Enantioselective Addition of Azlactones to Ethylene Sulfonyl Fluoride via Dual Catalysis

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28 examples
Up to 96% yield and 99% ee

80% yield, 90% ee

84% yield, 98% ee
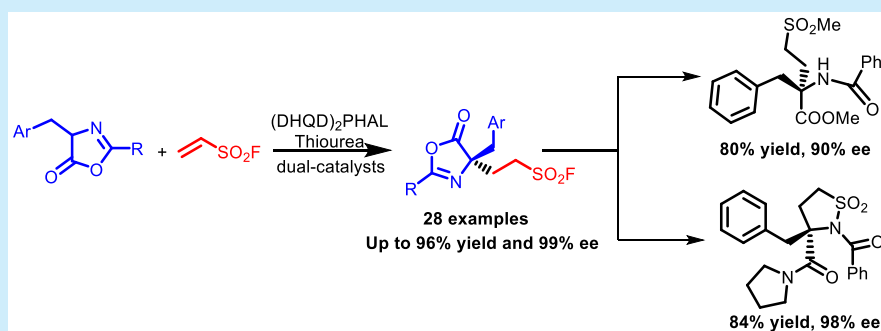
ABSTRACT: Enantioselective conjugate addition of azlactones to ethylene sulfonyl fluoride has been achieved via the cooperative catalysis with (DHQD)$_2$PHAL and a hydrogen-bond donor (HBD). This approach furnishes a facile access to a range of structurally diverse azlactone sulfonyl fluoride derivatives with good to excellent yields and enantioselectivities. The combination of azlactone and sulfonyl fluoride group produces valuable unnatural α-quaternary amino acid derivatives for the drug discovery.

Sulfonyl fluoride is a valuable synthetic motif that has great prospects in the area of pharmaceuticals, agrochemicals, and materials.[1] Sulfonyl fluoride is also known to be a potential irreversible inhibitor or protein probe, because of its high thermodynamic stability, controllable reactivity, and biocompatibility.[2] However, the availability of sulfonyl fluoride derivatives is still challenging.[3] Mostly, ethenesulfonyl fluoride (ESF), which is a strong Michael acceptor as well as Diels−Alder dienophile, is a useful reagent for the introduction of a sulfonyl fluoride group.[4] In 2014, Sharpless and co-workers reviewed the reactions of ESF with amines, N-containing heterocyclic compounds, and amino acids.[5] Sharpless, Qin, and other groups then developed more transformations of ESF.[6] Despite the progresses, asymmetric transformation of ESF had rarely been explored before. In 2019, Leung group reported phosphapalladacycle catalyzed enantioselective hydrophosphination reaction of β-arylethenesulfonyl fluorides.[7] In the same year, Rh-diene catalyzed enantioselective conjugate addition of arylboronic acid to β-arylethenesulfonyl fluorides[8] was reported by the Qin group. Recently, our group developed enantioselective conjugate additions of 3-amido-2-oxindoles to ESF[9] catalyzed by quinine-derived squaramides. In addition, the enantioselective conjugate addition of N-2,2,2-trifluoroethylisatin ketimines to ESF was also achieved.[10]

Given the unique value of azlactones[11] and sulfonyl fluoride, we are interested in an asymmetric reaction of azlactones and ESF. The transformation can offer an appealing way to access α-quaternary amino acid derivatives with sulfonyl fluoride

group. These products are valuable for drug discovery, because of their conformationally constrained nature of α-quaternary amino acid and covalent warhead of sulfonyl fluoride. Here, we report an enantioselective conjugate addition of azlactones to ESF via the cooperative catalysis with (DHQD)$_2$PHAL and a hydrogen-bond donor (HBD). A series of azlactone sulfonyl fluoride derivatives were obtained with good to excellent yields and enantioselectivities.

