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Enantioselective [4 + 2] Cycloaddition of Cyclic *N*-Sulfimines and Acyclic Enones or Ynones: A Concise Route to Sulfamidate-Fused 2,6-Disubstituted Piperidin-4-ones

Yong Liu,[†] Tai-Ran Kang,*[,†,‡] Quan-Zhong Liu,*[,†] Lian-Mei Chen,[†] Ya-Chuan Wang,[†] Jie Liu,[‡] Yong-Mei Xie,[‡] Jin-Liang Yang,[‡] and Long He*[,†]

Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry & Chemical Engineering, China West Normal University, Nanchong 637009, China, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

kangtairan@sina.com; quanzhongliu@sohu.com; longhe@cwnu.edu.cn

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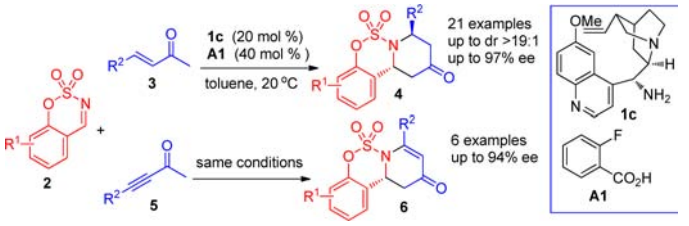
ABSTRACT



A concise route to valuable sulfamate-fused 2,6-disubstituted piperidin-4-ones or 2,3-dihydropyridin-4(1*H*)-ones in good yield with high diastereo- and enantioselectivity is presented. The combination of chiral primary amine and *o*-fluorobenzoic acid efficiently promoted an asymmetric [4 + 2] cycloaddition reaction of *N*-sulfonylimines and enones or ynones. The cycloaddition reaction between cyclic *N*-sulfonylimines and ynones is first reported.

Many 2,6-disubstituted piperidin-4-ones are found to possess useful biological activities,[1] such as anti-inflammatory, antihistaminic, hypotensive, anticancer, and depressant.[1b] The sulfamidate-fused compounds present in many pharmaceutical agents[2] are attractive synthetic intermediates in organic synthesis. Cyclic *N*-sulfonylimines (benzoxathiazine 2,2-dioxides), which are stable compared to the acyclic *N*-sulfonylimines,[3] have been employed in recent years,[4] including phosphane[4g−i] and the NHC-catalyzed[4j,k] cycloaddition reaction. Very recently, Tong reported the amine-promoted asymmetric [4 + 2] cycloaddition reaction between benzoxathiazine-2,2-dioxide (**2a**) and 2-(acetoxymethyl)buta-2,3-dienoate, providing sulfamate-fused piperidines, albeit with very low ee.[4a] To the

[†] China West Normal University.
[‡] Sichuan University.

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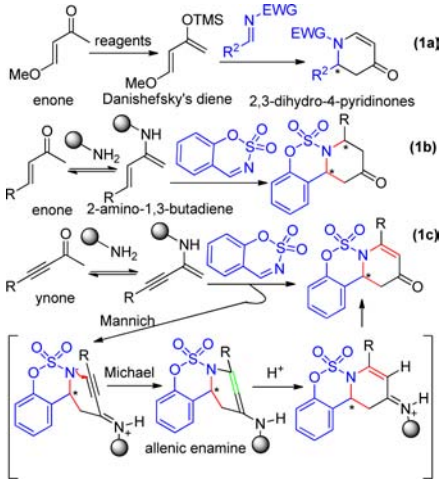
best of our knowledge, the enantioselective synthesis of sulfamate-fused 2,6-disubstituted piperidines-4-ones are rarely reported. Consequently, the development of efficient methods to access these valuable compounds is an attractive goal.

