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Additive-free selective methylation of amines with formic acid over a Pd/In₂O₃ catalyst

Caroline Genre,^{*a} Idir Benaissa,^a Timothé Godou,^a Mathieu Pinault,^a and Thibault Cantat^{*a}

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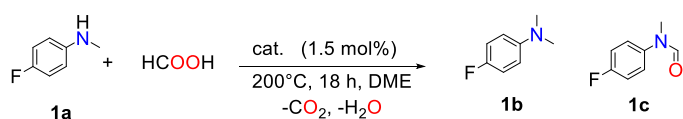
Abstract: Formic acid is used as the sole carbon and hydrogen source in the methylation of aromatic and aliphatic amines to methylamines. The reaction proceeds *via* a formylation/transfer hydrogenation pathway over a solid Pd/In₂O₃ catalyst without the need for any additive.

Methylamines are widely utilized compounds in both fine and bulk chemical industries. They are used as intermediates for the synthesis of agrochemicals, polymers, dyes, pharmaceuticals and are valuable organic building blocks.¹ Methylation of an amine in a drug molecule can have a strong effect on its lipophilicity and potency.² For these reasons, the development of methylation methods continues to attract the interest of chemists. The most common methods for synthesizing methylamines involve stoichiometric quantities of highly toxic methylating agents such as methyl iodide, formaldehyde, diazomethane or dimethylsulfate and generate abundant waste.³ In the quest for greener more sustainable reactions, catalytic methods utilizing renewable C1 sources (CO₂, HCOOH (FA)) associated to reductants (silanes, boranes, H₂) or additives (acids, salts) have been developed. Examples of such catalytic systems involve organometallic complexes of ruthenium⁴, rhodium⁵ or iron⁶. Amines were successfully methylated by CO₂/H₂ over solid catalysts as well, such as CuAlOx⁷, Pt-MoO_x/TiO₂⁸, PdGa/TiO₂⁹ or Cu/TiO₂¹⁰. These systems, however, require a high pressure of H₂. This issue can be solved with the use of liquid FA instead of a mix of gases, as it can act as both a carbon source and a reductant. Moreover, a now mature technology has been developed to promote its synthesis from the 2-electron reduction of CO₂ in an electrochemical cell over electro-catalysts, making FA a renewable reagent.¹¹ A few heterogeneous catalysts have been described for the methylation of amines with FA. Kim and co-workers reported the successful additive-free methylation of aromatic amines with FA catalyzed by a supported PdAg alloy in 2015¹². In 2016, Zhu et al. achieved this reaction over a Pd/C catalyst, albeit using hydrosilanes as reductants¹³. In order to expand the range

of possible catalysts for this reaction, we sought to exploit the association of a catalyst known for its CO₂ reduction activity and metal species active in reduction processes. We report here on the additive-free, one pot methylation of a variety of amines with an easily synthesized, water and air resistant catalyst. To our delight, we observed that Pd supported on indium oxide is active in the FA-mediated methylation of amines with yields up to 99%.

In₂O₃ was recently shown to be a highly efficient and specific catalyst for the hydrogenation of CO₂ to methanol.¹⁴ In a first attempt, we tested whether this oxide showed activity for the methylation of *p*-fluoro-*N*-methylaniline (**1a**) with FA (Table 1, entry 2). The catalytic reaction was conducted in a sealed autoclave under atmospheric pressure. A low *p*-fluoro-*N,N*-dimethylaniline (**1b**) yield of about 11 % was observed, as well as a 74% yield of *p*-fluoro-*N*-methylformanilide (**1c**). It thus appears that In₂O₃ is capable of methylating **1a** to **1b** with FA but the activity remains low. For this reason, In₂O₃-based catalysts doped with metals known for their hydrogenation properties (Pd, Pt, Ru) were synthesized and tested. The results are listed in Table 1. The catalysts were synthesized by an impregnation technique followed by calcination of the resulting powder at 400°C for 3 h under air. Pre-reducing the catalysts (20 bar H₂, 200°C, 1h) did not improve their activity nor their selectivity, therefore they were used as such. GC analysis of the atmosphere in the autoclave at the end of the reaction showed the presence of significant quantities of H₂ and CO₂ (Fig. S1). We thus postulate that *in situ* reduction of the catalysts was achieved from H₂ resulting from the decomposition of FA over the catalyst.

