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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.

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.[1e] 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 synthesis[3] 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*-Bu_4NBr and K_2CO_3. However, palladium catalyzed reductive homocoupling of aryl halides using ionic liquid[7] and zinc powder-formate salt[8] are also known.

Keywords: Symmetric biaryls; Palladium catalyzed reaction; Homocoupling; Ullmann reaction; Biaryl chiral diamides.
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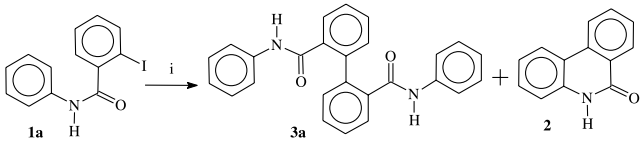
2. Results and discussion

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 $(Ph_3P)_2PdCl_2$ as a catalyst, we have unexpectedly isolated an intramolecularly coupled product **2** (15–20%) as a minor product (Scheme 1).

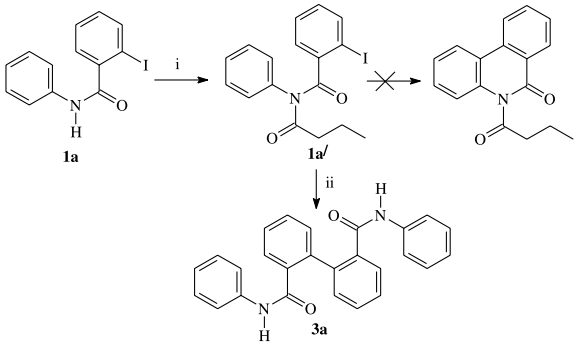


Scheme 1. (i) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF, 120 °C, 12 h.

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,$N^{2\prime}$-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

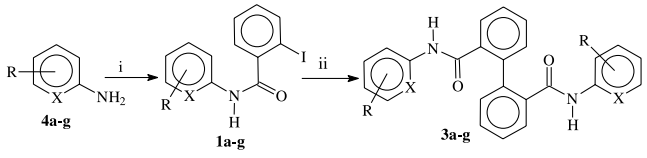
and chiral diamido biaryls and their interesting supramolecular networks.

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, Et_3N, dry C_6H_6, reflux, 24 h; (ii) $Pd(OAc)_2$, $(o\text{-tol})_3P$, Na_2CO_3, 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 $Pd(PPh_3)_2Cl_2$ 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 Ph_3P and Et_3N, 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, $Pd(Ph_3P)_2Cl_2$/CuI, $Pd(OAc)_2/Ph_3P$/CuI, $Pd(OAc)_2/(o\text{-tolyl})_3P$/CuI in DMF or acetonitrile and with a base, Et_3N. However, the best conditions were to use a catalytic amount of $Pd(OAc)_2/Ph_3P$/CuI and Et_3N 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).



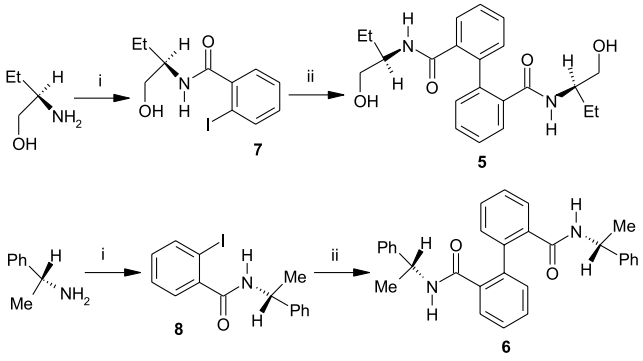
Scheme 3. (i) 2-Iodobenzoyl chloride (1.1 equiv), dry CH_2Cl_2, Et_3N, rt; (ii) $Pd(OAc)_2$, PPh_3, CuI, Et_3N, acetonitrile, reflux, 6–8 h.

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

Entry	2-Iodo-*N*-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_2Et	**3e**: X=CH, R=4-CO_2Et	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.



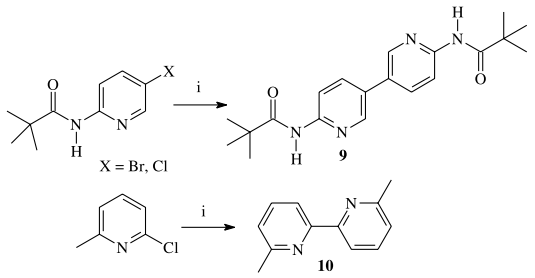
Scheme 4. (i) 2-Iodobenzoyl chloride, dry CH_2Cl_2, Et_3N, rt, 6 h; (ii) $Pd(OAc)_2$, Ph_3P, CuI, Et_3N, CH_3CN, reflux, 6–8 h.

