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Organocatalytic Biomimetic Decarboxylative Aldol Reaction of Fluorinated β-Keto Acids with Unprotected Isatins

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Abstract. A facile asymmetric synthesis of fluorinated 3-hydroxyoxindoles through the biomimetic decarboxylative aldol reaction of fluorinated β-keto acids with unprotected isatins catalyzed by quinine-derived urea catalyst has been achieved. One of the features of this work is that the easily available α, α-difluoro/α-monofluoro-β-keto acids have been first applied in the enantioselective synthesis of fluorinated compounds as the masked fluoroenolates. Furthermore, the utility of this method was demonstrated by its ability to access a series of difluorinated 3-hydroxyoxindoles with up to 95% ee and monofluorinated 3-hydroxyoxindoles with up to 90:10 d.r. and 94% ee.

Keywords: aldol reaction; fluorinated β-keto acids; di/monofluorinated oxindoles; organocatalysis

Introduction

Organofluorine chemistry is one of the most promising research fields because the introduction of fluorine atom into molecules could result in beneficial properties, and its application in modern life is extensively exploited in materials, medicines and agrochemicals.[1] Considering the fact that the fluorine substituents are virtually absent in natural products, the installation of fluoroalkyl groups relies heavily on the development of selective and effective fluorinating reagents.[2] Although numerous fluorine-containing synthons have emerged during the past decades, and the asymmetric synthesis of organofluorine compounds has particularly been the focus of intensive research efforts,[3] it is still challenging to assemble fluoroalkyl groups in enantioselective versions.

3-Hydroxy-2-oxindole is an appealing structural motif exists in a large variety of biologically active molecules (Figure 1).[4] Synthetically, isatins are the prevalent candidates for constructing those attractive frameworks, and the catalytic asymmetric aldol reaction provide an efficient access to the enantioenriched 3-hydroxy-2-oxindoles.[5] As the fluorinated building blocks could exert positive effects on evaluation of structure-activity

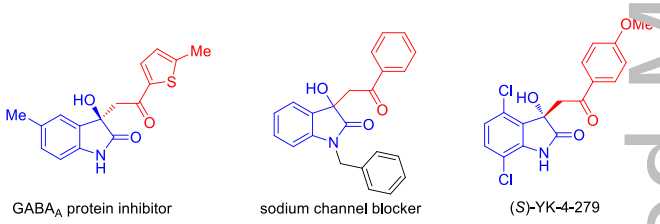

Figure 1. Biologically active 3-hydroxy-2- oxindoles.

relationships, several distinct strategies have been advanced to achieve 3-hydroxy-2-oxindoles as fluorinated versions in recent years. For example, Zhou and co-workers reported the first example of highly enantioselective synthesis of 3-difluoroalkyl substituted 3-hydroxyoxindoles using difluoroenol silyl ethers as nucleophiles. However, the acyclic monofluorinated silyl enol ether for synthesis of monofluorinated 3-hydroxyoxindole was realized with lower enantioselectivity (Scheme 1, eq a).[6] Afterwards, Fang and Wu et al. developed an asymmetric aldol reaction of trifluoromethyl α-fluorinated *gem*-diols with *N*-benzyl isatins, with the reaction of the corresponding difluoroenolate precursors being failed to provide difluorinated oxindoles (Scheme 1, eq b).[7] More recently, Zhang and Yi groups illustrated the aldol addition of difluoroenlates derived from 2,2-difluoro-1,3-diketones with *N*-benzyl isatins. Unfortunately, the monofluorinated 3-hydroxyoxindole was afforded with racemic mixture form (Scheme 1, eq c).[8]

