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Ruthenium-Catalyzed Methylation of Amines with Paraformaldehyde in Water under Mild Conditions

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Methylated amines are highly important for a variety of pharmaceutical and agrochemical applications. Existing routes for their formation result in the production of large amounts of waste or require high reaction temperatures, both of which impact the ecological and economical footprint of the methodologies. Herein, we report the ruthenium-catalyzed reductive methylation of a range of aliphatic amines, using paraformaldehyde as both substrate and hydrogen source, in combination with water. This reaction proceeds under mild aqueous reaction conditions. Additionally the use of a secondary phase for catalyst retention and recycling has been investigated with promising results.

Methylamines are ubiquitous in both natural products as well as throughout synthetic organic molecules. Key examples include their use in drug molecules[1,2] as well as their occurrence within natural molecules such as neurotransmitters.[3–5]

One existing method for the methylation of amines involves the use of a methylating agents, which, whilst effective, can result in over-methylation to yield quaternary amine salts.[6] Alternative single-carbon sources have also been investigated. A recent seminal publication by Leitner et al. reports the use of CO_2 as the C_1 source for the methylation of anilinic amines using a ruthenium catalyst. The proposed mechanism is believed to proceed through the formation of a formamide followed by subsequent reduction.[7] This work was built upon in a later publication detailing the reductive methylation of imines.[8] Beller et al. reported an alternative ruthenium system with an expanded substrate scope that included aliphatic amines.[9] Formic acid has been reported as a C_1 source in the direct methylation of a range of primary and secondary aromatic amines as recently reported by Cantat et al.[10] In analogy to CO_2 protocols, a ruthenium triphos catalyst with triflimide additive has been used to activate formic acid instead of CO_2. It has been proposed that the reaction proceeds through a mechanism involving the formation of a formamide intermediate with subsequent reduction. The reaction substrate scope was, however, noted to be limited, and reaction temperatures of 150 °C were required. Similarly, the classical amine methylation Eschweiler–Clarke reaction,[11] which needs an excess of both formic acid and formaldehyde, requires high temperatures, 120–160 °C, with long reaction times and results in the formation of various side products.[6] In these reactions, the formaldehyde is believed to condense with the amine, with the resulting imine becoming reduced by the formic acid. The use of a metal catalyst to directly hydrogenate the imine intermediate or substrate has been reported to negate the need for the formic acid; many, primarily noble metal, catalysts have been reported for this methodology.[12–14]

Our interest in formaldehyde as a C_1 building block originated from the recent publications whereby aqueous formaldehyde solutions were shown to liberate H_2 in the presence of a robust ruthenium catalyst, $[Ru(p\text{-cymene})Cl_2]_2$.[15–17] This mechanism was thought to proceed through the dehydrogenation of methanediol, the favourable product formed upon formaldehyde hydration, to formic acid. Further work showed that formaldehyde could be trapped as an intermediate in the catalytic reforming of paraformaldehyde (pFA) in aqueous solutions to yield methanol.[18] It was speculated that the use of a nucleophilic substrate, such as an amine, could attack the formaldehyde intermediate yielding an iminium cation and then undergo subsequent reduction to lead to a single substrate acting as both the carbon and hydrogen source in the methylation of amines for synthetic applications (Scheme 1).

The high importance of formaldehyde as a chemical reagent for current and future technologies is reflected in more than 50 industrial processes in which formaldehyde plays a key role for the manufacture of products used in daily life.[15,19–21] The product variety covers processed wood, paints, cosmetics, resins, polymers, adhesives besides many others. Formaldehyde is usually processed in the liquid and even aqueous phase. All these industries merge to a multi-billion-dollar market based on more than 30 mega tons per year of formaldehyde as building block and cross-linker.[15,19–21] Currently, >35% of the world methanol production is converted into formaldehyde, which turns formaldehyde into the number one product directly derived from methanol. In this context, it is feasible to find further processes using paraformaldehyde owing to its safe handling, availability and the fact that it can be derived from biomass (currently via syngas and methanol synthesis); this will turn paraformaldehyde into a bulk reagent available from renewable sources in future biomass- and C_1-based industries.[15–17,19–21] Additionally, there are processes under development to decompose residual formaldehyde from

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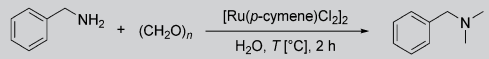
industrial wastewater; therefore, aqueous-phase processes using formaldehyde may turn even greener in the near future.[15]

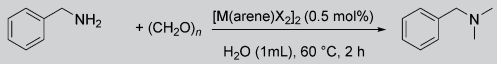
Table 1. Optimisation of reaction parameters for methylation reactions.



