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Ligand and base-free Heck reaction with heteroaryl halides

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ABSTRACT

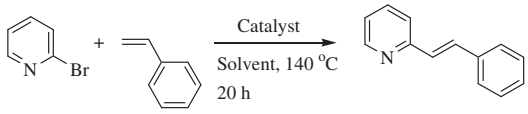
$Pd(CH_3CN)_2Cl_2$-catalyzed Heck reaction of different heteroaryl halides with olefins is carried out in the absence of both the ligand and base to obtain the corresponding coupling products in good yields.

Among the different Pd catalyzed C–C bond forming reactions, the Heck reaction is important in palladium catalysis.[1] Since its discovery in the early 1970's, it has been used in the synthesis of natural products, pharmaceuticals, and materials.[2] Its broad functional group tolerance, mild reaction conditions, and performance with a variety of aryl halides and olefins make the Heck reaction very attractive in the field of synthetic organic chemistry. Significant advances have been made in the past two decades on the Heck reaction using different phosphine ligands[3], palladacylces[4], and non-phosphine Pd-catalysts, such as N-heterocyclic[5], carbocyclic carbenes[6], and *N*, *O*, *S*- donor[7] atoms containing Pd-catalysts. However, the industrial application of this reaction is limited owing to the high cost of the ligands and catalysts.[8]

Although the first protocol of the Heck reaction of aryl iodides under ligand-free conditions has been known for years[9], $Pd(OAc)_2$ in combination with a suitable base has been traditionally used as an effective catalyst for the coupling of aryl bromides with terminal olefins.[10] It has been shown that the palladium catalyst, irrespective of the nature of its precursor, is rapidly reduced to Pd(0) at high temperature, which has a strong tendency to form colloids,[11] and the palladium nanoparticles that are present in these colloids catalyze the Heck reaction. However, the ligand-free approaches are usually limited to aryl iodides and aryl bromides.

It is well known that the synthesis of substituted heteroaryl derivatives is of great importance because they are present in a variety of biologically active compounds.[12] Prompted by the recent work on ligand-free Heck reactions with aryl halides,[10] we hypothesized that it was possible to accomplish the Heck reaction with different heteroaryl halides under ligand-free conditions. There are early indications that, the base-free Heck type reactions are possible with inorganic Pd(II) salts. For example, coupling of aryl diazonium salts with olefins can be catalyzed by Pd salts under

Table 1
Optimization of $Pd(CH_3CN)_2Cl_2$-catalyzed Heck reaction[a]



Entry[a]	Catalyst	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	DMA	57[c]
2	$Pd(OAc)_2$	DMA	30
3	$Pd(CH_3CN)_2Cl_2$	DMA	40
4	$PdCl_2$	DMA	25
5	$Pd_2(dba)_3$	DMA	10
6	$Pd(CH_3CN)_2Cl_2$	Toluene	0
7	$Pd(CH_3CN)_2Cl_2$	DMSO	<5
8	$Pd(CH_3CN)_2Cl_2$	DMF	55
9	$Pd(CH_3CN)_2Cl_2$	DMF	20[d]
10	$Pd(CH_3CN)_2Cl_2$	DMF	25[e]

[a] The reactions were carried out with 2-bromopyridine (1 mmol), styrene (2 mmol), catalyst (4 mol %) in 2.5 mL solvent at 140 °C for 20 h.
[b] Isolated yields.
[c] In the presence of LiOH (2 mmol).
[d] Reaction at 120 °C.
[e] Reaction with 2 mol % catalyst.

