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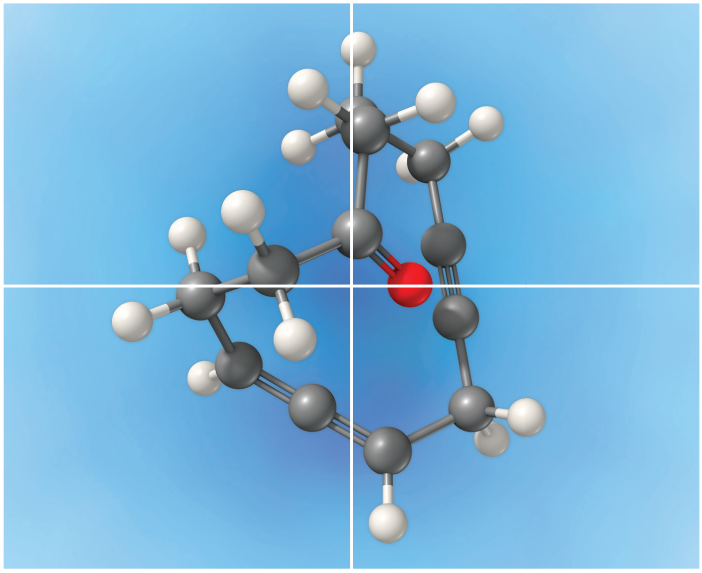

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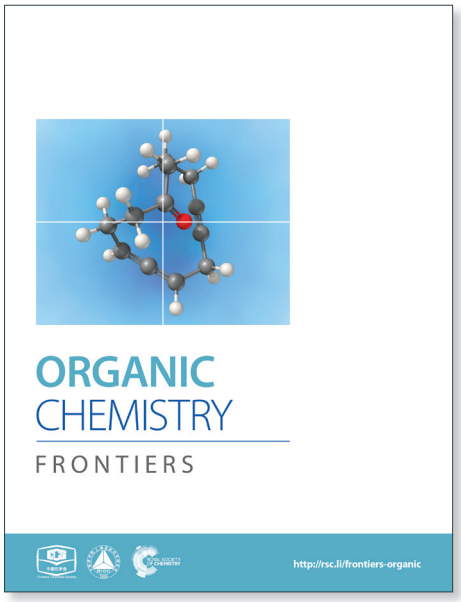

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ARTICLE

Palladium nanoparticles in glycerol: clear-cut catalyst for one-pot multi-step processes applied in the synthesis of heterocyclic compounds

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Palladium nanoparticles immobilised in a glycerol phase have been successfully applied in multi-step syntheses of heterocycles by a one-pot/one catalytic precursor approach. Actually, two- and three-component carbonylative couplings followed by an intramolecular cyclisation led to N-substituted (na)phthalimides, isoindole-1-ones and tetrahydroisoquinolin-1,3-diones in high isolated yields. 2-Benzofurans and dihydrobenzofurans could be likewise obtained by Cu-free Sonogashira coupling/hetero-cyclisation tandem processes. Drawing on the dual homogeneous/heterogeneous catalytic behaviour of PdNPs, sequential coupling/cyclisation/hydrogenation transformations were efficiently carried out, without isolation of intermediates. The Pd-based catalytic glycerol phase was recycled up to ten times preserving its activity and selectivity.

Introduction

Heterocycles are building blocks commonly present in a large variety of products, such as molecular materials, natural and biologically active compounds and also in regularly marketed drugs. For that reason, sustainable synthetic strategies have turned into a crucial current research. From this viewpoint, one-pot procedures involving metal-catalysed multi-step transformations represent powerful methodological means, which prevent the isolation (and purification) of intermediates leading to selective and advantageous processes.[1] As very well-established, palladium is a potent tool in organic synthesis, mainly due to its high efficiency, selectivity and ability to perform a wide range of appealing transformations (C-C and C-heteroatom bond formation reactions, hydrogenations and carbonylations, among the most representative ones).[2,3] In particular, Pd-catalysed reactions have found a great success in the synthesis of heterocyclic compounds, mostly those containing nitrogen and oxygen as heteroatoms.[4,5] In the main part of reports, molecular-based palladium catalytic species are generated in situ from metallic salts in the presence of ligands (in the most cases, phosphines),[6] although ligand-free systems can also give the expected heterocycles, often using relative high amounts of catalysts (higher than 2 mol%) and/or hazardous solvents.[7]

