

Selective Activation of Alcohols in the Presence of Reactive Amines over Intermetallic PdZn: Efficient Catalysis for Alcohol-Based *N*-Alkylation of Various Amines

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Supporting Information

ABSTRACT: Pd-based intermetallic compounds supported on Al₂O₃ (Pd_xM_y/Al₂O₃, where M = Bi, Cu, Fe, Ga, In, Pb, Sn, or Zn) were prepared and tested as catalysts for the selective activation of alcohols in the presence of reactive amines, which is highly challenging and is the key strategy for alcohol-based *N*-alkylation of amines. Although the Pd/Al₂O₃ catalyst exhibited a high catalytic activity, undesired side reactions such as amine dimerization (via amine activation) and C–O bond scission occurred, resulting in a poor yield of the *N*-alkylation product. In contrast, the PdZn/Al₂O₃ catalyst acted as an efficient catalyst for this reaction, displaying high catalytic activities, selectivities, and atom efficiencies and a wide substrate scope. Detailed kinetic and computational studies revealed



that the relative affinity of Pd for alcohol and amine drastically changes by the formation of a PdZn intermetallic phase. On monometallic Pd, the adsorption and activation of amines are preferred over those of alcohols in terms of thermodynamic and kinetic aspects, respectively. However, this trend is inverted on PdZn, allowing preferential adsorption and activation of alcohols and, hence, selective *N*-alkylation.

KEYWORDS: N-alkylation, amine, alcohol, PdZn, intermetallic, catalyst

INTRODUCTION

N-Alkylamines are important building blocks comprising a variety of functional organic molecules such as polymers, pharmaceuticals, herbicides, and bioactive molecules.¹ They are typically synthesized by *N*-alkylation of lower amines, a key synthetic methodology for C–N bond formation. Conventional methods for *N*-alkylation of amines rely on the use of alkylating agents such as aldehydes (in reductive amination) or alkyl halides. However, the former requires a high H₂ pressure or reducing agents such as hydrides, and the latter yields a stoichiometric amount of halogen waste.¹ Thus, more efficient, environmentally friendly protocols are required for *N*-alkylation of amines.

Recently, alcohol-based *N*-alkylation of amines has been favored as a highly efficient synthetic methodology for producing *N*-alkylamines. This reaction proceeds via a combination of alcohol dehydrogenation and subsequent reductive amination, where hydrogen transfer from the alcohol to the intermediate imine is catalyzed by a transition metal, such as Au,² Ag,³ Cu,⁴ Pt,⁵ Pd,⁶ Ni,⁷ Ir, Rh, Ru,⁸ or Fe.^{9,10} Alcohol acts as both an alkylating reagent and a hydrogen source, thereby providing high atom efficiency, environmental benignity, and easy handling under atmospheric pressure. However, amines, in general, are more reactive than alcohols; this leads to the frequent occurrence of undesired side reactions such as amine dimerization and fragmentation (C–N bond

cleavage), which eventually decrease the product yield. This drawback has restricted the substrate scope of amines to less reactive α -hydrogen-free amines such as aniline and its derivatives. For other reactive amines, an excess of amine or alcohol substrate is frequently used to obtain high product yields. However, a stoichiometric feed of alcohol and amine is highly desired for atom efficiency. To achieve efficient catalysis for this reaction with a wide substrate scope, a specific reaction system that activates alcohols, preferentially to amines, is required. In homogeneous catalysis, much effort has been devoted to developing efficient catalysts,¹¹ and an excellent Febased catalyst has recently been reported by Feringa and coworkers.^{9,10} However, developing such a system in heterogeneous catalysis is highly challenging, and no promising catalyst design has been reported in the literature. To overcome this challenge, a drastic change in the chemical properties of active metals may be needed.

Promising candidates for catalyst materials that provide such well-modified reaction sites are intermetallic compounds. Unlike solid—solution alloys, intermetallic compounds typically comprise metal elements with significantly different chemical properties and display well-defined bimetallic surfaces originat-

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ing from their specific crystal structures. An appropriate combination of two metal elements provides not only a substantially modified electronic structure of the active metal component but also a uniform reaction environment. Indeed, we have reported that some Pd-based intermetallic compounds are highly active and act as selective catalysts for various organic reactions, such as amine oxidation^{12,13} and chemoselective hydrogenation of nitrostyrenes,¹⁴ where monometallic Pd catalysts exhibit poor catalytic performances.

