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A Bifunctional Pd/MgO Solid Catalyst for the One-Pot Selective N-Monoalkylation of Amines with Alcohols

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Abstract: It has been found that a bifunctional metal Pd/base (MgO) catalyst performs the selective monoalkylation of amines with alcohols. The reaction goes through a series of consecutive steps in a cascade mode that involves: 1) the abstraction of hydrogen from the alcohol that produces the metal hydride and the carbonyl compound; 2) condensation of the carbonyl with the amine to give an imine, and 3) hydrogenation of the imine with the surface hydrogen atoms from the metal hydride. Based on isotopic and spectroscopic studies and on the rate of each elementary step, a global reaction mechanism has been proposed. The controlling step of the process is the hydride transfer from the metal to the imine. By changing the crystallite size of the Pd, it is demonstrated that this is a structure-sensitive reaction, whereas the competing processes that lead to subproducts are not. On these bases, a highly selective catalyst has been obtained with Pd crystallite size below 2.5 nm in diameter. The high efficiency of the catalytic system has allowed us to extend the process to the one-pot synthesis of piperazines.

Keywords: heterogeneous catalysis • hydrogen transfer • magnesium oxide • monoalkylation • palladium

Introduction

Monoalkylation of amines with alcohols is a reaction that produces C–N bonds yielding substituted amines.[1] It has been reported that Ru^{II} and Ir^{I} complexes are able to catalyze the direct alkylation of amines and sulfonamides by alcohols under transfer hydrogenation conditions.[2,3a–f] However, these reactions usually require an excess of a soluble base and the valuable catalysts are difficult to recover.

Despite the fundamental and practical interest of the reaction, there is only one precedent of a heterogeneous catalyst (Raney Ni) able to perform the monoalkylation of amines working with an excess of alcohol (3 g) and a large amount of catalyst. The global reaction mechanism was unknown, although the formation of radical intermediates was considered to be involved.

We will show here that, by using a Pd on MgO bifunctional solid catalyst, it is possible to catalyze the monoalkylation of amines through a series of consecutive reactions in a cascade mode with high selectivity. The process involves the abstraction of hydrogen from the alcohol that produces the metal hydride and the carbonyl compound from the alcohol. The carbonyl compound condenses with the amine to give an imine, which is hydrogenated to a final monoalkylated amine with the surface hydrogen atoms from the metal hydrides.

We show that this system can be applied to build organic molecules of industrial interest such as piperazines,[4,5] which are used as building blocks in medicine through the step-by-step introduction of different pharmacophoric moieties. It is worth noting that at present piperazines are synthesized by the reduction of the corresponding (di)ketopiperazines or by various cyclization reactions, for example, by dialkylation of amines with bis(2-chloroethyl)amine, by intramolecular reductive coupling of diamines,[6–9] or the recent alkylation of diamines with alcohols mediated by iridium and ruthenium.[2,3]

In this work, a series of bifunctional catalysts based on metals with different abilities to form hydrides and to give back the hydrogen—that is, Pd, Pt, and Au—have been supported on MgO.[10] Among them, Pd/MgO is able to perform the N-monoalkylation of amines with high selectivity and with a turnover frequency (TOF) about four times higher than that of the homogeneous Ru or Ir catalysts[3d] working under similar reaction conditions.

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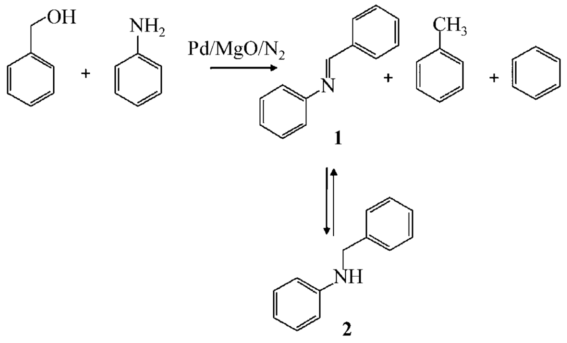
Mechanistic studies show that the controlling step of the global process is the hydride transfer from the metal to the imine, and that this is a structure-sensitive reaction. Therefore a metal catalyst prepared within the form of small crystallites that can easily take and give back hydride ions gives the best performance for this reaction. We have seen that the solid catalyst maintains activity and selectivity after being reused twice.

Results and Discussion

For proving the concept we have used the reaction between benzylic alcohol and aniline. Thus, when benzylic alcohol was allowed to react with aniline in trifluorotoluene at 180 °C with Pd/MgO as catalyst, the products obtained were the imine **1** and the amine **2**. These products account for 92 % of the converted material, with the rest of the products being toluene and benzene (see Scheme 1 and entry 1 in Table 1).



Scheme 1. Product distribution obtained in the N-alkylation reaction of aniline with benzyl alcohol catalyzed by Pd/MgO (0.8 % Pd) at 180 °C.