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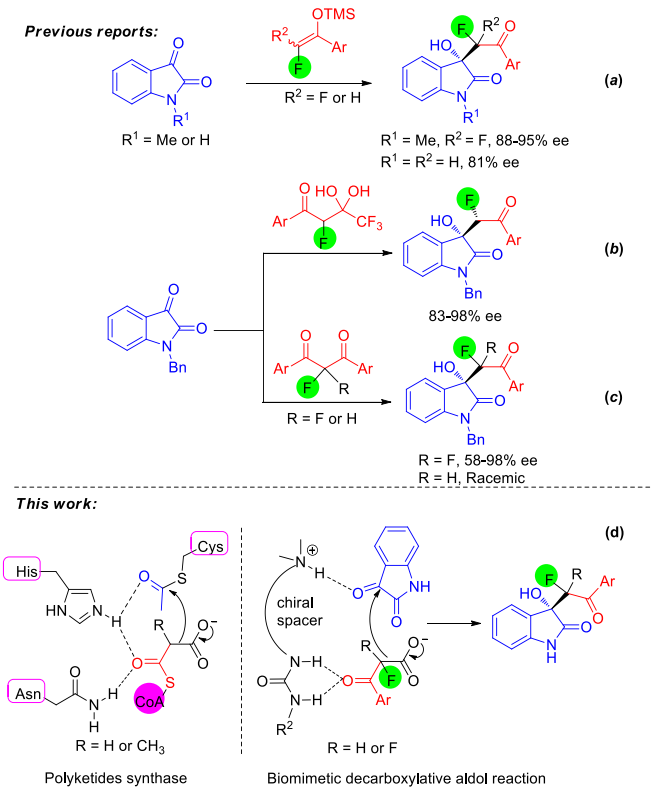


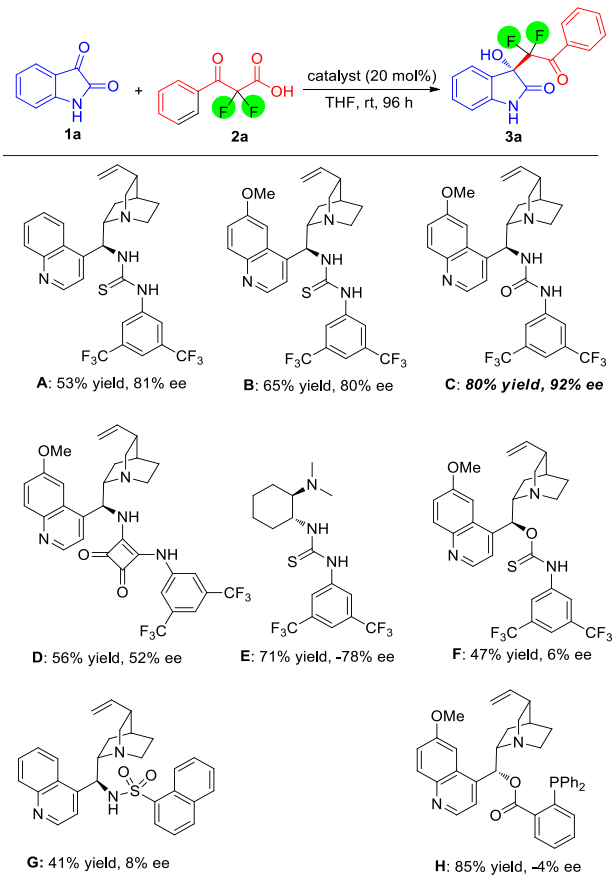
Scheme 1. Enantioselective synthesis of fluorinated 3-hydroxy-2-oxindoles.

Although the above mentioned methods have been established, several challenging problems remain to be solved. For example, these methods were restricted to the syntheses of either difluorinated or monofluorinated oxindoles, and *N*-protecting groups were usually required in order to get high enantioselectivities. Therefore, the further exploration of novel fluorinating precursors in the stereoselective synthesis of fluorinated oxindole analogues is still desirable. On the other hand, inspired by the polyketide biosynthesis via the activation of malonic acid half thioesters (MAHTs) by polyketide synthases (PKSs), a great number of organocatalytic enantioselective decarboxylative aldol reactions have been developed. Recently, Wennemers group reported an enantioselective organocatalyzed aldol reactions of fluoromalonic acid halfthioesters as a masked fluorinated thioacetate enolate with aldehyde.[9] In addition to being masked enolates, β-keto acids are safe and readily available starting materials, which largely enable their applications in the area of asymmetric decarboxylative aldol reaction as well as fluorination reaction.[10] But to the best of our knowledge, the reports on using fluorinated β-keto acids as fluorinating precursors remain very limited, especially the further extension of fluorinated β-keto acids in enantioselective synthesis was rarely recognized.[11] In this regard, we wish to report herein the asymmetric synthesis of di/mono-fluorinated 3-hydroxyoxindoles via organocatalytic biomimetic decarboxylative aldol reactions of α,α-difluoro/α-monofluoro-β-keto acids with unprotected isatins (Scheme 1, eq d).

