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Stereoselective Synthesis of 3,3'-Bisindolines by Organocatalytic Michael Additions of Fluorooxindole Enolates to Isatylidene Malononitriles in Aqueous Solution

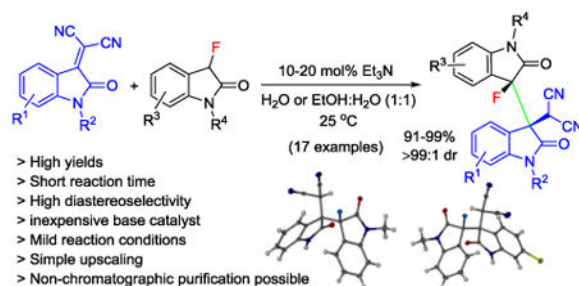
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Abstract

A highly diastereoselective organocatalytic reaction for the synthesis of fluorinated 3,3'-bisindolines exhibiting adjacent tetrasubstituted carbon stereocenters is described. A broad variety of heterochiral bisindolines was prepared in 91-99% yield using 3-fluorooxindoles and isatylidene malononitriles in the presence of catalytic amounts of triethylamine in water or aqueous solution. The reaction can be upscaled without compromising yield and diastereoselectivity and the general usefulness of this method was demonstrated with various Michael acceptors and extended to aldol and Mannich reactions.

Graphical abstract



Keywords

organocatalysis; Michael addition; 3, 3'-bisindolines; organofluorines; green chemistry

The high impact of fluoroorganic chemistry in the materials and medicinal sciences continues to spark great interest in synthetic methods that provide practical access to complex fluorinated compounds.^[1] The presence of fluorine often affects the lipophilicity, acidity, conformational bias, metabolic stability and other important properties of pharmaceuticals and agrochemicals. Similarly, the reactivity of fluorinated electrophiles and nucleophiles can vary significantly from that of the nonfluorinated analogues. The unique nucleophilicity, propensity to decomposition and unexpected side reactions of fluoroenolates

complicate stereoselective carbon-carbon bond formation and this generally requires the development of new methods.^[2] The construction of fluorinated tetrasubstituted carbon stereocenters with intermediate fluoroenolates remains particularly difficult.

The 3,3-disubstituted oxindole moiety is a frequently encountered substructure in natural products and drugs and has become a popular synthetic target.^[3] To this end, the simultaneous incorporation of contiguous stereocenters has attracted increasing attention.^[4] The discovery of the potassium ion channel modulator Maxipost^[5] and other biologically active fluorooxindoles has stimulated the development of various fluorination protocols that utilize readily available 3-alkyl and 3-aryloxindoles as starting material.^[6] The alternative approach based on C-C bond formation with 3-fluorooxindoles bears relatively unexplored synthetic potential.^[7]

Despite the general demand and the progress mentioned above, the synthesis of complex 3-fluorooxindoles exhibiting multiple functional groups and contiguous stereocenters often involves anhydrous conditions, inert atmosphere and low temperatures which increases energy consumption and cost. Encouraged by a report on the “on water” Michael addition of *O*-silyl difluoroenolates to isatylidene malonitriles,^[8] we have developed an environmentally benign method that addresses these issues and produces consistently heterochiral 3,3'-bisindolines from fluorooxindoles using inexpensive Et₃N as catalyst (Scheme 1). While the heterogeneous “on water” reaction is limited to preformed difluoroenoxy silanes used in excess and at elevated temperature, our method utilizes stoichiometric amounts of monofluorinated oxindole as the nucleophile precursor at room temperature in water or aqueous ethanol solutions. The reaction affords two adjacent tetrasubstituted carbon stereocenters in almost quantitative yields and with excellent diastereoselectivity. The 3,3'-bisindoline scaffold formed under these conditions is a common structural motif in dimeric alkaloids.^[9]