In the study presented here, we prepared a series of Pd-based intermetallic compounds supported on Al_2O_3 (Pd_xM_y/Al_2O_3 , where M = Bi, Cu, Fe, Ga, In, Pb, Sn, or Zn) and examined their catalytic performances in alcohol-based *N*-alkylation of various amines. The observed catalytic performances were rationalized on an atomic level on the basis of kinetic and computational studies. Herein, we report a novel and highly efficient catalytic system for *N*-alkylation of Pd-based intermetallic compounds.

EXPERIMENTAL SECTION

Catalyst Preparation. Pd-based catalysts $(Pd_{v}M_{v}/Al_{2}O_{3};$ Pd loading, 3.0 wt %; M = Bi, Cu, Fe, Ga, In, Pb, Sn, or Zn) were prepared by the successive impregnation (where M = Cu, Ga, In, Pb, or Sn) or co-impregnation (where M = Bi, Fe, or Zn) method using Al₂O₃ (JRC-ALO-8, $\gamma + \theta$ phase; $S_{BET} = 148$ $m^2 g^{-1}$) as a catalyst support. A specific amount of an aqueous solution containing $(NH_4)_2PdCl_4$ alone or both $(NH_4)_2PdCl_4$ and a second metal salt [typically, a nitrate except (NH₄)SnCl₆] in a 1:1 molar ratio (2:1 for PdGa) was added dropwise to a vigorously stirred aqueous slurry of Al₂O₃ (15 mL of ionexchanged water/g of Al_2O_3). After being stirred for 15 min under an air atmosphere, the slurry was completely dried on a hot plate and ground to a fine powder. The sample was then reduced in a quartz tube under a hydrogen flow (60 mL min⁻¹) at a predetermined temperature for 1 h (Pd, 500 °C; Pd-Bi, 600 °C; Pd-Cu, Pd-Ga, Pd-In, Pd-Pb, Pd-Sn, and Pd-Zn, 800 °C; Fe, 900 °C). For successive impregnation, this procedure was repeated using Pd/Al₂O₃ instead of bare Al₂O₃. For the preparation of PdBi/Al₂O₃, a nitric acid solution of $Bi(NO_3)_3 \cdot 5H_2O$ was added dropwise to a vigorously stirred aqueous slurry of impregnated (unreduced) Pd/Al₂O₃ as the mixture of Pd and Bi solutions formed an insoluble precipitate.

Catalytic Reaction. A catalyst (100 mg) was placed in a 50 mL three-neck round-bottom flask equipped with a silicone rubber septum, a reflux condenser, and a gas storage balloon (2 L) and pretreated under a H₂ stream (50 mL min⁻¹) at 400 $^{\circ}$ C for 0.5 h using a mantle heater. After the pretreatment, dry Ar $(20 \text{ mL} \cdot \text{min}^{-1})$ was passed into the flask to replace the residual H₂, and the flask was cooled to room temperature. A reaction mixture containing a solvent (p-xylene, 3 mL), amine (1.0 mmol), alcohol (1.0 mmol), and an internal standard (biphenyl, 0.1 mmol) was added to the flask through the septum. The catalytic reaction was initiated by immersing the reaction apparatus into a preheated oil bath under 1 atm of dry Ar. The temperature of the oil bath was controlled to maintain an actual reaction temperature of 110 °C. The products were quantified by flame ionization detection gas chromatography (Shimadzu GC-2025 equipped with an InertCap Pure-WAX capillary column, GL Sciences). The turnover frequency was determined as the consumption rate of amine (millimoles per hour) per amount of exposed Pd (mmol) estimated by CO chemisorption. The initial consumption rates were typically obtained below 30% conversion (conv.). Deuterated substrates (benzylamine- $\alpha_1\alpha$ - d_2_2 , CDN Isotopes, 99.3 atom % D, and benzyl alcohol- $\alpha_1\alpha$ - d_2_2 , ISOTEC, 98 atom % D) were used for estimation of the kinetic isotope effect on α -C–H bond activation. For recycling tests, the catalyst after reaction was washed by decantation in the reactor with *p*-xylene three times and finally once with *n*-hexane. The *n*-hexane rinse was completely removed by decantation and subsequent drying under an Ar flow (20 mL min⁻¹) at room temperature. The washed catalyst was reused after the pretreatment step outlined above.

