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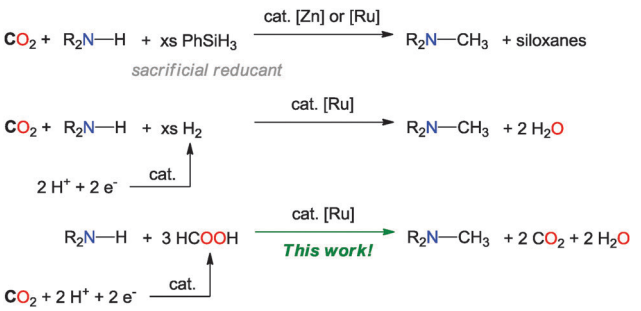
Catalytic methylation of aromatic amines with formic acid as the unique carbon and hydrogen source†

Solène Savourey, Guillaume Lefèvre, Jean-Claude Berthet and Thibault Cantat*

A novel methodology is presented for the direct methylation of amines, using formic acid as a unique source of carbon and hydrogen. Based on ruthenium(II) catalysts, the formation of the N–CH_3 group proceeds *via* an efficient formylation/transfer hydrogenation pathway.

The use of CO_2 as a building block for the production of value-added chemicals has recently attracted interest as it is a cheap and renewable resource. While CO_2 is already used for the industrial production of urea (Bosch-Meiser process), CO_2 conversion to methylamines has only been developed since 2013, to by-pass the use of formaldehyde or toxic methylating reagents such as methyl iodide, dimethyl sulfate or diazomethane.[1] The methylation of amines with CO_2 has first been unveiled, in parallel by our group and the Beller group, using hydrosilanes as reductants (Scheme 1).[2] Shortly afterwards, Klankermayer *et al.* and Beller *et al.* described the hydrogen version of this reaction.[3,4] Notably, H_2 could be considered as a renewable reductant, if it is produced by carbon-free (photo)-electro-reduction of water, and it advantageously circumvents the formation of siloxanes by-products resulting from the oxidation of hydrosilanes reductants. Nonetheless, the utilization of H_2 comes with a kinetic price and the methylation of amines with CO_2/H_2 still requires a high pressure of H_2 which results in a low hydrogen yield and, hence, a low faradaic efficiency.

From another standpoint, efficient electrocatalysts have been developed over the past decade to promote the 2-electron reduction of CO_2 to formic acid (HCOOH), in an electrochemical cell, and this technology is becoming mature.[5] In this context, an appealing strategy could emerge by utilizing HCOOH as a unique carbon and hydrogen source for the methylation of amines. This approach would thus benefit from the low bond dissociation energy (BDE) of 91 kcal mol^{-1} for the C–H bond in HCOOH (*vs.* 104 and 92 kcal mol^{-1} for the H–H and Si–H bonds, respectively), while producing only H_2O and CO_2 as by-products. Yet, the direct methylation of amines with HCOOH remains unknown to date. The closest example to such a reaction is represented by the recent utilization of HCOOH as a carbon source for the methylation of amines, with hydrosilanes as sacrificial reductants.[6,7]



Scheme 1 Strategies for the methylation of amines with CO_2 and HCOOH.

