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Facile synthesis of chiral ε-sultams *via* an organocatalytic aza-Friedel–Crafts reaction†

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Chiral ε-sultams, with their unique strain cyclic structure, are a type of molecule with important biological activities. A facile enantioselective aza-Friedel–Crafts reaction of seven-membered cyclic *N*-sulfonylimines with naphthols was developed with a cinchona alkaloid-based bifunctional organocatalyst, giving chiral ε-sultams with an enantiomeric excess of up to 92%.

The sulfonamide unit is an important pharmacophore in medicinal molecules, it possesses a broad spectrum of biological activities, such as antiviral, antibacterial, antitumor and so forth.[1] Moreover, sulfonamides can also be used as reagents,[2] chiral auxiliaries[3] and as key intermediates for the synthesis of other important drugs and biologically active compounds. Among the huge number of compounds in this family, seven-membered cyclic sulfonamides (ε-sultams) show a distinctive feature of a unique strain cyclic structure and have some important biological activities. They can be used as apical sodium co-dependent bile acid transporter (ASBT) inhibitors (**I**), non-nucleoside inhibitors of the HIV-1 reverse transcriptase (NNRTIs, **II**) and as a CaSR receptor (**III**) (Fig. 1).[4]

To date, a variety of powerful approaches have been developed for the synthesis of sulfonamides, such as the Pictet–Spengler reactions,[1e] Friedel–Crafts reactions,[5] intramolecular cycloadditions,[6] transition-metal catalyzed cyclizations,[7] and so forth.[8] However, there are few reports on the synthesis of chiral ε-sultams. Several groups such as Zhou, Baudoin and Zhang reported metal-catalyzed reactions for the synthesis of the ε-sultams in an enantioselective manner, respectively.[9] Very recently, our group presented a direct method for the palladium-catalyzed arylation of the seven-membered cyclic *N*-sulfonylimine for synthesis of chiral ε-sultams.[10] All of the above mentioned reports mainly focused on metal-catalyzed reactions, but the organocatalytic enantioselective reaction is still rare.

The addition of aromatic compounds to imines presents a fundamental carbon–carbon bond-forming process, namely an aza-Friedel–Crafts reaction.[11] The enantioselective variant of this reaction has been regarded as a convenient approach to obtaining chiral benzylic amines. Indoles and pyrroles are the aromatic nucleophiles most often used in this reaction for their excellent reactivities.[11b–h,l,m] Naphthols or phenols, although they have a low nucleophilicity, could also act as an optional aromatic nucleophile. Recently, asymmetric aza-Friedel–Crafts reactions involving naphthols or phenols have attracted significant attention. In 2010, Hui's group reported the asymmetric aza-Friedel–Crafts reactions of 2-naphthols and *N*-tosylimines using a stoichiometric amount of a chiral dinuclear zinc complex.[12] Subsequently, Wang[13] and Chimni[14] independently developed an organocatalytic enantioselective aza-Friedel–Crafts reaction for naphthols with aldimines using bifunctional catalysts derived from cinchona alkaloids. Qu's group developed an enantioselective aza-Friedel–Crafts reaction between electron-rich phenols and *N*-tosylaldimines in 2012.[15] Soon after, this reaction was widely studied by other research groups.[16] However, most of the reported works are limited to the activated linear aldimines containing sulfonyl groups (Scheme 1a). Apart from these, there are few reports on cyclic *N*-sulfonyl imines. In 2015, Pedro and co-workers pre-

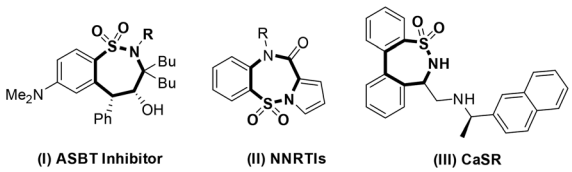

Fig. 1 Bioactive seven-membered cyclic sulfonamides.