Entry	T [°C]	Cat. [mol%]	Amine/pFA[a]	Conv.[b] [%]
1	50	0.5	1:3	6
2	60	0.5	1:3	40
3	70	0.5	1:3	55
4	70	2	1:3	58
5	60	0.5	1:5	85
6	60	2	1:5	95
7	70	0.5	1:10	>99
8	60	0.5	1:5	91
9	60	0.5	1:5	61

[a] Reactions were run on a 2 mmol (1 M) scale of benzylamine, except entries 8 (2 M) and 9 (0.5 M). [b] Conversions were determined by analysis of the ^{1}H NMR spectra.

Table 2. Catalyst screen for the methylation of benzylamine.



Entry	Metal	Arene	X	Conv.[a,b] [%]
1	Ru	toluene	Cl	>99
2	Ru	benzene	Cl	56
3	Os	*p*-cymene	Cl	10
4	Ru	benzene	Br	86
5	Ru	*p*-cymene	SCN	10
6	Ru	*p*-cymene	I	>99
7	Ru	2-phenoxyethanol	Cl	77
8	Ru	1-phenethyl-2,3,-dimethyl-imidazolium chloride	Cl	83

[a] Reactions run on a 2 mmol scale with 5 equiv. of pFA. [b] Conversions determined by analysis of the ^{1}H NMR spectra.

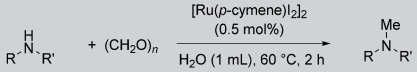
We herein report the use of arene ruthenium halide catalysts for the methylation of a range of primary and secondary amines with pFA under mild reaction conditions in short reaction times. Initial investigations employed benzylamine as the exemplary substrate and the reaction parameters were optimised using the commercially available $[Ru(p\text{-cymene})Cl_2]_2$ catalyst as shown in Table 1.

Whilst increases in temperature and catalyst loadings were noted to be favourable for methylation, it was seen that reactions at 60 °C with low catalyst loadings of 0.5 mol% gave acceptable conversions provided a 2:5 ratio of pFA per N–H group was used. An excess of pFA is required as some is lost to the competing reactions of dehydrogenation and methanol reformation. It was noted that higher reaction concentrations led to higher conversions (entries 7 and 8).

Taking the optimised reaction parameters, the use of a range of similar ruthenium catalysts was investigated. Table 2 shows that whilst alternative halide bridging anions, such as iodide and bromide, were compatible to the reaction with iodide showing quantitative conversion, the use of others such as the thiocyanate-bridged catalyst gave almost no conversion. Similarly, the replacement of the ruthenium catalyst with the osmium analogue (entry 3) gave low conversions.

Further reactions with the three best catalysts; $[Ru(toluene)Cl_2]_2$, $[Ru(p\text{-cymene})Cl_2]_2$ and $[Ru(p\text{-cymene})I_2]_2$, over a shorter reaction time of 1 h led to conversions of 41%, 61% and 76%, respectively. Having determined that $[Ru(p\text{-cymene})I_2]_2$ was the optimum catalyst, we proceeded to investigate the substrate scope available to the reaction. Table 3 shows a range of amines that could be methylated. With the exception of entry 5, all of the reactions proceeded in good-to-quantitative conversions and it can be seen that both primary and secondary amines, including cyclic and acyclic examples, were susceptible to methylation under the reaction conditions. Having demonstrated wide substrate scope availability, we decided to test the limitations of the reaction methodology. Challenging nitrogen nucleophiles such as sulfonamides and amides were investigated although no conversion to either the corresponding methylated or formylated products was observed even after 24 h under the reaction conditions; this is presumed to be due to lack of nucleophilicity required to form

Table 3. Amine methylation substrate scope.