^a Université Paris-Saclay, CEA, CNRS, NIMBE, 91191 Gif-sur-Yvette (France). E-mail: caroline.genre@cea.fr; thibault.cantat@cea.fr

Table 1. Methylation of 4-fluoro-N-methylaniline (**1a**) with FA over various catalysts.^a

Entry	Cat.	Conv. (%)	Yield 1b (%)	Yield 1c (%)
1	None	97	Traces	96
2	In ₂ O ₃	98	11	74
3	Pd/In ₂ O ₃	100	94	4
4	Pd/C	88	9	72
5	Pt/In ₂ O ₃	85	30	51
6	Pt/C	58	5	47
7	Ru/In ₂ O ₃	82	14	59
8	Ru/C	75	8	44

^a Reaction conditions: **1a** (5 mmol), catalyst 1.5 mol%, FA (60 mmol), DME (10 mL), 200°C, 18 h. Yields determined by GC/MS using isoctane as an internal standard, after calibration.

4-fluoro-N-methylaniline was retained as a benchmark substrate. Among the various catalysts tested, Pd/In₂O₃ afforded the best activity for N-methylation (yield: 94%). Remarkably, Pd/In₂O₃ showed better activity than both In₂O₃ and Pd/C, indicating that a positive synergistic effect occurs between the oxidic support and the Pd catalytic species. The same observation can be made with Ru and Pt containing catalysts (entries 5-8).

Pd/In₂O₃ displays higher activity than the Pt and Ru containing analogues (100% conversion vs 85 and 82%, respectively), and higher selectivity towards **1b** (94% yield vs 30 and 14% respectively). The reaction conditions for the methylation of various amines were therefore optimized with this catalyst (see Table S1). When the reaction is conducted at 150°C, there is total conversion of **1a** but the yield in **1b** is limited to 22% after 12 h (entry 2). The results are much better at 200°C, with an 85% yield in the desired product. This is consistent with reports showing that In₂O₃ is more active for CO₂ hydrogenation above this temperature.¹⁴ Screening different solvents revealed that DME is the best suited for the methylation reaction (entry 1), while yields fall when the reaction is conducted in hexane (entry 3). With THF, significant degradation of the solvent is observed, making its use impractical (entry 4).

A 12h reaction time with 4-fluoro-N-methylaniline as a substrate leads to a 100% conversion with a 85% yield of **1b** (Table S1, entry 1), which increased to 94% after 18h (entry 5). Longer reaction times did not provide better yields (entry 6).

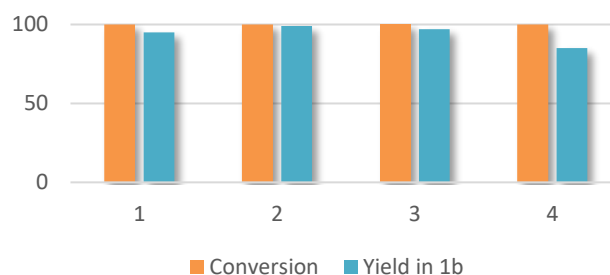
The quantity of FA relative to the substrate was also optimized. Tests were made with 2, 4, 8 and 12 equivalents of FA (entries 5 and 7-9). The best conversion (100% vs 58, 73, and 93%, respectively) and **1b** yield (94% vs 6, 16 and 23%

respectively) were obtained with 12 eq. FA (entry 5). This stoichiometry was thus selected for further catalytic reactions.

The Pd/In₂O₃ catalyst is a brown powder that turns to black after it is reduced. EDX mappings of a brown powder sample show that Pd, In, and O are spread uniformly (Fig. S3). XPS spectra of the samples were recorded before and after reaction with a substrate. They confirmed the presence of In, Pd and O in the samples. In the as-prepared state, the Pd3d signal at 337.0 eV is ascribed to PdO (Fig. S4).¹⁵ The In3d_{5/2} signal was detected at 444.4 eV, characteristic of In₂O₃ (Fig. S5)¹⁶. A shift of the Pd3d signal to 335.1 eV is observed for the reacted catalyst sample, which according to literature corresponds to elemental Pd.¹⁵ The In 3d_{5/2} signal was recorded at 444.7 eV, signaling that indium oxide was not significantly reduced during the reaction. The In/Pd ratio of the near surface region increased from nearly 1.0 for as-prepared catalyst to 12.1 in the reacted catalyst (Table S2). Such an evolution of the In/Pd ratio upon utilization of a similar Pd/In₂O₃ catalyst was reported by Neumann *et al.* and ascribed to the formation of intermetallic Pd-In particles and their subsequent covering by oxidic indium species migrating from the bulk to the surface of the material.¹⁶ In order to ensure that there is no contribution from Pd possibly leached from the solid catalyst, our benchmark reaction was carried out with pure In₂O₃ powder in the liquid phase recovered from a previous run of the reaction, but only extremely limited activity for amine methylation could be observed (3%).

It is likely that Pd in the catalyst is reduced by either FA or H₂ (produced upon FA decomposition), and that this metallic Pd on In oxide is the active catalytic species.