In a first approximation, the formation of products **1** and **2** can be explained by means of oxidative removal of hydrogen from benzylic alcohol to a afford benzaldehyde (detected only when aniline is not present) and a characteristic metal monohydride and/or dihydride.[11] The aldehyde reacts with aniline to give the condensation product **1**, which is hydrogenated by the palladium hydride to afford the new monoalkylated amine **2**. A control experiment shows that in the absence of the basic solid support MgO, Pd (Pd/C) can still catalyze the reaction, albeit affording much lower yield and selectivity of product **2** (see entry 2 in Table 1). It has also to be noticed that benzaldehyde and aniline react in the absence of catalyst, though at much lower reaction rate, thus making the polymerization of aniline more competitive and resulting in a decreased yield of **2**.

Pd/MgO is still highly selective toward the N-monoalkylated amine **2**, even when using equimolar amounts of the amine and the alcohol under milder conditions (110 °C; entry 4, Table 1). Moreover, the solid can be recovered and reused up to three times with only a slight loss of activity upon recycling. Nonetheless, the selectivity and yields of products can be kept by extending the reaction time (entry 3, Table 1).

When Pd is supported on two other basic supports, that is, Al–Mg hydrotalcite (HT) and hydroxyapatite (HAP), the resulting catalysts are active but the yield and selectivity to **2**, and even to **1**+**2**, are lower than in the case of MgO (see entries 5 and 6 in Table 1). As far as the metal is concerned, we chose two additional metals (Pt and Au) and their activity was compared with Pd. It is known that gold has a low tendency to form hydrides and they are quite unstable.[12–14] In clear contrast, Pt has an ample precedent in the literature for forming hydride complexes with a very strong metal–hydrogen bond.[15,16] Thus, gold and platinum were supported on MgO (for details on the preparation, see the Experimental Section) and their performance as catalysts for the monoalkylation of aniline was studied and compared with that of palladium (Figure 1).

With Pd/MgO as catalyst, we noticed a slight reduction in the yield of amine **2**, which became rapidly stabilized in a steady state with time (see Figure 1, bottom). We interpreted this result by assuming that the reverse reaction, that is, dehydrogenation from **2** to afford the imine **1**, occurs simultaneously, so that both compounds interconvert one to another until reaching an equilibrium concentration.[17]

With gold as catalyst, benzyl alcohol afforded reasonable yields of benzaldehyde, which

Table 1. N-Alkylation of anilines with benzyl alcohol catalyzed with diverse bifunctional solid catalysts.[a]

Entry	Catalyst	C [%][b]	Yield [%][c]				*t* [h]	TON[d]
			1	2	benzene	toluene		
1	Pd/MgO (0.8 %)	99	13	79	traces	7	0.25	192
2	Pd/C (5 %)	91	23	28	3	16	2.3	198
3[f]	Pd/MgO (0.8 %)	96	12	84	0	0	6	97[e]
4[g]	Pd/MgO (0.8 %)	90	8	80	traces	1	0.8	172
5	Pd/HT (0.55 %)	100	11	49	5	34	2	182
6	Pd/HAP (0.55 %)	100	39	26	3	31	2	167
7	Au/MgO (1.0 %)	93	49	38	3	2	5	156
8	Pt/MgO (1.0 %)	98	21	61	6	11	1	145
9[h]	AuPd/MgO	76	7	59	2	7	2	123[e]
10[i]	AuPt/MgO	87	42	36	8	2	2	149[e]
11[i]	PdPt/MgO	100	10	80	3	7	0.75	148[e]
12	Pd/MgO (2.0 %)	84	16	47	6	16	0.75	561
13	Pd/MgO (5.0 %)	75	13	38	8	15	1	521
14	Pd/MgO (10.0 %)	66	11	30	9	16	1	408

[a] Reaction conditions: benzyl alcohol (1 mmol), aniline (3 mmol), *n*-dodecane (0.1 mmol), catalyst (0.0075 mmol Pd, Pt, or Au), trifluorotoluene (1 mL), $T = 180\,^{\circ}C$. [b] Conversions were determined by GC on the basis of benzyl alcohol consumption. [c] Determined by GC. [d] Turnover number calculated as mmol of converted alcohol/mmol of catalyst (total Pd content). [e] Turnover number calculated as mmol of converted alcohol/mmol of surface Pd atoms. [f] After two uses. [g] Reaction conditions: benzyl alcohol (1 mmol), aniline (1 mmol), *n*-dodecane (0.1 mmol), catalyst (0.025 mmol Pd), trifluorotoluene (1 mL), $T = 110\,^{\circ}C$. [h] 0.0075 mmol Pd. [i] 0.0075 mmol Pt.

