Cite this paper: Gu, Z.; Wu, B.; Jiang, G.-F.; Zhou, Y.-G. *Chin. J. Chem.* **2018**, *36*, 1130—1134.

Concise Report

DOI: 10.1002/cjoc.201800330

Synthesis of Benzofuran-fused 1,4-Dihydropyridines *via* Bifunctional Squaramide-catalyzed Formal [4+2] Cycloaddition of Azadienes with Malononitrile†

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ABSTRACT An efficient bifunctional squaramide-catalyzed Michael addition/cyclization of azadienes with malononitrile has been successfully developed, providing a facile access to chiral benzofuran-fused 1,4-dihydropyridines with excellent yields, wide substrate scope and up to 99% ee. Additionally, this formal [4+2] cycloaddition can be performed in gram scale without noticeable loss of yield and enantioselectivity.

KEYWORDS 1,4-dihydropyridines, cycloaddition, azadienes, tandem reactions, organocatalysis, asymmetric synthesis

Introduction

1,4-Dihydropyridines (1,4-DHPs) are recognized as prominent structural scaffolds owing to their prevalence in natural products, pharmaceuticals and biologically active compounds.[1,2] For instance, the ZD 0947 is a novel urinary bladder selective ATP-sensitive potassium channel (K_{ATP} channel) opener and causes a significant relaxation in detrusor muscle.[3] Nilvadipine[4] and amlodipine[5] are long-acting calcium channel blockers used in the treatment of angina, congestive heart failure and hypertension. Notably, amlodipine is used in its enantiomeric mixture of salt forms, but the two enantiomers of amlodipine and their salts have different pharmacological properties. The (*S*)-(–)-isomer is the more potent calcium channel blocker showing about 2000-fold potency in vitro evaluation in the rat aorta than the (*R*)-(+)-isomer[5b] (Figure 1). Due to the remarkable importance of chiral 1,4-dihydropyridine frameworks, it is not surprising that the synthesis of optically active 1,4-dihydropyridines has attracted considerable attention. Chiral 1,4-dihydropyridines have been prepared using chiral reagents[6] and chiral resolutions.[7] In spite of great progress, there are only few examples of organocatalytic enantioselective syntheses of 1,4-dihydropyridines.[8] Hence, the asymmetric catalytic construction of chiral 1,4-dihydropyridines is still an active challenging task and highly desirable.

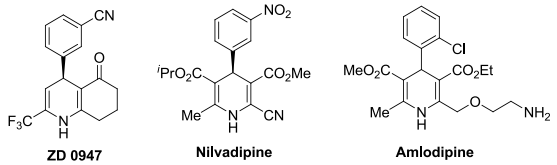
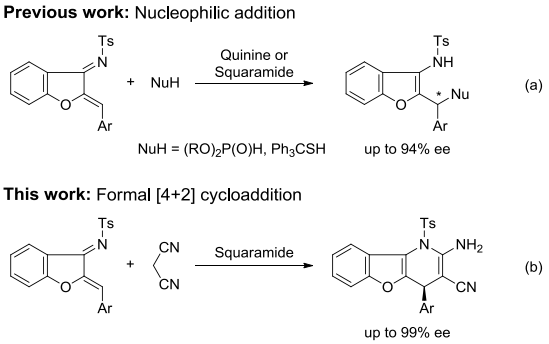


Figure 1 Bioactive 1,4-dihydropyridine derivatives.