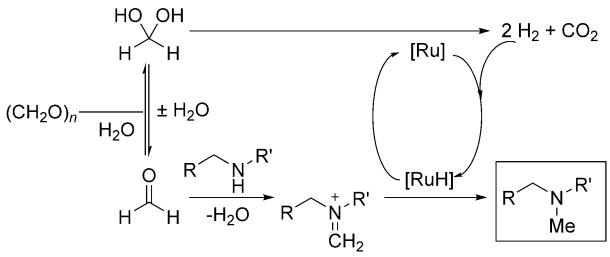


Entry	Amine[a]	Product amine	Equiv. pFA	Isolated yield [%]
1	cyclohexylamine	*N,N*-dimethyl cyclohexylamine	5	78
2	benzylamine	*N,N*-dimethyl benzylamine	5	80
3	morpholine	*N*-methyl morpholine	2.5	89
4	phenethylamine	*N,N*-dimethyl phenethylamine	5	86
5	5-amino-1-pentanol	*N,N*-dimethyl 5-amino-1-pentanol	5	73
6	piperidine	*N*-methyl piperidine	2.5	95
7	dibutylamine	*N*-methyl dibutylamine	2.5	97

[a] Reactions run on a 2 mmol scale.

the imine intermediate. Investigated anilines formed only intractable mixtures thought to be caused by polymerisation, and carbon nucleophiles showed no detectable methylation or formylation (Supporting Information, Table 2).

Having seen that methylated products were formed rather than the formamide products seen through similar methodologies,[22] the presence of a formamide intermediate, which could undergo subsequent reduction to the methylated product, was looked for in both the ^{1}H and ^{13}C NMR spectra. No corresponding peaks were seen, suggesting that this is not a reaction intermediate; this conclusion was further corroborated by submitting test amides, namely dimethyl formamide and benzamide, to the reaction conditions with no reduction seen in either case. Further ^{1}H and ^{13}C NMR analysis was conducted with initial build-up of the monomethylated product followed by subsequent decrease as conversion to the dimethylated product swiftly occurred, as determined by ^{1}H NMR analysis (Supporting Information, Figure 1). ^{13}C NMR spectroscopy was used to identify reaction intermediates present shortly after initiation of the reaction. As expected, signals corresponding to both the mono- and dimethylated product were present as was a signal indicative of the proposed Mannich-type imine intermediate.[23] This has led to the proposed reaction mechanism (Scheme 1) detailing the bifunctional use of formaldehyde as both substrate and reducing agent, in the hydrated form of methanediol in our ongoing research.[18]

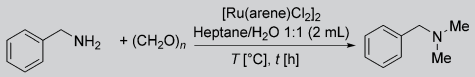


Scheme 1. Possible pathway for amine methylation with pFA.

Having shown that the reaction could be conducted in a monophasic system, leading to high yielding methylation of amines, it was postulated that the methodology might be expanded to allow for a biphasic system; this could enable catalyst separation and reuse. As arene ruthenium catalysts show high affinity for the aqueous phase, it was decided to investigate the potential for conducting biphasic methylation reactions with retention of the catalyst in the aqueous phase. To ensure a high aqueous solubility of the ruthenium catalyst, a ruthenium catalyst with a charged imidazolium functionality attached as part of the aryl group was investigated.[18,24] The results, shown in Table 1 in the Supporting Information, demonstrate compatibility of the methylation of benzylamine with a range of organic solvents, from the highly polar to the highly hydrophobic. It was evident that the water/heptane biphasic mixture visibly showed the least leaching of the catalyst into the organic phase; hence, this system was taken forward for optimisation despite it not showing the highest levels of methylation.

Retaining the use of the imidazolium ruthenium catalyst, optimisation of the biphasic system was carried out (Table 4). These results indicate that again the use of an excess of pFA is required with a 2:5 optimum ratio for each free N–H group to be methylated. It was encouraging to note that the use of low catalyst loadings was possible without a corresponding decline in the conversions.

Table 4. Reaction parameter optimisation for biphasic methylations.



