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Keywords
ii, synthesis, catalysed, reaction, intramolecular, c, h, functionalisation, ready, 6, biindole, biisatin, via, palladium, CMMB

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Synthesis of reaction-ready 6,6′-biindole and 6,6′-biisatin *via* palladium(II)-catalysed intramolecular C–H functionalisation†

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The first synthesis of a 6,6′-biindole and 6,6′-biisatin scaffold is reported with the penultimate step being the formation of the di-heterocyclic ring by Pd(II)-catalysed intramolecular C–H functionalisation and Sandmeyer cyclisation, respectively.

Nature provides a rich source of biaryl compounds with significant biological activity[1] and numerous methods exist for the synthesis of structurally diverse biaryls *e.g.* by transition-metal catalysis[2,3] or oxidative coupling.[3] As part of our ongoing investigations into the biological activities of homo- and hetero-dimeric aromatic systems,[4,5] we have been investigating biindoles as bioisosteres of binaphthyl units. In particular we are interested in privileged heterocyclic scaffolds having the potential for multiple functionalisations in often unreactive positions. Although the synthesis of symmetrical biindoles has been reported,[6] symmetrical 6,6′-biindoles and 6,6′-biisatins have no literature precedence. Herein we report the first synthesis of the symmetrical 6,6′-biindole **1** and 6,6′-biisatin **2** biaryl scaffolds with strategically positioned 'reaction-ready' functional groups in the 2-, 3- and usually unreactive 4-positions, upon which chemical libraries can be built in search of bioactive compounds (Fig. 1).

Bromide was selected for the reactive handles in the normally deactivated 4,4′-positions, thus, the key intermediate was bianiline **8**,[7] which allowed for a convergent synthesis to both targets. A 2,3-dicarboxylate substituent pattern on the indole nucleus[8] also allowed for future derivatisation, while reducing the reactivity of these positions during subsequent aryl bromide reactions. Thus, **8** was synthesised *via* a modified procedure in six steps from commercially available 2,2′-biphenol **3**, without the need for column chromatography in an overall yield of 52% (Scheme 1).[9,10] Key was the selective nitration of **6**, followed by protection of the phenolic groups to provide **7**, which was further reduced under ultrasound in the presence of iron[11] to afford bianiline **8**.

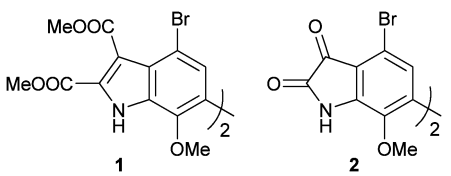

Fig. 1 Reaction ready 6,6′-biindole **1** and 6,6′-biisatin **2** target scaffolds.

Transition-metal-catalysed direct arylation *via* C–H insertion has undergone rapid development, and is still receiving significant attention.[12] A recent report[12d] outlined the synthesis of indoles from simple anilines and alkynes *via* a Pd(II)-catalysed C–H activation using dioxygen, however, at the outset of our work, the only reports of a 2,3-disubstituted methyl ester indole *via* Pd(II)-catalysis involved an excess of $Pd(OAc)_2$ (2 equiv.).[13] For cyclisation of **8** to biindole **1**, a catalytic method tolerating an aryl bromide substituent was required. Thus, the synthesis of enaminone **10** *via* Michael addition of dimethyl acetylenedicarboxylate to aniline **7** allowed for the optimisation of Pd(II)-catalysed C–H insertion and intramolecular cyclisation *via* indole **11** (Scheme 2).[14]

Intriguingly, solvent plays an important role in the mechanism for reaction. In the case of the Pd(II)-cyclisation of enaminones, it has not been discussed in detail, however, compounds of similar structure to **10** are capable of forming a stable six-membered intramolecular hydrogen bond (Scheme 3),[15] preventing the orientation required for intramolecular cyclisation to indole **11**. Proton transfer can occur, allowing for both an enaminone **10A** and imino–enol **10B** tautomer, with equilibrium shifted to favour **10A** as solvent polarity increases.[15] On the basis of the previous experiments (Scheme 2)[14] we postulate that both DMA and acetonitrile can competitively H-bond to the N–H enaminone proton, disrupting the stable six-membered ring conformer **10A** and establishing an equilibrium with the desired **10AA** enaminone intermediate. However, DMA participates more aggressively in H-bonding (Scheme 3),[16] and thus, **10AA** is expected to predominate in DMA.