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 diffraction[11] studies in two cases (achiral **3a** and chiral **6**) confirmed their biphenyl structures.



Scheme 5. (i) $Pd(OAc)_2$, Ph_3P, CuI, Et_3N, CH_3CN, reflux, 12–40 h.

As depicted in Figure 1, the biaryl **3a** is biphenyl-2,2′-dicarboxylic acid 2′-amide 2-phenylamide. Interestingly, the supramolecular structure of the biphenyl diamide shows that one amide oxygen accepts two intermolecular hydrogen bonds {N–H and C–H from another molecule, graph set $C(4)$, $R_2^1(6)$, N···O 2.857(6) Å and C···O 3.313(8) Å with N–H···O/C–H···O 165 and 137°, respectively} together with the *trans* amide NH which forms one intramolecular hydrogen bond with amide oxygen, set $S(9)$, N···O 2.857(6) Å N···O 2.919(6) Å. These geometric values have similar dimensions to those found in related intermolecular hydrogen bonding amide···amide systems as *N*-H···O=C hydrogen bonds with graph-set C(4).[12]

However, the intermolecular hydrogen bonding in **3a** displays a six-membered hydrogen bonding motif involving the adjacent amido NH and phenyl CH moieties interacting with the amide oxygen of a symmetry related molecule. This motif is absent in the chiral analogue **6** (Fig. 2), which only shows the normal N–H···O=C type hydrogen bonding, N···O 2.912(3) Å, N–H···O 163°. This is perhaps due to the extra rigidity of the geometry in **6** together with the presence of a chiral centre between the amide NH and the phenyl group.

In both the biphenyl diamides (achiral **3a** and chiral **6**), the biphenyl rings are shown close to be perpendicular by the presence of only one amide group at the α position to each ring. The central rings are at angles 78.9° for **3a** (in tetragonal system) and 78.38° (in orthorhombic system).

3. Conclusion

We thus present here an efficient method for the preparation

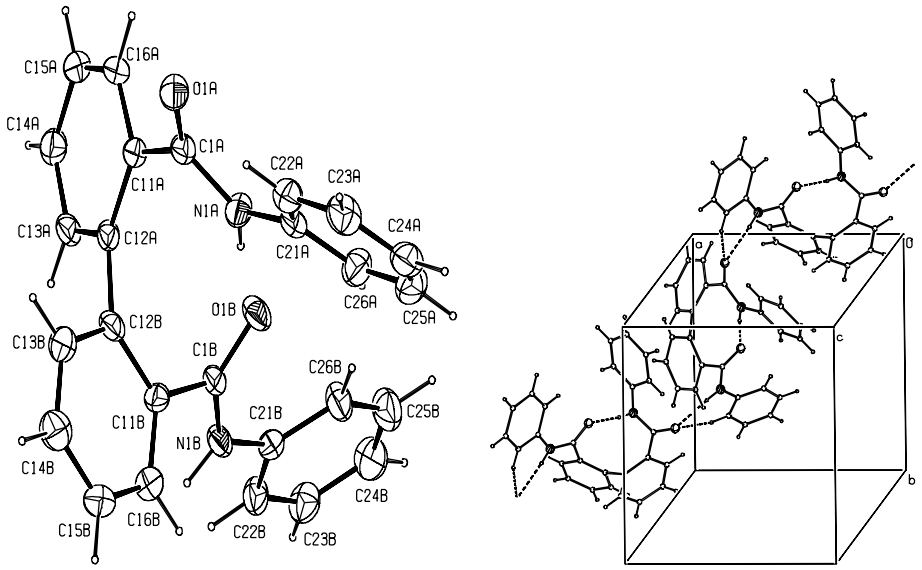


Figure 1. X-ray crystal structure of **3a** (above left) together with a view of the interactions (above right).

