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Diastereo- and Enantioselective Synthesis of Oxazine and Oxazolidine Derivatives with a Chiral Quaternary Carbon Center under Multifunctional Catalysis

Zhichao Jin, Xiao Wang, Huicai Huang, Xinmiao Liang, and Jinxing Ye*

Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

yejx@ecust.edu.cn

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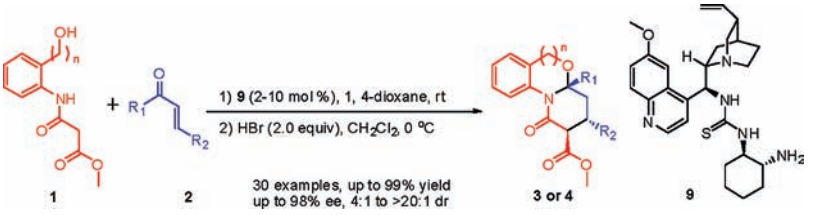
ABSTRACT



An easy one-pot, multistep cascade reaction which could afford a series of substituted benzo[d]pyrido[2,1-b]oxazolidine and [1,3]oxazine derivatives in a highly enantio- (up to 98% ee) and diastereoselective (4:1 to >20:1 dr) manner with generally good to excellent yields (up to 99%) has been developed. This well designed strategy could be applied to a wide scope of substrates under mild conditions with simple operations.

Nitrogen-containing multiple cycles have been considered as one of the most important fragments for drug discovery, and their synthesis has attracted more attention.[1] Among those compounds, the construction of oxazines and oxazolidines containing both a nitrogen and an oxygen atom is representative of some of the interesting endeavors. Various methodologies have been developed with the purpose of preparing these molecules efficiently.[2] For example, an efficient one-pot gold-catalyzed cascade reaction was developed to synthesize a series of pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones and pyrrolo/pyrido [2,1-*a*]-quinazolinones.[3] Eycken et al. reported the preparation of different pyridopyridazines and quinolines through a solvent-free procedure.[4] However, both of the studies did not involve asymmetric induction. Therefore, the preparation of this type of chiral heterocyclic compound, especially with a chiral quaternary carbon center, has remained a challenging task in organic synthesis.

Recently, the organocatalytic cascade reaction emerged as one of the most efficient strategies for the construction of cyclic compounds.[5,6] Scientists have also succeeded in the

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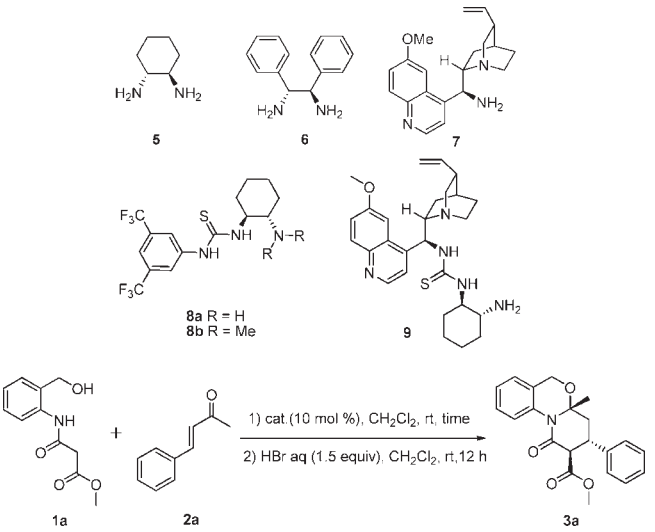
synthesis of fused heterocyclic compounds employing this metal-free strategy.[7−9] However, compared with the glorious achievements in the cascade reactions employing proline-derived catalysts, the cascade methodology of α,β-unsaturated ketones catalyzed by primary amine catalysts still represents a great challenge for chemists.[10]

We have been interested in the activation of α,β-unsaturated ketones and achieved great success in the asymmetric Michael additions of different nucleophiles to α,β-unsaturated ketones under multifunctional catalysis.[11] We have also made great efforts in the exploitation of cascade reactions from which complex compounds could be afforded in a highly stereoselective manner and a simple one-pot operation. In this letter, we report a one-pot cascade procedure for the synthesis of a series of enantio- and diastereoenriched oxazine and oxazolidine derivatives based on the rational design of bifunctional nucleophiles and the activation of vinyl ketones. Notably, a chiral quaternary carbon center with satisfactory selectivities has been constructed in the final annulation step by using a simple Brønsted acid.

