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Unexpected chiral vicinal tetrasubstituted diamines via borylcopper-mediated homocoupling of isatin imines

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Abstract
Addressing the asymmetric synthesis of oxindole-based α-amino boronic acids, instead of the expected products we disclosed the efficient homocoupling of oxindole-based N-*tert*-butanesulfinyl imines, with the generation of chiral, quaternary 1,2-diamines in a mild and completely stereoselective way. The obtained 3,3'-bisoxindoles derivatives were fully characterised by NMR and single-crystal X-ray diffraction analysis and proved to be single diastereoisomers and atropoisomers. A plausible mechanism for the one-pot Cu(II)-catalysed Bpin-addition to the isatin-derived ketimine and subsequent homocoupling is detailed.

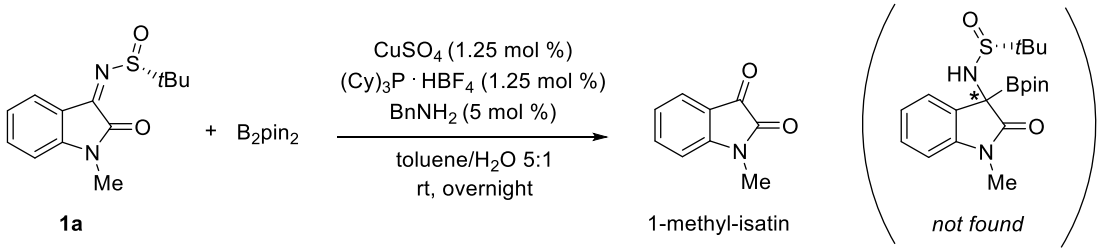
Keywords
N-tert-butanesulfinyl ketimine; bis(pinacolato)diboron; 3,3'-bisoxindole; homocoupling; atropoisomer.

Introduction

As bioisosteres of carboxylic acid derivatives, boronic acids have recently emerged as a novel chemotype in drug design, with a number of boron-containing compounds recently being approved by FDA.[1] In particular, α- and β-amino boronic acids are commonly utilized as key intermediates for the synthesis of boron-containing peptidomimetics, which have been demonstrated to be efficient covalent ligands and valuable protease inhibitors endowed with various biological activities.[2]
Relying on our long-standing studies on the asymmetric synthesis of 3,3-disubstituted oxindole derivatives,[3] we recently exploited a molecular hybridization strategy, pursuing the synthesis of chiral oxindole-based β-amino boronic acids and spiro derivatives. By merging the two biologically relevant oxindole and β-amino boronic acid moieties into a new scaffold, we accessed unexplored and potentially drug-like chemical space.[4] Indeed, incorporation of boron atom within chiral oxindoles had been reported only quite recently, exploiting Cu-catalysed enantioselective intramolecular transformations.[5]
Going on from such previous work, next we looked at the copper-mediated reaction of isatin-derived, optically pure sulfinyl ketimines with bis(pinacolato)diboron, as a potential way to access oxindole-based α-aminoboronates. The asymmetric synthesis of diverse α-amino boronic acids by diastereoselective Cu(I)-catalyzed borylation of N-*tert*-butanesulfinyl aldimines was described by Ellman and co-workers for the first time in 2008[6] and next further developed with a more stable Cu(II) catalyst in 2014.[7]
Herein we describe the unexpected results achieved by our work, that is the obtainment of unprecedented, bisoxindole-based, vicinal, tetrasubstituted diamines. Bisoxindoles represent a particularly intriguing class of compounds, for their interesting biological activities and because they can serve as key synthetic intermediates in the construction of complex natural products.[8] Particularly challenging is the placement of the two C3/C3' contiguous quaternary stereogenic centers, just as they are found in various alkaloids, such as those belonging to the bis(cyclotryptamine) family.[9]
In light of these considerations and as, to our knowledge, no borylcopper-mediated homocoupling of N-*tert*-butanesulfinyl imines have been documented before, we consider useful to share our findings and to accurately describe the obtained products.