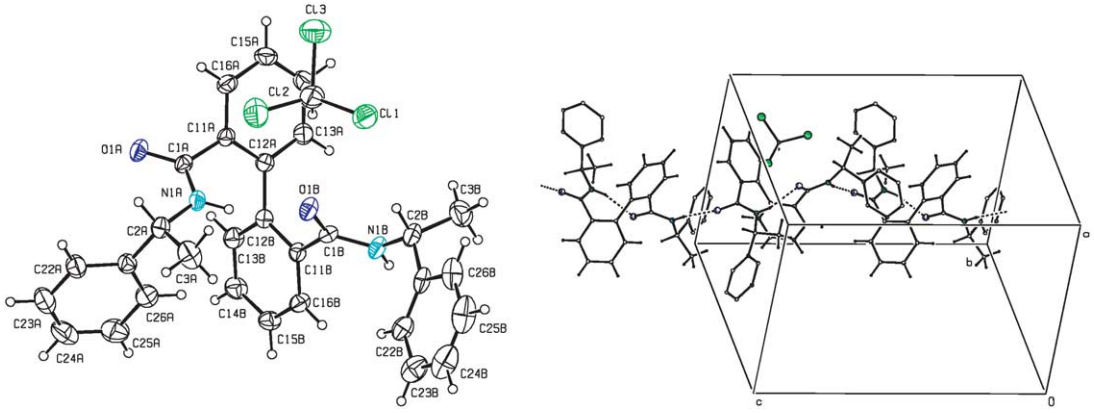


Figure 2. X-ray crystal structure of **6** (above left) together with a view of the interactions (above right).

of symmetrical diamido biaryls by palladium catalyzed homocoupling reaction as well as for the preparation of biphenyl chiral amides. The advantage is that we get the reductive coupling instead of dehalogenative coupling or simple reduction products, even though we have used palladium salt in the presence of Et_3N in an aprotic solvent like CH_3CN or DMF. The coupling reaction also works well in the synthesis of biheterocycles, for example, functionalized bipyridyls depending on the position of halogens. The crystal structures of achiral **3a** and chiral **6** were solved to confirm their structures along with exploring the amide–amide hydrogen bond induced supramolecular network in biphenyl 1,1′-diamides. We are currently investigating the application of this methodology in the synthesis of biphenyl or biheterocyclic designed molecules containing suitable amide substrates for studies in molecular recognition and supramolecular chemistry.

4. Experimental

All the reactions were carried out under nitrogen atmosphere in anhydrous solvents. CH_2Cl_2, DMF and Et_3N were distilled over CaH_2 and CH_3CN over P_2O_5. All chromatographic separations were performed on silica gel (100–200 mesh). For preparative thin layer chromatographic (PTLC) purification, the layer was formed on a glass plate using water gel-GF 254 silica gel. The petroleum ether used has a boiling range of 40–60 °C. Mps were uncorrected. ^{1}H NMR spectra were recorded either on a Bruker AM 300L MHz or a Bruker 500 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer. For NMR spectra, $CDCl_3$ was used as solvent unless otherwise mentioned using TMS as internal standard. Chemical shifts are expressed in δ unit and ^{1}H–^{1}H, ^{1}H–C coupling constants in Hz. IR spectra were recorded on a Perkin–Elmer Spectrum I spectrophotometer using KBr discs. Optical rotations are measured in a JASCO DIP 360 polarimeter. Mass spectra (JEOL JMS600) were obtained from the Indian Institute of Chemical Biology, Kolkata and the Philipps-Universitat, Marburg, Germany.

4.1. General procedure for the preparation of 2-iodo-*N*-arylbenzamides

To a magnetically stirred solution of the amines (1.0 mmol) in dry CH_2Cl_2 (20 ml) and freshly distilled Et_3N (1.2 equiv), was added 2-iodobenzoyl chloride (1.1 equiv), and stirring was continued for 6–12 h. The triethylamine hydrochloride was filtered off, and the organic layer after washing with water was dried (anhydrous Na_2SO_4) and then the solvent was removed under reduced pressure. The residue was purified using silica-gel chromatography to afford the corresponding 2-iodo-*N*-arylbenzamides (**1a**–**g**), **7** and **8** in almost quantitative yields.

Representative data for iodoarylbenzamides were as follows.

4.1.1. 2-Iodo-*N*-phenyl-benzamide (1a). Yield: (98%); off-white powder; mp 140–142 °C [lit.[13] 143–145 °C]. FT-IR (KBr): 3446, 2360, 1698, 1299, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm)=7.97 (d, 1H, J=7.8 Hz), 7.70–7.39 (m, 6H), 7.25–7.17 (m, 2H), 6.60 (br. S, 1H, N*H*, D_2O exchangeable).

