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Enantioselective Organocatalytic Synthesis of Oxazolidine Derivatives through a One-Pot Cascade Reaction

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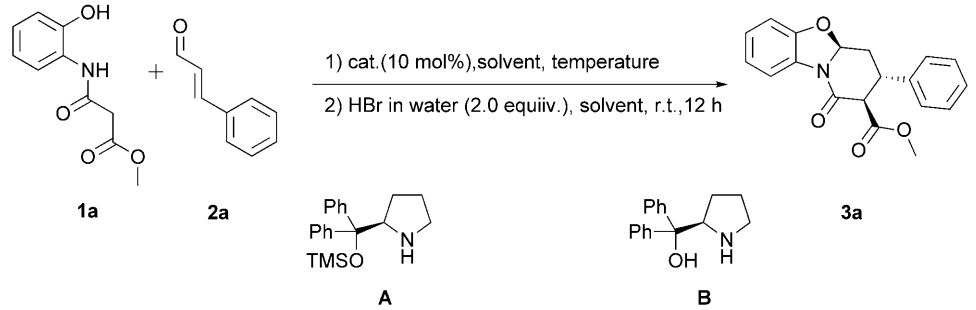
Abstract: An asymmetric organocatalytic cascade reaction which can afford a series of oxazolidine derivatives has been developed. The one-pot reaction reported here can produce an oxazolidine derivative in a highly enantioselective manner and good yield with good to excellent diastereomeric ratio.

Keywords: asymmetric catalysis; cascade reactions; one-pot process; oxazolidines; vinyl aldehydes

The development of asymmetric organocatalytic reactions has provided an efficient way in which scientists are able to synthesize highly enantioenriched compounds.[1] With its simple operation, low toxicity and ready availability, this method is attractive both to natural product synthesis and pharmaceutical engineering.[2] Of these well developed reactions, the enantioselective organocatalytic cascade reaction has become one of the most efficient strategies from which complex products with multiple chiral centres and bond formations can be obtained in a highly stereoselective manner and a simple one-pot operation.[3] Up to now, large numbers of excellent works have been reported with both ingenious designs and good to excellent results.[4] For example, Enders and coworkers have reported a three-component domino reaction in the synthesis of enantioenriched substituted cyclohexenes as one of the most outstanding starting principles in this field,[5] and a number of delicately designed two-component multistep Michael–Henry sequences for the synthesis of similar structures have been performed by Hayashi[6] and Zhong[7] et al. Recently, several highly efficient protocols for the synthesis of a series of optically active quinolizidine derivatives by an enantioselective secondary amine-catalyzed conjugate addition have been accomplished by Franzén[8] and Zhao,[9] respectively. These strategies were well established and the results were good. Nevertheless, both of the strategies resulted in a C–C bond formation between an electron-enriched aryl ring and an activated iminium intermediate in the annulation step. Herein, we report an efficient protocol by which a series of oxazolidine derivatives can be prepared through a C–O bond formation in a highly enantioselective manner by means of an easy one-pot operation. Notably, this oxazolidine structure can be found in a number of biologically active natural and non-natural compounds and is of great potential importance in the future exploitations in drug discoveries.[10]