Thus, we postulate a similar mechanism to Jiao and co-workers,[12d] with an emphasis on the importance of a strong H-bond acceptor solvent such as DMA (Scheme 3). Acting as a Lewis-base donor,[16] coordination of DMA sets up an equilibrium thought to favour the conformation of **10AA**, and increases the nucleophilicity of the α-carbon and arene through weakening of the N–H bond. C–H insertion *via* electrophilic palladation[12d] of **10AA** and reconjugation of the DMA stabilised cationic imine intermediate affords **10AB**, with subsequent electrophilic aromatic substitution and re-aromatisation providing palladacycle **10AC**. Reductive elimination of **10AC** gives the desired indole **11**, with the Pd(0) generated reoxidized by a Cu(II) salt. Alternatively, C−H activation *via* an electrophilic aromatic substitution reaction could precede enaminone C−H insertion, especially in an electron-rich arene such as **10**. However, in less electrophilic arenes, previous intramolecular isotope effect studies for

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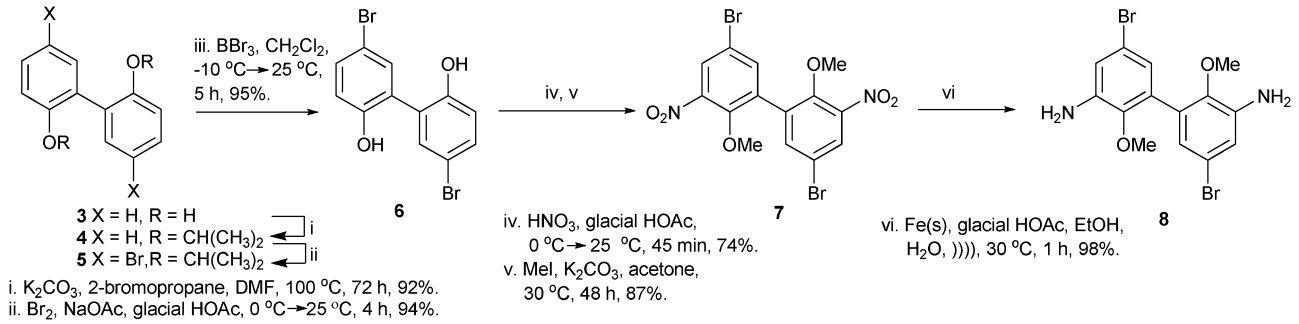
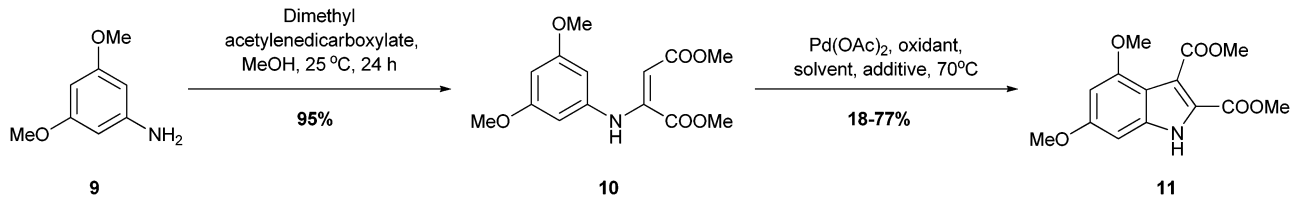
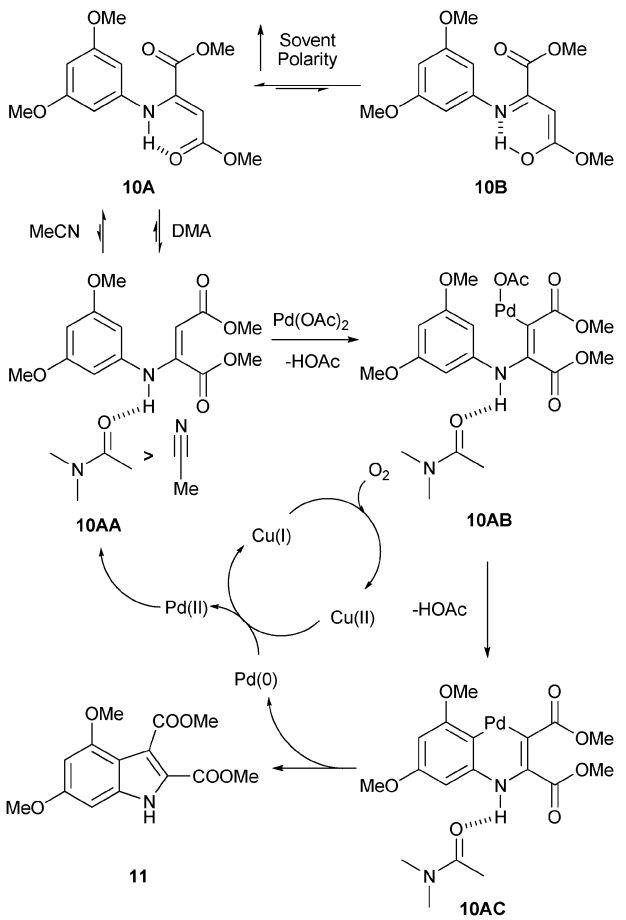
† Electronic supplementary information (ESI) available: Details of experimental procedures, optimisation details and discussion for cyclisation to indole monomers, ^1H and ^{13}C NMR spectra for biindole **1** and biisatin **2**. See DOI: 10.1039/c002098b