With the aim to recycle the catalytic phase, Pd-supported catalytic systems have led to the synthesis of heterocyclic compounds, mainly on carbon[8] and carbon nanotubes.[9] However, few studies using preformed palladium nanoparticles (PdNPs) have been applied in this frame.[10,11]

Looking for versatile Pd-based catalysts for the preparation of heterocycles, we decided to use the palladium catalytic system based on metal nanoparticles dispersed in neat glycerol (**PdNP**, stabilised by TPPTS, meaning Tris(3-sulfoPhenyl)Phosphine TriSodium salt), upon previously proving their efficiency and recyclability in C-C cross-couplings, C-heteroatom bond formations and C=C bond hydrogenations.[12] Actually, we have recently reported the application of metal nanoparticles homogeneously dispersed in neat glycerol (based on Pd and Cu_2O) in several organic transformations.[12,13] This eco-friendly solvent offers, among others, the significant advantage to suitably immobilise the catalyst, allowing an easy recycling of the catalytic phase.[14]

To the best of our knowledge, preformed PdNPs immobilised in a liquid phase were not used in the synthesis of heterocycles before this present work. We then planned to synthesise N- and O-containing heterocycles (Fig. 1), by means of Pd-catalysed one-pot protocols in glycerol medium.

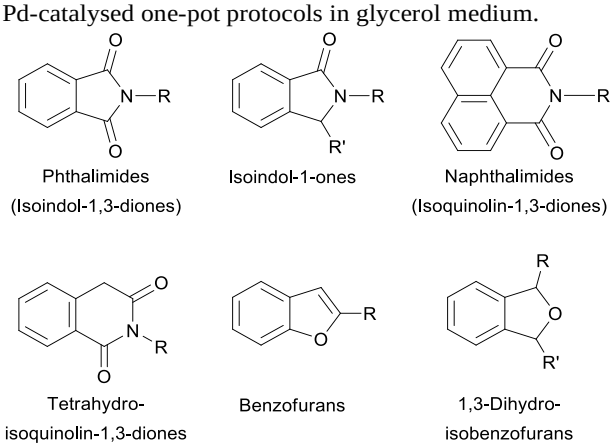
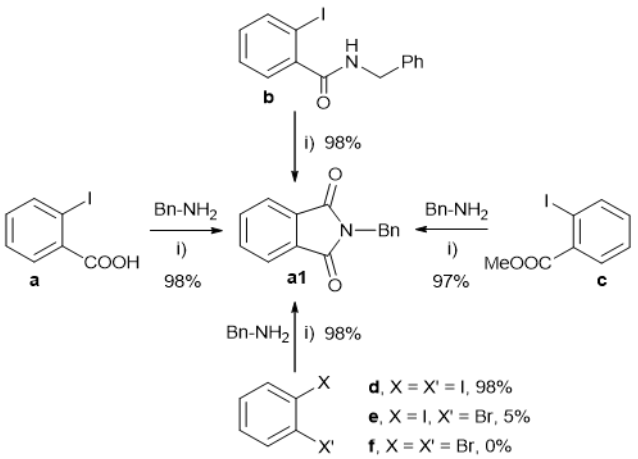


Fig. 1 Heterocyclic compounds synthesised through Pd-catalysed one-pot procedures.

Results and discussion

Pd-catalysed carbonylation/intramolecular amination domino processes

Both N-substituted indol-1,3-diones and isoquinolin-1,3-diones find many interesting applications in different fields such as medicinal chemistry and materials (*e.g.* polymers, fluorosensors).[4c] Phthalimides and naphthalimides are conventionally prepared via condensation of the corresponding anhydrides with primary amines, often requiring harsh conditions especially when steric hindered alkyl amines are involved.[15] Since the pioneering works of Heck concerning Pd-catalysed carbonylations,[16] many groups have applied this strategy in particular for the synthesis of heterocyclic compounds.[4c] The main part of works concerns homogeneous catalysts based on the assembly of Pd(II) salts and phosphines in usual organic solvents.[17] More recently Alper has employed phosphonium-based ionic liquids as solvents, recycling only twice the catalytic phase.[18] Bhanage has found efficient supported catalytic systems based on Pd-NHC complexes on polymers[19a] and palladium salts/imidazolium ionic liquids on silica,[19b] for the synthesis of phthalimides, allowing a catalyst recycling up to four times. The heterogeneous Pd/C catalyst was also efficient under harsh conditions, showing in addition the advantage of its recyclability (up to 8 times).[19c] However preformed non-supported PdNPs dispersed in a liquid phase for the synthesis of heterocycles, have not previously reported.[10]



Scheme 1. Pd-catalysed carbonylative cyclisation for the synthesis of **a1**. Reaction conditions i): 2.5 mol % **PdNP**, glycerol, 0.5 bar CO, DABCO, 120 °C, 0.5 h.

