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“On water” direct organocatalytic cyanoarylmethylation of isatins for the diastereoselective synthesis of 3-hydroxy-3-cyanomethyl oxindoles

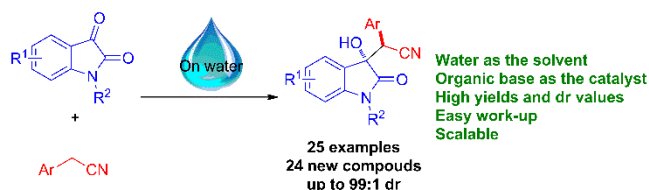
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ABSTRACT: An “on water” organocatalytic cyanoarylmethylation of aryl acetonitrile to isatins is developed, giving products in high yields and up to excellent diastereoselectivities. A remarkable enhancement on reaction rates and diastereoselectivities by water was observed under mild conditions. Moreover, this approach provides a highly efficient and environmental access to thermodynamic 3-hydroxy-3-cyanomethyl oxindoles.

INTRODUCTION

Water, in contrast to organic solvents, is an unquestionably cheap, safe, and environmentally benign solvent in nature. Use of water will reduce the use of harmful organic solvents and represents an important subject in green chemistry.¹ In addition, due to its unique physicochemical properties, water can give completely new reactivity as compared to commonly used organic solvents.² In many cases, significant improvement on reaction rates and selectivities are observed in water.³ Furthermore, in some cases, the reaction does not take place in the absence of water.⁴ Therefore, extensive research efforts have focused on the use of water as a reaction medium in

organic synthesis, and great success has been achieved.⁵ However, pursuing practical organic reactions in water for stereoselective synthesis of value-added products are still highly desirable.

Alkyl nitriles constitute an important class of nitrogen-containing compounds frequently found in many natural products and pharmaceutically interesting compounds (Figure 1).⁶ Moreover, the nitrile group can be easily converted into other functional groups, such as amine, aldehyde, amide and carboxylic acid.⁷ Therefore, great effort has been devoted to the synthesis of functional alkyl nitriles.⁸ In this contribution, the aldol-type cyanoalkylation of aldehydes have been intensively studied⁹, giving versatile functionalized β -hydroxy nitriles. In contrast, the use of more challenging ketones, as acceptors in cyanoalkylations is rare. To realize such transformations, metal catalysts¹⁰, metalated alkyl nitriles¹¹ or excess base¹² were found to be necessary. There are, however, no reports on metal-free catalytic stereoselective addition of simple alkyl nitriles to ketone. As part of our continuing interest in “on water” reactions^{3f,13}, herein we report the first organocatalytic direct cyanoarylmethylation of isatins on water (Scheme 1). This approach provides a facile access to diastereoselective synthesis of 3-hydroxy-3-cyanomethyl oxindoles.

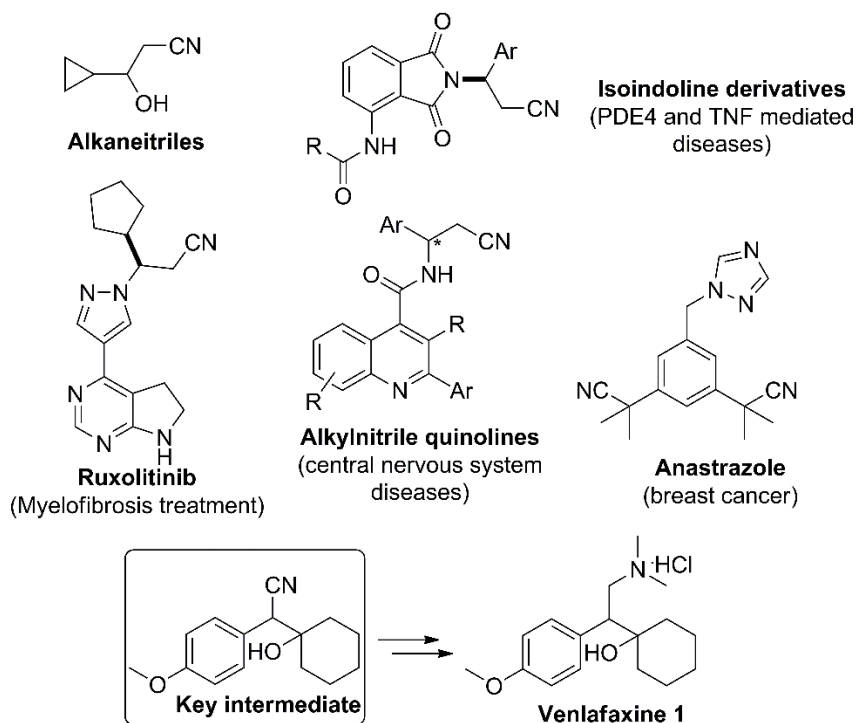
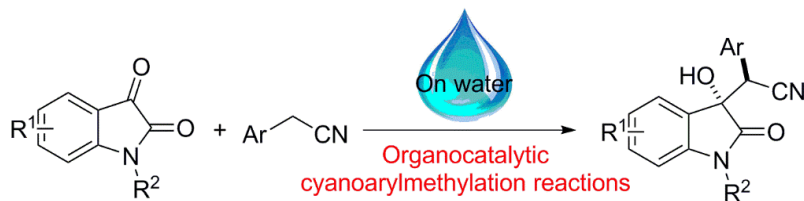


Figure 1. Representative natural products and pharmaceuticals.

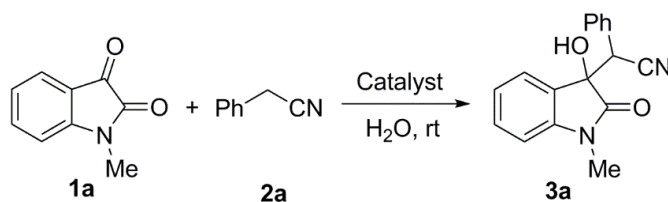


Scheme 1. On water organocatalytic cyanoarylmethylation of isatins.

RESULTS AND DISCUSSION

Initially, the model reaction of the *N*-methyl isatin **1a** and phenyl acetonitrile **2a** was investigated under various base catalytic conditions (Table 1). Using water as the reaction medium, we were pleased to find that the reaction catalyzed by diethylamine afforded the desired β -hydroxy nitrile **3a** in 83% yield with a diastereomeric ratio of 88:12 (entry 1). Screening of the base catalysts found that DBU improved both the yield and the diastereomeric ratio (entry 2), whereas other bases such as DMAP, DABCO, imidazole, K_2CO_3 and KOH displayed inferior catalytic activities. We also tested some chiral base catalysts to see if this reaction can proceed with enantioselectivity control. However, poor results (<10% ee) has been obtained for the moment (see supporting information for details).

Table 1 Screening of catalysts for the cyanoarylmethylation reaction of *N*-methyl isatin **1a** with phenyl acetonitrile **2a**^a

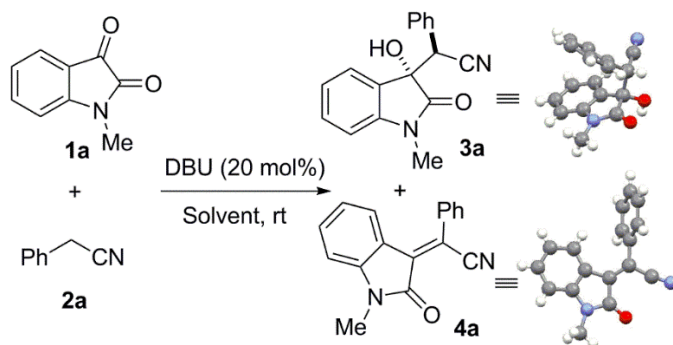


Entry	Cat.	t [h]	Yield [%] ^b	dr [%] ^c
1	Et ₂ NH	10	83	88:12
2	DBU	4	96	98:2
3	DMAP	26	82	70:30
4	DABCO	48	46	68:32
5	Imidazole	48	<5	nd
6	KOH	48	52	73:27

^a Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a**, 0.24 mmol of **2a** and 20 mol% of catalyst in 0.5 mL water. ^b Isolated yield. ^c Determined by ¹H NMR analysis. 20 mol% catalyst was used.

Subsequently, the solvent effect on the reaction outcome was examined with DBU as the catalyst (Table 2). It was found that this catalytic process is quite solvent dependent. Several organic solvents were evaluated and gave much lower transformation efficiency, even with a prolonged reaction time (48 h). In addition, the dehydration product **4a** instead of **3a** was obtained as the major product when organic solvents such as DCM, MeCN and MeOH were used. The reaction was greatly accelerated under “on water” condition to give the β -hydroxy nitrile **3a** in very good yield (96%) with excellent diastereoselectivity (98:2). Interestingly, the dehydration process was completely suppressed under such “on water” condition. Additional experiment showed that the catalyst loading could be lowered to 10 mol% with only a slight effect on reaction efficiency (entry 10). Single-crystal X-ray analysis of **3a** unambiguously confirmed that the cyanoarylmethylation product has an *anti*-configuration¹⁴.

