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A novel ruthenium-catalyzed amination of primary and secondary alcohols

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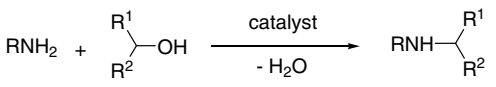
Abstract—An improved method for the N-alkylation of primary amines with primary and secondary alcohols has been developed. Novel, effective catalyst systems, for example, $Ru_3(CO)_{12}$ combined with tri-*o*-tolylphosphine or *n*-butyl-di-1-adamantylphosphine, allow for aminations in a good yield under comparatively mild conditions.

The catalytic formation of carbon–nitrogen bonds is of a broad interest to synthetic organic chemists since a large number of nitrogen-containing molecules are of importance for both the bulk and fine chemical industries, for example, for the production of solvents and emulsifiers. In addition, a variety of naturally occurring bio-active compounds such as alkaloids, amino acids and nucleotides contain amino groups, which are particularly useful for the development of new pharmaceuticals and agrochemicals.[1] Thus, the development of improved methods for the synthesis of amines continues to be a challenging and active area of research.[2]

Among the various catalytic amination methods, palladium-catalyzed amination of aryl halides,[3] hydroamination,[4] and hydroaminomethylation[5] of olefins or alkynes has received special attention in the last decade. Less interest has been paid to the further development of catalytic alkylations of amines.[6] Compared to the frequently applied N-alkylations with alkyl halides and reductive aminations, an economically and environmentally attractive method is the N-alkylation of amines using primary and secondary alcohols (Scheme 1).



R, R^1, R^2 = H, alkyl, aryl

Scheme 1. Catalytic N-alkylation of amines with alcohols.

This consecutive domino reaction consists of an initial dehydrogenation of the alcohol, subsequent imine formation followed by reduction with the initially produced hydrogen. The advantages of this method are the ubiquitous availability of alcohols and high atom efficiency, for example, no salt formation, water as the only by-product. Moreover, compared to reductive aminations, it is possible to run these reactions in the absence of hydrogen pressure.

The general principle of alkylation of amines with alcohols is well known.[7] The methylation of lower aliphatic amines with methanol is even performed on an industrial scale.[8] Until now mainly heterogeneous catalysts are used for N-alkylation at a high temperature and pressure. For example, alkylations of aryl amines are catalyzed by Raney-Ni,[9] alumina,[10] silica and montmorillonite at temperatures >200 °C.[11]

The first homogeneous catalysts were introduced by Grigg et al.[12] and Watanabe et al.[13] in 1981. Thereafter, ruthenium,[14] rhodium,[15] platinum,[16] and iridium complexes[15,17] have been introduced as molecular-defined transition metal catalysts for such reactions. Similar to heterogeneous systems the drawbacks of the known homogeneous catalysts are the high reaction temperatures (up to 215 °C) and long reaction times, which are required to obtain sufficient yields. In addition, the scope of these reactions is limited. With regard to the alcohol, mainly primary alcohols have been used as substrates. These are more reactive compared to secondary alcohols. With the exception of $[IrCp^*Cl_2]$, which was introduced by Fujita et al.[18] no efficient catalyst is known for the N-alkylation with secondary alcohols.

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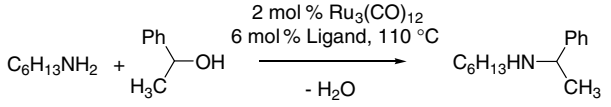
Thus, a major challenge in this area is the development of more active catalysts that work under milder conditions and allow a broader substrate scope. Clearly, the demands on improved catalysts for the N-alkylation of amines with alcohols are: (1) High activity for the dehydrogenation of alcohols to ketones and the hydrogenation of the resulting imines to amines via a transfer hydrogenation process, and (2) low sensitivity to water and functional groups on the substrate. From an environmental point of view the use of additional base for the activation of the catalyst should be avoided.

