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Microwave Assisted Solvent Free Catalytic Amino-Carbonylation of Aryl Bromide by Using μ-Dichloro-*bis*(benzylidene aniline)palladium(II) Complex as Catalyst

B. PANT[1], D. PRAKASH[2] and P. SAGAR[1,*]

[1]Department of Chemistry, Kumaun University, S.S.J. Campus, Almora-263601, India
[2]Department of Chemistry, Uttarakhand Open Univesity, Haldwani-263139, India

*Corresponding author: E-mail: sagarpriyanka2006@gmail.com

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Solvent-free aminocarbonylation (Heck carbonylation) of aryl halide, catalyzed by μ-dichloro-*bis*(benzylidene aniline)palladium(II) complex yields dimethyl benzamide and their substitutes, has several useful industrial applications. In present work, dimethylformamide (DMF) serves as an effective *in situ* supplier of dimethyl amine and carbon monoxide. Bromobenzene along with more electron-rich aryl bromide generally undergo these reactions very smoothly, but the yield of respective products is less. To increase the yields of aryl amide, it is needed to be add amines from the external sources to the reaction mixture. Imidazole and aniline were used as good reaction partners, or amines, in this experiment. For obtaining the best results, several reactions were conducted in the presence of base *i.e.* potassium *tert*-butoxide. Potassium *tert*-butoxide was responsible for the better decomposition of DMF and imidazole as an additive. The carbonylation reactions described here depend on the efficiency of *in situ* generation of carbon monoxide, which can be a suitable unconventional route to traditional carbonylation procedures for small-scale operation when a quick reaction time is sought where direct use of CO gas is not possible.

Keywords: Transition metal, Catalysis, Catalytic carbonylation, Green methodology, Solvent-free reaction, Microwave reactions.

INTRODUCTION

While several different approaches exist for preparing amides, doing so in a way that minimizes the chemical wastes or avoids the use of potentially harmful chemicals can be challenging. Generally, carboxylic acid derivatives like acyl chloride, ester and anhydride give amides on reaction with amines where the use of coupling reagents is frequently required [1]. So the most important aim of synthetic organic chemistry is to find more environmental friendly, time and atom-efficient methodologies for amide synthesis [2]. Catalytic systems allow the use of inert substrates for amide synthesis and less waste formation. As a result, amide synthesis *via* the catalytic route has drawn the attention of many researchers in the past few years and several methods have been developed [3]. For instance, Milstein *et al*. [4] developed a ruthenium catalyst that allows the coupling of an amine and alcohol to produce an amide.

Catalytic carbonylation of aryl halide is a convenient method of producing aryl amides directly. Several metal complexes, such as palladium and platinum complexes, were used to catalyze the reaction. In these reactions, the most common source of the carbonyl group is CO gas [5]. The process commonly uses CO, which is an odorless, but highly inflammable and toxic gas. The use of a pressurized CO gasoline cylinder restricted the carbonylation reaction for the commercial and industrial uses. So, it is a conservation opportunity to store and transport the CO cylinder. To solve this problem cylindrical CO gas-free carbonylation has gained great attention.

Metal carbonyls like $Mo(CO)_6$ by Kaiser *et al.* [6] and $Co_2(CO)_8$ by Larhed *et al.* [7] used as CO sources in various carbonylation reactions more than three decades ago. This method of *in situ* CO administration is ideal for high throughput organic synthesis. The method could be easily handled if inexpensive material mainly solvent itself behave as a CO source. Metal carbonyl compounds have been synthesized using the common solvent DMF [8,9]. Herein, the catalytic carbonylation of aryl bromide in addition to aniline (nucleophile), imidazole (an as additive) and a base potassium *tert*-butoxide in DMF

medium as a CO source is reported. Aryl amide was the product when isolated from a reaction that was performed for 15-20 min at 210 ºC under microwave heating.

