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Impregnated Palladium on Magnetite as Water Compatible Catalyst for the Cycloisomerization of Alkynoic Acid Derivatives

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This work describes the catalytic activity of palladium(II) species, in the cycloisomerization of alkynoic acids and their derivatives in aqueous media as well as in Deep Eutectic Solvents (DESs), with one of the lowest metal catalyst loadings reported so far in the literature. Different substrates such as terminal and internal alkynes or alkynyl sulfonylimides were studied obtaining selectivity either the cyclic compound or the hydrolysed keto derivative. This new system avoids the use of harmful solvents and employs very efficient and recoverable heterogeneous catalyst.

Introduction

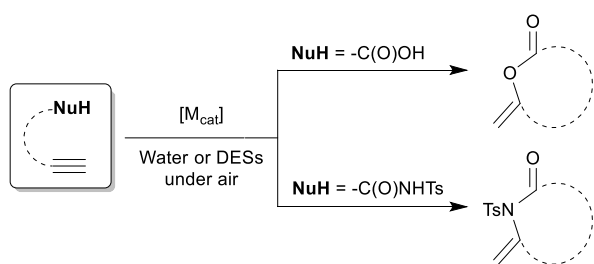
Cycloisomerization processes¹ are amongst the most valuable transformations according to the *Principles of Green Chemistry*,² since they showed the highest atom and step economy.³ The metal-catalyzed intramolecular cycloaddition of heteroatomic nucleophiles to an alkyne is a straightforward and highly selective methodology for the synthesis of heterocyclic products, which usually present an increased structural complexity when compared with their acyclic starting materials (Scheme 1).¹ Some of the crucial points to bear in mind when designing *Catalytic Green Chemical Processes* involve: *i*) the use of safe, nontoxic, cheap and sustainable solvents [like water and Deep Eutectic Solvents (DESs)];^{4,5} *ii*) the absence of co-catalyst (usually bases, acids or halogen abstractors are employed) and;

iii) the use of aerobic conditions (without protecting atmosphere).

Over the years, numerous protocols for the cycloisomerization of alkynoic acid derivatives catalyzed by transition metals have been reported, giving rise to a reliable and forthright synthetic tool for the production of highly substituted cyclic enol-lactones,^{6,7} with palladium species being the most used catalyst. Although, homogeneous⁶ catalysts were initially used, there are some examples in the literature which use heterogeneous palladium catalysts.⁷ However, most of these catalysts required: *i*) protocols with high catalyst loadings; *ii*) additives (such as co-catalysts or bases); and *iii*) the use of volatile organic solvents. Thus, only a few catalytic systems were able to carry out the cycloisomerization of alkynoic acid derivatives using sustainable solvents.⁸

On the other hand, the utilization of heterogeneous catalysts in organic synthesis presents important and obvious advantages including their easy isolation and the possible recycling, among others.⁹ In this sense, magnetite¹⁰ used as support, is particular attractive since its magnetic properties allows easily separation of the catalyst from the reaction mixture; just using an external magnet (magnetic decantation) without the need of tedious, time-consuming and waste-production (filtration, centrifugation or membrane separation steps). These unique properties make magnetite an excellent support for many different metallic catalysts.¹¹

With all these precedents in mind, herein we report a simple and heterogeneous catalyst based on palladium(II) oxide nanoparticles supported on magnetite for the cycloisomerization of alkynoic acid derivatives in aqueous media or Deep Eutectic Solvents (DESs). It is important to note that: *i*) a higher activity is achieved by using palladium(II) oxide impregnated on magnetite as catalyst; *ii*) the reactions proceed in water or DES under aerobic conditions and without the assistance of any co-catalyst, and *iii*) the use of water as reaction media allows the catalyst recycling (up to 4 consecutive times) without loss of catalytic activity or selectivity.



Scheme 1. Metal-catalyzed cycloisomerization of alkynoic acids or alkynyl sulfonylimides using sustainable solvents as reaction media in the presence of air.

