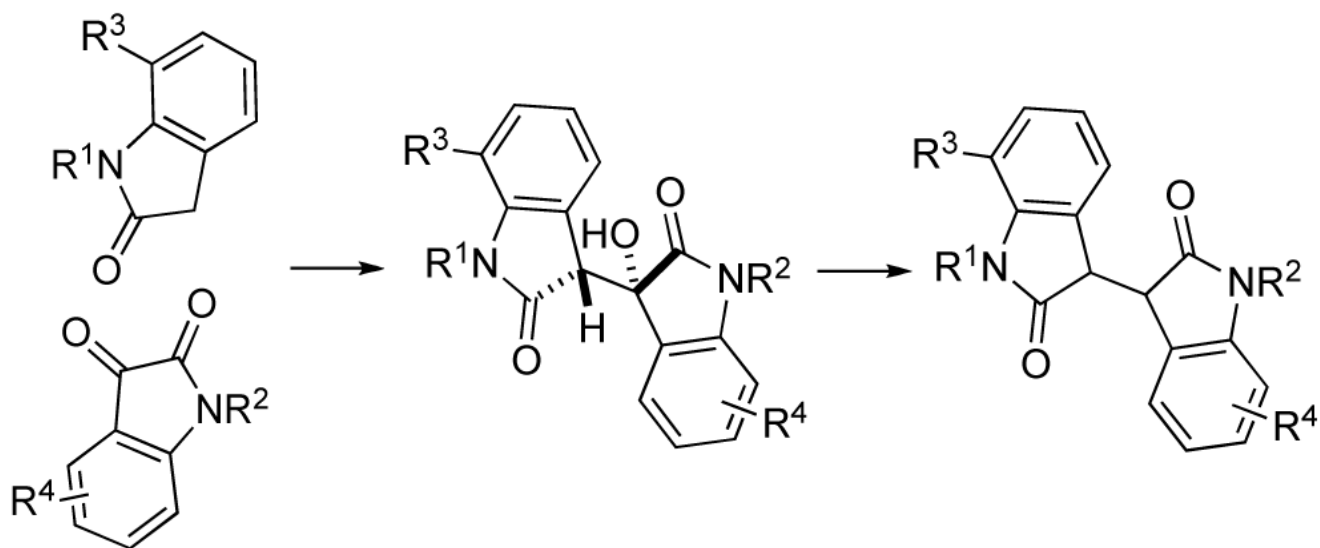# A Versatile Synthesis of Unsymmetrical 3,3′-Bioxindoles:

Stereoselective Mukaiyama Aldol Reactions of 2-Siloxyindoles with Isatins

J. Michael Ellis, **Larry E. Overman**, **Huw R. Tanner**, and **Jocelyn Wang**
Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025 leoverma@uci.edu

Abstract

A new synthesis of 3,3′-bioxindoles is reported that is well suited for the preparation of unsymmetrical structures. In the key step, 3-hydroxy-3,3′-bioxindoles are constructed by Mukaiyama aldol reaction of 2-siloxyindoles with isatins These tertiary carb inols are formed in high diastereoselectivities, with substitution at various positions of the isatin and the 2-siloxyindole being tolerated.

3,3′-Bioxindoles (**1**) are precursors to a variety of complex nitrogen heterocycles (Figure 1). In the alkaloid field, they have been used to synthesize a number of cyclotryptamine alkaloids,[1,2] exemplified by (+)-chimonanthine (**2**),[3] *meso*-calycanthine (**3**)[4] and (-)-idiospermuline (**4**).[5] 3,3′-Bioxindoles have also been employed to access heterocycles containing other polycyclic motifs, such as hexahydrodiazachrysene **5**.[6] In our laboratories, the reaction of dienolates of 3,3′-bioxindoles (**1**) with enantiomerically pure tartrate-derived dielectrophiles has been employed for the enantioselective construction of contiguous quaternary carbon stereocenters.[7,8]

3,3′-Bioxindoles (**1**) are commonly prepared by acidpromoted condensation of an isatin and an oxindole to generate an isoindigo, **8**, followed by saturation of the double bond (Scheme 1).[5–9] In ongoing studies, we required access to a series of unsymmetrical 3,3′-bioxindoles (**1**) having variation in both the nitrogen protecting group and the substituents on the two aromatic rings.[10] As some of the substituents are acid sensitive, the classical sequence illustrated in Scheme 1 was not viable. We report herein that the Mukaiyama aldol reaction[11] between 2-siloxyindoles[12] and isatins provides access to a variety of 3-

hydroxy-3,3′-bioxindoles,[13] intermediates that are readily converted to 3,3′-bioxindoles. We also disclose that the aldol addition occurs with high stereoselectivity to preferentially generate the *syn* aldol stereoisomer.