Ru^{II} complexes are potent hydrogenation catalysts and they have been successfully utilized in CO_2 hydrogenation.[3,4] In addition, we have recently shown that Ru(COD)(methylallyl)$_2$, associated with $CH_3C(CH_2PPh_2)_3$(triphos), could efficiently catalyze the disproportionation of HCOOH to methanol in up to 50% yield.[8] Because this catalytic system is also able to promote the methylation of amines with CO_2/H_2, we investigated its reactivity in the presence of amines and HCOOH. To our delight, we observed that heating a THF solution of aniline **1a** with 3 equiv. HCOOH in the presence of 1.0 mol% Ru(COD)(methylallyl)$_2$, 1.0 mol% triphos and 1.5 mol% MSA (methanesulfonic acid) led to the complete consumption of HCOOH and 43% conversion of aniline **1a** to *N*-methylaniline **2a** (41% yield) and *N*,*N*-dimethylaniline **3a** (2% yield), after 17 h in a sealed autoclave at 150 °C (entry 2, Table 1). ^1H and ^{13}C NMR monitoring of the crude mixture revealed the formation of two side-products, in addition to the expected CO_2 and water: methanol (<5%) which results from the disproportionation of HCOOH, and H_2 which results from its dehydrogenation. Similarly to the ruthenium-catalyzed methylation of amines with CO_2/H_2,[3a] the presence of an acid promoter, in addition to the ruthenium precursor and phosphine ligand, is crucial to ensure the

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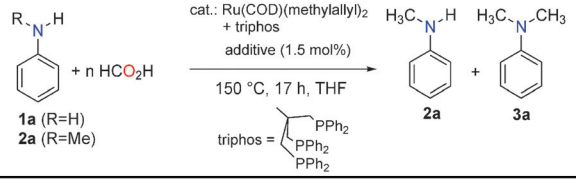
Table 1 Ruthenium-catalyzed methylation of **1a** and **2a** with HCOOH[a]



Entry	R	Cat. (mol%)	Triphos (mol%)	Additive	*n*	Conv. (%)	Yield (%) 2a	3a
1	H	1.0	1.0	—	3.0	36	2	<1
2	H	1.0	1.0	MSA	3.0	43	41	2
3	H	2.5	2.5	MSA	3.0	40	40	<1
4	H	1.0	1.0	MSA	6.0	88	71	17
5	H	1.0	1.0	$HNTf_2$	6.0	79	19	40
6	H	1.0	1.0	$HNTf_2$	9.0	70	23	47
7	H	1.0	1.0	$HNTf_2$[b]	6.0	69	23	46
8[c]	H	1.0	1.0	MSA	6.0	88	61	22
9	Me	1.0	1.0	$HNTf_2$	6.0	85	<1	85
10[d]	Me	0.8	0.8	$HNTf_2$	6.0	>99	<1	>99
11	H or Me	1.0	—	MSA	6.0	>99	<1	<1
12	H or Me	—	—	—	6.0	>99	<1	<1

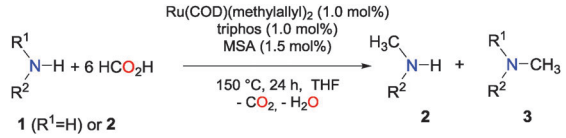
[a] Reaction conditions: substrate (8.3 mmol), $Ru(COD)(methylallyl)_2$, triphos, formic acid (*n* equiv.), additive (1.5 mol%), 150 °C, 17 h. Yield determined by GC/MS using hexamethylbenzene as an internal standard, after calibration. [b] $HNTf_2$ (3.0 mol%). [c] Reaction carried out at 80 °C. [d] Substrate **2a** (0.4 mmol) in a sapphire tube, yield determined by ^1H NMR spectroscopy with mesitylene as an internal standard.

