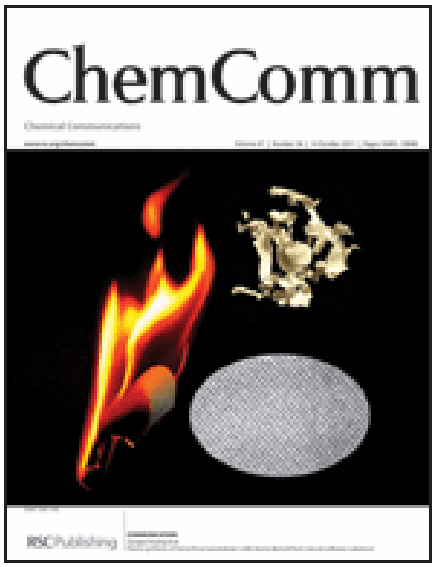

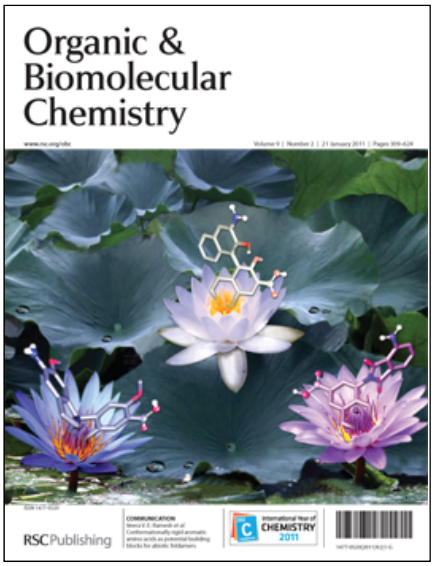

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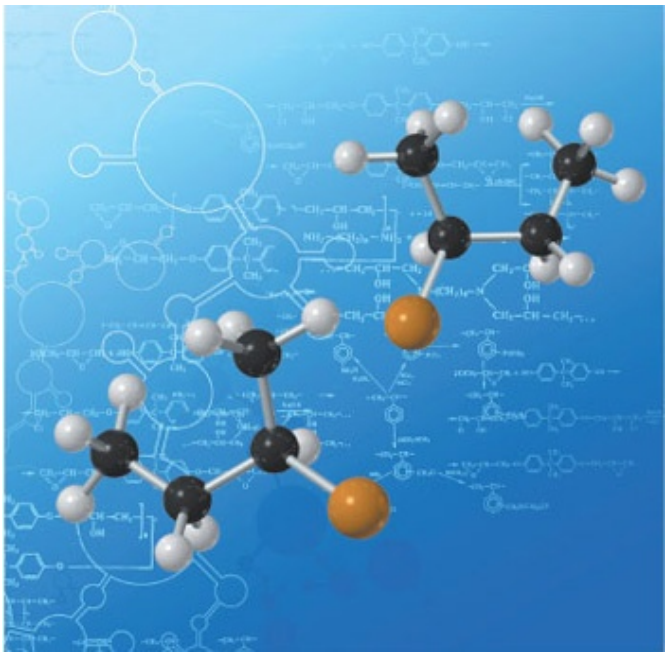

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Dioxindole in asymmetric catalytic synthesis: direct access to 3-substituted 3-hydroxy-2-oxindoles *via* 1,4-additions to nitroalkenes†‡

Michele Retini,§[a] Giulia Bergonzini[a] and Paolo Melchiorre*[ab]

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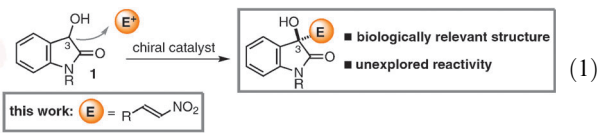
The asymmetric Michael addition of dioxindoles to β-substituted nitroalkenes is reported. The bifunctional primary amine-thiourea A, by means of a non-covalent-based mode of catalysis, secures direct access to 3-substituted 3-hydroxyoxindole derivatives with high stereocontrol.