Our initial studies focused on the union of (2-(trimethylsilyl)ethoxy)methyl (SEM)-protected oxindole **9** and 4-vinylisatin **10** (Scheme 2). Addition of the lithium enolate of oxindole **9** to isatin **10** generated aldol adduct **11a** and its epimer (3:1 dr, *syn*:*anti*);[14] however, the yield was low. In contrast, Mukaiyama aldol reaction of the 2-siloxyindole derivative of **9** with 2 equiv of isatin **10** in the presence of excess $BF_3 \cdot OEt_2$ (8 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 7 equiv) beginning at −78 °C, then warming to −50 °C, yielded aldol adduct **11a** in 78% yield and high diastereoselectivity (>19:1 *syn*:*anti*). Further investigation revealed that the optimal conditions for this transformation involved the use of 1.0 equiv of the isatin, 2.0 equiv of $BF_3 \cdot OEt_2$, and 2.5 equiv of DTBMP at −78 to −50 °C, conditions that provided adduct **11a** in 77% yield.

The scope of this aldol reaction is illustrated by the examples summarized in Table 1. Crude 2-siloxyindoles were employed, which were isolated by adding a small volume of methanol to the silylation reaction mixture, removing volatiles under reduced pressure, extracting the resultant oil with pentane, and concentration. *N*-Methyl, *N*-benzyl, and *N*-SEM substituents were tolerated on both the oxindole and the isatin. Substitution at each position on the aromatic ring of the isatin had no adverse effect on the aldol reaction (entries 1, 4–8). Substitution at the 7-position of the oxindole was also viable (entries 1, 2, 8). Additionally, the Mukaiyama aldol reaction was effective for a substrate containing a pyridine appended to the isatin (entry 7), although the yield in this case was slightly lower. In all reactions, diastereoselectivity was high (>11:1).[15] The reactions summarized in Table 1 were carried out at various scales (0.50 mmol to 40 mmol), with the best result being observed in the largest scale reaction (entry 2). Although only oxindoles having substituents at C7 of the aromatic ring were included in this study, we anticipate that oxindoles having substituents at C4—C6 will also successfully undergo Mukaiyama aldol condensation with isatins.

The *syn* relative configuration of aldol adduct **11c** was established by single crystal X-ray analysis. [16] The pre-transition state arrangement **12** of the 2-siloxyindole and the isatin, depicted in Figure 2, would be consistent with the observed *syn* stereoselection. This orientation places the bulky silyl group away from the aromatic ring of the isatin, and also allows for some degree of π-overlap of the two aromatic moieties.[17,18]

The conversion of the aldol adducts to the corresponding 3,3′-bioxindole was best accomplished by reaction with $SOCl_2$ and diisopropylethylamine[19] to give the corresponding isoindigo, which without purification was reduced with zinc and acetic acid.[20–22] Representative examples are shown in Table 2.

In conclusion, Mukaiyama aldol reaction of 2-siloxyindoles with isatins takes place in good yield and with high stereoselectivity to give *syn* diastereomers of 3-hydroxy-3,3′-bioxindoles. These aldol products can be reduced in good yield to give the corresponding 3,3′-bioxindoles. By use of this method, a variety of substituents, including those that are acid-sensitive, can be introduced at various positions of the 3,3′-bioxindole product.

Experimental Section

Representative Procedure for Generating 2-Siloxyindole Intermediates and Their Mukaiyama Aldol Reaction with Isatins. Preparation of 3-Hydroxy-7′-methoxy-*N'*-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)-3,3′-biindoline-2,2′-dione (11b)

To a stirring solution of 7-methoxy-*N*-methyloxindole (**S5**) (6.60 g, 37.3 mmol, 1.0 equiv), triethylamine (15.6 mL, 112 mmol, 3.0 equiv) and dichloromethane (700 mL) at 0 °C was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (12.8 mL, 55.9 mmol, 1.5 equiv). The resultant solution was maintained at 0 °C for 25 min and then allowed to warm to rt. Methanol (1.5 mL, 37 mmol, 1.0 equiv) was added, and the solution was concentrated under reduced pressure (~30 mmHg). The resulting biphasic mixture was extracted with pentanes (3 × 120 mL), and the combined organic extracts were concentrated under reduced pressure to provide the corresponding 2-siloxyindole as a pale red/pink solid, which was used in the subsequent reaction without further purification.