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Results and discussion

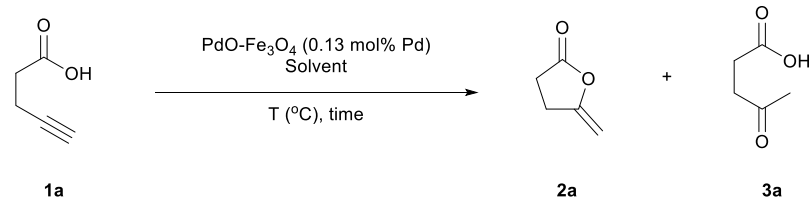
To start with this study, the cycloisomerization reaction was evaluated using palladium(II) oxide impregnated on magnetite as catalyst, and commercially available 4-pentynoic acid (**1a**), as the model for the reaction condition optimization (Table 1).

Initially, the reaction was performed using different DESs as sustainable solvents (Table 1, entries 1-12), obtaining the best result with the choline chloride-based eutectic mixture [ChCl:urea/1:2] (entry 7).¹² When the reaction was carried out in pure water as solvent (entry 13-31) the yield was substantially improved even at room temperature (entry 14). Then, a study on the evolution of the reaction was carried out at different temperatures (see Supporting Information). The ketoacid **3a** was obtained as minor product of the tandem process cycloisomerization/hydrolysis after 4 days at room temperature

(entry 20). The compound **3a** was the only obtained product after 7 days at room temperature (entry 21), 4 days at 50 °C (entry 25) or 7 h at 90 °C (entry 31). These results showed the selectivity of catalyst, capable of performing regioselectively the 5-*exo*-dig cyclization with no hydrolysis.

It should be also pointed out that the complete hydrolysis of previously isolated compound **2a** to the ketoacid **3a** took place after 17 h in water at 90 °C in absence of impregnated palladium on magnetite catalyst, while in the presence of catalyst the whole process took only 7 h (compare with entry 31). These experiments showed that the impregnated palladium on magnetite catalyst also catalyzed the final hydrolysis. Moreover, the increase of the temperature enhanced the reaction rate obtaining the enol-lactone **2a** in 60 min at room temperature (entry 14), in 30 min at 50 °C (entry 23), or only in 10 min at 90 °C (entry 27).

Table 1. Optimization of the reaction conditions.^a



Entry	Solvent	T (°C)	time	2a (%) ^b	3a (%) ^b
1	ChCl:urea (1:2)	25	45 min	0	0
2	ChCl:glycerol (1:2)	25	45 min	2	0
3	ChCl:ethylene glycol (1:2)	25	45 min	3	0
4	AcChCl:urea (1:2) ^c	25	45 min	2	0
5	ChCl:resorcinol (1:1)	25	45 min	30	0
6	ChCl:acetamide (1:2)	25	45 min	5	0
7	ChCl:urea (1:2)	90	10 min	81	0
8	ChCl:glycerol (1:2)	90	10 min	32	0
9	ChCl:ethylene glycol (1:2)	90	10 min	36	0
10	AcChCl:urea (1:2)	90	10 min	67	0
11	ChCl:resorcinol (1:1)	90	10 min	65	0
12	ChCl:acetamide (1:2)	90	10 min	25	0
13	H ₂ O	25	30 min	37	0
14	H ₂ O	25	60 min	100	0
15	H ₂ O	25	90 min	100	0
16	H ₂ O	25	2 h	100	0
17	H ₂ O	25	4 h	100	0
18	H ₂ O	25	1 d	92	8
19	H ₂ O	25	2 d	93	7
20	H ₂ O	25	4 d	67	33
21	H ₂ O	25	7 d	0	100
22	H ₂ O	50	10 min	67	0
23	H ₂ O	50	30 min	100	0
24	H ₂ O	50	2 h	100	0
25	H ₂ O	50	4 d	0	100
26	H ₂ O	90	5 min	90	0
27	H ₂ O	90	10 min	100	0
28	H ₂ O	90	30 min	100	0
29	H ₂ O	90	60 min	100	0
30	H ₂ O	90	2 h	73	27
31	H ₂ O	90	7 h	0	100

^a Reaction carried out using compound **1a** (0.1 mmol), 0.5 mg of catalyst (0.13 mol% Pd) in 0.2 mL of solvent. ^b Conversion determined by GC using tridecane as internal standard. ^c AcChCl (acetylcholine chloride).

