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Palladium-Catalyzed Heck Coupling-Hydrogenation: Highly Efficient One-Pot Synthesis of Dibenzyls and Alkyl Phenyl Esters

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Abstract: An efficient method for the synthesis of industrially important dibenzyls and alkyl phenyl esters *via* sequential Heck coupling and hydrogenation of the alkenyl double bond in one pot with a single recyclable catalyst under mild conditions has been realised. The catalyst was recovered by simple filteration and reused for several cycles with consistent activity.

Keywords: dibenzyls; molecular hydrogen; nanocrystalline magnesium oxide; one-pot synthesis; palladium(0)

Introduction

Organic synthesis employing heterogeneous catalysts has several beneficial effects on the environment since it involves the reuse of precious metal catalysts, thus forming less waste and resulting in lower metal contamination in the final pharmaceutically important molecules.[1] In an ideal setting one could make a double benefit of the heterogeneous catalysis by using the same active system for multiple reactions in one-pot.

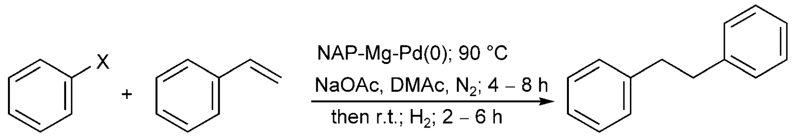
One of the major challenges faced by the fine chemicals industry in recent times is the synthesis of these target molecules by a large number of different reaction steps involving elaborate work-up and refining procedures.[2] The recently introduced one-pot synthetic approach[3] not only helps to improve atom economy, but also reduces the number of steps in isolation and purification of the intermediate compounds in the case of a multistep synthesis.[4]

A series of homogeneously catalyzed reactions reportedly illustrate the applicability of this strategy.[5] However, the negative mutual interactions taking place when all the reactions are run in the presence of the same catalysts poses a problem.[6] To overcome this problem, Arai and co-workers[7] have reported the application of bimetallic Pd and Ru immobilized on silica for the simultaneous hydrogenation of C=O and C=C bonds and consecutive Heck reaction followed by hydroformylation. The limitation in this system is that the activity of the catalyst remains connected to the individual activity of the single supported metal and a number of different metal complexes are required to be immobilized. Thus, a single supported metal catalyst, which is applicable to the overall reaction, is most useful in this context.

The versatility of palladium catalysts is established in a variety of transformations in organic synthesis.[1,8] Therefore, supported palladium catalysts became the best choice to be applied to multistep catalytic syntheses.

Dibenzyls form important substructures of several natural and synthetic compounds such as lunularic acid, an antifungal agent and bifluranol,[9] an anti-androgen agent. Recently, Djakovitch and co-workers[10] reported the synthesis of dibenzyls in one pot by using Pd on activated carbon. A palladium-catalyzed synthesis of biaryl derivatives *via* tandem Heck arylation-hydrogenation was reported by Fagnou and co-workers.[11] Later Corma and co-workers[12] synthesized important fragrances like alkyl phenyl esters by using heterogeneous palladium catalysts.

We have earlier reported Suzuki and Stille cross-coupling reactions[13] using a ligand-free nanocrystalline magnesium oxide-stabilized palladium(0) catalyst. Later, we have applied the same catalyst for the effi-



Scheme 1. Palladium-catalyzed synthesis of dibenzyl *via* Heck coupling and *in situ* reduction.

cient synthesis of organic amines from the corresponding nitro compounds in the presence of molecular hydrogen as the reductant under ambient conditions.[14]

Herein, we report a practical and atom economic synthesis of dibenzyls in good to excellent yields by a sequential Heck coupling reaction of haloarenes (chloro, bromo and iodo) and styrenes followed by hydrogenation of the resulting stilbenes by employing molecular hydrogen under atmospheric pressure (Scheme 1) using nanocrystalline magnesium oxide-stabilized palladium [NAP-Mg-Pd(0)] catalyst.

Results and Discussion

All the catalysts were prepared by counterionic stabilization of $PdCl_4$ as described in the literature.[13,14]

To identify the ideal reaction conditions, a diverse range of supported palladium catalysts were screened using bromobenzene and styrene as model substrates for the sequential reaction and results are summarized in Table 1. A variety of solvents and bases are also screened (see Supporting Information). After the completion of the Heck reaction under an N_2 atmosphere, the reaction mixture was cooled to room temperature and the atmosphere of the reaction vessel was replaced by hydrogen after flushing out the remaining nitrogen.

