



Heterogeneous palladium multi-task catalyst for sequential Heck-reduction–cyclization (HRC) reactions: influence of the support

Oier Ibarguren^a, Cécile Zakri^b, Eric Fouquet^a, François-Xavier Felpin^{a,*}

^a Université de Bordeaux, CNRS, Institut des Sciences Moléculaires (ISM), 351 Cours de la Libération, 33405 Talence, France

^b Université de Bordeaux, CNRS, Centre de Recherche Paul Pascal, Avenue Schweitzer, 33600 Pessac, France

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ABSTRACT

An evaluation study of various palladium supports led to the selection of charcoal as the most efficient system for the preparation of oxindoles by sequential Heck-reduction–cyclization (HRC) reactions. The in situ prepared Pd/C was not recyclable for further cross-coupling reactions but remains still highly active for reduction processes. The sustainable chemistry described herein allows extremely simple experimental protocol under mild conditions, free of any base, ligand and additive.

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In the context of sustainable chemistry, the development of transition metal-based heterogeneous multi-task catalysts is a recent concept which shows good promise for carrying out one-pot reactions.¹ Preparative procedures in which two or more consecutive transformations are carried out in the same reaction vessel offer a number of advantages to the organic chemist: especially, they result in a reduced number of operations, giving significant time-cost, labour, resource management and waste generation benefits.² Moreover, they allow the preparation of elaborated structures from relatively simple starting materials.

Two different approaches have been proposed for executing several transformations in the same reaction vessel with heterogeneous multi-task catalysts. (1) The first approach involves a heterogeneous mono-metallic catalyst in which the metal is able to promote several consecutive reactions. Conceptually straightforward to establish for consecutive reactions having a similar mechanism,³ this approach remains much more challenging when different mechanisms are involved in a one-pot process due to the high specificity of the metal.⁴ (2) This issue has been addressed, in a second approach, by using heterogeneous multi-metallic catalysts.⁵ Such a strategy appears much more convenient and flexible since each metal plays a specific and often unique role in promoting the one-pot multi-step sequence. However, the preparation of

heterogeneous multi-metallic catalysts is a quite difficult task and has limited further developments in this area. It should be noted that while a heterogeneous multi-metallic catalyst considered as a unique entity could be classified as a multi-task catalyst, each metal considered independently could not.

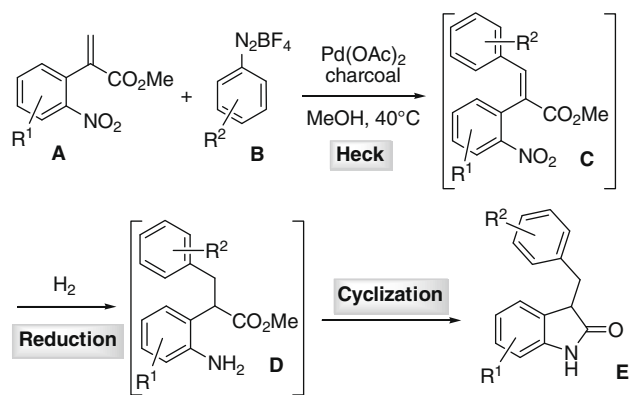
We recently reported our own contribution relating the use of Pd/C as catalyst for the preparation of novel oxindoles by sequential Heck-reduction–cyclization (HRC) reactions.⁶ Our strategy exploited the dual reactivities⁷ of an in situ-generated Pd/C catalyst with an experimentally simple protocol making use of highly reactive diazonium salts under base-free, ligand-free and additive-free conditions.⁸ We selected charcoal as the support for its low cost, inertness, stability and high surface area. Moreover, charcoal is prepared from renewable resources (vegetal or animal), a crucial point for the development of sustainable chemistry.

However, we were interested in evaluating other kinds of supports which feature similar advantages to charcoal including low cost and high surface area. In this Letter we wish to report our investigations towards the selection of the most efficient support for the HRC strategy (Scheme 1).

