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Enantioselective (3+2) Cycloaddition *via N*-Heterocyclic Carbene-Catalyzed Addition of Homoenolate to Cyclic *N*-Sulfonyl Trifluoromethylated Ketimines: Synthesis of Fused *N*-Heterocycle γ-Lactams

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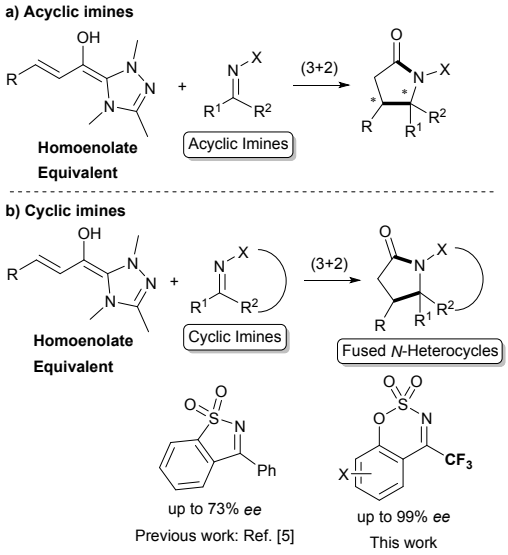
An enantioselective (3+2) cycloaddition of enals and cyclic *N*-sulfonyl trifluoromethyl ketimines *via N*-heterocyclic carbene-catalyzed homoenolate addition is described. This reaction can efficiently construct fused *N*-heterocycle γ-lactams bearing two adjacent chiral centers with >20:1 *dr* and 94–99% *ee*, with one chiral center as trifluoromethylated α-tetrasubstituted carbon stereocenter.

In the past few decades, *N*-heterocyclic carbenes (NHCs) have been used as a powerful organocatalyst for various enantioselective reactions to construct cyclic molecules.[1] The NHC catalysis with aldehydes can generate several types of reactive intermediates. A typical example is based on the a^3-d^3 umpolung of aldehydes to form the homoenolate intermediate by the nucleophilic addition of NHC catalysts to enals.[1b-c,1j] The homoenolates can be considered as d^3-nucleophiles for addition to 1,2-unsaturated activated double bond, followed by cyclization to regenerate NHC catalyst, resulting in formal catalytic (3+2) cycloaddition reaction. Obviously, the addition of homoenolate to electrophilic C=N is an efficient strategy to construct *N*-heterocycle γ-lactams.[2] In 2005, Bode and coworkers reported NHC-catalyzed racemic (3+2) cycloaddition of enals with *N*-sulfonylimines to produce γ-lactams.[3] Subsequently, several asymmetric (3+2) cycloadditions were reported *via* the NHC-catalyzed key enantioselective addition of homoenolate to the C=N of acyclic imines,[4] affording γ-lactams with high enantioselectivities[4a-f] (Scheme 1a). However, very little attention has been paid to using cyclic imines containing an endocyclic carbon–nitrogen double bond as electrophiles in the NHC-catalyzed (3+2) cycloaddition to obtain the fused *N*-heterocycle γ-lactams (Scheme 1b).[5] Only one five-membered cyclic *N*-sulfonyl ketimine was used for the enantioselective (3+2) cycloaddition, affording fused *N*-heterocycle γ-lactams with up to 73% *ee* and 6/1 *dr* after screening many chiral NHC catalysts.[5] The (3+2) cycloaddition reaction of cyclic imines *via* the NHC-catalyzed addition of homoenolate has not been investigated in detail, especially focusing on high enantioselectivities. Herein, we report highly enantioselective (3+2) cycloaddition of enals with cyclic *N*-sulfonyl trifluoromethylated ketimines *via* the NHC-catalyzed homoenolate addition, affording the fused *N*-heterocycle γ-lactams (Scheme 1b).



Scheme 1 Enantioselective (3+2) cycloadditions *via* NHC-catalyzed addition of homoenolate intermediate to imines.

