Note

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DBU-mediated Diastereoselective Aldol-type Cyanomethylation of Isatins

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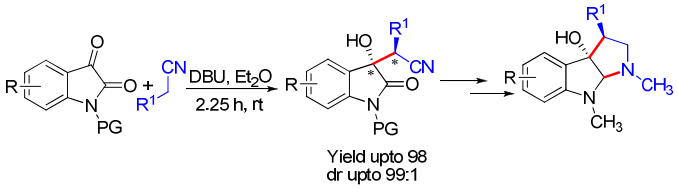
Supporting Information Placeholder

TOC GRAFIC & ABSTRACT:



An efficient, metal free approach to 3-substituted 3-hydroxy oxindole by DBU mediated highly diastereoselective addition of aryl acetonitrile to *N*-protected isatin under mild condition has been developed. The reaction proceeds smoothly to produce respective cyanomethylated adducts in good yield and excellent diastereoselectivity. Further transformation of the cyanide group allowed the synthesis of an advance intermediate of corresponding (+/-) CPC analogue. The mechanistic insight towards the aldol type cyanomethylation of *N*-trityl isatin with benzyl cyanide was obtained by DFT calculation.

Cyanoalkyls, an ubiquitous nitrogen-containing compounds, found in many molecular scaffolds of natural products and pharmaceuticals,[1] provides an easy access to many bioactive functionalities.[2] For instance, γ-amino alcohols, a functional group present in a number of neuronal uptake inhibitors,[3] can be easily synthesized through β-hydroxy cyanoalkyls. Considering its wide application, significant work has been done towards the synthesis of functional cyanoalkyls.

Specifically stereochemical addition of nitrile enolates to aldehydes has been well investigated.[4] Although addition of nitrile enolates on ketones remains relatively less explored. In case where such additions have been attempted, the reaction has been low yielding due to its reversible nature. In such transformations, the position of the equilibrium is greatly influenced by the structure of methylated nitriles as well as the carbonyl compounds.

Few decades ago, Kaiser and Hauser demonstrated that the reaction of hindered carbonyl compound with hindered α-alkali nitriles proceeded with a strained alkoxide intermediate and delivered lower yield of β-hydroxy nitrile.[5] Interestingly, it was found that addition of chelating metal such as Mg and Al cations, were helpful in shifting the equilibrium towards the product and resulted in higher yield of beta hydroxyl nitriles than those of the corresponding lithio acetonitrile. In 1998, Timberlake and co-workers showed that CeCl3-mediated aldol reaction of α-lithiated nitrile with alkyl and aryl ketones gave good yield of the corresponding β-hydroxy nitriles.[6] Later, Fleming and coworkers used the *in situ* generated β-hydroxy nitriles obtained from the reaction of α-lithiated nitriles and various unsymmetrical ketone, to transform it into corresponding α, β-unsaturated nitrile in presence of $MgBr_2$ and MeMgCl.[7] In a more recent report, Sarvanan and coworkers have reported a large scale procedure for the addition of 4-methoxy phenyl acetonitrile to symmetrical ketone, cyclohexanone, in presence of a high amount of base.[8] However, there is no report till date about diasterioselective phenyl acetonitrile addition to ketones due to poor steric control of the substrate. Difficulties associated mainly with the catalytic generation of active species, eg. α-cyano carbanions on metal ions, hampers the use of alkylnitriles as pro-nucleophile in selective C-C bond forming reaction. We hypothesize that use of soft bases such as metal free organocatalysts for the generation of α-cyano carbanions can help in dramatically shifting the equilibrium towards alkoxides as it might stabilize the intermediate generated *via* hydrogen bonding (Fig 1).

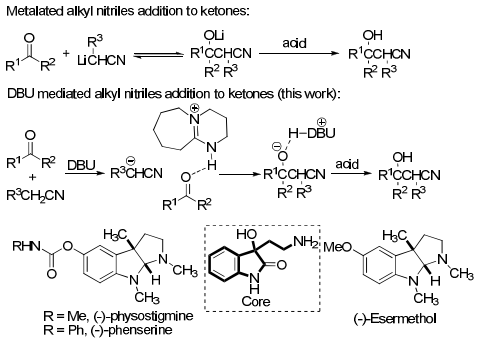
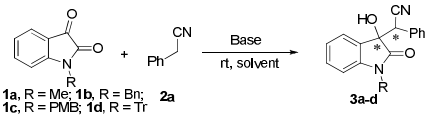


Figure 1. Strategies for cyanomethylation of ketones and natural products with 3-hydroxy-2-oxindole core.

Organocatalyst with high reactivity, have gathered attention being an environmentally green and economically viable alternative to metal catalyst. Organocatalyst such as tertiary amine DBU, have been shown to produce corresponding adducts in high yield for aldol reaction between reactive ketone derived enolates as donor and unsymmetrical ketones as acceptors.[9] The catalyst worked equally well for the homo-aldol reaction of 2-oxocarboxylic esters.[10] Recently, aryl and trifluromethyl substituted tertiary alcohols were synthesized by the aldol reaction of ketones as donor and aryl trifluoromethyl ketone as acceptor in presence of DBU as catalyst.[11] Recently, our group as well as others have demonstrated the cyanomethylation by using TMSAN (trimethyl

silyl acetonitrile) as cyanomethylating agents.[12] Here we report, DBU mediated direct alkylnitrile addition to isatins, a facile access to 3-hydroxy-3-cyanomethyl oxindoles.