Benzylamine and carbon monoxide in the presence of DABCO using **PdNP** in glycerol as catalyst were chosen as benchmark conditions in order to evaluate the nature of substrates in the synthesis of N-substituted phthalimides (Scheme 1 and Scheme S1 in the Supporting Information for the synthesis of **PdNP**). No important differences were found using the most typical starting materials, it means the 2-iodobenzamide (**b**, methyl 2-iodobenzoate (**c**) and 1,2-diiodobenzene (**d**). Bromo-aryl derivatives, such as 2-bromoiodobenzene (**e**) and 1,2-dibromobenzene (**f**) were not active. But using 2-iodobenzoic acid (**a**), more convenient and cheaper substrate, the efficiency of the catalytic system was preserved. It is important to underline the low CO pressure (0.5 bar) and high activity of the catalytic system (full conversion was achieved in 0.5h) to give 98% yield of **a1**. The catalytic phase was reused up to 10 times without loss of activity, isolating the phthalimide **a1** with yields ranging between 94 and 98%, by extraction with dichloromethane from the glycerol phase (Fig. 2). The catalytic solution remained stable after recycling as evidenced by TEM analysis (see Fig. S1 in the Supporting Information). No palladium was detected by ICP-AES analyses for the isolated products obtained after each run.

We then extended the scope of this protocol for the synthesis of N-substituted phthalimides using different primary amines (Table 1). Heterocycles with yields higher than 90% were obtained: benzyl- (**a1**-**a8**) and alkyl- (**a9**-**a16**) derivatives, including bulky primary amines (**a11**, **a15**-**a16**). The catalytic system was also compatible with different functions, such as alkynes (**a17**), alkenes (**a18**-**a21**), amino- (**a22**-**a23**) and oxygen-based (**a8**, **a24**-**a28**) functionalities. Some optically pure amine were also used as reagents (**4**, **6**, **13**, **16**); no racemization was observed under the catalytic conditions employed (as shown by HPLC analysis of **a4**; see Supporting Information).

This Pd-catalysed three-component reaction was also successfully applied in the synthesis of 1,8-naphthalimides (**g6, g8-9, g12, g16** and **g24,** Table 1), using 1,8-diiodonaphthalene as substrate, commonly employed in the literature.[20]

Unfortunately, the **PdNP** catalytic system was not active when anilines were involved as nucleophiles.

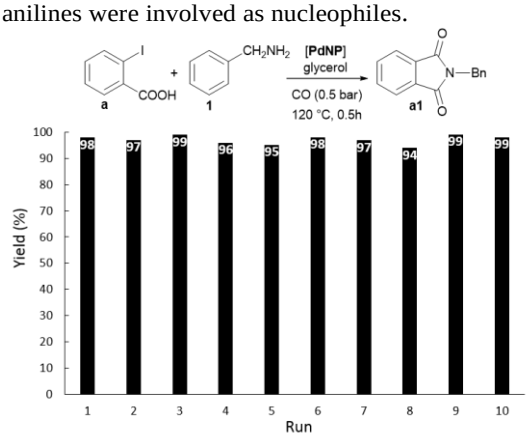


Fig. 2 Pd-catalysed aminocarbonylation of 2-iodobenzoic acid and benzylamine. Diagram showing the recycling of the catalytic phase. Figures indicate the isolated yield of **a1** after each run.

Polyheterocyclic compounds could be also synthesised from the bis(amines) **29**-**31** and tris-benzylic amine **32** by reaction with 2-iodobenzoic acid, giving the corresponding bis- (**a29**-**a31**) and tris-phthlamides (**a32**) in high yields (90-98%) (Fig. 3 and Scheme S2 for their syntheses).

