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COMMUNICATION

Selective cross-coupling of amines by alumina-supported palladium nanocluster catalysts[†]

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 Al_2O_3 -supported Pd nanoclusters with an average particle size of 1.8 nm act as a reusable catalyst for the selective crosscoupling of amines. The reaction is a structure-sensitive reaction, demanding coordinatively unsaturated Pd atoms on a metallic nanocluster. The support also affects the activity, an amphoteric oxide (Al_2O_3) is most effective.

Supported metal nanoparticles or nanoclusters play an important role in many heterogeneous catalytic reactions for green organic synthesis.¹⁻³ Current interest is focused on the development of supported metal catalysts for multi-step organic reactions, which provide a key technology for the green synthesis of fine chemicals.¹⁻⁷ Supported Pd metal catalysts have been widely used in organic reactions such as hydrogenation,^{8,9} selective oxidation,^{1,10,11} and multi-step one-pot reactions.⁵⁻⁷ To be able to move towards a rational design for heterogeneous synthetic catalysts, we need to understand the factors that affect the catalytic performance of Pd catalysts. Previous work has demonstrated that the size and support material have strong influence over the catalytic properties of Pd, but most of these fundamental attempts were focused on conventional reactions such as hydrogenation^{8,9} and selective oxidation.^{10,11} To establish a concept for the rational design of multi-functional Pd catalysts, a systematic study of the structure-activity relationship in Pd catalyzed one-pot organic reactions should be carried out. However, such fundamental information is not known to the degree necessary to design a new multi-functional heterogeneous Pd catalyst.

Amines are intermediates and products of enormous importance for chemical and life science applications. In addition to the well established Pd-catalyzed aminations of aryl halides¹² and the metal-catalyzed amination of alcohols,^{13,14} the transition-metal-catalyzed alkylation of amines by amines is an attractive alternative method of alkylamine synthesis.^{6,7,14-22} The reaction proceeds through a hydrogen-borrowing (hydrogen

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auto-transfer) mechanism.14-18 The process begins with the dehydrogenation of an alkylamine to the corresponding imine. The imine undergoes addition of another nucleophilic amine and elimination of ammonia to form an N-alkyl imine, which is hydrogenated by an in situ formed hydride species to the secondary amine product. Ru15,16 and Ir17,18 complexes are successful catalytic systems for selective amine cross-coupling of different amines, leaving ammonia as the only by-product. The [Cp*IrI2] complex developed by Williams and co-workers18 is of particular importance as the first example of selective amine alkylation when both of the amines are capable of undergoing oxidation to imines. From the environmental and economic viewpoints, it is preferable to accomplish the selective cross-coupling reaction using reusable heterogeneous catalysts. There are many reports of heterogeneous catalysis for the self-14,23-25 and cross-coupling6,7,14,19-22 of amines. However, previous examples of cross-coupling reactions suffer from low selectivity for cross-coupling different amines,²² reusability,⁶ low turnover number (TON), and the need for stoichiometric amounts of additives²¹ or special reaction methods (microwave heating,7,21 electrocatalysis19 and photocatalysis20). Recently, a Pd/C-catalyzed cross-coupling reaction was reported as the first example of a reusable heterogeneous catalyst for this reaction, but the system requires microwave heating.7 In addition, there are no systematic reports on the effects of metal particle size and nature of supports on the catalytic activity.

We report herein that γ -alumina-supported Pd nanoclusters act as reusable heterogeneous catalysts for amine cross-coupling reactions. To establish the structure–activity relationship, the effects of the Pd particle size, support basicity (acidity) and nature of transition metals on turnover frequency (TOF) (defined as the activity per unit of exposed Pd surface), are examined, and a design concept of the supported Pd metal catalyst for the present reaction is discussed.

Supported Pd catalysts were prepared by the impregnation method, followed by calcination and by H₂-reduction. To control the metal particle size, temperatures of calcination (T_{cal}) and reduction (T_{H2}) were changed (Table 1). The catalysts are designated as Mx/Al₂O₃-D, where x is the content (wt%) of metal (M) and D is the metal particle sizes (nm). Pd1/Al₂O₃-1.8 is the standard catalyst.