The rationally designed nucleophilic reagent **1a** was selected as the Michael donor to participate in the cascade reaction with 4-phenylbut-3-en-2-one **2a** under several different conditions to form the desired oxazolidine derivative **3a**. Based on the former studies[8,9] we assumed that the enantiopurity of the final product would be dominantly determined by the first step of the cascade procedure. Thus the reaction conditions for the Michael addition were first investigated to optimize the enantioselectivity of the cascade reaction (Table 1). Poor enantioselectivity was obtained using the diamine catalysts **5** and **6** (entries 1 to 2). Moderate stereoselectivity could be acquired using the famous catalyst 9-amino (9-deoxy) epiquinine **7** (entry 3). When the thiourea motif was imported, great improvement

Table 1. Screening of the Reaction Conditions for the First Step of the Tandem Reaction[a]



entry	cat.	solvent	t (h)[b]	conv %[c]	ee %[d]	dr[e]
1	**5**	CH_2Cl_2	48	89	30	4:1
2	**6**	CH_2Cl_2	48	51	35	4:1
3	**7**	CH_2Cl_2	48	80	−51	4:1
4	**8a**	CH_2Cl_2	48	70	85	4:1
5	**8b**	CH_2Cl_2	48	0	--	--
6	**9**	CH_2Cl_2	24	>95	86	4:1
7	**9**	Toluene	24	>95	77	1:1
8	**9**	1,4-dioxane	24	>95	91	1:1
9	**9**	THF	24	>95	89	1:1
10	**9**[f]	1,4-dioxane	24	>95	91	1:1
11	**9**[g]	1,4-dioxane	24	>95	92	1:1
12	**9**[g]	1,4-dioxane[h]	72	>95	94	1:1
13	**9**[g]	1,4-dioxane[i]	144	64	95	1:1
14	**9**[g]	1,4-dioxane[j]	144	50	94	1:1
15	**9**[g]	1,4-dioxane[k]	72	>95	94	9:1[k]

[a] Unless otherwise noticed, all reactions were carried out using 1.0 equiv of **1a** (0.10 mmol), 1.5 equiv of **2a**, 0.1 equiv of catalyst, 0.2 mL of solvent, and 1.5 equiv of HBr in water (40%). [b] t represented the reaction time 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 after the certain time given. [d] Enantiomeric excess of **3a**, determined by chiral HPLC. [e] Determined by ^{1}H NMR on the crude reaction mixture 12 h after adding 1.5 equiv of HBr aq into the isolated intermediate (0.25 M). [f] 5.0 mol % catalyst was used. [g] 2.0 mol % catalyst was used. [h] The Michael addition was carried out at 0.2 M using 0.5 mL of 1,4-dioxane. [i] The Michael addition was carried out at 0.1 M using 1.0 mL of 1,4-dioxane. [j] The Michael addition was carried out at 0.067 M using 1.5 mL of 1,4-dioxane. [k] The annulation step was carried out at 0.067 M using 6 mL of CH_2Cl_2 under 0 °C.

in the ee value was implemented using catalyst **8a**, with 70% conversion within 48 h (entry 4). However, no reaction occurred when the primary amine was protected (entry 5). Finally, when the multifunctional catalyst **9** was employed both the reaction rate and ee value were acceptable (entry 6). After the screening of different solvents, 1,4-dioxane appeared to be the most suitable reaction media for the Michael addition (entry 8).[12] Further optimizations of the

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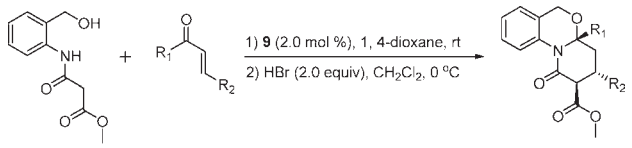
(12) For more details, see Supporting Information.

