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Aza-Henry Reaction of Isatin Ketimines with Methyl 4-Nitrobutyrate en Route to Spiro[piperidine-3,3′-oxindoles]

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Abstract: A new enantioselective route to spiro[piperidine-3,3′-oxindoles] from isatin ketimines is described. The aza-Henry reaction of *N*-Boc-isatin ketimines with methyl 4-nitrobutyrate in the presence of a Ph_2BOX-$CuBr_2$ complex provided the corresponding nitro amino esters with good diastereoselectivity and excellent enantioselectivity (up to >99% *ee*). The aza-Henry adducts were transformed into spiro[piperidine-3,3′-oxindoles] after reduction of the nitro group to oxime, and cleavage of the *N*-Boc group and lactamisation.

Keywords: asymmetric catalysis; copper; lactams; nitrogen heterocycles; nucleophilic addition

3,3′-Spirocyclic oxindoles are attractive targets in organic synthesis due to the presence of this structural motif in numerous naturally occurring alkaloids and pharmaceutically active compounds,[1,2] exhibiting antitumour,[3] antibacterial,[4] analgesic[5] or antituberculosis[6] activities, among others. Many 3,3′-spirocyclic oxindoles feature a heterocyclic spiranic ring with a nitrogen atom at the 2 position of the oxindole nucleus.[7] Among these, oxindoles bearing a spiranic piperidine ring, either alone, or fused with an aromatic or heteroaromatic system have attracted great interest on account of their biological profile. Examples (Figure 1) include tetrahydro-β-carboline spirooxindoles (spiroindolinones) with anticonvulsive activity,[8] the experimental drug NITD609, which has recently been identified as a potential treatment for malaria,[9] or (iso)quinoline spirooxindoles with potential antitumour activity.[10] Some simple spiro[piperidine-3,3′-oxindoles] have shown analgesic properties[11] while others are being investigated as peptide isosteres which are able to mimetise a type II β-turn in the search for new enzyme inhibitors.[12]

The molecular and stereochemical complexity that characterises this class of compounds represents a significant synthetic challenge;[13] in particular, the construction of a highly hindered, strained spirocyclic quaternary chiral centre is not trivial, especially in an enantioselective manner.[14] Therefore, only a limited number of synthetic approaches to these kinds of spirooxindoles in enantioselective manner are available. For instance, tetrahydro-β-carboline spirooxindoles have been prepared by means of the Pictet–Spengler reaction between tryptamines and isatins in either a non-enantioselective[15] or an enantioselective fashion,[16] and *via* cyclization of alkynylanilines in racemic form.[17] On the other hand, quinoline spirooxindoles have been obtained *via* a Povarov reaction from isatin ketimines.[10,18] Alternatively, formation of the spiranic ring can be accomplished from 3-substituted-3-aminooxindoles *via* cyclization procedures[19] such as lactamisation.[20] However, the synthesis of enantioenriched spirooxindoles by using this strategy requires procedures for the highly stereoselective formation of the amino-substituted quaternary stereocentre at the position 3 of the oxindole, and the introduction of a properly functionalised chain at this position.

Recently, the aza-Henry reaction with ketimines has experienced considerable progress,[21] and several

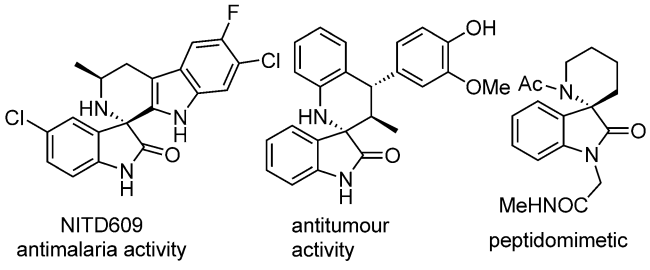
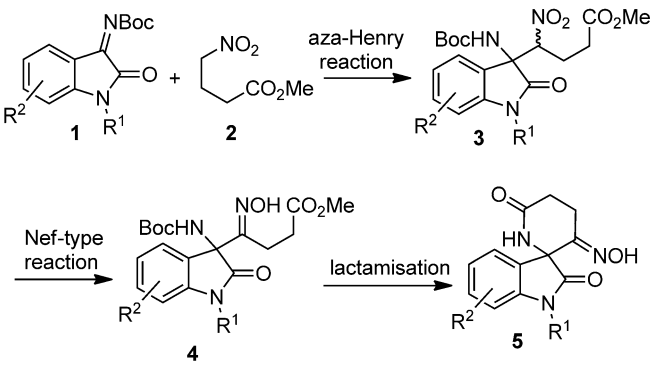


