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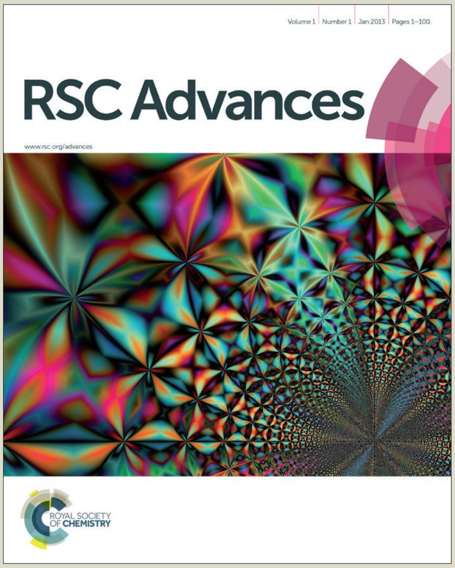

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A facile and practical copper diacetate mediated, ligand free C-N cross coupling of trivalent organobismuth compounds with amines and N-Heteroarenes

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Abstract

In present work, efficient Cu (OAc)$_2$.H$_2$O catalyzed protocol in absence of any additional ligand has been developed for the *N*-arylation of amines and nitrogen containing heterocycles using trivalent organobismuth reagents under mild conditions. This protocol tolerates variety of functional groups on amines and the organobismuth reagent with high degree of chemoselectivity.

Key words:

Organobismuth, N-Arylation, heterocycles, chemoselectivity

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Introduction

The *N*-aryl nitrogen heterocycles such as arylpyrroles, arylpyrazoles, arylimidazoles, aryltriazoles, arylindoles, arylcarbazoles, diarylamines etc. are unique building blocks in bioactive natural products and pharmaceutically interesting compounds.[1] As a more efficient and facile method for N-arylation, the transition-metal-catalyzed coupling of aryl halides and amines is powerful method in both academic and industrial laboratories.[2] However, current methods have some potential limitations because these reactions are environmental unfriendly as they require stoichiometric amounts of copper or copper salts, which produce significant amounts of wastes, high reaction temperatures and also uses expensive transition-metal catalysts such as palladium[3] and rhodium[4]. There are few reports where low cost nickel[5]and cobalt[6] complexes were used as catalyst but their selectivity was not good. Thus screening inexpensive and environmental benign metal catalysts for the arylation reaction still remains a great challenge. In recent years, Buchwald and Hartwig initiated the use of inexpensive copper catalysts bearing various ligands that have provided a highly economical and efficient method for the N-arylation of nitrogen-containing heterocycles with aryl halides.[7] The ligands employed in the Cu-catalyzed reactions includes beta-diketones[8], 1, 2-diamines[9], phenanthrolines[10], bipyridines[11], amino acids[12], phosphines[13] and others.[14] These chelating ligands play an important role in controlling the concentration of active catalytic species, but they may contaminate the final products.[15] Therefore use of ligand-free catalysts seems to be a good alternative to avoid the inconvenience of ligand removal from reaction mixtures.

It is noted that simple inorganic copper (II) salts without extra ligands for catalyzing such coupling reactions is of limited scope. [18] There are few reports on the amination of aryl halides with amines promoted by copper (II) salts without using organic ligands, they often required large amounts of Cu $(OAc)_2$ [18a, b] or copper oxide nanoparticles[18c], which raised the cost of the reaction. Choudary and coworkers reported an efficient catalytic N-arylation reaction using the copper (II) apatite as the catalyst but require high catalyst loading.[18d] To this end, the development of a simple, easily available, economical copper catalyst with a low catalyst loading in the absence of any additional ligands for such coupling reactions would be highly demanding.