In the last few years, azadienes have been regarded as an effective four-atom synthon in the construction of benzofuran-fused heterocyclic compounds owing to the driving force of aromatization.[9,10,11] In 2016, Zhao's group reported highly efficient catalytic aza-Diels-Alder reactions of azadienes to access either diastereomeric series of benzofuran-fused lactams and tetrahydropyridines in excellent stereoselectivities.[9a] Subsequently, Lu and co-workers developed enantioselective phosphine-catalyzed formal [4+4] cycloaddition of azadienes with allene ketones, giving azocines in high yields and enantioselectivities.[9b] Recently, palladium-catalyzed asymmetric formal cycloaddition of azadienes to prepare benzofuran-fused nine-membered and ten-membered heterocycles has been realized by Zhao's group.[9c-9e] During our studies on the employment of azadienes, we focused on bifunctional organocatalytic reactions of azadienes.[12-14] Recently, we reported the chiral bifunctional Brønsted base-catalyzed asymmetric nucleophilic addition of phosphites[14a] or thiols[14b] with azadienes, giving the corresponding products with excellent enantioselectivities (Scheme 1a). Considering that malononitrile has been widely used as nucleophilic reagent in enantioselective Michael addition[15] and served as two-atom synthon in asymmetric formal cycloaddition,[16] we envisioned that the combination of malononitrile and azadienes could enable facile synthesis of chiral benzofuran-fused 1,4-dihydropyridines by an asymmetric formal cycloaddition (Scheme 1b). Herein, we present bifunctional squaramide-catalyzed Michael addition/cyclization of the azadienes with malononitrile for facile synthesis of chiral benzofuran-fused 1,4-dihydropyridines with excellent enantioselectivities and broad substrate scope.

Scheme 1 Bifunctional chiral Brønsted base-catalyzed asymmetric reactions of azadienes



Results and Discussion

To test the viability of our proposed protocol, azadiene **1a** and malononitrile **2** were selected as model substrates for condition optimization. Pleasingly, the reaction proceeded smoothly to completion in 3 h and the desired product **3a** was isolated in 92% yield with 89% of enantioselectivity by employing cinchona alkaloid based squaramide catalyst **4a** as the catalyst (Table 1, entry

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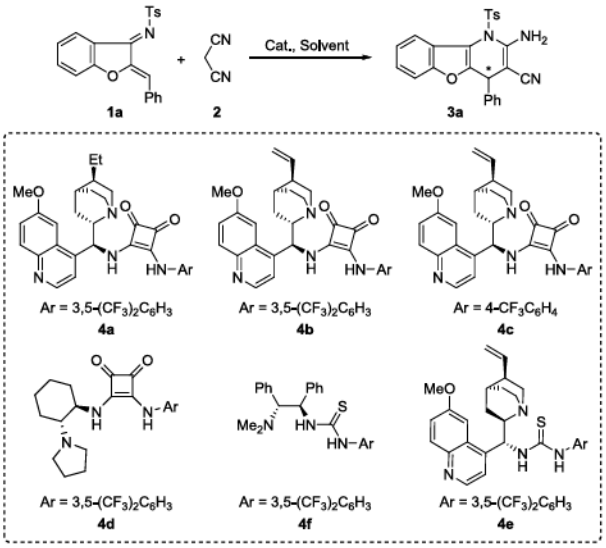
† Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

1). Subsequently, various solvents were examined, and it was found that solvent effect played a crucial role in the reactivities and enantioselectivities (Table 1, entries 2—6). In terms of enantioselectivity and yield, chloroform was chosen as the optimal solvent (Table 1, entry 3). Subsequently, several chiral bifunctional organocatalysts were evaluated. Cinchona alkaloid-based squaramide catalysts gave higher reactivities and enantioselectivities in comparison with the corresponding thiourea catalysts. The quinidine-based squaramide catalyst **4c** gave the desired product **3a** with 97% yield and 94% ee (Table 1, entries 7—11). To further improve the enantioselectivity, the effect of temperature was examined. When the reaction temperature was decreased to 0 °C, enantioselectivity was slightly enhanced, while, the reactivity was lower (Table 1, entry 12). We monitored the reaction process and found this reaction was two-steps formal cycloaddition including Michael addition and intramolecular cyclization. The enantio-determining step Michael addition is fast due to driving force of aromatization and the intramolecular cyclization is very slow at lower temperature. Therefore, we hypothesized that Michael addition should conduct at lower temperature which would be beneficial to the control of enatioselectivity, and intramolecular cyclization should perform in the higher temperature. In accordance with our prediction, 95% ee and excellent yield of the desired product were obtained when Michael addition was run at 0 °C until azadiene **1a** was completely consumed and the intramolecular cyclization took place at 30 °C (Table 1, entry 13). Satisfactorily, 96% ee was observed when the first step Michael addition occurred at −20 °C (Table 1, entry 14). Notably, the enantioselectivity and reactivity could be maintained when the catalyst loading was reduced to 5 mol% (Table 1, entry 15). Therefore, the optimal condition was established: using squaramide **4c** as catalyst and chloroform as the solvent to perform the reaction at −20 °C for 1 h, then at 30 °C for 5 h.