Optimum yield of the product (98%) was obtained by using [NAP-Mg-Pd(0)] (Table 1, entry 1). No products were formed when the reaction was carried out in the absence of palladium. When the reaction was carried out in the presence of $Pd\text{-}SiO_2$ and added base, the Heck coupling step proceeded very sluggishly to form stilbene (5%), but the hydrogenation step did not proceed even at elevated temperatures (Table 1, entry 2). Pd-C also failed to form any perceptible amount of product in the hydrogenation step although a small amount of stilbene was formed in the coupling step under our reaction conditions (Table 1, entry 3). Pd-MgLaO showed equal efficiency in the Heck coupling reaction albeit the hydrogenation step proceeded with only moderate yield of product (70%) (Table 1, entry 4). Pd-LDH (Mg-Al layered double hydroxides) also catalyzed the coupling reaction with equal ease but was inactive for the hydrogenation step under ambient pressure (Table 1, entry 5), whereas $Pd\text{-}Al_2O_3$ and $Pd\text{-}TiO_2$, yielded the coupling product in good yields but the hydrogenated product was obtained under a hydrogen pressure of 5 bar (Table 1, entries 6 and 7). Homogeneous $PdCl_2$ required a much higher temperature to yield a trace amount of the Heck coupled product, but no product was detected in the hydrogenation step (Table 1, entry 8).

Table 1. Screening of different palladium-supported catalysts for the synthesis of dibenzyls.[a]

Entry	Catalyst	Time [h][b]	Conversion [%][c]	Time [h][d]	Conversion [%][e]
1	NAP-Mg-Pd(0)	4.0	98	3.0	98
2	$Pd\text{-}SiO_2$	4.0	5	3.0	-
3	Pd-C	4.0	8	3.0	-
4	Pd-Mg-LaO	4.0	98	3.0	70
5	Pd-LDH	4.0	98	3.0	-
6	$Pd\text{-}Al_2O_3$[f]	4.0	52	15.0	83
7	$Pd\text{-}TiO_2$[f]	4.0	98	15.0	80
8	$PdCl_2$	4.0	5[g]	3.0	-

[a] *Reaction conditions:* bromobenzene (1.0 mmol), styrene (1.2 mmol), NaOAc (1.2 mmol), catalyst (1.43 mol%) and DMAc (4.0 mL) were stirred at 100 °C for an appropriate time under an N_2 atmosphere. The reaction mixture was then cooled to room temperature and stirred under an H_2 atmosphere.

[b] Time required for the formation of stilbene.

[c] GC yields of stilbene.

[d] Time required for hydrogenation of stilbene to dibenzyl.

[e] GC yields of dibenzyl.

[f] 0.2 mol% Pd is used, reaction temperature 120 °C; yield is recorded under a hydrogen flow of 5 $mL\,min^{-1}$ (5 bar).[12]

[g] Reaction temperature 135 °C.

The enhanced activity of the catalyst [NAP-Mg-Pd(0)] over the different supported palladium catalysts screened as well as its homogeneous counterparts can be explained by the high basicity and surface area [600 $m^2 g^{-1}$] of nanocrystalline magnesium oxide. The presence of edge-corner and other defect sites allows the nanostructured MgO materials to possess a high concentration of reactive surface ions. The reactive sites on the surface of MgO are as follows: 1)

Table 2. Palladium-catalyzed one-pot synthesis of dibenzyls from haloarenes and styrenes.[a]

