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Synthesis of Symmetrical Biaryls through Palladium-Catalyzed Ligand-Free Homocoupling of Aryliodine(III) Diacetates

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Abstract An efficient process for the synthesis of symmetrical biaryls from readily available and bench-stable aryliodine(III) diacetates has been developed with high regional selectivity. The process exhibited high selectivities and good functional group tolerance with respect to methyl, bromo, chloro and cyano groups. Mechanistic studies revealed that the transformation involved in situ generation of aryl iodide from heating-promoted degradation of aryliodine(III) diacetate, followed by Ullmann-type homocoupling.

Key words biaryls, palladium, homogeneous catalysis, coupling, chemoselectivity

As important structural motifs, biaryls are widely found in many functional materials, natural products and pharmaceuticals.¹ Additionally, biaryl fragments are also usually employed as useful building blocks in organic catalysts and ligands in organic synthesis to construct complex molecules (Figure 1).² Therefore, their fundamental importance in synthetic organic chemistry has led to intensive studies to develop a number of transformations to create various biaryl compounds, and great progress has been achieved by transition-metal-catalyzed cross-coupling and homocoupling reactions in the synthesis of symmetrical and unsymmetrical biaryls.³ Among them, transition-metal-catalyzed homocoupling reactions are the most straightforward and concise route for preparing symmetrical biaryl compounds from only one substrate. In this regard, the Ullmann coupling reaction has gained much attention as an efficient process, although it has been known for over a century.^{3d,e} Over the past decade, major advances have been made in transition-metal-mediated oxidative coupling reactions between two nucleophilic partners to construct various chemical bonds, including $C_{sp2}-C_{sp3}$, $C_{sp2}-C_{sp2}$, and $C_{sp}-C_{sp3}$



bonds.⁴ Thus, oxidative dimerization of *sp*² arylmetal reagents has emerged as a method of choice to synthesize symmetrical biaryls.⁵ For example, Yamamoto,^{5a} Luo^{5b} and other groups^{5c,d} reported transition-metal-promoted homocoupling reactions of boronic acids, Lei^{5e} disclosed the Pd-catalyzed Negishi-type oxidative homocoupling of arylzinc reagent by utilizing desyl chloride as the oxidant, Hayashi^{5f} and Severin^{5g} independently revealed Fe-mediated oxidative homocoupling of aryl Grignard reagents by using 1,2-dichloroethane and nitrous oxide as the oxidant. Unfortunately, many of the arylmetal reagents are sensitive, expensive, and tedious to prepare. To address these issues, transition-metal-catalyzed oxidative homocoupling of *sp*²

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arene C-H bond has been employed as a powerful tool for direct synthesis of valuable biaryl products.⁶ In contrast to oxidative dimerization of sp² arylmetal reagents, oxidative homocoupling of sp² arene C-H bond is the most widely accepted green chemical processes to form symmetrical biaryls. However, this method often lacks selectivity and/or usually requires directing group, to some extent, limiting the widespread application of this protocol in organic synthesis. Recently, aromatic carboxylic acids, sodium arylsulfinates and N'-tosyl arylhydrazines have gained much attention owing to their broad availability, high stability and low cost, thus, employing them as the single arvl precursor in transition-metal-catalyzed homocoupling provides an attractive alternative for the synthesis of symmetrical biarvl compounds. Su disclosed for the synthesis of biarvls a Pd/Ag-mediated decarboxylative coupling reaction between two different (hetero)aryl carboxylic acids.^{7a} Larrosa,^{7b} Tan and Deng^{7c} independently reported Pd/Ag-mediated decarboxylative homocoupling of (hetero)aromatic carboxylic acids with good and moderate yields. Luo7d and Forgione.^{7e} each developed a Pd-catalyzed desulfitative homocoupling of sodium arylsulfinates under aerobic conditions for the synthesis of symmetrical biaryls. Lu illustrated the preparation of biarvl compounds via Pd-catalyzed homocoupling of N'-tosyl arylhydrazines.^{7f} Therefore, the further exploration of efficient procedure for the preparation of symmetrical biaryls from transition-metal-catalyzed homocoupling is currently of great interest in organic synthesis. Herein, we exhibit an attempt to use bench-stable aryliodine(III) diacetate ArI(OAc)₂ as single aryl precursor in Pd-catalyzed ligand-free homocoupling transformation to generate symmetrical biaryl derivatives.

