Supporting Information for:

Dioxindole in asymmetric catalytic synthesis: direct access to 3-substituted 3-hydroxy-2-oxindoles via 1,4-additions to nitroalkenes

Michele Retini,[1†] Giulia Bergonzini[1] & Paolo Melchiorre[1,2*]

[1] ICIQ - *Institute of Chemical Research of Catalonia, Avenida Països Catalans 16 - 43007 Tarragona, Spain*

[2] ICREA - *Institució Catalana de Recerca i Estudis Avançats, Passeig Lluís Companys 23 - 08010 Barcelona, Spain*

[†] Present address: Università degli Studi di Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino (PU), Italy

*To whom correspondence should be addressed. E-mail: pmelchiorre@iciq.es

Supporting Information

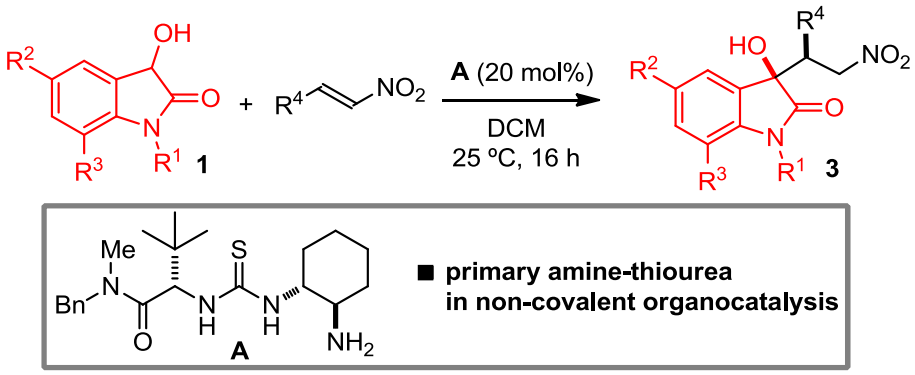


Table of Contents

A. General Information

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. When necessary, ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; bs, broad signal.

High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionization (EI). X-ray data were obtained from the ICIQ X-Ray Unit using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector. Optical rotations are reported as follows: $[\alpha]_D^{rt}$ (*c* in g per 100 mL, solvent). Melting points were measured using open glass capillaries in a Mettler Toledo MP70 apparatus.

The authors are indebted to the team of the Research Support Area at ICIQ, in particular to: Dr. Noemí Cabello (HRMS Unit); Dr. Marta Martínez and Eduardo Escudero-Adan (X-ray Unit). We thank Grace Fox for proofreading the manuscript.

General Procedures. All the reactions were set up under air and using freshly distilled solvents, without any precautions to exclude moisture, unless otherwise noted - open air chemistry on the benchtop.

Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Determination of Diastereomeric Ratios

The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture on the Michael addition products **3**.

Determination of Enantiomeric Purity. HPLC analysis on chiral stationary phase was performed on an Agilent 1200-series instrumentation. Daicel Chiralpak AD-H, IA, IB or IC columns with *i*-PrOH/hexane as the eluent were used.

HPLC traces were compared to racemic samples prepared by purification of the compounds obtained using DABCO (1,4-Diazabicyclo[2.2.2]octane) as the catalyst of the reaction. Note that DABCO induces a marked preference for the *anti* diastereoisomer (as it can be observed by the HPLC traces for the racemic compounds **3**), while catalyst **A** affords preferentially the *syn* product.

Determination of Yield and Conversion in the Optimization Studies. The conversion of the starting materials and the yield of product in the optimization studies related to the model reaction depicted in Table 1 and Scheme 1 of the main manuscript were determined by ^{1}H NMR spectroscopy adding an internal standard in the crude reaction: hexamethylbenzene: δ 2.22 ppm (s, 18H). Since in all instances the conversion of nitrostyrene was equal to the yield of product, in some cases the yield was determined by

integration of the signals of the unreacted nitrostyrene in the ^{1}H NMR spectra (nitrostyrene ^{1}H NMR signal: δ 8.01 ppm (d); 1-benzyl-3-hydroxyindolin-2-one **1c** H NMR signal: δ 5.16 ppm (s)).

Materials. Commercial grade reagents and solvents were purchased from Sigma Aldrich, Fluka, and Alfa Aesar and used as received, without further purification; otherwise, where necessary, they were purified as recommended.[1] Catalyst **A** (S)-2-[[(1R,2R)-2-Aminocyclohexyl] thioureido]-N-benzyl-N,3,3-trimethylbutanamide is commercially available (Aldrich); all the other catalysts were synthesized according to literature procedures.[2] Dioxindole derivatives **1a-c** have been synthesized starting from commercial available isatins following the procedure described within Section G, page S12.
trans-β-Nitrostyrene **2** was purchased from Aldrich and used as received. All the other nitrostyrene substrates were synthesized according to literature procedures.[3] Nitroethylene (used in the studies detailed in Section F, page S12) was synthesized from commercial available nitroethanol following the procedure reported in the literature.[4]

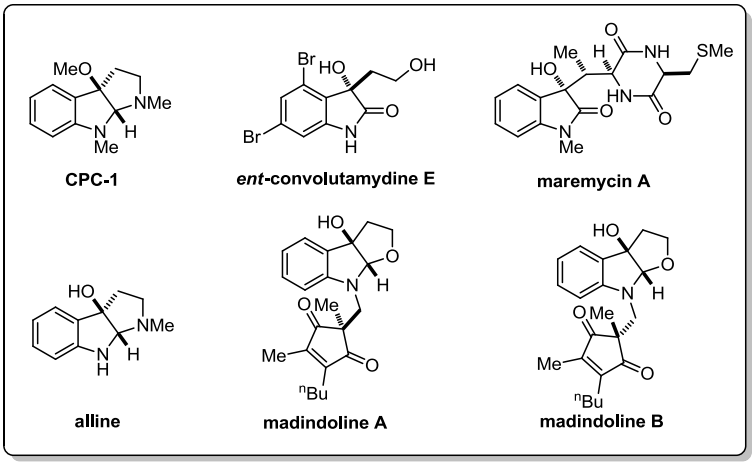


Figure S1. Examples of natural products possessing the 3-hydroxyindole moiety

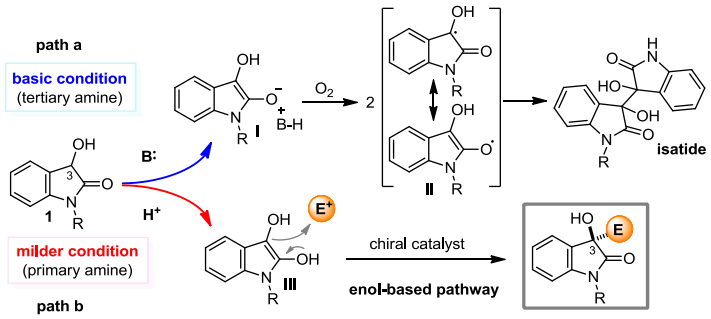
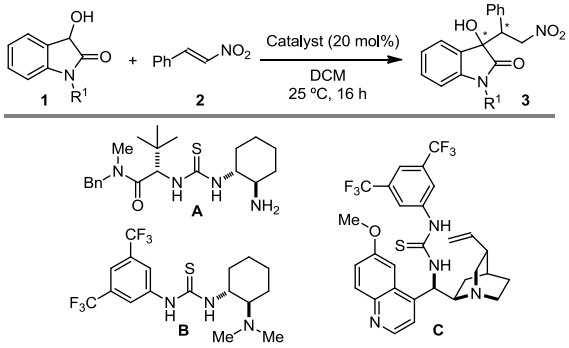


Figure S2. Taming the dioxindole **1** reactivity: in the presence of a tertiary amine and trace of oxygen, an oxidative enolate coupling leads to the formation of the dimeric isatide (path a). Milder reaction conditions (i.e. the use of a primary amine) preserve the intrinsic high nucleophilic power of **1** (path b). This channels the intrinsically nucleophilic character of dioxindole toward a productive conjugate addition manifold, mainly through an enol-directed pathway (enediol intermediate **III**).

[1] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
[2] (a) A. G. Wenzel; E. N. Jacobsen; *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965. (b) P. Vachal; E. N. Jacobsen; *Org. Lett.* **2000**, *2*, 867-870.
[3] Y. Liu; M. Nappi; E. Arceo; S. Vera; P. Melchiorre; *J. Am. Chem. Soc.* **2011**, *133*, 15212-15218.
[4] Y. C. Li Guo; N. A. Kopf; S. H. Gellman; *J. Am. Chem. Soc.***2008**, *130*, 5608-5609.

B. Optimisation Studies

Table S1. Catalyst compatibility with dioxindole and optimisation studies [a]



entry	catalyst	R^1	**2** (equiv)	conversion [%] isatide[b]	conversion [%] **3**	dr *anti: syn*	ee (%) *anti: syn*
1	quinine	H (**1a**)	1.2	50	21	5:1	35/<5
2	**B**	H (**1a**)	1.2	55	22	3:1	12/nd
3	quinine	H (**1a**)	-	64	-	-	-
4	**B**	H (**1a**)	-	32	-	-	-
5	**A**	H (**1a**)	1.2	30	54	1:2.1	11/57
6	**A**	H (**1a**)	-	15	-	-	-
7	**A**	Me(**1b**)	1.2	26[c]	44	1:2.1	35/80
8	**A**	Bn (**1c**)	1.2	15[c]	69	1:2.1	50/87
9	**B**	Bn (**1c**)	1.2	24[c]	30	2.4:1	39/15
10	**C**	Bn (**1c**)	1.2	40[c]	58	2.3:1	32/<5
11	**A**	Bn (**1c**)	1[d]	9[c]	>95	1:2.5	43/89
12[e]	**A**	Bn (**1c**)	1[d]	<5[c]	60	1:2.4	33/85
13[f]	**A**	Bn (**1c**)	1[d]	<5[c]	35	1:2	30/75
14[g]	**A**	Bn (**1c**)	1[d]	<5[c]	95	1:4	57/94

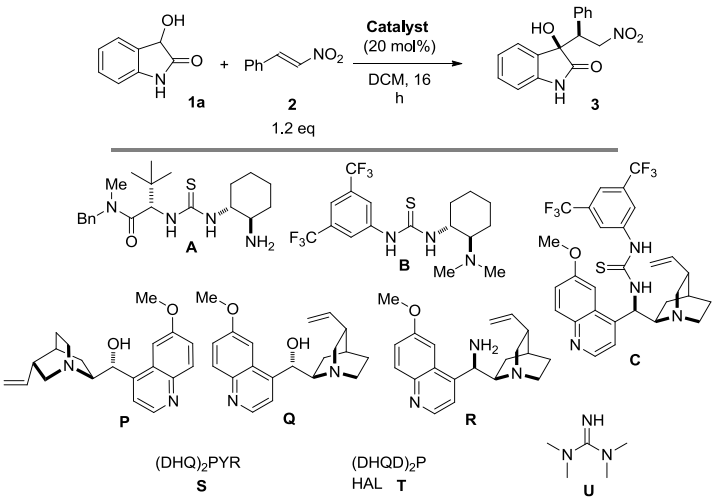
[a] Reactions performed on a 0.05 mmol scale using 1.2 equiv of **2** with $[\mathbf{1}]_0$ = 0.25 M in DCM, without any precaution for excluding air. Both diastereomeric ratios (dr) and conversion were determined by ^{1}H NMR analysis of the crude reaction mixture using hexamethyl benzene as the internal standard. Enantiomeric excess (ee) values were determined by HPLC analysis on commercially available chiral stationary phases. [b] The value refers to the conversion of **1a** into isatide (see eqn (2) for details). [c] With N-protected dioxindoles **1b-c**, the isatides generated through the oxidative coupling likely undergo a disproportionation leading to dioxindole and isatin (see Ref. 13d and Figures S5-6 in the ESI for more details). The reported values refer to the amount of the corresponding isatins detected. [d] Performed with 1.5 equiv of **1c**. [e] Reaction performed at 0°C. [f] Reaction performed at -20°C. [g] $[\mathbf{2}]_0$ = 0.05 M in DCM.

Comment to Table S1. Quinine and the Takemoto catalyst **B** are chiral bases classically used for deprotonative activation. When using either of these, only a minor amount of the conjugate addition product **3** was formed (with a moderate preference for the *anti* diastereoisomer), while the dioxindole **1a** was consumed through a fast degradation pathway (entries 1-2). Control experiments revealed that exposing a solution of dioxindole **1a** in dichloromethane (DCM) to an aerobic atmosphere and in the presence of tertiary amines led to the fast and almost quantitative formation of isatide, the pinacol dimeric form of **1** (entries 3-4).