Results and Discussion

At the outset of our work, the unprotected isatin **1a** and α,α-difluoro-β-keto acid **2a** were selected as the model substrates to evaluate various chiral organocatalysts (Table 1). To our delight, using the cinchona alkaloid-derived bifunctional thiourea **A** as catalyst and THF as solvent, the desired product **3a** was obtained in 53% yield and 81% ee. Encouraged by this result, the related H-bond donor quinine derivatives were examined and the thiourea catalyst **B** could afford **3a** with enhanced yield (65%) and similar enantioselectivity (80% ee). In the following, the quinine-derived urea **C** was found to be the most promising catalyst, furnishing the difluorinated 3-hydroxy oxindole in 80% yield with excellent enantioselectivity (92% ee). While the use of the squaramide-based catalyst **D** and the Takemoto's catalyst **E** led to the decrease of yields and ee values. Noteworthy, the dual H-bond donors of the catalyst seemed to be important for realizing effective enantiocontrol, due to the fact that catalysts **F-H** possessing one or no H-bond donor, the enantioselectivities of **3a** dropped significantly.

Table 1. Representative results of the catalyst evaluation.[a]



[a]Conditions: **1a** (0.15 mmol), **2a** (0.225 mmol), catalyst (20 mol%), THF (1.5 mL), rt for 96 h, isolated yield, ee was determined by HPLC analysis.

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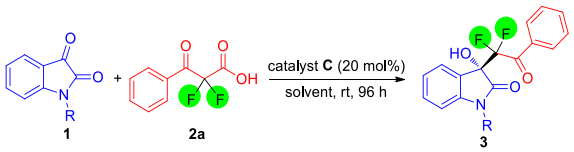
Table 2. Substitution effect of the nitrogen atom of isatin and optimization of the reaction conditions.[a]



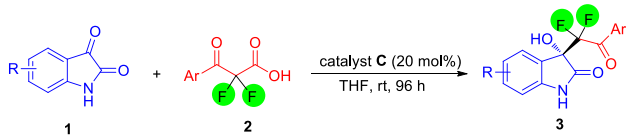
Entry	R	Solvent	Yield (%)[b]	ee (%)[c]
1	H	THF	80 (**3a**)	92
2	Me	THF	85 (**3b**)	91
3	Bn	THF	71 (**3c**)	88
4	H	CH_2Cl_2	60 (**3a**)	40
5	H	toluene	35 (**3a**)	14
6	H	CH_3CN	57 (**3a**)	20
7	H	MeOH	47 (**3a**)	0
8	H	DMF	83 (**3a**)	74
9[d]	H	THF	67 (**3a**)	92

