Organocatalytic regio- and enantioselective formal [4 + 2]-annulation of chiral nitrogen-containing dipoles

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Received: 30 Dec 2022 First Decision: 19 Jan 2023 Revised: 31 Jan 2023 Accepted: 6 Feb 2023 Published: 15 Feb 2023

Academic Editors: Bao-Lian Su, Da-Gang Yu Copy Editor: Ke-Cui Yang Production Editor: Ke-Cui Yang

Abstract
Quinidine-catalyzed regio- and enantioselective formal [4 + 2]-cycloadditions of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates with N-tosyl-2-methylenebut-3-enoates and 2-methylene-3-oxoalkanoates have been developed for the first time. The reaction features the in situ formation of chiral nitrogen-containing dipolar intermediates, a ring-opening/Michael addition/annulation cascade reaction, and works well over a broad substrate scope to furnish the tetrahydroquinolines in high yields with high asymmetric induction under mild conditions.

Keywords: Annulation, benzoxazine, diene, organocatalysis, tetrahydroquinoline

INTRODUCTION
The enantioenriched tetrahydroquinoline subunit is widely present in compounds with a wide range of biological activities [Scheme 1A][1]. Moreover, chiral 1,2,3,4-tetrahydroquinoline phosphoramidites have also been proven to be promising ligands in Ir-catalyzed asymmetric reactions[2]. Accordingly, the development of new methodologies for the catalyzed asymmetric synthesis of these significant frameworks continues to be a very active field of research[3-7]. Particularly, metal-catalyzed decarboxylative transformations of vinyl benzoxazinones have been identified as a powerful and versatile tool for the
asymmetric synthesis of chiral 1,2,3,4-tetrahydroquinolines, which featured a chiral metal-stabilized 1,4-zwitterionic intermediate [Scheme 1B][8].

Notably, organocatalytic asymmetric annulations have emerged as a key platform for the asymmetric construction of functionalized carbo- and heterocycles[9-12], but the organocatalytic asymmetric reactions of benzoxazinones for the construction of chiral tetrahydroquinoline motif remained a challenge [Scheme 1C].

An important breakthrough in the field of the organocatalytic asymmetric reactions of benzoxazinones was reported by Lu et al. in 2018[13]. They replaced the vinyl group of vinyl benzoxazinones with an alkynyl residue, enabling the formation of chiral N-heterocyclic carbene (NHC)-azolium enolate intermediate followed by [4 + 2]-annulation to furnish the chiral 3,4-dihydroquinolin-2(1H)-ones [Scheme 2A]. Based on our work on organocatalytic asymmetric reactions of Morita-Baylis-Hillman (MBH) adducts[14], we modified the structure of vinyl benzoxazinones and successfully developed 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates as new synthons to realize the chiral phosphine-catalyzed enantioselective formal [4 + 2]-cycloadditions via chiral phosphine-dipole intermediate [Scheme 2B][15]. To develop new catalytic systems and explore reactions of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates, we here reported a chiral amine-catalyzed regio- and enantioselective formal [4 + 2]-annulation of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates with α, β-unsaturated carbonyl derivatives for the asymmetric construction of enantioenriched 1,2,3,4-tetrahydroquinolines [Scheme 2C]. Importantly, the strategy represents the first time the chiral amine catalyzed the formal [4 + 2]-annulation of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates via a chiral amine-dipole intermediate.

**EXPERIMENTAL**

To a solution of CH₂Cl₂ (0.1 mL) were added 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates 1 (0.1 mmol), α,β-
unsaturated carbonyl derivatives 2 or 4 (0.2 mmol) and quinidine C5 (0.01 mmol, catalyst). The mixture was stirred at 35 °C for 96 h. After removing the solvent under vacuum, the residue was purified by flash chromatography (petroleum ether/ethyl acetate = 4/1, v/v) to afford the desired products 3 or 5.