We reasoned that using of a milder, less basic organic catalyst could minimise the amount of transiently generated intermediate **I** and the subsequent oxidative enolate coupling, thus channeling the intrinsically nucleophilic character of dioxindole toward a productive conjugate addition manifold, mainly through an enol-directed pathway (see Figure S2 in the previous page). The bifunctional primary amine thiourea **A** was identified as a promising catalyst. This is because it induced the formation of the adduct **3** with interesting stereoselectivity (entry 5) while preserving the integrity of dioxindole (entry 6).

It is worth noting that tertiary amine-thiourea catalysts **B**-**C** induced a substantial dioxindole degradation and a low stereoselectivity in the 1,4-addition of N-benzyl dioxindole **1c** to **2** (entries 9-10)

Table S2. Catalyst screening using dioxindole **1a** as the nucleophile[a]

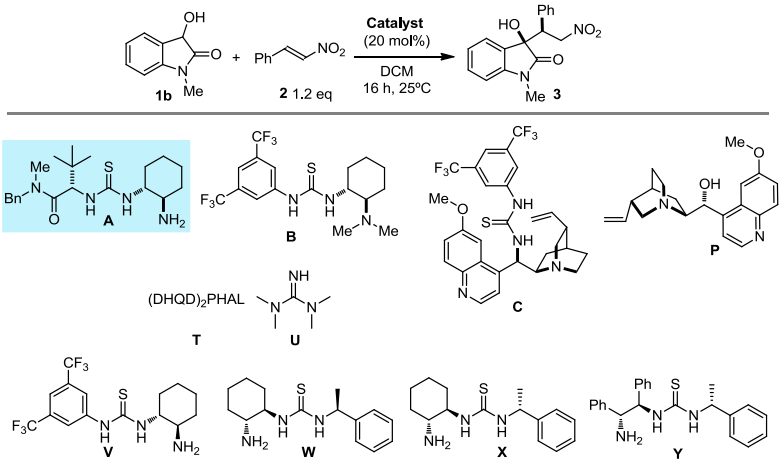


Entry	Catalyst	T (ºC)	Conversion (%)[b] 3	d.r.[b] anty:syn	Ee (%)[c] Anti:syn
1	**P**	25	21	5:1	35/0
2	**P**	-20	40	5:1	27/0
3	**Q**	-20	35	4:1	37[d]/0
4	**C**	0	16	3:1	n.d.
5	**C**[e]	25	45	3:1	0/0
6	**R**	-20	<5	n.d.	n.d.
7	**S**	0	25	4:1	17/n.d.
8	**T**	0	22	4:1	17[d]/n.d.
9	**U**	25	70	3:1	-
10	**B**	25	22	3:1	12/n.d.
11	**A**	**25**	**54**[f]	**1:2**	**11/57**

[a] Reactions performed on a 0.05 mmol scale with $[\mathbf{1a}]_0$ = 0.25 M in DCM, without any precaution for excluding air. [b] Both diastereomeric ratios (dr) and conversion were determined by ^{1}H NMR analysis of the crude reaction mixture using hexamethyl benzene as the internal standard. [c] Enantiomeric excess (ee) values were determined by HPLC analysis on commercially available chiral stationary phases. [d] The opposite enantiomer was obtained. [e] Reaction performed using Toluene as solvent. [f] Isolated yield.

Comment to Table S2. Exposure of a solution of dioxindole **1a** in dichloromethane to an aerobic atmosphere and in the presence of a base as catalyst (enties 1-10) led mainly to the formation of isatide, the pinacol dimeric form of **1**, see Figure S2 for more details. Under classical base catalysis conditions (deprotonative activation by a tertiary amine), the product **3**:isatide ratio can be substantially increased when performing the reaction at low temperature, since under cryogenic conditions the oxidative coupling is substantially inhibited (entries 1,2). Interestingly, the guanidine catalyst **U** seems compatible with dioxindole. This screening identified the thiourea primary amine **A** as the best candidate to develop an effective asymmetric conjugate addition to nitrostyrene.

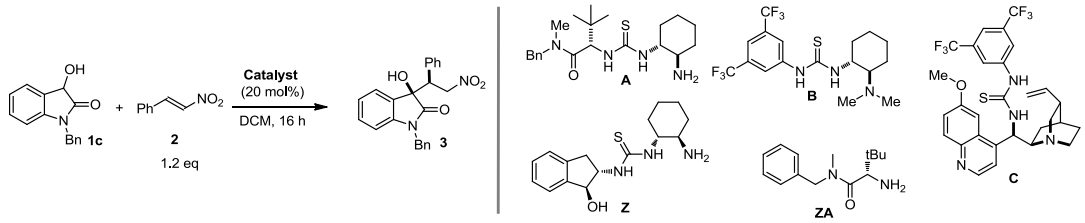
Table S3. Catalyst screening using 3-hydroxy-1-methylindolin-2-one **1b** [a]



Entry	Catalyst	Conversion (%) 3	d.r. anty:syn	ee (%) anti:syn
1	**P**	28	3:1	31[b]/n.d.
2	**T**	50	4.4:1	13/n.d.
3	**B**	30	2.2:1	25/23
4[c]	**C**	30	2:1	0/n.d.
5	**U**	50	2:1	-
6	**V**	45	1.6:1	7/n.d.
7	**W**	44	1.8:1	5/11
8	**X**	40	1.5:1	0/0
9	**Y**	37	1.5:1	7/n.d.
10	**A**	**44**	**1:2**	**35/80**

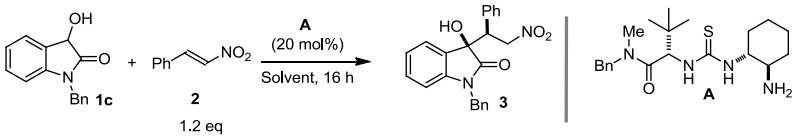
[a] Reactions performed on a 0.05 mmol scale with $[\mathbf{1}]_0$ = 0.25 M in DCM. [b] The opposite enantiomer was obtained. [c] Reaction in Toluene as solvent.

Table S4. Catalyst screening using 1-benzyl-3-hydroxyindolin-2-one **1c**



Entry	Catalyst	Conversion (%) 3	d.r. anty:syn	ee (%)
1	**B**	30	2.4:1	39/15
2	**C**	31	1.4:1	27/0
3	**Z**	26	1.8:1	15/0
4	**ZA**	<5	n.d.	n.d.
5	**A**	**68**	**1:2.1**	**50/87**

Table S5. Solvent screening using 1-benzyl-3- hydroxyindolin-2-one **1c**[a]

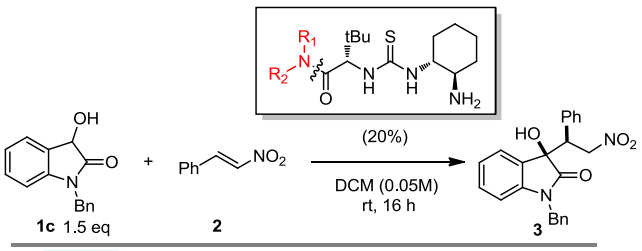


Entry	Solvent	Conversion (%) 3	d.r. anty:syn	Ee (%) Anti:syn
1	Toluene	33	1:1.4	33/77
2	$CHCl_3$	45	1:2.4	40/82
3	THF	45	1:1.6	33/77
4	Acetone	21	1:1.5	n.d.
5	DCE	43	1:1.8	35/80
6	MTBE	41	1:1.7	30/80
7	MeCN	37	1:1.8	39/75
8	DMF	70	1:1	0/0
9	EtOH	70	1:1	7/19
10	EtOAc	44	1:2.5	39/89
11	DCM	68	1:2.1	50/87
12[b]	DCM	full	1 :2.5	43/89

[a] Reactions performed on a 0.05 mmol scale with $[\mathbf{1}]_0$ = 0.25 M in DCM. [b] Reaction performed with 1.5 equiv of **1c**.

C. Catalyst structure/reactivity and stereoselectivity correlation studies

Table S6: Catalyst optimisation: the amide moiety [a]

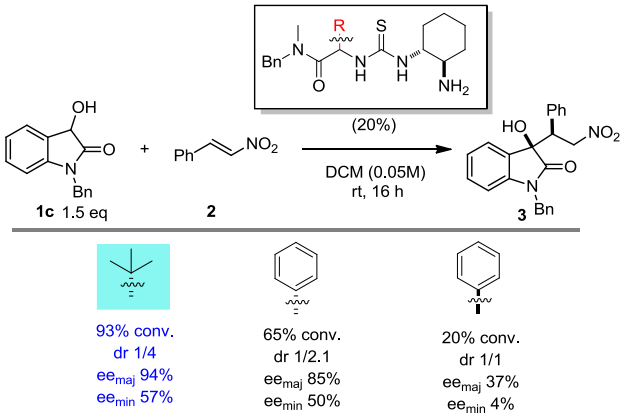


Me, Bn, N	H, Bn, N	Bn, Bn, N	i-Bu, i-Bu, N
93% conv. dr 1/4 ee_{maj} 94% ee_{min} 57%	65% conv. dr 1/2.4 ee_{maj} 85% ee_{min} 25%	70% conv. dr 1/3.2 ee_{maj} 92% ee_{min} 50%	55% conv. dr 1/3.2 ee_{maj} 87% ee_{min} 23%

[a] Reactions performed on a 0.05 mmol scale using 1.5 equiv of **1c** with $[\mathbf{2}]_0$ = 0.05 M in DCM, without any precaution for excluding air.

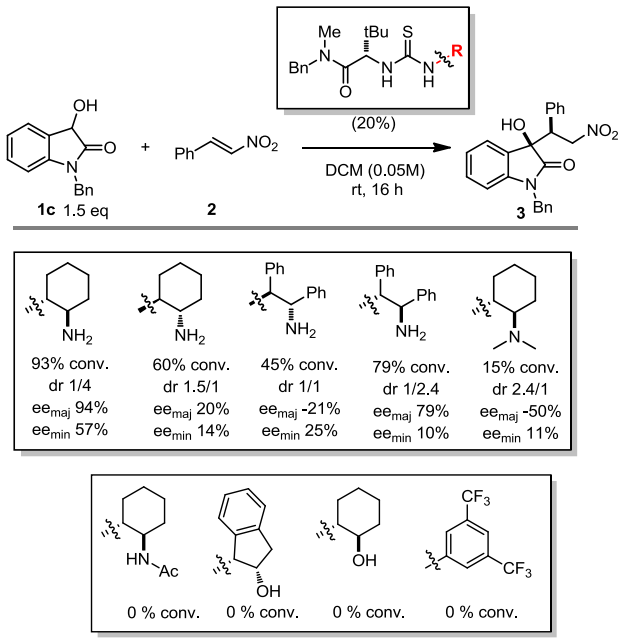
Comment to Table S6. The amide scaffold did not alter the stereochemical outcome of the Michael reaction to a significant extent.

Table S7: Catalyst optimisation: the aminoacid moiety [a]



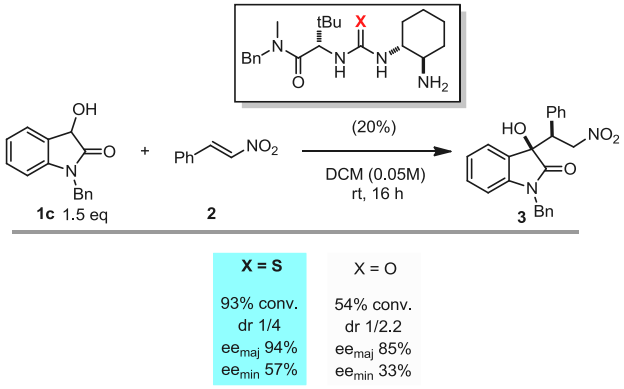
[a] Reactions performed on a 0.05 mmol scale using 1.5 equiv of **1c** with $[\mathbf{2}]_0$ = 0.05 M in DCM, without any precaution for excluding air.

Table S8: Catalyst optimisation: the amino moiety [a]



[a] Reactions performed on a 0.05 mmol scale using 1.5 equiv of **1c** with $[\mathbf{2}]_0$ = 0.05 M in DCM, without any precaution for excluding air.

Table S9: Catalyst optimisation: urea or thiourea? [a]



[a] Reactions performed on a 0.05 mmol scale using 1.5 equiv of **1c** with $[\mathbf{2}]_0$ = 0.05 M in DCM, without any precaution for excluding air.

Sum-up: Catalyst structure/reactivity and stereoselectivity correlation studies.

