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ARTICLE TYPE

Pd(II)/Mg-La mixed oxide catalyst for cyanation of aryl C–H bonds and tandem Suzuki-cyanation reactions

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Abstract. Palladium(II)/magnesium-lanthanum mixed oxide (Pd(II)/Mg-La) catalyst is a **reusable** catalyst for cyanation of aromatic C–H bonds by using the combination of NH₄HCO₃ and DMSO as the “CN” source. Moderate to good yields of aromatic nitriles were obtained. An excellent regioselectivity was achieved using the present protocol. A tandem process involving Suzuki coupling followed by cyanation reaction was also developed using the heterogeneous (Pd(II)/Mg-La) catalyst. This cascade process resulted in the formation of aromatic nitrile from simple 2-halopyridine. The catalyst was recovered by centrifugation and reused for three consecutive cycles with nearly consistent activity and selectivity.

Keywords: cyanation, heterogeneous catalysis, palladium, magnesium-lanthanum mixed oxide, tandem reactions, Suzuki coupling, recyclability.

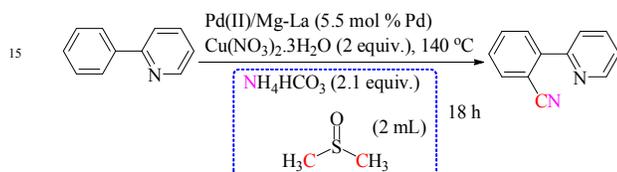
Introduction

Aryl nitriles are valuable intermediates in synthetic organic chemistry since the nitrile group is an important precursor for a broad range of functional group transformations leading to the formation of amines, aldehydes, acids, ketones, amides and heterocycles.¹ Aryl nitriles are also key motifs in pharmaceuticals, agrochemicals, dyes and natural products.² The classical methods for the synthesis of nitrile containing compounds requires pre-functionalization of the arenes with aryl iodides/bromides (Rosenmund-von Braun reaction)³ and aryl diazonium compounds (Sandmeyer reaction).⁴ Other precursors such as aldehydes (Schmidt reaction), aldoximes or primary **carboxamides** are also used in cyanation reactions.^{5–7} In industry, ammoxidation reaction is used to synthesise nitriles from toluene derivatives in the presence of oxygen and ammonia using heterogeneous catalysts at high temperature (around 500 °C) and high pressure. However, these approaches suffer from multiple synthetic steps, high cost, harsh reaction conditions, limited functional group tolerance, and use of toxic cyano sources. Efforts have therefore been directed towards catalytic routes for synthesising aryl nitriles via transition-metal-catalyzed cyanation of haloarenes using the metal bound precursor MCN (M = Cu, Na, K, Zn), TMSCN or K₄Fe(CN)₆ as the source of “CN” unit.^{8–13} Transition-metal-catalyzed C–H bond functionalization reactions have now emerged as one of the most efficient tools in the formation of C–C and C–hetero atom bonds.¹⁴ However, direct cyanation of aryl C–H bonds is comparatively underdeveloped compared to other types of C–H functionalization reactions. The first example of Cu-mediated direct C–H bond cyanation was reported by Yu’s group in 2006. They used 2-arylpyridine as a

substrate and TMSCN or CH₃NO₂ as the “CN” source.¹⁵ Other cyanide sources such as metal cyanides,¹⁶ isocyanides,¹⁷ TsCN,¹⁸ Me₃SiN₃,¹⁹ BrCN²⁰ and acetone cyanohydrine²¹ have been used in transition-metal-catalyzed oxidative cyanation through C–H bond activation. In pursuit of greener and safer “CN” sources for cyanation reaction, recently, Chang and his co-workers reported an elegant and effective cyanation process through Pd catalyzed direct C–H bond functionalization using a combination of DMF and ammonia²² or ammonium iodide²³ as a “CN” source. Very recently, Jiao et al. reported the novel cyanation of heterocycles by using DMF as the cyanating source and as a solvent.²⁴ Cheng et al. pioneered the combined use of NH₄HCO₃ and DMSO as the source of cyanide in the Pd-catalyzed direct cyanation of indoles.²⁵