Figure 1. Some examples of bioactive 3-aminospiro[piperidine-3,3′-oxindoles].

groups[22] including ours[23] have developed efficient procedures for the enantioselective aza-Henry reaction with isatin ketimines leading to 3-aminooxindoles bearing a quaternary stereogenic centre. These studies with isatins have been limited to unfunctionalised nitroalkanes. We envisioned that the addition of alkyl nitrobutyrates to isatin ketimines[24,25] would provide chiral 3-aminooxindoles with an ester-functionalised chain at the 3 position of the oxindole which would make possible the access to highly enantioenriched spiro[piperidine-3,3′-oxindoles] after lactamisation (Scheme 1).[26]

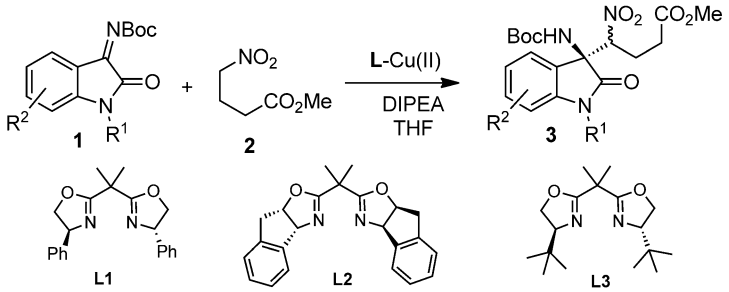
In our previous work[23] we performed the enantioselective addition of nitromethane to *N*-Boc-isatin ketimines using a copper(II)-Ph_2BOX (**L1**) catalyst with excellent enantiomeric excesses. Election of the copper salt was crucial for the success of this reaction as the use of copper(II) triflate caused the hydrolysis of the *N*-Boc-imine, being detrimental to the yield.



Scheme 1. Enantioselective approach to spiro[piperidine-3,3′-oxindoles] based on the aza-Henry reaction with methyl 4-nitrobutyrate.

This undesired reaction could be avoided by using other copper salts, the best results in terms of yield

Table 1. BOX-Cu(II)-catalysed aza-Henry reaction of methyl-4-nitrobutyrate with *N*-Boc–isatin ketimines.[a]



Entry	**1**	R^1	R^2	**3**	*t* [h]	Yield [%]	*dr*[b]	*ee*[c] [%]
1[d]	**1a**	H	H	**3a**	19	58	93:07	99/99
2	**1a**	H	H	**3a**	19	84	90:10	99/98[e]
3	**1b**	Me	H	**3b**	14	84	60:40	99/99
4	**1c**	Bn	H	**3c**	15	90	83:17	91/99[e]
5	**1d**	MOM	H	**3d**	14	96	84:16	99/99[e]
6	**1e**	H	5-Me	**3e**	16	98	91:09	99/96
7	**1f**	H	5-MeO	**3f**	15	87	91:09	98/96
8	**1g**	H	5-Br	**3g**	16	88	82:18	98/90
9	**1h**	H	5-Cl	**3h**	14	89	85:15	97/93[e]
10	**1i**	H	6-Cl	**3i**	21	97	69:31	96/96[e]
11	**1j**	H	7-Me	**3j**	15	87	90:10	98/96
12	**1k**	H	7-Cl	**3k**	16	94	83:17	99/98[e]
13	**1l**	H	7-F	**3l**	14	90	86:14	99/99[e]
14	**1m**	H	5,7-Me_2	**3m**	16	94	90:10	99/98
15[f]	**1a**	H	H	**3a**	19	84	76:24	76/73[h]
16[g]	**1a**	H	H	**3a**	19	86	76:24	2/2