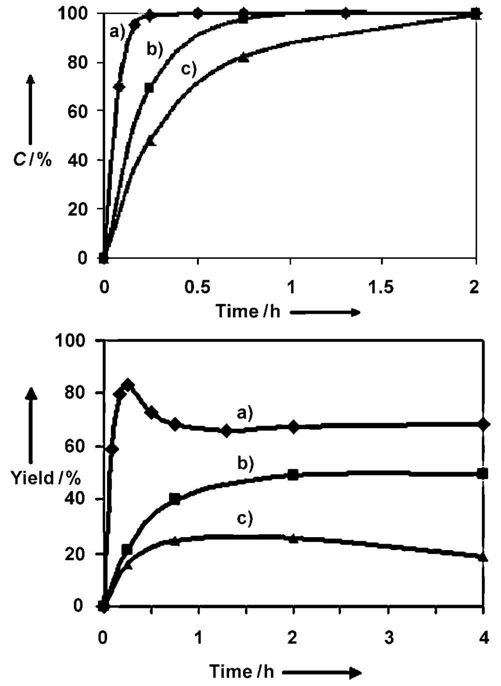


Figure 1. Comparative plots showing the conversion (C) of benzyl alcohol against time (top) and the yield of compound **2** versus time in the N-alkylation reaction of aniline with benzyl alcohol catalyzed (bottom) by a) Pd/MgO (0.8%; 0.0075 mmol Pd), b) Pt/MgO (0.75%, 0.0075 mmol), and c) Au/MgO (1%, 0.0075 mmol).

underwent reaction with aniline to afford compound **1** as the major product, with the saturated product **2** being formed in moderate yields (entry 7 in Table 1 and Figure 1). With platinum supported on MgO, the alcohol was completely transformed into benzaldehyde and the yields of amine **2** were higher than those obtained with gold, albeit lower than with palladium (entry 8 in Table 1 and Figure 1).

The clear superiority of palladium over gold and platinum for catalyzing this reaction can be explained by taking into account that the stability of gold and platinum hydrides are either too low or too high, respectively, and consequently they are less reactive than palladium hydrides.[12–14,18] This explanation suggests that the controlling step of the reaction should be the hydrogenation of the imine through hydrogen transfer from the metal hydride, and the surface hydride concentration and its ability to release the hydrogen will determine the activity and selectivity of the catalyst.

To check the hypothesis, we have measured the initial reaction rates for each one of the reactions occurring in a sequential mode on Pd/MgO (0.8% Pd; see Scheme 2). The results obtained clearly show that the slowest reaction step is indeed the hydrogenation of the imine by the surface hydrides.

Taking this into account, it is not surprising that the activity of the metals follows the order Pd > Pt > Au (see entries 1, 7, and 8 in Table 1; and Figure 1). In the case of bimetallic catalysts (entries 9–11 in Table 1), the activity is most probably dominated by Pd.

$$1)\ PhCH_2OH + Pd^0 \rightleftharpoons PhCHO + Pd\text{-}H\ (r_0^1 = 0.1896\ \text{mmol h}^{-1})$$

$$2)\ PhCHO + PhNH_2 \longrightarrow PhN{=}CHPh\ (r_0^2 = 0.2898\ \text{mmol h}^{-1})$$

$$3)\ PhN{=}CHPh + Pd\text{-}H \longrightarrow PhNHCH_2Ph + Pd^0 (r_0^3 = 0.0627\ \text{mmol h}^{-1})$$

Scheme 2. Initial reaction rates (*r*) calculated for the sequential transformation between benzyl alcohol and aniline catalyzed by Pd/MgO (0.8% Pd) at 180 °C.

Influence of metal crystallite size on reactivity: Since the reaction-controlling step is the hydrogenation of the imine by the surface hydrides and hydrogenations are in many cases structure-sensitive reactions, we have studied the influence of the Pd crystallite size on the initial rate of formation of product **2**. To do this, a series of Pd/MgO catalysts with different Pd crystallite sizes were prepared (see characterization details in Table S1 in the Supporting Information; the crystallite size distribution measured by TEM is also given in the Supporting Information, Figure S1). The number of Pd surface atoms in each sample was calculated by taking into account the total metal content, crystal-size distribution, and the calculation procedure given in ref. [19].

When the initial reaction rate per metal surface atom (turnover frequency, or TOF) is plotted versus the average crystallite size for Pd (see Figure 2), it can be seen that the initial reaction rates for the formation of the amine (product **2**) as well as the formation of benzaldehyde increase exponentially as the Pd crystallite size decreases.

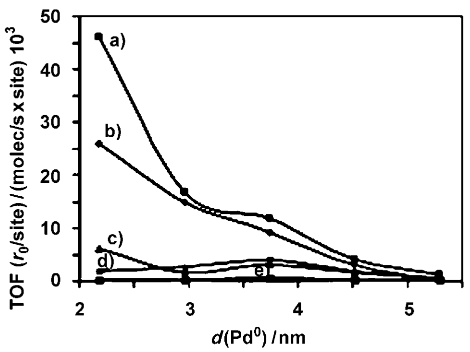


Figure 2. Plots showing the initial reaction rates (r_0) per surface atom as a function of metal particle size (*d*) for a) the hydrogenation transfer reaction to afford **2**; b) dehydrogenation of benzyl alcohol to afford benzaldehyde; c) condensation reaction to give **1**; d) hydrogenolysis reaction to give toluene; and e) decarbonylation reaction to afford benzene.