These cyanating processes not only obviate the need to pre-functionalize the arenes but also use non-toxic single or combined “CN” sources. However, despite their exceptional performance, there are several challenges that have prevented the widespread practical application of transition-metal-catalyzed oxidative cyanation process through C–H bond activation. One such challenge arises due to the inability to recover and reuse expensive transition-metals. Industry favors catalytic processes induced by a heterogeneous catalyst over the homogeneous one in view of its ease of handling, simple workup, and regenerability. Recently, highly basic magnesium-lanthanum mixed oxide (Mg-La mixed oxide) has found excellent applications as a solid base catalyst for various organic transformations.^{26–28} Different transition-metals impregnated Mg-La mixed oxide catalysts have also been developed and used as effective heterogeneous catalysts in **Heck**^{29a} and **Kumada** coupling^{29b} and oxidation reactions.^{29c} Recently, we have

explored the activity of air- and moisture-stable palladium impregnated on Mg-La mixed oxide catalyst (Pd/Mg-La) in chemoselective hydrogenation of olefinic bonds and oxidative sp^2 C-H bond acylation reaction.³⁰ In search for a suitable heterogeneous catalyst for the cyanation of aryl C-H bonds in the presence of other functional groups, we envisaged that Pd(II)/Mg-La mixed oxide could exhibit interesting catalytic activities. Herein, we have explored the activity of this Pd(II)/Mg-La mixed oxide catalyst towards the cyanation of aromatic C-H bonds by using a combination of NH_4HCO_3 and DMSO as the "CN" source to provide aromatic nitriles (Scheme 1).



Scheme 1 Pd(II)/Mg-La mixed oxide catalyzed cyanation of aryl C-H bonds.

Results and Discussion

Preparation of catalyst

The Mg-La mixed oxide was synthesized by co-precipitation of Mg- and La nitrates.^{29a} The Pd-doped Mg-La mixed oxide catalyst (Pd(II)/Mg-La mixed oxide) was prepared by impregnation method (see experimental section, supporting information).

X-ray diffraction patterns

The X-ray diffraction patterns of the fresh and used Pd(II)/Mg-La catalysts revealed the presence of both $\text{La}_2\text{O}_2(\text{CO}_3)$ and PdO phases (Figure 1). Diffraction lines appeared at $2\theta = 29.55^\circ$, 22.84° , 13.1° [ICDD # 23-0435] and

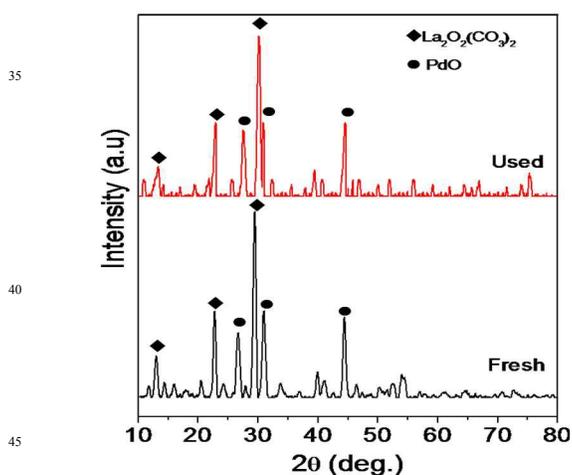


Fig. 1 XRD patterns of the fresh and used Pd(II)/Mg-La mixed oxide catalysts.

their corresponding inter planar spacing values (d) 0.302, 0.389 and 0.675 nm are attributed to lanthanum oxide carbonate phase. The diffraction peaks are observed due to PdO phase at $2\theta = 31.7^\circ$, 45.54° , 27.33° with the corresponding d values of 0.282, 0.199, 0.326 nm that are in good agreement with ICDD # 46-1211. There is no change in the crystal structure of PdO and $\text{La}_2\text{O}_2(\text{CO}_3)$ phases in both fresh and used form of catalysts.

Transmission electron microscope

The transmission electron microscope (TEM) images of fresh and used (after 1st cycle) Pd(II)/Mg-La catalysts are reported in Figure 2a and 2b. The average Pd particle size is measured from TEM and found to be 25 and 33 nm for fresh and used catalysts respectively. Interestingly, it is observed that the shape of the particles remains unchanged. This suggests that the structure and morphology of the palladium particles remains same even after recycling.

