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Asymmetric [4+2] annulation of *N*-sulfonyl ketimines: access to *N*-heterocycles bearing 1,3-nonadjacent stereocenters with a quaternary carbon center

Tengfei Xuan[1], Wei Han[1], Ruochen Pang[1], Yuxin Tian[1], Weiwu Ren[1,2,*]

[1]Molecular Synthesis Center & Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, Shandong, China.
[2]Laboratory for Marine Drugs and Bioproducts, Laoshan Laboratory, Qingdao 266237, Shandong, China.

[*]**Correspondence to:** Prof. Weiwu Ren, Molecular Synthesis Center & Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao 266003, China. E-mail: renweiwu@ouc.edu.cn

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Abstract

An organocatalytic [4+2] annulation of *N*-sulfonyl ketimines with aminochalcones has been developed to afford the benzenesulfonamide fused tetrahydroquinazoline compounds under mild conditions with excellent stereoselectivity (up to 99% ee). This method provides a concise and efficient approach for the construction of *N*-heterocyclic compounds bearing 1,3-nonadjacent stereocenters with a quaternary carbon center.

Keywords: Benzenesulfonamide, tetrahydroquinazoline, 1, 3-nonadjacent stereocenters, aminochalcones, *N*-sulfonyl ketimines, [4+2] annulation

INTRODUCTION

Chiral benzofused 5-membered sultam with a quaternary stereocenter as an important structural motif shows a broad spectrum of biological activities[1-4], such as HIV-1 inhibitors, γ-secretase inhibitors and aldose reductase inhibitors [Figure 1]. It is also used as chiral auxiliaries in asymmetric chemistry[5]. On the

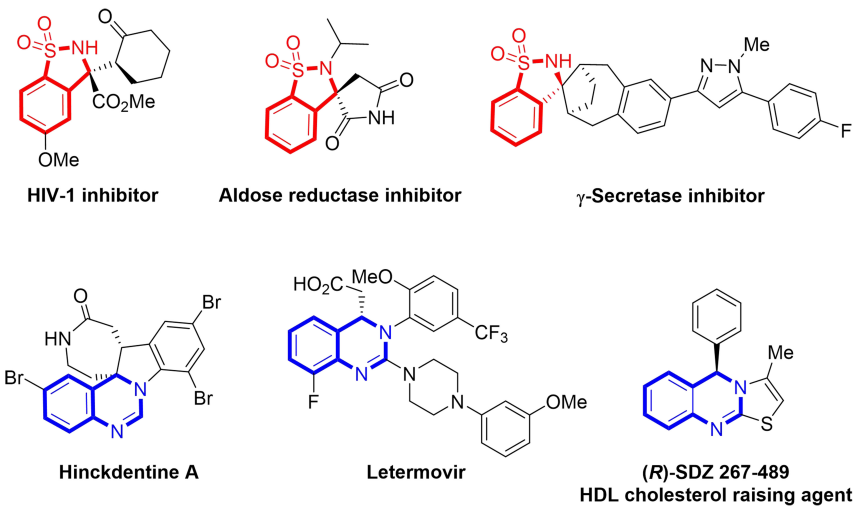
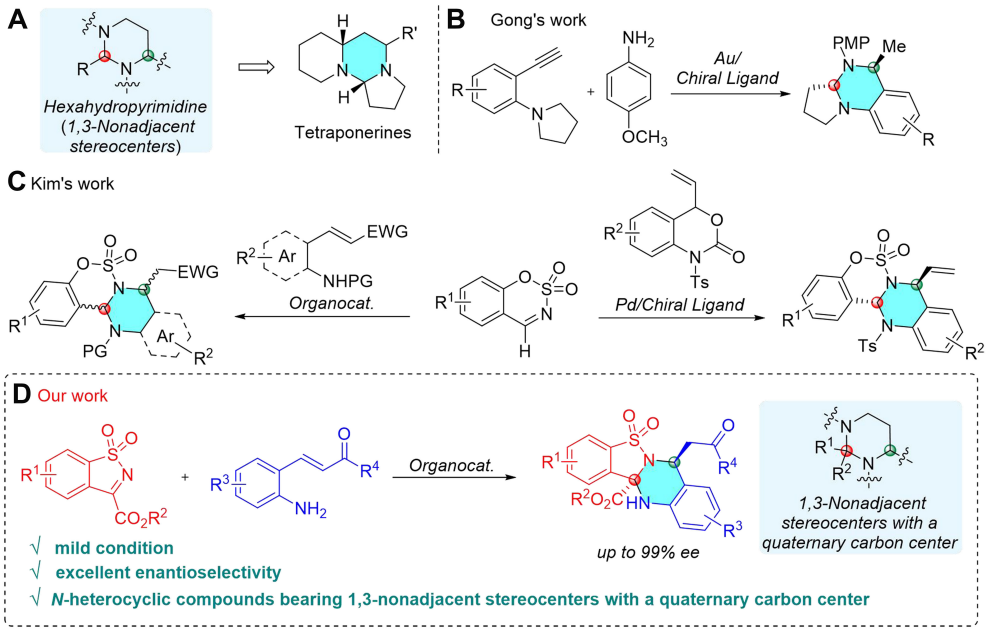


