Communication

Manganese-Catalyzed Aminomethylation of Aromatic Compounds with Methanol as Sustainable C1 Building Block

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Manganese-Catalyzed Aminomethylation of Aromatic Compounds with Methanol as Sustainable C1 Building Block

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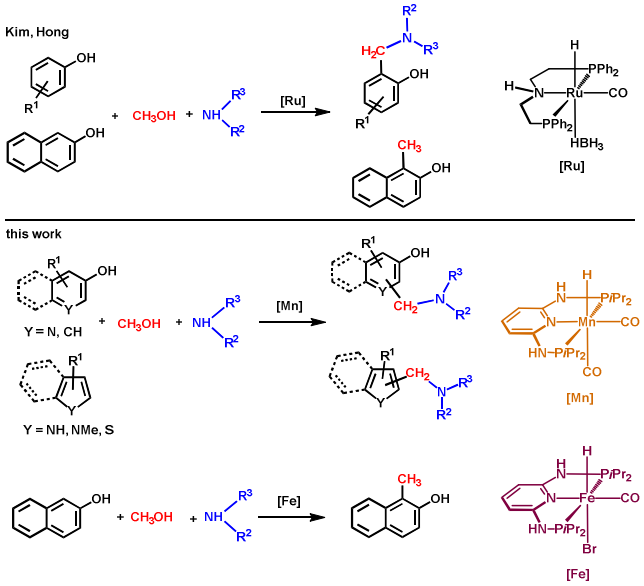
ABSTRACT: This study represents the first example of a manganese-catalyzed environmentally benign, and practical three-component aminomethylation of activated aromatic compounds including naphtols, phenols, pyridines, indoles, carbazoles, and thiophenes in combination with amines and MeOH as C1 source. These reactions proceed with high atom-efficiency *via* a sequence of dehydrogenation and condensation steps which give rise to selective C-C and C-N bond formations, thereby releasing hydrogen and water. A well-defined hydride Mn(I) PNP pincer complex, recently developed in our laboratory, catalyzes this process in a very efficient way and a total of 28 different aminomethylated products were synthesized and isolated yields of up to 91 %. In a preliminary study, a related Fe(II) PNP pincer complex was shown to catalyze the methylation of 2-naphtol rather than its aminomethylation displaying again the divergent behavior of isoelectronic Mn(I) and Fe(II) PNP pincer systems.

During the past decade, the acceptorless dehydrogenation (AD) of alcohols,[1] an oxidant-free, atom-economical approach to yield carbonyl compounds, has emerged as powerful tool for the benign construction of valuable complex organic molecules. Alcohols are sustainable and abundant building blocks as they are readily available by a variety of industrial processes and can be obtained renewably *via* fermentation or catalytic conversion of lignocellulosic biomass.[2,3] Ketones and aldehydes generated *in situ* can be converted into other useful organic materials such as amines, imines, amides, or heterocycles. In the course of these transformations only dihydrogen and water as nontoxic byproducts are generated. Due to the significance of C-C and C-N bond forming reactions, in recent years several efficient homogeneous catalysts based on non-precious, inexpensive, earth abundant metals like Mn,[4,5,6,7] Fe,[8,9,10] Co[11,12,13] or Ni[14] have been developed which are highly active for AD of alcohols as well as in the opposite reaction, i.e. the hydrogenation of carbonyl compounds. In particular AD reactions catalyzed by Mn(I) pincer complexes became a very important research topic, after seminal reports in 2016 by the groups of Milstein,[5a,b] Beller,[5f,g] and us[5d,e] on dehydrogenative coupling reactions of alcohols and amines to yield imines, α-alkylation of ketones with primary alcohols, and multicomponent reactions to form heterocycles such as quinolines and pyrimidines. Within the following months a remarkable number of intriguing developments in catalytic transformations with Mn pincer complexes has been achieved. The group of Kempe[5c] and our group[5d,e] reported the dehydrogenative coupling of alcohols with amines and amidines to form pyrimidines. Beller *et al.* described the Mn-catalyzed dehydrogenation of MeOH,[5h] and the Milstein group described the *N*-formylation of amines with MeOH.[5m] Gauvin *et al* described an acceptorless dehydrogenative coupling of alcohols to esters,[5j] and the group of Darcel and Sortais reported the mono-N-methylation of anilines with MeOH.[5k]

Inspired by these rapidly growing developments in Mn(I) catalysis, we describe here an efficient three-component aminomethylation of activated aromatic and hetero aromatic compounds with MeOH as key feedstock (Scheme 1). A Ru-catalyzed aminomethylation of phenol derivatives utilizing MeOH as C1 source was recently described by Kim and Hong (Scheme 1).[15] Surprisingly, when 2-naphthol was employed instead of phenol, only methylation was observed.