Table 1. Optimization of Cyanomethylation reaction of isatins 1 with Benzylcyanide **2a**[a,d]



1a, R = Me; **1b**, R = Bn; **1c**, R = PMB; **1d**, R = Tr **2a** **3a-d**

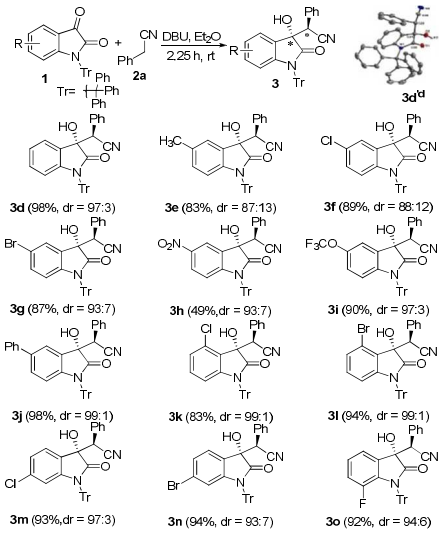
entry	R	Base	solvent	yield (%)[b]	diastereomeric ratio[c]
1	Me	DBU	CH_2Cl_2	54	72:28
2	Bn	DBU	CH_2Cl_2	57	76:24
3	PMB	DBU	CH_2Cl_2	32	79:21
4	Tr	DBU	CH_2Cl_2	65	82:18
5	Tr	DMAP	CH_2Cl_2	0	0
6	Tr	DABCO	CH_2Cl_2	~5	-
7	Tr	CH_3ONa	CH_2Cl_2	23	70:30
8	Tr	PhONa	CH_2Cl_2	0	0
9	Tr	DBU	CH_2Cl_2	75	83:17
10	Tr	DBU	THF	77	80:20
11	Tr	DBU	Et_2O	>98	97:3
12	Tr	DBU	MTBE	98	93:7
13	Tr	DBU	Toluene	26	81:19
14	Me	DBU	Et_2O	70	73:27
15	Bn	DBU	Et_2O	76	50:50
16	PMB	DBU	Et_2O	72	86:14

[a]Unless noted all reactions were performed under argon with 0.1 mmol of **1** and 0.12 mmol of **2a** in 1.0 mL of solvent with 0.12 mmol of base. [b]Isolated combined yield based on **1**. [c]Ratios determined by ^{1}H NMR analysis of crude mixtures. [d]Reactions (9-16) performed under argon with 0.1 mmol of **1** and 0.12 mmol of **2a** in 1.0 mL of solvent and 0.18 mmol of base.

We initiated the optimization of the reaction conditions on *N*-protected isatin core due to its importance in natural and bioactive molecules.[13] We first explored the cyanomethylation reaction of 1 equivalent of *N*-methyl isatin (entry 1, table 1) with 1.2 equivalent of phenyl acetonitrile and 1.2 equivalent of DBU as a base at room temperature in dichloromethane as a solvent. The desired *β*-hydroxy nitrile **3a** was obtained in moderate yield of 54% with lower diastereoselectivity of 72:28. Encouraged by the initial yield and selectivity, the cyanomethylation reactions of different *N*-substituted isatins were screened (table 1, entry 2-4). It was observed that the reaction on *N*-benzyl isatin, yielded the corresponding cyano-methylated product (57%, entry 2, table 1) in moderate yield and diastereoselectivity, whereas *N*-PMB isatin pro duced comparatively lower yield and slightly improved selectivity (32%, dr 79:21 entry 3, table 1). The use of bulkier *N*-protecting group such as *N*-tritylisatin resulted in an enhanced reactivity as well as improved stereocontrol (65%, dr 82:18, entry 4, table 1). To further improve the reactivity and selectivity, we screened various organic bases such as DMAP, DABCO, CH_3ONa and PhONa for the reaction of *N*-tritylisatin with benzylcyanide in dichloromethane (entry 5-8, table 1). Surprisingly, none of the base showed better reactivity than DBU. We then decided to explore the impact of the base amount on the selectivity and reactivity. Increasing the amount of DBU to 1.8 equivalent at room temperature resulted in good yield (75%) and increased selectivity (83:17) of desired product (entry 9, table 1). We then screened various solvents such as THF, Et_2O, MTBE and toluene for the cyanomethylation reaction of *N*-trityl isatin at room temperature (table 1,

entries 10-13). Surprisingly, Et_2O turned out to be very effective (2h 15 min) with quantitative yield (>98%, entry 11) and excellent diastereo selectivity (97:3). The other etherial solvent, MTBE, also provided quantitative yield with good diastereoselectivity (98%, dr 93:7, entry 12, table 2), while solvents such as THF and Toluene showed no effect on reactivity. After optimizing Et_2O as the most efficient solvent, we re-examined the reactivity of *N*-Me, Bn, PMB protected isatins in Et_2O. No significant improvement in yield and selectivity for various *N*-protected isatins was observed (table 1, entry 14-16).

Table 2. Cyanomethylation reaction of various isatins 1 and benzylcyanide **2a** [a,b,c]

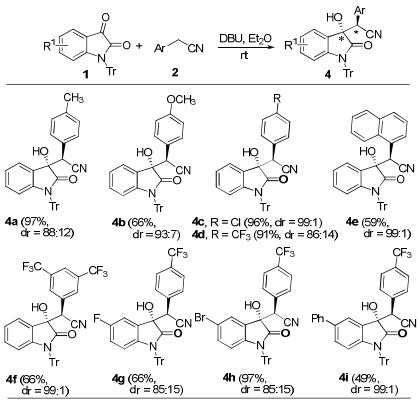


[a]Unless noted reactions were performed under argon with 0.1 mmol of **1d-1o** and 0.12 mmol of **2a** in 1.0 mL of solvent with 0.18 mmol of base. [b]Isolated yield of **3d-3o**. [c]Ratios determined by ^{1}H NMR analysis of crude mixtures. [d]X-ray crystal structure of adduct **3d (**see SI).

