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# Manganese Catalyzed Reductive Amination of Aldehydes using Hydrogen as Reductant

Duo Wei,<sup>a</sup> Antoine Bruneau-Voisine,<sup>a,b</sup> Dmitry A. Valyaev,<sup>b</sup> Noël Lugan<sup>b</sup> and Jean-Baptiste Sortais<sup>\*b,c</sup>

**A one-pot two-steps procedure was developed for the alkylation of amines *via* reductive amination of aldehydes using molecular dihydrogen as reductant in the presence of manganese pyridinyl-phosphine complex as pre-catalyst. After the initial condensation step, the reduction of the imines formed *in situ* is applied under mild conditions (50-100 °C) with 2 mol% of catalyst and 5 mol% of *t*BuOK under 50 bar of hydrogen. Excellent yields (> 90%) were obtained for a large combination of aldehydes and amines (38 examples), including aliphatic aldehydes and amino-alcohols.**

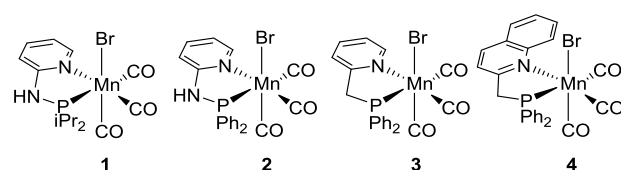
In the last two years, the use of manganese as a sustainable alternative to precious transition metals in hydrogenation and hydrogen borrowing reactions has achieved an impressive explosion.<sup>1</sup> Starting from the hydrogenation of aldehydes, ketones and nitriles,<sup>2</sup> the scope of reducible functional group was rapidly enlarged to esters,<sup>2d, 3</sup> amides,<sup>3c, 4</sup> and CO<sub>2</sub>.<sup>5</sup> Soon after, hydrogen transfer reactions using isopropanol as reductant<sup>6</sup> and asymmetric reduction<sup>2d, 7</sup> have been disclosed. In the field of hydrogen borrowing reactions, the first manganese-catalyzed dehydrogenative coupling of alcohols and amines to form imines<sup>8</sup> was rapidly complemented by the synthesis of esters<sup>9</sup> from alcohols, and amides<sup>10</sup> from alcohols and amines. In the field of C-C bond formation reactions,  $\alpha$ -alkylation of ketones with alcohols,<sup>11</sup> and olefination of nitriles<sup>12</sup> were also achieved. Interestingly, the upgrading of ethanol in butanol,<sup>13</sup> the dehydrogenation of methanol<sup>14</sup> to H<sub>2</sub> and CO<sub>2</sub>, or the deoxygenation of alcohols<sup>15</sup> were also found to be catalyzed by manganese complexes. Finally, the access to various higher amine derivatives using alcohols as alkylating reagents was developed,<sup>16</sup> including the *N*-monomethylation of amines,<sup>16-17</sup> aminomethylation of [hetero]arenes with methanol/amines,<sup>18</sup>

and multi-component synthesis of quinolines,<sup>19</sup> pyrroles<sup>20</sup> and pyrimidines.<sup>21</sup>

Reductive amination<sup>22</sup> is one of the chemical reaction in the chemist tool-box for the preparation of amines.<sup>23</sup> It relies on the *in situ* condensation of a ketone or aldehyde with an amine to form the corresponding imine, which is subsequently reduced to the desired amine. When using molecular hydrogen as reductant, it appears that the key step in the reaction sequence is the hydrogenation of the intermediate imine.

In line with our previous work on manganese catalyzed reactions<sup>24</sup> and catalytic amines synthesis using first-row transition metals complexes,<sup>25</sup> we report thereafter the first alkylation of amines *via* reductive amination of aldehydes using molecular hydrogen as reductant and well-defined manganese complexes as pre-catalysts.

We have selected complexes **1-4** as candidates for this study (Scheme 1) as we recently demonstrated that manganese (I) bromo-tricarbonyl complexes bearing bidendate pyridinyl-phosphine ligands were good catalysts for the hydrogenation of carbonyl derivatives, and especially complex **2** featuring diphenyl-(2-aminopyridinyl)-phosphine ligand.<sup>26</sup>



**Scheme 1.** Manganese complexes used in this study.

We initially focused on the direct hydrogenation of *N*-benzylideneaniline **c1** as model substrate, using catalyst **2** and a base, under 50 bar of H<sub>2</sub>, based on previously optimized conditions for the hydrogenation of ketones. First, we found that alcohols, and notably ethanol, were suitable solvents for the hydrogenation step (See Table S1 in S.I.) as a green solvent alternative to toluene. It then appeared that the nature of the base had little influence on the reaction, NaOtBu, KOtBu, KHMDS, or Cs<sub>2</sub>CO<sub>3</sub> leading to satisfactory conversions (**2** (1

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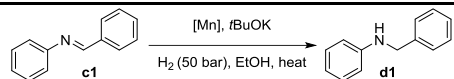
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mol%), base (2 mol%), 100 °C, EtOH, 22h, 41% to 64% yield, see Table S2 in S.I.). The activity of complexes **1-4** was compared at 80 °C with 1 mol% catalyst and 2 mol% of *t*BuOK (Table 1, entries 1-4) and complex **2** appeared to be the most active one. Increasing the catalyst loading to 2 mol% led to a full conversion (entry 5). Interestingly, the temperature could be decreased to 50 °C without any detrimental effect on activity (entry 6), and even to 30 °C where a decent conversion still occurred (76%, entry 7).

