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PAPER

Enantioselective organocatalytic oxyamination of unprotected 3-substituted oxindoles†‡

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An enantioselective α-oxyamination of unprotected 3-substituted oxindoles with nitrosobenzene catalyzed by tertiary amine–thiourea bifunctional organocatalysts has been developed and affords the corresponding 3-amino-2-oxindole derivatives in good yields and with moderate to excellent enantioselectivities (up to > 99.9 : 0.1 er when the product is isolated by direct filtration from the reaction mixture). The absolute configuration of the major enantiomers of the products has been established both by chemical correlation and by comparison between the theoretically calculated and the experimental ECD.

Introduction

The 3-amino-2-oxindole moiety is present in drug candidates such as the gastrin/CCK-B receptor antagonist AG-041R,[1] the vasopressin VIb receptor antagonist SSR-14945,[2] the antimalarial NITD609,[3] and some HIV protease inhibitors;[4] on the other hand, marine alkaloids such as the chartellines A–C[5] and psychotrimine, a terrestrial alkaloid isolated from the leaves of the Malaysian plant *Psychotria rostrata*,[6] contain 3-aminoindole substructures that can be accessed from quaternary 3-aminooxindoles (Fig. 1).[7,8]

Although several different procedures are known for the synthesis of tetrasubstituted 3-amino-2-oxindoles in racemic form,[9] few methodologies are presently available for the efficient asymmetric preparation of these compounds, especially in a catalytic fashion.[10] In 2008, Kündig and co-workers[11] reported that the palladium-catalysed intramolecular α-arylation of α-nitrogenated amide enolates gave chiral 3-aminooxindoles in high yield and with variable enantioselectivities (87 : 13–95 : 5 er) when a chiral *N*-heterocyclic carbene ligand was used. Shortly afterwards, the direct, highly efficient asymmetric organocatalytic amination of 3-substituted oxindoles with azodicarboxylates was almost simultaneously achieved by Liu and Chen,[12] Zhou,[13] and Barbas III,[14] using dimeric Cinchona-alkaloid derivatives as catalysts. The nickel-catalyzed enantioselective amination of 3-substituted oxindoles with azodicarboxylates was concurrently disclosed by Matsunaga, Shibasaki *et al.*[15] Very recently, an organocatalytic asymmetric Strecker reaction of ketimine isatin derivatives with trimethylsilyl cyanide, taking place with moderate yields and enantioselectivities (70 : 30–87 : 13 er), has been reported by Zhou *et al.*[16]

The catalytic asymmetric nitroso-aldol reaction[17] has emerged as an efficient tool for the enantioselective formation of carbon–oxygen bonds (α-aminoxylation)[18] and, in a few instances, of carbon–nitrogen bonds (α-oxyamination)[19] at the α-position of

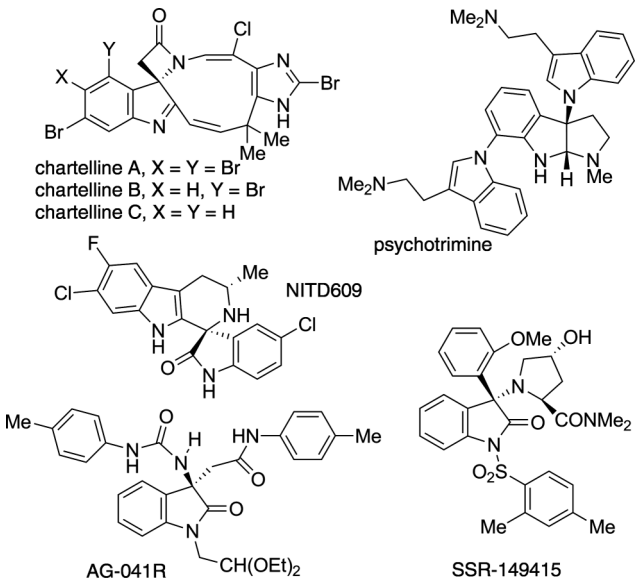

Fig. 1 Representative natural products and bioactive compounds with 3-aminoindole or 3-aminooxindole framework.

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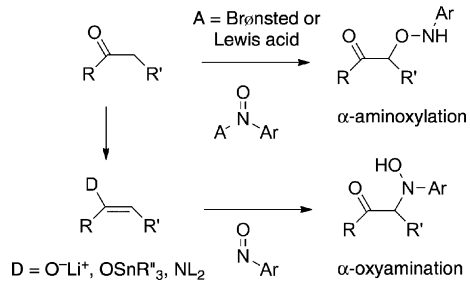
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra and HPLC traces of compounds **3a–3i**. CCDC reference numbers 831712 and 831713. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06503c

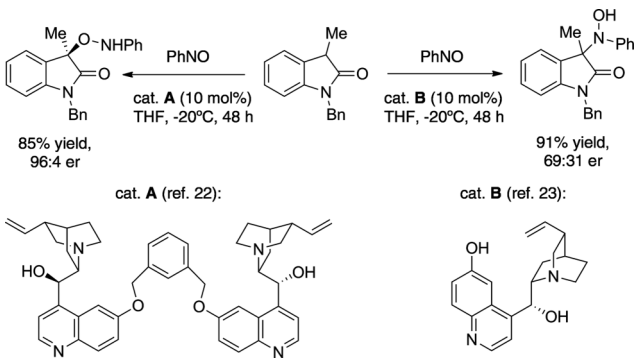
‡ Dedicated to Prof. Miquel A. Pericàs on the occasion of his 60th birthday.

enolizable carbonyl compounds. The regioselectivity of the reaction appears to be controlled by the nature of the catalyst (Scheme 1). Thus, Yamamoto showed that the uncatalyzed reaction of alkali-metal and tin enolates with nitrosobenzene took place with almost exclusive N-selectivity,[20] while the use of Lewis-acid catalysis with silyl enol ethers resulted in high O-selectivities.[18a,20,21] In a similar way, organocatalysts having Brønsted-acid sites give α-aminoxylation products,[18b–h] and chiral secondary amine catalysts afford α-oxyamination adducts.[19]



Scheme 1 Possible products from the nitroso-aldol reaction.

