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Chemoselective hydrogenations controlling the binomial architecture of metal particles and acid–base properties of the support: Synthesis of heterocycles with nitrogen and oxygen by reductive heterocyclization.

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ABSTRACT

2,1-Benzisoxazoles have been produced by reductive heterocyclization of 2-nitroacylarenes using supported Pt nanoparticles. The reaction involves a cascade process in which the first step is the reduction of the nitro group into hydroxylamine which subsequently cycles to 2,1-benzisoxazole through the nucleophilic attack to the carbonyl group in 2-position. The reaction was performed on Pt/C, Pt/TiO_2 and Pt/MgO using hydrogen as reducing agent under mild reaction conditions. The results showed that Pt/MgO was the most active and selective catalyst. The study of the influence of the crystal size of the metal on the activity and selectivity, combined with the reaction mechanism by *in situ* FTIR spectroscopy of the adsorbed reactant, showed that maximum activity and selectivity to the target compound can be achieved by controlling the architecture of metal particles and acid-base properties of the support. The effect of the temperature on the selectivity, the stability of Pt/MgO catalyst, as well as the scope of the reaction have been studied. Finally, the reductive cyclization using different metals (Pd and Au) supported on MgO has been also performed.

Keywords: reductive heterocyclization, 2,1-benzisoxazole, Pt/MgO, 2-nitroacylarene**s,** cascade process.

INTRODUCTION

2,1-Benzisoxazoles (anthranils) are fused heteroaromatic systems useful as building blocks to prepare a broad class of compounds with important biological properties and industrial applications. For instance, 2,1-benzisoxazole derivatives are employed in the treatment of some disorders of the central nervous system, as for instance Alzheimer's disease, other forms of dementia, and cerebral infarct.[1] They are also used as antiplasmodial, antimicrobial[2] and anti-inflammatory agents.[3] Anthranils and their salts can also be used as starting materials to prepare other heterocyclic systems for tranquilizers drugs such as Valium,[4] or acridones (in the production of dyes and pharmaceutical products.[5]

Different approaches can be used to synthesize 2,1-benzisoxazoles as, for instance, the reaction of substituted nitroarenes and arylacetonitriles in concentrated strong base alcoholic solution,[6] and in the presence of silylating agents,[7] heterocyclization of 2-azido aryl ketones,[8] and addition of glyoxylate esters to nitrosoarenes catalyzed by Lewis acid.[9] However, the most common method to prepare 2,1-benzisoxazoles involves the reductive heterocyclization of 2-nitroacylbenzene derivatives. This transformation occurs through the partial reduction of the nitro group to the hydroxylamine function followed by heterocyclization through the nucleophilic attack of the hydroxylamine group to the carbonyl of the acyl group and further dehydration[10] (see Scheme 1).

Classically, the reaction is carried out using Sn or $SnCl_2$ in concentrated HCl,[10,11] although other approaches use $SnCl_2$ $2H_2O$[12] or indium metal with different additives in water or methanol to promote the reductive heterocyclization of 2-nitroacylbenzenes. However, temperature and

concentration of reducing agent should be controlled since over-reduction of 2,1-benzisoxazole into the corresponding 2-aminoacyl compound by reductive cleavage can occur yielding the corresponding 2,1-benzisoxazoles in low selectivity[13] (Scheme 2).

In general, through the above methods, 2,1-benzisoxazole derivatives are obtained after long reaction times and with non-reusable catalysts. Therefore a sustainable route to prepare 2,1-benzisoxazole derivatives involving the use of an active, selective and reusable heterogeneous catalyst based on metal supported nanoparticles and hydrogen as reducing agent would be of interest. However, this route is not easy because the catalytic hydrogenation can promote not only the reductive cleavage of 2,1-benzisoxazoles into to 2-aminoacylbenzenes but also the complete and fast reduction of the nitro into amino group as well as, the reduction of the carbonyl group of the nitroacylarene. In fact, in the reports on hydrogenation of 2-nitroacylarene derivatives using Pt (colloidal Pt solution)[14] or Pd/C[15] catalysts a mixture of 2,1-benzisoxazole and 2-aminoacyl derivative, with low selectivity to the former are obtained. It appears that to perform successfully the reaction to obtain high yield and selectivity to the 2,1-benzisoxazol, a catalyst is required that promotes the formation of the hydroxylamine intermediate and the fast nucleophilic attack to the carbonyl group of the acyl group, while avoiding the reductive cleavage of the 2,1-benzisoxazole.

In the present work we will show that by controlling the binomial architecture of the metal nanoparticles and the nature of the support a non selective catalyst such as Pt, can be transformed to obtain, 2,1-benzisoxazoles in excellent yields and selectivity by reductive heterocyclization of 2-nitroacylarenes.

EXPERIMENTAL SECTION

2-Nitroacylarenes (>99%), Toluene (≥99%), and Dodecane ((≥99%), were purchased from Aldrich. Gold(III) chloride trihydrate (99.9%), platinum (II) acetylacetonate (97%), palladium (II) acetylacetonate (99%), were purchased from Aldrich. MgO sample with a surface area of 670 m^2g^{-1} was purchased from NanoScale Materials. TiO_2 (P-25, Degussa) and active carbon (Darco KB-B) supports were supplied by Evonik Industries and Aldrich, respectively.

0.2wt%Pt/TiO_2, sample with a Pt crystal size of 1.5 nm was prepared by incipient wetness following previously reported procedure[16] and reduced at 450^{o}C.

Pt/MgO samples with different Pt loading were prepared by impregnation of the support with the corresponding amount of a solution or platinum (II) acetylacetonate, in water free toluene (12.5 mL) which was added to 1 g of oxide support. The mixture was stirred for 12 h at room temperature and the solvent was removed at reduced pressure, and dried overnight under vacuum. The samples were calcined 3.5 h at 550 ^{o}C with an N_2 flow of 100 $mLmin^{-1}$ and activated by calcination at 450 ^{o}C with an H_2 flow of 100 $mLmin^{-1}$ during 3 h. Pd/MgO and Au/MgO samples were prepared following the same procedure.

A sample with 0.2 wt% of Pt onto porous active carbon (Darco KB-B, 100 mesh) was obtained by incipient wetness impregnation with a solution (2mL) containing the desired amount of metal (10.56 mg of $H_2PtCl_6 \cdot 6H_2O$) to form a thick paste (2 g). The catalyst paste was mixed thoroughly with a spatula for 10min. Then, the sample was dried at 100ºC for 12h. The final catalyst was

activated by reduction in a fix bed reactor with and H_2 flow of 100mL/min at 450ºC for 3h.

The amount of metal supported on the different catalysts was determined by ICP analysis in a Varian SpectrAA-10 Plus. Average metal size of the different catalysts was measured by HRTEM images, which were acquired by using a JEM 1010 transmission electron microscopy operated at 100 kV. The samples were prepared directly by dispersing the powders onto carbon copper grids.