The quest to assemble biologically relevant yet synthetically challenging target structures continues to spur the development of novel, more effective, enantioselective catalytic strategies.[1] A recent hot topic in asymmetric catalytic synthesis is the enantioselective addition of racemic 3-substituted oxindoles to a wide variety of electrophiles.[2] This is because the chemistry provides rapid access to structurally complex chiral 3,3-disubstituted oxindole frameworks.[3] These are attractive targets due to their promising biological activities[3a] and wide-ranging use as synthetic intermediates for alkaloids and drug candidates.[3b,c] In particular, the asymmetric 1,4-addition to nitroalkenes has become a benchmark for measuring progress within the field. The pioneering, independent contributions by the groups of Barbas III[4] and Shibasaki[5] on the use of *N*-Boc protected 3-alkyloxindoles have been followed by the studies of Maruoka and colleagues,[6] who exploited the high reactivity of *N*-Boc protected 3-aryloxindoles to design a base-free phase transfer reaction with nitroolefins in a water rich solvent. Very recently, Zhou and co-workers nicely expanded the scope of this reaction to include *N*-unprotected 3-aryl and 3-alkyloxindoles.[7]

Here, we report our contribution to the progress of the catalytic asymmetric 1,4-addition of 3-substituted oxindoles to nitroalkenes, demonstrating that dioxindole **1** is a competent nucleophile of this transformation. The chemistry provides unconventional access to valuable 3-substituted 3-hydroxyoxindole derivatives.[8] Key factors in our success were the ability to channel the inherently high nucleophilic power of **1** toward a productive reaction pathway and the use of a chiral primary amine thiourea as an effective H-bonding catalyst.

This research endeavour was motivated by our interest in devising a new and versatile strategy for stereoselectively accessing 3-substituted 3-hydroxyoxindole derivatives. Many biologically active compounds and natural products possess an oxindole framework with a C3-hydroxy-bearing tetrasubstituted stereogenic centre (for a selection see Fig. S1 in ESI‡).[9] Very recently, we wondered about the reactivity of dioxindole **1**.[10] The nucleophilic addition of **1** to an electrophile (*i.e.* a Michael acceptor) would directly install the valuable hydroxyl moiety at the C3-oxindole position, providing an unexplored and versatile strategy for stereoselectively accessing chiral frameworks of high synthetic value (eqn (1)).



(1)

Given this synthetic potential, it is surprising that dioxindole has never been used as a competent nucleophile in conjugate addition pathways.[10] Although the literature records no such reactions,[11] we believed that dioxindole would probably alkylate as readily as or more readily than 3-alkyloxindoles through deprotonative activation under basic conditions. This prompted us to assess the feasibility of an organocatalytic stereocontrolled 1,4-addition of **1a** (easily derived from isatin by simple reduction) to *trans*-β-nitrostyrene **2** under general base activation by chiral tertiary amines.[4,7] Extensive studies are reported in Tables S1–S9 in the ESI‡, with selected results summarised in Table 1.

Quinine and the Takemoto catalyst **B**[12] 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 and 2). Control experiments revealed that exposing a solution of dioxindole **1a** in dichloromethane (DCM) to an aerobic atmosphere in the presence of tertiary amines led to the fast and almost quantitative formation of isatide, the pinacol dimeric form of **1** (studies reported in Table S1 in the ESI‡).[13] This oxidative dimerisation pathway under basic conditions has already been reported.[13a,b] It is driven by oxidation of the enolate intermediate **I** to

[a] *ICIQ - Institute of Chemical Research of Catalonia, Av. Països Catalans 16, 43007 Tarragona, Spain. E-mail: pmelchiorre@iciq.es; Tel: +34 977920208*
[b] *ICREA - Institució Catalana de Recerca i Estudis Avançats, Pg. Lluís Companys 23, 08010 Barcelona, Spain*

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‡ Electronic supplementary information (ESI) available: Experimental, NMR and HPLC data. CCDC 859399 (**3k**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc30198a

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

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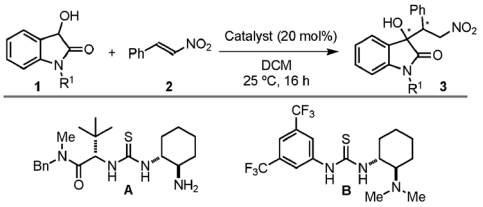
Table 1 Selected optimisation studies[a]