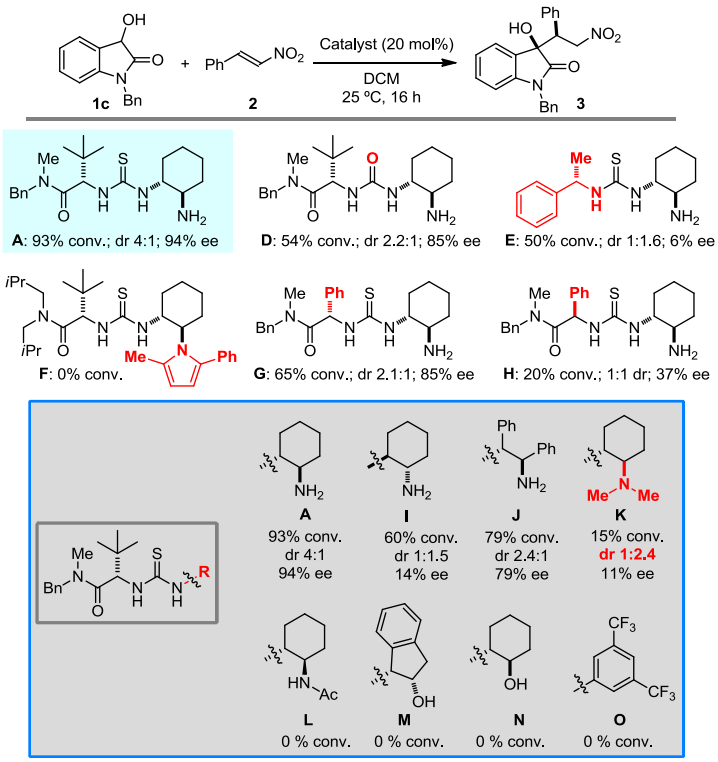


Figure S3: Reaction conditions: 20 mol% of the catalyst, 1.5 equiv of *N*-benzyl dioxindole **1c** and [nitrostyrene **2**]$_0$ = 0.05 M in DCM, 25 °C, 16 hours reaction time.

Comment to Figure S3. We focused on extensive structure/stereoselectivity correlation studies in order to understand the importance of the structural and stereochemical elements of the organocatalyst **A** in dictating the selectivity of the reaction. Our motivation was that primary amine thiourea derivatives of type **A** were originally conceived (and then successfully used) by Jacobsen and colleagues to synergistically combine hydrogen-bonding catalysis with the covalent activation of aldehydes and ketones, through the intermediacy of covalently bounded catalyst-enamine species.[5] Since the substrates involved in the present chemistry do not provide the chemical handle necessary for covalent activation, we wished to identify the structural elements that make the primary amine thiourea **A** effective in the realm of hydrogen-bonding catalysis (non-covalent activation mode). We investigated the addition of dioxindole **1c** to **2** in DCM using modified thiourea derivatives. This was to identify a role for each functional group of the catalyst scaffold, and to gain insight into the mechanism of stereoinduction. The results are reported in Figure S3.

The urea catalyst **D** was slightly less reactive and stereoselective than its thiourea analogue **A**. This indicates that these catalysts likely operate by similar mechanisms as H-bond donors; that is, the Lewis basicity of sulphur in **A** probably does not play a direct role during the catalysis. The amido-moiety[6] and the primary

[5] (a) H. Huang and E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; (b) M. P. Lalonde, Y. Chen and E. N. Jacobsen, *Angew. Chem., Int. Ed.* **2006**, *45*, 6366; (c) A. R. Brown, W.-H. Kuo and E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286. An analogue of primary amine thiourea **A** provided high catalytic activity in the cyanosilylation of ketones operating via non-covalent activation, but affording low stereocontrol, see: (d) D. E. Fuerst and E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964.

[6] We extensively modified the amide scaffold, either by introducing more sterically demanding substituents or by using a secondary amide moiety. This did not alter the stereochemical outcome of the Michael reaction to a significant extent, see Table S6.

amine were soon recognised as essential elements for catalysis, since their absence dramatically affected the outcome of the reaction (catalysts **E**-**F**). It appeared that only a well-defined relative spatial arrangement of the catalytic moieties, as dictated by the absolute configurations of three stereocentres, brought about an effective catalysis. The stereochemistry and the nature of the substituent within the amino acid component were both important for securing high stereoselectivity, with (*S*)-*tert*-leucine providing optimal results (compare catalysts **A**, **G**, and **H**). In addition, a specific stereochemistry of the diaminocyclohexane backbone was required (**A** against **I**). Surprisingly, replacing the primary amine in **A** with the corresponding *N*,*N*-dimethyl tertiary amine (**K**) caused an inversion of the diastereoselectivity together with a complete loss of enantiocontrol. This suggests an uncommon mechanistic scenario where the primary amino moiety is not operating as a Brønsted base, but serving as a suitable chemical handle for hydrogen-bonding activation. The need for a primary amine for catalytic activity is clearly suggested by the results obtained with catalysts (**L**, **M**, **N**), which bear functional groups with slightly different hydrogen-bonding abilities with respect to **A**. All these results suggest a cooperative mechanism of catalysis of the thiourea, the amido group, and the primary amino moiety, which synergistically channel the process toward a highly stereoselective pathway by concomitant activation of both the electrophilic and nucleophilic partners. On the basis of the absolute configuration of product **3k**, a plausible mechanism was proposed to reconcile the catalyst structure/reactivity and stereoselectivity correlation studies (Figure S4).

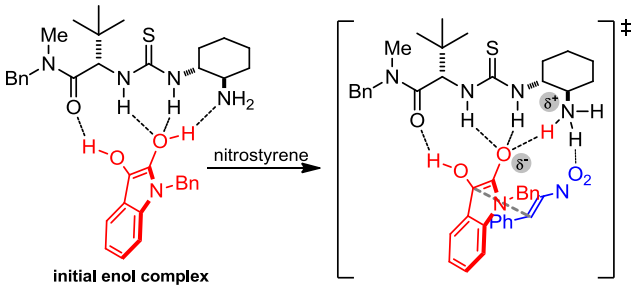


Figure S4: Proposed enol-based mechanism using primary amine-thiourea catalyst **A**.

It is plausible that the primary amine-thiourea catalyst **A** stabilises the enol form of the dioxindole through hydrogen bonding instead of promoting the formation of an enolate intermediate (intermediate **I** in eqn (2)).[7] During the C-C bond-forming event, the nascent negative charge is stabilised by the thiourea unit, while the build-up of the positive charge on the ammonium ion directs the approach of the nitrostryrene. This is consistent with the striking difference in the reaction outcome observed when using catalyst **K**, and with the fact that catalyst **A** greatly minimises the oxidative coupling pattern (which is driven by oxidation of the enolate intermediate **I**). In addition, the potential of primary amine-thiourea catalyst to operate trough enol-based chemistry has already been demonstrated.[8] The proposed cooperative catalysis system[9] takes advantage of the consolidated spectacular ability of thiourea derivatives to recognise anions and negative charges.[10]

[7] NMR analysis of a mixture of catalyst **A** and dioxindole **1c** in CD_2Cl_2 did not result in any detectable binding interactions, indicating that spectroscopically observable substrate binding does not occur in the present system.
[8] D. A. Yalalov, S. V. Tsogoeva, T. E. Shubina, I. M. Martynova and T. Clark, *Angew. Chem., Int. Ed.* **2008**, *47*, 6624.
[9] Protection of the hydroxyl dioxindole moiety in **1c** completely suppressed the reactivity of the addition to **2** under the optimal reaction conditions, while the THP-O protected derivative of **1a** provided a racemic product (see Figure S5 for more details). These results indicate that the OH moiety of the dioxindole is engaged in a key interaction with catalyst **A** to build-up a well structured transition state.
[10] (a) R. R. Knowles and E. N. Jacobsen, *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678; (b) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; (c) S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

Nucleophile structure-reactivity studies

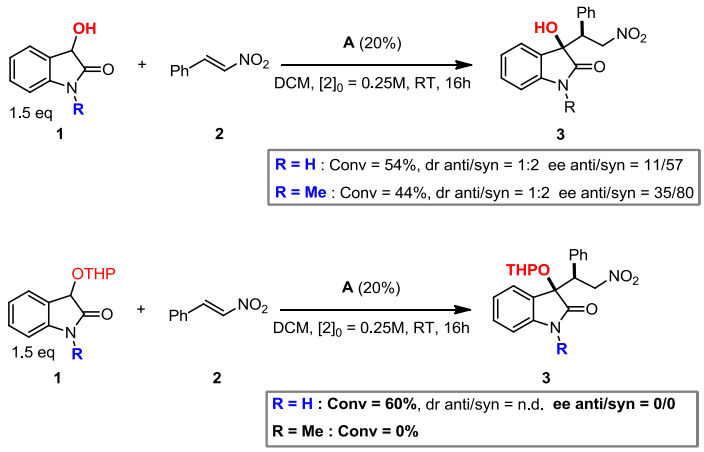
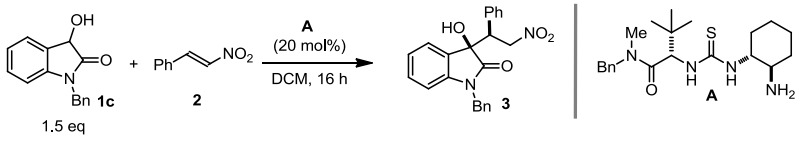


Figure S5: A strong influence of the substitution pattern of the dioxindole **1** was observed. Protection of the hydroxyl group dramatically affects the outcome of the reaction as the nucleophile looses an essential element for selectively binding to the catalyst.

D. Catalyst Self-Association Studies

Table S10. Temperature and concentration effect[a]



Entry	Temperature (ºC)	$[2]_0$	Conversion (%)[b] 3	d.r.[b] anty:syn	Ee (%)[c] Anti:syn
1	25	0.25	full	1:2.5	43/89
2	0	0.25	60	1 :2.4	33/85
3	**-20**	**0.25**	**35**	**1 :2**	**30/75**
4	**25**	**1**	**full**	**1 :1.6**	**23/63**
5	25	0.25	full	1 :2.5	43/89
6	25	0.1	87	1 :2.7	50/90
7	**25**	**0.05**	**93**	**1 :4**	**57/94**

[a] Reactions performed on a 0.05 mmol scale in DCM, without any precaution for excluding air. [b] Both diastereomeric ratios (dr) and conversion were determined by ^{1}H NMR analysis of the crude reaction mixture using hexamethyl benzene as the internal standard. [c] Enantiomeric excess (ee) values were determined by HPLC analysis on commercially available chiral stationary phases.

Comment to Table S10. An unusual correlation between reaction temperature, concentration, and stereoselectivity has been observed (reduced ee observed at lower temperature and higher concentration). This was rationalised on the basis of a self-aggregation of the catalyst. This phenomenon is not uncommon for bifunctional thiourea-based catalysts[11] and it may determine the formation of monomer and dimer (or higher) aggregates characterised by different catalytic and/or stereoselective profiles. See Table S11 in the following page for more details.

[11] (a) H. B. Jang, H. S. Rho, J. S. Oh, E. H. Nam, S. E. Park, H. Y. Bae, C. E. Song, *Org. Biomol. Chem.* **2010**, *8*, 3918; b) G. Tárkányi, P. Király, S. Varga, B. Vakulya, T. Soós, *Chem. Eur. J.* **2008**, *14*, 6078.