Figure 1. Bioactive compounds containing benzofused sultams and quinazolines.

other hand, quinazoline skeleton widely exists in natural products[6-9] and marketed drugs [Figure 1]. For instance, antiviral drug Letermovir[10], with 3,4-dihydroquinazoline, has potent anti-cytomegaloviral activity both *in vitro* and *in vivo*, and it is used clinically to treat patients who are seropositive for cytomegalovirus after undergoing allogeneic hematopoietic stem cell transplantation. The serum high-density lipoprotein cholesterol raising agent (*R*)-SDZ 267-489[11] can reduce the risk of atherosclerosis by raising cholesterol levels.

The combination of two pharmacophores through covalent bonds to create new bioactive molecules is a traditional method of drug design. We envisioned that the *N*-heterocyclic compounds, combining the two chiral structures mentioned above containing 1,3-nonadjacent stereocenters, might possess potential biological activities. Meanwhile, *N*-heterocyclic compounds bearing 1,3-nonadjacent stereocenters also serve as the fundamental structure of biologically active natural products[12-15], such as tetraponerines, which act as inhibitors of neuronal nicotinic acetylcholine receptors [Scheme 1A]. Moreover, in the total synthesis of this class of natural products, the construction of 1,3-nonadjacent stereocenters usually starts with chiral substrates[16-18] or requires the participation of chiral auxiliaries[19,20]. There is only one example of asymmetric catalytic approach, which requires the stepwise introduction of two chiral centers to construct the chiral hexahydropyrimidine skeleton[21]. Therefore, the development of an efficient approach to the construction of benzenesulfonamide fused tetrahydroquinazoline compounds bearing 1,3-nonadjacent stereocenters in a direct, concise and stereoselective manner is of great importance. Currently, there are limited asymmetric catalytic synthetic methods available for constructing *N*-heterocyclic compounds with 1,3-nonadjacent stereocenters. As shown in Scheme 1, He *et al.* developed a cascade hydroamination/redox reaction for the synthesis of cyclic aminals under the combined catalysis of gold complexes and Brønsted acid[22]. Sim *et al.* developed organocatalyzed stereoselective [4+2] annulations of cyclic *N*-sulfimines, affording benzosulfamidate fused tetrahydroquinazoline and hexahydropyrimidine derivatives, respectively[23,24]. Mun *et al.* also developed a palladium-catalyzed decarboxylative [4+2] annulation of vinyl benzoxazinanones with cyclic *N*-sulfimines for the synthesis of benzosulfamidate fused tetrahydroquinazolines[25].

It is widely recognized that quaternary carbon chiral centers represent a prominent research focus and challenge in the field of asymmetric catalysis due to their steric hindrance. Therefore, the development of



Scheme 1. Asymmetric synthesis of *N*-heterocycles bearing 1,3-nonadjacent stereocenters.

1,3-nonadjacent stereocenters with a quaternary carbon center is of great significance. Notably, there is lack of documented techniques for producing *N*-heterocyclic frameworks bearing 1,3-nonadjacent stereocenters with a quaternary carbon center, as illustrated in Scheme 1. Herein, we reported a catalytic enantioselective [4+2] annulation of *N*-sulfonyl ketimines with aminochalcones to access benzenesulfonamide fused tetrahydroquinazoline compounds bearing 1,3-nonadjacent stereocenters with a quaternary carbon center.

