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Asymmetric Conjugate Addition of Ethylene Sulfonyl Fluorides to 3-Amido-2-oxindoles: Synthesis of Chiral Spirocyclic Oxindole Sultams

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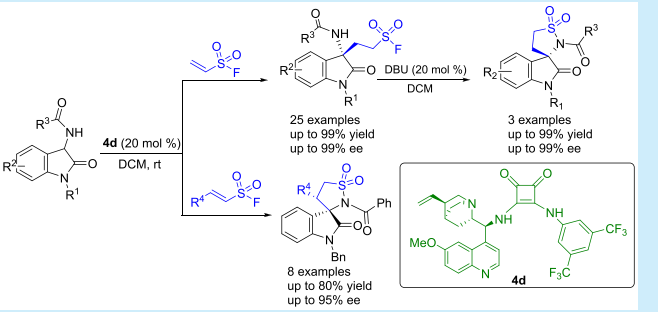
Supporting Information

ABSTRACT: An enantioselective conjugate addition of ethylene sulfonyl fluorides to 3-amido-2-oxindoles has been developed. Quinine-derived squaramides were identified as efficient catalysts. A series of spirocyclic oxindole sultams were prepared with excellent yields and enantioselectivities. A reaction mechanism via bifunctional activation was proposed.



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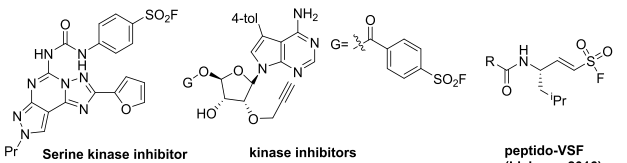
In recent years, sulfonyl fluorides have received great attention in organic synthesis and medicinal chemistry.[1] Sharpless and co-workers have developed several sulfur(VI) fluoride exchange (SuFEx) reactions with excellent chemo- and regioselectivities. Unlike conventional sulfonyl chlorides, sulfonyl fluorides have unique physicochemical properties, such as the resistance to the reduction, high thermodynamic stability, controllable reactivity, and strong interaction of hydrogen bonding. Therefore, sulfonyl fluorides were widely explored as irreversible inhibitors or probes against protein and nucleic acid targets (Scheme 1).[2]

Scheme 1. Representative Drugs and Probes Containing a Sulfonyl Fluoride Group



Among the various methods for the introduction of a sulfonyl fluoride group, the reactions with ethylene sulfonyl fluorides (ESFs) are extremely valuable due to their excellent reactivity.[1a,3,4] ESFs could be used as dienophiles in Diels−Alder reactions.[5] They were also used as excellent Michael acceptors in a variety of transformations.[6] During the reactions, the SO_2F group generally remains unaffected. The further elaborations of the SO_2F group were achieved under more forced conditions or in the presence of appropriate catalysts. Lupton and co-workers reported an N-heterocyclic carbene (NHC) catalyzed addition of arylethenesulfonyl fluorides to trimethylsilylated 1,3-dicarbonyl compounds. A series of unsaturated δ-sultones were prepared in good yields.[6b] Recently, Qin and co-workers utilized ESF to synthesize a variety of fused δ-sultone heterocycles.[6c,d] Despite this progress, catalytic asymmetric reaction of ESFs had rarely been explored before. Recently, Leung and co-workers reported an enantioselective hydrophosphination reaction of β-arylethenesulfonyl fluorides.[7a] Qin and co-workers also developed an enantioselective conjugate addition of arylboronic acid to β-arylethenesulfonyl fluorides.[7b] As a continuous effort to develop organocatalytic asymmetric reactions, we envisioned that ESFs are suitable Michael acceptors.[8] The new reactions will provide chiral sulfonyl fluorides, which are useful candidates as covalent inhibitors and protein probes.

3-Amino-2-oxindoles are a class of attracting nucleophiles in the organocatalytic conjugate additions.[9] The resulting chiral 3,3-disubstituted 2-oxindoles are valuable for the synthesis of oxindole-derived natural products and the screening of new drug candidates.[10] Herein, we would like to report an asymmetric conjugate addition of 3-amide oxindoles to ESFs. A series of chiral sulfonyl fluorides with 3,3-disubstituted 2-oxindole scaffolds were prepared with excellent yields and enantioselectivities. Furthermore, the products were readily transformed to chiral spirocyclic oxindole sultams without loss of the optical purity.