Based on our previous research in intermolecular hydroaminations of olefins and alkynes,[19] we recently became interested in the development of novel ruthenium complexes for the amination of alcohols, especially secondary alcohols. Herein, we report our results from this study and present $Ru_3(CO)_{12}$/ligand-systems which are active for the N-alkylation of amines with different alcohols at 100–110 °C.

Initial studies were performed using *n*-hexylamine and 1-phenylethanol as the substrates in the presence of different ruthenium sources. As a result of these reactions the ruthenium cluster $Ru_3(CO)_{12}$ was tested in the presence of different phosphine ligands. Typically, the catalytic reactions were run without a solvent using 2 mol % $Ru_3(CO)_{12}$ and 6 (3) mol % of monodentate (bidentate) ligands at 110 °C. The selected results and the ligands used are shown in Table 1 and Scheme 2.

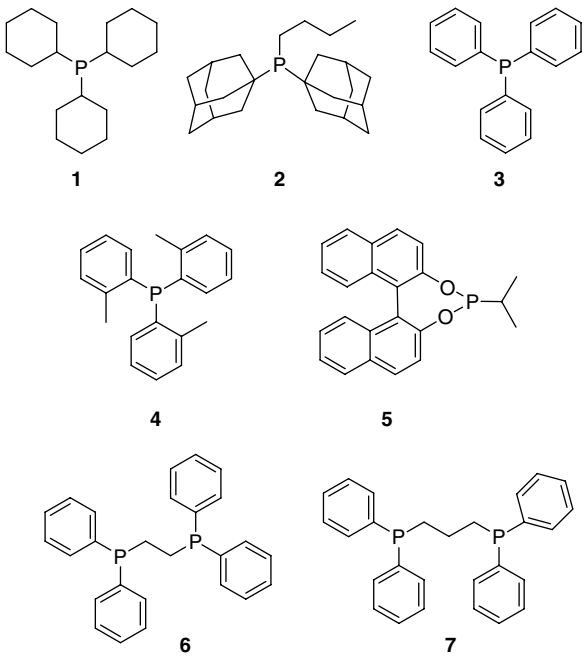
Notably, the reaction proceeds in a good yield (74%) in the presence of the ruthenium carbonyl cluster (Table 1, entry 1). With respect to the used ligands, there was no clear trend observed. For example electron-rich bulky phosphines such as tricyclohexylphosphine **1** and *n*-butyl-di-1-adamantyl-phosphine[20] **2** behaved quite differently (Table 1, entries 2 and 3). Similar divergent behaviour was observed with aryl phosphines **3** and **4** (Table 1, entries 4 and 5). The best results were obtained with **2** and **4** (>90% of *N*-(1-phenyl-ethyl)hexylamine).

Table 1. N-Alkylation of *n*-hexylamine with 1-phenyl-ethanol in the presence of $Ru_3(CO)_{12}$ and different ligands[a]



Entry	Ligand	Conversion (%)	Yield (%)
1	None	100	74
2	**1**	100	59
3	**2**	**100**	**90**
4	**3**	81	47
5	**4**	**100**	**97**
6	**5**	56	33
7	**6**	85	30
8	**7**	82	34

[a] Reaction conditions: 2 mmol *n*-hexylamine, 10 mmol 1-phenylethanol, 0.04 mmol $Ru_3(CO)_{12}$, 0.12 mmol monodentate ligand (or 0.06 mmol bidentate ligand), 110 °C, 24 h, conversion and yield were determined by GC analysis with hexadecane as the internal standard.



Scheme 2. Ligands for N-alkylation of amines with alcohols.

For all other tested ligands the conversion of substrate was significantly higher than the yield of the desired product. In these cases the corresponding imine was observed as the major side product. Thus, the hydrogenation of the imine appears problematic.

Next, critical reaction parameters of the model reaction were studied in more detail (Table 2). The $Ru_3(CO)_{12}$/tri(*o*-tolyl)-phosphine catalyst system **4** was chosen for its high yield, robustness and favourable price.