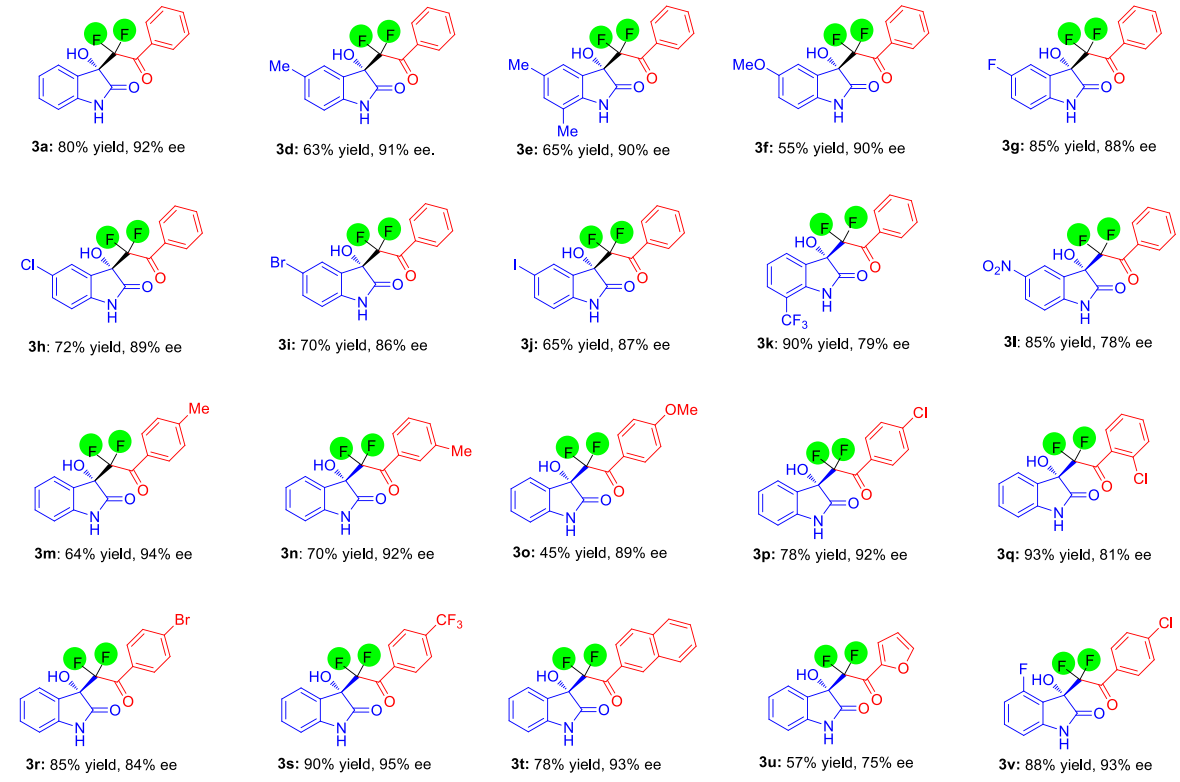
[a]Conditions: **1** (0.15 mmol), **2a** (0.225 mmol), catalyst **C** (20 mol%), solvent (1.5 mL), rt for 96 h. [b]Isolated yield. [c]ee was determined by HPLC analysis. [d]10 mol% of catalyst **C** was used.

After identified the suitable catalyst **C**, we set out to further optimize the reaction conditions (Table 2). The substitution effect of the nitrogen atom of isatin was first investigated. In addition to the unprotected isatin, *N*-methyl isatin and *N*-benzyl isatin also afforded the desired products (**3b** and **3c**) with good yields and enantioselectivities (Table 2, entries 2 and 3). Moreover, screening of different solvents revealed that CH_2Cl_2, toluene, CH_3CN and MeOH resulted in the remarkable decrease of yields and enantioselectivies (Table 2, entries 4 to 7). The employment of DMF has a negative impaction on the enantioselectivity, albeit with the yield being increased to 83% (Table 2, entry 8). By reducing the catalyst loading to 10 mol%, the enantioselectivity was maintained with 92% ee, but a diminished yield was observed (67%, Table 2, entry 9).

Having established the optimal conditions, we then studied the substrate scope of this newly established method. The representative results are depicted in Table 3. Generally, various isatins bearing both electron-donating and electron-withdrawing groups were employable, generating difluorinated oxindoles in good to excellent yields and enantioselectivities (Table 3, **3d** to **3l**). For instance, the methyl and methoxy substituted isatins exhibited 55-65% yields

Table 3. Substrate scope of isatins and α,α-difluoro-β-keto acids.[a]





[a]Conditions: **1** (0.15 mmol), **2** (0.225 mmol), catalyst **C** (20 mol%), THF (1.5 mL), rt for 96 h. Yields of isolated products are given. ee was determined by HPLC analysis.