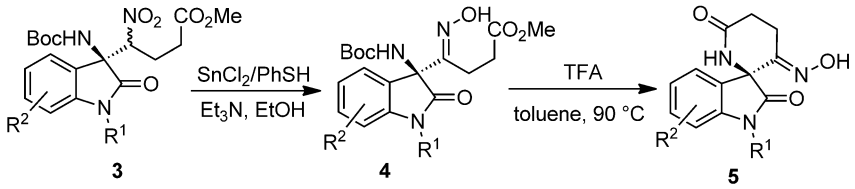
[a] $CuBr_2$ (10 mol%), **L1** (10 mol%), DIPEA (14 mol%), methyl 4-nitrobutyrate (5 equiv.), room temperature.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC.
[d] $Cu(BF_4)_2$ was used instead of $CuBr_2$.
[e] The *ee* values may experience some minor deviations (1–2% *ee*) due to experimental error caused by partial overlapping of peaks in HPLC traces.
[f] **L2** was used instead of **L1**.
[g] **L3** was used instead of **L1**.
[h] The enantiomer with the opposite configuration at the quaternary stereogenic centre was obtained.

and enantioselectivity being obtained with copper(II) tetrafluoroborate hydrate. However, when these conditions were applied to the addition of methyl 4-nitrobutyrate (**2**) to isatin ketimine **1a** (Table 1, entry 1), the expected nitroamine was obtained with excellent enantioselectivity although in low yield (58%), together with products arising from the hydrolysis of the ketimine. It seemed that addition of the bulkier methyl 4-nitrobutyrate does not take place at a sufficient rate to avoid completely the hydrolysis of the imine as in the case of the more reactive nitromethane. Fortunately, the use of copper(II) bromide (Table 1, entry 2) instead of copper(II) tetrafluoroborate hydrate allowed us to obtain the aza-Henry product **3a** with high yield (84%), good diastereoselectivity (90:10) and excellent enantiomeric excesses for both diastereomers (99% and 98%, respectively). Although in the view of these results further optimisation was not considered necessary, we also assessed two more commercially available BOX ligands **L2** and **L3** in this reaction (Table 1, entries 15 and 16). The reaction in the presence of **L2**-$CuBr_2$ provided compound **3a** with good yield and fair diastereo- and enantioselectivity, while the use of ligand **L3** delivered the diastereomeric mixture of compound **3a** in almost racemic form.

The optimised conditions for the aza-Henry reaction with methyl 4-nitrobutyrate were applied to a number of isatin *N*-Boc-ketimines **1b–1m** substituted at either the N-1 atom of the heteroaromatic ring or at different positions of the homoaromatic ring (Table 1, entries 3–14). The aza-Henry products **3b–3m** were obtained in high yields and remarkable diastereoselectivities ($dr > 80{:}20$) for most of the examples tested. Although protection of the N-1 is not required, isatin ketimines substituted at this position reacted also with good yields, diastereoselectivity and enantioselectivity (Table 1, entries 3–5), the diastereoselectivity was low only in the case of the imine **1b** derived from 1-methylisatin (Table 1, entry 3). The reaction also allowed the presence of electron-donating (entries 6, 7, 11 and 14) or electron-withdrawing (entries 8–10, 12 and 13) groups on the homoaromatic ring, providing the expected products with good yields and diastereoselectivities. Remarkably, both diastereomers were obtained with high enantioselectivity. Thus the major diastereomer was obtained with enantiomeric excesses above 91% and the minor diastereomer was obtained with enantiomeric excesses above 90% for all the ketimines tested.

Next we studied the formation of the spiranic ring *via* lactamisation. To avoid any retro-Henry reaction while keeping a functional group on the side chain, the nitro group was first converted into an oxime *via* a reductive Nef-type reaction with $SnCl_2$/thiophenol.[27] The corresponding oximes **4** were obtained predominantly with the *E* geometry in fair to good yields without detrimental effects on the enantiomeric excesses (Table 2). After that we attempted the deprotection of the *N*-Boc group and lactamisation. Al-

Table 2. Transformation of aza-Henry adducts **3** into spiro[piperidine-3,3′-oxindoles].[a,b]