The first application of the nitroso-aldol reaction for the asymmetric heterofunctionalization of 3-substituted oxindoles has been recently reported by the Barbas III group.[22] After testing several chiral tertiary amine catalysts, these authors found that a newly designed quinidine dimer (**A**) promoted the enantioselective addition of nitrosobenzene to a series of 3-substituted *N*-benzyl oxindoles with good yields (65–85% yield) and stereoselectivities (87 : 13–98 : 2 er). In most cases, the reaction was *O*-selective (less than 15% of oxyamination products were formed), a fact that was accounted for by invoking hydrogen-bonding between an hydroxyl group of the catalyst and the nitrogen atom of nitrosobenzene. Subsequently, Liu, Chen and co-workers[23] have disclosed that other *Cinchona*-alkaloid catalysts such as demethylquinine (**B**) give preferentially rise to the oxyamination of *N*-benzyl 3-methyl oxindole, although with low enantioselectivity (Scheme 2). Since demethylquinine also led to the oxyamination of *N*-unprotected oxindoles (enantioselectivities ranging from 79.5 : 20.5 to 86 : 14 er), these authors concluded that the regioselectivity of the nitroso-aldol reaction largely depended on the structure of the catalyst.



Scheme 2 Catalyst-dependent regioselectivity in the nitroso-aldol reaction of 3-methyl-*N*-benzyloxindole.

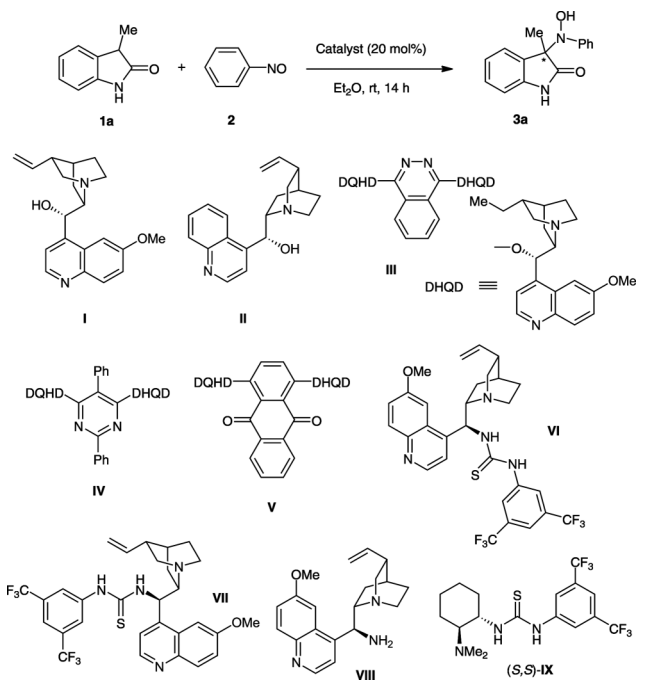
In the light of these precedents, and given our interest on the development of new methodology for asymmetric organocatalysis,[24,25] we undertook a re-examination of the chiral amine-catalyzed enantioselective reactions of *N*-unprotected, 3-substituted oxindoles with nitrosobenzene.[26] We present herein a full account of our results in this topic.

Results and discussion

As a benchmark process, we selected the reaction between 3-methyloxindole (**1a**) and nitrosobenzene (**2**). This reaction took readily place in diethyl ether in the presence of 20 mol% of triethylamine, affording exclusively the α-oxyamination product **3a** in quantitative yield after only 2 h at room temperature. The structure of **3a** was unambiguously established by X-ray diffraction analysis of a monocrystal (see later), and its spectral data were moreover found to be coincident with those reported by Liu *et al.*[23] We decided then to examine the same reaction using several chiral tertiary amine catalysts (Table 1).

Several interesting conclusions can be drawn from inspection of the data gathered in Table 1. On the first place, and irrespective

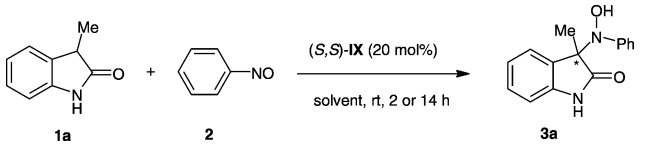
Table 1 Catalyst screening in the reaction between 3-methyl-2-oxindole (**1a**) and nitrosobenzene (**2**)[a]



Entry	Catalyst	Conversion[b] (%)	Er[c] (*R* : *S*)
1	NEt_3	100[d]	—
2	**I**	100	70 : 30
3	**II**	100	40 : 60
4	**III**	100	66 : 34
5	**IV**	100	61 : 39
6	**V**	100	66 : 34
7	**VI**	100	14 : 86
8	**VII**	100	78 : 22
9	**VIII**	100	50 : 50
10	(*S*,*S*)-**IX**	100[d]	15 : 85

[a] *Experimental conditions*: A mixture of **1a** (0.10 mmol), nitrosobenzene **2** (0.12 mmol) and catalyst (0.02 mmol) in diethyl ether (1 mL) was stirred at room temperature during 14 h. [b] Determined by ^{1}H NMR analysis of the reaction mixture. [c] Determined by HPLC analysis. [d] Conversion was already complete after 2 h at rt.

Table 2 Solvent screening in the reaction between 3-methyl-2-oxindole (**1a**) and nitrosobenzene (**2**) catalyzed by (*S*,*S*)-**IX**[a]

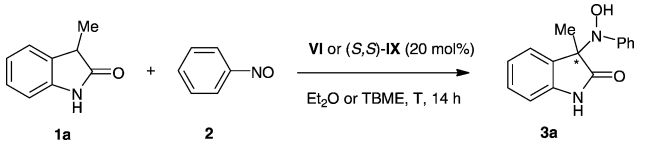


1a 2 3a

Entry	Solvent	Conversion[b] (%)	Er[c] (*R* : *S*)
1	Et_2O	100	15 : 85
2	MeOH	< 5 (62[d])	50 : 50
3	$Cl(CH_2)_2Cl$	100	19 : 81
4	CH_2Cl_2	100	18 : 82
5	THF	100	50 : 50
6	DME	100	20 : 80
7	TBME	100	14 : 86
8	nBu_2O	100	15 : 85
9	$nPent_2O$	100	25 : 75

[a] *Experimental conditions*: A mixture of **1a** (0.10 mmol), **2** (0.12 mmol) and catalyst (*S*,*S*)-**IX** (0.02 mmol) in the solvent specified (1 mL) was stirred at room temperature for 2 h. [b] Determined by ^{1}H NMR analysis of the reaction mixture. [c] Determined by HPLC. [d] Conversion after 24 h reaction.