With the aforementioned optimal reaction conditions, we investigated the substrate scope of formal [4+2] cycloaddition of azadienes **1** with malononitrile **2**. As expected, the transformations conducted smoothly under the standard reaction conditions. A series of azadienes with different aryl substituents were suitable reaction partners, delivering the corresponding chiral benzofuran-fused 1,4-dihydropyridines in excellent enantioselectivities and yields. (Table 2, entries 1—11). The electronic and steric properties of the substituent on the aromatic ring had only marginal influence on yields and enantioselectivities. The methyl substituent at the 6-position of benzofuryl ring was tolerated and the corresponding adduct **3l** was obtained in 95% ee and 94% yield (Table 2, entry 12). Furthermore, the conversion was successful for various sulfonylimines regardless of steric hindrance (Table 2, entries 13—15). Notably, for bulky 2,4,6-trimethylbenzenesulfonyl imines **1o**—**1q**, the reaction afforded the desired products in almost quantitative yields and excellent enantio-

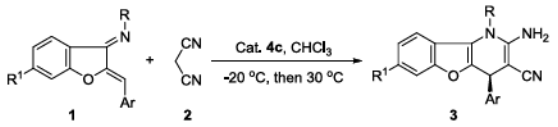
Table 1 The evaluation of reaction parameters[a]



Entry	Solvent	Cat.	Yield[b]/%	ee[c]/%
1	DCM	**4a**	92	89
2	DCE	**4a**	94	89
3	$CHCl_3$	**4a**	97	88
4	toluene	**4a**	86	85
5	*p*-xylene	**4a**	91	85
6	THF	**4a**	trace	—
7	$CHCl_3$	**4b**	94	89
8	$CHCl_3$	**4c**	97	94
9	$CHCl_3$	**4d**	96	67
10	$CHCl_3$	**4e**	36	62
11	$CHCl_3$	**4f**	65	58
12[d]	$CHCl_3$	**4c**	85	96
13[e]	$CHCl_3$	**4c**	99	95
14[f]	$CHCl_3$	**4c**	>99	96
15[f,g]	$CHCl_3$	**4c**	97	96

[a] Conditions: **1a** (0.20 mmol), **2** (0.24 mmol), Cat. (10 mol %), solvent (2.0 mL), 30 °C, 3 h. [b] Isolated yields. [c] Determined by HPLC. [d] 0 °C, 24 h. [e] 0 °C (1 h), then 30 °C (5 h). [f] −20 °C (1 h), then 30 °C (5 h). [g] Catalyst loading was reduced to 5 mol%.

Table 2 Substrate scope[a]