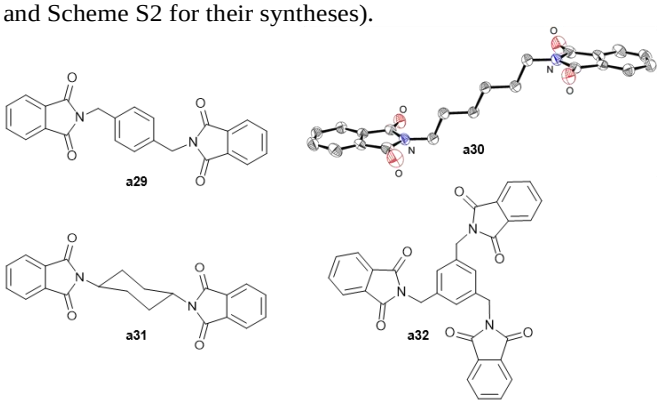
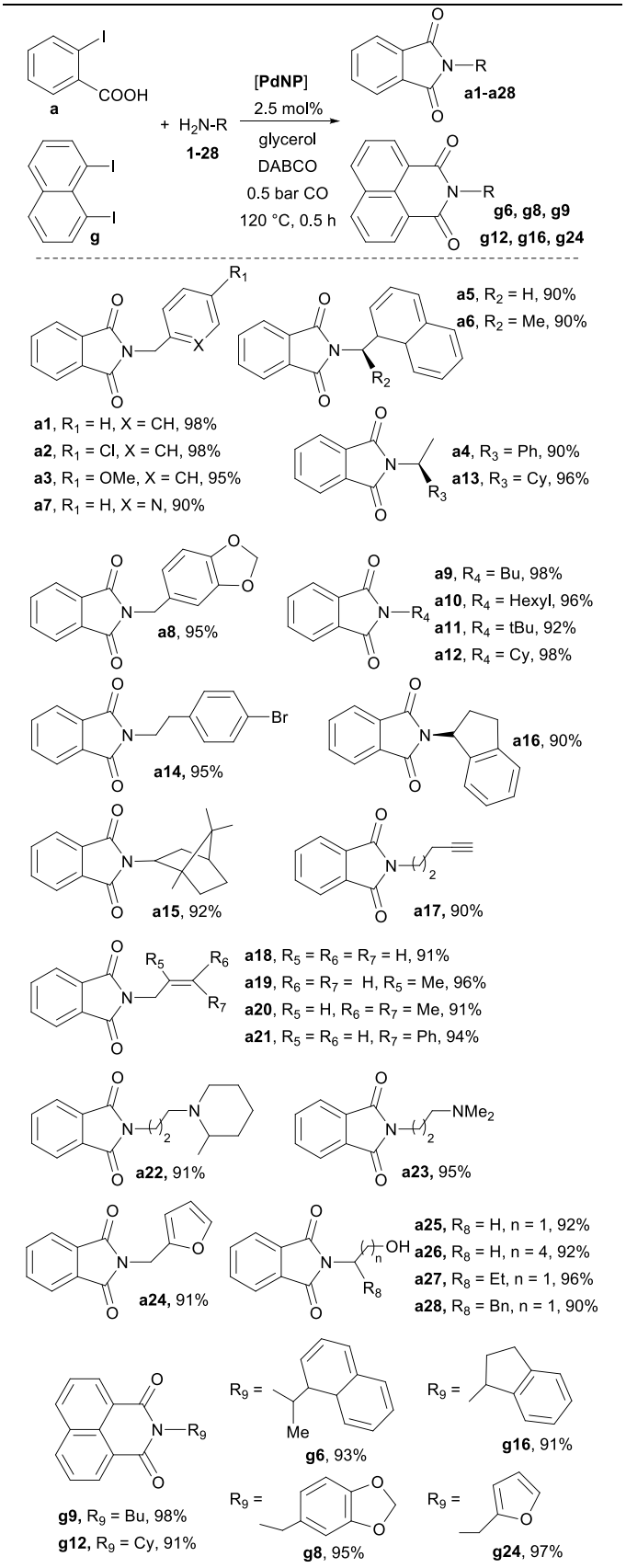


Fig. 3 Poly-phthalimides **a29**-**a32** synthesised by one-pot Pd-catalysed aminocarbonylation. For **a30**, a molecular view (ellipsoids drawn at 50% probability) of its X-ray diffraction structure is given; hydrogen atoms are omitted for clarity.

