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

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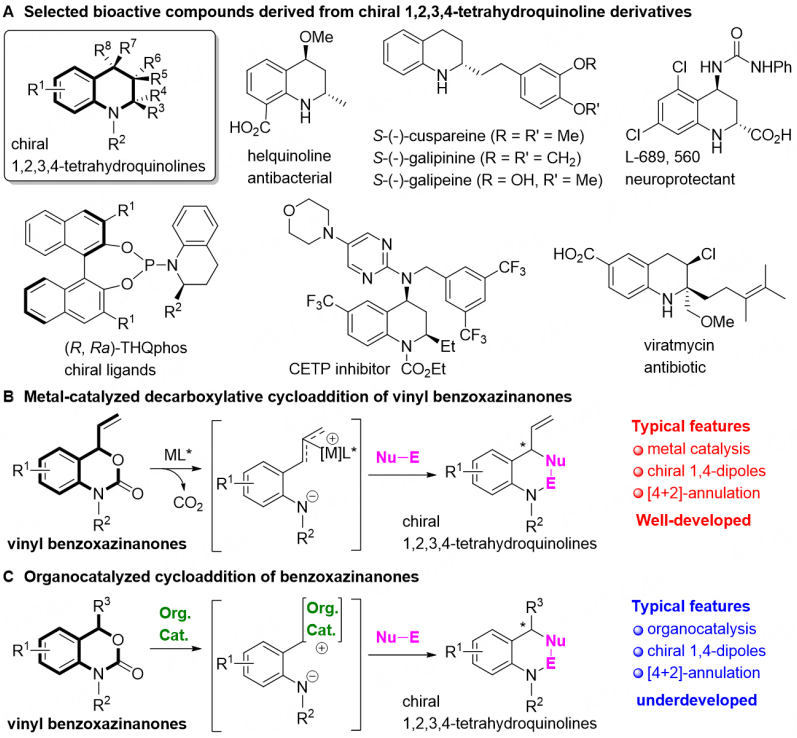
Abstract

Quinidine-catalyzed regio- and enantioselective formal [4 + 2]-cycloadditions of 2-(4*H*-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



Scheme 1. Selected chiral 1,2,3,4-tetrahydroquinolines and related reactions.

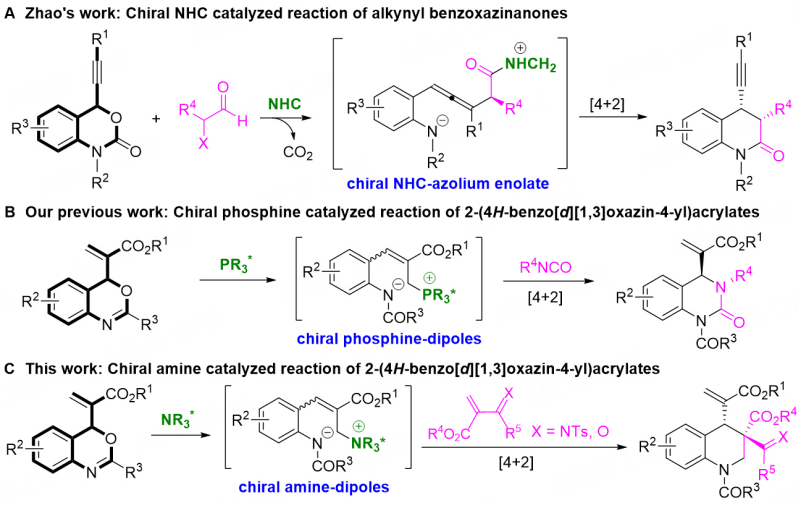
asymmetric synthesis of chiral 1,2,3,4-tetrahydroquinolines, which featured a chiral metal-stabilized 1,4-zwitterionic intermediate [Scheme 1B][8].

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(1*H*)-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-(4*H*-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-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates, we here reported a chiral amine-catalyzed regio- and enantioselective formal [4 + 2]-annulation of 2-(4*H*-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-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates via a chiral amine-dipole intermediate.

EXPERIMENTAL

To a solution of CH_2Cl_2 (0.1 mL) were added 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates **1** (0.1 mmol), α,β-



Scheme 2. Organocatalytic reactions of benzoxazinanone-related compounds.