Table 2 Solvent effect on the DBU catalyzed addition of 2a to 1a^a



Entry	Solvent	t [h]	3a/4a Yield [%] ^b	dr [%] ^c
1	DCM	48 h	9/67	nd
2	MeCN	48 h	9/64	nd
3	DMF	48 h	38/25	65:35
4	DMSO	48 h	66/28	65:35
5	Dioxane	48 h	52/3	76:24
6	THF	48 h	70/7	79:21

7	Toluene	48 h	81/8	96:4
8	MeOH	48 h	trace/92	nd
9	H ₂ O	4 h	96/0	98:2
10 ^d	H ₂ O	18 h	86/0	99:1

^a Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a**, 0.24 mmol of **2a** and 20 mol% of catalyst in 0.5 mL solvent. ^b Isolated yield by column chromatography. ^c Determined by ¹H NMR analysis. ^d 10 mol% of the catalyst was used, isolated yield by washing process.

Most importantly, this “on water” reaction is operationally straightforward and scalable to gram scale (Figure 2). After the complete conversion of *N*-methyl isatin (indicated by a color change from red to yellow), the desired product **3a** was obtained in highly pure form by simple filtration and washing with water and petroleum ether, which is a key intermediate for the synthesis of (±)-CPC-1 analogue **6**.

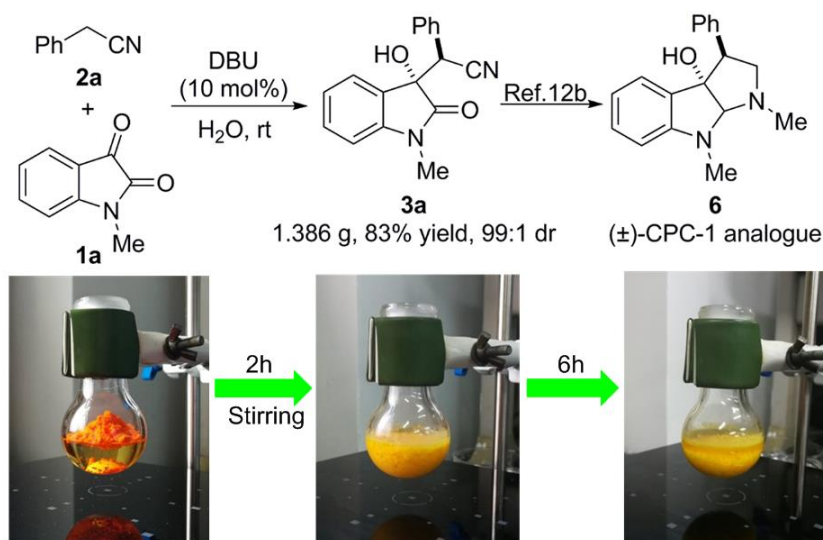
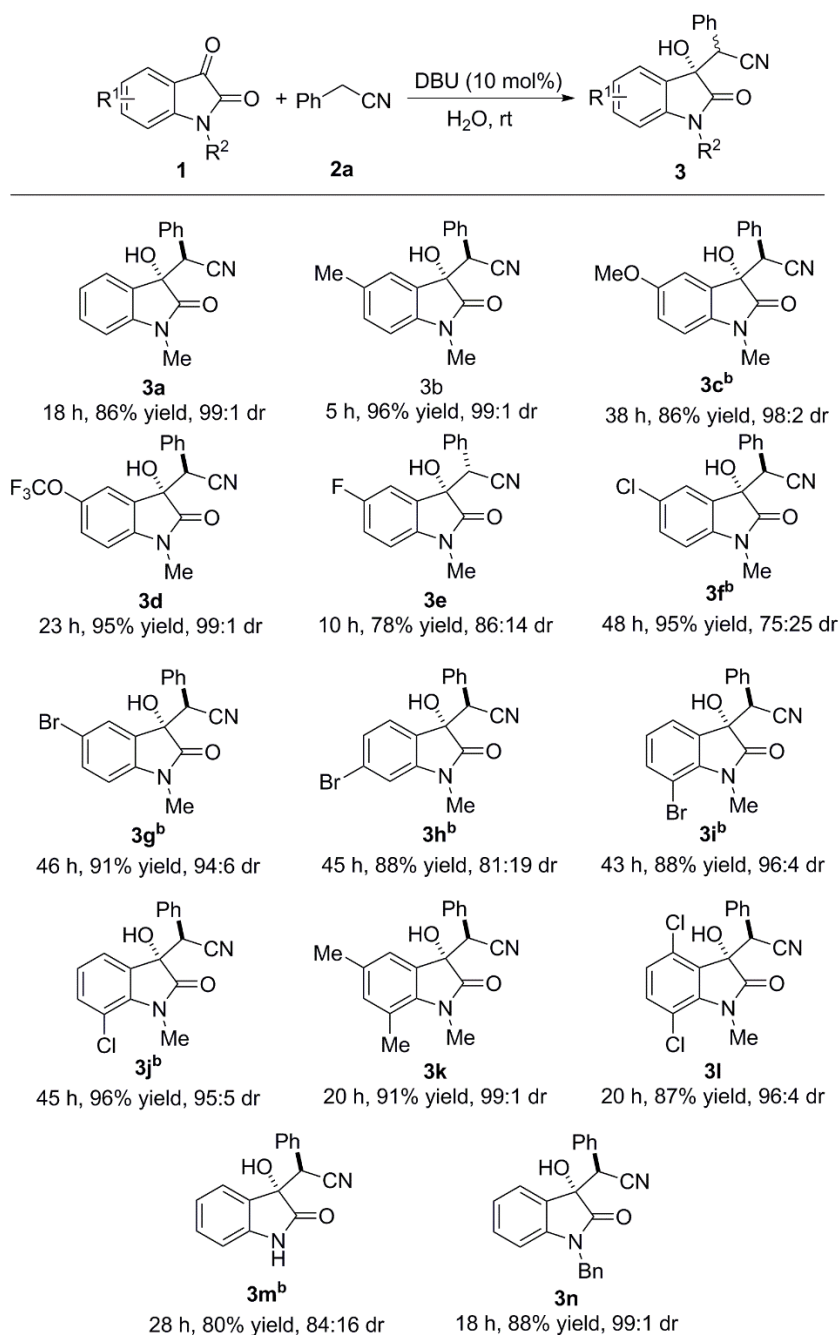


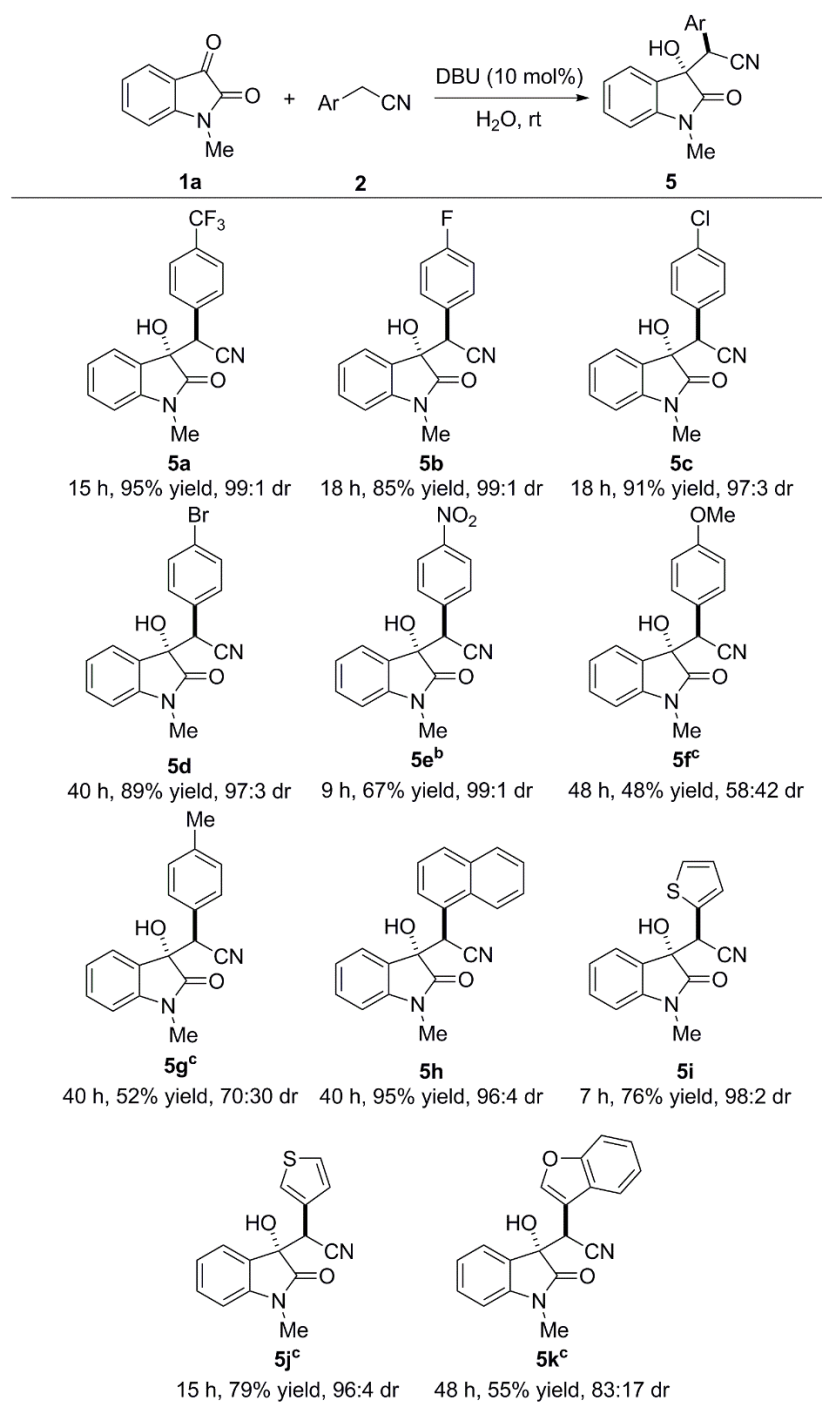
Figure 2. Gram scale synthesis of 3a.