As a first screening, we examined the N-alkylation of morpholine (2a) with benzyl amine (1a) using various transition

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Catalysts-x ^a	M/wt%	$T_{\rm cal}/^{\circ}{\rm C}^{b}$	$T_{\rm H2}/^{\circ}{\rm C}^c$	D/nmª
$Pd1/Al_2O_3-1.8$	1	500	200	1.8
$Pd1/Al_{2}O_{3}-4.2$	1	700	500	4.2
$Pd5/Al_2O_3-8.7$	5	800	500	8.7
$Pd5/Al_2O_3-15$	5	1000	500	15.2
$Pd1/CeO_2-2.4$	1	700	500	2.4
Pd1/MgO-4.0	1	600	500	4.0
$Pd1/ZrO_2-4.6$	1	500	300	4.6
$Pd1/SiO_2-4.9$	1	500	400	4.9
Pd5/C-3.3	5		300	3.3
Pd black	100		100	22.7
Ag5/Al ₂ O ₃ -0.9	5	600	300	0.9^{d}
$Au1/Al_2O_3-2.3$	1	300	_	2.3 ^e
Pt5/Al ₂ O ₃ -1.2	5	500	500	1.2
Rh5/Al ₂ O ₃ -1.9	5	500	300	1.9
Ru5/Al ₂ O ₃ -1.9	5	500	300	1.9

^{*a*} Average particle size (nm) of supported metal estimated from CO adsorption experiments. ^{*b*} Temperature of calcination. ^{*c*} Temperature of reduction in H₂. ^{*d*} Size of the Ag particle was estimated from EXAFS in our previous study.⁴ ^{*c*} Size of the Au particle was estimated from TEM in our previous study.²⁹

metal-based heterogeneous catalysts (Table 2). For the Pd1/Al₂O₃-1.8 catalyst, benzyl amine (1a) was selectively converted to *N*-benzyl-morpholine (3a) as a desired product with 88% yield, while the total yield of byproducts was 12%. In contrast, for other catalysts such as Pd1/SiO₂-4.9, benzyl amine, (1a) was not only converted to 3a but also various byproducts. The self coupling of 1a gave *N*-benzylidenebenzylamine (5a) and its hydrogenation product, dibenzylamine (4a). Toluene (6a) was also produced by elimination of NH₃ from 1a. The rate of 3a formation was also measured under the conditions where conversion of aniline was below 40%, and TOF was calculated using the rate and the number of surface metal

atoms estimated by CO adsorption. The yield of 3a and TOF depended strongly on the nature of the transition metals, support materials, and Pd particle size. Among various transition metal nanoclusters (Pd, Ag, Au, Pt, Rh, Ru) supported on Al₂O₃ (Table 2, entries 1,17–21) with similar metal particle size (0.9–2.3 nm), Pd1/Al₂O₃-1.8 showed the highest **3a** yield and TOF. Among the Pd catalysts (Table 2, entries 2, 9-13) with similar size (2.4-4.9 nm), but with different support materials (Al_2O_3 , CeO_2 , MgO, ZrO₂, SiO₂, C), Pd1/Al₂O₃-4.2 was the most effective in terms of 3a yield and TOF. As shown in Table 1, we prepared a series of Pd/Al₂O₃ catalysts with different Pd particle size. The catalytic results (Table 2, entries 1-4) showed that the Pd/Al₂O₃ catalyst with the smallest Pd size, Pd1/Al₂O₃-1.8, was the best catalyst. Consequently, Pd1/Al₂O₃-1.8 was found to be the most effective catalyst. In the literature, there are two examples of heterogeneous Pd catalysts for cross-coupling reactions of amines using Pd black⁶ and Pd/C.⁷ Table 2 shows that Pd1/Al₂O₃-1.8 is more efficient than commercially available Pd black and Pd/C in terms of activity (TOF) and selectivity for cross-coupling.

Next, we examined reactions of benzylic amines with various cyclic amines using Pd1/Al₂O₃-1.8 (Table 3, entries 1–12). *p*-Substituted benzyl amines with electron-donating substituents (Table 3, entries 2–3) proceeded with good yields, while those with an electron-withdrawing substituent were not successful (Table 3, entry 4). An aliphatic primary amine (Table 3, entry 6) was also tolerated. The catalyst was applicable to heterocyclic amines containing an oxygen or nitrogen atom (Table 3, entries 7–8). The reaction of benzyl amine **1a** with various cyclic secondary amines leads to the formation of the corresponding *N*-alkylated amines in good to moderate yields (Table 3, entries 9–12). The catalyst was also applicable to the selective mono-*N*-alkylation of 4-methoxyaniline using di-*iso*-propylamine