We began our search for a method that yields the targeted 3,3'-bisindoline scaffold under mild homogeneous conditions using commonly used organic solvents and base additives. After initial screening we found that the reaction between isatylidene malonitrile, **1a**, and 3-fluorooxindole, **2a**, in the presence of 10 mol% of Et₃N as catalyst in THF at 25 °C proceeded smoothly and gave exclusively the 3,3'-bisindoline **3** in 99% yield and with >99:1 diastereoselectivity (Table 1, entry 1). It is noteworthy to mention that the reaction can easily be monitored by the disappearance of the dark red color of the isatylidene malonitrile derivatives as the 3,3'-bisindoline products are colorless. This initial result prompted us to further investigate the role of catalyst and solvent. As expected, formation of product **3** was not observed under strictly heterogeneous “on water” conditions in the absence of base (Table 1, entry 2). Further screening revealed that the reaction occurs in a variety of solvents including acetone, dichloromethane and ethanol (Table 1, entries 3-5). However, when acetone was used as solvent, 23% of 2-(2-oxo-3-(2-oxopropyl)indolin-3-yl)malonitrile along with 76% of 3,3'-bisindoline **3** was obtained due to competition of the Michael addition of acetone to **1a**. Having found a remarkable solvent compatibility, we envisioned a green protocol and investigated water and aqueous solutions as solvent in the presence of 10 mol% of Et₃N as catalyst. Fortunately, all these reactions yielded **3** in quantitative amounts and excellent diastereoselectivity (Table 1, entries 6-8). The addition of

small amounts of the base allows partial dissolution of **1a** and **2a** in the form of its enolate in water. The reaction then occurs within 3 hours in the water phase rather than “on water”. The absence of any “on water” reaction acceleration is in agreement with the observation that the formation of **3** is even faster under perfectly homogeneous conditions when a water/ethanol mixture is used as solvent (compare entries 7 and 8). It is noteworthy that replacement of Et₃N by inorganic bases such as NaHCO₃, Na₂CO₃ or K₂CO₃ led to lower yield and longer reaction times (Table 1, entries 9-11). Changes in the catalyst loading only affected the reaction rate but did not compromise the stereoselectivity (entries 12 and 13).

With the optimized reaction protocol in hand, we continued with exploring the substrate scope. 3-Fluorooxindoles containing a methyl or phenyl group at the oxindole nitrogen were treated with a series of isatylidene malononitriles under optimized reaction conditions. The 3,3'-bisindolines **3** and **4** were obtained in 94-99% yield and with >99:1 dr (Scheme 2). As expected, protection of the nitrogen atom in the isatylidene Michael acceptor does not affect the reaction outcome and we obtained **5** and **6** in 93-95% yield and with excellent stereoselectivity (>99:1 dr). More variations around the aryl ring in **1** revealed that electronically diverse acceptors containing 5-Me, 7-CF₃, 5-F, 6-Cl, 5-NO₂ or 5-OMe substituents are well tolerated. The corresponding 3,3'-bisindolines **7-12** were produced in very good yields (91-99%) and with unchanged diastereoselectivity. Interestingly, complete precipitation of *N,N'*-protected-3,3'-bisindolines from the homogenous reaction mixture allowed nonchromatographic product isolation which minimizes labor and solvent waste production.^[10]

The crystalline nature of the bisindolines greatly facilitates X-ray examination of the relative configuration of the oxindole dimers. Slow evaporation of solutions of compounds **3-6** and **10** in hexanes and ethylacetate gave single crystals suitable for crystallography which proved that all compounds investigated were present in the heterochiral form (Figure 1).^[11]

We then applied 3-fluorooxindoles carrying removable *N*-protecting groups such as benzyl, *p*-methoxyphenyl (PMP), *p*-benzyloxyphenyl (PBP) and diphenylmethyl in essentially the same protocol (Scheme 3). The corresponding products **13-18** were obtained in 91-99% yield and with excellent diastereoselectivity. Altogether, the presence of protecting groups either in the 3-fluorooxindole moiety or in the isatylidene malononitrile Michael acceptor is well tolerated and this can be useful for further selective synthetic modifications of the 3,3'-bisindolines. The reaction however, also proceeds smoothly in the absence of any protecting groups and we obtained **19** in 98% yield with >99:1 dr. Again, crystallographic analysis of single crystals obtained from **18** confirmed that the heterochiral dimer is consistently formed.