Results and Discussion

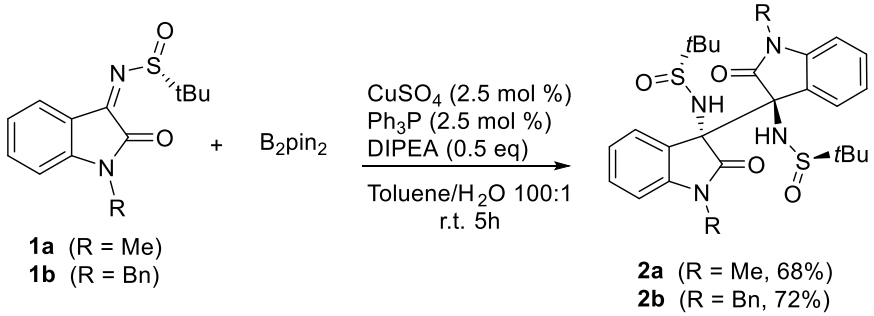
We began our investigation using the known (*R*)-1-methylisatin-derived N-*tert*-butanesulfinyl ketimine **1a**, bis(pinacolato)diboron, $CuSO_4$/$(Cy)_3P$ catalyst and benzylamine, as reported in Scheme 1. The first reaction was carried out at room temperature in toluene/water (5:1), as described by Ellman and co-workers, but the expected α-amino-boronate could not be isolated. Extensive hydrolysis of the starting ketimine occurred, allowing the only recovery of the 1-methyl-isatin precursor.



Scheme 1. Reaction conducted according to the Ellman protocol.

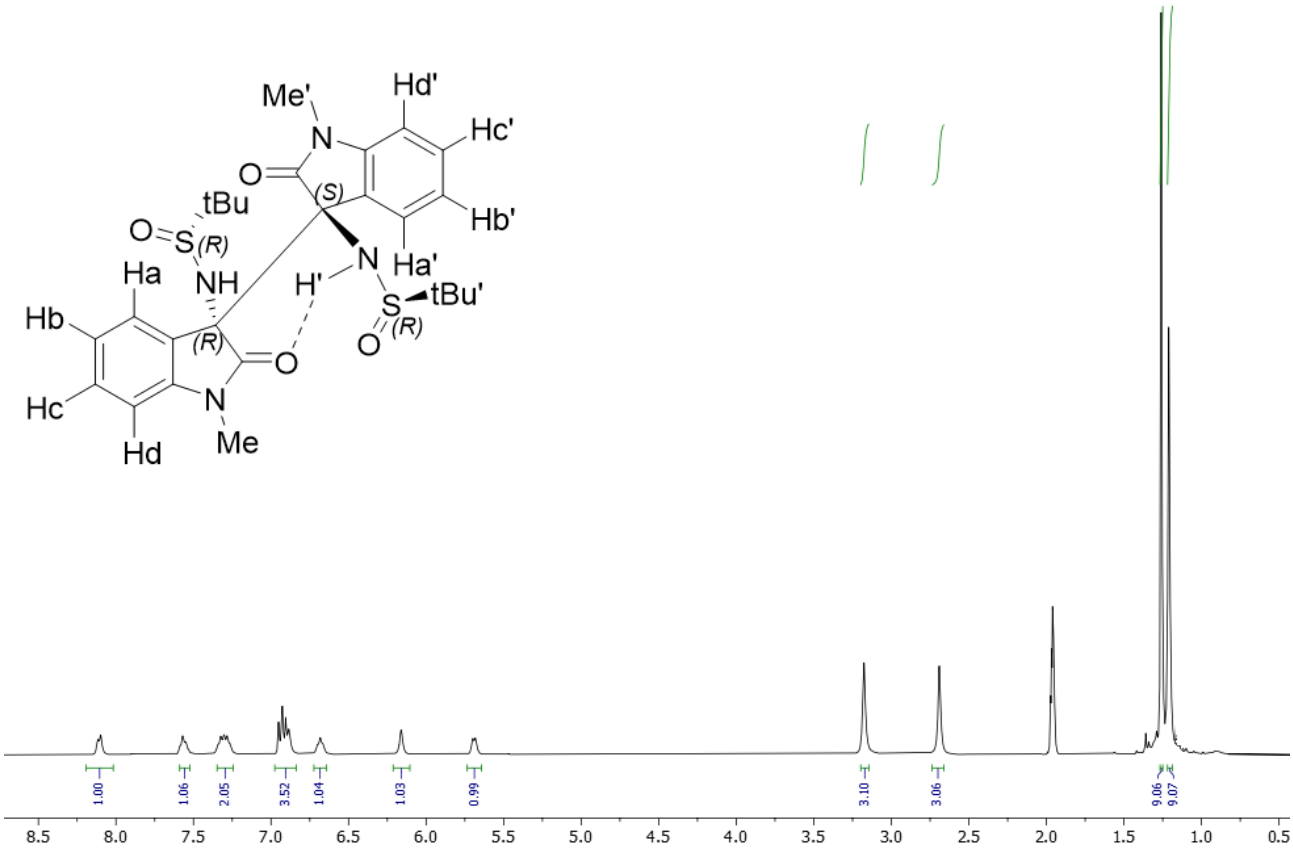
In the light of this initial outcome, we considered to reduce the amount of water to the minimum necessary to solubilize the copper sulfate. Thus, performing the reaction in toluene/water 100:1, ketimine hydrolysis was almost entirely prevented and a new product could be detected, even if together with various impurities. As part of a consequent, detailed screening of reaction conditions, we evaluated many amines (pyridine, 4-picoline, p-methoxy-pyridine, triethylamine, DIPEA, DMAP, DABCO) in place of benzylamine. DIPEA proved to be the best choice, while, with regard to the ligand, Ph_3P behaved more effectively than $(Cy)_3P{\cdot}HBF_4$, maximizing the conversion of the substrate to a single product.