EXPERIMENTAL

Analytical grade chemicals of Aldrich, Fluka and E-Merk brands were used throughout. Solvents of the highest quality were utilized and distilled under a nitrogen/argon atmosphere before use. Thin-layer chromatography (20 cm × 20 cm) on silica gel F-254 precoated plates was used to analyze the resulting mixture. The results were seen using either UV light or ninhydrin in ethanol. The molecular weight was determined using a Knauer Dampefdruck osmometer. The IR spectra of the complex were recorded using a Perkin-Elmer 1800 (FT-IR) spectrophotometer with KBr Phase from 4000-400 cm^{-1} and a CsI phase from 400-200 cm^{-1}. The Schiff base ligand and their complex were synthesized as per the literature method [10,11].

General procedure

Synthesis of *N*-[(*E*)-phenylmethylidene]aniline (L_A) Schiff base ligand: An equimolar proportion of aniline (15 mL, 163.4 mmol) was mixed with benzaldehyde (16.5 mL, 163.4 mmol) in methanol (12 mL). The mixture was stirred occasionally and refluxed for 1 h. The mixture so obtained undergoes distillation under reduced pressure. Brown crystals of *N*-(phenylmethylidene)aniline (L_A) were separated, washed, recrystallized with methanol and then finally dried under vacuum conditions.

Synthesis of di-μ-chloro-*bis*(benzylideneaniline-C^1N') palladium(II) [$Pd_2(L_A)_2Cl_2$] (1A) complex: Palladium chloride (2.44 mmol) and Schiff base (4.88 mmol) were mixed dropwise while stirring continuously at 30 ºC to a 15 mL methanolic solution. The mixture was thoroughly mixed after L_A had been added. The solution turned into a greenish yellow precipitate, which was washed thoroughly with methanol and then dried in vaccum. The complex was found to be stable in solid state and could be stored under a nitrogen atmosphere for several months without experiencing any discernible alteration.

Cataytic aminocarbonylation of aryl halide: A vial was prepared with aryl bromide (0.75 mmol), aniline (3 mmol), catalyst (0.04 mmol), potassium *tert*-butoxide (0.75 mmol), imidazole (0.75 mmol) and DMF (1 mL). First, the reaction setup was thoroughly tightened after being evacuated, purged and filled with pure dry nitrogen. For 20 min, the vessel was submitted to microwave radiation at 210 ºC. After allowing the vessel to cool to room temperature, the mixture was extracted using ethyl acetate. The solvent was extracted at reduced pressure after the organic layer had been washed with brine and water and dried on potassium carbonate. The reaction progress was monitored by taking out the reaction mixture at the initial stage and finally after 20 min at the end of reaction.

***N*-[(*E*)-Phenylmethylidene]aniline (L_A):** Yield: 80%, colour: Brown. IR (KBr, ν_{max}, cm^{-1}): 1626 (C=N), 1584 (C=C), 1310 (C-N), 759, 692 (C-H benzene out of the plane), ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.4 (s, 1H), 7.3-7.5 (m, 5H), 7.8-7.9 (m, 5H).

Di-μ-chloro-*bis*(benzylideneaniline-C^1N') palladium(II): Yield: 80 %, colour: greenish yellow, m.p.: 245 ºC decomp. IR (KBr, ν_{max}, cm^{-1}): 1599 (C=N), 1572 (C=C), 1317 (C-N), 765, 760, 752, 692 (C-H benzene out of the plane); 763 (*ortho* metallation), 310-360 (Pd-Cl): ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.4 (s,1H), 7.3-7.5 (m, 5H), 7.8-7.9 (m, 5H).

***N*,*N*-Dimethylbenzamide (1a):** Yield: 92%, white solid; MS *m/z* (M^+): 149.1 ^{1}H NMR (400 MHz, DMSO): δ 7.88 (d, J= 7.64, 2H), 7.99 (bs, 1H), 7.45 (t, *J* = 7.36, 2H), 7.37 (bs, 1H), 7.52 (t, *J* = 7.76, 1H) ppm. ^{13}C NMR (75 MHz, DMSO): δ 168.3, 134.7, 131.6, 128.6, 127.9 ppm.

***N*,*N*-3-Trimethylbenzamide (1b)**: White solid; Yield: (116 mg, 0.85 mmol, 86%). MS *m/z* (M^+): 164.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (bs, 2H), 7.34 (d, *J* = 5.38 Hz, 2H), 7.65 (s, 1H), 2.40 (s, 3H), 7.60 (s, 1H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 138.5, 132.8, 128.5, 128.2, 124.4, 21.3 ppm.

