VIP CO_2 Utilization

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Ruthenium-Catalyzed Direct Methylation of Primary and Secondary Aromatic Amines Using Carbon Dioxide and Molecular Hydrogen**

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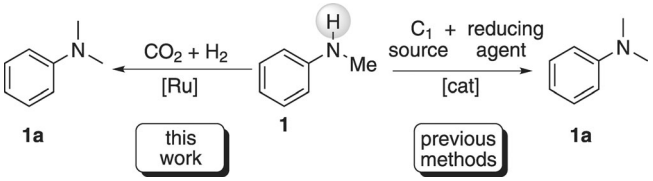
Dedicated to the Bayer company on the occasion of its 150th anniversary

In the last two decades the utilization of renewable resources as chemical building block, solvent, or additive has emerged as important research area for the development of sustainable chemical processes. In this respect, carbon dioxide (CO_2) is an important renewable C_1 resource, which is already used as a raw material for the production of important industrial chemicals in certain cases and intensively researched for novel transformations.[1,2] In particular, organometallic catalytic methods for the hydrogenation of CO_2 to the valuable C_1 chemicals formic acid[3] and methanol[4] are finding great interest. With primary or secondary amine substrates, the hydrogenation of CO_2 results in the formation of formamide derivatives using organometallic catalysts including rhodium, iridium, and ruthenium complexes.[3,5] Recently, Cole-Hamilton et al. could demonstrate the use of a catalytic system based on [Ru(acac)$_3$] and the tridentate ligand triphos (triphos: 1,1,1-tris(diphenylphosphinomethyl)ethane) for the reduction of amides with molecular hydrogen, leading to the corresponding alkyl amines.[6] Based on this background, we envisaged the possibility for direct N-methylation of amines using CO_2 and molecular hydrogen.

Although the hydrogenation of CO_2 is broadly investigated, the direct alkylation of amines remains presently elusive. Traditional pathways for N-methylation include alkylation with methyl iodide, orthoesters, or dimethyl carbonate or reductive alkylations such as the Eschweiler–Clark method using formaldehyde and formic acid as C_1 source.[7] Two very recent reports describe the use of CO_2 as C_1 source for the methylation of anilines employing excess phenyl silane ($PhSiH_3$) as the reducing agent (Scheme 1, right).[8]

Herein, we disclose the homogenously catalyzed direct N-methylation of anilines using CO_2 and H_2 as the only sources for the construction of the methyl group (Scheme 1, left). The starting point for the investigation was the well-established triphos-based[9] ruthenium system, which provides excellent homogeneous catalysts for the hydrogenation of amides, esters, and carboxylic acids.[6,10] In particular, the stable and readily accessible complex [Ru(triphos)(tmm)] (tmm: trimethylene methane) has been recently used successfully as molecularly defined catalyst including the hydrogenation of CO_2 to methanol under relatively mild reaction conditions (Figure 1).[4c,11]



Scheme 1. Direct N-methylation of *N*-methylaniline with CO_2 and H_2 (left) compared to state-of-the-art reductive methylation methods (right).

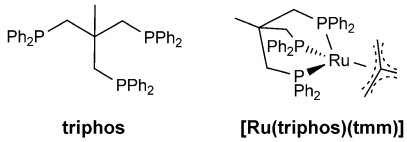


Figure 1. Tridentate ligand triphos and the corresponding ruthenium trimethylene methane complex.

The model substrate for the initial screening was *N*-methylaniline (**1**) leading to *N*,*N*-dimethylaniline (**1a**) with the possibility of formation of methanol as a side product. As expected, the presence of an organic acid is crucial for the conversion of **1** (Table 1, entries 1–4). This is in accordance with recent mechanistic investigations that suggested a ruthenium species of type $[Ru(triphos)H]^+$ comprising the facially coordinated tripodal ligand to facilitate hydride transfer and protonolysis as key steps for the addition of hydrogen to carboxylate groups.[12] In absence of any acid, only traces of **1a** were detected (Table 1, entry 1), whereas the use 5 mol% of trifluoromethanesulfonylimide ($HNTf_2$) improved the yield up to 97% at 140°C (Table 1, entry 4). Lowering the reaction temperature to 120°C resulted still in a conversion of 81% after 22 h, and at 100°C 58% of **1a** were obtained (Table 1, entries 5 and 6). Increasing the reaction temperature slightly to 150°C at 2.5 mol% catalyst loading resulted in full

