



Palladium catalyzed N-alkylation of amines with alcohols

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ABSTRACT

An iron oxide immobilized palladium catalyst was prepared for the N-alkylation of amines with alcohols under base and organic ligand free conditions. Applying the optimized reaction conditions, the coupling reactions of amines and alcohols with various structures could be realized with up to 99% isolated yields. The catalysts were studied by XRD, BET, and XPS and the mechanism was studied by DFT calculations.

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N-alkyl amine is one of the key functional groups in organic chemistry.¹ It plays a major role in the elaboration and composition of biological and chemical systems. N-alkyl amines are typically synthesized by using conventional alkylating agents, such as alkyl halides, however, this procedure can be problematic due to over-alkylation and the toxic nature of many alkyl halides and related alkylating agents.² The use of alcohols instead of alkyl halides to achieve the N-alkyl amines is an attractive method because it produces only water as byproduct and does not need special equipment. A variety of transition metal complexes such as ruthenium, iridium, rhodium, platinum, gold, nickel, copper, and iron catalysts are known to be good catalysts for the N-alkylation of amines and alcohols.^{3–12} Unfortunately, for the most of known homogeneous catalysts, the recovery and reuse of expensive catalysts, and the indispensable use of co-catalysts such as base and stabilizing ligand are unavoidable.^{13,14} The development of easily recoverable and recyclable heterogeneous catalysts can solve the problems of the homogeneous systems and has received a particular research interests.¹⁵ Although there are several reports on the N-alkylation using heterogeneous catalysts such as solid acids and transition metal-based catalysts, most of them require high reaction temperatures and high pressure and the scope of substrates is limited.^{16,17} Previously, the N-alkylation of benzyl alcohol with alkyl amine has been investigated in the presence of heterogeneous palladium catalyst but the system was still not general enough.¹⁸ The development of efficient heterogeneous catalyst for N-alkylation system with alcohol is still a challenging topic. Here, we report our results about Pd/Fe₂O₃ catalyzed coupling reaction of

amine with alcohol in the absence of additional base and organic ligands.

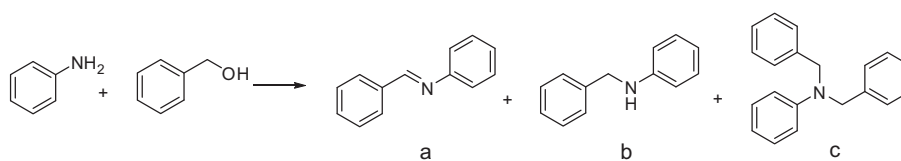
Initially, the N-alkylation of aniline with benzyl alcohol in the absence of base and organic ligand was explored using various iron oxide-supported and palladium-based catalysts (Table 1). All the catalysts were characterized by XRD, XPS and BET. XRD analysis confirmed the formation of crystal Fe₂O₃ (Fig. S1). No crystal Pd, Ru, and Ir could be detected by XRD, which indicate that the Pd, Ru, and Ir species are highly dispersed. Among the catalysts examined, Pd/Fe₂O₃ showed the highest catalytic activity with 95% conversion. Under the same reaction conditions, Ru/Fe₂O₃ and Ir/Fe₂O₃ only gave conversions <13% (entries 1–3). The effect of base on the catalytic activity of Pd/Fe₂O₃ was further checked. Surprisingly, the addition of catalytic amount of base (5 mol % K₂CO₃, K-O-t-Bu, K₃PO₄) as co-catalyst did not improve the conversion and selectivity (entries 4–6). Apparently, our catalyst system was active enough in the absence of base. By tuning the ratio of aniline and benzyl alcohol, the desired product, i.e. N-benzylaniline, could be achieved with higher conversion and selectivity (entries 7–9). If the catalyst was recovered and reused for the second time, 94% conversion, and 71% selectivity to N-benzyl amine and 28% selectivity to imine were obtained. So the reuse of the catalyst was possible.