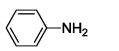
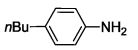
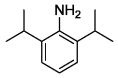
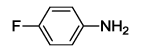
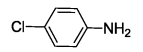
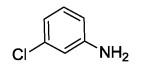
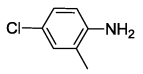
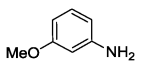
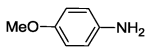
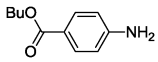
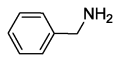
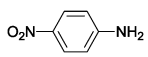
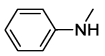
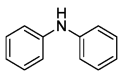
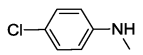
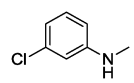
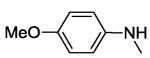
catalytic activity and, in the absence of MSA, only 2% **2a** were observed (entries 1, 11 and 12, Table 1). Increasing the HCOOH loading to 6 equiv. facilitated the formation of N–CH_3 groups and **2a** and **3a** were obtained in 71 and 17% yield, respectively (entry 4), while no improvement was observed with 9 equiv. HCOOH nor by increasing the catalyst loading from 1 to 2.5 mol% (entries 3 and 6, Table 1 and Table S1, ESI†). Importantly, while the methylation of **1a** is efficient at 150 °C, it also proceeds well at 80 °C (entry 8). Interestingly, the more acidic $HNTf_2$ additive increases the activity of the catalytic system and favors the bis-methylation of aniline **1a** (entries 4 and 5 in Table 1). With 3.0 mol% $HNTf_2$, the methylation of **1a** with 6 equiv. HCOOH provided the bismethylated product **3a** in 46% yield and **2a** in 23% yield (entry 7, Table 1). As such, 57% of the C–H bonds in HCOOH are efficiently converted to C–H bonds in the N–CH_3 products, while the remaining 43% of the C–H bonds mainly evolved into H_2. Consequently, the methylation of the secondary amine **2a** is more efficient with $HNTf_2$ (Table 1 and Table S1, ESI†). Based on these findings, the efficient methylation of **2a** was achieved on a 0.4 mmol scale, in 17 h in a sealed sapphire NMR tube, with 6 equiv. HCOOH and 1.0 mol% $Ru(COD)(methylallyl)_2$/triphos + $HNTf_2$ (1.5 mol%), yielding **3a** in quantitative yield (entry 10, Table 1). This result corresponds to a 50% faradaic efficiency and to a catalyst turnover number (TON) of 100 (TOF 5.9 h^{-1}). In comparison, similar TONs and TOFs were obtained for the methylation of amines with H_2 and CO_2 with $Ru(COD)(methylallyl)_2$ + triphos after 24 h at 150 °C, lower faradaic efficiencies were obtained, ranging from 0.4 (ref. 4) to 28%.[3a]

The methylation of N–H bonds in a variety of amines was then carried out to explore the potential of this novel catalytic transformation (Table 2). Using 6 equiv. HCOOH, the methylation of primary anilines **1a–j** is efficient with cumulative yields to the methylation products **2** and **3** ranging from 51 to 88%, after 24 h at 150 °C with 1.0 mol% [$Ru(COD)(methylallyl)_2$ + triphos] and 1.5 mol% MSA. Interestingly, the selectivity of the mono- *vs.* bis-methylation of primary anilines depends on the electronic nature of the substituents on the aryl ring. With strong electronic withdrawing groups (characterized by a Hammett constant $\sigma > 0.2$), the selective formation of **2** is favored and **3** was obtained in low yield (<9%, for **3e–g** and **3j**) (Table 2). The bulky aniline **1c** gave **2c** in a low 13% yield (entry 3, Table 2) and the formamide derivative was identified as the major product in this reaction (traces of the iminium product were also detected by GC/MS chromatography).[9] While the ester group in **1j** is found unaffected, methylation of **1l** is accompanied with the complete reduction of the nitro group to afford 4-aminoaniline in 77% yield and 4-amino-*N*-methylaniline in 23% yield (entry 12 in Table 2).[7c] Additionally, keto, cyano and non-conjugated C=C groups are not well tolerated in the present methodology, whereas amide functions are compatible with the methylation of an aromatic –NH_2 group (Table S2, ESI†). Basic amines such as aliphatic amines were shown to exhibit a lower reactivity in the methylation strategies utilizing CO_2 with $PhSiH_3$ or H_2.[2,3a,4] This trend is also marked in the present methylation of amines with HCOOH and, for example, methylation of benzylamine **1k** was found unproductive (entry 11 and Table S2, ESI†). Nonetheless, modest to good yields were also obtained for the methylation of secondary anilines with $HNTf_2$ (entries 13 and 17–19). Indole **1n** gave **3n** in a low 2% yield without hydrogenation of the C=C double bond (entry 16).

