

A convenient palladium catalyzed synthesis of symmetric biaryls, biheterocycles and biaryl chiral diamides

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Abstract—A series of symmetrical diamido biaryls has been synthesized in good yield by direct homocoupling of iodoarylbenzamides by palladium-catalysis. No cross product has been isolated from the reaction mixture of two different iodoarylbenzamides under similar conditions. However, only in the case of 2-iodo-*N*-phenylbenzamide, the intramolecularly coupled product phenanthridone has been isolated as a minor product along with the major intermolecularly coupled product. Biphenyl chiral diamides have been synthesized by this coupling method. This coupling reaction also works well with the reductive dimerization of functionalized heterocyclic compounds. Thus 6,6'-dipivaloylamino-3,3'-bipyridine and 6,6'-dimethyl-2,2'-bipyridine have been efficiently synthesized. In two cases, the X-ray crystal structures have been solved to establish the structures of symmetrical and chiral diamido biaryls and their supramolecular networks.
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1. Introduction

Highly functionalized symmetrical biaryl subunits are present in a large number of natural products such as tellimagrandins,^{1a} (–) gossypol^{1b} and are also used in materials science as precursors to rigid liquid crystals^{1c} as well as semi conducting complexes, and consequently gain much attention for their synthesis.^{1c} There are various coupling methods, and the application of these methods have been recently reviewed.² The most convenient method for the synthesis of symmetrical biaryls is reductive homocoupling of arylhalides either by Ullmann synthesis³ or by oxidative coupling of arylboronic acid,^{4a} arylzinc,^{4b} arylstannanes^{4c} and aryl mesylates.^{4d} However, palladium catalyzed coupling reactions are among the most important C–C bond forming reactions in organic synthesis.⁵ Lemaire et al.⁶ have synthesized functionalized symmetrical biaryls and biheterocycles via the homocoupling of aryl halides using Pd(OAc)₂ in the presence of *n*-Bu₄NBr and K₂CO₃. However, palladium catalyzed reductive homocoupling of aryl halides using ionic liquid⁷ and zinc powder-formate salt⁸ are also known.

Keywords: Symmetric biaryls; Palladium catalyzed reaction; Homocoupling; Ullmann reaction; Biaryl chiral diamides.

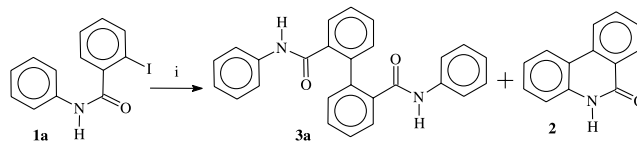
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2. Results and discussion

We report here the results of our observation of palladium catalyzed reaction of iodoarylbenzamides to prepare symmetrical biaryl diamides, including biaryl chiral diamides, by a modified procedure. During our investigation of the palladium catalyzed homocoupling reaction of **1a** by using (Ph₃P)₂PdCl₂ as a catalyst, we have unexpectedly isolated an intramolecularly coupled product **2** (15–20%) as a minor product (Scheme 1).

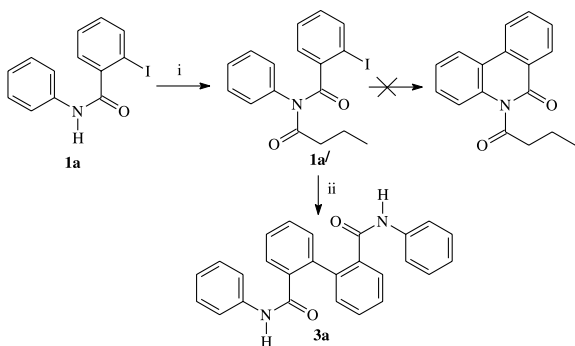


Scheme 1. (i) (Ph₃P)₂PdCl₂, CuI, Et₃N, DMF, 120 °C, 12 h.

The symmetrical diamido biaryls **3a–g** was synthesized in good yields from direct self-coupling of iodoarylbenzamides **1a–g** along with the biaryl chiral diamides **5** and **6** by palladium catalyzed reactions. No cross product was isolated from the reaction mixture of **1a** and **1b** under similar conditions. Only in the case of **1a**, did cyclization leading to a phenanthridone **2** occur. The crystal structures of **3a** (*N*²,*N*^{2'}-diphenyl [1,1'-biphenyl]-2,2'-dicarboxamide) and **6** (biphenyl-2,2'-dicarboxylic acid bis-[(1*R*-phenylethyl)-amide]) reveal the detailed structures of symmetrical

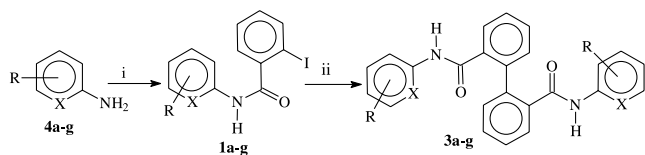
and chiral diamido biaryls and their interesting supra-molecular networks.

According to the reported procedure,^{9a} it is necessary to protect the N–H function of **1a** with an alkyl group to obtain the cyclized product **2** (*N*-protected) by a palladium catalyzed dehydrohalogenation reaction since palladium forms a cyclic complex between the halogen bearing carbon and the N–H function. However, the *N*-butyryl protected derivative of 2-iodo-*N*-phenyl-benzamide **1a'** formed the intermolecularly coupled product **3a** in the Heck reaction^{9b} using tri-*o*-tolylphosphine, palladium acetate and sodium carbonate in DMF under reflux for one and a half hours where selective deprotection of the *N*-butyryl group occurred (Scheme 2).



