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Pd-catalyzed coupling of aryl iodides with triarylbismuths as atom-economic multi-coupling organometallic nucleophiles under mild conditions

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ABSTRACT

The facile cross-coupling reactivity of triarylbismuth compounds with aryl iodides was achieved under mild heating conditions. The established catalytic protocol using $Pd(OAc)_2(Cy_2NH)_2$ system exhibited high coupling reactivity with a variety of triarylbismuth and aryl iodide compounds under mild conditions. These coupling reactions were completed in short reaction time affording good to high yields of functionalized biaryl products. The studies of multi-coupling reactions with tris(4-iodophenyl)amine, **8** also furnished moderate to good yields of coupled products, **8a–8f**.

There is a growing importance to coupling methodology using organometallic reagents for C–C bond formations in organic synthesis.[1] Organobismuth compounds being non-toxic[2a] are emerging as prospective organometallic green reagents for coupling reactions in organic synthesis.[2,3] With the program of developing atom-efficient or atom-economic multi-coupling organometallic reagents useful for organic synthesis, we have demonstrated the potential use of triarylbismuth compounds for coupling reactions with various organic electrophiles.[3] The Suzuki–Miyaura, Stille, and Hiyama coupling reactions now can be easily carried out at room temperature conditions.[4–6] However, the studies with new ligands are still continuing to enrich these methods.[7,8] Thus, several protocols with a variety of ligands based on amines,[7] carbenes,[8a] oximes,[8b] and imidazolium[8c] salts in addition to phosphines[8d] are reported with promising reactivity in coupling reactions.

In continuation of our studies with triarylbismuths as reagents for organic synthesis, it was of interest to achieve $BiAr_3$ couplings under mild heating conditions. So far the known palladium catalyzed cross-coupling reactions of $BiAr_3$ compounds were performed under 90–100 °C conditions with aryl halides and triflates.[2b,g,3d–f] However, the homo-couplings[9] of triarylbismuth compounds readily occur either at room temperature[9a] or under heating[9b] conditions. In this context, we report here a facile palladium catalyzed coupling reaction of triarylbismuth compounds with aryl iodides under mild heating condition.

To develop an efficient catalytic protocol we have chosen a simple palladium catalyst, $Pd(OAc)_2$ with an amine as ligand for this study, as this combination showed novel reactivity in coupling reactions of aryl boronic acids with aryl bromides under room temperature condition.[7c,d] As part of these efforts, a systematic screening was carried out using 4-iodoacetophenone and $BiPh_3$ as a model reaction under different base, solvent, and temperature conditions (Table 1).

For example, this reaction was studied with $Pd(OAc)_2/2Cy_2NH$ system and potassium acetate base in different solvents such as *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and acetonitrile at 90 °C (entries 1–4). This revealed DMF as a suitable solvent to give high conversion to product **1a** (entry 1). However, the reaction with cyclohexylamine as ligand provided only moderate conversion to the desired product (entry 5). Incidentally, the base K_3PO_4 was proven to be effective in DMF under different heating conditions with dicylohexyl amine ligand (entries 6–9). At this stage we prepared $Pd(OAc)_2(Cy_2NH)_2$ complex (DAPCy) using the literature procedure[7c] in order to use it in our study. Encouragingly, the reaction using DAPCy complex also showed good reactivity at 60 °C in DMF as solvent (entry 10). From this, it was clear that the catalytic system is equally effective with either $Pd(OAc)_2/2Cy_2NH$ or preformed DAPCy system. Further check with different bases revealed that KOAc is a better choice under similar conditions (entries 11–13). In most of these reactions the

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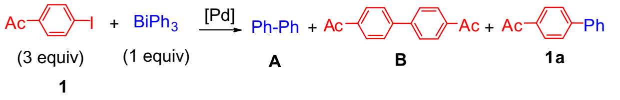
Table 1
Screening conditions[a,b,c]