As a carbon source, we focused on the low toxic organobismuth compounds [19] for use in copper-mediated C-N bond formation with amines and imides. N- phenylation of aliphatic and aromatic amines by Ph_3Bi under copper salt catalysis giving moderate yield of mono or

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diphenylated amines under mild conditions was reported by Barton *et a1.*[20] Good yields of mono and diphenylated derivatives was achieved in presence of metallic copper at room temperature but substrate scope is limited. In another study Finet *et al.* [21] used triphenylbismuth diacetate as aryl source which reacts with various N-H containing heteroarenes in the presence of a catalytic amount of copper diacetate to afford moderate yields of the N-phenyl heteroarenes. Indoles are C_3 or N-phenylated by triphenylbismuth bis-trifluoroacetate under copper catalyst.[22] Combes and Finet [23] reported reaction of triarylbismuthanes with iodobenzene diacetate in DCM under mild, neutral conditions to afford triarylbismuth diacetates, which can be isolated in good yields. The reagents can also be directly used in a one-pot copper catalyzed N-arylatlon of anilines to give near quantitative yields of the corresponding diarylamines. Various hydrazine derivatives were studied with respect to arylation by triarylbismuthane and triarylbismuth diacetate reagents with emphasis on scope and limitations by Tsubrik *et al.*[24] Among these reagents, a few contained bulky substituents in their aromatic rings and substrates spanned a range from simple hydrazides to triply protected hydrazines. Organobismuth derivatives of pyrocatechol fragment for arylation of piperazines using copper acetate as catalyst in DCM was reported by Vassileva *et al.* [25] which was used to synthesize Eltoptazine [l-(2,3-dihydro- 1,4-benzodioxine-5-yl)-piperazine] a potential anxiolytic and antidepressant drug. Recently copper-catalyzed coupling reaction between alkynyl (triaryl) bismuthonium salts and five-membered imides was reported by Sueda *et al.*[26] which was utilized to synthesize 4-Amino-1, 2, 3-triazole. In above cases they combined the corresponding trivalent and in few cases pentavalent organobismuth compounds with a stoichiometric amount of copper salt. Recently Petiot *et al.*[27] used copper catalyzed N-arylation of azoles and diazoles using functionalized organobismuth (III) reagents. In addition they extended this protocol to N-arylate protected tryptophan derivatives promoted by a substoichiometric amount of copper acetate.

In this paper, we report a simple reagent system consisting of the easily accessible organonobismuth (III) reagents and copper diacetate which catalyzes the *N*-arylation of various amines and N-heteroarenes in absence of any ligand. Optimization of reaction parameters such as amount of catalyst, role of bases, role of solvents, role of oxygen and mole ratio of organobismuth (III) reagents is also studied.

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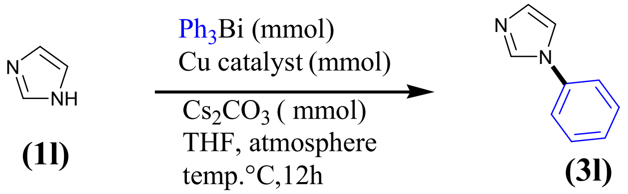
Results and discussion

Usually pentavalent organobismuth species are prepared from their corresponding trivalent analogues, our main goals is to develop conditions that would operate directly with trivalent organobismuthanes. Another objective is to develop a protocol that would allow the use of substoichiometric amounts of catalyst and tolerate a wide diversity of functional groups on both coupling partners. With these goals in mind we initiated our investigation by examining the conditions under which coupling reaction of imidazole and triphenyl bismuthine proceed efficiently (Scheme 1).



Scheme 1 Optimization of reaction conditions for the N-phenylation of imidazole **1**with triphenylbismuthine

Screening of catalyst

Copper salts appear to be the most effective in coupling with poorly nucleophilic nitrogen sources such as amides and imides. In determining the effect of the copper salt for C-N cross coupling, both copper (I) and copper (II) salts were tested with imidazole (1.2mmol) and triphenyl bismuthine (1.0 mmol) as model substrates (Scheme1). Results from screening experiment are summarized in Table 1.

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Table 1 Influence of various copper salts on N-arylation of imidazole with triphenyl bismuthine in THF[a] at 80°C

Entry	Cu salt (1.5 mmol)	Reaction time (h)	Yield [b] (%)
1	$CuSO_4$	12 h	Trace
2	Cu powder	12 h	55
3	Cu $(OAc)_2$	12 h	85
4	CuI	12 h	45
5	CuBr	12 h	35
6	CuCl	12 h	25
7	CuO	12 h	15
8	--	12 h	None

[a] Reaction conditions: Triphenyl bismuthine (1 mmol), imidazole (1.2 mmol), Cs_2CO_3 (2 mmol)
[b] Isolated yields