Entry	Equiv. pFA	Catalyst [mol%]	T [°C]	t [h]	Conv.[a] [%]
1	1.33	1.0	80	16	13
2	2	1.0	80	16	20
3	3	1.0	80	16	25
4	5	1.0	80	16	38
5	5	0.25	90	2	32
6	5	0.5	90	2	37
7	5	1.0	90	2	35
8	5	2.0	90	2	42

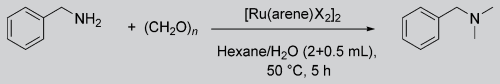
[a] Reactions run on a 2 mmol scale, 0.5 mL H_2O and 2 mL heptane used as solvent with $[Ru(arene)Cl_2]_2$ (arene: 1-phenethyl-2,3,-dimethyl-imidazolium chloride).

Interestingly, the reduction of the reaction temperature led to greater conversions; however, below 50 °C there was a sharp decrease in activity. This was attributed both to avoiding competitive reaction pathways, such as dehydrogenation of aqueous formaldehyde, that were expedited by high temperatures as well as circumventing the entropically favourable hydrolysis of the proposed imine intermediate at the higher temperatures. Having optimised the reaction conditions at 50 °C, a screen of potential ruthenium catalysts was conducted for the biphasic reaction (Table 5).

With the optimised system in hand, a substrate scope for amines was undertaken as shown in Table 6. The use of simple, low boiling amines was also investigated. For these substrates an alternative method for isolation was required; thus, ethereal HCl was applied to generate the hydrochloride salts, which led to the high yields recorded in entries 6–9 in Table 6. As with the monophasic reaction system, a range of primary and secondary amines could be isolated in good-to-excellent yields.

In consequence of the successful biphasic reactions and the ability to retain the catalyst in the aqueous phase, this system was further investigated. Dibutylamine was chosen as the exemplary substrate for methylation and was submitted to a set of recycling experiments, the results of which are reported in Figure 1 below and SI-Figure 2 in the Supporting Information. It is apparent that the turnover numbers remain high for each of the recycling steps with little reduction in efficiency. Notably, the addition of a phosphate buffer helped to stabilise the catalyst over repeated use.

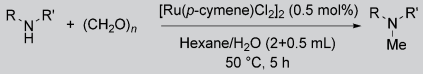
Table 5. Catalyst screen for the biphasic methylation of benzylamine.



Entry	Arene	Halogen	Conv.[a] [%]
1	*p*-cymene	Cl	90
2	toluene	Cl	53
3	2-phenoxyethanol	Cl	39
4	benzene	Br	29
5	*p*-cymene	I	78
6	1-phenethyl-2,3,-dimethyl-imidazolium chloride	Cl	43
7	*N,N,N*-triethyl-phenethyl ammonium mesolate	Cl	52

[a] Reactions run on a 2 mmol scale with 5 equiv. of pFA. Conversions determined by analysis of the ^{1}H NMR spectra. Hexane used rather than heptane simply for practical convenience.

Table 6. Substrate screen for biphasic methylations.



Entry	Amine	Equiv. pFA	Isolated yield[a] [%]
1	cyclohexylamine	5	88
2	benzylamine	5	83
3	phenethylamine	5	93
4	dibutylamine	2.5	87
5	octylamine	5	98
6	diethylamine	2.5	83[b]
7	isobutylamine	5	83[b]
8	*tert*-butylamine	5	77[b]
9	diisopropylamine	2.5	71[b]

[a] Reactions run on a 2 mmol scale. [b] Isolated yield determined by comparison of isolated HCl salt against a 1,4-dioxane standard.

