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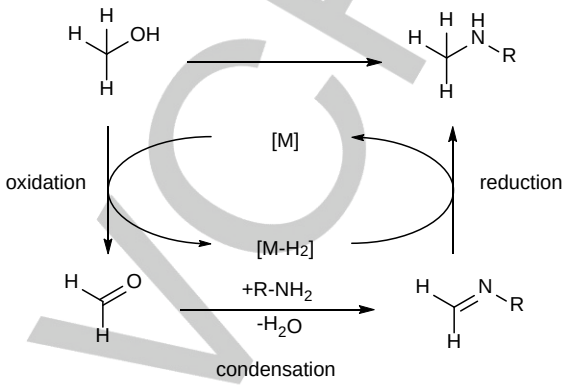
Improved And General Manganese Catalyzed N-Methylation of Aromatic Amines Using Methanol

Jacob Neumann[a], Saravanakumar Elangovan[a, b], Anke Spannenberg[a], Kathrin Junge[a] and Matthias Beller*[a]

Abstract: A novel lutidine based manganese PNP pincer complex has been synthesized for the selective N-methylation of aromatic amines with methanol. Using borrowing hydrogen methodology a selection of different functionalized aniline derivatives is methylated selectively in good yields.

The selective *N*-methylation of amines is one of the most used methodologies for the synthesis of pharmaceuticals and fine chemicals.[1] In general, Eschweiler-Clarke type reactions, applying formaldehyde, are preferred for such industrial products. On the other hand, on laboratory scale methylation of amines is still often based on reagents such as methyl iodide, dimethyl sulfate or diazomethane. Clearly, those reactions suffer not only from the utilization of carcinogenic reagents but also from the low selectivity of the processes leading to multiple methylation products. An additional drawback of these latter procedures is the formation of stoichiometric amounts of waste. Therefore more environmental benign processes, using safer methylation agents, continue to interest chemists in industry and academia. In this respect, in the last decade greener alternatives such as dimethyl carbonate, carbon dioxide and formic acid have been intensively studied for methylation of amines.[2] In addition, the so-called borrowing hydrogen (BH) strategy enables the use of methanol as a convenient methylation reagent.[3] First examples for the homogenously catalyzed methylation of amines using methanol were published already in the early 1980´s and 1990´s, respectively.[4]

Since then, only very few homogenous catalysts were developed for the methanol derived *N*-methylation of amines, which are mainly based on precious metals such as ruthenium, iridium or silver. Until today in heterogeneous catalysis non-noble metal catalysts prevail for methylation of amines.[5] However, these catalysts, often copper-based, require high temperatures (>200°C) for sufficient activity. On the other hand, homogeneous non-noble metal catalyzed *N*-methylation of amines remains challenging, even though examples for the *N*-alkylation based on iron and cobalt were published by the groups of Barta and Kempe.[6]



Scheme 1. Catalytic methylation of amines using borrowing hydrogen strategy

Very recently, we developed the first homogenous manganese pincer complex (**1**) which catalyzes the *N*-methylation of amines using the BH strategy as well as the reduction of carboxylic acid derivatives.[7] Motivated by these results and the actual interest in molecularly-defined manganese pincer-type complexes (Figure 1),[8] here we report a second generation manganese catalyst, which allows for the methylation of amines under milder conditions with high efficiencies.

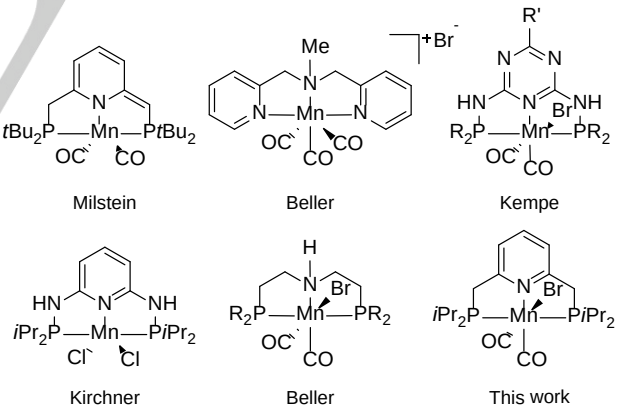


Figure 1. Recently published manganese pincer complexes which were applied in homogeneous catalysed reactions.

