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## Ligand-free palladium catalyzed ullmann biaryl synthesis: 'household' reagents and mild reaction conditions

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A palladium catalysed Ullmann biaryl synthesis has been developed using hydrazine hydrate as the reducing reagent under room temperature. The combination of  $Pd(OAc)_2$  and hydrazine hydrate works smoothly for the coupling of both electron-rich and electron-deficient aryl iodides, as well as hetero-aryl iodides, leading to a wide range of biaryls in good to excellent yields. The reaction requires only 1 mol%  $Pd(OAc)_2$  and the in-situ generated palladium naoparticles is found to be active catalysis.

Biaryls are core structures that can be found in pharmaceuticals, agrochemicals<sup>1</sup>, natural products<sup>2</sup>, organic functional materials<sup>3</sup>, and ligands<sup>4</sup>. For decades, the coupling of two aromatic units has evolved to be one of the most important methods for the biaryl synthesis.<sup>5,6</sup> While the past century has witnessed significant advances in transition metalcatalyzed cross-couplings between aryl halides and organometallic reagents (e.g. Suzuki, Stille, Negishi and Hiyama coupling reactions), Ullmann biary synthesis<sup>7</sup> is still recognized as a straightforward method for the synthesis of numerous symmetrical and unsymmetrical biaryls from aryl halides without the need for preformation of organometallic species.<sup>8</sup> However, this reaction usually requires stoichiometric input of Cu(0) or Cu(I) salts and relatively harsh conditions (> 200 °C), which somewhat limits its practical application in organic synthesis. As a consequence, the search for milder variations has become a major research interest in this field. Palladium has been found to catalyze the couplings of aryl halides in the presence of reducing reagents such as hydroquinone, alcohol, amines, triphenylarsine, formate salt, zinc, and indium. For example, Rawal and co-workers developed a convenient procedure for both inter- and intramolecular homocoupling of aryl halides using catalytic palladium in the presence of

<sup>+</sup> Footnotes relating to the title and/or authors should appear here.

of aryl halides for the synthesis of symmetrical biaryls either in aqueous acetone or in water by using zinc as the reducing reagent.<sup>10</sup> Another advance in this area is the development of various Pd complexes/nanoparticles<sup>11,12</sup> that can catalyze the couplings of aryl halides, however, still requiring elevated temperature. Also the cost and availability of those specific Pd complexes/nanoparticles may further limit their application in practical synthesis. In comparison, reports on the practical coupling reaction for biaryl synthesis employing cheap and readily available catalysts/reagents as well as mild reaction conditions, have to date remained scarce. In connection with our interest in hydrazine chemistry<sup>13</sup>, we discovered that hydrazine hydrate can serve as the reducing reagent in ligandfree Pd(OAc)<sub>2</sub> catalyzed coupling of aryl halides under room temperature with N<sub>2</sub> instead of inorganic salts as the byproduct, permitting a mild and practical biary synthesis using readily available reagents and catalysts (scheme 1).

hydroquinone.<sup>9</sup> Li and co-workers realized the homocoupling



 $M = B(OR)_2, SnR_3, ZnX, SiR_3, MgX et al.$ 

b) Conventional Ullmann biaryl synthesis



c) Pd-catalyzed Ullmann-type biaryl synthesis





Initially, the coupling product was isolated with 86% yield from a 2-hour reaction of 1-chloro-4-iodobenzene in DMSO in

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the presence of Pd(OAc)<sub>2</sub> (20 mol%) and hydrazine hydrate (2 equiv.) under room temperature (Table 1, entry 1). The same coupling product can also be generated using DMF as the solvent, however, with lower reaction rate and yield (Table 1, entry 2). Surprisingly this reaction was totally inhibited under room temperature in other solvents, such as acetone, ethyl acetate, THF, ethanol, dichloromethane and acetonitrile (Table 1, entries 3-8). To lower the catalyst loading, reactions with 10 mol%, 5 mol%, 2.5 mol% of  $Pd(OAc)_2$  were carried out individually (Table 1, entries 9-11), and it was found that the reaction went much slower with less  $Pd(OAc)_2$  as the one with 2.5 mol% Pd(OAc)<sub>2</sub> hardly made any progress over a 48-hour period. Then a mixture of DMF and DMSO (v/v, 3:1) was tested as the solvent, and improved reactivity was observed as shown in entries 12-13 compared to entries 10-11. Interestingly, the addition of a hard base like K<sub>3</sub>PO<sub>4</sub>, could significantly enhance the reactivity, as 2.5 mol% Pd(OAc)<sub>2</sub> was able to consume all the starting materials in 6 hours, leading to the desired biaryl product with 86% yield (Table 1, entry 14) and 1 mol% Pd(OAc)<sub>2</sub> could accomplish the reaction in 10 hours with 82% yield (Table 1, entry 15). Finally, by using 4 equivalents of hydrazine hydrate, 1 equivalent of  $K_3PO_4$  and 1 mol% Pd(OAc)<sub>2</sub>, the reaction went smoothly to a full conversion in 10 hours, resulting in the desired biaryl with 87% yield (Table 1, entry 16). Notably, unlike most Pd-catalyzed reactions, this reaction proceeds soomthly under air without any protection, thus simplifying the operation.