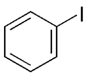
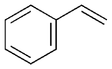
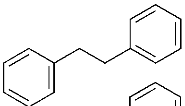
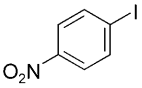
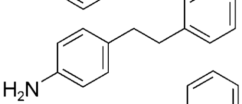
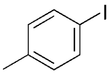
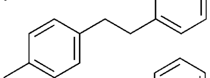
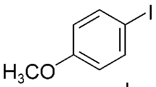
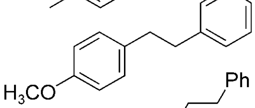
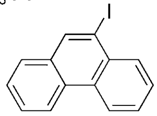
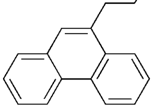
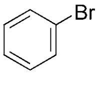
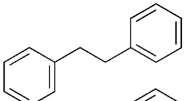
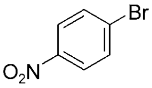
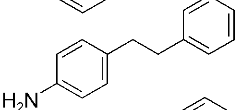
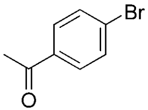
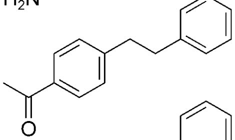
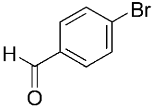
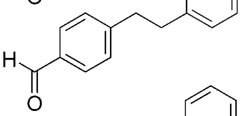
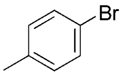
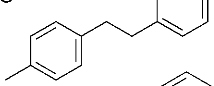
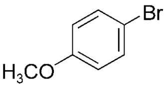
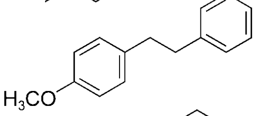
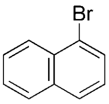
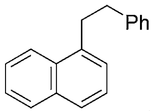
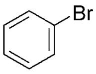
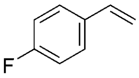
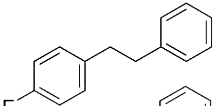
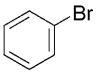
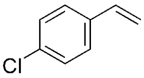
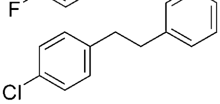
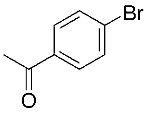
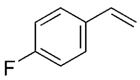
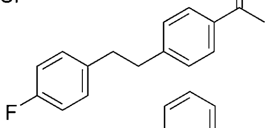
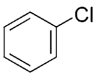
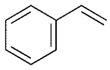
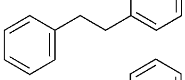
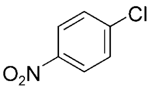
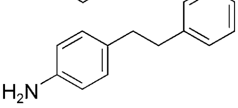
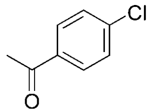
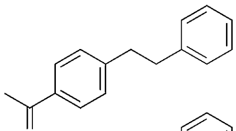
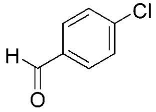
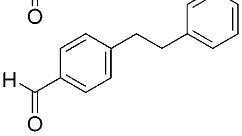
Entry	Haloarene	Alkene	Product[b]	Yield [%][c]
1				98, 96[d]
2				98
3				85
4				82
5				95
6				98
7				98
8				98
9				96
10				85
11				82
12				95
13				98
14				98
15				98
16				75
17				83

Table 2. (Continued)

Entry	Haloarene	Alkene	Product[b]	Yield [%][c]
18				80
19				78

[a] Reaction conditions: aryl halide (1.0 mmol), styrene (1.2 mmol), NaOAc (1.2 mmol), NAP-Mg-Pd(0) (1.43 mol%) and DMAc (4 mL) were stirred at 100 °C for an appropriate time under an N_2 atmosphere. [TBAB (0.2 mmol) was used in the reactions of chloroarenes]. The reaction mixture was then cooled to room temperature and stirred under an H_2 atmosphere (balloon).

[b] All products are characterized by NMR and mass spectroscopy (see Supporting Information).

[c] Isolated yields after column chromatography.

[d] Yield after sixth cycle.

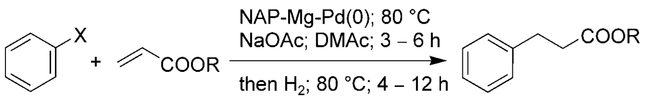
the Mg^{2+} site, which is of the Lewis acid type, 2) the O^{2-} site which is of the Lewis base type, 3) lattice-bound and 4) isolated hydroxy groups and anionic and cationic vacancies. An edge or even more so, a corner O^{2-} anion is coordinatively unsaturated and is seeking Lewis acids to help stabilize and delocalize its negative charge. Conversely, an Mg^{2+} ion on an edge or corner is seeking Lewis bases to stabilize and delocalize its positive charge. Therefore, these coordinatively unsaturated O^{2-} and Mg^{2+} ions readily accept incoming reagents with Lewis acid or Lewis base character.[15,16]

The optimum temperature of the Heck coupling is found to be 90–100°C and the hydrogenation of the resulting stilbenes takes place at room temperature under ambient pressure. Other conditions were then optimized using the same model substrates and [NAP-Mg-Pd(0)] as catalyst (see Supporting Information). The reaction was most productive when dimethylacetamide (DMAc) was used as the solvent and sodium acetate (NaOAc) as base. The use of triethylamine or K_2CO_3 gave the product of Heck coupling but failed to form any hydrogenated product. In the absence of any added base, the highly basic NAP-MgO acts as a base in the case of the Heck coupling reaction to produce the arylated product in 5% yield but no product was obtained from the subsequent step. This is in agreement with the currently accepted mechanism for the Heck reaction which requires stoichiometric neutralization of the hydrohalogenic acid by an appropriate base.[17] Other solvents like dioxane and NMP were found to be less effective. The use of less polar solvents such as toluene drastically decreases the yield of the coupling product (10%). Under these optimized conditions, a number of different haloarenes and styrenes were subjected to this sequence of reactions to produce the corresponding dibenzyls in good to excellent yields (Table 2).