Scheme 1 The synthesis of substituted bianiline **8**.



Scheme 2 Investigation into the Pd(II)-catalysed C–H activation of enaminone **10**, affording 2,3-disubstituted indole **11**.

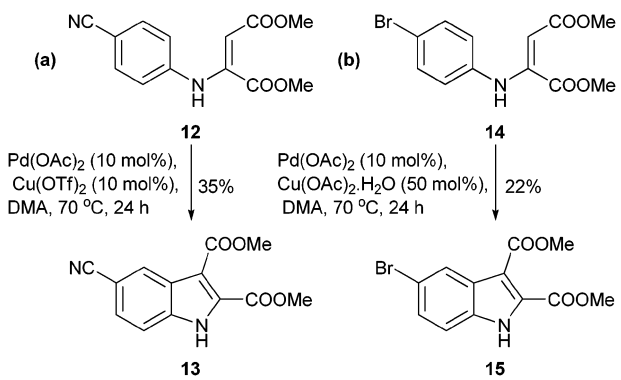


Scheme 3 Proposed mechanism for 2,3-dicarboxylate indole synthesis *via* Pd(II)-catalysed C–H functionalisation in DMA.

oxidative Pd(II)-catalysed conditions[12d] support the formation of an enaminone intermediate analogous to **10AB**.

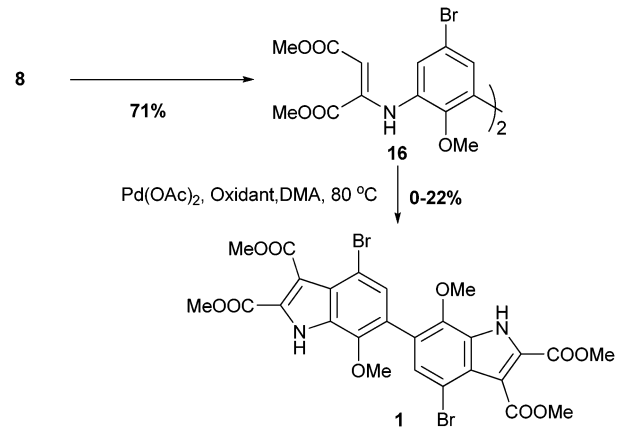
Only limited examples of this reaction using substrates with strongly deactivating and/or potentially labile functional groups have been reported.[12d] Therefore we examined the tolerance of our optimised conditions[14b] using two electron-deficient arenes (Scheme 4). Indole **11** was isolated in modest yield (35%) and 5-bromo indole **15** in a poorer yield (18%). A higher catalyst loading and 50 mol% $Cu(OAc)_2{\cdot}H_2O$ as co-oxidant marginally increased the yield of indole **15** to 22%. Although not optimised, these indolisation conditions tolerate electron-deficient and aryl bromide functional groups, and could be utilised in the synthesis of the 6,6′-biindole **1**.