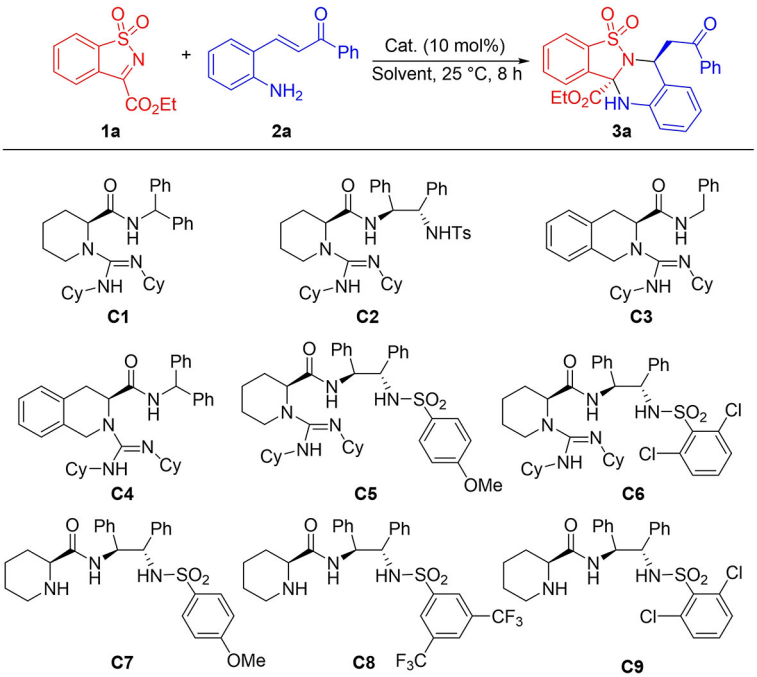
EXPERIMENTAL

To a stirred solution of cyclic *N*-sulfonyl ketimine **1** (0.10 mmol, 1.0 equiv) and aminochalcone **2** (0.15 mmol, 1.5 equiv) in $CHCl_3$ (1.0 mL) was added catalyst (0.01 mmol, 10 mol%) at 25 °C. Then, the resulting mixture was stirred at the same temperature. After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was directly charged to column chromatography on silica gel (petroleum ether/ethyl acetate = 20/1 to 5/1) to give the product **3**.

RESULTS AND DISCUSSION

To evaluate the practical feasibility of our proposal, the model reaction between *N*-sulfonyl ketimine **1a** and aminochalcone **2a** was carried out in MeCN at 25 °C. As indicated in Table 1, several chiral catalysts with hydrogen bond donors and acceptors were first examined. Cyclohexyl guanidine catalysts **C1**, **C2**, **C5**, **C6** and benzocyclohexyl guanidine catalysts **C3**, **C4** were tested first (Table 1, entries 1 to 6). It was found that catalyst **C2** led to the best enantioselectivity, and the reaction proceeded well, producing the desired [4+2] cycloadducts in 54% yield with 89% ee (Table 1, entry 2). We then tested different types of cyclohexyl catalysts without guanidino **C7**-**C9**. To our delight, the enantioselectivity was further improved, and **C8** exhibited the most effective catalytic effect (7:1 dr, 95% ee) (Table 1, entry 8), which is supposed to follow the catalytic pathway of the catalyst to form a ketimine intermediate with the aminochalcone to catalyze the reaction. Next, the reaction conditions were further optimized by varying solvents (Table 1, entries 10-15). When halogenated hydrocarbon solvents were tested, the enantioselectivity improved, and $CHCl_3$ as the solvent gave the best enantioselectivity (99% ee) and diastereoselectivity (10:1 dr) (Table 1, entry 14).