Table 3 Solvent and temperature screening in the reaction between 3-methyl-2-oxindole (**1a**) and nitrosobenzene (**2**) catalyzed by **VI** and by (*S*,*S*)-**IX**[a]



1a 2 3a

Entry	Catalyst	Solvent	*T*/°C	Er[b] (*R* : *S*)
1	**VI**	Et_2O	*rt*	14 : 86
2	**VI**	Et_2O	–20	25 : 75
3	**VI**	TBME	*rt*	12.5 : 87.5
4	**VI**	TBME	50	13.5 : 86.5
5	(*S*,*S*)-**IX**	Et_2O	*rt*	15 : 85
6	(*S*,*S*)-**IX**	TBME	*rt*	14 : 86
7	(*S*,*S*)-**IX**	Et_2O	4	16.5 : 83.5
8	(*S*,*S*)-**IX**	Et_2O	–20	20 : 80

[a] *Experimental conditions*: A mixture of **1a** (0.10 mmol), nitrosobenzene **2** (0.12 mmol) and catalyst **VI** or (*S*,*S*)-**IX** (0.02 mmol) in diethyl ether or in *tert*-butyl methyl ether (1 mL) was stirred at the temperature indicated for 14 h. Full conversion was observed in all instances. [b] Determined by HPLC analysis of the reaction mixture.

of the nature of the catalyst, complete and exclusive conversion of **1a** to the oxyamination product **3a** was observed. Among the chiral amine catalysts examined, only 9-amino-9-epiquinine **VIII** gave a racemic product (entry 9 in Table 1). As it was logical to expect, quinidine-derived catalysts (entries 2, 4, 5, 6 and 8) showed opposite enantioselectivities to quinine (or cinchonidine) derived catalysts (entries 3 and 7). The presence of a hydrogen-bond donor thiourea moiety greatly increases the enantioselectivity of the process. Thus, the highest enantiomeric ratios were obtained with the 9-amino-9-epiquinine thiourea catalyst **VI** (entry 7) and with Takemoto's thiourea catalyst **IX** (entry 10). We decided next to examine the effect of the solvent in the Takemoto's thiourea-catalyzed oxyamination of 3-methyloxindole **1a** (Table 2).

When the reaction was run in methanol (entry 2 in Table 2), it became very slow (62% conversion was achieved after 14 h), and only racemic product **3a** was obtained. Good conversions were again recovered with the use of chlorinated solvents (entries 3 and 4), but the enantioselectivity of the process was eroded. These results seem to indicate that the hydrogen bonding provided by the catalyst plays a key role in the stereochemical outcome of the oxyamination. Other ethereal solvents were then investigated (entries 5–9 in Table 2). Complete conversion was achieved in all instances after 2 h at r. t., but the enantiomeric excess of **3a** was strongly dependent on the structure of the solvent. Thus, tetrahydrofuran (entry 5) unexpectedly led to the formation of racemic product, and only with *tert*-butyl methyl ether (TBME, entry 7) the enantiomeric ratio previously achieved with diethyl ether (entry 1) could be slightly improved. In a further effort to improve the performance of the reaction, and having selected diethyl ether and TBME as the most suitable solvents, we examined the effect of the temperature in oxyaminations catalyzed by **VI** or **IX** (Table 3).

Both in diethyl ether and in *tert*-butyl methyl ether the enantioselectivity of the process decreased when performed at reduced temperatures, both with catalyst **VI** (entries 1–3) and with catalyst **IX** (entries 5–8). Increasing the temperature in TBME to 50°C did not lead to any improvement (entry 4). The optimal conditions for the asymmetric oxyamination of **1a** involve therefore the use of either **VI** or **IX** as the catalyst, in *tert*-butyl methyl ether at room temperature. In view of the commercial availability of **IX** in both enantiomeric forms,[27] and taking also into account that the pseudo-enantiomeric form of **VI** (*i.e.*, the quinidine–thiourea derivative **VII**) gave substantially lower enantioselectivity (compare entries 7 and 8 in Table 1), the scope of the oxyamination of a set of 3-substituted, *N*-unprotected 2-oxindoles **1a–i** was examined with Takemoto's thiourea **IX** (Table 4).

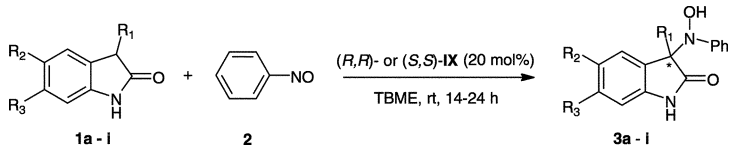
The *N*-nitroso-aldol adducts **3a–i** were isolated, after chromatographic purification, in good yields (up to 96%) and with moderate enantioselectivities. The highest enantiomeric purities (up to 86 : 14 er) were achieved when the 3-substituent was methyl (entries 1–3 in Table 4) or ethyl (entry 4). When bulkier substituents were placed in the 3-position, the enantioselectivity decreased considerably; for example 3-isobutyloxindole **1e** afforded the oxyamination adduct compound **3e** in excellent yield (93%) but with poor enantioselectivity (entry 5 in Table 4). In summary, catalyst **IX** exhibits enantioselectivities similar to those reported by Chen and co-workers with demethylquinine.[23]

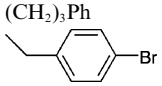
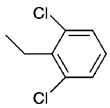
On the other hand, in some of the reactions summarized in Table 4 we observed the gradual precipitation of the product. We collected this solid by simple filtration when the reaction was complete, and we were delighted to find that in all instances the enantiomeric purity of the precipitated product was much higher than that resulting from the work up of the complete reaction crude (Table 5).

