

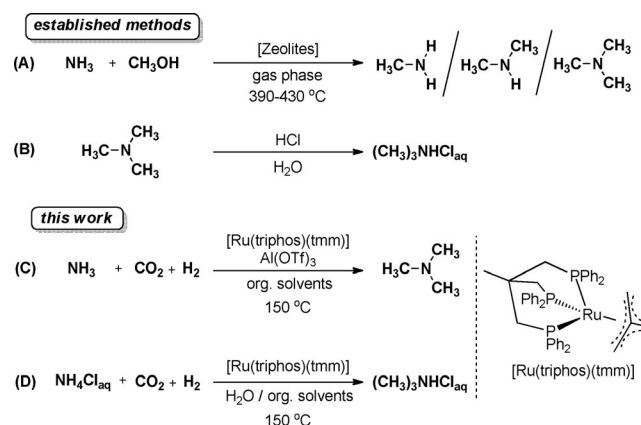
Selective Synthesis of Trimethylamine by Catalytic *N*-Methylation of Ammonia and Ammonium Chloride by utilizing Carbon Dioxide and Molecular Hydrogen

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The synthesis of trimethylamine (TMA) through a multicomponent combination of ammonia with carbon dioxide and molecular hydrogen by using a homogeneous ruthenium catalyst was explored. The use of [Ru(triphos)(tmm)] [triphos: 1,1,1-tris(diphenylphosphinomethyl)ethane, tmm: trimethylene methane] together with aluminum trifluoromethanesulfonate as a co-catalyst resulted in high ammonia conversion and excellent selectivity for TMA in organic solvents. Aqueous solutions of ammonium chloride were methylated almost quantitatively to the corresponding hydrochloride salt (i.e., TMA·HCl) in a biphasic solvent system by using the same Ru complex without the need for any co-catalyst.

Methylamines, the simplest members of the aliphatic amine family, represent highly important and versatile intermediates within the chemical supply chain. The industrial significance of methylamines is reflected by a worldwide annual production larger than 1.3×10^6 t with a growing rate of 3.5% per annum.^[1] These basic chemicals are generally used as valuable building blocks for the synthesis of solvents, surfactants, ion-exchange resins, and synthetic fibers, as well as agrochemical and pharmaceutical products.^[2]

Methylamines are prepared on industrial scale by the exothermic reaction of ammonia (NH₃) and methanol (CH₃OH) with an amorphous silica–alumina catalyst in fixed-bed reactors at 390–430 °C (Scheme 1A). The composite equilibria within the reaction network result in complex product mixtures, and the three possible methylamines (mono-, di-, and trimethylamine: MMA, DMA and TMA) are generally produced with moderate selectivity for the individual product, largely controlled by the NH₃/CH₃OH feed ratio.^[2,3] Moreover, MMA, DMA, TMA, and NH₃ form an azeotropic mixture, and the use of zeolite-based catalysts in combination with methanol results



Scheme 1. A) Industrial production of TMA by using CH₃OH and NH₃, and B) formation of the hydrochloride. New approach for the synthesis of TMA and its hydrochloride starting from C) NH₃ or D) NH₄Cl by using CO₂/H₂.

in dimethyl ether (DME) as an additional byproduct.^[4] Consequently, the downstream purification process is laborious and requires a train of four to five distillation columns, which finally results in integrated production plants at economy of scale.^[2a,5] The synthesis of the ammonium chlorides is typically achieved in a subsequent step (Scheme 1B).

Herein, we report a novel catalytic approach for the selective synthesis of trimethylamine and its hydrochloride by using carbon dioxide (CO₂) as a renewable C₁ building block for the formation of the three methyl groups on ammonia in the presence of molecular hydrogen.^[6] In previous work from our group, a well-defined and highly versatile [Ru(triphos)(tmm)] [triphos: 1,1,1-tris(diphenylphosphinomethyl)ethane, tmm: trimethylene methane] catalyst was developed for the hydrogenation of CO₂ to methanol and the utilization of CO₂ and H₂ for the *N*-methylation of primary and secondary amines.^[7] On the basis of these investigations, the direct triple *N*-methylation of NH₃ (Scheme 1C) or NH₄Cl (Scheme 1D) by using a combination of CO₂ and H₂ was targeted.