A solution of the crude 2-siloxyindole, *N*-((2-(trimethylsilyl)ethoxy)methyl)isatin (10.4 g, 37.6 mmol, 1.01 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (19.1 g, 93.2 mmol, 2.5 equiv), and dichloromethane (630 mL) was cooled to −78 °C, and boron trifluoride diethyl ether complex (9.20 mL, 74.6 mmol, 2.0 equiv) was added dropwise. After 2 h at −78 °C, the solution was allowed to warm to −50 °C where it was maintained overnight. This solution was then poured into water (250 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 250 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated under reduced pressure to provide a brown oil. Purification of this oil by silica gel flash column chromatography (dry loaded on Celite, gradient: 1:6 EtOAc-hexanes to 1:3 EtOAc-hexanes) provided alcohol **11b** (14.8 g, 87%) as a pale brown solid: mp 129–132 °C; R_f 0.54 (1:4 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4, 1H), 7.42 (ddd, *J* = 8.8, 8.0, 7.7, 1H), 7.24 (t, *J* = 7.6, 1H), 7.02 (d, *J* = 7.7, 1H), 6.76 (d, *J* = 8.3, 1H), 6.67 (dd, *J* = 8.3, 7.7, 1H), 6.45 (br s, 1H), 5.60 (d, *J* = 7.6, 1H), 4.90 (d, *J* = 11.4, 1H), 4.82 (d, *J* = 11.4, 1H), 3.91(s, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 3.10 (ddd, *J* = 10.4, 9.9, 6.4, 1H), 3.02 (ddd, *J* = 10.4, 9.9, 6.1, 1H), 0.80–0.66 (m, 2H), −0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0 (C), 175.5 (C), 145.5 (C), 143.0 (C), 132.8 (C), 130.8 (CH), 127.5 (C), 124.5 (CH), 124.1 (C), 123.9 (CH), 123.1 (CH), 116.6 (CH), 112.8 (CH), 110.2 (CH), 77.4 (C), 69.2 (CH_2), 65.6 (CH_2), 55.8 (CH_3), 49.3 (CH), 29.8 (CH_3), 17.5 (CH_2), −1.3 (CH_3); IR (film) 3365, 2952, 1733, 1713, 1615 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{24}H_{30}N_2NaO_5Si$: 477.1822; found: 477.1823.

Representative Procedure for Converting Aldol Adducts to 3,3′-Bioxindoles. Preparation of 7′-Methoxy-*N'*-methyl-*N*-(2-(trimethylsilyl)ethoxymethyl)-3,3′-dihydroisoindigo (13a)

To a solution of tertiary alcohol **11b** (14.8 g, 32.5 mmol, 1.0 equiv) and dichloromethane (275 mL) at 0 °C was added over 5 min diisopropylethylamine (17.0 mL, 97.5 mmol, 3.0 equiv) and then freshly distilled thionyl chloride (2.85 mL, 39.0 mmol, 1.2 equiv). The resulting solution was maintained for 25 min at 0 °C, before being allowed to warm to rt where it was maintained for 45 min. The reaction mixture was then poured into a saturated aqueous solution of sodium hydrogen carbonate (150 mL). The aqueous layer was separated and extracted with dichloromethane (4 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure to yield a brown oil that was used without further purification in the subsequent reaction.

