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Rhodium catalyzed cyanide-free cyanation of aryl halide by using formamide as a cyanide source

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ABSTRACT

This work reports rhodium–xantphos as a new catalytic system for cyanide-free cyanation of aryl halides to aryl nitriles. The reaction takes place in the presence of phosphorous oxychloride as an acid and formamide as a cyanide source cum solvent. The developed protocol avoids the use of highly toxic metal cyanides. This methodology is a simple, single step reaction involving formamide as a safe and nontoxic source of cyanation. A variety of aryl iodides/bromides were well tolerated under optimized reaction conditions providing moderate to excellent yield of corresponding cyanides.

Synthesis of aryl nitriles is an important transformation in incorporation of various functional groups like amide, ketones, aldehydes, amines, amidines, tetrazoles, oximes, oxazolidines, carboxylic acid, and its derivatives. They also have great importance in the synthesis of various natural products, agrochemicals, pigments, dyes, herbicides, therapeutic drugs, and their intermediates.[1] The nitriles are core structure of numerous pharmaceutical products such as Bicalutamid casodex (Zeneca)®, Fadrozole Arensin (Ciba–Giegy), Periciazine, Citalopram Cipramil (Promonta Lundbeck)®, Escitalopram®, and Etravirine® which are having applications like non steroidal antiandrogen, antineoplastic, anticancer, non steroidal aromatase inhibitor, antipsychotic, antidepressant, selective serotonin uptake inhibitor, Tranquilizer, 5HT reuptake inhibitor, and reverse transcriptase inhibitor (Fig. 1).[2]

Aryl nitriles are usually synthesized by using aryl halides. The most powerful methods for the synthesis of nitriles are Sandmeyer[3] and Rosenmund-von Braun[4] methods. However, these methods have major drawbacks like harsh reaction conditions and multistep synthesis. Various cyanating reagents such as CuCN,[5] KCN,[6] $Zn(CN)_2$,[7] and NaCN,[8] are used for the synthesis of nitriles, but these reagents are highly toxic and environmentally hazardous. Recently reported $K_4Fe(CN)_6$ reagent is not toxic, but it is prepared by using toxic metal cyanide source.[9] Another less toxic trimethylsilyl cyanide (Me_3SiCN) reagent is also used as a cyanide source in several methods for cyanation of aryl halide, however, it gives hydrogen cyanide as a side product which is extremely poisonous, also it is expensive and sensitive to moisture.[10] Some groups have reported the transition metal catalyzed synthesis of nitriles by using copper and palladium.[11] The cyanation of unreactive aryl halides like bromides and chlorides are also reported using toxic

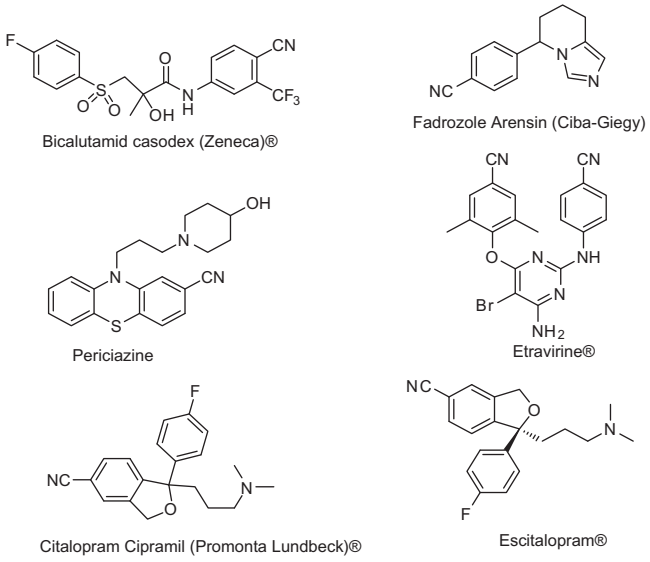

Figure 1. Various pharmaceutical products containing benzonitrile.

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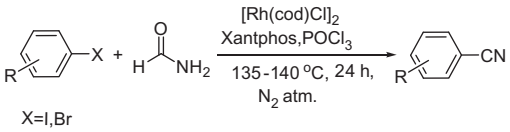
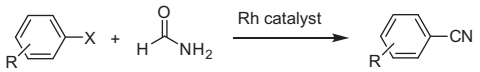


Scheme 1. Cyanation of aryl halide using formamide.

