Synthetic Methods

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Dioxindole in Asymmetric Catalytic Synthesis: Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and the Preparation of Maremycin A**

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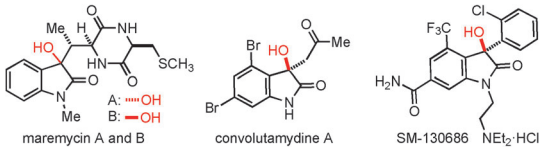
Dedicated to Professor Giuseppe Bartoli

Many biologically active compounds and natural products possess an oxindole framework with a hydroxy-bearing tetrasubstituted stereogenic center at C3 (Scheme 1).[1] It



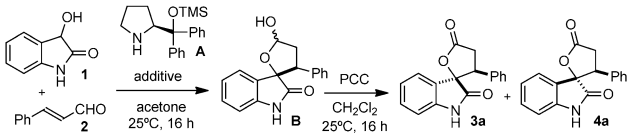
Scheme 1. Naturally occurring and biologically active 3-hydroxyoxindole derivatives.

has been shown that a defined three-dimensional spatial arrangement of this structural element greatly influences the biological activity.[1a] This observation has provided the impetus to develop highly stereoselective routes to this particular target structure.

In the last few years, different catalytic asymmetric methodologies have been reported, including metal-based and organocatalytic methods.[2] These strategies mainly relied on 1) nucleophilic additions to isatins,[3] 2) intramolecular arylation reactions,[4] and 3) the direct hydroxylation of 3-alkyl-substituted oxindoles.[5] Herein, we describe an unprecedented synthetic strategy to access 3-substituted 3-hydroxyoxindole derivatives in excellent yields and enantioselectivities. At the heart of the study is the use of dioxindole **1** and the possibility to channel its inherently high nucleophilicity toward a productive reaction pathway.

The deprotonative activation of racemic 3-alkyl- or 3-aryl-substituted oxindoles under basic conditions and the subsequent asymmetric addition to a number of electrophiles has recently been identified as a versatile strategy to stereoselectively construct tetrasubstituted carbon stereocenters at the C3 position of oxindole.[2,5,6] In contrast, dioxindole **1**, which would directly install the valuable hydroxy moiety at C3, has never been used as a competent nucleophile in analogous reaction pathways.[7] This is rather surprising, because the electron induction of the hydroxy moiety could be expected to increase the acidity of the hydrogen atom at C3 and the propensity toward an alkylation pathway. Although such reactions have not been reported,[8] we believed that dioxindole could probably alkylate equally or more readily than 3-alkyloxindoles. We thus investigated the reactivity profile of compound **1** (easily derived from isatin by simple reduction) under different reaction conditions in order to evaluate our reasoning. Extensive studies are reported in Tables S1–S5 in the Supporting Information, with selected results summarized in Table 1. Scheme 2 provides a rationalization of our efforts, which eventually allowed us to tame the inherently strong nucleophilic character of dioxindole **1**.

Table 1: Understanding the dioxindole reactivity: selected optimization studies.[a]



Entry	**A** [mol%]	Additive ([mol%])	**2** [equiv]	Yield [%][b] isatide[c]	**3a**+**4a**	*ee* [%][d] **3a**/**4a**
1	–	DABCO (5)	–	39[c]	–	–
2	–	quinine (5)	–	37[c]	–	–
3	5	–	–	11[c]	–	–
4	5	–	1.2	6	24	96/97
5	5	2-FBA (5)	1.2	<5	85	97/97
6	1	2-FBA (50)	1.2	–	99	97/97
7	0.5	2-FBA (50)	1.2	–	81	97/97
8[e]	1	2-FBA (1)	1.2	12[c]	<5	n.d.

[a] Reactions performed on a 0.05 mmol scale using 1.2 equiv of **2** with $[\mathbf{2}]_0 = 0.6$ M in acetone. All reactions afforded a poor diastereomeric distribution (ranging from 1.4:1 to 1:1). A Michael addition/hemiacetalization sequence led to a mixture of the two anomers of hemiacetal **B**. Oxidation of the crude mixture with PCC (3 equiv; CH_2Cl_2, 16 h) gave the corresponding products **3a** and **4a**. [b] Yield determined by ^{1}H NMR analysis of the crude reaction mixture with 2,5-dimethylfuran as internal standard. [c] The maximum yield for isatide is 50%, because two oxindole units are merged. [d] *ee* values of isolated compounds **3a** and **4a**, n.d. = not determined. [e] $[\mathbf{2}]_0 = 0.06$ M in acetone. DABCO = 1,4-diazabicyclo [2.2.2]octane, 2-FBA = *ortho*-fluorobenzoic acid, PCC = pyridine chlorochromate, TMS = trimethylsilyl.

