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Amine Synthesis

One-Pot Synthesis of Symmetrical Tertiary and Secondary Amines from Carbonyl Compounds, Ammonium Carbonate and Carbon Monoxide as a Reductant

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Abstract: Rh-catalyzed one-step synthesis of tertiary and secondary amines from aldehydes and ketones, ammonium carbonate serving as nitrogen source, and carbon monoxide as a reducing agent has been developed. Aliphatic and aromatic aldehydes lead to the corresponding tertiary symmetrical amines in 69–83 % yields. Aromatic and aliphatic ketones lead to the corresponding secondary symmetrical amines which were obtained in 62–79 % yields.

Introduction

Amines are a widespread class of organic compounds. This structural motif can be found in many biologically active compounds, such as alkaloids, pharmaceuticals and agrochemicals.[1–5] Amines are also used as ligands, extractants, building blocks for nitrogen-containing organic compounds and synthetic polymers.[6–9] In particular, they can be successfully utilized in optoelectronics due to their ability to function as a hole transport materials.[10,11] Some symmetrical tertiary and secondary amines are of industrial importance. For example, dibenzylamine is used in rubber vulcanization process,[12] dicyclohexylamine is useful in manufacture of corrosion inhibitors,[13] whereas diisopropylamine is mostly used for agrochemicals and rubber accelerators such as DIBS (*N*,*N*-diisopropyl-2-benzothiazylsulfenamide).[13] Numerous methods have been developed for the synthesis of amines in the past few decades.[14] They generally fall into several groups: amination of halogen derivatives,[14a–14d,14p,14t,14u] hydrogen borrowing methodology,[14e–14h,14m–14o] hydroaminoalkylation[14i,14j,14q,14r,14s,14v,14w,14x,14y] of alkenes and reductive amination/alkylation.[14k] The use of the latter in the synthesis of tertiary amines is very attractive due to the easy availability of the starting materials and catalysts. Moreover, according to recent research, reductive amination reaction is increasingly used in the pharmaceutical industry.[15]

It is possible to synthesize symmetrical tertiary/secondary amines from aldehydes or ketones and ammonia. However, reactions with ammonia may be inconvenient due to the difficulties with transportation, storage and requirements for special equipment. On the other hand, ammonium salts may be a good alternative to ammonia in this reaction due to their operational easiness. Standard protocols for the synthesis of tertiary amines from aldehydes and ammonium salts often require the use of borohydride reductants[16] or excess of other reducing agents to effectively conduct the reaction.[14k] In our previous research we have shown that carbon monoxide can be potentially one of the most selective and atom-economical alternatives to the classical reductants in this process.[17]

We have also recently reported a novel method for the synthesis of symmetrical tertiary amines from aldehydes without an external hydrogen source.[18] The amine source in this reaction is acetamide. Herein we report a more convenient protocol for conducting this reaction (Scheme 1). The obvious improvements are the use of cheaper and easier to handle reagents, the substantial lowering of the catalyst loading in a number of cases and the extension of substrate scope from aromatic aldehydes to aromatic and aliphatic aldehydes and even aromatic and aliphatic ketones.

Results and Discussion

We started our investigation with catalysts and solvents screening in the model reaction between 4-mehylbenzaldehyde and ammonium carbonate (Table 1). Initially, a number of rhodium and ruthenium metal complexes were screened, among them $IndRhI_2$,[19] rhodium(II) acetate and rhodium(III) chloride showed the most promising catalytic activity (Table 1, entries 3, 6–7). It was found that reaction proceeded smoothly in water in case of $IndRhI_2$ and $RhCl_3$ (Table 1, entries 6–7). After a number of experiments rhodium(III) chloride was chosen for further optimization because of its lower price. We found that the best reaction medium was MeOH/H_2O mixture (Table 1, entry 10). Decreasing the pressure from 50 to 40 atm slightly decreases

