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Enantioseletive Fluorination of 3-Functionalized Oxindoles Using Electron-rich Amino Urea Catalyst

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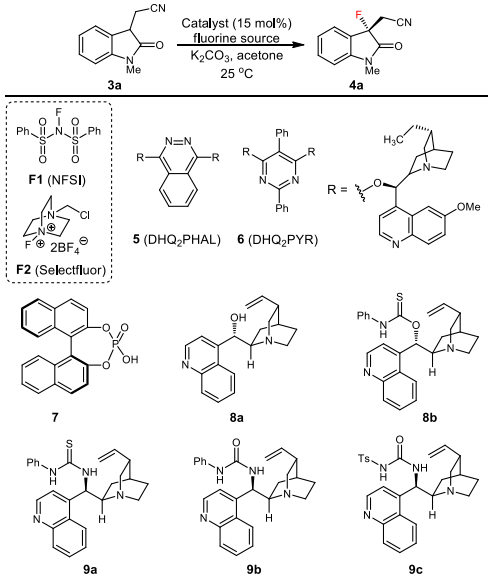
Abstract. An enantioselective fluorination of 3-functionalized oxindoles using electron-rich amino urea catalyst is described. Various 3-functionalized 3-fluoro-2-oxindoles were obtained in good yields and enantio-selectivity. The resulting enantioenriched 3-methylene nitrile 3-fluoro-2-oxindole product was found to inhibit indoleamine 2,3-dioxygenase considerably.

Keywords: Asymmetric catalysis; Fluorination; 3-Functionalized oxindoles; Catalyst; Anti-cancer agent

Oxindole motifs present in many biologically active compounds[1] and natural products.[2] Thanks to the unique features of organofluorine compounds,[3] fluorinated indoles become a common modification in improving the bioactivity of relevant pharmaceutical products.[1e,g] In particular, it was found that enantioenriched 3-substituted 3-fluoro-2-oxindoles exhibit broad applications in medicinal chemistry.[1e,f] Owing to the potential of medical applications of 3-substituted 3-fluoro-2-oxindoles, several groups have developed enantioselective fluorination of 3-aryl and 3-alkyloxindoles.[4] Other relevant approaches include asymmetric aldol reaction with fluoroenolates[5] and palladium-catalyzed cyclization[6] were documented. However, majority of these methods rely on transition metal catalysis and require the protection of the N-H indole moiety. While Shibata and co-workers reported that cinchona alkaloid-derived organocatalysts could promote the enantioselective fluorination of 2-oxindoles, the scope is limited to 3-aryl-substituted substrates.[4d] Therefore, new methods to devise enantioenriched 3-functionalized 3-fluoro-2-oxindoles is still highly desired. Herein, we describe a novel synthetic strategy to produce diverse enantioenriched 3-fluoro-2-oxindoles bearing cyano, hydroxyl, amide, sulfonamide, ester, allyl and, alkyl functionalities using electron-rich urea organocatalyst. Moreover, it was identified that some of the fluorinated products exhibit significant anti-cancer activity.

Nitrile moiety is useful in many pharmaceutical structures, including bioactive molecules[1d] and natural products[2d]. Initially, the organocatalytic fluorination was performed using substrate 3-alkyl-2-oxindole **3a** in the presence of potassium carbonate in acetone. *N*-Fluorobenzenesulfonimide (**F1**, NFSI) was used as the electrophilic fluorinating agent (Table 1). While Shibata and co-workers reported that DHQ_2PHAL (**5**) and DHQ_2PYR (**6**) could promote the 3-fluorination of 3-aryl-2-oxindoles in moderate enantioselectivity,[4d] they were found to be ineffective in catalyzing the asymmetric fluorination of 3-alkyl-2-oxindole **3a** although satisfactory yield of product **4a** was obtained (entries 1 and 2). BINOL-derived phosphoric acid catalyst **7**, cinchonine (**8a**),

Table 1. Evaluation of Catalysts.