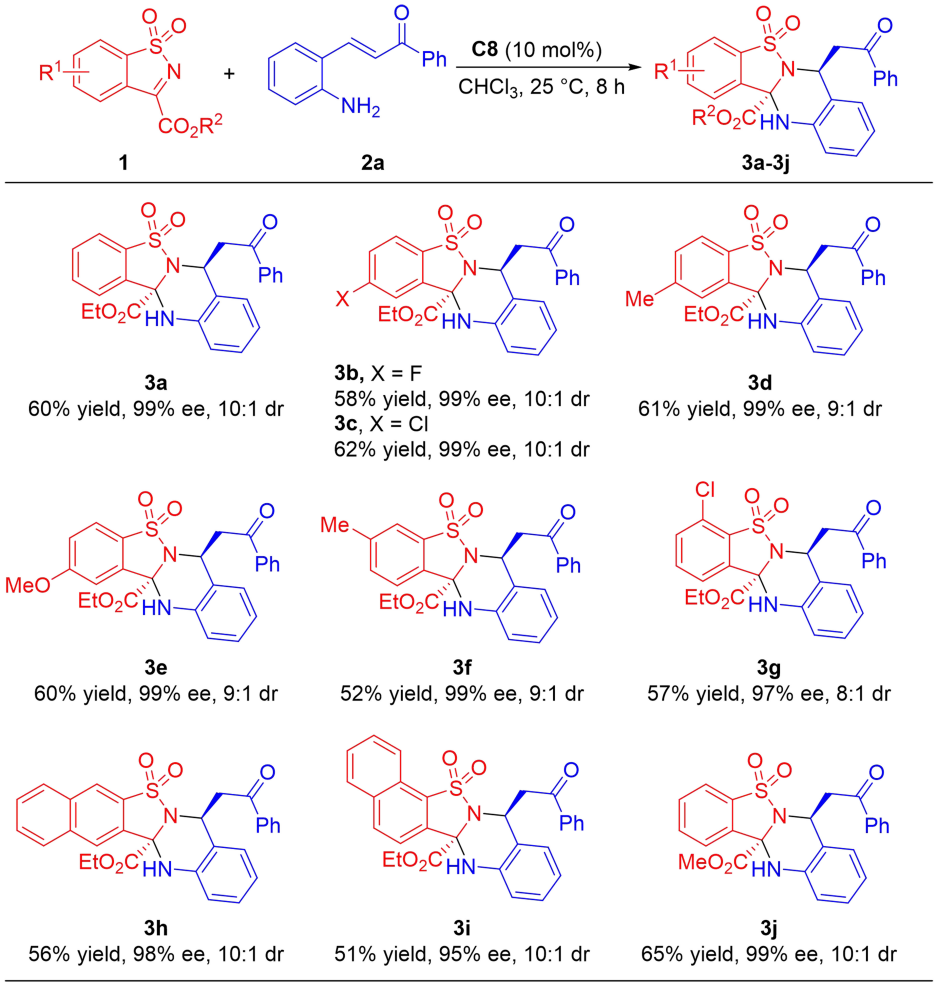
Table 1. Evaluation of catalysts and optimization of reaction conditions[a]



Entry	Cat.	Solvent	Yield (%)[b]	Dr[c]	Ee (%)[d]
1	**C1**	MeCN	42	2:1	0
2	**C2**	MeCN	54	2:1	89
3	**C3**	MeCN	39	1:1	11
4	**C4**	MeCN	< 5	-	-
5	**C5**	MeCN	51	2:1	76
6	**C6**	MeCN	58	2:1	81
7	**C7**	MeCN	56	5:1	92
8	**C8**	MeCN	52	7:1	95
9	**C9**	MeCN	55	5:1	91
10	**C8**	EtOAc	21	2:1	80
11	**C8**	Toluene	45	2:1	74
12	**C8**	THF	35	5:1	88
13	**C8**	Et_2O	52	2:1	78
14	**C8**	$CHCl_3$	60	10:1	99
15	**C8**	DCM	41	7:1	92

[a]Conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), and catalyst (0.01 mmol) in solvent (1.0 mL) at 25 °C; [b]Isolated yield; [c]Determined by ^{1}H NMR of the crude reaction mixture; [d]The ee values were determined by chiral HPLC analysis. THF: Tetrahydrofuran; DCM: dichloromethane.