Among the tested copper salts, Cu $(OAc)_2$ was found to be the best catalyst, which afforded 85% yield of 1-phenyl imidazole(**3l**) in presence of Cs_2CO_3 as base for 12 h at 80°C (Table 1, entry 3). Cu powder and CuI giving **3l** in moderate yields (Table 1, entry 2 and 4), but Cu powder catalyst require acetic acid as non aqueous reaction medium. In case of $CuSO_4$ and CuO, poor yield of **3l** was obtained (Table 1, entry 1 and 7). CuBr, and CuCl catalyst are more efficient than $CuSO_4$ and CuO produced 35 % and 25 % yields of **3l** (Table 1, entry 5 and 6). It is interesting to note that in CuBr catalysis cleavage of CAr-Bi bonds resulted in self coupling of triphenyl bismuthine giving isolated biphenyl in 45% yield along with 35% yield of N-phenyl imidazole using column chromatographic separation. Since CuBr and CuCl are more expensive and oxidizes very readily, so their use in C-N cross coupling is avoided. Hence the most efficient, inexpensive, and air-stable Cu $(OAc)_2$ was selected as the catalyst for all further reactions. It has been found that 1.5mmol copper acetate catalyst under optimized reaction conditions provide excellent yields. Controlled experiment conducted in the absence of catalyst indicate no desired C-N cross coupled product (Table 1, entry 8) the only detected and separated products were unreacted starting material and small amount of biphenyl formed due to self

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coupling of organobismuthine ,which is known reactivity of organobismuthine under metal catalysis.

Screening of bases

The efficiency of arylation with the Ar_3Bi / Cu (OAc)$_2$ system is highly dependent on basicity of amine as shown by Barton[20]. To select the appropriate base for N-arylation reaction, we carried out (Scheme1) in presence of various bases under optimized reaction conditions. The results are summarized in Table 2.

Table 2 Effect of different bases on N-arylation of imidazole with triphenyl bismuthine in THF[a], at 80°C

Entry	Base	Reaction time (h)	Yield[b] (%)
1	KOH	12h	68
2	K_2CO_3	12h	75
3	K_3PO_4	12h	25
4	CsF	12h	20
5	Cs_2CO_3	12h	85
6	NaOH	12h	35
7	KF	12h	45
8	TEA	12h	65
9	--	12h	No reaction

[a] Reaction conditions: catalyst (1.5mmol), Triphenyl bismuthine (1 mmol), Imidazole (1.2 mmol), Base (2 mmol),

[b] Isolated yields

The study shows that, the reaction proceeds smoothly in presence of Cs_2CO_3 which gives 85% yield of N-phenyl imidazole (Table 2, entry 5). Other bases namely K_3PO_4, CsF and NaOH afforded low yields of **3l** (Table 2, entries 3, 4, 6). KOH and K_2CO_3 are other better choices in C-N cross coupling which gives excellent yields (Table 2, entries 1 and 2). In case of TEA,

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moderate yield of C-N cross coupled product was obtained (Table 2, entry 8).The coupling reaction does not proceed in the absence of base (Table 2, entry 9).

Screening of Solvents

It is well known fact that the choice of solvent significantly influences the C-N cross coupling reaction. To study the effect of different solvents in our system, we performed (Scheme1) using Cs_2CO_3 as base and Cu (OAc) $_2$ as catalyst. Typical solvent effects are summarized in Table 3.

Table 3 Influence of solvent in N-arylation of imidazole with triphenyl bismuthine[a]

Entry	Solvent	T (°C)	Yield[b] (%)
1	DMF	120	40
2	DMSO	120	35
3	$C_6H_5CH_3$	120	55[c]
4	MeCN	80	10
5	DCM	80	65[c]
6	THF	80	85
7	THF	50	45
8	THF	60	60
9	THF	70	70
10	H_2O	100	0
11	MeOH	80	0

[a] Reaction conditions: Catalyst (1.5 mmol), Triphenyl bismuthine (1 mmol), Imidazole (1.2 mmol), Cs_2CO_3 (2 mmol), 12 h

[b] Isolated yields

[c] Catalyst loading (2 mmol)

As seen from Table 3, the reaction proceeds in both non-polar and polar solvent with significant variation in yield. $C_6H_5CH_3$ and DCM which are non polar solvents favored the formation of **3l** and gives moderate yield (Table 3, entry3 and 5) but require high catalyst loading