In the mid-1990s, the group of Baiker worked on this challenging transformation and described the use of CO₂/H₂ for the methylation of NH₃ by using Cu- and Pd-based heterogeneous catalysts. The formation of methylamines was achieved, but the system suffered from drawbacks such as low yield, low selectivity, and the necessity of high reaction temperatures (200–300 °C).^[2b,8] With respect to molecular catalysts, the group of Vaska observed trimethylamine as a minor product in the Ru- and Os-catalyzed transformations of dimethylamine with

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CO₂/H₂ to dimethylformamide (DMF).^[9] The formation of the third methyl group was supposed to arise from hydrogenation of DMF or the dismutation of the DMA substrate.^[9,10]

Given this rather limited precedence, we were very pleased to find that the direct methylation of ammonia occurred efficiently by using the [Ru(triphos)(tmm)] catalyst in dioxane solution under mild conditions at 150 °C and an initial total pressure of 80 bar [*p*(CO₂)/*p*(H₂) = 1:3; 1 bar = 0.1 MPa]. Activation of the catalyst by the addition of acid^[11] was found to be necessary for the reaction (Table 1, entry 1). The use of [Ru(triphos)(tmm)] (2.5 mol%) together with trifluoromethanesulfo-

Table 1. Ruthenium-catalyzed methylation of NH₃ with CO₂ and molecular hydrogen.^[a]

$$\text{NH}_3 + \text{CO}_2 + \text{H}_2 \xrightarrow[\text{dioxane, 150}^\circ\text{C}]{\text{[Ru(triphos)(tmm)] co-catalyst}} \text{H}_3\text{C}-\overset{\text{CH}_3}{\text{N}}-\text{CH}_3$$

20 bar 60 bar

Entry	Catalyst [mol %]	Co-catalyst [mol %]	Time [h]	Yield ^[b] [%]
1	2.5	none	20	–
2	2.5	HNTf ₂ (20)	24	23
3	2.5	Al(OTf) ₃ (20)	24	67
4	1.5	Al(OTf) ₃ (10)	24	36
5	2.5	Al(OTf) ₃ /HNTf ₂ (20:5)	24	73
6	2.5	Al(OTf) ₃ /HNTf ₂ (20:10)	24	77

[a] Reaction conditions: [Ru(triphos)(tmm)], co-catalyst, 0.32 M NH₃ in dioxane (2 mL), CO₂/H₂ (20:60 bar), 150 °C. [b] TMA yield in the reaction solution was determined by NMR spectroscopy by using mesitylene as an internal standard.

nylimide (HNTf₂, 20 mol%) resulted in the formation of TMA in 23% yield as the only methylated amine product detectable in the reaction solution (Table 1, entry 2). A larger excess amount of HNTf₂ gave a lower yield of TMA and methanol was formed as the major product.

In addition to protic acids, Lewis acids such as Al(OTf)₃ (aluminum trifluoromethanesulfonate) were recently reported as co-catalysts for hydrogenation reactions by using ruthenium-triphos catalysts.^[12] Replacing HNTf₂ with Al(OTf)₃ resulted in a largely improved performance of the Ru catalyst and led to selective formation of TMA in a high yield of 67% (Table 1, entry 3). Decreasing the loading of [Ru(triphos)(tmm)]/Al(OTf)₃ to 1.5:10 mol% led to a drop in the TMA yield to 36% (Table 1, entry 4). Interestingly, the use of a Brønsted acid in addition to Al(OTf)₃ improved the activity even further to afford TMA in yields of 73 and 77% at HNTf₂ loadings of 5 and 10 mol%, respectively (Table 1, entries 5 and 6).