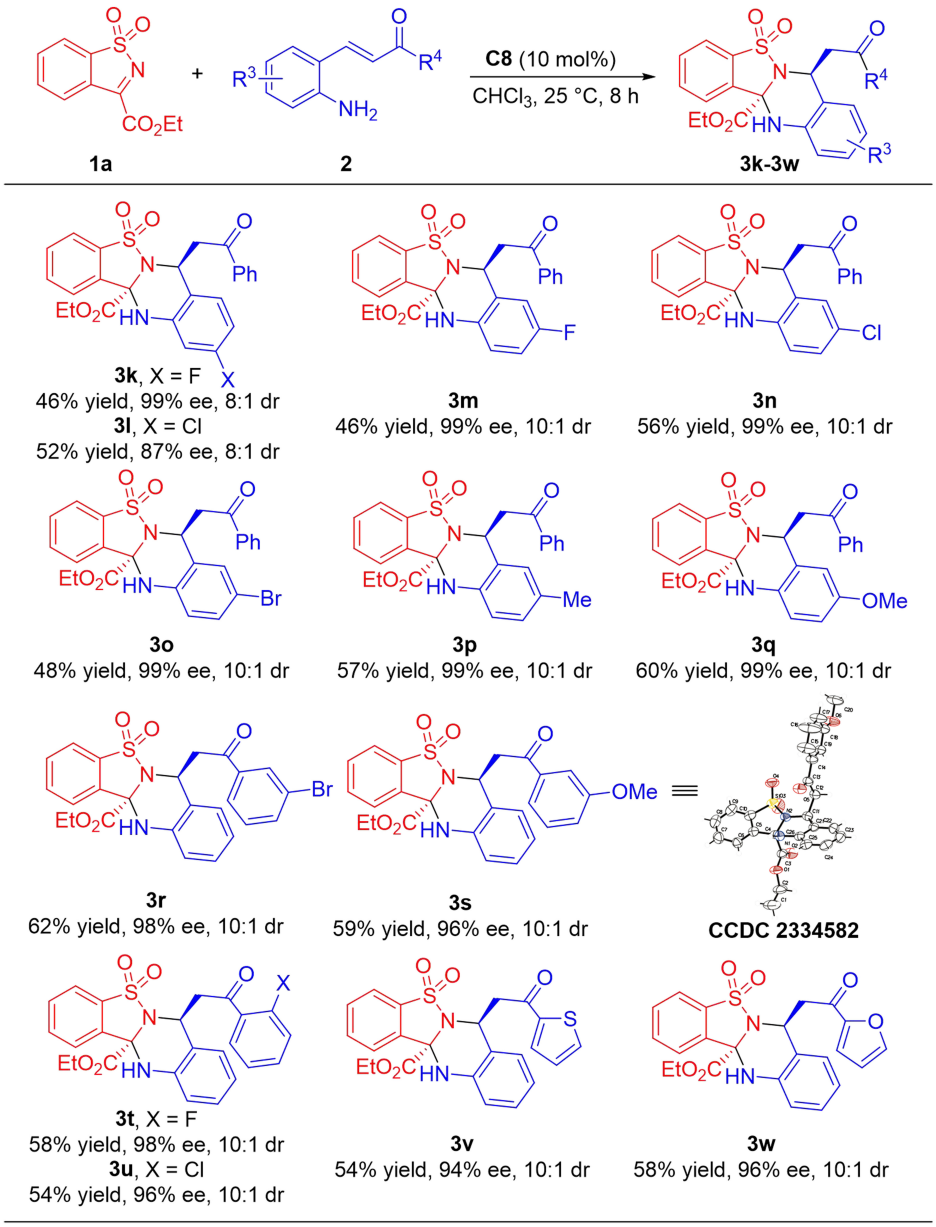
With the optimal reaction condition in hand, we then investigated the substrate scope of *N*-sulfonyl ketimines **1** and aminochalcones **2**. As shown in Scheme 2, a range of substituted *N*-sulfonyl ketimines were evaluated to examine the generality of the method. The electron-withdrawing groups and electron-donating groups at different positions of the aromatic ring of **1** were tolerated well in this catalytic reaction, giving the corresponding chiral benzenesulfonamide fused tetrahydroquinazoline products **3b**-**3g** with good diastereoselectivities (> 8:1) and excellent enantioselectivities (97%-99% ee). When replacing the benzene