The optimized conditions were then used to explore the generality of the reaction with various substituents on the aromatic ring of *N*-tritylisatins. All reactions reached completion at rt in about 2.25 h. Generally good yield and excellent selectivities were obtained in presence of almost all kinds of substituents including electron-donating groups (**3e**), halogen substituents at various positions (**3f**, **3g** , **3k** and **3o**) and other electron-withdrawing groups (**3h-3i**), (Table 2) on the aromatic ring of oxindole **1**. In almost all cases we observed quantitative yield and excellent streocontrol. We achieved good yield and excellent diastereoselectivity (99:1) with 5-phenyl and 4-halo substituted isatin (table 2, entry **3j**, **3k** and **3l**), whereas the 6-halo and 7-halo substitution resulted in very high yield and excellent diastereocontrol (entry **3m-3o**). The relative configuration of the Aldol adduct was determined by X-ray crystal structure analysis of **3d** and the relative configuration of the major stereoisomer was established to be *anti***.**

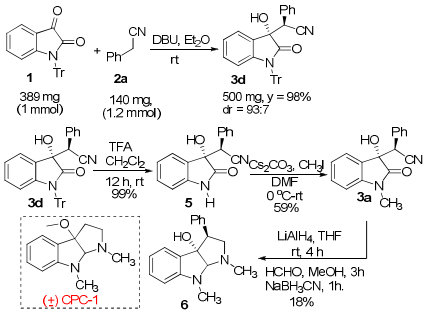
We also investigated the reaction with various substituted benzylcyanides (**2b-2g**, Table 3). Substitution at 4- position of benzyl cyanide afforded very high selectivity in all the cases. Selectivity for reactions of 4-chloro, 2-naphthyl acetonitrile and 3, 5-bis trifluoromethyl benzyl acetonitriles was very high with *dr* up to 99:1 (**4c, 4e** and **4f**). Since, trifluoromethylated compounds are commonly used in drug discovery; we tried an alternative access to these compounds by addition of 4-trifluorometyl benzyl cyanide to 5-F, 5-Br, 5-Ph substituted tritylisatins. For

Table 3. Cyanomethylation reaction of various isatins with substituted benzylcyanides 2 [a,b,c]



[a]Unless noted reactions were performed under argon with 0.1 mmol of **1** and 0.12mmol of **2** in 1.0 mL of solvent with 0.18 mmol of base. [b]Isolated combined yield **4a-4i**. [c]Ratios determined by ^{1}H NMR analysis of crude mixtures.

Scheme 1. Scale-up and Transformation of cyanomethyl adduct **3d**.



all three, good yield with high diastereoselectivity (**4g-4i**, table 3) was observed. Further, to demonstrate the synthetic utility of the cyanomethyl adduct **3d**, a simple 1 mmol scale-up of the reaction was performed, gave corresponding adduct **3d** in excellent yield with very high diastereoselectivity under standard reaction condition. The **3d** was also transformed to an advance intermediate of (±)□CPC□1 analogue (scheme 1).[14]

In order to understand the mechanism and formation of the *syn* (VI) and the *anti* (IX) products, full quantum chemical calculations were done with density functional theory (DFT) at the PBE/TZVP level of theory. [for computational method details please see Supporting Information (SI)]. The reaction can proceed *via* two pathways: the *syn* pathway and the *anti* pathway (Figure 2) In the observed highly selective base catalyzed cyanomethylation the reactant complex (RC) consisting

of DBU, benzyl cyanide and *N*-tritylisatins goes through the transition state II, where DBU abstracts a proton from benzyl cyanide to make intermediate III, which is 8.8 kcal/mol (ΔG) higher in energy than the RC.

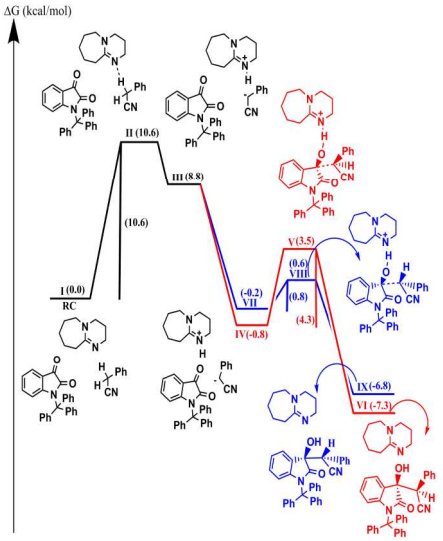


Figure 2. Density functional theory calculations comparing the free energy profiles: red (*syn* product pathway) and blue (*anti* product pathway).

The activation energy barrier corresponding to the first transition state is found to be 10.6 kcal/mol. Subsequent to this step, intermediate III can reorient itself and form intermediates VII and IV, which are more stable by 9.0 kcal/mol and 9.6 kcal/mol respectively than intermediate III. Intermediate IV would lead to the *syn* pathway, while VII leads to the *anti* pathway. As there are two possibilities of nucleophilic attack by the carbanion of benzyl cyanide to the carbonyl carbon of *N*-tritylisatin, followed by deprotonation from $DBUH^+$, leading to the formation of the *syn* (VI) and the *anti* (IX) cyanomethylated products. The *syn* product pathway (shown in red, Figure 2) is seen to have a barrier of 4.3 kcal/mol, passing through the transition state V *en route* to forming the final *syn* product VI, which was seen to be more stable in comparison to RC, by 7.3 kcal/mol. However, the more facile pathway is the one shown in blue, having a barrier of only 0.8 kcal/mol, corresponding to the formation of the *anti* product (see Figure. 2). Hence, the calculations indicate that the major diastereoselective product formed that would be the *anti* product, which corroborates the experimental results. Thus, the reaction pathway and the eventual outcome is governed by the kinetics of the two reactions: the major product being the one with the lower barrier, i.e. the *anti* product here. This product is preferred because of the less sterically hindered transition state in the *anti* case in comparison to the *syn* (Figure S3 in the Supporting Information file).

In conclusion, we have demonstrated a direct DBU mediated alkyl nitrile addition to various isatins, which can be further exploited to directly access quaternary 3-hydroxy-3-cyanomethyl oxindoles. The versatility of the cyanomethylation reaction is also demonstrated by converting the direct cyanomethyl adduct to an advance intermediate of a natural product analogue in simple steps.

EXPERIMENTAL SECTION

General Information. Bruker AV-300 instrument (300 MHz and 75 MHz, respectively) was used to record ^{1}H and ^{13}C NMR spectra in deuterated solvents with residual protonated solvent signals as internal reference.^{1}H NMR's data is reported as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, coupling constant (Hz). ^{13}C NMR's data is recorded in terms of chemical shift (δ, ppm). FT-IR Spectrometer was used to record infrared spectra and are reported in frequency of absorption. MS-TOF mass spectrometer and ESI mass spectrometer were used to record low resolution and high resolution mass spectra. Column chromatographic separations were carried out on silica gel (100–200 mesh).