Thus, enantiomerically pure (>99.7 : 0.3 er) compounds **3a** and **3b** can be obtained in practical yields and in both enantiomeric forms (see entries 1–3 in Table 5). A substantial improvement in the enantiomeric purity of the 3-isobutyloxyndole *N*-nitroso-aldol adduct **3e** (from 31.5 : 68.5 to 11.5 : 89.5 er) was also achieved in this way (compare entry 5 in Table 4 with entry 4 in Table 5).[28]

In order to find some explanation for this crystallization effect in the enantiomeric purity of the product, we performed X-ray

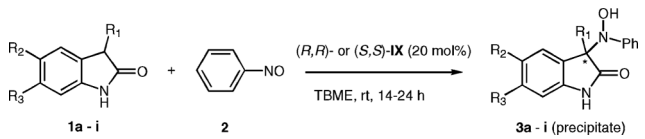
Table 4 Scope of the reaction between 3-substituted-2-oxindoles (**1a–i**) and nitrosobenzene (**2**) catalyzed by **IX**[a]



Entry	Oxindole	R_1	R_2	R_3	Catalyst	Product	Yield[b] (%)	Er[c] ($R:S$)
1	**1a**	Me	H	H	(*S*,*S*)-**IX**	**3a**	82	14 : 86
2	**1b**	Me	Br	H	(*S*,*S*)-**IX**	**3b**	92	15 : 85
3	**1c**	Me	H	Cl	(*S*,*S*)-**IX**	**3c**	96	19 : 81
4	**1d**	Et	H	H	(*R*,*R*)-**IX**	**3d**	93	85 : 15
5	**1e**	CH_2CHMe_2	H	H	(*S*,*S*)-**IX**	**3e**	93	31.5 : 68.5
6	**1f**	$(CH_2)_2CHMe_2$	H	H	(*S*,*S*)-**IX**	**3f**	75	28.5 : 71.5
7	**1g**	$(CH_2)_3Ph$	H	H	(*S*,*S*)-**IX**	**3g**	68	23 : 77
8	**1h**		H	H	(*S*,*S*)-**IX**	**3h**	54	38.5 : 61.5
9	**1i**		H	H	(*R*,*R*)-**IX**	**3i**	87	82 : 18

[a] *Experimental conditions*: A mixture of 3-substituted oxindole **1a–i** (0.10 mmol), nitrosobenzene **2** (0.12 mmol) and catalyst **IX** (0.02 mmol) in *tert*-butyl methyl ether (1 mL) was stirred at room temperature until complete conversion (TLC). [b] Yield of isolated product after chromatographic purification. [c] Determined by HPLC analysis. See text for the assignment of absolute configurations.

Table 5 Oxyamination of 3-substituted-2-oxindoles with filtration of the product precipitate[a]



Entry	Catalyst	Product	Yield[b] (%)	Er[c] ($R:S$)
1	(*S*,*S*)-**IX**	**3a**	58	< 0.1 : 99.9
2	(*R*,*R*)-**IX**	**3a**	60	> 99.7 : 0.3
3	(*R*,*R*)-**IX**	**3b**	42	> 99.9 : 0.1
4	(*S*,*S*)-**IX**	**3e**	68	11.5 : 89.5
5	(*S*,*S*)-**IX**	**3h**	78	31 : 69
6	(*R*,*R*)-**IX**	**3i**	72	88 : 12

[a] *Experimental conditions*: A mixture of 3-substituted oxindole **1a**, **1b**, **1e** or **1e** (0.10 mmol), nitrosobenzene **2** (0.12 mmol) and catalyst **IX** (0.020 mmol) in *tert*-butyl methyl ether (1 mL) was stirred at rt during 14–24 h (conversion complete by TLC analysis). [b] Yield of isolated product after filtration of the reaction mixture. [c] Determined by HPLC analysis.

diffraction analyses of both the racemic and of the enantiopure crystals of **3a**.[29] The presence of an amide functional group and a *N*-hydroxy group in adduct **3a** makes it a potential building block for the assembly of hydrogen-bonded supramolecular aggregates. The single-crystal X-ray diffraction analysis of the racemic compound **3a** confirmed the existence of this hydrogen bond network (Fig. 2). Racemic **3a** crystallizes in the achiral space group $P\bar{1}$. In the solid state, the (*R*)-enantiomer selectively recognizes the (*S*)-enantiomer by two types of hydrogen bond-pairs: a pair involves the two carboxamide moieties of two enantiomeric molecules, while another pair is formed between the *N*-hydroxy amine moieties. As a result, the centrosymmetric dimers are further linked to form an infinite chain-like structure.

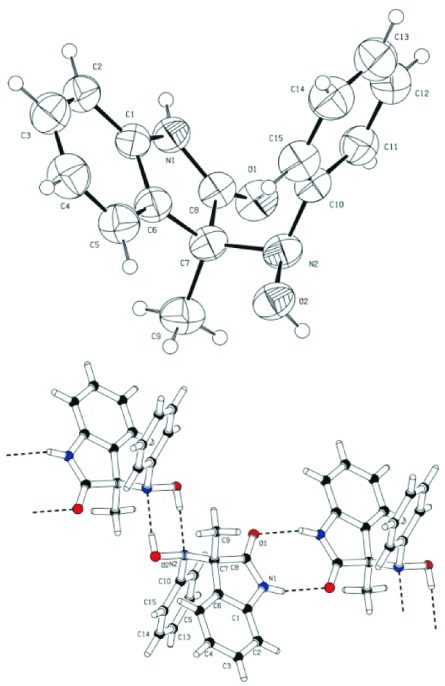


Fig. 2 Solid-state structure of racemic **3a**.