Since bisindolines are key building blocks for the synthesis of several alkaloids, many radical dimerization procedures for the synthesis of 3,3'-bridged bisoxindoles have been reported.^[12] Because radical dimerization of oxindoles often suffers from low stereoselectivity, the introductions of complementary approaches that overcome this problem has remained important. To the best of our knowledge the 3,3'-bisoxindoline **3-19** have not been reported to date and our organocatalytic method generates a single diastereomer in one step under environmentally benign condition. In addition, this synthetic protocol can easily be upscaled

without compromising results. The formation of **3** using 4.0 mmol of **1a** and 4.0 mmol of **2a** in 10 mL of water gave 1.38 g of **3** with 96% yield and >99:1 diastereoselectivity.

To broaden the general utility of our green chemistry protocol, we employed *N*-methyl and *N*-phenyl 3-fluorooxindoles in other Michael additions, an aldol type reaction and a Mannich reaction (Scheme 4). The addition of *N*-phenyl-3-fluorooxindole (**2b**) to acrylonitrile gave **20** in 92% yield. Compound **21** was obtained from *N*-methyl-3-fluorooxindole (**2a**) and methyl vinyl ketone in 96% yield. We noticed that the reactions catalyzed by a weak organic base (20 mol% of Et₃N) takes 2 to 2.5 days whereas the use of stronger base (20 mol% DBU) under identical reaction conditions decreased the reaction time to 2 hours. We were pleased to find that the aldol reaction with diethyl ketomalonate gave **22** in 97% yield and aminomethylation of 3-fluorooxindole using Eschenmoser's salt gave **23** in 99% yield, which altogether underscore the versatility and practicality of C-C bond formation with fluoroenolates in aqueous solution.

In summary, we have developed a highly diastereoselective organocatalytic method for the synthesis of 3,3'-bisindolines containing two adjacent quarternary chiral centers. Excellent yields and stereoselectivities were achieved using inexpensive Et₃N as catalyst in water or aqueous solutions at room temperature. This organocatalytic protocol favorably compares to previously reported "on water" Michael additions to isatylidene malonitriles. Furthermore, analysis of a series of single crystal structures of six products revealed that this reaction consistently favors formation of the heterochiral dimer representing an important scaffold observed in cyclotryptamine alkaloids. The general usefulness of this reaction procedure goes beyond the synthesis of fluorinated 3,3'-bisindolines which was demonstrated with the addition of fluorooxindoles to methyl vinyl ketone, acrylonitrile, diethyl ketomalonate and Eschenmoser's salt.

Experimental Section

Representative Procedure for the Organocatalytic Michael addition

2-(2-Oxoindolin-3-ylidene)malononitrile (39 mg, 0.2 mmol) and 3-fluoro-1-methylindolin-2-one (33 mg, 0.2 mmol) were added together with 10 mol% Et₃N into 0.5 mL of water. The reaction was stirred at room temperature and monitored by TLC. After 3 hours, the mixture was poured onto brine (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes-ethyl acetate as mobile phase to give 3,3'-bisindoline **3** as a colorless solid in 99% yield (71 mg, 0.198 mmol). *R*_f = 0.4 (hexanes/EtOAc, 1:1); ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.17 (s, 1H), 7.86 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.61 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.43 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.13 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.82 (dd, *J* = 7.8, 7.7 Hz, 1H), 6.09 (s, 1H), 5.82 (dd, *J* = 7.7, 1.8 Hz, 1H), 3.20 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ = 170.7 (d, *J*_{C-F} = 9.3 Hz), 168.9 (d, *J*_{C-F} = 21.2 Hz), 144.7 (d, *J*_{C-F} = 5.1 Hz), 143.7, 133.6 (d, *J*_{C-F} = 3.1 Hz), 132.5, 126.4 (d, *J*_{C-F} = 2.7 Hz), 124.6, 123.9, 123.5 (d, *J*_{C-F} = 2.7 Hz), 122.6, 121.1 (d, *J*_{C-F} = 18.2 Hz), 112.7, 112.1, 111.5, 110.6, 91.3 (d, *J*_{C-F} = 198.7 Hz), 56.8 (d,