Characterizations. The crystal structures of the catalysts were determined by powder X-ray diffraction (XRD) with a Rigaku RINT2400 diffractometer using a Cu K α X-ray source. Differential XRD patterns were obtained by subtracting the pattern for the Al₂O₃ support from that of the supported catalysts. Transmission electron microscopy (TEM) was conducted using a JEOL JEM-2010F microscope at an accelerating voltage of 200 kV. To prepare the TEM specimen, all samples were sonicated in tetrachloromethane and then dispersed on a Cu grid supported by an ultrathin carbon film. CO pulse chemisorption was performed to estimate the Pd dispersion in the prepared catalysts. Prior to chemisorption, the catalyst was pretreated under a H₂ flow (60 mL min⁻¹) for 0.5 h. After the reduction pretreatment, He was introduced at the same temperature for 30 min to remove the chemisorbed hydrogen, followed by cooling to room temperature. A 5% CO/He pulse was introduced into the reactor, and the passed supplied CO was quantified downstream by a thermal conductivity detector. Inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the catalysts was performed using a Shimadzu ICPE-9000 spectrometer. The catalysts were dissolved using aqua regia and a HF solution.

Computational Details. Periodic density functional theory calculations for surface reactions were performed using the CASTEP code¹⁵ with Vanderbilt-type ultrasoft pseudopotentials¹⁶ and a revised Perdew-Burke-Ernzerhof exchangecorrelation functional^{17,18} based on the generalized gradient approximation. The plane-wave basis set was truncated at a kinetic energy of 370 eV, and a Fermi smearing of 0.1 eV was utilized. In this study, we chose the Pd(111), PdCu(110), and PdZn(111) planes as the most stable surfaces. Monkhorst-Pack k-point meshes¹⁹ of $2 \times 3 \times 1$ [for Pd(111) and PdCu(110)] and $2 \times 2 \times 1$ [for PdZn(111)] were used. For the calculation of methoxide and methylamide, surfaces were modeled using (3×4) and (2×2) unit cells for Pd(111) and PdZn(111), respectively, with a four-atom-thick layer and a 13 Å vacuum spacing between the two surfaces. The atomic coordinates were fully relaxed, while the lattice constants were fixed. Convergence criteria comprised (a) a self-consistent field tolerance of 2.0×10^{-6} eV/atom, (b) an energy tolerance of 2.0 \times 10⁻⁵ eV/atom, (c) a maximal force tolerance of 0.05 eV/Å, and (d) a maximal displacement tolerance of 2.0×10^{-3} Å for structure optimization and energy calculation. The transition state (TS) search was performed using the complete linear synchronous transit (LST)/quadratic synchronous transit (QST) method.^{20,21} An LST maximization was performed, followed by an energy minimization in the directions conjugating to the reaction pathway. The approximated TS structure was subjected to a QST maximization with conjugate gradient minimization refinements. This cycle was repeated until a stationary point was found. The convergence criterion for TS calculations was set to a root-mean-square force tolerance of 0.10 eV/Å.

The adsorption energy is defined using eq 1:

$$\Delta E_{\rm ad} = E_{\rm A-S} - (E_{\rm S} + E_{\rm A}) \tag{1}$$

where E_{A-S} is the energy of the slab with the adsorbate, E_A is the total energy of the free adsorbate, and E_S is the total energy of the bare slab.

RESULTS AND DISCUSSION

The Pd-based intermetallic compounds were prepared using an impregnation method with Al_2O_3 as a support (Pd_xM_y/Al_2O_3 , where M = Bi, Cu, Fe, Ga, In, Sn, Pd, or Zn). The crystallite phases of the prepared catalysts were analyzed by XRD (Figure 1). For most catalysts, the desired intermetallic phases were formed with high phase purities. One-to-one alloy phases were observed for the Pd–Cu and Pd–Fe catalysts.



Figure 1. X-ray diffraction (XRD) patterns of Pd-based bimetallic catalysts supported on Al_2O_3 . For the sake of clarity, diffraction of the Al_2O_3 support was subtracted from the original patterns. Crystallite sizes estimated using the Scherrer equation are also shown.

Further characterization was performed for the catalysts that presented broad diffraction peaks. Panels a and b of Figure 2 show the TEM image of $PdZn/Al_2O_3$ and the size distribution of the nanoparticles, respectively. The particle sizes range from 3 to 7 nm, and the mean volume diameter is 6.0 nm, which are consistent with the crystallite size estimated using XRD (5 nm). Panels c and d of Figure 2 show a high-resolution TEM image of a single nanoparticle and the magnification of the region (designated by a yellow square in Figure 2c), respectively. These images clearly show lattice fringes [spacing of 2.22 nm (Figure 2d, yellow lines)] that correspond to those of the PdZn(101) planes [2.19 nm, ICDD-PDF 00-006-0620 (Figure 2d, light blue lines)]. Moreover, the observed atomic arrays closely match the corresponding crystal structure viewed along the [111] direction.