1. General reaction procedure for Cyanomethylation Reaction.

To a solution of *N*-protected isatin **1** (0.1 mmol) in solvent (specified below) (1 ml) was added Phenyl acetonitrile (0.12 mmol) at room temperature under N_2. The resulting mixture was stirred for 1 min at the same temperature and then DBU (0.18 mmol) was added drop wise. The resulting mixture was stirred for 2.25h at room temperature. The progress of the reaction was monitored by thin layer chromatography. Once the reaction completed it was quenched by addition of 1M HCl (1.0 mL) solution. The resulting mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide an oily residue that was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1/3, *v*/*v*). The ratio of diastereomers was determined by ^{1}H NMR.

2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3d): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (97:3) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.29 ppm, δ minor: 4.38 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (50 mg, 98% yield, *anti/syn* = 97:3), MP 198-199 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.29 (s, 1H), 5.28 (d, *J* = 8.1 Hz, 1H), 6.80-6.86 (m, 7H), 6.97-7.05 (m, 2H), 7.07-7.09 (m, 9H), 7.18 (s, 1H), 7.24-7.29 (m, 2H), 7.33-7.38 (m, 1H), 7.86 (d, *J* = 7.16 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.1, 75.1, 76.3, 116.8, 118.4, 123.1, 124.3, 125.5, 127.1, 127.5, 127.6, 128.7, 129.3, 129.4, 129.6, 140.7, 143.6, 176.6; **FTIR** (KBr) cm^{-1}, 3379, 2361, 1736, 1489, 1124, 749; **HRMS ESI:** $[M+Na]^{+}$, Calcd for $C_{35}H_{26}O_2N_2Na$ 529.1886 ; found 529.1871.

2-(3-hydroxy-5-methyl-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3e): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1e** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (87:13) was determined by ^{1}H NMR

analysis of the crude product (δ major: 4.36 ppm, δ minor: 4.45 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (50.3 mg, 83% yield, *anti/syn* = 87:13), MP 193-194 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.36 (s, 1H), 5.95 (d, *J* = 8.29 Hz, 1H), 6.70 (d, *J* = 8.29 Hz, 1H), 6.94 (bs, 5H), 7.17-7.22 (m, 11H), 7.36-7.42 (m, 4H), 7.75 (s, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 20.8, 47.0, 75.0, 76.4, 116.5, 118.5, 124.8, 125.5, 127.0, 127.4, 127.6, 128.7, 129.3, 129.4, 129.6, 129.8, 132.9, 140.8, 141.2, 176.6; **FTIR** (KBr) cm^{-1}, 3419, 2923, 2856, 1703, 1488, 1260, 1093, 745; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{28}O_2N_2Na$ 543.2042; found 543.2027.

2-(5-chloro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3f): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1f** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (88:12) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.37 ppm, δ minor: 4.46 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (48mg, 89% yield, *anti/syn* = 88:12), MP 182-183 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.37 (s, 1H), 6.00 (d, *J* = 8.67 Hz, 1H), 6.90-6.92 (m, 6H), 7.17-7.23 (m, 12H), 7.39-7.47 (m, 3H), 7.92 (s, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.0, 75.4, 76.3, 117.8, 118.0, 124.7, 127.3, 127.6, 127.8, 128.6, 128.9, 129.3, 129.4, 129.6, 129.8, 140.4, 140.8, 142.2, 176.3; **FTIR** (KBr) cm^{-1}, 3400, 2924, 2854, 1720, 1460, 1097, 1606, 804; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Cl_1Na$ 563.1496; found 563.1468.

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2-(5-bromo-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3g): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1g** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (93:7) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.45 ppm, δ minor: 4.52 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (51 mg, 87% yield, *anti/syn* = 93:7), MP 196-197 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.40 (s, 1H), 4.45 (s,1H), 6.03 (d, *J* = 8.67 Hz, 1H), 6.98-7.01 (m, 6H), 7.10 (dd, J_1 = 1.88 Hz, J_2 = 8.67 Hz, 1H), 7.22-7.25 (m, 5H), 7.32-7.35 (m, 5H), 7.45-7.58 (m, 4H), 8.13 (d, *J* = 1.70 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ; 47.0, 75.4, 76.1, 116.3, 118.0, 118.2, 127.3, 127.4, 127.5, 127.6, 128.9, 129.2, 129.4, 129.6, 129.6, 132.3, 140.4, 142.8, 176.1; **FTIR** (KBr) cm^{-1}, 3422, 2895, 2382, 1639,1057, 898; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Br_1Na$ 607.0991; found 607.0977.

2-(3-hydroxy-5-nitro-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3h): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1h** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (93:7) was determined by ^{1}H NMR analysis

of the crude product (δ major: 4.35ppm, δ minor: 4.43 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (27 mg, 49% yield, *anti/syn* = 93:7), 175-176 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.63 (bs, 1H), 4.35 (s, 1H), 6.14 (d, J = 9.04 Hz, 1H), 6.84-6.86 (m, 6H), 7.05-7.09 (m, 2H), 7.11-7.13 (m, 6H), 7.17-7.19 (m, 3H), 7.29-7.33(m, 2H), 7.38-7.40 (m, 1H), 7.75 (dd, J_1 = 2.07 Hz, J_2 = 9.04 Hz, 1H), 8.67 (d, J = 2.07 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.0, 75.8, 76.0, 116.6, 117.5, 120.0, 125.5, 126.7, 127.6, 127.8, 128.7, 129.1, 129.3, 129.5, 129.9, 139.9, 143.5, 149.4, 176.7; **FTIR** (KBr) cm^{-1}, 3363, 2923, 2358, 1760, 1721, 1486, 1195, 746; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_4N_3Na$ 574.1737; found 574.1720.