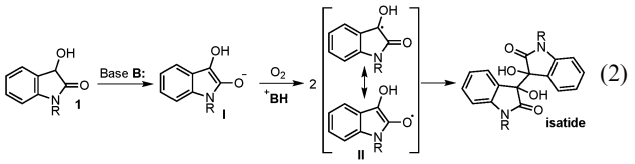


Entry	Catalyst	R^1	2 (equiv.)	Conversion [%] Isatide[b]	3	dr *anti* : *syn*	ee (%) *anti* : *syn*
1	Quinine	H (**1a**)	1.2	50	21	5 : 1	35/< 5
2	**B**	H (**1a**)	1.2	55	22	3 : 1	12/nd
3	**A**	H (**1a**)	1.2	30	54	1 : 2.1	11/57
4	**A**	Me (**1b**)	1.2	26[c]	44	1 : 2.1	35/80
5	**A**	Bn (**1c**)	1.2	15[c]	69	1 : 2.1	50/87
6	**A**	Bn (**1c**)	1[d]	9[c]	> 95	1 : 2.5	43/89
7[e]	**A**	Bn (**1c**)	1[d]	< 5[c]	35	1 : 2	30/75
8[f]	**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. Both dr and conversion were determined by ^{1}H NMR analysis of the crude reaction mixture using hexamethyl benzene as the internal standard. ee values determined by HPLC analysis. [b] The value refers to the conversion of **1a** into isatide (see eqn (2) for details). [c] With dioxindoles **1b–c**, the isatides generated *via* the oxidative coupling likely undergo a disproportionation leading to dioxindole and isatin (see ref. 13*c* and Fig. S7 and S8 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] Performed at −20 °C. [f] $[\mathbf{2}]_0$ = 0.05 M in DCM.

form an isatin radical **II**, see (eqn (2)). We reasoned that use 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 Fig. S2 in the ESI‡ for more details).

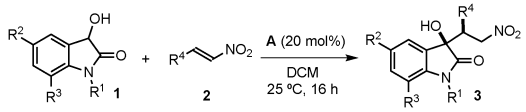
The bifunctional primary amine thiourea **A**[14] was identified as a promising catalyst. This is because it induced the formation of the adduct **3** with interesting stereoselectivity (entry 3) while preserving the integrity of dioxindole (entry 6, Table S1, ESI‡). Interestingly, catalyst **A** switched the diastereoselectivity of the process, leading to the preferential formation of the *syn*-**3** isomer. This bifunctional catalyst was selected for further optimisations.



(2)

Protecting the nitrogen of dioxindole with a methyl or a benzyl group markedly increased the enantioselectivity of the process (entries 4 and 5). Better results were obtained using a slight excess of dioxindole (1.5 equiv., entry 6). Further studies on the **A**-catalysed 1,4-addition of dioxindole **1c** to nitrostyrene **2** revealed an unusual correlation between reaction temperature and stereoselectivity (reduced ee observed at lower temperature, entry 7). This was rationalised on the basis of a self-aggregation of the catalyst,[15] which may determine the formation of monomer and dimer (or higher) aggregates characterised by different catalytic and/or stereoselective profiles. Table S11 and Fig. S6 in ESI‡ report the DOSY (diffusion ordered spectroscopy) and dilution spectroscopic NMR experiments that we carried out to gain insights into the self-association of the catalyst **A**. These investigations have confirmed that the diffusion coefficient of catalyst **A** significantly decreases upon increasing its concentration. This gave us the idea of using a more diluted reaction system, which generally favours a catalyst monomeric form. Using a $[\mathbf{2}]_0$ = 0.05 M in DCM resulted in a higher level of both diastereo- and enantio-selectivity (4 : 1 dr, 94% ee, entry 8). These conditions were selected to examine the scope of the Michael addition by evaluating a variety of nitroalkenes (Table 2, entries 1–8). Different substituents at the aromatic moiety of β-nitrostyrene derivatives were well-tolerated, regardless of their electronic properties. The corresponding adducts **3** were obtained in good to high yield and *syn* diastereoselectivity with very high control over the absolute stereochemistry (ee up to 96%). As a limitation of the system, aliphatic nitroalkenes did not react under the described conditions. A series of dioxindole derivatives bearing different substituents at the C5 and C7 positions proved to be competent nucleophiles of the conjugate addition to nitrostyrene (entries 9–12). The presence of a different substituent at the dioxindole nitrogen atom (*i.e.* a methyl group, entry 13) was well-tolerated, while the absence of a substituent slightly affected the efficiency of the catalytic system (entry 14). Importantly, for most of the products **3** a simple flash chromatography on silica gel afforded the major *syn* adduct as a single diastereoisomer and in synthetically useful chemical yield. Crystals from bromide **3k** were suitable for anomalous dispersion X-ray analysis, which established the absolute configuration of the Michael reaction as well as its *syn* stereochemical outcome.