In contrast, the crystal of enantiopure compound **3a** shows a different hydrogen-bond network. In the enantiopure crystal (belonging to the $P2_12_12_1$ space group) there is only one type of hydrogen bond interaction, involving the hydroxylamine and the carboxamide moieties of two adjacent homochiral molecules, and as a result the monomer forms a chain even more stable and structured than the racemic one (Fig. 3). This could explain the high enhancement in the enantiomeric purity observed in the

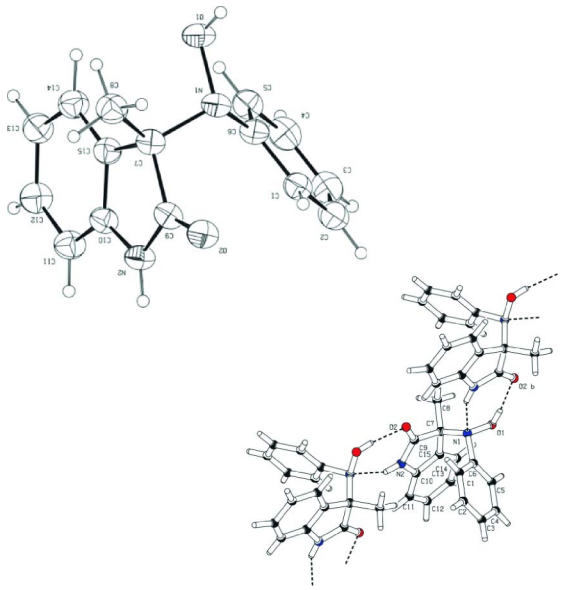


Fig. 3 Solid-state structure of enantiomerically pure **3a**.

precipitate. Coherent with this explanation is the fact that the enantiomeric purity of precipitated **3a** depends on the concentration of the reaction. When the oxyamination of **1a** is performed either at 0.1 M (standard conditions) or at 0.2 M concentration of the substrate, enantiomerically pure **3a** is obtained upon filtration. When the concentration is increased to 0.5 M, the enantiomeric ratio of the solid **3a** goes down to 70 : 30, indicating that in this case the more soluble racemic crystal begins to precipitate from the reaction mixture.

In the course of their study on the oxyamination of 3-substituted oxindoles with demethylquinine,[23] Liu, Chen and co-workers were able to determine the absolute configuration of the *N*-nitroso-aldol adduct derived from 3-(3-chlorobenzyl)-2-oxindole by X-ray diffraction analysis; the stereochemistry of the remaining adducts (including that of **3a**) was assigned by analogy. In order to have an alternative proof, we undertook a combined experimental and theoretical study (using a time-dependent density functional theory approach, TDDFT) of the electronic circular dichroism (ECD) of **3a**. This technique has been shown to predict circular dichroism spectra with high accuracy and has been used successfully to ascertain the absolute configuration of chiral organic molecules.[30]

The minimum energy conformers of **3a** were located by using DFT methods (see ESI† for details). The most stable conformation of (*S*)-**3a** (accounting for 96% of the total conformer population) was then used in a time-dependent DFT calculation, at the B3LYP/6-311++G(d,p) level, to simulate the ECD and it was compared with the experimental spectrum of enantiomerically pure (+)-**3a** in methanol ($c = 10^{-4}$ M). As it can be seen from Fig. 4, the agreement in the 220–320 nm range is excellent, and we concluded that the oxyamination of **1a**, by using both Takemoto's thiourea (*S*,*S*)-**IX** and the quinine-derived thiourea **VI** as catalysts, preferentially leads to the formation of the (*S*)-enantiomer of **3a**. This configurational assignment agrees with that made by Liu and Chen for the same compound.[23]

On the other hand, enantiomerically pure (+)-**3a** was conveniently reduced to (–)-3-methyl-3-(phenylamino)-2-oxindole **4a** by treatment with indium,[31] acetic acid and acetic anhydride in

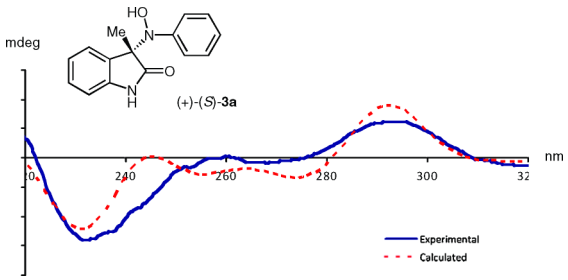
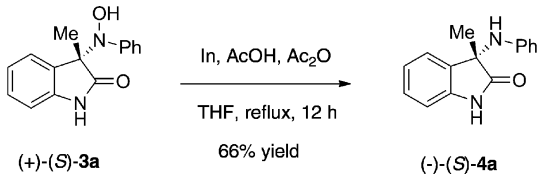


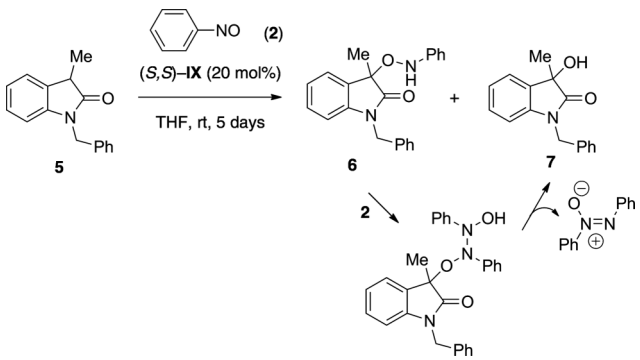
Fig. 4 Comparison of the calculated ECD spectrum of (*S*)-**3a** with the experimental ECD spectrum of (+)-**3a**.

tetrahydrofuran (Scheme 3). This transformation further validated our stereochemical assignment, since (*R*)-(+)-**4a** has been correlated with (*R*)-3-amino-3-methyl-2-oxindole.[26]



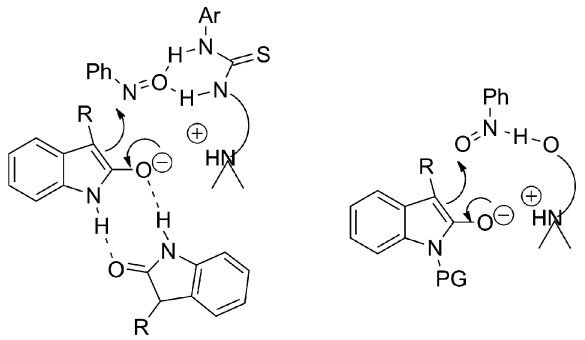
Scheme 3 Reductive cleavage of the N–O bond in **3a**.