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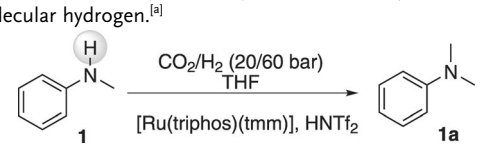
Table 1: Ruthenium-catalyzed methylation of *N*-methyl aniline with CO_2 and molecular hydrogen.[a]



Entry	Acid (mol%)	*T* [C°]	*t* [h]	Yield [%][b]
1	–	140	10	2
2	$HNTf_2$ (0.5)	140	22	11
3	$HNTf_2$ (2.5)	140	22	84
4	$HNTf_2$ (5)	140	22	97
5	$HNTf_2$ (5)	120	22	81
6	$HNTf_2$ (5)	100	22	58
7	$HNTf_2$ (5)	150	10	99

[a] Reaction conditions: *N*-methylaniline **1** (1.0 mmol), [Ru(triphos)(tmm)] (2.5 mol%), THF (2 mL), CO_2/H_2 (20/60 bar); [b] Yield determined by gas chromatography using *n*-dodecane as internal standard.

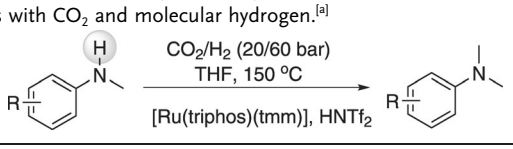
conversion of **1** in 10 h affording **1a** in 99% yield (Table 1, entry 7). The conversion/time profile under these conditions is shown in the Supporting Information. In subsequent experiments, full conversion of the starting material was also achieved when using different acids such as methanesulfonic acid (MSA) and *p*-toluenesulfonic acid (*p*-TsOH; see the Supporting Information for details).

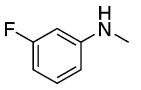
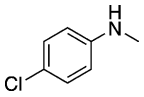
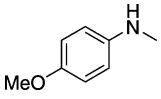
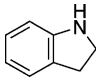
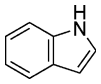
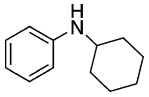
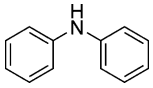
The methylation of various substituted secondary anilines under the standard reaction conditions was investigated (Table 2). When halogen-substituted anilines were used, the desired products were obtained in high yields up to 90% for 3-fluoro-*N,N*-dimethylaniline (**2a**; Table 2, entry 1) and 4-chloro-*N,N*-dimethylaniline (**3a**; Table 2, entry 2). The electron-donating methoxy group in the 4-position of the aromatic ring of **4** significantly reduced the reactivity (Table 2, entry 3). When indoline **5** was used, the corresponding N-methylated product **5a** was obtained in respectable 73% yield (Table 2, entry 4). Indole **6** gave the same product **5a** in similar yield through concomitant hydrogenation of the C=C double bond (Table 2, entry 5). A slightly lower yield of 64% was obtained for the direct methylation of *N*-cyclohexylaniline (**7**; Table 2, entry 6). Diphenylamine (**8**) showed very low reactivity (Table 2, entry 7), and secondary alkyl amines were not methylated.

For the aryl,alkyl-amines **1**–**6** the results suggest a qualitative trend towards lower reactivity with increasing basicity of the substrate. This was tentatively associated with a reduced availability of protons inhibiting the formation of the active $[Ru(triphos)H]^+$ species. In agreement with this consideration, higher loadings of the acid cocatalyst were found to highly promote the reactivity of 4-methoxy-*N*-methylaniline (**4**; for more details see the Supporting Information).

The dimethyl aniline moiety is widely found in many bioactive compounds, pharmaceuticals, and materials such as edrophonium-based compounds, which are used as cholinesterase inhibitor,[13] mifepristone, which is a progestational hormone antagonist,[14] and eserine, which is a binding agent for molecularly imprinted polymers (MIPs) used in molecular imprinting technology.[15] Thus we attempted to extend the scope of the direct methylation reaction to primary substituted anilines leading directly to the corresponding substituted *N,N*-dimethylanilines (Table 3). The use of aniline (**9**) itself afforded the corresponding dimethyl aniline **1a** in 94% yield (Table 3, entry 1). 4-Chloroaniline (**10**) gave 4-chloro-*N,N*-dimethylaniline (**3a**) in 93% yield (Table 3, entry 2), providing an interesting building block for further functionalization at the chloro substituent. Fluorine-containing primary anilines, such as 2-fluoroaniline (**11**) and 3-trifluoromethyl-*p*-toluidine (**12**) also provided the dimethlyated products in excellent yields (Table 3, entries 3 and 4), thereby giving access to fluorine-substituted tracers for ^{19}F-NMR-based screening in metabolism studies.[16] Even highly substituted 2,4,6-trimethylaniline (**13**) afforded **13a** with a yield of 84% (Table 3, entry 5).