In a separate experiment, purification of this product by silica gel flash column chromatography (1:9 EtOAc-hexanes) gave the corresponding isoindigo **S20** as a dark burgundy solid: mp 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, *J* = 8.0, 1H), 8.73 (m, 1H), 7.36 (td, *J* = 7.7, 0.9, 1H), 7.09 (d, *J* = 7.5, 1H), 7.01 (d, *J* = 7.8, 1H), 6.96 (m, 2H), 5.24 (s, 2H), 3.87 (s, 3H),

3.62 (t, J = 8.2, 2H), 3.57 (s, 3H), 0.94 (t, J = 8.2, 2H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, CDCl3) δ 168.2, 168.0, 144.8, 143.8, 134.8, 134.3, 133.7, 133.3, 132.6, 129.6, 122.9, 122.7, 122.3, 121.6, 116.8, 109.1, 69.5, 66.2, 56.3, 29.7, 17.9, −1.4; IR (film) 2954, 1698, 1609 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{24}H_{29}N_2O_4Si$, 437.1897; found, 437.1912.

The unpurified isoindigo intermediate was dissolved in THF (315 mL) and cooled to 0 °C. To this solution was added zinc dust (12.8 g, 195 mmol, 6.0 equiv) and glacial acetic acid (3.2 mL, 180 mmol, 5.6 equiv). The resulting suspension was vigorously stirred at 0 °C for 1.5 h, and then allowed to warm to rt over 45 min. The reaction mixture was then filtered through a pad of Celite eluting with EtOAc (250 mL). The organic solution was washed with saturated aqueous sodium hydrogen carbonate (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield a black foamy oil. This residue was further purified by silica gel flash column chromatography (dry loaded on Celite, gradient: 1:4 EtOAchexanes to 1:1 EtOAc-hexanes) to afford bioxindole **13a** as a 1.6:1 mixture of epimers (12.4 g, 87%) as an orange foam: R_f 0.20 (1:1 EtOAc-hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.28 (t, J = 7.8, 0.6H), 7.12 (t, J = 7.7, 0.4H), 7.06–7.02 (m, 0.6H), 6.99 (t, J = 7.3, 0.6H), 6.93–6.80 (m, 3.0H), 6.74–6.65 (m, 0.8H), 6.55 (d, J = 7.2, 0.3H), 6.33 (m, 0.5H), 5.22 (d, J = 10.8, 0.4H), 5.18 (d, J = 10.9, 0.4H), 5.04 (s, 1.2H), 4.34 (d, J = 3.5, 0.3H), 4.25 (m, 0.8H), 4.12 (d, J = 3.3, 0.6H), 3.87–3.81 (m, 1.9H), 3.80–3.74 (m, 1.1H), 3.59–3.52 (m, 1.1H), 3.47 (s, 0.5H), 3.55–3.44 (m, 2.7H), 0.97 (m, 0.8H), 0.84 (t, J = 7.8, 1.3H), 0.10 (s, 3.2H), −0.05 (s, 5.8H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.4 (C), 175.9 (C), 175.0 (C), 174.8 (C), 145.2 (C), 145.1 (C), 143.4 (C), 142.7 (C), 132.9 (C), 131.9 (C), 128.7 (CH), 128.3 (CH), 127.1 (C), 126.3 (C), 125.5 (C), 124.4 (C), 123.4 (CH), 123.3 (CH), 122.9 (CH), 122.82 (CH), 122.78 (CH), 122.75 (CH), 116.1 (CH), 115.9 (CH), 112.6 (CH), 112.3 (CH), 109.8 (CH), 109.4 (CH), 69.8 (CH$_2$), 69.3 (CH$_2$), 66.6 (CH$_2$), 65.8 (CH$_2$), 55.74 (CH$_3$), 55.71 (CH$_3$), 46.5 (CH), 46.2 (CH), 46.0 (CH), 29.6 (CH$_3$), 29.5 (CH$_3$), 17.9 (CH$_2$), 17.6 (CH$_2$), −1.4 (CH$_3$), −1.5 (CH$_3$); IR (film) 2950, 1716, 1612 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{24}H_{31}N_2O_4Si$, 439.2053; found, 439.2048.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

References

(1)(a). Hino T. Chem. Pharm. Bull 1961;9:979–988. (b) Hino T, Yamada S. Tetrahedron Lett 1963;4:1757–1760.

(2). For a recent brief review, see: Steven A, Overman LE. Angew. Chem., Int. Ed 2007;46:5488–5508.

(3). Overman LE, Larrow JF, Stearns BA, Vance JM. Angew. Chem., Int. Ed 2000;39:213–215.

(4). Link JT, Overman LE. J. Am. Chem. Soc 1996;118:8166–8167.

(5). Overman LE, Peterson EA. Angew. Chem., Int. Ed 2003;42:2525–2528.