Initially, the reaction of 3-benzamido oxindole **1a** with ESF **2a** was examined in the presence of chiral organocatalysts **4a**−**4j**, and the results are summarized in Table 1. Quinine **4a**

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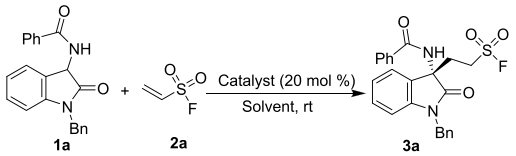
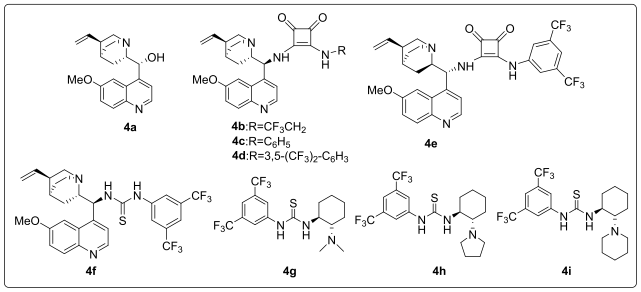
Table 1. Optimization of the Reaction Conditions[a]





entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**4a**	DCM	86	-
2	**4b**	DCM	71	91
3	**4c**	DCM	97	94
4	**4d**	DCM	98	99
5	**4e**	DCM	97	−91
6	**4f**	DCM	93	97
7	**4g**	DCM	55	−88
8	**4h**	DCM	32	−85
9	**4i**	DCM	72	−91
10	**4d**	$CHCl_3$	95	98
11	**4d**	DCE	91	98
12	**4d**	toluene	87	99
13	**4d**	THF	71	96
14	**4d**	Et_2O	67	89
15	**4d**	EtOAc	78	96
16	**4d**	1,4-dioxane	88	98
17	**4d**	MeCN	69	88
18	**4d**	MeOH	66	72
19[d]	**4d**	DCM	83	99
20[e]	**4d**	DCM	76	99

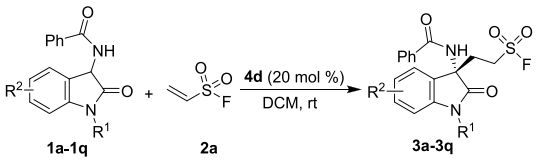
[a]The reactions were conducted with **1a** (0.10 mmol), **2a** (0.12 mmol), and catalysts **4a**−**4i** (0.02 mmol) in 1.0 mL of solvent at room temperature for 12 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]15 mol % of **4d** was used. [e]10 mol % of **4d** was used.

could catalyze the reaction, but only racemic product **3a** was obtained (Table 1, entry 1). To our delight, quinine-derived squaramides **4b**−**4d** provided **3a** in good yields and with excellent enantioselectivities (Table 1, entries 2−4). The quinidine-derived squaramide **4e** gave the opposite enantiomer of **3a** with excellent enantioselectivity (Table 1, entry 5). The quinine-derived thiourea **4f** is also efficient. The excellent yield and enantioselectivity were obtained (Table 1, entry 6). The chiral cyclohexane-1,2-diamine-derived thioureas **4g**−**4i** also catalyzed the transformation, however with inferior yields and enantioselectivities (Table 1, entries 7−9).

Furthermore, a series of reaction solvents were screened using **4d** as the catalyst. Generally, excellent yields and enantioselectivities were achieved in less polar solvent such as chloroform, dichloroethane, toluene, THF, ether, ethyl acetate, and 1,4-dioxane (Table 1, entries 10−16). Lower yields and enantioselectivities were obtained in polar solvents including acetonitrile and methanol (Table 1, entries 17−18). The effect of the loading of catalyst **4d** was also examined. Although the enantioselectivities were kept well at the loading of 15 mol % and 10 mol % **4d**, the yields were gradually reduced (Table 1, entries 19−20).

