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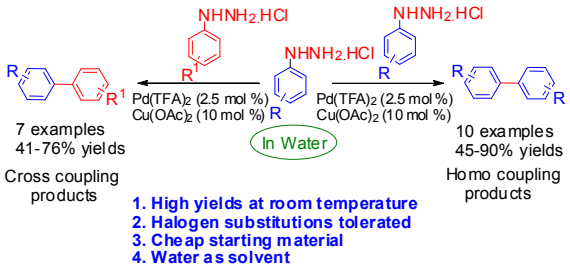

An efficient methodology for the synthesis of biaryls via Pd/Cu catalyzed coupling of unprotected phenylhydrazines in water is reported.

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ARTICLE TYPE

Palladium and copper-catalyzed ligand-free coupling of phenylhydrazines in water

Parul Chauhan,‡[a] Makthala Ravi,‡[a] Shikha Singh,[a] Kanumuri S. R. Raju,[c] Vikas Bajpai,[b] Brijesh Kumar,[b] Wahajuddin,[c] Prem. P. Yadav*[a]

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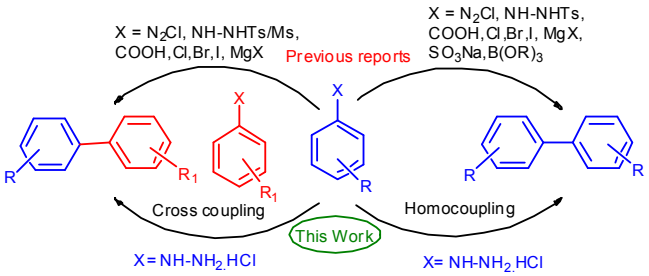
An efficient protocol has been developed for the synthesis of biaryls via Pd/Cu catalyzed coupling of phenylhydrazines in water. Homo and cross couplings were successfully achieved in a ligand-free catalytic system, at room temperature and water as sole reaction medium.

The palladium catalyzed carbon-carbon bond forming reactions are the most important synthetic routes for the generation of biaryls towards construction of natural products and medicinally important molecules. Over the past few decades organometallic methods have impacted tremendously on selective biaryl couplings. Use of water as solvent in these reactions is more recent and limited because of sensitivity, poor solubility of substrate/ligand and use of co-solvent or phase transfer agents.[1] Various biaryl couplings of suitably functionalized arenes such as aryl halides,[2] aryl triflates,[3] aryl diazonium salts,[4] arylboronic acids,[5] aryl acids,[6] aryl magnesium salt,[7] aryl tosyl/mesyl hydrazines,[8] etc are well known in the literature (Scheme 1). All these processes have provided alternative methodologies for biaryl couplings with associated limitations. In the recent past, Cu/Ag has gained special attention as a co-catalyst to facilitate reactions by crucial transmetallation to deliver an aryl-Pd(II) complex in Pd(0)/Pd(II) catalytic cycle. Among, most notable processes are decarboxylative cross coupling processes in which a Cu(I)/Ag(I) co-catalyst catalyzes the expulsion of CO_2 followed by transmetallation and reductive elimination to deliver biaryls.[9] Also a bimetallic Pd/Cu catalyzed desulfitative C-C coupling of sodium salt of aryl sulfinates was reported in water.[10] Inspired by the bimetallic processes[11] and vast literature on biaryl synthesis from functionalized hydrazines[12] and hydrazones,[13] we designed a Pd/Cu catalytic system to achieve an easy and efficient homo and cross coupling of phenylhydrazines. We hypothesized that water soluble phenylhydrazine hydrochloride salts can be easily converted into diazene by a Cu(II) oxidant and the resulted diazene may be subjected to Pd catalyzed C-C bond formation to afford biaryls. To investigate our hypothesis we chose 4-fluorophenyl hydrazine as a model substrate.