***N*,*N*-3,4-Tetramethylbenzamide (1c)**: White solid; yield: (110 mg, 0.73 mmol, 74%). MS *m/z* (M^+):168.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.76 Hz, 2H), 7.55 (d, *J* = 7.84 Hz, 1H), 7.63 (s, 1H), 6.08 (bs, 1H), 2.33 (s, 6H), 5.85 (bs, 1H) ppm. ^{13}C NMR (75 MHz, DMSO): δ 168.4, 140.1, 136.4, 129.6, 129.0, 125.5, 124.8, 20.3, 19.8 ppm.

4-(*Tert*-butyl)-*N*,*N*-dimethylbenzamide (1d): Ivory solid, yield: (145 mg, 0.81 mmol, 82%); MS *m/z* (M^+):178.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 9H), 6.11 (bs, 2H), 7.47 (d, *J* = 8.04 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 155.6, 130.8, 127.2, 125.5, 34.9, 31.1 ppm.

4-Fluoro-*N*,*N*-dimethylbenzamide (1e): White solid; Yield: (119 mg, 0.86 mmol, 85%). MS *m/z* (M^+): 206.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 (bs, 2H), 7.13 (m, 2H), 7.85 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 166.3, 168.3, 129.8, 129.7, 115.8, 115.6 ppm.

***N*-Phenyl-benzamide (2)**: White solid; Yield: (122.7 mg, 0.93 mmol, 93%). MS *m/z* (M^+): 197.1; ^{1}H NMR (500 MHz, DMSO): δ 7.39-7.11 (m, 5H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.96 (brs, 1H) ppm. ^{13}C NMR (125 MHz, DMSO) δ 165.7, 142.3, 132.0, 138.0, 129.3, 129.0, 127.0, 124.4, 120.1, 21.5 ppm; GC (retention time): 21 min, 44 s.

RESULTS AND DISCUSSION

In present study, *N*-[(*E*)-phenylmethylidene]aniline (L_A) Schiff base ligand and their corresponding μ-dichloro-*bis*-(benzylidene aniline-C^1N')palladium(II) complex were synthesized and characterized by spectroscopic methods and molecular weight determination.

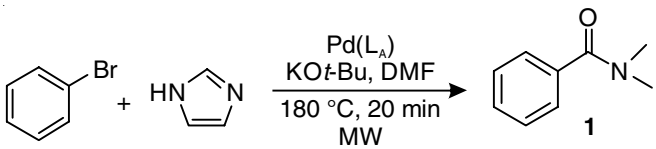
The determined molecular weight of the synthesized palladium(II) complex was found to be lower than as compared to their formulation. This suggests partial or complete dissociation of the dinuclear palladium compound to the corresponding mononuclear one in solution according to eq. 1 and further synthesis was carried out with this Pd(II) complex.

$$Pd_2(L_A)_2Cl_2 + DMF \rightleftharpoons 2PdLa{\cdot}DMF{\cdot}Cl$$

IR bands of free *N*-[(*E*)-phenylmethylidene]aniline (L_A) shows two bands in the region of 1650-1570 cm^{-1} [12]. The band at 1626 cm^{-1} is assigned to C=N stretching mode while 1584 cm^{-1} band assigned to the aromatic ring stretching mode. In case of μ-dichloro-*bis*(benzylidene aniline-C^1N') palladium(II),

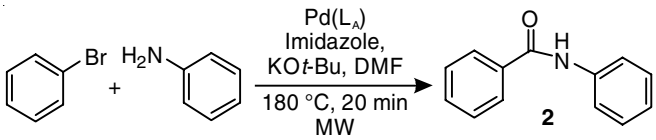
the complex shows a shift of C=N and C=C stretching mode to lower frequency *i.e.* 1599 and 1572 cm^{-1}.