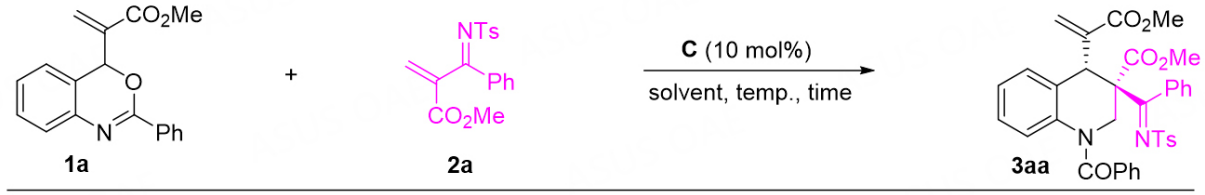
unsaturated carbonyl derivatives **2** or **4** (0.2 mmol) and quinidine **C5** (0.01 mmol, catalyst). The mixture was stirred at 35 °C for 96 h. After removing the solvent under vacuum, the residue was purified by flash chromatography (petroleum ether/ethyl acetate = 4/1, v/v) to afford the desired products **3** or **5**.

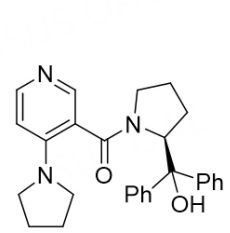
RESULTS AND DISCUSSION

At the outset, we wanted to develop an organocatalytic [4 + 4]-annulation of 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates with 2-[aryl(tosylimino)methyl]acrylates[16]. 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-4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylate **1a**, leading to the formation of racemic 1,2,3,4-tetrahydroquinoline-3-carboxylate **3aa**[17]. 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-4*H*-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 (CH_2Cl_2) 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 CH_2Cl_2 (0.1 mL) at 35 °C after 96 h [Table 1, entry 27].

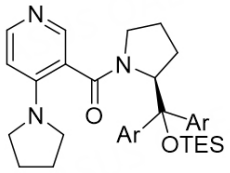
With the optimal conditions in hand, we then investigated the substrate scope. The scope of 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates **1** was firstly examined by the **C5**-catalyzed reaction of methyl 2-[phenyl(tosylimino)methyl]acrylate **2a** [Scheme 3]. Notably, all the probed 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates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

Table 1. Condition optimization

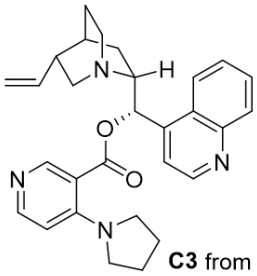




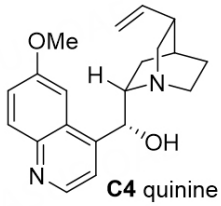
C1 from *L*-proline



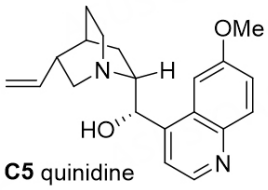
C2 from *L*-proline
Ar = 3,5-$(CF_3)_2C_6H_3$