4.1.2. 2-Iodo-*N*-*o*-tolyl-benzamide (1b).[14] Yield: (96%); white crystalline solid; mp 195–197 °C. FT-IR (KBr): 3342, 1649, 1523, 1456, 1310, 1016, 753, 669 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.01 (d, 1H, J=7.9 Hz), 7.92 (d, 1H, J=7.8 Hz), 7.55 (d, 1H, J=7.2 Hz), 7.45 (t, 1H, J=7.3 Hz), 7.31–7.22 (m, 2H), 7.25 (br s, 1H, N*H*), 7.19–7.11 (m, 2H), 2.36 (s, 3H).

4.1.3. 2-Iodo-*N*-*m*-tolyl-benzamide (1c).[14] Yield: (95%); white solid; mp 155–157 °C. FT-IR (KBr): 3243, 1652, 1541, 1316, 779, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.92 (d, 1H, J=7.9 Hz), 7.51 (s, 1H), 7.46–7.41 (m, 3H), 7.38 (br s, 1H, N*H*), 7.29–7.24 (m, 1H), 7.15 (t, 1H, J=7.6 Hz), 6.99 (d, 1H, J=7.4 Hz), 2.39 (s, 3H).

4.1.4. 2-Iodo-*N*-(4-methoxy-phenyl)-benzamide (1d).[14] Yield: (95%); white solid; mp 155–157 °C. FT-IR (KBr): 3308, 1651, 1513, 825, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.90 (d, 1H, J=7.8 Hz), 7.57–7.50 (m, 3H), 7.42 (t, 1H, J=7.3 Hz), 7.37 (br s, 1H, N*H*), 7.14 (t, 1H, J=7.6 Hz), 6.92 (d, 2HH, J=8.9 Hz), 3.81 (s, 3H).

4.1.5. 4-(2-Iodo-benzoylamino)-benzoic acid ethyl ester (1e). Yield: (90%); cream colored solid; mp 110–112 °C. FT-IR (KBr): 3331, 1701, 1664, 1598, 1533, 1405, 1281, 1174, 1017, 769, 752, cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.07 (d, 1H, J=8.6 Hz), 7.93 (d, 1H, J=7.7 Hz), 7.85 (d, 1H, J=8.6 Hz), 7.72 (d, 1H, J=8.4 Hz), 7.65 (br s, 1H, N*H*), 7.54 (d, 1H, J=8.5 Hz), 7.45 (d, 1H, J=7.4 Hz), 7.17 (t, 1H, J=7.5 Hz), 6.64 (d, 1H, J=6.9 Hz), 4.37 (q, 2H, J=7.1 Hz), 1.40 (t, 3H, J=7.1 Hz). Anal. Calcd for $C_{16}H_{14}NO_3I$: C, 48.62; H, 3.57; N, 3.54. Found: C, 48.60; H, 3.60; N, 3.58.

4.1.6. 2-Iodo-*N*-pyridin-2-yl-benzamide (1f). Yield: (88%); cream colored solid; mp 92–94 °C. FT-IR (KBr): 2977, 1681, 1579, 1433, 1309, 1015, 780 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=10.15 (br s, 1H, N*H*), 8.52 (d, 1H, J=8.4 Hz), 8.23 (d, 1H, J=6.8 Hz), 8.00 (d, 1H, J=8.1 Hz), 7.94 (t, 1H, J=7.0 Hz), 7.88 (t, 1H, J=7.6 Hz), 7.61 (d, 1H, J=7.8 Hz), 7.48–7.38 (m, 1H), 7.15 (t, 1H, J=6.5 Hz).

4.1.7. 2-Iodo-*N*-(6-methyl-pyridin-2-yl)-benzamide (1g). Yield: (92%); white crystalline solid; mp 101–103 °C. FT-IR (KBr): 3240, 2983, 1683, 1576, 1454, 1136, 1016, 798, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.35 (br s, 1H, N*H*), 8.17 (d, 1H, J=8.1 Hz), 7.91 (d, 1H, J=8.0 Hz), 7.66 (t, 1H, J=7.8 Hz), 7.49 (d, 1H, J=7.5 Hz), 7.40 (t, 1H, J=7.5 Hz), 7.14 (t, 1H, J=7.7 Hz), 6.93 (d, 1H, J=7.5 Hz), 2.45 (s, 3H). Anal. Calcd for $C_{13}H_{11}N_2OI$: C, 46.17; H, 3.27; N, 8.28. Found: C, 46.15; H, 3.30; N, 8.30.