This result clearly indicates that both reactions (i.e., the hydride-transfer reaction to the imine as well as dehydrogenation of the alcohol) are structure-sensitive reactions.[20] On the other hand, since the initial reaction rate per metal surface atom remains constant with particle size for the competing reactions that give toluene and benzene, one can increase the selectivity to product **2** by preparing catalysts with smaller Pd crystallite sizes.

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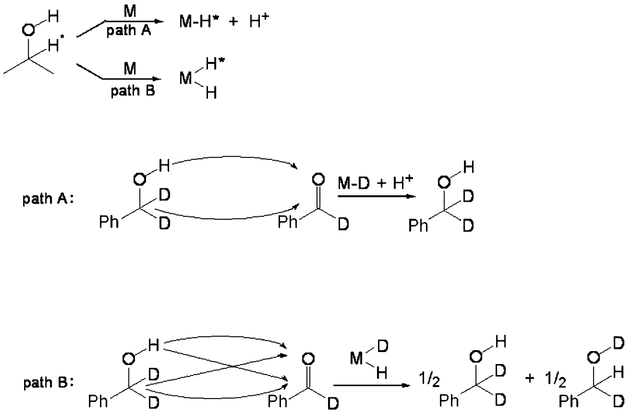
Reaction mechanism: As already mentioned, the N-alkylation of amines with alcohols on Pd/MgO occurs through a series of consecutive reactions in which the first step must be the abstraction of hydrogen from the alcohol by Pd^0 to give the corresponding carbonyl compound and a divalent metal hydride. To prove this, we have followed the reaction using in situ diffuse reflectance (DR) UV/Vis spectroscopy, and the results given in Figure S2 in the Supporting Information show that the freshly prepared Pd/MgO catalyst gives a spectrum with a broad and structureless band that has been assigned to Pd^0 reduction.[21] The spectrum of the catalyst recovered after completing the benzylic alcohol transformation to benzaldehyde (in the absence of amine) was very similar to that of $[Pd(acac)_2]$ (acac = acetylacetonate; Figure S2 in the Supporting Information), thus suggesting an initial oxidative addition process from Pd^0 to afford the intermediate Pd^{2+} mono- or dihydride with the simultaneous formation of benzaldehyde. Experiments based on in situ IR techniques were undertaken to confirm the formation of this palladium hydride bond. In this case, the course of the reaction was followed from the changes in the infrared spectrum of Pd/MgO during the cascade reaction, but the characteristic vibration band of palladium hydride bonds was not detected by IR spectroscopy.[22] Instead of this, the IR spectra showed three defined bands at 3480, 3684, and 1325 cm^{-1}. The former two bands were assigned to hydroxyl vibrations of MgOH species, whereas the third one was assigned to Mg–H.[23] Formation of this magnesium hydride could be explained by taking into account that migration of atomic hydrogen over the palladium metal surface to a different phase (the MgO support) can easily take place. This migration, which is the basis for the "spillover" phenomenon, has been widely documented, and the same can be applied for the "reverse spillover" effect (hydrogen migration from the MgO support to the metal palladium), since both processes are energetically favorable.[23]

After establishing that the process involves the formation of the hydride and the controlling step of the reaction corresponds to the transfer of hydride to the imine, we have studied in detail how and what type of hydride species are formed.

To do this, we have assumed that when the hydride intermediate is formed, the metal hydride should arise either from the α-C–H (see Scheme 3, path A) of the hydrogen donor or from both the α-C–H and the O–H of the alcohol (path B).[24]

For path B, any of the hydrides on the metal may add to the imine carbon, since the catalyst would not distinguish between the proton from the OH and the hydride formed from the α-C–H to perform the hydrogenation, thus losing their identity. Therefore, to find out whether path A or B is operating with Pd/MgO, an experiment was carried out by putting $PhCD_2OH$ into contact with Pd/MgO at 180 °C. After reaching the equilibrium with the formation of benzaldehyde (after 1.5 h), we searched the ^1H NMR spectrum of the alcohol to see if H/D scrambling had occurred (Figure S3 in the Supporting Information).