Scheme 2. Substrate scope of cyclic *N*-sulfonyl ketimines **1**[a]. [a]Conditions: **1** (0.10 mmol), **2a** (0.15 mmol), and catalyst (0.01 mmol) in $CHCl_3$ (1.0 mL) at 25 °C; [b]Isolated yield; [c]Determined by ^1H NMR of the crude reaction mixture; [d]The ee values were determined by chiral HPLC analysis.

ring with naphthalene rings of *N*-sulfonyl ketimines **1**, the transformation also maintained excellent enantioselectivities, affording **3h** in 98% ee and **3i** in 95% ee. Additionally, the replacement of ethyl ester with methyl ester in *N*-sulfonyl ketimines **1** also worked well to give the desired product **3j** with 10:1 dr and 99% ee.

Next, a variety of aminochalcones **2** were investigated. Firstly, we tried different R^3 substituents on the benzene ring. As shown in Scheme 3, electron-withdrawing R^3 groups (4-F, 4-Cl, 4-Br, 5-F, 5-Cl) and electron-donating R^3 groups (4-Me, 4-OMe) worked well, delivering products **3k-3q** with good diastereoselectivities and excellent enantioselectivities. In addition, the R^4 groups of **2**, which involved a phenyl ring containing electron-withdrawing or donating substituents, were all well tolerated. The reactions proceeded smoothly with excellent efficiency, furnishing products **3r-3u** with 10:1 dr and excellent enantioselectivities (96%-98% ee). Heterocyclic aromatic rings such as thienyl and furyl also worked well, and the reactions proceeded efficiently to afford the corresponding products **3v** and **3w** with excellent enantioselectivities. The absolute configuration of **3s** was confirmed by X-ray single crystal diffraction (detailed data are in Supplementary Materials) and those of other products were assigned accordingly.

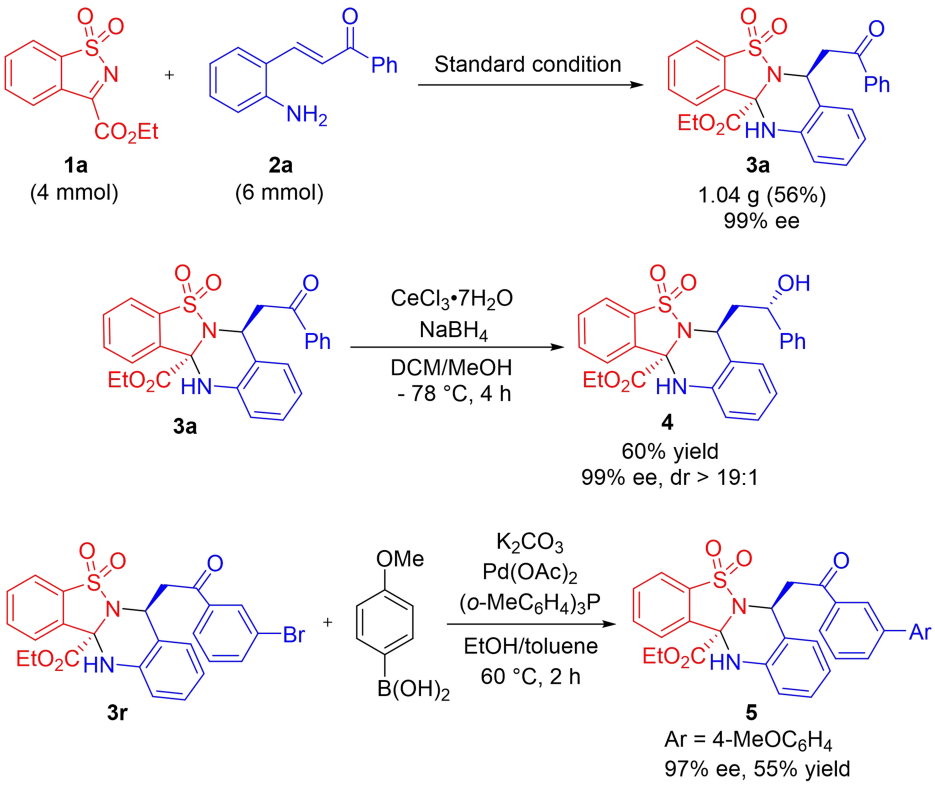


Scheme 3. Substrate scope of aminochalcones **2**[a]. [a]Conditions: **1a** (0.10 mmol), **2** (0.15 mmol), and catalyst (0.01 mmol) in $CHCl_3$ (1.0 mL) at 25 °C; [b]Isolated yield; [c]Determined by ^1H NMR of the crude reaction mixture; [d]The ee values were determined by chiral HPLC analysis.