(6). Papageorgiou C, Borer X. Helv. Chim. Acta 1988;71:1079–1083.

(7)(a). Hoyt SB, Overman LE. Org. Lett 2000;2:3241–3244. [PubMed: 11009391] (b) Overman LE, Peterson EA. Angew. Chem., Int. Ed 2003;42:2525–2528.

(8). 3,3′-Bioxindoles have also been employed in double Steglich rearrangements for the diastereoselective synthesis of contiguous quaternary stereocenters, see: Menozzi C, Dalko PI, Cossy J. Heterocycles 2007;72:199–204.

(9). Hansen CW. Ann. Chim. (Paris) 1924:94–134.

(10)(a). Only two unsymmetrical 3,3′-bioxindoles were found by a substructure search of SciFinder conducted on 8/20/08.(b)For one example of the challenges involved in preparing unsymmetrical 3,3′-bioxindoles, see: OvermanLEPetersonEATetrahedron20035969056919

(11). Mukaiyama T, Banno K, Narasaka K. J. Am. Chem. Soc 1974;96:7503–7509.

(12)(a). Sawada T, Fuerst DE, Wood JL. Tetrahedron Lett 2003;44:4919–4921. (b) Nicolaou KC, Hao J, Reddy MV, Rao PB, Rassias G, Snyder SA, Huang X, Chen DY-K, Brenzovich WE, Giuseppone N, Giannakakou P, O'Brate A. J. Am. Chem. Soc 2004;126:12897–12906. [PubMed: 15469287] (c) Alcaraz M-L, Atkinson S, Cornwall P, Foster AC, Gill DM, Humphries LA, Keegan PS, Kemp R, Merifield E, Nixon RA, Noble AJ, O'Beirne D, Patel ZM, Perkins J, Rowan P, Sadler P, Singleton JT, Tornos J, Watts AJ, Woodland IA. Org. Process Res. Dev 2005;9:555–569. (d) Trost BM, Brennan MK. Org. Lett 2006;8:2027–2030. [PubMed: 16671773] (e) Overman LE, Shin Y. Org. Lett 2007;9:339–341. [PubMed: 17217299] (f) Poulsen TB, Bernardi L, Aleman J, Overgaard J, Jorgensen KA. J. Am. Chem. Soc 2007;129:441–449. [PubMed: 17212424] (g) Corkey BK, Toste FD. J. Am. Chem. Soc 2007;129:2764–2765. [PubMed: 17305344]

(13). For an earlier report of the utility of 2-siloxyindoles in Mukaiyama aldol reactions, see: Adhikari S, Caille S, Hanbauer M, Ngo VX, Overman LE. Org. Lett 2005;7:2795–2797. [PubMed: 15957949]

(14). Relative configuration is assigned in analogy to **11c** (vide infra).

(15). ^{1}H NMR analysis of the crude reaction product prior to purification typically showed the presence of only one stereoisomer.

(16). The relative configurations of other aldol adducts were assigned in analogy to **11c**

(17). Open transition states with the enoxysilane and carbonyl π-bonds antiperiplanar are typically proposed for Mukaiyama aldol reactions, see: Marhwald R. Chem. Rev 1999;99:1095–1120. [PubMed: 11749441]

(18). The yield of the aldol reaction was somewhat lower when the 7-position of the oxindole and the 4-position of the isatin were both substituted (entry 8). The 7-position of the oxindole and 4-position of the isatin would be in close proximity in pre-transition state ensemble **12**

(19). Heymann H, Fieser LF. J. Am. Chem. Soc 1951;73:5252–5265.

(20). Additional methods have been demonstrated for the conversion of 3-hydroxy-3,3′-bioxindoles to 3,3′-bioxindoles. These include: acid-mediated dehydration of the tertiary alcohol to afford an isoindigo that is subsequently reduced by catalytic hydrogenation,[6–9] and direct reduction with trimethylsilyl iodide[21] or HI.[22]

(21)(a). Sakai T, Miyata K, Utaka M, Takeda A. Tetrahedron Lett 1987;28:3817–3818.(b)For an example of the reduction of a 3-hydroxy-3,3′-bioxindole, see: PetersonEAPh. D. Dissertation2005University of CaliforniaIrvine