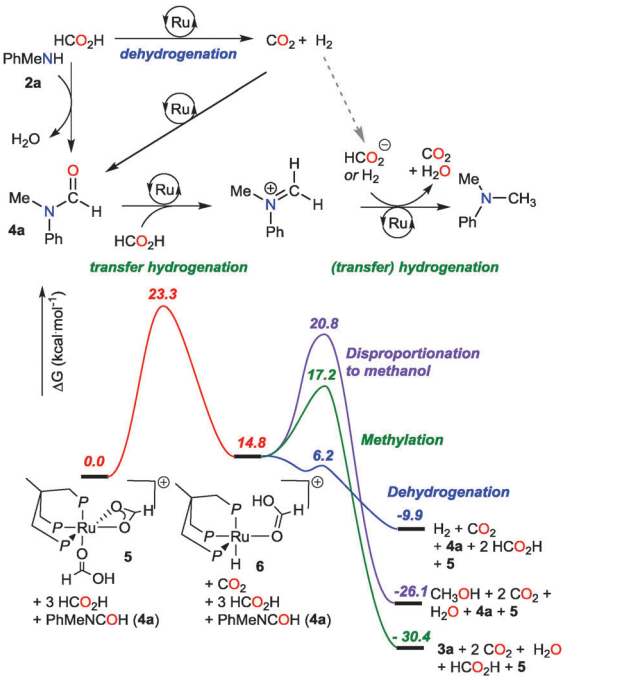
Beyond the proof of concept, the methylation of amines with HCOOH still suffers from a limited scope and we therefore investigated the mechanism of this novel reaction so as to guide the design of future catalysts. Based on the organic species detected in solution (formamide and iminium intermediates, methanol and CO_2), a plausible pathway for the methylation of the N–H bond with HCOOH involves the formation of a formamide intermediate which is reduced to an iminium species, prior to its reduction to a N–CH_3 group (Scheme 2). In fact, formylation of **2a** is thermally available and formamide **4a** was obtained in quantitative yield after 1 h at 150 °C.[10] Subsequent reduction of formamide **4a** afforded 67% of **3a** (Fig. S3, ESI†). A control reaction confirmed that methanol, issued from the disproportionation of HCOOH, is not a methylating agent, since no methylation of **2a** was observed with $Ru(COD)(methylallyl)_2$/triphos + MSA and methanol after 24 h at 150 °C. Monitoring the products distribution over time by ^1H NMR spectroscopy revealed that HCOOH undergoes dehydrogenation at the earlier stages of the methylation of **2a** and serves in parallel as a formylation agent to yield **4a** (Fig. S4, ESI†). HCOOH is then fully consumed and the quantity of H_2 in solution decreases while **3a** is produced, suggesting that the reduction of **4a** proceeds both *via* transfer hydrogenation (from HCOOH) and hydrogenation. Competition between the methylation of **2a**, the dehydrogenation of HCOOH and its disproportionation to MeOH has been investigated using DFT calculations, with the simplified $CH_3C(CH_2PMe_2)_3$ ligand in place of triphos. A schematic summary of the results is presented in Scheme 2 and the computed potential energy surface is given in the ESI† (Fig. S5). In the presence of an acid promoter, such as MSA or $HNTf_2$, protonation of the reactive Ru(triphos)(κ^1–OCHO)(κ^2–OCHO)

Table 2 Ruthenium-catalyzed methylation of substituted amines with formic acid[a]