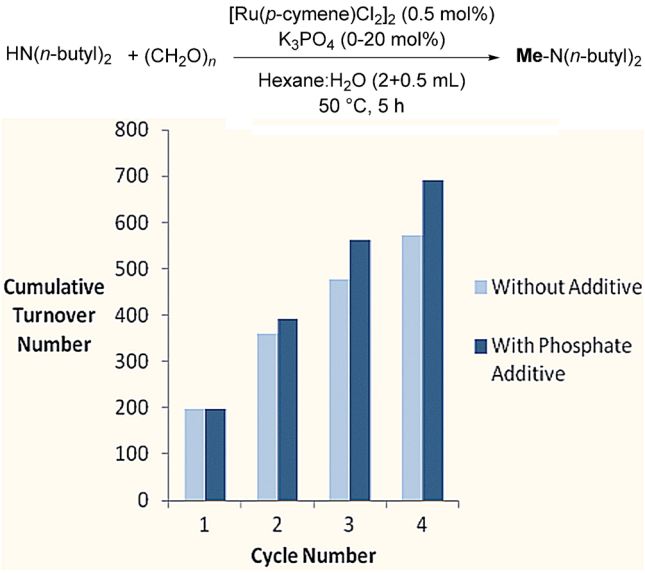


Figure 1. Biphasic catalyst recycling experiments.

In conclusion, we have herein reported simple, mild and efficient mono- and biphasic methodologies for the methylation of a wide variety of aliphatic amines. Low catalyst loadings and short reaction times for the aqueous monophasic reaction enhance its green credentials whilst the use of a secondary phase allows for good levels of catalyst retention. Methods for the immobilisation of the optimised catalysts upon a secondary solid phase are ongoing.

Experimental Section

Exemplary monophasic reaction: Into a screw-neck vial, [Ru(*p*-cymene)I_2]$_2$ (9.8 mg; 0.01 mmol, 0.5 mol%) and pFA (300 mg; 10 mmol) were added. Water (1.0 mL) was added, which was followed by addition of benzylamine (2 mmol; 218 μL); the vial was closed and then placed into a preheated aluminium block at 60 °C and stirred for 2 h. After this time, the vial was cooled to room temperature and NaOH solution (2 mL, 2 M) was added; the aqueous phase was washed three times with 10 mL dichloromethane. Organic fractions were combined, dried over $MgSO_4$ and Al_2O_3 and solvent was reduced in vacuo to yield the desired amine.

Exemplary biphasic reaction: Into a screw-neck vial, [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg; 0.01 mmol, 0.5 mol%) and pFA (300 mg; 10 mmol) were added. Hexane (2 mL) and water (0.5 mL) were added, which was followed by addition of benzylamine (2 mmol; 218 μL); the vial was closed and then placed into a preheated aluminium block at 50 °C and stirred for 5 h. After this time, the vial was cooled to room temperature, neutralised and separated as per the monophasic system (see above).

Recycling experiment protocol: [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 0.01 mmol, 0.5 mol%) and pFA (150 mg; 5 mmol) were added to a screw-cap vial, which was followed by addition of hexane (2 mL), water (0.5 mL) and dibutylamine (340 μL; 2 mmol). After sealing and heating at 50 °C for 5 h, the organic layer was extracted and solvents were removed in vacuo. The residue was analysed by ^{1}H NMR spectroscopy. For each cycle, hexane (2 mL), dibutylamine (340 μL; 2 mmol) and pFA (150 mg; 5 mmol) were recharged into the reaction vial containing the ruthenium catalysts in the aqueous phase.

Acknowledgements

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Keywords: amination · homogeneous catalysis · methylation · paraformaldehyde · ruthenium

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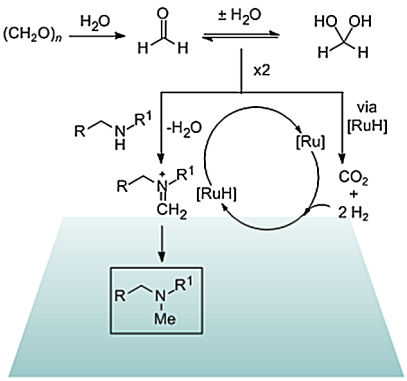
Ruthenium-Catalyzed Methylation of Amines with Paraformaldehyde in Water under Mild Conditions



Paraformaldehyde can do it easily: Methylated molecules are highly important for a variety of applications. Existing routes for their formation result in the production of large amounts of waste or require high reaction temperatures. To solve this, a simple methylation of aliphatic amines with paraformaldehyde in a biphasic reaction consisting of water and organic solvent is presented. The ruthenium catalyst is immobilized in the aqueous phase and suitable for recycling.