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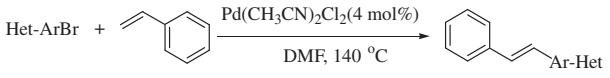
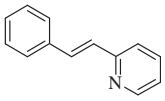
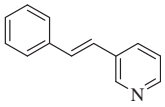
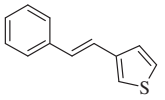
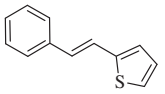
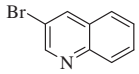
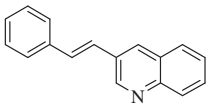
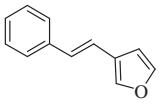
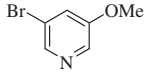
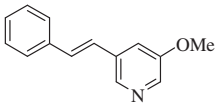
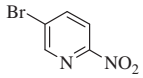
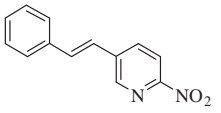
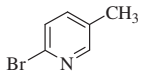
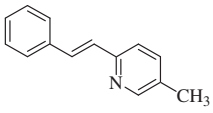
Table 2
Heck reaction of various heteroaryl bromides with styrene catalyzed by $Pd(CH_3CN)_2Cl_2$[a]



Entry	HE-ArBr	Product	Yeild[b] (%)
1			55
2			80
3			84
4			82
5			80
6			82
7			76
8			86
9			5

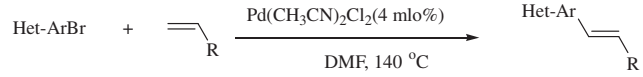
[a] Reactions and conditions: heteroaryl halide (1 mmol), styrene (2 mmol), 4 mol % $Pd(CH_3CN)_2Cl_2$ and 2.5 mL DMF at 140 °**C** for 20 h.
[b] Isolated yield.

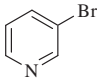
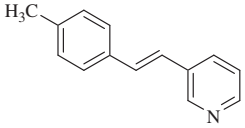
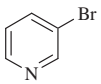
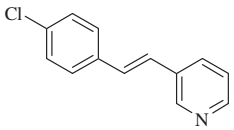
base-free conditions.[13] Likewise, it is expected that the Pd salts catalyze the Heck reaction of heteroaryl halides with styrene under base-free conditions. Herein, we report the $Pd(CH_3CN)_2Cl_2$ catalyzed Heck reaction of heteroaryl bromides under both ligand and base-free conditions. This novel method is economically attractive since, in contrast to the traditional Pd-catalyzed Heck reactions,[3,4a,14] it does not use any ligand and base.

Initially, the Heck reaction between the 2-bromopyridine and styrene was carried out using $Pd(OAc)_2$ as a catalyst and LiOH as a base in *N,N*-dimethylacetamide (DMA) without using any phosphine or non-phosphine ligands and the reaction gave the corresponding product 2-styryl-pyridine in 57% yield (Table 1, entry 1). Later, we examined the same reaction in the absence of both the ligand and the base to make the protocol more attractive to the industry. Surprisingly, the reaction even in the absence of base afforded the product in 30% yield (entry 2). Further, the reaction was optimized with different palladium salts and solvents to increase the efficiency of this reaction; results are summarized in Table 1. As shown in Table 1, different palladium salts, such as $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$, and $Pd(CH_3CN)_2Cl_2$ were screened for this reaction in the absence of both the ligand and the base by using DMA as solvent at 140 °C (Table 1, entries 2–5). The choice of palladium precursor has a profound effect on the reaction in terms of the yield of the Heck product. The maximum yield was obtained when $Pd(CH_3CN)_2Cl_2$ was used as a catalyst (entry 3). Further, we have screened different solvents and *N,N*-dimethylformamide (DMF) proved to be the best solvent and the product was formed in good yield (entry 8). When the reaction was carried out at 120 °C, the reaction provided only 20% yield, which shows that temperature 140 °C is mandatory to obtain the maximum yield of the product (entry 9). Next, the reaction was carried out with 2 mol % of $Pd(CH_3CN)_2Cl_2$ (entry 10) and it was found that 4 mol % of $Pd(CH_3CN)_2Cl_2$ was the most effective catalytic loading.