Entry	Catalyst/ligand	Base (equiv)	Solvent	Time (h)	Temp (°C)	**1** (%)	**A** (%)	**B** (%)	**1a** (%)
1	$Pd(OAc)_2/2Cy_2NH$	KOAc (4)	DMF	4	90	2	10	12	76
2	$Pd(OAc)_2/2Cy_2NH$	KOAc (4)	THF	4	90	50	11	8	9
3	$Pd(OAc)_2/2Cy_2NH$	KOAc (4)	DME	4	90	56	18	10	16
4	$Pd(OAc)_2/2Cy_2NH$	KOAc (4)	MeCN	4	90	47	11	4	34
5	$Pd(OAc)_2/2CyNH_2$	K_3PO_4 (4)	DMF	4	90	2	15	15	66
6	$Pd(OAc)_2/2Cy_2NH$	K_3PO_4 (4)	DMF	4	90	0	16	6	78
7	$Pd(OAc)_2/2Cy_2NH$	K_3PO_4 (4)	DMF	1	90	0	12	10	77
8	$Pd(OAc)_2/2Cy_2NH$	K_3PO_4 (4)	DMF	1	80	4	15	6	75
9	$Pd(OAc)_2/2Cy_2NH$	K_3PO_4 (4)	DMF	1	60	11	13	0	75
10	$Pd(OAc)_2(Cy_2NH)_2$	K_3PO_4 (4)	DMF	1	60	10	14	3	72
11	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (4)	DMF	2	60	7	9	6	77
12	$Pd(OAc)_2(Cy_2NH)_2$	K_2CO_3 (4)	DMF	2	60	15	11	4	69
13	$Pd(OAc)_2(Cy_2NH)_2$	AgOAc (4)	DMF	2	60	42	34	0	24
14	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (4)	DMF	2	40	9	9	0	81 [73]
15	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (4)	DMF	2	35	7	4	0	80 [81]
16	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (4)	DMF	2	25	35	10	0	55 [45]
17	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (3)	DMF	2	35	7	4	0	89 [89]
18	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (2)	DMF	2	35	24	12	0	64
19	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (1)	DMF	2	35	46	13	0	41
20	$Pd(OAc)_2(Cy_2NH)_2$	None	DMF	2	35	63	20	0	17
21	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (3)	DMF	1	35	10	9	0	80
22	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (3)	DMF	2	35	40	6	0	52 [44][d]
23	$Pd(OAc)_2(Cy_2NH)_2$	KOAc (3)	DMF	2	35	23	8	0	65 [65][e]
24	None	KOAc (3)	DMF	2	35	93	0	0	0

[a] Reaction conditions: $BiPh_3$ (0.25 mmol, 1 equiv), 4-iodoacetophenone (0.825 mmol, 3.3 equiv), $Pd(OAc)_2$ (0.0225 mmol, 0.09 equiv), amine ligand (0.045 mmol, 0.18 equiv), base, solvent (3 mL), temperature, and time.

[b] $Pd(OAc)_2(Cy_2NH)_2$ (0.0225 mmol, 0.09 equiv) was employed.

[c] GC conversions are given and isolated yields are given in parenthesis. Isolated yields are calculated considering three aryls from $BiPh_3$ for couplings. Thus, 0.75 mmol of product as 100% yield.

[d] With 3 mol % of $Pd(OAc)_2(Cy_2NH)_2$.

[e] With 6 mol % of $Pd(OAc)_2(Cy_2NH)_2$.

formation of biphenyl (**A**) from $BiPh_3$ and homo-coupled product (**B**) from aryl iodide were formed as the side products.

To suppress these homo-couplings and to further enhance cross-coupling reactivity, the reactions were further carried out by lowering the temperature (entries 14–16). Overall, this reaction was found to be effective even at mild heating conditions either at 35 °C or 40 °C with a high cross-coupling yield and minimized side products (entries 14 and 15). However, the reaction was found to be moderate at room temperature (entry 16). Thus, it was clear that the cross-coupling is facile between 35 and 40 °C temperatures with high cross-coupling yield. Further study using different amounts of KOAc base between 1 and 3 equiv revealed that 3 equiv of base is good enough to get high coupling yield of **1a** (entries 17–19). In this case, the product **1a** was isolated in 89% yield (entry 17). It is to be noted that a control reaction without a base afforded very poor conversion to the product (entry 20). At this stage, we have checked the reaction with 1 h reaction time and this furnished lower yield of the product (entry 21). Importantly, with 3 and 6 mol % of the catalyst loading the reaction delivered lower yields of **1a** (entries 22 and 23). Further, in the absence of a catalyst, formation of the cross-coupled product was not observed (entry 24). Hence, the presence of a catalyst and its amount is important to obtain higher yield of the coupling product (entry 17).

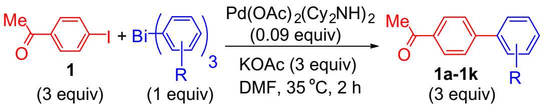
With these studies, it was clear that the coupling reaction is effective with 3 equiv of KOAc base to provide high yield of the product in 2 h reaction time (entry 17). Essentially, the condition with KOAc (3 equiv) using $Pd(OAc)_2(Cy_2NH)_2$ (0.09 equiv) catalyst in DMF as solvent at 35 °C in 2 h emerged as an optimal condition for this reaction (entry 17). This is a remarkable reactivity from the view point that the cross-coupling of $BiPh_3$ as multi-coupling organometallic nucleophile is demonstrated under mild heating conditions.