^{1}H NMR Spectroscopic Data for Self-Association of Catalyst A

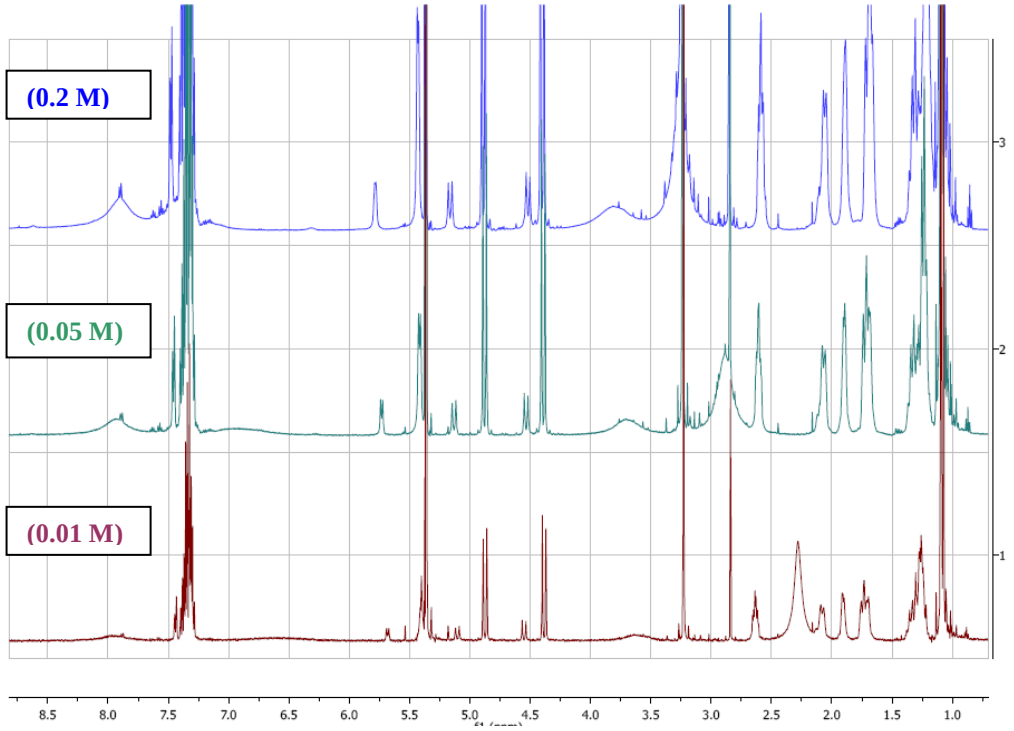
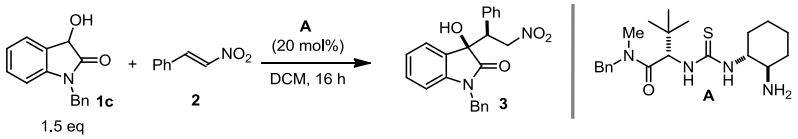


Figure S6: 1H NMR dilution experiments of **A** were carried out in CD_2Cl_2. Marked concentration dependencies were observed for the chemical shift of –C(=S)N(H) proton and –NH_2 protons. The chemical shift of the primary amine protons was downfield-shifted from 2.2 to 3.2 ppm upon increasing its concentration from 0.01 M to 0.2 M and the chemical shift of the –C(=S)N(H) proton was downfield-shifted from 6.5 to 7.2 ppm. This concentration dependency is consistent with the hydrogen-bonded self-association of **A**. Blu spectrum: catalyst **A** (0.2 M in CD_2Cl_2, 25ºC); green spectrum: catalyst **A** (0.05 M in CD_2Cl_2, 25ºC); red spectrum: catalyst **A** (0.01 M in CD_2Cl_2, 25ºC)

Table S11. DOSY (diffusion ordered spectroscopy) spectroscopic NMR experiments [a]



2 Conc. (M)	A Conc. (M)	d.r.[a]	Ee_{maj} (%)[b]	Ee_{min} (%)[b]	D ($10^{-10}m^2s^{-1}$)[c]
1	0.2	1.6:1	63	23	**3.23**
0.25	0.05	2.5 :1	89	43	**9.74**
0.05	0.01	4:1	94	57	**12.02**

[a] Determined by ^{1}H NMR of the crude mixture. [b] Determined by chiral HPLC analysis on a chiral stationary phase
[c] Diffusion coefficient D obtained by DOSY experiments on samples of catalyst solutions in CD_2Cl_2. The experiments were carried on a Bruker Avance spectrometer, 500 MHz, equipped with a 5-mm broadband observe (BBO) z axis gradient probes capable of generating 55 G/cm field strengths.

Comment to Table S11. The DOSY NMR technique has recently been regarded as an invaluable tool for studying self-association phemonena in solution.[11] The diffusion coefficients of the amino thiourea **A** significantly decreased upon increasing its concentration. The ee values obtained at different concentrations are fairly consistent with the diffusion coefficients (D) of the catalyst, indicating that the catalyst degree of self-association plays a crucial role in determining the enantioselectivity. The obtained results suggest that the catalyst monomeric form, favoured under more diluted reaction condition, is the most selective species.

E. The Dioxindole Stability

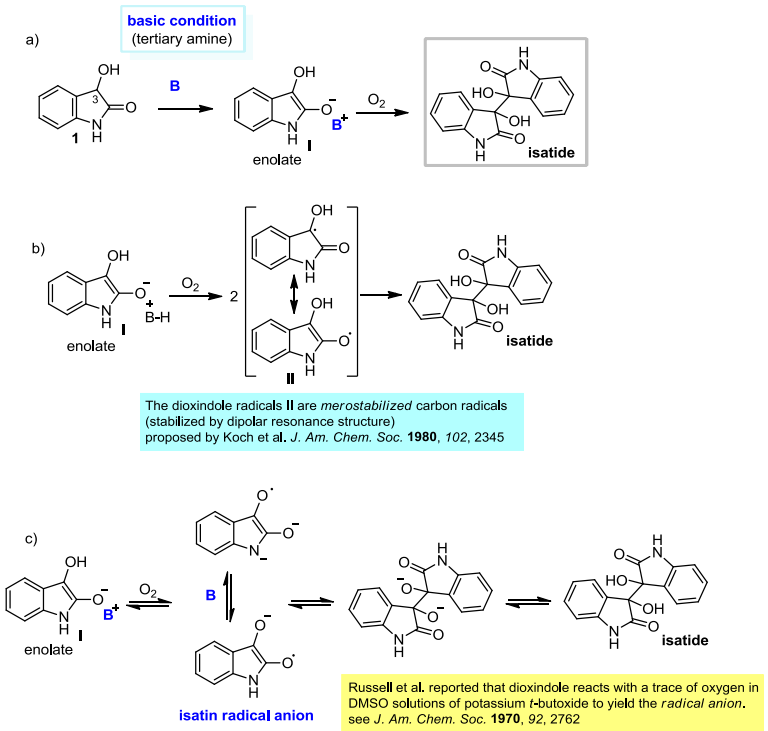


Figure S7. The dioxindole oxidative coupling pathway leading to isatide. a) The oxidative dimerization pathway under basic conditions and in the presence of oxygen has been reported several times.[12,13,14,15] **b**) Koch et al.[13] proposed that the dioxindole radicals **II** are *merostabilized* carbon free radicals. They are stabilized by dipolar resonance structure, since the radical center lies between the electron-donating hydroxyl substituent and the electron-withdrawing carbamido substituent. This phenomenon is known as the *captodative* effect (Ref. 13b). **c**) A different oxidative pathway has been proposed by Russell et al.[14]: in highly basic conditions (DMSO solutions of potassium t-butoxide) dioxindole is believed to react with a trace of oxygen to yield the corresponding radical (di)anion. It should be noted that this pathway is an equilibrium: indeed, isatide can undergo a disproportionation under basic conditions, leading to dioxindole and isatin (as reported in Refs 14&15).

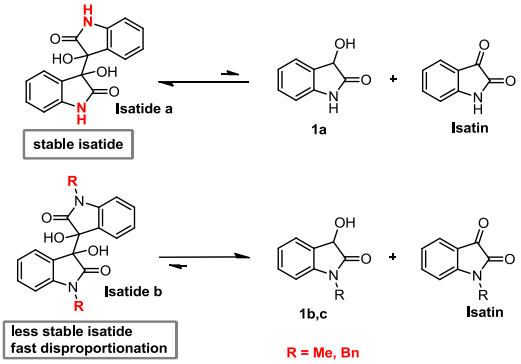
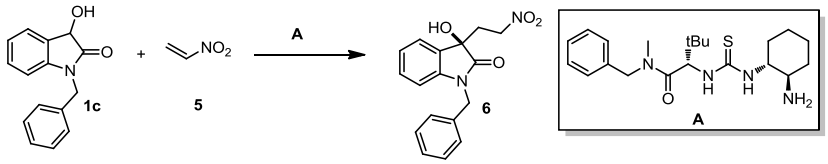


Figure S8. The disproportionation of isatide. When using dioxindole **1a** as the nucleophile of the conjugate addition (mainly in the presence of a tertiary amine), we have detected the formation of a large amount of isatide. In contrast, using *N*-protected dioxindoles no traces of isatide were detected, even in the presence of a tertiary amine. However, a large amount of the corresponding isatin was detected, in addition to the reactants and the product of the reaction. This observation can be rationalized taking into account the different stability of the isatides derived from N-unprotected or N–protected dioxindoles, **a** and **b** respectively. It has been already reported that the N-protected isatide **b** easily undergoes a disproportionation, leading to the corresponding dioxindole and isatin (Refs 14&15).

[12] E. Ziegler; T. Kappe; R. Salvador; *Mh. Chem.* **1963**, *94*, 453.
[13] R.W. Bennett; D. L. Wharry; T. H. Koch; *J. Am. Chem. Soc.* **1980**, *102*, 2345; b) H. G. Viehe, Z. Janousek, R. Merenyi, L. Stella, *Acc. Chem. Res.* **1985**, *18*, 148.
[14] G. A. Russell; C. L. Myers; P. Bruni; F. A. Neugebauer; R. Blankespoor; *J. Am. Chem. Soc.* **1970**, *92*, 2762.
[15] O. J. Sonderegger; T. Bürgi; L. K. Limbach; A. Baiker; *Journal of Molecular Catalysis A* **2004**, *217*, 93.

F. The Oxindole Addition to Nitroethylene

Table S12

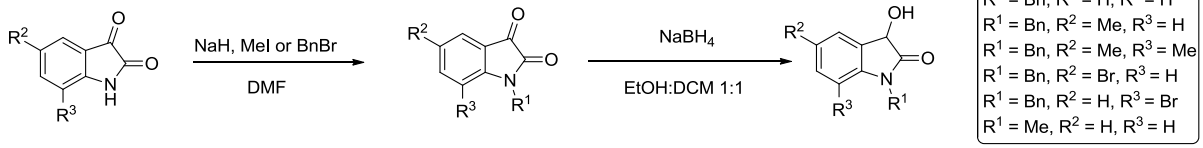


Entry	A mol%	Solvent	1c : 5 ratio	[1c]$_0$	T (ºC)	Time (h)	Conv[b] (%)	e.e.[c]
1	**20**	**DCM**	**1.5:1**	**0.075**	**rt**	**46**	**<10**	**92**
2[d]	20	DCM	1:1.5	0.25	rt	12[e]+48	<5	nd
3[d]	20	DCM	1:1.5	1	rt	12[e] +48	20	nd
4	20	AcOEt	1:1.5	1	40	60	16	nd
5[d]	30	DCM	1.5:1	0.11	35	18[e] +5	23	nd
6	30	AcOEt	1.5:1	0.075	50	22	17	nd
7	30	DCM	1.5:1	0.5	30	20[e] +48	<5	nd
8[d]	30	AcOEt	1.5:1	0.5	30	20[e] +48	22	-11
9[d]	30	DCM	1.5:1	0.5	30	20[e] +48	5	10

[a] Reactions performed on a 0.05 mmol scale, without any precaution for excluding air. [b] Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Enantiomeric excess (ee) values were determined by HPLC analysis on commercially available chiral stationary phases. [d] The reaction was performed adding a 1M solution of nitroethylene in DCM via syringe pump. [e] Nitroethylene solution addition time (h)

G. Preparation of the Starting Materials

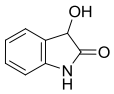
Synthesis of Dioxindole Derivatives



Procedure: a solution of commercially available isatins (5 mmol) in 15 mL of dry DMF was slowly added to a suspension of sodium hydride (6.5 mmol, 1.3 eq, 60 % in mineral oil) in 15 mL of dry DMF at 0 ºC. The suspension was stirred for 2h at 0 ºC. Then, 1.5 equivalent of the alkylating agent (methyl iodide or benzil bromide) was added. The mixture was stirred for 2 h at room temperature and water was added until precipitation of the N-protected isatin. Crystallization from hexane/ethyl acetate afforded the pure products in about 70% yield. The pure N-protected isatins (2 mmol) were added in small portions to a stirred suspension of sodium borohydride (3 mmol, 113 mg, 1.5 eq) in 12 mL of a 1:1 dichloromethane/ethanol mixture at 0 ºC. The mixture was vigorously stirred at this temperature until the suspension became colourless (about 5 min). Then water (0.2 mL) was added and the reaction mixture was stirred until bubbling stop. The mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified by

chromatography on silica gel using a 1:1 mixture of hexane/diethyl ether, or crystallized by ethyl acetate/hexane to separate the N-protected-3-hydroxy-2-oxoindole derivatives from the pigments formed during the extraction and evaporation procedures.

Starting materials NMR data

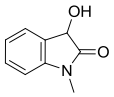


3-hydroxyindolin-2-one.

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.82 (d, 1H, J = 7.50 Hz), 6.15 (d, 1H, J = 7.50 Hz), 6.15 (d, 1H, J = 7.54 Hz), 6.78 (d, 1H, J = 7.65 Hz), 6.96 (t, 1H, J = 7.62 Hz), 7.20 (t, 1H, J = 7.68 Hz), 7.28 (d, 1H, J = 7.28 Hz), 10.22 (br s, 1H).