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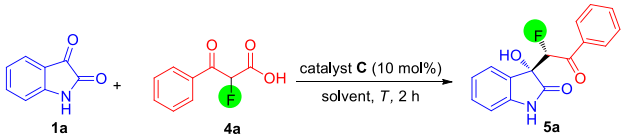
and 90-91% ee (**3d** to **3f**). Meanwhile, a variety of halogen-substituted isatins also furnished the desired products in satisfactory enantioselectivities (86-89% ee, **3g** to **3j**). The substrates with strong electron-withdrawing groups (CF_3, NO_2) afforded high yields of the corresponding products. However, lower enantioselectivies were observed in these two cases (78-79% ee, **3k** and **3l**). Subsequently, the scope of α,α-difluoro-β-keto acids was investigated (Table 3, **3m** to **3u**). Difluoro-β-keto acids appended with electron-rich groups (methyl and methoxy) were proved competent in the decarboxylative reaction, affording the desired products in 89-94% ee (**3m** to **3o**). Substrates containing halogen substituents in the *ortho*- and *para*-position of the aromatic ring were also tolerated well in the reaction, with high yields and enantioselectivities being obtained (78-93% yields, 81-92% ee, **3p** to **3r**). Of note is that the trifluoromethyl-substituted difluoro-β-keto acid could afford the product with up to 90% yield and 95% ee. (**3s**). In addition, naphthyl and heteroaryl substituents also gave the corresponding difluorinated oxindoles in 93% ee and 75% ee, respectively (**3t** and **3u**). Furthermore, the substituent at the 4-position of isatin had no obvious effect on the yield and enantioselectivity (Table 3, **3v**).

Table 4. Optimization of the mono-fluorinated 3-hydroxy oxindole synthesis.[a]

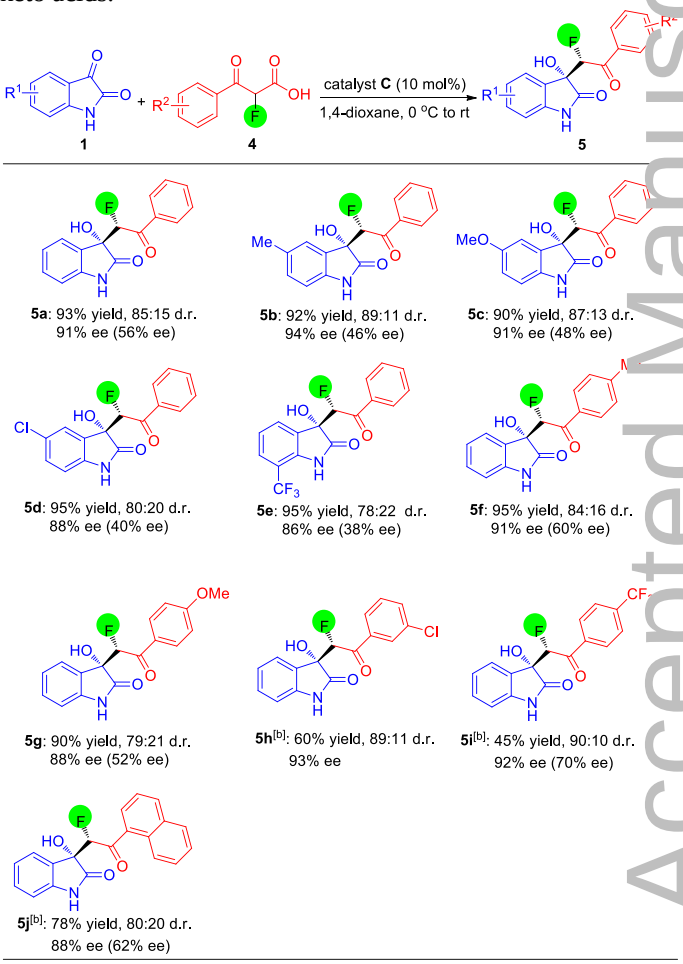


Entry	Solvent	*T* (°C)	Yield (%)[b]	d.r.[c]	ee (%)[c]
1[d]	THF	25	95	82:18	87
2	THF	25	93	82:18	90
3	CH_2Cl_2	25	42	54:46	37
4	DMF	25	84	81:19	88
5	toluene	25	35	63:37	50
6	MeOH	25	88	69:31	62
7	MTBE	25	78	69:31	62
8	1,4-dioxane	25	93	85:15	90
9	1,4-dioxane	10	92	82:18	90
10[e]	1,4-dioxane	0 to 25	93	85:15	91