Platinum dispersions were determined by H_2 chemisorption at 35°C in an ASAP 2010C Micromeritics equipment by extrapolating the total gas uptakes in the adsorption isotherms at zero pressure. Prior to the measurements the samples (about 300 mg) were reduced under flowing pure H_2 at 450 °C for 3 h. Active metal surface area were estimated from the total amount of chemisorbed H_2, assuming an adsorption stoichiometry Pt/H of 2, the Pt content (from ICP-OES), and considering spherical particle geometry with a surface atomic density of 8 nm^2/atom

Powder X-Ray diffraction patterns were collected in Philips X' PERT diffractometer equipped with a proportional detector and a secondary graphite monochromator. Data were collected stepwise over the $2^o \leq 2\theta \leq 40^o$ angular region, with steps of 0.02^o 2θ , 20s/step accumulation time and Cu KR (λ = 1.54178 Å) radiation.

In situ FTIR experiments have been performed with a Nexus 8700 FTIR spectrometer using a DTGS detector and acquiring at 4 cm^{-1} resolution. For the *in situ* catalytic IR experiments a quartz IR cell allowing *in situ* treatments in controlled atmosphere and temperatures from 25 ºC to 600 ºC has been

connected to a vacuum system with gas dosing facility. Prior to the adsorption experiments the samples were treated at 120 ºC in H_2 flow (20 ml·min^{-1}) for 1.5 h followed by evacuation at 10^{-5} mbar at the same temperature for 1h.Then the samples were cooled down to 25 ºC under dynamic vacuum conditions followed by co-adsorption of 2-nitrobenzaldehyde (8mbar) and H_2 (40mbar). IR spectra were recorded with time. For the IR studies of CO adsorption a homemade stainless steel IR cell allowing in situ treatments in controlled atmosphere and temperatures from -170 ºC to 500 ºC has been used. Samples have been activated as before, followed by cooling down to -170ºC under dynamic vacuum conditions. CO dosing are performed at -170ºC and at increasing pressure (0.05-0.5 mbar). IR spectra were recorded after each dosage. Origin software has been used for spectra treatment.

General procedure for reduction of 2-nitroacylarenes . In a 5 mL autoclave, the catalyst and a solution of 2-nitroacylarene (1 mmol, 165 mg), dodecane as internal standard (40 mg, 0.23 mmol) in 2 mL of toluene were placed. The autoclave was pressurized at 9 bar of hydrogen and heated at 30 ^{o}C under vigorous stirring.

In all reactions, samples were taken at regular intervals, diluted with dichloromethane and analyzed by GC equipped with a HP5 capillary column of 30 m x 0.25mm and 0.25mm cross-linked 5% phenylmethylsiloxane and a FID as the detector. In all cases the molar balance was ≥ 95%. Mass spectra were performed by GC–MS HP Agilent 5973 with a 6980 mass selective detector.

The products were purified by recrystallization from ethanol and identified by GC-MS and ^{13}C and ^{1}H NMR. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C at 75 MHz in a Bruker Avance 300 spectrometer, and the chemical shifts in

parts per million (ppm) were reported to internal TMS.

For catalyst recycling studies, the solid was collected by filtration, washed thoroughly with CH_2Cl_2 and calcined at 550 ºC in nitrogen flow during 3 h and then with hydrogen flow 3 h more.

Spectral data of products

3-Methyl-2,1-benzoisoxazole (2a):

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.45 (d, 8.82 Hz, 1H); 7.32 (d, 9.09 Hz, 1H); 7.16 (dd, 9.09, 6.3 Hz, 1H); 6.8 (dd, 8.82, 6.3 Hz, 1H); 3.14 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75MHz): δ 206 (C), 167 (C), 158 (C), 132 (CH), 123 (CH), 121 (CH), 116 (CH), 12 (CH_3). MS m/z (%)$M^+\cdot$ 133(100), 104(60), 90(10), 78(27), 62(16), 51(10), 43(49), 15(1).

2,1-Benzoisoxazole (2b):

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.12 (s, 1H); 7.6 (d, 9.09 Hz, 1H); 7.5 (d, 8.82 Hz, 1H); 7.29 (dd, 9.09, 6.4 Hz, 1H); 6.9 (dd, 8.82, 6.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75MHz): δ 156 (CH), 155 (C), 131 (CH), 124 (CH), 120 (CH), 118 (C), 115 (CH). MS m/z (%)$M^+\cdot$ 119(87), 92(100), 64(60), 38(18), 28(49).

3-methyl-[1,3]dioxolo[4',5':4,5]benzoisoxazole (2c):

^{1}H-NMR ($CDCl_3$, 300MHz): δ 6.62 (,s 1H); 6.45 (s, 1H); 5.88 (s, 2H); 3.22 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75MHz): δ 163 (C), 156 (C), 153 (C), 146 (C), 102 (CH_2), 92 (CH), 89 (CH), 112 (C), 12 (CH_3). MS m/z (%)$M^+\cdot$177(69), 148(100), 121(7), 105(7), 91(10), 77(12), 68(12), 53(22), 43(43), 28(27).

5-methoxy-2,1,benzoisoxazole (2d):

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.91 (s, 1H); 7.5 (d, 9.57 Hz, 1H); 7 (dd, 9.57, 2.2 Hz, 1H); 6.6 (s, 1H); 3.6 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75MHz): δ 156 (C), 154 (C), 152 (CH), 128 (CH), 118 (C), 116 (CH), 93 (CH), 55 (CH_3). MS m/z (%) $M^{+}\cdot$ 149 (54), 133 (7), 122 (19), 106(100), 79(19), 52(19), 29(7).

5-bromo-3-methyl-2,1-benzoisoxazole (2e):

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.52 (s, 1H); 7.3 (d, 9.42 Hz, 1H); 7.18 (dd, 9.42, 1.59 Hz, 1H); 2.66 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75MHz): 165 (C), 155 (C), 135 (CH), 122 (CH), 117(CH), 117 (CH), 116 (C), 12 (CH_3). MS m/z (%) $M^{+}\cdot$212(79), 211(84), 183(91), 182(98), 158(19), 156(28), 132(5), 117(10), 104(19), 90(25), 77(31), 61(25), 50(13), 43(100), 38(13), 15(3).

RESULTS AND DISCUSSION

It has been reported in literature that for the reduction of nitroaromatics into phenylhydroxylamine derivatives using catalyst based on Pd and, especially, Pt are preferred over supported metals such as Rh, Ir, Ru, and Os due to the higher activity and selectivity of the former.[17] In fact, we recently showed that 0.2wt%Pt/C controlled crystal sizes is an efficient catalyst for the coupling of nitroarenes with aldehydes in the presence of H_2 to obtain nitrones[18] in where the mechanism involves the condensation of the hydroxylamine intermediate generated *in situ* with the benzaldehyde in a cascade type reaction. It was demonstrated that the formation of the hydroxylamine intermediate is favored by the presence of highly unsaturated Pt species. Furthermore, it has been reported recently in an interesting work that nitroaromatics can be

chemoselectively reduced into phenylhydroxylamines in high yields using nanoparticles of Pt supported on carbon.[19]

From these precedents and considering that the reductive heterocyclization of 2-nitroacylarenes to 2,1-benzisoxazol involves the cyclization of the hydroxylamine intermediate by attack of the hydroxylamine group to the carbonyl group at the 2-position (see Scheme 1), we envisaged that a properly designed Pt/C catalyst could be a selective catalysts to prepare 2,1-benzisoxazol derivatives by reductive heterocyclization of 2-nitroacylarenes through a cascade type process.