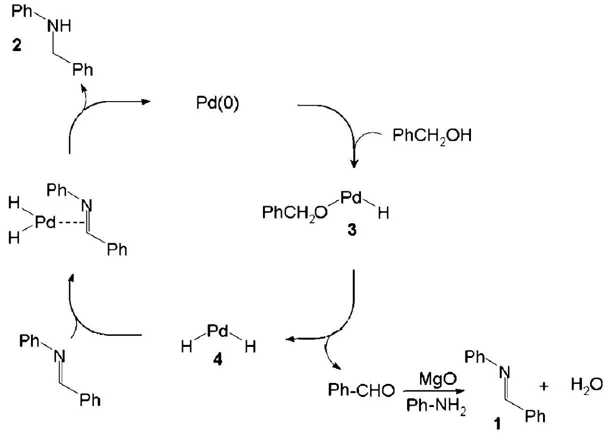


Scheme 3. Incorporation of deuterium in the α-position and/or hydroxyl group of benzyl alcohol catalyzed by palladium at 180 °C, through A) the monohydride and B) the dihydride mechanism.

If palladium follows path A, no H/D scrambling should occur and the deuterium would exclusively go back to the α-C of the alcohol, thereby giving $PhCD_2OH$ as the only product. On the contrary, if path B is operative, then the deuterium would scramble between carbon and oxygen (CD/OD ≈ 1:1) and two different deuterated alcohols would be detected at the end (see Scheme 3 and Figure S3).[24]

In our case, the ^1H and ^{13}C NMR spectra of the reaction mixture showed the formation of monodeuterated chemical species Ph(CαD–H)OH as well as the unlabeled compound $PhCH_2OH$, which should arise from a second deuterium abstraction from Ph(CαD–H)OH (see Figure S3 in the Supporting Information). Since, in addition to this, the CD_2 carbon was not detected in the ^{13}C NMR spectrum, we can propose that with Pd/MgO as catalyst the formation of metal hydride species proceeds exclusively through path B.

Thus, by taking into account all the above results, we can propose the following tentative reaction mechanism for the monoalkylation of amine with alcohols on the Pd/MgO catalysts (see Scheme 4).



Scheme 4. Proposed reaction mechanism for the monoalkylation of aniline with benzyl alcohol catalyzed by Pd/MgO.

In this mechanism, a palladium dihydride species Pd–H_2 (**4**) is formed upon direct interaction with the alcohol (and/or through formation of a palladium alkoxylate intermediate **3**). The dihydride metal species **4** would react with the unsaturated compound **1** formed by condensation of the aldehyde with the amine on the basic sites of MgO.

Scope of the reaction: The reaction has been successfully extended to other alcohols and amines and the results are given in Table S2 in the Supporting Information.

The aliphatic alcohol 1-octanol reacts more slowly than the aromatic benzyl alcohol (see entries 1 and 2 in Table S2), and the yield of the final monoalkylated amine P_2 was lower for the aliphatic than for the aromatic alcohol (entries 1 and 2 in Table S2). Notably, the yield of the monoalkylated aniline improved when a double bond was present at the α,β-position in the allylic alcohol *trans*-2-hexenol. However, no transfer hydrogenation occurred for this imine bond in the presence of the conjugated C=C bond, so that the reduction of the latter occurred with complete chemoselectivity (see entry 3, Table S2).

The yield of N-alkylated aniline improved significantly when the monoalkylation of aniline was carried out with the isomer *cis*-2-hexenol, and again the selective transfer hydrogenation of the α,β-unsaturated imine intermediate P_1 afforded the saturated imine P_2 (see entry 4, Table S2). As expected, a strong reduction in the yield of hydrogenated product P_2 was observed when the double bond was sterically hindered (see entry 5, Table S2 in the Supporting Information).

In close connection to this, and just to check if the reactivity of the C=N bond towards hydrogenation increases when this functionality is far away from the C=C group, we attempted the monoalkylation of aniline with 5-hexenol. In this case, a complex mixture of products derived from hydrogenation of the C=C bond, the imine, as well as both multiple bonds was obtained (see entry 6, Table S2 in the Supporting Information).

From these results it can be concluded that the substitution and the position of the double bond relative to the C=N group has a strong influence on the chemoselectivity of the process. Thus, the C=C double bond is hydrogenated with difficulty when it is sterically hindered or when it is far from the C=N group. On the other hand, in conjugated systems, the activated double bond is exclusively hydrogenated with preference over the C=N bond.

Interestingly, the monoalkylation reaction of the aliphatic amine 1-cyclohexylethylamine with benzyl alcohol proceeds rapidly. It affords products derived exclusively from the oxidative dehydrogenation of the alcohol (see entry 7, Table S2).

One-pot synthesis of piperazines: Owing to the success of Pd/MgO in catalyzing the monoalkylation of aniline with alcohols, we have attempted the reaction between different 1,2-diamines and 1,2-diols to achieve the one-pot synthesis of piperazines. The reactions were performed using equimolar amounts of 1,2-diamines and ethylene glycol derivatives at 160°C in acetonitrile and good yields of the respective heterocycles were obtained (see Table S3 in the Supporting Information). The results collected in Table S3 indicate that, by following this approach, 1,2-diamines are also amenable to a cyclocondensation/N-alkylation reaction following a hydrogen-transfer route over the Pd/MgO bifunctional catalyst.