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(2mmol).THF gave the best results with Cs_2CO_3 as base at 80°C (Table 3, entry 6) with 0.5mmol copper catalyst. In case of MeCN, very poor yield of N-phenyl imidazole(**3l)** was obtained at 80°C (Table 3, entry 4).With increase in polarity of solvents, the cleavage of the CAr-Bi bond was found to be enhanced, and in DMF (Table 3, entry 1) the predominant product was the homo coupled biphenyl along with **3l** .When reactions were conducted with optimal solvent, THF at 70°C, 60°C and 50°Cdecrease in yield of N-phenyl imidazole was noticed (Table 3, entries 7, 8 and 9). In H_2O and MeOH under reflux (Table 3, entry10 and 11), no C-N cross coupling was observed instead white suspension got accumulated on the inner walls of the reaction flask suggesting the decomposition of triphenyl bismuthine to bismuth hydroxide.

It is worth mentioning that, the reaction temperature, 110-130 °C which was proved to be necessary for other Cu-catalyzed *N*-arylations of amines and *N*-heterocycles with aryl halides, our catalytic system reduce reaction temperature to 80°C.

Effect of Oxygen, Air and inert atmosphere

An inert atmosphere was not essential requirement during the reaction, but protection from atmospheric moisture is needed. Beneficial effect of oxygen on O-arylation of phenols using trivalent organobismuthanes was investigated by Crifar *et al*.[28] To check the effect of oxygen on N-arylation, we tested the model reaction (Scheme1) under different reaction atmosphere. Results from the reaction atmosphere are presented in Table 4.

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Table 4 Effect of oxygen, air and N_2 atmosphere on the N-phenylation of imidazole **1** using triphenyl bismuthine[a] at 80°C

Entry	Ph_3Bi (mmol)	Cu (OAc)$_2$ (mmol)	Atm.	Yield[b] (%)
1	1.0	1.5	Air	90
2	1.0	1.5	O_2	85
3	1.0	1.5	N_2	70
4	0.7	1.5	Air	81
5	0.33	1.5	Air	50
6	1.0	1.0	Air	70
7	1.0	1.5	Air	65[c]
8	1.0	0.5	Air	55
9	1.0	0.1	Air	30

[a] Reaction conditions: Triphenyl bismuthine, imidazole (1.2 mmol),Cs_2CO_3 (2 mmol) in 5mLTHF

[b] Isolated yields

[c] Reaction was conducted in 50 mL flask

On reacting 1.0 mmol of triphenylbismuth with imidazole (**1l**) in the presence of 1.5 mmol of copper acetate and 2.0 mmol of Cs_2CO_3 under air atmosphere, we obtained **3l** in 90 % yield (Table 4, entry 1). When the reaction was carried out under same stoichiometric ratio but in the pure O_2 atmosphere, 85% yield was noticed (Table 4, entry 2). To validate the importance of oxygen, we performed the reaction under nitrogen atmosphere and noticed a drop in the yield of **3l** (Table 4, entry 3) thereby suggesting the role of air/O_2 during catalytic cycle under Cu-acetate. In addition when the reaction was carried out in a two neck round bottom flask of 50 mL capacity wherein more space existed due to which the yield was depressed, thus reflecting effect of molecular oxygen on reaction (Table 4, entry 7).The detail explanation is given in discussion part of mechanism. When 0.5mmol of copper acetate was used, it has been found that the yield

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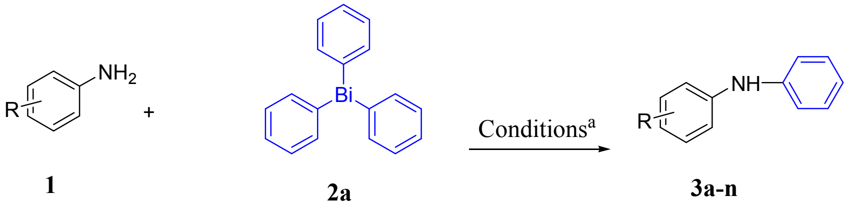
was further decreased up to 55 % (Table 4, entry 8). However, further reduction in the catalyst loading was not tolerated where merely 30% yield of desired product was obtained (Table 4, entry 9).