RESULTS AND DISCUSSION
At the outset, we wanted to develop an organocatalytic [4 + 4]-annulation of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates with 2-[(aryl(tosylimino)methyl)acrylates. Exceptionally, methyl 2-[phenyl(tosylimino)methyl]acrylate 2a was found to act as a two-atom synthon in the N,N-dimethylpyridin-4-amine (DMAP) catalyzed reaction of methyl 2-(2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)acrylate 1a, leading to the formation of racemic 1,2,3,4-tetrahydroquinoline-3-carboxylate 3aa. To achieve an organocatalytic asymmetric [4 + 2]-annulation for the construction of chiral 1,2,3,4-tetrahydroquinolines, we then started our investigation with a model reaction between methyl 2-(2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)acrylate 1a and methyl 2-[(phenyl(tosylimino)methyl)acrylate 2a in the presence of different chiral amines C in dichloromethane (CH₂Cl₂) at room temperature (rt) for 24 h. Initially, the C1-catalyzed formal [4 + 2]-annulation furnished the desired product 3aa in 60% yield with 18% ee and > 20:1 dr [Table 1, entry 1]. Other chiral organocatalysts C2-3 bearing pyridine ring also afforded unsatisfactory enantioselectivity, respectively [Table 1, entries 2-3]. An essential enhancement of enantioselectivity was achieved when quinine C4 was employed as a catalyst, giving the desired product 3aa in 13% yield with 91% ee [Table 1, entry 4]. Further screening of cinchona alkaloids identified quinidine C5 as a suitable catalyst to afford 3aa in 30% yield with 90% ee [Table 1, entries 5-7]. To our delight, systematic screening studies including the effect of solvents [Table 1, entries 8-13], concentration [Table 1, entries 14-18], reaction temperature [Table 1, entries 19-22], the molar ratio of reactants and temperature [Table 1, entries 23-27] revealed that quinidine C5 enabled the formation of 3aa in 95% yield with 89% ee in CH₂Cl₂ (0.1 mL) at 35 °C after 96 h [Table 1, entry 27].

With the optimal conditions in hand, we then investigated the substrate scope. The scope of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates 1 was firstly examined by the C5-catalyzed reaction of methyl 2-[(phenyl(tosylimino)methyl)acrylate 2a [Scheme 3]. Notably, all the probed 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates could react smoothly to afford the corresponding products in high yields with asymmetric induction. In detail, the reaction of ethyl 2-(2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)acrylate 1b (R¹ = Et)
### Table 1. Condition optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
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<td>87</td>
<td>89</td>
</tr>
<tr>
<td>25</td>
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<td>CH₂Cl₂ (0.1 mL)</td>
<td>35 °C</td>
<td>96</td>
<td>90</td>
<td>89</td>
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</table>
Scheme 3. Substrate scope of the reaction between benzoxazines 1 and N-tosyl-2-methylenebut-3-enoates 2. A mixture of 1 (0.1 mmol), 2 (0.2 mmol), and C5 (10 mol%) in CH2Cl2 (0.1 mL) was stirred at 35 °C for 96 h. All dr > 20:1, determined by 1H NMR. Products 3 were obtained in isolated yield. The enantiomeric excess (ee) was determined by chiral-HPLC analysis.

furnished the desired product 3ba in 78% yield with 86% ee and > 20:1 dr. Various substituents (R2), either electron-withdrawing (F, Cl, Br) or electron-donating group (Me), could be introduced into the aromatic ring of 2-([4H-benzo[d][1,3]oxazin-4-yl]acrylates with a slight effect on the reaction, affording the corresponding products 3ca-fa in 73%-97% yields with 82%-92% ee and > 20:1 dr. A series of product 3ga-ja with different acyl (R3) were also obtained in 82%-94% yield with 84%-89% ee and > 20:1 dr. No significant electronic effect on the aromatic moiety was observed. With these encouraging data in hand, we turned our attention to the scope of methyl 2-[aryl(tosylimino)methyl]acrylates 2. It was found that the aromatic ring functionality (R4) of 2-[aryl(tosylimino)methyl]acrylates had a large influence on the yield, and the corresponding products 3ab-ad were obtained in 48%-75% yields with 88%-93% ee and > 20:1 dr. The hetero-aromatic 2-[aryl(tosylimino)methyl]acrylate 2e was also compatible to afford the desired product 3ae in 47% yield with 87% ee and > 20:1 dr. Notably, the formation of side products led to a relatively low yield of the desired product. Pleasingly, it was confirmed by these results that the C5-mediated asymmetric
Scheme 4. Substrate scope of the reaction between benzoxazines 1 and 2-methylene-3-oxoalkanoates 4. A mixture of 1 (0.1 mmol), 4 (0.2 mmol), and C5 (10 mol%) in CH$_2$Cl$_2$ (0.1 mL) was stirred at 35 °C for 96 h. All dr > 20:1, determined by $^1$H NMR. Products 5 were obtained in isolated yield. The enantiomeric excess (ee) was determined by chiral-HPLC analysis.