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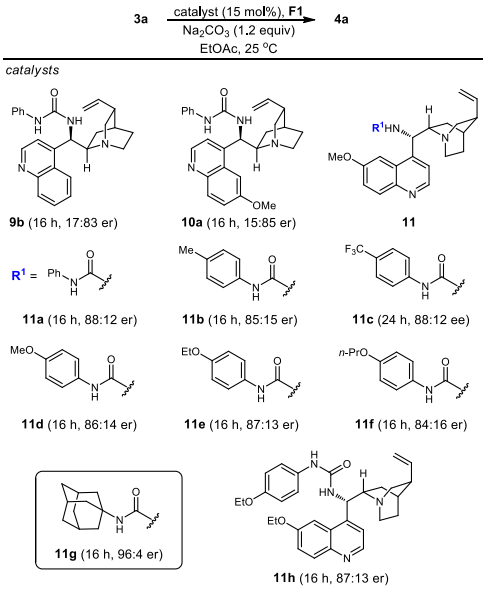
Entry[a)]	F	Catalyst	Time (d)	Yield (%)[b)]	er[c)]
1	**F1**	**5**	2	73	50:50
2	**F1**	**6**	2	76	5842
3	**F1**	**7**	4	trace	ND
4	**F2**	**7**	4	trace	ND
5	**F1**	**8a**	4	trace	ND
6	**F2**	**8a**	4	trace	ND
7	**F1**	**8b**	4	trace	ND
8	**F2**	**8b**	4	trace	ND
9	**F1**	**9a**	4	trace	ND
10	**F1**	**9b**	1	34	35:65
11	**F1**	**9c**	1	45	61:39
12	**F2**	**9b**	4	trace	ND

[a)] Reactions were carried out with substrate **3a** (0.1 mmol), catalyst (0.015 mmol), K_2CO_3 (0.12 mmol) and fluorine source (0.12 mmol) in acetone (3 mL) at 25 °C. [b)] Isolated yield. [c)] Determined by chiral HPLC. Ts = 4-toluenesulfonyl.

amino-thiocarbamate (**8b**), and amino-thiourea (**9a**) also failed in promoting the fluorination of **3a** (entries 3–9). To our delight, appreciable yields and enantiomeric ratio (er) of the desired product **4a** could be obtained when cinchona alkaloid-derived urea catalyst **9b** or **9c** was applied (entries 10 and 11). The reaction was sluggish when changing the fluorinating agent to selectfluor (**F2**) (entry 12).

A brief survey on solvents and bases revealed the superior performance of EtOAc with sodium carbonate, providing **4a** in 17:83 er when catalyst **9b** was used (Table 2).[7] The use of catalyst **10a** with a quinidine skeleton increased the er to 15:85. Switching the catalyst backbone to the quinine-derived catalyst **11a** further improved the enantioselectivity to 88:12 er. Although it is well-documented that electronic demand on the urea-system is often a crucial factor in organocatalytic enantioselective reaction,[8–9] it was found that neither

Table 2. Study on Effect of The Substituent on The Urea Catalysts.[a)]

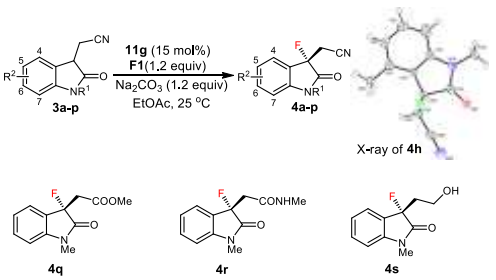


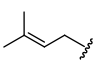
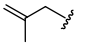
[a)] Reactions were carried out with substrate **3a** (0.1 mmol), catalyst (0.015 mmol), Na_2CO_3 (0.12 mmol) and **F1** (0.12 mmol) in EtOAc (3 mL) at 25 °C.

electron-rich nor electron-deficient urea catalysts (**11b**-**11f**) could alter the er substantially. Nonetheless, further modification of the urea moiety leading us to the discovery that catalyst **11g** bearing an admantyl substituent returned a 96:4 er. Increasing the bulkiness of the quinoline moiety (**11h** vs **11e**) returned equal enantiomeric ratio (87:13 er).

After identifying the optimal catalyst, we continued to investigate the substrate scope of this reaction (Table 3). The catalytic fluorination protocol was found to be compatible with a range of oxindoles with different *N*-substituents such as methyl and ethyl groups (entries 1-2). Unsaturated compounds are sensitive towards electrophilic fluorination. Nonetheless, olefinic (**3c**-**3e**) and propargyl (**3f**) substrates were well-tolerated under the reaction conditions (entries 3-6). *N*-Phenyl oxindole **3g** also worked well in the system (entry 7). A series of *N*-methyl oxindoles with different electron-rich or electron-deficient substitutions at the aryl system were also examined and good yields and enantioselectivity were generally observed (entries 8-16). The absolute configuration of the product **4h** was determined by X-ray diffraction analysis on the single-crystal sample.[7] It's noteworthy that substrates bearing an ester, an amide or a hydroxyl group returned high yield and enantio-control (entries 17-19). In addition, the reaction was scable in excellent yield with equal high er ratio (entry 20).

