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Organocatalytic Asymmetric Cascade Reaction of 2-Hydroxyphenyl-Substituted Enones and Isocyanates To Construct 1,3-Benzoxazin-2-ones

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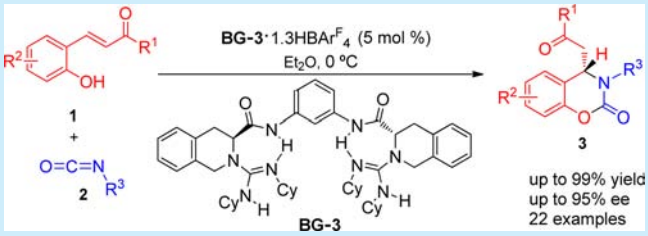
Supporting Information

ABSTRACT: The development of a new bisguanidinium salt as a multifunctional organocatalyst for asymmetric cascade esterification/aza-Michael reaction between 2-hydroxyphenyl-substituted enones and isocyanates is reported. A high level of enantioinduction and excellent isolated yields were achieved under mild reaction conditions. Enantiomerically enriched 1,3-benzoxazin-2-ones were constructed, and a possible catalytic model was suggested based on the mechanism-driven experiments.



1,3-Benzoxazinone derivatives represent a kind of heterocycle which possesses diverse biological properties as potential antimicrobial and analgesic agents.[1] Some 3,4-dihydro-4-acyl-2*H*-1,3-benzoxazin-2-one derivatives show molluscicidal activity against the *Biomphalaria alexandrina* snails which are the intermediate host of *Schistosoma mansoni*.[1d] The synthesis of 4-acyl-2*H*-1,3-benzoxazin-2-ones could be realized from the esterification/aza-Michael cascade between 2-hydroxyphenyl-substituted enones and isocyanates.[2] However, it suffers from drawbacks, including the formation of the open-chain carbamate product, strong base of KOH for cyclization, and reflux conditions in benzene. Moreover, only racemic products were obtained which is not conducive for screening pharmacological activities. Consequently, it is necessary to develop a chiral catalyst for the synthesis of enantiomerically enriched 4-substituted 1,3-benzoxazin-2-one derivatives.

An asymmetric intramolecular aza-Michael reaction allows the straightforward preparation of enantiomerically enriched nitrogen heterocycles.[3] A variety of nitrogen nucleophiles and Michael acceptors have been used for the construction of chiral five- or six-membered heterocycles,[4] such as substituted tetrahydroquinolines,[4a,b] tetrahydroisoquinolines,[4a−d] 2,3-dihydroquinolin-4-ones,[4e] piperidin-2-ones,[4f,g] pyrrolidines,[4g−k] and others.[4l−w] Nevertheless, *in situ* generation of carbamate nitrogen-nucleophile to participate in enantioselective intramolecular aza-Michael reaction is rare. The Matsubara group reported an asymmetric formal [3 + 2] cycloaddition for 2-oxazolidinone synthesis via carbamate intermediates generated *in situ* from *γ*-hydroxy-*α*,*β*-unsaturated carbonyl compounds with isocyanate.[4u] Although an enantioselectivity switch could be obtained the results were unsatisfactory. To accomplish a process that generates 1,3-benzoxazin-2-one derivatives in a highly enantiomerically enriched manner, we elected to study the catalytic asymmetric cascade reaction between 2-hydroxyphenyl-substituted enones and isocyanates. We questioned whether such a reaction could be realized using chiral guanidine bifunctional organocatalysts[5] that acted as a strong organic base and that housed multihydrogen that would confer high activity to go along with enantioselectivity.[6] Herein, we report a new bifunctional bisguanidinium salt that has proven to be effective and efficient in the esterification/aza-Michael reaction for the preparation of enantioenriched 4-acyl 1,3-benzoxazin-2-ones. The reactions between various 2-hydroxyphenyl-substituted enones and isocyanates performed well, and good yields (up to 99%) and high enantioselectivities (up to 95% ee) were given under mild reaction conditions.