To further explore the scope of the C5-mediated asymmetric formal [4 + 2]-annulation of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates with 2-[aryl(tosylimino)methyl]acrylates was established.

To demonstrate the utility of this methodology, more investigations were carried out. Pleasingly, the C5-catalyzed reaction was easily scaled up [Scheme 5A]. Under the standard conditions, 5.0 mmol of 2-(2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)acrylate 1a reacted smoothly with 10.0 mmol of 2-[phenyl(tosylimino)methyl]acrylate 2a, affording 2.4 g (75% yield) of 3aa with 89% ee and > 20:1 dr. Treated with N-hydroxybenzimidoyl chloride/Et$_3$N, product 6aa was obtained in 96% yield with 79% ee and > 20:1 dr [Scheme 5B]. Notably, replacing catalyst C5 with C5-Me, poor results were obtained from the reaction of 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylate 1a with methyl 2-[phenyl(tosylimino)methyl]acrylate 2a [Scheme 5C]. These results indicated that the free hydroxy group of catalyst C5 is essential to achieve high efficiency and asymmetric induction.

As shown in Scheme 6, the absolute configuration of the enantioenriched 1,2,3,4-tetrahydroquinoline-3-carboxylate 3aa was determined by ECD (see Supplementary Materials for details). Accordingly, a possible reaction mechanism was proposed in Scheme 7. The initial nucleophilic addition of C5 to 2-(2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)acrylate 1a to form the key chiral amine-dipole intermediate I. Then, methyl 2-[phenyl(tosylimino)methyl]acrylate 2a was activated and arranged spatially by hydrogen-bond interaction
to react with the chiral amine-dipole to generate 1,4-adduct intermediate II. The subsequent asymmetric intramolecular conjugate addition afforded cycloaddition product intermediate III, followed by the removal of organocatalyst C5 to re-generate the catalyst and afford the desired product 3aa.

CONCLUSIONS
In conclusion, this work demonstrated the in situ formation of chiral amine-dipoles from 2-(4H-benzo[d][1,3]oxazin-4-yl)acrylates and nucleophilic quinidine. This newly developed nucleophilic catalysis was successfully applied to the organocatalytic regio- and enantioselective formal [4 + 2]-annulations of N-tosyl-2-methylenebut-3-enoates and 2-methylene-3-oxoalkanoates for the first time. Particularly, this catalytic system allows for the rapid construction of a broad scope of enantioenriched 1,2,3,4-tetrahydroquinoline derivatives. The investigation of the new chiral amine-dipoles as a means of synthesizing other high added-value compounds is ongoing in our lab.
DECLARATIONS

Acknowledgments
We gratefully thank the assistance of SUSTech Core Research Facilities, Yang Yu (HRMS, SUSTech). Computational work was supported by the Center for Computational Science and Engineering at SUSTech, and the CHEM high-performance supercomputer cluster (CHEM-HPC) located at the Department of Chemistry, SUSTech.

Authors’ contributions
Designing the experiments, writing the manuscript, and being responsible for the whole work: Li P
Performing the experiments: Wang T
Synthesizing the substrates and data review: Wang T, Chen X, Wan Q
Determining the absolute configuration of product 3aa: Shen B, Yu P

Availability of data and materials
Detailed experimental procedures and spectroscopic data were published as Supplementary Materials in the journal.

Financial support and sponsorship
The authors acknowledge the financial support from National Natural Science Foundation of China (21871128), Guangdong Innovative Program (2019BT02Y335), and the Guangdong Provincial Key Laboratory of Catalysis (2020B121201002).

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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