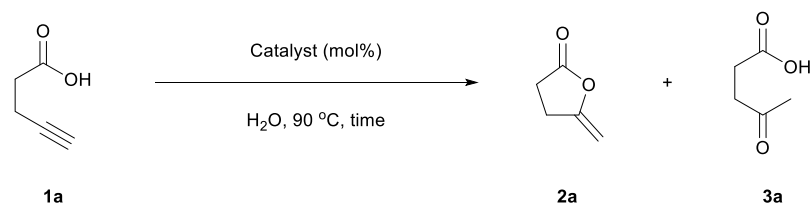
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At this point, it should be highlighted that this reaction time is one of the lowest reported so far in the literature⁸ for this cycloisomerization process in sustainable solvents.

Once the optimal conditions were determined (entry 27 in Table 1, or entry 1 in Table 2), other catalysts were tested in the model catalytic reaction (Table 2). Prior to these studies we proved that the reaction without catalyst failed in the aforementioned optimized reaction conditions (entry 2). For completeness of the possible blank experiments, we also evaluated the activity of the magnetite support by its own. Nanoparticles or microparticles of magnetite were used as catalysts with the results showing the inactivity of the support (entries 3 and 4). After the no-activity of magnetite was tested, different metal oxides impregnated on magnetite (entries 5-16) were evaluated

as catalyst, observing that only PtO/Pt₂O-Fe₃O₄ and PdO/Cu-Fe₃O₄ showed some catalytic activity (entries 5 and 16). However, the selectivity was poor, since the ketoacid **3a** was detected. Once palladium was found to be the most active metal, other commercially available palladium species were tested (being either homogenous or heterogeneous catalysts) under the previously optimized catalytic conditions (water at 90 °C). In all the palladium catalysts tests, the amount of loading required to obtain a complete conversion was higher than that using magnetite as support (compare entries 1, 17, 19, 21, 23 and 25), thus highlighting the superior catalytic activity of the magnetite-based palladium catalyst. At lower reaction times, the obtained yield was not quantitative: for instance, PdO-H₂O (1.42 mol%) or Pd(MeCN)₂Cl₂ (0.1 mol%) gave product **2a** in 71

Table 2. Optimization of the catalyst.^a



Entry	Catalyst	time	2a (%) ^b	3a (%) ^b
1	PdO-Fe ₃ O ₄ (0.13)	10 min	100	0
2	-	10 min	0	0
3	Nano-Fe ₃ O ₄ (6.48)	10 min	0	0
4	Micro-Fe ₃ O ₄ (6.48)	10 min	0	0
5	PtO/Pt ₂ O-Fe ₃ O ₄ (0.13)	10 min	40	7
6	Au ₂ O ₃ -Fe ₃ O ₄ (0.13)	10 min	0	0
7	Cu/CuO-Fe ₃ O ₄ (0.13)	10 min	0	0
8	Ru ₂ O ₃ -Fe ₃ O ₄ (0.13)	10 min	0	0
9	IrO ₂ -Fe ₃ O ₄ (0.13)	10 min	0	0
10	CoO-Fe ₃ O ₄ (0.13)	10 min	0	0
11	NiO-Fe ₃ O ₄ (0.13)	10 min	0	0
12	Rh ₂ O ₃ -Fe ₃ O ₄ (0.13)	10 min	0	0
13	Ag ₂ O/Ag-Fe ₃ O ₄ (0.13)	10 min	0	0
14	OsO ₂ /OsO ₂ (OH) ₂ -Fe ₃ O ₄ (0.13)	10 min	0	0
15	NiO/Cu-Fe ₃ O ₄ (0.19/0.22)	10 min	0	0
16	PdO/Cu-Fe ₃ O ₄ (0.17/0.13)	10 min	76	22
17	Pd/C (1.18)	10 min	100	0
18	Pd/C (1.10)	7 h	70	30
19	PdO-H ₂ O (1.85)	10 min	100	0
20	PdO-H ₂ O (2.06)	7 h	0	100
21	PdCl ₂ (3.87)	10 min	100	0
22	PdCl ₂ (4.05)	7 h	0	100
23	Pd(AcO) ₂ (0.10)	10 min	100	0
24	Pd(AcO) ₂ (0.10)	7 h	100	0
25	Pd(MeCN) ₂ Cl ₂ (0.10)	10 min	100	0
26	Pd(MeCN) ₂ Cl ₂ (0.10)	7 h	100	0

^a Reaction carried out using compound **1a** (0.1 mmol) in 0.2 mL of solvent. ^b Conversion determined by GC using tridecane as internal standard.