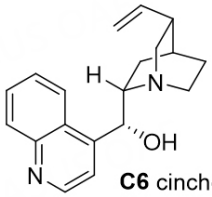
C3 from cinchonine



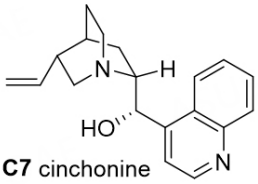
C4 quinine



C5 quinidine



C6 cinchonidine

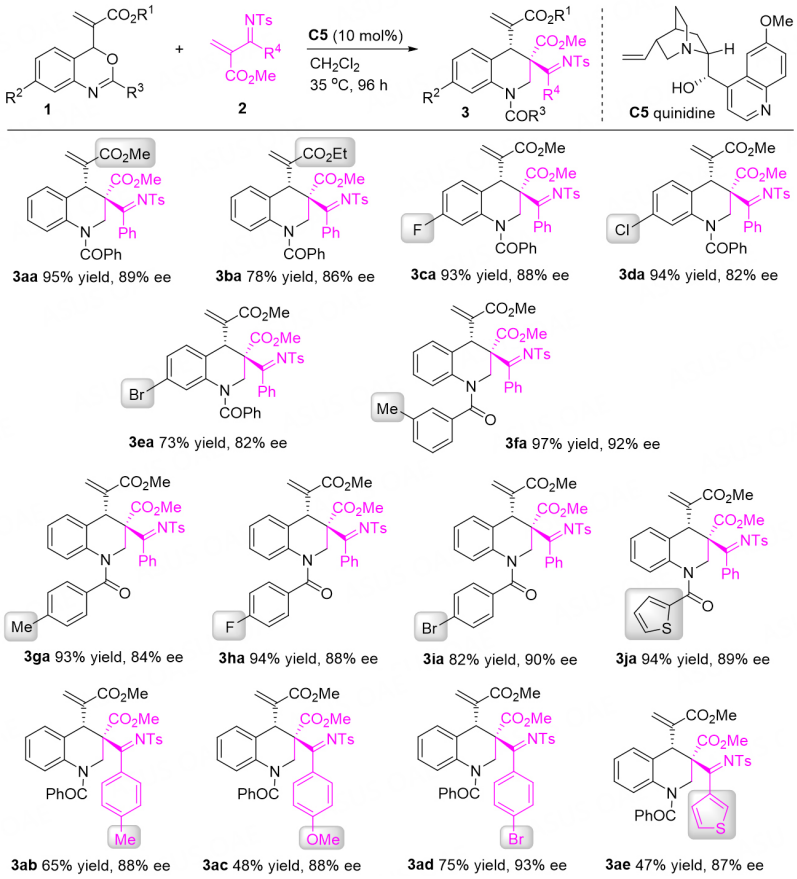


C7 cinchonine

Entry[a]	Catalyst	Solvent	Temp.	Time (h)	Yield (%)[b]	ee (%)[c]
1	**C1**	CH_2Cl_2	rt	24	60	18
2	**C2**	CH_2Cl_2	rt	24	47	40
3	**C3**	CH_2Cl_2	rt	24	14	5
4	**C4**	CH_2Cl_2	rt	24	13	91
5	**C5**	CH_2Cl_2	rt	24	30	90
6	**C6**	CH_2Cl_2	rt	24	9	85
7	**C7**	CH_2Cl_2	rt	24	13	89
8	**C5**	$CHCl_3$	rt	36	15	89
9	**C5**	$ClCH_2CH_2Cl$	rt	36	trace	-
10	**C5**	EtOAc	rt	36	trace	-
11	**C5**	toluene	rt	36	trace	-
12	**C5**	THF	rt	36	trace	-
13	**C5**	MeCN	rt	36	20	87
14	**C5**	CH_2Cl_2 (0.4 mL)	rt	36	35	89
15	**C5**	CH_2Cl_2 (0.3 mL)	rt	36	38	89
16	**C5**	CH_2Cl_2 (0.2 mL)	rt	36	44	89
17	**C5**	CH_2Cl_2 (0.1 mL)	rt	36	52	89
18	**C5**	CH_2Cl_2 (0.05 mL)	rt	36	43	89
19	**C5**	CH_2Cl_2 (0.1 mL)	rt	72	73	89
20	**C5**	CH_2Cl_2 (0.1 mL)	rt	96	78	89
21	**C5**	CH_2Cl_2 (0.1 mL)	rt	120	81	89
22	**C5**	CH_2Cl_2 (0.1 mL)	rt	144	84	89
23[d]	**C5**	CH_2Cl_2 (0.1 mL)	rt	96	80	89
24[e]	**C5**	CH_2Cl_2 (0.1 mL)	rt	96	87	89
25[e]	**C5**	CH_2Cl_2 (0.1 mL)	35 °C	96	90	89