$J_{C-F} = 23.7$ Hz), 26.9, 25.4; ^{19}F NMR (376 MHz, DMSO- d_6) $\delta = -164.2$; Anal. Calcd. For $\text{C}_{20}\text{H}_{13}\text{FN}_4\text{O}_2$: C, 66.66; H, 3.64; N, 15.55. Found: C, 66.61; H, 3.81; N, 15.78.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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10. For example, 3,3'-bisindoline 5 was quantitatively isolated after reaction of 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile and 3-fluoro-1-methylindolin-2-one in EtOH:H₂O (1:1) in the presence of 10 mol% of Et₃N after 3 hours. The precipitate was washed twice with small portions of ethanol to give pure product.
11. The CCDC numbers 1569588, 1569590, 1569589, 1569587, 1569585, 1569586 and 1569584 contain the the supplementary crystallographic data for compounds 3, 4, 5, 6, 10, 18 and 23, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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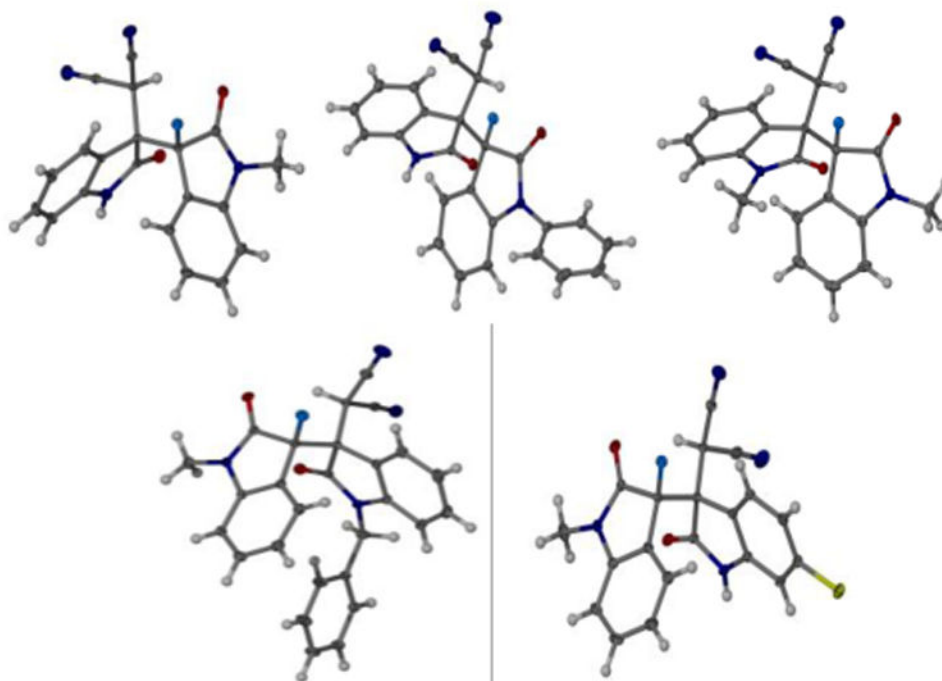
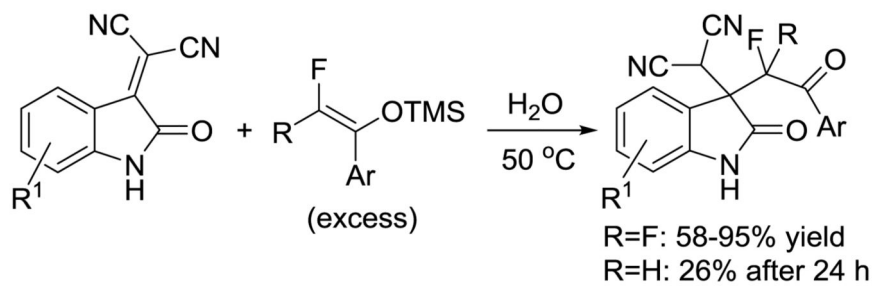
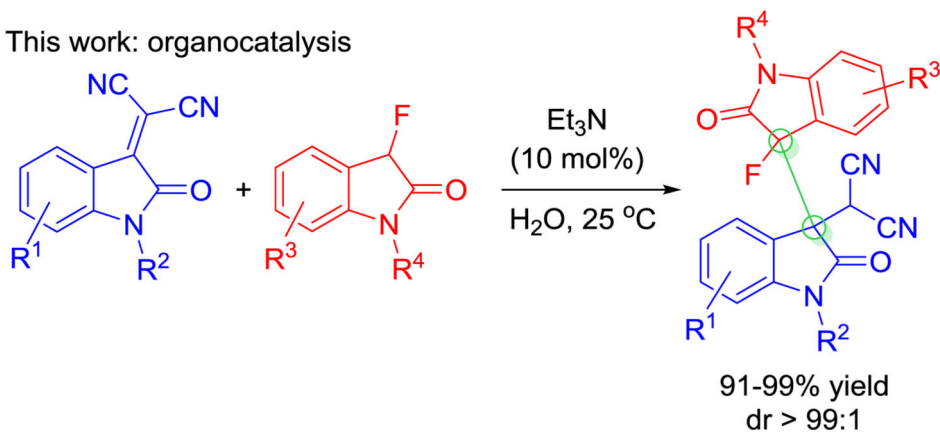