Our studies began with evaluation of the chiral guanidine catalysts for the cascade reaction shown in Table 1. Treatment of 2-hydroxyphenyl-substituted enone **1a** with 4-methoxyl isocyanatobenzene **2a** in CH_2Cl_2 at 30 °C in the presence of chiral guanidine-amides **G-1**−**G-3** provided initial disappointing results (entries 1−3). The use of chiral **G-1** predominantly yielded the carbamate intermediate **4aa**, **G-2** gave the racemic cyclization product **3aa** in high yield, and only **G-3** gave the desired cyclization product **3aa** in 45% yield and 24% ee, accompanied by **4aa** in 52% yield. Bisguanidines could efficiently promote the esterification/aza-Michael process, and only a small amount of byproduct **4aa** was detected (entries 4−6). **BG-1**, which was efficient in several asymmetric organocatalytic reactions in our previous study,[6j,k,n,q] resulted in up to 88% yield but without stereocontrol (entry 4). Bisguanidine **BG-2**[6l] bearing an achiral benzene-1,3-diamine linkage could provide a reasonable level of conversion (98% yield) and 9% ee (entry 5). A set of encouraging results were obtained when bisguanidine **BG-3** and its salt were used. **BG-3** prepared from

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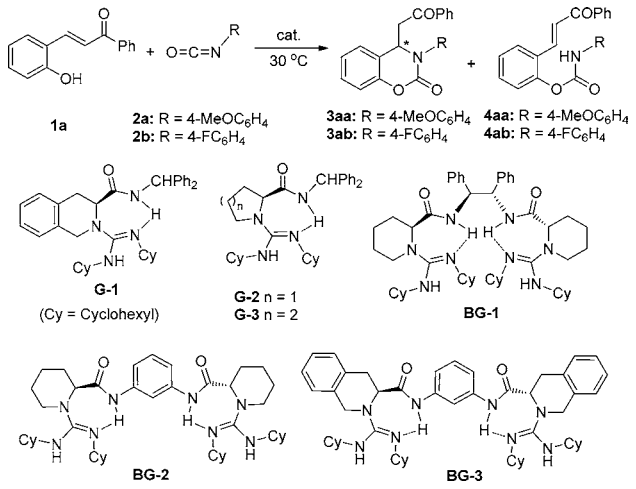
Table 1. Optimization of the Reaction Conditions[a]



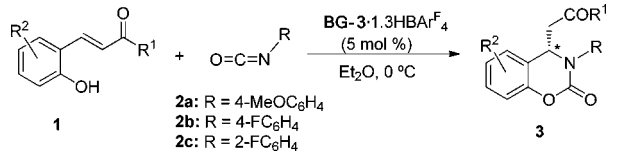
entry	cat.	solvent	yield (%)[b] 3; 4	ee of 3 (%)[c]
1	**G-1**	CH_2Cl_2	<6; 93	11
2	**G-2**	CH_2Cl_2	91; trace	0
3	**G-3**	CH_2Cl_2	45; 52	24
4	**BG-1**	CH_2Cl_2	88; trace	0
5	**BG-2**	CH_2Cl_2	98; trace	9
6	**BG-3**	CH_2Cl_2	81; trace	25
7	**BG-3**·$HBAr^F_4$	CH_2Cl_2	80; trace	70
8	**BG-3**·$HBAr^F_4$	toluene	90; trace	65
9	**BG-3**·$HBAr^F_4$	Et_2O	99; trace	72
10	**BG-3**·$HBAr^F_4$	THF	trace; 23	–
11[d]	**BG-3**·$HBAr^F_4$	Et_2O	96; trace	80
12[d,e]	**BG-3**·$HBAr^F_4$	Et_2O	98; trace	84
13[d,e]	**BG-3**·1.3$HBAr^F_4$	Et_2O	99; trace	89
14[d,e,f]	**BG-3**·1.3$HBAr^F_4$	Et_2O	99; trace	93

[a]Unless otherwise noted, the reactions were carried out with the catalyst (10 mol %), **1a** (0.1 mmol), and **2a** (1.2 equiv) in solvent (1.0 mL) at 30 °C for 18−46 h. [b]Isolated yield of **3** and **4**, respectively. [c]Determined by HPLC analysis. [d]Catalyst (10 mol %), **1a** (0.05 mmol), and **2a** (1.5 equiv) in Et_2O (1.2 mL) at 0 °C. [e]The catalyst loading was 5 mol %. [f]The reaction was performed with **1a** (0.05 mmol), **2b** (1.5 equiv) in Et_2O (1.5 mL). $HBAr^F$ = HB[3,5-$(F_3C)_2C_6H_3]_4$; **BG-3**·1.3$HBAr^F_4$ is prepared from a mixture of **BG-3** (35%) and **BG-3**·2$HBAr^F_4$ (65%).

