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Mono-*N*-methylation of anilines with methanol catalyzed by a manganese pincer-complex

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ABSTRACT

The selective mono-*N*-methylation of anilines derivatives was achieved under mild conditions using inexpensive methanol as C1 source. Under hydrogen borrowing conditions, using a tridentate PN^3P manganese pre-catalyst (5 mol%), a catalytic amount of base (20 mol%), for 24 h at 120 °C, a large variety of anilines derivatives was methylated in good to excellent yield. Mechanistic investigations allowed us to isolate and characterize by X-ray diffraction studies a de-aromatized manganese intermediate.

1. Introduction

Amines are important building blocks that have found widespread applications in agrochemicals, pharmaceuticals, natural products, dyes and polymers [1–3]. In particular, *N*-methylamines are key intermediates and building blocks in organic synthesis. As an alternative to hazardous classical methylation reagents, such as methyl iodide, methyl triflate or dimethyl sulfate, or to formaldehyde, new greener sources of "CH_3" have recently drawn the attention of chemists [4,5]. Among them, CO_2 was used as C1 source for the methylation of amines under reductive conditions with hydrosilanes or H_2 [6–16], as well as formic acid [17–19] and stable and non-toxic dialkyl carbonates [20–22]. The simplest alcohol, methanol is also an attractive reagent for the methylation of amines, as it is readily available, inexpensive and a renewable feedstock [23–27]. Utilizing the hydrogen borrowing methodology [28–39], methanol is first activated upon dehydrogenation into formaldehyde, which is then condensed with an amine to afford the corresponding imine, which is finally reduced *in situ* to the *N*-methylated amine, water being the sole by-product. Such methodology was originally developed with transition metals such as ruthenium and iridium [40–45]. In the quest for green and sustainable chemistry, the use of earth abundant raw material is essential [46], but their transformations with the help of non-noble metal catalysts is a still a challenge [47,48]. Tremendous advances were recently achieved with iron [49], notably in hydrogen borrowing reactions [50–61]. However, methylation of amines with methanol is still a difficult reaction, probably due to the high activation barrier of the dehydrogenation step compared to heavier alcohols [62,63]. In this context, manganese, which is the third most abundant transition metal after iron and titanium, is arguably an economical, non-toxic and environmentally benign metal, highly attractive for sustainable chemistry and catalysis [64–66].

In reduction area, manganese complexes have been applied lately in the hydrosilylation of ketones and carboxylic acid derivatives [67–72]. However, until this year, manganese was not known as a catalyst for hydrogenation of carbonyl substrates or for related hydrogen borrowing reactions [64–66].

Beller described the first example of hydrogenation of carbonyl derivatives, nitriles [73], and esters [74] using aminodiphosphine (PNHP) manganese complexes such as **1**, followed very recently by Kempe, who developed a catalytic system based on 2,6-(diaminotriazinyl)-diphosphine (PN^5P) ligand [75] and us [76]. On the other hand, Milstein [77,78], using the PNP pincer complex **2**,

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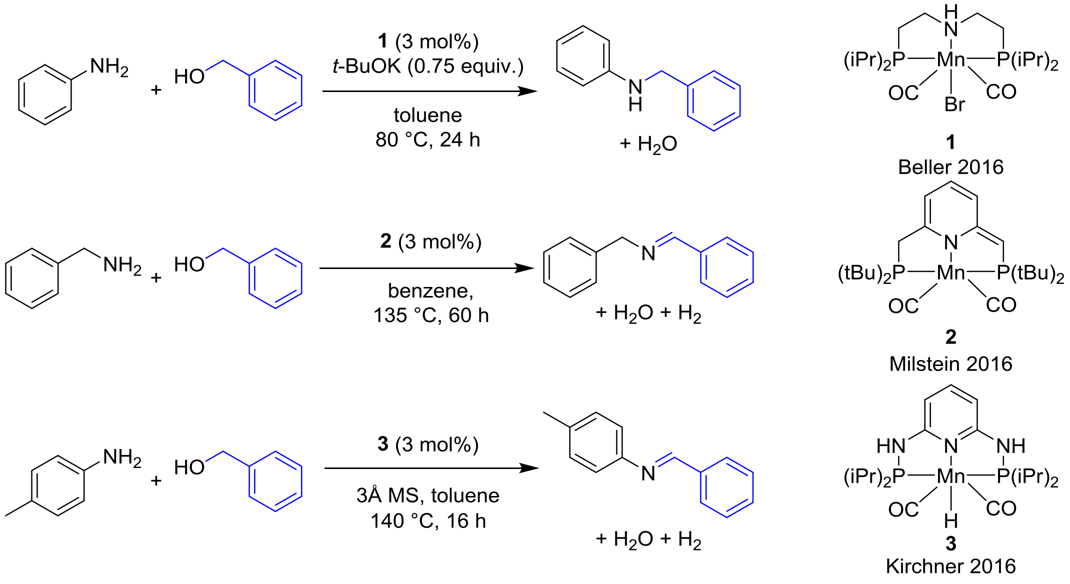
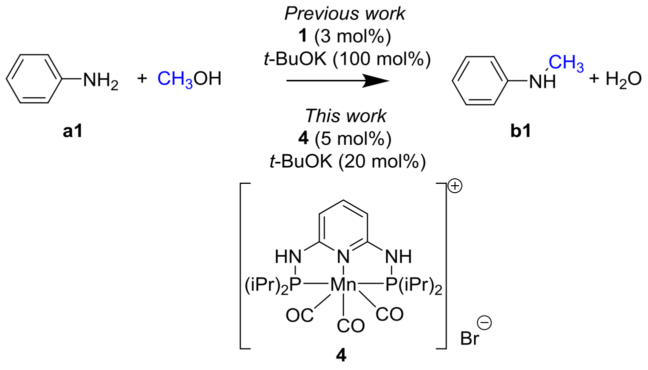