4.1.8. *N*-(1*R*-Hydroxymethyl-propyl)-2-iodo-benzamide (7). Yield: (94%); off-white solid; mp 106–108 °C. FT-IR (KBr): 3264, 2962, 1644, 1540, 1042, 725 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.77 (d, 1H, J=7.8 Hz), 7.35–7.27 (m, 2H), 7.05–6.99 (m, 1H), 5.90 (d, 1H, J=7.8 Hz, N*H*), 4.03–3.98 (m, 1H), 3.77 (dd, 1H, J=3.5,

3.5 Hz), 3.65 (dd, 1H, J=5.1, 5.1 Hz), 2.40 (br s, 1H, OH), 1.71–1.51 (m, 2H), 0.98 (t, 3H, J=7.4 Hz). Anal. Calcd for $C_{11}H_{14}NO_2I$: C, 41.39; H, 4.42; N, 4.38. Found: C, 41.35; H, 4.45; N, 4.40.

4.1.9. *N*-(1*R*-Phenyl-ethyl)-2-iodo-benzamide (8). Yield: (96%); off-white solid; mp 85–87 °C. FT-IR (KBr): 3299, 1640, 1529, 1447, 1317, 1014, 873, 743, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.84 (d, 1H, J= 7.8 Hz), 7.44–7.25 (m, 7H), 7.10–7.05 (m, 1H), 6.00 (br s, 1H, N*H*), 5.34 (p, 1H, J=7.3 Hz), 1.64 (d, 3H, J=6.9 Hz). Anal. Calcd for $C_{15}H_{14}NOI$: C, 51.29; H, 4.01; N, 3.98. Found: C, 51.26; H, 4.10; N, 4.00.

4.2. 5*H*-Phenanthridin-6-one (2) and biphenyl-2,2′-dicarboxylic acid bis-phenylamide (3a)

In a typical reaction procedure, a mixture of 2-iodo-*N*-phenyl-benzamide **1a** (340 mg, 1.05 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 0.015 mmol), CuI (2.85 mg, 0.015 mmol), Et_3N (0.5 ml) and dry DMF (5.0 ml) was stirred at 120 °C for 12 h under nitrogen atmosphere. DMF was then distilled off, methylene chloride was then added and filtered through a pad of celite (3–4 cm). The organic layer was washed well with water followed by brine and then dried (Na_2SO_4). Removal of solvent followed by column chromatography furnished white solid **2** (30 mg, 15%) followed by **3a** (60 mg, 58%) as white crystalline solid.

4.2.1. 5*H*-Phenanthridin-6-one (2). Mp 198 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm)=9.46 (bs, 1H), 7.75–7.08 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=169.5, 138.16, 132.27, 132.07, 130.19, 129.80, 128.93, 128.74, 128.50, 128.15, 127.38, 124.47, 120.09. MS (EI): m/z (%)=195.1 (M^+, 14%), 122.1 (70%), 106.1 (100%). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.96; H, 4.64; N, 7.15.

4.2.2. Biphenyl-2,2′-dicarboxylic acid bis-phenylamide (3a). Mp 228–229 °C [lit.[15] 229–230 °C]. UV/vis ($CHCl_3$): λ_{max} (log ε)=258 nm (8.7). FT-IR (KBr): 3444, 3251, 1644, 1540, 1488, 1321, 776 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.81 (bs, 2H), 7.26 (d, 2H, J=8.6 Hz), 7.36–7.31 (m, 8H), 7.19 (t, 4H, J=7.8 Hz), 7.12 (d, 2H, J=8.5 Hz), 7.00 (t, 2H, J=7.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.75, 139.51, 138.35, 136.53, 130.58, 130.13, 129.30, 128.52, 127.62, 124.88, 120.40. MS (EI): m/z (%)= 392.1 (M^+, 34%), 271.9 (31%), 181 (100%), 28 (75%). Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.59; H, 5.10; N, 7.14. Found: C, 79.55; H, 5.14; N, 7.23.