(*S*)-tetrahydroisoquinoline-3-carboxylic acid and benzene-1,3-diamine provided good conversion (81% yield) and 25% ee (entry 6). The application of bisguanidinium hemisalt **BG-3**·$HBAr^F_4$ led to a striking result, wherein the product **3aa** could be isolated with an 80% yield and 70% ee (entry 7). In comparison with an ethane-1,2-diamine linker, a phenyl linker is conformationally stable, and the chiral environment created would make quite a difference.[6l−n] Next, the influence of the reaction solvent was investigated (entries 7−10). It revealed that the reaction in Et_2O delivered an ee value of 72% with a 99% yield (entry 9), which increased to 80% ee after the reaction temperature was reduced to 0 °C and the concentration was diluted (entry 11). Further decreasing the catalyst loading to 5 mol % resulted in an 84% ee and 98% yield (entry 12). In view of the fact that equilibrium among **BG**, **BG**·2HX, **BG**·HX existed in the bisguanidinium salt catalyst,[6n] we next tuned the ratio between bisguanidine and the acid $HBAr^F_4$, which might influence the equilibrium and give more reactive and enantioselective catalytic species. To our delight, a slight enhancement in enantioselectivity was observed with **BG-3**·1.3$HBAr^F_4$ (89% ee and 99% yield; entry 13). Other ratios deviating from 1:1.3 resulted in decreased yields and enantioselectivities. CD spectra related to the catalysts with variable ratio confirmed the effect of the acid on the conformation of the catalyst (see the Supporting Information (SI) for details). Furthermore, the use of 4-fluoro-substituted isocyanatobenzene **2b** could undergo the reaction in the presence of 5 mol % of **BG-3**·1.3$HBAr^F_4$, giving the corresponding product **3ab** in 99% yield and 93% ee (entry 14).

With an effective catalyst in hand (Table 1, entries 13−14), a wide range of substituted enones **1** reacted with isocyanatobenzene **2** were investigated. As shown in Table 2, variations to the benzoyl substituent of 2-hydroxyphenyl-substituted enones

Table 2. Scope of 2-Hydroxyphenyl-Substituted Enones and Isocyanates[a]



entry	R^1, R^2	yield (%)[b]	ee (%)[c]
1	Ph, H (**1a**)	99 (**3ab**)	93
2[d]	4-MeC_6H_4, H (**1b**)	93 (**3bb**)	93
3[d]	3-MeC_6H_4, H (**1c**)	73 (**3cb**)	92
4	2-FC_6H_4, H (**1d**)	79 (**3db**)	93
5	2-ClC_6H_4, H (**1e**)	81 (**3eb**)	89
6	3-FC_6H_4, H (**1f**)	80 (**3fb**)	90
7[d]	4-FC_6H_4, H (**1g**)	73 (**3gb**)	94
8	4-ClC_6H_4, H (**1h**)	89 (**3hb**)	89
9[e]	4-BrC_6H_4, H (**1i**)	80 (**3ib**)	91
10[e]	4-*t*BuC_6H_4, H (**1j**)	99 (**3jb**)	93
11[e]	4-$F_3CC_6H_4$, H (**1k**)	99 (**3kb**)	91
12[d]	4-PhC_6H_4, H (**1l**)	99 (**3lb**)	95
13[e]	 , H (**1m**)	99 (**3mb**)	89
14	Ph, 4′-FC_6H_4 (**1n**)	99 (**3nb**)	85
15	Ph, 4′-ClC_6H_4 (**1o**)	99 (**3ob**)	86
16	Ph, 4′-BrC_6H_4 (**1p**)	99 (**3pb**)	91
17	Ph, 5′-ClC_6H_4 (**1q**)	94 (**3qb**)	90
18[e]	Ph, 5′-$MeOC_6H_4$ (**1r**)	76 (**3rb**)	91
19	2-naphthyl, H (**1s**)	97 (**3sa**)	85
20	2-furyl, H (**1t**)	92 (**3ta**)	85
21	Ph, H (**1a**)	99 (**3aa**)	89
22	Ph, H (**1a**)	97 (**3ac**)	89