Conclusion

The Pd/MgO catalyst is able to perform the N-monoalkylation of amines with high selectivity and a turnover frequencies (TOF), about four times higher than that of homogeneous Ru or Ir catalysts, even when working under similar reaction conditions.

The catalyst temporarily removes hydrogen from an alcohol to form the more reactive aldehyde and a metal hydride. The aldehyde is converted in situ into an imine through a condensation reaction with an amine. The hydrogen is given to the imine, thereby yielding a new amine with the overall formation of a C–N bond.

We have found that the rate-controlling step of the process is the hydrogenation of the imine by hydride transfer. This reaction behaves as a structure-sensitive reaction with respect to the Pd. According to this, both activity and selectivity values are higher when the crystallite size is smaller.

Pd is more active and selective than Au or Pt on MgO.

Hydrogenation of the C=N double bond in the presence of a C=C group has been studied by using allylic alcohols as well as unsaturated alcohols as alkylating agents. In general, we have observed that the steric hindrance and the position of the double bond relative to the imine group are crucial in determining the chemoselectivity for the unsaturated amine with this catalytic system. In conjugated systems, we can confirm that no transfer hydrogenation occurs for the imine bond in the presence of the C=C bond, so that reduction of the latter takes place with complete chemoselectivity. In nonconjugated systems, a marked reduction of chemoselectivity is observed, since now the C=N as well as the C=C bond are simultaneously hydrogenated.

Since the reaction is applicable to the alkylation of anilines as well as aliphatic amines, a closely related strategy has been used to prepare piperazines through a new synthetic route.

Experimental Section

Hydroxyapatite and hydrotalcite were prepared by following previously reported procedures.[24,25] An MgO sample with a surface area of 670 $m^2 g^{-1}$ was purchased from NanoScale Materials. Inorganic salts [$Pd(acac)_2$], $NaAuCl_4$, and $KAu(CN)_2$ were purchased from Aldrich, whereas [$Au(CH_3)_2(acac)$] and [$Pt(acac)_2$] were supplied by Strem and Acros, respectively. The products were used as received.

Preparation of metal/MgO (metal = Pd, Pt, Au) bifunctional catalysts: Pd/MgO (0.8 wt% palladium) was prepared by following the procedure reported in ref. [10]. Pt/MgO (1 wt% metal loading) was obtained by adding MgO (1 g, 670 m^{2}g^{-1}) to a solution of [Pt(acac)$_2$] (24.01 mg, 0.078 mmol) in anhydrous dichloromethane (30 mL) while stirring for 12 h. After evaporation of the solvent at reduced pressure, the solid was dried overnight at 353 K under vacuum and then calcined under a nitrogen flow at 823 K (ramp rate: 5 °C min^{-1}) for 3.5 h. The sample was activated before reaction by heating the solid at 723 K under an atmosphere of air for 5 h and then for 5 h under nitrogen. Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90:10) for 2 h.

Au/MgO (1 wt% metal loading) was prepared by following a reported procedure, albeit with modifications:[26] MgO (1 g, 670 m^{2}g^{-1}) was added to a solution of [Au(CH$_3$)$_2$(acac)] (17.963 mg, 0.055 mmol) in ethanol (30 mL) while stirring for 12 h. The solvent was evaporated at reduced pressure. The solid was dried overnight at 353 K under vacuum and then calcined in a nitrogen flow at 823 K (ramp rate: 5 °C min^{-1}) for 3.5 h. The sample was activated before reaction by heating the solid at 723 K under air for 5 h and then for 5 h under nitrogen. Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90:10) for 2 h.

Preparation of bimetallic supported catalysts (PdPt/MgO, AuPd/MgO, AuPt/MgO):[27] AuPt/MgO (0.75 wt% Pt and 2.5 wt% Au) was prepared by co-impregnation of MgO with two solutions of [Pt(acac)$_2$] (9.015 mg, 0.023 mmol) and [Au(CH$_3$)$_2$(acac)] (25.15 mg, 0.077 mmol) in dichloromethane (15 mL). The mixture was stirred for 12 h at room temperature. The solvent was evaporated at reduced pressure and the solid was dried at 80 °C for 12 h under vacuum. The material was calcined at 450 °C under a N_2 flow for 4.5 h (5 °C min^{-1}). Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90:10) for 2 h.

AuPd/MgO (0.75 wt% Pd and 2.5 wt% Au) was prepared by co-impregnation of MgO with two solutions of [Pd(acac)$_2$] (12.795 mg, 0.042 mmol) and [Au(CH$_3$)$_2$(acac)] (25.15 mg, 0.077 mmol) in acetone (15 mL). The mixture was stirred for 12 h at room temperature. The solvent was evaporated at reduced pressure and the solid was dried at 80 °C for 12 h under vacuum. The material was calcined at 450 °C under a N_2 flow for 4.5 h (5 °C min^{-1}). Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90:10) for 2 h.