To obtain insight into the progress of the reaction, experiments at various reaction times were analyzed (Table 2). After 12 h, selective formation of TMA in 21% yield was determined (Table 2, entry 1), and the yield increased to 30% within 15 h (Table 2, entry 2). Together with the yield of 67% obtained after 24 h (Table 1, entry 3), these data indicate an induction period for the catalytic system to reach its full activity. Conducting the reaction at temperatures of 120 and 180 °C in

Table 2. Parameter variation in the ruthenium-catalyzed methylation of NH₃ with CO₂ and molecular hydrogen.^[a]

$$\text{NH}_3 + \text{CO}_2 + \text{H}_2 \xrightarrow[\text{solvent, T, t}]{\text{[Ru(triphos)(tmm)] (2.5 mol\%) Al(OTf)_3 (20 mol\%)}} \text{H}_3\text{C}-\overset{\text{CH}_3}{\text{N}}-\text{CH}_3$$

20 bar 60 bar

Entry	Solvent	Temperature [°C]	Time [h]	Yield ^[b] [%]
1	dioxane	150	12	21
2	dioxane	150	15	30
3	dioxane	120	20	16
4	dioxane	180	20	34
5 ^[b]	THF	150	24	52
6 ^[c]	dioxane/H ₂ O	150	24	53

[a] Reaction conditions: [Ru(triphos)(tmm)] (2.5 mol%), Al(OTf)₃ (20 mol%), 0.32 M NH₃ in dioxane (2 mL), CO₂/H₂ (20:60 bar). [b] TMA yield in the reaction solution was determined by NMR spectroscopy by using mesitylene as an internal standard. [c] 0.4 M NH₃ in THF (2 mL). [d] H₂O (0.5 mL) was added.

both cases resulted in lower yields than those obtained under the standard conditions at 150 °C (Table 2, entries 3 and 4). Changing the reaction solvent to THF gave TMA in a slightly lower 52% yield (Table 2, entry 5) than that obtained in dioxane under comparable conditions. Interestingly, the addition of water (dioxane/H₂O = 4:1) still afforded TMA in a good yield of 53% (Table 2, entry 6), which confirmed the stability of the catalyst system in aqueous media.

This finding prompted us to investigate the possible use of ammonium chloride (NH₄Cl) in aqueous solution as the nitrogen source for the direct synthesis of trimethylamine hydrochloride (TMA·HCl). However, the use of the established conditions in the presence of Al(OTf)₃ gave no methylation product. Conversely, in the absence of Al(OTf)₃, the NH₄Cl feed was converted smoothly into TMA·HCl in 46% yield by using a 4:1 mixture of dioxane/H₂O (Table 3, entry 1). Increasing the pressure of the gas mixture and in particular the partial pressure of CO₂ resulted in increased yields of 60 and 88%, respectively (Table 3, entries 2 and 3). Finally, a practically quantitative yield

Table 3. Direct synthesis of TMA·HCl in aqueous solution by the [Ru(triphos)(tmm)]-catalyzed methylation of NH₄Cl with CO₂ and H₂.^[a]

$$\text{NH}_4\text{Cl}_{\text{aq}} + \text{CO}_2 + \text{H}_2 \xrightarrow[\text{Dioxane/water (4/1 mL), 150}^\circ\text{C, 24 h}]{\text{[Ru(triphos)(tmm)]}} (\text{CH}_3)_3\text{NHCl}_{\text{aq}}$$

Entry	[Ru] [mol %]	CO ₂ [bar]	H ₂ [bar]	Yield ^[b] [%]
1	2.5	20	60	46
2	2.5	30	90	60
3 ^[c]	2.5	40	90	88
4	5	40	90	> 99

[a] Reaction conditions: [Ru(triphos)(tmm)] (2.5 or 5 mol%), NH₄Cl (1 mL NH₄Cl in H₂O solution, 2 M, 2.0 mmol), dioxane (4 mL). [b] TMA yield in the reaction solution was determined by NMR spectroscopy by using mesitylene as an internal standard. [c] A total of 2 mL of H₂O was used.