We selected methyl 2-(2-nitrophenyl)acrylate **1** and 4-(methoxycarbonyl)benzene-diazonium tetrafluoroborate **2** as coupling partners in our model system (Table 1). Preliminary experiments showed that the Heck cross-coupling works well either with or without addition of charcoal. This observation suggests that a quasi-homogeneous catalysis is operating, as already observed by other groups.⁹ If such, the active catalyst is soluble

* Corresponding author. Tel.: +33 4000 6285; fax: +33 4000 6286.

E-mail addresses: fx.felpin@ism.u-bordeaux1.fr, fx.felpin@lcoo.u-bordeaux1.fr (F.-X. Felpin).



Scheme 1. General strategy of the HRC approach.

Table 1
Screening of various supports

Entry ^a	Support	$\text{Pd}(\text{OAc})_2$ (mol %)	Yield ^b (%)
1	—	5	52
2	PANI	5	20
3	CeO_2	5	65
4	MgO	5	— ^c
5	Zeolite	5	74
6	Graphite	5	65
7	MWNT ^d	5	78
8	MWNT	2	70
9	Charcoal	5	83
10	Charcoal	2	63
11	Charcoal ^e	2	70
12	Charcoal ^f	2	75
13	Charcoal	0	0

^a Reaction conditions: Acrylate (1 mmol), diazonium salt (1.2 mmol), $\text{Pd}(\text{OAc})_2$ (1–5 mol %) and support (90%Pd, w/w) in MeOH (6 mL) at 40 °C for 0.5–1 h (Heck coupling), then H_2 for 24 h.

^b Yield of isolated product.

^c Degradation.

^d MeOH (10 mL) was used.

^e The reduction was carried out for 48 h.

^f One equivalent of HBF_4 was added.

palladium nanoparticles leached in the solvent resulting in similar mechanism whatever the homogeneous or heterogeneous nature of the pre-catalyst. However, in the absence of a support the subsequent reduction–cyclization steps proceeded partially, resulting in a moderate yield of oxindole **3** (entry 1). This result clearly indicated the requirement of a support able to promote smoothly the reduction stage. The use of polyaniline (PANI) as an organic support proved to be incompatible with the reaction conditions due to its extensive decomposition (entry 2). Metallic oxides are not useful on the whole process although Pd/MgO has been recently described as an efficient catalyst for sequential Heck–reduction reactions.^{7f} The use of zeolite led to oxindole **3** along with unidentified by-products (entry 5). Moreover, after filtration of the catalyst, at the end of the HRC process, an important leaching of palladium was detected in solution leading to an unacceptable contamination level. We finally screened three different forms of carbon-based material including graphite, multi-wall carbon

nanotubes (MWNTs) and activated charcoal. From these three supports, charcoal gave the highest results while graphite produced non-negligible quantities of *N*-hydroxyoxindole due to the partial reduction of the nitro group along with the expected oxindole **3**. This by-product was also detected in very minor quantity with MWNT and charcoal at a 5-mol % palladium loading. However, decreasing the amount of palladium to 2 mol % resulted in the formation of larger quantities of *N*-hydroxyoxindole (corresponding to a partial reduction of the nitro group) and, consequently, lower yields of **3**. Charcoal proved to be the best support in our system, leading to high yield (83%) of oxindoles **3** at 5 mol % Pd. This result could be explained by the strong affinity of palladium nanoparticles with charcoal as confirmed by ICP-MS analysis of the filtered solution. Indeed, more than 99.99% of the initial quantity of introduced palladium under the form of $\text{Pd}(\text{OAc})_2$ is retained on the charcoal after the HRC process. Moreover, the HBF_4 produced during the Heck cross-coupling (1 equiv/diazonium salt) is not detrimental to the integrity of the charcoal while an opposite behaviour has been observed with PANI. We also observed a slight increase in the yield when one additional equivalent of HBF_4 is added to the reaction mixture¹⁰ during the reduction–cyclization sequence (entry 12). When palladium was omitted no reaction occurred indicating a genuine palladium-catalyzed reaction (entry 13).

