl alcohol (0.3)	1:1.5	92 (76)
8[e]		 **13**	–	1:5	85 (63)

[a] Reaction conditions: amine (1.0 mmol), alcohol (1.5–5.0 mmol), $[Ru_3(CO)_{12}]$ (2.0 mol-%), cataCXium® PCy (6.0 mol-%), without or with *tert*-amyl alcohol (0.20–0.40 mL), 140 °C with piperidine and 120 °C with pyrrolidine, 24 h. [b] Yields were determined by GC analysis with hexadecane as internal standard, isolated yields are given in parenthesis. [c] 91% conversion. [d] Reaction without ligand. [e] 130 °C.



Scheme 3. *N*-Alkylation of di-*n*-butylamine with 1-phenylethanol and transalkylation of di-*n*-butylamine.

(Table 2, Entry 3). However, by column chromatography the two diastereomers could be separated.

Apart from cyclic amines, we also tested acyclic substrates such as di-*n*-butylamine, *N*-methyl-*N*-octylamine, *N*-cyclohexyl-*N*-methylamine, and dibenzylamine (Table 2, Entry 8). Here, in general transalkylation of the different alkyl groups to the aliphatic amine was observed as a side reaction.[23,27] For example, in the case of the reaction of di-*n*-butylamine with 1-phenylethanol, three *n*-butyl-substituted products were observed. Unexpectedly, dehydrogenation of the aliphatic amine occurred to a considerable amount and led to tri-*n*-butylamine and *n*-butylamine. The latter product also reacts with 1-phenylethanol. Noteworthy, the product ratio can be influenced by the reaction conditions (Scheme 3). By applying mixed acyclic amines, a variety of alkylated products was observed by GC as a result of the various transalkylation reactions.

Finally, piperidine and pyrrolidine were treated with arylalkyl alcohols as well as with linear and cyclic aliphatic alcohols to give the corresponding tertiary amines in high yields (85–97%; Table 3). To our delight also some functionalized and heterocyclic derivatives such as 1-methoxy-2-butanol and 1-(2-furyl)ethanol provided the desired products in 85 and 75% yield, respectively (Table 3, Entries 3 and 8). With respect to the mechanism, it is interesting to note that only small amounts (<5%) of the respective ketones were found in the reaction mixtures.

Conclusions

In summary, we present a salt-free amination of secondary alcohols to give various tertiary amines. In the presence of an in situ generated ruthenium catalyst selective amination takes place in high yield and selectivity with secondary cyclic amines such as piperidine, pyrrolidine, and piperazine. The reaction is atom efficient leaving only water as a side product and can be conveniently carried out without additional pressure. In the case of secondary alkylamines, transalkylations occur as side reactions.

Experimental Section

General Procedure for *N*-Alkylation Reaction with Solvent: In a pressure tube (ACE) under an argon atmosphere $[Ru_3(CO)_{12}]$ (0.02 mmol) and ligand (0.06 mmol) were dissolved in *tert*-amyl alcohol (0.2–0.5 mL). Then, the corresponding alcohol (1.5 or 3 mmol) and secondary amine (1 mmol) were added. The pressure tube was fitted with a Teflon cap and stirred at 120–140 °C for 24 h. The solvent was removed in vacuo, and the crude product was purified by column chromatography.

General Procedure for *N*-Alkylation Reaction without Solvent: In a pressure tube (ACE) under an argon atmosphere $[Ru_3(CO)_{12}]$ (0.2 mmol) and ligand (0.6 mmol) were dissolved in the corresponding alcohol (50 mmol) and secondary amine (10 mmol). The pressure tube was fitted with a Teflon cap and stirred at 130–140 °C for 24 h. The excess alcohol was distilled, and the crude product was purified by column chromatography.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for compounds **1**–**6** and **8**–**13**.

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