[a]Unless otherwise noted, all reactions were carried out with **BG-3**·1.3$HBAr^F_4$ (5 mol %), **1** (0.05 mmol), and **2** (1.5 equiv) in Et_2O (1.5 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis. [d]**BG-3**·1.3$HBAr^F_4$ (10 mol %). [e]**BG-3**·1.3$HBAr^F_4$ (7.5 mol %).

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impacted the conversion greatly and the enantioselectivity slightly (73−99% yields and 89−95% ee; entries 1−12). The introduction of a methyl substituent at the *metho*-position and electron-withdrawing substituent led to a lower conversion (entries 5−9), and the corresponding uncyclization byproducts **4** were detected. Benzofuran-substituted α,β-unsaturated ketone **1m** was tolerable, delivering the corresponding cyclization product **3mb** in 99% yield and 89% ee, whose structure shows a broad spectrum of biological activities[7] (entry 13). The substituent at the β-aryl group had an effect on the outcomes depending on both the electronic nature and position of the substituent (entries 14−18). A halo-substituent at the C′-4 position and 4-methyloxyl-substituent at the C′-5 position reduced the yield or enantioselectivity, respectively (entries 14, 15, and 18). Unfortunately, aliphatic ketones are poor partners in this protocol. Next, simple variations to the isocyanatobenzenes were tested. 4-Methyloxyl and 2-fluoro-substituted isocyanatobenzene **2a** and **2c** participated in the esterification/aza-Michael reaction well, giving the desired products with slightly reduced enantioselectivities (entries 21−22). Using 4-methyloxyl isocyanatobenzene **2a** as the reactant, naphthalen-2-yl, and furan-2-yl substituted 2-hydroxyl-enones **1s** and **1t** exhibited excellent reactivity and good enantioselectivities (entries 19−20). 1,3-Benzoxazin-2-one **3ta**, which shows molluscicidal activity,[1d] was given in 92% yield and 85% ee (entry 20). Unfortunately, alkyl-substituted isocyanates are inert under these reaction conditions.

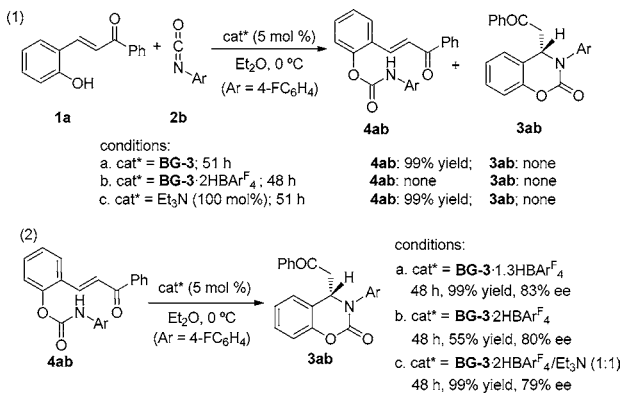
It is noteworthy that the reaction could be carried out at gram-scale. In the presence of 5 mol % of **BG-3**·1.3HBAr$^F_4$ catalyst, the reaction between 2-hydroxyphenyl-substituted enones **1a** (2.93 mmol) and isocyanate **2b** performed smoothly, delivering the corresponding product **3ab** in 99% yield and 94% ee (see the SI for details). The absolute configuration of the product **3ab** was determined to be *S* by X-ray single crystal analysis.[8] Comparison of the Cotton effect with **3ab** showed that the absolute configurations of the other 1,3-benzoxazin-2-ones **3** were *S* (see the SI for details).