2-(3-hydroxy-2-oxo-5-(trifluoromethoxy)-1-tritylindolin-3-yl)-2-phenylacetonitrile (3i): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1i** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (97:3) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.38 ppm, δ minor: 4.43 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (53.3 mg, 90% yield, *anti/syn* = 97:3), MP 187-188 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.32 (bs, 1H), 4.38 (s, 1H), 6.07 (d, J = 8.85 Hz, 1H), 6.77 (d, J = 7.54 Hz, 1H), 6.91-6.93 (m, 6H), 7.11-7.23 (m, 11H), 7.35-7.40 (m, 2H), 7.44-7.49 (m, 1H), 7.83 (s, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.1, 75.5, 76.1, 117.5, 117.9, 122.0, 127.1, 127.3, 127.7, 127.8, 128.9, 129.1, 129.2, 129.4, 129.5, 129.6, 140.3, 142.2, 144.8 (q, J_1 = 2.19 Hz, J_2 = 3.84 Hz), 176.5; **FTIR** (KBr) cm^{-1}, 3837, 3406, 2724, 2311, 1717, 1219, 896; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{25}O_3N_2F_3Na$ 613.1709; found 613.1741.

2-(3-hydroxy-2-oxo-5-phenyl-1-tritylindolin-3-yl)-2-phenylacetonitrile (3j): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1j** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.35 ppm, δ minor: 4.42 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (57.1 mg, 98% yield, *anti/syn* = 99:1), 202-203 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.55 (bs, 1H), 4.35 (s, 1H), 6.06 (d, J = 7.72 Hz, 1H), 6.87 (bs, 6H), 7.09-7.16 (m, 12H), 7.28-7.34 (m, 6H), 7.50 (m, 2H), 8.14 (s, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.0, 75.2, 77.2, 117.0, 118.4, 122.7, 126.1, 126.1, 126.6, 127.1, 127.3, 127.5, 127.8, 128.8, 129.4, 129.4, 129.5, 129.6, 136.1, 139.5, 140.7, 142.8, 176.7; **FTIR** (KBr) cm^{-1}, 3408, 2954, 2590, 1727, 1053, 768; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{41}H_{30}O_2N_2Na$ 605.2199; found 605.2172.

2-(4-chloro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3k): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1k** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The

reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^{1}H NMR analysis of the crude product ((δ major: 4.27 ppm, δ minor: 4.34 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (45 mg, 83% yield, *anti/syn* = 99:1), MP 194-195 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.21 (bs, 1H), 4.27 (s, 1H), 5.97 (s, 1H), 6.83 (bs, 6H), 6.97-7.04 (m, 3H), 7.11-7.18 (m, 9H), 7.30-7.38 (m, 3H), 7.76 (d, *J* = 7.72 Hz, 1H) ; **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.05, 75.5, 76.0, 117.2, 118.2, 123.3, 123.9, 125.2, 127.3, 127.6, 127.8, 128.9, 129.3, 129.5, 129.6, 135.2, 140.3, 144.9, 176.5; **FTIR** (KBr) cm^{-1}, 3373, 2924, 2360, 1743, 1453, 1089, 809; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Cl_1Na$ 563.1496; found 563.1494.

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2-(4-bromo-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3l):

DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1l** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^{1}H NMR analysis of the crude product (δ major: 5.32 ppm, δ minor: 5.55 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (55.1 mg, 94% yield, *anti/syn* = 99:1), MP 192-193 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.54 (bs, 1H), 5.32 (s, 1H), 5.92 (d, *J* = 8.10 Hz, 1H), 6.63 (t, *J* = 8.10 Hz, 1H), 6.80-6.82 (m, 6H), 7.04-7.17 (m, 12H), 7.29 (t, *J* = 7.16 Hz, 2H), 7.36 (d, *J* = 7.16 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 43.4, 75.4, 77.2, 115.9, 116.6, 118.7, 124.0, 127.0, 127.2, 127.6, 128.8, 129.1, 129.3, 130.2, 140.5, 146.0, 175.2; **FTIR** (KBr) cm^{-1}, 3372, 3032, 2205, 1632, 997; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Br_1Na$ 607.0992 ; found 607.0981.

2-(6-chloro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3m): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1m** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (97:3) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.37 ppm, δ minor: 4.43 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (50.5 mg, 93% yield, *anti/syn* = 97:3), MP 202-203 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.37 (s, 1H), 6.07 (s, 1H), 6.91-6.93 (m, 6H), 7.06-7.15 (m,3H), 7.18-7.24 (m, 9H), 7.36-7.41 (m, 2H), 7.45-7.50 (m, 1H), 7.85 (d, *J* = 8.10 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.0, 75.5, 76.0, 117.2, 118.2, 123.3, 124.0, 125.2, 127.3, 127.6, 128.9, 129.3, 129.3, 129.5, 129.6, 135.2, 140.3, 144.9, 176.5; **FTIR** (KBr) cm^{-1}, 3353, 2923, 2070, 1738, 1184, 828; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Cl_1Na$ 563.1496; found 563.1486.

2-(6-bromo-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3n): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1n** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The

reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (93:7) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.36 ppm, δ minor: 4.42 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (55 mg, 94% yield, *anti/syn* = 93:7), MP 206-207 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.36 (s, 1H), 6.21 (s, 1H), 6.90-6.92 (m, 6H), 7.10-7.13 (m, 2H), 7.18-7.25 (m, 10H), 7.37-7.42 (m, 2H), 7.45-7.47 (m, 1H), 7.79 (d, *J* = 7.91 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.9, 75.5, 76.0, 118.1, 120.0, 123.2, 124.5, 125.5, 126.2, 127.3, 127.6, 128.9, 129.2, 129.3, 129.5, 129.6, 140.3, 144.9, 176.4; **FTIR** (KBr) cm^{-1}, 3367, 2902, 2330, 1926, 1601, 1051, 802; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Br_1Na$ 607.0991; found 607.0966.