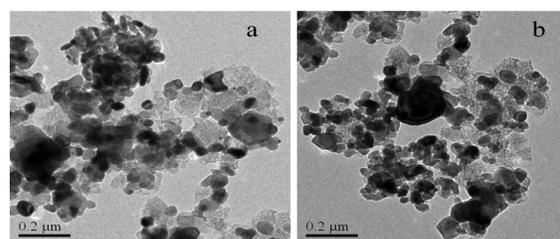


Fig. 2 TEM images of the Pd(II)/Mg-La mixed oxide: a) fresh and b) used catalyst.

X-ray photoelectron spectroscopic analysis

The X-ray photoelectron spectroscopic (XPS) analysis of the fresh and used (after 4th cycle) Pd(II)/Mg-La mixed oxide catalyst is presented in Figure 3. The complete XPS spectrum of Pd(II)/Mg-La (Figure 1, SI) shows XPS signal at binding energy 50.5 eV which corresponds to magnesium in oxidised form.^{30c}

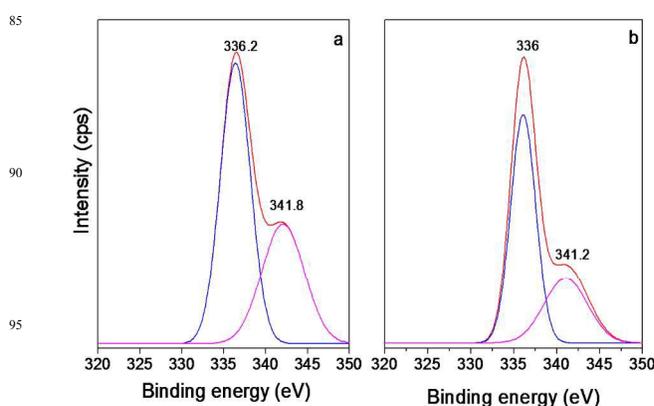


Fig. 3 The XPS spectra of (Pd 3d_{5/2}, 3d_{3/2}) a) fresh and b) used Pd(II)/Mg-La mixed oxide catalysts.

The presence of PdO species on the near surface of the fresh catalyst is confirmed by the appearance of XPS signals at 336.2 eV and 341.8 eV, which corresponds to Pd $3d_{5/2}$ and Pd $3d_{3/2}$ binding energies respectively. The XPS of the recovered catalyst after the fourth cycle showed the $3d_{5/2}$ and $3d_{3/2}$ peaks at 336 eV and 341.2 eV respectively.^{30d}

Optimization conditions

The optimization studies were performed by using 2-phenylpyridine as the model substrate. When 30 mg of Pd(II)/Mg-La mixed oxide catalyst (5.5 mol % of Pd), 1 equiv of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and a combination of NH_4HCO_3 (1 equiv) and DMSO (2 mL) as the cyanating agent were used, the desired product 2-(pyridin-2-yl)benzotrile was obtained in 43% yield (Table 1, entry 1). Encouraged by this result, several optimization studies were conducted by altering the oxidant, nitrogen source and solvents. Results from these studies are summarized in Table 1. An improvement in the product yield is observed when the amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and NH_4HCO_3 is increased from 1 equivalent to 2 and 2.1 equivalents respectively (Table 1, entries 1-3).

Table 1 Screening of reaction parameters.^a

Entry	Oxidant/ equiv.	Nitrogen source/ equiv.	Solvent	Yield (%)
1	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/1$	$\text{NH}_4\text{HCO}_3/1$	DMSO	43
2	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/1$	DMSO	61
3	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	92
4	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	87, 66^b
5	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	48^c, 66^d, 70^e
6	$\text{K}_2\text{S}_2\text{O}_8/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	0
7	TBHP(70% aqueous)/2	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	0
8	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	NH_3 (25% aq)/2.1	DMSO	20
9	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMF	58
10	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	60 ^f
11	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	58 ^g
12	-	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	0
13	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/2$	$\text{NH}_4\text{HCO}_3/2.1$	DMSO	0 ^h

^a Reaction conditions: 30 mg Pd(II)/Mg-La (5.5 mol % of Pd), 2-phenylpyridine (0.5 mmol), solvent (2 mL), 140 °C, 18h, ^b 20 mg catalyst (3.6 mol % of Pd), ^c 10 mg catalyst (1.8 mol % of Pd), ^d 12 h reaction, ^e reaction at 120 °C, ^f using Pd(II)/MgO catalyst, ^g using Pd(II)/La₂O₃ catalyst, ^h without catalyst.