Benzo[*e*][1,2,3]oxathiazine 2,2-dioxide, a class of cyclic sulfamidates heterocycles,[6] can be considered as a *N*-sulfonyl cyclic imine. In our previous research, this type of cyclic aldimines was used for the phosphane-catalyzed (3+2) cycloaddition[7] and highly enantioselective Mannich reactions catalyzed by primary amine organocatalysts[8]. The trifluoromethyl (CF_3) group-containing organic molecules are widely used in medicinal chemistry, attributing to the characteristic molecular properties such as improved polarity,

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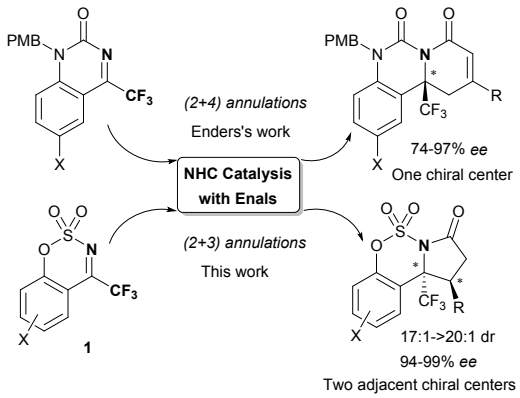
†Electronic Supplementary Information (ESI) available: CCDC 1919445. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

metabolic stability, lipophilicity, and bioavailability imparted by fluorine.[9] We envisaged incorporation of a CF_3 group at the C=N double bond[10] of the benzo[*e*][1,2,3]oxathiazine 2,2-dioxides to get cyclic *N*-sulfonyl trifluoromethylated ketimines **1**,[7,11] which were viewed as more challenging imine substrates for catalytic asymmetric transformations.[12] Inspired by the powerful NHC organocatalysis for diverse reactions to build complex chiral scaffolds,[1] we became interested in exploring NHC-catalyzed enantioselective reactions of the cyclic ketimines **1**. Although NHC-catalyzed enantioselective annulation of cyclic trifluoromethylated ketimines is one of the most powerful tools to generate polycyclic trifluoromethylated *N*-heterocycles bearing a tetrasubstituted chiral stereocenter, it is still a challenging task (Scheme 2). In this pioneering field, Enders and coworkers realized the enantioselective (4+2) annulations of trifluoromethyl 2(1*H*)-quinazolinones.[13] In this study, enantioselective (3+2) annulations of trifluoromethyl benzo[*e*][1,2,3]oxathiazine 2,2-dioxide were developed, affording γ-lactam products bearing two adjacent chiral centers with excellent stereoselectivties.



Scheme 2 NHC-Catalyzed enantioselective annulations of cyclic trifluoromethylated ketimines.

Cyclic *N*-sulfonyl CF_3 ketimine **1a** was chosen as a substrate of the model reaction with cinnamaldehyde **2a** under NHC catalysis (Table 1). Triazolium salt **C-1** was chosen as the NHC precatalyst (preNHC) and TEA as the base in DCM at 40°C, affording the desired product **3a** in 78% yield with 4:1 *dr* and 85% *ee* (entry 1). Encouraged by this promising result, reaction conditions were optimized. First, some bases were screened, resulting in comparatively less enantioselectivities in the range 82–86% *ee* (entries 1–10). By taking the yields and *ee* value into account, *N*,*N*-diisopropylethylamine (DIPEA) was chosen as the optimized base for the reaction (entry 10). Next, different chiral catalysts were examined. Catalysts with different scaffolds greatly affected this (3+2) cycloaddition, and indanol-derived triazolium catalysts were selected for further screening (entries 10–15). The results showed that nitro-substituted indanol-derived triazolium **C-6** was the most efficient catalyst,[14] affording excellent stereoselectivities with 20/1 *dr* and 98% *ee* (entry 15). Further, various solvents were screened for this reaction, and the best reactivity and stereoselectivity was obtained using DCM as the solvent (entry 15). To the best of our surprise, the reaction proceeds smoothly at room temperature, affording single diastereoisomer product in the nearly enantiopure form (entry 19).[15]