After establishing the reaction conditions for the synthesis of amide from corresponding aryl bromide and DMF, various substituted aryl halides were also followed by same procedure. The approach, as shown in Table-1, several electronic and steric factors on aryl bromide substituents, resulting various patterns of good to excellent yields of the aryl amides (**1a-e**). It was observed that bromobenzene among various aryl bromide gives better results in the given conditions so present study is focused mainly on bromobenzene. Further reaction was improved by following bromobenzene as sunstituent and imidazole as additional reactants and DMF as CO source in a simulated reaction. Surprisingly, no change was observed in the primary product. It was again dimethyl amide **1** as primary product with a high yield (**Scheme-I**) instead of expected product *i.e.* aryl imidazole by microwave heating at 210 ºC for 20 min. This finding prompted us to conduct a more indepth examination of DMF's potential and limitations as a carbon monoxide precursor for carbonylation operations.



Scheme-I: Pd(II) catalyzed carbonylation of aryl bromide

To determine whether other byproducts besides the primary product were obtained or not, the present investigation now further upgraded by using aniline as an external amine. So, bromobenzene (0.75 mmol), aniline (3 mmol), KO^t-Bu (0.75 mmol), imidazole (0.75 mmol) and palladium Schiff base complex (0.04 mmol) at 210 ºC in DMF was heated in microwave synthesizer. A 64% yield of *N*-phenyl benzamide (**2**) was obtained after 20 min reaction period (**Scheme-II**).



Scheme-II: Synthesis of *N*-phenyl benzamide (**2**) by catalytic carbonylation

TABLE-1
Pd(II) CATALYZED CARBONYLATION OF ARYL HALIDE AND SUBSTITUTED ARYL HALIDE

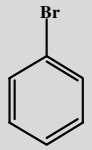
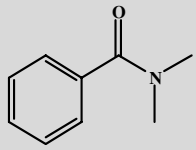
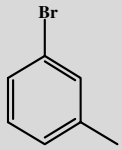
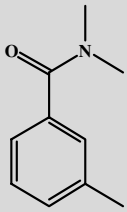
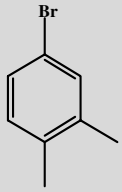
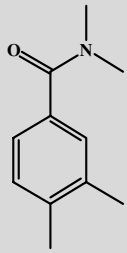
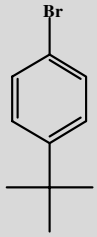
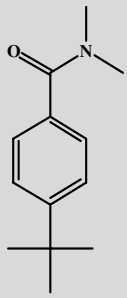
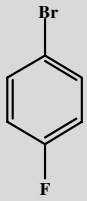
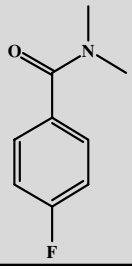
Compd.	Substrate	Product	Yield (%)
1a			59
1b			48
1c			40
1d			45
1e			44

Table-2 displays the outcomes from the reaction under different conditions. Furthermore, the results demonstrated that bidentate ligands yield the desired results (entry 2) but monodentate ligands do not. Due to the inability to carry out the reaction with $PdCl_4$ in the absence of a ligand (entry 3), the reaction vessel experienced extraordinarily high pressure and in some cases, the solution of the reaction vessel erupted. The Pyrex wall accumulating metallic palladium may have caused high pressure by interfering with the temperature microwave feedback regulation. Furthermore, the absence of imidazole

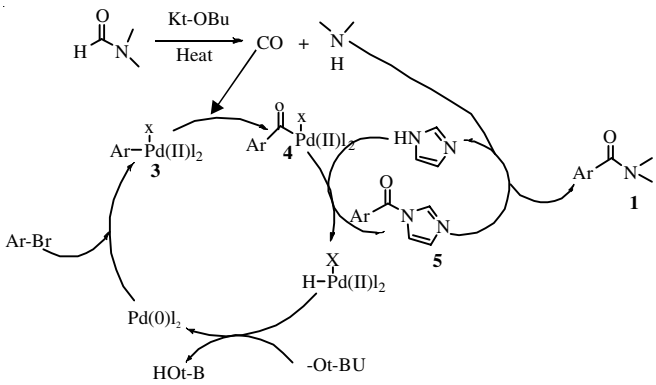
TABLE-2
PALLADIUM-CATALYZED CARBONYLATION OF ARYL BROMIDE UNDER DIFFERENT REACTION CONDITIONS

