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Efficient palladium-catalyzed cyanation and C-S coupling reactions in green media

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Abstract: Application of an easy-prepared efficient and stable palladium complex in excellent high yields cyanation and C-S coupling of a wide variety of aryl halides, including aryl chlorides have been reported. However, a convenient and effective protocol has been developed that has several superior advantages, including reusable and very low amount used catalyst, wide range of substrate tolerance, excellent yields, short reaction times and very simple procedure.

Keywords: Cyanation, C-S coupling, Pd(II) complex, Green media.

Introduction

The nitrile functional group is widespread in organic materials [1], polymers [2], dyes [3], pesticides [4], natural products [5] and pharmaceuticals [6]. Nitrile moiety is an important functional group in pharmaceutical chemistry due to its hydrogen bond accepting ability [7, 8]. The nitrile-containing bioactive molecules have been applied to treat a broad spectrum of ailments such as depression, breast cancer, HIV and Parkinson’s disease [6]. Variety of functional groups such as amides, ketones, amines and alcohols are synthesis through nitriles, excellently.

Recently, palladium-catalyzed cross coupling of aryl halides and metallonucleophiles have been advanced [9-13]. In concern to toxicity of palladium residuals and this fact that ppm level of palladium traces in pharmaceuticals is acceptable, application of efficient and recyclable catalysts is valuable. Furthermore, due to economical and environmental factors, catalytic systems without expensive and toxic phosphine ligands are favorable.

Therefore, more convenient selective approaches using a palladium catalyst are required.

Also, synthesis of biologically important organic sulfides by metal complexes catalyzed sulfonation coupling reactions attracted the scientist attention [14]. Diaryl sulfides create an important class of therapeutic agents in medicinal chemistry [15-19]. So, the development of efficient method for the synthesis of these compounds is important. Traditional approaches for synthesis of diaryl/aryl alkyl sulfides include reduction of aryl sulfones or aryl sulfoxides using strong reducing agents or harsh reaction conditions [20]. However, metal catalyzed cross-coupling systems method have been developed to overcome these drawbacks. Some of them involves reaction of aryl diazoniumfluoroborate and diaryl disulfides [21], coupling of aryl or alkyl thiols with aryl halides [22-26], cross-coupling reaction of aryl halides and ethyl potassium xanthogenate [27] reaction of phenolic esters with alkyl halides by using thiourea [28], reaction of aryl halides with aminothiourea [29], oxidative sulfidation of diaryl disulfides [30] and reaction of

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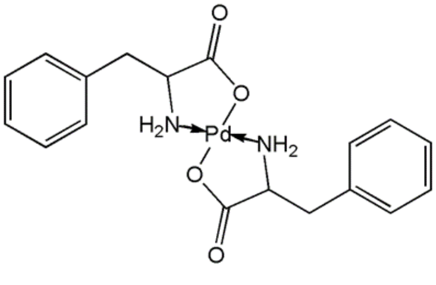
thiourea with aryl halides [31]. These methods usually require harsh reaction conditions, such as use of stoichiometric amounts of the catalyst, use of ligands together with metal salts and more importantly non-reusable catalysts.

Palladium complex were used as catalysts for a variety of organic substrates due to their ready availability, less time for synthesis and their chemical and thermal stability; these are known as the most effective catalysts for cross-coupling reactions yet. However, the separation and recycling of such catalysts may be become very difficult. To overcome such problems, researchers have anchored the metal complexes on solid base which almost of them were obtained difficultly in long boring multi-steps preparation methods with spent mush cost and time. Hence, presents a novel recyclable homogenous phosphine-free palladium complex seems logical. In continuation of our recent investigations about development of cross-coupling reaction [32-37], in this paper, we describe a methodology for cyanation and C-Scross-coupling reactions using a high-efficient and easy prepared reusable palladium catalyst.

Learning from the nature, employing biomolecules is highly favorable in chemical transformations. In the past ten years, amino acids are the most attractive organic compounds and used widely in organic reactions [38-41]. In the best of our knowledge, their practical application of phenylalanine as to generate palladium complex have never been reported for the cyanation and C-S cross-coupling reactions.

Result and Discussion

Herein, Phe-Pd complex was synthesized from l-phenylalanine (Scheme 1). The catalyst was characterized with CHN, ^{1}HNMR and FT-IR, the results was given in supplemental data. In continuous, the efficiency of this catalyst was investigated in cyanation and C-S cross-coupling reactions.