From the reaction run in the optimized conditions, the unprecedented bisoxindole **2a** could be isolated in 68% yield, after flash chromatography. Quite similarly, starting from (*R*)-1-benzylisatin-derived N-*tert*-butanesulfinyl ketimine **1b**, compound **2b** could be obtained in comparable yield (Scheme 2).



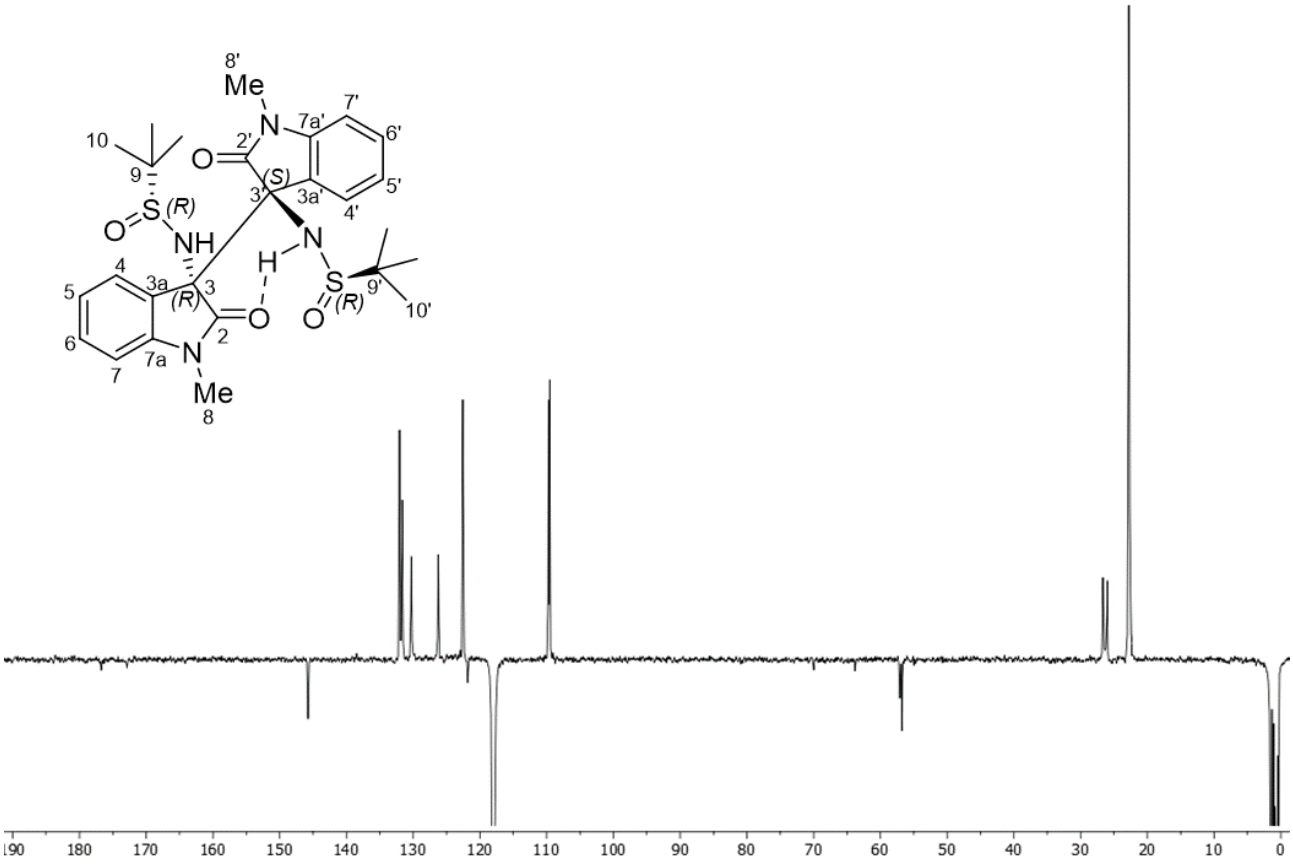
Scheme 2. Reactions conducted in the optimized conditions.

Compounds **2a** and **2b** were fully characterized by high-resolution mass spectrometry and by mono- and bi-dimensional NMR analysis. In particular, from HSQC, HMBC e COSY experiments all single frequencies could be safely assigned in ^1H and ^{13}C NMR spectra, as reported in Tables 1 and 2 for **2a**, allowing the complete spin systems reconstruction for both the oxindole-based units (for **2b**, see Supporting Information). Furthermore, from NOESY experiment, the unique *anti* disposition of the two *t*Bu-SO-NH substituents along the C3-C3' bond could be assessed, thus demonstrating the complete diastereoselecivity of the reaction.