Thus, taking 2-nitroacetophenone as reactant model, we tested first 0.2wt%Pt/C (average crystal size of 1.6 nm) that was active for preparing nitrones.[18] The reduction was performed at 30 ^{o}C under 9 bar of H_2 in toluene as a solvent and in Figure 1 the kinetic plot of the reaction is presented. As can be observed there, the 2-aminoacetophenone appears as a primary and secondary product which can be formed by fast hydrogenation of the 2-nitroacetophenone into amino (primary character), as well as by further reduction of the desired 2,1-benzisoxazole (see Scheme 2), that appears as a primary and unstable product,

From these results we can conclude that although the 0.2wt%Pt/C catalyst promotes the formation of 2,1-benzisoxazole through the formation of the hydroxylamine intermediate, under our reaction conditions, this intermediate undergoes a fast reduction into 2-aminoacetophenone. Moreover, the catalyst also promotes the reductive cleavage of 2,1-benzisoxazole in high extension.

Similar results were obtained when the hydrogenation was performed with Pt supported on TiO_2 (0.2wt%Pt/TiO_2) activated at 450 ^oC in the presence of hydrogen (see Figure 2), although in this case the results are not surprising due to the role attributed to TiO_2 in minimizing the formation of hydroxylamine intermediate during the hydrogenation of nitro compounds.[20]

It has been demonstrated in our previous study[21] that the basicity of surface oxygen species favors the stabilization of nitroso and hydroxylamine intermediate compounds. Then, in an attempt to stabilize the intermediate hydroxylamine, enhancing the cyclization reaction, we have selected MgO as a basic support for Pt.

Then, a catalyst was prepared that contains 0.2wt% of Pt on MgO (0.2wt%Pt/MgO). The average Pt crystallite size in this catalyst was 2.4 nm (see Table S1). The catalytic results given in Figure 3 show that the concentration of 2,1-benzisoxazole reach a maximum yield of approximately 80% at 100 % reactant conversion when working with the Pt/MgO catalyst. Longer reaction times lead to further hydrogenation of 2,1-benzisoxazole into 2-aminoacetophenone, which correspondingly, show a marked character as secondary product. Moreover, a minor amount of a compound which was tentatively assigned to a dimmer of the nitrosobenzene intermediate (azodioxide) was also detected during the reaction.

Notice that in the case of 0.2wt%Pt/MgO which gives better catalytic results than 0.2wt%Pt/C, not only the support has been changed, but the average of crystallite size of the Pt was also different.

Therefore we cannot conclude if the improvement is only due to an intrinsic effect of the support on the catalytic process or to an indirect effect of the support on metal dispersion. To gain a better physico-chemical understanding of our catalytic system, while improving its catalytic behavior, different Pt on MgO catalysts were prepared in where, the Pt dispersion was changed. By doing this we could have Pt/MgO samples with different average metal Pt crystallite sizes. Thus, by changing the metal crystallite size, one can not only change the ratio of exposed to non–exposed metal atoms, that may reflect on total conversion, but it will also change the relative ratio of accessible Pt atoms located at the crystal corners (less saturated metal atoms) versus the accessible Pt atoms located on crystal faces, being this ratio higher when smaller is the crystal size. Since the electronic properties of those more unsaturated Pt atoms should be different, the activity (as per turnover frequency) and selectivity of the final catalyst could be modified by changing the crystal size of the metal nanoparticle**.**

Then three additional Pt/MgO samples with 0.1, 0.5 and 1 wt% of Pt were prepared (see experimental section) in which average crystallite sizes obtained from the corresponding histograms are given in Table S1.

Kinetic curves for the conversion of 2-nitroacetophenone with these new samples are given in Figures S1-S4**.** In Table 1 are summarized the results of the turnover frequency (TOF), conversion and selectivity to 3-methyl-1,2-benzoisoxazole obtained with the different catalysts. It can be seen from those that the TOF (calculated as initial rate of formation of benzisoxazole divided by mole of surface Pt atoms) increases when decreasing the Pt metal crystallite size. This would indicate that the less saturated Pt metal atoms located at the

corners play a key role in this multistep reaction. Very importantly, the maximum yield of the 3-methyl-2,1-benzisoxazole (**2**) (94%) obtained at 100% conversion of 2-nitroacetophenone is obtained with the Pt/MgO catalyst (TON of 4700) with the smallest crystallite size (1.1 nm). From these results, we can then conclude that when the crystal size of the metal Pt decreases and the relative amount of less saturated Pt atoms on the surface increases the catalyst became more active for the reductive heterocyclization and less active for the reductive cleavage that shows a marked sensitiveness to the architecture of the Pt nanoparticles.

Nevertheless, we want to point out that while the average crystallite size of the most active and selective Pt/MgO (1.1 nm) is not that different of that of Pt/C (1.6 nm), TOF and selectivity to 2,1-benzisoxazole is much lower in the second one (990 h^{-1} and 5% selectivity at 100% conversion for the Pt/C versus 7220 h^{-1} and 94% selectivity at the same conversion for the Pt/MgO). This observation indicates either a direct effect of the support or an indirect effect where the support may influence the shape of the Pt crystals. In order to discern between both effects, a detailed spectroscopic study based on IR spectroscopy have been performed on the 0.2wt%Pt/C and 0.2wt%Pt/MgO samples. Differences in particle shape are hard to be visualized by means of our HRTEM study; therefore we have used IR spectroscopy of CO adsorption as a more convenient way to titrate the nature of surface sites. The IR spectra of CO adsorption (Figure 4) shows less saturated Pt surface sites on the 0.2wt%Pt/C sample (IR band at 2040 cm^{-1}) than on the 0.2wt%Pt/MgO sample (IR band at 2060 cm^{-1}), being the last one more selective to 2,1-benzisoxazole. Thus we can say that the selectivity to 2,1-benzisoxazole is not only related to the

presence of unsaturated surface sites and has to be related to other factors than particle size and shape.

To unravel this behavior, the reaction mechanism has been followed *in situ* by IR spectroscopy taking 2-nitrobenzaldehyde as reactant model. Thus, 2-nitrobenzaldehyde and H_2 have been co-adsorbed in the presence of the catalyst, and the evolution of reaction intermediate surface species monitored with time by means of IR spectroscopy. On the 0.2wt%Pt/C sample (Figure 5) 2-aminobenzaldehyde has been detected on the catalyst surface in the first minutes of the reaction (IR bands at 1601, 1570 and 1558 cm^{-1}) while no other intermediate products could be visualized, indicating a fast hydrogenation rate of the nitro to amino group.

In opposite, on the 0.2wt%Pt/MgO sample (Figure 6), nitrosobenzaldehyde (IR band at 1485 cm^{-1}) and hydroxylamine (1490 cm^{-1}) are detected in the first minutes of the reaction (see inset of Figure 6), while at increasing reaction time new IR bands at 1638, 1539, 1515 and 1482 cm^{-1} could be envisage, corresponding to 2,1-benzisoxazole. 2-Aminobenzaldehyde was hard to detect, specifically considering the bad quality of the IR spectra due to the high amount of carbonate species on the support.

