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Nanocrystalline magnesium oxide-stabilized palladium(0): the Heck reaction of heteroaryl bromides in the absence of additional ligands and base†

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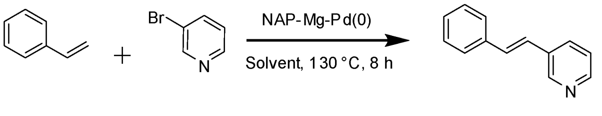
An efficient and user-friendly protocol has been realized for the Heck reaction of heteroaryl bromides by using a reusable nanocrystalline magnesium oxide-stabilized palladium(0) catalyst without the aid of additional ligands and base. Dimethylamine generated under *in situ* conditions by the decomposition of DMF serves as the base in this reaction. The catalyst was reused with consistent activity up to four cycles.

The palladium-catalyzed Heck reaction has become one of the most important C–C bond forming reactions due to its functional group tolerance and its application to a broad range of endeavors, ranging from synthetic organic chemistry to materials science.[1] In particular, the Heck reaction of heteroaryl halides has received considerable attention as heteroaryl derivatives are present in a variety of biologically active compounds and pharmaceuticals.[2] In recent years, palladium catalysts, in conjunction with tertiary aryl or alkyl phosphine ligands,[3] N-heterocyclic,[4] and carbocyclic carbenes,[5] have been used for the Heck reaction of aryl and heteroaryl halides in the presence of a base. Further progress has been made by performing the reactions under ligand-free conditions[6] or using reusable catalysts.[7] There are few examples[3f,g] of palladium-catalyzed Heck reactions in the presence of a ligand and base for the synthesis of heteroaryl derivatives. Very recently, an economical method for the Heck reaction of heteroaryl bromides was developed by us under both ligand- and base-free conditions using a homogeneous palladium catalyst.[8] It is highly desirable to develop a recoverable and reusable palladium catalytic system from an industrial and environmental point of view.

Nanocrystalline metal oxides have recently received much attention in view of their potential usefulness as materials[9] and more importantly as catalysts.[10] Nanocrystalline magnesium oxide (NAP-MgO) possesses a high concentration of reactive sites on the surface, such as Lewis acid Mg^{2+} and Lewis base O^{2-}, lattice bound and isolated hydroxyl groups and anionic and cationic vacancies. Earlier, we reported the effective C–C bond forming reactions using Mg–Al layered hydroxide and NAP-MgO-supported palladium catalysts.[11] Moreover, the enhanced activity of NAP-MgO-stabilized osmate, palladate and tungstate systems over their homogeneous counterparts has also been reported.[12] Herein, we report a convenient and reusable NAP-MgO–Pd(0) catalyst for the Heck coupling of heteroaryl bromides with olefins in the absence of additional ligands and base (Scheme 1).

For optimization of the reaction conditions, a simple representative model system consisting of 3-bromopyridine and styrene was chosen and the results of this optimization study are summarized in Table 1. For this study, based on our previous results,[8] DMF was chosen as the solvent. This reaction was carried out using NAP-Mg–Pd(0) (0.020 g, 9 wt%) as the catalyst at 130 °C for 8 hours to give an 86% yield of the desired C–C coupled product (Table 1, entry 1). As it is always advisable to compare the activity with commercially available and reusable Pd-catalysts,[6,7] the reaction was repeated under the same conditions using Pd/C, LDH–Pd(0) and Mg–La–Pd(0) catalysts, however there was no evidence for the formation of the desired C–C coupled product (Table 1, entries 2 and 3), but in the case of Mg–La–Pd(0) 20% yield of the C–C coupled product was obtained (Table 1, entry 4). Although DMF was initially chosen as the solvent, the reaction was also performed in a variety of



Scheme 1 The Heck reaction of styrene with 3-bromopyridine.