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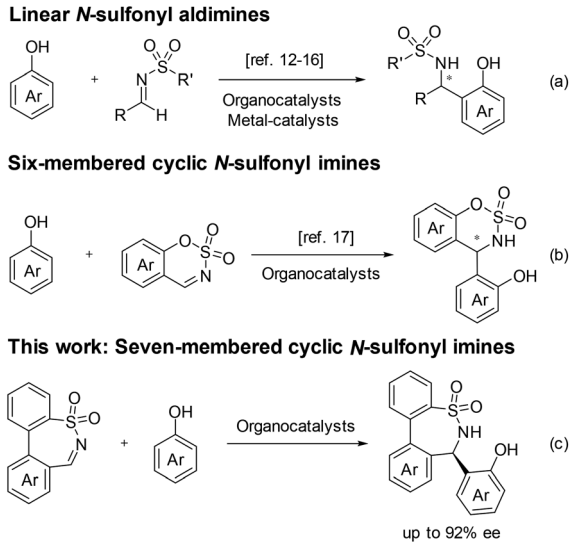
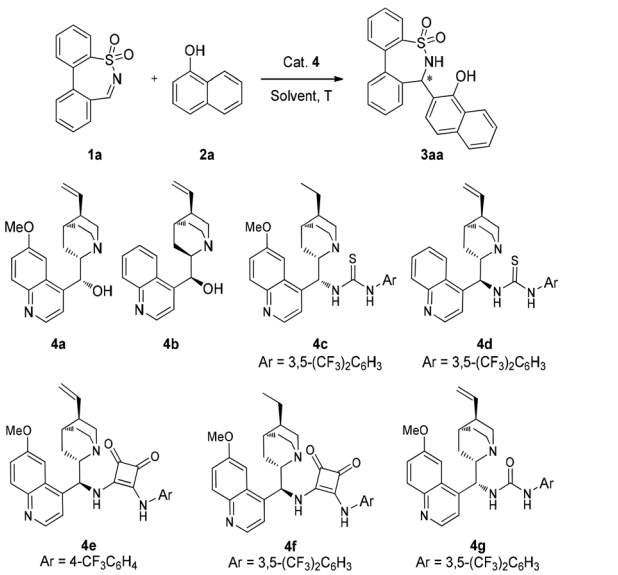


Scheme 1 The catalytic asymmetric aza-Friedel–Crafts reaction of *N*-sulfonylimines with naphthols or phenols.

sented an organo-catalytic aza-Friedel–Crafts reaction employing naphthols and benzoxathiazine 2,2-dioxides as reaction partners and using a quinine-derived bifunctional catalyst, providing the desired products in moderate yields with an enantiomeric excess (ee) up to 96% (Scheme 1b).[17] To the best of our knowledge, the asymmetric aza-Friedel–Crafts reactions between naphthols and seven-membered cyclic *N*-sulfonyl aldimines have not been reported to date. In this paper, we present an asymmetric aza-Friedel–Crafts reaction of the seven-membered cyclic *N*-sulfonyl aldimines and naphthols with a cinchona alkaloid-derived organocatalyst, giving chiral ε-sultams with excellent yields and enantioselectivities up to 92% (Scheme 1c).

At the outset, we chose seven-membered cyclic *N*-sulfonyl aldimines (**1a**) and 1-naphthol (**2a**) as model substrates for the aza-Friedel–Crafts reaction. The results of the optimization of the conditions are summarized in Table 1. To our delight, the reaction could be carried out smoothly by using the cinchona alkaloid catalyst **4a**. The desired product was obtained in a 97% yield, albeit with a moderate 64% ee (Table 1, entry 1). Subsequently, we turned our attention to the screening of the organocatalysts. A series of organocatalysts were evaluated including the cinchona alkaloid, cinchona alkaloid-based thiourea, squaramide and urea catalysts. In the case of the organocatalyst **4b**, a high yield and an 83% ee were observed (entry 2). The thiourea catalysts and squaramide catalysts only obtained modest enantioselectivities (entries 3–6). Next, a number of different solvents were extensively examined with catalyst **4b** (entries 8–13). It was found that chloroform was the best choice in terms of yield and enantioselectivity (entry 10). Considering the effect of temperature on the enantioselectivity, we tried to reduce the temperature in order to improve the enantioselectivity. Fortunately, the reaction provided the corresponding product with a 95% yield and an 89% ee value