The Fe₂O₃-supported palladium catalyzed N-alkylation reactions of various amines and alcohols were further investigated as shown in Table 2. The coupling of benzyl alcohol and aniline proceeded efficiently with 90% isolated yield (entry 1). Next, various alcohols were further tested. For (2-methoxyphenyl) methanol, which contains electron-donating substituent, 99% yield was obtained (entry 2). Also, heteroatom containing alcohol, i.e. pyridin-3-ylmethanol, was converted into the corresponding

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Table 1
Catalyst screening under various reaction conditions^a



Entry	Catalyst	Base	Conv. ^b (%)	Sel. ^c (%)		
				a	b	c
1	Pd/Fe ₂ O ₃	—	95	25	74	<1
2	Ru/Fe ₂ O ₃	—	13	99	—	—
3	Ir/Fe ₂ O ₃	—	6	99	—	—
4	Pd/Fe ₂ O ₃	K ₂ CO ₃	84	35	65	<1
5	Pd/Fe ₂ O ₃	KOt-Bu	94	34	66	<1
6	Pd/Fe ₂ O ₃	K ₃ PO ₄	94	28	72	—
7 ^d	Pd/Fe ₂ O ₃	—	97	16	83	<1
8 ^e	Pd/Fe ₂ O ₃	—	100	2	94	4

^a 5 mmol aniline, 7.5 mmol benzyl alcohol, 40 mg catalyst (2.28 wt%Pd/Fe₂O₃, 0.17 mol Pd% to aniline), 140 °C, 12 h, Ar.

^b Conversion of aniline with GC-MS.

^c Selectivities by GC-MS analysis based on the aniline consumed.

^d Aniline:benzyl alcohol = 1:2, 160 °C, 2 h.

^E Aniline:benzyl alcohol = 1:3, 160 °C, 2 h.

Table 2
Results of the alkylation reactions with amines and alcohols^a

Entry	R ¹ NH ₂	R ² OH	t (h)	Product	Yield ^b (%)
1			2		90
2			18		99
3			12		96
4			24		86
5			24		80
6			12		98
7			5		95
8			4		81 ^c
9			10		78
10			12		91

(continued on next page)

Table 2 (continued)

Entry	R ¹ NH ₂	R ² OH	t (h)	Product	Yield ^b (%)
11			12		85
12			20		95
13			20		72
14			18		95
15			18		85
16			28		91
17			28		95
18			28		84
19			12		87
20			24		93
21			24		79

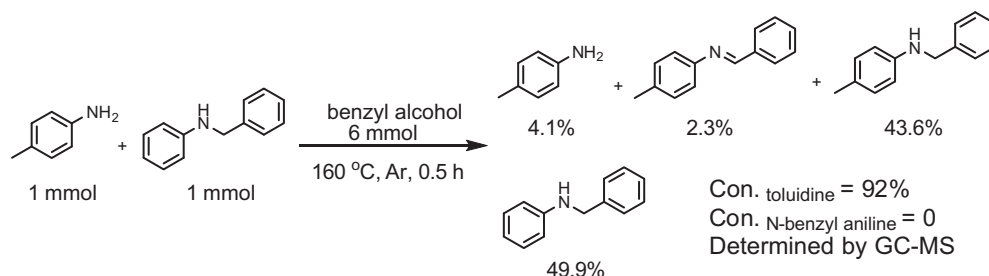
^a 2 mmol amine, 6 mmol alcohol, 40 mg catalyst (0.43 mol % Pd to amines), Ar. Entries 1, 3, 6–11, 16–19, 160 °C. Entries 2, 14, 15, 20, 21, 170 °C. Entries 4, 5, 13, 150 °C, entry 12, 140 °C.

^b Isolated yield.

^c Determined by GC–MS. The conversion was 100% and the selectivity to *N*-heptyl-octyl amine was 81%. The byproduct was triheptylamine.