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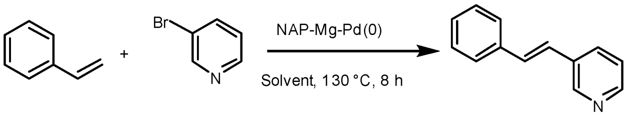
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cy00404j

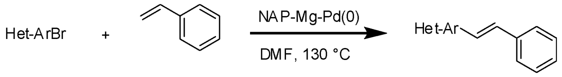
Table 1 Optimization of reaction conditions

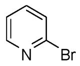
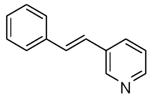
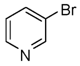
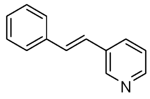
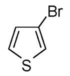
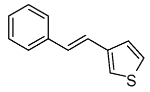
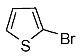
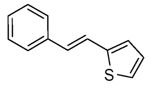
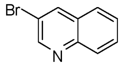
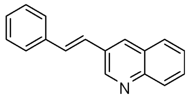
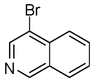
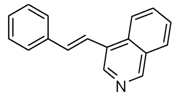
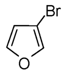
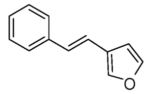
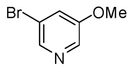
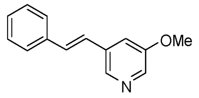
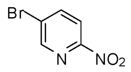
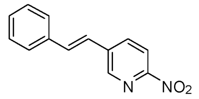
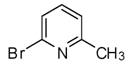
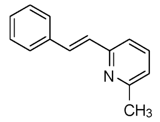


Entry[a]	Catalyst	Solvent	Yield[b] (%)
1	NAP-Mg–Pd(0)	DMF	86
2	Pd–C	DMF	0
3	LDH–Pd(0)	DMF	0[c]
4	Mg-La–Pd(0)	DMF	20[d]
5	NAP-Mg–Pd(0)	DMA	20
6	NAP-Mg–Pd(0)	DMSO	0
7	NAP-Mg–Pd(0)	Toluene	<5
8	NAP-Mg–Pd(0)	DMF	55[e]
9	NAP-Mg–Pd(0)	DMF	40[f]
10	NAP-Mg–Pd(0)	DMF	20[g]

[a] The reactions were carried out with 3-bromopyridine (1 mmol), styrene (2 mmol) and catalyst (0.020 g) in 2.5 mL of solvent at 130 °C for 8 h. [b] Isolated yields. [c] Reaction with the catalyst (0.030 g). [d] Reaction with the catalyst (0.030 g). [e] Reaction at 110 °C. [f] Reaction with the catalyst (0.015 g). [g] Reaction with the catalyst (0.010 g).

Table 2 The Heck reaction of different heteroaryl bromides catalyzed by NAP-Mg–Pd(0)



Entry[a]	Het-ArBr	Product	Yield[b] (%)
1			74
2			86
3			85
4			82
5			87
6			75
7			83
8			81
9			90
10			60

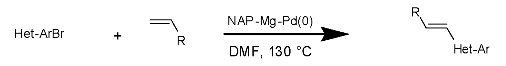
[a] The reactions (entries 1–10) were carried out with heteroaryl bromides (1 mmol), styrene (2 mmol) and catalyst (0.020 g) in 2.5 mL of solvent at 130 °C for 8 h. [b] Isolated yields.

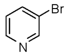
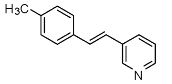
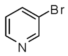
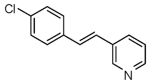
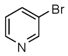
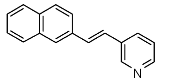
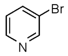
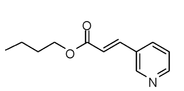
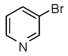
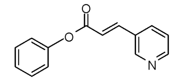
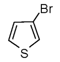
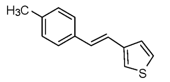
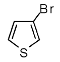
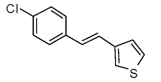
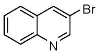
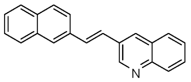
solvents; however only poor yields of the C–C coupled products were obtained when DMA, DMSO and toluene were employed (Table 1, entries 5–7). The reaction was also carried out at low temperature (Table 1, entry 8) and with low catalyst loadings (Table 1, entries 9 and 10), but in these cases only moderate yields of the C–C coupled products were obtained. From the above results, the following optimized reaction conditions were established with respect to the heteroaryl halide: 20 mg of NAP-Mg–Pd(0) as the catalyst in 2.5 mL of DMF as the solvent at 130 °C for 8 h.