At the start of this work, we further investigated the application of manganese pincer complexes. Therefore, in addition to the previously shown complex (**1**) we decided to test pyridine based manganese PNP pincer complexes such as **2** and **3** because this structure motif has been successfully adopted in the past for a number of catalytic reactions.[9]

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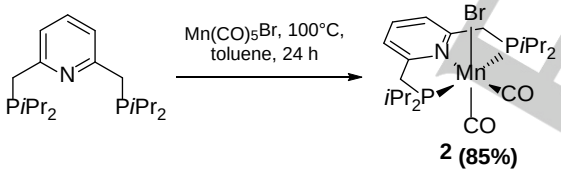
Complexes **2** and **3** are easily synthesized in a one-step reaction of the corresponding 2,6-bis(di-alkyl phosphinomethyl)pyridine ligand (PNP^{iPr}) or (PNP^{tBu}) and $Mn(CO)_5Br$ in very high yields (83%-85%). Complex **3** was originally described by Milstein's group.[8c] While the *iso*-propyl substituted PNP Mn pincer complex **2** forms the neutral species (Scheme 2), compound **3** is isolated as cationic tris-carbonyl complex with a bromide counter anion. Crystals suitable for X-ray analysis were obtained from slow cooling of a hot saturated solution of **2** in benzene. As shown in Figure 2 the distorted-octahedral manganese center is surrounded by three meridional placed donor atoms of the PNP pincer ligand. The two carbonyl ligands and the bromine atom occupy the remaining positions while the two CO are arranged in *cis* coordination. The IR spectrum of **2** shows two strong absorptions at 1819 and 1909 cm^{-1} for the CO ligands. The ^{31}P NMR of complex **2** shows a signal at 85.76 ppm, indicating two chemically equivalent phosphorus atoms. In the aromatic region of the proton NMR two signals are to be found. One triplet at 7.53 ppm with a coupling constant of 7.5 Hz and a doublet at 7.26 ppm which again has a coupling constant of 7.5 Hz. The spectrum also contains four multiplets in the aliphatic region (δ = 4.08 – 3.69; 3.62 – 3.38; 3.16 – 2.80; 2.70 – 2.37) with an area similar to the doublet in the aromatic region. Those signals can be ascribed to diastereotopic protons of the CH_2 and the C*H* protons of the isopropyl group. In the carbon NMR three signals can be seen in the aromatic region (163.96 (t, *J* = 5.8 Hz); 137.29; 120.85 (t, *J* = 4.5 Hz)). In the aliphatic area altogether seven signals can be found (41.56 (t, *J* = 8.3 Hz); 26.97 (t, *J* = 10.2 Hz); 26.28 (t, *J* = 8.1 Hz); 20.25 – 20.01 (m); 19.96; 19.72; 18.93). To determine which carbon signal matches with which proton signal, a HSQC experiment was carried out (see SI).



Scheme 2. Synthesis of Mn PNP pincer complex **2**.

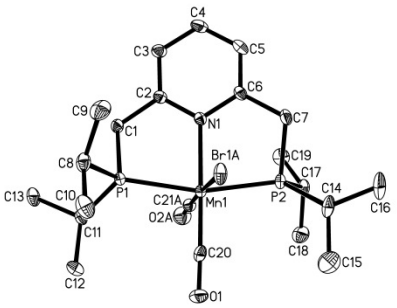
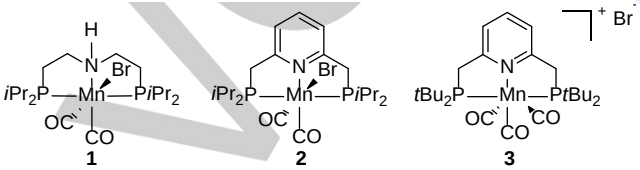
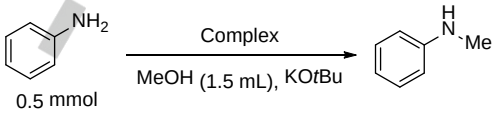


Figure 2. ORTEP diagram of [Mn(PNP^{iPr})(CO)$_2$Br] (**2**) with thermal ellipsoids at 30% probability. Hydrogen atoms are omitted for clarity.

With these manganese pre-catalysts (**1**-**3**) in hand, we studied the *N*-methylation of aniline with methanol as model reaction. Starting from the previously optimized conditions (Table 1, entry 3), we first lowered the catalyst loading from 3 mol% to 1 mol%. In the case of complex **1** this led to a decreased overall yield of 90% (Table 1, entry 4). When complex **2** was used, still a full conversion of aniline towards *N*-methylaniline was obtained. With 1 equivalent of base and even shorter reaction times full conversion of aniline was observed (Table 1, entries 7, 8). A halving of the base loading led to a decreased conversion of 92% after 6 h (Table 1, entry 9) and 97% after 16 h (Table 1, entry 10), respectively. Surprisingly, in the presence of complex **3** no reaction towards the desired product was obtained (Table 1, entry 11), demonstrating the strong influence of the phosphorous substituents.