Bromobenzene reacted with styrene quantitatively to produce *trans*-stilbene selectively in the presence of [NAP-Mg-Pd(0)] (Table 2, entry 6). In all the reactions, the ratio of haloarenes to styrenes is 1:1.2 which gives the optimum yield of the product. Under these conditions neither the formation of biaryls resulting from competing homocoupling reaction nor branched derivatives were detected as by-products. To ensure the active species of palladium, which takes part in the reaction, the same reaction (Table 2, entry 6) was run using NAP-Mg-$PdCl_4$ as catalyst instead of [NAP-Mg-Pd(0)] under the same conditions. It was seen that only 10% of the desired product is obtained. Leaching of Pd was noticed during the course of the reaction as determined by atomic absorption spectroscopy (AAS). This is in agreement with the observations reported by Djakovitch and Koehler.[18]

Aryl bromides and iodides containing a variety of substituents underwent this cascade reaction with equal ease. Aryl chlorides (Table 2, entries 16–19) although less reactive, are more desirable substrates than their bromide and iodide counterparts in terms of cost and availability.[19] The reactions with aryl chlorides also proceeded smoothly albeit with slightly lower yields compared to their bromide and iodide analogues. The nitro group present on the aryl bromides and iodides was cleanly reduced to its corresponding amine in addition to the alkenyl double bond under these reaction conditions (Table 2, entries 2, 7, and 17), whereas ketone and aldehyde functionality was preserved (Table 2, entries 8, 9, 15, 18 and 19). The reaction was more facile with haloarenes possessing an electron-withdrawing group in the *para*-position (Table 2, entries 2, 7, 8, 9, and 15). However, presence of an *ortho*-substituent gave only trace amount or no products, this can be attributed to the steric factor. In presence of an electron-donating group, the reaction was found to be slower (Table 2, entries 3, 4, 10, 11). This methodology was further extended to polyaromatic haloarenes (Table 2, entries 5 and 12) successfully.

Later, we successfully extended the scope of the methodology using acrylates as coupling partners under the similar reaction conditions (Scheme 2) to produce alkyl phenylpropionates, which are useful compounds in fragrances and fine chemicals industries.[12]

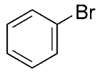
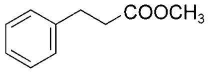
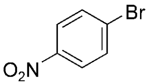
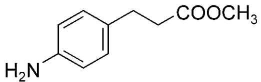
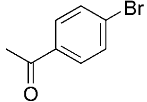
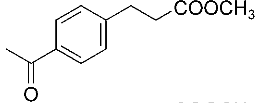
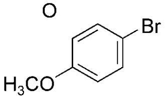
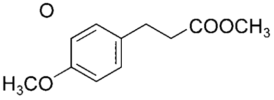
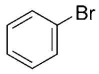
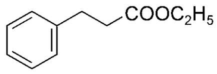
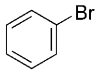
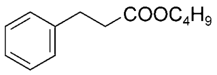
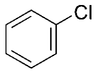
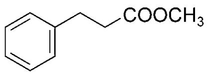
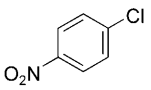
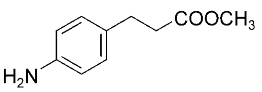


Scheme 2. Synthesis of alkyl phenylpropionates.

The coupling reaction proceeded faster with the acrylates, than with their styrene counterparts, albeit the hydrogenation step was comparatively slower and proceeded only at elevated temperatures. Aryl bromides and chlorides coupled with acrylates with equal efficiency in this cascade reaction and results are summarized in Table 3.

The nitro group was cleanly reduced to the corresponding amine along with the alkenyl moiety (Table 3, entries 2 and 8), while the keto functionally was greatly tolerated under the present reaction conditions (Table 3, entry 3). In the presence of an electron-donating group, the reaction proceeds at higher temperature, and takes a longer time (Table 3, entry 4). Interestingly, the formation of 4-methoxyphenyl propionic acid (20%) was also observed in this case, which may be attributed to the higher temperatures and longer reaction time.