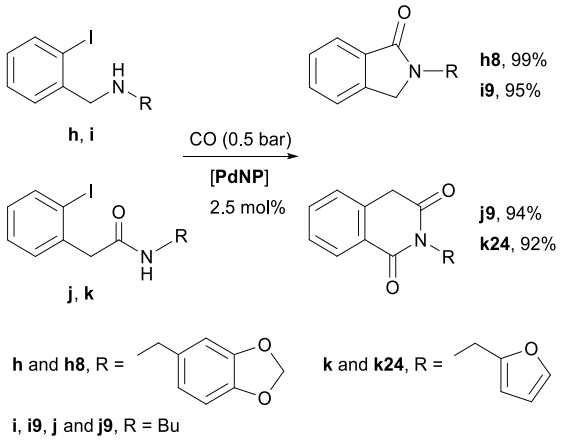
Table 1. Pd-catalysed three-component carbonylative cyclisations for the synthesis of N-substituted isoindol-1,3-diones (**a1**-**a28**) and isoquinolin-1,3-diones (**g** derivatives).[a]



[a] Reaction conditions: 1 mL of glycerol using a iodo-based substrate/amine/palladium ratio = 40/40/1. Yields refer to

isolated products. See Table S1 for reagents and products structures.

Preformed substrates (**h-k**) allowed the synthesis of isoindole-1-ones (**h8**, **i9**) and tetrahydroisoquinoline-1,3-diones (**j9**, **k24**) through a Pd-catalysed two-component carbonylative cyclisation process under the same catalytic conditions described above for the preparation of (na)phthalimides (Scheme 2).



Scheme 2. Pd-catalysed two-component carbonylative cyclisations for the synthesis of N-substituted isoindole-1-ones (**h8, i9**) and tetrahydroisoquinolin-1,3-diones (**j9, k24**). Reaction conditions: glycerol, DABCO, 120 °C, 0.5 h.

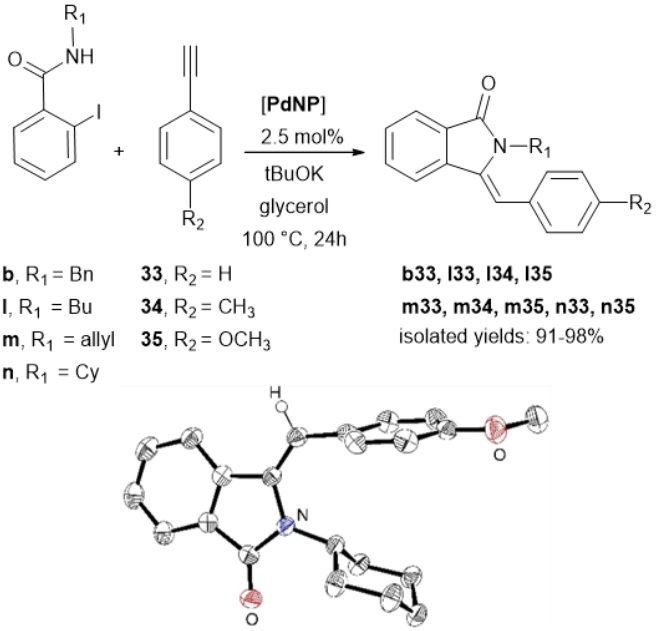
Pd-catalysed C-C Sonogashira cross-coupling/intramolecular cyclisation domino processes

The synthesis of highly substituted heterocyclic compounds represents an intense research axis due to their presence in frequent natural compounds and drugs.[21] Several metal-catalysed methodologies have been developed including domino Cu-catalysed tandem reactions,[22] Sonogashira carbonylative couplings in ionic liquids[23] or Heck/Suzuki-Miyaura domino processes,[24] also under microwaves activations.[25]

In this frame, we planned the synthesis of N-substituted 3-(arylmethylene)isoindolin-1-ones through Pd-catalysed Cu-free Sonogashira coupling followed by intramolecular cyclisation, under CO-free conditions starting from 2-halobenzamides and the corresponding terminal alkynes (Scheme 3).[26]

