DOI: 10.1002/adsc.200800353

Ruthenium-Catalyzed Synthesis of Secondary Alkylamines: Selective Alkylation with Aliphatic Amines

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Received: June 6, 2008; Published online: August 13, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800353.

Abstract: The chemoselective *N*-alkylation of *tert*-alkylamines applying aliphatic amines is described for the first time. In the presence of the Shvo catalyst **1**, *tert*-octylamine **4** and 1-adamantylamine **5** are alkylated using primary, secondary, and even tertiary amines to give the corresponding monoalkylated *tert*-alkylamine in moderate to very good yields and excellent selectivity. This novel reaction proceeds without an additional hydrogen source and ammonia is formed as the only by-product.

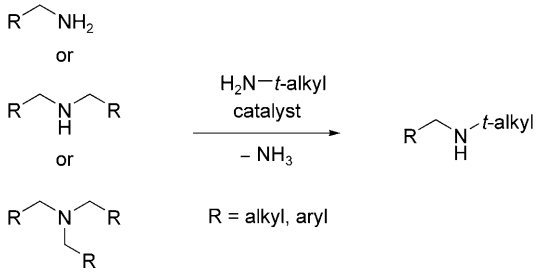
Keywords: alkylation; amines; homogeneous catalysis; hydrogen transfer; ruthenium

Amines are of significant importance for the bulk and fine chemical industry. Due to their numerous applications in polymers, dyes, agrochemicals, and pharmaceuticals,[1] there is an ongoing interest for improved and new synthetic preparations.[2] Besides the well known *N*-alkylations of amines with alkyl halides,[2,3] catalytic methodologies such as reductive amination,[2,4] hydroaminations,[5] and hydroaminomethylations[6] of olefins or alkynes have been developed for the synthesis of aliphatic amines within the last decade. In addition, the environmentally friendly *N*-alkylation of amines using primary[7] and secondary alcohols[8,9] has attracted considerable interest.

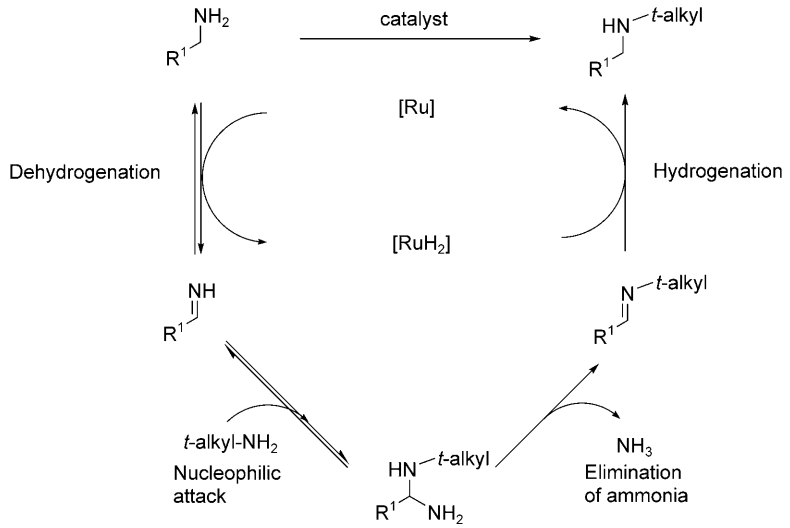
Recently, we demonstrated that aliphatic amines can be used as alkylating agents instead of the corresponding alcohol. Although this transformation – alkylation of amines with amines – seems to be unusual at first sight, there is significant industrial interest in analogous transalkylations.[10] More specifically, we discovered that anilines are converted in high yield to *N*-alkylanilines.[11] This atom-efficient alkyl transfer proceeds with primary as well as secondary and tertiary aliphatic amines leaving ammonia as the only by-product.[12] Based on these reactions, we also became interested in the selective alkylation of aliphatic amines (Scheme 1). The resulting *tert*-alkylamines are of interest as intermediates; for example, this structural element is found in pharmaceuticals[13] like vildagliptin.[14]

From a mechanistic viewpoint the alkylation of amines proceeds *via* a so-called borrowing hydrogen sequence which is shown in Scheme 2.[15] Initially, the ruthenium-catalyzed dehydrogenation of the alkylamine should occur *via* coordination and ß-hydride elimination. Then, nucleophilic attack of the *tert*-alkylamine on the resulting imine and elimination of ammonia yields the corresponding secondary imine. Subsequent catalytic hydrogenation leads to the alkylated *tert*-alkylamine. Notably, applying secondary or even tertiary amines, in the first reaction cycle a primary or secondary amine is eliminated instead of ammonia.