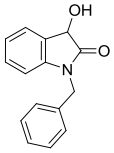
^{13}C NMR (100 MHz, DMSO-d_6): δ 69.6, 109.9, 121.9, 125.2, 129.4, 129.8, 142.6, 178.4 ppm.

3-hydroxy-1-methylindolin-2-one



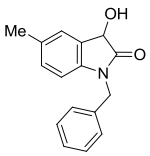
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.17 (s, 3H), 4.66 (br s, 1H), 5.10 (s, 1H), 6.81 (d, 1H, J = 7.92 Hz), 7.10 (dt, 1H, J_1 = 7.52 Hz, J_2 = 0.92 Hz), 7.32 (t, 1H, J = 7.64 Hz), 7.46 (d, 1H, J = 7.46 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 70.0, 108.6, 123.4, 125.3, 126.9, 130.0, 144.0, 176.9 ppm.

1-benzyl-3-hydroxyindolin-2-one



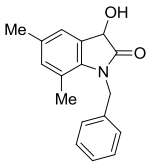
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (br s, 1H), 4.88 (complex system, 2H), 5.17-5.21 (m, 1H), 6.72 (d, 1H, J = 7.93 Hz), 7.07 (dt, 1H, J_t = 7.54, J_d = 0.89 Hz), 7.18-7.34 (m, 6H), 7.47 (d, 1H, 7.45 Hz. ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.0, 70.0, 109.6, 123.4, 125.3, 127.1, 127.4, 127.9, 128.9, 129.8, 135.4, 143.1, 177.3 ppm.

1-benzyl-3-hydroxy-5-methylindolin-2-one



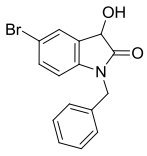
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.99 (br s, 1H), 4.85 (complex system, 2H), 5.16 (s, 1H), 6.59 (d, 1H, J = 7.95 Hz), 6.98-7.03 (m, 1H), 7.22-7.34 (m, 6H,) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 43.8, 69.9, 109.2, 126.05, 126.9, 127.3, 127.71, 128.8, 129.9, 132.9, 135.4, 140.5, 177.0 ppm.

1-benzyl-3-hydroxy-5,7-dimethylindolin-2-one



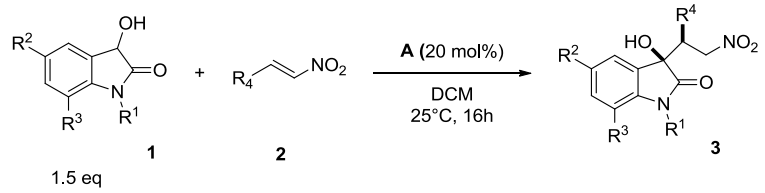
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.29 (s, 3H) 3.81(d, 1H, J = 4.97 Hz), 5.13-5.18 (m, 3H), 6.82 (s, 1H), 7.14-7.21 (m, 3H), 7.23-7.36 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 20.6, 45.0, 69.4, 120.0, 123.9, 125.6, 127.3, 127.7, 128.9, 133.0, 134.0, 137.0, 138.5, 177.9 ppm.

1-benzyl-5-bromo-3-hydroxyindolin-2-one

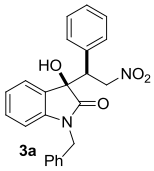


^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (d, 1H, J = 4.60 Hz), 4.89 (complex system, 2H), δ 5.18 (d, 1H, J = 4.08 Hz), 6.60 (d, J = 8.41 Hz), 7.25-7.39 (m, 6H), 7.59-7.61 (m. 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9, 69.5, 111.0, 116.0, 127.2, 127.9, 128.5, 128.6, 128.9, 132.6, 134.8, 142.0, 176.3 ppm.

H. General Procedure for the Michael Addition of Dioxindole to Nitrostyrene



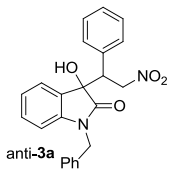
All the reactions were carried out in dichloromethane (CHROMASOLV for HPLC anhydrous) without any precaution for excluding air and moisture (open air chemistry on the benchtop). An ordinary round bottom flask equipped with a Teflon-coated stir bar and a plastic cap was charged with the trans-β-nitrostyrene **2** (0.2 mmol) and the dioxindole derivative **1** (0.3 mmol, 1.5 equiv). Then, (S)-2-[[(1R,2R)-2-aminocyclohexyl] thioureido]-*N*-benzyl-*N*,3,3-trimethylbutanamide **A** (0.04 mmol, 20 mol%) was added in one portion and the reaction was started by the addition of dichloromethane (4 ml). The round bottom flask was closed and stirring continued over 16 hours at 25 ºC. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (10 ml). Solvent was removed in vacuo and the diastereomeric ratio (d.r.) was determined by 1H NMR analysis of the crude mixture. The product **3** was isolated by flash column chromatography on silica gel.



(R)-1-benzyl-3-hydroxy-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3a - Table **2**, entry **1)**

Major diastereoisomer. The reaction was carried out following the general procedure to furnish the crude products as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.46 ppm (d), δ_{minor} 6.41 ppm (d). $R_{f\ maj}$ = 0.24, $R_{f\ min}$ = 0.28 (dichloromethane/diethyl ether 98/2). The title compound **3a** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.24) in 69% yield (53.5 mg, yellow solid, mp = 72.5-74.5 ºC). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.6 min, τ_{minor} = 14.0 min. $[\alpha]_D^{26}$= -51.4 (c = 0.56, $CHCl_3$, 94% ee). HRMS *calcd* for ($C_{23}H_{20}N_2O_4$+Na): 411.1321, found 411.1321.

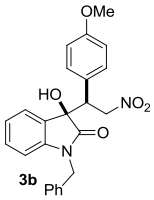
^{1}H NMR (400 MHz, $CDCl_3$): δ3.19 (bs, 1H), 4.24 (dd, 1H, J_1 = 10.65 Hz, J_2 = 4.58 Hz), 4.32 (d, 1H, J = 15.91), 4.90 (d, 1H, J = 15.91 Hz), 5.03 (dd, 1H, J_1 = 13.01 Hz, J_2 = 10.65 Hz), 5.54 (dd, 1H, J_1 = 13.01 Hz, J_2 = 4.58 Hz), 6.46 (d, 1H, J = 7.85 Hz), 6.55 (d, 2H, J = 7.10 Hz), 6.86 (d, 2H, J = 7.20 Hz). 7.08-7.35 (m, 9H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ44.3, 51.8, 75.9, 78.3, 110.5, 111.3, 123.5, 125.0, 126.9, 127.8, 12.8, 129.0, 129.4, 130.9, 133.6, 134.7, 138.6, 143.4, 176.8 ppm.



The **minor diastereoisomer** *anti*-**3a** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.28) in 13% yield (10 mg, yellow solid). The enantiomeric excess was determined to be 62% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 6.4 min, τ_{minor} = 11.3 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.96 (bs, 1H), 4.34 (dd, 1H, J_1 = 9.76 Hz, J_2 = 5.05 Hz), 4.48-4.58 (m, 1H), 4.72-4.82 (m, 1H), 5.27-5.38 (m, 1H), 5.48-5.59 (m, 1H), 6.35-6.43 (m, 1H), 6.81-6.88 (m, 2H), 6.90-6.97 (m, 2H), 6.98-7.06 (m, 2H), 7.06-7.15 (m, 3H),

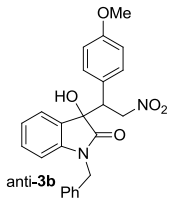
7.16-7.23 (m, 3H), 7.51-7.57 (m, 1H) ppm.[13]C NMR (100 MHz, $CDCl_3$): δ 43.8, 50.9, 74.2, 109.6, 123.3, 123.8, 127.0, 127.6, 127.9, 128.3, 128.7, 128.8, 130.3, 133.1, 134.5, 142.3, 175.7 ppm.

(R)-1-benzyl-3-hydroxy-3-((S)-1-(4-methoxyphenyl)-2-nitroethyl)indolin-2-one (3b – Table **2**, entry **2)**



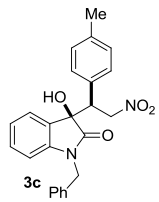
The reaction was carried out following the general procedure to furnish the crude products as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 3.73 ppm (s), δ_{minor} 3.71 ppm (s). $R_{f\ maj}$ = 0.26, $R_{f\ min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.26) in 75% yield (63.0 mg, pale yellow solid, mp = 69–71 ºC). The enantiomeric excess was determined to be 93% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.5 min, τ_{minor} = 30.1 min. $[\alpha]_D^{26}$= -87.6 (c = 0.80, $CHCl_3$, 93% ee). HRMS *calcd* for ($C_{24}H_{22}N_2O_5$+Na): 441.1426, found 441.1432.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.65 (bs, 1H), 3.73 (s, 3H), 4.23-4.31(m, 2H), 4.92-5.06 (m, 2H), 5.53 (dd, 1H, J_1 = 12.86 Hz, J_2 = 4.43 Hz), 6.48 (d, 1H, J = 7.76 Hz), 6.55 (d, 2H, J = 7.40 Hz), 6.63 (d, 2H, J = 8.50 Hz), 6.77 (d, 2H, J = 8.50 Hz), 7.09-7.19 (m, 4H), 7.23 (dt, 1H, J_t = 7.86 Hz, J_d = 1.13 Hz), 7.33-7.37 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.3, 51.2, 55.4, 76.2, 78.4, 110.5, 114.3, 123.5, 124.9, 125.3, 126.9, 127.8, 128.9, 129.4, 130.4, 130.9, 134.7, 143.5, 160.0, 176.9 ppm.



The **minor diastereoisomer** *anti*-**3b** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.30) in 11% yield (9 mg, yellow solid). The enantiomeric excess was determined to be 42% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 11.7 min, τ_{minor} = 23.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (bs, 1H), 3.67 (s, 3H), 4.28 (dd, 1H, J_1 = 9.74 Hz, J_2 = 4.95 Hz), 4.46-4.53 (m, 1H), 4.83 (d, J = 15.84 Hz, 1H), 5.25-5.34 (m, 1H), 5.45-5.25 (m, 1H), 6.39-6.45 (m, 1H), 6.51-6.56 (m, 2H), 6.80-6.86 (m, 4H), 7.07-7.15 (m, 2H), 7.16-7.23 (m, 3H), 7.51-7.55 (m, 1H) ppm.[13]C NMR (100 MHz, $CDCl_3$): δ 43.8, 50.0, 55.0, 74.3, 109.7, 119.7, 123.3, 123.7, 124.8, 127.0, 127.4, 127.6, 128.6, 129.02, 129.06, 129.9, 130.3, 134.5, 142.4, 159.1, 175.8 ppm.

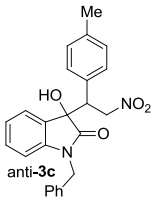
(R)-1-benzyl-3-hydroxy-3-((S)-2-nitro-1-(p-tolyl)ethyl)indolin-2-one (3c – Table **2**, entry **3)**



The reaction was carried out following the general procedure to furnish the crude products as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 2.29 ppm (s), δ_{minor} 2.20 ppm (s). $R_{f\ maj}$ = 0.25, $R_{f\ min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.25) in 74% yield (59.5 mg, yellow solid, mp = 75.0–76.0 ºC.). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.9 min, τ_{minor} = 24.7 min. $[\alpha]_D^{26}$= -67.2 (c = 0.97, $CHCl_3$, 94% ee). HRMS *calcd* for ($C_{24}H_{22}N_2O_4$+Na): 425.1477, found 425.1489.

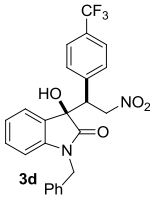
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.44 (bs, 1H), 4.22-4.31 (m, 2H), 4.95 (d, 1H, J = 15.77 Hz), 5.01 (dd, 1H, J_1 = 12.92 Hz, J_2 = 10.65 Hz), 5.52 (dd, 1H, J_1 = 12.92 Hz, J_2 = 4.45 Hz), 6.47 (d, 1H, J = 7.76 Hz), 6.57 (d, 2H, J = 7.38 Hz), 6.73 (d, 2H, J = 7.97 Hz), 6.92 (d, 2H, J = 7.97 Hz), 7.08-7.24 (m, 5H),

7.32-7.36 (m, 1H) ppm.^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 44.3, 51.5, 53.8, 76.1, 78.3, 110.5, 123.5, 125.0, 127.0, 127.8, 128.9, 129.2, 129.6, 130.4, 130.9, 134.8, 138.5, 143.5, 176.8 ppm.