Scheme 2. (i) Butyryl chloride, Et₃N, dry C₆H₆, reflux, 24 h; (ii) Pd(OAc)₂, (*o*-tol)₃P, Na₂CO₃, DMF, reflux, 1.5 h.

Intramolecular palladium catalyzed reactions are well established in the synthesis of benzo[*c*]phenanthridine or fully aromatized phenanthridine alkaloids.^{9b–e} Interestingly when **1a** was subjected to Pd(PPh₃)₂Cl₂ catalyzed coupling reaction, the major product was the intermolecularly coupled diphenyl diamide **3a** along with the minor intramolecularly coupled product phenanthridinone **2**. Then **1a** was subjected to a reaction using Pd(OAc)₂ as the catalyst with Ph₃P and Et₃N, and no intramolecularly coupled product **2** was obtained but the only isolated product was the biaryl, **3a**. This homocoupling reaction was then performed with a series of 2-iodo-*N*-arylbenzamides **1a–e** using a variety of catalysts and solvents, for example, Pd(Ph₃P)₂Cl₂/CuI, Pd(OAc)₂/Ph₃P/CuI, Pd(OAc)₂/*o*-tolyl₃P/CuI in DMF or acetonitrile and with a base, Et₃N. However, the best conditions were to use a catalytic amount of Pd(OAc)₂/Ph₃P/CuI and Et₃N in refluxing acetonitrile. This catalyst system was also examined with heterocyclic compounds, for example, 2-iodo-*N*-pyridin-2-ylbenzamides **1f–g**. In all these cases, 2-iodo-*N*-arylbenzamides **1a–g** (obtained from the corresponding amines **4a–g**) underwent conversion only to biaryls **3a–g** in good yields showing the generality of this method for the intermolecular biaryl coupling reactions (Scheme 3).



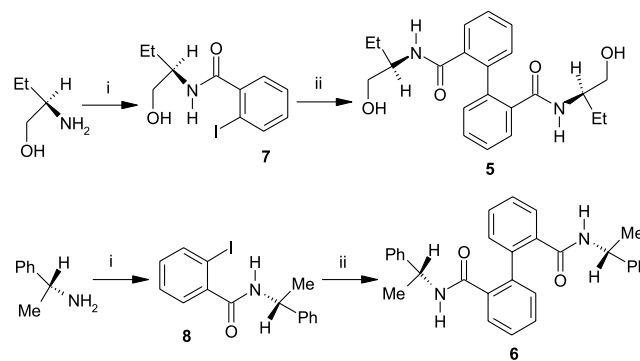
Scheme 3. (i) 2-Iodobenzoyl chloride (1.1 equiv), dry CH₂Cl₂, Et₃N, rt; (ii) Pd(OAc)₂, PPh₃, CuI, Et₃N, acetonitrile, reflux, 6–8 h.

Table 1. Yield of products (**3a–g**) of palladium catalyzed coupling reactions of **1a–g**

Entry	2-Iodo- <i>N</i> -arylbenzamides (1a–g)	Symmetrical diamido-biaryls (3a–g)	Yield (%)
1.	1a : X=CH, R=H	3a : X=CH, R=H	70
2.	1b : X=CH, R=2-Me	3b : X=CH, R=2-Me	66
3.	1c : X=CH, R=3-Me	3c : X=CH, R=3-Me	70
4.	1d : X=CH, R=4-OMe	3d : X=CH, R=4-OMe	68
5.	1e : X=CH, R=4-CO ₂ Et	3e : X=CH, R=4-CO ₂ Et	56
6.	1f : X=N, R=H	3f : X=N, R=H	54
7.	1g : X=N, R=6-Me	3g : X=N, R=6-Me	65

The results of the palladium catalyzed homocoupling reactions of various iodoarylbenzamides are shown in Table 1.

We have prepared the biphenyl chiral diamides **5** and **6** from **7** and **8**, respectively, (Scheme 4). Protection of the hydroxyl group in *R*(–)-2-amino-1-butanol was not necessary as evident by the following observation. Reaction of *R*(–)-2-amino-1-butanol with 2-iodobenzoyl chloride afforded the chiral 2-iodobenzamide **7**. Subsequent coupling of **7** gave the biphenyl chiral diamide **5** as a brown-semi solid in 54% yield using similar conditions as before.



Scheme 4. (i) 2-Iodobenzoyl chloride, dry CH₂Cl₂, Et₃N, rt, 6 h; (ii) Pd(OAc)₂, Ph₃P, CuI, Et₃N, CH₃CN, reflux, 6–8 h.

Similarly, *R*(+)- α -methylbenzylamine was converted to the iodobenzamide **8** which on palladium catalyzed coupling reaction afforded the biphenyl chiral diamide **6** as a white crystalline solid in 70% yield.

The coupling reaction using these conditions was also found to be successful with the synthesis of homocoupled bi-heterocyclic compounds. These compounds are useful for molecular recognition research and in metal directed assembly and also in the synthesis of metal helicates.¹⁰

Thus 3,3'- and 2,2'- coupled functionalized bipyridyl compounds **9** and **10** were synthesized efficiently by this method (Scheme 5). For the 3,3'-coupling reaction, 2-*N*-pivaloyl-3-bromopyridine required 12 h at reflux in comparison to the chloro analog, which required 46 h.

All of the biaryls were characterized by ¹H NMR and also by mass spectrometric studies. Single crystal X-ray diffraction¹¹ studies in two cases (achiral **3a** and chiral **6**) confirmed their biphenyl structures.

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