Aryliodine(III) diacetate is one of the most useful hypervalent iodine reagents with the characteristics of easy availability (benzene + I_2),⁸ high stability and low cost. Therefore, it is widely used in organic synthesis and represents rich chemistry, for example, it is not only used as a surrogate for toxic oxidants in oxidative transformations,⁹ but is also employed in radical reactions to generate oxygen- and carbon-centered radicals.¹⁰ Furthermore, aryliodine(III) diacetate can serve as acetoxy and aryl sources in oxidative transformations.^{11,12} On this point, Suna^{11a} and others^{11b,c} reported Pd-catalyzed acetoxylation of (hetero)arenes or alkenes with the employment of aryliodine(III) diacetate. Mao,^{12a} Magedov,^{12b} Cheng,^{12c} and Fairlamb^{12d} revealed Pdcatalyzed arylation of olefins, and benzoxazole C-H bonds with aryliodine(III) diacetate. Recently, we have reported an efficient Pd-catalyzed direct arylation of electron-deficient polyfluoroarenes with aryliodine(III) diacetates to afford the corresponding polyfluorobiaryls with moderate to good yields.¹³ Among these transformations, to the best of our knowledge, the synthesis of symmetrical biaryls via the homocoupling of aryliodine(III) diacetates as single aryl precursors has not been developed.

A variety of reaction parameters were screened for the homocoupling of phenyliodine(III) diacetate (1a) as the model reaction under an air atmosphere. Selected results that illustrated the effect of catalyst, base and other factors on the reaction outcome are listed in Table 1. Initially, we observed that the homocoupling reaction of phenyliodine(III) diacetate (1a) in DMF in the presence of 10 mol% of $Pd(OAc)_2$ as catalyst, 4 equivalents of K_2CO_3 as base and one equivalent of ammonium phosphomolybdate hydrate (PMA) as additive at 110 °C smoothly furnished the desired product biphenyl (2a) in 71% yield (Table 1, entry 1). Unfortunately, either drastically reduced vield (20%) was obtained when the amount of K₂CO₃ was decreased to 2 equivalents, or trace amounts of product 2a was observed when K₂PO₄, Cs₂CO₂ and *t*-BuOK were employed instead of K₂CO₃ under otherwise identical conditions, respectively (Table 1, entries 2-5). Thus, K_2CO_3 appeared to be the best choice for this transformation to provide a satisfactory yield. The effect of additive was then evaluated, and studies showed that moderate yields were obtained when ammonium phosphomolybdate hydrate was replaced with $Cu(OAc)_2$ and $Cu(OTf)_2$ (Table 1, entries 6 and 7). To our delight, a comparable yield (73%) was delivered when additive was absent (Table 1, entry 8), and the result indicated that the phenyliodine(III) diacetate might act both as the aryl precursor and as an oxidant in this transformation. However, a nitrogen atmosphere was detrimental to the transformation (Table 1, entry 9). The reaction temperature played a key role in the reaction conversion, and lowering reaction temperature to 80 °C did not lead to the product (Table 1, entry 10). Then, different reaction times were screened under otherwise equivalent conditions. It was found that a short reaction time (2 h) could gave a comparable yield (66%), whereas much shorter time (1 h) furnished a decreased yield (55%; Table 1, entries 12 and 13). The influence of solvent on the catalytic process was also investigated, and results showed that inferior yields were obtained in the screened solvents than that in DMF (Table 1, entries 14-16). Decreasing the loading of $Pd(OAc)_2$ led to an unsatisfactory yield (26%; entry 17). Finally, replacing $Pd(OAc)_2$ with Cul in the reaction furnished none of the desired product (Table 1, entry 18), which demonstrated that the Pd catalyst played an essential role in the catalytic reaction.

With the optimized conditions in hand, the scope of this reaction with respect to easily available aryliodine(III) diacetate substrate was explored under the standard conditions of entry 12 in Table 1. As shown in Table 2, beside phenyliodine(III) diacetate (**1a**), this Pd-catalyzed ligand-free homo-coupling reaction was shown to be effective for a wide array of aryliodine(III) diacetates with different function groups to furnish the corresponding symmetrical biaryls in moderate to good yields. Electron-rich and -deficient substituents such as methyl, bromo, chloro and cyano groups all could be quite well tolerated. It was also observed that electronic properties of the aromatic moiety in this homocoupling

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		I(OAc) ₂	catalyst base, additive solvent, time	• \\\\		
		1a	air, 110 °C	2a		
Entry	Catalyst (mol%) ^b	Base (equiv)	Additive (equiv)	Solvent	Time (h)	Isolated yield (%)
1	Pd(OAc) ₂ (10)	K ₂ CO ₃ (4)	PMA (1)	DMF	20	71
2	Pd(OAc) ₂ (10)	K ₂ CO ₃ (2)	PMA (1)	DMF	20	20
3	Pd(OAc) ₂ (10)	K ₃ PO ₄ (2)	PMA (1)	DMF	20	trace
4	$Pd(OAc)_2$ (10)	Cs ₂ CO ₃ (2)	PMA (1)	DMF	20	trace
5	$Pd(OAc)_2$ (10)	<i>t</i> -BuOK (2)	PMA (1)	DMF	20	trace
6	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	$Cu(OAc)_2$ (1.5)	DMF	20	52
7	Pd(OAc) ₂ (10)	K ₂ CO ₃ (4)	Cu(OTf) ₂ (1.5)	DMF	20	48
8	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	-	DMF	20	73
9 ^c	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	-	DMF	20	67
10 ^d	$Pd(OAc)_2$ (10)	K ₂ CO ₃ (4)	-	DMF	20	trace
11	Pd(OAc) ₂ (10)	K ₂ CO ₃ (4)	-	DMF	10	68
12	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	-	DMF	2	66
13	Pd(OAc) ₂ (10)	K ₂ CO ₃ (4)	-	DMF	1	55
14	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	-	toluene	2	55
15	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	-	dioxane	2	10
16	$Pd(OAc)_2$ (10)	$K_2CO_3(4)$	-	MeCN	2	8
17	$Pd(OAc)_2(5)$	K ₂ CO ₃ (4)	-	DMF	2	26
18	Cul (10)	K ₂ CO ₃ (4)	-	DMF	2	0