Table 1. Effect of Reaction Parameters on coupling reaction <sup>a</sup>						
сі—		OAc) <sub>2</sub> ( <b>x</b> ₄·H <sub>2</sub> O ( <b>y</b> om temp	mol %) equiv.	) ) → CI		Сі
entry	solvent	х	у	additive	time	yield <sup>b</sup> /%
1	DMSO	20	2		2 h	86
2	DMF	20	2		12 h	67
3	Acetone	20	2		8 h	0
4	AcOEt	20	2		8 h	0
5	THF	20	2		8 h	0
6	$C_2H_5OH$	20	2		8 h	0
7	$CH_2Cl_2$	20	2		8 h	0
8	CH₃CN	20	2		17 h	0
9	DMSO	10	2		18 h	85
10	DMSO	5	2		48 h	63
11	DMSO	2.5	2		48 h	<5
12	DMF:DMSO <sup>c</sup>	5	2		10h	84
13	DMF:DMSO <sup>c</sup>	2.5	2		72 h	76
14	DMF:DMSO <sup>c</sup>	2.5	2	$K_3 PO_4^{d}$	6 h	86
15	DMF:DMSO <sup>c</sup>	1	2	$K_3PO_4^{\ d}$	10 h	82
16	DMF:DMSO <sup>c</sup>	1	4	K <sub>3</sub> PO <sub>4</sub> <sup>d</sup>	8 h	87
$^a$ 1.0 mmol of 1-chloro-4-iodobenzene in solvent (1.0 mL) at room temperature bisolated yield; $^c\nu/\nu,$ 3:1; $^d$ 1.0 equiv. of $K_3PO_4$						

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After establishing suitable conditions, the scope, of homocoupling of various aryl halides was explored (ମିକ୍ଷାହିସ୍ଥ)ି । ମିଶିଶ୍ୱାହିନ୍ aryl iodides with various aromatic/hetero aromatic rings were investigated (2a-2k), and most of the para-substituted aryl iodides were found to undergo the desired transformation affording yields greater than 80% (2b, 2e-i, and 2k), while meta-substituted substrate also showed comparable activity leading to desired biaryl product in good yield (2c). But when steric pressure was applied at the ortho position, the reactivity decreased so dramatically that no desired coupling product was isolated under current conditions (2d). This observation indicates that the reaction is very susceptible to steric hindrance. The electronic nature of the substrates was shown to have little influence on the reaction efficiency, and aryl iodides with electron-donating or electron-withdrawing substituents on the aromatic ring could be converted to corresponding biaryls in good to excellent yields (2b, 2h vs 2i, 2k). Notably hetero aryl iodide like 2-iodopyridine also worked smoothly under current conditions affording an excellent yield of 89%. Finally, aryl bromides and chlorides were evaluated under current conditions, but none of them showed enough activity to give isolable product, indicating that oxidative addition of C-X to Pd maybe the rate-determining step for this transformation. To demonstrate the synthetic utilities of this strategy, we also conducted a gram-scale reaction of 1i, which provided 2i in 89% yield.



In the reaction of 1-iodo-2-methylbenzene 1d, although no coupling product 2d was isolated, we observed the formation of toluene which is the simple reducing product from 1-iodo-2methylbenzene. To investigate the steric effect, we carried on to test more substrates including sterically hindered aryl iodides and more complicated aryl iodides. As shown in Table 3, without any exception, all the ortho-substituted aryl iodides

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(11-o) were reduced to simple aromatic compounds in good yields under the standard conditions. The same reduction was observed in the reaction of the complicated substrate 1p which was designed to undergo an intramolecular coupling originally. However, substrate 1q that is structurally similar to substrate 1p remained intact under the standard conditions. The same results were found with 2-iodothiophene 1r and 1-iodonaphthalene 1s, as neither coupling nor reducing product were isolated.

Table 3. The reaction of sterically hindered and complicated aryl iodides <sup>a</sup>



# $^{\rm s}1.0$ mmol of 1,~2.2 mg Pd(OAc), 4.0 mmol of hydrazine hydrate, 1.0 mmol of $K_3\text{PO}_4,~0.75$ mL DMF + 0.25 mL DMSO, room temperature, isolated yield.