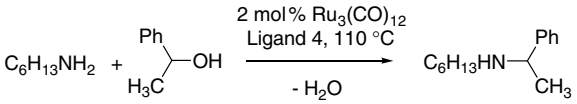
Reducing the catalyst loading from 2 to 1 mol %, the conversion decreased from 100% to 79%, and the yield of secondary amine dropped to 37%. Variation of the alcohol/amine ratio demonstrated the importance of the alcohol concentration for the hydrogenation step (Table 2, entries 2–5). Although the conversion decreased only slightly to around 80%, the product yield decreased steadily to only 29%. Reducing the reaction time to 7 h showed that almost 24 h are necessary for a full conversion (Table 2, entry 8).

The two best catalysts identified from these studies were applied to the alkylation of various amines under the optimized conditions (Table 3).

In addition to the model reaction described above, the N-alkylation of *n*-octylamine and benzylamine with 1-phenylethanol proceeded in moderate yield (64% and 49%, respectively) (Table 3, entries 4 and 8). Cyclooctylamine gave 29% of the corresponding alkylated amine (Table 3, entry 6). In all cases ligand **4** gave better product yields than **2**.

Finally, different alcohols were examined in the N-alkylation of *n*-hexylamine (Table 4). Again, all substrates were tested in the presence of ligands **2** and **4**. Notably,

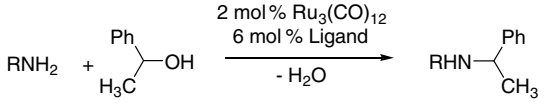
Table 2. N-Alkylation of *n*-hexylamine with 1-phenylethanol in the presence of $Ru_3(CO)_{12}$ and tri(*o*-tolyl)phosphine (**4**)[a]



Entry	Catalyst (mol %)	Amine/alcohol	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)
1	1	1:5	110	24	79	37
2	2	1:5	110	24	100	97
3	2	1:4	110	24	88	58
4	2	1:3	110	24	80	38
5	2	1:2	110	24	82	29
6	2	1:5	100	24	90	52
7	2	1:5	90	24	38	10
8	2	1:5	110	7	58	22

[a] Reaction conditions: 2 mmol *n*-hexylamine, 10 mmol 1-phenylethanol, 0.04 mmol $Ru_3(CO)_{12}$, 0.12 mmol **4**, conversion and yield were determined by GC analysis with hexadecane as the internal standard.

Table 3. N-Alkylation of different amines with 1-phenyl-ethanol in the presence of $Ru_3(CO)_{12}$/**2** or **4**[a]



Entry	Amine	Ligand	Conversion (%)	Yield (%)
1	Hexylamine	**2**	100	90
2	Hexylamine	**4**	100	97
3	Octylamine	**2**	100	35
4	Octylamine	**4**	100	64
5	Cyclooctylamine	**2**	56	21
6	Cyclooctylamine	**4**	44	29
7	Benzylamine	**2**	81	19
8	Benzylamine	**4**	72	49

[a] Reaction conditions: 1 mmol amine, 5 mmol 1-phenylethanol, 0.02 mmol $Ru_3(CO)_{12}$, 0.06 mmol ligand, 110 °C, 24 h, conversion and yield were determined by GC analysis with hexadecane as

secondary aliphatic alcohols such as 2-octanol and cyclohexanol gave *N*-hexyl-2-octylamine and *N*-hexyl-cyclohexylamine in excellent yields (90–94%) (Table 4, entries 1–4). We were also pleased to find that hetero-aromatic alcohols, for example, 1-(2-furyl)-ethanol (Table 4, entries 5 and 6), furan-2-yl-methanol (Table 4, entries 7 and 8), and thiophen-2-yl-methanol (Table 4, entries 9 and 10) were converted to the corresponding secondary *N*-hexylamines in moderate to good yields. Ligand **4** was again superior to **2** in all cases studied.

In conclusion, we present a novel ruthenium-catalyzed N-alkylation of amines with alcohols in the presence of different sterically hindered phosphine ligands. The reactions can be performed under significantly milder conditions (110 °C) compared to the known ruthenium catalysts and proceed with good yields.

