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Cadmium(II)-Catalyzed C–N Cross-Coupling of Amines with Aryl Iodides

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Abstract: Cadmium diacetate dihydrate [Cd(OAc)$_2$·2H$_2$O] in combination with ethylene glycol catalyzes efficiently the C–N cross-coupling of amines with aryl iodides by a benzyne mechanism. Alkyl, aryl and heterocyclic amines are compatible with this system affording the aminated products in high to excellent yield.

Keywords: amination; aryl halides; benzyne mechanism; cadmium; C–N cross-coupling

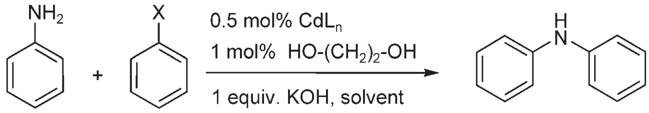
The amination of aryl halides represents a powerful means for the preparation of numerous compounds in biological, pharmaceutical and material sciences.[1] The traditional methods available for this purpose, however, often require stoichiometric amounts of metal reagents, which, on scale-up, leads to a problem of waste disposal.[2] To overcome these drawbacks, considerable attention has been recently focused to develop catalytic systems for this purpose by cross-coupling reactions.[3] In 1983 Migita and co-workers first reported the cross-coupling of tributyltin amide with aryl bromide catalyzed by PdCl$_2${P(*o*-C$_6$H$_4$Me)$_3$}$_2$.[4] Since then palladium complexes bearing sterically hindered phosphine ligands[5] and copper complexes having electron-rich ligands such as amines,[6] ethylene glycol,[7a] *N*,*N*-diethylsalicylamide,[7b] 1,10-phenanthroline,[8] *N*-oximes,[9] thiophencarboxylates,[10] amino acids[11] and 1,3-dicarbonyl compound[12] have been studied for the coupling of amines with aryl halides. In this contribution, we report that Cd(OAc)$_2$·2H$_2$O in combination with ethylene glycol catalyzes efficiently the C–N cross-coupling of amines with aryl iodides in excellent yield. The procedure is compatible with alkyl, aryl and N-heterocyclic amines and takes place at moderate temperatures in air.

First, we studied the reaction of aniline with iodobenzene as model substrates (Table 1). The reaction occurred to provide the desired C–N cross-coupled diphenylamine in 92% yield when the substrates were stirred for 2 h at 110 °C in the presence of 0.5 mol% Cd(OAc)$_2$·2H$_2$O, 1 mol% ethylene glycol and 1 equiv. KOH in dimethyl sulfoxide (DMSO). CdCl$_2$, CdCl$_2$·2H$_2$O and CdI$_2$ were also investigated as the catalysts, but they were less effective in comparison to Cd(OAc)$_2$·2H$_2$O. Among the solvents studied, DMSO, toluene, dioxane and DMF, the former provided the best results. The reaction with KOH was superior to that using K$_2$CO$_3$, Cs$_2$CO$_3$, NEt$_3$ and pyridine. Among the aryl halides, iodobenzene was more reactive compared to bromo- and chlorobenzene.

Next, to study the scope of the procedure, the reaction of other amines with iodobenzene was studied (Table 2, Table 3, and Table 4). 4-Bromo-, 4-chloro-, 2-methyl-, 2-methoxy-, 4-methoxy-, 4-nitro- and 2,4-dimethylaniline underwent the reaction to provide the corresponding C–N cross-coupled products in 70–98% yield (Table 2). Anilines having electron-donating groups were more reactive in comparison to those with electron-withdrawing groups. Similar result was observed with alkylamines, benzylamine, furfurylamine, *n*-butylamine, cyclohexylamine, pyrrolidine, piperidine and morpholine, affording the C–N cross-coupled products in 82–98% yield (Table 3). N-Heterocyclic compounds such as pyrrole, indole, imidazole, 2-methylimidazole and benzimidazole underwent the reaction to give the aminated products in 96–98% yield (Table 4). The imidazole derivatives were less reactive in comparison to alkyl- and arylamines.