Table 2. Scope of the Tandem Reaction[a]



1a 2 3

entry	R_1	R_2	t_1 (d)[b]	t_2 (d)[c]	yield (%)[d]	product	ee (%)[e]	dr[f]
1	Me	Ph	3	1	88	**3a**	93	9:1
2	Me	2-FPh	2	1	85	**3b**	97	9:1
3	Me	4-FPh	9[g]	1	76	**3c**	95	8:1
4	Me	2-ClPh	3	1	95	**3d**	95	14:1
5	Me	3-ClPh	4	1	96	**3e**	95	7:1
6	Me	4-ClPh	3	1	89	**3f**	92	8:1
7	Me	3-BrPh	3	1	95	**3g**	90	8:1
8	Me	4-BrPh	5	1	91	**3h**	93	8:1
9	Me	2-MeOPh	2	1	93	**3i**	97	>20:1
10	Me	3-MeOPh	9[g]	1	88	**3j**	87	7:1
11	Me	4-MeOPh	9[g]	1	82	**3k**	95	11:1
12	Me	2-MePh	9[g]	1	77	**3l**	92	10:1
13	Me	3-MePh	7	1	99	**3m**	90	11:1
14	Me	4-MePh	9[g]	1	78	**3n**	90	11:1
15	Me	2,3-$(MeO)_2$Ph	3	1	89	**3o**	94	14:1
16	Me	2,4-$(MeO)_2$Ph	3	1	89	**3p**	90	19:1
17	Me	2-naphthyl	6	1	87	**3q**	85	10:1
18	Me	2-furanyl	5[h]	1	82	**3r**	95	4:1
19	Me	2-thiophenyl	9[g]	1	82	**3s**	93	6:1
20	Me	2-NO_2Ph	8[h]	1	64	**3t**	96	7:1
21	Me	3-NO_2Ph	5	1	82	**3u**	90	5:1
22	Me	4-NO_2Ph	6	1	83	**3v**	84	4:1
23	Me	*n*-Pr	5[h]	1	91	**3w**	95	15:1
24	Me	*i*-Bu	2[h]	1	97	**3x**	98	16:1
25	Et	Me	5[h]	1	96	**3y**	90	8:1

[a] Unless otherwise noticed, all reactions were carried out using 1.0 equiv of **1a** (0.20 mmol), 1.5 equiv of **2**, 0.02 equiv of **9**, 1.0 mL of 1,4-dioxane, 6 mL of CH_2Cl_2, and 2.0 equiv of HBr in water (40%). [b] The time needed for the first step of Michael addition, which is determined by TLC of the disappearance of the nucleophilic reagent **1**. [c] The time needed for the annulation step of the tandem reaction. [d] Isolated yield of the product mixture of both diastereoisomers. [e] Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC. [f] Determined by ^{1}H NMR on the product mixture. [g] Without full conversion of **1**. [h] 10 mol % of **9** was employed.

catalyst loading and the reaction concentration could afford the oxazolidine product with up to 95% ee and only 2% of catalyst loading (entry 13).

As the optimized reaction conditions for the Michael addition had been acquired, we next exploited the diastereoselectivities of the cascade procedure, which were determined completely by the annulation step initiated by a strong acid. The effects of different solvents were first surveyed by adding aqueous HBr into the isolated Michael product under the same concentration as that for the first step, which is summarized in the last column of Table 1 (entries 6−15). From these data we could see that CH_2Cl_2 and $CHCl_3$ showed a sharp distinction from other solvents and afforded the highest diastereomeric ratios of the final products. Then different acidic additives were screened to find the most suitable acid for the annulation step. Aqueous HBr produced a 4:1 diastereomeric ratio in the final step.[12] With an efficient and diastereoselective annulation reaction was in hand, we next investigated a catalytic one-pot process without separation of the intermediates. After a series of examinations, the dr value could be increased to more than 9:1 when diluting the reaction mixture into 0.03 M under 0 °C with CH_2Cl_2 as the solvent (entry 15).

With the best reaction conditions for both steps of the one-pot cascade process in hand, the scope of the asymmetric process was next examined using nucleophilic reagents **1a** and vinyl ketones **2** (Table 2). Data showed that this well developed strategy could be applied to a large variety of vinyl ketones involving both aromatic and aliphatic substituents. Most of the desired oxazine derivative products could be afforded in excellent yields with excellent enantio- and diastereoselectivities using only 2.0 mol % of catalyst **9**. Substrate generality under the present reaction conditions was broad, covering aryl and linear enones. Examination of substituent effects revealed that substituted moieties did not strongly affect enantioselectivity but slightly affected the reaction rates and the dr values of the final products.