Entry	R	R^1	Ar	Yield[b]/%	ee[c]/%
1	Ts	H	Ph	97 (**3a**)	96
2	Ts	H	2-MeC_6H_4	98 (**3b**)	96
3	Ts	H	3-MeC_6H_4	99 (**3c**)	96
4	Ts	H	4-MeC_6H_4	95 (**3d**)	97
5	Ts	H	4-$^{i}PrC_6H_4$	90 (**3e**)	97
6	Ts	H	4-$^{t}BuC_6H_4$	97 (**3f**)	96
7	Ts	H	2-Naphthyl	97 (**3g**)	95
8	Ts	H	4-$MeOC_6H_4$	98 (**3h**)	99
9	Ts	H	3-ClC_6H_4	97 (**3i**)	93
10	Ts	H	3-BrC_6H_4	96 (**3j**)	92
11	Ts	H	4-ClC_6H_4	97 (**3k**)	95
12	Ts	Me	Ph	94 (**3l**)	95
13	Ns	H	Ph	96 (**3m**)	93
14	Ms	H	Ph	98 (**3n**)	97
15	SO_2Mes	H	Ph	98 (**3o**)	99
16	SO_2Mes	H	4-$MeOC_6H_4$	96 (**3p**)	98
17	SO_2Mes	H	2-Naphthyl	94 (**3q**)	98

[a] Conditions: **1** (0.20 mmol), **2** (0.24 mmol), Cat. **4c** (5 mol%), $CHCl_3$ (2.0 mL), −20 °C (1—29 h), then 30 °C (4—26 h). [b] Isolated yields. [c] Determined by HPLC.

selectivities (Table 2, entries 15—17). Unfortunately, when 2-tosylacetonitrile was used instead of malononitrile, only Michael addition product was obtained in low diastereoselectivity.[17] The absolute configuration of the product (+)-**3a** was unambiguously assigned to be *R* by X-ray crystallographic analysis after recrystallization with diethyl ether (Figure 2).[18]

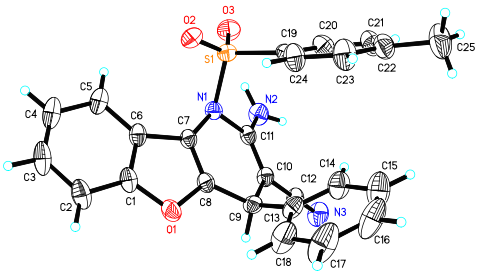
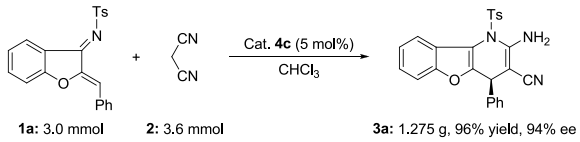


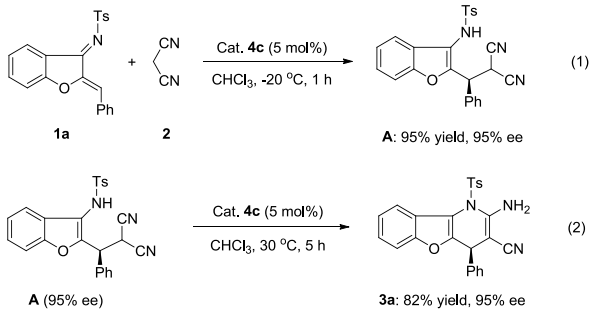
Figure 2 X-ray crystal structure of 1,4-dihydropyridine (+)-**3a**.

In order to further demonstrate the practicality of this methodology, the formal [4+2] cycloaddition of azadiene **1a** with malononitrile **2** was conducted at gram scale, giving the desired product in 96% yield and 94% ee without noticeable loss of yield and enantioselectivity (Scheme 2).

Scheme 2 Scale-up experiment



To identify that this reaction was two-steps formal cycloaddition, we carried out control experiments. The reaction of azadiene **1a** and malononitrile **2** was stopped after 1 h, the Michael addition intermediate **A** was isolated in 95% ee (Eq. 1). Then, intramolecular cyclization of intermediate **A** took place at 30 °C in 5 h, delivering cyclization product **3a** in 95% ee (Eq. 2). The above results indicated that the reaction involved enantio-determining step Michael addition and intramolecular cyclization.