The substrate scope of the reaction was investigated after deriving the optimized reaction conditions. First, we studied variation of the isatins (Table 3). Both electron-donating (5-Me and 5-OMe) and electron-withdrawing (5-OCF₃, 5-F, 5-Cl and 5-Br) groups on the oxindole were

tolerable to afford the desired β -hydroxy nitriles in good to excellent yields and diastereoselectivities (**3b-3g**). Moreover, substitution was viable at the 4-position, 6-position and 7-position of the oxindole, and disubstitution was also feasible. In all the cases, the desired product was formed in excellent yields and very good dr values (**3h-3l**). It is worth noting that *N*-benzylisatin and isatin with a free NH group were also well-tolerated to furnish the desired product in high yields with good to excellent dr values (**3m**, **3n**). Other ketones, such as trifluoroacetophenone, acetophenone, methyl benzoylformate and cyclohexanone were not suitable for this cyanoarylmethylation reaction under our conditions. In addition, the reaction of benzaldehyde with phenyl acetonitrile led to the formation of a dehydrated product (see supporting information for details).

Table 3 The scope of addition reaction^a

^a Unless otherwise noted, the reaction was performed with 0.2 mmol of **1**, 0.24 mmol of **2a** and 10 mol% of catalyst in 0.5 mL water. The yield refers to the isolated product. The dr value determined by ¹H NMR analysis. ^b 20 mol% of the catalyst was used.

Table 4 The scope of addition reaction^a

^a Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a**, 0.24 mmol of **2** and 10 mol% of DBU in 0.5 mL water. The yield refers to the isolated product. The dr value determined by ¹H NMR analysis.

^b DABCO was used as the catalyst. ^c 20 mol% of DBU was used.

Next, we investigated variation on the benzyl nitriles. As shown in Table 4. The electronic nature of benzyl nitriles has a noticeable influence on the reaction yields and diastereoselectivities. Generally, benzyl nitriles bearing electron-withdrawing (4-CF₃, 4-F, 4-Cl, 4-Br and 4-NO₂) groups gave more satisfactory results than those with electron-donating (4-OMe and 4-Me) groups. The sterically more demanding 1-naphthyl substrate had no negative effect on the reaction (**5h**). Pleasingly, satisfactory results in term of yield and diastereoselectivity were also achieved with the nitriles containing heterocycles such as thiophene and benzofuran (**5i**, **5j** and **5k**).

During the investigation of substrate scope, a time-dependent dr changes of some products were observed (Figure 3). For instance, the reaction of *N*-methyl-5-fluoro isatin (**1e**) with phenyl acetonitrile **2a** was *anti*-selective at early stage. Upon prolonging the reaction time, the diastereoselectivity of this reaction changed from *anti* to *syn*. After stirring for 18 hours, the product **3e** was obtained in excellent *syn*-selectivity (95:5), and no more changes in the dr was observed from then on. Moreover, when products (**3e-3g**) with low dr were treated with 20 mol% DBU in water for 20 h, a significant improvement of dr was observed. These results suggested that the reaction is reversible in the presence of DBU when using water as the reaction medium, and thermodynamically controlled leading to the more stable adduct. To the best of our knowledge, this reaction represents the first example of “on water” mediated diastereoselective changes.

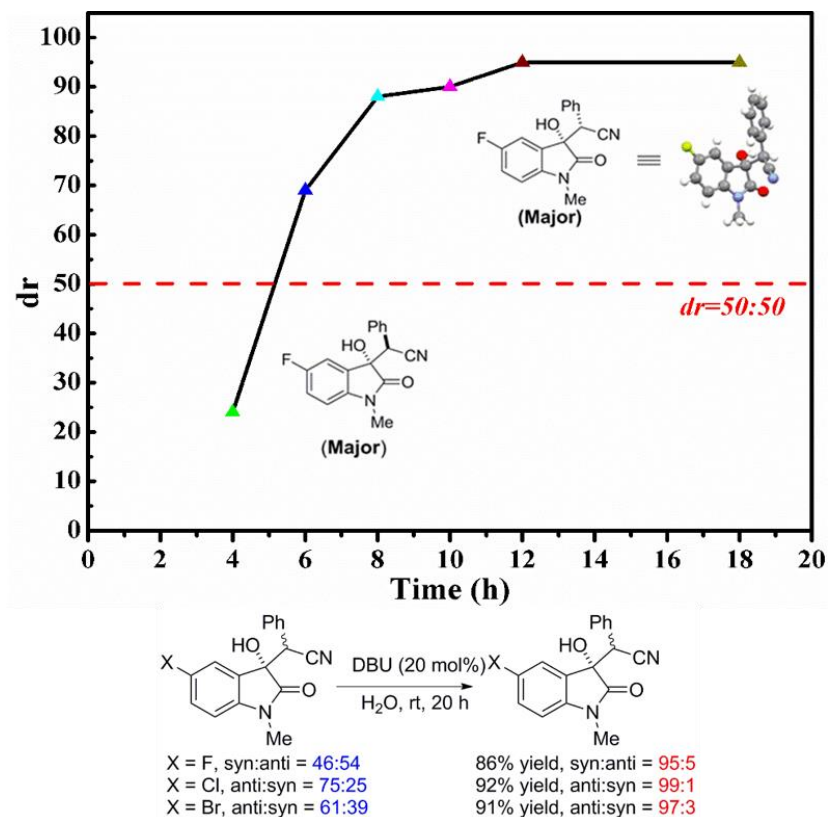


Figure 3. Time dependent changes in diastereomeric ratio.

To understand the effect of thermodynamic stability on the product diastereoselectivity, we performed DFT calculations to compare the energy differences between the *syn*- and *anti*-adducts for **3a** and **3e** (Figure 4). As the products show poor solubility in water solvent, both the molecular state in water solvent and the solid state were analyzed using cluster and periodic models (16 molecules per unit cell), respectively. For both **3a** and **3e**, the molecular *anti*-isomer shows a higher stability than its *syn*-isomer with a lower energy of 6 kJ/mol. However, the further calculations on periodic unit cells indicate that although the *anti-3a* still shows a higher stability than *syn-3a* with a favored energy by 50 kJ/mol, the stability of *syn-3e* unit cell increases significantly with a decreased energy by -110 kJ/mol in comparison with the *anti-3e*. This indicates that the *syn*-isomer of **3e** is the thermodynamic product in its solid state, which is consistent with the experimental observations. As the products are mostly insoluble in reaction conditions, we speculate the selectivity of thermodynamic products for different substrates is controlled by the diastereomer

stability at solid state, and such stability differences may be induced by the different stacking of the diastereomer molecules with distinct hydrogen-bonding interaction and steric effect in the crystals.

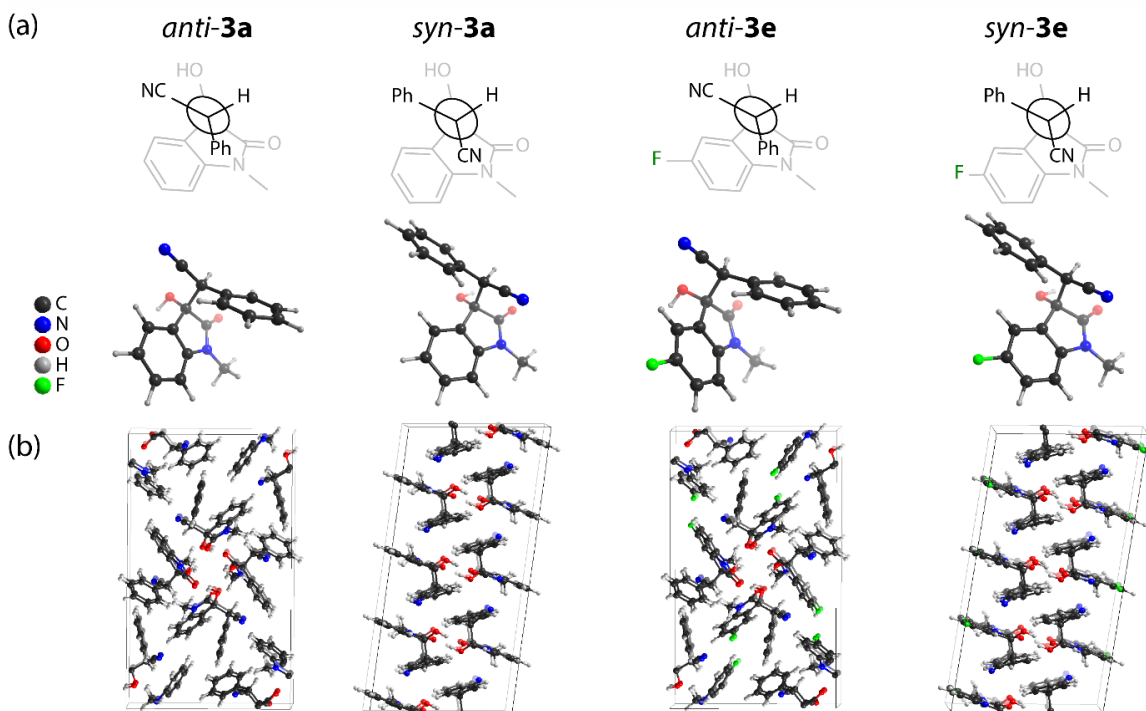


Figure 4. Optimized product structures of (a) cluster models and (b) respective periodic unit cells.