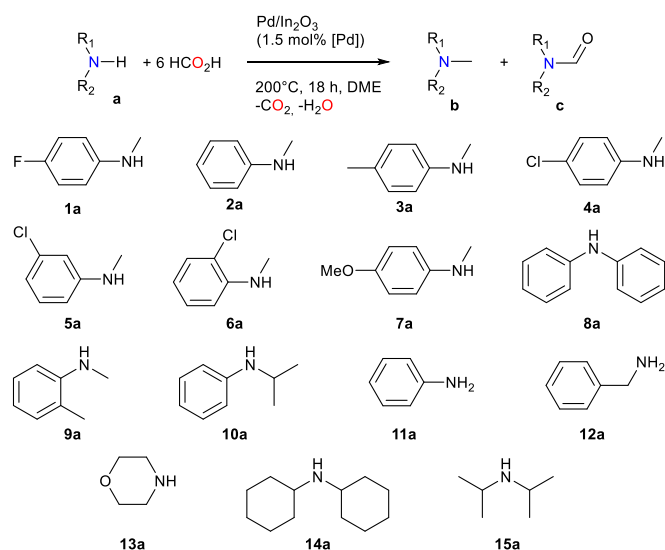
Recycling experiments were carried out with **1b** as a substrate (Fig. 1). After each run, the recovered catalyst was annealed under air at 400°C for 3h. Full conversion and excellent specificity were obtained with a second and third run of the catalyst. In a fourth run, specificity decreased to 85% of the desired product.

Fig. 1 Conversion and yield in **1b** (%) catalyst over Pd/In₂O₃ after 1, 2, 3 and 4 runs

The methylation of a variety of primary and secondary amines was carried out to explore the potential of this novel catalytic transformation. Using 12 equivalents of FA, the methylation of secondary aromatic amines (entries 1-7) is efficient, with yields ranging between 30 and 93% (18h, 200°C, 1.5 mol% [Pd]). The catalytic system tolerates a variety of

substituents on the aromatic ring. Interestingly, no hydrogenation of the aromatic cycle was observed, as can be the case with other Pd containing catalysts during hydrogenation of aromatic species including amides¹⁷. With aniline and *N*-methylaniline coupling by-products, mostly 4,4'-methylenebis(*N,N*-dimethylaniline), were observed. The same kind of coupling was observed with **5a** and **10a**, yielding 4,4'-methylenebis(3-chloro-*N,N*-dimethylaniline) and 4,4'-methylenebis(*N*-isopropyl-*N*-methylaniline) as side products. The catalytic system displayed only limited activity with aliphatic amines (entries 9-13), the best yield was obtained with morpholine (60%).

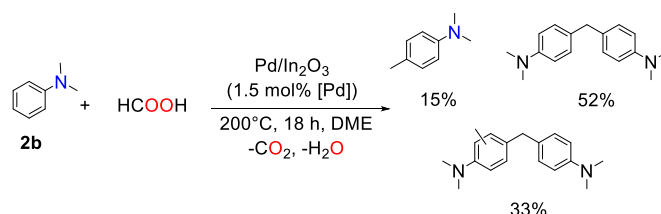
Table 2. Pd/In₂O₃ catalyzed methylation of aromatic and aliphatic amines with FA



Entry	Substrate	Conv. (%)	Yield b (%)	Yield c (%)
1	1a	100	94	traces
2	2a	100	84	8
3	3a	100	90	traces
4 ^a	4a	100	76	24
5	5a	100	77	traces ^b
6	6a	95	70	traces
7	7a	100	78	22
8	8a	100	99	traces
9	9a	100	82	16
10	10a	100	80	traces ^c
11	11a	89	29 (12 ^d)	20
12	12a	88 ^e	40 (1 ^f)	20 ^g
13	13a	100	60	38
14	14a	98	31	65
15	15a	100	25	73

^a4.5 mol% catalyst; ^bside-product: 4,4'-methylenebis(3-chloro-*N,N*-dimethylaniline) ^cside-product: methylenebis(*N*-isopropyl-*N*-methylaniline) ^d*N*-methylaniline; ^emix of various products including starting material and ethylated products; ^f*N*-methylbenzylamine; ^gmix of *N*-benzylformamide, *N*-benzyl-*N*-methylformamide, *N*-benzyl-*N*-formylformamide

With aromatic amines, products of methylation of the aromatic cycle were observed *via* Friedel-Crafts reaction: The reaction of *N,N*-dimethylaniline with FA over Pd/In₂O₃ (DME, 200°C, 18h) yielded 15% of *N,N*,4-trimethylaniline, 52% of 4,4'-methylenebis(*N,N*-dimethylaniline), and a mixture of various methylated derivatives of the latter (Scheme 1). This is further indication that the reaction time must be chosen accurately to avoid over-methylation