Table 2	Reaction of 1a with 2a by various catalysts ^a

	NH ₂ + HN	2 mmol 1 mol% catal o-xylene, reflution 1 h	yst ux		$\bigcirc \bigcirc$	N (
	1a	2a	3a	4a	l	5a	6a
Entry	Catalysts-x	1a conv. (%)	3a yield (%)	4a yield (%)	5a yield (%)	6a yield (%)	TOF/h
1	Pd1/Al ₂ O ₃ -1.8	100	88	4	0	8	610
2	$Pd1/Al_2O_3-4.2$	100	80	3	4	11	460
3	Pd5/Al ₂ O ₃ -8.7	64	32	14	4	2	290
4	Pd5/Al ₂ O ₃ -15	18	5	4	2	0	170
9	Pd1/CeO ₂ -2.4	73	32	19	9	4	120
10	Pd1/MgO-4.0	89	50	19	8.5	7	290
11	$Pd1/ZrO_2-4.6$	100	57	21	16.3	5	330
12	$Pd1/SiO_2-4.9$	100	41	26	16.4	14	340
13	Pd5/C-3.3	100	74	5	13.4	1	315
14	Pd black	38	12	3	7.6	5	74
15	PdO	26	3	3	9.8	8	_
16	$Pd(CH_3COO)_2$	23	2	3	8.7	4	_
17	Ag5/Al ₂ O ₃ -0.9	6	0	0	3.3	0	0
18	$Au1/Al_2O_3-2.3$	6	0	0	3.9	0	0
19	Pt5/Al ₂ O ₃ -1.2	31	21	0	5.2	4	11
20	Rh5/Al ₂ O ₃ -1.9	26	17	0	4.0	5	15
21	Ru5/Al ₂ O ₃ -1.9	34	20	0	6.8	3	19

^{*a*} Conversion of **1a** and yields were determined by GC. TOF calculated using the number of surface metal atoms and the rate of **3a** formation measured under the conditions where conversions were below 40%.

Table 3 Cross-coupling of amines by Pd1/Al₂O₃-1.8^a

	R ₁ —NH ₂ + 1.0 mmol 1	R ₂ —NH ₂ <u>1 mol%</u> 2.0 mmol o-xyle 2	$\frac{\text{Pd1/Al}_2\text{O}_3-1.8}{\text{ene, reflux, 1 h}} \text{R}_1^{\prime}$	$ \begin{array}{cccc} H & H \\ N & R_2 & R_1 & N \\ 3 & 4 \end{array} $	R ₁ R ₁	N _{R1}	
					Yield (%)		
Entry	1	2	Product	Conv. (%)	3	4	5
1	NH ₂	HNO		100	88	4	0
2	NH ₂	HNO	N NO	100	85	5	4
3	NH ₂	HNO		100	88	3	3
4	F ₃ C NH ₂	HNO	F3C NO	100	44	5	6
5	NH ₂	HNO		100	76	8	9
6	NH ₂	HNO	N N	100	79	4	11
7	NH ₂	HNO		100	78	9	6
8	NH ₂	HNO		94	72	8	13
9 ^b	NH ₂	HN		100	81	6	2
10 ^b	NH ₂	HN		100	72	11	6
11 ^b	NH ₂	↓ ₽	N V	100	78	5	9
12 ^b	NH2	N H		100	66	16	10
13 ^{c,d}	↓ ↓ H	NH ₂		78	71	_	
14 ^{<i>d</i>,<i>e</i>}	N N	NH ₂	, , , , , , , , , , , , , , , , , , ,	100	76	_	—

^{*a*} Conversion of **1** and yields were determined by GC. ^{*b*} T = 125 °C. ^{*c*} t = 20 h. ^{*d*} 1/2 = 2 mmol/1 mmol. Yield of **3** is based on **2**. ^{*c*} Tertiary amine (18% yield) was also produced.

(Table 3, entry 13) and triethylamine (Table 3, entry 14) as alkylation reagents.

After the reaction of **1a** and **2a** (Table 3, entry 1), the catalyst was easily separated from the reaction mixture by centrifugation. ICP analysis of the filtrate confirmed that the contents of Pd in the solution were below the detection limit (<0.1 ppm). The separated catalyst was washed with acetone (5 mL) and distilled water (5 mL), followed by calcining at 500 °C for 1 h, and by reducing in H₂ at 200 °C for 10 min. The recovered catalyst showed a high yield of **3a** in the first (86%) and the second (85%) recycle tests. The total turnover number (TON) based on total Pd reached 261, which is higher than that of a homogeneous Ir catalyst (TON = 98) for a similar reaction.¹⁸ The above results clearly demonstrate that Pd1/Al₂O₃-1.8 is a highly efficient heterogeneous catalyst for the present reaction.