(>99%) of TMA·HCl was obtained at an increased catalysts loading of 5 mol% (Table 3, entry 4).

Under the optimized conditions, the aqueous/organic biphasic system also allowed for convenient separation of the catalyst and product (Figure 1). Upon removing the reaction mix-

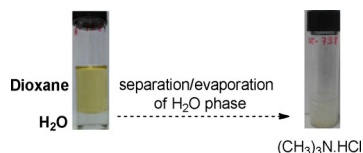
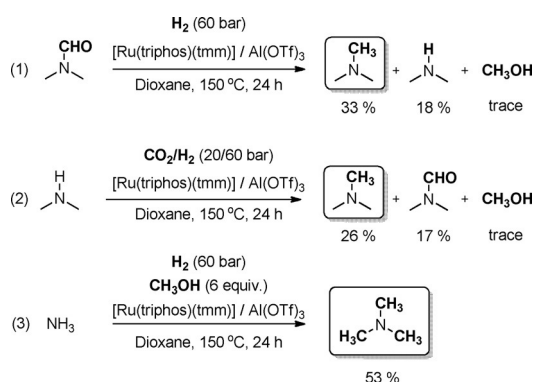


Figure 1. The aqueous/organic biphasic system after the reaction.

ture from the high-pressure reactor, the two liquid phases separated spontaneously with the catalyst partitioning into the organic dioxane phase with high preference, as judged from the coloration. TMA·HCl formed was isolated as a colorless solid after separation/evaporation of the aqueous phase (Figure 1). This beneficial phase behavior opens the possibility for integrated reaction/separation sequences under recycling of the organic catalyst phase.

To gain insight into the pathway of the selective formation of TMA starting from the $\text{NH}_3/\text{CO}_2/\text{H}_2$ feed, we conducted a set of experiments with different possible intermediates for TMA formation. Formamides were previously suggested as intermediates for the direct *N*-methylation of amines.^[6b,13] Under the standard reaction conditions but in the absence of CO_2 , the hydrogenation of DMF gave TMA in a yield of 33% in addition to trace amounts of methanol and 18% of DMA, which most likely resulted from catalytic decarbonylation of DMF [Scheme 2, Eq. (1)]. If dimethylamine was used as a substrate

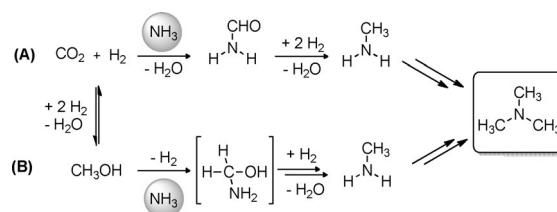


Scheme 2. Control reactions to elucidate possible pathways for the [Ru(triphos)(tmm)]-catalyzed methylation of ammonia starting from DMF, DMA, or NH_3 .

under CO_2/H_2 pressure, TMA was obtained in 26% yield, and in addition, DMF was detected as a byproduct [Scheme 2, Eq. (2)]. Again, however, methanol was observed in trace amounts under these conditions. This prompted us to probe the direct methylation of ammonia with methanol under these mild conditions. Indeed, TMA was obtained in 53% yield if the

reaction was performed in the presence of methanol and the absence of CO_2 [Scheme 2, Eq. (3)].

Taken together, these results suggest, in principle, two possible pathways for the methylation of ammonia and ammonium chloride with the novel catalytic process (Scheme 3). In pathway A, the methylation occurs via formamide intermediates,



Scheme 3. Possible reaction pathways for the [Ru(triphos)(tmm)]-catalyzed methylation of ammonia by using CO_2/H_2 as a C_1 synthon.

which are well known to be formed from amines, CO_2 , and H_2 .^[6] In pathway B, methanol is formed from CO_2 and H_2 and acts as a methylating agent through typical alcohol-amination mechanisms.^[14] As Ru-triphos is known to catalyze the hydrogenation of amides^[15] as well as the hydrogenation of CO_2 to methanol,^[7] distinction between the two pathways is currently not plausible. Given the possible equilibria between the involved species, they may well occur in parallel under the catalytic action of the Ru-triphos system.