Scheme 1: The structure of Phe-Pd catalyst

Our initial experiments focused on the cyanation of bromobenzene with $K_4Fe(CN)_6$ (Table **1**). We chose potassium ferrocyanide as the nucleophile meanwhile it is commercially available and inexpensive with significant low toxicity.

These studies were carried out using a range of different bases (Na_2CO_3, K_2CO_3, K_3PO_4, t-BuOH and KOH). Among these bases Na_2CO_3 was the best. Optimization with respect to the solvent displayed that the reaction precedes best in DMAc. This solvent gave better results than other solvents, such as NMP, DMSO, MeOH and DMF. Screening was also performed at different temperatures and results showed that no significant reaction improvement was occurred at below 100 ℃. Finally, the optimal temperature was found to be 130 ℃. Lastly, the amounts of the catalyst was tested and it was found that 0.03 mol% of Pd gave the most consistent results. Running the reaction in the presence of lower amounts of the catalyst (0.01 mol%) did not meet with major success and no more yield was obtained in large amount of catalyst (0.1).

The scope of the reaction was investigated; so, the cyanation reaction of various alkyl halides with $K_4Fe(CN)_6$ was performed (Table **2**). Among all of the aryl halides studied by this reaction, both electron-donating substituents and electron-withdrawing substituents are found to be compatible; however, aryl halides contain electron-withdrawing are more active than other. The reaction was found sensitive to steric hindrance by a substituent ortho to the halide and these were done in low yields.

The good obtained results from cyanation reaction motivated us to study the potential activity of catalyst in C─S coupling reaction.

For studying the efficacy of catalyst in C-S coupling reaction; firstly, the reaction of bromobenzene and KSCN was selected as a model reaction (Table 3). The effect of several factors including the kind of base and solvent, amount of catalyst and reaction temperature in model reaction was examined and among them, KOH was selected as the best one. Then, the reaction was done in different solvents, DMSO was found as the most effective solvent. The effect of the amount of catalyst was also explored and the best result is obtained by 0.04 mol% Pd. The reaction temperature on the model reaction was also considered and 130 ℃ was chosen as the optimized conditions.

Table 1: Optimization of Phe-Pd catalyzed coupling of bromobenzene with $K_4Fe(CN)_6$ under various conditions.[a]

Entry	Solvent	Base	Cat. (mol% Pd)	T (°C)	Yield (%)
1	DMAc	Na_2CO_3	0.03	130	83
2	DMAc	K_3PO_4	0.03	130	65
3	DMAc	K_2CO_3	0.03	130	20
4	DMAc	KOH	0.03	130	57
5	DMAc	t-BuOH	0.03	130	-
6	MeOH	Na_2CO_3	0.03	130	36
7	DMSO	Na_2CO_3	0.03	130	75
8	DMF	Na_2CO_3	0.03	130	69
9	NMP	Na_2CO_3	0.03	130	51
10	DMAc	Na_2CO_3	0.03	110	77
11	DMAc	Na_2CO_3	0.03	60	46
12	DMAc	Na_2CO_3	0.1	130	87
13	DMAc	Na_2CO_3	0.01	130	36

[a] Reaction conditions: bromobenzene (0.5 mmol), $K_4Fe(CN)_6$ (0.5 mmol), cat., base, solvent (1 mL).

[b] GC conversions.

Table 2: Scope of the reaction of aryl halides and $K_4Fe(CN)_6$, catalyzed by Phe-Pd.[a]

Entry	X	R	Yield[b](%)
1	I	H	85
2	I	4-OMe	65
3	I	4-NO_2	97
4	Br	H	83
5	Br	4-OMe	58
6	Br	4-NO_2	95
7	Br	4-Cl	85
8	Br	3-Cl	60
9	Br	2-Cl	9
10	Br	4-CHO	95
11	Br	4-$COCH_3$	97
12	Br	3-$COCH_3$	80
13	Br	2-$COCH_3$	10
14	Cl	H	41
15	Cl	4-NO_2	93
16	Cl	4-CHO	89

[a] Reaction conditions: aryhalide (1 mmol), aniline (1.2 mmol), KOH (4 equiv.), DMSO (3 mL) and 80 ℃, for 3 h.