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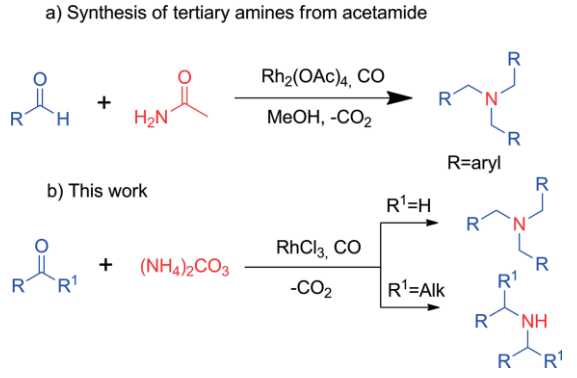
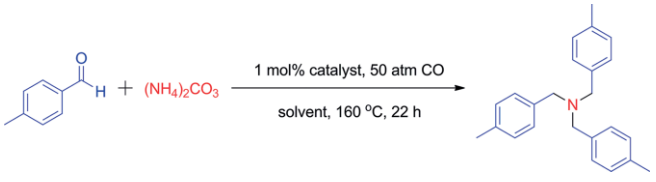


Scheme 1. Synthesis of symmetrical secondary and tertiary amines from carbonyl compounds and CO.

the yield (Table 1, entry 11). However, further decreasing to 20 atm drops the yield significantly (Table 1, entry 12). Advantageously, when the catalyst loading was lowered to 0.2 mol-% the yield maintained at appreciable level of 80 % (Table 1, entry 13).

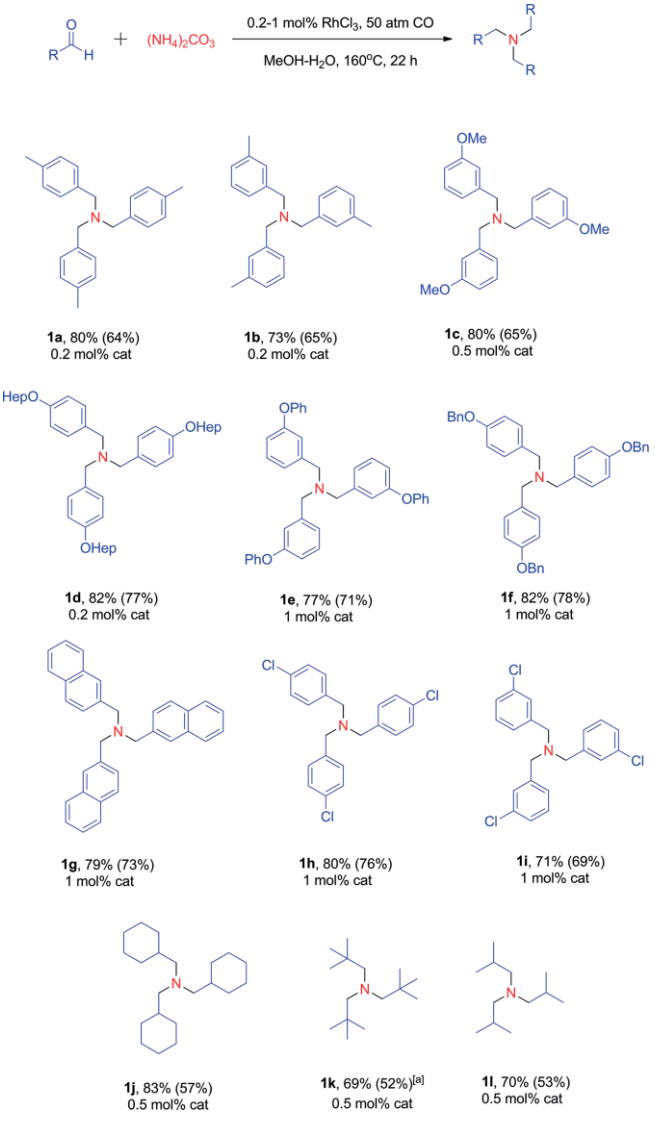
Table 1. Selected optimization studies.