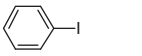
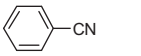
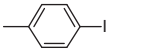
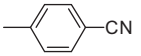
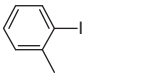
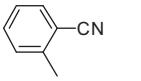
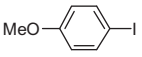
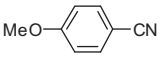
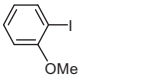
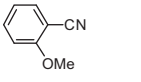
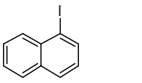
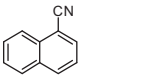
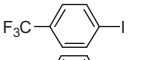
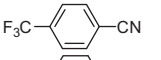
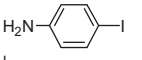
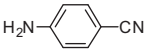
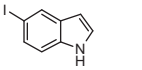
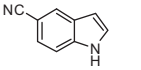
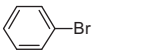
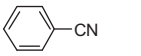
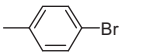
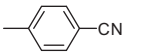
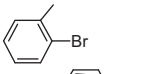
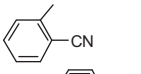
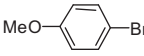
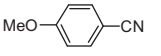
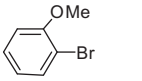
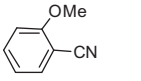
Table 1
Optimization of reaction parameters[a]



Entry	Catalyst	Catalyst loading	Ligand	Yield[b] (%)
1	$RhCl_3{\cdot}3H_2O$	5 mol %	Xantphos	10
2	$Rh(acac)(CO)_2$	5 mol %	Xantphos	18
3	$HRh(CO)(PPh)_3$	5 mol %	Xantphos	12
4	$[Rh(cod)Cl]_2$	5 mol %	Xantphos	80
5	$[Rh(cod)Cl]_2$	2.5 mol %	Xantphos	45
6[c]	$[Rh(cod)Cl]_2$	5 mol %	Xantphos	30
7	$[Rh(cod)Cl]_2$	5 mol %	Dppm	Trace
8	$[Rh(cod)Cl]_2$	5 mol %	Dppp	Trace
9	$[Rh(cod)Cl]_2$	5 mol %	Dppf	60
10	$Pd(OAc)_2$	5 mol %	Xantphos	61
11[d]	$[Rh(cod)Cl]_2$	5 mol %	Xantphos	0
12[e]	$[Rh(cod)Cl]_2$	5 mol %	Xantphos	70
13[f]	$[Rh(cod)Cl]_2$	5 mol %	Xantphos	81

[a] Reaction conditions: 4-iodotoluene (1 mmol), formamide (10 ml/mmol), catalyst as indicated, ligand (10 mol %), $POCl_3$ (2 mmol), 24 h, 135–140 °C under nitrogen atmosphere.
[b] GC yield.
[c] Reaction temp 120 °C.
[d] Without $POCl_3$.
[e] Reaction time 18 h.
[f] Reaction time 30 h.

Table 2
Substrate study for cyanation[a]

Entry	Aryl halide	Product	Yield[b] (%)
1			71
2			80
3			74
4			85
5			77
6			87
7			30
8			35
9			50
10			40
11			44
12			42
13			45
14			42

[a] Reaction conditions: aryl halide (1 mmol), formamide (10 ml/mmol), $[Rh(cod)Cl]_2$ (5 mol %), Xantphos (10 mol %), $POCl_3$ (2 mmol), 24 h, 135–140 °C, under nitrogen atmosphere.
[b] GC yield.

cyanide sources. Recently nitriles have been prepared by C–H activation of aromatic compounds using toxic metal cyanide source which forms stable cyano complexes that deactivate the transition metal catalyst.[12]

Due to the drawbacks of cyanation using such toxic cyanide sources, many groups gave emphasis on developing cyanide free cyanation by using non toxic cyanide source like dimethyl formamide (DMF)[13] and sodium azide.[14] In this context, recently our group have explored formamide as a non toxic cyanide source and successfully applied for cyanation of aryl halides using palladium catalyst in 48 h.[15] In the present work we have developed rhodium catalyzed cyanide free synthesis of nitriles using formamide as a nitrile source (Scheme 1). The protocol was well optimized with different reaction parameters and applied to a variety of aryl halides.