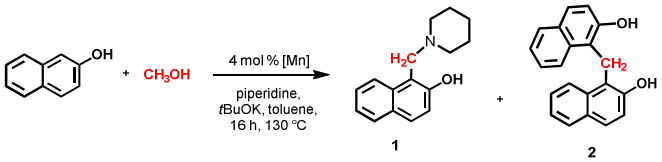
Scheme 1. Catalytic aminomethylations of aromatic compounds utilizing amines and MeOH as C1 source.



First, the reaction conditions were optimized for the three component reaction of 2-naphtol, piperidine and MeOH (in a 1:1.1:1.3 ratio) as model system in toluene (4 mL) in the presence of 1.3 equiv KO*t*Bu and 4 mol% **[Mn]** at 130 °C (Table 1). The products were analyzed by ^{1}H and ^{13}C{^{1}H} NMR and identified

by comparison with authentic samples. In general, isolated yields after purification by column chromatography are reported. Under these reactions conditions 1-(piperidin-1-yl-methyl)naphthalene-2-ol (**1**) was selectively formed in 86 % isolated yield (Table 1, entry 1). Shorter reaction times led to a drop in yield (Table 1, entry 2), while longer reaction time did not lead to an improvement of the yield (Table 1, entry 3). Lowering the temperature to 110 °C resulted in low yields (Table 1, entry 5). Likewise, also lowering of the catalyst loading (2 mol %) led to a reduced yield (Table 1, entry 4). When the reaction was performed in the absence of amine, dimerization of 2-naphtol through a bridging methylene group took place to give 1,1'-methylenedinaphthalene-2-ol (**2**) in 63 % isolated yield (Table 1, entry 6).

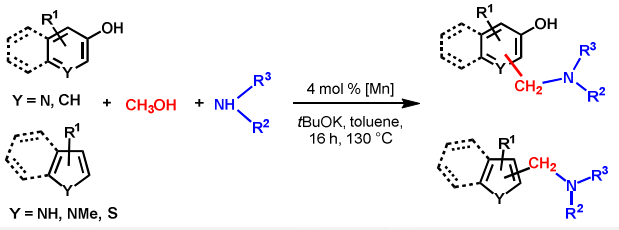
Table 1. Optimization of the reaction conditions for the aminomethylation of aromatic compounds.[a,b]

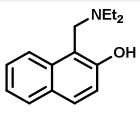
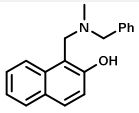
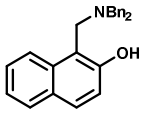
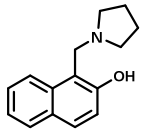
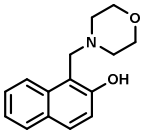
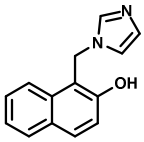
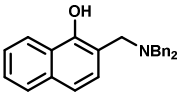
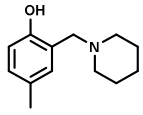
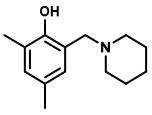
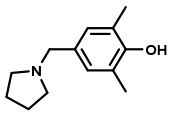
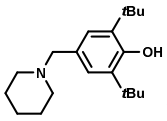
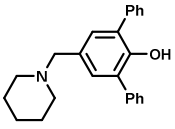
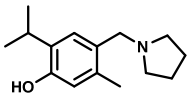
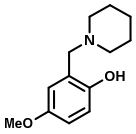
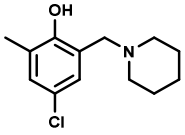
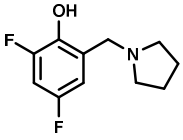
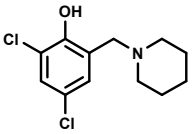
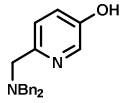
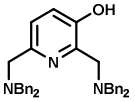
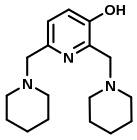
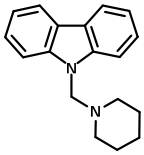
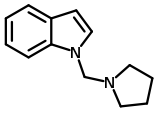