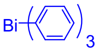
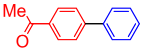
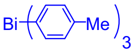
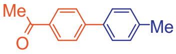
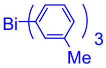
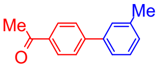
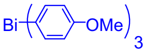
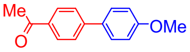
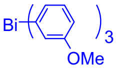
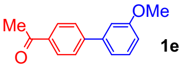
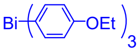
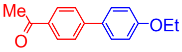
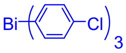
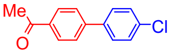
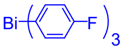
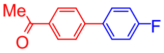
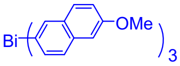
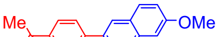
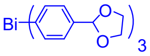
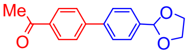
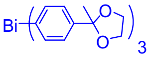
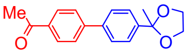
This prompted us to extend the scope of this study with different $BiAr_3$ compounds as given in Table 2.[10] The coupling reactions using 4-iodoacetophenone as an organic electrophile with triarylbismuths as atom-efficient multi-coupling organometallic nucleophiles afforded good to excellent yields of functionalized biphenyls. Effective participation of both electron-rich and -deficient $BiAr_3$ compounds as multi-coupling nucleophiles was demonstrated in all these reactions. The coupling reactions of triarylbismuths with phenyl group containing protected formyl and acetyl groups also fared well under the optimized conditions.

Further, we have also carried out couplings with a diverse range of aryl iodides under the optimized condition. These results are summarized in Table 3. This study also revealed efficient couplings with electron-deficient aryl iodides furnishing excellent yields of functionalized biaryls. The reactivity of electron-rich iodides was found to be impressive with moderate yields as these substrates are otherwise poor substrates in such couplings. The reactions of ortho-substituted aryl iodide with different $BiAr_3$ compounds also furnished good yield of products.

Then, we turned our attention to establish the multi-coupling reactivity of aryl iodides. For this, we have chosen tris(4-iodophenyl)amine (**8**) for the reaction with different $BiAr_3$ compounds in a one-pot operation (Scheme 1). These multi-couplings with

Table 2
Cross-couplings with different $BiAr_3$ compounds[a,b,c]



Entry	Ar_3Bi	Biaryl	Yield (%)
1		 1a	89
2		 1b	90
3		 1c	85
4		 1d	86
5		 1e	80
6		 1f	85
7		 1g	70
8		 1h	78
9		 1i	60
10		 1j	70
11		 1k	70

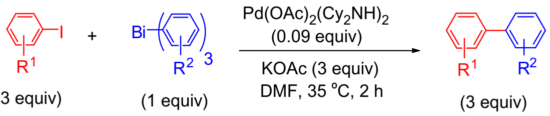
[a] Reaction conditions: 4-iodoacetophenone (0.825 mmol, 3.3 equiv), $BiAr_3$ (0.25 mmol, 1 equiv), $Pd(OAc)_2(Cy_2NH)_2$ (0.0225 mmol, 0.09 equiv), KOAc (0.75 mmol, 3 equiv), DMF (3 mL), 35 °C, 2 h.
[b] Isolated yields were calculated considering three aryl from $BiAr_3$ and 0.75 mmol of cross-coupling product as 100% yield.
[c] All the products were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS analysis.

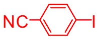
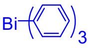
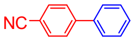
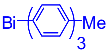
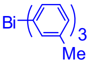
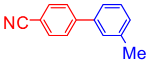
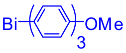
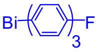
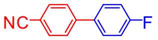
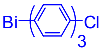
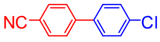
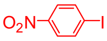
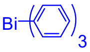
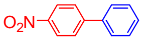
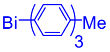
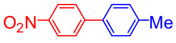
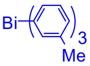
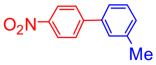
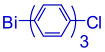
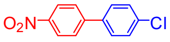
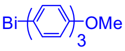
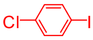
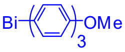
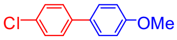
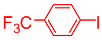
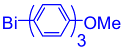
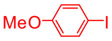
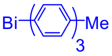
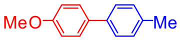
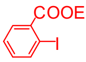
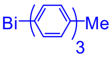
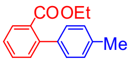
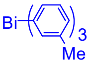
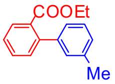
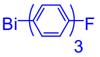
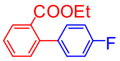
tris(4-iodophenyl)amine under the conditions studied provided moderate to high yields of the coupling products, **8a–8f**. However, biaryls as side products were also formed in these reactions as we have used 0.5 equiv excess of triarylbismuths to facilitate the multi-coupling process with **8**. The excess amount was used to compensate the loss of $BiAr_3$ due to homo-couplings. Although not optimized for multi-couplings with **8**, the coupling studies provided moderate to high yield of the products. Thus, the novel coupling reactivity of $BiAr_3$ compounds was also demonstrated in the synthesis of molecular motifs useful for photo-physical applications.[12]