The reaction of 4-iodotoluene with formamide in the presence of $POCl_3$ as an additive using rhodium/xantphos catalyst system was chosen as a model reaction (Table 1). Various rhodium precursors like $RhCl_3{\cdot}3H_2O$, $Rh(acac)(CO)_2$, and $HRh(CO)(PPh_3)_3$ were screened and they gave a very low yield of 4-methyl benzonitrile (Table 1, entries 1–3). Among all the screened metal precursors, $[Rh(cod)Cl]_2$ was found to provide admirable yield (80%) of desired product (Table 1, entry 4). Decreasing the catalyst loading from 5 mol % to 2.5 mol % decreases the yield of desired product (Table 1, entries 4 and 5).

Furthermore, the effect of various bidentate phosphine ligands was also studied and it was observed that dppm and dppp provided low yields of the desired product (Table 1, entries 7 and 8), but interestingly sterically hindered and large bite angle phosphine ligands like xantphos and dppf provide 80% and 60% yields of benzonitrile, respectively, (Table 1, entries 4 and 9). When reaction temperature was decreased from 140 to 120 °C lower yield of the desired product was obtained (Table 1, entry 6). It can be seen that previously reported palladium catalyst gives lower conversion than rhodium under similar reaction conditions (Table 1, entry 10). The reaction was also studied in the absence of $POCl_3$. It was observed that there is no product formation indicating necessity of $POCl_3$ in the reaction (Table 1, entry 11). We have also studied the effect of time and it was observed that the yield of desired product decreases with decrease in the reaction time. Further increase in reaction time showed no prominent effect on the reaction outcome (Table 1, entries 12 and 13).

Thus the optimized reaction parameters are: aryl iodide (1 mmol), $[Rh(cod)Cl]_2$ (5 mol %), Xantphos (10 mol %), $POCl_3$ (2 mmol), and formamide (10 ml/mmol) for 24 h at 135–140 °C under nitrogen atmosphere. A variety of aryl halides bearing the electron donating and withdrawing groups were screened with formamide under optimized reaction parameters and results are summarized in Table 2.[16]

Under these optimized reaction parameters, iodobenzene reacts moderately with formamide giving 71% yield of benzonitrile (Table 2, entry 1). Aryl iodides bearing electron donating groups like $-CH_3$, $-OCH_3$ at *ortho* or *para* position furnish an excellent yield of

corresponding nitrile (Table 2, entries 2–5). 1-Iodonapthalene provides an excellent yield of 1-naphthonitrile (Table 2, entry 6). Aryl halide bearing an electron withdrawing substituent provided lower yield of expected product under present reaction conditions (Table 2, entry 7). Free amino group bearing substrate that is 4-iodo aniline also gives 4-aminobenzonitrile product in moderate yield (Table 2, entry 8). Heterocyclic aryl iodide also works under optimized reaction conditions and furnishes a moderate yield of 1*H*-indole-5-carbonitrile (Table 2, entry 9).

It was observed that various aryl bromides also work under optimized reaction conditions and furnish moderate to acceptable yields of their corresponding nitrile product (Table 2, entries 10–14).

In conclusion, we have developed a non-toxic, convenient, and cyanide free protocol for cyanation of aryl halides. The developed protocol proves to be an attractive alternative to the reported toxic methods for nitrile synthesis. A variety of aryl halides containing electron donating and withdrawing groups are also tolerated in present reaction conditions.

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16. Typical experimental procedure:- in an oven dried 25 ml two-necked round-bottom flask equipped with a condenser was placed a mixture of aryl halide (1 mmol), $[Rh(cod)Cl]_2$ (0.05 mmol, 5 mol %), and Xantphos (0.1 mmol, 10 mol %) in 10 ml/mol formamide at room temperature and stirred for 2–3 min. Then $POCl_3$ (2 mmol) was added to the reaction mixture which was then heated in an oil bath at 135–140 °C for 24 h with continuous stirring under nitrogen atmosphere. After 24 h the reaction mixture was cooled to room temperature and poured into 40 ml saturated solution of $NaHCO_3$. The product was extracted into ethyl acetate (3×15 ml). After drying over anhydrous Na_2SO_4, the combined ethyl acetate layer was concentrated by rotary evaporation. All the prepared compounds were characterized by GC–MS (Shimadzu QP 2010).