Next, the cross-coupling was evaluated by subjecting two different aryl iodides (1:1 mol) to the standard conditions. As shown in Table 4, different combination of two aryl iodides showed diverse selectivity. Major homo-coupling products were observed with aryl iodide bearing strong electrondonating group (e.g. -OMe) in the reaction with an aryl iodide bearing weak electron-donating groups (entries 1-4). The reaction of 1-iodo-4-methoxybenzene with hetero aryl iodide (2-iodopyridine) was also found to prefer homo-coupling (entry 5). Interestingly, the reactions involving aryl iodides with strong electron-withdrawing groups (e.g. -CN, -F, -CF<sub>3</sub>) tended to give more cross-coupling products (entries 6-9), except for the reaction between 4-iodobenzonitrile and 1chloro-4-iodobenzene (entry 10). The highest cross-coupling selectivity was obtained in the reaction of 1-iodo-4methoxybenzene with 1-fluoro-4-iodobenzene, from which three biaryl products were isolated with total 90% yield and 56% of the them was unsymmetrical biaryl product (entry 6). This cross-coupling selectivity can be improved by using one of the two substrates in excess amount (entries 11-14). The reaction of 2.0 equivalents of 1-fluoro-4-iodobenzene with 1.0 equivalent of 1-iodo-4-methoxybenzene led to a ratio of 67:33 for unsymmetrical/symmetrical biaryl (entry 11). Further study revealed that higher loading of 1-fluoro-4-iodobenzene can enhance the selectivity of cross-coupling and the ratio can be increased to 78:22 when 5.0 equivalents of 1-fluoro-4iodobenzene was used (entry 14). To seek other possible ways to improve the selectivity, some ligands and additives were tested. As shown in Table 5, phosphine ligands including PPh<sub>3</sub>, dppp and dppe were found to inhibit the reaction, as it only gave a conversion less than 10% in the presence of PPh<sub>3</sub> while being totally shut down in the presence of dppp or dppe (entries 1-3). 2,2-bipyridine and TBAC were also employed as ligand/additive in this reaction, but none of them was able to improve the selectivity significantly (entries 4-5).

Table 4.	Evaluation	of cro	ss-coui	olinga
	Lvaluation	01 010	33 COU	JIIIG

Ar <sup>1</sup> I +	Ar <sup>2</sup> l standard	conditions Ar <sup>1-</sup>	$-Ar^1 + Ar^1 - Ar^2 +$	Ar <sup>2</sup> -Ar <sup>2</sup>
74 1	7.1.1	3	4	5
entry	Ar <sup>1</sup>	Ar <sup>2</sup>	ratio ( <b>3:4:5</b> )	yield <sup>b</sup> /%
1	Ph	4-OMe-Ph	25: 31: 44	81
2	4-Me-Ph	4-OMe-Ph	25: 30: 45	77
3	3-Me-Ph	4-OMe-Ph	34: 21: 45	75
4	4-Br-Ph	4-OMe-Ph	22: 38: 40	83
5	2-Ру	4-OMe-Ph	25: 33: 44	84
6	4-F-Ph	4-OMe-Ph	29: 56: 15	90
7	4-OMe-Ph	4-CN-Ph	20: 50: 30	92
8	4-F-Ph	4-CN-Ph	20: 46: 34	83
9	4-CF <sub>3</sub> -Ph	4-CN-Ph	22: 48: 30	89
10	4-Cl-Ph	4-CN-Ph	27: 33: 40	85
11 <sup>c</sup>	4-F-Ph	4-OMe-Ph	: 67: 33	89
12 <sup>d</sup>	4-F-Ph	4-OMe-Ph	: 68: 32	87
13 <sup>e</sup>	4-F-Ph	4-OMe-Ph	: 71: 29	87
14 <sup>f</sup>	4-F-Ph	4-OMe-Ph	: 78: 22	86

 $^{\rm s}1.0\,$  mmol of Ar¹I, 1.0 mmol of Ar²I, 4.4 mg Pd(OAc), 8.0 mmol of hydrazine hydrate, 2.0 mmol of K<sub>3</sub>PO<sub>4</sub>, 1.5 mL DMF + 0.5 mL DMSO, room temperature. <code>bisolated yield. '2.0 mmol of Ar¹I, 1.0 mmol of Ar²I. '4.0 mmol of Ar¹I, 1.0 mmol of Ar²I. '5.0 mmol of Ar¹I, 1.0 mmol of Ar²I. '4.0 mmol of Ar¹I, 1.0 mmol of Ar²I. '5.0 mmol of Ar¹I, 1.0 mmol of Ar²I. '4.0 mmol of Ar²I.'</code>