A variety of heteroaryl bromides were reacted using the above optimized reaction conditions and the results are presented in Table 2. The Heck reaction of π-electron deficient heteroaryl bromides, such as 3-bromopyridine, 2-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline, with styrene afforded high yields of the C–C coupled products (Table 2, entries 1–4). As shown in our previous report,[8] the position of the bromo-substituent on pyridine can influence the yield of the product (entries 1 *vs.* 2). In the case of π-electron-rich heteroaryl halides, such as 2-and 3-bromothiophenes and 3-bromofuran, the yield of the products under the optimized conditions are nearly the same as in the cases of π-electron-deficient heteroaryl halides (Table 2, entries 5–7). Similarly, comparable yields were obtained from the reaction of styrene with 5-methoxy-3-bromopyridine and 2-nitro-5-bromopyridine (Table 2, entries 8 and 9). The reaction of electron-rich 6-methyl-2-bromopyridine gave the Heck coupled product in 60% yield under the same reaction conditions (Table 2, entry 10); this was one of the first compounds to be developed that acts as a selective antagonist for the metabotropic glutamate receptor.[13]

Next, we investigated the use of NAP-Mg–Pd(0) to catalyze the reaction between various heteroaryl bromides and substituted styrenes, *n*-butylacrylates and phenylacrylates, and the results are presented in Table 3. The reaction of 4-methylstyrene, 4-chlorostyrene and 2-naphthylstyrene with the π-electron-deficient heterocycles such as 3-bromopyridine and 3-bromoquinoline afforded good yields (85–91%) of the coupled products (Table 3, entries 1–3 and 7). Only 65% of the desired product was obtained from the reaction of the activated olefin *n*-butylacrylate and phenylacrylate with 3-bromopyridine (Table 3, entries 4 and 5). Slightly lower yields were observed in the case of π-electron-rich 3-bromothiophene with 4-methylstyrene

Table 3 The NAP-Mg–Pd(0) catalyzed Heck reaction of heteroaryl bromides and olefins



Entry[a]	Het-ArBr	R	Product	Yield[b] (%)
1		4-Me-C_6H_4		91
2		4-Cl-C_6H_4		88
3		$C_{10}H_7$		89
4		${}^nBu$-CO_2		65
5		Ph-CO_2		75
6		4-Me-C_6H_4		75
7		4-Cl-C_6H_4		76
8		$C_{10}H_7$		85

[a] The reactions (entries 1–10) were carried out with heteroaryl bromides (1 mmol), styrene (2 mmol) and catalyst (0.020 g) in 2.5 mL of solvent at 130 °C for 8 h. [b] Isolated yields.

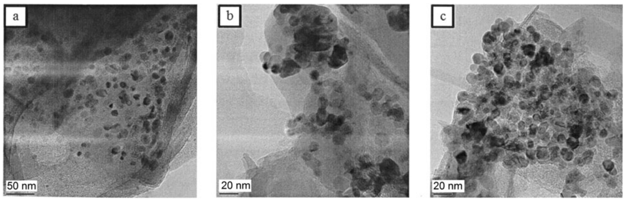


Fig. 1 Transmission electron micrographs of fresh (a) and used (b) NAP-Mg–Pd(0), and the catalyst after the 5th cycle (c).

and 4-chlorostyrene when compared to π-electron-deficient 3-bromopyridine (Table 3, entries 5 and 6). It is clear from these results that regardless of the electron-withdrawing or donating groups on the aromatic ring of the substituted styrenes, both π-electron-rich and π-electron-deficient heterocycles showed similar activity in the Heck reaction (Table 3, entries 1 *vs.* 2 and 5 *vs.* 6). However, the reaction of aryl halides that lack a heteroatom, for example, 4-bromoanisole and 4-chloronitrobenzene failed under the standard conditions. Therefore, it is assumed that presence of heteroatoms in aryl halides is essential for the success of the reaction.