According to previous studies performed in our group,[21] the higher basicity of the MgO support, may explain the stabilization of the hydroxylamine intermediate compound, where accumulation of hydroxylamine on the catalyst surface would favor their cyclization versus hydrogenation. In a similar way, the basicity of the support enhances stabilization of 2,1-benzisoxazole. This has been proved by a control experiment where 2,1-benzisoxazole has been

adsorbed on a fresh 0.2wt%Pt/MgO sample where it remains stable even after vacuum treatment (see supporting information for details Figure S5) and in the presence of H_2 as observed in figure 6.

From these results we can then conclude that the higher basicity of the MgO support plays a key role enhancing the selectivity to 2,1-benzisoxazole. Moreover, the higher rate of 2-aminoacylarene formation observed on the 0.2wt%Pt/C sample, in both the IR as in the catalytic studies, can be related to a more pronounce activation of the carbonyl functional group in the case of the 0.2wt%Pt/C sample. Indeed, the carbonyl group of adsorbed 2-nitrobenzaldehyde is shifted to lower frequencies in the 0.2wt%Pt/C sample (1695 cm^{-1}) versus the 0.2wt%PtMgO sample (1702 cm^{-1}) (see Figure S6). In this case, we can assume that activation of the carbonyl group causes an electronic withdrawing effect that enhances the electrophylicity of the nitro group increasing their hydrogenation rate to amino group. Similar effects have already been reported in the literature.[19]

Influence of the Temperature of Reaction

In order to study the influence of the reaction temperature on the selectivity, the process was performed at increased temperatures (50, 70 and 90 ^{o}C) using 0.1wt%Pt/MgO sample. In Figure 7 is presented the yield of 3-methyl-2,1-benzisoxazole versus conversion. As can be observed, an increase of temperature leads to a decrease in selectivity to 2,1-benzisoxazole, indicating that the reductive cleavage should have a higher activation energy.

Stability and reusability of the Pt/MgO

To investigate if the catalytic process involves possible Pt leached into the solution, an additional experiment was carried out where the reduction of 2-nitroacetophenone with 0.2wt%Pt/MgO was stopped after 30 min. At this point, the catalyst was filtered off in hot and the reaction was continued for an additional 1h, but no further conversion was detected (Figure S7).

To check the reusability of the catalyst, after a first run, the 0.1wt%Pt/MgO sample was recovered by filtration, washed thoroughly with dichloromethane and used in a second cycle. The results showed an important decrease in activity (only 10 % yield of 2,1-bezisoxazole was obtained) indicating strong catalyst deactivation, which could be caused by strong adsorption of organic material on the catalyst surface. Indeed the TG analysis of the used catalyst showed that 32 wt% (with respect to the amount of catalyst) of organic material remained on the catalyst. However, another possible cause of catalyst deactivation could be the existence of structural changes of the support. XRD analysis of the used catalyst showed the appearance of diffraction peaks corresponding to $Mg(OH)_2$ (see Figure S8) which will be produced by hydration of MgO by the water produced during reaction. These observations suggest that deactivation of the catalyst could be originated not only by adsorption of organic material but also by changes in basicity of the support as $Mg(OH)_2$ is less basic than MgO.[22] However the initial catalytic activity could be recovered by submitting the catalyst to calcination at 550 ºC under air flow followed by reduction under H_2 flow at 450 ºC. Following this protocol, the catalyst could be reused three consecutive cycles without loss of activity and selectivity (see Figure 8). Moreover, the ICP analysis of the catalyst after

reaction showed that the amount of Pt on the catalyst remains constant during the three cycles.

Since other metals such as Au and Pd have been reported as potential chemoselective catalyst for hydrogenation of nitro groups 0.1wt%Pd/MgO and 0.1wt%Au/MgO were prepared following the same methodology and tested in the reduction of 2-nitroacetophenone. However, as can be observed in Table 2 0.1wt%Pd/MgO (1.9 nm Pd crystal size) was less active than Pt/MgO although the selectivity to 2,1-benzoisoxazole was rather acceptable, while the Au/MgO (2.3 nm Au crystal size) showed very low activity in this reaction.

Scope of the reaction

Finally the 0.1wt%Pt/MgO catalyst was tested for the reductive heterocyclization of various 2-nitroarylketone and 2-nitrobenzaldehyde derivatives (Table 3). Good conversion and selectivities to the corresponding 2,1-benzoisoxazole derivatives were obtained with substrates bearing electron-donating groups in the aromatic ring (entries 3 and 4) or with withdrawing groups such as Br (entry 5) while in this case dehalogenation as side reaction was not observed. However, when the carbonyl group in *ortho* position is integrated in an ester group the reductive heterocyclization was not observed at all, and the only observed compound was the corresponding 2-aminoester (entry 6). This result agrees with the previously reported results using $SnCl_2$ for reducing 2-nitroesters.[12]

CONCLUSIONS

2,1-Benzisoxazoles have been obtained by reductive heterocyclization of 2-nitroacylarenes using supported Pt nanoparticles. The reductive

heterocyclization of 2-nitroacetophenone performed with Pt nanoparticles on different supports (C, TiO_2 and MgO) showed that Pt/MgO was the most active and selective catalyst. Kinetic experiments combined with Operando IR spectroscopy and HRTEM showed that while small Pt nanoparticles (~1nm) are necessary for a successful catalyst, this is not the only requisite to achieve high activity and selectivity. The reaction mechanism studied by *in situ* IR spectroscopy of the adsorbed reactant, showed that the reduction of the nitro group on the Pt goes through the formation of the corresponding nitroso, hydroxylamine and aniline derivatives. However, the relative rate of the different hydrogenation steps can be modified by the basicity of the support. Thus, it is possible to stabilize the hydroxylamine intermediate on the Pt/MgO surface favoring their cyclization to the target compound versus hydrogenation. Moreover, the basicity of the support enhances the stabilization of the desired 2,1-benzisoxazole avoiding their further reductive cleavage. Then, maximum activity and selectivity to the target compound can be achieved by controlling the architecture of metal particles and acid-base properties of the support. The optimized Pt/MgO catalyst could be reused several times without loss of activity and could be applied to the synthesis of a variety of 2,1-benzisoxazole derivatives with high yields.

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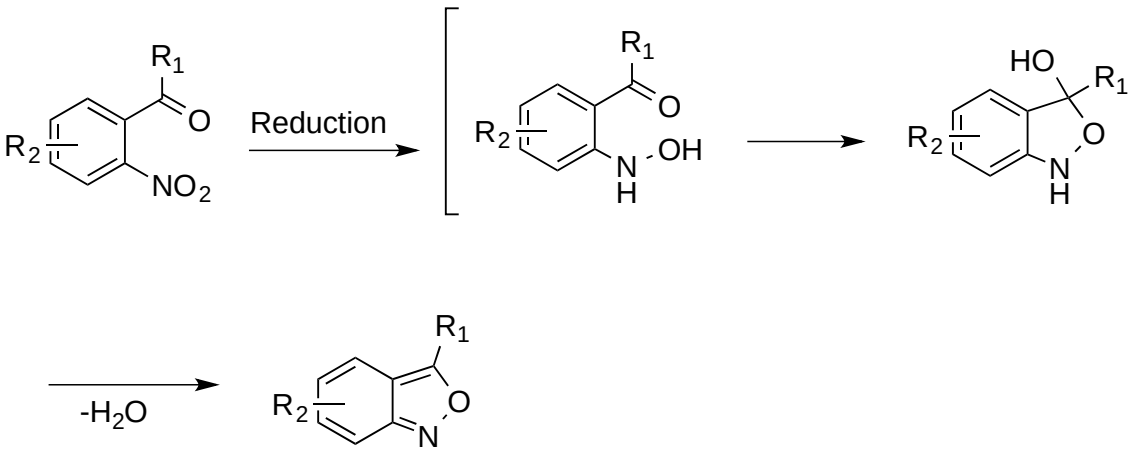
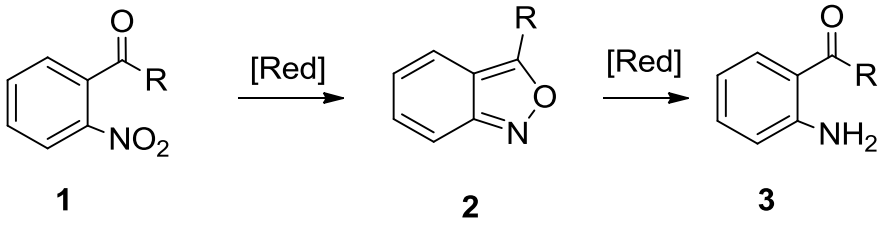