Using the above mentioned optimized reaction conditions,[16] we further extended the scope of reaction with a variety of heteroaryl halides, using 4 mol % of $Pd(CH_3CN)_2Cl_2$ catalyst, and the results are presented in Table 2. The Heck reaction of 3-bromopyridine with styrene has given high yield of the product when compared to 2-bromopyridine under the optimized conditions (entries 1 vs 2). Thus the position of the bromo substituent on pyridines influences the yield of the products.[15] Similar tendency was not found in the case of π-electron excessive heteroaryl halides such as 2- and 3-bromothiophenes and the yield of the products in both the cases under the same reaction conditions was nearly the same (entries 3 vs 4). With these interesting results, we further examined

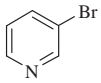
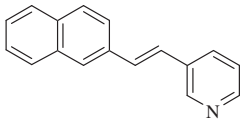
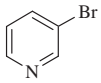
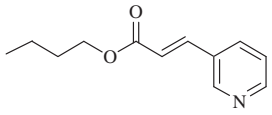
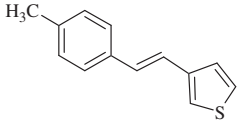
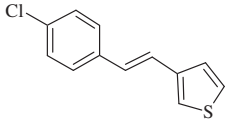
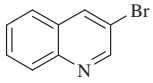
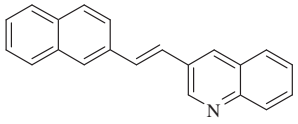
Table 3
Heck reaction of various heteroaryl bromides with olefins catalyzed by $Pd(CH_3CN)_2Cl_2$[a]



Entry	Het-Br	R	Product	Yeild (%)[b]
1		4-Me-C_6H_4		82
2		4-Cl-C_6H_4		80

(*continued on next page*)

Table 3 (*continued*)

Entry	Het-Br	R	Product	Yeild (%)[b]
3		$C_{10}H_7$		84
4		$^{n}Bu\text{-}CO_2$		60
5		4-Me-C_6H_4		73
6		4-Cl-C_6H_4		72
7		$C_{10}H_7$		85

[a] Reactions and conditions: heteroaryl halide (1 mmol), olefin (2 mmol), $Pd(CH_3CN)_2Cl_2$ (4 mol %) and 2.5 mL DMF at 140 °C for 20 h.
[b] Isolated yield.

the reaction of 3-bromoquinoline and 3-bromofuran with styrene, where the products were formed in essentially good yields (entries 5 and 6). Furthermore, it was found that the reaction also proceeded nicely with the electron-rich and electro-deficient 3-bromohetero arenes, such as 5-methoxy-3-bromopyridine and 2-nitro-5-bromopyridine with styrene in 76% and 86% yield, respectively (entries 7 and 8), whereas the reaction with electron-rich 5-methyl-2-bromopyridine gave the product in only 5% yield under the same reaction conditions (entry 9). No product was formed when 2- or 3-chlorohetero arenes were used under the above optimized conditions.

Next, we studied the application of this new method to various styrenes and *n*-butyl acrylate and the results are shown in Table 3. The reaction of π–electron deficient heterocycles, such as 3-bromopyridine and 3-bromoquinoline with different styrenes such as 4-methylstyrene, 4-chlorostyrene, and 2-naphthylstyrene afforded good yields in the range of 80–85% (entries 1–3 and 7). In the case of activated olefin *n*-butyl acrylate the reaction of 3-bromopyridine gave a moderate yield of the desired product (entry 4). Finally, the reaction with the π-electron excessive heterocycle, 3-bromothiophene was performed with different styrenes and the yields obtained were slightly lower than the π-electron deficient heterocycles (entries 5 and 6).

In conclusion, we have developed a more convenient and economical method for the Heck reaction with heteroaryl halides using $Pd(CH_3CN)_2Cl_2$ under both the ligand and base-free conditions. This method is applicable to a wide range of heteroaryl halides. Since this method is developed under neutral conditions in the absence of ligand and base, it should find practical and industrial usage with a wide functional group tolerance for the synthesis of biologically active heteroaryl derivatives.

Acknowledgments

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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.2011.06.081.

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16. *General procedure*: The reaction vessel was charged with aryl halide (1 mmol), alkene (2 mmol), and the catalyst $Pd(CH_3CN)_2Cl_2$ (4 mol %) in *N,N*-dimethylformamide (2.5 mL). The reaction mixture was heated at 140 °C for the desired time 20 h and the progress of reaction was monitored by TLC. At the end of the reaction, the reaction mixture was cooled to room temperature and was diluted with EtOAc (20 mL), and, washed with water. The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and hexane (1:9) to afford the desired product in high purity.