[a]Conditions: **1a** (0.15 mmol), **4a** (0.75 mmol), catalyst **C** (10 mol%), solvent (1.5 mL), 2 h. [b]Isolated yield. [c] d.r. and ee (major isomer) were determined by HPLC analysis. [d] 20 mol% of catalyst **C** was used. [e] Reaction solution was stirred at 0 °C for 10 min, and then warmed to 25 °C. MTBE = methyl *tert*-butyl ether

To further demonstrate the versatility of the present method, the exploration of the mono-fluorinated 3-hydroxy oxindole synthesis was carried out (Table 4). Under the established conditions, the organocatalytic biomimetic decarboxylative aldol reaction of α-fluoro-β-keto acid **4a** with isatin delivered an excellent yield with 82:18 d.r. and 87% ee after 2 h (Table 4, entry 1). We were pleased to find that the amount of catalyst **C** decreased to 10 mol% could slightly enhance the steroselectivity (82:18 d.r., 90% ee, Table 4, entry 2). Extensive screening of solvents revealed CH_2Cl_2, DMF, toluene, MeOH and MTBE failed to give superior results (Table 4, entries 3 to 7). The subsequent investigation showed that 1,4-dioxane was the more suitable solvent, 85:15 d.r. and 91% ee were obtained by running the reaction at the temperature of 0 °C to 25 °C (Table 4, entry 10).

Table 5. Substrate scope of isatins and α-monofluoro-β-keto acids.[a]



[a]Conditions: **1** (0.15 mmol), **4** (0.75 mmol), catalyst **C** (10 mol%), 1,4-dioxane (1.5 mL), 0 °C for 10 min, and then warmed to 25 °C. Yields of isolated products are given. Values in brackets refer to the ee of the minor isomer, d.r. and ee were determined by HPLC analysis. [b]Reacted for 12 h.

With the optimal conditions in hand, the substrate scope of different isatins and α-fluoro-β-keto acids **4** was conducted and the results are illustrated in Table 5. Notably, the introductions of methyl and methoxy groups to isatins were generally beneficial for the diastereoselectivities, delivering the corresponding products with excellent enantioselectivities (94% and 91% ee, **5b** and **5c**). Halogen atom and trifluoromethyl group-modified isatins successfully gave the mono-fluorinated 3-hydroxyoxindoles in excellent yields (95%) and good steroselectivities (80:20 and 78:22 d.r., 88% and 86% ee, **5d** and **5e**). Additionally, other substituted α-fluoro-β-keto acids also could be employed in the asymmetric decarboxylative reaction without compromising the enantioselectivities (88-93% ee, **5f** to **5i**). The present reaction conditions were also compatible with the naphthyl-substituted α-fluoro-β-keto acid and the corresponding product could be isolated in 78% yield along with good stereoselectivity (80:20 d.r. and 92% ee, **5j**).

Conclusion

In summary, we have developed an asymmetric biomimetic decarboxylative aldol reaction utilizing fluorinated β-keto acids as the novel building blocks. In the presence of quinine-derived urea catalyst, various difluorinated 3-hydroxyoxindoles bearing a fully substituted carbon were obtained in moderate to good yields (45-93%) and good to excellent enantioselectivities (75-95% ee). Particularly, the present methodology also enables a highly efficient and valuable access to the enantioenriched monofluorinated 3-hydroxyoxindoles exhibiting vicinal chiral centers, good diastereoselectivities (d.r. up to 90:10) and excellent enantioselectivities (ee up to 94%) were observed. We hope this protocol will facilitate other applications of fluorinated β-keto acids in the stereoselective synthesis of numerous bioactive molecules.