Entry	Catalyst[a]	Solvent	Yield
1[b]	$Rh_2(OAc)_4$	MeOH	50 %
2[b]	$Rh_2(OAc)_4$	MeOH/H_2O(10 %)	61 %
3[b]	$Rh_2(OAc)_4$	MeOH/H_2O(20 %)	69 %
4[b]	$Rh_2(OAc)_4$	EtOH	43 %
5[b]	$RuCl_3$	MeOH	14 %
6[b]	$IndRhI_2$	H_2O	80 %
7[b]	$RhCl_3$	H_2O	78 %
8[b]	$Rh_2(OAc)_4$	H_2O	58 %
9[b]	$Rh_2(OAc)_4$	MeOH/H_2O(60 %)	79 %
10[c]	$RhCl_3$	MeOH/H_2O(60 %)	87 %
11[c,d]	$RhCl_3$	MeOH/H_2O(60 %)	78 %
12[c,e]	$RhCl_3$	MeOH/H_2O(60 %)	58 %
13[c,f]	$RhCl_3$	MeOH/H_2O(60 %)	80 %
14[c,g]	$RhCl_3$	MeOH/H_2O(60 %)	67 %

[a] In case of $Rh_2(OAc)_4$ 1 mol-% per metal was used. [b] 0.66 mmol of aldehyde, 0.22 mmol of ammonium carbonate. [c] 1.32 mmol of aldehyde, 0.22 mmol of ammonium carbonate. [d] 40 atm CO. [e] 20 atm CO. [f] 0.2 mol-% of catalyst were used. [g] 0.1 mol-% of catalyst were used.

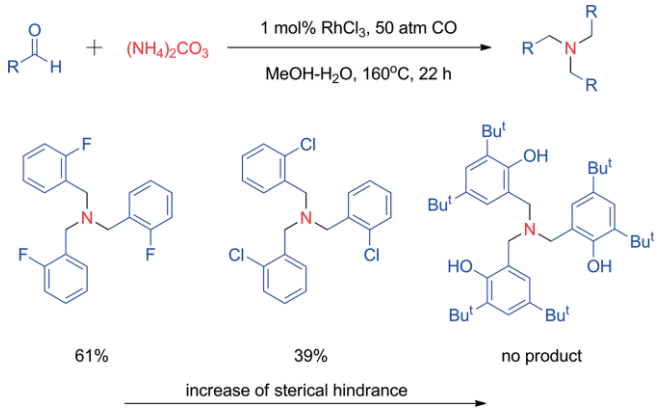
With the optimal conditions in hand, we next investigated the substrate scope of this reaction (Scheme 2). High yields were observed for substrates with various substitution patterns (**1a**–**1l**). The transformation of aromatic aldehydes with methyl (**1a**, **1b**), methoxy (**1c**), heptyloxy (**1d**), chloride (**1h**, **1i**) groups successfully proceeded with high yields. The protocol proved to be acceptable for such condensed aromatic structure as 2-naphthaldehyde giving the corresponding tertiary amine **1g** in 79 % yield. It was found that aliphatic aldehydes (cyclohexylcarbaldehyde, pivaldehyde, isobutyraldehyde) can also be involved in this reaction with good yields of the resulting products (**1j**–**1l**). On the contrary, the majority of *ortho*-substituted aldehydes showed poor results. This observation is in good correlation with the increase of the steric hindrance of substituents (Scheme 3).



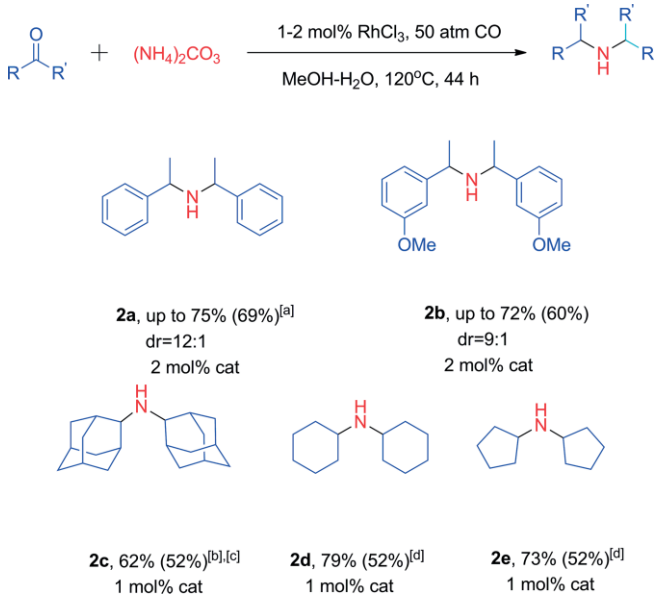
Scheme 2. Scope of tertiary amines. 0.5 equiv. of. $(NH_4)_2CO_3$ (1 eq [NH_3]) and 3 equiv. of. aldehyde were used [a] isolated as hydrochloride.