On the basis of previous reports¹⁵, a transition state involving an oil-water interface was assumed to explain the high efficiency of this process. As illustrated in Figure 5, the deprotonation of phenyl acetonitrile **2a** is facilitated by the synergistic effect of water and base. Through the interactions with hydrogen-bond networks at the phase boundary, the dicarbonyl group of the electrophile and nitrile group of the pro-nucleophile might be organized at the periphery of the oil droplet, while the hydrophobic part is orientated within the hydrophobic interior. Consequently, the free hydroxyl groups at the interface effectively activated the reactants and stabilized the transition state. Moreover, the dehydration process could be suppressed when using water as the sole solvent.

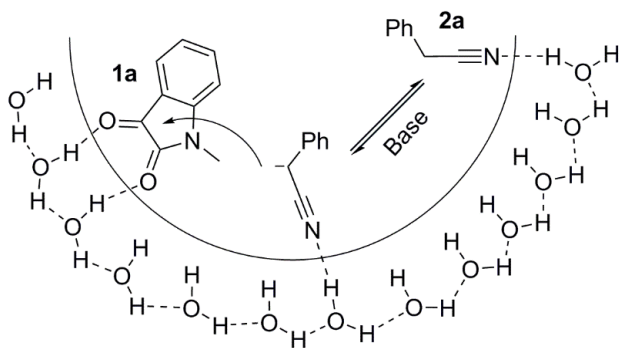


Figure 5. Proposed reaction mechanism.

In summary, we have developed an “on water” efficient strategy for the organocatalytic addition of aryl acetonitriles to isatins. The reaction rate and selectivity were greatly enhanced under “on water” conditions. The changes of diastereoselectivity was observed in this “on water” catalytic process. Moreover, this process provides a highly efficient and environmentally benign approach for the diastereoselective synthesis of 3-hydroxy-3-cyanomethyl oxindoles, a structural scaffold for various natural product analogues and pharmaceutical agents.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a liquid NMR spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using CDCl_3 as the solvent. The residual proton in CDCl_3 ($\delta = 7.27$) served as an internal standard for ^1H NMR, and the ^{13}C -atom of CDCl_3 was used as an internal standard ($\delta = 77.16$) for ^{13}C NMR. Chemical shifts are reported in ppm and the coupling constants J are given in Hz. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Infrared spectra were recorded on an FT-IR spectrometer, and only major peaks were reported in cm^{-1} . The high-resolution mass spectra (HRMS) were recorded on an electrospray ionization (ESI) apparatus using Orbitrap mass spectrometry. General procedure for the preparation of starting materials isatins and benzyl nitriles were commercially available. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.

General procedure for the synthesis of *N*-protected isatins 1 (GP-1)¹⁶: *N*-alkylated isatin

derivatives were prepared from commercially available isatins with different alkyl halides in the presence of K_2CO_3 in DMF at room temperature. MeI or BnBr (10.2 mmol, 3.0 equiv) was added to a stirred solution of isatin (3.4 mmol, 1.0 equiv) and K_2CO_3 (8.5 mmol, 2.5 equiv) in DMF and stirred for 12 h at room temperature. The reaction mixture was quenched with water and extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The crude residue was then purified by column chromatography (eluent: PE/EA = 10/1-4/1, v/v) to provide compounds **1**.

1-methylindoline-2,3-dione (1a)¹⁶: Compound **1a** was prepared by GP-1. Red solid, 465.8 mg, 85% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63-7.60 (m, 2H), 7.14 (t, $J = 7.6$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 3.26 (s, 3H).

1,5-dimethylindoline-2,3-dione (1b)¹⁷: Compound **1b** was prepared by GP-1. Red solid, 327.6 mg, 55% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.40 (m, 2H), 6.80-6.78 (m, 1H), 3.23 (s, 3H), 2.34 (s, 3H).

5-methoxy-1-methylindoline-2,3-dione (1c)¹⁷: Compound **1c** was prepared by GP-1. Red solid, 227.5 mg, 35% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.17-7.13 (m, 2H), 6.81 (d, $J = 8.0$ Hz, 1H), 3.80 (s, 3H), 3.22 (s, 3H).

1-methyl-5-(trifluoromethoxy)indoline-2,3-dione (1d)¹⁸: Compound **1d** was prepared by GP-1. Orange solid, 291.7 mg, 35% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49-7.48 (m, 2H), 6.96-6.94 (m, 1H), 3.28 (s, 3H).

5-fluoro-1-methylindoline-2,3-dione (1e)¹⁸: Compound **1e** was prepared by GP-1. Red solid, 304.6 mg, 50% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36-7.32 (m, 2H), 6.89-6.86 (m, 1H), 3.26 (s, 3H).

5-chloro-1-methylindoline-2,3-dione (1f)¹⁸: Compound **1f** was prepared by GP-1. Red solid, 365.8 mg, 55% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59-7.57 (m, 2H), 6.87 (d, $J = 8.0$ Hz, 1H), 3.26 (s, 3H).

5-bromo-1-methylindoline-2,3-dione (1g)¹⁷: Compound **1g** was prepared by GP-1. Red solid, 571.3 mg, 70% yield. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74-7.71 (m, 2H), 6.82 (d, $J = 8.0$ Hz,

1H), 3.26 (s, 3H).

6-bromo-1-methylindoline-2,3-dione (1h)¹⁸: Compound **1h** was prepared by GP-1. Orange solid, 653.0 mg, 80% yield. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.46 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.09 (d, J = 1.6 Hz, 1H), 3.25 (s, 3H).

7-bromo-1-methylindoline-2,3-dione (1i)¹⁹: Compound **1i** was prepared by GP-1. Red solid, 285.7 mg, 35% yield. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.72 (dd, J = 8.0, 1.2 Hz, 1H), 7.58 (dd, J = 7.2, 1.2 Hz, 1H), 7.02-6.69 (m, 1H), 3.66 (s, 3H).

7-chloro-1-methylindoline-2,3-dione (1j)²⁰: Compound **1j** was prepared by GP-1. Red solid, 332.5 mg, 50% yield. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.55-7.52 (m, 2H), 7.09-7.05 (m, 1H), 3.64 (s, 3H).

1,5,7-trimethylindoline-2,3-dione (1k)¹⁷: Compound **1k** was prepared by GP-1. Red solid, 321.7 mg, 50% yield. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.25 (s, 1H), 7.14 (s, 1H), 3.48 (s, 3H), 2.51 (s, 3H), 2.27 (s, 3H).

4,7-dichloro-1-methylindoline-2,3-dione (1l)²¹: Compound **1l** was prepared by GP-1. Orange solid, 625.7 mg, 80% yield. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.44 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 3.64 (s, 3H).

1-benzylindoline-2,3-dione (1n)¹⁶: Compound **1n** was prepared by GP-1. Red solid, 766.4 mg, 95% yield. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.63-7.61 (m, 1H), 7.49 (td, J = 8.0, 1.2 Hz, 1H), 7.38-7.27 (m, 5H), 7.10 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.94 (s, 2H).

General reaction procedure for “On water” cyanoarylmethylation reaction. *N*-protected isatin **1a** (32.2 mg, 0.20 mmol), phenyl acetonitrile **2a** (28.1 mg, 0.24 mmol) and 0.5 mL H₂O were stirred at room temperature, then DBU (3.0 μ L, 0.02 mmol) was added. The reaction mixture was stirred for the indicated time. After the reaction was completed (indicated by color change from red to yellow), the solid product was filtered, washed by water and dried under vacuum to afford the product **3a** in high yield, purity and diastereoselectivity. Some products were purified by column

chromatography (eluent: PE/EA = 4/1, v/v).

2-(3-hydroxy-1-methyl-2-oxindolin-3-yl)-2-phenylacetonitrile (3a): pale yellow solid; 47.9 mg, 86% yield, 99:1 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.96 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.23-7.19 (m, 1H), 7.17-7.14 (m, 1H), 7.07-7.04 (m, 2H), 6.75 (d, *J* = 7.2 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H), 3.73 (s, 1H), 2.84 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.6, 143.4, 131.0, 129.0, 128.8, 128.7, 128.2, 126.2, 125.0, 123.6, 118.5, 109.1, 77.6, 46.2, 26.2. IR (KBr): ν 3348 2921 2245 1735 1709 1613 1469 1114 694 cm⁻¹. HRMS (ESI/Orbitrap) m/z: [M + Na]⁺ Calcd for C₁₇H₁₄N₂O₂Na 301.0947; Found 301.0955.