The fact that the reaction of *N*-unprotected 3-substituted oxindoles with nitrosobenzene gives exclusively rise to α-oxyamination products, irrespectively of the amine organocatalyst used, is at variance with the commonly accepted hypothesis that the regioselectivity of this process is controlled by the nature of the catalyst.[17,22,23] We decided therefore to test the reaction of *N*-benzyl 3-methyl-2-oxindole **5**[32] with **2** in the presence of a 20% molar amount of (*S*,*S*)-**IX** in tetrahydrofuran at room temperature (Scheme 4).



Scheme 4 Reaction of *N*-benzyl-3-methyl-2-oxindole **5** with nitrosobenzene **2** catalyzed by (*S*,*S*)-**IX**.

The nitroso-aldol reaction of the *N*-protected derivative **5** was very sluggish under these conditions, and after five days we were able to isolate in low yield and after careful chromatographic purification, the α-aminoxylation product **6** (identified by comparison of its spectral data with those reported by Barbas and co-workers)[22] and the known[33] *N*-benzyl-3-hydroxy-3-methyl-2-oxindole **7**. As depicted in Scheme 4, compound **7** probably arises from reaction of **6** with nitrosobenzene **2**, followed by loss of azobenzene from the intermediate adduct.[18h,34] We can conclude therefore that the regiochemical outcome of the reaction between



oxyamination reaction (this work) aminoxylation reaction (ref.22)

Fig. 5 Proposed transition states for the nitroso-aldol reaction of *N*-unprotected (left) and *N*-protected (right) 3-substituted-2-oxindoles.

nitrosobenzene and 3-substituted-2-oxindoles under catalysis by amino-thiourea bifunctional catalysts such as **IX** also depends on the structure of the starting oxindole. We hypothesize that this change of regioselectivity is driven by intermolecular-hydrogen bonding of the enolate oxygen in unprotected 3-substituted oxindoles (Fig. 5).

Conclusions

In summary, we have found that the tertiary amine-catalyzed nitroso-aldol reaction between *N*-unprotected 3-substituted-2-oxindoles and nitrosobenzene takes place with N-selectivity, and the corresponding α-oxyamination adducts are obtained with good yields and enantioselectivities, especially so when bifunctional amino-thioureas such as **IX** are used as the catalysts (up to 86 : 14 er) in ethereal solvents such as *tert*-butyl methyl ether. From a practical point of view, it is worth noting that in some of these reactions gradual precipitation of the product takes place, and isolation of this solid by simple filtration gives rise in all instances to products with increased enantiomeric purity. Thus, essentially enantiopure (er > 99.7 : 0.3) compounds **3a** and **3b** can be easily obtained in this way. When using the (*S*,*S*)-enantiomer of Takemoto's thiourea **IX** as the catalyst, (*S*)-configured α-oxyamination products are primarily obtained. In the same conditions, *N*-benzyl-3-methyl-2-oxindole **5** mainly affords α-aminoxylation products. Work aiming at the elucidation of this dependence of the regioselectivity of the nitroso-aldol reaction on the presence of a nitrogen-protecting group in the starting 3-substituted oxindole is currently being pursued in our laboratory.

Note added in proof

After the submission of this manuscript, a report on the asymmetric oxyamination of *N*-benzyl-3-(arylmethyl)oxindole derivatives by chiral bifunctional tertiary amine thiourea catalysts was published online.[37]

Experimental section

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Specific rotations were measured at room temperature in a Perkin-Elmer 241 MC polarimeter, using a sodium lamp (λ = 589 nm) and a 1 dm-long 1 mL cell. NMR spectra were recorded in DMSO-d^6 solution at room temperature. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) were obtained on a Varian Unity 300 or on a Unity-Innova 300 spectrometer; ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) were obtained on a Mercury 400 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS for ^{1}H NMR and to DMSO-d^6 (d 39.4) for ^{13}C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; coupling constants (J) are quoted in hertz. High-resolution mass spectra (HRMS) were obtained with the ESI (+ or −) technique at the 'Unitat d' Espectrometria de Masses' of Barcelona University in a Bruker MirOTOF spectrometer. Enantiomeric purities were determined by HPLC using Daicel Chiralpak® IA or IB columns in a Shimadzu LC-20AD instrument with UV detection. Reactions were generally run with magnetic stirring in loosely stoppered glass vials under air. Commercially available reagents, catalysts and solvents were used as received. 3-Substituted oxindoles **1b–i** were prepared according to a literature procedure.[35] Catalysts **VI**, **VII** and **VIII** were obtained from quinine or from quinidine as described by Sóos and co-workers.[36] Silica gel (0.040–0.063 mm) was used for chromatographic purifications. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by UV irradiation.

General experimental procedure for the oxyamination of 3-substituted indoles

To a stirred solution of the 3-substituted oxindole **1a–i** (0.10 mmol) and of the catalyst (*S*,*S*)- or (*R*,*R*)-**IX** (0.02 mmol) in *tert*-butyl methyl ether (1 mL), nitrosobenzene **2** (0.12 mmol) was added in one portion. The reaction mixture was stirred at room temperature until the starting oxindole was not detected by ^{1}H-NMR or by TLC.

A. Standard work-up. Dichloromethane was added dropwise until a clear solution was obtained (1–2 mL), and the reaction crude was directly purified by column chromatography on silica gel (hexane–ethyl acetate mixtures) to afford the a-oxyaminated product **3a–i**.

B. Filtration work-up. The crude reaction mixture was filtered with suction through a Büchner funnel. The precipitate was washed twice with cold hexane, collected, and dried under vacuum. Racemic products were obtained from the corresponding substrates by catalysis with triethylamine.

(*S*)-3-(Hydroxy(phenyl)amino)-3-methylindolin-2-one (3a)

Colorless solid. Er > 99.9 : 0.1. Mp 138–140 °C (lit.:[9] 137–138 °C). $[\alpha]_D^{20}$ = +52.4 (*c* 0.5, THF) [lit.:[9] $[\alpha]_D^{20}$ = +43.4 (*c* 0.5, THF)]. ^{1}H NMR (300 MHz) δ 1.48 (s, 3H), 6.69 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.04–7.19 (m, 6H), 8.91 (s, 1H). ^{13}C NMR (100.6 MHz) δ 22.4, 70.3, 109.1, 120.7, 122.4, 124.1, 124.6, 126.9, 127.8, 129.7, 140.7, 149.2, 177.8. HRMS (ESI) calc. from $C_{30}H_{29}N_4O_4$ $(2M + H)^+$: 509.2183; found: 509.2186. HPLC conditions: Daicel Chiralpak® IA column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 19.3 min, t_{minor} = 16.4 min.