With the optimal reaction conditions in hand, a series of 3-benzamido-2-oxindoles were examined, and the results are summarized in Table 2. The N1 substituent exerted a slight

Table 2. Asymmetric Addition of ESF to 3-Benzamido-2-oxindoles 1a−1q[a]



entry	1	R^1/R^2	yield (%)[b]	ee (%)[c]
1	**1a**	Bn/H	98	99
2	**1b**	Ph/H	88	99
3	**1c**	Me/H	85	99
4	**1d**	Bn/5-F	97	98
5	**1e**	Bn/5-Cl	99	98
6	**1f**	Bn/5-Br	98	99
7	**1g**	Bn/5-Me	98	99
8	**1h**	Bn/5-MeO	99	98
9	**1i**	Bn/6-F	91	99
10	**1j**	Bn/6-Cl	92	97
11	**1k**	Bn/6-Br	93	99
12	**1l**	Bn/6-MeO	99	98
13	**1m**	Bn/7-F	99	98
14	**1n**	Bn/7-Cl	93	99
15	**1o**	Bn/7-Br	93	98
16	**1p**	Bn/7-CF_3	86	98
17	**1q**	Bn/5,7-diMe	83	99

[a]The reactions were conducted with **1a**−**1q** (0.10 mmol), **2a** (0.12 mmol), and **4d** (0.02 mmol) in DCM (1.0 mL) at room temperature for 12 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

influence on the yield, but the enantioselectivity was not disturbed (Table 2, entries 1−3). 5-Substitution on oxindole was tolerated very well. 5-Halogenated (F, Cl, Br), 5-methyl, and 5-methoxyl substrates provided excellent yields and enantioselectivities (Table 2, entries 4−8). 6-Substituted substrates **1i**−**1l** also afforded excellent enantioselectivities; however, slightly low yields were obtained (Table 2, entries 9−12). 7-Substituted substrates were also examined. Excellent yields and enantioselectivities were obtained for **1m**−**1o** (Table 2, entries 13−15). Lower yields were observed for 7-CF_3- and 5,7-dimethyl-substituted substrates **1p**−**1q** (Table 2, entries 16−17).

Further exploration of the substrate scope was focused on different 3-amido-2-oxindoles **1r**−**1y**, and the results are summarized in Scheme 2. Excellent yields and enantioselectivities were generally obtained for 2-oxindoles with the 3-arylamido group (such as 2-naphthamido, 3-indolecarboxamido, 2-thiophencarboxamido, and 2-furancarboxamido). 3-Cyclopropanecarboxamido-2-oxindole **1v** and cyclopentanecarboxamido-2-oxindole **1w** are also suitable substrates. Good yields and excellent enantioselectivities were obtained. For 4-tetrahydropyrancarboxamido-2-oxindole **1x**, although excellent enantioselectivity was achieved, low yield was obtained. 3-Ethoxycarboxamido-2-oxindole **1y** was also applicable. Good yield and enantioselectivity were obtained. A single crystal of

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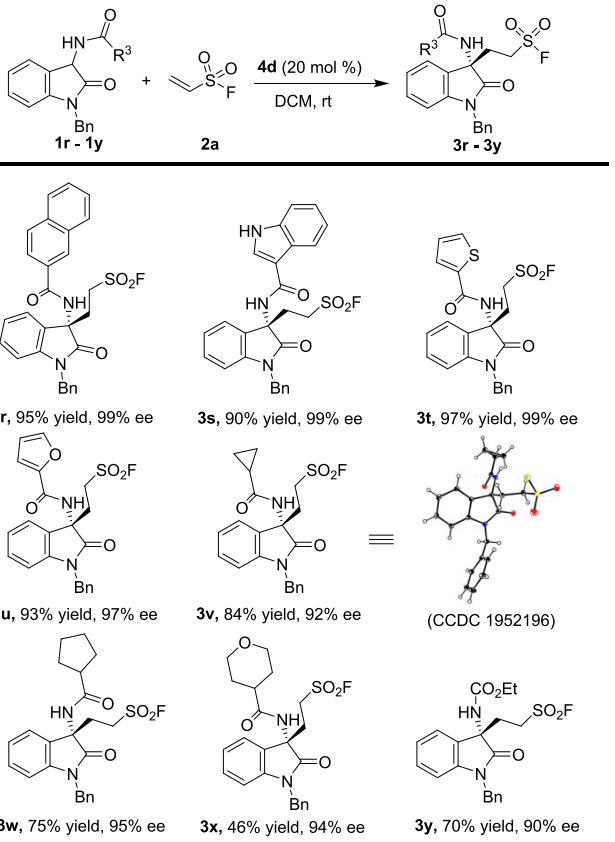
Scheme 2. Asymmetric Addition of ESF to 3-Amido-2-oxindoles 1r−1y[a]



[a]The reactions were conducted with **1r−1y** (0.10 mmol), **2a** (0.12 mmol), and catalyst **4d** (0.02 mmol) in DCM (1.0 mL) at room temperature for 12 h.