2-(3-hydroxy-1,5-dimethyl-2-oxindolin-3-yl)-2-phenylacetonitrile (3b): yellow solid; 56.1 mg, 96% yield, 99:1 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.78 (s, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.12-7.05 (m, 3H), 6.78 (d, *J* = 7.6 Hz, 2H), 6.50 (d, *J* = 7.6 Hz, 1H), 4.89 (s, 1H), 3.80 (s, 1H), 2.82 (s, 3H), 2.41 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.4, 141.0, 133.4, 131.2, 129.2, 128.8, 128.8, 128.2, 126.2, 125.7, 118.5, 108.7, 77.7, 46.4, 26.2, 21.3. IR (KBr): ν 3265 2918 2245 1713 1620 1498 1367 1117 699 cm⁻¹. HRMS (ESI/Orbitrap) m/z: [M + Na]⁺ Calcd for C₁₈H₁₆N₂O₂Na 315.1104; Found 315.1113.

2-(3-hydroxy-5-methoxy-1-methyl-2-oxindolin-3-yl)-2-phenylacetonitrile (3c): white solid; 53.0 mg, 86% yield, 98:2 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.56 (d, *J* = 2.0 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 2H), 6.89-6.83 (m, 3H), 6.49 (d, *J* = 8.8 Hz, 1H), 4.84 (s, 1H), 4.16 (s, 1H), 3.86 (s, 3H), 2.80 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.2, 156.7, 136.5, 129.1, 128.8, 128.7, 128.2, 127.2, 118.4, 115.9, 111.7, 109.5, 78.0, 56.1, 46.5, 26.2. IR (KBr): ν 3296 2836 2245 1703 1495 1291 1050 697 cm⁻¹. HRMS (ESI/Orbitrap) m/z: [M + H]⁺ Calcd for C₁₈H₁₆N₂O₃H 309.1234; Found 309.1227.

2-(3-hydroxy-1-methyl-2-oxo-5-(trifluoromethoxy)indolin-3-yl)-2-phenylacetonitrile (3d): yellow solid; 68.8 mg, 95% yield, 99:1 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.79 (s, 1H), 7.23-7.19 (m, 2H), 7.15-7.11 (m, 2H), 6.96-6.92 (m, 2H), 6.56 (d, *J* = 8.8 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 4.16 (br, 1H), 2.86 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.2, 145.4 (q, ³*J*_{CF=}

2.1 Hz), 141.8, 129.2, 128.6, 128.5, 127.4, 124.2, 119.3, 117.8, 109.4, 77.7, 46.6, 26.3. IR (KBr): ν 3270 2932 2250 1714 1496 1254 1214 1167 1113 703 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3\text{H}$ 363.0951; Found 363.0949.

2-(5-fluoro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3e): white solid; 14.3 mg, 86% yield, 95:5 dr; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm) 7.23-7.22 (m, 3H), 7.16-7.06 (m, 5H), 6.81-6.78 (m, 1H), 4.95 (s, 1H), 2.89 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO-}d_6$) δ (ppm) 173.9, 157.7 (d, $^1J_{\text{CF}} = 237.0$ Hz), 139.3 (d, $^4J_{\text{CF}} = 1.6$ Hz), 130.0, 129.3 (d, $^3J_{\text{CF}} = 7.9$ Hz), 129.0, 128.5, 128.0, 118.2, 116.2 (d, $^2J_{\text{CF}} = 23.1$ Hz), 112.6 (d, $^2J_{\text{CF}} = 25.1$ Hz), 109.5 (d, $^3J_{\text{CF}} = 8.2$ Hz), 76.3, 43.7, 25.8. IR (KBr): ν 3334 2923 2239 1703 1625 1490 1474 1112 662 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}_2\text{Na}$ 319.0853; Found 319.0858.

2-(5-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3f): pale yellow solid; 37.2 mg, 92% yield, 99:1 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.90 (s, 1H), 7.31 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.21 (t, $J = 7.2$ Hz, 1H), 7.15-7.11 (m, 2H), 6.89-6.87 (m, 2H), 6.53 (d, $J = 8.4$ Hz, 1H), 4.78 (br, 1H), 4.08 (s, 1H), 2.83 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100MHz, CDCl_3) δ (ppm) 175.3, 141.9, 131.0, 129.3, 129.1, 128.7, 128.5, 128.5, 127.8, 125.5, 118.1, 110.0, 77.6, 46.4, 26.3. IR (KBr): ν 3269 3068 2945 2250 1713 1609 1490 1364 1117 700 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_2\text{Na}$ 335.0558; Found 335.0564.

2-(5-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3g): white solid; 33.9 mg, 91% yield, 97:3 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.02 (d, $J = 2.0$ Hz, 1H), 7.47 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.23-7.20 (m, 1H), 7.16-7.13 (m, 2H), 6.93 (d, $J = 7.2$ Hz, 2H), 6.47 (d, $J = 8.4$ Hz, 1H), 4.34 (s, 1H), 4.26 (s, 1H), 2.83 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 174.6, 142.4, 134.0, 129.2, 128.8, 128.6, 128.5, 128.3, 127.9, 117.9, 116.5, 110.2, 46.6, 26.2. IR (KBr): ν 3263 2967 2250 1712 1605 1487 1114 699 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}_2\text{Na}$ 379.0053; Found 379.0061.

2-(6-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3h): white solid; 62.8 mg, 88% yield, 81:19 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.76 (d, $J = 8.0$ Hz, 1H), 7.34-

7.31 (m, 1H), 7.22-7.18 (m, 1H), 7.17-7.12 (m, 2H), 6.94-6.90 (m, 2H), 6.72 (d, $J = 2.0$ Hz, 1H), 4.65 (s, 1H), 4.44 (s, 1H), 2.79 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 175.0, 144.5, 129.7, 129.2, 128.8, 128.5, 126.6, 126.4, 124.9, 124.8, 118.1, 112.2, 77.4, 46.5, 26.2. IR (KBr): ν 3385 2924 2250 1718 1607 1493 1373 1062 698 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}_2\text{Na}$ 379.0053; Found 379.0062.

2-(7-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3i): pale yellow solid; 62.8 mg, 88% yield, 96:4 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.86 (d, $J = 7.6$ Hz, 1H), 7.46-7.44 (m, 1H), 7.25 (d, $J = 7.2$ Hz, 1H), 7.18-7.14 (m, 2H), 7.09-7.05 (m, 1H), 6.90 (d, $J = 8.0$ Hz, 2H), 4.44 (s, 1H), 3.86 (br, 1H), 3.19 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 175.7, 140.6, 136.6, 129.3, 129.0, 128.7, 128.5, 124.9, 124.1, 117.9, 102.9, 77.1, 47.0, 29.8. IR (KBr): ν 3357 2924 2248 1710 1454 1116 699 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}_2\text{Na}$ 379.0053; Found 379.0060.

2-(7-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3j): yellow solid; 59.8 mg, 96% yield, 95:5 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.83 (dd, $J = 7.2$ Hz, 1.2 Hz, 1H), 7.26-7.22 (m, 2H), 7.16-7.11 (m, 3H), 6.88 (d, $J = 7.6$ Hz, 2H), 4.55 (s, 1H), 4.44 (s, 1H), 3.16 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 175.5, 139.2, 133.3, 129.3, 128.7, 128.7, 128.5, 124.5, 123.6, 117.9, 116.2, 47.0, 29.6. IR (KBr): ν 3282 2926 2248 1713 1606 1461 1116 699 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_2\text{Na}$ 335.0558; Found 335.0563.

2-(3-hydroxy-1,5,7-trimethyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3k): white solid; 56.0 mg, 91% yield, 99:1 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.62 (s, 1H), 7.18 (d, $J = 6.8$ Hz, 1H), 7.10-7.09 (m, 2H), 6.85 (s, 1H), 6.74 (d, $J = 6.0$ Hz, 2H), 4.84 (s, 1H), 3.69 (s, 1H), 3.07 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 176.1, 138.8, 135.1, 133.2, 129.5, 128.8, 128.8, 128.1, 126.9, 123.4, 120.4, 118.4, 77.1, 46.6, 29.5, 21.0, 18.6. IR (KBr): ν 3422 2921 2242 1728 1704 1105 700 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$ 329.1260; Found 329.1270.

2-(4,7-dichloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3l): white solid; 60.4 mg, 87% yield, 96:4 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.25 (d, *J* = 7.6 Hz, 1H), 7.19-7.15 (m, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.02-6.99 (m, 3H), 5.05 (s, 1H), 3.80 (s, 1H), 3.23 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 173.6, 141.2, 134.1, 130.4, 129.4, 128.8, 128.6, 128.3, 125.1, 125.1, 116.7, 114.8, 77.4, 43.9, 29.5. IR (KBr): ν 3385 2935 2248 1709 1600 1449 1112 699 cm⁻¹. HRMS (ESI/Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₇H₁₂Cl₂N₂O₂H 347.0349; Found 347.0354.

2-(3-hydroxy-2-oxoindolin-3-yl)-2-phenylacetonitrile (3m): white solid; 42.3mg, 80% yield, 84:16 dr; ¹H NMR (400 MHz, MeOD) δ (ppm) 7.79 (d, *J* = 8.0 Hz, 1H), 7.28-7.18 (m, 3H), 7.15-7.10 (m, 3H), 6.97-6.95 (m, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.52 (s, 1H); ¹³C {¹H} NMR (100 MHz, MeOD) δ (ppm) 178.6, 143.2, 131.7, 131.1, 130.2, 129.7, 129.3, 128.5, 126.2, 123.6, 120.0, 111.2, 78.5, 46.7. IR (KBr): ν 3345 3181 2926 2248 1735 1709 1613 1469 1114 752 cm⁻¹. HRMS (ESI/Orbitrap) *m/z*: [M + Na]⁺ Calcd for C₁₆H₁₂N₂O₂Na 287.0791; Found 287.0798.