Table 1 Optimization of reaction the parameters[a]



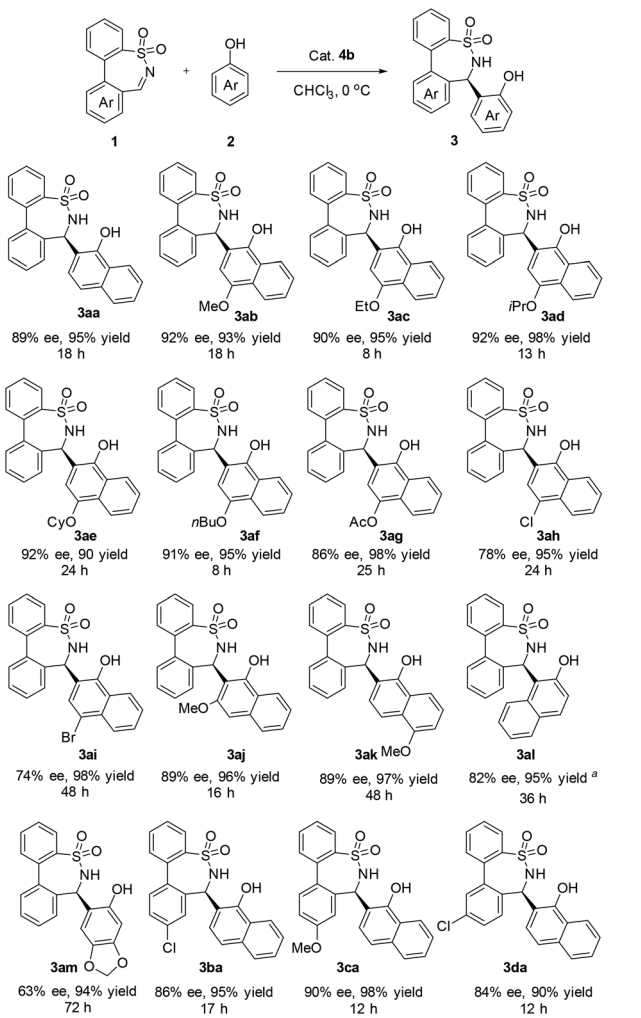
Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**4a**	Toluene	97	64
2	**4b**	Toluene	99	83
3	**4c**	Toluene	94	66
4	**4d**	Toluene	95	74
5	**4e**	Toluene	92	73
6	**4f**	Toluene	98	55
7	**4g**	Toluene	92	64
8	**4b**	DCM	95	83
9	**4b**	DCE	95	83
10	**4b**	$CHCl_3$	97	85
11	**4b**	THF	68	45
12	**4b**	$PhCF_3$	93	75
13	**4b**	EtOAc	86	50
14[d]	**4b**	$CHCl_3$	95	89
15[e]	**4b**	$CHCl_3$	95	88
16[f]	**4b**	$CHCl_3$	96	90
17[g]	**4b**	$CHCl_3$	95[h]	89
18[i]	**4b**	$CHCl_3$	95[h]	86

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), Cat. **4** (10 mol%), solvent (3.0 mL), 25 °C, 3–24 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] 0 °C. [e] −10 °C. [f] 0 °C, $CHCl_3$ (4.0 mL). [g] **1a** (0.20 mmol), **2a** (0.30 mmol), **4b** (10 mol%), $CHCl_3$ (12.0 mL), 0 °C, 18 h. [h] Isolated yield. [i] **1a** (0.20 mmol), **2a** (0.30 mmol), **4b** (5 mol%), $CHCl_3$ (12.0 mL), 0 °C, 28 h.

at 0 °C (entry 14). However, the value of ee for the product did not increase when we further reduced the temperature to −10 °C (entry 15). To our delight, increasing the amount of solvent gave an excellent yield and a slightly higher 90% ee value (entry 16). The increase of the ee value may be due to inhibition of the background reaction by reducing the concentration. Furthermore, upon doubling the scale of the reaction the high level of reactivity and enantioselectivity was maintained, delivering the product in a 95% yield and a 89% ee (entry 17). When the amount of catalyst was reduced to 5 mol%, the ee value of the reaction was reduced to 86% (entry 18). Therefore, the optimal conditions were established

as: **4b** as the catalyst (10 mol%), chloroform as the solvent and a temperature 0 °C.