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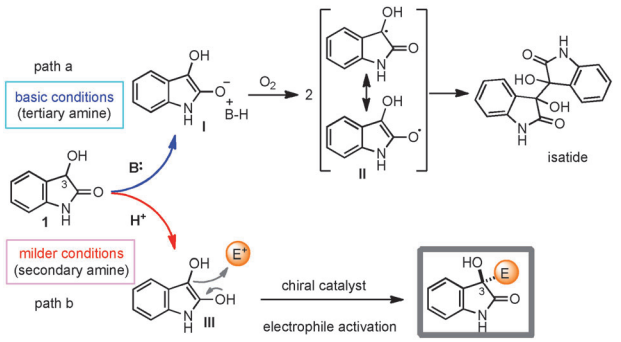


Scheme 2. Taming the dioxindole **1** reactivity: an oxidative enolate coupling in the presence of a tertiary amine and traces of oxygen leads to the formation of the dimeric isatide (path a). Milder reaction conditions (i.e., the use of a secondary amine) preserve the intrinsic high nucleophilic power of **1** (path b). B = base.

Exposure of a solution of dioxindole **1** in acetone to an aerobic atmosphere in the presence of a base (e.g., a tertiary amine such as DABCO or quinine, see entries 1 and 2 in Table 1) led to the fast and almost quantitative formation of isatide, the dimeric form of **1**.[7b,9] This oxidative dimerization pathway under basic conditions has already been reported,[9a,b] and is driven by oxidation of the enolate intermediate **I** to form an isatin radical **II** (Scheme 2, path a).[9]

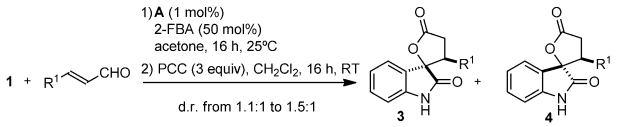
With the aim of minimizing the oxidative coupling pattern, we evaluated the compatibility of dioxindole with a milder, less basic organic catalyst. We found that the chiral secondary amine **A**[10] can indeed coexist with **1** (Table 1, entry 3),[8] which is a necessary condition to preserve the intrinsically nucleophilic character of dioxindole. This observation provided the foundation for the design of an unprecedented direct catalytic asymmetric route to enantioenriched 3-substituted 3-hydroxyoxindoles.

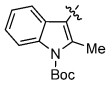
Given the established ability of catalyst **A** to promote the stereoselective conjugate addition of a variety of nucleophiles to α,β-unsaturated aldehydes[10c] under iminium ion activation, we focused on the reaction between **1** and cinnamaldehyde **2**.[11] The addition was followed by a fast hemiacetalization, which led to a mixture of the two anomers of hemiacetal **B**. Direct oxidation of the crude mixture with pyridine chlorochromate (PCC) gave the corresponding spiro oxindole γ butyrolactones[12] **3a** and **4a** with high optical purity (Table 1, entry 4). Rather unexpectedly, we observed that use of *ortho*-fluorobenzoic acid (2-FBA) as a co-catalyst induced a tremendous acceleration of the Michael addition, while completely minimizing the amount of isatide, which was formed through the oxidative pathway (Table 1, entries 5 and 6, and Tables S3 and S4). A large excess of 2-FBA (50 mol% with regard to amine **A**) allowed us to reduce the amine catalyst loading to 1 mol%, while maintaining high enantioselectivity and reactivity (the reaction reaches completion over 16 h; Table 1, entry 6). Experimental observations suggest that this uncommon reaction acceleration mainly depends on solubility issues (see Figure S1 and Table S6 in the Supporting Information). Indeed, under the reaction conditions (initial concentration of aldehyde **2** is 0.6 M in acetone) the dioxindole is only partially soluble, a condition that prevents reagent degradation.[13] The addition of an acid could probably induce the formation of the more soluble enediol intermediate **III** (Scheme 2, path b),[14] thus assuring a constant yet low amount of nucleophile in the organic solvent. Attempts to dilute the mixture to a concentration of 0.06 M in order to enhance the dioxindole solubility and avoid the large excess of 2-FBA resulted in an incomparably lower reactivity (Table 1, entry 8). For this reason, we selected the conditions reported in Table 1, entry 6 (**A**: 1 mol%; 2-FBA: 50 mol%) to evaluate the scope of the reaction.