To demonstrate the potential application of this protocol, the scale-up reaction of *N*-sulfonyl ketimines **1a** with aminochalcone **2a** was carried out under the standard condition [Scheme 4], and the corresponding product **3a** could be obtained in 56% yield (1.04 g) with 99% ee. Then, the reduction of the carbonyl group of **3a** using $NaBH_4$ and $CeCl_3·7H_2O$ furnished the hydroxy-functionalized compound **4** in 60% yield. We also tried the Suzuki coupling of **3r**, and the desired product **5** was obtained with a 55% yield.

CONCLUSIONS

In summary, we have developed a concise and efficient [4+2] annulation of *N*-sulfonyl ketimines and aminochalcones. The reaction proceeds with excellent enantioselectivity under mild conditions, providing a



Scheme 4. Scale-up reaction and further synthetic transformation.

convenient approach to benzenesulfonamide fused tetrahydroquinazoline compounds with 1,3-nonadjacent stereocenters containing a quaternary carbon center. This straightforward synthetic protocol exhibited excellent yields with a wide substrate scope. Studies on the bioactivities of the benzenesulfonamide fused tetrahydroquinazoline compounds are in progress in our laboratory. Additionally, the GAP (Group-assisted purification) protection groups[26-28] could be further considered for catalyst recycling/recovery purposes for this reaction, especially for large-scale synthesis with larger loading of catalysts.

DECLARATIONS

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We sincerely thank all the team members who participated in this study.

Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Ren W
Performing the majority of the experiments: Xuan T
Conducting some of the experiments: Han W, Tian Y
Initially trying the model reaction: Pang R

Availability of data and materials

The raw data supporting the findings of this study are available within this Article and its Supplementary Materials. Further data are available from the corresponding authors upon reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Tengfei Xuan

Tengfei Xuan obtained his B.Sc. in Pharmacy from Xinxiang Medical University in 2017. He then received his M.Sc. in Medicinal Chemistry from Jinan University in 2020 and his Ph.D. in Medicinal Chemistry from Ocean University of China in 2024. His current research interests focus on the total synthesis of natural products and the development of novel synthetic methodologies for total synthesis.

Wei Han

Wei Han obtained his B.Sc. in Pharmacy from Qilu University of Technology in 2020. He then received his M.Sc. in Pharmacy from Ocean University of China. Subsequently, he joined Prof. Zhonglin Tao's group at Hunan University as a doctoral candidate. His research interests center on organometallic chemistry.

Ruochen Pang

Ruochen Pang obtained his B.Sc. in Pharmacy from Jinan University in 2020, followed by an MSc in Medicinal Chemistry from Ocean University of China in 2023. He is currently employed at Pharmaron.

Yuxin Tian

Yuxin Tian obtained his B.Sc. in Chemical Engineering from Qingdao University of Science and Technology in 2023. He is currently pursuing postgraduate studies in pharmacy at Ocean University of China, with a research focus on organocatalysis.

Weiwu Ren

Weiwu Ren received his B.Sc. in Chemistry from Nankai University in 2006 and his Ph.D. in Organic Chemistry from Peking University in 2011 under the supervision of Prof. Zhen Yang. He then worked as a research assistant at Tsinghua University under the supervision of Prof. Yefeng Tang from 2011 to 2012. From 2012 to 2016, he conducted postdoctoral research at the École Polytechnique Fédérale de Lausanne (EPFL), followed by a postdoctoral position at Simon Fraser University in Canada from 2016 to 2019. In 2019, he joined the faculty of School of Medicine and Pharmacy at Ocean University of China. His current research interests lie in the total synthesis of bioactive marine natural products, the development of novel synthetic methodologies, and the biological functions of marine natural products and their analogs.