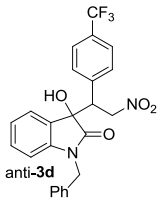
The **minor diastereoisomer** *anti*-**3c** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.30) in 9% yield (7.5 mg, yellow solid). The enantiomeric excess was determined to be 64% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 9.1 min, τ_{minor} = 19.0 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.64 (s, 3H), 3.46 (bs, 1H), 4.69-4.78 (m, 1H), 4.87-4.97 (m, 1H), 5.23-5.31 (m, 1H), 5.67-5.77 (m, 1H), 5.87-5.98 (m, 1H), 6.80-6.86 (m, 1H), 7.20-7.31 (m, 6H), 7.48-7.68 (m, 5H), 7.92-8.00 (m, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ21.0, 43.8, 50.4, 74.3, 109.7, 123.3, 123.8, 127.0, 127.5, 128.6, 128.7, 129.0, 129.1, 129.9, 130.3, 134.6, 137.6, 142.4, 175.8 ppm.

(R)-1-benzyl-3-hydroxy-3-((S)-2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)indolin-2-one (3d – Table **2**, entry **4)**



The reaction was carried out following the general procedure to furnish the crude products as a 3.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.54 ppm (d), δ_{minor} 6.50 ppm (d). $R_{f\,maj}$ = 0.26, $R_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.26) in 56% yield (51.0 mg, yellow solid, mp = 76.0–78.0 ºC). The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak AD-H column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.3 min, τ_{minor} = 23.6 min. $[\alpha]_D^{25}$= -27.5 (c = 0.88, $CHCl_3$, 90% ee). HRMS *calcd* for ($C_{24}H_{19}F_3N_2O_4$+Na): 479.1195, found 479.1186.

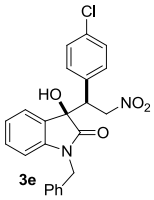
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (bs, 1H), 4.32 (d, 1H, J = 15.8 Hz), 4.38 (dd, 1H, J_1 = 11.13 Hz, J_2 = 3.82 Hz), 4.87 (d, 1H, J = 15.8 Hz), 5.06 (dd, 1H, J_1 = 13.33 Hz, J_2 = 4.03 Hz), 5.61 (dd, 1H, J_1 = 13.33 Hz, J_2 = 4.03 Hz), 6.54 (d, 1H, J = 7.72 Hz), 6.65 (d, 2H, J = 7.24 Hz), 7.00 (d, 2H, J = 8.12 Hz), 7.11-7.21 (m, 4H), 7.23-7.34 (m, 2H), 7.37 (d, 2H, J = 8.13 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.5, 51.5, 75.6, 77.9, 110.7, 123.8, 125.0, 125.8, 126.8, 126.9, 128.1, 129.1, 129.8, 130.9, 131.3, 134.55, 137.8, 143.3, 176.7 ppm.



The **minor diastereoisomer** *anti*-**3d** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.30) in 15% yield (13.5 mg, yellow solid). The enantiomeric excess was determined to be 37% by HPLC analysis on a Daicel Chiralpak IC column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.4 min, τ_{minor} = 17.7 min.

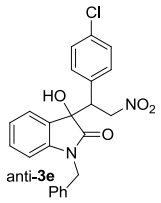
^{1}H NMR (400 MHz, $CDCl_3$): δ4.38 (dd, J_1= 10.24 Hz, J_2 = 4.77 Hz, 1H), 4.44-4.53 (m, 1H), 4.83 (d, 1H, J = 15.74 Hz), 5.30-5.42 (m, 1H), 5.47-5.57 (m, 1H), 6.45-6.52 (m, 1H), 6.85-6.92 (m, 1H), 7.01-7.26 (m, 8H), 7.55 (dd, 1H, J_1= 7.64 Hz, J_2 = 0.82 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ44.0, 50.6, 73.8, 109.8, 123.5, 123.7, 125.1, 125.23, 125.26, 127.1, 127.9, 128.2, 128.7, 129.2, 130.8, 134.4, 137.2, 142.2, 175.3 ppm.

(R)-1-benzyl-3-((S)-1-(4-chlorophenyl)-2-nitroethyl)-3-hydroxyindolin-2-one (3e - Table **2**, entry **5**)



The reaction was carried out following the general procedure to furnish the crude products as a 3.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.52 ppm (d), δ_{minor} 6.48 ppm (d). $R_{f\ maj}$ = 0.27, $R_{f\ min}$ = 0.31(dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.27) in 60% yield (53.5 mg, yellow solid, mp = 84.0–86.0 ºC). The enantiomeric excess was determined to be 84% by HPLC analysis on a Daicel Chiralpak AD-H column: 90:10 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 30.8 min, τ_{minor} = 43.8 min. $[\alpha]_D^{26}$= -58.7 (c = 1.14, $CHCl_3$, 84% ee). HRMS *calcd* for ($C_{23}H_{19}ClN_2O_4$+Na): 445.0931, found 445.0927.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (bs, 1H), 4.25-4.32 (m, 2H), 4.92-5.03 (m, 2H), 5.56 (dd, 1H, J_1 = 13.11 Hz, J_2 = 4.08 Hz), 6.52 (d, 1H, J = 7.73 Hz), 6.54-6.59 (m, 2H), 6.78 (d, 2H, J = 8.46 Hz), 7.05-7.10 (m, 2H), 7.14 (dt, 1H, J_t = 7.73 Hz, J_d = 1.01 Hz), 7.18-7.27 (m, 4H), 7.35 (d, 1H, J = 7.91 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.4, 51.2, 75.8, 78.1, 110.6, 123.7, 124.9, 126.9, 126.95, 128.0, 129.0, 129.2, 130.7, 131.1, 132.1, 134.5, 134.9, 143.4, 176.7 ppm.

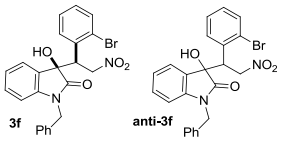


The **minor diastereoisomer** *anti*-**3e** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.31) in 13% yield (11.0 mg, yellow solid). The enantiomeric excess was determined to be 15% by HPLC analysis on a Daicel Chiralpak IC column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major}= 38.7 min, τ_{minor}= 34.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (bs, 1H), 4.30 (dd, J_1= 10.17 Hz, J_2 = 4.78 Hz, 1H), 4.43-4.52 (m, 1H), 4.83 (d, 1H, J = 16.32 Hz), 5.27-5.34 (m, 1H), 5.45-5.54 (m, 1H), 6.47 (d, 1H, J = 7.88), 6.80-6.88 (m, 1H), 6.93-7.00 (m, 2H), 7.08-7.19 (m, 2H), 7.21-7.27 (m, 1H), 7.53 (dd, 1H, J_1= 7.17 Hz, J_2 = 1.00 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 43.8, 50.2, 73.9, 109.8, 123.5, 123.7, 127.0, 127.8, 128.5, 128.6, 128.7, 130.1, 130.6, 131.5, 134.0, 134.4, 142.3, 175.5 ppm.

(R)-1-benzyl-3-((S)-1-(2-bromophenyl)-2-nitroethyl)-3-hydroxyindolin-2-one (3f)

The reaction was carried out following the general procedure to furnish the crude product as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{maj} 6.43 ppm (d), δ_{min}6.55 ppm (d).

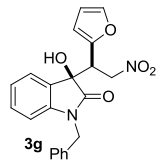


(3**f** – Table **2**, entry **6**). The title compound was isolated as a 5.2:1 diastereomeric mixture by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.30) in 60% overall yield (56.0 mg) as a pale yellow solid. The enantiomeric excess was determined to be 85% for the compound **3f** by HPLC analysis on a Daicel Chiralpak IA column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.4 min, τ_{minor} = 20.5 min. The enantiomeric excess was determined to be 22% for the compound *anti*-**3f** by HPLC analysis on a Daicel Chiralpak IA column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.5 min, τ_{minor} = 17.1 min. $[\alpha]_D^{25}$= +18.7 (*c* = 0.81, $CHCl_3$, 5.2:1 mixture of diastereoisomers **3f** and **3f**'; ee_{3f} = 85%, ee_{3f}' = 22%). HRMS *calcd* for ($C_{23}H_{19}Br_2NO_4$+Na): 489.0426, found 489.0446.

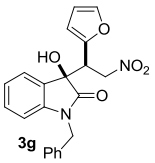
^{1}H NMR (400 MHz, $CDCl_3$, 5.2:1 mixture of diastereoisomers **3f** and *anti*-**3f**): δ 4.61 (d, 1H$_{maj}$, J_1 = 16.05 Hz), 4.68-4.76 (m, , 1H$_{maj}$, 1H$_{min}$), 4.82-4.91 (m, , 1H$_{min}$), 5.03-5.15 (m, 2H$_{maj}$, 1H$_{min}$), 5.16-5.25 (m, 1H$_{min}$), 5.44-5.52 (m, , 1H$_{min}$), 5.73 (dd, 1H$_{maj}$, J_1 = 13.84 Hz, J_2 = 4.18 Hz), 6.39-6.47 (m, , 1H$_{maj}$), 6.54-6.58 (m, , 1H$_{min}$), 6.67 (d, 1H$_{maj}$, J_1 = 7.90 Hz), 6.89 (dt, 1H$_{maj}$, J_t = 7.60 Hz, J_d = 0.82 Hz), 6.95-6.99 (m, 1H$_{min}$), 7.08-

7.12 (m, 2H$_{maj}$), 7.14-7.39 (m, 7H$_{maj}$, 10H$_{min}$), 7.50 (dd, 1H$_{maj}$, J_1 = 8.00 Hz, J_2 = 1.40 Hz), 7.70-7.74 (m, 1H$_{min}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 5.2:1 mixture of diastereoisomers **3f** and *anti*-**3f**) δ 43.9, 47.6, 53.4, 74.8, 76.9, 109.8, 123.1, 124.9, 126.9, 127.5, 127.8, 128.9, 129.8, 130.5, 133.3, 134.1, 134.8, 142.4, 176.6 ppm.

(R)-1-benzyl-3-((S)-1-(furan-2-yl)-2-nitroethyl)-3-hydroxyindolin-2-one (3g – Table **2**, entry **7)**

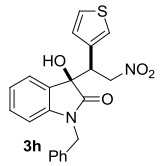


The reaction was carried out following the general procedure to furnish the crude products as a 3.6:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.34 ppm (dd), δ_{minor} 4.46 ppm (dd). $R_{f\,maj}$ = 0.25, $R_{f\,min}$ = 0.29 (dichloromethane/diethyl ether = 98/2). The title compound was isolated by flash column chromatography as a 11:1 mixture of diastereoisomers (dichloromethane/diethyl ether 98/2, R_f = 0.25) in 60% yield (45.0 mg, white solid, mp = 56.0– 57.0 ºC). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IB column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.1 min, τ_{minor} = 13.2 min. $[\alpha]_D^{25}$= -22.4 (c = 0.50, $CHCl_3$, 96% ee). HRMS *calcd* for ($C_{21}H_{18}N_2O_5$+Na): 401.1113, found 401.1107. ^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer): δ 3.24 (bs, 1H), 4.34 (dd, 1H, J_1 = 10.61 Hz, J_2 = 4.25 Hz), 4.60 (d, 1H, J = 15.74 Hz), 4.92 (d, 1H, J = 15.74 Hz), 5.05 (dd, 1H, J_1 = 13.33 Hz, J_2 = 10.59 Hz), 5.48 (dd, 1H, J_1 = 13.31 Hz, J_2 = 4.05 Hz), 6.04 (d, 1H, J = 3.31 Hz), 6.19 (dd, 1H, J_1 = 3.31 Hz, J_2 = 1.83 Hz), 6.63 (d, 1H, J = 8.06 Hz), 7.02-7.11 (m, 4H), 7.15 (dd, 1H, J_1 = 1.83 Hz, J_2 = 0.75 Hz), 7.20-7.29 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, major diastereoisomer): δ 44.4, 45.3, 73.9, 77.2, 110.2, 110.3, 110.8, 123.6, 124.8, 127.5, 127.7, 128.1, 129.1, 130.7, 135.0, 142.9, 143.1, 147.9, 176.6 ppm.