Chemical analysis was also performed for the prepared $PdZn/Al_2O_3$ catalyst, which contains a component that has a low boiling point (Zn; 907 °C), using ICP-AES. A small portion of Zn was lost (1:0.79 Pd:Zn) during the catalyst preparation, probably because of the high vapor pressure and the high reduction temperature used (800 °C). The loss of Zn from PdZn at high temperature has been previously reported.²² According to the phase diagram of the Pd–Zn system,²³ intermetallic PdZn has a composition width (Pd, 44–63%).

Therefore, the prepared $PdZn/Al_2O_3$ catalyst seems to have a slightly Pd-rich PdZn phase ($Pd_{0.56}Zn_{0.44}$). The small deviation of the lattice fringe spacing from the value in the literature observed in Figure 2d may be attributed to the slightly enriched Pd: the larger atomic radius of Pd (140 pm) compared to that of Zn (135 pm)²⁴ increases the lattice constant.

We also performed Fourier transform infrared (FT-IR) experiments with CO adsorption to characterize the surface of the prepared catalysts (Figure 3). Pd/Al₂O₃ presents some peaks, which are assigned to the stretching vibration of CO adsorbed in linear (2090 cm⁻¹) and bridging [1995 cm⁻¹ on Pd(100), 1950 cm⁻¹ on Pd(111)] features.²⁵ The contribution of the bridging CO was dominant compared with that of the linear-type CO on Pd/Al₂O₃. Conversely, for PdZn/Al₂O₃, linear-type CO was predominantly observed, indicating that the Pd–Pd ensembles almost disappeared by the formation of the intermetallic phase. The peak position of linear CO on PdZn/Al₂O₃ agreed with the values in the literature for PdZn²⁶ and was red-shifted compared with that on Pd/Al₂O₃. The latter indicates that the Pd atoms in PdZn were slightly electron-enriched by the charge transfer from Zn.

The prepared Pd-based catalysts were tested as catalysts for alcohol-based N-alkylation of amines. First, aniline and benzyl alcohol were used as model substrates. The obtained conversions of benzyl alcohol and selectivities for the product N-benzylaniline are listed in Table 1. For all catalytic reactions, the products were typically N-benzylaniline, N-benzylideneaniline (i.e., the intermediate imine), and toluene. Only a negligible amount of benzaldehyde (<0.5%) was detected for each reaction period, indicating that the condensation of benzaldehyde and aniline to N-benzylideneaniline was sufficiently fast. Monometallic Pd/Al₂O₃ exhibited moderate aniline conversion and selectivity (sel.) for N-benzylaniline (entry 1). A longer reaction time resulted in a slight increase in aniline conversion and significant reduction in product selectivity (entry 10). The limited aniline conversion can be attributed to the hydrogenolysis of benzyl alcohol to toluene occurring as a side reaction (Figure S1a), which irreversibly wasted the alkylating agent and hydrogen. The decrease in product selectivity may be explained by the fragmentation of Nbenzylaniline into toluene and aniline. This was demonstrated by a control experiment using N-benzylaniline alone as a substrate, which resulted in the formation of toluene and aniline in a 1:1 molar ratio (Figure S1b). Here, N-benzylaniline itself acted as a hydrogen source, and dehydrogenated Nbenzylideneaniline was formed. Thus, undesired C-O and/or C-N bond cleavage significantly occurred when monometallic Pd/Al₂O₃ was used. Although Pd₂Ga and PdCu displayed selectivities and yields higher than those of monometallic Pd (entries 3 and 4, respectively), the product yields did not increase even under much longer reaction times (entries 11 and 12. respectively). This is also because of the formation of toluene, which limited aniline conversion and N-benzylideneaniline hydrogenation (Figure S1c). Thus, for this reaction, undesired C-O and/or C-N bond scissions significantly influence the product selectivity and should be avoided to achieve high yields. Intermetallic catalysts with Fe, Sn, In, Bi, and Pb exhibited considerably low catalytic performances (entries 5-9, respectively). In contrast, PdZn exhibited excellent catalytic activity and selectivity (entry 2 and Figure S1d) with minimal toluene formation during the reaction period (Figure S1d), allowing almost stoichiometric conversion to the product N-benzylaniline.