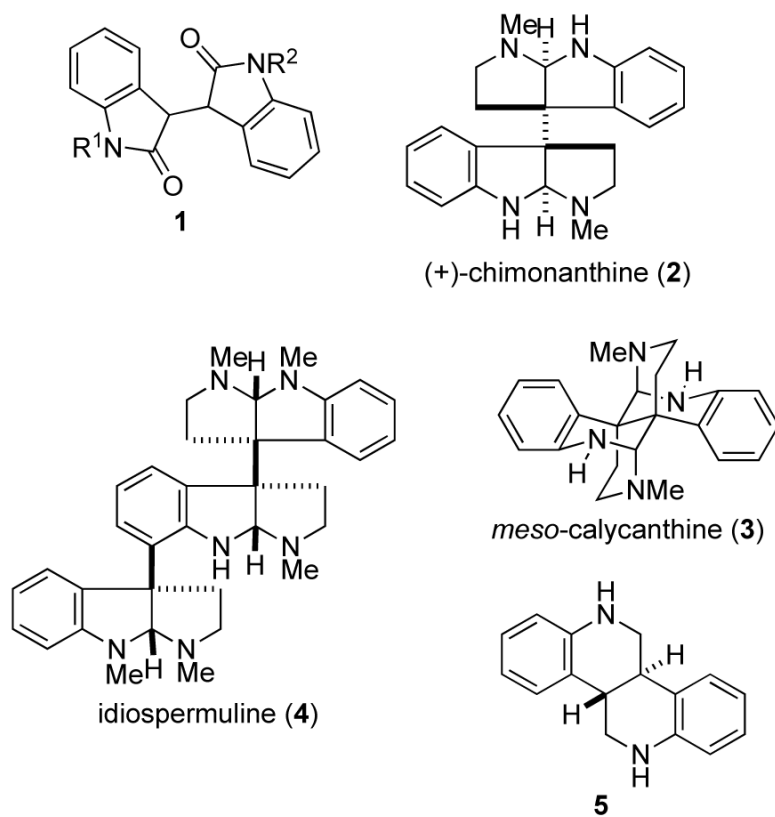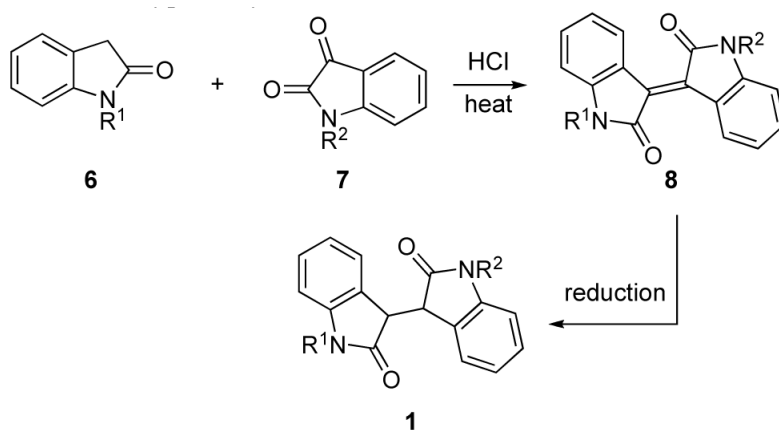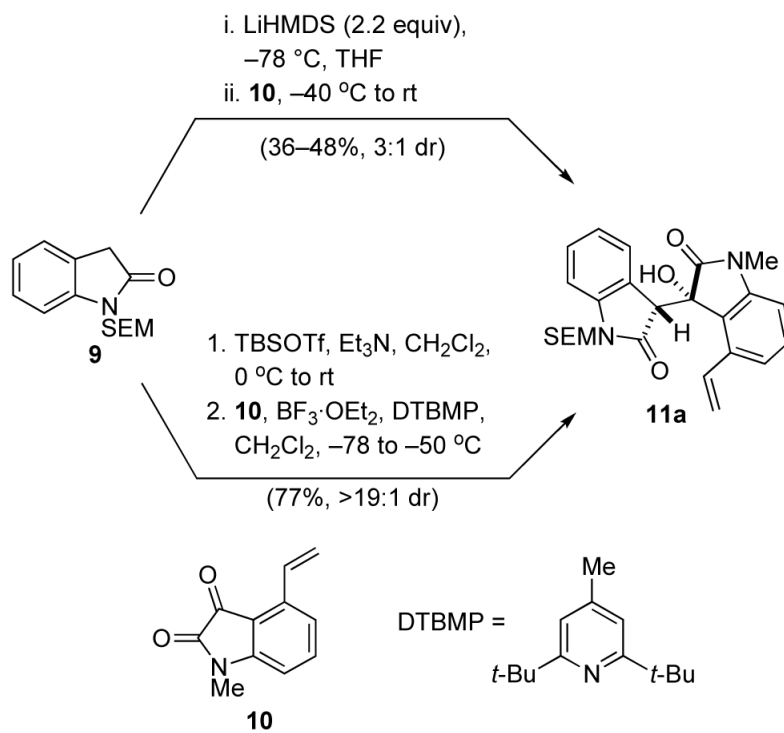(22). Metwally SAM, Younes MI, Abbas HH. Acta Chim. Hung 1989;126:591–597.