To evaluate the transferability of second aryl group from the triphenylbismuthane ,we performed the reaction using 0.7 mmol and observed a significant drop in yield of N-phenyl imidazole(Table 4 , entry 4).This clearly indicates only one aryl group can be transferred from triarylbismuthane. Further reduction in mole ratio of triphenylbismuthine (0.33mmol) delivers only 50 % yield of product (Table 4, entry 5) which also supports above observation. This phenomenon is well known in copper catalysis involving organobismuth reagents.[27,28] From above results it has been concluded that, the yield of N-phenylated product was dependent upon the amount of Cu $(OAc)_2$.

Hence the optimum conditions for cross-coupling reactions in THF consist of the combination of Cu $(OAc)_2$ (1.5mmol) and Cs_2CO_3 (2.0 mmol) at 80°C for 12 h without protection of air. The reactions were monitored by TLC as well as by the color change from the initial deep blue to turquoise green, with the simultaneous precipitation of grayish Cu (I) salt.

After optimizing the reaction conditions, the reaction scope was extended with electronically different anilines and triphenyl bismuthine (Scheme 2).



Scheme 2: N-Arylation of Amines (**1a-f**), Amides (**1g-h**), Sulphonamine (**1k**), Imidazole (**1l**) and Indole (**1m**) using triphenylbismuthane (**2a**)

We chose several nitrogenated compounds possessing various functional groups for our study. Typical results are summarized in Table 5.

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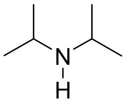
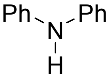
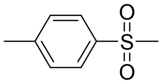
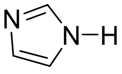
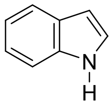
Table 5 N-Arylation of amines with triphenyl bismuthine[a]

Entry	Amine R (**1**)	N-arylated product (**3**)	Yield[b] (%)
1	H (**1a**)	**3a**	78
2	*p*-Br (**1b**)	**3b**	70
3	*p*-Cl (**1c**)	**3c**	65
4	*p*-NO_2 (**1d**)	**3d**	65
5	*p*-OCH_3 (**1e**)	**3e**	88
6	*p*-CH_3 (**1f**)	**3f**	86
7	C_6H_5CO (**1g**)	**3g**	45
8	CH_3CO (**1h**)	**3h**	32
9	 (**1i**)	**3i**	--
10	 (**1j**)	**3j**	--
11	 (**1k**)	**3k**	40
12	 (**1l**)	**3l**	80
13[c]	(**1l**)	**3m**	75
14	 (**1m**)	**3n**	75

[a] Conditions: Amine (1.0 mmol), Ph_3Bi (1.2 mmol), Cu $(OAc)_2$ (1.5mmol), Cs_2CO_3 (2.0mmol), THF (5 mL), 80°C, 12h

[b] Isolated yields.

[c] Reaction was carried out by *p*-tolylbismuthine(2d).

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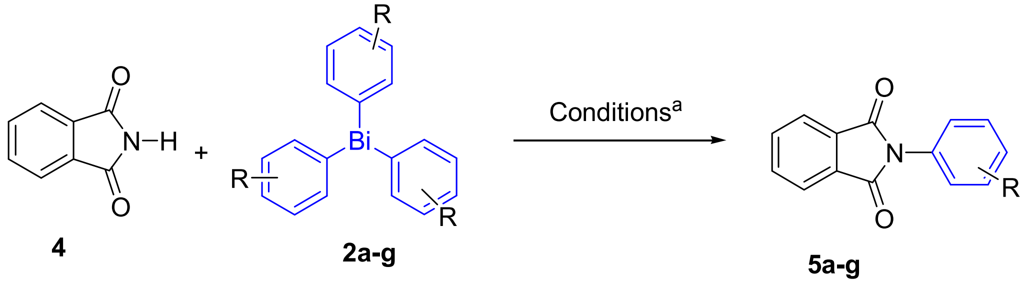
As illustrated in Table 5, aniline was monoarylated successfully using triphenyl bismuthine (Table 5, entry1). Aromatic amines bearing either electron donating groups (Table 5, Entry 6) or electron withdrawing groups (Table 5, entries 4 and 5) gave corresponding unsymmetrical diarylamines in good yield. Notably, halo substituent on the aryl amine remained unaffected under these reaction conditions. Thus, reaction of p-bromoanilline with triphenyl bismuthine gives desired secondary amine in good yield (Table 5, entry 2). Imidazole and Indole was cross-coupled with triphenyl bismuthine affording excellent yields of corresponding N-phenyl derivatives (Table 5, entries 12 and 14). Imidazole on coupling with p-tolylbismuthine provides 75% yield of 1-*p*-tolyl-1*H*-imidazole thereby suggesting the effect of methyl substituent on cross coupling yield (Table 5, entry13[c]).