Table 3. Substrate Scope of Fluorination of *N*-Substituted Oxindole **3**.



Entry[a)]	R^1	R^2	Time (h)	4	Yield[b)], er[c)]
1	Me	H	16	**4a**	65, 96:4
2	Et	H	16	**4b**	68, 90:10
3	Allyl	H	16	**4c**	69, 90:10
4		H	20	**4d**	70, 89:11
5		H	20	**4e**	69, 92:8
6	Proparyl	H	16	**4f**	67, 91:9
7	Ph	H	24	**4g**	71, 95:5
8	Me	4-Me	16	**4h**	85, 95:5
9	Me	5-Me	16	**4i**	85, 96:4
10	Me	6-Me	16	**4j**	86, 97:3
11	Me	7-Me	16	**4k**	79, 94:6

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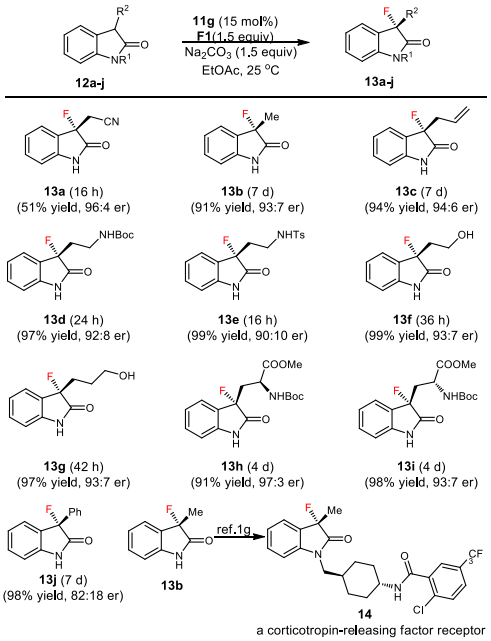
12	Me	6-F	24	**4l**	75, 95:5
13	Me	5-Cl	24	**4m**	68, 91:9
14	Me	5-Br	20	**4n**	66, 96:4
15	Me	6-Br	20	**4o**	62, 92:8
16	Me	5-OMe	18	**4p**	69, 92:8
17	-	-	168	**4q**	93, 95:5
18	-	-	24	**4r**	98, 95:5
19	-	-	168	**4s**	96, 90:10
20[d)]	-	-	36	**4r**	99, 95:5

[a)] Reactions were carried out with **3** (0.2 mmol), catalyst **11g** (0.03 mmol), Na_2CO_3 (0.24 mmol) and **F1** (0.24 mmol) in EtOAc (6 mL) at 25 °C. [b)] Isolated yield. [c)] Determined by chiral HPLC. [d)] The reaction was conducted on a 1 mmol scale.

It is worth-mentioning that *N*-protection-free 3-fluoro-2-oxindoles could be useful in the preparation of pharmaceutically important compounds without going through the laborious protection/deprotection procedures. To the best of our knowledge, however, only one literature reported the enantioselective fluorination of unprotected 3-substituted oxindoles with substrate scope limited to 3-alkyl and 3-aryl substitions.[4e]

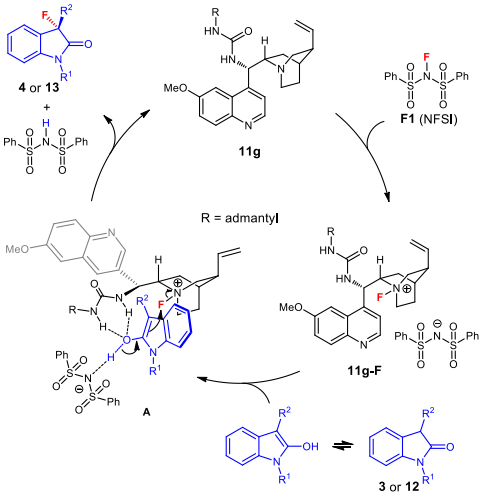
Table 4. Substrate Scope of Fluorination of **12**.[a)]



[a)] Reactions were carried out with **12** (0.2 mmol), catalyst **11g** (0.03 mmol), Na_2CO_3 (0.24 mmol) and **F1** (0.24 mmol) in EtOAc (6 mL) at 25 °C. Isolated yields were recorded. Er was determined by chiral HPLC.