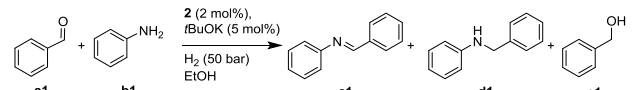
**Table 1.** Optimization of the reactions conditions of the hydrogenation of benzylideneaniline **c1** with manganese catalysts **1-4**.

				
Entry <sup>[a]</sup>	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%) <sup>[c]</sup>
1 <sup>[a]</sup>	<b>1</b> (1)	80	19	40
2 <sup>[a]</sup>	<b>2</b> (1)	80	24	74
3 <sup>[a]</sup>	<b>3</b> (1)	80	19	17
4 <sup>[a]</sup>	<b>4</b> (1)	80	19	1
5 <sup>[b]</sup>	<b>2</b> (2)	80	17	> 98
6 <sup>[b]</sup>	<b>2</b> (2)	50	17	> 98
7 <sup>[b]</sup>	<b>2</b> (2)	30	24	76

[a] Conditions: an autoclave was charged in a glovebox with, in this order, **c1** (181 mg, 1.0 mmol), EtOH (4.0 mL), Mn-complex (1 mol%), *t*BuOK (2.2 mg, 2 mol%), and then pressurized with H<sub>2</sub> (50 bar) and heated. [b] **c1** (91 mg, 0.5 mmol), EtOH (2.0 mL), **2** (5.0 mg, 2 mol%), *t*BuOK (2.8 mg, 5 mol%). [c] Yield was determined by <sup>1</sup>H NMR spectroscopy and GC on the crude mixture.

In terms of practical and economical synthesis, direct reductive amination of aldehydes is more desirable than hydrogenation of corresponding isolated imines. Hence, we turned our attention towards the direct synthesis of benzylaniline **d1** from benzaldehyde **a1** and aniline **b1**. In a first attempt, all the components, *i.e.* **2**, **a1**, **b1**, *t*BuOK, and H<sub>2</sub>, were introduced in an autoclave being heated at 80 °C overnight (Scheme 2, conditions A). Disappointingly, a mixture of benzylalcohol **e1** (44%), imine **c1** (38%), and the desired amine **d1** (18%) was obtained, showing that the hydrogenation of benzaldehyde occurred faster than the condensation with aniline. In a second strategy, the condensation step was carried out in the presence of the catalyst and the base at 80 °C for 5 h, then the reaction mixture was pressurized under H<sub>2</sub> and stirred at 80 °C overnight (conditions B). Unfortunately, the main products were again alcohol **e1** (61%) and imine **c1** (29%). Finally, we decided to perform first the condensation of the aldehyde with the amine in EtOH, imine **c1** being formed in 90% yield after 24 h at 100 °C, and then to add the precatalyst, the base, and H<sub>2</sub> to the crude imine before heating under stirring at 80 °C overnight (Conditions C). To our delight, under these conditions, the desired *N*-benzylaniline **d1** was obtained in high yield (87%). Here after, 1.2 equivalent of amines **b** were used to ensure the

full conversion of the aldehyde **a** into the imines **c** before the hydrogenation step (Table 2). We next probe the scope of this first manganese catalyzed reductive amination system thus defined.

			
Conditions A:	<b>c1</b> 38	<b>d1</b> 18	<b>e1</b> 44
Conditions B:	29	7	61
Conditions C:	2	87	11

**Scheme 2.** Optimization of the procedure for reductive amination of benzaldehyde with aniline under the catalysis of manganese complex **2**. See main text for conditions definition and SI Table S4 for experimental details.

