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Copper-Mediated Construction of Spirocyclic Bis-oxindoles via a Double C−H, Ar−H Coupling Process

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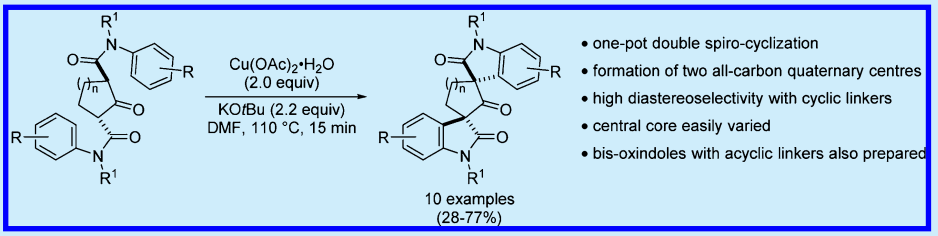
Supporting Information



ABSTRACT: A double C−H, Ar−H coupling process for the conversion of bis-anilides into spirocyclic bis-oxindoles, enabling the concomitant formation of two all-carbon quaternary centers at oxindole 3-positions in a diastereoselective manner, is described. The optimum cyclization conditions utilize stoichiometric $Cu(OAc)_2 \cdot H_2O$/KO*t*Bu in DMF at 110 °C and have been applied to prepare a range of structurally diverse bis-spirooxindoles in fair to good yields (28−77%); the method has also been extended to prepare bis-oxindoles linked by a functionalized acyclic carbon chain.

Over the past decade, there has been a significant resurgence of interest in oxindoles, as these structures represent validated targets in the search for new drug candidates and form the cornerstone of numerous alkaloids of biological interest.[1] More recently, bis-oxindoles have attracted considerable attention (Figure 1). For example,

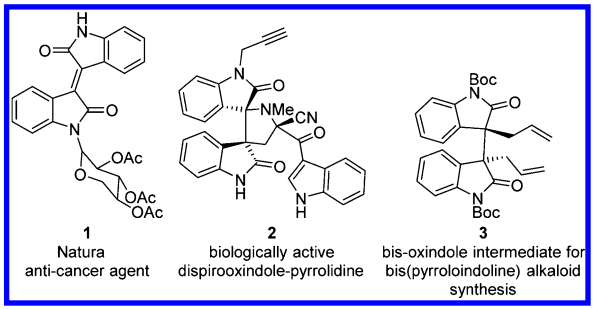
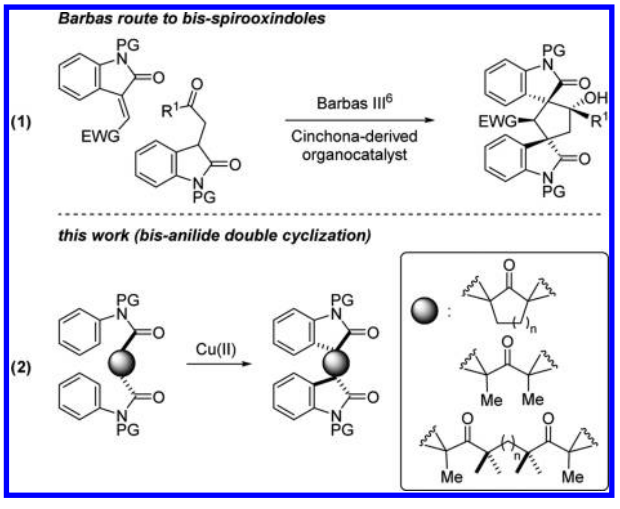


Figure 1. Examples of bis-oxindole targets.

Natura (**1**) is representative of a family of isoindigo-based anticancer agents (CDK inhibitors)[2] and compound **2** is typical of a range of dispirooxindole-pyrrolidine derivatives recently shown to possess significant antibacterial and anticancer activities (against A549 human lung adenocarcinoma).[3] Moreover, bis-oxindoles have long been employed as precursors of bis(pyrroloindoline) alkaloids,[4] most recently with compound **3** being used as a cornerstone for the synthesis of a diverse range of cyclotryptamine alkaloids.[4d]

Many synthetic strategies have been established to access the oxindole motif,[5] but only limited examples have been reported to date on bis-oxindoles, probably because of their highly functionalized polycyclic skeletons, particularly those containing multiple spiro-quaternary carbon centers. The majority of approaches rely on the linking together of preformed oxindoles,[2−4] a strategy most beautifully illustrated by Barbas who developed an organocatalytic asymmetric Michael addition/aldol cascade reaction between 3-substituted oxindoles and methyleneindolinones which proceeds with excellent diastereo- and enantiocontrol (Scheme 1, eq 1).[6] Related variants have subsequently been reported[7] but all commence with preformed oxindoles and all produce bis-oxindole