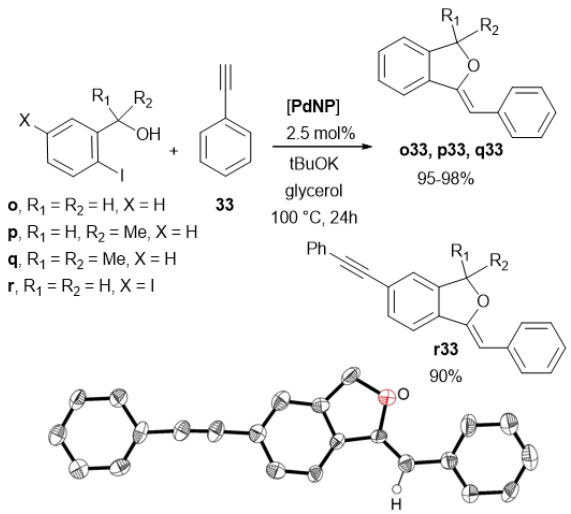
The heterocyclic compounds were isolated in yields higher than 90%, exclusively giving the *Z* isomer, proved by the X-ray diffraction structure of **n35**. These results are in agreement with those reported using Pd/Cu-catalysed C-C coupling/heteroannulation domino reactions, demonstrating that after the C-C coupling, the alkynyl compound triggers an *anti*-addition leading to the corresponding heterocycle.[27,28]

Following the same domino strategy but using 2-iodo benzyl alcohols (**o**-**r**) and phenols (**s**, **t**) as substrates, **PdNP** in glycerol efficiently gave the regio- and stereo-selective synthesis of (Z)-1-methylene-1,3-dihydroisobenzofurans (Scheme 4) and 2-substituted benzofurans (Table 2), respectively. The diiodo-benzyl alcohol **r** led to the bifunctional compound **r33** using the same catalyst; its X-ray diffraction structure also confirmed the (*Z*)-stereochemistry (Scheme 4).



Scheme 3. Pd-catalysed Sonogashira coupling followed by intramolecular amination for the synthesis of (*Z*)-3-(arylmethylene)isoindolin-1-ones. For **n35**, a molecular view (ellipsoids drawn at 50% probability) of its X-ray diffraction structure is given; hydrogen atoms are omitted for clarity, except that involved in the exocyclic C=C bond.

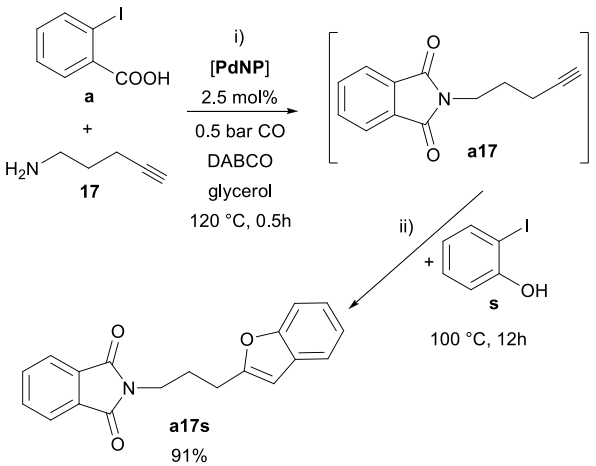
In relation to benzofurans (Table 2), it is important to note the behaviour observed using 1,7-octadiyne (**40**); the relative ratio of the phenol **s** and dialkyne **40** (**s**/**40** = 1/1 or **s**/**40** = 2/1), gave the alkyne-benzofuran **s40** or the bis(bezofuran) **s40s**, respectively (Table 2). This selectivity permitted to isolate **s40** in high yield, which in turn could be involved in the synthesis of polyheterocyclic compounds such as **s40u** (Scheme 6).



Scheme 4. Pd-catalysed Sonogashira coupling followed by intramolecular amination for the synthesis of (*Z*)-1-methylene-1,3-dihydroisobenzofurans. For **r33**, a molecular view (ellipsoids drawn at 50% probability) of its X-ray diffraction structure is given; hydrogen atoms are omitted for clarity, except that involved in the exocyclic C=C bond.

Drawing on the versatility and robustness exhibited by **PdNP** in glycerol together with its compatibility vis-à-vis different kind of reagents, we carried out a one-pot methodology for the synthesis of a polyfunctional molecule containing two different heterocycles by one-pot sequential process: carbonylation/intramolecular amination followed by a Sonogashira coupling (Scheme 5). Actually, the bis(heterocyclic) **a17s** was selectively obtained, without isolation of the phthalimide intermediate (**a17**).

With the same aim on mind, we coupled two different catalysts in the same medium, **PdNP** and **Cu_2ONP**,[12,13] which gave bis(heterocyclic) compounds bearing a benzofuran or phthalimide moiety and a triazole group, without isolation of the corresponding intermediates **a17** and **s40** (Scheme 6). Both compounds were obtained in excellent yields and fully characterised, including their X-ray diffraction structures.