Figure 2. (a) Transmission electron microscopy (TEM) image of $PdZn/Al_2O_3$ and (b) size distribution of the nanoparticles. (c) High-resolution TEM image of a single nanoparticle. (d) Close-up of the region marked by the yellow square in panel c. The crystal structure of PdZn viewed along the [111] direction is overlapped with the TEM image. Yellow and light blue lines represent experimental and literature values for *d* spacings, respectively. (e) Fast Fourier transform (FT) of the image in panel c. (f) Rhombitruncated octahedron model of a PdZn nanoparticle with {110} and {101} facets viewed along the [111] direction.



Figure 3. FT-IR spectra of CO chemisorbed on the Pd/Al_2O_3 and $PdZn/Al_2O_3$ catalysts.

Next, the catalysts exhibiting moderate to high aniline conversions were tested for N-alkylation of 4-methylbenzylamine, a highly reactive amine, with benzyl alcohol (Table 2; the time course of the product yields is shown in Figure S2). In this reaction, the desired N-alkylation yields an asymmetric amine (1) and the corresponding imine (2), whereas the undesired amine dimerization forms a symmetric amine (3)and the corresponding imine (4). The preference for Nalkylation over amine dimerization can be quantified by the rate ratio of these reactions, r_A/r_D , where r_A and r_D represent the Nalkylation rate (rate of formation of 1 and 2) and amine dimerization rate (rate of formation of 3 and 4), respectively. Note that such a preference cannot be evaluated using benzylamine and benzyl alcohol because the N-alkylation products are identical to the dimerization products. In the case of monometallic Pd, N-alkylation and dimerization proceeded at comparable rates, affording an r_A/r_D value close to unity (Table 2, entry 1). This indicates that monometallic Pd shows little preference for N-alkylation. Other byproducts such as toluene were also formed, as observed in the aniline Nalkylation. Although Pd2Ga and PdCu showed relatively high $r_{\rm A}/r_{\rm D}$ values (Table 2, entries 2 and 3, respectively), the selectivities for the desired amine 1 were moderate. This is

Table 1. Catalytic Performances of Pd-Based Intermetallic Compounds Supported on Al₂O₃ in *N*-Alkylation of Aniline with Benzyl Alcohol^{*a*}

(OH 1	+	NH ₂ F 2 ·	PdM/Al ₂ – H ₂ O		N 3
			conv.	. (%)		
entry	catalyst	time (h)	1	2	sel. of $3\ (\%)$	yield of 3 (%)
1	Pd	0.5	77	50	29	22
2	PdZn	0.5	100	99	99	99
3	Pd_2Ga	0.5	64	52	65	42
4	PdCu	0.5	45	45	72	32
5	PdFe	0.5	48	27	19	9
6	$Pd_{20}Sn_{13}$	0.5	9	7	36	3
7	PdIn	0.5	7	3	9	1
8	PdBi	0.5	3	3	8	<1
9	Pd ₁₃ Pb ₉	0.5	3	3	<1	<1
10	Pd	5	100	58	7	7
11	Pd_2Ga	3	100	75	49	49
12	PdCu	7	99	82	64	63
13	PdFe	4	100	66	35	35

^aReaction conditions: amine, 1.0 mmol; alcohol, 1.0 mmol; solvent, 3 mL (*p*-xylene); PdZn/Al₂O₃, 100 mg (2.8 mol % Pd); temperature, 110 °C; atmosphere, 1 atm of Ar.

because the involvement of amine dimerization and other side reactions such as toluene formation remains significant. Conversely, PdZn exhibited excellent selectivity for the desired amine 1 and an r_A/r_D value that is 1 order of magnitude higher than those of Pd₂Ga and PdCu (Table 2, entry 4). Thus, the PdZn catalyst allows preferential activation of the alcohol in the presence of a highly reactive amine.

The substrate scope of the $PdZn/Al_2O_3$ catalyst in the alcohol-based *N*-alkylation of amines was investigated, as summarized in Table 3. The reaction between benzyl alcohol

Table 2. Catalytic Performances of Pd-Based Catalysts in N-Alkylation of 4-Methylbenzylamine with Benzyl Alcohol^a

	+ OH	PdM/Al ₂ O ₃		NH 1 NH 3				2 7 8 1 1 1 4	
					selec	tivity (mol 9	%)	
entry	v catalyst	time (min)	N conv. (%)	1	2	3	4	others	$r_{\rm A}/r_{ m D}$
1	Pd	15	100	29	1	23	5	42	1.5
2	Pd ₂ Ga	30	97	61	4	9	5	18	7.7
3	PdCu	45	94	63	2	8	4	17	11
4	PdZn	40	100	92	3	2	1	2	104
an								1 6	

^aReaction conditions are identical to those cited in the footnote of Table 1.