Table 1. Methylation of aniline: Testing different manganese complexes.[a]





Entry	Complex	Loading [mol%]	KO*t*Bu [eq.]	Time [h]	Yield [b] [%]
1	-	-	1	24	-
2	$Mn(CO)_5Br$	2	1	24	-
3	**1**	3	1	24	95
4	**1**	1	1	24	90
5	**1**	2	0.5	16	69
6	**2**	1	1	24	>99
7	**2**	1	1	16	>99
8	**2**	1	1	6	>99
9	**2**	1	0.5	6	92
10	**2**	2	0.5	16	97
11	**3**	1	1	24	-

[a] Reaction conditions: 0.5 mmol aniline, 100 °C. [b] Yield determined by GC analysis using *n*-hexadecane as an internal standard.

In order to prove the general applicability of the improved catalyst **2** under the optimized catalytic conditions we investigated the methylation reaction of different functionalized aromatic amines (Table 2). In general, amines carrying electron donating or electron withdrawing groups were selectively mono-methylated to give the corresponding *N*-methylamines in good to very good yields (Table 2, entries 1, 2, 4, 6). In the case of *ortho* substituted aniline derivatives the desired products were obtained in moderate yields (Table 2, entries 3, 5, 6). This finding indicates that sterically demanding substrates are less active compared to *para* or *meta* substituted ones. This

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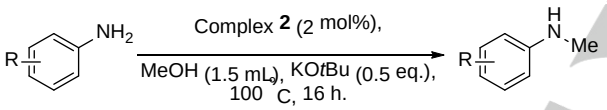
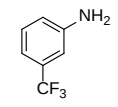
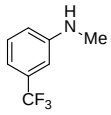
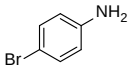
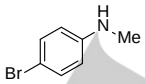
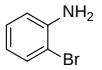
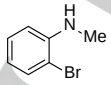
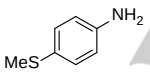
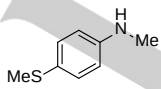
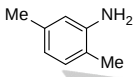
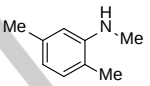
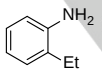
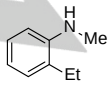
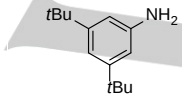
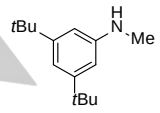
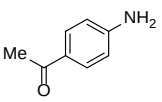
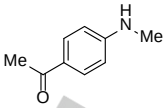
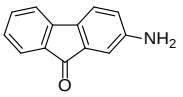
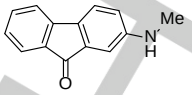
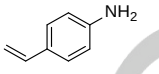
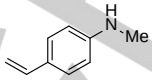
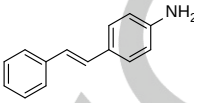
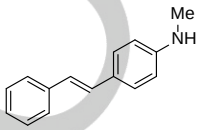
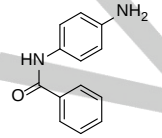
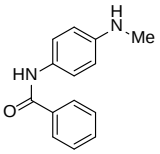
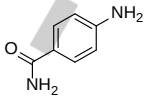
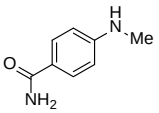
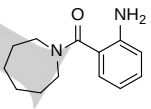
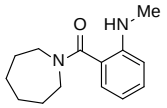
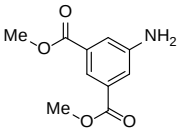
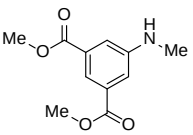
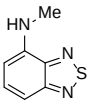
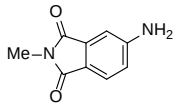
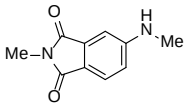
assumption is supported by the finding that 2,4,6-tritertbutylaniline showed no reactivity at all, while 3,5-ditertbutylaniline was completely converted (Table 2, entry 7). Interestingly, 4-aminoacetophenone was monomethylated without any reduction of the ketone (Table 2, entry 8). In contrast, the more electron deficient 2-amino-fluoren-9-one was partially reduced to the corresponding alcohol (Table 2, entry 9). Notably, aniline derivatives containing a vinyl group as well as stilbene group were selectively mono-methylated without any hydrogenation of the C-C double bonds (Table 2, entries 10, 11). Furthermore amides containing *N*-methylanilines were synthesized in good to very good yields without any reduction or hydrolysis of the amide moiety (Table 2, entries 12-14). Furthermore, the diester dimethyl-5-aminoisophthalate was methylated to 65% of the desired product using NaOMe as a base (Table 2, entry 15). In this case, the difference between yield and conversion can be explained by the formation of carboxylic acid derivatives of the diester through hydrolysis. Those compounds have strong interactions with the GC column and were difficult to detect by this methodology. Finally, heterocyclic compounds were selectively monomethylated using complex **2** (Table 2, entries 16, 17). Regarding functional group tolerance it should be mentioned that nitrile containing anilines were not transformed to the desired product indicating an inhibition of the reaction in this case.