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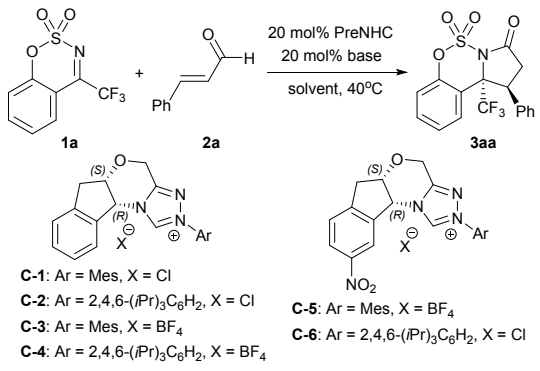
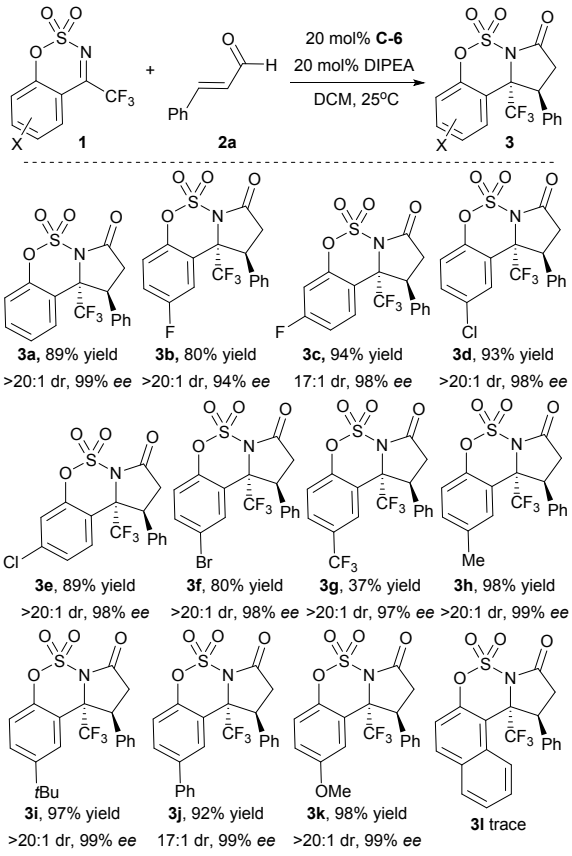
Table 1 Condition optimization[a]



Entry	PreNHC	Solvent	Base	Yield[b] (%)	dr[c]	ee[d] (%)
1	**C-1**	DCM	TEA	78	4:1	85
2	**C-1**	DCM	K_3PO_4	91	4:1	83
3	**C-1**	DCM	KOAc	63	4:1	85
4	**C-1**	DCM	Cs_2CO_3	90	4:1	82
5	**C-1**	DCM	TMG	93	4:1	83
6	**C-1**	DCM	Quinine	89	4:1	85
7	**C-1**	DCM	Quinidine	80	6:1	85
8	**C-1**	DCM	DMAP	85	5:1	85
9	**C-1**	DCM	HMTA	89	5:1	85
10	**C-1**	DCM	DIPEA	91	4:1	86
11	**C-2**	DCM	DIPEA	91	4:1	91
12	**C-3**	DCM	DIPEA	84	6:1	85
13	**C-4**	DCM	DIPEA	64	4:1	92
14	**C-5**	DCM	DIPEA	90	20:1	97
15	**C-6**	DCM	DIPEA	90	20:1	98
16	**C-6**	THF	DIPEA	87	20:1	96
17	**C-6**	toluene	DIPEA	93	20:1	97
18	**C-6**	MeCN	DIPEA	trace	--	--
19[e]	**C-6**	DCM	DIPEA	91	>20:1	99

[a] Reaction conditions: imine **1a** (0.05 mmol), enal **2a** (0.15 mmol), PreNHC (20 mol%), base (20 mol%), solvent (0.5 ml), 40°C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC using a chiral column. [e] 1 mL of DCM and 25°C.