PdPt/MgO (0.75 wt% Pd and 0.1 wt% Pt) was prepared by co-impregnation of MgO with two solutions of [Pd(acac)$_2$] (26.7 mg, 0.0888 mmol) and [Pt(acac)$_2$] (4.5 mg, 0.011 mmol) in dichloromethane (20 mL). The mixture was stirred for 12 h at room temperature. The solvent was evaporated at reduced pressure and the solid was dried at 80 °C for 12 h under vacuum. The material was calcined at 450 °C under a N_2 flow for 4.5 h (5 °C min^{-1}). Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90:10) for 2 h.

Catalyzed N-alkylation of amines with alcohols: A mixture of alcohol (1 mmol), amine (3 mmol), Pd/MgO (0.0998 g; Pd: 0.0075 mmol), trifluorotoluene (1 mL), and *n*-dodecane (20 μL) as internal standard were placed into an autoclave. The resulting mixture was vigorously stirred at 180 °C under nitrogen. The reaction was monitored by GC.

Study of the monohydride and/or dihydride mechanism: Pd/MgO (147.3 mg, 0.8%) and PhCD$_2$OH (125.8 mg) were added into an autoclave containing trifluorotoluene (1 mL) under nitrogen. The reaction mixture was heated at 180 °C while being vigorously stirred. The reaction was monitored by GC. The catalyst was filtered off (after 1.5 h) and trifluorotoluene was eliminated with heating under reduced pressure. The ^{1}H and ^{13}C NMR spectra of the reaction mixture were recorded using [D$_6$]DMSO as solvent and TMS as the internal reference.

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[1] a) Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi, T. Ohta, *J. Org. Chem.* **1984**, *49*, 3359–3363; b) R. A. T. M. Abbenhuis, J. Boersma , G. Van Koten, *J. Org. Chem.* **1998**, *63*, 4282–4290; c) Y. Tsuji, K-T. Hu, Y. Watanabe, *Tetrahedron Lett.* **1986**, *27*, 377–380; d) Y. Tsuji, K-T. Hu, Y. Watanabe, *J. Org. Chem.* **1987**, *52*, 1673–1680; e) Y. Tsuji, S. Kotachi, K-T. Hu, Y. Yokohama, Y. Watanabe, *J. Org. Chem.* **1990**, *55*, 580–584; f) Y. Watanabe, Y. Morisaki, T. Kondo, T. Mitsudo, *J. Org. Chem.* **1996**, *61*, 4214–4218; g) D. Hollmann, S. Bahn, A. Tillack, R. Parton, R. Altink, M. Beller, *Tetrahedron Lett.* **2008**, *49*, 5742–5745.

[2] a) G. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey, J. M. Williams, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535–537; b) K. I. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 3525–3528; c) K. I. Fujita, Z. Li, N. Ozeki, R. Yamaguchi, *Tetrahedron Lett.* **2003**, *44*, 2687–2690.

[3] a) M. H. S. A. Hamid, J. M. J. Williams, *Chem. Commun.* **2007**, 725–727; b) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J.* **2007**, *2*, 403–410; c) G. Jenner, G. Bitsi, *J. Mol. Catal.* **1988**, *45*, 165–168; d) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774; e) K. Kujita, Y. Enoki, R. Yamaguchi, *Tetrahedron* **2008**, *64*, 1943–1954; f) B. Blank, S. Michlik, R. Kempe, *Chem. Eur. J.* **2009**, *15*, 3790–3799; g) J. L. García Ruano, A. Parra, J. Aleman, F. Yuste, V. M. Mastranzo, *Chem. Commun.* **2009**, 404–406.

[4] a) R. M. Nieto, A. Coelho, A. Martinez, A. Stefanachi, E. Sotelo, E. Raviña, *Chem. Pharm. Bull.* **2003**, *9*, 1025–1028; b) M. Vieth, M. G. Siegel, R. E. Higgs, I. A. Watson, D. H. Robertson, K. A. Savin, G. L. Durst, P. A. Hipskind, *J. Med. Chem.* **2004**, *47*, 224–232.

[5] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

[6] a) S. Soukara, B. Wünch, *Synthesis* **1999**, 1739–1746; b) M. E. Jung, J. C. Rohloff, *J. Org. Chem.* **1985**, *50*, 4909–4913.

[7] a) C. Macleod, B. I. Martinez-Teipel, W. M. Barker, R. E. Dolle, *J. Comb. Chem.* **2006**, *8*, 132–140; b) K. G. Liu, A. J. Robichaud, *Tetrahedron Lett.* **2005**, *46*, 7921–7922.

[8] a) P. Vairaprakash, M. Periasamy, *J. Org. Chem.* **2006**, *71*, 3636–3638; b) G. J. Mercer, M. S. Sigman, *Org. Lett.* **2003**, *5*, 1591–1594.