The **minor diastereoisomer** *anti*-**3g** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.29) in 16% yield (12.0 mg, yellow solid). The enantiomeric excess was determined to be 66% by HPLC analysis on a Daicel Chiralpak IC column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.2 min, τ_{minor} = 9.0 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.99 (bs, 1H), 4.44 (dd, 1H, J_1= 10.21 Hz, J_2 = 5.93 Hz), 4.56-4.66 (m, 1H), 4.87-4.95 (m, 1H), 5.18-5.24 (m, 1H), 5.25-5.31 (m, 1H), 5.89 (d, 1H, J = 3.16 Hz), 6.08 (dd, 1H, J_1= 3.30 Hz, J_2 = 1.85 Hz), 6.60 (d, 1H, J = 7.86 Hz), 7.01-7.16 (m, 4H), 7.19 (dt, 1H, J_t= 7.74 Hz, J_d = 1.17 Hz), 7.26-7.30 (m, 3H), 7.39-7.43 (m, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ44.0, 45.0, 73.0, 76.1, 109.4, 109.6, 110.3, 123.4, 123.9, 127.4, 127.8, 128.7, 130.5, 134.8, 142.5, 147.5, 175.4ppm.

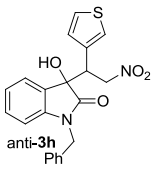
(R)-1-benzyl-3-hydroxy-3-((S)-2-nitro-1-(thiophen-3-yl)ethyl)indolin-2-one (3h – Table **2**, entry **8)**



The reaction was carried out following the general procedure to furnish the crude products as a 2.7:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.48 ppm (d), δ_{minor} 6.43 ppm (d). $R_{f\,maj}$ = 0.27, $R_{f\,min}$ = 0.31 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.27) in 62% yield (49.0 mg, yellow solid, mp = 66.0–68.0 ºC.). The enantiomeric excess was determined to be 95% by HPLC analysis on a Daicel Chiralpak IA column: 75:25 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 215, 254 nm: τ_{major} = 16.5 min, τ_{minor} = 20.0 min. $[\alpha]_D^{26}$= -49.8 (c = 0.85, $CHCl_3$, 95% ee). HRMS *calcd* for ($C_{21}H_{18}N_2O_4S$+Na): 417.0885, found 417.0865.

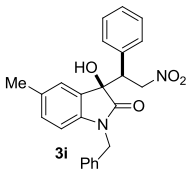
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.78 (bs, 1H), 4.39 (d, 1H, J = 15.95 Hz), 4.48 (dd, 1H, J_1 = 10.58 Hz, J_2 = 4.40 Hz), 4.86-4.99 (m, 2H), 5.52 (dd, 1H, J_1 = 12.88 Hz, J_2 = 4.40 Hz), 6.48 (dd, 1H, J_1 = 4.98 Hz, J_2 = 1.19

Hz), 6.53 (d, 1H, J = 7.90 Hz), 6.70-6.76 (m, 2H), 6.87 (dd, 1H, J_1 = 2.93 Hz, J_2 = 1.19 Hz), 7.06-7.14 (m, 2H), 7.18-7.25 (m, 4H), 7.30-7.33 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.3, 47.3, 76.3, 77.9, 110.5, 123.6, 124.9, 125.4, 126.3, 127.0, 127.4, 127.5, 127.9, 129.1, 130.9, 134.2, 134.8, 143.4, 176.9 ppm.



The **minor diastereoisomer** *anti*-**3h** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.31) in 11% yield (8.5 mg, yellow solid). The enantiomeric excess was determined to be 59% by HPLC analysis on a Daicel Chiralpak IC column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 21.4 min, τ_{minor} = 22.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (bs, 1H), 4.43–4.58 (m, 2H), 4.73-4.82 (m, 1H), 5.22-5.32 (m, 1H), 5.41-5.51 (m, 1H), 6.43-6.50 (m, 1H), 6.55 (dd, 1H, J_1 = 4.95 Hz, J_2 = 1.22 Hz), 6.80-6.85 (m, 1H, J_1 = 3.30 Hz, J_2 = 1.85 Hz), 6.60 (d, 1H, J = 7.86 Hz), 7.01-7.16 (m, 4H), 7.19 (dt, 1H), 6.86-6.94 (m, 1H), 6.99 (dd, 1H, J_1 = 5.04 Hz, J_2 = 2.97 Hz), 7.09-7.19 (m, 2H), 7.20-7.25 (m, 1H), 7.50-7.55 (m, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 43.8, 46.3, 74.4, 109.7, 123.4, 123.5, 124.0, 125.5, 127.0, 127.5, 127.6, 128.7, 129.1, 130.5, 133.7, 134.6, 142.5, 175.6 ppm.

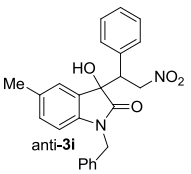
(R)-1-benzyl-3-hydroxy-5-methyl-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3i – Table **2**, entry **9)**



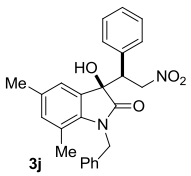
The reaction was carried out following the general procedure to furnish the crude products as a 3.3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.34 ppm (d), δ_{minor} 6.29 ppm (d). $R_{f\,maj}$ = 0.26, $R_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated by flash column chromatography as a single diastereoisomer (R_f = 0.26 dichloromethane/diethyl ether 98/2) in 58% yield (46.5 mg, yellow solid, mp = 85.0–86.0 ºC.). The enantiomeric excess was determined to be 95% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 9.9 min, τ_{minor} = 24.7 min. $[\alpha]_D^{25}$= -93.3 (c = 0.47, $CHCl_3$, 95% ee). HRMS *calcd* for ($C_{24}H_{22}N_2O_4$+Na): 425.1477, found 425.1476.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.40 (bs, 1H), 4.22-4.33 (m, 2H), 4.86 (d, 1H, J = 15.87 Hz), 5.05 (dd, 1H, J_1 = 12.98 Hz, J_2 = 10.81 Hz), 5.54 (dd, 1H, J_1 = 12.98 Hz, J_2 = 4.30 Hz), 6.34 (d, 1H, J = 7.96 Hz), 6.53 (d, 1H, J = 7.29 Hz), 6.87 (d, 2H, J = 7.29 Hz), 7.01 (d, 1H, J = 8.13 Hz), 7.08-7.19 (m, 6H), 7.22-7.28 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 44.3, 51.9, 76.0, 78.4, 110.3, 125.7, 126.8, 127.2, 127.7, 128.8, 128.9, 129.0, 129.4, 131.2, 133.3, 133.6, 134.8, 141.0, 176.7 ppm.

The **minor diastereoisomer** *anti*-**3i** was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.30) in 13% yield (10.0 mg, yellow solid). The enantiomeric excess was determined to be 63% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.8 min, τ_{minor} = 20.5 min.



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (σ, 3H), 2.94 (bs, 1H), 4.32 (δδ, 1H, J_1 = 9.62 Hz, J_2 = 5.01 Hz), 4.44–4.54 (m, 1H), 4.76 (d, 1H, J = 15.89 Hz), 5.27-5.38 (m, 1H), 5.47-5.59 (m, 1H), 6.27 (d, 1H, J = 7.94 Hz), 6.78-6.85 (m, 2H), 6.88-6.98 (m, 3H), 7.00-7.08 (m, 2H), 7.10-7.24 (m, 4H), 7.36 (bs, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 43.8, 50.8, 74.3, 109.4, 124.4, 127.0, 127.5, 127.9, 128.3, 128.6, 128.83, 128.86, 130.6, 133.0, 133.2, 134.6, 139.9, 175.6 ppm

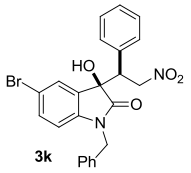


(R)-1-benzyl-3-hydroxy-5,7-dimethyl-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3j – Table **2**, entry **10)**

The reaction was carried out following the general procedure to furnish the crude products as a 2.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 2.33 ppm (s), δ_{minor} 2.27 ppm (d). $R_{f\,maj}$ = 0.24, $R_{f\,min}$ = 0.29 (dichloromethane/diethyl ether = 99/1). The title compound was isolated by flash column chromatography as a 9:1 mixture of diastereoisomers (R_f = 0.24 dichloromethane/diethyl ether 99/1) in 59% yield (49.0 mg, yellow solid, mp = 109.0–112.0 ºC.). The enantiomeric excess was determined to be 87% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 7.6 min, τ_{minor} = 19.5 min. $[\alpha]_D^{25}$= -53.0 (c = 0.76, $CHCl_3$, 87% ee). HRMS *calcd* for ($C_{25}H_{24}N_2O_4$+Na): 439.1634, found 439.1631.

^{1}H NMR (400 MHz, $CDCl_3$, major diasteroisomer): δ 1.97 (s, 3H), 2.33 (s, 3H), 3.46 (bs, 1H), 4.25 (dd, 1H, J_1 = 10.95 Hz, J_2 = 4.23 Hz), 4.65 (d, 1H, J = 17.2 Hz), 4.97 (d, 1H, J = 17.2 Hz), 5.05 (dd, 1H, J_1 = 12.88 Hz, J_2 = 10.80 Hz), 5.53, (dd, 1H, J_1 = 13.06 Hz, J_2 = 4.23 Hz), 6.42 (d, 2H, J = 7.10 Hz), 6.82-6.90 (m, 3H), 7.01 (s, 1H), 7.07-7.2 (m, 5H), 7.26-7.34 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major diasteroisomer): δ 18.7, 21.2, 45.5, 52.1, 76.1, 77.5, 120.9, 123.6, 125.4, 127.3, 128.1, 128.8, 128.9, 129.1, 129.5, 133.3, 133.8, 135.3, 136.9, 139.1, 177.7 ppm.

(R)-1-benzyl-5-bromo-3-hydroxy-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3k – Table **2**, entry **11)**

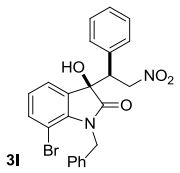


The reaction was carried out following the general procedure to furnish the crude products as a 2.6:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.32 ppm (d), δ_{minor} 6.23 ppm (d). $R_{f\,maj}$ = 0.29, $R_{f\,min}$ = 0.24 (dichloromethane/diethyl ether = 99/1). The title compound was isolated by flash column chromatography as a single diastereoisomer (dichloromethane/diethyl ether 99/1, R_f = 0.24) in 61% yield (59.0 mg, colourless solid). The enantiomeric excess was determined to be 88% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 6.0 min, τ_{minor} = 10.8 min. $[\alpha]_D^{26}$= -64.9 (c = 0.99, $CHCl_3$, 88% ee). HRMS *calcd* for ($C_{23}H_{19}BrN_2O_4$+Na): 489.0426, found 489.0439.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 1H), 4.23-4.35 (m, 2H), 4.85 (d, 1H, J = 16.05 Hz), 5.04 (dd, 1H, J_1 = 13.15 Hz, J_2 = 10.77 Hz), 5.53 (dd, 1H, J_1 = 13.16 Hz, J_2 = 4.43 Hz), 6.33 (d, 1H, J = 8.55 Hz), 6.51-6.57 (m, 2H), 6.89-6.94 (m, 2H), 7.09-7.21 (m, 5H), 7.26-7.37 (m, 2H), 7.37-7.41 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.0, 51.3, 75.3, 78.0, 111.6, 116.0, 126.5, 127.6, 127.9, 128.73, 128.78, 128.8, 129.0, 129.1, 132.9, 133.3, 133.8, 141.9, 176.2 ppm.

The relative and absolute configuration for **3k** was unambiguously inferred by anomalous dispersion X-ray crystallographic analysis, see X-ray Crystallographic Data section.

(R)-1-benzyl-7-bromo-3-hydroxy-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3l – Table **2**, entry **12)**

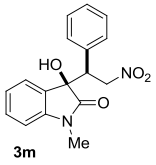


The reaction was carried out following the general procedure to furnish the crude products as a 2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.22 ppm (dd), δ_{minor} 4.33 ppm (dd). $R_{f\ maj}$ = 0.26, $R_{f\ min}$ = 0.30 (dichloromethane/diethyl ether = 99/1). The title compound was isolated by flash column chromatography as an 11/1 diastereomeric mixture (dichloromethane/diethyl ether 99/1, R_f = 0.26) in 46% yield (42.5 mg, yellow solid). The enantiomeric excess was determined to be 73% by HPLC

analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 7.6 min, τ_{minor} = 19.5 min. $[\alpha]_D^{24}$= +6.1 (c = 1.22, $CHCl_3$, 73% ee). HRMS *calcd* for ($C_{23}H_{19}BrN_2O_4$+Na): 489.0426, found 489.0430.

^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ 3.30 (bs, 1H), 4.23 (dd, 1H, J_1 = 10.55 Hz, J_2 = 4.41 Hz), 4.97-5.14 (m, 3H), 5.51 (dd, 1H, J_1 = 13.13 Hz, J_2 = 4.41 Hz), 6.58-6.65 (m, 2H), 6.85-6.91 (m, 2H), 6.98-7.75 (m, 1H), 7.15-7.26 (m, 5H), 7.29-7.37 (m, 2H), 7.45 (dd, 1H, J_1 = 8.21 Hz, J_2 = 1.19 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major distereoisomer): δ 45.2, 51.9, 75.6, 77.4, 103.6, 124.3, 124.7, 126.1, 127.3, 128.9, 129.1, 129.3, 130.6, 133.2, 136.7, 136.9, 141.0, 144.5, 177.7 ppm.