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or 89% yield respectively, after 5 min. Moreover, standard palladium homogeneous catalyst like Pd(AcO)₂ or Pd(MeCN)₂Cl₂ were unable to promote the hydrolysis reaction at longer reaction times, recovering quantitatively the compound **2a** unchanged (Table 2, entries 24 and 26).

Once the best catalytic settings were established (in terms of catalyst and reaction conditions), the scope of this catalytic transformation was evaluated (Table 3). The magnetite-impregnated Pd catalyst showed a wide applicability and tolerance to functional groups at α position of the acid function with one of the lowest metal catalyst loadings reported.^{7,8} Lower temperatures (50 °C) were required when aliphatic substituents were attached at that position (entry 3) in order to perform the reaction selectively. The influence of the length of aliphatic chain was also studied; when a methylene unit was added to the alkynoic acid, the cycloisomerization process was turned slower, compared with the final hydrolysis, finding only a small amount of **2c** (detected by GC), with the ketoacid **3c** being the main product (entry 5). As previously observed for

other catalytic systems,^{7,8} alkynoic acids containing longer aliphatic chain ($n = 3$) were inactive towards cycloisomerization (entry 6). Once the length of alkyl chain was discovered as a crucial parameter, the relative position of the triple C-C bond was also evaluated. Thus, the reaction using a highly challenging internal alkynoic acid gave the expected cyclic compound **2e** with an excellent result (entry 7), although the reaction time must be increased. This observed experimental fact is consistent with the *trans* addition of the acid/imide group on the alkyne, which is activated by π -coordination to Pd. It should also be pointed out that for this internal alkyne: *i*) the addition was regioselective, since only Z-product was detected in the crude mixture; and *ii*) no traces of the corresponding 6-membered ring, resulting from an *endo* instead of an *exo* cyclization, were detected, thus providing a new insight of the high selectivity of the catalytic system. As expected, the corresponding ketoacid **3e** was obtained just by increasing the reaction time (entry 8). After the good results obtained for the cycloisomerization of alkynoic acids in water, we decided to

Table 3. Scope of the cyclization of alkynoic acids and derivatives by PdO-Fe₃O₄.

Entry ^a	R ¹	R ²	R ³	X-Z	n	time	Product	Yield (%) ^b
1	H	H	H	O	1	10 min	2a	100 ^c
2	H	H	H	O	1	7 h	3a	100
3	Me	Me	H	O	1	1 d	2b	55 ^d
4	Me	Me	H	O	1	1 d	3b	92
5	H	H	H	O	2	45 h	3c	98
6	H	H	H	O	3	3 d	3d	0 ^e
7	H	H	Ph	O	1	1 d	2e	96
8	H	H	Ph	O	1	4 d	3e	75
9	H	H	H	N-Ts	1	8 h	2f	30 ^f
10	H	H	H	N-Ts	1	1 d	3f	95
11	CO ₂ Me	H	H	N-Ts	1	5 h	2g	95 ^g
12	CO ₂ Me	H	H	N-Ts	1	2 d	3g	83
13	CO ₂ Me	Allyl	H	N-Ts	1	2 d	2h	97
14	CO ₂ Et	Me	H	N-Ts	1	5 h	2i	95 ^g
15	CO ₂ Et	Me	Et	N-Ts	1	4 d	2j	76

^a Reaction carried out using compounds **1a-j** (0.1 mmol), 0.5 mg of catalyst (0.13 mol% Pd) in 0.2 mL of solvent. ^b Isolated yield. ^c Yield determined by GC using an internal standard. ^d Reaction carried out at 25 °C. ^e The starting compound **1d** was recovered unchanged.

^f 25% of **3f** and 40% of starting **1f** were detected by ¹H NMR of crude mixture. ^g Reaction carried out at 50 °C.

focus our attention in the cycloisomerization of alkynyl sulfonylimides, in which the intramolecular addition of a N-H bond across the carbon-carbon triple bond facilitates the formation of the corresponding alkylidene lactams (Scheme 1).^{6p,13} Cycloisomerization of alkynyl imides is usually more challenging than that of their corresponding carboxylic acid counterparts as typically demands the employment of organic solvents as reaction media. Thus, there are really few examples in the literature which describe the cycloisomerization of alkynyl imides in water and under aerobic conditions.^{8j, n} Bearing in mind the mentioned precedents, we observed that the magnetite-impregnated Pd catalyst also proved to be compatible with *N*-tosyl derivatives (entries 9-15, Table 3). Cyclization of **2f** (entry 9) proceed so slowly in comparison with the hydrolysis reaction (entry 10) that only 30% of compound **2f** could be isolated after 8 h, with the starting reagent and keto derivative **3f** being detected in the crude mixture. Functional groups such as ester (entries 11 and 14) or allyl (entry 13) were compatible with the cyclization, finding that in these cases the process was totally selective.