Scheme 1. Mechanism of the reductive heterocyclization of 2-nitroacylarenes



Scheme 2. Pathway of the reduction of 2-nitroacylarenes

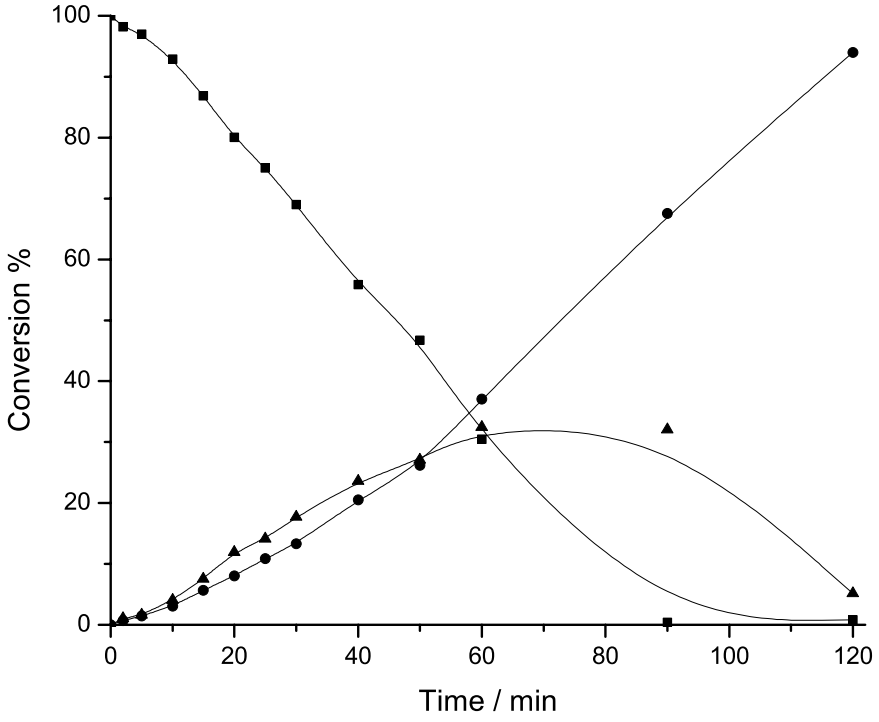


Figure 1. Hydrogenation of 2-nitroacetophenone using 0.2wt%Pt/C as catalyst; 2-nitroacetophenone (■),3-methyl-2,1-benzoisoxazole (▲), 2-aminoacetophenone (●). Reaction conditions: 0.2wt%Pt/C (40 mg), 2-nitroacetophenone (1 mmol), Toluene (2 mL), 9 bar H_2 at 30 ^{o}C.

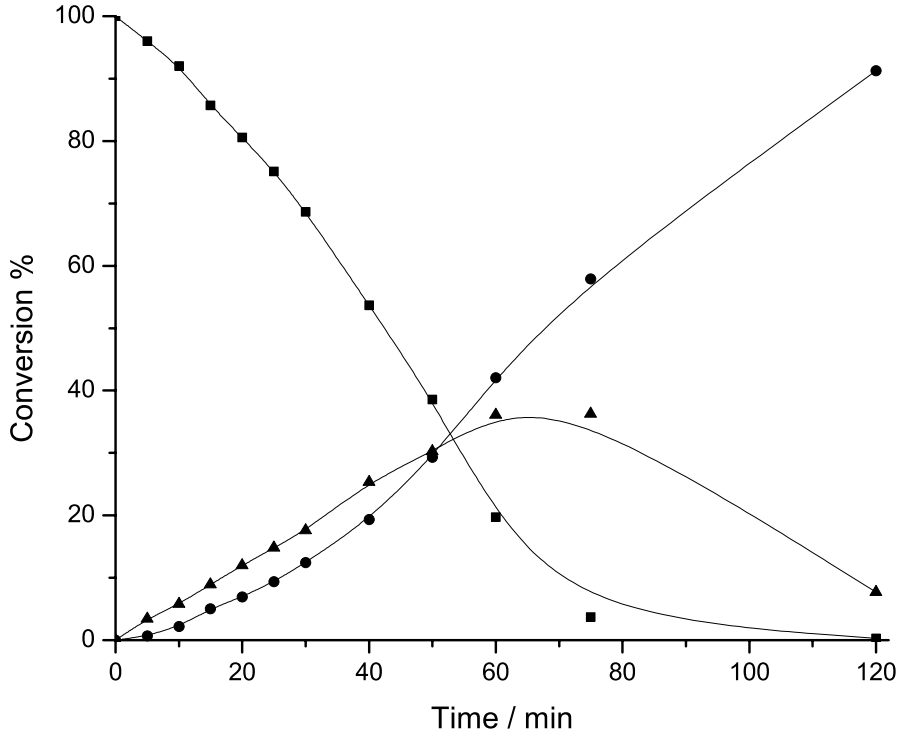


Figure 2. Hydrogenation of 2-nitroacetophenone using 0.2wt%Pt/TiO_2 catalyst; 2-nitroacetophenone (■), 2-aminoacetophenone (●), 3-methyl-2,1-benzoisoxazole (▲). Reaction conditions: 0.2wt%Pt/TiO_2, (40 mg), 2-nitroacetophenone (1 mmol), Toluene (2 mL), 9 bar H_2, at 30 ^oC.