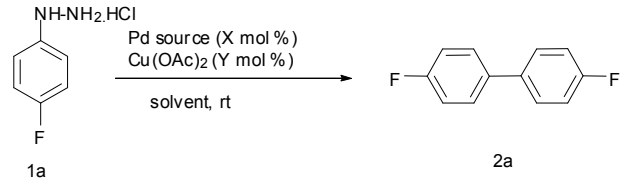
We started the reaction of 1a in the presence of palladium acetate (5 mol%) and copper acetate (10 mol%) in water for 20 min at r.t. To our delight, the reaction proceeded smoothly and provided biaryl 2a in 80 % yield (Table 1, entry 1). To the best of our knowledge, this is the first report on Pd catalyzed synthesis of biaryls from phenylhydrazines using Cu as an oxidant in water.



Scheme 1 Strategies for the synthesis of biaryls

Encouraged by these results, we next evaluated various Pd(II) sources (Table 1, entries 1-6) and found that $Pd(TFA)_2$ (2.5 mol%) is the best Pd source, affording 90% yield of 2a (Table 1, entry 2). Increasing the catalytic loading of palladium from 2.5 mol% to 5 mol% there was no improvement in yield (Table 1, entry 2 versus entry 3). Further a set of reactions were performed to investigate the influence of catalytic amount of copper acetate and found that 10 mol% copper acetate provided best yield (Table 1, entry 2), 5 mol% of copper acetate led to reduction of yield to 78% (Table 1, entry 7) and no further improvement was observed while increasing catalytic loading to 20 mol% (Table 1, entry 8). Other copper sources such as $CuCl_2$ and $CuBr_2$ provided moderate yields (Table 2, entries 1-2), whereas Cu(I) sources such as CuI and Cu_2O resulted in abrupt reduction in yields (Table 2, entries 3-4). Non-copper oxidants such as Ag_2CO_3, TBHP and Iodine were also screened (Table 2, entries 5-7) and none of them were more efficient than the copper acetate for this conversion. Other organic solvents (Table 1, entries 9-14) were also screened and found to give moderate to high yield of 2a where reaction in DMF provided almost comparable yield as compared to water (Table 1, entries 9 and 5-18). After having promising results in hand for the model system, the scope of substituted phenylhydrazines was investigated (Table 3). Optimized protocol was applied to a range of mono (Table 3, entries 1-6 and 8) and disubstituted (Table 3, entries 7 and 9) phenylhydrazines to afford good to excellent yield of corresponding biaryls. Reactions of phenylhydrazines having electron withdrawing groups such as fluoro, chloro, bromo, cyano, nitro and dichloro (Table 3, entries 1a-1c and 1e-1g) and

Table 1 Optimization of catalyst for coupling reaction[a]

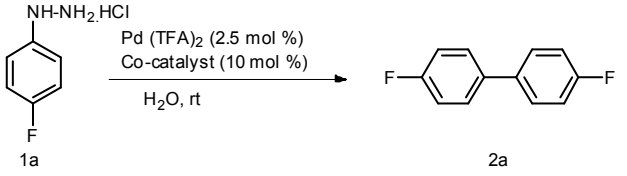


1a 2a

Entry	Pd source	X	Y	Solvent	Time	Yield(%)[b]
1	$Pd(OAc)_2$	5	10	H_2O	20 min	80
2	$Pd(TFA)_2$	2.5	10	H_2O	15 min	90
3	$Pd(TFA)_2$	5	10	H_2O	15 min	90
4	$PdCl_2$	5	10	H_2O	1 h	75
5	$Pd(PPh_3)_2Cl_2$	5	10	H_2O	2 h	65
6	$Pd(PPh_3)_4$	5	10	H_2O	3.5 h	41
7	$Pd(TFA)_2$	2.5	5	H_2O	2 h	78
8	$Pd(TFA)_2$	2.5	20	H_2O	15 min	90
9	$Pd(TFA)_2$	2.5	10	DMF	15 min	90
10	$Pd(TFA)_2$	2.5	10	EtOH	20 min	80
11	$Pd(TFA)_2$	2.5	10	THF	20 min	80
12	$Pd(TFA)_2$	2.5	10	MeOH	20 min	75
13	$Pd(TFA)_2$	2.5	10	DMSO	20 min	85
14	$Pd(TFA)_2$	2.5	10	Toluene	20 min	65
15	$PdCl_2$	2.5	10	DMF	1 h	79
16	$Pd(PPh_3)_2Cl_2$	2.5	10	DMF	2 h	67
17	$Pd(PPh_3)_4$	2.5	10	DMF	3.5 h	42
18	$Pd(OAc)_2$	2.5	10	DMF	2 h	80
19	$Pd(TFA)_2$	1[c]	-	H_2O	15min	0
20	-	-	1[c]	H_2O	15 min	0

[a]Reaction condition: 1a (0.62 mmol), catalyst (X mol %), $Cu(OAc)_2$ (Y mol %), solvent (10 mL) at rt. [b]Isolated yields, [c]Equivalents.