A wide range of β-substituted enals are well-tolerated, including differently substituted aryl groups as well as heteroaryl, alkenyl, and alkyl moieties (Table 2). The spiro oxindole γ butyrolactones **3** and **4** were isolated in good to high chemical yields with high to excellent enantiomeric excess. As a limitation of the system, an ester moiety led to a moderate level of enantioselectivity (Table 2, entry 11). Although the conjugate addition proceeds with poor control over the relative configuration,[15] the possibility to easily isolate the two diastereoisomers for almost all of the adducts **3** and **4** by column chromatography testifies to the synthetic utility of the process. The absolute and relative configuration of the stereogenic centers of compound **3e** was unambiguously determined by anomalous dispersion X-ray crystallographic analysis.[16]

Further investigations of the conjugate addition reaction were carried out to delineate the scope of the nucleophilic component. Dioxindole derivatives that bear different sub-

Table 2: Aldehyde substrate scope.[a]

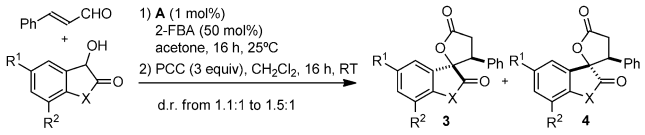


Entry	R^1	Products	Yield [%][b] total (**3**/**4**)	*ee* [%][c] **3**/**4**
1	Ph	**3a**, **4a**	98 (43/55)	97/97
2	4-MeO-C_6H_4	**3b**, **4b**	63 (24/39)	97/98
3	4-NO_2-C_6H_4	**3c**, **4c**	89 (47/42)	88/92
4	2-NO_2-C_6H_4	**3d**, **4d**	92 (43/49)	94/98
5	4-Cl-C_6H_4	**3e**, **4e**	93 (39/54)	97/98
6	2-furanyl	**3f**, **4f**	65 (30/35)	96/97
7	3-thiophenyl	**3g**, **4g**	91 (38/53)	99/99
8		**3h**, **4h**	74 (39/35)	96/97
9	CH=CHCH$_3$	**3i**, **4i**	79 (29/50)	89/97
10[d]	pentyl	**3j**, **4j**	63	98/86
11	CO_2Et	**3k**, **4k**	72	66/70

[a] Reactions performed on a 0.2 mmol scale using 1.2 equiv of enal with $[\mathbf{2}]_0 = 0.6$ M in acetone (ACS-grade reagent). All reactions afforded a poor diastereomeric distribution (ranging from 1.5:1 to 1:1). [b] The total yield of the spiro γ butyrolactones (obtained by oxidation of the crude with PCC) is reported; the values in brackets refer to the yield of isolated diastereomerically pure compounds **3** and **4**, which can be easily separated by column chromatography on silica gel. The yields reflect the degree of conversion. [c] Determined by HPLC analyses of isolated compounds **3** and **4** on chiral stationary phases. [d] 5 mol% of both the catalyst **A** and of 2-FBA was used. Boc = *tert*-butoxycarbonyl.

stituents at the C5 and C7 positions performed well under the reaction conditions (Table 3, entries 1–4), while the presence of a substituent at the nitrogen atom slightly lowered the

Table 3: Scope of dioxindole derivatives.[a]



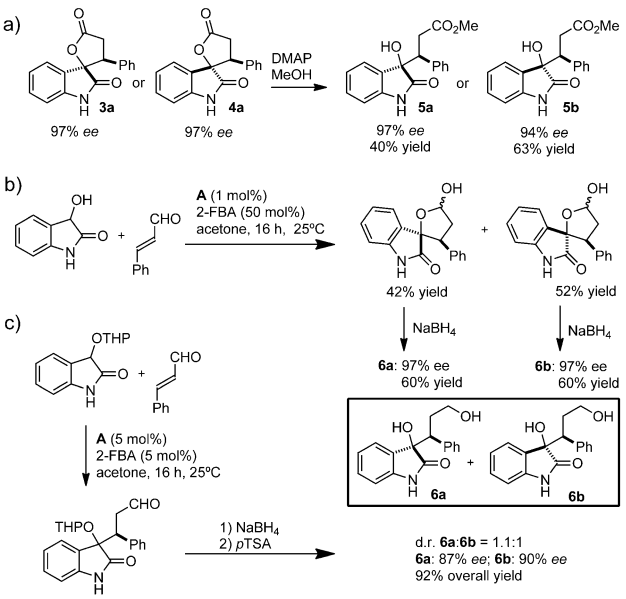
Entry	R^1	R^2	X	Product	Yield [%][b] total (**3**/**4**)	*ee* [%][c] **3**/**4**
1	Me	H	N-H	**3l**, **4l**	89 (32/57)	97/97
2	CF_3O	H	N-H	**3m**, **4m**	92 (44/48)	97/93
3	Br	H	N-H	**3n**, **4n**	64 (24/40)	96/96
4	H	Br	N-H	**3o**, **4o**	93	95/95
5[d]	H	H	N-Me	**3p**, **4p**	67 (39/28)	90/94
6[d]	H	H	N-Bn	**3q**, **4q**	92	95/95
7[d]	*t*Bu	*t*Bu	O	**3r**, **4r**	72 (30/42)	96/97

[a] Reactions carried on a 0.2 mmol scale using 1.2 equiv of cinnamaldehyde with $[\mathbf{2}]_0 = 0.6$ M in acetone. [b] The total yield of the spiro γ butyrolactones (obtained by oxidation of the crude with PCC) is reported; the values in brackets refer to the yield of the isolated diastereomerically pure compounds **3** and **4**, which can be easily separated by column chromatography on silica gel, see the Supporting Information for details. [c] Determined by HPLC analyses of the isolated compounds **3** and **4** on chiral stationary phases. [d] 5 mol% of the catalyst **A** and of 2-FBA was used.