Entry	Substrate		Conversion (%)	Products distribution (%)	
1		**1a**	100	**2a**, 71 (58)	**3a**, 17 (12)
2		**1b**	84	**2b**, 56	**3b**, 19
3		**1c**	88	**2c**, 13	**3c**, <1
4		**1d**	86	**2d**, 63	**3d**, 23
5		**1e**	51	**2e**, 51	**3e**, <1
6		**1f**	70	**2f**, 51	**3f**, 9
7		**1g**	51	**2g**, 50	**3g**, <1
8		**1h**	80	**2h**, 62 (53)	**3h**, 17 (10)
9		**1i**	86	**2i**, 57[c]	**3i**, 29[c]
10		**1j**	65	**2j**, 54	**3j**, <1
11		**1k**	37	**2k**, <1	**3k**, <1
12		**1l**	100	**2l**, 23	
13[b]		**2a**	85	**3a**, 85 (69)	
14[b]		**2m**	9	**3m**, 9	
16[b]		**2n**	2	**3n**, 2	
17[b]		**2o**	66	**3o**, 66 (52)	
18[b]		**2p**	51	**3p**, 44 (33)	
19[b]		**2q**	77	**3q**, 77[c]	

[a] Reaction conditions: substrate (8.3 mmol), Ru(COD)(methylallyl)$_2$ (1.0 mol%), triphos (1.0 mol%), MSA (1.5 mol%), formic acid (6 equiv.), 150 °C, 24 h. Yield determined by GC/MS chromatography using hexamethylbenzene as an internal standard, after calibration. Isolated yields are given in parenthesis. [b] MSA was replaced with $HNTf_2$ (1.5 mol%). [c] Reaction carried out in a sapphire tube: substrate (0.4 mmol); yield determined by ^{1}H NMR spectroscopy. Note: unless otherwise noted, formamide derivatives were observed as the only side-products when the yields of **2** and **3** don't add up to the conversion of **1**.



Scheme 2 Computed (DFT) pathways for the methylation of **2a** to **3a**.

complex is expected to form **5**. The activation energy associated with the decarboxylation of **5** was computed at 23.3 kcal mol^{-1} to yield hydride complex **6**. In agreement with our previous findings on the disproportionation of HCOOH, generation of the reactive hydride intermediate is the rate determining step, meaning that the selectivity of the reaction is mostly under thermodynamic control. **6** is able to promote either the reduction of formamide **4a** (en route to the methylation of **2a**) or a second molecule of HCOOH (leading to the disproportionation pathway). Alternatively, the Ru–H function can be quenched by the acidic proton of HCOOH to yield H_2 and complete the dehydrogenation of HCOOH. The three divergent routes present different thermodynamic and kinetic characteristics. From **6**, release of H_2 is essentially barrier less. However, the dehydrogenation of HCOOH has a low exergonicity (−9.9 kcal mol^{-1} and −29.7 kcal mol^{-1} for the dehydrogenation of 3HCOOH) and it is therefore reversible under the applied conditions. H_2 can thus lead to the re-formation of **6** and, in turn, be utilized for the reduction of **4a**. In contrast, conversion of **6** to the hemiaminal complex **14** (ESI†) requires an activation energy of 17.2 kcal mol^{-1} and it is irreversible, yielding the methylamine product **3a**, with an overall energy balance of −30.4 kcal mol^{-1}. This mechanism is thus in agreement with the experimental results pointing to a convergent reduction of **4a** *via* both transfer hydrogenation from HCOOH and hydrogenation. Importantly, this mechanism also shows that the disproportionation of HCOOH to methanol is less favored than the reduction of **4a** as it requires an activation energy of 20.8 kcal mol^{-1} for an exergonicity of −26.1 kcal mol^{-1}. Nevertheless, methanol formation is unproductive in the methylation of **2a** because the energy barrier required to regenerate **6** from formaldehyde exceeds 24.8 kcal mol^{-1} (Fig. S5, ESI†). Finally, it

is remarkable that the mechanism of this unprecedented methylation of amines with HCOOH differs completely from the classical Eschweiler–Clarke reaction, which relies on the condensation of an amine substrate onto formaldehyde and subsequent reduction of the resulting imine with HCOOH.[11]

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