2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-phenylacetonitrile (3n): white solid; 62.4 mg, 88% yield, 99:1 dr; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.74 (d, *J* = 7.2 Hz, 1H), 7.36 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.27-7.11 (m, 8H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.61 (d, *J* = 6.8 Hz, 2H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 1H), 4.72 (d, *J* = 16.4 Hz, 1H), 4.47 (d, *J* = 16.4 Hz, 1H); ¹³C {¹H} NMR (100 MHz, DMSO-*d*₆) δ (ppm) 174.2, 142.5, 135.1, 130.3, 129.8, 129.0, 128.7, 128.4, 128.3, 127.0, 126.9, 126.4, 124.4, 122.7, 119.3, 109.4, 76.2, 44.7, 42.6. IR (KBr): ν 3438 3034 2907 2248 1724 1613 1491 1368 1048 697 cm⁻¹. HRMS (ESI/Orbitrap) *m/z*: [M + H]⁺ Calcd for C₂₃H₁₈N₂O₂H 355.1441; Found 355.1446.

2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-(4-(trifluoromethyl) phenyl)acetonitrile (5a): white solid; 65.8 mg, 95% yield, 99:1 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.98 (d, *J* = 7.6 Hz, 1H), 7.38-7.32 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.50 (s, 1H), 3.54 (s, 1H), 2.87 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.5, 143.3,

133.0, 131.4, 131.1 (q, $^2J_{CF} = 32.8$ Hz), 129.2, 125.8, 125.1 (q, $^3J_{CF} = 3.7$ Hz), 125.0, 123.8, 123.7 (q, $^1J_{CF} = 270.8$ Hz), 117.9, 109.6, 45.8, 26.3. IR (KBr): ν 3410 2921 2359 1707 1613 1325 1116 1069 755 cm^{-1} . HRMS (ESI/Orbitrap) m/z: $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{Na}$ 369.0821; Found 369.0823.

2-(4-fluorophenyl)-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetonitrile (5b): white solid; 50.4 mg, 85% yield, 99:1 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.92 (d, $J = 7.6$ Hz, 1H), 7.36 (td, $J = 7.6$ Hz, 1.2 Hz, 1H), 7.24-7.20 (m, 1H), 6.89-6.87 (m, 2H), 6.82-6.78 (m, 2H), 6.61 (d, $J = 7.6$ Hz, 1H), 4.36 (s, 1H), 4.12 (br, 1H), 2.87 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 175.4, 162.9 (d, $^1J_{CF} = 247.5$ Hz), 143.4, 131.2, 130.6 (d, $^3J_{CF} = 8.4$ Hz), 125.9, 125.0, 125.0 (d, $^4J_{CF} = 3.3$ Hz), 123.8, 118.3, 115.3 (d, $^2J_{CF} = 21.7$ Hz), 109.1, 77.6, 45.6, 26.2. IR (KBr): ν 3340 2926 2248 1713 1698 1613 1511 1246 1116 757 cm^{-1} . HRMS (ESI/Orbitrap) m/z: $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}_2\text{Na}$ 319.0853; Found 319.0862.

2-(4-chlorophenyl)-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetonitrile (5c): white solid; 56.7 mg, 91% yield, 97:3 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.93 (d, $J = 7.6$ Hz, 1H), 7.34 (td, $J = 8.0$ Hz, 1.2 Hz, 1H), 7.22-7.18 (m, 1H), 7.04 (d, $J = 8.4$ Hz, 2H), 6.69-6.66 (m, 3H), 5.34 (s, 1H), 3.65 (s, 1H), 2.89 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 175.4, 143.4, 135.1, 131.2, 130.1, 128.5, 127.7, 125.9, 125.0, 123.7, 118.1, 109.3, 45.6, 26.3. IR (KBr): ν 3397 2923 2250 1708 1613 1494 1470 1093 757 cm^{-1} . HRMS (ESI/Orbitrap) m/z: $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_2\text{Na}$ 335.0558; Found 335.0565.

2-(4-bromophenyl)-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetonitrile (5d): white solid; 63.6 mg, 89% yield, 97:3 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.92 (d, $J = 8.0$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.23-7.19 (m, 3H), 6.72-6.70 (m, 2H), 6.65 (d, $J = 7.6$ Hz, 1H), 4.78 (s, 1H), 4.04 (br, 1H), 2.89 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) 175.1, 143.3, 131.5, 131.3, 130.4, 128.1, 125.7, 125.0, 123.9, 123.3, 118.0, 109.2, 77.4, 45.8, 26.3. IR (KBr): ν 3386 2914 2245 1707 1613 1493 1470 1115 755 cm^{-1} . HRMS (ESI/Orbitrap) m/z: $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}_2\text{Na}$ 379.0053; Found 379.0062.

2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-(4-nitrophenyl)acetonitrile (5e): white solid; 43.5 mg, 67% yield (this compound was found to be relatively unstable in organic solvent), 99:1 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.99-7.97 (m, 2H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.39 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.26-7.24 (m, 1H), 7.14-7.12 (m, 2H), 6.64 (d, *J* = 7.6 Hz, 1H), 4.42 (s, 1H), 4.17 (s, 1H), 2.90 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 174.4, 148.2, 143.1, 136.1, 131.7, 130.0, 125.1, 125.0, 124.2, 123.5, 117.2, 109.2, 77.3, 46.2, 26.3. IR (KBr): ν 3324 3075 2905 2247 1701 1616 1521 1345 1112 764 cm⁻¹. HRMS (ESI/Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₇H₁₃N₃O₄H 324.0979; Found 324.0986.

2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-(4-methoxyphenyl)acetonitrile (5f): pale yellow solid; 29.5 mg, 48% yield, 58:42 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.91 (d, *J* = 7.2 Hz, 1H), 7.34-7.31 (m, 1H), 7.22-7.19 (m, 1H), 6.80 (d, *J* = 2.0 Hz, 2H), 6.61-6.58 (m, 3H), 4.36 (s, 1H), 4.16 (s, 1H), 3.70 (s, 3H), 2.85 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.0, 159.8, 143.3, 131.0, 130.0, 125.9, 125.0, 123.7, 120.9, 118.5, 113.7, 108.7, 77.5, 55.3, 45.8, 26.2. IR (KBr): ν 3385 3066 2922 2243 1708 1614 1513 1470 1252 755 cm⁻¹. HRMS (ESI/Orbitrap) *m/z*: [M + Na]⁺ Calcd for C₁₈H₁₆N₂O₃Na 331.1053; Found 331.1063.

2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-(4-methoxyphenyl)acetonitrile (5g): white solid; 30.4 mg, 52% yield, 70:30 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.92 (d, *J* = 7.2 Hz, 1H), 7.35-7.32 (m, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 7.6 Hz, 2H), 6.59 (d, *J* = 8 Hz, 1H), 4.31 (s, 2H), 2.85 (s, 3H), 2.22 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ (ppm) 175.0, 143.4, 138.8, 131.0, 129.6, 129.1, 129.0, 128.7, 126.0, 125.1, 123.7, 118.5, 108.7, 77.5, 46.3, 26.1, 21.2. IR (KBr): ν 3275 3057 2919 2243 1708 1614 1469 1114 759 cm⁻¹. HRMS (ESI/Orbitrap) *m/z*: [M + Na]⁺ Calcd for C₁₈H₁₆N₂O₂Na 315.1104; Found 315.1109.

2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-(naphthalen-1-yl)acetonitrile (5h): pale yellow solid; 62.6 mg, 95% yield, 96:4 dr; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.04 (d, *J* = 8.4 Hz, 1H), 7.85-7.79 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.56-7.52 (m, 1H), 7.50-7.46 (m, 1H), 7.35 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.20 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.05 (dd, *J* = 7.2 Hz,

0.8 Hz, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 5.33 (s, 1H), 3.72 (s, 1H), 2.58 (s, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ (ppm) 174.9, 143.6, 133.6, 131.1, 130.7, 129.9, 128.8, 128.1, 126.8, 126.3, 126.2, 125.4, 125.2, 124.6, 123.7, 122.9, 118.8, 108.6, 77.4, 41.8, 26.0. IR (KBr): ν 3298 3055 2929 2253 1698 1617 1469 1093 756 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_2\text{Na}$ 351.1104; Found 351.1112.

2-(3-hydroxy-1-methyl-2-oxindolin-3-yl)-2-(thiophen-2-yl)acetonitrile (5i): pale yellow solid; 43.2 mg, 76% yield, 98:2 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.93 (d, $J = 7.6$ Hz, 1H), 7.41 (td, $J = 7.6$ Hz, 1.2 Hz, 1H), 7.26-7.24 (m, 1H), 7.10-7.08 (m, 1H), 6.76-6.71 (m, 2H), 6.65 (d, $J = 3.2$ Hz, 1H), 4.46 (s, 1H), 4.42 (s, 1H), 2.96 (s, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ (ppm) 175.0, 144.0, 131.4, 130.2, 128.9, 127.1, 126.6, 126.0, 125.1, 124.0, 117.8, 109.0, 41.6, 26.4. IR (KBr): ν 3262 2935 2253 1709 1613 1469 1112 759 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2\text{SNa}$ 307.0512; Found 307.0518.