Finally, most of the substrates (either cyclic lactones or lactams) underwent successfully the hydrolysis reaction, giving rise to the corresponding keto acids or imides (entries 2, 4, 5, 8, 10 and 12). However, when the bulkiness of substitution at α position was increased, the corresponding hydrolysis products were not observed (entries 13-15).

Taking into account the following noteworthy catalytic features: *i*) the aforementioned higher activity of impregnated palladium on magnetite on the cycloisomerization of compound **1a**; *ii*) the possibility of reusing the aqueous reaction media for further transformations;¹⁴ and *iii*) the easy catalyst recycling (just by using an external magnet) after its use;¹⁵ we decide to study the recyclability of our catalytic system (Figure 1), which is considered to be a crucial point in the direction of *Sustainable Chemistry* for many industrial processes.¹⁵

For this purpose, after the completion of the reaction, the mixture was extracted with ethyl acetate, in order to remove all

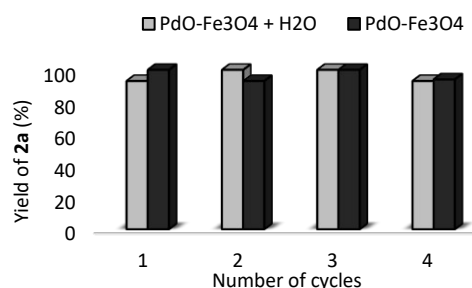


Figure 1. Recyclability of the PdO-Fe₃O₄ + H₂O and PdO-Fe₃O₄.

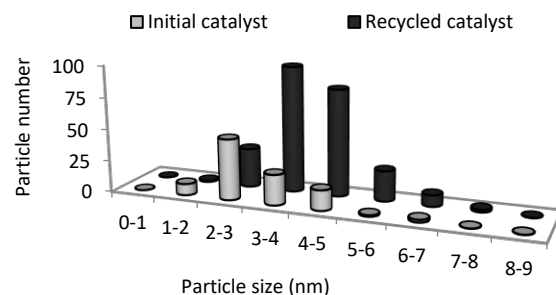


Figure 2. Particle size distribution of fresh and recycled catalyst

organic compounds, and the mixture of water and catalyst, were reused under the same reaction conditions. Taking advantage of the magnetic properties of our catalyst we also investigated its recovery by magnetic decantation and fresh solvent was used. In both cases, the catalytic system could be recycled up to 4 consecutive times without any decrease in catalytic activity or selectivity.

In order to study the heterogeneity of the reaction, a simple hot-filtration experiment was carried out. Thus, the cycloisomerization reaction of **1e** was performed under standard conditions and after 5 h the catalyst was recovered by magnetic decantation and the alkynoic acid **1a** was added to the homogeneous solution. After 10 minutes at 90 °C, the GC analysis of crude mixture showed the presence of compounds **2e** (40%) and **2a** (37%). This experimental result seems to indicate that a partial lixiviation of the active species from the surface of catalyst to the water solution occurs.

The nanosize distribution of the palladium heterogeneous catalyst was measured after recycling process (Figure 2). The particle size distribution showed a small overall increase, observing that, after the reaction, nanoparticles tend to sinter, giving a mean value of 4.0 ± 1.1 nm in comparison with the initial mean value of 3.1 ± 1.0 nm.