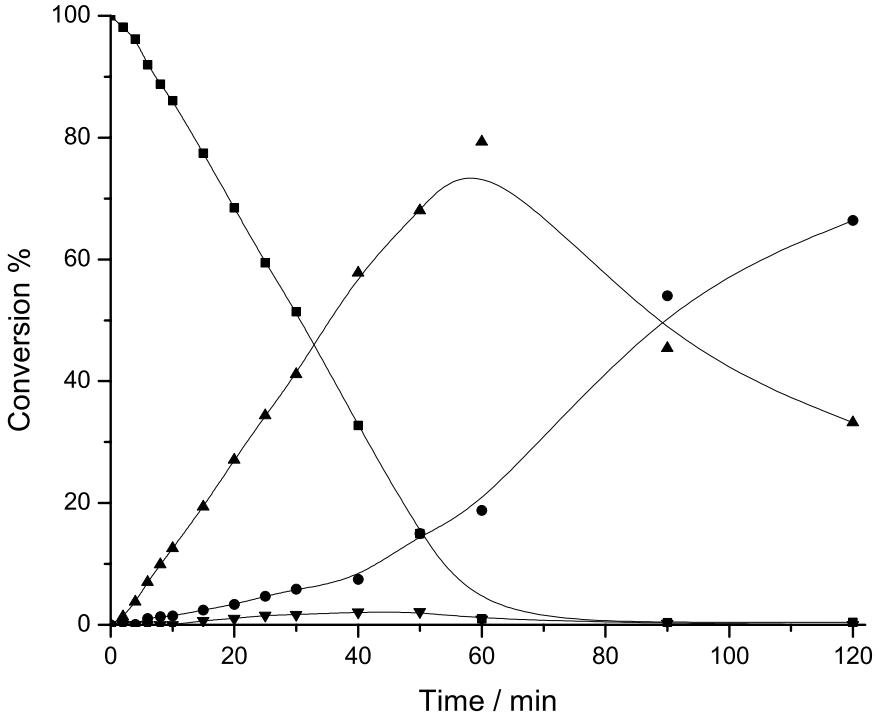


Figure 3. Hydrogenation of 2-nitroacetophenone using 0.2wt%Pt/MgO as a catalyst; 2-nitroacetophenone (■), 3-methyl-2,1-benzoisoxazole (▲), 2-aminoacetophenone (●), azodioxide (Mr=266 g/mol) (▼).Reaction conditions: 0.2wt%Pt/MgO (40 mg), 2-nitroacetophenone (1 mmol), Toluene (2 mL), 9 bar H_2 at 30 ^{o}C;

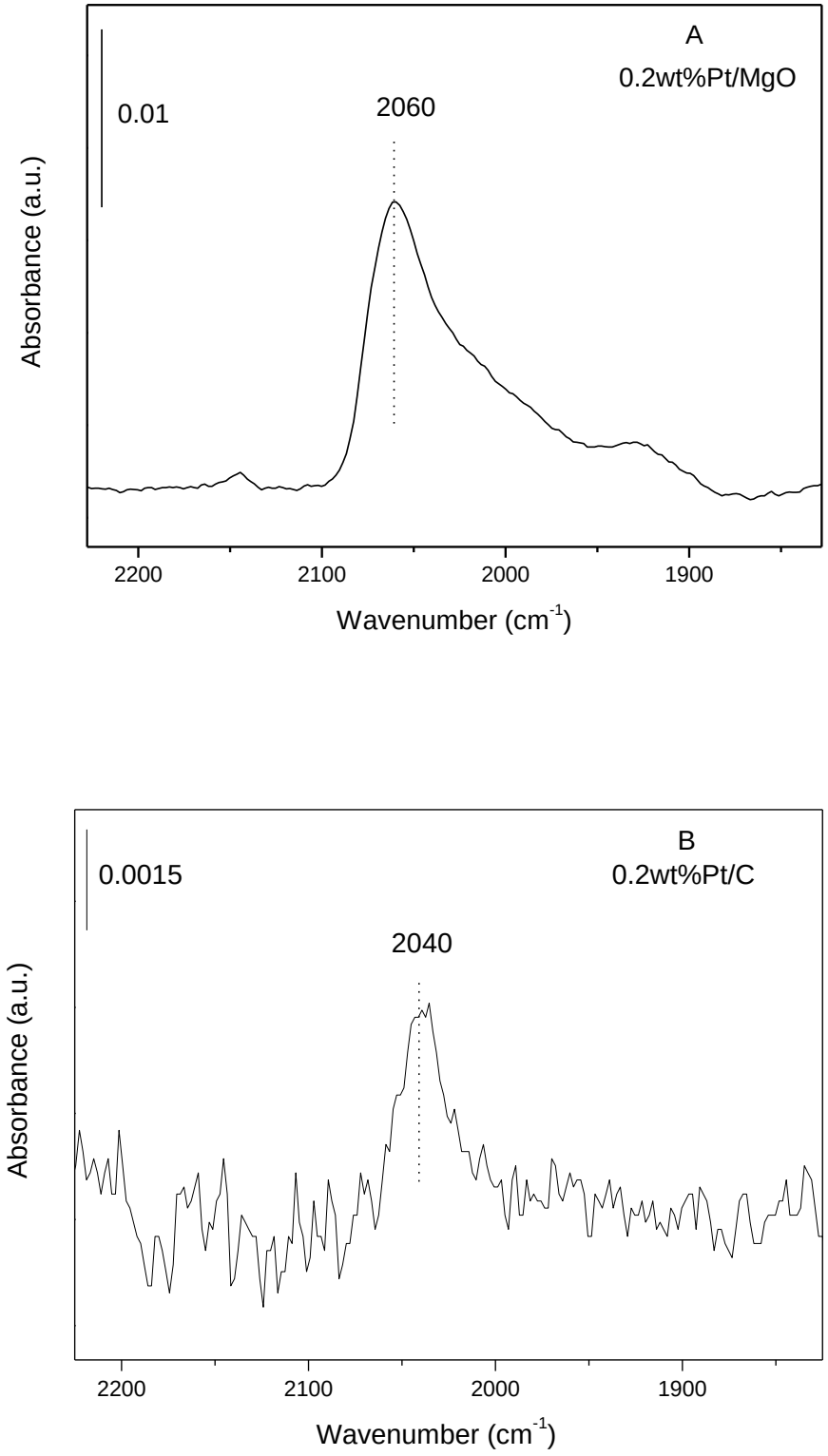


Figure 4. IR spectra of CO adsorption on 0.2wt%Pt/MgO (A) and 0.2wt% Pt/C (B) acquired at -170 ºC and 0.5 mbar CO.