Scheme 1. Example of the Cascade Reaction of **1a** with Cyclic Enone

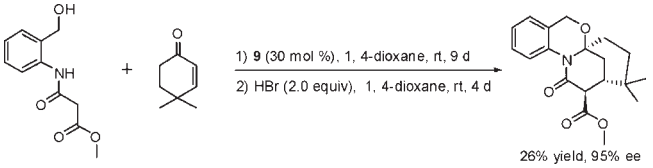
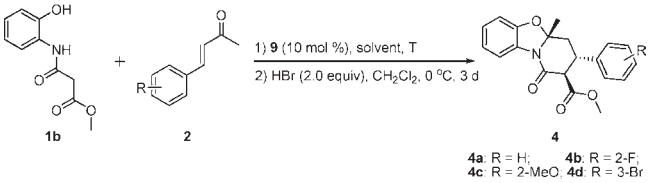


Table 3. Cascade Reactions of **1b** with Different Vinyl Ketones[a]



1b 2 4

entry	solvent	concn (M)[b]	temp (°C)[c]	t (d)[d]	yield (%)[e]	4	ee (%)[f]	dr[g]
1	dioxane	0.5	rt	2	nd	**4a**	65	10:1
2	mixture[h]	0.1	0	9	45	**4a**	83	10:1
3	mixture[h]	0.1	0	9	53	**4b**	80	9:1
4	mixture[h]	0.1	0	9	54	**4c**	73	6:1
5	mixture[h]	0.1	0	9	41	**4d**	82	7:1

[a] Unless otherwise noticed, all reactions were carried out using 1.0 equiv of **1b** (0.20 mmol), 1.5 equiv of **2**, 0.1 equiv of **9** for the first step and 6 mL of CH_2Cl_2, 2.0 equiv of HBr in water (40%) for the annulation step. [b] The concentration of the reaction mixture for the first step was based on **1b**. [c] The reaction temperature for the first step of the tandem reaction. [d] The reaction time for the first step. [e] Isolated yield of both diastereomers. [f] Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC. [g] Determined by ^{1}H NMR in the product mixture. [h] The mixture of dioxane/THF = 9/1.

Moreover, this one-pot strategy could even be applied to a cyclic vinyl ketone to afford a much more congested multicyclic compound in a highly enantioselective manner as a single diastereomer with a relatively unsatisfactory yield. An example is shown in Scheme 1.

A more challenging oxazolidine derivative was selected as the target of the cascade reaction. When using the other nucleophilic reagent **1b**, an oxazolidine derivative was obtained with moderate stereoselectivity and yield. This was probably attributed to the stereohindrance in the formation of five-membered ring oxazolidine. We continued investigate optimal conditions by screening solvents and temperature to improve the stereoselectivities in the formation of the desired oxazolidine products. After several screenings, those oxazolidine derivatives could be afforded in good stereoselectivities, but in moderate yields (Table 3).

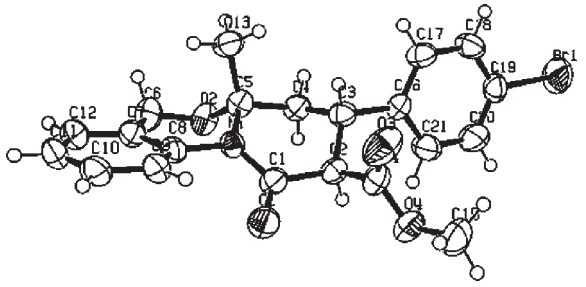


Figure 1. X-ray analysis of **3h**.

The bromide product **3h** was recrystallized from CH_2Cl_2, and the single crystal was subjected to X-ray analysis to determine the absolute configuration (Figure 1).[12]

In summary, an efficient one-pot multistep cascade reaction has been developed to afford a series of oxazine and oxazolidine derivatives. This new process could be applied to a wide scope of substrates in a highly enantio- and diastereoselective manner with generally good to excellent yields.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products and cif file of enantiopure **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.