Experimental Section

General procedure for the asymmetric synthesis of 3-difluoroalkyl-3-hydroxyoxindoles 3.

To a solution of isatin **1** (0.15 mmol) in THF (1.5 mL) was added catalyst **C** (17.3 mg, 0.03 mmol) and α,α-difluoro-β-keto acid **2** (0.225 mmol) at room temperature. The reaction mixture was stirred vigorously at room temperature for 96 h, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; gradient eluent: petroleum ether to 30% EtOAc in petroleum ether) to provide the 3-difluoroalkyl-3-hydroxyoxindole.

(*S*)-3-(1,1-difluoro-2-oxo-2-phenylethyl)-3-hydroxyindolin-2-one (3a). Yield: 80%, 36 mg, white solid, mp: 150-151 °C, R_f = 0.29 (30% EtOAc/petroleum ether); 92% ee, HPLC conditions: Daicel Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.5 mL/min, 254 nm; t_r (major) = 5.005 min, t_r (minor) = 8.963 min. Optical rotation: $[\alpha]_D^{15}$ = -353.7 (*c* = 0.41, MeOH). ^{1}H NMR (600 MHz, Acetone-d_6) δ 6.20 (brs, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 2H), 7.73 (t, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 7.7 Hz, 2H), 9.65 (brs, 1H). ^{19}F NMR (376 MHz, Acetone-d_6) δ -109.94 (s, 2F). ^{13}C NMR (151 MHz, Acetone-d_6) δ 76.9 (t, *J* = 25.6 Hz), 111.0, 117.9 (t, *J* = 262.7 Hz), 122.9, 126.8, 127.2, 129.6, 131.1 (t, *J* = 3.3 Hz), 131.7, 133.8, 135.4, 144.12, 174.0, 188.9 (t, *J* = 29.1 Hz). HRMS (ESI): *m/z* calcd for $C_{16}H_{11}F_2NNaO_3$ $(M+Na)^+$ 326.0605, found 326.0595.

General procedure for the asymmetric synthesis of 3-fluoroalkyl-3-hydroxyoxindoles 5.

The solution of isatin **1** (0.15 mmol) and catalyst **C** (8.7 mg, 0.015 mmol) in 1,4-dioxane (0.5 mL) was stirred at room temperature for 10 min. Then the reaction mixture was cooled to 0 °C, followed by the solution of freshly prepared α-fluoro-β-keto acid **4** (4.0-5.0 equiv) in 1,4-dioxane (1.0 mL) was added. After 10 min, the reaction slowly warmed to room temperature and further stirred for the reported time. The solvent was removed under reduced pressure, the crude product was purified by flash column chromatography (SiO_2; gradient eluent: petroleum ether to 30% EtOAc in petroleum ether) to provide the 3-fluoroalkyl-3-hydroxyoxindoles.

(*S*)-3-((*S*)-1-fluoro-2-oxo-2-phenylethyl)-3-hydroxyindolin-2-one (5a). Yield: 93%, 40 mg, colorless oil, R_f = 0.38 (40% EtOAc/petroleum ether); d.r. 85:15, 91% ee (major isomer), HPLC conditions: Daicel Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.5 mL/min, 254 nm; t_r (major) = 4.795 min, t_r (minor) = 6.637 min. Optical rotation: $[\alpha]_D^{15}$ = +25.6 (*c* = 0.43, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.97 (brs, 1H), 5.96 (d, *J* = 46.2 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 7.11 – 7.22 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 9.07 (brs, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.10 –193.35 (m, 1F). ^{13}C NMR (151 MHz, $CDCl_3$) δ 76.7 (d, *J* = 25.2 Hz), 91.2 (d, *J* = 190.7 Hz), 111.1, 123.1, 125.8, 126.1, 128.7, 129.5 (d, *J* = 3.5 Hz), 130.8, 134.5, 135.2, 141.6, 177.1, 195.3 (d, *J* = 19.4 Hz). HRMS (ESI): *m/z* calcd for $C_{16}H_{12}FNNaO_3$ $(M+Na)^+$ 308.0699, found 308.0706.

Acknowledgements

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FULL PAPER

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