Table 2 Effect of co-catalyst (oxidant)[a]



1a 2a

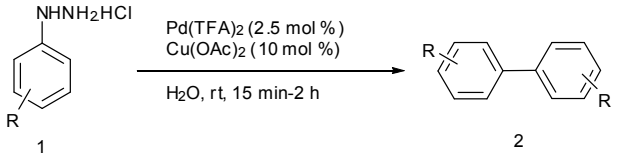
Entry	Co-catalyst	Time	Yield[b]
1	$CuCl_2$	30 min	68
2	$CuBr_2$	30 min	85
3	CuI	1 h	35
4	Cu_2O	2 h	None
5	Ag_2CO_3	30 min	60
6	TBHP[c]	1 h	55
7	Iodine	30 min	51
8	TBHP + CuI[d]	20 min	85

[a]Reaction condition: 1a (0.62 mmol), $Pd(TFA)_2$ (2.5 mol %), co-catalyst (10 mol %), water (10 mL) at rt. [b]Isolated yields. [c]TBHP (1 equivalent). [d]TBHP (1 equivalent) + CuI (10 mol %).

electron donating groups such as methoxy and dimethyl (Table 3, entries 8 and 9) proceeded with similar efficiency and afforded 2a–2i in 68–90% yields (Table 3, entries 1-9).

Notably, halogen groups were compatible with this reaction (2a-2c). Most of the C-C coupling strategies use aryl halides as aryl source, whereas in our process halides are retained in the coupled product. Further cyano and nitro groups are also compatible with present methodology. These functional groups are important post coupling diversification points in medicinal chemistry.[14]

Table 3 Homocoupling of substituted phenylhydrazines[a]

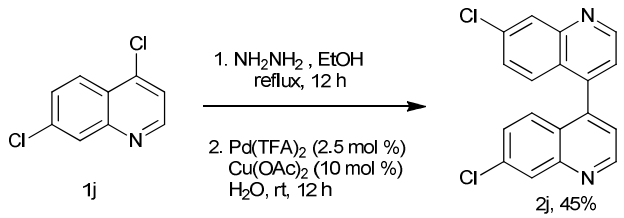


1 2

Entry	R	Product	Time	Yield(%)[b]
1	4-F	2a	15 min	90
2	4-Br	2b	20 min	85
3	4-Cl	2c	15 min	90
4	H	2d	20 min	82
5	4-CN	2e	1 h	69
6	4-NO_2	2f	30 min	81
7	3,4-Di-Cl	2g	25 min	79
8	4-OMe	2h	2 h	68
9	3,4-Di-Me	2i	1 h	80

[a]Reaction condition: 1a (0.62 mmol), $Pd(TFA)_2$ (2.5 mol %), oxidant (10 mol %), water (10 mL) at rt. [b]Isolated yields.

The present method also afforded unique 4,4'-biquinoline efficiently and may prove to be a key process for synthesis of biologically active biheterocycles.[15]

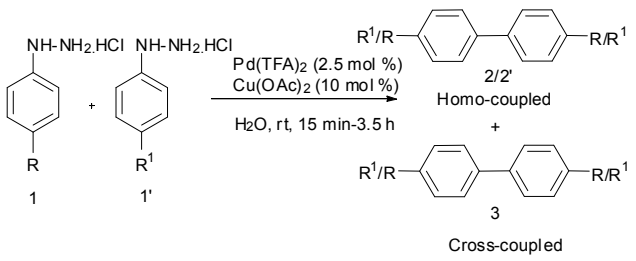


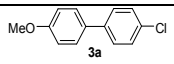
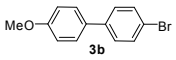
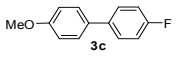
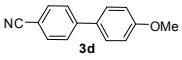
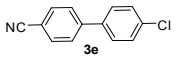
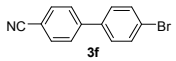
1j