Figure 1. X-ray structures of the 3,3'-bisindolines **3-6** and **10** (top left to right bottom). All products are heterochiral. Only one enantiomer is shown for simplicity.

Previous work: "on water"

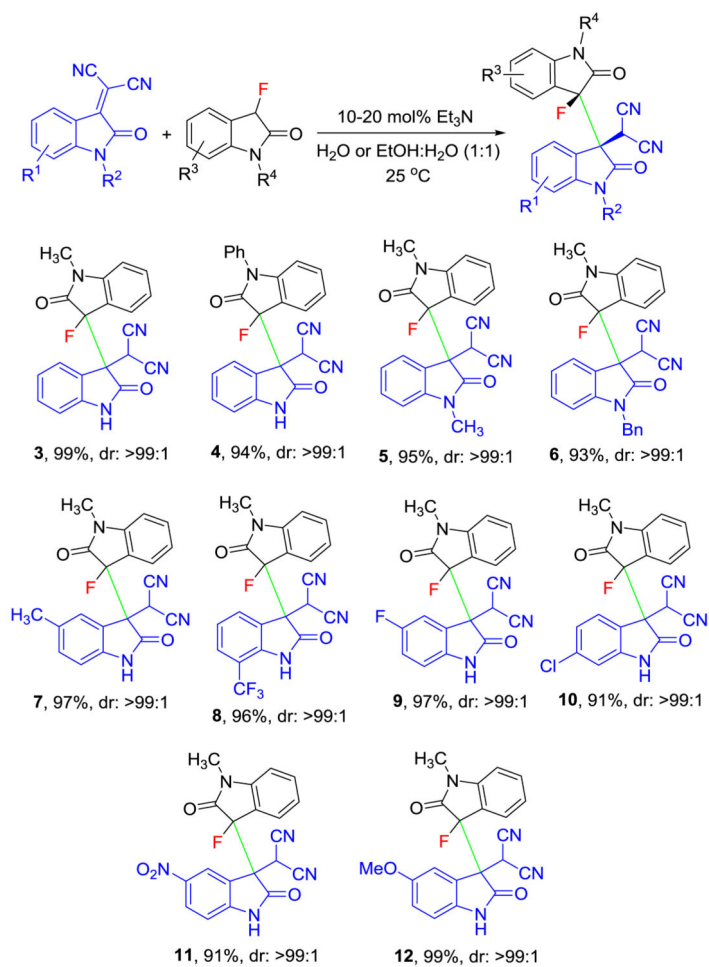


This work: organocatalysis

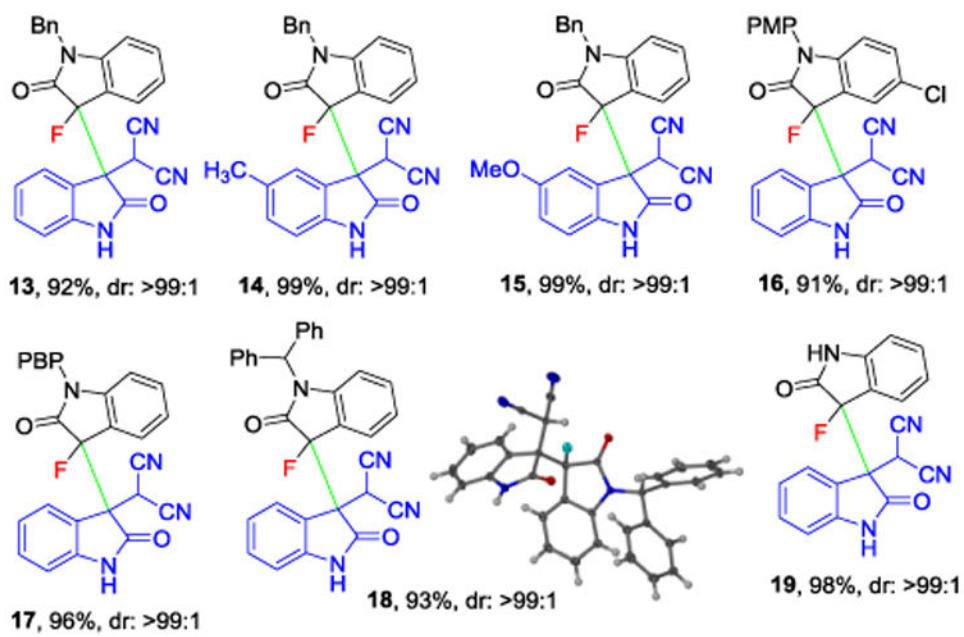


Scheme 1.

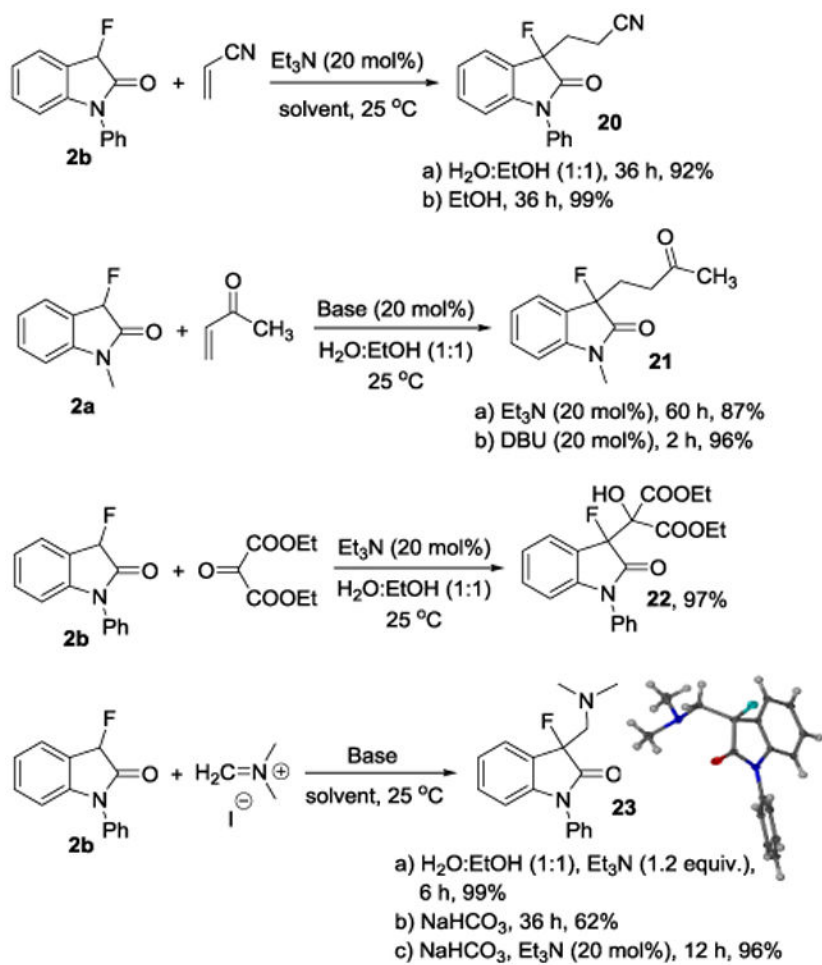
Fluoroenolate Michael additions to isatylidene malononitriles.