Entry	**3**	R^1	R^2	**4**	Yield of **4** [%]	*ee* of **4** [%][c]	**5**	Yield of **5** [%]	*ee* of **5** [%][c]
1	**3a**	H	H	**4a**	82	97	**5a**	82	99
2	**3b**	Me	H	**4b**	68	97	**5b**	68	99
3	**3c**	Bn	H	**4c**	76	99	–	–	–
4	**3d**	MOM	H	**4d**	59	98	–	–	–
5	**3e**	H	5-Me	**4e**	92	99	**5e**	92	92
6	**3f**	H	5-MeO	**4f**	86	98	**5f**	86	95
7	**3g**	H	5-Br	**4g**	97	99	**5g**	97	99
8	**3h**	H	5-Cl	**4h**	88	97	**5h**	88	97
9	**3i**	H	6-Cl	**4i**	78	96	**5i**	78	99
10	**3j**	H	7-Me	**4j**	67	99	**5j**	67	99
11	**3k**	H	7-Cl	**4k**	80	97	**5k**	80	99
12	**3l**	H	7-F	**4l**	88	99	**5l**	88	99
13	**3m**	H	5,7-Me_2	**4m**	81	99	**5m**	81	99

[a] **3** (1 equiv.), $SnCl_2$ (2 equiv.), PhSH (6 equiv.), Et_3N (6 equiv.), EtOH, 20 min.
[b] **4** (1 equiv.), TFA (2 equiv.), toluene, 90 °C.
[c] Determined by HPLC.

though cyclisation to δ-lactams from amino esters usually takes place readily,[26] in our case the lactamisation reaction was difficult due to the strain associated with the formation of the spiranic ring and required treatment of compounds **4** with trifluoroacetic acid in toluene at 90 °C. Under these conditions the *N*-Boc group was removed and the resulting free NH_2 group underwent intramolecular amidation to give the expected spiro[piperidine-3,3′-oxindoles] **5**. Compounds **5** were insoluble in toluene and precipitated from the reaction mixture upon cooling, making their purification easy. Compounds **5** were obtained with fair to good yields and with excellent enantiomeric excesses, except for compound **5c**, which decomposed during this treatment, and compound **5d** having an acid sensitive group attached to N-1. Remarkably, no products resulting from oxime hydrolysis or Beckmann rearrangement were observed.

X-ray analysis of compound **5k** (Figure 2) confirmed the formation of the spiranic system and allowed determination of the configuration of the quaternary stereogenic centre, as well as the geometry of the C=N double bond in the oxime.[28] For the rest of products the absolute stereochemistry was assigned upon the assumption of a uniform stereochemical mechanism.

The observed *S* configuration in the quaternary stereogenic centre is in good agreement with the model proposed in Figure 3.

In this model,[29] we propose that the isatin ketimine coordinates the catalyst Cu(II) centre in a bidentate fashion giving a distorted square planar complex with both the oxygen atom of the amide carbonyl group and the imine nitrogen occupying the most acidic equatorial positions for the maximum electrophilic activation. In this disposition access to the *re* face of the C–N imine is hampered by one of the phenyl groups of the ligand. The nitronate is positioned in one of the apical positions of the Cu(II) centre being activated as a nucleophile, so that nucleophilic attack takes place from the *si* face of the imine, to give the corresponding nitroamide with the *S* configuration at the newly formed quaternary stereogenic centre.

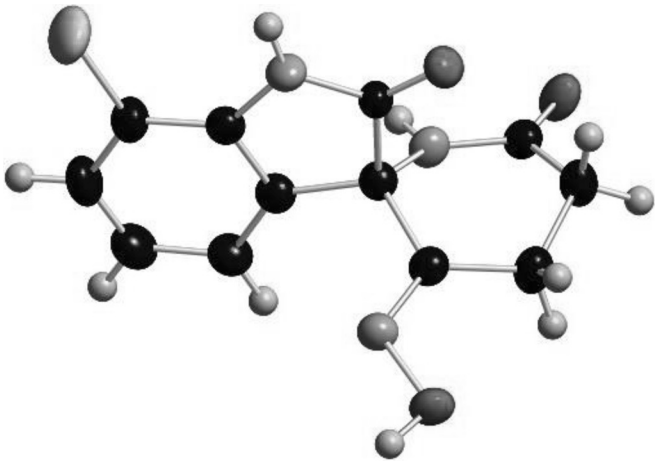


Figure 2. ORTEP plot for the X-ray structure of compound **5k**. The thermal ellipsoids are drawn at the 50% probability level.