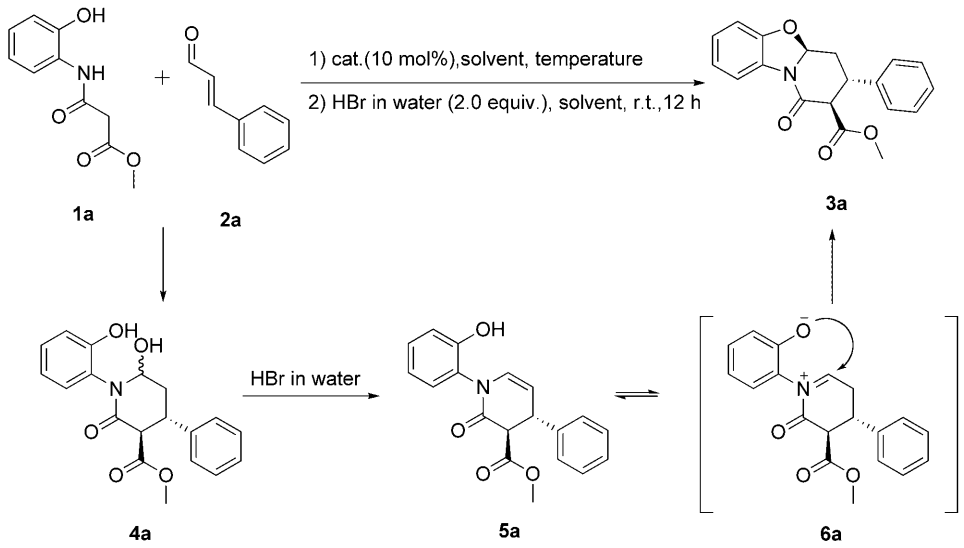
Initially, the cascade reaction of the rationally designed aryl amide **1a**[11] and cinnamyl aldehyde **2a** was carried out at room temperature by using the Jørgensen catalyst **A**[12], which was derived from *R*-proline, for the first step of Michael addition and then adding aqueous HBr solution to the reaction system for the annulation step. To our surprise and great delight, the Michael addition of **1a** and **2a** proceeded much faster than the results reported before,[8,9] probably due to the formation of an intramolecular hydrogen bond in the aryl amide,[13] and the sequence proved to go on smoothly. However, only moderate enantioseletivity was observed. Assuming that the *ee* value was predominately determined by the Michael addition step and that the annulation step would only effect the total yield and the diastereomeric ratio of the final product,[8,9] the optimization of the Michael addition was firstly investigated based on the *ee* value of **3a** and the formation of the isolable intermediate **4a** (Table 1). The results showed that both the temperature and the solvent had significant effects on the conversion of the Michael addition and the enantio purity of the final product. After screening a number

Table 1. Screening of the reaction conditions for the Michael addition of the aryl amide **1a** to cinnamyl aldehyde **2a**.[a]



Entry	Catalyst	Solvent	Temperature [°C][b]	Conversion[c] [%]	*ee*[d] [%]
1	**A**	CH_2Cl_2	r.t.	full (1.5 h)	77
2	**B**	CH_2Cl_2	r.t.	full (12 h)	59
3	**A**	CH_2Cl_2	−20	full (4.5 h)	96
4	**A**	THF	−20	21 (4.5 h)	90
5	**A**	toluene	−20	73 (4.5 h)	91
6	**A**	Et_2O	−20	46 (4.5 h)	82
7	**A**	CH_3CN	−20	44 (4.5 h)	71
8	**A**	DMF	−20	<10 (4.5 h)	nd
9	**A**	EtOAc	−20	31 (4.5 h)	55
10	**A**	2-propanol	−20	36 (4.5 h)	–[e]

[a] All reactions were carried out using 1.0 equiv. of **1a** (0.20 mmol), 1.5 equiv. of **2a**, 0.10 equiv. of catalyst, 0.4 mL solvent and 2.0 equiv. of HBr (40% in water).
[b] This represents the reaction temperature of the first step of the tandem reaction.
[c] The conversion of the Michael addition which was determined by ^{1}H NMR on the crude reaction mixture based on **4a** and **1a** after the certain time given within the parentheses.
[d] Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC.
[e] No final product was isolated after 12 h since the acid aqueous HBr had been added.



Scheme 1. Process of the one-pot cascade reaction.

of different conditions, the results proved best using catalyst **A** under −20 °C for the first step of the cascade reaction in CH_2Cl_2 (entry 3). The reaction proceeded well in several non-polar solvents with good to excellent enantioselectivities, albeit with relatively low conversions compared with that in CH_2Cl_2 (entries 4 to 6). However, strong polar solvents presented poor results either in reaction rates or in enantioselectivities (entries 8 to 10).