[b] Isolated yield

Table 3: Optimization of reaction conditions on C-S coupling reaction of bromobenzene with KSCN in the presence of catalyst.[a]

Entry	Solvent	Base	Cat. (mol% Pd)	T (°C)	Yield[b](%)
1	DMF	KOH	0.04	130	78
2	DMSO	KOH	0.04	130	88
3	NMP	KOH	0.04	130	36
4	H2O	KOH	0.04	130	7
5	CH3CN	KOH	0.04	130	10
6	DMSO	K_2CO_3	0.04	130	76
7	DMSO	t-BuOK	0.04	130	16
8	DMSO	Na_2CO_3	0.04	130	39
9	DMSO	NaOAc	0.04	130	71
10	DMSO	KOH	0.04	110	74
11	DMSO	KOH	0.02	90	56
12	DMSO	KOH	0.1	130	80

[a]The reaction was carried out with bromobenzene (1.0 mmol), KSCN (1.2 mmol), base (4 eq.) solvent (3.0 mL) for 30 min.
[b]GC yield

With the optimized conditions in hand, the substrate scope of the C-S coupling reaction of aryl halides was considered (Table 4). So, the wide range of activated and inactivated aryl iodides, bromides and even chlorides was applied. As can be seen in Table 4, aryl iodides were converted to the corresponding products in good yields. The reactivity in aryl iodides, aryl bromides and aryl chlorides was decrease. The starting materials with electron-withdrawing group in more active than aryl halides contained electron-releasing substituent.

The cross-couplings was done efficiency in short reaction time with high yields of products. High activities of Phe-Pd can be related to the very good dispersion of homogenous catalyst in reaction medium. Considering to our goals to develop a highly efficient and green catalytic system, reusalability of catalyst was investigated. This Phe-Pd complex was reused without any classical separation techniques such as filtration and centrifugation. The reaction of bromobenzene with KSCN was selected as model reaction and after the first use of catalyst in C-S coupling reaction, the products was extracted with ethyl acetate (2 × 25 mL). In this process the catalyst stayed in the aqueous phase and the recovered aqueous phase having catalyst was concentrated and loaded with fresh coupling partner and base. The palladium content of the first extracted aqueous phase was measured by ICP and compared with palladium content of last run and no significant changes was observed. The result was given in Table 5.

Conclusion

In summary, we reported on the synthesis of aryl nitriles and symmetrical aryl sulfides from electron-rich and electron-deficient aryl halides. Our methodology is fast and involves the use of a non-toxic solvent in air atmosphere.

Experimental section

Materials and methods:

The chemicals were obtained from commercial sources. All new compounds have been characterized by 1H and ^{13}C NMR, IR spectroscopy and elemental analysis.1H and 13C NMR spectra were obtained on a BrukerAvance III 500 (500MHz, ^{1}H; 125MHz, ^{13}C) Spectrometer. All spectra were taken in $CDCl_3$ and the chemical shifts are given in ppm with respect to tetramethylsilane (TMS) used as an internal standard. Near IR spectra were obtained on a Perkin Elmer Precisely Spectrum 400 FT-IR/FT-FIR Spectrometer.

Procedure for the preparation of Phe-Pd:

In a round-bottom flask with a magnet stirrer and condenser, a solution of phenylalanine (20%, w/v) in acetic acid (2%, w/v) was prepared and ethanol solvent of palladium acetate (20%, w/v) was added to it. This solution was stirred for 12 h at room temperature to obtain the palladium complex. Then, the complex was separated from the reaction mixture.

General procedure for cyanation reaction:

In a round-bottom flask equipped with a magnetic stirrer and condenser, 0.006 mg of catalyst contain 0.03 mol% of Pd catalyst was added to a mixture of Na_2CO_3 (4 eq.), aryl halide (1 mmol) and $K_4Fe(CN)_6$ (1 mmol), and suspended in DMAc (3 mL), stirred at 130 ℃ for 30 minutes. The progress of the reaction was checked by gas chromatography (GC), after completion of reaction, the organic layer was dried with (Na_2SO_4). The solvent was evaporated under reduced pressure, and the crude mixture was purified by silica gel column chromatography eluting with hexane.

General procedure for C-S coupling reaction:

In a round-bottom flask equipped with a magnet stirrer and condenser, 0.008 g of catalyst contain 0.04 mol% of Pd catalyst was added to a mixture of KOH (4 eq.), aryl halide (1 mmol) and KSCN (1 mmol), and suspended in DMSO (3 mL), stirred at 130 ℃ for 30 minutes. The progress of the reaction was checked by gas chromatography (GC), after completion of reaction, the organic layer was dried with (Na_2SO_4). The solvent was evaporated under reduced pressure, and the crude mixture was purified by silica gel column chromatography eluting with hexane.

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