Entry	Catalyst	Ligand	Additive	Base	Solvent	Yield of **2** (%)
1	$Pd(Cl)_4$	L_A	Imidazole	KO*t*-Bu	DMF	64.07
2	$Pd(Cl)_4$	PPh_3	Imidazole	KO*t*-Bu	DMF	0
3	$Pd(Cl)_4$	–	Imidazole	KO*t*-Bu	DMF	a
4	$Pd(Cl)_4$	L_A	–	KO*t*-Bu	DMF	b
5	$Pd(Cl)_4$	–	–	K_2CO_3	DMF	c

L_A = N-[(*E*)-phenylmethylidene]aniline; *Reaction condition: Bromobenzene (0.75 mmol), aniline (3 mmol), additive (0.75 mmol), KO*t*-Bu (0.75 mmol), Pd Schiff base complex (0.04 mmol), [a]Vial eruption, [b]Diphenylamine was the major product. [c]N-Phenylformamide was the major product.

results in the formation of compound **2** (< 1% by GC/MS, entry 4) and using potassium carbonate in place of potassium *tert*-butoxide results in the formulation of aniline and getting back starting material (entry 5). At 210 ºC, the reaction was carried out with 1.0 equiv. of KO^t-Bu. The basic amount was than increased to 1.5 equiv. which increasing the yield of **2** to 68%. Table-3 displays the outcomes with bromobenzene with or without external amine. Although secondary amine, aniline and benzylamine are suitable for the reactions by employing aniline, giving the isolated yield of amide (entry 2). The yield of compound **1a**, which relies on the release of dimethylamine from the solvent was marginally lower (59%, entry 1).

The aminocarbonylation processes are assumed to proceed in the manner as shown in **Scheme-III**. It is generally known that when DMF decarbonylates upon heating, producing carbon monoxide and dimethylamine when a base is present [13]. To our knowledge, this methodology is the first instance in which solvent itself generates CO and is effectively used in the carbonylation procedure [14].



Scheme-III: Proposed mechanistic cycle for catalytic carbonylation of aryl bromide

In contrast to imidazole or the palladium catalyst, KO^t-Bu appears to speed up this breakdown [15]. The liberation of these gases was represented by a pressure graph on heating at 210 ºC (Fig. 1). Since, the aminocarbonylation reaction combines the two products of the DMF decarbonylation reaction into **1**, it is revealed that the internal pressure of the vessel is not so high (Fig. 2).

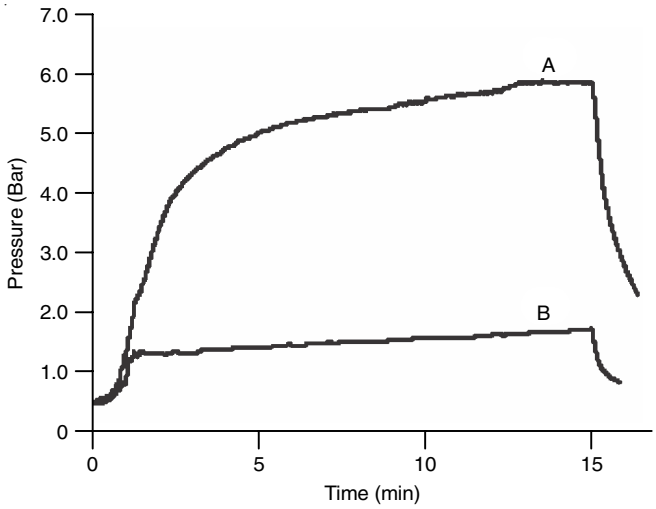


Fig. 1. Pressure-time curve observed from MW heating for 20 min: (A) solvent, base: (B) solvent, additive, substrate, catalyst and base