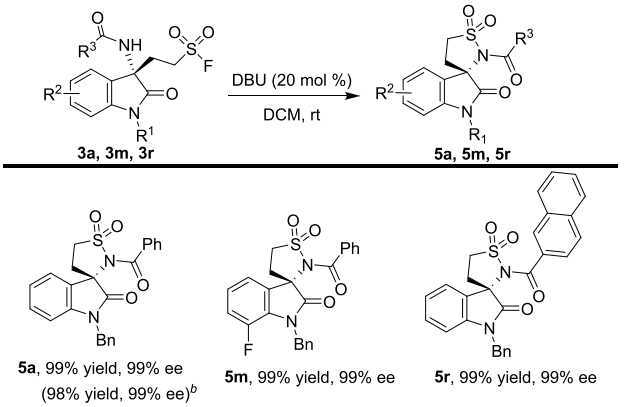
product **3v** was obtained, and the absolute configuration was confirmed as *S* by X-ray diffraction analysis. Other products were supposed to have *S* configuration analogously. We also examined the reaction of ESF with 3-benzoxy-2-oxindole, 3-hydroxy-2-oxindole, 3-phenylthio-2-oxindole, and 3-phenyl-2-oxindole; however, no expected addition products were obtained.[11]

While the products **3a**, **3m**, and **3r** were treated with DBU, the intramolecular cyclization occurred to give spirocyclic oxindole sultams **5a**, **5m**, and **5r** with excellent yields and enantioselectivities (Scheme 3). The similar spirocyclic oxindoles were reported to possess a variety of interesting biological activities.[12] We expect that spirocyclic oxindole sultams are also highly valuable for the studies of medicinal chemistry.

A reaction of 3-benzamido-2-oxindole **1a** and ESF in 3 mmol scale was also examined. The product **3a** was obtained with excellent yield and enantioselectivity (1.3 g, 96% yield, 99% ee, Scheme 4). To demonstrate the applications of the products in SuFEx chemistry, the reactions of **3a** with pyrrolidine and *p*-methoxyphenyl TBS ether were examined, respectively. The corresponding sulfamide **7a** and sulfonate **8a** were obtained in good yields and with excellent enantioselectivities (Scheme 4). In both cases, a small amount of **5a** was observed due to the competitive intramolecular cyclization.

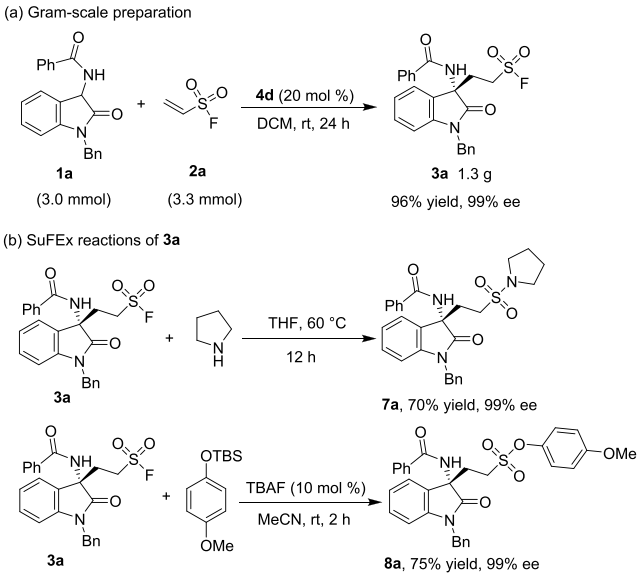
To further demonstrate the generality of this reaction, a series of *β*-arylethenesulfonyl fluorides were examined, and the

Scheme 3. Synthesis of Chiral Spirocyclic Oxindole Sultams[a]



[a]The reactions were conducted with **3** (0.10 mmol) and DBU (0.02 mmol) in DCM (1.0 mL) at room temperature for 12 h. [b]Scale-up reaction of **3a** (1.5 mmol).