Proton	Chemical Shift (ppm)	Proton	Chemical Shift (ppm)
Ha	5.69	Ha’	8.11
Hb	6.69	Hb’	7.29
Hc	7.33	Hc’	7.58
Hd	6.94	Hd’	6.92
NH	6.16	NH’	6.88
Me	3.18	Me’	2.69
tBu	1.26	tBu’	1.21

Table 1. ^{1}H NMR (CD_3CN, 400 MHz) and assignments for compound **2a**



Carbon	Chemical Shift (ppm)	Carbon	Chemical Shift (ppm)
C-2	176.7	C-2’	172.9
C-3	63.8	C-3’	70.0
C-4	126.2	C-4’	130.3
C-5	122.63	C-5’	122.57
C-6	131.6	C-6’	132.1
C-7	109.7	C-7’	109.5
C-8	26.7	C-8’	26.0
C-9	57.1	C-9’	56.7
C-10	22.76	C-10’	22.79
C-3a and C-3a’	121.8	C-7a and C-7a’	145.8

Table 2. ^{13}C NMR (CD_3CN, 100 MHz) and assignments for compound **2a**

All stereochemical implications were fully confirmed by single-crystal X-ray diffraction analysis, which was performed on well-formed prismatic crystals of compound **2a** (Figure 1).[10]