In the case of tertiary amines, we assume that initially an iminium ion is generated by ß-hydride elimination. Another possible reaction mechanism involving hydrolysis of the amines to form ketones[16] could be excluded. For this purpose, reactions under strict water-free conditions and in the presence of small amount of water (5 mol%) were performed, however the results do not indicate any influence of water.



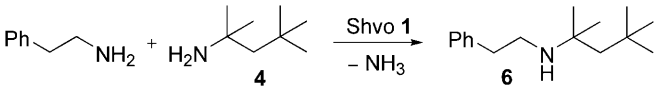
Scheme 1. Selective *N*-alkylation of *tert*-alkylamines.



Scheme 2. Catalytic hydrogen transfer in *N*-alkylation of *tert*-alkylamines with aliphatic amines.

The formed alkylamine reacts further until all alkyl chains are transferred to the *tert*-alkylamine. Clearly, dehydrogenation of the *tert*-alkyl group is not feasible because ß-hydride elimination is not possible. Hence, a selective alkyl transfer takes place.

Table 1. Influence of the catalyst on the reaction of *tert*-octylamine **4** and phenethylamine.[a]



Entry	Catalyst	Yield [%][b]
1	Shvo **1**	49
2	Shvo-H_2 **2**	19
3	Shvo PPh_3	14
4	Shvo cataCXium®PCy[e]	12
5	[Ru[(+)-BINAP]$(Cl)_2$][e]	<1
6	[{Ru(*p*-cymene)$(Cl)_2$}$_2$][c]	–
7	[{Ru(*p*-cymene)$(Cl)_2$}$_2$]/TsDPEN[e] **3**[d]	–
8	[{Ru(*p*-cymene)$(Cl)_2$}$_2$]/dppf[d,e]	–
9	[$Ru_3(CO)_{12}$]/cataCXium®PCy[e]	<1

[a] *Reaction conditions*: 1 mmol phenethylamine, 2 mmol *tert*-octylamine **4**, 1 mol% ruthenium catalyst relative to phenethylamine, 24 h, 160 °C.

[b] Yields were determined by GC with hexadecane as internal standard and are based on phenethyl-(1,1,3,3-tetramethylbutyl)-amine **6**.

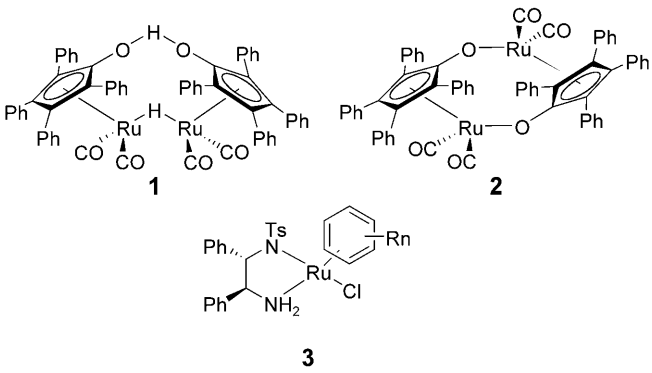
[c] 4 mol% K_2CO_3.

[d] 2 mol% ligand, 4 mol% K_2CO_3.

[e] BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, TsDPEN = *N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine, dppf = 1,1′-bis(diphenyl-phosphanyl)ferrocene, cataCXium®PCy = *N*-phenyl-2-(dicyclohexylphosphino)-pyrrole.