Scheme 1. [4 + 2] Cycloaddition Reaction between Imines and Unsaturated Ketones



HOMO-activated 2-amino-1,3-butadienes derived from enones and chiral amine catalysts are valuable intermediates in organic synthesis.[5] Barbas and co-workers first reported the amine-catalyzed [4 + 2] cycloaddition of nitroalkenes and 2-amino-1,3-butadienes in 2002.[6] After this event, tremendous chemists have dedicated to amine catalyzed cycloaddition reaction of enones and various electron-deficient dienophiles.[7] It is known that imines are reactive in the hetero Diels–Alder reactions of siloxybutadiene derivatives as dienes, such as Danishefsky's diene [Scheme 1, (1a)] in the presence of a Lewis or Brønsted acid.[8] However, acyclic enones or ynones are seldeom employed in the aminocatalyzed [4 + 2] cycloaddition reactions of imines.[8,9] Very recently, Jacobsen reported the primary aminothiourea-catalyzed cycloaddition of enone and cyclic imine, affording high enantioselective indolo- and benzoquinolizidine.[9c]

Inspired by our interest in the amino-catalyzed addition reaction,[10] we surmised that the enamine formed in situ from enones or ynones might react with cyclic *N*-sulfonylimines in the presence of primary amine,[11] providing a concise route to valuable sulfamate-fused 2,6-disubstituted piperidin-4-ones or 2,3-dihydropyridin-4(1*H*)-ones (Scheme 1, b and c). The primary amine-catalyzed cycloaddition between cyclic *N*-sulfonylimines and ynones[12,13] has never been reported to date. Prominent features of this reaction include a Mannich/reflexive-Michael/protonation reaction sequence via enamine–iminium–allenic enamine–iminium cascade catalysis. The chiral allenamine intermediate[14–16] would be formed in situ and then act as the nucleophile in a subsequent reaction (Scheme 1, c).

Initially, we explored the [4 + 2] cycloaddition reaction of benzoxathiazine-2,2-dioxide **2a** and (*E*)-4-phenylbut-3-en-2-one **3a** in toluene at 40 °C in the presence of *o*-fluorobenzoic acid (**A1**) by using 20 mol % chiral primary amines catalyst **1**, which was derived from natural

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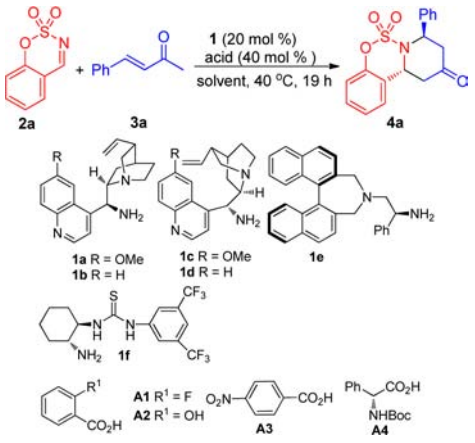
Table 1. Optimization of the Cycloaddition Reaction[a]

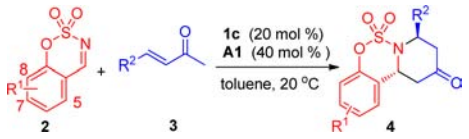


entry	1	acid	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**A1**	toluene	76	>19:1	82 (*S*,*S*)
2	**1b**	**A1**	toluene	74	>19:1	76 (*S*,*S*)
3	**1c**	**A1**	toluene	85	>19:1	90 (*R*,*R*)
4	**1d**	**A1**	toluene	73	>19:1	89 (*R*,*R*)
5	**1e**	**A1**	toluene	80	18:1	78 (*S*,*S*)
6	**1f**	**A1**	toluene	64	>19:1	77 (*R*,*R*)
7	**1c**	**A2**	toluene	76	>19:1	88 (*R*,*R*)
8	**1c**	**A3**	toluene	61	18:1	84 (*R*,*R*)
9	**1c**	**A4**	toluene	67	>19:1	86 (*R*,*R*)
10	**1c**	**A1**	DCE	88	18:1	53 (*R*,*R*)
11	**1c**	**A1**	$CHCl_3$	82	18:1	61 (*R*,*R*)
12	**1c**	**A1**	THF	60	>19:1	87 (*R*,*R*)
13[e]	**1c**	**A1**	toluene	80	>19:1	97 (*R*,*R*)

[a] Reaction conditions: cyclic *N*-sulfonylimine **2a** (0.1 mmol), (*E*)-4-phenylbut-3-en-2-one **3a** (0.15 mmol), catalyst **1** (20 mol %), and acid (40 mol %) in 0.5 mL of solvent at 40 °C for 19 h. [b] Yield of the isolated major diastereomer. [c] Determined by crude ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] Reaction at 20 °C for 24 h.