Scheme 2 Synthesis of 4,4'-biquinoline

We tested our methodology for cross coupling reactions of chloro, bromo, fluoro and cyano substituted phenylhydrazines with methoxy and cyano substituted phenylhydrazine under optimized reaction condition (Table 1, entry 2). Cross coupling proceeded smoothly and afforded desired unsymmetrical biaryls (3) in 41-76% yields (Table 4, entries 1-6).

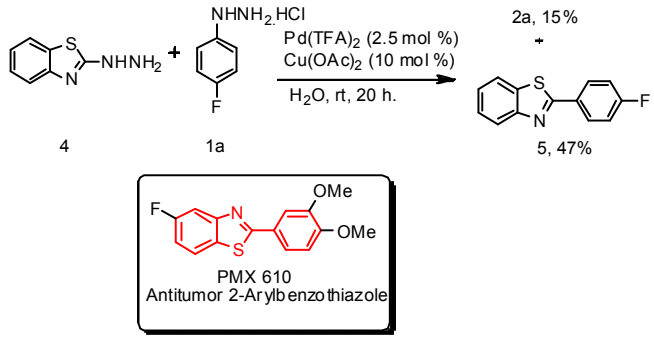
Table 4 Cross-coupling of substituted phenylhydrazines[a]



Entry	R	R^1	Cross coupling product (3)	Time	Yield(%)[b] (3, 2, 2′)
1.	Cl	OMe	 **3a**	2 h	76, 2, 21
2.	Br	OMe	 **3b**	2.5 h	75, 6, 19
3.	F	OMe	 **3c**	2 h	71, 13, 15
4.	CN	OMe	 **3d**	3.5 h	41, 55, 3
5.	Cl	CN	 **3e**	2.5 h	59, 11, 30
6.	Br	CN	 **3f**	2.5 h	64, 25, 10

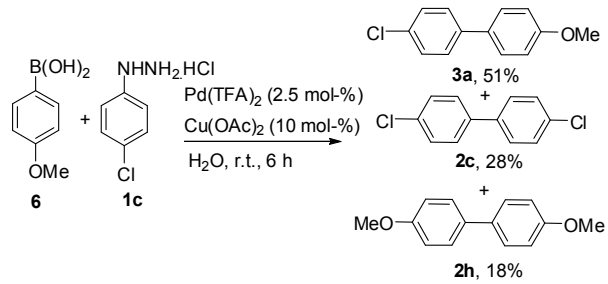
[a]Reaction condition: 1 (0.57 mmol), 1' (0.68 mmol), $Pd(TFA)_2$, (2.5 mol %), $Cu(OAc)_2$ (10 mol %), water (10 mL) at rt. [b]HPLC yields.

The methodology was further extended for synthesis of anticancer pharmacophore 2-arylbenzothiazole[16] (Scheme 3) and Suzuki coupling of aryl boronic acids with phenylhydrazines (Scheme 4).



Scheme 3 Synthesis of 2-arylbenzothiazole.

Recently, Zhao et al., reported Pd-catalyzed Suzuki coupling of phenylhydrazines with arylboronic acid using phosphine ligands, acids and NMP as solvent at 90 ºC.[17] Peng et al., also reported Pd-catalyzed Suzuki coupling of phenylhydrazines with arylboronic acid while using TsCl for activation of hydrazine, SDS as PTC in water at 60 ºC.[18] We herein executed Suzuki cross-coupling of 4-methoxyphenylboronic acid with 4-chlorophenylhydrazine (Scheme 4) under our optimized conditions in water at room temperature without using any hydrazine activation agents like TsCl, ligand and PTC. Further optimization of yield is under progress.



Scheme 4 Pd/Cu catalyzed Suzuki coupling of arylhydrazines hydrochloride in water.