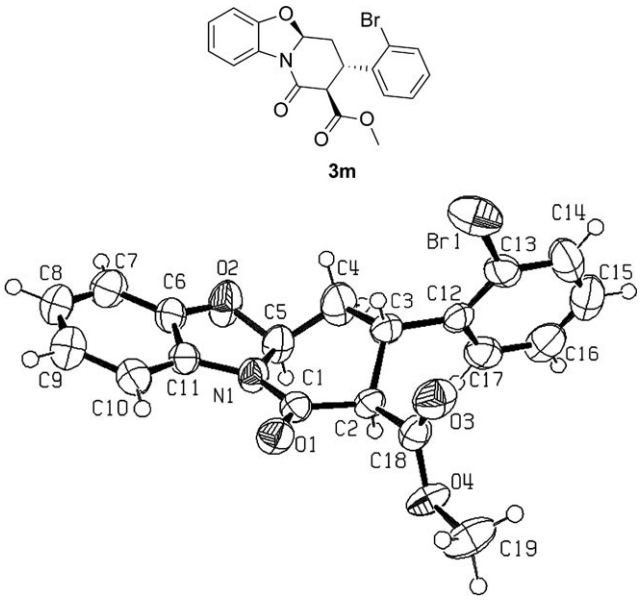


Figure 1. X-ray crystal structure of **3m**.

Having established the most effective reaction conditions for the Michael addition step, the annulation procedure promoted by acid additives was subsequently investigated. After adding excess aqueous HBr solution to the reaction system, we observed that the intermediate **4a** had diminished within 1 h to afford a small amount of the isolable intermediate **5a** and the main product **3a** (Scheme 1). Therefore, a variety of acid additives were screened at first mainly based on the conversion of **3a** from **5a** and the diastereomeric ratio of the final product (Table 2). Results showed that the annulation could not be promoted by acids that were relatively weak (entries 4 to 5). When using a strong acid, the procedure proceeded well with generally good to excellent diastereomeric ratio

Table 2. Screening of the acid additives for the annulation step of the tandem reaction.[a]

Entry	Acid additive	Equiv.	t[b]	Conv.[c] [%]	dr[d]
1	37% aqueous HCl	2.0	12 h	66	95:5
2	40% aqueous HBr	2.0	12 h	79	90:10
3	TFA	2.0	12 h	81	86:14
4	PhCOOH	2.0	12 h	NR	–
5	CH_3COOH	2.0	12 h	NR	–
6	diphenyl phosphate	2.0	12 h	76	91:9
7	Amberlyst 15	2.0	12 h	61	90:10
8	$TsOH{\cdot}H_2O$	2.0	12 h	95	93:7
9	$TsOH{\cdot}H_2O$	0.1	12 h	trace	nd
10	$TsOH{\cdot}H_2O$	0.2	12 h	69	nd
11	$TsOH{\cdot}H_2O$	0.5	12 h	82	nd
12	$TsOH{\cdot}H_2O$	1.0	12 h	87	nd
13	$TsOH{\cdot}H_2O$	2.0	1 h	83	93:7
14	$TsOH{\cdot}H_2O$	2.0	2 h	83	93:7
15	$TsOH{\cdot}H_2O$	2.0	4 h	86	93:7
16	$TsOH{\cdot}H_2O$	2.0	8 h	89	93:7

[a] All reactions were carried out using 1.0 equiv. of **1a** (0.20 mmol), 1.5 equiv. of **2a**, 0.10 equiv. of catalyst, 0.4 mL CH_2Cl_2 and the stated amount of the acid additives.

[b] Time t represents the reaction time of the annulation step.

[c] The conversion of the cyclization step of the tandem reaction which was determined by ^{1}H NMR on the crude reaction mixture based on **3a** and **5a**.

[d] Determined by ^{1}H NMR on the crude reaction mixture after stirring for a certain time since the acid had been added.