cinchona alkaloids,[17] BINOL[18] and (1*R*,2*R*)-cyclohexane-1,2-diamine,[19] respectively. The results are summarized in Table 1. All of the primary amines catalyzed the reaction to generate sulfamate-fused 2,6-disubstituted piperidin-4-ones **4**, and the most optimal catalyst turned out to be **1c** in terms of the yield and enantioselectivity (entry 3). Other primary amines (**1a**,**b** and **1d**) derived from cinchona alkaloids also provided similar results (entries 1−2 and 4), the primary amine **1e** developed early by our group and the aminothiourea **1f** only afforded 78% ee and 80% ee (entries 5 and 6), respectively. It is worth noting that all the chiral primary amines afforded excellent diastereoselectivities. Screening of different acids indicated that both the yield and enantioselectivity were dependent on the acid used (entries 7−9). In terms of yield and enantioselectivity, *o*-fluorobenzoic acid (**A1**) was optimal. A solvent screening indicated that the solvent employed affected the reaction performance dramatically. Toluene delivered the best among the solvents screened (entries 10−12 vs 3). Performing the reaction at lower temperature resulted in a significant increase of enantioselectivity, albeit with a slight decrease in the yield (entry 13).

Table 2. Substrate Scope of Cycloaddition Reaction[a]



entry	R^1	R^2	4	yield[b] (%)	dr[c]	ee[d] (%)
1	H	C_6H_5	**4a**	80	>19:1	97
2	H	4-MeC_6H_4	**4b**	81	19:1	94
3	H	4-$MeOC_6H_4$	**4c**	75	19:1	95
4	H	4-ClC_6H_4	**4d**	85	19:1	92
5	H	4-BrC_6H_4	**4e**	80	19:1	91
6	H	4-$CF_3C_6H_4$	**4f**	70	18:1	94
7	H	4-FC_6H_4	**4g**	73	19:1	92
8	H	3-MeC_6H_4	**4h**	83	>19:1	95
9	H	3-$MeOC_6H_4$	**4i**	81	19:1	92
10	H	3-ClC_6H_4	**4j**	85	>19:1	97
11	H	3-BrC_6H_4	**4k**	82	>19:1	97
12[e]	H	2-BrC_6H_4	**4l**	61	18:1	90
13	H	2-furyl	**4m**	80	19:1	95
14	H	2-thiophenyl	**4n**	84	>19:1	93
15	H	cyclohexyl	**4o**	60	>19:1	97
16	H	Pr	**4p**	83	>19:1	95
17	7-Cl	C_6H_5	**4q**	65	>19:1	93
18	7-MeO	C_6H_5	**4r**	74	>19:1	93
19	6-Cl	C_6H_5	**4s**	76	16:1	93
20	6-MeO	C_6H_5	**4t**	66	>19:1	95
21	6,8-tBu	C_6H_5	**4u**	60	>19:1	97

[a] General conditions: cyclic *N*-sulfonylimines **2** (0.1 mmol), enones **3** (0.15 mmol), catalyst **1c** (20 mol %), and **A1** (40 mol %) in 0.5 mL of solvent at 20 °C for 12−30 h. [b] Yield of the isolated major diastereomer. [c] Determined by crude ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] Reaction at 40 °C for 24 h.

With the optimized reaction conditions in hand, a variety of cyclic *N*-sulfonylimines **2** and enones **3** were subjected to the enantioselective cycloaddition reaction. As summarized in Table 2, various enones bearing either electron-donating or -withdrawing groups at *β*-position reacted smoothly to afford sulfamate-fused 2,6-disubstituted piperidin-4-ones **4a**−**l** in good yields (60−85%) and with excellent diastereo- 16:1−19:1 and enantioselectivities (90−97%) (entries 1−11). It is worth noting that the enone **3l** bearing bromine atom substitutent at the 2-position of phenyl group seems to have a detrimental effect on the reaction rate, and the product **4l** was obtained in 60% yield and 18:1 dr with 90% ee when the reactions were carried out at 40 °C for longer reaction time (entry 12). The substrates with heteroaromatic rings such as furyl and thiopheneyl at the *β*-position of enones proceeded smoothly in the cycloaddition as well (entries 13 and 14). Gratifyingly, the cycloaddition reactions can be extended to enones such as **3o** and **3p** with aliphatic substituents

(17) For chiral primary amine derived from cinchona alkaloids in organic synthesis, see ref 11f and references cited therein.
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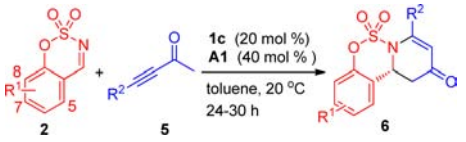
attached at β-position (entries 15 and 16) giving rise to piperidin-4-ones with 97% ee and 95% ee, respectively. Finally, several *N*-sulfonylimines were also investigated, and the piperidin-4-ones were obtained with moderate yields and excellent enantioselectivities (93−97% ee, entries 17−21).