(*S*)-5-Bromo-3-(hydroxy(phenyl)amino)-3-methylindolin-2-one (3b)

Yellowish solid. Er = 85 : 15. $[\alpha]_D^{20}$ = +14.2 (*c* 0.25, DMSO). ^{1}H NMR (300 MHz) δ 1.46 (s, 3H), 6.67 (d, J = 7.3 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 7.08–7.13 (m, 2H), 7.15–7.25 (m, 3H), 7.32 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 9.02 (s, 1H), 10.43 (s, 1H). ^{13}C NMR (100.6 MHz) δ 22.7, 70.3, 111.2, 112.6, 122.3, 124.3, 127.4, 127.5, 130.9, 132.9, 140.7, 149.4, 176.6. HRMS (ESI) calc. from $C_{30}H_{27}Br_2N_4O_4$ (2M + H)$^+$: 665.0394; found: 665.0392. HPLC conditions: Daicel Chiralpak® IA column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 24.3 min, t_{minor} = 16.1 min.

(*S*)-6-Chloro-3-(hydroxy(phenyl)amino)-3-methylindolin-2-one (3c)

Colorless oil. Er = 81.5 : 19.5. $[\alpha]_D^{20}$ = +13.8 (*c* 0.5, DMSO). ^{1}H NMR (300 MHz) δ 1.47 (s, 3H), 6.71 (d, J = 1.95 Hz, 1H), 6.93 (dd, J_1 = 8.1 Hz, J_2 = 1.95 Hz, 1H), 7.06–7.11 (m, 2H), 7.15–7.21 (m, 2H), 8.98 (s, 1H), 10.42 (s, 1H). ^{13}C NMR (100.6 MHz) δ 22.7, 69.9, 109.2, 120.6, 122.3, 124.3, 126.1, 127.5, 129.2, 132.5, 142.9, 149.5, 177.0. HRMS (ESI) calc. from $C_{30}H_{27}Cl_2N_4O_4$ (2M + H)$^+$: 577.1404; found: 577.1399. HPLC conditions: Daicel Chiralpak® IB column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 14.5 min, t_{minor} = 8.0 min.

(*R*)-3-Ethyl-3-(hydroxy(phenyl)amino)indolin-2-one (3d)

Colorless oil. Er = 85 : 15. $[\alpha]_D^{20}$ = –22.3 (*c* 0.75, DMSO). ^{1}H NMR (300 MHz) δ 0.53 (t, J = 7.5 Hz, 3H), 1.97–2.15 (m, 2H), 6.65 (d, J = 7.7 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.1 Hz, 1H), 7.03–7.15 (m, 6H), 8.87 (s, 1H), 10.23 (s, 1H). ^{13}C NMR (100.6 MHz) δ 7.8, 28.7, 75.1, 108.9, 120.9, 122.6, 124.2, 124.9, 127.3, 128.2, 128.3, 142.3, 150.1, 176.2. HRMS (ESI) calc. from $C_{16}H_{17}N_2O_2$ (M + H)$^+$: 269.1285; found: 269.1283. HPLC conditions: Daicel Chiralpak® IB column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 7.8 min, t_{minor} = 9.5 min.

(*S*)-3-(Hydroxy(phenyl)amino)-3-isobutylindolin-2-one (3e)

Yellowish waxy solid. Er = 89.5 : 10.5. $[\alpha]_D^{20}$ = +27.0 (*c* 0.1, DMSO). ^{1}H NMR (300 MHz) δ 0.48 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 6.4 Hz, 3H), 1.19 (hept, J = 6.4 Hz, 1H), 2.07 (d, J = 6.2 Hz, 2H), 6.63 (d, J = 7.4 Hz, 1H), 6.91 (t, J = 7.2 Hz, 1H), 6.95–7.04 (m, 3H), 7.06–7.18 (m, 4H), 8.84 (s, 1H), 10.20 (s, 1H). ^{13}C NMR (100.6 MHz) δ 25.9, 26.2, 26.3, 46.1, 76.5, 111.2, 116.7, 122.9, 125.6, 126.7, 128.0, 129.4, 130.7, 144.5, 152.0, 178.8. HRMS (ESI) calc. from $C_{18}H_{20}NaN_2O_2$ (M + Na)$^+$: 319.1413; found: 319.1413. HPLC conditions: Daicel Chiralpak® IB column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 9.0 min, t_{minor} = 7.3 min.

(*S*)-3-(Hydroxy(phenyl)amino)-3-isopentylindolin-2-one (3f)

Yellowish waxy solid. Er = 71.5 : 28.5. $[\alpha]_D^{20}$ = +16.3 (*c* 0.25, DMSO). ^{1}H NMR (300 MHz) δ 0.48–0.64 (m, 1H), 0.71 (d, J = 6.2 Hz, 3H), 0.76 (d, J = 6.2 Hz, 3H), 0.82–0.97 (m, 1H), 1.38 (hept, J = 6.2 Hz, 1H), 1.94–2.15 (m, 2H), 6.63 (d, J = 7.4 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 7.1 Hz, 1H), 7.01–7.17 (m, 6H), 8.86 (s, 1H), 10.19 (s, 1H). ^{13}C NMR (100.6 MHz) δ 23.0, 23.1, 28.4, 32.7, 34.5, 75.3, 109.7, 121.7, 123.5, 125.0, 128.1, 129.1, 129.3, 142.8, 150.8, 177.1. HRMS (ESI) calc. from $C_{19}H_{22}NaN_2O_2$ (M + Na)$^+$: 333.1573; found: 333.1579. HPLC conditions: Daicel Chiralpak® IA column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 19.9 min, t_{minor} = 13.7 min.