4.3. Synthesis of biphenyl-2,2′-dicarboxylic acid bis-phenylamide (3a). A general representative reaction procedure for symmetrical biaryls

A mixture of 2-iodo-*N*-phenyl-benzamide **1a** (120 mg, 0.37 mmol), $Pd(OAc)_2$ (3.36 mg, 0.015 mmol), CuI (2.85 mg, 0.015 mmol), Ph_3P (10 mg, 0.03 mmol), Et_3N (0.25 ml) and CH_3CN (5.0 ml) was stirred at 82 °C for 6 h under nitrogen atmosphere. The reaction mixture was then evaporated to dryness, CH_2Cl_2 was added and filtered through a pad of celite (3–4 cm). The organic layer was washed well with water followed by brine and then dried (Na_2SO_4). Removal of solvent followed by column chromatography afforded the white crystalline solid **3a** (25 mg, 70%) identical in all respects with the material described above. This protocol was successfully applied for other iodoarylbenzamides **1b–g** and for chiral **7** and **8**.

4.3.1. *N*-Butyryl-2-iodo-*N*-phenyl-benzamide (1a′). A mixture of 2-iodo-*N*-phenyl-benzamide **1a** (324 mg, 1 mmol), butyryl chloride (0.114 ml, 1.1 mmol) and Et_3N (0.153 ml, 1.1 mmol) in dry benzene was refluxed for 24 h under N_2 atmosphere. The product was purified by silica gel chromatography [CH_2Cl_2 and pet-ether (1:1)] to afford the butyryl protected derivative **1a′** as a cream-colored semi solid.

FT-IR (KBr): 3446, 2360, 1698, 1299, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.68 (d, 1H, J=8.1 Hz), 7.34–7.17 (m, 7H), 6.95 (m, 1H), 2.51 (t, 2H, J=5.6 Hz), 1.65–1.52 (m, 2H), 0.84 (t, 3H, J=7.4 Hz). Anal. Calcd for $C_{17}H_{16}NO_2I$: C, 51.91; H, 4.10; N, 3.56. Found: C, 51.90; H, 4.12; N, 3.60.

4.4. Palladium catalyzed coupling of butyryl protected derivative (1a′)

A mixture of butyryl protected derivative **1a′** (100 mg, 0.264 mmol), $Pd(OAc)_2$ (2.97 mg, 0.0132 mmol), (o-tol)$_3$P (4.02 mg, 0.0132 mmol) and Na_2CO_3 (23.34 mg) in dry DMF (5.0 ml) was stirred at 150 °C for 1.5 h under nitrogen atmosphere. The reaction mixture was then evaporated to dryness, CH_2Cl_2 was added and filtered through a pad of celite (3–4 cm). After usual work-up and purifications, **3a** was isolated as a white crystalline solid (31 mg, 60%) identical in all respects with the above.

4.4.1. Biphenyl-2,2′-dicarboxylic acid bis-*o*-tolylamide (3b). Cream colored solid; mp 230–232 °C [lit.[16] 236 °C]. UV/vis ($CHCl_3$): λ_{max} (log ε)=247 nm (8.4). FT-IR (KBr): 3434, 2922, 1644, 1527, 1458, 1317, 1059, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.35 (bs, 2H), 6.63 (d, 2H, J=8.8 Hz), 7.40–7.37 (m, 4H), 7.34 (d, 2H, J=7.9 Hz), 7.22 (d, 2H, J=8.7 Hz), 7.04 (t, 4H, J=6.5 Hz), 6.98 (t, 2H, J=7.0 Hz), 1.99 (s, 6H). MS (EI): m/z (%)=420 (M^+, 30%), 286 (25%), 181 (100%), 91 (28%). Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 80.00; H, 5.74; N, 6.70.

4.4.2. Biphenyl-2,2′-dicarboxylic acid bis-*m*-tolylamide (3c). White crystalline solid; mp 208–210 °C. UV/vis ($CHCl_3$): λ_{max} (log ε)=256 nm (10.7). FT-IR (KBr): 3443, 3264, 2925, 1645, 1598, 1550, 1440, 1331, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.68 (bs, 2H), 7.62 (d, 2H, J=8.5 Hz), 7.36–7.31 (m, 4H), 7.24 (s, 2H), 7.13 (d, 2H, J=8.5 Hz), 7.10–7.05 (m, 4H), 6.82 (d, 2H, J=6.9 Hz), 2.24 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.70, 139.52, 139.22, 138.29, 136.62, 130.53, 130.12, 129.08, 128.48, 127.63, 125.69, 121.03, 117.54, 21.87. MS (EI): m/z (%)=420.4 (M^+, 40%), 286.2 (35%), 181 (100%), 116 (41%). Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.95; H, 5.76; N, 6.68.