Finally, we studied the C–N cross-coupling of pyrrolidine with the substituted iodobenzenes, 2-methoxy-, 4-methoxy-, 4-nitro- and 2,4-dimethyliodobenzene (Table 5). The reactions occurred to afford a mixture of regioisomers in high yield. The reactivity of an aryl iodide with an electron-withdrawing group was greater in comparison to that having an electron-

Table 1. Reaction of aniline with aryl halides.

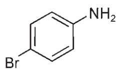
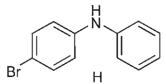
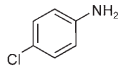
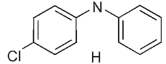
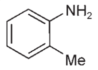
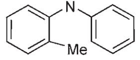
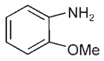
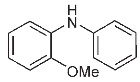
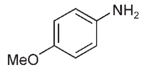
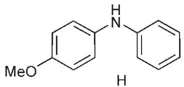
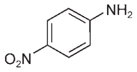
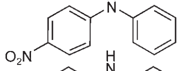
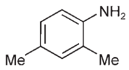
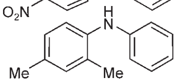


Catalyst	X	Solvent	Base	Temp. [°C]	Time [h]	Yield [%][a,b]
$CdCl_2$	I	DMSO	KOH	110	6	86
CdI_2	I	DMSO	KOH	110	6	86
$CdCl_2 \cdot 2H_2O$	I	DMSO	KOH	110	6	90
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	KOH	110	2	92
$Cd(OAc)_2 \cdot 2H_2O$	I	toluene	KOH	110	12	40
$Cd(OAc)_2 \cdot 2H_2O$	I	DMF	KOH	110	12	15
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	KOH	90	12	30
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	KOH	25	12	trace
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	K_2CO_3	110	10	20
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	Cs_2CO_3	110	10	50
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	NEt_3	110	8	0
$Cd(OAc)_2 \cdot 2H_2O$	I	DMSO	pyridine	110	8	5
$Cd(OAc)_2 \cdot 2H_2O$	Br	DMSO	KOH	110	9	85
$Cd(OAc)_2 \cdot 2H_2O$	Cl	DMSO	KOH	110	12	65

[a] Catalyst (0.5 mol%), ethylene glycol (1 mol%), aryl halide (1 mmol), aniline (1.2 mmol), KOH (1 mmol) and solvent (1 mL) were stirred in air.

[b] Isolated yield.

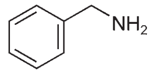
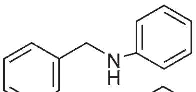
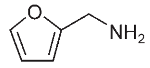
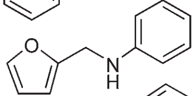
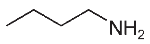
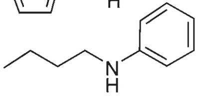
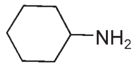
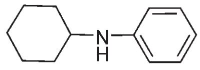
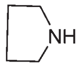
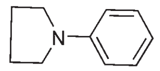
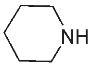
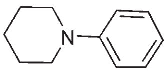
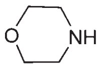
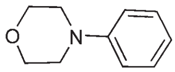
Table 2. Reaction of arylamines with iodobenzene.

Entry	Amine	Product	Time [h]	Yield [%][a,b]
1			5	88
2			6	90
3			4	98
4			4.5	94
5			1.5	91
6			10	70
7			5	92

[a] $Cd(OAc)_2 \cdot 2H_2O$ (0.5 mol%), ethylene glycol (1 mol%), iodobenzene (1 mmol), amine (1.2 mmol) and KOH (1 mmol) were stirred at 110 °C in DMSO (1 mL) in air.

[b] Isolated yield.

Table 3. Reaction of alkylamines with iodobenzene.

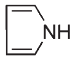
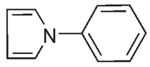
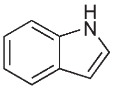
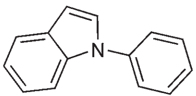
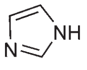
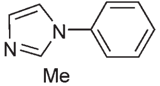
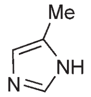
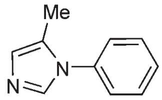
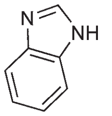
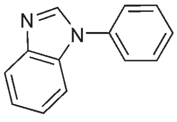
Entry	Amine	Product	Temp. [°C]	Time [h]	Yield [%][a,b]
1			110	6	98
2			110	8	82
3			80	7.5	92
4			110	4	90
5			85	5	94
6			110	3.5	98
7			110	5.5	97

[a] $Cd(OAc)_2 \cdot 2H_2O$ (0.5 mol%), ethylene glycol (1 mol%), iodobenzene (1 mmol), amine (1.2 mmol) and KOH (1 mmol) were stirred at appropriate temperature in DMSO (1 mL) under air.