Table 3. N-Alkylation of Various Amines Using PdZn/Al₂O₃ Catalysts⁴

	R₁−OH +	R ₂ ⁻ ^H _N cata	alyst, 1 atm N ₂ ►	R ₁ N ^R 3	³ + H ₂ O	
		<i>p</i> -	xylene, 110°C	R ₂		
entry	R_1	R ₂	R ₃	time (h)	conv. (%)	sel. (%)
1	Bn	Ph	Н	0.5	100	99
2 ^b	Bn	Ph	Н	2.5	100	>99
3 ^c	Bn	Ph	Н	24	100	97
4 ^{<i>d</i>}	$n - C_8 H_{17}$	Ph	Н	6	92	>99
5 ^d	$c-C_6H_{11}$	Ph	Н	8	90	94
6	furfuryl	Ph	Н	4	91	85
7	Bn	$n-C_8H_{17}$	Н	2	97	95
8 ^d	$n - C_8 H_{17}$	$n - C_8 H_{17}$	Н	7	98	96
9 ^d	$c-C_6H_{11}$	$n - C_8 H_{17}$	Н	2	96	94
10^d	$n - C_8 H_{17}$	$n - C_8 H_{17}$	$n - C_8 H_{17}$	7	92	>99
11	Bn	Bn	Н	1	100	95
12	Bn	4-F-Bn	Н	0.75	100	88
13	Bn	4-Me-Bn	Н	0.67	100	92
14	Bn	4-MeO-Bn	Н	0.75	100	67
15 ^{d,e}	$n - C_8 H_{17}$	Bn	Н	2	100	48

^aReaction conditions: amine, 1.0 mmol; alcohol, 1.0 mmol; solvent, 3 mL (p-xylene); PdZn/Al₂O₃, 100 mg (2.8 mol % Pd); temperature, 110 °C; atmosphere, 1 atm of Ar. ^bTemperature, 75 °C. ^cSubstrates, 10 mmol; solvent (p-xylene), 30 mL. ^dPdZn/Al₂O₃, 200 mg. ^eAlcohol, 3.0 mmol.

and aniline proceeded stoichiometrically even at a lower temperature (75 °C, entry 2). The gram-scale reaction was also well-catalyzed (entry 3), affording a turnover number of 2380 based on the Pd dispersion measured by CO adsorption (7.1%).

Recycling experiments revealed that the PdZn/Al₂O₃ catalyst can be used at least four times without significant loss of catalytic performance (Figure S3). Although a decrease in the catalytic performance (0.5 h, 55% conv. and 90% sel.) was apparent in the fifth run, increasing the reaction time led to a high product yield (2 h, 92% conv. and 92% sel.). Inductively coupled plasma atomic emission spectrometry analysis revealed that a small amount of Zn (\sim 6%) was leached during the four initial catalytic runs, which may be the reason for the loss of catalytic performance. In addition, aliphatic (primary and secondary) and heteroaromatic alcohols could also be used as alkylating agents for anilines with excellent catalytic performances (entries 4–6). For aliphatic primary amines, alkylation by benzyl and aliphatic (primary and secondary) alcohols was selectively catalyzed with high yields (entries 7-9). Alkylation of secondary amines to the corresponding tertiary amines proceeded successfully (entry 10). Benzylic amines, which are highly reactive amines, were successfully converted to the corresponding N-alkylated amines with good to excellent yields (entries 11-14). Alkylation of benzylamine with an aliphatic alcohol (i.e., a highly reactive amine and a less reactive alcohol), which is an extremely challenging reaction, resulted in a moderate yield when triple the amount of alcohol was used (entry 15). Note that most reactions in Table 3 (except entry 15) proceeded with equimolar amounts of amine and alcohol. Thus, an efficient catalytic system for N-alkylation of amines with high catalytic performances, a wide substrate scope, and high atom efficiency was developed using intermetallic PdZn/ Al_2O_3 .