As seen in Table 1, the choice of oxidant has a crucial role in the reaction outcome. Excellent yields of the product was obtained when the oxidant is either $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ or $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (Table 1, entries 1-4). However, we chose to continue the reaction with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, since it is considerably cheaper than $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$. When the amount of palladium was reduced, a decrease in the yield of the product was observed (Table 1, entry 4). Performing the reaction at a lower temperature of 120 °C or for a shorter period of 12 h, has a detrimental effect on the product yield (Table 1, entry 5). Interestingly, there is no reaction using other oxidants such as $\text{K}_2\text{S}_2\text{O}_8$ and aqueous *tert*-butyl hydroperoxide (TBHP) (Table 1, entries 6 and 7). Importantly, we found that the NH_4HCO_3 is a better source of nitrogen in the cyanation reaction than ammonia (Table 1, entry 3 and 8) wherein the yield is 20% only. Remarkably, changing the solvent from DMSO to DMF had a detrimental effect on the yield of the product as only 58% yield was obtained (Table 1, entry 9). The use of other heterogeneous palladium catalysts such as Pd(II)/MgO and Pd(II)/La₂O₃ exhibited inferior yields of the product than the Pd(II)/Mg-La mixed oxide catalyst (Table 1, entries 10 and 11). It is important to note that the presence of both palladium and copper is necessary for the formation of the product (Table 1, entries 12 and 13).

Substrate Scope

Eventually, the catalytic system consisting of Pd(II)/Mg-La (30 mg, 5.5 mol % of Pd), $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (2 equiv.) as the oxidant and the combination of NH_4HCO_3 (2.1 equiv.) and DMSO (2 mL) as the cyanating reagent at 140 °C temperature was chosen for the cyanation reaction of an array of 2-phenylpyridine derivatives and the results are summarized in Figure 4. With 4-methyl 2-phenylpyridine, the corresponding mono cyano derivative was obtained in 82% yield (Figure 4, entry 2). To some extent, the reaction was sensitive to methyl substitution on the meta position of the 2-phenyl ring (Figure 4, entry 3), delivering the product in slightly lower yield than its para counterpart (Figure 4, entries 2 and 3). In contrast, for an electron deficient 4-fluoro, -chloro and -bromo substituted analogues, moderate yields of the products were obtained (Figure 4, entries 4, 5 and 6). Other functional groups such as -CF₃, -CN and -OMe also survived the reaction conditions, giving the corresponding cyano derivatives of 2-phenylpyridine in moderate yields (Figure 4, entries 7, 8, 9 and 10). Remarkably, bulkier 2-naphthyl and 1-naphthyl derivatives of pyridine also furnished the cyanation product with moderate yields under the present reaction conditions (Figure 4, entries 11 and 12). Interestingly, isoquinoline and quinoline could act as directing groups as well, delivering the corresponding aryl nitriles in 79% and 73% yields respectively (Figure 4, entries 13 and 14). Gratifyingly, benzo[*h*]quinoline also demonstrated good efficiency in the current cyanation reaction and produced the corresponding cyanated product in 63% yield (Figure 4, entry 15).