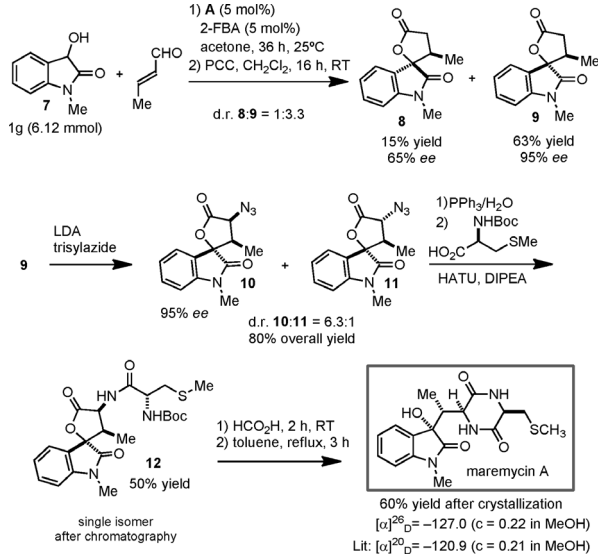
reactivity of the catalytic system, but preserved the high enantioselectivity (Table 3, entries 5 and 6). Finally, we demonstrated that a 3-hydroxy-substituted benzofuranone derivative is also a competent substrate for the present reaction (Table 3, entry 7).

The synthesized spiro oxindole γ butyrolactones **3** and **4** are valuable, complex compounds.[12] However, the central goal of our studies was to devise a novel and versatile strategy to stereoselectively access 3-substituted 3-hydroxyoxindole derivatives. Standard manipulations of the products easily led to the target compounds **5** and **6** (Scheme 3a,b). A complementary approach to 3-hydroxyoxindoles **6a**,**b** can be envisaged through the use of an O-protected dioxindole derivative as the nucleophile[7] in the Michael addition, followed by a simple reduction/deprotection sequence (Scheme 3c).

The application of a new synthetic strategy to streamline the preparation of complex natural products is generally considered an important validation of its synthetic potential and usefulness. By exploiting the dioxindole reactivity, we envisioned a straightforward access to maremycin A,[17] a diketopiperazine alkaloid that was recently isolated from the culture broth of marine *Streptomyces* species B 9173. Our synthetic plan started with the addition of N-Me dioxindole **7** to crotonaldehyde on a gram scale (Scheme 4). After oxidation with PCC, the major diastereoisomer of the spiro oxindole γ butyrolactone **9** was isolated by chromatography in good yield and with 95% *ee*. Formation of the corresponding lithium enolate and treatment with trisylazide gave azide **10**,[18a] which has the desired three-dimensional arrangement, as the major isomer (d.r. = 6.3:1). The Staudinger reaction



Scheme 3. DMAP = 4-dimethylaminopyridine, *p*TSA = *para*-toluenesulfonic acid, THP = tetrahydropyranyl.



Scheme 4. Stereocontrolled synthesis of maremycin A. DIPEA = *N*,*N*-diisopropylethylamine, HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, LDA = lithium diisopropylamide.

was followed by condensation with N-Boc-S-methyl-L-cysteine.[17b] After purification, this reaction afforded compound **12** as a single stereoisomer. Maremycin A was finally accessed after removal of the Boc protective group and formation of the diketopiperazine ring[18b] in 15% overall yield starting from dioxindole **7**.

Understanding the reactivity of dioxindole under different reaction conditions has allowed us to channel its inherently high nucleophilicity toward a productive reaction pathway. We believe that this previously unexplored reactivity will rapidly find applications in the design of other catalytic asymmetric transformations, thus opening new

opportunities to access enantioenriched 3-substituted 3-hydroxyoxindole derivatives.

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[11] The use of a tertiary amine (i.e., quinine) to promote the reaction between **1** and **2** resulted in the formation of a large amount of isatide, together with a minor product, which was identified as the corresponding aldol adduct; see Figure S2 in the Supporting Information for more details.

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[14] Both a tertiary amine and an acid are able to reduce the optical purity of enantioenriched dioxindole **1** by promoting keto–enol tautomerization, see: O. J. Sonderegger, T. Bürgi, L. K. Limbach, A. Baiker, *J. Mol. Catal. A* **2004**, *217*, 93.

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[16] CCDC 848635 (**3e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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