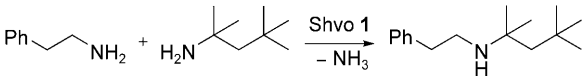
As model system the alkylation of *tert*-octylamine **4** (1,1,3,3-tetramethylbutlamine) was performed with phenethylamine. Different ruthenium complexes were tested by applying 1 mol% ruthenium catalyst and 2 equivalents of *tert*-octylamine **4** at 160 °C in a pressure tube without additional solvent (Table 1). The different pre-catalysts investigated included the ruthenium/TsDPEN system **3** reported by Noyori and co-workers[17] (Table 1, entry 7), the ruthenium/dppf system of Hamid and Williams[7c] (Table 1, entry 8), and our ruthenium carbonyl/phosphine system (Table 1, entry 9).[9a] However, similar to the alkylation of anilines[11] the Shvo catalyst {[2,3,4,5-$Ph_4(\eta^5$-$C_4CO)]_2H$}$Ru_2(CO)_4(\mu$-H) **1**, shown in Scheme 3, provided the best result (Table 1, entry 1). Surprisingly, catalyst **2** was less reactive. So far, we cannot explain this observation.

Next, we investigated the influence of different reaction conditions (Table 2). Without solvent, the opti-



Scheme 3. Different ruthenium catalysts for the alkylation of *tert*-alkylamines.

Table 2. Optimization of the reaction conditions.[a]



Entry	T [°C]	Solvent	Shvo **1** [mol%]	*tert*-Octylamine **4** [equiv.]	Yield [%][b]
1	140	–	1	2	16
2	150	–	1	2	35
3	160	–	1	2	49
4	170	–	1	2	34
5	160	Heptane	1	2	38
6	160	DME	1	2	48
7	160	NMP	1	2	44
8	170	Heptane	1	2	60
9	170	DME	1	2	69
10	170	NMP	1	2	35
11	160	–	1	1	23
12	160	–	1	3	55
13	160	–	0.5	2	41
14	160	–	2	2	48
15[c]	170	DME	1	2	44
16[d]	170	DME	1	2	70
17[e]	170	DME	1	2	60
18[f]	170	DME	1	2	51
19	170	DME	1	3	75

[a] *Reaction conditions*: 2 mmol phenethylamine, 24 h, 0.5 mL solvent.
[b] Yields were determined by GC with hexadecane as internal standard and are based on phenethyl-(1,1,3,3-tetramethylbutyl)-amine **6**.
[c] 12 h.
[d] 48 h.
[e] 0.25 mL solvent.
[f] 1 mL solvent.

mal yield is obtained at 160 °C (Table 2, entry 3). At lower temperature more diphenethylamine is formed, while a higher temperature gave triphenethylamine as by-product. Applying 1-methyl-pyrrolidin-2-one (NMP) as solvent decreased the chemoselectivity and significantly more triphenethylamine is obtained (Table 2, entries 7 and 10). In heptane as non-polar solvent the catalyst is less reactive but more selective and a moderate yield of 60% at 170 °C is achieved (Table 2, entry 8). An improved yield of 69% is observed in dimethoxyethane (DME) (Table 2, entry 9) and the best yield (75%) is achieved using an excess of 3 equiv. *tert*-octylamine **4** in DME (Table 2, entry 19).

Reactions in DMSO, 2-methylbutan-2-ol, dioxane, and toluene are comparable. Variation of the catalyst loading (Table 2, entries 13 and 14), reaction time (Table 2, entries 15 and 16), and solvent concentration (Table 2, entries 17 and 18) did not lead to any further improvement.

In order to demonstrate the generality of the alkyl transfer, different amines were investigated in the reaction with *tert*-octylamine **4**. The results are summarized in Table 3. Primary amines as well as secondary ones gave the desired products in good to excellent yield. Remarkably, even tertiary amines such as trioctylamine can be used as alkylating agents, although activation of these substrates is known to be difficult. However, tribenzylamine is less reactive and no reaction with *tert*-octylamine **4** or 1-adamantylamine **5** is observed (Table 3, entries 6 and 17). The more electron-rich 4-methoxybenzylamine showed increased reactivity compared to benzylamine (Table 3, entries 4 and 11). Moreover, aliphatic amino ethers are converted selectively to the secondary amines (Table 3, entry 10). We were pleased to find that 1-adamantylamine reacted with primary, secondary, and tertiary amines providing excellent yields of the corresponding *N*-alkyl-1-adamantylamines (Table 2, entries 12–14). In all cases, the reaction was highly selective towards monoalkylation. Neither the formation of dialkylated *tert*-alkylamines nor of the alkyl-di-*tert*-alkylamines was observed.