Subsequently, a kinetic study of the PdZn intermetallic compound (Table 4) was performed. For PdZn, positive kinetic isotope effect (KIE) values were obtained upon deuteration at the α -C–H bond of benzyl alcohol for N-benzylation of aniline $(k_{\rm H}/k_{\rm D} = 2.2)$ and at the α -C–H bond of benzylamine for its dimerization ($k_{\rm H}/k_{\rm D}$ = 2.3). This indicates that activation of the α -C-H bond is the rate-determining step for each reaction. The corresponding activation energies were estimated by Arrhenius-type plots (Figure S4), affording values of 77 and 96 kJ mol⁻¹ for benzyl alcohol and benzylamine, respectively. These results demonstrate that alcohol is activated much more easily than amine on the surface of PdZn. Although a similar kinetic study was performed for monometallic Pd, no KIE was observed upon deuteration at the α -C–H bond of benzylamine, suggesting that the rate-determining step of amine dimerization is not α -C–H bond activation. We previously reported that, for oxidative dehydrogenation of amine on monometallic Pd, desorption of the product imine is the rate-determining step because of its strong adsorption property. Similarly, product desorption can also be the rate-determining step of benzylamine dimerization over Pd. Thus, Arrhenius-type analysis of the Pd catalyst cannot compare the activation energies of α -C-H bond scissions. Therefore, we performed a first-principle calculation for the C–H bond activation steps over a Pd(111) surface using methoxide and methylamide as model adsorbates. Although these adsorbates on Pd(111) have been theoretically

Table 4. Summary of the Results of a Kinetic Study of N-Alkylation and Amine Dimerization over PdZn/Al₂O₃ and Pd/Al₂O₃

		reaction order			kinetic isotope effect			
catalyst	substrate	[alcohol]	[amine]	$E_{\rm a}$ (kJ mol ⁻¹)	deuteration	$k_{\rm H}/k_{\rm D}$	rate-determining step	
PdZn	$PhNH_2 + BnOH$	0.01	0.20	77	$\alpha_{,}\alpha_{-}d_{2}$ -BnOH	2.2	C-H bond activation (BnOH)	
	BnNH ₂	-	-	96	$\alpha_{1}\alpha_{2}$ -BnNH ₂	2.3	C–H bond activation (BnNH ₂)	
Pd	$PhNH_2 + BnOH$	0.45	-0.25	56	$\alpha_{1}\alpha_{2}$ -BnOH	2.8	C–H bond activation (BnOH)	
	BnNH ₂	_	_	78	$\alpha_{,}\alpha_{-}d_{2}$ -BnNH ₂	1.0	imine desorption	

studied and the stable adsorption geometries have also been clarified,^{27–31} there are no reports about the comparison of C– H bond activation energies for methoxide and methylamide under the same conditions. Figure 4 shows the energy diagram



Figure 4. Energy diagrams for C–H bond activation of methoxide and methylamide over a Pd(111) surface. All energies are relative to gasphase methanol or methylamine with the bare slab. The total energy of bare slab and gas-phase methanol or methylamine was set to zero. For each model, a hydrogen atom was adsorbed on an fcc hollow site at the opposite surface of the slab to balance the number of atoms.

of C–H bond activation from methoxide to formaldehyde and from methylamide to methanimine (TS structures are shown in Figure S5). As the most stable adsorption sites, fcc hollow, bridge, and $\mu - \eta^2$ sites were selected for methoxide, methylamide, and the dehydrogenated products (formaldehyde and methanimine), respectively. The C–H bond activation energy for methylamide (65 kJ mol⁻¹) was 24 kJ mol⁻¹ lower than that for methoxide (89 kJ mol⁻¹), supporting the fact that amine is more easily activated than alcohol over a monometallic Pd surface. On the basis of these results, it can be said that the formation of a PdZn intermetallic phase inverts the C–H bond activation favorability to alcohol and amine.

Besides the aforementioned C-H bond activation properties, the relative adsorption affinity of the substrates was also considered. The dependence of the reaction rate of aniline Nbenzylation on the substrate concentration was examined, as listed in Table 4 (the corresponding plots are shown in Figure S6). When monometallic Pd was used as a catalyst, positive and negative reaction orders were observed for alcohol and amine, respectively, suggesting competitive adsorption of amine with alcohol. In contrast, for PdZn, both reaction orders were nearly zero. Considering the rate-determining step being α -C-H bond activation of benzyl alcohol, the saturation coverage of alcohol on the catalyst surface is likely. These results indicate that alcohol adsorption is much more favorable than amine adsorption on the PdZn surface. Figure 5 summarizes the calculated adsorption energies of oxygen (E_0) and nitrogen $(E_{\rm N})$ atoms on the surfaces of Pd, PdCu, and PdZn. As the surfaces that are the most stable and likely to be exposed, the Pd(111), PdCu(110), and PdZn(111) planes were considered. Pd-rich hollow sites (Pd fcc, Pd₂Cu, and Pd₂Zn hollow sites) were chosen as the adsorption sites. In the case of the Pd(111)surface, nitrogen showed an adsorption energy slightly higher than that of oxygen ($\Delta E_{O-N} = E_O - E_N = -23$ kJ mol⁻¹). This indicates the intrinsic adsorption favorability of nitrogen atoms to monometallic Pd compared with that of oxygen atoms; i.e.,