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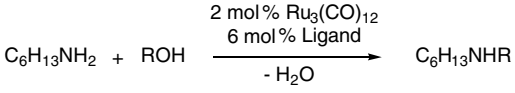
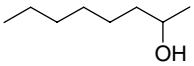
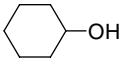
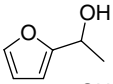
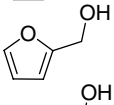
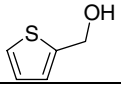
Table 4. N-Alkylation of *n*-hexylamine with different alcohols in the presence of $Ru_3(CO)_{12}$/**2** or **4**[a 21]



Entry	Alcohol	Ligand	Temperature (°C)	Conversion (°C)	Yield (%)
1		**2**	110	100	92
2		**4**	110	100	90
3		**2**	120	100	94
4		**4**	120	100	93
5		**2**	110	100	17
6		**4**	110	100	49
7		**2**	110	100	33
8		**4**	110	100	60
9		**2**	110	66	7
10		**4**	110	100	70

[a] Reaction conditions: 2 mol % catalyst, 24 h, conversion and yield were determined by GC analysis with hexadecane as internal standard.

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21. Preparative procedure for the amination reaction: In an Ace-pressure tube under an argon atmosphere $Ru_3(CO)_{12}$ (0.1 mmol) and ligand **4** (0.3 mmol) were dissolved in thiophen-2-yl-methanol (25 mmol) and hexylamine (5 mmol). The pressure tube was fitted with a Teflon cap and heated at 110 °C for 48 h in an oil bath. The excess alcohol was distilled (40 °C, 0.88 mbar). The residue was extracted with 1 N HCl (3×5 mL). The combined HCl-phases were spiked with 15 N NaOH solution, extracted with dichloromethane (5×5 mL), dried over magnesium sulfate and reduced in vacuo to yield *N*-(thiophen-2-ylmethyl)hexan-1-amine hydrochloride as a brown powder. Isolated yield: 317 mg (32%). ^{1}H NMR (500.13, $CDCl_3$, δ): 0.84 (t, 3H, $^3J = 6.9$ Hz, H-6); 1.21–1.35 (m, 6H, H-3,4,5); 1.84 (m, 2H, H-2); 2.81 (m, 2H, H-1); 4.26 (m, 2H, H-7); 7.03 (dd, 1H, $^3J_{10,11} = 5.2$ Hz, $^3J_{9,10} = 3.6$ Hz, H-10); 7.34 (dd, 1H, $^3J_{10,11} = 5.2$ Hz, $^4J_{9,11} = 1.0$ Hz, H-11); 7.42 (dd, 1H, $^3J_{9,10} = 3.6$ Hz, $^4J_{9,11} = 1.0$ Hz, H-9); 9.80 (br, 2H, NH_2). ^{13}C NMR ($CDCl_3$, 125.8 MHz, δ): 13.9 (C-6); 22.4 (C-5);

25.8 (C-2); 26.4 (C-3); 31.1 (C-4); 44.3 (C-7); 45.6 (C-1); 127.9 (2) (C-10, C-11); 130.9 (C-8); 131.3 (C-9). MS (EI, 70 eV) *m*/*z* (rel. intensity): 197 (1) [M^+], 126 (24) [M^+–C_5H_{11}], 112 (9) [M^+–C_4H_3S], 97 (100) [M^+–$C_6H_{14}N$]. FT IR (KBr, cm^{-1}): 3070 (w, C-H_{ar}), 2932 (s), 2862 (s), 2794 (s), 2740 (s), 2550 (m), 2421 (m), 1581 (m), 1472 (s), 853 (m), 717 (m), 696 (s). Anal. Calcd for $C_{11}H_{19}NS$·HCl: C, 56.51; H, 8.62; N, 5.99; S, 13.71; Cl, 15.16. Found: C, 56.30; H, 9.08; N, 5.75; S, 13.42; Cl, 14.37. HRMS calcd for $C_{11}H_{19}NS$: 197.12327. Found: 197.12334.