Scheme 1. Manganese complexes in hydrogen borrowing reactions.



Scheme 2. Mono-*N*-methylation of aniline derivatives with methanol under the catalysis of manganese complexes.

and Kirchner [79,80], using the PN^3P pincer hydride complex **3**, reported the dehydrogenative coupling of alcohols and amines to form imines, whereas catalyst **1** led to the alkylated amines [81] (Scheme 1). Boncella, using the same catalytic system as Beller, accomplished the decomposition of formic acid into hydrogen and carbon dioxide [82]. Finally, Beller also reported the α-alkylation of ketones with primary alcohols under hydrogen borrowing [83] and the reduction of ketones though hydrogen transfer reaction [84].

In the course of our investigation on the alkylation of amines with alcohols under hydrogen borrowing conditions to produce the alkylated amines, we have recently described the first selective mono-methylation of anilines using methanol catalyzed by PNHP-Mn catalyst **1** [81]. The reaction was operating at 100 °C, in the presence of 1 equiv. of *t*-BuOK and 3 mol% of catalyst. Herein, we describe a new catalytic system, based on manganese catalyst **4** bearing a bis-(diaminopyridine)phosphine ligand (PN^3P) and the methylation is now operating under catalytic amount of base (20 mol%) (Scheme 2).

2. Experimental

Typical catalytic methylation. In an argon filled glove box, a Schlenk tube was charged with the desired amine (0.5 mmol), toluene (1 mL), MeOH (1 mL), Mn complex **4** (14 mg, 5 mol%) followed by *t*-BuOK (11.2 mg, 20 mol%), in this order. The mixture was stirred for 24 h at 120 °C in an oil bath. The solution was then

Table 1
Optimization of the reaction conditions for the methylation of aniline under the catalysis of **4**.[a]

Entry	Base (mol%)	Time (h)	Temp. (°C)	Conv.[b] (yield[c]) (%)
1	*t*-BuOK (100)	62	120	98 (98)
2	*t*-BuOK (10)	22	120	83 (83)
3	*t*-BuOK (5)	22	120	37 (37)
4	*t*-BuOK (10)	22	110	73 (73)
5	*t*-BuOK (10)	22	130	84 (84)
6	Cs_2CO_3 (10)	22	120	81 (81)
7	K_2CO_3 (10)	22	120	78 (78)
8	NaOH (10)	22	120	38 (38)
9	KOH (10)	22	120	33 (33)
10[d]	*t*-BuOK (20)	24	120	0 (0)
11	*t*-BuOK (20)	24	120	96 (94)

[a] Reaction conditions: aniline **a1** (0.5 mmol), methanol (1 mL), toluene (1 mL), catalyst **4** (5 mol%), and the base were mixed in this order and heated in a closed Schlenk tube in an oil bath.

[b] Conversion of **a1** was determined by GC and ^1H NMR on the crude reaction mixture.

[c] Yield in **b1** was determined by GC and ^1H NMR on the crude reaction mixture.

[d] $Mn(CO)_5Br$ as catalyst.