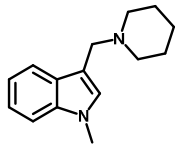
entry[a]	base	T [°C]	time [h]	yield[b] **1** [%]	yield[b] **2** [%]
1	*t*BuOK	130	16	86	
2	*t*BuOK	130	8	72	
3	*t*BuOK	130	24	87	
4[c]	*t*BuOK	130	16	78	
5	*t*BuOK	110	16	37	
6[d]	*t*BuOK	130	16		63
7		130	16	traces	

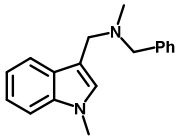
[a] Reaction conditions: 1.3 mmol MeOH, 1.0 mmol 2-naphthol, 1.1 mmol piperidine, 1.3 mmol *t*BuOK, 4 mL toluene, 130 °C. [b] Isolated yields. [c] 2 mol % **[Mn]**. [d] In the absence of amine.

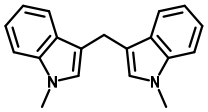
Table 2. Aminomethylation of aromatic compounds with MeOH and amines catalyzed by [Mn].[a,b]

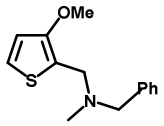


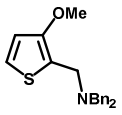
entry	product	entry	product
1	 **3** (72 %)	2	 **4** (91 %)
3	 **5** (92 %)	4	 **6** (85 %)
5	 **7** (84 %)	6	 **8** (49 %)
7	 **9** (60 %)	8	 **10** (78 %)
9	 **11** (81 %)	10	 **12** (78 %)
11	 **13** (81 %)	12	 **14** (87 %)
13	 **15** (61 %)	14	 **16** (82 %)
15	 **17** (77 %)	16	 **18** (68 %)
17	 **19** (55 %)	18	 **20** (64 %)
19[c]	 **21** (43 %)	20[c]	 **22** (44 %)
21	 **23** (75 %)	22	 **24** (52 %)

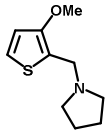
23  **25** (74 %)

24  **26** (81 %)

25[d]  **27** (64 %)

26  **28** (74 %)

27  **29** (76 %)

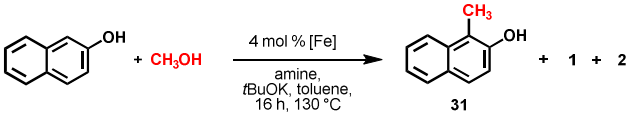
28  **30** (59 %)

[a] Reaction conditions: 1.3 mmol MeOH, 1.0 mmol substrate, 1.1 mmol amine, 1.3 mmol *t*BuOK, 4 mol % **[Mn]**, 4 mL toluene, 130 °C. [b] Isolated yields. [c] 2.2 mmol MeOH, 1.0 mmol substrate, 2.2 mmol amine, 2.6 mmol *t*BuOK, 7 mol % **[Mn]**, 4 mL toluene. [d] Imidazole as N-nucleophile.

Having established the optimal reaction conditions, this methodology was applied to other aromatic and heteroaromatic compounds in combination with different amines and MeOH (Table 2). 2-Naphtol (Table 2, entries 1-6), 1-naphtol (Table 2, entry 7), phenols (Table 2, entries 8-17), 3-hydroxypyridine (Table 2, entries 18-20), carbazole (Table 2, entry 21), indole (Table 2, entry 22), 1-methylindole (Table 2, entries 23 and 24) and 3-methoxythiophene (Table 2, entries 26-28) were treated with diethylamine, benzylamine, methylbenzylamine, piperidine, pyrollidine, morpholine, imidazole and 1.3 equiv of MeOH to afford the corresponding aminomethylated products in good to high isolated yields. Methylation was not observed in any of the investigated cases, as observed by Kim and Hong[15] when 2-naphthol was employed instead of phenol. 2-Naphtol affords selectively the respective 1-aminomethylated products (Table 2, entries 1-6), while 1-naphtol yields the 2-aminomethylated compound (entry 7). Phenols, depending on the substitution pattern, yield selectively either 2- or-4-aminometylated products (Table 2, entries 8-17). The reaction of 3-hydroxypyridine with 1 or 2 equiv of benzylamine and MeOH resulted in the formation of 6-(dibenzylaminomethyl)pyridin-3-ol and 2,6-bis(dibenzylaminomethyl)pyridin-3-ol, respectively (Table 2, entries 18 and 20). With carbazole and indole aminomethylation occurred at the nitrogen site rather than at a C-position yielding 1-(pyrrolidin-1-ylmethyl)-1H-indole and 9-(piperidin-1-ylmethyl)-9H-carbazole (Table 2, entries 21 and 22). The reaction of 1-methylindole with imidazole resulted in dimerization rather than aminomethylation to give bis(1-methyl-1H-indole-3-yl)methane (Table 2, entry 25). 3-Methoxythiophenes afforded selectively 2-aminomethylated products (Table 2, entries 26-28).