Table 2: Ruthenium-catalyzed methylation of substituted aromatic amines with CO_2 and molecular hydrogen.[a]



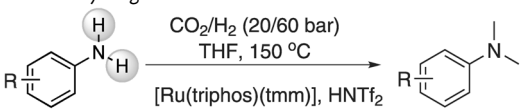
Entry	Aniline	Product		*t* [h]	Yield [%][b]
1		**2**	**2a**	22	90
2		**3**	**3a**	10	90
3		**4**	**4a**	10	35
4[c]		**5**	**5a**	20	73
5[c]		**6**	**5a**	20	70
6		**7**	**7a**	15	64
7		**8**	**8a**	48	27

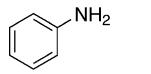
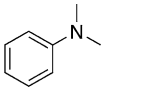
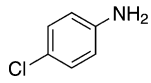
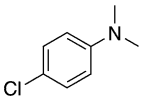
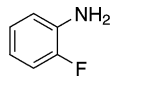
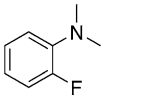
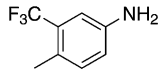
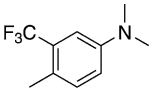
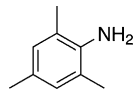
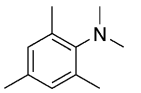
[a] Reaction conditions: Substituted aromatic amine (1.0 mmol), [Ru(triphos)(tmm)] (2.5 mol%), $HNTf_2$ (5 mol%), THF (2 mL), CO_2/H_2 (20/60 bar), 150°C; [b] Yield determined by GC using *n*-dodecane as internal standard. [c] Yield determined by NMR spectroscopy.

Finally, we investigated the possibility to use this new N-methylation reaction in a sequential hydrogenation/methylation reaction to access unsymmetrical methyl/alkyl anilines from the corresponding amides. As prototypical substrate, acetanilide (**14**) was transformed successfully to *N*-ethyl-*N*-methylaniline (**14a**) in 69% yield (Scheme 2). Since monoamidation is much more readily achieved than monoalkylation, this unprecedented sequence offers a synthetically powerful method for the construction of unsymmetrical dialkyl anilines using CO_2 and H_2.

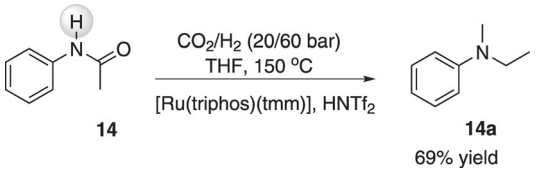
Since amides are readily reduced under the established catalytic conditions, a plausible reaction pathway for the

Table 3: Ruthenium-catalyzed methylation of primary anilines with CO_2 and molecular hydrogen.[a]



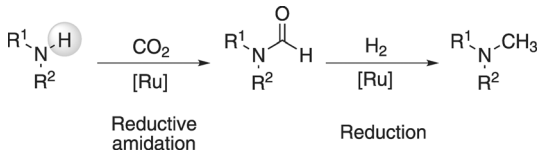
Entry	Aniline		Product		*t* [h]	Yield [%][b]
1		**9**		**1a**	15	94
2		**10**		**3a**	10	93
3		**11**		**11a**	24	93
4		**12**		**12a**	20	94
5		**13**		**13a**	15	84

[a] Reaction conditions: Substituted primary aniline (1.0 mmol), [Ru(triphos)(tmm)] (2.5 mol%), $HNTf_2$ (5 mol%), THF (2 mL), CO_2/H_2 (20/60 bar), 150°C; [b] Yield determined by GC using *n*-dodecane as internal standard.



Scheme 2. Sequential hydrogenation/N-methylation of acetanilide **14**.

construction of the methyl group involves amidation of the aniline by CO_2 hydrogenation followed by the reduction of the formamide intermediate to the corresponding N-methylated product (Scheme 3). Both steps are known to be



Scheme 3. Proposed reaction pathway for the catalytic formation of methylamine from CO_2 and molecular hydrogen.

catalyzed by ruthenium–phosphine catalysts. Indeed, *N*-methylformanilide was quantitatively converted under 60 bar of molecular hydrogen under otherwise standard reaction conditions and dimethylaniline **1a** was formed in 73% yield. However, a major by-product (22%) was the monoalkylated product **1**, resulting from decarbonylation.[12,17] Notably, the decarbonylation was suppressed almost completely when the reaction was carried out in the presence of additional 20 bar of CO_2, resulting in a 60:1 mixture of **1a** and **1** from a 1:1 mixture of *N*-methylformanilide and **1**.