The few reported methods to arylate amides and imides using the organobismuth alone, or in the presence of copper, either failed completely or gave very unsatisfactory yields. Almost all of these reactions require the use of high temperatures, very basic conditions, and long reaction time. For amide substrates such as benzamide and acetamide the N-phenyaltion under present reaction conditions produces low yields (45 % and 32%) of N-Arylated products (Table 5, entries 7 and 8). *p*-toluenesulfonamide afforded the corresponding N-arylated product in 40% yield (Table 5, entry11). Attempts with both aliphatic and aromatic secondary amines (Table 5, entries 9 and 10) were unsuccessful.

The catalytic activity of this protocol under optimized condition was evaluated with electronically different substituted bismuthines and pthalimide as per Scheme 3.



Scheme 3: Steric and electronic effects of functionalized organobismuthanes (**2a-g**) on the N-arylation of **4**

The results are summarized in Table 5.

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Table 6 The N-arylation of pthalimide (**4**) with functionalized organobismuthanes[a]

Entry	Triaryl bismuthane (**2**) R		N-arylated product (**5**)	Yield[b] (%)
1	H	**(2a)**	**5a**	93
2	*o*-Me	**(2b)**	**5b**	65
3	*m*-Me	**(2c)**	**5c**	70
4	*p*-Me	**(2d)**	**5d**	87
5	*p*-OMe	**(2e)**	**5e**	95
6	*p*-Br	**(2f)**	**5f**	65
7	*p*-Cl	**(2g)**	**5g**	45

[a] Conditions: Pthalimide (1.0 mmol), Ar_3Bi (1.2 mmol), Cu $(OAc)_2$ (1.5mmol), Cs_2CO_3 (2.0mmol), THF (5 mL), 80°C, 12h

[b] Isolated yields.

It has been observed from Table 6 that, in copper-catalyzed reactions, the steric hindrance of the organobismuth reagent plays a significant role, probably at the stage of the transmetallation from bismuth to copper. When this transfer is very easy (by coordination of the copper species with an amine), the steric effect induces less important consequences. Most of bismuthines allows the arylation of the pthalimide heterocycle under mild and normal practical conditions with good yields. The reaction activities of bromo and chloro bismuthines are however less (Table 6, entry 6 and 7), when substituted with electron withdrawing group, particularly methoxy, reacts well with pthalimide giving 95% yield of **5e** (Table 6, entry 5). Electron donating group at *para*- position favour the formation of cross coupled product over *ortho* and *meta* substitution (Table 6, entries 2, 3 and 4) affording excellent yields. In the case of *ortho*-tolylbismuthine, the influence of sterically hindered methyl substituent on aryl group gives diacetate during reaction course which was clearly seen by its moderate yield (Table 6, entry 2).