2-(7-fluoro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-phenylacetonitrile (3o):

DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1o** (0.1 mmol) and Phenyl acetonitrile (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (94:6) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.37 ppm, δ minor: 4.47 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (48 mg, 92% yield, *anti/syn* = 94:6), MP 182-183 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.27 (bs, 1H), 4.37 (s, 1H), 6.71-6.77 (m, 1H), 6.88-6.91 (m, 6H), 7.09-7.21 (m, 12H), 7.34-7.39 (t, *J* = 7.35 Hz, 2H), 7.45-7.49 (m, 1H), 7.87 (d, *J* = 7.35 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 47.3, 76.1, 77.2, 118.2, 120.0 (d, *J* = 23.60 Hz), 120.8 (d, *J* = 3.29 Hz), 125.3 (d, *J* = 7.14 Hz), 127.0, 127.3, 128.3, 128.9, 129.0, 129.1, 129.5, 129.7, 130.7 (d, *J* = 8.23 Hz), 142.3 (d, J = 2.20 Hz), 144.9 (d, *J* = 251.93 Hz), 176.2; **FTIR** (KBr) cm^{-1}, 3690, 3501, 3088, 2315, 1740, 1448, 968; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2F_1Na$ 547.1792; found 547.1799.

2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-p-tolylacetonitrile (**4a**): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile **2b** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (88:12) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.36 ppm, δ minor: 4.44 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (50.2 mg, 97% yield, *anti/syn* = 88:12), MP 205-206 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.38 (bs, 1H), 4.36 (s, 1H), 6.08 (d, *J* = 8.10 Hz, 1H), 6.89-7.01 (m, 8H), 7.06-7.08 (m, 1H), 7.16-7.27 (m, 12H), 7.94 (d, *J* = 7.16 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 21.3, 46.7, 75.2, 76.4, 116.8, 118.5, 123.1, 124.3, 125.6, 126.6, 127.1, 127.4, 127.6, 129.2, 129.4, 129.5, 139.4, 140.8, 143.7, 176.7; **FTIR** (KBr) cm^{-1}, 3575, 2813, 2329, 1716, 1330, 1060, 811; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{28}O_2N_2Na$ 543.2042; found 543.2047.

2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-(4-methoxyphenyl)acetonitrile (4b):

DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile **2c** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (93:7) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.32 ppm, δ minor: 4.42 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (35.5 mg, 66% yield, *anti/syn* = 93:7), MP187-188 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.32 (s, 1H), 6.07 (d, *J* = 8.10 Hz, 1H), 6.82-6.85 (m, 2H), 6.89-7.02 (m, 9H), 7.06-7.11 (m, 1H), 7.16-7.23 (m, 9H), 7.92 (d, *J* = 7.16 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.4, 55.3, 75.1, 76.4, 114.1, 116.8, 118.6, 121.4, 123.1, 124.3, 125.5, 127.1, 127.4, 129.3, 129.5, 130.8, 140.8, 143.8, 160.5, 176.7; **FTIR** (KBr) cm^{-1}, 3406, 2925, 2311, 1717, 1261, 1023, 820; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{28}O_3N_2Na$ 559.1992; found 559.1977.

2-(4-chlorophenyl)-2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetonitrile (4c):

DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile **2d** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.78 ppm, δ minor: 5.02 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (51 mg, 96% yield, *anti/syn* = 99:1), MP 201-202 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, dmso-d_6) δ 4.78 (s, 1H), 6.02 (d, *J* = 7.91 Hz, 1H), 6.91-6.93 (m, 5H), 7.00-7.02 (m, 2H), 7.06-7.14 (m, 2H), 7.18-7.20 (m, 10H), 7.42-7.52 (m, 2H), 7.69 (d, *J* = 7.16 Hz, 1H); **^{13}C-NMR** (75 MHz, dmso-d_6) δ 44.6, 74.0, 75.4, 79.1, 115.9, 119.1, 122.3, 123.9, 126.7, 126.9, 127.4, 128.7, 128.9, 129.1, 131.2, 134.3, 141.0, 142.9, 175.6; **FTIR** (KBr) cm^{-1}, 3353, 2923, 2667, 2070, 1738, 1609, 1490, 1035, 828; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{35}H_{25}O_2N_2Cl_1Na$ 563.1496; found 563.1498.

2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (4d):

DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile **2e** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (86:14) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.49 ppm, δ minor: 4.46 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (52 mg, 91% yield, *anti/syn* = 86:14), MP 194-195 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.49 (s, 1H), 6.10 (d, *J* = 8.29 Hz, 1H), 6.95-6.97 (m, 6H), 7.07-7.26 (m, 11H), 7.35-7.46 (m, 2H), 7.57-7.66 (m, 2H), 7.93 (d, *J* = 7.35 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.4, 75.3, 76.2, 117.0, 117.8, 123.4 (d, *J* = 74.65 Hz), 125.2, 125.6 (q, J_1 = 3.29 Hz, J_2 = 6.59 Hz), 127.2, 127.5, 127.7, 129.3, 129.6, 130.1, 130.5, 133.6, 140.7,

141.1, 143.6, 176.2; **FTIR** (KBr) cm^{-1}, 3471, 3232, 2813, 2329, 1716, 1331, 1060, 896; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{25}O_2N_2F_3Na$ 597.1760; found 597.1761.

2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-(naphthalen-1-yl)acetonitrile (4e): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile **2f** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^1H NMR analysis of the crude product (δ major: 5.32 ppm, δ minor: 5.41 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (33 mg, 59% yield, *anti/syn* = 99:1), MP 198-199 ^oC. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 5.32 (s, 1H), 6.05 (d, *J* = 7.91 Hz, 1H), 6.53-6.55 (m, 6H), 6.92-7.00 (m, 7H), 7.06-7.16 (m, 5H), 7.36-7.42 (m, 1H), 7.56-7.64 (m, 2H), 7.88 (d, *J* = 6.59 Hz, 1H), 7.96 (d, *J* = 8.10 Hz, 1H), 8.04 (t, *J* = 7.91 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 41.9, 75.1, 77.2, 116.9, 119.1, 123.2, 124.5, 124.7, 125.9, 126.1, 126.3, 126.8, 127.3, 127.4, 127.7, 128.2, 129.0, 129.2, 129.3, 130.1, 130.7, 133.9, 140.8, 143.7, 176.8; **FTIR** (KBr) cm^{-1}, 3803, 3365, 2931, 1641, 896; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{39}H_{28}O_2N_2Na$ 579.2042; found 579.2042.