As previously proposed by Murahashi et al.6 for the Pd black catalysed amine cross-coupling, it is most probable that the present amine cross-coupling reaction proceeds through the hydrogen borrowing pathway (Fig. 1), in which the reaction is initiated by temporary removal of hydrogen from benzyl amine 1a to generate a benzyl imine 1a' and Pd-H species. For the reaction of p-substituted benzyl amines with 2a by Pd1/Al₂O₃-1.8, the reaction rate decreased with an increase in the Brown-Okamoto parameter (σ^+) in the order of CH₃O > CH₃ > H > CF₃. The relationship between $log(k_x/k_H)$ and σ^+ (Fig. S1 in the ESI[†]) gives a fairly good straight line ($r^2 = 0.94$) with a negative slope ($\rho^+ = -0.52$), indicating that a transition state of the rate-determining step involves a positive charge at the α carbon atom adjacent to the phenyl ring. Since an induction period was not observed in the course of 3a formation (Fig. S2[†]), the hydrogenation of **3a'** to **3a** is not a slow step. Thus, it is suggested that the C-H cleavage of **1a** by Pd to produce $C^{\delta+}$ and Pd-H^{&-} species is the rate-determining step in the present reaction.



Fig. 1 A possible reaction mechanism.

Finally, we discuss a structure–activity relationship. In Fig. 2, the TOF based on the number of surface metal atoms (from entries 1–4 in Table 2) are plotted as a function of Pd particle size in Pd/Al₂O₃. In a size range of 1.8-15.2 nm, the TOF decreases with the particle size, indicating that the present reaction is a structure-sensitive reaction demanding a coordinatively unsaturated Pd site. The unsaturated Pd sites should play an important role in the rate-determining C–H dissociation of **1a**. This result is consistent with the theoretical study by Liu and Hu; the stepped surface of Pd clusters, containing coordinatively unsaturated Pd, has a lower dissociation barrier in C–H bond



Fig. 2 TOF based on the number of surface Pd atoms for the reaction of 1a with 2a νs . average particle size of Pd in Pd/Al₂O₃ (Table 2, entries 1–4).

cleavage than the flat Pd (111) surface.²⁶ To discuss the role of the support in the Pd catalyzed reaction of 1a and 2a, we prepared a series of supported Pd catalysts with the same Pd content (1 wt%) and similar particle size (2.4-4.9 nm), but with a variety of supports. It is established that the O 1s binding energy (BE) of metal oxides decreases with an increase in the basicity of the metal oxide.²⁷ In Fig. 3, TOF is plotted as a function of the O 1s BE of the support oxides. There is a volcano-type relationship between TOF and O 1s BE, and Al₂O₃ as an amphoteric oxide gives the highest activity. A possible explanation of the support dependent activity is based on a metal-support bi-functional mechanism, where acid-base sites on the support take part in a certain step of the catalytic cycle. Basic sites on the support may play a role in the C-H abstraction of 1a, and acid sites may be effective in the polarization of the C=N bond of iminium cations and thus may promote hydrogenation of imines. Another possibility is the electronic effect of supports on the electronic state of Pd clusters. Recently, Raybaud et al. reported a DFT study on the metal-support interactions at the interface of a Pd13 cluster and γ -Al₂O₃ and showed that the Pd metal atoms interacting with hydroxyls on the support became positively charged, whereas the other Pd atoms located further from the interface were nucleophilic centers.28 This polarized nature of Pd atoms may be effective in the C-H bond cleavage of 1a, leading to the high activity of the Al₂O₃-supported Pd catalyst.



Fig. 3 Effect of the O ls binding energy of oxygen atoms in the supports on the catalytic activity of Pd catalysts with similar metal particle size (nm) shown in parentheses.

 Al_2O_3 -supported Pd nanoclusters with an average particle size of 1.8 nm act as a heterogeneous catalyst for the cross-coupling of amines, providing the first example of a reusable Pd catalyst for cross-coupling of amines both of which are able to undergo dehydrogenation. The reaction is a structure-sensitive reaction, demanding coordinatively unsaturated Pd atoms on the metallic nanocluster. The support also affects the activity, and the amphoteric oxide (Al₂O₃) gives the highest activity.

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