Interestingly, the strategy can be adapted to ketones as well. In this reaction, ketones give secondary amines as the products, probably, due to the steric factors (Scheme 4). No significant amounts of corresponding tertiary amines were found. In order to get a better yield, an increased reaction time (44 h) and lower temperature were required (120 °C). It was found that aliphatic ketones generally work better than aromatic ones (1 mol-% of the catalyst vs. 2 mol-%). Even such sterically hindered ketone as 2-adamantanone can be transformed to the corresponding secondary amine with moderate yield (**2c**, 62 %).

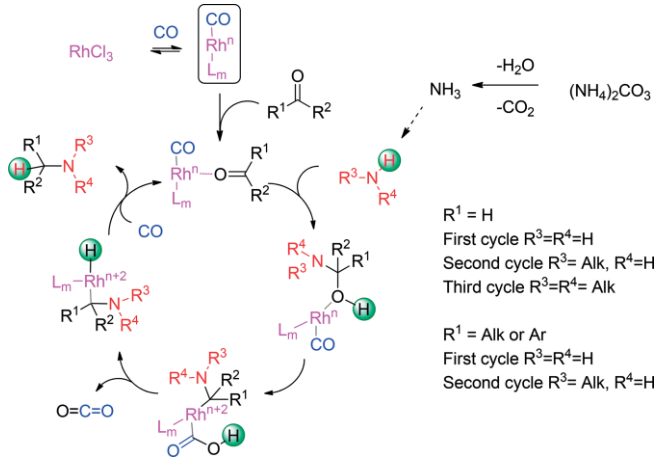
To our delight, compounds **2a** and **2b** were obtained with 12:1 and 9:1 diastereoselectivity correspondingly. The minor diastereomer is *meso* form. This assignment was made on the basis of the previous work.[20]



Scheme 3. Scope of *ortho*-substituted tertiary amines in the reaction. 0.5 equiv. of. $(NH_4)_2CO_3$ (1 eq [NH_3]) and 3 equiv. of. aldehyde were used.



Scheme 4. Scope of secondary amines. 0.5 equiv. of. $(NH_4)_2CO_3$ (1 eq [NH_3]) and 2 equiv. of. ketone were used [a] 50 h; [b] 160 °C; [c] 1 equiv. of. $(NH_4)_2CO_3$ (2 eq [NH_3]) and 1 equiv. of ketone were used [d] isolated as hydrochloride.



Scheme 5. Plausible mechanism of the transformation.

The plausible mechanism for the catalytic transformation is depicted in the Scheme 5.

Conclusions

In summary, we developed a method for the one-step preparation of symmetrical tertiary and secondary amines by direct reductive amination using ammonium carbonate as a nitrogen source and carbon monoxide as a reducing agent. A variety of aliphatic and aromatic aldehydes and aromatic and aliphatic ketones were applied. The limitations such as increased steric hindrance in aromatic aldehydes in *ortho*-position were demonstrated.

Experimental Section

General Procedure for the Tertiary Amine Synthesis: A glass vial in a 10 mL stainless steel autoclave was charged with the catalyst (0.2–2 mol-%), ammonium carbonate, the corresponding solvent, an aldehyde or ketone. The autoclave was sealed, flushed with CO (3 × 10 atm), and then charged with the indicated pressure of CO. The reactor was placed into a preheated oil bath. After the indicated time, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane rinsing were combined and then concentrated on a rotary evaporator. The residue was purified by chromatography on silica gel.

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Keywords: Aldehydes · Ketones · Tertiary amines · Secondary amines · Carbon monoxide

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