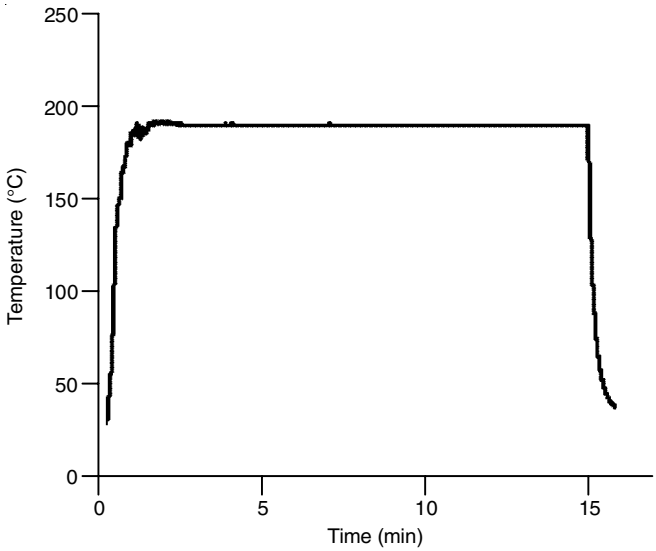
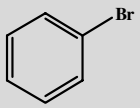
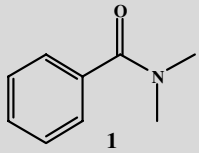
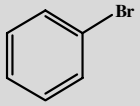
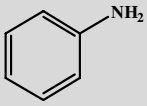
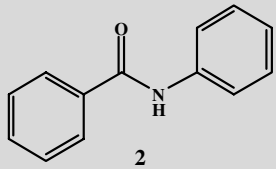


Fig. 2. Variation of temperature and time for a reaction mixture under microwave heating (Table-3. entry 2)

The chemical process consumes dimethylamine and carbon monoxide, which results in the pressure drop. The mechanistic

TABLE-3
CARBONYLATION OF BROMOBENZENE WITH DMF AS CO SOURCE CATALYZED BY Pd SCHIFF BASE COMPLEX

Entry	Aryl bromide	Amine	Product	Time (min)	Temp. (°C)	Isolated yield (%)
1		–	 **1**	20	210	59
2			 **2**	20	210	64

*Reaction condition: Bromobenzene (0.75 mmol), aniline (3 mmol), additive (0.75 mmol), KO*t*-Bu (0.75 mmol), Pd Schiff base complex (0.04 mmol), DMF (mL), microwave heating.

pathway explains that in the first step palladium(0) and aryl bromide form aryl palladium complex (**3**) by oxidative addition, which coordinates to carbon monoxide. As a result, compound **4** aroylpalladium is synthesized. The reactive aroylpalladium species should be easily attacked by amine to form amide **1** [16]. Aroylimidazoles appear to be necessary for the process to proceed, as substituting imidazole for *N*-methylimidazole has a negative effect on the synthesis.

In coordination with dimethylamine, excess aniline (4 eqn.) was added to the reaction mixture as nucleophile. Additionally, additional KO^t-Bu was added to assure the release of carbon monoxide and dimethylamine. When the bidentate ligand was employed in place of the monodentate ligand, the product was obtained effectively. This is consistent with the observation that inactive palladium carbonyl complexes can't form when Pd atoms accumulate due to the inhibition of bidentate ligands [17,18].

A non-favoured insertion of carbon monoxide into the aroylpalladium complex to produce the arylpalladiumcarbonyl complex explains, at least in part, why electron-deficient aryl bromides do not produce aryl amides. The earlier finding that electron-deficient halides are substantially more likely than their electron-rich analogs to undergo decarbonylation support this theory [19].

Schnyder *et al.* [16] used formamide as an ammonia synthon to synthesize successfully some primary aromatic halides under carbon monoxide atmosphere. For these reactions, a nucleophilic Lewis base like imidazole or DMAP was combined with a palladium catalyst. An aryl dimethylamide was obtained in 89% yield. Here, imidazole served as the base and DMF served as both the solvent and source. At the carbon monoxide 5 bar pressure, the reaction was continued for 18 h. It is significant to observe that the amide production required the introduction of carbon monoxide gas into the reaction vessel.

Conclusion

In this methodology, the carbonylation of aryl bromide and substituted aryl halide was performed using microwave heating. It was found that among the different aryl halide, electron-rich halides generally give better results in comparison to electron-deficient species. A novel technique for the synthesis of *N*,*N*-dimethyl substituted amide as well aryl amide from aryl halides by carbonylation involving di-μ-dichloro-*bis*(benzylidene aniline)palladium(II) complex system free from the initial pressure of carbon monoxide. Here, DMF itself behaves *in situ* source generator of both carbon monoxide and dimethylamine. From the investigated reaction path, the results confirmed that the reaction has proceeded through DMF decomposition with subsequent aminocarbonylation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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