The conjugate addition of azlactone **1a** to ESF was used as the model reaction. A variety of chiral organocatalysts were examined, and the results are listed in Table 1. In our previous works, the bifunctional organocatalyst **2a** was found to be the best catalyst for the conjugate reaction of ESF.[9,10] However, in the present reaction, catalyst **2a** gave almost racemic product **4a** with poor yield (Table 1, entry 1). The thiourea analog **2b** also provided low yield and enantioselectivity (Table 1, entry 2). The quinine **2c** and cinchonine **2d** were found to give improved yields; however, the enantioselectivities were unsatisfactory (Table 1, entries 3 and 4). A number of other organocatalysts were also tried, but only low to moderate yields and poor enantioselectivities were obtained (see details
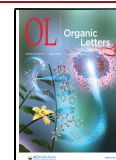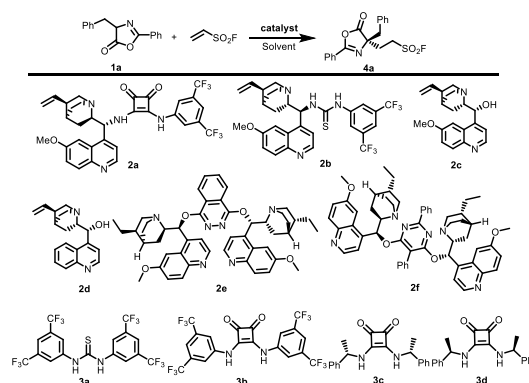
Table 1. Optimization of the Reaction Conditions[a]

entry	Cat. 2	Cat. 3	solvent	temperature, T (°C)	yield[b] (%)	enantiomeric excess, ee[c] (%)
1	2a	–	DCM	rt	18	−1
2	2b	–	DCM	rt	46	−11
3	2c	–	DCM	rt	65	−7
4	2d	–	DCM	rt	60	−5
5	2e	–	DCM	rt	79	37
6	2f	–	DCM	rt	78	17
7	2e	3a	DCM	rt	95	47
8	2e	3b	DCM	rt	94	43
9	2e	3c	DCM	rt	94	45
10	2e	3d	DCM	rt	94	45
11	2e	3a	Tol	rt	85	37
12	2e	3a	THF	rt	84	51
13	2e	3a	DCE	rt	89	37
14	2e	3a	CHCl₃	rt	97	59
15[d]	2e	3a	CHCl₃	rt	92	65
16[e]	2e	3a	CHCl₃	rt	91	60
17[d]	2e	3a	CHCl₃	0	92	71
18[d]	2e	3a	CHCl₃	−20	91	77
19[d]	2e	3a	CHCl₃	−40	90	85
20[d]	2e	3a	CHCl₃	−60	90	86
21[d]	2e	3a	CHCl₃	−78	90(86)[f]	90
22[d,g]	2e	3a	CHCl₃	−78	90	88

[a]Reaction conditions: **1a** (0.10 mmol), ESF (0.10 mmol), catalyst **2** (0.02 mmol) and **3** (0.02 mmol) in 1.0 mL solvent for 12 h. [b]Determined by ¹H NMR analysis of the crude product, using 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by chiral HPLC analysis. [d]2.0 mL of CHCl₃ was used. [e]3.0 mL of CHCl₃ was used. [f]Isolated yield was given in the parentheses. [g]10 mol % of **2e** and **3a** were used and the reaction time was 38 h.

in Scheme S1 in the Supporting Information (SI)). When cinchona alkaloid dimer (DHQD)₂PHAL **2e** was used, product **4a** was obtained with 79% yield and 37% ee (Table 1, entry 5). The similar catalyst **2f** gave 78% yield, but with inferior enantioselectivity (entry 6). Considering HBD catalysts can activate ESF,[9,10] the thiourea **3a** was added as a cocatalyst with **2e**. To our delight, the product **4a** was achieved with excellent yield and improved enantioselectivity (Table 1, entry 7). The squaramide **3b** provided the similar yield and slightly lower enantioselectivity (Table 1, entry 8). Two chiral squaramides **3c** and **3d** were also tested, and similar yields and enantioselectivities were observed (entries 9–10). The chiral structure of the squaramide seems to exert negligible effect on the enantioselectivity. The screening of reaction solvents revealed that chloroform could increase the yield and enantioselectivity (Table 1, entries 11–14). Better enantioselectivity was obtained when the reaction was conducted in a more dilute solution (Table 1, entry 15). The decrease of the reaction temperature showed beneficial effect on the enantioselectivity (Table 1, entries 17–21). While the reaction

was performed at −78 °C, the product **4a** was obtained with 86% isolated yield and 90% ee (Table 1, entry 21). Decreasing the catalyst loading from 20 mol % to 10 mol % did not influence the yield, but slightly eroded the enantioselectivity and prolonged the reaction time (Table1, entry 22). Finally, the optimal reaction conditions were identified as **1a** (0.10 mmol), ESF (0.10 mmol), **2e** (20 mol %), and **3a** (20 mol %) in CHCl₃ (2 mL), at −78 °C.