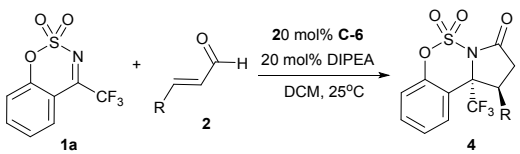
With the optimized reaction conditions in hand, different substituted imine substrates were evaluated for the enantioselective (3+2) cycloadditions, and the results are summarized in Scheme 2. Various cyclic *N*-sulfonyl trifluoromethylated ketimines **1**, bearing both electron-donating and electron-withdrawing substituents, such as fluoride, chloride, bromide, trifluoromethyl, methyl, *tert*-butyl, phenyl and methoxyl, in the fused phenyl ring all were well tolerated under the reaction conditions, affording the fused *N*-heterocycle γ-lactams **3a–k** as the *trans*-diastereoisomer products with excellent stereoselectivities of 17:1–>20:1 *dr* and 97–99% *ee*. However, only 37% yield was obtained for imine **2g**. Unfortunately, very low conversion was observed for 1,2-naphthylene-ring-containing imine **1l**, probably because of steric hindrance caused by the *ortho*-substitution of sulfamidate heterocycle.



Scheme 3 Scope of cyclic trifluoromethylated ketimines. (0.1 mmol reaction scale)

Subsequently, the scope of enals **2** was investigated using the conditions similar to those used for the imine substrates. As listed in Table 2, substantial generality of the (3+2) cycloadditions for enals **2** displayed a broad substrate scope, and both aromatic and aliphatic β-substituted enals were well tolerated, affording the corresponding γ-lactams **4** with excellent diastereoselectivities and enantioselectivities. Both electron-withdrawing and electron-donating substituents were tolerated on the *para* position of the phenyl ring in enals **2b–g** (entries 1–6). The substrate with substituent at the *meta* position of the phenyl ring in enal **2h** afforded low yield of the product, but still retained excellent enantio- and diastereoselectivity (entry 7), and very low reactivity was observed for enal **2i** bearing *ortho* substituent (entry 8). The enals with β-substituted naphthyl (**2j**) and heterocyclic furan group (**2k**) were also suited for this reaction (entries 9–10). Instead of aromatic enals, four aliphatic enals such as **2l–o** were also applied to the (3+2) cycloadditions, and slightly lower enantioselectivity (94–96% *ee*) were obtained in fairly good yields (entries 11–14).

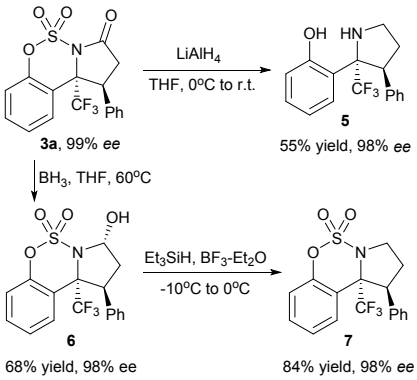
Table 2 Scope of enals.



Entry	R	4	Yield (%)	dr	ee (%)
1	4-F-C_6H_4 (**1b**)	**4b**	97	17:1	99
2	4-Cl-C_6H_4 (**1c**)	**4c**	96	17:1	98
3	4-Br-C_6H_4 (**1d**)	**4d**	97	17:1	99
4	4-Me-C_6H_4 (**1e**)	**4e**	97	20:1	99
5	4-MeO-C_6H_4 (**1f**)	**4f**	90	20:1	99
6	4-NO_2-C_6H_4 (**1g**)	**4g**	83	>20:1	99
7	3-Cl-C_6H_4 (**1h**)	**4h**	43	>20:1	99
8	2-Cl-C_6H_4 (**1i**)	-	trace	-	-
9	2-naphthyl (**1j**)	**4j**	98	>20:1	99
10	2-furanyl (**1k**)	**4k**	93	>20:1	95
11	Et (**1l**)	**4l**	82	>20:1	95
12	*n*-Pr (**1m**)	**4m**	99	>20:1	94
13	*i*-Pr (**1n**)	**4n**	99	>20:1	96
14	*n*-Heptyl (**1o**)	**4o**	84	>20:1	95