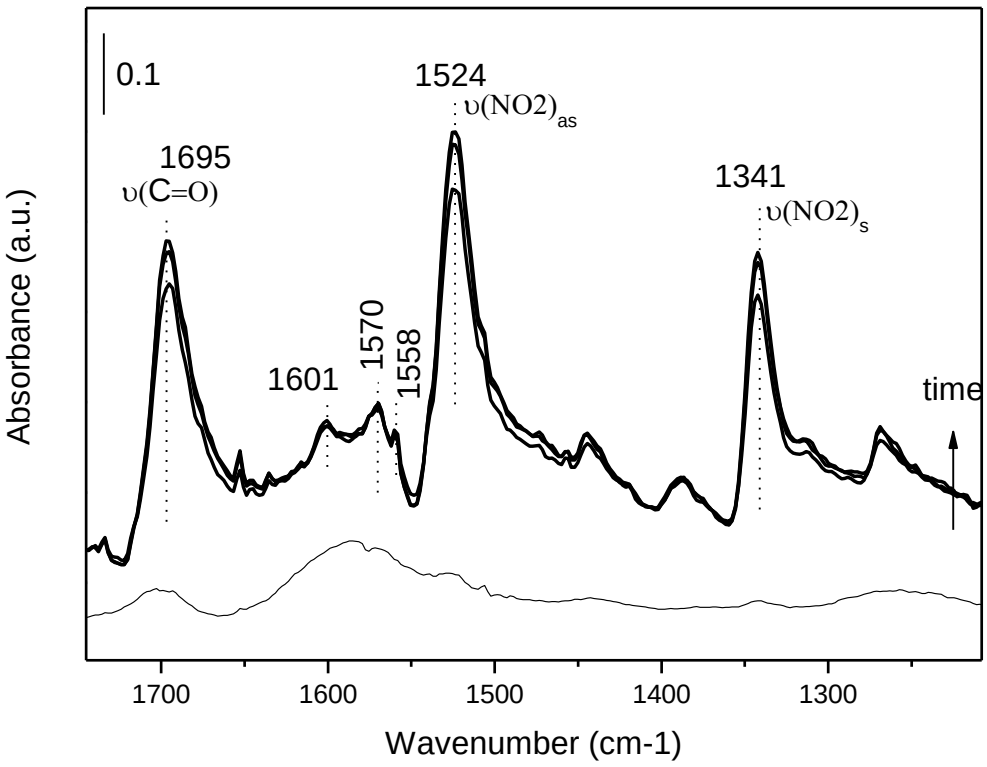


Figure 5. Time evolution of IR surface species on the 0.2wt%Pt/C catalyst during the hydrogenation of 2-nitrobenzaldehyde (8mbar 2-nitrobenzaldehyde and 40 mbar H_2 at 25 ºC). In black thin line the sample before reaction and in bold line the sample during the reaction. Spectra are acquired at 7 min, 52 min and 150 min of reaction. IR bands at 1695, 1524 and 1341 cm^{-1} are due to 2-nitrobenzaldehyde.

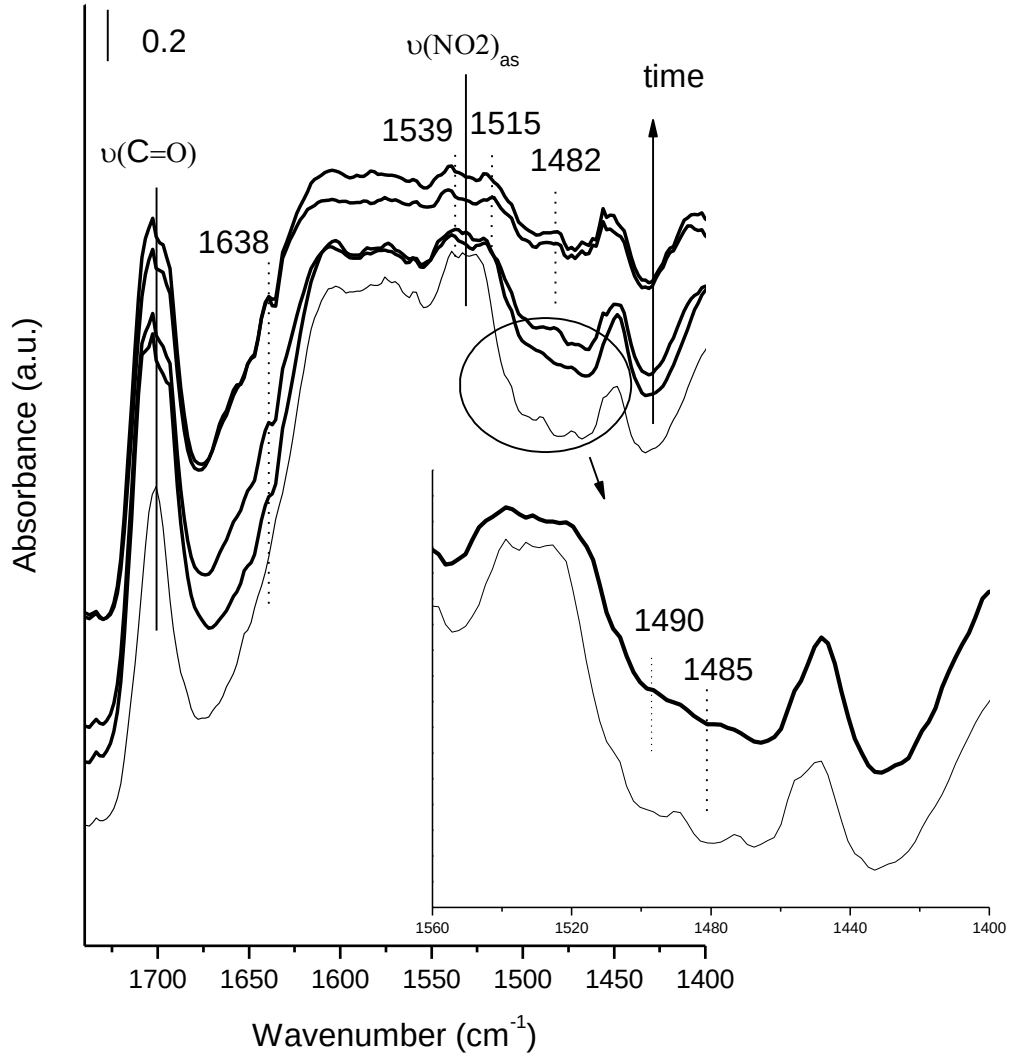


Figure 6 Time evolution of IR surface species on the 0.2wt%Pt/MgO catalyst during the hydrogenation of 2-nitrobenzaldehyde (8mbar 2-nitrobenzaldehyde and 40 mbar H_2 at 25 ºC). In black thin line the sample before reaction and in bold line the sample during the reaction. Spectra are acquired at 7 min, 52 min, 110 min and 200 min of reaction.

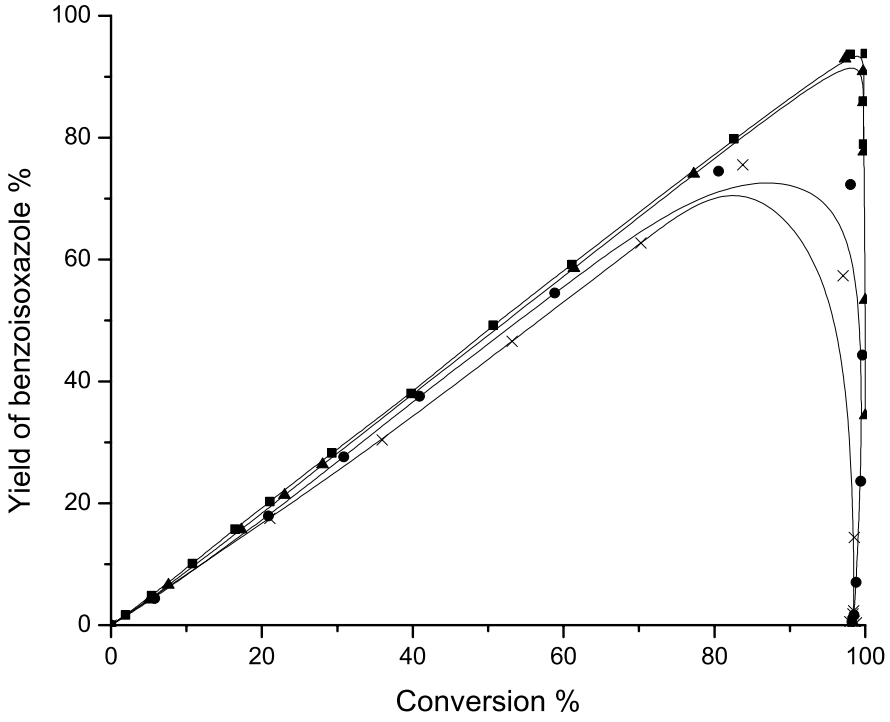


Figure 7. Influence of the reaction temperature on the selectivity to 3-methyl-2,1-benzisoxazole using 0.1wt%Pt/MgO as catalyst. Reaction Conditions: 0.1wt%Pt/MgO (40 mg), 2-nitroacetophenone (1 mmol), Toluene (2 mL), 9 bar H_2, Temperature (^oC): 30(■), 50(▲), 70(•),90 (x).