We next conducted some experiments to investigate the role of metals in this reaction. When phenylhydrazine 1a was reacted under optimized conditions with $Pd(TFA)_2$ in absence of Cu(II), no product was observed (Table 1, entry 19). Similarly reaction without $Pd(TFA)_2$ but with $Cu(OAc)_2$ under optimized condition did not afford any biaryl product indicating that both of these metals are essential for coupling (Table 1, entry 20). Also TEMPO displayed a negligible effect on the reaction of 1a in the presence of Pd/Cu to afford 2a, ruling out a radical pathway.

Although a detailed study is required to fully understand the exact mechanism of homo and cross coupling of phenylhydrazines and role of Cu in catalytic cycle, a tentative pathway can be proposed on the basis of our observations and previous reports on phenylhydrazine couplings[8,19] (Figure 1). Phenylhydrazine A undergoes oxidation in the presence of Cu(II) to form diazene intermediate B or complex C, which subsequently undergoes transmetalation with Pd(II) followed by expulsion of N_2 to afford intermediate D. A second transmetalation of intermediate E with C or B to produce a bis-aryl palladium (II) species F, which subsequently undergoes reductive elimination to afford the desired homo and cross-coupled product G and Pd(0). Finally Pd(0) undergo oxidation to Pd(II) completing the catalytic cycle.

Conclusions

In conclusion, biphenyls were synthesized by an efficient Pd/Cu catalytic system from unprotected phenylhydrazines in water. The reaction displayed a better functional group tolerance towards electron donating as well as electron withdrawing groups. Interestingly unsymmetrical biaryl products have moderate selectivity over symmetrical ones in cross coupling reactions. Air and water tolerance, ligand-free catalysis along with high yields at room temperature are key features of this methodology. Further scope of this reaction is in progress for construction of biologically important compounds in our laboratory.

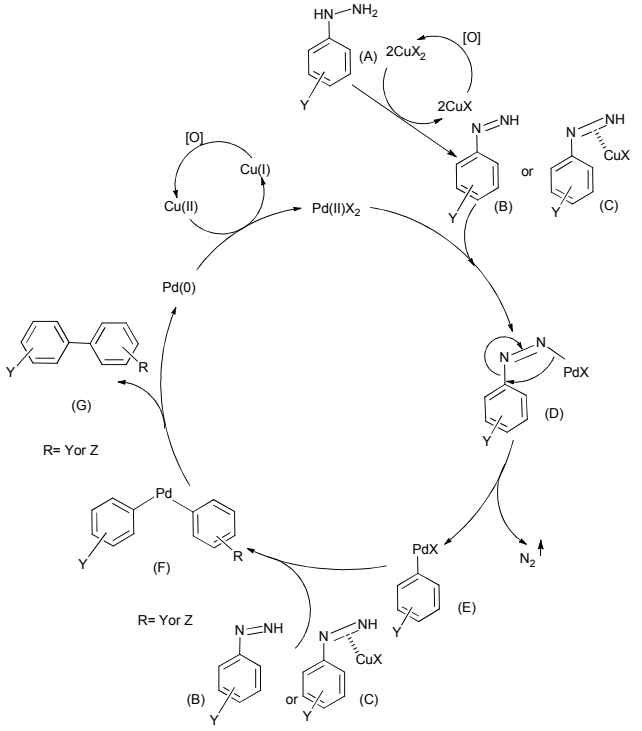


Figure 1 Proposed mechanism.

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Notes and references

[a] *Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow-226031, India. Fax: +91-522-2623405/2623938; Tel: :+91-522-2612411-18, Ext. 4761/4762; E-mail: pp_yadav@cdri.res.in; ppy_cdri@yahoo.co.in*

[b] *Sophisticated Analytical Instrument Facility, CSIR-Central Drug Research Institute, Lucknow-226031, India.*

[c] *Division of Pharmacokinetics and Metabolism, CSIR-Central Drug Research Institute, Lucknow-226031, India.*

† Electronic Supplementary Information (ESI) available: Experimental procedures, data and NMR spectra of all the final compounds. See DOI: 10.1039/b000000x/

‡ P.C and M.R. contributed equally to this work.

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