In conclusion, we have demonstrated the catalytic N-methylation of secondary and primary aromatic amines using CO_2 as C_1 source and molecular hydrogen directly as reducing agent. The use of the molecularly defined and stable precursor complex [Ru(triphos)(tmm)], which can be obtained in one step from commercially available triphos and $[(cod)Ru(metallyl)_2]$,[11] together with appropriate amounts of readily available organic acids as cocatalysts affords the mono- or dimethylation in good to excellent yields. Unsymmetrical dialkyl anilines are accessible through sequential hydrogenation/methylation of the corresponding anilides. These transformations provide an atom-efficient alternative to traditional N-methylation methodologies and utilize CO_2 as carbon source. Especially if hydrogen is provided from renewable sources, the new synthetic route clearly has the potential to significantly reduce the carbon footprint of N-methylation processes.

Experimental Section

General procedure for the methylation reaction in a 10 mL stainless-steel high pressure reactor: [Ru(triphos)(tmm)] (0.019 g, 0.025 mmol), $HNTf_2$ (0.014 g, 0.05 mmol), aniline substrate (1.0 mmol), and THF (2 mL) were added through a cannula under argon to an autoclave equipped with a glass liner containing a stir bar. The autoclave was pressurized with CO_2 to 20 bar and then H_2 was added up to a total pressure of 80 bar. The reaction mixture was stirred and heated to 150°C in an oil bath. After the specified time period, the autoclave was cooled to room temperature and then to ca. 0°C in an ice bath, and carefully vented. The composition of the reaction solution was analyzed by ^1H NMR spectroscopy with mesitylene as internal standard and the results confirmed by gas chromatography using dodecane as internal standard.

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[1] a) H. Arakawa, M. Aresta, J. N. Armor, M. A. Barteau, E. J. Beckman, A. T. Bell, J. E. Bercaw, C. Creutz, E. Dinjus, D. A. Dixon, K. Domen, D. L. DuBois, J. Eckert, E. Fujita, D. H. Gibson, W. A. Goddard, D. W. Goodman, J. Keller, G. J. Kubas, H. H. Kung, J. E. Lyons, L. E. Manzer, T. J. Marks, K. Morokuma, K. M. Nicholas, R. Periana, L. Que, J. Rostrup-Nielson, W. M. H. Sachtler, L. D. Schmidt, A. Sen, G. A. Somorjai, P. C. Stair, B. R. Stults, W. Tumas, *Chem. Rev.* **2001**, *101*, 953; b) A. Behr, *Carbon Dioxide Activation by Metal Complexes*, Wiley-VCH, Weinheim, **1988**; c) *Carbon Dioxide as Chemical Feedstock* (Ed.: M. Aresta), Wiley-VCH, Weinheim, **2010**.

[2] a) D. Walther, *Coord. Chem. Rev.* **1987**, *79*, 135; b) W. Leitner, *Coord. Chem. Rev.* **1996**, *153*, 257; c) T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365; d) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kühn, *Angew. Chem.* **2011**, *123*, 8662; *Angew. Chem. Int. Ed.* **2011**, *50*, 8510; e) M. Peters, B. Köhler, W. Kuckshinrichs, W. Leitner, P. Markewitz, T. E. Müller, *ChemSusChem* **2011**, *4*, 1216.

[3] a) W. Leitner, *Angew. Chem.* **1995**, *107*, 2391; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2207; b) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1995**, *95*, 259; c) P. G. Jessop in *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 489 – 511; d) C. Federsel, R. Jackstell, M. Beller, *Angew. Chem.* **2010**, *122*, 6392; *Angew. Chem. Int. Ed.* **2010**, *49*, 6254.

[4] a) E. Balaraman, C. Gunanathan, J. Zhang, L. J. W. Shimon, D. Milstein, *Nat. Chem.* **2011**, *3*, 609; b) C. Huff, M. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18122; c) S. Wesselbaum, T. vom Stein, J. Klankermayer, W. Leitner, *Angew. Chem.* **2012**, *124*, 7617; *Angew. Chem. Int. Ed.* **2012**, *51*, 7499; d) Z. Han, L. Rong, J. Wu, L. Zhang, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 13218; *Angew. Chem. Int. Ed.* **2012**, *51*, 13041.