Scheme 5. Synthesis of the bis(heterocyclic) phthalimide/benzofuran compound **a17s** by a one-pot sequential process catalysed by **PdNP** in glycerol.

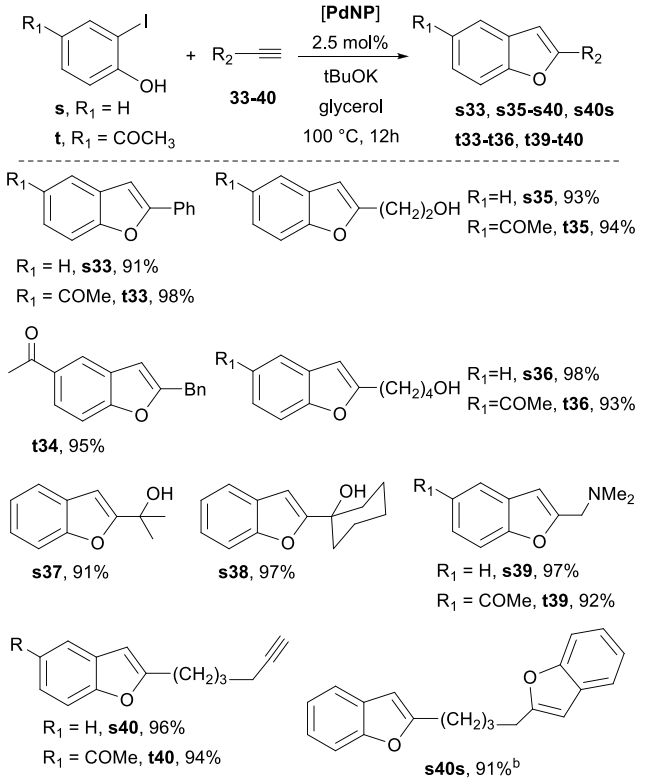
Pd-catalysed heterocycle formation followed by hydrogenation

After proving the efficiency of **PdNP** in glycerol in the synthesis of different kinds of heterocycles by C-C bond formations and heteroannulations, we decided to use the same catalytic system in one-pot sequential processes involving a hydrogenation step, taking advantage of the dual catalytic reactivity exhibited by MNPs dispersed in a liquid phase, *i.e.* their molecular- and surface-like reactivity behaviour.[12,29]

For that, we carried out the sequential coupling/cyclisation/hydrogenation process, using **PdNP** as single catalytic precursor (Scheme 7). Therefore, upon formation of the phthalimides **a18**-**a21**, the system was pressurised with dihydrogen (1 bar) without isolation of the phthalimide intermediates; the corresponding hydrogenated compounds **a18H**-**a21H** were obtained in high yields (> 90%) (Scheme 7a).

Following the same approach, 1-benzyl-1,3-dihydroisobenzofuran (**o33H**) and the 3-(4-substituted-benzyl)isoindolin-1-one derivatives **l33H-l35H**, **m33H-m35H** and **n35H** were efficiently prepared (Scheme 7b and 7c).

Table 2. Synthesis of 2-substituted benzofurans (**s33**, **s35-s40**, **t33-t36** and **t39-t40**) by Pd-catalysed Sonogashira coupling followed by intramolecular cyclisation.[a]