Table 2 Addition of dioxindole derivatives to nitroalkenes[a]



Entry	R^1	R^2	R^3	R^4	3	dr	Yield[b] (%)	ee[c] (%)
1	Bn	H	H	Ph	**a**	4 : 1	91 (69)	94
2	Bn	H	H	4-MeO–C_6H_4	**b**	4 : 1	98 (75)	93
3	Bn	H	H	4-Me–C_6H_4	**c**	4 : 1	96 (74)	94
4	Bn	H	H	4-CF_3–C_6H_4	**d**	3.2 : 1	78 (56)	90
5	Bn	H	H	4-Cl–C_6H_4	**e**	3.2 : 1	80 (60)	84
6	Bn	H	H	2-Br–C_6H_4	**f**	4 : 1	60	85
7	Bn	H	H	Furan-2-yl	**g**	3.6 : 1	94 (60)	96
8	Bn	H	H	Thiophen-3-yl	**h**	2.7 : 1	89 (62)	95
9	Bn	Me	H	Ph	**i**	3.3 : 1	78 (58)	95
10	Bn	Me	Me	Ph	**j**	2.8 : 1	78 (59)	87
11	Bn	Br	H	Ph	**k**	2.8 : 1	76 (61)	88
12	Bn	H	Br	Ph	**l**	2 : 1	75 (46)	73
13	Me	H	H	Ph	**m**	3 : 1	73 (48)	90
14	H	H	H	Ph	**n**	2 : 1	50	66

[a] Reactions performed on a 0.2 mmol scale using 20 mol% of catalyst **A**, 1.5 equiv. of dioxindoles and $[\mathbf{2}]_0$ = 0.05 M in DCM at rt over 16 h. [b] The total yield of the isolated products is given; the values between brackets refer to the yield of the isolated diastereomerically pure compounds *syn*-**3**, which can easily be separated by standard chromatography on silica gel. [c] ee values refer to the major *syn* diastereoisomer **3**.

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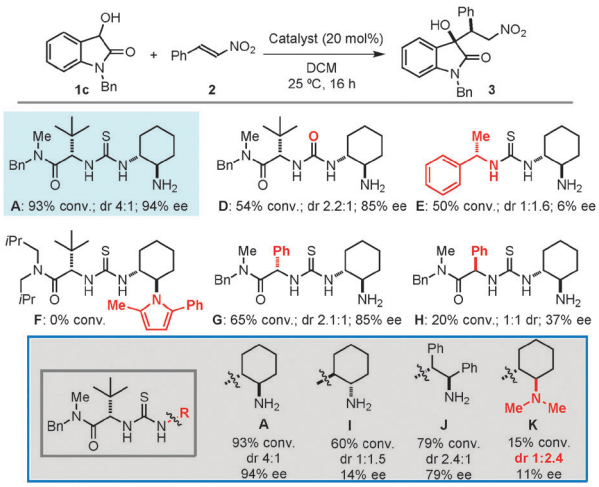
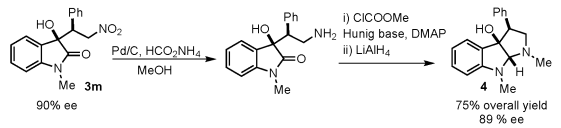


Scheme 1 Catalyst structure/reactivity and stereoselectivity correlation studies. Reaction conditions: 20 mol% of the catalyst, 1.5 equiv. of **1c**, $[\mathbf{2}]_0$ = 0.05 M in DCM, 25 °C, 16 hours reaction time.

The straightforward preparation of compound **4**—which bears the hexahydropyrrolo[2,3-*b*]indole unit found in many natural molecules—through standard manipulations of compound **3m** testifies to the potential synthetic usefulness of this previously unexplored reactivity (eqn (3)).



(3)

We then 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. We investigated the addition of dioxindole **1c** to **2** in DCM using modified thiourea derivatives. Selected results are reported in Scheme 1, with an in depth discussion detailed in Fig. S3 in the ESI.‡ The amido-moiety and the primary 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 the three stereocentres, brought about an effective catalysis. The stereochemistry and the nature of the substituent within the amino acid part were both important for securing high stereoselectivity, while 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. It is plausible that the primary amine-thiourea catalyst **A** stabilises the enol form[16] of the dioxindole through hydrogen bonding instead of promoting the formation of an enolate intermediate. A mechanistic model to reconcile the catalyst structure/reactivity and stereoselectivity correlation studies is proposed in Fig. S4 of the ESI.‡

The asymmetric addition of dioxindoles to nitroolefins was developed. Two factors are central to the successful implementation of the chemistry: the reactivity of dioxindole, and the ability of **A** to catalyse the reaction through the cooperation of multiple weak attractive interactions with the substrates.

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