Furthermore, the ICP-MS analysis of the solution after the catalytic reaction showed the leaching of a small amount of palladium (7.1% of the initial amount) and iron (0.1% of the initial amount), which is in accordance with the results obtained in the hot-filtration experiment. Other experiments were carried out in order to study palladium leaching. When Pd/C was employed as catalyst under optimized conditions the ICP-MS analysis of water solution showed a similar leaching of palladium in comparison with PdO-Fe₃O₄ (6.4% of the initial

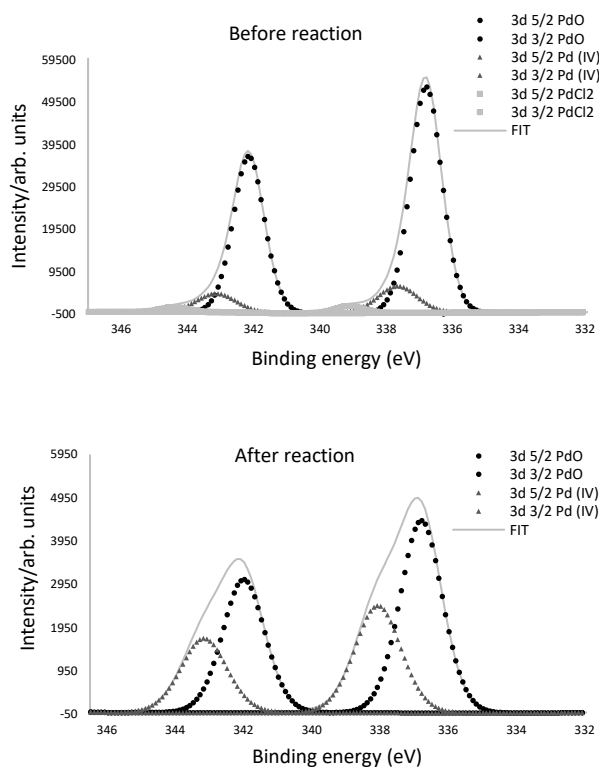
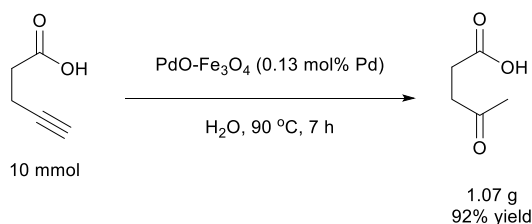


Figure 3. XPS of fresh and recycled palladium catalyst.

amount). However, no leaching of palladium was observed when PdO-Fe₃O₄ was treated with either an acid (butyric acid) and alkyne (1-hexyne) substrate (proportion 1:1) in water or only in the presence of water at 90 °C.

XPS analysis was performed to confirm the oxidation state of the catalyst after the catalytic reactions. Thus, this analysis showed that a portion of the initial palladium(II) is oxidized to palladium(IV), but this slightly modification seemed not to change the initial activity of the catalyst (Figure 3).

Finally, to prove the applicability of the process, the model reaction was performed on a gram-scale (Scheme 2). This reaction, performed with 4-pentynoic acid **1a** (10 mmol) in 20 mL of water as solvent was stirred at 90 °C for 7 hours, cooled to room temperature and extracted with 2-MeTHF (5 mL), a potential sustainable alternative solvent. The organic phase was evaporated to dryness and analysed by ¹H NMR (see Supporting Information) to afford 1.07 g of pure product **3a** (92% yield) without the need of chromatography purification.



Scheme 2. Gram-scale reaction. Isolated product **3a** in 92% yield without chromatography purification.

Experimental

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General

Solvents and reagents were used as obtained from commercial sources and without purification. ¹H NMR (300 MHz) spectra were recorded on Bruker AC-300 NMR spectrometers respectively in proton coupled mode. ¹³C NMR (75.5 MHz) spectra were recorded on Bruker AC-300 NMR spectrometers respectively in proton decoupled mode at 20 °C; chemical shifts are given in δ (parts per million) and coupling constants (*J*) in Hertz. Low-resolution mass spectra (EI) were obtained at 70 eV on an Agilent Technologies GC/MS-5973N spectrometer or Agilent 5973 Network spectrometer with Direct Insertion Probe (73DIP-1), giving fragment ions in *m/z* with relative intensities (%) in parentheses. High-resolution mass spectra (EI) were obtained at 70 eV on an Agilent 7200 flight (Q-TOF) spectrometer with Direct Insertion Probe (73DIP-1), giving fragment ions in *m/z* with relative intensities (%) in parentheses. Infrared spectra were measured on a Jasco FT/IR-4100 Fourier Transform Infrared Spectrometer. Melting points were obtained with a Reichert Thermovar apparatus. XPS analyses were carried out on a VG-Microtech Mutilab. TEM images were obtained on a JEOL, model JEM-2010 equipped with an X-ray detector OXFORD INCA Energy TEM 100 for microanalysis (EDS). XRF analyses were obtained on a PHILIPS MAGIX PRO (PW2400) X-ray spectrometer equipped with a rhodium X-ray tube and a beryllium window. The chromatographic analyses (GC) were determined with a Younglin 6100 instrument equipped with a flame ionization detector and 30 m HP-5 capillary column (0.25 mm diam, 0.33 mm film thickness), using nitrogen (2 mL/min) as a carrier gas, *T*_{injector} = 270 °C, *T*_{column} = 60 °C (3 min) and 60-270 °C (15 °C/min), *P* = 12 psi. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV₂₅₄ light. Column chromatography was performed using silica gel 60 of 40-63 mesh. The ICP-MS analyses were carried out on a Thermo Elemental VG PQ-ExCell spectrometer.