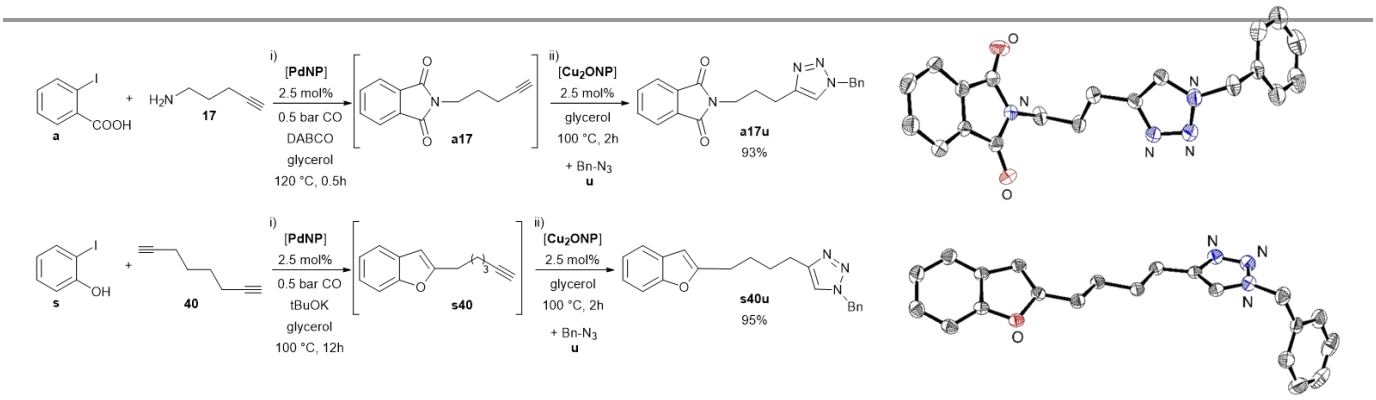


[a] Reaction conditions: 1 mL of glycerol using a iodo-based substrate/alkyne/palladium ratio = 40/40/1. Yields refer to isolated products. [b] Iodo-based substrate/alkyne/palladium ratio = 80/40/1. See Table S2 for reagents and products structures.

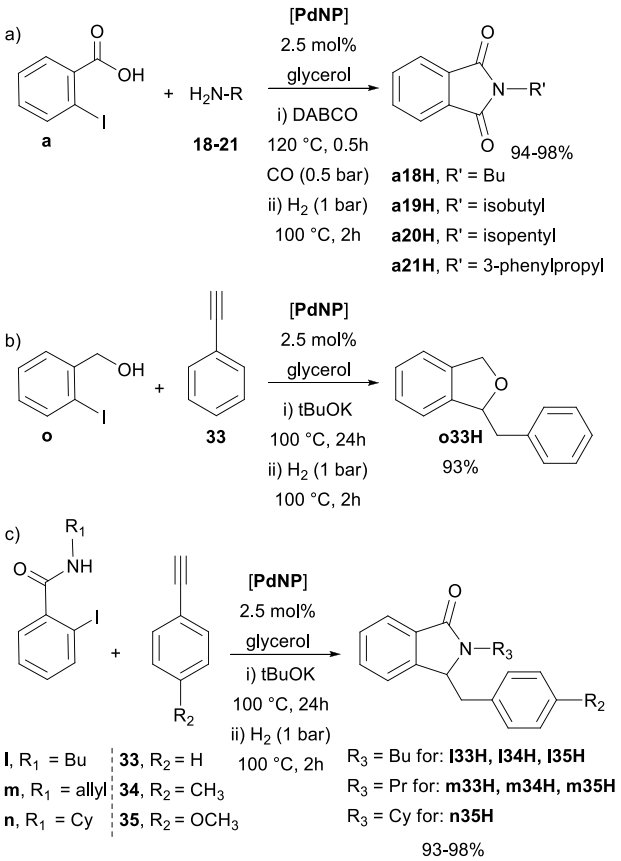
Conclusions

To sum up, we could efficiently applied PdNPs dispersed in neat glycerol and stabilised by TPPTS in a large panel of reaction conditions, leading to the synthesis of heterocyclic compounds: (na)phthalimides, isoindole-1-ones, tetrahydroisoquinolin-1,3-diones, (*Z*)-3-(arylmethylene)isoindolin-1-one and (*Z*)-1-methylene-1,3-dihydroisobenzofurans. One-pot tandem and/or sequential methodologies gave the desired products without isolation of the generated intermediates. Furthermore compounds containing two heterocycles could be isolated, even using in the same medium two different catalysts, Pd and Cu_2O based nanoparticles. The Pd-based glycerol phase could be recycled up to ten times without loss of reactivity.

Applications of palladium nanocatalysts stabilised by chiral agents in enantioselective processes are currently underway.



Scheme 6. Pd- and Cu-catalysed one-pot multi-step sequential processes for the synthesis of polyheterocyclic compounds, **a17u** and **s40u**. Molecular views (ellipsoids drawn at 50% probability) of their X-ray diffraction structures are given; hydrogen atoms are omitted for clarity



Scheme 7. One-pot coupling/cyclisation/hydrogenation multi-step processes catalysed by **PdNP** in glycerol.

Acknowledgements

Financial support from the Centre National de la Recherche Scientifique (CNRS) and the Université Paul Sabatier are gratefully acknowledged. F. C. thanks the CNRS and Région Midi-Pyrénées for a PhD grant.

Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: Experimental procedures, copies of NMR spectra and X-ray diffraction data. See DOI: 10.1039/b000000x/

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