Table 3. Palladium-catalyzed synthesis of alkyl phenylpropionates from haloarenes and acrylates.[a]

Entry	Aryl halide	Alkene	Product[b]	Yield [%][c]
1				85
2				90
3				90
4				78[d]
5				85
6				85
7				78
8				82

[a] *Reaction conditions:* aryl halide (1.0 mmol), acrylate (1.2 mmol), NaOAc (1.2 mmol), NAP-Mg-Pd(0) (1.43 mol%) and DMAc (4 mL) were stirred at 80 °C for an appropriate time under an N_2 atmosphere. The reaction mixture was then cooled to room temperature and stirred under an H_2 atmosphere under ambient pressure at 80 °C.

[b] All products are characterized by NMR and mass spectroscopy (see Supporting Information).

[c] Isolated yields.

[d] Reaction temperature: 120 °C; Reaction time: 12 h.

Reusability of the Catalyst

The final product was isolated from the catalyst by simple filtration after the reaction. The catalyst was washed first with water and then with diethyl ether to remove any excess base and organic material. It was then dried at room temperature and used without any regeneration for further cycles. It was observed that the catalyst showed consistent activity until sixth cycle (Table 1, entry 1). The TEM image of the used catalyst did not show any change in the shape and size of the support as well as the active species, Pd(0). Thus, the morphology of the catalyst remains the same even after several recycles (Figure 1 a and b).

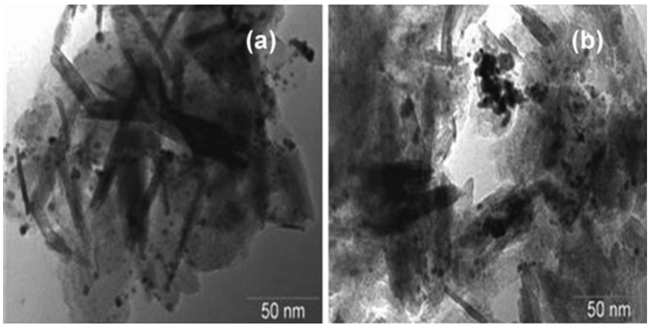


Figure 1. Transmission electron micrographs of (**a**) fresh catalyst, (**b**) used catalyst.

A slight decrease in activity was observed in the subsequent cycles, which may be attributed to the decrease in the surface area due to hydration of the catalyst by water formed in the reaction.[20] No quantifiable amount of leached Pd was detected in the filtrate by AAS.

The effect of the highly basic nanocrystalline magnesium oxide as demonstrated in the formation of the dibenzyls and alkyl phenylpropionates, coupled with the absence of any leached metal in the filtrate suggests that the catalytic process is truly heterogeneous and the reaction occurs on the solid surface.[8c,13,21]

Conclusions

In summary, we have devised a very efficient method for synthesizing industrially important dibenzyls and alkyl phenylpropionates *via* a sequence of a Heck coupling followed by hydrogenation of the alkenyl double bond. Both of these steps are efficiently catalyzed by the recoverable and reusable ligand-free nanocrystalline MgO-stabilized palladium(0) catalyst. The catalyst is easy to handle, shows consistent activity for six cycles, and is cost effective for industrial use.

Experimental Section

The catalyst [NAP-Mg-Pd(0)] was prepared according to the procedure reported in the literature[13,14] (see Supporting Information for details). All other catalysts used were synthesized based on the literature reports.[17,22]

General Procedure for the Synthesis of Dibenzyls and Alkyl Phenylpropionates

In an oven-dried, 10-mL, two-necked round-bottom flask was charged the haloarene (1.0 mmol), styrene or acrylate (1.2 mmol), NaOAc (1.2 mmol), [NAP-Mg-Pd(0)] (0.015 g, 1.43 mol%) and dimethylacetamide (4.0 mL) and the mixture stirred at 100 °C (80 °C for acrylates) under a nitrogen atmosphere for an appropriate time (4–8 h for styrene substrates and 3–6 h for acrylates) The progress of the reaction was monitored by thin layer chromatography (TLC). On the complete formation of the Heck product from the first step, the reaction mixture was cooled to room temperature and the nitrogen atmosphere was replaced by flushing with H_2 *via* a hydrogen-filled balloon. The mixture was then again stirred at room temperature (80 °C for acrylates) under a hydrogen atmosphere for an appropriate time (2–6 h for styrene substrates and 3–12 h for acrylates). After the completion of the reaction as judged by TLC, the reaction mixture was diluted with water (20 mL), and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product, followed by flash chromatography over silica gel (60–120 mesh) column using ethyl acetate/hexane (2:100) v/v as an eluent to afford the pure product.

Supporting Information

Complete experimental details for catalyst synthesis, solvent screening, catalyst optimization studies, ^1H and ^{13}C NMR spectra of the products synthesized are given in the Supporting Information.

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