**Scheme 2.**

Organocatalytic synthesis of 3,3'-bisindolines **3-12** from 3-fluoroindoles and isatylidene malononitriles. Reaction conditions: 0.2 mmol of isatylidene malononitrile and 0.2 mmol of 3-fluoroindole in 0.5 mL of solvent, 10-20 mol% of catalyst, 25 °C. See SI for details.

**Scheme 3.**

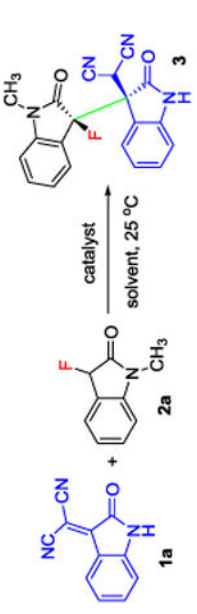
3,3'-Bisindolines carrying a protecting group in the fluorooxindole moiety. See Scheme 2 for reaction conditions.

**Scheme 4.**

Organocatalytic 1,2- and 1,4-additions with fluoroindole enolates in aqueous solutions.

Table 1

Optimization of the Michael addition of 3-fluorooxindole **2a** to the isatylidene malononitrile **1a**.^a



Entry	Catalyst	Solvent	Time (h)	Yield (%) ^b	d ^r c
1	Et ₃ N	THF	2	99	>99 : 1
2	No base	H ₂ O	12	nr	--
3	Et ₃ N	Acetone	1	76	>99 : 1
4	Et ₃ N	CH ₂ Cl ₂	2	93	>99 : 1
5	Et ₃ N	EtOH	1	97	>99 : 1
6	Et ₃ N	THF:H ₂ O (1:1)	2	99	>99 : 1
7	Et ₃ N	EtOH:H ₂ O (1:1)	2	98	>99 : 1
8	Et ₃ N	H ₂ O	3	99	>99 : 1
9 ^d	NaHCO ₃	H ₂ O	18	16	>99 : 1
10	Na ₂ CO ₃	H ₂ O	18	45	>99 : 1
11	K ₂ CO ₃	H ₂ O	18	78	>99 : 1
12 ^e	Et ₃ N	H ₂ O	2	99	>99 : 1
13 ^f	Et ₃ N	H ₂ O	7	81	>99 : 1

^aReaction conditions: 0.2 mmol of **1a** and 0.2 mmol of **2a** in 0.5 mL of solvent, 10 mol% of catalyst, 25 °C.

^bIsolated yield.

^cDetermined by ¹H and ¹⁹F NMR.

^d0.5 mL of sat. NaHCO₃.

^e20 mol% of Et₃N.

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