Our further attempts to establish the reactivity using aryl bromide and aryl triflates with $BiAr_3$ compounds provided mixed results under the established conditions. While the reaction with aryl bromide furnished poor yield of the coupling product, aryl triflate did not furnish the desired coupling.

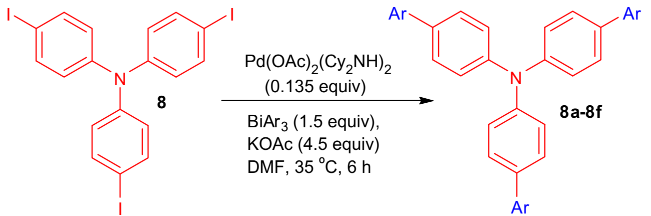
In conclusion, we have demonstrated an efficient cross-coupling of aryl iodides with $BiAr_3$ compounds as atom-efficient multi-coupling organometallic nucleophiles using mild heating conditions under palladium catalysis. Overall, the catalytic system with an easily available palladium precursor and dicyclohexylamine as ligand proved to be very effective for cross-couplings with triarylbismuth compounds. Further efforts are under way to broaden the scope of these couplings in organic synthesis.

Table 3
Couplings of aryl iodides with $BiAr_3$ compounds[a,b,c]



Entry	Aryl iodide	$BiAr_3$	Biaryl	Yield (%)
1	 (2)		 2a	80
2	2		 2b	87
3	2		 2c	82
4	2		 2d	84
5	2		 2e	78
6	2		 2f	75
7	 (3)		 3a	75
8	3		 3b	88
9	3		 3c	86
10	3		 3d	75
11	3		 3e	84
12	 (4)		 4a	75
13	 (5)		 5a	75
14	 (6)		 6a	50
15	 (7)		 7a	65
16	7		 7b	61
17	7		 7c	60

[a] Reaction conditions: aryl iodide (0.825 mmol, 3.3 equiv), $BiAr_3$ (0.25 mmol, 1 equiv), $Pd(OAc)_2(Cy_2NH)_2$ (0.0225 mmol, 0.09 equiv), KOAc (0.75 mmol, 3 equiv), DMF (3 mL), 35 °C, 2 h.
[b] Isolated yields were calculated considering three aryl from $BiAr_3$ and 0.75 mmol of product as 100% yield.
[c] All the products were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS analysis.



8a, Ar = *m*-tolyl(73%)
8b, Ar = p-tolyl (75%)
8c, Ar = *p*-trifluoromethylphenyl (55%)
8d, Ar = *m*-trifluoromethylphenyl (60%)
8e, Ar = *p*-ethoxyphenyl (61%)
8f, Ar = *m*-methoxyphenyl (61%)

Scheme 1. Multi-coupling reactions of tris(4-iodophenyl)amine.[11]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.053.

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10. *General procedure*: A hot-oven dried Schlenk tube was charged with aryl iodide (3.3 equiv, 0.825 mmol), followed by triarylbismuth (1 equiv, 0.25 mmol), KOAc (3 equiv, 0.75 mmol, 0.075 g), $Pd(OAc)_2(Cy_2NH)_2$ (0.09 equiv, 0.0225 mmol, 0.0132 g) and dry DMF (3 mL) solvent under nitrogen atmosphere. The reaction mixture was stirred in an oil bath maintained at 35 °C for 2 h. The contents of the mixture were quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extract was washed with water (2 × 10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, and was concentrated to get a crude product. The crude was subjected to silica gel column chromatography using 2–5% ethyl acetate/petroleum ether as eluent to obtain a biaryl product. Isolated yield of biaryl was calculated considering three aryls from $BiAr_3$.Thus, 0.75 mmol of product is 100% yield.
11. [a]Reaction conditions: tris(4-iodophenyl)amine (0.16 mmol, 1 equiv), $BiAr_3$ (0.24 mmol, 1.5 equiv), $Pd(OAc)_2(Cy_2NH)_2$ (0.0216 mmol, 0.135 equiv), KOAc (0.72 mmol, 4.5 equiv), DMF (6 mL), 35 °C, 6 h. [b]Isolated yields. [c]The 0.16 mmol of **8a**–**8f** correspond to 100% yield.
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