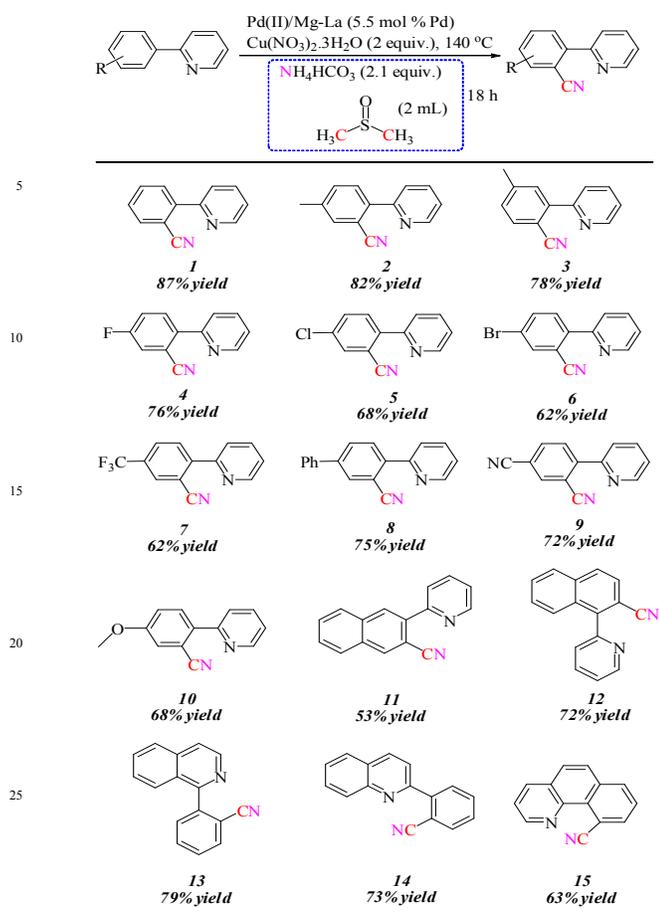


Fig. 4 Substrate scope of the cyanation reaction.

Test of Recyclability

The feasibility of repeated use of Pd(II)/Mg-La mixed oxide catalyst in the cyanation reaction was also examined. In Figure 5, we present the results from the investigation of recycling of the catalyst using 2-phenylpyridine as the model substrate on 1.5 mmol scale. The Pd(II)/Mg-La mixed oxide catalyst shows consistent activity and selectivity up to 4 cycles. After each cycle, Pd(II)/Mg-La mixed oxide catalyst was recovered by simple centrifugation, washed with water (100 mL), oven-dried and used directly for the next cycle without any further purification. No loss of catalytic activity was observed for the catalyst in the cyanation of aryl C–H bonds. Moreover, leaching of the palladium metal after each cycle was determined by AAS (Table 1, SI). From Table 1 (SI) it could be observed that the amount of palladium is nearly consistent in each of the cycles, which indicates the absence of leached palladium species in the solution.

To know the heterogeneity of the catalyst, we have carried out two experiments. In the first experiment, the reaction was terminated after three hours. At this juncture, the catalyst was separated from the reaction mixture at the reaction temperature (140 °C) and the reaction was continued with the filtrate for an additional 18 hours. The conversion was found

to remain almost identical before and after removal of catalyst. In the second experiment, the Pd(II)/Mg-La mixed oxide catalyst was stirred at 140 °C for ten hours and the filtrate was used for the cyanation reaction. No product formation was observed. Hence from these two experiments, it could be concluded that the reaction proceeds under heterogeneous conditions and that there are no leached palladium species in the solution.

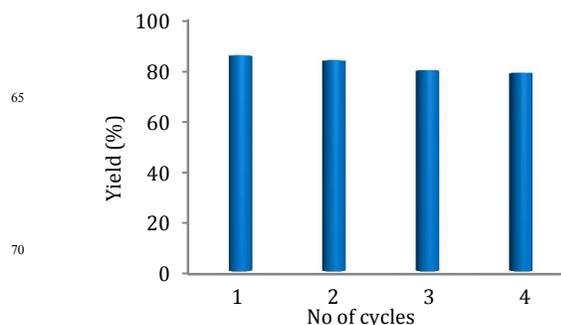
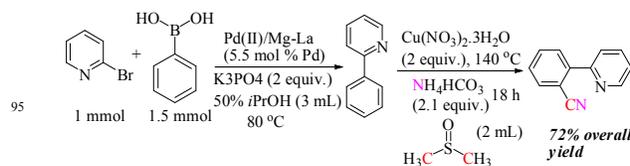


Fig. 5 Recyclability of the catalyst in the cyanation reaction.

Tandem Suzuki-Cyanation Reaction

Tandem reactions represent an important avenue to improve synthetic efficiency by rapidly increasing molecular complexity while minimizing the number of isolation and purification steps.³¹ For the preparation of starting materials for the cyanation reactions, we have used the Pd(II)/Mg-La mixed oxide catalyzed Suzuki coupling reaction (Figure 1, SI, entries c-m and o). The heterogeneous Pd(II)/Mg-La mixed oxide catalyst produced excellent yields of the coupled product. Intrigued with these results, we got interested in developing tandem process where starting from 2-halopyridine derivatives, cyano derivatives of 2-phenylpyridine could be synthesised in a single pot without any intermediary separation and isolation steps. The tandem Suzuki-cyanation reaction of 2-bromopyridine produced the desired cyanated product 2-(pyridin-2-yl) benzonitrile in moderate yields of 72% (Scheme 2).