(R)-3-hydroxy-1-methyl-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3m – Table **2**, entry **13)**



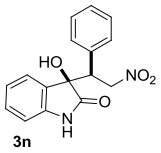
3m

The reaction was carried out following the general procedure to furnish the crude products as a 3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.08 ppm (dd), δ_{minor} 4.25 ppm (dd). $R_{f\,maj}$ = 0.26, $R_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 95/5). The title compound was isolated by flash column chromatography as a 9:1 diastereoisomers mixture (dichloromethane/diethyl ether 95/5, R_f = 0.26) in 48% yield (30 mg, yellow solid). The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 8.2 min, τ_{minor} = 12.0 min. $[\alpha]_D^{24}$= -18.7 (c = 1.23, $CHCl_3$, 87% ee). HRMS *calcd* for ($C_{17}H_{16}N_2O_4$+Na): 335.1008, found 335.1016.

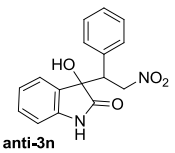
^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer): δ 2.81 (s, 3H), 3.67 (bs, 1H), 4.08 (dd, 1H, J_1 = 10.86 Hz, J_2 = 4.58 Hz), 5.02 (dd, 1H, J_1 = 10.68 Hz, J_2 = 13.27 Hz), 5.52 (dd, 1H, J_1 = 13.27 Hz, J_2 = 4.43 Hz), 6.62 (d, 1H, J = 7.89 Hz), 6.82-6.87 (m, 2H), 7.06-7.13 (m, 4H), 7.14-7.20 (m, 1H), 7.29-7.36 (m, 1H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer): δ 26.2, 51.6, 75.3, 78.5, 108.9, 123.4, 125.0, 127.4, 128.4, 128.7, 129.0, 130.8, 133.6, 143.7, 176.8 ppm.

(R)-3-hydroxy-3-((S)-2-nitro-1-phenylethyl)indolin-2-one (3n)

The reaction was carried out following the general procedure to furnish the crude products as a 2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.02 ppm (dd), δ_{minor} 4.25 ppm (dd).



3n



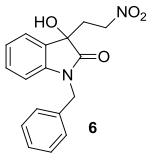
anti-3n

(**3n** – Table **2**, entry **14**). The mixture of the diastereoisomers **3n** and **anti-3n** was isolated by flash column chromatography (dichloromethane/diethyl ether = 80/20; R_f = 0.28) in 50% overall yield (30.0 mg) as a pale yellow solid. The enantiomeric excess was determined to be 66% for the compound **3n** by HPLC analysis on a Daicel Chiralpak IA column: 48.5:48.5:3 hexane/dichloromethane/i-PrOH, flow rate 1 mL/min, λ = 215, 254 nm: τ_{major} = 34.7 min, τ_{minor} = 36.8 min. The enantiomeric excess was determined to be 0% for the compound **anti-3n** by HPLC analysis on a Daicel Chiralpak IA column: 48.5:48.5:3 hexane/dichloromethane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 38.9 min, τ_{minor} = 23.3 min. $[\alpha]_D^{25}$= -0.7 (*c* = 1.46, $CHCl_3$, 2:1 mixture of diastereoisomers **3n** and **4n'**; ee_{3n} = 66%, $ee_{4n'}$ = 0%).HRMS *calcd* for ($C_{16}H_{14}N_2O_4$+Na): 321.0851, found 321.0836.

^{1}H NMR (400 MHz, $CDCl_3$, 2:1 mixture of diastereoisomers **3n** and **anti-3n**): δ 3.17-3.49 (m, $1H_{maj}$, $1H_{min}$), 4.02 (dd, $1H_{maj}$, J_1 = 10.51 Hz, J_2 = 4.42 Hz), 4.25 (dd, $1H_{min}$, J_1 = 9.91 Hz, J_2 = 4.92 Hz), 4.99 (dd, $1H_{maj}$, J_1 = 13.27 Hz, J_2 = 10.63 Hz), 5.16-5.26 (m, $1H_{min}$), 5.39-5.50 (m, $1H_{maj}$, $1H_{min}$), 6.57 (d, $1H_{min}$, J = 7.59 Hz), 6.71 (d, $1H_{maj}$, J = 7.89 Hz), 6.85-6.90 (m, $2H_{maj}$), 6.90-7.01 (m, $2H_{min}$), 7.02-7.23 (m, $4H_{maj}$, $3H_{min}$), 7.24-

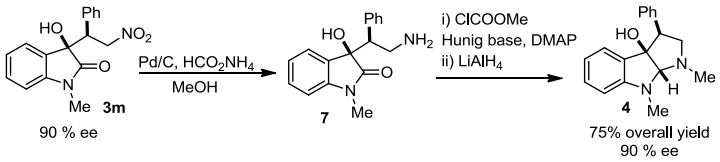
7.31 (m, 1H$_{maj}$, 1H$_{min}$), 7.37-7.61 (m, 2H$_{maj}$, 1H$_{min}$) ppm.^{13}C NMR (100 MHz, $CDCl_3$ 2:1 mixture of diastereoisomers **3n** and **anti-3n**): δ 51.1, 51.4, 74.5, 75.4, 78.1, 78.4, 110.7, 110.8, 111.0, 111.1, 123.5, 123.7, 124.6, 125.5, 127.9, 128.4, 128.5, 128.6, 128.8, 129.0, 129.3, 130.6, 130.9, 133.3, 135.5, 140.1, 140.7, 178.7, 178.9 ppm.

1-benzyl-3-hydroxy-3-(2-nitroethyl)indolin-2-one (6)



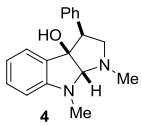
The title compound was isolated by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.26). HRMS *calcd* for ($C_{17}H_{16}N_2O_4$+Na): 335.1008, found 335.1003. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58-2.70 (m, 2H), 2.72 (bs, 1H), 4.63-4.99 (m, 4H), 6.78 (d, 1H, J = 7.61 Hz), 7.10 (dt, 1H, J_t = 7.47 Hz, J_d = 1.07 Hz), 7.24-7.44 (m, 7H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 35.1, 43.9, 69.9, 73.9, 110.0, 123.6, 123.8, 127.3, 128.0, 128.92, 128.99, 130.5, 135.0, 142.0 ppm.

I. Product Derivatisations



Synthesis of (3S,3aR,8aR)-1,8-dimethyl-3-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-ol (4)

To a stirred solution of compound **3m** (27.1 mg, 0.087 mmol) in CH_3OH (1 mL) were sequentially added Pd/C 10%, 50%wet (6 mg) and $HCOONH_4$ (38.2 mg, 0.6 mmol). The reaction mixture was refluxed 1 h, then filtered on a celite pad, the pad washed several times with CH_3OH and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with sat. Na_2CO_3, and the aqueous phase extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated affording the title compound as a yellow oil. The material obtained in this step was dissolved in dry methylene chloride (1 mL) under an argon atmosphere. To this resultant solution at 0 ºC was added Hunig's base (68 µL, 0.39 mmol, 4.5 equiv.), chloromethyl formate (27 µL, 0.34 mmol, 4 equiv.) and DMAP (4.2 mg, 0.035 mmol, 40 mol%). After the addition, the reaction was allowed to warm to room temperature and stirred over 4 h. Next, the reaction was first diluted with methylene chloride and then quenched with a saturated aqueous sodium bicarbonate solution. The aqueous layer was separated and extracted with methylene chloride (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The material obtained was dissolved in 3 mL of dry THF and $LiAlH_4$ (27 mg, 0.69 mmol, 8 eq) was added at 0 ºC. The resulting mixture was heated to reflux for 2 h and then cooled to 0 ºC. Ethyl acetate (20 mL) and saturated aqueous $NaHCO_3$ (10 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Preparative TLC (AcOEt/MeOH, 92/8) afforded 18.3 mg (75%) of the desired product **4**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94 (bs, 1H), 2.76 (s, 3H), 2.99 (s, 3H), 3.22-3.27 (m, 2H), 3.47 (dd, 1H, J_1 = 8.67 Hz, J_2 = 7.64 Hz), 4.24 (s, 1H), 6.53 (d, 1H, J = 8.02



Hz), 6.69 (dt, 1H, J_1 = 7.53 Hz, J_2 = 0.83 Hz), 6.87 (dd, 1H, J_1 = 7.48 Hz, J_2 = 0.88 Hz), 7.20 (dt, 1H, J_1 = 7.65 Hz, J_2 = 1.44 Hz), 7.31-7.42 (m, 5H) ppm. ^{13}C NMR (125 MHz,$CDCl_3$): 35.2, 41.4, 54.2, 59.3, 87.7, 100.0, 107.8, 117.7, 122.6, 127.5, 128.4, 129.7, 129.8, 131.3, 13 6.2, 151.2 ppm. The enantiomeric excess was determined to be 89% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.46 min, τ_{minor} = 5.02 min. $[\alpha]_D^{25}$= -17.4 (*c* = 0.25, $CHCl_3$, ee = 89%) HRMS *calcd* for ($C_{18}H_{20}N_2O$+H): 281.1654, found 281.1656.

J. X-ray Crystallographic Data

Single Crystal X-ray Diffraction Data for compound 3k

The relative and absolute configuration for compound **3k** was unambiguously inferred by anomalous dispersion X-ray crystallographic analysis, which established the absolute configuration of the Michael reaction as well as its *syn* stereochemical outcome. The relative and absolute configuration for all the other products of the Michael reaction was assigned by analogy, assuming a constant and homogeneous mechanism of catalysis.

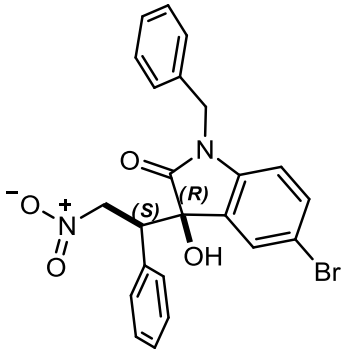
X-ray structure determinations: Crystals of compound **3k** were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature (starting from a diastereomerically pure compound, with 88% ee). The measured crystals were unstable under atmosphere conditions; they were prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation.

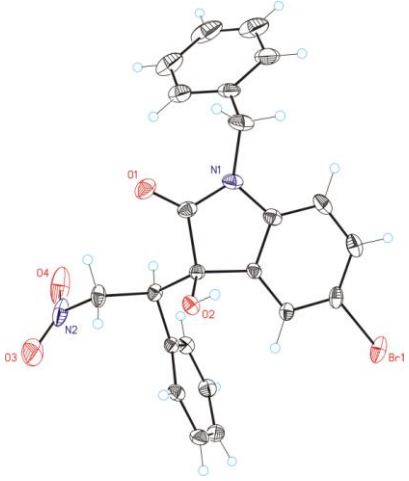
Data Collection. Measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with $Mo_{K\alpha}$ radiation, Montel mirrors and a Cryostream Plus low temperature device (*T* = 100K). Full-sphere data collection was used with ω and φ scans.

Programs used: Data collection Apex2 V2009.11 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correction TWINABS V. 2008-1 (2008).

Structure Solution. SIR2008

Structure Refinement. SHELXTL V6.14





Crystal data for **3k** at 100 K: **CCDC 85939**

Empirical formula	C23 H19 Br N2 O4	
Formula weight	467.31	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.1970(8) Å	α= 90.00 °.
	b = 7.4443(5) Å	β = 98.003(2) °.
	c = 12.4368(9) Å	γ = 90.00 °.
Volume	1026.56(13) $Å^3$	
Z	2	
Density (calculated)	1.512 Mg/m^3	
Absorption coefficient	2.035 mm^{-1}	
F(000)	476	
Crystal size	0.10 x 0.10 x 0.05 mm^3	
Theta range for data collection	1.84 to 32.65 °.	
Index ranges	-16 <=h<=16 ,-11 <=k<=11 ,-18 <=l<=18	
Reflections collected	17795	
Independent reflections	6761 [R(int) = 0.0204]	
Completeness to theta =32.65 °	0.937 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9051 and 0.8224	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6761 / 1 / 272	
Goodness-of-fit on F^2	0.696	
Final R indices [I>2sigma(I)]	R1 = 0.0288 , wR2 = 0.0841	
R indices (all data)	R1 = 0.0325 , wR2 = 0.0883	
Absolute Structure Flack parameter	x =-0.008(5)	
Largest diff. peak and hole	0.704 and -0.248 $e.Å^{-3}$	