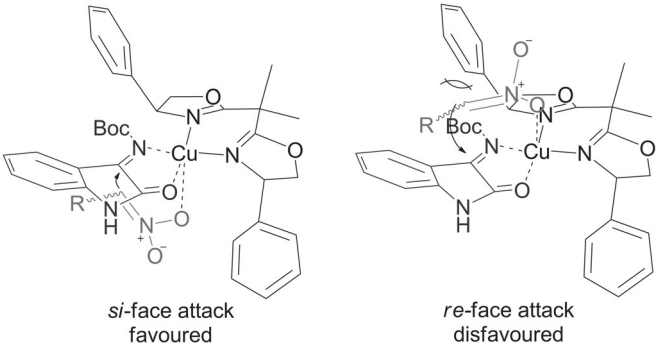


Figure 3. Stereochemical model for the aza-Henry reaction.

In summary, a highly catalytic enantioselective aza-Henry reaction of methyl 4-nitrobutyrate with ketimines is reported. The addition of methyl 4-nitrobutyrate[30] to *N*-Boc-isatin ketimines in the presence of a Ph_2BOX-$CuBr_2$ complex provided the corresponding nitro amino esters with good diastereoselectivity and excellent enantioselectivity (up to 99% *ee*). The selection of the copper salt was essential to obtain good yields. The aza-Henry adducts were transformed into highly enantioenriched spiro[piperidine-3,3′-oxindoles] after reduction of the nitro group to oxime, and cleavage of the *N*-Boc group and lactamisation.

Experimental Section

General Procedure for the Enantioselective Addition of Methyl 4-Nitrobutyrate to Isatin Ketimines

Copper(II) bromide (8.4 mg, 0.038 mmol) contained in a Schlenk tube was dried under vacuum and the tube was filled with nitrogen. A solution of ligand Ph_2BOX (**L1**, 12.5 mg, 0.038 mmol) and methyl 4-nitrobutyrate (**2**, 276 mg, 240 μL, 1.9 mmol) in THF (0.38 mL) was added *via* syringe. After stirring for 1 h, a solution of ketimine **1** (0.38 mmol) and *N,N*-diisopropylethylamine (9.1 μL, 0.053 mmol) in THF (0.57 mL) was added. The reaction mixture was stirred at room temperature until completion (monitored by TLC). The reaction mixture was diluted with EtOAc (30 mL), washed with 0.5 M aqueous HCl (1 mL), brine (2×1 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **3**. Racemic compounds **3** for comparative purposes were prepared following the same procedure by using 2,2′-bipyridine as substitutive for Ph_2BOX.

General Procedure for the Synthesis of Oximes 4

Compound **3** (0.28 mmol) was added to a solution of $SnCl_2{\cdot}2H_2O$ (126.4 mg, 0.56 mmol), thiophenol (185.1 mg, 173 μL, 1.68 mmol) and triethylamine (170.0 mg, 234 μL, 1.68 mmol) in absolute EtOH (1.4 mL) at room temperature. After 20 min, the reaction mixture was poured into 1 M aqueous HCl (2 mL) and CH_2Cl_2 (4 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (4 mL), brine (3 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed through a short plug of silica gel eluting with hexane/EtOAc 8:2 to remove the excess of thiophenol and then with EtOAc. The EtOAc fraction was concentrated under reduced pressure to give oximes **4**.

General Procedure for the Synthesis of Spiranic δ-Lactams 5

Trifluoroacetic acid (36.5 mg, 25 μL, 0.32 mmol) was added to a solution of compound **4** (0.16 mmol) in dry toluene (1.6 mL) at room temperature under a nitrogen atmosphere. The mixture was heated at 90 °C for 3–4 h, and allowed to cool down to room temperature. The supernatant liquid was removed and the solid washed with DCM/toluene mixtures to give compounds **5**. Alternatively, after the reaction time, the mixture was concentrated under reduced pressure and the residue washed with DCM/toluene mixtures to give compounds **5**.

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