Scheme 1. Strategies for the Synthesis of Bis-oxindoles



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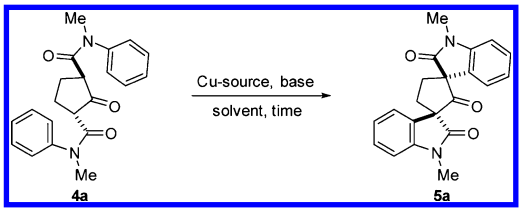
products linked at the 3,3-positions by another 5-membered ring generated in a formal [3 + 2]-cyclization process.[8]

Our objective was to establish a more general route to bis-oxindoles (Scheme 1, eq 2) which would utilize readily accessible bis-anilide precursors[9] and would be applicable to the formation of a range of diverse bis-oxindole products with, for the first time, great variability in the linking central core units. As shown, the plan was to utilize a copper(II)-mediated bis-anilide cyclization approach (a formal C−H, Ar−H coupling) based on the chemistry devised for the preparation of oxindoles[10,11] and related heterocycles[12] by the groups of Taylor and Kündig in 2009. Herein, we wish to disclose the success of this approach to access a range of bis-spirooxindoles featuring central core units of different ring sizes and, in addition, functionalized acyclic linker units.

The cyclopentanone 2,5-dicarboxamide **4a** was chosen as the bis-anilide for preliminary studies (Table 1). Compound **4a** was

Table 1. Optimization of the Reaction Conditions



entry	base	Cu source	solvent (temp)	time (h)	yield
1	–	$Cu(OAc)_2·H_2O$ (1.0 equiv)	mesitylene (170 °C)	0.5	<5%
2	–	$Cu(OAc)_2·H_2O$ (1.0 equiv)	toluene (100 °C)	0.5	24%
3	–	$Cu(OAc)_2·H_2O$ (1.0 equiv)	toluene (80 °C)	3	17%
4	**KO*t*Bu (2.2 equiv)**	**$Cu(OAc)_2·H_2O$[a] (2.0 equiv)**	**DMF (110 °C)**	**0.25**	**67%**

[a]In a control experiment carried out using KO*t*Bu (2.2 equiv) but without $Cu(OAc)_2·H_2O$, no product was observed in the ^1H NMR spectrum of the crude reaction mixture. Instead, residual starting material and products from amide hydrolysis as well as decomposition were observed.

prepared in two steps by amide coupling between adipic acid and *N*-methylaniline followed by a novel ring closure using carbonyldiimidazole (CDI; see Supporting Information for details). The thermodynamically more stable *trans*-bis-anilide diastereoisomer was the only product of the reaction (confirmed by X-ray crystallography).[13] The double spirocyclization was then investigated, initially using $Cu(OAc)_2·H_2O$ in mesitylene at 170 °C, conditions optimized for the formation of simple oxindoles.[10b,c] However, only traces of cyclized product **5a** were detected under these conditions (Table 1, entry 1). Carrying out the reaction in toluene at reflux gave a useful 24% yield (entry 2) but further reductions in temperature resulted in lower yields, even after extended reaction times (e.g., entry 3). However, changing to $Cu(OAc)_2·H_2O$ and KO*t*Bu in DMF (conditions employed in our original study[10a]) gave the desired spirocyclic bis-oxindole **5a** in a gratifying 67% yield (entry 4). This double cyclization proceeded with complete diastereoselectivity to give only the *trans*-diastereoisomer illustrated, in which the two oxindole units are orthogonal (confirmed by X-ray crystallographic analysis, Figure 2).[14]

Having established successful conditions for the double cyclization on the model system **4a**, we went on to test the