Table 4 Recyclability test of the catalyst with different substrates

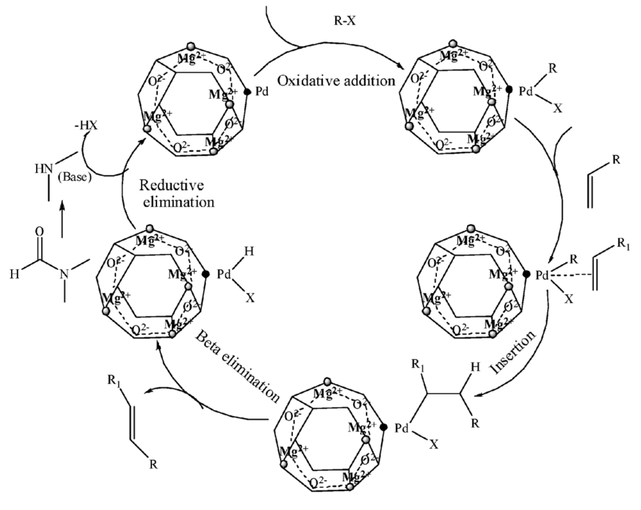
	Yield[b]				
Substrate[a]	Fresh	Run 1	Run 2	Run 3	Run 4
3-Bromopyridine	86	85	83	80	80
3-Bromothiophene	84	84	84	83	80
3-Bromoquinoline	87	85	84	83	83

[a] The reactions were carried out with heteroaryl bromides (1 mmol), styrene (2 mmol) and catalyst (0.020 g) in 2.5 mL of solvent at 130 °C for 8 h. [b] Isolated yields.

The C–C coupled products were isolated from the catalyst by simple filtration after completion of the reaction. The catalyst was washed first with water and then with diethyl ether to remove any organic material. It was dried at room temperature and used for reusability studies. It was observed that the catalyst shows almost consistent activity up to four cycles (Table 4). The TEM image of the used catalyst did not show any change in the shape and size of the support or active Pd(0) centers. The slight decrease in the observed activity in the subsequent cycles may be attributed to a decrease in the surface area due to hydration of the catalyst by water formed in the reaction.[14] No quantifiable amount of leached palladium was detected in the filtrate by AAS.

The TEM images of the fresh and used NAP-Mg–Pd(0) catalysts are shown in Fig. 1. It appears that there is not much change in the shape and size of the Pd particles in both fresh and used catalysts. TEM analysis indicated that the nano Pd particles had a mean diameter of 10 and 12 nm for fresh and used catalysts. The morphology of the catalyst remains the same even after 4 recycles.

The proposed mechanism involves the initial oxidative addition of heteroaryl halides to the palladium(0) catalyst (Scheme 2). In the second step, the palladium(II) catalyst forms a π complex with olefin followed by insertion of alkene into the



Scheme 2 A plausible mechanism for the Nap-MgO–Pd(0) catalyzed Heck reaction of heteroaryl bromides (for the sake of convenience only one palladium nano particle is shown on the support).

Pd–R bond. This is ensued by the formation of the required product by a beta elimination step. Subsequently, palladium(0) is regenerated by a reductive elimination step. It is important to note that for the reductive elimination step to proceed, the presence of base is essential. On the other hand, the reaction described here is performed without the addition of base. Notably, it is documented in the literature that DMF can serve as a precursor of dimethylamine.[15] Therefore, it is conceived that dimethylamine generated from the decomposition of DMF serves as the base in the reaction. Moreover, the presence of dimethylamine was detected in the reaction solution by GCMS headspace analysis (see ESI†).

Conclusions

The Heck reaction of heteroaryl bromides with olefins had been accomplished by using a reusable heterogeneous NAP-Mg–Pd(0) catalyst. The catalyst was recovered and reused up to four cycles with almost consistent activity. The simple procedure, easy recovery, reusability, and catalytic activity are expected to be cost effective for industrial use.

Notes and references

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