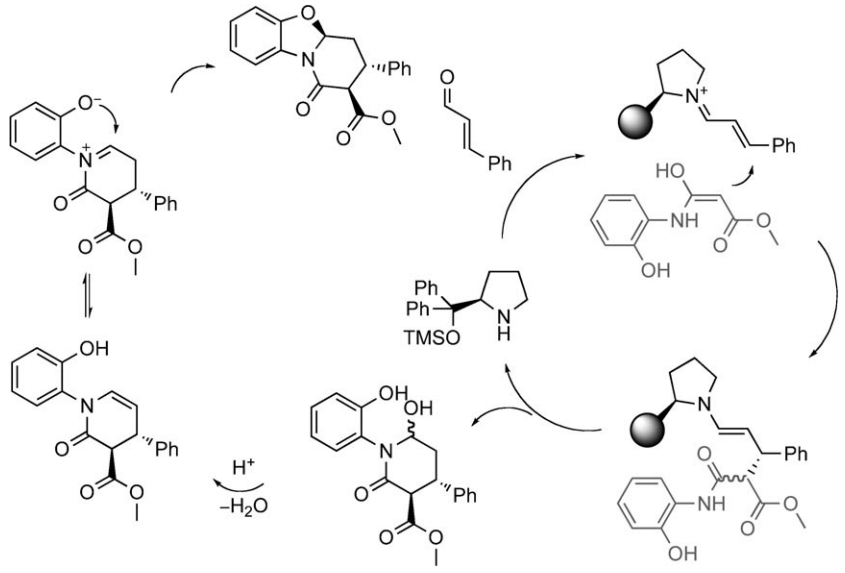
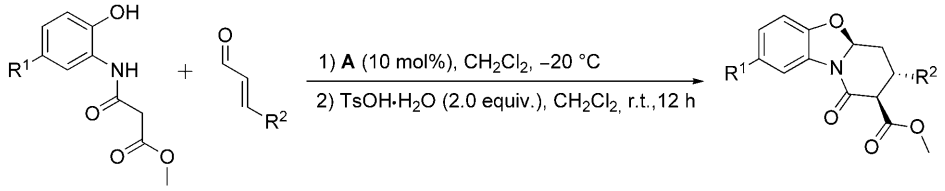


Figure 2. Prposed model of the cascade reaction.

Table 3. The scope of the tandem reaction of the aryl amide **1** and different vinyl aldehyde **2**.[a]



R^1 = H, **1a**; CH_3, **1b**; Cl, **1c**.

Entry	**1**	R^2	t[b]	Yield[c] [%]	Product	ee[d] [%]	dr[e]
1	**1a**	Ph	4.5 h	90	**3a**	96	92:8
2	**1a**	4-$NO_2C_6H_4$	4.5 h	55[g,h]	**3b**	94	93:7
3	**1a**	4-FC_6H_4	3 d[f]	64	**3c**	98	95:5
4	**1a**	4-$CH_3C_6H_4$	9 h	83	**3d**	90	92:8
5	**1a**	4-BrC_6H_4	5.5 h	76[g,h]	**3e**	90	85:15
6	**1a**	4-ClC_6H_4	3.5 h	53[g]	**3f**	92	85:15
7	**1a**	3-$CH_3C_6H_4$	9 h	90	**3g**	95	96:4
8	**1a**	3-ClC_6H_4	3 d[f]	65	**3h**	97	93:7
9	**1a**	2-ClC_6H_4	24 h	70	**3i**	97	96:4
10	**1a**	2-$CH_3OC_6H_4$	14 h	87	**3j**	96	93:7
11	**1a**	4-$CH_3OC_6H_4$	2 d	82	**3k**	85	92:8
12	**1a**	2-FC_6H_4	3 d	89	**3l**	98	93:7
13	**1a**	2-BrC_6H_4	14 h	69	**3m**	97	95:5
14	**1a**	CH_3	11 h	93	**3n**	92:87	73:27[i]
15	**1a**	CH_3CH_2	3 d[f]	60	**3o**	96:95	67:33[i]
16	**1b**	4-$CH_3C_6H_4$	9.5 h	86	**3p**	94	93:7
17	**1b**	4-ClC_6H_4	8.5 h	81	**3q**	96	94:6
18	**1c**	3-$CH_3C_6H_4$	12 h	54	**3r**	96	95:5
19	**1c**	2-ClC_6H_4	3 d	53	**3s**	99	93:7
20	**1a**	$CH_3(CH_2)_2$	5 d[f]	50	**3t**	97:95	69:31[i]
21	**1a**	$(CH_3)_2CH$	5 d[f]	72	**3u**	99:99	55:45[i]
22	**1a**	$CH_3(CH_2)_6$	5 d[f]	27	**3v**	98:98	54:46[i]