[5] a) P. Haynes, L. H. Slaugh, J. F. Kohnle, *Tetrahedron Lett.* **1970**, *11*, 365; b) P. G. Jessop, Y. Hsiao, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1994**, *116*, 8851; c) P. G. Jessop, Y. Hsiao, T. Ikariya, R. Noyori *J. Am. Chem. Soc.* **1996**, *118*, 344; d) O. Kroecher, R. A. Koeppel, A. Baiker, *Chem. Commun.* **1997**, 453; e) L. Schmid, M. Rohr, A. Baiker, *Chem. Commun.* **1999**, 2303; f) F. Liu, M. B. Abrams, T. R. Baker, W. Tumas, *Chem. Commun.* **2001**, 433.

[6] a) A. A. Núñez Magro, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 3154; b) D. L. Dodds, J. Coetzee, J. Klankermayer, S. Brosinski, W. Leitner, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 3154; published addition (Nov 2011); c) 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 – 11050.

[7] For example: a) W. Eschweiler, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 880; b) H. T. Clarke, H. B. Gillespie, S. Z. Weisshaus, *J. Am. Chem. Soc.* **1933**, *55*, 4571; c) E. Farkas, C. J. Sunman, *J. Org. Chem.* **1985**, *50*, 1110; d) P. Tundo, M. Selva, *Acc. Chem. Res.* **2002**, *35*, 706; e) Y. Zhao, S. W. Foo, S. Saito, *Angew. Chem.* **2011**, *123*, 3062; *Angew. Chem. Int. Ed.* **2011**, *50*, 3006.

[8] a) O. Jacquet, X. Frogneux, C. Das Neves Gomes, T. Cantat, *Chem. Sci.* **2013**, *4*, 2127; b) Y. Li, X. Fang, K. Junge, M. Beller, *Angew. Chem.* **2013**, *125*, 9746 – 9749; *Angew. Chem. Int. Ed.* **2013**, *36*, 9568 – 9571.

[9] For pioneering work on the use of triphos ligand in catalysis, see: C. Bianchini, A. Meli, M. Peruzzini, F. Vizza, F. Zanobini, *Coord. Chem. Rev.* **1992**, *120*, 193.

[10] a) H. T. Teunissen, C. J. Elsevier, *Chem. Commun.* **1997**, 667; b) H. T. Teunissen, C. J. Elsevier, *Chem. Commun.* **1998**, 1367; c) M. C. Van Engelen, H. T. Teunissen, J. G. de Vries, C. J. Elsevier, *J. Mol. Catal. A* **2003**, *206*, 185; d) B. Boardman, M. J. Hanton, H. Van Rensburg, R. P. Tooze, *Chem. Commun.* **2006**, 2289; e) F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer, W. Leitner, *Angew. Chem.* **2010**, *122*, 5642; *Angew. Chem. Int. Ed.* **2010**, *49*, 5510.

[11] For the synthesis of [(triphos)Ru(tmm)], see: T. vom Stein, T. Weigand, C. Merkens, J. Klankermayer, W. Leitner, *ChemCatChem* **2013**, *5*, 439.

[12] F. M. A. Geilen, B. Engendahl, M. Hölscher, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2011**, *133*, 14349.

[13] F. Leonetti, M. Catto, O. Nicolotti, L. Pisani, A. Cappa, A. Stefanachi, A. Carotti, *Bioorg. Med. Chem.* **2008**, *16*, 7450.

[14] S. L. Wempe, C. D. Gamarra-Luques, C. M. Telleria, *Cancer Growth Metastasis* **2013**, *6*, 1.

[15] E. J. Enholm, F. Allais, R. T. Martin, R. Mohamed, *Macromolecules* **2006**, *39*, 7859.

[16] a) M. Leone, R. A. Rodriguez-Mias, M. Pellecchia, *ChemBioChem* **2003**, *4*, 649; b) T. Tengel, T. Fex, H. Emtenäs, F. Almqvist, I. Sethson, J. Kihlberg, *Org. Biomol. Chem.* **2004**, *2*, 725; c) A. Mutlib, R. Espina, J. Atherton, J. Wang, R. Talaat, J. Scatina, A. Chandrasekaran, *Chem. Res. Toxicol.* **2012**, *25*, 572.

[17] T. vom Stein, M. Meuresch, D. Limper, M. Hölscher, J. Coetzee, A. M. Z. Slawin, D. J. Cole-Hamilton, J. Klankermayer, W. Leitner, unpublished results.