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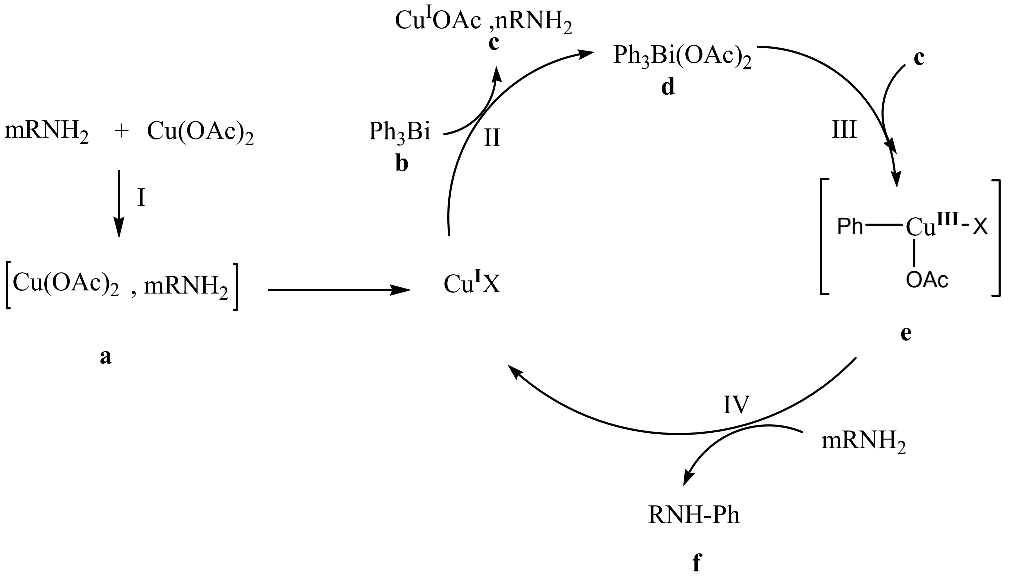
It is important to note that, present protocol tolerate thermally sensitive functional groups in the substrate along with high levels of chemo selectivity, avoiding the occurrence of other competitive coupling reactions such as *O*-arylation and aryl amidation.

Possible Mechanism of N-Phenylation

The mechanism of the present N-arylation reaction with triarylbismuthane is not clear at present. We consider similar mechanisms for the N-arylation with pentavalent bismuth compounds proposed by Barton *et al.*[20], reaction with arylboronic acids proposed by Collman *et al*[29a,b] and the S-arylation with arylsilanes as proposed by Luo *et al.*[30], which may be relevant to the N-arylation demonstrated here. Possible mechanism of the reaction between triarylbismuthanes and amine in the formation of diaryl amines is depicted in Scheme 4.



Scheme 4: Possible Mechanism of N-Phenylation of amine

In the step I catalyst activation takes place in the presence of aromatic amine and generates copper diacetate amine complex (**a**).This complex in step II undergoes oxidative addition with trivalent organobismuth reagent Ar_3Bi (**b**) which leads to the formation of Cu^I complex(**c**) and pentavalent organobismuth diacetate $Ar_3Bi(OAc)_2$(**d**) as key intermediate. In Step III ligand coupling takes place between (**c**) and (**d**) where phenyl copper (III) species (**e**) get formed. This Species in step IV phenylate amine to afford N-arylated product (**f**) and Cu^IX and catalytic cycle was continued.

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Oxygen is a highly atom-economical, environmentally benign, and abundant oxidant, which makes it ideal in many ways.[31] The chemistry of copper in combination with molecular oxygen, increases exponentially since oxygen can act as either a sink for electrons (oxidase activity) or a source of oxygen atoms that are incorporated into the product (oxygenase activity) or both[32]. The oxidation of copper with oxygen is a facile process allowing catalytic turnover in net oxidative processes and ready access to the higher Cu^{III} oxidation state, which facilitates a variety of transformations including two-electron reductive elimination to Cu^{I}. Molecular oxygen does not generate toxic byproducts, which get either reduced to water, occasionally via H_2O_2 or get incorporated into the target structure. Such oxidations using oxygen or air (21% oxygen) have been employed safely in numerous commodity chemical continuous and batch processes.[32]

As discussed previously an inert atmosphere was not essential, when the reaction was carried out in the pure O_2 atmosphere or in a two neck round bottom flask of 50 mL capacity, lower yields of desired product was noticed (Table 4, entries 2and 7).These results hints that molecular oxygen plays a critical role in a copper catalyzed reaction and suggest the catalytically active species to be Cu (I), which was formed in situ by oxidizing triarylbismuthine with O_2 from air during the reaction. The formation of Cu (I) species was supported by the observation of characteristic pale green colour of solution. A sequential color changes observed during the N-arylation reaction indicate that the oxidation of organobismuth (III) compound with subsequent Cu (II) to Cu (I) should be a complex process. The presence of a suitable amount of air in the round bottom flask is crucial to the formation of Bi (V) intermediate. An excess amount of air (or oxygen) is unfavorable to the reaction since the Cu (I) species was further oxidized to less active Cu (II) species, as evidenced by the distinctive blue colored copper amine complex.