(*S*)-3-(Hydroxy(phenyl)amino)-3-(3-phenylpropyl)indolin-2-one (3g)

Colorless oil. Er = 77 : 23. $[\alpha]_D^{20}$ = +8.6 (*c* 0.25, DMSO). ^{1}H NMR (300 MHz) δ 0.95–1.11 (m, 1H), 1.25–1.44 (m, 1H), 1.97–2.19 (m, 2H), 2.39–2.54 (m, 2H), 6.62 (d, J = 7.7 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.1 Hz, 1H), 7.00–7.15 (m, 9H), 7.17–7.25 (m, 2H), 8.81 (s, 1H), 10.21 (s, 1H). ^{13}C NMR (100.6 MHz) δ 27.6, 37.4, 37.7, 76.7, 111.3, 123.2, 124.9, 126.5, 127.3, 127.9, 129.6, 130.3, 130.4, 130.7, 130.8, 143.9, 144.3, 152.2, 178.5. HRMS (ESI) calc. from $C_{46}H_{45}N_4O_4$ (2M + H)$^+$: 717.3435; found: 717.3430. HPLC conditions: Daicel Chiralpak® IA column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 28.1 min, t_{minor} = 17.9 min.

(*S*)-3-(4-Bromobenzyl)-3-(hydroxy(phenyl)amino)indolin-2-one (3h)

Yellowish waxy solid. Er = 61.5 : 38.5. $[\alpha]_D^{20}$ = +37.1 (*c* 0.4, DMSO). ^{1}H NMR (300 MHz) δ 3.37 (d, J = 12.5 Hz, 1H), 3.45 (d, J = 12.5 Hz, 1H), 6.37 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.95–7.00 (m, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.07–7.16 (m, 4H), 7.21 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 1H), 9.13 (s, 1H), 9.97 (s, 1H). ^{13}C NMR (100.6 MHz) δ 40.9, 75.8, 108.8, 119.6, 120.8, 122.8, 124.4, 125.9, 127.2, 127.4, 128.6, 130.2, 130.3, 132.3, 132.4, 134.3, 141.7, 149.8, 175.2. HRMS (ESI) calc. from $C_{21}H_{18}BrN_2O_2$ (M + H)$^+$: 409.0546; found: 409.0548. HPLC conditions: Daicel Chiralpak® IA column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 22.7 min, t_{minor} = 21.1 min.

(*R*)-3-(2,6-Dichlorobenzyl)-3-(hydroxy(phenyl)amino)indolin-2-one (3i)

Yellowish waxy solid. Er = 88 : 12. $[\alpha]_D^{20}$ = –60.7 (*c* 0.25, DMSO). ^{1}H NMR (300 MHz) δ 3.83 (d, J = 13.9 Hz, 1H), 4.18 (d, J = 13.9 Hz, 1H), 6.41 (d, J = 7.7 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 6.73–6.85 (m, 1H), 6.91–7.27 (m, 6H), 7.23 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.3 Hz, 1H), 9.21 (s, 1H), 10.05 (s, 1H). ^{13}C NMR (100.6 MHz) δ 36.5, 74.8, 108.6, 114.3, 120.1, 124.1, 124.9, 126.8, 127.1, 128.1, 128.2, 128.8, 134.1, 135.8, 142.0, 149.4, 176.1. HRMS (ESI) calc. from $C_{21}H_{17}Cl_2N_2O_2$ (M + H)$^+$: 399.0662; found: 399.0664. HPLC conditions: Daicel Chiralpak® IA column, *i*-PrOH–hexane 10 : 90, flow rate 1 mL min^{-1}, UV detection at 254 nm, t_{major} = 27.4 min, t_{minor} = 17.0 min.

(*S*)-3-Methyl-3-(phenylamino)indolin-2-one (4a)[23]

To a stirred solution of enantiomerically pure (*S*)-**3a** (0.27 mmol, 1 equiv.) in dry THF (2 mL), Ac_2O (0.15 mL, 6 equiv.), AcOH (0.06 mL, 4 equiv) and indium (62 mg, 2 equiv.) were added sequentially. The mixture was heated at reflux until total consumption of the starting material (monitored by TLC analyses, about 12 h). The reaction was cooled to 0°C and water (2 ml) and

aqueous saturated K_2CO_3 (2 ml) were added. The organic layer was separated and the aqueous layer was extracted three times with AcOEt (10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to afford the crude product, that was purified by flash chromatography on silica gel (hexane–AcOEt 1 : 1) to give **4a** as a waxy solid (41 mg, 66% yield). $[\alpha]_D^{20} = -20$ (*c* 0.5, DMSO). ^{1}H NMR (300 MHz) δ 1.46 (s, 3H), 6.15 (d, J = 7.7 Hz, 2H), 6.38 (s, 1H), 6.45 (t, J = 7.3 Hz, 1H), 6.84–6.97 (m, 4H), 7.15 (d, J = 7.1 Hz, 1H), 7.21 (td, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 10.6 (s, 1H). HRMS (ESI) calc. from $C_{15}H_{15}N_2O$ $(M + H)^+$: 239.1179; found: 239.1176.

N-Benzyl-3-methyl-3-(phenylaminoxy)indolin-2-one (6)[22]

Colorless oil. ^{1}H NMR (300 MHz) δ 1.72 (s, 3H), 4.63 (part A of AB system, J = 15.3 Hz, 1H), 5.01 (part B of AB system, J = 15.3 Hz, 1H), 6.54 (d, J = 7.9 Hz, 1H), 6.96–7.02 (m, 3H), 7.08–7.24 (m, 10H). HRMS (ESI) calc. from $C_{22}H_{21}N_2O_2$ $(M + H)^+$: 345.1598; found: 345.1604.

N-Benzyl-3-hydroxy-3-methylindolin-2-one (7)[36]

Colorless oil. ^{1}H NMR (300 MHz) δ 1.70 (s, 3H), 3.47 (br s, 1H), 4.81 (part A of AB system, J = 15.5 Hz, 1H), 4.96 (part B of AB system, J = 15.5 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 7.06 (td, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.19 (td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.23–7.33 (m, 5H), 7.41 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100.6 MHz) δ 25.0, 43.7, 73.7, 109.5, 123.2, 123.4, 127.1, 127.6, 128.8, 129.4, 131.4, 135.4, 141.8, 178.7. HRMS (ESI) calc. from $C_{16}H_{16}NO_2$ $(M + H)^+$: 245.1176; found: 245.1173.

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