N-benzyl-pyridin-3-amine with 96% yield (entry 3). Importantly, 80–86% yields were achieved for aliphatic alcohols as alkylating agents (entries 4–5). In addition, the coupling reaction of benzyl alcohol with heteroatom-containing pyridin-3-amine and *p*-toluidine were also successful with 95–98% isolated yields (entries 6 and 7). Notably, the coupling of aliphatic alcohol with aliphatic amine also gave good yields (78–81%, entries 8 and 9). These results suggested that Pd/Fe₂O₃ showed high catalytic activities for the

coupling of benzylic, heteroatom-containing and especially aliphatic alcohols, and amines to give secondary amines. Interestingly, tertiary amines could also be obtained by varying the reaction conditions. The transformation of aniline and *p*-toluidine efficiently proceeded to afford the corresponding benzylic tertiary amines in high yields, i.e. 85% and 91% (entries 10 and 11). Excellent results were obtained in the transformation of aliphatic primary alcohols or aliphatic primary amines. The corresponding



Scheme 1. The competition reaction between *p*-toluidine and *N*-benzyl aniline.

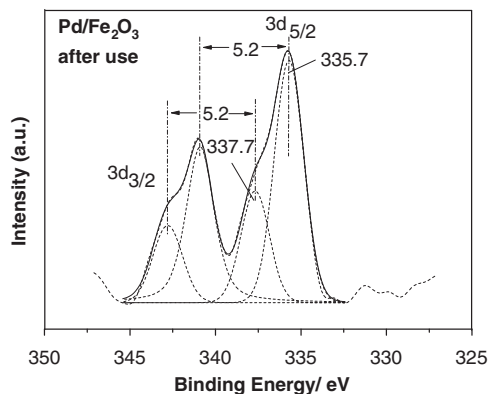
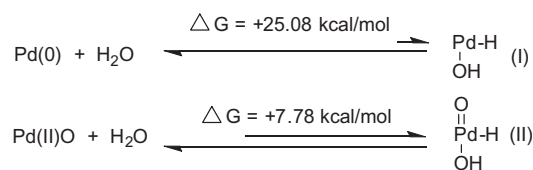


Figure 1. XPS spectra of Pd/Fe₂O₃ after use.



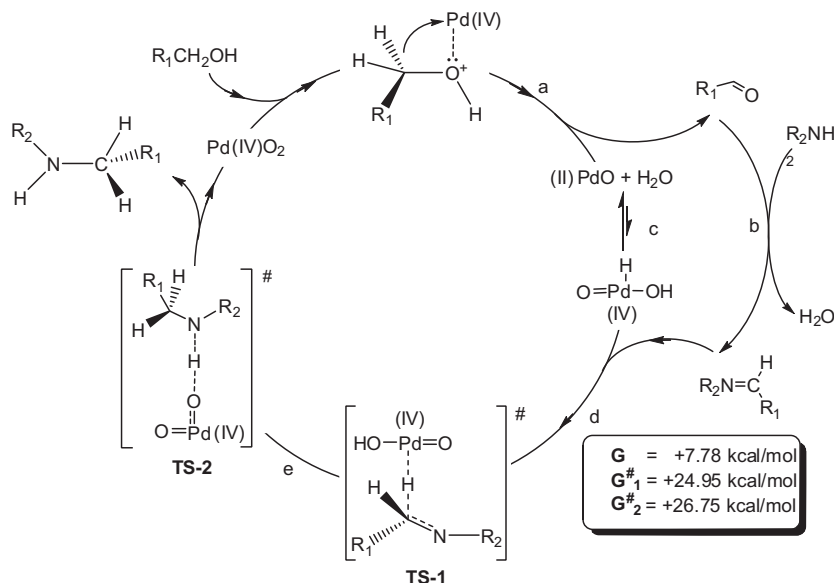
Scheme 2. Possible catalytic active palladium species.

our simple Fe₂O₃-supported palladium catalysts under base and organic ligand free conditions.