Scheme 2 Tandem Suzuki-cyanation reaction.

Conclusions

In conclusion, we have developed a simple and efficient method for the cyanation of aromatic C–H bonds by using Pd(II)/Mg-La mixed oxide catalyst using a combination of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as

an oxidant, NH_4HCO_3 and DMSO as the “CN” source to provide aromatic nitriles in moderate to good yields with excellent regioselectivity. A tandem process involving Suzuki coupling followed by cyanation reaction was also developed using the heterogeneous (Pd(II)/Mg-La) catalyst. The catalyst can be readily recovered by simple centrifugation and reused with consistent activity and selectivity for three cycles. We hope that this methodology may find widespread use in the synthesis of aromatic nitriles.

Experimental Section

A 10 mL round bottom flask was charged with 2-phenylpyridine (77.59 mg, 0.5 mmol), NH_4HCO_3 (83 mg, 1.05 mmol, 2.1 equiv.), Pd(II)/Mg-La (30 mg, 5.5 mol % of Pd), $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (187.5 mg, 1 mmol, 2 equiv.) and DMSO (2 mL). The reaction mixture was stirred at 140 °C for 18 h. After the completion of the reaction, as monitored by TLC, 5 mL of ethyl acetate was added in the reaction mixture. The catalyst was separated by simple centrifugation and the reaction mixture was treated with brine (10 mL). The organic layer was separated and the aqueous layer was back extracted with ethyl acetate (3×5 mL). The combined ethyl acetate extract was dried with anhydrous Na_2SO_4 (50 gm) and was concentrated under reduced pressure. The pure product was isolated by flash column chromatography on silica gel using ethyl acetate/hexane (10%) as an eluent (pale yellow oil, 156 mg, 87% yield).

Recyclability test: The recyclability of the catalyst was checked using 2-phenylpyridine as the model substrate on 1.5 mmol scale. A 25 mL round bottom flask was charged with 2-phenylpyridine (232.7 mg, 1.5 mmol), Pd(II)/Mg-La catalyst (90 mg, 5.5 mol % of Pd), $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (562.5 mg, 2 equiv.), NH_4HCO_3 (249 mg, 2.1 equiv.), DMSO (6 mL) and stirred at 140 °C for 18 h. After the completion of the reaction, as monitored by TLC, 15 mL of ethyl acetate was added in the reaction mixture. The catalyst was recovered by simple centrifugation, washed with water (100 mL), air-dried and used directly for the next cycle without further purification. The Pd(II)/Mg-La mixed oxide catalyst shows consistent activity and selectivity up to 4 cycles. Leaching of Pd species from the solid catalyst after the first cycle was determined by atomic absorption spectroscopy (AAS) and was found to be negligible. The Pd content of the fresh catalyst was 9.76% and in the case of used catalyst after the first cycle was found to be 9.68% as measured by AAS. Table 1 (SI) contains the Pd loading of the catalysts in each of the reaction cycles.

General catalytic procedure for the tandem Suzuki-cyanation reaction: A 25 mL round bottom flask was charged with 2-bromopyridine (96 mg, 1 mmol), phenylboronic acid (182 mg, 1.5 mmol), Pd(II)/Mg-La (40 mg), $\text{K}_3\text{PO}_4 \cdot 7\text{H}_2\text{O}$ (424 mg, 2 mmol) and 50% aqueous isopropanol (3 mL). The reaction mixture was stirred at 80 °C and was monitored by TLC. After the completion of the reaction (3 h), the reaction mixture was brought under room temperature and charged with NH_4HCO_3 (236 mg, 3 mmol), $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (454 mg, 2.5 mmol) and DMSO (2 mL). The reaction was continued at 140 °C for another 18 h. After the completion of the reaction, as monitored by TLC, 10 mL of ethyl acetate was added and the catalyst was separated by simple centrifugation. The reaction mixture was treated with brine (10 mL) and the organic layer was separated. The aqueous layer was back extracted with ethyl acetate (3×5 mL). The combined ethyl acetate extract was dried with anhydrous Na_2SO_4 (50 gm) and was concentrated under reduced pressure. The pure product

was isolated by flash column chromatography on silica gel using ethyl acetate/hexane (10%) as an eluent (pale yellow oil, 129 mg, 72% yield).

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Notes and references

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