With the optimized reaction conditions in hand, azlactones **1a–1ab** were investigated (see Scheme 1). The substituted 2-phenyl azlactones were first explored. The electronic property of the substituent on the benzene ring exerted obvious influence on the enantioselectivity of the reaction. The *para*-methyl substituted substrate **1b** gave product **4b** with excellent yield and good enantioselectivity. *para*-Br and *para*-COOMe substituted substrates **1c** and **1d** afforded lower enantioselectivities. The steric hindrance of the substituent significantly influenced the enantioselectivity. The enantioselectivity was improved when the substitutions were changed from *para*- to *meta*- to *ortho*-position (**4b**, **4e**, and **4g**). *ortho*-Substituted

Scheme 1. Asymmetric Addition of Azlactone 1a–1ab to ESF[a]

4a, 86%yield, 90%ee   4b, 97%yield, 82%ee   4c, 89%yield, 70%ee   4d, 88%yield, 74%ee

4e, 89%yield, 87%ee   4f, 86%yield, 80%ee   4g, 84%yield, 92%ee   4h, 87%yield, 94%ee

4i, 83%yield, 92%ee   4j, 82%yield, 88%ee   4k, 87%yield, 92%ee   4l, 63%yield, 86%ee

4m, 88%yield, 86%ee   4n, 87%yield, 80%ee   4o, 80%yield, 66%ee   4p, 82%yield, 53%ee

4q, 93%yield, 81%ee   4r, 96%yield, 95%ee   4s, 86%yield, 94%ee   4t, 86%yield, 74%ee

4u, 90%yield, 84%ee   4v, 95%yield, 60%ee   4w, 82%yield, 79%ee   4x, 89%yield, 96%ee

4y, 86%yield, 97%ee   4z, 87%yield, 98%ee   4aa, 82%yield, 95%ee   4ab, 85%yield, 99%ee

[a]Reaction conditions: **1a–1ab** (0.10 mmol), ESF (0.10 mmol), and catalyst **2e** (0.02 mmol) and **3a** (0.02 mmol) in CHCl$_3$ (2.0 mL) at −78 °C for 12 h. Isolated yields.

substrates **1h** and **1i** generally gave the products with excellent enantioselectivities, probably because of favorable steric interactions with the catalyst (DHQD)$_2$PHAL **2e**. The reaction of 1-naphthyl azlactone **1k** provided the product **4k** with 87% yield and 92% ee. 2-Heteroaryl azlactones **1l–1n** were also applicable. The products were obtained with moderate to good yields and enantioselectivities. The reaction of 2-methyl azlactone **1o** afforded the product **4o** in a good yield but with moderate enantioselectivity.

Furthermore, a variety of 4-substituted azlactones were explored. 4-Phenyl azlactone **1p** gave inferior yield and enantioselectivity in comparison with 4-benzyl azlactone **1a**. The result showed that 4-benzyl substitution was more favorable for the enantioselectivity. Substrates with 4-methyl and 4-isopropyl groups were tried; **S4c** and **S4d** were obtained with excellent yields, but the enantioselectivities were moderate (see details in Scheme S2 in the SI). The reaction of 4-MeO-benzyl azlactone **1q** provided the product **4q** with excellent yield and good enantioselectivity. 3-Bromobenzyl azlactone **1r** and 3-CF$_3$-benzyl azlactone **1s** afforded excellent yields and enantioselectivities. In contrast, 2-bromobenzyl azlactone **1t** provided low enantioselectivity. 1-Naphthylmethyl and 3-indolylmethyl azlactones were also examined. Good yields and moderate enantioselectivities were obtained. The results showed that large 2-substitutents may have adverse effects on the enantioselectivity. 2-Thienylmethyl azlactone **1w** was also applicable. The product **4w** was obtained with good