[b] Isolated yield.

donating group. These results suggest that reaction takes place by a benzyne mechanism (Scheme 1). The reaction of aryl iodide with $Cd(OAc)_2 \cdot 2H_2O$ can give an intermediate ***a*** which can react with base to provide the benzyne intermediate ***b***. Addition of amine with the intermediate ***b*** can lead to the C–N cross-coupled products as a mixture of regioisomers.

Table 4. Reaction of N-heterocyclic compounds with iodobenzene.

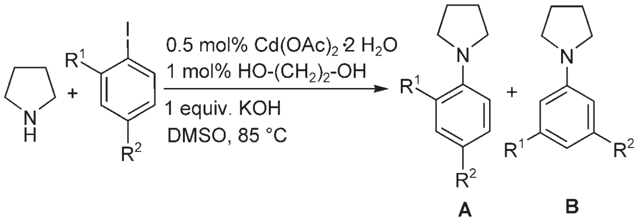
Entry	Amine	Product	Time [h]	Yield [%][a,b]
1			6	96
2			8	97
3			12	98[c]
4			13	96[c]
5'			18	98[c]

[a] $Cd(OAc)_2 \cdot 2H_2O$ (0.5 mol%), ethylene glycol (1 mol%), amine (1.2 mmol), iodobenzene (1 mmol) and KOH (1 mmol) were stirred at 110 °C in DMSO (1 mL) under air.

[b] Isolated yield.

[c] Catalyst (1 mol%) used.

Table 5. Reaction of substituted iodobenzenes with pyrrolidine.[a]

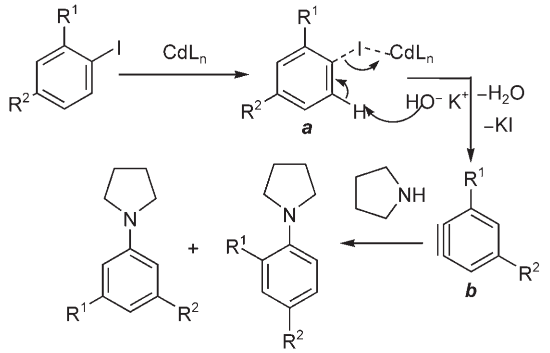


Entry	R^1	R^2	Time [h]	**A** [Yield%][b]	**B** [Yield,%][b]
1	OMe	H	12	22	35
2	H	OMe	8	26	42
3	H	NO_2	2.5	77	18
4	Me	Me	15	37	55

[a] Catalyst (0.5 mol%), ethylene glycol (1 mol%), aryl iodide (1 mmol), pyrrolidine (1.2 mmol) and KOH (1 mmol) were stirred in DMSO (1 mL) under air.

[b] Isolated yield.

In conclusion, the C–N cross-coupling of amines with aryl iodides by the combined use of $Cd(OAc)_2 \cdot 2H_2O$ and ethylene glycol has been found to take place in high yield. The reaction is simple, efficient and functions in air by a benzyne mechanism. Further optimization of this reaction with other aryl halides is currently being studied.



Scheme 1.

Experimental Section

General Procedure

To a stirred solution of amine (1.2 mmol), aryl iodide (1 mmol) and KOH (1 mmol) in DMSO (1 mL), a homogeneous stock solution prepared from $Cd(OAc)_2 \cdot 2H_2O$ (0.5 mol%) and ethylene glycol (1 mol%) in (DMSO) (50 μL) was added. The solution was heated at 80–110 °C for the appropriate time under air (Table 1–Table 5). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and treated with ethyl acetate (5 mL) and water (2 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic solution, after successively being washed with brine (3 × 5 mL) and water (1 × 5 mL), was dried (Na_2SO_4) and passed through celite. Evaporation of the solvent usually provided analytically pure aminated products which do not require further purification. Wherever the reaction was incomplete, the product was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.

Acknowledgements

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