With the goal of understanding how species of the catalyst and the substrate might interact to selectively afford the desired product, we did some control experiments (Scheme 1). The reaction between 2-hydroxyphenyl-substituted enones **1a** and isocyanate **2b** in the presence of 5 mol % of bisguanidine catalyst **BG-3** gave only the carbamate intermediate **4ab** in complete conversion at 0 °C (Scheme 1, eq 1a). The cyclization product **3ab** was obtained at improved reaction temperature (30 °C; Table 1, entry 6), indicating that the intramolecular aza-Michael reaction should be the rate-determining step. However, no reaction occurred if bisguanidium salt **BG-3**·2HBAr$^F_4$ was used as the catalyst instead (Scheme 1, eq 1b). It implies that a basic guanidine unit might benefit the oxa-addition of the hydroxyl group of 2-hydroxyphenyl-substituted enones to isocyanate. Additionally, Et_3N could only promote the formation of intermediate **4ab** (Scheme 1, eq 1c). Next, when the carbamate intermediate **4ab** was subjected to chiral catalyst conditions, the desired cyclization product **3ab** was given in 99% yield and 83% ee for **BG-3**·1.3HBAr$^F_4$ (Scheme 1, eq 2a), and in 55% yield and 80% ee for **BG-3**·2HBAr$^F_4$ (Scheme 1, eq 2b). Moreover, the yield increased to 99% after 5 mol % of Et_3N was added into the latter case (Scheme 1, eq 2c). It seems possible that the presence of the guanidinium salt and amide is necessary for hydrogen bonding that is crucial for the enantioselective intramolecular aza-Michael reaction, and the guanidine unit might benefit the deprotonation of carbamate **4ab** and accelerate the cyclization.

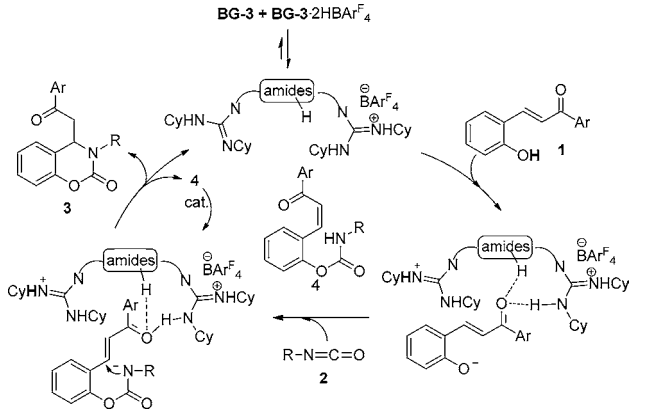
On the basis of these results, we presumed a possible catalytic model. As shown in Scheme 2, the guanidine unit of the catalyst abstracts the proton of the 2-hydroxyphenyl-substituted enones, forming the oxygen nucleophile;[9] meanwhile, the chalcone moiety is bonded via hydrogen bonds of the guanidinium and amide. The oxa-addition to isocyanate **2** forms the carbamate species, which then undergoes enantioselective aza-Michael reaction, following a protonation from the guanidinium cation, generating the desired cyclization product 4-acyl 1,3-benzoxazin-2-ones **3**. In the presence of the bisguanidinium salt, the intermediate **4** could further undergo deprotonation and aza-Michael reaction to give the final product **3**.

In summary, we have developed a convenient and efficient method to construct 1,3-benzoxazin-2-ones. A bifunctional bisguanidinium salt allowed for the asymmetric esterification/aza-Michael cascade between 2-hydroxyphenyl-substituted enones and isocyanates. Excellent yields and high enantioselectivities were given under mild reaction conditions. The reaction enables the synthesis of optically active 1,3-benzoxazin-2-ones with biological activity. We anticipate that chiral guanidine and guanidinium may find utility in other cascade reactions.

Scheme 1. Mechanism-Driven Experiments



Scheme 2. Proposed Catalytic Cycle



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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02522.

Crystallographic data (CIF)

Experimental details, analytic data (NMR, HPLC, CD, ESI-HRMS data) (PDF)

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Notes

The authors declare no competing financial interest.

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