Based on the ICP-MS results showing a total adsorption of palladium on the charcoal, we assume that a 10% w/w Pd/C was generated in situ. After a simple filtration, the catalyst was separated from the reaction mixture and dried under vacuum.

TEM analysis showed a wide distribution of the nanoparticles with an average size of 30 nm and uniform dispersion on the charcoal (Fig. 1).

We explored the recycling potential of the in situ prepared Pd/C. Unfortunately, the recycled catalyst showed a strong deactivation for the Heck cross-coupling (Scheme 2, Eq. 1) involved in the preparation of oxindole **3**. This deactivation was also observed with a less demanding cross-coupling involving methyl acrylate **5** (Scheme 2, Eq. 2). We attributed these disappointing results to the reduced form (Pd^0) of the reused Pd/C catalyst. Indeed, we have previously reported that Heck reactions catalyzed by Pd/C require a Pd^{II} pre-catalyst.¹¹ We attempted without success a re-oxidation of the Pd^0/C to the more reactive $\text{Pd}^{\text{II}}/\text{C}$ using iodine as reported by de Vries and co-workers.¹² We noticed that the presence of iodine ions completely inhibited the catalytic activity. However that point

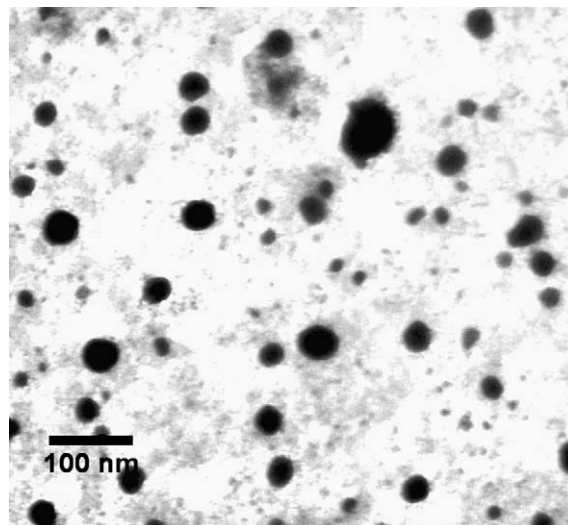
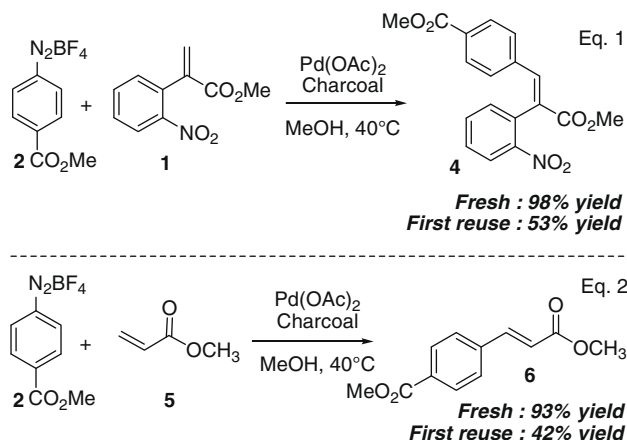


Figure 1. TEM images of the Pd/C catalyst in situ generated.