A competition experiment between *p*-toluidine and *N*-benzyl aniline was further carried out (Scheme 1). Clearly, *p*-toluidine was preferentially reacted with benzyl alcohol, affording only imine and mono-alkylation product, while *N*-benzyl aniline did not participate in the reaction and no tertiary amine was detected. Hence, mono-alkylation product and di-alkylation product could be synthesized by changing reaction time simply.

In order to get more information about the Pd/Fe₂O₃ catalyzed *N*-alkylation of aniline with alcohol, the catalyst Pd/Fe₂O₃ was measured by XPS after reaction, Figure 1. For the fresh Pd/Fe₂O₃ sample, the binding energy of palladium was 337.6 eV. This number was bigger than the typical binding energy of PdO,¹⁹ which was ~336.1 eV, but close to the binding energy of PdO₂,²⁰ which was ~337.6 eV. Interestingly, an additional strong peak at 335.7 eV could be observed after reaction. It was bigger than the

tertiary amines could be obtained with 85–95% yields (entries 12–15). On the other hand, secondary amines could be converted into the corresponding tertiary amines with up to 95% yields (entries 16–19). Finally, 93% yield was achieved for the *N*-alkylation reaction of indole with benzyl alcohol (entry 20). Methyl-indole-3-carboxylate was not stable enough under our reaction conditions, and the decarboxylated product was obtained (entry 21). All these results indicated that the product could be selectively modulated between secondary amines and tertiary amines by



Scheme 3. Mechanism of palladium catalyzed *N*-alkylation of amines with alcohols.

binding energy of Pd(0), which was 334.9–335.2 eV, but close to the binding energy of PdO, which was 336.1 eV.

According to the characterization results, we can hypothesize that the hydrogen-borrowing process might be realized through the cycle between 'PdO₂' and 'PdO' or 'PdO' and 'Pd'. Thus, it was further investigated by DFT calculations using GAUSSIAN 03 software (B3LYP/LANL2DZ).²¹ Undoubtedly, for the two cycles, they all start from the oxidation of alcohol to form the aldehyde.²² In the meanwhile, the palladium was transferred into 'PdO'/H₂O or 'Pd'/H₂O. Next, the active palladium species (I) or (II) would be generated by the reaction of 'PdO' or 'Pd' with H₂O. According to the calibration, it could be seen that the ΔG of Pd(0) + H₂O to form species (I) is +25.08 kcal/mol, which indicates that the formation of active palladium species (I) for the next step is rather difficult and the catalytic cycle between 'PdO' and 'Pd' is blocked. The ΔG of 'PdO' + H₂O to species (II) is +7.78 kcal/mol and thus the formation of active palladium species (II) is more reasonable, Scheme 2.

On the basis of the above experimental and DFT calculation results, a possible mechanism for 'PdO₂' and 'PdO' catalyzed N-alkylation of amines with alcohols is illustrated in Scheme 3. The first step of the reaction would involve the oxidation of an alcohol to the corresponding carbonyl compound, with the generation of a 'PdO' species (step a). The carbonyl intermediate would readily react with amine to afford an imine (step b). On the other hand, a reversible cycle between 'PdO' and compound (II) was happened (step c). We propose that the step is a reversible dis-proportionation of the Pd catalyst, which enters the catalytic cycle as the active intermediate with a free energy cost of +7.78 kcal/mol (step c).

Subsequently, the addition of the hydride palladium to the C=N bond of imine would occur to give a transition states TS-1, with free energy barrier +24.95 kcal/mol (step d). Then the transition states TS-1 transform to transition states TS-2, with free energy barrier of +26.75 kcal/mol (step e). Finally, the product was released and the 'PdO₂' species was regenerated.

In conclusion, a simple iron oxide-supported palladium catalyst was developed for the alkylation of amines with alcohols. The simple catalytic system exhibits high activity in the absence of base and organic ligand. In general, good to excellent yields are achieved using amines and alcohols containing various functional groups. Importantly, catalyst characterization and DFT studies suggested a novel mechanism with 'PdO₂/PdO' as possible intermediate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.059.

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