With the optimized conditions in hand, the reaction scope was then evaluated, and the results are summarized in Scheme 2. When introducing an alkoxy group to the 4-position of 1-naphthol, the reaction proceeded smoothly, providing the desired products with excellent enantioselectivities and high yields (**3ab–3af**). Furthermore, for the acetoxy substrate, a 98% isolated yield and 86% enantioselectivity were observed (**3ag**). The electronic properties of the substrates had a significant influence on the ee value (**3ah–3ai**). For example, the ee value decreased to 78% when the chloro atom was in the *para*-position of the hydroxyl group. This implies that the enantiocontrol of the alkoxy substituted substrates is better than that of the substrates bearing halogen groups. Subsequently, we investigated substituents at different positions of 1-naphthol. Both the alkoxy substituents at the 3-position and 5-position of 1-naphthol were tolerated, giving the products in good yields and an 89% ee (**3aj–3ak**). In addition, 2-naphthol and



Scheme 2 Substrate scope. Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), **4b** (10 mol%), $CHCl_3$ (12.0 mL), 0 °C. [a] **4f** (10 mol%), toluene (12.0 mL).

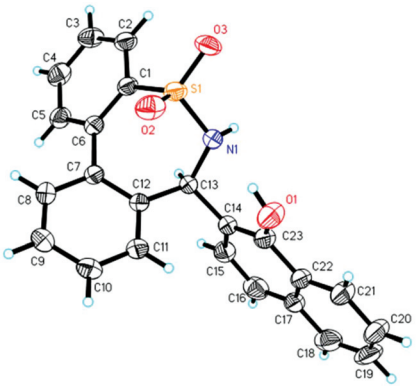


Fig. 2 X-ray crystal structure of compound (–)-**3aa**.

sesamol (4-hydroxy-1,3-benzodioxole) were amenable to the present reaction. Through simple optimization, 2-naphthol could give rise to **3al** in an 82% ee and 95% yield. It is worth noting that the position and electronic properties of the substituents on the biphenyl motif had a slight effect on the results (**3ba–3da**). However, unfortunately, 1,4-dihydroxynaphthalene and one methyl protected 1,8-dihydroxynaphthalene did not provide the corresponding product, which could be ascribed to the intramolecular or intermolecular hydrogen bonding interaction, thereby further affecting contact with the catalyst and substrate. Moreover, other nucleophiles such as pyrrole and indole were also investigated under standard reaction conditions. The results showed that pyrrole could give trace products and low enantioselectivities. When indole was used as a reaction substrate, unfortunately, no desired product was observed.

The absolute configuration of the product (–)-**3aa** was unambiguously determined to be *R* using X-ray diffraction of the single crystals after a simple recrystallization process using ethyl acetate and *n*-hexane (Fig. 2).

Based on the above experimental results and the relevant literature,[13–14,16a,17] the stereochemistry of this reaction could be explained by the plausible transition state model shown in Fig. 3. The cinchona alkaloid derived catalysts promote the reaction in a dual activation manner: activating the seven-membered cyclic *N*-sulfonylimines and naphthols *via* a hydrogen-bonding interaction. By enhancing the nucleophilicity of the naphthols, the reaction was conducted smoothly through a *Si*-face attack to aldimines to afford the *R*-configured products.

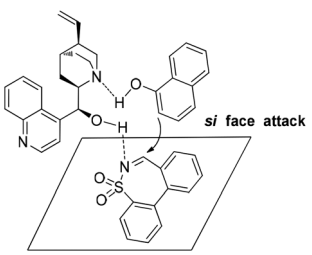


Fig. 3 Proposed transition state model.

Conclusions

In summary, we have developed an efficient method for the synthesis of chiral ε-sultams through an organocatalytic aza-Friedel–Crafts reaction of the seven-membered cyclic *N*-sulfonyl aldimines with naphthols in good yields with up to 92% ee. Furthermore, the development of other macrocyclic structures is under progress and the results will be presented in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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