Table 2. Mn-catalyzed selective monomethylation of anilines using methanol.[a]



Entry	Substrate	Product	Conv. [%][b]	Yield [%][c]
1			85	73
2			99	89
3			65	59
4			99	92
5			70	51
6			74	63
7			99	91
8[d]			88	63
9[e]			99	39
10			99	83
11			99	92
12[f]			99	93
13[f]			99	88
14[f]			99	86
15[g]			99	65
16			99	95
17[f]			99	85

[a] Standard reaction conditions: amine (1 mmol), complex **2** (2 mol%) MeOH (1.5 mL), KO*t*Bu (0.5 mmol), 100 °C, 16 h. [b] Determined by GC using *n*-hexadecane as internal standard. [c] Isolated yield. [d] Decreased yield through the formation of 4-(*N*-methylamino)propiophenone (7% isolated yield). [e] Decreased yield through the formation of 2-methylamino-fluoren-9-ol (50% isolated yield). [f] Complex **2** (4 mol%), 120 °C were used. [g] NaOMe (1 mmol) was used.

Indeed, carrying out a reaction of aniline under the optimized conditions in the presence of 10 mol% 4-aminobenzonitrile gave only 3% of *N*-methylaniline under these conditions confirming this assumption. Applying benzyl or hexyl amine as substrates formation of the corresponding imine was observed as the main product.

In summary, we have synthesized the manganese PNP pincer complex **2** and showed that this catalyst is suitable for the selective mono-methylation of aromatic amines with inexpensive methanol. Compared to our previously described manganese

catalysts, this novel complex allowed for methylations under milder conditions in better yields. From a synthetic point of view it is interesting that functional groups such as ketone, C-C double bonds or amides are well tolerated. Notably, structurally closely related complexes such as **3** do not show any activity under our optimal conditions.

Experimental Section

An oven dried pressure tube was charged with Mn precursor **2** (10.6 mg, 0.02 mmol) and *t*-BuOK (56 mg, 0.5 mmol). Amines (1 mmol) were weighed into the pressure tube under air, and the pressure tube was connected to a Schlenk line and vacuum-argon exchange was performed three times. Dry, degassed methanol (1.5 mL) and amines (in case of liquid ones) were charged under an argon stream after the three vacuum-argon exchanges. The pressure tube was closed with a Teflon® stopper and was heated to 100 °C. After 16 h the reaction mixture was cooled to room temperature and extracted with ethyl acetate / water. The organic layer was dried over $MgSO_4$ and transferred into a round bottom flask. SiO_2 (350 mg) was added to the mixture. The solvent was removed *in vacuo* and the product was purified by column chromatography using pentane and ethyl acetate (100:0 to 0:100). The product was analyzed by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectroscopy using EI (70eV) as ionization method.

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Keywords: Borrowing hydrogen • amines • methylation • manganese • pincer complex

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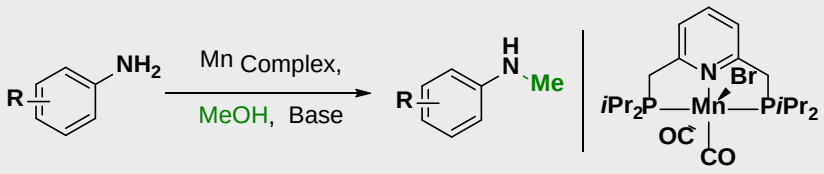

A manganese pincer complex has been employed for the selective N-methylation of aromatic amines using methanol via borrowing hydrogen methodology. A selection of different functionalized aniline derivatives is selectively mono-methylated in good yields.

*Jacob Neumann, Saravanakumar Elangovan, Anke Spannenberg, Kathrin Junge and Matthias Beller**

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Improved And General Manganese Catalyzed N-Methylation of Amines Using Methanol