Since the isoelectronic Mn(I) and Fe(II) PNP pincer complexes **[Mn]** and **[Fe]**, respectively, exhibited divergent reactivities in the dehydrogenative coupling of alcohols with amines,[5d] we also studied the three component reaction of 2-naphtol, piperidine and MeOH with 4 mol% **[Fe]** as catalyst (Table 3). In contrast to the Mn-catalyzed reaction under identical reaction conditions, the methylated product 1-methylnaphthalene-2-ol (**31**) was formed as major product (48 % yield), together with the aminomethylated and dimerized compounds **1** and **2**, respectively, as minor products (Table 3, entry 1). In the absence of amine, **2** was the major product (54 % yield), with **1** being formed in only 17 % yield. (Table 3, entry 2). In the absence of KO*t*Bu no products were obtained at all. If the reaction is performed in the presence of 0.2 equiv of piperidine, the major product is the methylated 2-naphtol **31**, with only 13 % of dimerized product (Table 3, entry 4). The yield of **31** could be further increased to 75 %, if the temperature is raised to 140 °C (Table 3, entry 5).

Table3. Optimization of the reaction conditions for the methylation of 2-naphthol.[a,b]



entry[a]	base	amine	yield[b] **29** [%]	yield[b] **1** [%]	yield[b] **2** [%]
1	*t*BuOK	piperidine	48	28	17
2	*t*BuOK		17		54
3		piperidine	traces	traces	traces
4[c]	*t*BuOK	piperidine	67	traces	14
5[c,d]	*t*BuOK	piperidine	75	traces	13

[a] Reaction conditions: 1.3 mmol MeOH, 1.0 mmol 2-naphthol, 1.1 mmol amine, 1.3 mmol *t*BuOK, 4 mol % **[Fe]**, 4 mL toluene, 130 °C. [b] Isolated yields.[c] 0.2 mmol amine. [d] 140 °C.

In conclusion, this study represents the first example of a manganese-catalyzed environmentally benign, and practical three-component aminomethylation of aromatic compounds including naphtols, phenols, pyridines, indoles, carbazoles, and thiophenes in combination with amines and MeOH as C1 source. These reactions proceed with high atom-efficiency *via* a sequence of dehydrogenation and condensation steps which give rise to selective C-C and C-N bond formations, thereby releasing hydrogen and water. Moreover, in a preliminary study a related Fe(II) PNP pincer complex was shown to catalyze the methylation of 2-naphtol rather than its aminomethylation underlining again the divergent reactivity of isoelectronic Mn(I) and Fe(II) PNP pincer systems. As described recently,[5d] both Mn and Fe catalysts are able to form coordinatively unsaturated intermediates upon deprotonation of the PNP ligand (bifunctional behavior). The important difference is that Mn contains two, Fe only one inert CO co-ligand, but Fe additionally contains a hydride ligand which can participate in the catalytic reaction. Accordingly, the Mn catalyst is able to perform only dehydrogenation reactions, while the Fe system (in analogy to many Ru systems) is capable of performing both dehydrogenations and hydrogenations (*via* an insertion mechanism). This study demonstrates that base metal catalysts begin to challenge precious metal catalysts and may contribute to a further advancement of waste-free sustainable base metal catalysis.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI: xxxxx

Synthetic procedures, ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra of all organic products (PDF).

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Notes

The authors declare no competing financial interest.

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