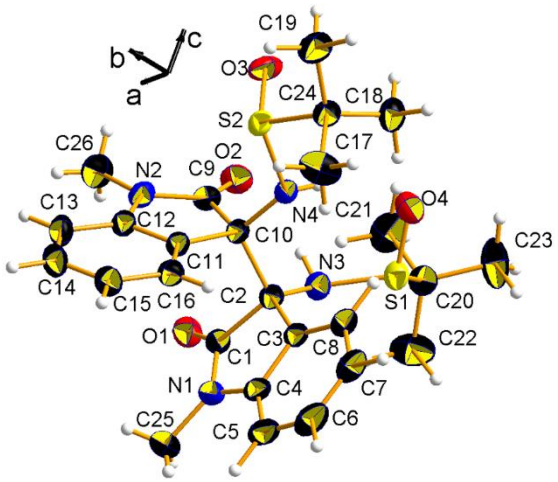
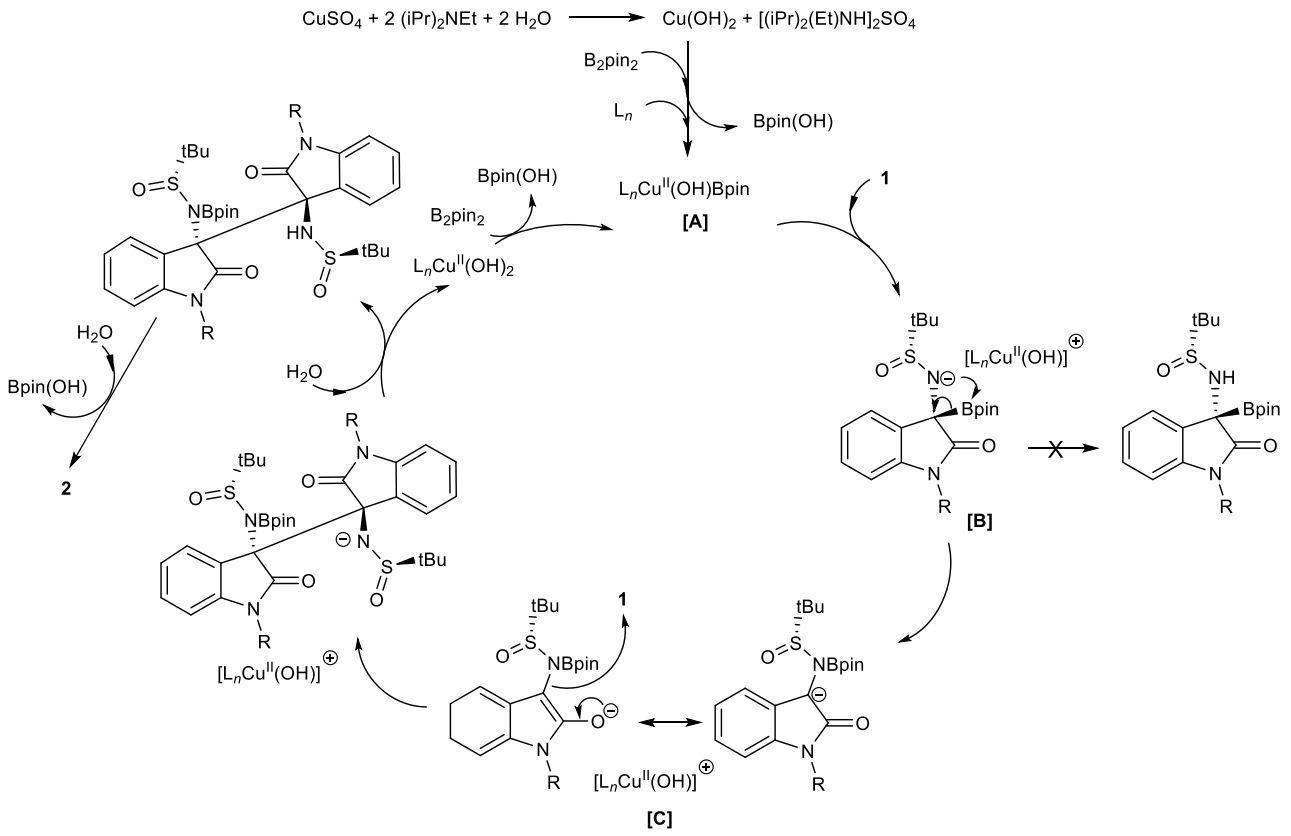


Figure 1. Asymmetric unit of **2a**, with the atom-numbering scheme. The crystallographic reference system is also shown. Thermal ellipsoids at RT were drawn at the 50 % probability level. Atoms are represented with the usual colour code (C: black; N: blue; O: red; S: yellow; H: white).