[9] a) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267–278; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705.

[10] M. J. Climent, A. Corma, S. Iborra, M. Mifsud, *J. Catal.* **2007**, *247*, 223–230.

[11] Y. R. S. Laxmi, J.-E. Bäckvall, *Chem. Commun.* **2000**, 611–612.

[12] a) J.-P. Deng, W.-C. Shih, C.-Y. Mou, *ChemPhysChem* **2005**, *6*, 2021–2025; b) A. S. K. Hashmi, R. Salathe, T. M. Frost, L. Schwarz, J.-H. Choi, *Appl. Catal. A* **2005**, *291*, 238–246.

[13] a) M. C. Gimeno, A. Laguna in *Comprehensive Coordination Chemistry II, Vol. 6* (Ed.: D. E. Fenton), Elsevier, Amsterdam, Chapter 6.7, p. 911; b) R. J. Puddephatt in *Comprehensive Coordination Chemistry, Vol. 5* (Ed.: G. Wilkinson), Elsevier, Amsterdam, Chapter 55, p. 861.

[14] G. N. Khairallah, R. A. J. O'Hair, M. I. Bruced, *Dalton Trans.* **2006**, 3699–3707.

[15] a) R. H. Crabtree in *Modern Coordination Chemistry* (Eds.: G. J. Leigh, N. Winterton), RSC, Cambridge, **2002**; b) R. H. Crabtree in *Recent Advances in Hydride Chemistry* (Eds.: M. Peruzzini, R. Poli), Elsevier, Amsterdam, **2001**; c) R. H. Crabtree in *Transition Metal Hydrides* (Ed.: A. Dedieu), VCH, Weinheim, **1992**.

[16] For a review on gas-phase transition-metal hydrides, see: P. B. Armentrout, L. S. Sunderlin in *Transition Metal Hydrides* (Ed.: A. Dedieu), VCH, Weinheim, Chapter 1k, **1992**.

[17] J. S. M. Samec, A. H. Ell, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327–2334.

[18] a) E. Suchanek, N. Lange, G. Auffermann, W. Bronger, H. D. Lutz, *J. Raman Spectrosc.* **1999**, *30*, 981–986; b) Raman studies, which are a valuable tool in elucidating the relative strength of metal–hydrogen (MH) bonds in transition-metal hydrido complexes, confirms that MH stretching modes display much stronger bonds in the case

of 5d metal atoms than the 3d and 4d metal atoms; c) P. Pyykkö, *Chem. Rev.* **1988**, *88*, 563–594.

[19] a) N. Mahata, V. Vishwanathan, *J. Catal.* **2000**, *196*, 262–270; b) S. Domínguez-Domínguez, A. Berenguer-Murcia, A. Linares-Solano, D. Cazorla-Amorós, *J. Catal.* **2008**, *257*, 87–95; c) R. Van Hardeveld, F. Hartog, *Surf. Sci.* **1969**, *15*, 189–230; d) R. E. Benfield, *J. Chem. Soc. Faraday Trans.* **1992**, *88*, 1107–1110.

[20] M. Boudart, *Chem. Rev.* **1995**, *95*, 661–666.

[21] a) A. Corma, H. García, A. Leyva, *Mol. Catal. A* **2005**, *230*, 97–105; b) A. Corma, H. García, A. Leyva, *J. Catal.* **2004**, *225*, 350–358.

[22] W. Grochala, P. P. Edwards, *Chem. Rev.* **2004**, *104*, 1283–1316.

[23] a) E. Knözinger, K. H. Jacob, P. Hofmann, *J. Chem. Soc. Faraday Trans.* **1993**, 1101; b) W. M. Bartczak, J. Stawowska, *Mater. Sci.-Pol.* **2006**, 24.

[24] a) O. Pàmies, J-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058; b) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237–248; c) Y. R. S. Laxmi, J.-E. Bäckvall, *Chem. Commun.* **2000**, 611–612; d) J. E. Bäckvall, *J. Organomet. Chem.* **2002**, *652*, 105–111.

[25] a) K. Mori, T. Hara, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2004**, *126*, 10657–10666; b) A. Abad, C. Almela, A. Corma, H. García, *Tetrahedron* **2006**, *62*, 6666–6672; c) C. Elliot, *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*, Elsevier, New York, **1994**; d) S. Sugiyama, T. Minami, H. Hayashi, M. Tanaka, N. Shigemoto, J. B. Moffat, *J. Chem. Soc. Faraday Trans.* **1996**, *92*, 293.

[26] M. J. Climent, A. Corma, S. Iborra, K. Epping, A. Velty, *J. Catal.* **2004**, *225*, 316–326.

[27] Y. Hao, M. Mihaylov, E. Ivanova, K. Hadjiivanov, H. Knözinger, B. C. Gates, *J. Catal.* **2009**, *261*, 137–149.

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