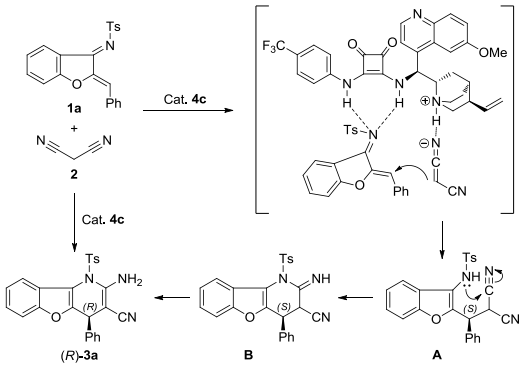


Based on the above results and previous literature report,[16c] a plausible reaction mechanism is depicted in Scheme 3. Initially, Michael addition of azadiene **1a** with malononitrile **2** forms (*S*)-configured intermediate **A** catalyzed by quinidine-based squaramide **4c**. Subsequently, the intramolecular aza-nucleophilic addition of nitrile group affords the cyclization intermediate **B**, followed by tautomerization to furnish the final annulation product **3a**.

Conclusions

In summary, we have successfully developed the highly

Scheme 3 Proposed reaction mechanism



enantioselective formal [4+2] cycloaddition of the azadienes with malononitrile using bifunctional squaramide as catalyst, providing a facile access to chiral benzofuran-fused 1,4-dihydropyridines with excellent yields and up to 99% ee. Further studies on the extension of this strategy to synthesize other chiral heterocyclic compounds are ongoing in our laboratory.

Experimental

General information

Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on 400 MHz instrument with TMS (tetramethylsilane) as internal standard. Optical rotations were measured with JASCO P-1010 polarimeter. Flash column chromatography was performed on silica gel (200—300 mesh). All reactions were monitored by TLC analysis.

General procedure for the synthesis of product 3

A mixture of azadienes **1** (0.2 mmol), malononitrile **2** (15.9 mg, 0.24 mmol) and organocatalyst **4c** (5.6 mg, 0.01 mmol) was stirred in chloroform ($CHCl_3$, 2.0 mL) at –20 °C until the full consumption of **1** (1—29 h). Subsequently, the reaction mixture was stirred at 30 °C for 4—26 h. The solvent was removed under reduced pressure and the crude product was directly purified by flash chromatography on silica gel using dichloromethane, diethyl ether and hexanes (1/1/5) as eluent to give the chiral products **3**.

(*R*)-2-Amino-4-phenyl-1-tosyl-1,4-dihydrobenzofuro[3,2-*b*]-pyridine-3-carbonitrile (3a). 86 mg, 97% yield, new compound, white solid, m.p. = 161—163 °C, R_f = 0.50 (dichloromethane/diethyl ether/hexanes = 1/1/2), 96% ee, $[\alpha]^{20}_D$ = +141.44 (*c* 0.83, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05—8.03 (m, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.42—7.36 (m, 1H), 7.36—7.28 (m, 2H), 7.19—7.05 (m, 5H), 6.70 (d, J = 7.5 Hz, 2H), 5.65 (s, 2H), 4.63 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6, 151.8, 147.2, 146.1, 138.6, 130.9, 130.1, 128.6, 128.5, 127.3, 127.1, 125.1, 123.8, 123.6, 122.3, 119.2, 116.8, 111.6, 71.1, 39.9, 21.9. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 70/30, flow = 0.8 mL/min, retention time 14.2 min (major) and 18.5 min (minor). HRMS Calculated for $C_{25}H_{20}N_3O_3S$ $[M+H]^+$ 442.1220, found 442.1224.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.201800330.

Acknowledgement

Financial support from National Natural Science Foundation of

China (21532006), Dalian Bureau of Science and Technology (2016RD07), and Dalian Institute of Chemical Physics (ZZBS201602) is acknowledged.

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[17] The Michael addition product was obtained in 87% yield with 1:1 dr. However, the two diastereomers can't be separated on TLC plate and chromatography.

[18] CCDC 1838129 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Manuscript received: June 11, 2018
Manuscript revised: September 2, 2018
Manuscript accepted: September 5, 2018
Accepted manuscript online: September 9, 2018
Version of record online: XXXX, 2018