Scheme 1. Reaction of *N,N*-dimethylaniline with FA over Pd/In₂O₃

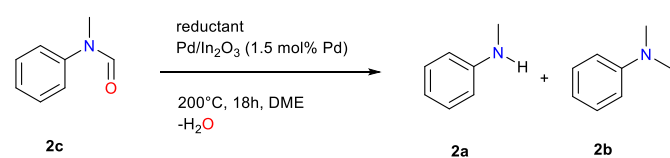
In light of these results, and in order to enhance the scope of this catalytic transformation, we investigated possible reaction pathways and intermediates. Based on the species detected at the end of the reaction, it is plausible that the methylation of the NH function involves the formation of a formamide intermediate, which is subsequently reduced.

Reaction of *N*-methylformamide **2c** with 12 equivalents of FA in our chosen conditions indeed provided *N,N*-dimethylaniline with an excellent 94% yield. A possible pathway is thus the conversion of the starting amine into the corresponding formamide, followed by either direct or transfer hydrogenation.

During the reaction, the pressure inside the autoclave increased to 30 bar. Gas chromatography analysis of the autoclave atmosphere confirms the presence of H₂ and CO₂, likely resulting from FA decomposition over the catalyst. It is thus possible that either FA or/and H₂ are responsible for formamide (transfer)-hydrogenation. To test these hypotheses, the hydrogenation of *N*-methylformamide was conducted in our preferred conditions with FA at 200°C and under a H₂ and a H₂/CO₂ atmosphere. At 160°C, conversion was extremely low, regardless the nature of the reductant, indicating that reduction of the amide is the rate determining step in the methylation of amines. A >99% conversion and excellent 94% yield of *N,N*-dimethylaniline were obtained with FA as a reductant (Table 3, entry 1) at 200°C. In contrast, the direct hydrogenation (30 bar H₂) of *N*-methylformamide **2c** provided a mixture of *N*-methylaniline **2a** and *N,N*-dimethylaniline **2b** with a 50 to 60% yield depending on the conditions. This is consistent with recent results published by Sorribes *et al.*,¹⁸ whereas only traces of the de-methylated product were observed with FA (Table 3, entries 2, 3). A higher H₂ pressure (50 bar) did not significantly modify the results, and a CO₂ pressure only had a marginal impact (Table 3, Entries 3, 4). This leads us to propose that FA, and not H₂ issued from its decomposition, is the principal reductant in the methylation of amines over Pd/In₂O₃ (Fig. 2).

Methanol was observed in the reaction medium, as could be anticipated from the fact that In_2O_3 catalyzes the hydrogenation of CO_2 to methanol. The use of 4 equivalents of methanol as a methylating agent was tested with *N*-methylaniline in our preferred conditions. The reaction yielded a moderate 22% yield of methylated product (conversion: 30%). It is thus possible that methanol issued from CO_2 hydrogenation is a minor contributor to amine methylation as well.

Table 3. Hydrogenation of *N*-methylformanilide with various reductants



Entry	Reductant	Pressure (bar)	Conv. (%)	Yield 2a (%)	Yield 2b (%)
1	FA (12 eq)	-	>99	Traces	94
2	H ₂	30	>99	32	60
3	H ₂	50	>99	50	49
4	H ₂ /CO ₂	30/30	>99	56	42

^a Reaction conditions: **1a** (5 mmol), Pd/ In_2O_3 80 mg, DME (10 mL), 200°C, 18 h. Yields determined by GC/MS using isooctane as an internal standard, after calibration.

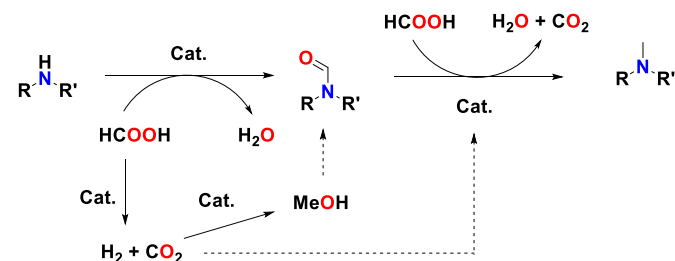


Figure 2. Proposed mechanism for the methylation of amines by FA

In conclusion, we have developed a simple, additive-free procedure for the *N*-methylation of amines with FA as a carbon and hydrogen source, by using a water and air resistant Pd/ In_2O_3 catalyst, without the need for an additional reductant. Aromatic amines are methylated with good yields and no reduction of the aromatic cycle is observed.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgments

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