In conclusion, the selective catalytic triple *N*-methylation of ammonia and ammonium chloride by using CO_2 as a C_1 source and molecular hydrogen as a reducing agent was demonstrated. The catalytic system comprised the readily available complex [Ru(triphos)(tmm)] [triphos: 1,1,1-tris(diphenylphosphino)methyl)ethane, tmm: trimethylene methane] as a precatalyst. For the selective synthesis of trimethylamine (TMA) from ammonia in organic solvents, a Lewis and/or Brønsted acid as co-catalyst was required. The conversion of ammonium chloride occurred very efficiently with practically quantitative yield in a two-phase aqueous/organic system. No co-catalyst was required in this case, probably because of the availability of the inherent proton from the substrate. Intermediate formation of formamides and/or methanol were identified as possible pathways for the construction of the methyl groups from the CO_2/H_2 mixture, and further mechanistic studies are underway to unravel the complex reaction network.

A salient feature of this new catalytic reaction is the use of ammonia, CO_2 , and H_2 as the only reagents: all three components are readily available at ammonia production sites. At present, the hydrogen for ammonia production is formed from fossil feedstocks, which results in concomitant CO_2 formation through the water gas shift equilibrium. Whereas the current technology to produce methylamines requires an additional unit operation for methanol production, the catalytic process described herein allows for direct utilization of the available gaseous production streams. Of course, the potential impact on the carbon footprint of the synthesis of TMA or TMA·HCl

will be even larger as hydrogen may become available from nonfossil sources exploiting excess renewable energy.

Experimental Section

General procedure for the one-step synthesis of trimethylamine starting from $\text{NH}_3/\text{CO}_2/\text{H}_2$

A solution of 0.32 M ammonia in dioxane (2.0 mL) was added under an argon atmosphere to a Schlenk tube containing [Ru(tri-phos)(tmm)] (0.012 g, 0.016 mmol) and $\text{Al}(\text{OTf})_3$ (0.061 g, 0.13 mmol). After stirring for 5 min, the solution was transferred to a carefully degassed and dried 20 mL stainless-steel autoclave. The autoclave was pressurized at room temperature with 20 bar CO_2 and then H_2 was added up to a total pressure of 80 bar. The mixture was agitated with a magnetic stir bar and was heated to 150 °C by using a preheated aluminum cone. After 24 h, the autoclave was cooled in an ice bath and was then carefully vented. The yield of trimethylamine in the solution was analyzed by ^1H NMR spectroscopy by using mesitylene as an internal standard.

General procedure for the one-step synthesis of trimethylamine starting from $\text{NH}_4\text{Cl}/\text{CO}_2/\text{H}_2$

A carefully degassed and dried 20 mL stainless-steel autoclave was charged under an argon atmosphere with a solution of 2 M NH_4Cl in water (1.0 mL). Under an argon atmosphere, [Ru(tri-phos)(tmm)] (0.039 g, 0.05 mmol) was dissolved in degassed dioxane (4 mL) in a Schlenk tube. The mixture was then transferred under an argon atmosphere by cannula to the autoclave. The autoclave was subsequently pressurized at room temperature with CO_2 to 20 bar and then H_2 was added up to a total pressure of 80 bar. The mixture was stirred and heated to 150 °C by using a preheated aluminum cone. After 24 h, the autoclave was cooled to room temperature, and the mixture was stirred for 2 h. The autoclave was then cooled in an ice bath and carefully vented. The reaction solution was analyzed by ^1H NMR spectroscopy by using mesitylene as an internal standard.