Synthetic procedures

General procedure for the preparation of PdO-Fe₃O₄ catalyst. To a stirred solution of PdCl₂ (345 mg, 2 mmol), KCl (2 g, 26 mmol, to increase the palladium solubility) in deionized water (240 mL) was added micro-Fe₃O₄ (8 g, 34 mmol). After 10 min at room temperature, the mixture was slowly basified with NaOH (1 M) until pH around 13. The mixture was stirred during 24 hours at room temperature in air. After that, the catalyst was filtered and washed with deionized water (3 x 10 mL). The solid was dried at 100 °C during 24 h in a standard glassware oven, obtaining the expected catalyst: incorporation of palladium of 2.74 % according to XRF.

General procedure for the preparation of DESSs. A mixture of hydrogen-bond donor and hydrogen-bond acceptor, with the previously specified molar ratio, was added in a round bottom flask under an inert atmosphere. The mixture was stirred for 60

minutes in a T range between 65 and 80 °C obtaining the corresponding DES.

General procedure for the preparation of starting material. 2,2-Dimethylpent-4-ynoic acid (**1b**), N-tosylpent-4-ynamide (**1f**) and 5-Phenylpent-4-ynoic acid (**1e**) were prepared according to reported procedures.¹³

General procedure of cycloisomerization reactions. In a 10 mL glass tube, the catalyst PdO-Fe₃O₄ (0.5 mg), the corresponding substrate (0.1 mmol) and the solvent (0.2 mL), were added. Subsequently, the tube was sealed with a septum and heated to the corresponding temperature for the time necessary for each starting reagent. After the reaction was completed, the tube was cooled. Then, the mixture was quenched with water and extracted with AcOEt (3 × 1 mL). The organic phases were dried over MgSO₄, followed by evaporation under reduced pressure to remove the solvent and purified by column chromatography.

Procedure for catalyst recycling. The reaction was performed according to the general procedure. After 10 minutes, the mixture was extracted with ethyl acetate, dissolving all organic compounds, in such a way that water and catalyst remained in the reaction tube. To the remaining mixture, compound **1a** was added, carrying out the reaction again under the same reaction conditions.

On the other hand, in order to recycle only the catalyst, we extracted the product with water and AcOEt (3 × 1 mL) and then, decanting the solution with the aid of a magnet, the catalyst remained in the reaction tube. Then, fresh water and compound **1a** were added to the tube, carrying out the new reaction under standard conditions.

Conclusions

In conclusion, we have demonstrated that palladium(II) oxide impregnated on magnetite is a cheap, selective, versatile and very active catalyst for the cycloisomerization of a variety of alkyne acids and their derivatives (*i.e.*, alkynyl imides). The little amount of palladium catalyst used is one of the lowest palladium catalyst loading ever reported. Moreover, the reactions were found: *i*) to be highly regio- and stereoselective, resulting in selective formation of the *exo*-dig products and, for internal alkynes, selective formation of the *Z* configuration product; *ii*) to take place under air and in sustainable solvents (water and DES); *iii*) to occur in the absence of co-catalysts (no bases, acids or halogen extractors are required); and *iv*) to be recycled in four consecutive runs without loss of activity or selectivity. Thus, and all-in-all, we have presented a highly efficient and sustainable methodology (that takes place under standard bench conditions) for the synthesis of highly-substituted heterocycles (either five-membered lactones or lactams) or acyclic keto-acids or keto-imides, that involves a maximum atomic economy and the use of green solvents, which makes the sustainability of the whole process extremely high.

Conflicts of interest

There are no conflicts to declare.

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