Nonetheless, we are delighted to realize that the catalytic protocol was also suitable to *N*-protection-free 2-oxindoles. For instance, 3-methyl-2-oxindole (**12b**) could readily be converted to the corresponding 3-fluorinated product **13b** in good enantioselectivity (Table 4). **13b** is the key advanced intermediate for the preparation of the bioactive compound **14**[1g] and our approach provides an easy access to such compound. Further attempt in diversifying the scope revealed that the current method is compatible with many functionalities at the C(3) position (Table 4). High enantio-control was observed when cyano group containing substrate was utilized (**12a**). Alkyl and allyl containing oxindole substrates **12b-c** were capable of delivering high enantioselectivities, though much longer time was required to obtain high yields. Substrates possessing NHBoc, NHTs and ester moiety provided products in excellent yields and high enantioselectivities (**12d-e, 12h-i**). High er values could also be acquired when hydroxyl-containing oxindole substrates were used (**12f-g**). Unfortunately, the current reaction conditions were not suitable for 3-aryl-substituted 2-oxindole substrate (**12j**).

A brief investigation on the possible intermediate was conducted by ^{19}F NMR experiment on a mixture of the catalyst **11g** and NSFI under basic condition. The fluorine signal exhibited a downfield-shift from –40.0 ppm (pure NSFI) to 42.4 ppm (the putative complex **11g-F**), which could be attributed to the coordination of the quinuclidine's nitrogen of **11g** to the fluorine of NSFI.[4d] Since the *N*-protection-free 2-oxindoles **12** also worked well under the catalytic protocol, we believe that the N-H in the oxindole substrate does not play a crucial role in the enantio-determining step. A proposed catalytic cycle is depicted in Scheme 1. We speculate that catalyst **11g** might firstly react with NSFI to generate the putative fluorinating species **11g-F**. The 2-oxindole **3** or **12** could then hydrogen-bond to the urea moiety to give intermediate **A** and subsequent fluorination to yield product **4** or **13**. Instead of an electron-withdrawing group, we suspect that the bulky admantyl group in **11g** might offer optimal steric demand for the effective asymmetric transformation.



Scheme 1. Proposed Mechanism.

Small-molecule inhibitors of indoleamine 2,3-dioxygenase (IDO) are currently being translated to clinic for evaluation as cancer therapeutics.[10] Recently, the indole-based compound Indoximod has been identified as a selective IDO_2 inhibitor and is currently under clinical trial for cancer treatment.[10b-c]

We also evaulated the IDO_2 inhibition effect of the newly synthesized 3-fluoro-2-oxindole derivatives. The starting material **12a** (table 5, entry 1) shown very poor effect on IDO_2, while **13a** inhibited IDO_2 substantially, indicating that α-fluorination is of critical importance to increase bioactivity. Compared to Indoximod, product **13a** was capable of inhibiting IDO_2 considerably (table 5, entry 2), while products **13e**, **13f** and **13g** could inhibit IDO_2 with moderate effect (table 5, entries 4−6).[7] Elaboration of these compounds is underway in order to develop potential anti-cancer agents. The resulting products bearing diverse functional groups allow for a rapid synthesis of fluorine-containing bioactive molecules.

Table 5. Results of IDO_2 Inhibition Effect.

Entry	Compound	IC_{50} of IDO_2 (μM)
1	**12a**	>1000
2	**13a**	16
3	**13c**	>1000
4	**13e**	102
5	**13f**	278
6	**13g**	81
7	**4q**	>1000
8	**4r**	>1000
9	**4s**	>1000
10	**Indoximod**	465

In summary, we have developed an efficient and highly enantioselective fluorination of 3-substituted 2-oxindoles in the presence of chiral urea catalyst. Various *N*-protected and *N*-unprotected tertiary 3-oxindoles bearing diverse functionalities were synthesized in excellent yields and high enantioselectivities. The method herein substantially broadens the scope of tertiary 3-fluoro-2-oxindoles, which is beneficial to organic and medicinal chemistry. Further studies to investigate the bioactivities and elaboration of these products are ongoing.

Experimental Section

General Procedure for Enantioselevtive Fluorination. To a EtOAc (6 mL) solution of 3-substituted oxindole substrates **3** or **12** (0.2 mmol, 1.0 equiv) and catalyst **11g** (15.0 mg, 0.03 mmol, 0.15 equiv) at room temperature, was added Fluorobenzenesulfonimide (**F1**, NFSI) (75.6mg, 0.24 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature and monitored by TLC. The solution was diluted with water (5 mL) and extrated with EtOAc, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc) to yield the corresponding 3-fluoro 3-functionalized oxindole products **4** or **13**.

Acknowledgements

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[7] The details present in the Supporting Information. CCDC 1860684 contains supplementary crystallographic data for compound **4h**.

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