2-(benzofuran-3-yl)-2-(3-hydroxy-1-methyl-2-oxindolin-3-yl)acetonitrile (5k): red solid; 35.0 mg, 55 % yield, 83:17 dr; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.01 (d, $J = 7.2$ Hz, 1H), 7.34-7.30 (m, 2H), 7.25-7.19 (m, 3H), 7.12-7.07 (m, 2H), 6.60 (d, $J = 8.0$ Hz, 1H), 5.25 (br, 1H), 4.26 (s, 1H), 2.77 (s, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ (ppm) 175.6, 154.8, 144.8, 143.6, 131.3, 126.6, 125.0, 124.9, 123.9, 123.1, 119.7, 117.7, 111.5, 109.9, 109.1, 76.9, 37.0, 26.2. IR (KBr): ν 3347 3056 2918 2250 1710 1616 1115 705 cm^{-1} . HRMS (ESI/Orbitrap) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ 341.0897; Found 341.0898.

General Procedure for the gram scale synthesis of 3a (Figure 2). *N*-protected isatin **1a** (967.0 mg, 6.0 mmol), phenyl acetonitrile **2a** (773.2 mg, 6.6 mmol) and H_2O (9.0 mL) were stirred at room temperature, then DBU (90.0 μL , 0.6 mmol) was added. The progress of the reaction can be monitored by visualization of the color change of the reaction mixture from red (at the start of the reaction) to yellow (at the end of the reaction). After stirring for the indicated time, the solid were filtered, washed by H_2O and Petroleum ether to afford 1.386 g (83%) of the desired product **3a** (99:1 dr).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: DFT computational details, full spectroscopic data for all new compounds and crystallographic data for **3a**, **4a** and **3e** (PDF)

Crystallographic file of product **3a** (CIF)

Crystallographic file of product **4a** (CIF)

Crystallographic file of product **3e** (CIF)

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REFERENCES

- [1] (a) Horváth, L. T.; Anastas, P. T. Introduction: Green Chemistry. *Chem. Rev.* **2007**, *107*, 2169-2173. (b) Li, C.-J.; Trost, B. M. Green Chemistry for Chemical Synthesis. *Pro. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13197-13202. (c) Breslow, R. The Principles and Reasons for Using Water as a Solvent for Green Chemistry. In *Handbook of Green Chemistry [Online]*; Anastas, P.-T., Li, C.-J., Eds.; Wiley-VCH: Weinheim, **2010**, *5*, 1-29. (d) Simon, M.-O.; Li, C.-J. Green Chemistry Oriented Organic Synthesis in Water. *Chem. Soc. Rev.* **2012**, *41*, 1415-1427.
- [2] (a) Otto, S.; Engberts, J. B. F. N. Hydrophobic Interactions and Chemical Reactivity. *Org. Biomol. Chem.* **2003**, *1*, 2809-2820. (b) Butler, R. N.; Coyne, A. G. Water: Nature's Reaction Enforcers-Comparative Effects for Organic Synthesis "In-Water" and "On-Water". *Chem. Rev.* **2010**, *110*, 6302-6337. (c)

Lipshutz, B. H.; Ghorai, S. Transitioning Organic Synthesis from Organic Solvents to Water. What's Your E Factor. *Green Chem.* **2014**, *16*, 3660-3679.

- [3] For selected examples, see: (a) Rideout, D. C.; Breslow, R. Hydrophobic Acceleration of Diels-Alder Reactions. *J. Am. Chem. Soc.* **1980**, *102*, 7816-7817. (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. "On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279. (c) Paladhi, S.; A. Chauhan; Dhara, K.; Tiwari, A. K.; Dash, J. An Uncatalyzed Aldol Reaction of Thiazolidinediones. *Green Chem.* **2012**, *14*, 2990-2995. (d) Paladhi, S.; Bhati, M.; Panda, D.; Dash, J. Thiazolidinedione-Isatin Conjugates via an Uncatalyzed Diastereoselective Aldol Reaction on Water. *J. Org. Chem.* **2014**, *79*, 1473-1480. (e) SaiPrathima, P.; Srinivas, K.; Rao, M. M. "On Water" Catalysis: an Expedient Approach for the Synthesis of Quaternary Centered 3-Hydroxy-3-(nitromethyl)indolin-2-one Derivatives. *Green Chem.* **2015**, *17*, 2339-2343. (f) Zhang, Y.; Wei, B.-W.; Lin, H.; Zhang, L.; Liu, J.-X.; Luo, H.-Q.; Fan, X.-L. "On Water" Direct Catalytic Vinylogous Henry (Nitroaldol) Reactions of Isatins for the Efficient Synthesis of Isoxazole Substituted 3-hydroxyindolin-2-ones. *Green Chem.* **2015**, *17*, 3266-3270. (g) Yu, J.-S.; Liu, Y.-L.; Tang, J., Wang, X.; Zhou, J. Highly Efficient "On Water" Catalyst-Free Nucleophilic Addition Reactions Using Difluoroenoxy silanes: Dramatic Fluorine Effects. *Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516. (h) Luque-Agudo, V.; Gil, M. V.; Román, E.; Serrano, J. A. "On Water" Reactivity between Carbohydrate-Derived Nitroalkenes and Furans. *Green Chem.* **2016**, *18*, 3844-3851. (i) Dilauro, G.; Dell'Aera, M.; Vitale, P.; Capriati, V.; Perna, F. M. Unprecedented Nucleophilic Additions of Highly Polar Organometallic Compounds to Imines and Nitriles Using Water as a Non-Innocent Reaction Medium. *Angew. Chem. Int. Ed.* **2017**, *56*, 10200-10203. (j) Hajra, S.; Roy, S. S.; Aziz, S. M.; Das, D. Catalyst-Free "On-Water" Regio- and Stereospecific Ring-Opening of Spiroaziridine Oxindole: Enantiopure Synthesis of Unsymmetrical 3,3'-Bisindoles. *Org. Lett.* **2017**, *19*, 4082-4085. (k) Zhu, S.; Chen, C.; Xiao, M.; Yu, L.; Wang, L.; Xiao, J. Construction of the Tetrahydroquinoline Spiro Skeleton via Cascade [1,5]-Hydride Transfer-Involved C(sp³)-H Functionalization "On Water". *Green Chem.* **2017**, *19*, 5653-5658. (l) Balaraman, K.; Ding, R. S.; Wolf, C. Stereoselective Synthesis of 3,3'-Bisindolines by Organocatalytic Michael Additions of Fluorooxindole Enolates to Isatylidene Malononitriles in Aqueous Solution. *Adv. Synth. Catal.* **2017**, *359*, 4165-4169. (m) Hikawa, H.; Ichinose, R.; Kikkawa, S.; Azumaya, I. A Palladium-Catalyzed Dehydrative N-Benzoylation/C-H Benzoylation Cascade of 2-Morpholinoanilines on Water. *Green Chem.* **2018**, *20*, 1297-1305. (n) Hikawa, H.; Ichinose, R.; Kikkawa, S.; Zumaya, I. A Palladium-Catalyzed Dehydrogenation of Benzyl Alcohols for Construction of 2-Arylbenzimidazoles "On Water". *Asian J. Org. Chem.* **2018**, *7*, 416-423.
- [4] (a) Li, C.-J. Organic Reactions in Aqueous Media with a Focus on Carbon-Carbon Bond Formations: A Decade Update. *Chem. Rev.* **2005**, *105*, 3095-3166. (b) Li, C.-J.; Chen, L. Organic Chemistry in Water. *Chem. Soc. Rev.* **2006**, *35*, 68-82. (c) Chan, T.-H.; Li, C.-J. Comprehensive Organic Reactions in Aqueous Media, Wiley, New York, **2007**. (d) Chanda, A.; Fokin, V. V. Organic Synthesis "On Water". *Chem. Rev.* **2009**, *109*, 725-748. (e) Gawande, M. B.; Bonifacio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. Benign by Design: Catalyst-Free in-Water, on-Water Green Chemical Methodologies in Organic Synthesis. *Chem. Soc. Rev.* **2013**, *42*, 5522-5551.