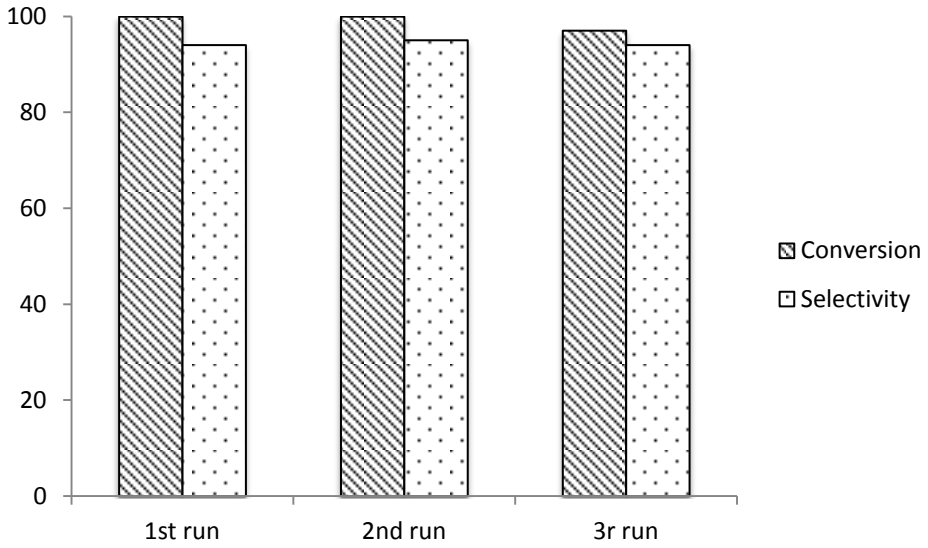


Figure 8. Reuses of the 0.1wt%Pt/MgO sample in the reductive cyclization of 2-nitroacetophenone.Reaction conditions: 0.1wt %Pt/MgO (40mg), 2-nitroacetophenone (1 mmol), Toluene (2 mL), 9 bar H_2 at 30^{o}C during 1h. After each use, the catalyst was calcined at 550 ^{o}C under air flow during 3h, and reduced at 450 ^{o}C under H_2 flow.

Table 1. Results of the reductive heterocyclization of 2-nitroacetophenone using Pt/MgO samples with different crystal sizes.

Entry	Pt loading (wt%)	Crystal size(nm)	$r^o \cdot 10^5$ mol/h	TOF(h^{-1})	Conv. **1**(%)	Select. **2**(%)
1	1.0	8.7	56.2	1220	100	56
2	0.5	3.0	73.7	2960	100	72
3	0.2	2.4	75.8	5820	100	75
4	0.1	1.1	120.6	7220	100	94

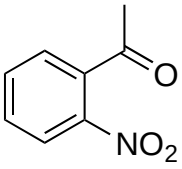
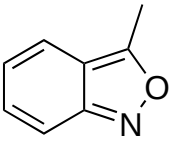
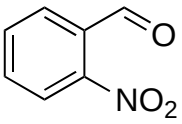
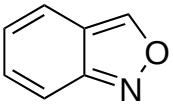
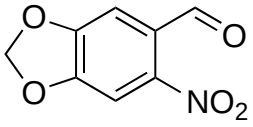
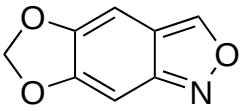
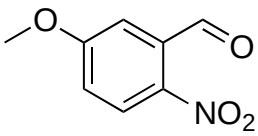
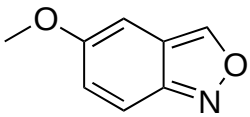
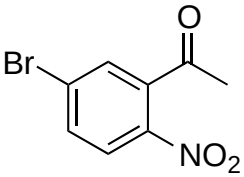
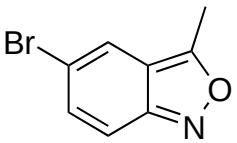
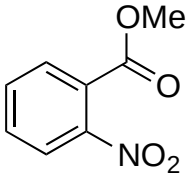
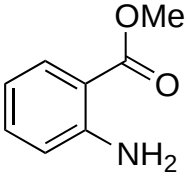
Reaction conditions: substrate/Pt=4877 (molar ratio), 2-nitroacetophenone (1 mmol), 30 ^oC, Toluene (2 mL), 9 bar P_{H2}, 60 min reaction time; r^o: initial rate of appearance of 3-methyl-2,1-benzoisoxazole. TOF: defined as the initial reaction rate of formation of 3-methyl-2,1-benzoisoxazole divided by mole of surface Pt atoms (determined by chemisorption of H_2).

Table 2. Results of the reductive heterocyclization of 2-nitroacetophenone using different metals supported on MgO

Catalyst	Cristal size (nm)	$r^o \cdot 10^5$ mol/h	Time (min)	Conv(%) **1**	Yield(%) **2**	Select(%) **2**
0.1 wt%Pd/MgO	1.9	35.90	90	100	63	63
0.1wt% Pt/MgO	1.1	120.60	60	100	94	94
0.1wt%Au/MgO[a]	2.3	0.08	120	3	2	57

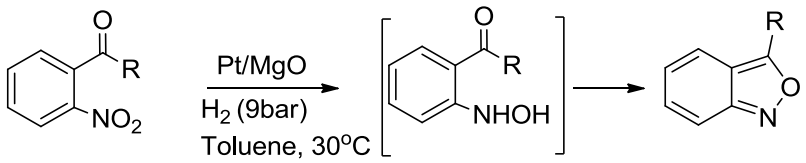
Reaction conditions: molar ratio substrate/metal=4877, 2-nitroacetophenone (1mmol), Toluene (2 mL), 9 bar P_{H2} at 30^{o}C.

Table 3. Reductive heterocyclization of different 2-nitroacylarenes using 0.1wt%Pt/MgO as catalyst.

Entry	Reactant	Time (h)	Conversion (%)	Product	Yield (%)
1		1	100	 **2a**	94
2	 **2b**	1	100	 **2b**	100
3		1.5	98	 **2c**	93
4		3	100	 **2d**	96
5		1.5	99	 **2e**	97
6		4	60		60

Reaction conditions: 0.1wt%Pt/MgO (40 mg), reactant (1 mmol), Toluene (2 mL), 9 bar PH_2 at 30^{o}C

GRAPHICAL ABSTRACT



2,1-Benzisoxazoles have been selectively synthesized through reductive heterocyclization of 2-nitroacylarenes by adjusting crystal size of Pt nanoparticles and acid-base properties of the support.