It is important to note here that ,we were able to isolate in situ formed intermediate (**d**) under our reaction condition and characterized it as $Ar_3Bi\ (OAc)_2$ by ^{1}HNMR and IR spectroscopy. This signifies the conversion of +3 oxidation state of bismuth to +5 state under copper catalyst in inert solvent. As byproduct during catalytic cycle were presumably H_2O_2 and CH_3COOH which exerts oxidizing action and get enhanced in the presence of added inorganic bases. This might be the reason for in situ oxidation triphenylbismuthine to $Ar_3Bi\ (OAc)_2$. There are reports where tris (2-methoxyphenyl) bismuth is oxidized to the corresponding diacetate in relatively good yields by iodobenzene diacetate under neutral conditions,[33] Oxidation of the trivalent bismuth compound was done by reaction with sodium perborate in acetic acid, [34]

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which led to the diacetate in 63% yield. On the other hand copper diacetate increases the rate of decomposition of triarylbismuth diacetate.[35]

It is interesting to note that, addition of catalytic amount of copper to intermediate (d) allows high yield and selective phenylation of pthalimide thereby suggesting the role of copper catalyst in N-phenylation. Attempts to isolate bismuth containing byproducts were unsuccessful due to their labile nature but small amount of biaryl were detected together with N-arylated product due to reactivity of triarylbismuthines.The presence of aryl radical species in the course of N-arylation reaction with triarylbismuthane and in situ generated pentavalent organobismuthane [$Ar_3Bi~(OAc)_2$] was over ruled which is in agreement with the Barton's procedure.

In N-Arylation of a different group of N-H containing compounds with triarylbismuth and cupric acetate, tertiary amine such as triethylamine or pyridine act as promoter.[36] They play important role in increasing the solubility of the substrate thereby allowing the reaction to proceed at low temperature and in good yields. We are employing Cs_2CO_3 as optimized base in presence of air atmosphere it also shows enhancement in the solubility of substrate thereby follows similar function as promoter. A base promoter has a remarkable effect in these arylation reactions where product formation in its absence in the case of imidazole is indicative (Table 2, entry 9) and thereby significantly improves the yield in the phenylation of 4-nitroaniline.

In the present study, key mechanistic features of N-arylation reaction were elucidated such as the identity of the catalyst inactive state and isolation of intermediate. In addition principles that motivate the ability of copper that tends to undergo one-electron redox changes, to mediate a two-electron oxidative coupling reaction with a four-electron oxidant (O_2) was identified.

Conclusions

We have successfully developed a highly efficient, simple, low temperature and easily accessible protocol to N-arylate nitrogenated compounds like amines, amides, sulfonamides and imides with organobismuth (III) compounds. The present coupling reaction gave moderate to excellent yields of N-substituted pthalimide in comparison with earlier reports. Methodology may be prominently suitable for synthesis of biologically active N-aryl heterocycles under copper diacetate catalysis.

Experimental

General

All reactions and manipulations were conducted under an air atmosphere. Organobismuth (III) compounds (**2a-g**) were synthesized by literature procedures.[37a, b] Copper acetate and heteroarenes were purchased from commercial sources and used without further purification. Solvents were distilled before use. IR spectra were recorded on a Shimadzu 8400 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian-300MHz spectrometer with $CDCl_3$ as the solvent and tetra methyl silane (TMS) as the internal standard. GCMS data were collected on a Shimadzu Gas chromatograph mass spectrometer QP5050. The reactions were monitored by TLC, and visualized with UV light followed by development in iodine chamber. Preparative column chromatography was carried out on a column 10cm x l.5cm with silica gel 60/120 mesh size. GCMS /CHNS analysis of few representative compounds is provided in characterization section.

General catalytic procedure for the N-arylation of nitrogen containing heterocycles with Organobismuth (III) reagents

To a solution of $Cu(OAc)_2.H_2O$ (1.5 mmol) in THF (5 mL) were added organobismuth (III) compound (1.2 mmol), amine or nitrogen-containing heterocycle (1.0 mmol), and Cs_2CO_3 (2.0 mmol) under air atmosphere. The mixture was stirred at 80°C for 12 h. After cooling to ambient temperature, the mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography on silica gel.

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Graphical Abstract

A facile and practical copper diacetate mediated, ligand free C-N cross coupling of trivalent organobismuth compounds with amines and N-Heteroarenes

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