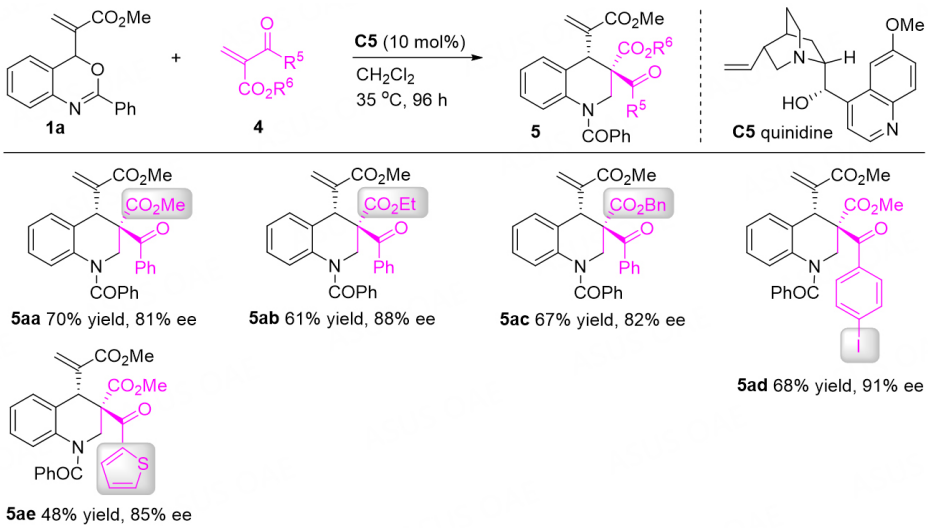
26[e]	**C5**	CH_2Cl_2 (0.1 mL)	40 °C	96	76	89
27[f]	**C5**	CH_2Cl_2 (0.1 mL)	35 °C	96	95	89

[a]Unless noted, a mixture of **1a** (0.05 mmol), **2a** (0.06 mmol), and **C** (10 mol%) in the solvent (0.5 mL) was stirred at room temperature (rt) for the time given. All dr > 20:1, determined by ^{1}H NMR; [b]isolated yield; [c]determined by chiral-HPLC analysis; [d]**2a** (0.075 mmol); [e]**2a** (0.10 mmol); [f]**1a** (0.10 mmol); **2a** (0.20 mmol).



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 CH_2Cl_2 (0.1 mL) was stirred at 35 °C for 96 h. All dr > 20:1, determined by ^{1}H 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 (R^2), either electron-withdrawing (F, Cl, Br) or electron-donating group (Me), could be introduced into the aromatic ring of 2-(4*H*-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 (R^3) 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 (R^4) 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



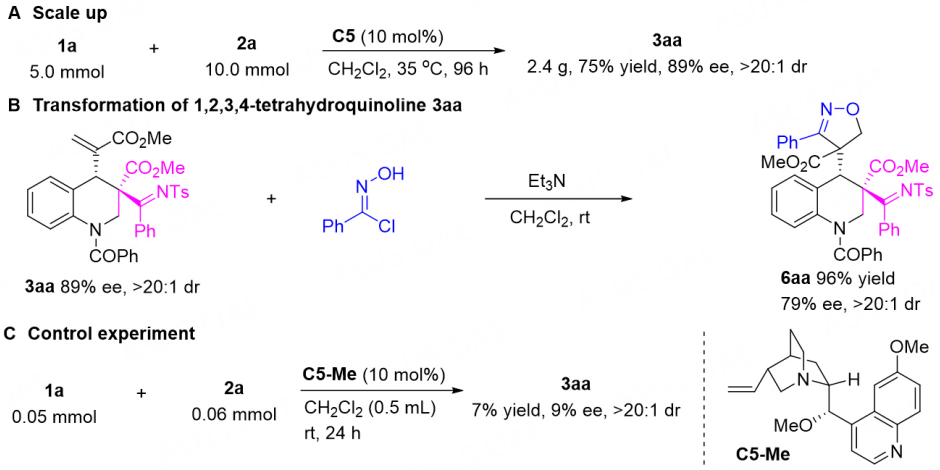
Scheme 4. Substrate scope of the reaction between benzoxazines **1** and 2-methylene-3-oxoalkanoates **4.** A mixture of **1** (0.1 mmol), **4** (0.2 mmol), and **C5** (10 mol%) in CH_2Cl_2 (0.1 mL) was stirred at 35 °C for 96 h. All dr > 20:1, determined by ^{1}H NMR. Products **5** were obtained in isolated yield. The enantiomeric excess (ee) was determined by chiral-HPLC analysis.

formal [4 + 2]-annulation of 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates with 2-[aryl(tosylimino)methyl]acrylates was established.