The absolute and relative configurations of product **3e** were determined to be *trans*-(1*S*, 10b*S*)-isomer in the γ-lactam group by single crystal X-ray diffraction (see ESI†). The configurations of all other products **3** (Scheme 3) and **4** (Table 2) were assigned by chemical analogy.

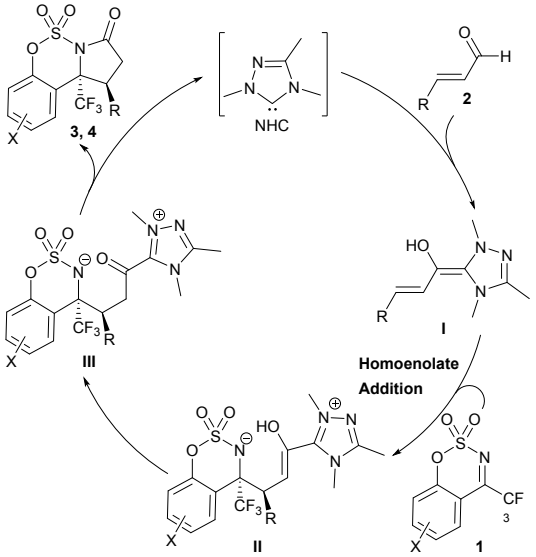
The reductive transformations of product **3a** were performed, and the corresponding results are shown in Scheme 4. The treatment of **3a** with $LiAlH_4$ allowed reductive cleavage of sulfamidate heterocycle and reduction of γ-lactam yielding *ortho*-hydroxylphenyl pyrrolidine **5** without loss of enantioselectivity. γ-Lactam **3a** was treated with borane in THF to generate cyclic hemiaminal **6** bearing three chiral centers. The stereochemistry of new generated hydroxyl substituted chiral carbon center was established by NOE experiments (see ESI,† Scheme S2). Subsequently, **6** was treated with triethylsilane and BF_3-Et_2O for dehydroxylation to afford compound **7**. The enantioselectivity of both compounds **6** and **7** was determined by chiral HPLC, indicating that the optical purity was maintained in the reaction processes.



Scheme 4 Reductive transformations of product **3a**.

Based on reported NHC-catalyzed cycloaddition reactions,[4-5] a plausible catalytic cycle for this enantioselective (3+2) cycloaddition, involving a key step of the homoenolate addition to the C=N double bond, is proposed, as shown in Scheme 5. The first step of the addition of NHC with enals **2** generated the Breslow intermediate I, which serves as homoenolate equivalents. The nucleophilic addition of the

homoenolates to cyclic sulfonyl trifluoromethylated ketimines **1** affords the intermediates II, along with generating two adjacent chiral centers. After tautomerization of the intermediates II, the resulting acyl azoliums III undergo intramolecular cyclization to afford the final products **3** or **4** and regenerate the NHC catalyst.



Scheme 5 Plausible catalytic cycle.

In conclusion, the enantioselective (3+2) cycloadditions of enals and cyclic *N*-sulfonyl trifluoromethylated ketimines were developed via the NHC-catalyzed addition of homoenolate to the ketimines. A series of novel fused *N*-heterocycle γ-Lactams bearing two adjacent chiral centers were produced with excellent enantio- and diastereoselectivity (94–99% *ee* and up to >20:1 *dr*). This study extended the scope of chiral NHC organocatalysis *via* the homoenolate addition using cyclic *N*-sulfonyl trifluoromethylated ketimines as the substrates.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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15 For more results on the reaction condition optimization, please see ESI,† Table S1 and Scheme S1).