[a] Unless otherwise noticed, all reactions were carried out using 1.0 equiv. of **1** (0.40 mmol), 1.5 equiv. of **2**, 0.10 equiv. of catalyst **A**, 0.8 mL CH_2Cl_2 and 2.0 equiv. of $TsOH{\cdot}H_2O$.
[b] The time needed for the first step of Michael addition, which was determined by TLC.
[c] Isolated yield of the product mixture **3** of both diastereoisomers.
[d] Enantiomeric excess of the major diastereoisomer (except for those $dr < 4:1$), which was determined by chiral HPLC.
[e] Determined by ^1H NMR on the product mixture.
[f] Without full conversion of **1**.
[g] The reaction mixture was stirred for 3 days at room temperature after the acid additive had been added.
[h] 0.8 mmol 40% aqueous HBr in 0.7 mL CH_2Cl_2 was added instead of the solid $TsOH{\cdot}H_2O$.
[i] Four different diastereoisomers were detected by chiral HPLC, and only the major two were recorded.

and moderate to good conversion (entries 1 to 3, 6 to 8). To our surprise, the acid $TsOH{\cdot}H_2O$ promoted the annulation step with much higher conversion than any other acid that had been examined and afforded excellent diastereoselectivity (entry 8). Then, a series of control experiments was carried out focusing respectively on the amount of $TsOH{\cdot}H_2O$ (entries 9 to 12) and the reaction time of the second step (entries 13 to 16) in order to find the best conditions for the annulation reaction. Experimental data showed that the final product **3a** could be afforded in 95% conversion from **5a** and with a 93:7 *dr* value using 2.0 equivalents of $TsOH{\cdot}H_2O$ after stirring for 12 h since the acid had been added.

With the optimized reaction conditions for both the Michael addition and the annulation steps in hand, the scope of the two-component, one-pot cascade reaction was then expended using either aromatic or aliphatic vinyl aldehydes under similar conditions (Table 3). Good to excellent enantio- and diastereoenriched products were obtained in moderate to good yields, with the exceptant of the low diastereomeric ratios observed when aliphatic vinyl aldehydes were employed (entries 14 and 15). It appeared that

the substituents on the phenyl ring of the cinnamyl aldehydes had little effect on the *ee* value but did impact the total yields greatly. The electron-donating group substituted cinnamyl aldehydes generally afforded highly yielded products while the electron-withdrawing group often resulted in only moderate yields. However, all the products were obtained with high *ee* values, regardless of the properties of the substituents either on the vinyl aldehydes **2** or the aryl amides **1**.

The absolute configuration of the isolated major diastereoisomer **3m** was determined by X-ray analysis of a single crystal[14] (Figure 1), which was identical to our predicted model (Figure 2) based on previous work by Jørgensen,[15] Franzén[8] and Rios.[16]

In summary, an easy one-pot cascade reaction which afforded an oxazolidine derivative in a highly enantioselective manner and moderate to good yield with good to excellent diastereomeric ratio has been developed. Further applications of this approach towards the preparations of more complex enantioenriched compounds are currently being investigated.

Experimental Section

Typical Procedure: (2*R*,3*S*,4a*S*)-Methyl 1-Oxo-3-phenyl-1,2,3,4,4a-pentahydrobenzo[*d*]pyrido[2,1-*b*]oxazole-2-carboxylate (3a)

A solution of methyl 3-(2-hydroxyphenylamino)-3-oxopropanoate **1a** (0.4 mmol) in CH_2Cl_2 (0.4 mL) was stirred at −20 °C for 5 min whereupon the solution of catalyst **A** (0.04 mmol) and cinnamyl aldehyde (0.6 mmol) in CH_2Cl_2 (0.4 mL) was added. After that the reaction mixture had been stirred at −20 °C until **1a** disappeared (determined by TLC), $TsOH{\cdot}H_2O$ (0.8 mmol) was then added into the mixture in one portion. After 10 min, the reaction mixture was allowed to warm to room temperature and was stirred overnight. Finally the reaction mixture was separated by column chromatography with petroleum ether:ethyl acetate = 10:1 as eluant to give the pure product **3a** as white crystals; yield: 90%. For more details, see Supporting Information.

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