Table 5. Effect of ligands/additives on cross-coupling selectivity <sup>a</sup>					
Ar <sup>1</sup> I + Ar <sup>1</sup> = 4-F Ar <sup>2</sup> = 4-C	Ar <sup>2</sup> I <u>standard conditions</u> E-Ph DMe-Ph	Ar <sup>1</sup> —Ar <sup>1</sup> + 3	- Ar <sup>1.</sup>	—Ar <sup>2</sup> + <b>1</b>	Ar <sup>2</sup> -Ar <sup>2</sup> 5
entry	ligand/additive	rati	o ( <b>3</b> :4	:5)	yield/% <sup>b</sup>
1	PPh <sub>3</sub> <sup>c</sup>				<10
2	dppp <sup>d</sup>				0
3	dppe <sup>d</sup>				0
4	bpy <sup>d</sup>	:	72: 3	28	82
5	TBAC <sup>e</sup>	:	76:	24	88
<sup>a</sup> Standard conditions: 5.0 mmol of 1-fluoro-4-iodobenzene, 1.0 mmol of 1-iodo- 4-methoxybenzene, 4.4 mg Pd(OAc), 8.0 mmol of hydrazine hydrate; 2.0 mmol of K <sub>3</sub> PO <sub>4</sub> , 1.5 mL DMF + 0.5 mL DMSO, room temperature; <sup>b</sup> isolated yield; <sup>c</sup> 10 mol%; <sup>c</sup> 5 mol%; <sup>c</sup> 20 mol%; dppp = 1,3-Bis(diphenylphosphino)propane; dppe = 1,2- Bis(diphenylphosphino)ethane; bpy = 2,2 -bipyridine; TBAC = Tetrabutylammonium chloride					

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For insight into the reaction mechanism, especially the high activity of palladium catalyst, it is noticed that some fine dark grey particles precipitated out during the reaction. This precipitate was found to be able to promote the coupling reaction, when being re-subjected to aryl iodides. So we wonder if the real catalytic species was some type of palladium nanoparticles (PdNPs)<sup>14</sup> and pre-formation of PdNPs was then carried out by treating Pd(OAc)<sub>2</sub> with excess hydrazine hydrate in the mixture of DMSO and DMF (1:3). The resulted precipitate was filtrated and washed to give a dark grey powder, from which PdNPs with dimensions of 50-100 nm were observed upon SEM measurement (Figure 1). Moreover, this pre-formed PdNPs, replacing Pd(OAc)<sub>2</sub>, demonstrated excellent catalytic activity in the homo-coupling of 4iodobenzonitrile under standard conditions (Scheme 2). Notably PdNPs can be recovered in good yields and its catalytic activity maintained after 3 cycles (table of Scheme 2).



Figure 1. (up) Preparation of PdNPs. (down) SEM image of PdNPs.



Scheme 2. PdNPs catalysed homo-coupling of 4-iodobenzonitrile.

On the basis of these experimental observations, a plausible mechanism is proposed (Scheme 3). The reaction is initiated by the reduction of Pd(OAc)<sub>2</sub> to Pd<sup>0</sup> in the presence hydrazine hydrate. Herein, the active Pd<sup>0</sup> species is found to be in the form of nanoparticles, which accounts for its high activity under room temperature. Then the oxidative addition of aryl iodide to Pd<sup>0</sup> results in the formation of Pd<sup>II</sup> complex **6**. The transmetallation between two molecules of Pd<sup>II</sup> complex **6** leads to intermediate **7**, along with PdI<sub>2</sub> which could also be reduced to Pd<sup>0</sup> by hydrazine hydrate. Final reductive elimination of intermediate **7** affords the desired coupling product, as well as the Pd<sup>0</sup> species which can re-enter the catalytic cycle.



#### Conclusions

In conclusion, we have developed a palladium catalysed Ullmann biaryl synthesis using hydrazine hydrate as the reducing reagent. This reaction avoids the need for metal reductants which is neither cost-effective nor environmentally benign. Instead, hydrazine hydrate that is readily available and cheap, serves a good partnership with  $Pd(OAc)_2$  in promoting the coupling reaction of aryl iodides under room temperature. The reaction works smoothly for both electron-rich and electron-deficient aryl iodides, as well as hetero-aryl iodides, leading to a wide range of biaryls in good to excellent yields. Preliminary mechanistic studies suggested active catalytic species for this transformation is palladium nanoparticles that can be easily prepared by treating Pd(OAc)<sub>2</sub> with hydrazine hydrate. Taken together with its operational simplicity, readily available reagents, broad substrates scope, and amenability to gram-scale synthesis, this green reaction will find practical application for the synthesis of biaryl compounds.

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## 'household' reagents and mild reaction conditions

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 $\mathbb{N}_{2}H_{4}$ · $H_{2}O$  replacing metal reductants:

Mild reaction conditionsConvenient operationLess inorganic waste