2-(3,5-bis(trifluoromethyl)phenyl)-2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetonitrile (4f):

DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1d** (0.1 mmol) and Phenyl acetonitrile **2g** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^1H NMR analysis of the crude product (δ major: 4.51 ppm, δ minor: 4.55 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (42.6 mg, 66% yield, *anti/syn* = 99:1), MP 139-140 ^oC. *Rf* = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.51 (s, 1H), 6.14 (d, *J* = 8.29 Hz, 1H), 6.89-6.91 (m, 5H), 6.99 (t, *J* = 7.72 Hz, 1H), 7.16-7.27 (m, 11H), 7.55 (s, 2H), 7.94-7.97 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.3, 75.7, 76.2, 117.1, 117.4, 120.8, 123.4 (q, J_1 = 3.29 Hz, J_2 = 7.14 Hz), 123.7, 124.2, 124.4 (d, *J* = 4.39 Hz), 127.4, 127.6, 129.2, 129.8 (d, *J* = 2.75 Hz), 130.0, 132.0, 132.5, 140.5, 143.5, 175.9; **FTIR** (KBr) cm^{-1}, 3347, 3059, 2923, 1719, 1608, 1278, 1137, 1035, 899; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{37}H_{24}O_2N_2F_6Na$ 665.1634; found 665.1610.

2-(5-fluoro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (4g): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1p** (0.1 mmol) and Phenyl acetonitrile **2e** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (85:15) was determined by ^1H NMR analysis of the crude product (δ major: 6.05 ppm, δ minor: 6.29 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (39.3 mg, 66% yield, *anti/syn* = 85:15), 192-193 ^oC. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2);

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.47 (s, 1H), 6.05 (dd, J_1 = 3.96 Hz, J_2 = 8.85 Hz, 1H), 6.63 (t, J = 8.67Hz, 1H), 6.94-6.95 (m, 5H), 7.18-7.31 (m, 12H), 7.62-7.69 (m, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.4, 75.5, 76.2, 112.0 (d, J = 24.70 Hz), 116.3 (d, J = 23.05 Hz), 117.4, 118.0 (d, J = 7.68 Hz), 125.8 (q, J_1 = 2.75 Hz, J_2 = 6.59 Hz), 127.4, 127.6, 127.8, 129.1, 129.2, 130.0, 130.4, 131.6 (d, J = 32.93 Hz), 133.2, 139.4 (d, J = 2.20 Hz), 140.3, 140.8, 157.3 (d, J = 245.35 Hz), 176.2; **FTIR** (KBr) cm^{-1}, 3584, 3410, 2913, 2373, 2202, 1614, 1497,1328, 1054,807; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{24}O_2N_2F_4Na$ 615.1666; found 615.1650.

2-(5-bromo-3-hydroxy-2-oxo-1-tritylindolin-3-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (4h): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1g** (0.1 mmol) and Phenyl acetonitrile **2e** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (85:15) was determined by ^{1}H NMR analysis of the crude product (δ major: 6.03 ppm, δ minor: 6.27 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (63 mg, 97% yield, *anti/syn* = 85:15), MP 189-190 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.54 (s, 1H), 6.03 (d, J = 8.67 Hz, 1H), 6.97-6.99 (m, 4H), 7.09-7.14 (m, 1H), 7.21-7.35 (m, 12H), 7.47 (d, J = 8.10 Hz, 1H), 7.67-7.75 (m, 2H), 8.08 (s, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.2, 75.5, 76.0, 115.9, 116.5, 117.4, 118.4, 125.7 (q, J_1 = 3.29 Hz, J_2 = 7.14 Hz), 127.2, 127.4, 127.4, 127.7, 127.8, 129.1, 129.2, 130.1, 130.4, 132.6, 133.1, 140.2, 140.7 (d, J = 144.90 Hz), 175.8; **FTIR** (KBr) cm^{-1}, 3382, 2739, 2104, 1602, 964, 832; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{36}H_{24}O_2N_2F_3Br_1Na$ 675.0865; found 675.0899.

2-(3-hydroxy-2-oxo-5-phenyl-1-tritylindolin-3-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (4i): DBU mediated (0.18 mmol) reaction of *N*-trityl isatin **1j** (0.1 mmol) and Phenyl acetonitrile **2e** (0.12 mmol) in Et_2O (1 ml) was run at room temperature for 2.25h under N_2. The reaction mixture was quenched according to the general procedure. The *anti/syn* ratio (99:1) was determined by ^{1}H NMR analysis of the crude product (δ major: 4.52 ppm, δ minor: 4.75 ppm). The crude mixture was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 30/70) to give the inseparable mixture of diastereomers as white solid (32 mg, 49% yield, *anti/syn* = 99:1), 199-200 ^{o}C. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.62 (bs, 1H), 4.52 (s, 1H), 6.18 (d, J = 8.48 Hz, 1H), 6.99-7.01 (m, 6H), 7.19-7.21 (m, 9H), 7.27-7.37 (m, 4H), 7.41-7.46 (m, 2H), 7.58-7.64 (m, 4H), 8.19 (s, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 46.5, 75.4, 76.2, 117.2, 117.8, 122.6, 125.3, 125.7 (q, J = 4.39 Hz), 126.7, 127.3, 127.5, 127.6, 127.8, 128.2, 128.8, 128.9, 129.3, 130.1, 131.5, 131.9, 133.5, 136.4, 139.3, 140.6, 142.8, 176.2; **FTIR** (KBr) cm^{-1}, 3478, 3282, 2894, 2362, 1718, 1602, 964, 866; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{42}H_{29}O_2N_2F_3Na$ 673.2073; found 673.2106.