4.4.3. Biphenyl-2,2′-dicarboxylic acid bis-[(4-methoxy-phenyl)-amide] (3d). White solid; mp 120–122 °C. UV/vis

($CHCl_3$): λ_{max} (log ε)=239 nm (10.1). FT-IR (KBr): 3307, 2955, 1650, 1512, 1232, 824, 741 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.82 (bs, 2H), 7.60 (d, 2H, J=8.6 Hz), 7.32–7.30 (m, 4H), 7.22 (d, 4H, J=6.9 Hz), 7.10 (d, 2H, J=6.4 Hz), 6.71 (d, 4H, J=6.9 Hz), 3.67 (s, 6H). MS (EI): m/z (%)=452.0 (M^+, 40%), 330 (30%), 181 (100%), 123 (85%). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.30; H, 5.38; N, 6.22.

4.4.4. Biphenyl-2,2′-dicarboxylic acid bis-[(4-bezoic acid ethyl ester)-amide] (3e). Light yellow gum. UV/vis ($CHCl_3$): λ_{max} (log ε)=237 nm (7.7). FT-IR (KBr): 2980, 2940, 1655, 1540, 1435, 1390, 1295, 1100, 770, 710, 565 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.09 (br s, 2H), 7.73–7.28 (m, 16H), 3.39 (q, 2H, J=7.1 Hz), 3.30 (q, 2H, J=7.1 Hz), 1.18 (t, 3H, J=7.1 Hz), 1.12 (t, 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.82, 168.51, 139.52, 138.29, 136.62, 125.69, 133.81, 133.46, 132.54, 130.65, 128.76, 126.09, 43.43, 14.71. MS (EI): m/z (%)=536.0 (M^+, 20%), 330 (30%), 181 (100%). Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.62; H, 5.25; N, 5.22. Found: C, 71.54; H, 5.28; N, 5.34.

4.4.5. Biphenyl-2,2′-dicarboxylic acid bis-pyridin-2-yl-amide (3f). Light yellow gum. UV/vis ($CHCl_3$): λ_{max} (log ε)=280 (8.5), 238 nm (9.3). FT-IR (KBr): 3450, 3085, 1690, 1610, 1580, 1550, 1460, 1400, 1310, 1240, 790, 755, 565 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.03 (bs, 2H), 7.92–7.80 (m, 4H), 7.46–7.35 (m, 4H), 7.21–7.02 (m, 8H). MS (EI): m/z (%)=366.4 (M^+, 40%), 234 (100%). Anal. Calcd for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found: C, 73.00; H, 4.58; N, 14.24.

4.4.6. Biphenyl-2,2′-dicarboxylic acid bis-[(6-methyl-pyridin-2-yl)-amide] (3g). Light brown solid; mp 176–178 °C (decomp). UV/cis ($CHCl_3$): λ_{max} (log ε)=285 (9.6), 240 nm (10.0). FT-IR (KBr): 3450, 3080, 1690, 1610, 1580, 1540, 1460, 1400, 1310, 1240, 790, 755, 715, 565 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm)=8.97 (bs, 2H), 7.92 (d, 2H, J=8.0 Hz), 7.70–7.68 (m, 2H), 7.53–7.38 (m, 6H), 7.24–7.21 (m, 2H), 6.80 (d, 2H, J=7.4 Hz), 2.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.52, 156.96, 150.93, 139.74, 139.02, 136.04, 130.87, 130.40, 128.39, 127.75, 119.70, 111.46, 22.90. MS (FAB): m/z (%)=423.3 (MH^+, 100%). Anal. Calcd for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.90; H, 5.30; N, 13.30.

4.4.7. Biphenyl-2,2′-dicarboxylic acid bis-[(1*R*-hydroxy-methyl-propyl)-amide] (5). Light brown semi solid. UV/vis ($CHCl_3$): λ_{max} (log ε)=259 (7.8), 239 nm (8.2). FT-IR (KBr): 3433, 2922, 2360, 1640, 1438, 1119, 722 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=7.67–7.63 (m, 4H), 7.55–7.41 (m, 4H), 6.50–6.44 (m, 2H, 2×N*H* amide), 4.52–4.48 (m, 1H), 4.23–4.19 (m, 1H), 4.01 (br s, 2H, OH), 3.75–3.71 (m, 2H), 3.68–3.65 (m, 2H), 1.87–84 (m, 2H), 1.70–1.63 (m, 2H), 1.07 (t, 3H, J=4.9 Hz), 0.99 (t, 3H, J=7.4 Hz). MS (EI): m/z (%)=384 (M^+, 20%), 330 (20%), 290 (40%), 249 (80%), 231 (100%), 105 (95%). Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.28. Found: C, 68.68; H, 7.38; N, 7.38.