In sharp contrast to these widely reported amine-catalyzed enones systems, the organocatalytic cascade reaction involving asymmetric conjugate addition to a ynone has rarely been reported.[13] It was found that the combination **1c/A1** was also an excellent catalyst with respect to the cascade recation of *N*-sulfonylimines **2** and ynones **5**, affording the sulfamate-fused 2,6-disubstituted 2,3-dihydropyridin-4(1*H*)-ones **6** in moderate yield with high to excellent enantioselectivity. The results are shown in Table 3. The presence of a carbon−carbon double bond at the products would be useful in the structurally diverse dihydropyridines molecules.

Table 3. Cycloaddition Reaction Involving Ynones **5**[a]



entry	R^1	R^2	**6**	yield[b] (%)	ee[c] (%)
1	H	C_6H_5	**6a**	80	91
2	7-MeO	C_6H_5	**6b**	70	90
3	6-Cl	C_6H_5	**6c**	64	87
4	6-MeO	C_6H_5	**6d**	65	90
5	6,8-tBu	C_6H_5	**6e**	60	87
6	H	Et	**6f**	65	94

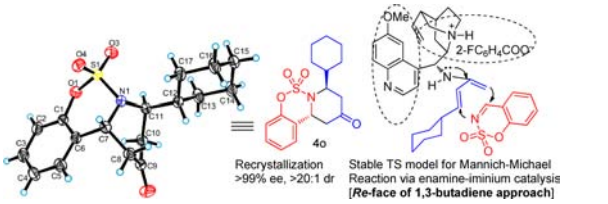
[a] General conditions: cyclic *N*-sulfonylimines **2** (0.1 mmol), ynones **5** (0.15 mmol), catalyst **1c** (20 mol %), and **A1** (40 mol %) in 0.5 mL of toluene at 20 °C for 24−30 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

The absolute configuration of **4o** was unambiguously determined to be (8*R*,11*R*) by X-ray crystal structure analysis.[20] It should be noted that the Mannich reaction product was observed in all the reaction of enones **3** and *N*-sulfonylimines **2**, albeit with low yield. We cannot definitely rule out a possible concerted mechanism,

(20) CCDC 956374 (**4o**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

(21) (a) Moran, A.; Hamilton, A.; Bo, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2013**, *135*, 9091.

Scheme 2. Proposed Catalytic Cycle for the Formation of **4o**



however, a stepwise Mannich−Michael addition manner seems to be plausible. Based on the detailed mechanistic study reported by Melchiorre's group,[21] we suppose a transition state to explain the observed stereochemical outcome of the enantioselective cycloaddition reaction (Scheme 2). The *Si*-face of the reactive $\pi-\pi$-system derived in situ is shielded by the quinolin ring and the 2-fluorobenzoate, which is engaged in the electrostatic interaction with the protonated tertiary amino moiety of the catalyst.[21] This induces the approach of the electrophile **2a** from the less congested *Re*-face of the $\pi-\pi$-system,[21] furnishing the cycloaddition reaction in an *endo* fashion, delivering the observed (8*R*,11*R*)-**4o**. The absolute configuration of 2,3-dihydropyridin-4(1*H*)-ones **6** was determined to be *R* on the basis of a presumed common catalytic mechanism in the first Mannich step similar to that of cycloadducts **4**.

In conclusion, we have developed an effective cycloaddition of enones or ynones with cyclic imines using primary amine as the catalyst. The present protocol provides a rapid and efficient method to construct valuable sulfamate-fused 2,6-disubstituted piperidin-4-ones **4** and 2,3-dihydropyridin-4(1*H*)-ones **6** with up to 87% yield and $>19/1$ dr with 97% ee under mild reaction conditions. Further studies toward the application of this methodology in the synthesis of pharmaceutical intermediates are ongoing.

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Supporting Information Available. Experimental details, characterization data, HPLC enantiomer analysis, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.