- [5] (a) Grieco, P. A. *Organic Synthesis in Water*. Blackie, London, **1998**. (b) Kobayashi, S.; Manabe, K. Development of Novel Lewis Acid Catalysts for Selective Organic Reactions in Aqueous Media. *Acc. Chem. Res.* **2002**, *35*, 209-217. (c) Sen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. Organoindium Reagents: The Preparation and Application in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 271-401. (d) Lindström, U. M. Stereoselective Organic Reactions in Water. *Chem. Rev.* **2002**, *102*, 2751-2772. (e) Butler, R. N.; Coyne, A. G. Organic Synthesis Reactions on-Water at the Organic-Liquid Water Interface. *Org. Biomol. Chem.* **2016**, *14*, 9945-9960. (f) Niu, R.; Xiao, J.; Liang, T.; Li, X.-W. Facile Synthesis of Azaarene-Substituted 3-Hydroxy-2-oxindoles via Brønsted Acid Catalyzed sp³ C-H Functionalization. *Org. Lett.* **2012**, *14*, 676-679. (g) Xiao, J.; Wen, H.; Wang, L.; Xu, L.-B.; Hao, Z.-H.; Shao, C.-L.; Wang, C.-Y. Catalyst-Free Dehydrative SN₁-Type Reaction of Indolyl Alcohols with Diverse Nucleophiles “on Water”. *Green Chem.* **2016**, *18*, 1032-1037. (h) Guo, W. G.; Liu, X. H.; Liu, Y.; Li, C. Chiral Catalysis at the Water/Oil Interface. *ACS Catal.* **2018**, *8*, 328-341. (i) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118*, 679-746. (j) Xie, P.-Z.; Wang, J.-Y.; Liu, Y.-N.; Fan, J.; Wo, X.-Y.; Fu, W.-S.; Sun, Z.-L.; Loh, T.-P. Water-Promoted C-S Bond Formation Reactions. *Nat. Commun.* **2018**, *9*, 1321.
- [6] (a) Fleming, F. F. Nitrile-Containing Natural Products. *Nat. Prod. Rep.* **1999**, *16*, 597-606. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902-7917. (c) Mesa, R. A.; Yasothan, U.; Kirkpatrick, P. Ruxolitinib. *Nat. Rev. Drug Discovery* **2012**, *11*, 103-104.
- [7] (a) Pappoport, Z.; Patai, S. *Chemistry of the Cyano Group*. Wiley, London, **1970**. (b) Fleming, F. F.; Wang, Q. Unsaturated Nitriles: Conjugate Additions of Carbon Nucleophiles to a Recalcitrant Class of Acceptors. *Chem. Rev.* **2003**, *103*, 2035-2078.
- [8] López, R.; Palomo, C. Cyanoalkylation: Alkyl nitriles in Catalytic C-C Bond-Forming Reactions. *Angew. Chem. Int. Ed.* **2015**, *54*, 13170-13184.
- [9] (a) Carlier, P. R.; Lam, W. W. F.; Wan, N. C.; Williams, I. D. Lithium Ephedrate Mediated Aldol Reaction of Arylacetonitriles: Thermodynamic Control of Enantioselectivity. *Angew. Chem. Int. Ed.* **1998**, *37*, 2252-2254. (b) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. P(RNCH₂CH₂)₃N-Catalyzed Synthesis of Beta-Hydroxy Nitriles. *J. Org. Chem.* **1999**, *64*, 3090-3094. (c) Carlier, P. R.; Lo, C. W. S.; Lo, M. M. C.; Wan, N. C.; Williams, I. D. HMPA Promotes Retro-Aldol Reaction, Resulting in Syn-Selective Addition of Lithiated 1-Naphthylacetonitrile to Aromatic Aldehydes. *Org. Lett.* **2000**, *2*, 2443-2445. (d) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. Direct Catalytic Aldol-Type Reactions Using RCH₂CN. *Org. Lett.* **2003**, *5*, 3147-3150. (e) Kumagai, N.; Matsunaga, S.; Shibasaki, M. Cooperative Catalysis of a Cationic Ruthenium Complex, Amine Base, and Na Salt: Catalytic Activation of Acetonitrile as a Nucleophile. *J. Am. Chem. Soc.* **2004**, *126*, 13632-13633. (f) Goto, A.; Endo, K.; Ukai, Y.; Irlé, S.; Saito, S. Rh^I-Catalyzed Aldol-Type Reaction of Organonitriles under Mild Conditions. *Chem. Commun.* **2008**, 2212-2214. (g) Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. A Robust Nickel Catalyst for Cyanomethylation of Aldehydes: Activation of Acetonitrile under Base-Free Conditions. *Angew. Chem. Int. Ed.* **2013**, *52*, 7523-7526. (h) Sureshkumar, D.; Ganesh, V.; Kumagai, N.; Shibasaki, M. Direct Catalytic Addition of Alkyl nitriles to Aldehydes by Transition-Metal/NHC Complexes. *Chem.-Eur. J.* **2014**, *20*, 15723-15726.

- [10] (a) Xiao, Z.; Timberlake, J. W. Cerium (III) Chloride Mediated Nitrile Aldol Reactions: Enhanced Diastereoselectivities Using a Chiral Organocerium Complex. *Tetrahedron*. **1998**, *54*, 4211-4222. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones. *J. Am. Chem. Soc.* **2009**, *131*, 3195-3197. (c) Yazaki, R.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones via Soft Lewis Acid/Hard Bronsted Base/Hard Lewis Base Catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 5522-5531. (d) Wang, G.-W.; Zhou, A.-X.; Wang, J.-J.; Hu, R.-B.; Yang, S.-D. Palladium-Catalyzed sp^2 and sp^3 C-H Bond Activation and Addition to Isatin toward 3-Hydroxy-2-oxindoles. *Org. Lett.* **2013**, *15*, 5270-5273.
- [11] (a) Kaiser, E. M.; Hauser, C. R. Influence of Metallic Cation in Carbonyl Addition Reactions of Certain Nitriles and Sulfones with Benzophenone. *J. Am. Chem. Soc.* **1967**, *89*, 4566-4567. (b) Fleming, F. F.; Shook, B. C. Unsaturated Nitriles: Stereoselective MgO Eliminations. *J. Org. Chem.* **2002**, *67*, 3668-3672.
- [12] (a) Saravanan, M.; Satyanarayana, B.; Reddy, P. P. An Improved and Impurity-Free Large-Scale Synthesis of Venlafaxine Hydrochloride. *Org. Process Res. Dev.* **2011**, *15*, 1392-1395. (b) Rao, V. U. B.; Kumar, K.; Das, T.; K. Vanka; Singh, R. P. DBU-Mediated Diastereoselective Aldol-Type Cyanomethylation of Isatins. *J. Org. Chem.* **2017**, *82*, 4489-4496.
- [13] (a) Zhang, Y.; Wei, B.-W.; Zou, L.-N.; Kang, M.-L.; Luo, H.-Q.; Fan, X.-L. "On Water" Direct Vinylogous Henry (Nitroaldol) Reactions of 3, 5-Dimethyl-4-nitroisoxazole with Aldehydes and Trifluoromethyl Ketones. *Tetrahedron*, **2016**, *72*, 2472-2475. (b) Zhang, Y.; Wei, B.-W.; Wang, W.-X.; Deng, L.-L.; Nie, L.-J.; Luo, H.-Q.; Fan, X.-L. Direct Vinylogous Oxidative Cross-Dehydrogenative Coupling of 4-Nitroisoxazoles with *N*-Aryl Tetrahydroisoquinolines in Water under Air Conditions. *RSC Adv.* **2017**, *7*, 1229-1232. (c) Han, M.-Y.; Lin, J.; Li, W.; Luan, W.-Y.; Mai, P.-L.; Zhang, Y. Catalyst-Free Nucleophilic Addition Reactions of Silyl Glyoxylates in Water. *Green Chem.* **2018**, *20*, 1228-1232.
- [14] CCDC 1846861, 1847207 and 1860176 contain the supporting crystallographic data for this paper.
- [15] (a) Jung, Y.; Marcus, R. A. On the Theory of Organic Catalysis on Water. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502. (b) Thomas, L. L.; Tirado-Rives, J.; Jorgensen, W. L. Quantum Mechanical/Molecular Mechanical Modeling Finds Diels-Alder Reactions Are Accelerated Less on the Surface of Water Than in Water. *J. Am. Chem. Soc.* **2010**, *132*, 3097-3104. (c) Manna, A.; Kumar, A. Why Does Water Accelerate Organic Reactions under Heterogeneous Condition? *J. Phys. Chem. A.* **2013**, *117*, 2446-2454. (d) Sela, T.; Vigalok, A. Organic Synthesis "on Water" vs "on Liquids": A Comparative Analysis. *Org. Lett.* **2014**, *16*, 1964-1967.
- [16] Dhara, K.; Mandal, T.; Das, I.; Dash, J. Synthesis of Carbazole Alkaloids by Ring-Closing Metathesis and Ring Rearrangement-Aromatization. *Angew. Chem. Int. Ed.* **2015**, *54*, 15831-15835.
- [17] Ji, H. H.; Zhu, Y. Z.; Shao, Y.; Liu, J.; Yuan, Y.; Jia, X. D. Active sp^3 C-H Bond Oxidation Initiated sp^3 - sp^2 Consecutive C-H Functionalization of *N*-Arylglycine Amides: Construction of Isatins. *J. Org. Chem.* **2017**, *82*, 9859-9865.
- [18] Lee, Y. C.; Patil, S. S.; Golz, C.; Strohmman, C.; Ziegler, S.; Kumar, K.; Waldmann, H. A Ligand-Directed Divergent Catalytic Approach to Establish Structural and Functional Scaffold Diversity. *Nat. Commun.*

2016, 8, 14043.

- [19] Luo, J. F; Zhao, Y. C; Xu, X; Zheng, J. L; Liang, H. Z. Cu-Catalyzed Oxidation of Indoles to Isatins. *Tetrahedron Lett.* **2017**, 58, 4591-4594.
- [20] Bredenkamp, A; Mohr, F; Kirsch, S. F. Synthesis of Isatins through Direct Oxidation of Indoles with IBX-SO₃K/NaI. *Synthesis-Stuttgart* **2015**, 47, 1937-1943.
- [21] Hamdy, A. M; Al-Masoudi, N. A; Pannecouque, C; Rahman, Q; Villinger, A; Langer, P. Regioselective Suzuki-Miyaura Reactions of 4, 7-Dichloro-*N*-methylisatin. Synthesis, Anti-HIV Activity and Modeling Study. *RSC Adv.* **2015**, 5, 107360-107369.