4.4.8. Biphenyl-2,2′-dicarboxylic acid bis-[(1*R*-phenyl-ethyl)-amide] (6). White crystalline solid; mp 140–142 °C. $[\alpha]_D^{34}$=+28.50 (c 0.66, $CHCl_3$). UV/vis ($CHCl_3$): λ_{max} (log ε)=239 nm (10.9). FT-IR (KBr): 3090, 2980, 1620, 1505, 1460, 1220, 1190, 1130, 1100, 1080, 1030, 1000, 750, 725, 540 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.55–7.07 (m, 18H), 6.94 (br s, 2H), 5.02 (br s, 2H), 1.36 (d, 3H, J=11.3 Hz), 1.14 (d, 3H, J=11.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=169.35, 143.34, 139.40, 136.86, 136.53, 129.90, 129.82, 128.88, 128.84, 128.19, 128.14, 127.56, 127.34, 126.59, 126.46, 49.51, 49.19, 22.18, 21.74. MS (FAB): m/z (%)=449.6 (MH^+, 90%), 471.5 (100%). Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 79.96; H, 6.71; N, 7.10. Found: C, 79.92; H, 6.82; N, 7.21.

4.4.9. 3,3′-Bipyridyl-6,6′-dipivaloylamide (9). Off-white solid; mp 167–169 °C. UV/vis ($CHCl_3$): λ_{max} (log ε)=298 nm (9.9). FT-IR (KBr): 3434, 2953, 2360, 1671, 1503, 1314, 1166, 827 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.46 (d, 2H, J=2.31 Hz), 8.34 (d, 2H, J=8.76 Hz), 8.08 (bs, 2H), 7.88 (dd, 2H, J=8.66 Hz), 1.35 (s, 18H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=177.51, 151.51, 145.91, 136.81, 129.67, 114.27, 40.24, 27.87. HRMS (FAB): m/z calculated for $C_{20}H_{26}N_4O_2$ $(M+Na)^+$: 377.1953; Found: 377.1952.

4.4.10. 6,6′-Dimethyl-2,2′-bipyridyl (10). Cream colored solid; mp 82–85 °C (lit.[17] 89–90 °C).

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11. *Crystallographic data* **3a**: Chemical formula $C_{26}H_{20}N_2O_2$, Molecular weight 392.44 g mol^{-1}, tetragonal, space group $P4_32_12$ (No. 96), $a=b=10.7822(9)$, $c=35.902(4)$ Å, $\alpha=\beta=\gamma=90°$, $V=4173.8(6)$ Å^3, $Z=8$, $T=294(2)$ K, density = 1.249 g cm^{-3} (calc.), $F(000)=1648$, $\mu=0.080$ cm^{-1}, 5203 reflections from 2–25°, 2235 unique (1342 with $I>2\sigma I$), 272 parameters, R-factor is 0.066, $wR_2=0.126$ [based on F^2 for reflections with $I>2\sigma I$)], $Gof=1.04$, density range in final Δ-map is -0.29 to $+0.28$ e.A^{-3}, (solved in SHELXL97, refined in SHELXL97). *Crystallographic data* **6**: Chemical formula $C_{31}H_{29}N_2O_2Cl_3$ (as chloroform solvate): Molecular weight 567.91 g mol^{-1}, orthorhombic, space group $P2_12_12_1$ (No. 19), $a=11.7763(7)$, $b=14.4974(12)$, $c=17.4072(17)$ Å, $\alpha=\beta=\gamma=90°$, $V=2971.9(4)$ Å^3, $Z=4$, $T=294(2)$ K, density = 1.269 g cm^{-3} (calc.), $F(000)=1148$, $\mu=0.338$ cm^{-1}, 5950 reflections from 2 to 25°, 5275 unique (3850 with $I>2\sigma I$), 346 parameters, R-factor is 0.043, $wR_2=0.078$ [based on F^2 for reflections with $I>2\sigma I$)], $Gof=1.03$, density range in final Δ-map is -0.20 to $+0.20$ e.A^{-3}, (solved in SHELXL97, refined in SHELXL97). The crystallographic data for **3a** and **6** have been deposited with the Cambridge Crystallographic Data Centre, CCDC as No. 190491 and 209565. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).
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