Reaction of dimethyl acetylenedicarboxylate with bianiline **8** provided di-enaminone **16** in 71% yield. Cyclisation *via* Pd(II)-catalysed oxidative coupling yielded 6,6′-biindole **1** in 22% yield (Table 1, entry 1). The higher catalyst and oxidant loading of 30 mol% (15 mol%/enaminone) and 100 mol% (50 mol%/enaminone), respectively, was used to promote more efficient oxidation of generated Pd(0). Further optimisation through catalyst and oxidant loading (Table 1, entries 2 and 3) did not improve the yield of **1**. Excess $Pd(OAc)_2$ in air resulted in complete consumption of **16**, however, **1** could only be isolated in 8% yield with multiple by-products formed. The observed product distribution was presumably a consequence



Scheme 4 Optimisation of C–H Pd insertion reactions to form indole monomers containing electron withdrawing substituents.

Table 1 Pd(II)-catalysed synthesis of 6,6′-biindole scaffold **1**



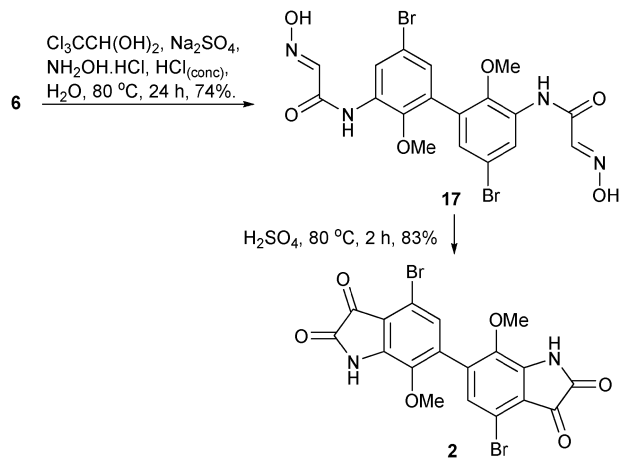
Entry	Catalyst (mol%)	Oxidant (mol%)	Time/h	Yield[a] (%)
1	$Pd(OAc)_2$ (30)	$Cu(OAc)_2{\cdot}H_2O$ (100)	18	22
2[b]	$Pd(OAc)_2$ (20)	$Cu(OAc)_2{\cdot}H_2O$ (20)	29	7.5
3	$Pd(OAc)_2$ (30)	$Cu(OTf)_2$ (100)	24	0
4	$Pd(OAc)_2$ (400)	None	18	8

[a] Isolated yield. [b] An additional 10 mol% $Pd(OAc)_2$ and 10 mol% $Cu(OAc)_2$ added after 23 h.

of Pd(0) not being efficiently reoxidised back to Pd(II), and thus, demonstrates the superiority of an oxidative catalytic method.[17]

6,6′-Biisatin **2** was realised in high yield over two steps from bianiline **8** *via* the robust and well precedented Sandmeyer method (Scheme 5).[18] Isonitrosoacetanilide **17** was prepared in good yield (74%), and subsequent heating of **17** in concentrated sulfuric acid allowed di-cyclisation to occur, with biisatin **2** isolated in 83% yield after precipitation on crushed ice, without the requirement for chromatography.

In conclusion, we have demonstrated the first syntheses of two novel symmetrical 6,6′-biheterocycles from a common bianiline intermediate. Both the 6,6′-biindole **1** and 6,6′-biisatin **2** represent scaffolds which contain 'reaction-ready' functionalities in previously unreactive positions of the benzene ring, while retaining the possibility for subsequent derivatisations on the heterocyclic ring.



Scheme 5 Synthesis of 6,6′-biisatin.

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