In conclusion, we present the first selective alkylation of aliphatic amines using amines. Proceeding under transfer hydrogenation conditions, no additional hydrogen is needed for the alkylation. In the presence of the Shvo catalyst **1**, selective alkyl transfer, using primary as well as secondary and tertiary aliphatic amines to *tert*-alkylamines proceeds selectively in high yield.

Experimental Section

General Procedure for the Selective Monoalkylation of *tert*-Alkylamines

In an ACE-pressure tube under an argon atmosphere alkylamine (2 mmol mono-, 1 mmol di-, or 0.67 mmol trialkylamine) and Shvo catalyst (21.7 mg, 0.02 mmol, 1 mol% per alkyl group) were dissolved in DME (0.5 mL) and *tert*-alkylamine (6 mmol, 3 equiv. per alkyl group). The pressure tube was fitted with a Teflon cap and stirred at 170 °C for 24 h. The solvent was removed under vacuum, and the crude product was purified by column chromatography.

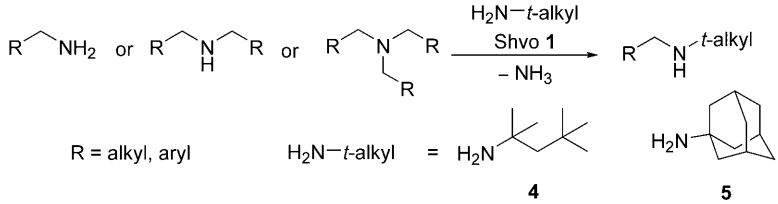
Supporting Information

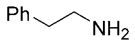
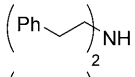
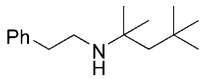
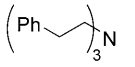
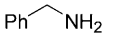
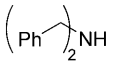
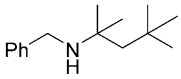
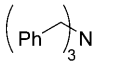
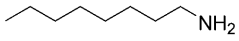
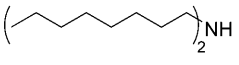
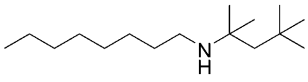
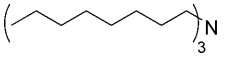
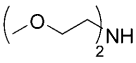
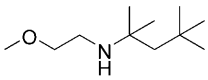
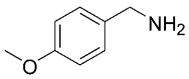
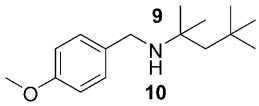
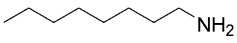
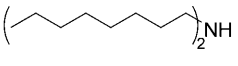
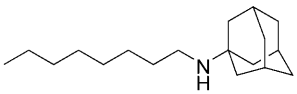
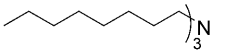
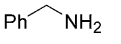
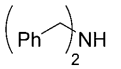
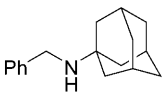
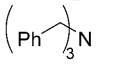
Experimental details and characterization data for compounds **6**–**12** are given in the Supporting Information.

Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), and the Deutsche Forschungsgemeinschaft (DFG BE 1931/16–1, Leibniz prize). We thank all members of the analytical group (LIKAT) for their support.

Table 3. Catalytic *N*-alkylation of *tert*-alkylamines.[a]



Entry	Substrate	*tert*-Alkylamine	Product	Yield [%][b]
1		**4**		75 (68)
2		**4**	 **6**	90
3		**4**		87 (75)
4		**4**		58 (49)
5		**4**	 **7**	76 (58)
6		**4**		<1
7		**4**		90 (61)
8		**4**	 **8**	89 (78)
9		**4**		85
10		**4**	 **9**	60 (43)
11		**4**	 **10**	89 (63)
12[c]		**5**		99 (94)
13[c]		**5**	 **11**	99
14[c]		**5**		99
15[c]		**5**		81 (67)
16[c]		**5**	 **12**	90
17[c]		**5**		<1

[a] *Reaction conditions*: 2 mmol mono-, 1 mmol di-, or 0.67 mmol trialkylamine, 6 mmol *tert*-alkylamine, 1 mol% Shvo catalyst **1** per alkyl group, 24 h, 0.5 mL DME.

[b] Yields were determined by GC with hexadecane as internal standard and are based on alkyl groups. Isolated yields in brackets.

[c] 1 mL DME.

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