In general, as far as the formation of the imines is not a limiting step,<sup>27</sup> the subsequent hydrogenation proceeds well for a wide variety of aldehydes and amines (Table 2). First, benzaldehydes derivatives bearing either electron donating or electron withdrawing groups both react with anilines to afford *in fine* the corresponding amines in good yield (entries 1-16). Noticeably, halogen substituents (**d6-d10**), including iodo substituent, were well tolerated with less than 10% diiodination in the cases of **d9** and **d10**. Esters and amides moieties were not reduced under these conditions (**d12-d13**). Interestingly, starting from 4-formylacetophenone **a14** in the presence of 2 equivalent of aniline **b1**, only the aldimine moieties was reduced in the transient di-imine intermediate **c14** affording the corresponding amino-ketimine **d14**,<sup>28</sup> while in the presence of 1 equivalent of **b1**, amino-ketone **d15** was obtained in good yield. In the same vein, the reductive amination of benzaldehyde **a1** with 4-acetyl-aniline **b16** led selectively to the corresponding 4-acetylaniline **d16** leaving the ketone functionality untouched. Organometallic ferrocenylaldehyde **a17** was also suitable for this protocol. Several heterocycles, including pyrrole, furane, pyridine, thiophene, and thiazole were well tolerated by the catalytic system (entries 18-23). It is noteworthy that this reductive amination protocol is not limited to aniline derivatives, as sulfonylamide **b24** as well as aliphatic primary **b25-b27** and secondary amines **b28-b30** were also successfully coupled. Ethylenediamine **b31** afforded the *N,N'*-dibenzylethylenediamine **d31**, without formation of imidazolines.<sup>29</sup> Remarkably, the amino-alcohols **b32-b34** were alkylated to afford selectively the corresponding hydroxyamines, the pending hydroxy group not entering into a potentially competitive *N*-alkylation process.<sup>16</sup> To complete the series of amines amenable for this transformation,  $\alpha$ -amino-esters **b35-b36** were alkylated with success. A series of aliphatic aldehydes (**a37-a40**), including butanal (**a37**), readily available by hydroformylation or bio-sourced aldehydes such as cinnamaldehyde (**a40**), were also successfully engaged in the present reductive amination protocol. Non-conjugated C=C were typically not reduced in the course of the reaction, while conjugated C=C bonds were reduced under harsher conditions,<sup>30</sup> which is in line with the selectivity observed for the reduction of  $\alpha,\beta$ -unsaturated ketones.<sup>26</sup>

$\text{R}^1\text{-CHO} + \text{HN(R}^2\text{)(R}^3\text{)} \xrightarrow[2) \text{ 2 (2 mol\%), tBuOK (5 mol\%), H}_2 \text{ (50 bar), T (}^\circ\text{C), t (h)}]{1) \text{ EtOH, 100 }^\circ\text{C, 24 h}}$					
Entry	Product	Temp. ( $^\circ\text{C}$ )	time (h)	Yield (%) <sup>[b]</sup>	
1		d1	50	18	93
2		d2	100	36	94
3		d3	100	48	72
4		d4	100	24	78 <sup>[c]</sup>
5		d5	50	48	87
6		d6	100	48	28
7		d7	80	36	90
8		d8	50	48	80
9		d9	100	36	98 <sup>[d]</sup>
10		d10	100	36	98 <sup>[d]</sup>
11		d11	80	36	97
12		d12	80	48	92
13		d13	100	48	95
14 <sup>[e]</sup>		d14	80	36	88
15		d15	50	18	73
16		d16	50	18	96
17		d17	80	48	98
18		d18	100	48	97
19		d19	100	48	90
20		d20	80	36	68
21		d21	80	48	55
22		d22	80	48	90

Entry	Product		Temp. (°C)	time (h)	Yield (%)
23		d23	80	48	92
24		d24	80	48	93
25		d25	100	48	90
26		d26	80	18	95
27		d27	80	48	94
28		d28	80	36	96
29		d29	80	36	94
30		d30	80	36	93
31 <sup>[f]</sup>		d31	100	48	95
32		d32	100	24	86
33		d33	100	24	83
34		d34	100	18	97
35 <sup>[g]</sup>		d35	100	18	90
36 <sup>[g]</sup>		d36	100	36	91
37		d37	50	48	96
38		d38	50	48	95
39		d39	50	36	96
40 <sup>[g]</sup>		d40	100	48	93

**Table 2.** Scope of the reductive amination of aldehydes with amines in presence of **2** as precatalyst.<sup>[a]</sup> [a] Typical reaction conditions: a solution of aldehyde **a** (0.5 mmol), amine **b** (0.6 mmol) and anhydrous EtOH (2.0 mL) was stirred at 100  $^\circ\text{C}$  for 24h, then transferred to a 20 mL autoclave followed by **2** (5.0 mg, 2 mol%) and tBuOK (2.8 mg, 5 mol%). The autoclave was subsequently charged with H<sub>2</sub> (50 bar) and heated. [b] Isolated yield after purification. [c] **a1** (4.3 mmol), condensation: 2 h, r.t. [d] c.a. 10% of deiodination product. [e] **b1** (100  $\mu\text{L}$ , 1.1 mmol). [f] **a1** (122  $\mu\text{L}$ , 1.2 mmol). [g] **2** (5 %mol), tBuOK (10 mol%).

Finally, it has to be noted that a few functional groups such as terminal alkyne, nitro group, or unprotected pyrrole were not tolerated.

In conclusion, we have shown that a well-defined manganese pre-catalyst featuring a readily available bidendate diphenyl-(2-aminopyridinyl)-phosphine ligand catalyzes efficiently the reductive amination of aldehydes using H<sub>2</sub> as reductant with a wide functional group tolerance. This higher amines synthesis protocol significantly enlarges the scope of reactions catalyzed by manganese complexes and nicely complements a previous approach based on alkylation of amines with alcohols.

## Conflicts of interest

There are no conflicts to declare.

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