The compound **2a** is chiral and crystallizes in the orthorhombic space group $P2_12_12_1$. The presence of sulphur anomalous scatters allowed to unequivocally establish the absolute configurations, which reads *S* at the chiral centre C2 and *R* at the C10 one (C numbering as in Figure 1). The absolute configuration of the two sulphur stereogenic centres is confirmed to be *R*. Interestingly, the molecule does not bear any pseudo–mirror plane, that is, the observed conformer is asymmetric (C1) in itself, regardless the configuration of the two sulfinamide substituents. This peculiarity is likely due to the hindered rotation across the newly formed C-C bond, joining the two oxindole unit. Such C2–C10 single bond is quite long (1.58 Å), as expected due to crowding of the two facing oxindole systems. In the crystal, NH groups set up intramolecular hydrogen bonds with the O acceptors of the sulfinamide moieties (see Table 3), likely contributing to further stabilize the observed conformer.

D–H···A	$d_{D\text{-}H}$ / Å	$d_{H\cdots A}$ / Å	$d_{D\text{-}A}$ / Å	α / deg	*Symmetry*
N3–H3N···O2	0.99(4)	2.03(4)	2.854(4)	139(3)	x, y, z
N4–H4N···O4	0.82(4)	2.21(4)	2.981(4)	157(4)	x, y, z

Table 3. Intramolecular hydrogen bonds in **2a** at room temperature, which involve the NH groups with one keto oxygen (O2) and one sulfinamide oxygen (O4). Atom numbering as in Figure 1. The asymmetry of such interactions reflects the intrinsic asymmetry of the solid–state conformer.



Scheme 3. Proposed mechanism for the borylcopper-mediated homocoupling of ketimines **1**.

In order to rationalize the formation of bisoxindole products, we refer to the underdeveloped umpolung reactions of imines, considering, in particular, the copper-catalysed process reported quite recently by Zhang, Hou and co-workers.[11] In our case, we presume the possible reaction mechanism shown in Scheme 3, which likely starts from the catalytic generation, in our experimental conditions, of the borylcopper(II) species **[A]**. Such copper complex proved to be not isolable, but could be easily generated in situ and may act as a genuine Cu(II) catalyst, with a labile coordination site.[12] According to Ellman's chemistry, the addition of Bpin to the C=N double bond of the ketimine substrate **1** should actually take place, affording the intermediate **[B]**, immediate precursor of our original target compound, namely the α-amino-boronate derivative. However, probably due to its high steric crowding, such intermediate spontaneously turns into the carbanion **[C]**, thus realizing the imine umpolung and allowing the cross-coupling reaction with the remaining electrophilic ketimine **1**. The complete diastereoselectivity would arise from the mutual approach of the two oxindole nuclei from the less hindered side, that is the one away from the bulky auxiliary *t*Bu group. The presence of two NH-SO*t*Bu substituents, preventing the free rotation around the C3/C3' bond, ensures the optical activity of the molecule, in accordance with the presence of a single atropoisomer (absence of any pseudo–mirror plane), as also determined by single-crystal X-ray diffraction analysis.

Conclusions

In summary, we have disclosed a reaction protocol that allows efficient homocoupling of oxindole-based N-*tert*-butanesulfinyl imines and generation of chiral, quaternary 1,2-diamines in a mild and completely stereoselective way. The one-pot, simple experimental procedure makes this process a convenient and straightforward approach for the synthesis of enantiomerically pure vicinal diamines and structurally challenging bisoxindole natural products.

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