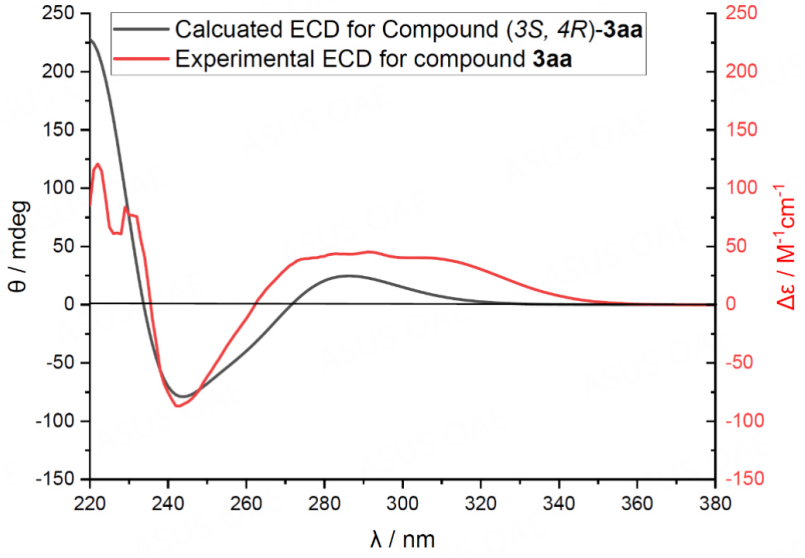
To further explore the scope of **C5**-mediated asymmetric formal [4 + 2]-annulation of 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates, reactions of the structurally related 2-methylene-3-oxoalkanoates **4** were investigated under the standard conditions [Scheme 4][18]. Importantly, a different ester group (R^6) of 2-methylene-3-oxoalkanoates was tolerated to generate the desired products **5aa**-**ac** in 61%-70% yields with 81%-88% ee and > 20:1 dr. Furthermore, both substituted aromatic and hetero-aromatic rings (R^5) were also compatible, furnishing the corresponding products **5ad** in 68% yield with 91% ee and > 20:1 dr and **5ae** in 48% yield with 85% ee and > 20:1 dr. Taken together, the **C5**-mediated region- and enantioselective formal [4 + 2]-annulation of 2-(4*H*-benzo[*d*][1,3]oxazin-4-yl)acrylates was successfully extended from 2-[aryl(tosylimino)methyl]acrylates to 2-methylene-3-oxoalkanoates.

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-4*H*-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_3N, 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-4*H*-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



Scheme 5. Further investigations.

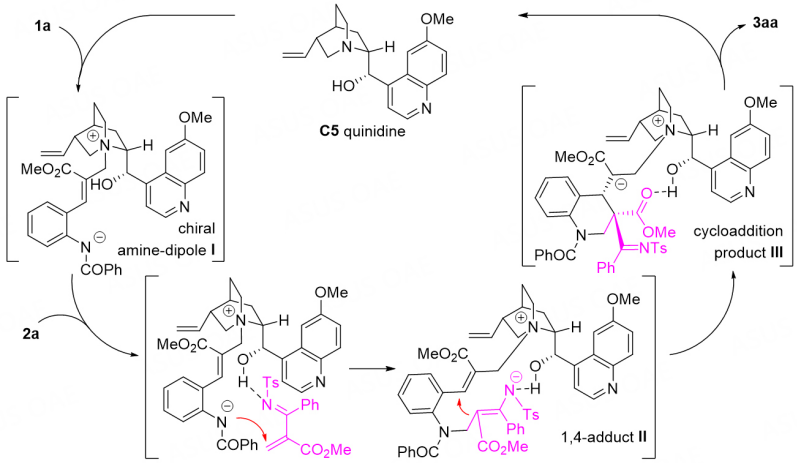


Scheme 6. Comparison of the calculated ECD of compound (*3S,4R*)-**3aa** with the experimental one of compound **3aa**.

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-(4*H*-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.



Scheme 7. Proposed reaction mechanism.

DECLARATIONS

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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.

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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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