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- [1] Chemical Economics Handbook (CEH): Market report alkylamines, Eaglewood, 2014.
- [2] a) P. Roose in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2015; b) D. R. Corbin, S. Schwarz, G. C. Sonnichsen, *Catal. Today* 1997, 37, 71.
- [3] a) P. Roose, M. G. Turcotte, J. W. Mitchell in *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, New York, 2000; b) C. Gründling, G. Eder-Mirth, J. A. Lercher, *J. Catal.* 1996, 160, 299.
- [4] K. Segawa, A. Sugiyama, H. Tachibana, Y. Kurusu, Nitto Chemical Industry Co., Ltd. US 5,210,308, Japan, 1993.
- [5] K. S. Hayes, *Appl. Catal. A* 2001, 221, 187.
- [6] a) W.-H. Wang, Y. Himeda, J. T. Muckerman, G. F. Manbeck, E. Fujita, *Chem. Rev.* 2015, DOI: 10.1021/acs.chemrev.5b00197; b) J. Klankermayer, S. Wesselbaum, K. Beydoun, W. Leitner, *Angew. Chem. Int. Ed.* 2015, DOI: 10.1002/anie.201507458; *Angew. Chem.* 2015, DOI: 10.1002/ange.201507458.
- [7] a) S. Wesselbaum, T. Vom Stein, J. Klankermayer, W. Leitner, *Angew. Chem. Int. Ed.* 2012, 51, 7499; *Angew. Chem.* 2012, 124, 7617; b) S. Wesselbaum, V. Moha, M. Meuresch, S. Brosinski, K. M. Thenert, J. Kothe, T. v. Stein, U. Englert, M. Hölscher, J. Klankermayer, W. Leitner, *Chem. Sci.* 2015, 6, 693; J. Klankermayer, W. Leitner, *Science* 2015, 350, 629.
- [8] a) S. V. Gredig, R. A. Koeppel, A. Baiker, *J. Chem. Soc. Chem. Commun.* 1995, 73; b) S. V. Gredig, R. Koeppel, A. Baiker, *Catal. Today* 1996, 29, 339; c) S. V. Gredig, R. A. Koeppel, A. Baiker, *Catal. Lett.* 1997, 46, 49.
- [9] S. Schreiner, J. Y. Yu, L. Vaska, *Inorg. Chim. Acta* 1988, 147, 139.
- [10] a) P. G. Jessop, Y. Hsiao, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* 1994, 116, 8851; b) L. Vaska, S. Schreiner, R. A. Felty, J. Y. Yu, *J. Mol. Catal.* 1989, 52, L11.
- [11] F. M. Geilen, B. Engendahl, M. Holscher, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* 2011, 133, 14349.
- [12] Y. Li, C. Topf, X. Cui, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* 2015, 54, 5196; *Angew. Chem.* 2015, 127, 5285.
- [13] a) K. Beydoun, T. vom Stein, J. Klankermayer, W. Leitner, *Angew. Chem. Int. Ed.* 2013, 52, 9554; *Angew. Chem.* 2013, 125, 9733; b) Y. Li, I. Sorribes, T. Yan, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* 2013, 52, 12156; *Angew. Chem.* 2013, 125, 12378; c) A. Tlili, E. Blondiaux, X. Frogneux, T. Cantat, *Green Chem.* 2015, 17, 157.
- [14] a) V. N. Tsarev, Y. Morioka, J. Caner, Q. Wang, R. Ushimaru, A. Kudo, H. Naka, S. Saito, *Org. Lett.* 2015, 17, 2530; b) T. T. Dang, B. Ramalingam, A. M. Seayad, *ACS Catal.* 2015, 5, 4082; c) E. J. Derrah, M. Hanauer, P. N. Plessow, M. Schelwies, M. K. da Silva, T. Schaub, *Organometallics* 2015, 34, 1872.
- [15] a) A. A. Núñez Magro, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* 2007, 3154; b) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin, D. J. Cole-Hamilton, *Chem. Eur. J.* 2013, 19, 11039; c) T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Hölscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* 2014, 136, 13217.

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