yield and enantioselectivity. Since 3-substituted-benzyl azlactones **1r–1s** showed superior yields and enantioselectivities, a series of new substrates with 3-bromobenzyl or 3-CF$_3$-benzyl were examined. Generally, azlactones **4x–4ab** were achieved with excellent yields and enantioselectivities. β-Phenylethenesulfonyl fluoride was also examined; however, the reaction gave messy products and most of the starting material was left. The absolute configuration of the product **4n** was confirmed as *S* by single-crystal X-ray diffraction (see Figure 1).
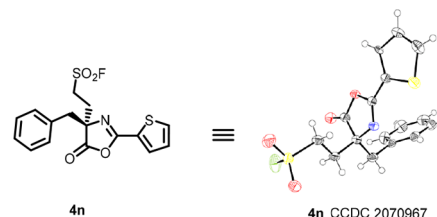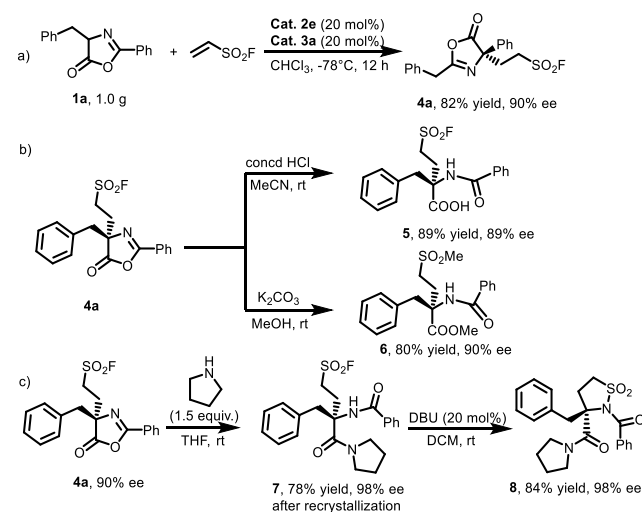

**Figure 1.** X-ray structure of product **4n** (ellipsoid contour at 50% probability).

Scheme 2. Gram-Scale Synthesis and Derivatizations of Product 4a

To demonstrate the synthetic potential of the reaction, a gram scale reaction of azlactone **1a** and ESF was performed (Scheme 2a). The product **4a** was obtained in 82% yield and with 90% ee. The subsequent derivations of the product **4a** were also conducted. Acidic hydrolysis of **4a** provided the α-quaternary amino acid **5** with sulfonyl fluoride group (the ee value was determined after esterification). However, the treatment of **4a** in methanol under basic conditions gave sulfonate-carboxylate **6** (Scheme 2b). Furthermore, the reaction of **4a** with pyrrolidine afforded the product **7** with 78% yield and 98% ee after recrystallization (Scheme 2c). The intramolecular cyclization of **7** with DBU provided sultam **8** with 84% yield and 98% ee. These products are attractive candidates for the drug discovery.[12]

Based on the reported activation models[13] of azlactone and (DHQD)$_2$PHAL, stereochemical models are proposed in Scheme 3. (DHQD)$_2$PHAL **2e** activates enol tautomer **1a′** via the hydrogen-bonding interaction. Simultaneously, ESF is activated by thiourea **3a** via the double hydrogen bonding. The steric shielding generated by (DHQD)$_2$PHAL triggers the attack from the *Si* face of **1a′**. Thus, *S*-**4a** is obtained as the

Scheme 3. Plausible Stereochemical Models

attack from Si face   attack from Re face
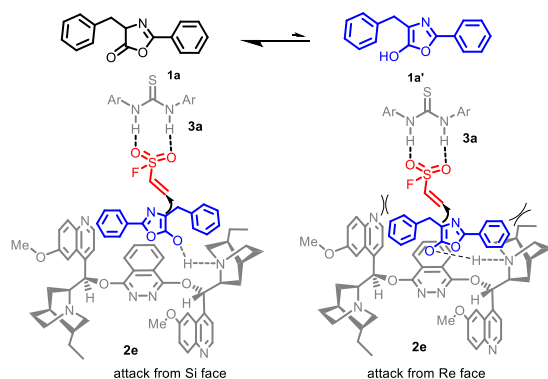
major enantiomer. The synergistic activation by two catalysts is crucial for high reaction rate and excellent enantioselectivity.

In summary, an enantioselective conjugate addition of azlactones to ESF has been developed via the cooperative catalysis of $(DHQD)_2PHAL$ and thiourea. A variety of 2-phenyl and 4-benzyl azlactones were obtained with good to excellent yields and enantioselectivities. This approach provides a facile access to a range of chiral azlactones with sulfonyl fluoride group. Notably, the products could be readily transformed to chiral sultams and α-quaternary amino acids derivatives which are useful candidates for drug discovery.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01193.

    NMR and HPLC spectra (PDF)

Accession Codes

CCDC 2070967 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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