2-(3-hydroxy-2-oxoindolin-3-yl)-2-phenylacetonitrile (5): To a solution of compound **3d** (101 mg, 0.2 mmol) in DCM (2 ml), trifluoroacetic acid (28.17 mmol, 2 ml) was dropwise added at room temperature. The resulting reaction mixture was run at same

temperature for next 12 h. The progress of the reaction was monitored by TLC. Once the reaction was completed, the reaction mixture was evaporated off under reduced pressure. The organic residue was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 80/20) to give the inseparable mixture of diastereomers as white solid (52.3 mg, yield = 99%). R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, CD_3OD) δ 4.52 (s, 1H), 6.60 (d, *J* = 7.72 Hz, 1H), 6.95 (d, *J* = 7.35 Hz, 2H), 7.09 (m, 3H), 7.18-7.29 (m, 2H), 7.77 (d, *J* = 7.35 Hz, 1H); **^{13}C-NMR** (75 MHz, CD_3OD) δ 46.7, 78.6, 111.4, 120.1, 123.7, 126.3, 128.6, 129.4, 129.8, 130.3, 131.2, 131.8, 143.2, 178.7; **FTIR** (KBr) cm^{-1}, 3741, 3414, 2487, 2355, 1702, 1616, 1482, 1362, 1026; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{16}H_{12}O_2N_2Na$ 287.0790; found 287.0777.

2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3a): To a solution of compound of **5** (53 mg, 0.2 mmol) in dry DMF (1.0 mL), Cs_2CO_3 (65.2 mg, 0.2 mmol) was added at 0 °C. The resulting mixture was stirred for 10 minutes at same temperature, then methyl iodide (0.22 mmol, 13.8 µL) was added to it. Subsequently, the reaction mixture was warmed to room temperature and stirred for next 12 h. The progress of the reaction was monitored by TLC. Once the reaction completed, it was quenched with water. The biphasic mixture was transferred to the separating funnel with help of EtOAc (2.0 mL). The organic layer was separated and washed with water (2.0 mLx3). The combined aqueous layer was extracted with EtOAc (2.0 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The organic residue was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 80/20) to give the inseparable mixture of diastereomers as white solid (33 mg, yield = 59%), MP 174-175 ^oC. R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR** (300 MHz, CDCl3) δ 2.81 (s, 3H), 4.21 (s, 1H), 4.55 (s, 1H), 6.55 (d, *J* = 7.72 Hz, 1H), 6.84 (d, *J* = 7.35 Hz, 2H), 7.05 (d, *J* = 7.35 Hz, 2H), 7.14-7.23 (m, 2H), 7.29-7.35 (m, 1H), 7.92 (d, *J* = 7.35 Hz, 1H); **^{13}C-NMR** (75 MHz, CDCl3) δ 25.9, 46.4, 77.5, 108.5, 118.1, 123.5, 124.9, 125.8, 128.1, 128.6, 128.9, 129.5, 130.8, 143.1, 174.9; **FTIR** (KBr) cm^{-1}, 3737, 3404, 2931, 2360, 1712, 1614, 1462, 1113, 1023, 932; **HRMS ESI:** $[M+Na]^+$, Calcd for $C_{17}H_{14}O_2N_2Na$ 301.0947; found 301.0951.

1,8-dimethyl-3-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-ol (6)[15] :

A solution of **3a** (55.6 mg, 0.2 mmol) in THF (4.0 mL) was cooled to 0 °C and $LiAlH_4$(31 mg, 0.8 mmol) was added in portions. The reaction was stirred for 4 hours at room temperature, quenched with water, and the suspension obtained was filtered over celite (washings with EtOAc). The crude product is subjected to next step, Formaldehyde (0.11 ml 1.38 mmol 37% in water) was added to a solution of crude product in MeOH (2 ml), the reaction mixture was stirred at RT for 3h, then the reaction mixture cooled to 0 ^oC and $NaBH_3CN$ (86.7 mg, 1.38 mmol) was added. After stirred at room temperature 1hour, the reaction quenched with water and filtered over celite (washing with EtOAc). The biphasic mixture was transferred to the separating funnel with help of EtOAc (2.0 mL). The organic layer was separated and washed with water (2.0 mLx3). The combined aqueous layer was extracted with EtOAc (2.0 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The organic residue was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 5/95 to 60/40) to give a pale yellow sticky solid **6** (10 mg, yield = 18%). R_f = 0.4 (ethyl acetate/petroleum ether = 1/2); **^{1}H-NMR**

(300 MHz, CDCl3) δ 3.15 (s, 3H), 3.21 (s, 3H), 3.41-3.52 (m, 1H), 3.62 (dd, J_1 = 6.03 Hz, J_2 = 10.55 Hz, 1H), 4.01 (dd, J_1 = 6.03 Hz, J_2 = 13.38 Hz, 1H), 4.59 (s, 1H), 6.65 (d, J = 8.10 Hz, 1H), 6.77 (td, J_1 = 0.75 Hz, J_2 = 7.35 Hz, 1H), 6.97 (dd, J_1 = 0.75 Hz, J_2 = 7.54 Hz, 1H), 7.31-7.33 (m, 1H), 7.41-7.49 (m, 5H); **^{13}C-NMR** (75 MHz, CD_3OD) δ 36.5, 50.7, 52.0, 64.0, 86.5, 104.6, 108.2, 119.2, 121.8, 128.5, 128.8, 130.0, 130.7, 130.9, 132.6, 150.8; **FTIR** (KBr) cm^{-1}, 3743, 3388, 2928, 2326, 1677, 1469, 1140; **HRMS ESI:** $[M+H]^+$, Calcd for $C_{18}H_{21}O_1N_2$ 281.1648; found 281.1638.

2. Details of DFT calculations

All the calculations in this study have been performed with density functional theory (DFT), with the aid of the Turbomole 6.4 suite of programs, using the PBE functional. The TZVP basis set has been employed. The resolution of identity (RI), along with the multipole accelerated resolution of identity (marij) approximations have been employed for an accurate and efficient treatment of the electronic Coulomb term in the DFT calculations. Solvent correction were incorporated with optimization calculations using the COSMO model, with diethyl ether (ε = 4.33) as the solvent. The values reported are ΔG values, with zero point energy corrections, internal energy and entropic contributions included through frequency calculations on the optimized minima with the temperature taken to be 298.15 K. Harmonic frequency calculations were performed for all stationary points to confirm them as a local minima or transition state structures (for details see SI).

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of compounds (^{1}H, ^{13}C NMR) including X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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