Figure 1.
3,3′-Bioxindole and representative heterocycles prepared from these intermediates

Scheme 1.
Typical Synthesis of 3,3′-Bioxindoles

i. LiHMDS (2.2 equiv),
   −78 °C, THF
ii. **10**, −40 °C to rt

(36–48%, 3:1 dr)

1. TBSOTf, Et₃N, CH₂Cl₂,
   0 °C to rt
2. **10**, BF₃·OEt₂, DTBMP,
   CH₂Cl₂, −78 to −50 °C

(77%, >19:1 dr)

9

11a

DTBMP =

10

Scheme 2.
Aldol Reaction of 2-Siloxyoxindoles with Isatins

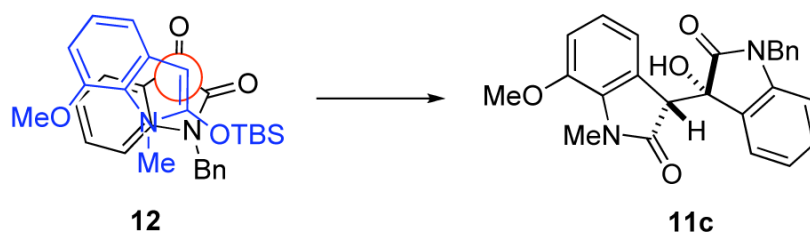**Figure 2.**
Pre-transition state model rationalizing *syn* selectivity

Table 1

Mukaiyama Aldol Reactions of 2-Siloxyindoles and Isatins[a]

11a-h
(dr >11:1)

entry	R[1]	R[3]	R[2]	R[4]	11	Yield (%)[b]
1	SEM	H	Me	4-vinyl	11a	77
2	Me	MeO	SEM	H	11b	87
3	Me	MeO	Bn	H	11c	80
4	SEM	H	Bn	H	11d	76
5	Bn	H	SEM	7-F	11e	83
6	SEM	H	Bn	6-phenyl	11f	84
7	SEM	H	Bn	5-(3-pyridyl)	11g	60
8	Me	MeO	Me	4-vinyl	11h	52[c]

[a]Conditions: Oxindole (1.0 equiv), isatin (1.0 equiv), BF$_3$·Et$_2$O (2.0 equiv), DTBMP (2.5 equiv), −78 °C to −50 °C.

[b]Yield over two steps of the aldol adduct after purification by silica gel flash column chromatography.

[c]The starting oxindole (15–20%) was recovered.

Table 2

3,3'-Bioxindole Formation from 3-Hydroxy-3,3'-Bioxindoles[a]

entry	11	R¹	R³	R²	13	R⁴	Yield (%)[b]
1	11b	Me	MeO	SEM	13a	H	87[c]
2	11c	Me	MeO	Bn	13b	H	89
3	11d	SEM	H	Bn	13c	H	85
4	11e	Bn	H	SEM	13d	7-F	79
5	11f	SEM	H	Bn	13e	6-Ph	90

[a]Conditions: step 1: **11** (1.0 equiv), SOCl2 (1.2 equiv), i-Pr2NEt (3.0 equiv), 0 °C to rt; step 2: Zn (30 equiv), AcOH (18 equiv), 0 °C to rt.

[b]Yield over two steps after purification of **13** by silica gel flash column chromatography.

[c]Reduction performed with a modified procedure: Zn (6.0 equiv), AcOH (5.6 equiv), 0 °C to rt.