Scheme 4. Gram-Scale Preparation and SuFEx Reactions of Product 3a



results are outlined in Scheme 5. The reaction afforded optically active spirocyclic oxindole sultams via a conjugate addition and spontaneous cyclization. *β*-Phenylethenesulfonyl fluoride and various substituted *β*-phenylethenesulfonyl fluorides were applied successfully. Good yields, enantioselectivities, and diastereoselectivities were achieved. The steric configuration of the major diastereoisomer of product **6ab** was determined via X-ray diffraction analysis. The inferior enantioselectivities in comparison with ESF may be caused by the unfavorable steric interaction of *β*-aryl with 3-benzamido-2-oxindole **1a**. The *β*-heteroarylethenesulfonyl fluorides **2g−2i** are also applicable. Moderate yields and good enantioselectivities were obtained; however, the diastereoselectivities were lower in comparison with *β*-phenylethenesulfonyl fluorides.

A tentative reaction mechanism is illustrated in Scheme 6. 3-Benzamido-2-oxindole **1a** is deprotonated by catalysts **4d** to generate an enolate anion. The electrostatic attraction and hydrogen bonding are expected between the ammonium cation

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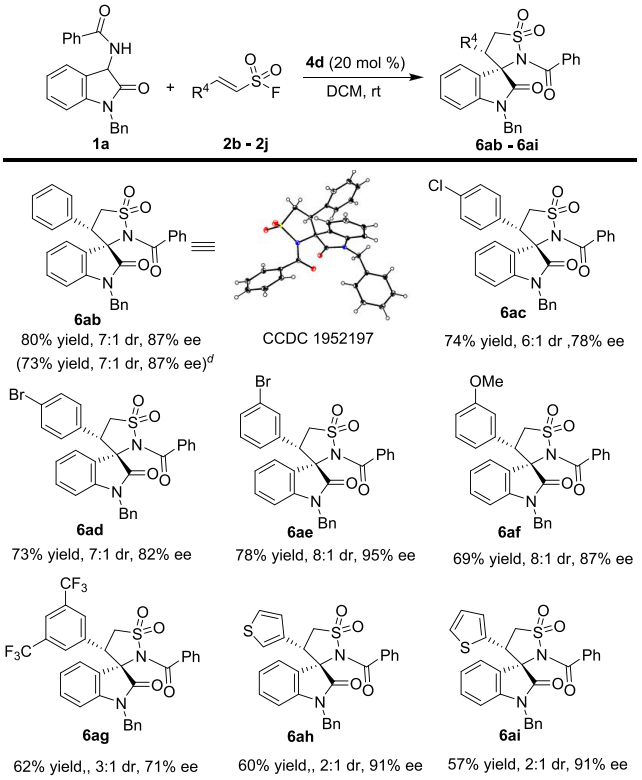
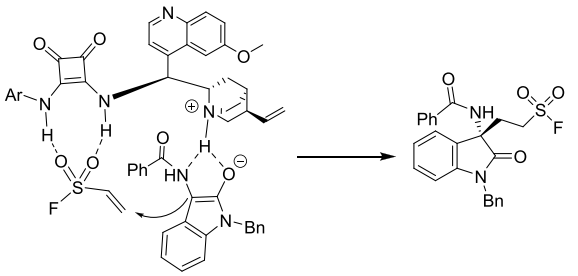
Scheme 5. Asymmetric Addition of β-Arylethenesulfonyl Fluorides to 1a[a–c]



[a]The reactions were conducted with **1a** (0.10 mmol), **2b–2j** (0.12 mmol), and **4d** (0.02 mmol) in DCM (1 mL) at room temperature for 24 h. [b]Only structural drawings of major diastereoisomers were provided. [c]The dr values were determined by ^{1}H NMR analysis. [d]Scale-up reaction of **1a** (1.5 mmol).

Scheme 6. Proposed Reaction Mechanism



and enolate anion. ESF is activated via the double hydrogen bonding with the squaramide group. The attack of ESF from the *Re* face of enolate leads to the product **3a**.

In summary, we have developed an asymmetric conjugate addition of 3-amido-2-oxindoles to ethenesulfonyl fluorides. Quinine-derived squaramides were found to be highly efficient catalysts. Excellent yields and enantioselectivities were obtained under mild reaction conditions. The further transformations to optically active spirocyclic oxindole γ-sultams, sulfamide, and sulfonate were achieved. The results demonstrate that ethenesulfonyl fluorides are suitable Michael acceptors for asymmetric organocatalytic transformations. Further applications of ethylenesulfonyl fluorides in catalytic asymmetric reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03911.

Complete experimental procedures and characterizations of new products; NMR spectra; and HPLC chromatograms (PDF)

Accession Codes

CCDC 1952196–1952197 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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