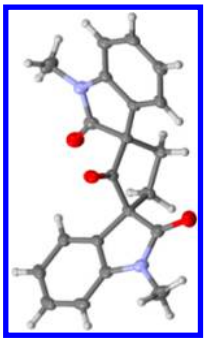
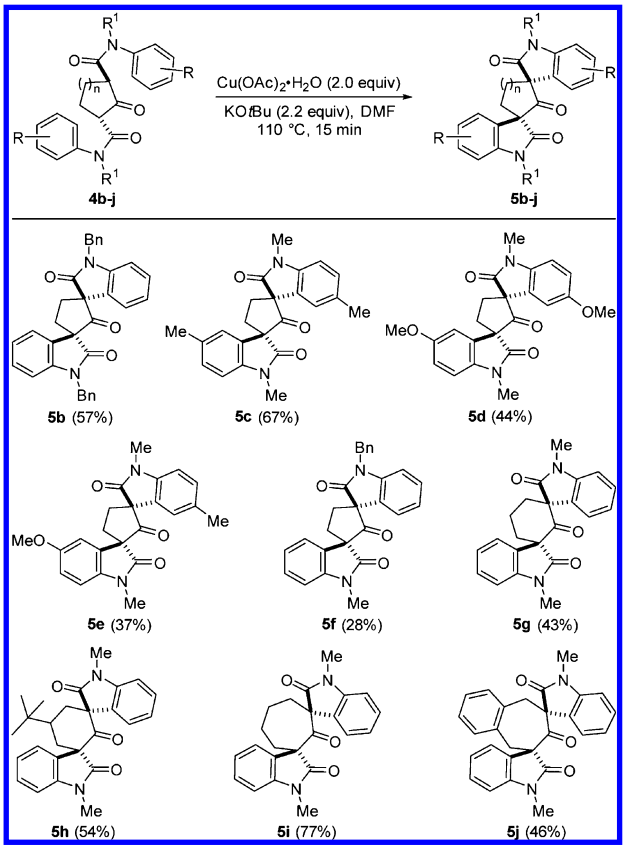


Figure 2. Crystal structure of **5a** (50% probability ellipsoids).

substrate scope using a range of substituted bis-anilides **4**.[15] First we ensured that the procedure was compatible with *N*-benzyl protection and found that adduct **5b** was formed in 57% yield. Substitution of the aromatic rings was studied next, and both 4-methyl- and 4-methoxy-substitution was well tolerated giving **5c** and **5d**, respectively. Unsymmetrical bis-oxindoles were also prepared with either differential ring substitution (**5e**) or differential *N*-protection (**5f**). Variation of the central ring size was also explored.[15] Thus, a cyclohexanone (**5g**) and a substituted cyclohexanone example (**5h**) were prepared, as were a 7-membered ring-containing bis-oxindole (**5i**, obtained in 77% yield) and a benzo-fused cycloheptanone example (**5j**). The yields of the cyclization products varied (28−77%), but it should be noted that all of the procedures in Scheme 2 used the standard conditions developed in Table 1 and none were optimized. It should also be noted that all of products in Scheme 2 were obtained as single *trans*-diastereoisomers.

Scheme 2. Bis-spirooxindole Substrate Scope



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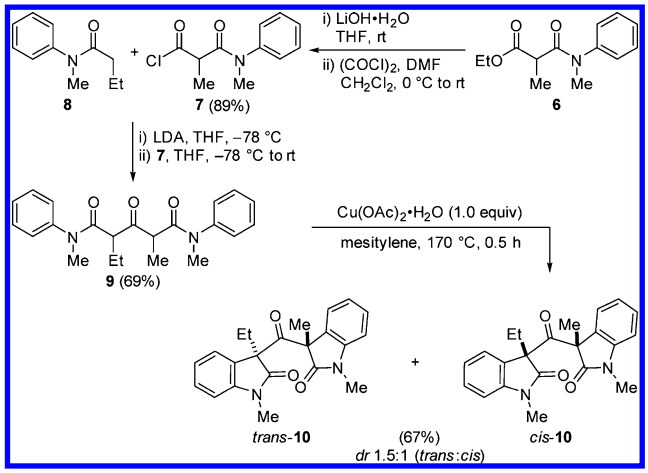
To further demonstrate the scope and versatility of the double anilide cyclization procedure, attention switched to the use of acyclic linker units. Initial studies were carried out on bis-anilide **9**, readily prepared as shown in Scheme 3. Thus, acid

Scheme 3. Bis-oxindole Synthesis with an Acyclic Linker



chloride **7** was synthesized from the respective ester anilide **6** in 89% yield over two steps. The enolate of **8** was trapped with acid chloride **7** and afforded bis-anilide **9** in 69% yield. In this case, the strongly basic procedure was not required, and treatment of precursor **9** with $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in mesitylene at 170 °C for 30 min afforded the desired bisoxindole **10** in 67% yield.[16] The keto-linked bis-oxindole **10** was obtained as a mixture of diastereoisomers (1.5:1 *trans*/*cis*) which were separable by column chromatography. The relative configurations of the diastereoisomeric products were determined by X-ray crystallography (Figure 3) indicating that the *trans*-isomer **10** was the major product.[17]