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^a Reaction conditions: 1a (0.2 mmol), solvent (2 mL), 110 °C, air atmosphere.

^b Relative to **1a**.

^c Reaction was conducted under an N₂ atmosphere.

^d Reaction was conducted at 80 °C.

transformation did not play a significant role, with good vields recorded for the homocoupling of **1a.b** and **1e** (albeit at a slightly elevated temperature; Table 2, entries 1, 2 and 5), whereas moderate yields were obtained for the homocoupling of 1c,d and 1f,g (Table 2, entries 3, 4 and 6, 7). It is worth noting that 4-chloro(diacetoxyiodo)benzene (1e) and 4-bromo(diacetoxyiodo)benzene (1f) formed the desired products (2e and 2f) with the halogen moieties (Cl, Br) remaining intact (Table 2, entries 5 and 6), which could be used for further functionalization of the C-Hal bond, exhibiting the potential application of this transformation. Interestingly, aryliodine(III) compound bonding with a different anion was also a suitable substrate for this protocol. For example, homocoupling of [bis(trifluoroacetoxy)iodo]benzene (1h) generated the hoped-for product 2a (Table 2, entry 8), albeit in a moderate yield (40%) under a slightly elevated temperature.

Some experiments were performed to gain a preliminary insight into the reaction mechanism. At first, heating phenyliodine(III) diacetate (**1a**) with 4 equivalents of K₂CO₃ in DMF at 110 °C for 0.5 hour generated iodobenzene in 40% isolated yield. This observation is consistent with the fact that phenyliodine(III) diacetate degrades to iodobenzene under heating conditions with a similar base (Cs_2CO_3 and Ag_2CO_3).^{12d,13} Next, reacting this freshly isolated iodobenzene with 10 mol% of Pd(OAc)₂ and 4 equivalents of K₂CO₃ under an air atmosphere for ten hours led to the biphenyl product **2a** in 58% isolated yield, as detected by GC–MS and NMR. Based on above observations, we can conclude that this transformation involves an in situ generation of aryl iodide from the thermal degradation of aryliodine(III) diacetate with a base, followed by an Ullmann-type homocoupling.

In summary, we have established a new Pd-catalyzed ligand-free homocoupling method for the direct synthesis of symmetrical biaryl compounds.¹⁴ This ligand-free transformation displays attractive features including using cheap and readily available aryliodine(III) diacetates as the single aryl precursors, a range of functional group tolerance, good chemoselectivity and moderate to good yields. With these features, the present protocol provides a broad utility in

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 Table 2
 Palladium-Catalyzed Ligand-Free Homocoupling of Arylio dine(III) Diacetates^a



Product

Entry Substrate





^a Reaction conditions: aryliodine(III) diacetate 1 (0.2 mmol), Pd(OAc)₂ (10 mol%), K2CO3 (4 equiv), DMF (2 mL), 110 °C, 2 h.

^b Average of two runs

^c Reaction was conducted at 130 °C.

synthesizing functional materials, natural products and pharmaceuticals in laboratory researches and industrial applications. Preliminary mechanistic studies disclosed that the reaction involved an in situ generation of aryl iodide from the heating of aryliodine diacetate in the presence of a base, followed by an Ullmann-type homocoupling to give the desired product. Efforts are currently underway to extend the substrate scope and improve the efficiency of this reaction further.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380320.

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- (14) **General Procedure (Preparation of 2)**: A mixture of aryliodine(III) diacetate **1** (0.2 mmol), K_2CO_3 (110.6 mg, 0.8 mmol, 4 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%) and DMF (2 mL) was stirred at 110 °C for 2 h. After cooling to r.t., the reaction mixtures were diluted with H₂O (10 mL) and filtered through a pad of silica gel that was then washed with Et₂O (3 × 10 mL). The combined organic phase was washed with brine (2 × 20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel to provide the corresponding product. The product was characterized by GC–MS and NMR spectroscopy.

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