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Figure 5. Calculated adsorption energy of oxygen $(E_{\rm O})$ and nitrogen $(E_{\rm N})$ atoms on various Pd-based surfaces. Optimized structures of the surfaces with oxygen atoms adsorbed on the hollow sites are shown.

the monometallic Pd surface is azophilic. This trend is also observed for methoxide and methylamide adsorbed on Pd(111), as shown in Figure 4. Energetically, the methylamide adsorbate is favored over methoxide adsorbate by 34 kJ mol⁻¹. Conversely, for PdCu(110), $E_{\rm O}$ was slightly higher than $E_{\rm N}$ ($\Delta E_{\rm O-N} = 22$ kJ mol⁻¹). For PdZn(111), $E_{\rm O}$ was much higher than $E_{\rm N}$ ($\Delta E_{\rm O-N} = 86$ kJ mol⁻¹), which is consistent with the preferential adsorption of alcohol over amine, as mentioned above (Table 4). Thus, the adsorption affinity was drastically modified by the formation of intermetallic phases. This may be attributed to the intrinsic oxophilic character of Zn or Cu, which is contrary to the azophilic character of Pd. The oxophilic character of Zn atoms in the PdZn phase has also been reported in the literature of computational studies.²⁸ As is evident in Figure 6, the $\Delta E_{\rm O-N}$ values for Pd, PdCu, and PdZn



Figure 6. Relation between $r_{\rm A}/r_{\rm D}$ and $\Delta E_{\rm O-N}$.

display a strong positive correlation with their $r_{\rm N}/r_{\rm D}$ ratios obtained in the *N*-alkylation. This indicates that the adsorption favorability of alcohol over amine plays a significant role in product selectivity. Thus, the obtained results demonstrate that the activation of alcohol over PdZn is preferred over the activation of amines from kinetic and thermodynamic perspectives, allowing highly efficient alcohol-based *N*-alkylation of amines.

Intermetallic PdZn is considered to be an effective catalyst for methanol steam re-forming with minimal byproduction of CO.²² The positive role of the PdZn phase has been extensively studied and proposed as inhibiting the dehydrogenation of the formaldehyde intermediate to CO,²² which differs from the key role suggested in this study. Besides this reaction, Pd–Zn bimetallic catalysts, including Pd/ZnO, have been widely examined and have shown to be effective for various catalytic reaction, such as selective hydrogenation, ^{32–37} water–gas shift reaction, ^{38–40} partial oxidation of methanol, ^{41–43} hydro-formylation of ethylene, ⁴⁴ and esterification. ⁴⁵ However, no reactions involving nitrogen have been reported, highlighting the novelty of PdZn catalysis for *N*-alkylation of amines.

CONCLUSION

In this study, the catalytic performance of Pd-based intermetallic compounds in alcohol-based N-alkylation of amines was investigated. PdZn/Al₂O₃ was observed as a highly efficient heterogeneous catalyst with high catalytic performance, a wide substrate scope, and high atom efficiency. The surface of intermetallic PdZn is capable of selective activation of alcohols over amines, which is necessary for alkylation of reactive amines such as benzylamine. The unique catalytic performance of PdZn originates from the fundamental change in the C-H activation property and adsorption affinity of the substrates, allowing preferential activation of alcohols over amines. The incorporation of the oxophilic Zn into the azophilic Pd at an atomic level and ordered fashion plays a significant role in this drastic change, which has rarely been observed using conventional monometallic or supported catalysts. To the best of our knowledge, this is the first report of the rationalization of this kind of selective activation at an atomic scale. Thus, the results obtained provide not only an efficient catalytic system for Nalkylation of amines but also an innovative concept for selective molecular recognition and activation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01677.

Reaction profile, recycling test, kinetic studies, and optimized structures (PDF)

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Notes

The authors declare no competing financial interest.

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