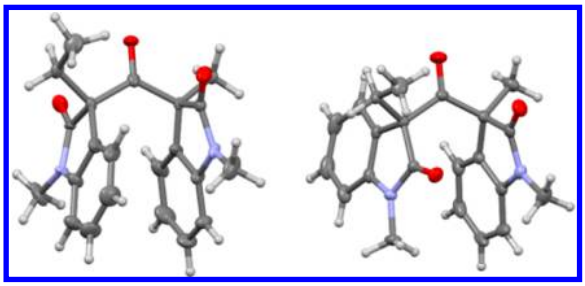
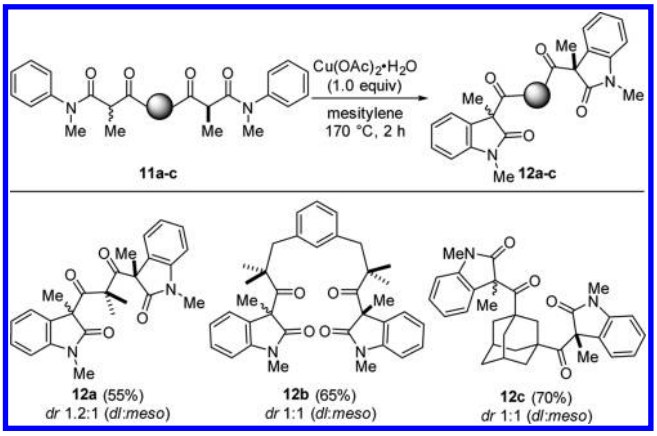


Figure 3. Crystal structures of *trans*-**10** (left) and *cis*-**10** (right).

Having established that this Cu(II) method could be employed to prepare bis-oxindoles with a keto-functionalized one-carbon linker, we sought to further extend the reaction scope (Scheme 4).

Compounds **11a–c** were easily obtained from the corresponding diacid chlorides using similar procedures to those employed in Scheme 3. Cyclization again occurred efficiently using $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in mesitylene at 170 °C, and again mixtures of diastereoisomers were produced. The diastereoisomers of bis-oxindole **12a**, linked by a three-carbon dicarbonyl chain, were separable, and the structures confirmed by X-ray analysis (Figure 4).[18] We also varied the linker chain length introducing an aromatic ring (**12b**) and prepared the adamantane-linked example **12c** using a similar procedure.

Scheme 4. Bis-oxindole Synthesis with Di-ketone Linkers



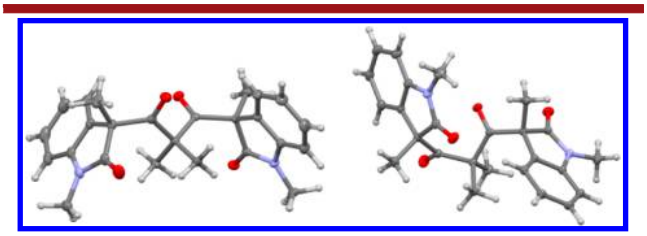


Figure 4. Crystal structures of DL-**12a** (left) and *meso*-**12a** (right).

In conclusion, we have developed a concise strategy to access a diverse range of spirocyclic bis-oxindoles using a one-pot, double Cu(II)-mediated bis-anilide cyclization by double C–H, Ar–H coupling. This method allows the installation of two all-carbon quaternary centers at the oxindole 3-position in a diastereoselective manner and great variability in the linking central core units for the first time. The method has been extended to prepare a number of bis-oxindoles linked by a functionalized acyclic carbon chain. We are currently investigating the use of chiral auxiliaries in these processes as well as exploring applications in target synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(13) X-ray data for **4a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1013303), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.
(14) X-ray data for **5a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1004040), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.
(15) The cyclopentanone precursors were prepared using the procedure described for **4a**; the 6- and 7-membered ring precursors **4g–j** were synthesized from cyclohexanone or -heptanone *via* double carboxylation with methyl magnesiumcarbonate: Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598. This was followed by double Mukaiyama amide coupling (see Supporting Information for details).
(16) The previous conditions ($Cu(OAc)_2 \cdot H_2O$, KO*t*Bu in DMF at 110 °C) were tried; however, the yield of the product was inferior (~54%). This drop in yield is mainly due to formation of oxidative cleavage byproducts, namely *N*-methyl-3-alkyl-3-hydroxyoxindoles. Formation of these byproducts is minimized under the $Cu(OAc)_2 \cdot H_2O$/toluene conditions.
(17) X-ray data for *cis*- and *trans*-**10** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1004041 and 1016758), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.
(18) X-ray data for *meso*-**12a** and *dl*-**12a** have been deposited with the Cambridge Crystallographic Data Centre (*meso*-**12a**: CCDC 1013389, DL-**12a**: CCDC 1013390), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif. See Supporting Information for crystallographic details.