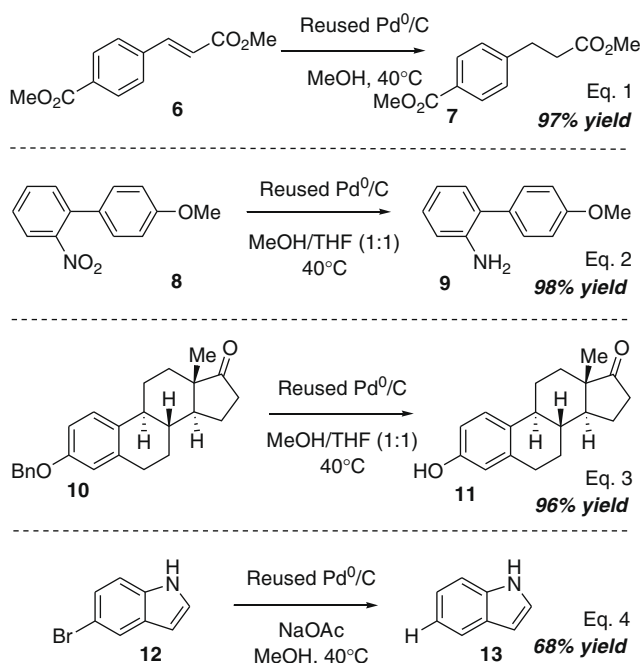


Scheme 2. Recycling studies for the Heck reaction.

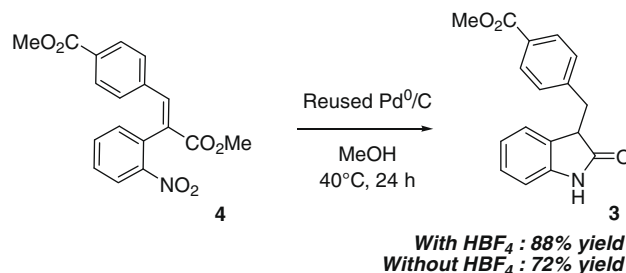
does not preclude the overall process as from an industrial point of view, heterogeneous catalysts are rarely reused directly after filtration and an inexpensive standard combustion procedure is preferred for the reactivation.

In order to support our hypothesis, we examined a set of reactions where a Pd^0 is required (Scheme 3). Therefore, we exploited the reductive properties of the recycled catalyst for the reduction of acrylate **6** (Eq. 1) and 2-nitrobiphenyl **8** (Eq. 2), the debenzyla-tion of oestrogen **10** (Eq. 3) and the debromination of bromoindole **12** (Eq. 4). In contrast with the recycling experiments conducted on the Heck reaction, we noticed a high activity of the catalyst involved in reduction processes leading to good to high yield of compounds **7**, **9**, **11** and **13**. These observations confirm that the prepared Pd^0/C remains an active catalyst for reduction purposes but cannot be used further for the Heck cross-coupling where a $\text{Pd}^{\text{II}}/\text{C}$ would be required.

During the optimization studies of the support, we established the beneficial effect of HBF_4 on the rate of the reduction (Table 1, entry 11). In order to understand in depth the role of HBF_4 in the HRC sequence, we compared the reduction of the Heck intermediate **4** for the synthesis of oxindole **3** (Scheme 4).



Scheme 3. Recycling studies for various reductive transformations.

Scheme 4. Study of the HBF_4 effect.

To our surprise, we noticed a decrease in the conversion in the absence of HBF_4 , resulting in a significant drop in the yield. Therefore, HBF_4 could not be considered as a waste of the first step (Heck cross-coupling) since it acts as a co-catalyst for the subsequent transformations. This intriguing behaviour has not been reported previously although a related concept has been recently described with an indium catalyst for a domino imine formation Diels–Alder reaction.¹³

In summary, this work showed that the strong affinity of palladium nanoparticles for robust, inexpensive and non-toxic charcoal could be efficiently exploited in one-pot sequential reactions. Our studies demonstrated that the experimental simplicity is not antagonist to the reaction efficiency. Indeed, the HRC strategy allows the succession of 4 steps in one pot under mild conditions with a simple in situ-generated Pd/C catalyst and does not require any base, ligand and additive. We believe that such a research of experimental simplicity associated to the synthesis of useful biologically relevant heterocycles will be of increased interest in the context of sustainable chemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.084.

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