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Highly Stereoselective [4+2] Cycloaddition of Azlactones to β,γ-Unsaturated α-Ketoesters Catalyzed by an Axially Chiral Guanidine Base

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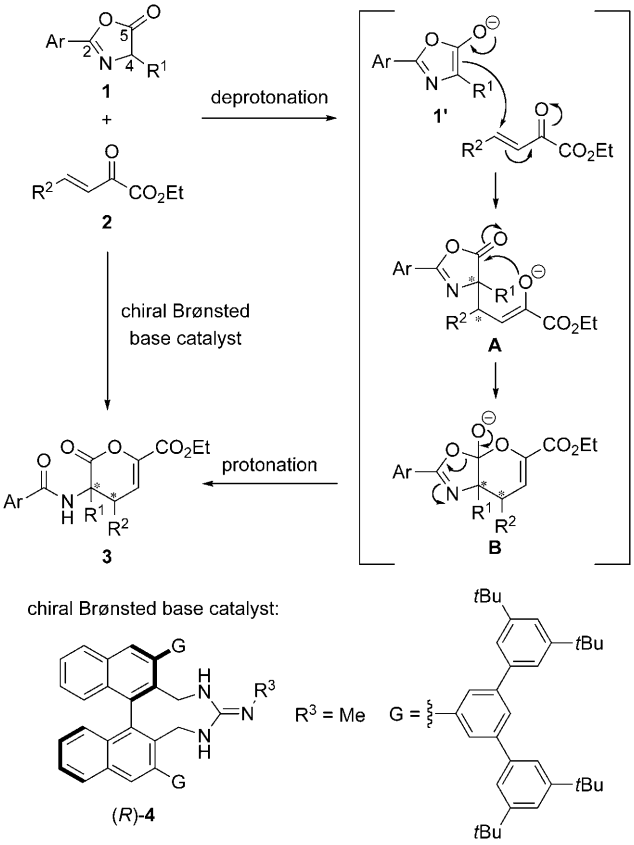
Dedicated to Professor Takeshi Nakai on the occasion of his 70th birthday

Oxazole-5-(4*H*)-ones, known as azlactones, possess multiple reactive sites. The acidic nature of the C4-position allows for the formation of an enol tautomer that functions as a nucleophilic site and reacts with a variety of electrophiles, whereas the electrophilic nature of the carbon atoms at the 2- and 5-positions allows for nucleophilic attack and the formation of ring-opened products.[1] The rich reactivity of the azlactone scaffold enables a wide variety of transformations, which makes azlactones extremely versatile reactants in synthetic organic chemistry. Among these transformations, cycloaddition reactions that utilize the multiple reactive sites of azlactones are attractive. For example, the nucleophilic C4 and electrophilic C2 atoms serve as a 1,3-dipole, which has been applied to [3+2] cycloaddition reactions and gives a general synthetic route to a variety of five-membered nitrogen heterocycles, including pyrrolines, imidazolines, and imidazoles.[1] In contrast, cycloaddition reactions that take advantage of the nucleophilic C4 and electrophilic C5 atoms have rarely been exploited.[2] Recently, Gong and co-workers demonstrated the enantioselective catalysis of the cycloaddition reactions of azlactones at C4 and C5 with 1,3-azabutadienes, affording enantioenriched α-amino-δ-lactams.[3] However, to the best of our knowledge, this is the sole example of such enantioselective catalysis.[4] Further synthetic applications of azlactones **1** to catalytic enantioselective cycloaddition reactions remains uncultivated despite the fact that the method provides efficient access to nitrogen-substituted cyclic compounds in an optically active form. Therefore, we envisioned the use of β,γ-unsaturated α-ketoesters **2** as novel reactants for the enantioselective cycloaddition reaction of the azlactone **1** with a chiral Brønsted base catalyst (Scheme 1). The proposed transformation would enable facile access to 2-amino sugar derivatives as pharmaceutically and biologically intriguing molecules. It can be assumed that the reaction involves three consecutive transformations:[5] 1) Michael addition of the enolate form of azlactone **1′** at the C4-position[6] to the β,γ-



Scheme 1. Cycloaddition reaction of the β,γ-unsaturated α-ketoesters **2** with azlactones **1** catalyzed by axially chiral guanidine base (*R*)-**4**.

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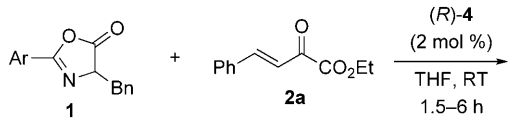
unsaturated α-ketoester **2** generates acyclic intermediate **A**; 2) Subsequent intramolecular nucleophilic addition of the enolate oxygen of **A** to the C5 atom of the azlactone subunit results in the formation of intermediate **B** as a formal [4+2] cycloaddition product; and 3) The consecutive process is terminated by ring-opening of the azlactone moiety, to give an α-amino-δ-lactone derivative **3** with a sugar framework. Herein, we report on the diastereoselective and enantioselective cycloaddition reaction of **1** with **2**, catalyzed by the axially chiral guanidine **4**, a chiral Brønsted base catalyst developed within our group.[7,8]

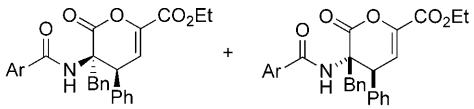
An initial investigation was conducted to explore the optimal aromatic substituent (Ar) at the C2 atom of azlactone **1**.[9] Substituted azlactones **1a**–**1h** were treated with a β,γ-unsaturated α-ketoester **2a** with guanidine (*R*)-**4** (2 mol%) as the base catalyst at room temperature in THF. As shown in Table 1, the desired cycloaddition products **3** were obtained in high yields, irrespective of the steric and electronic properties of the Ar substituent. However, the Ar substituent displayed a marked influence on both the enantio- and diastereoselectivity (Table 1, entries 1–8). Although the reaction provided the *cis* isomers predominantly in all cases, the introduction of electron-donating groups at the 3- and 5-positions led to a slight decrease in selectivity for the *cis* isomer (Table 1, entries 5 and 6). In contrast, dramatic positional effects on the aromatic ring were observed in terms of enantioselectivity. Introduction of the electron-donating methoxy group at the 4-position resulted in the formation of racemic products (Table 1, entries 2 and 8) whereas the slightly electron-donating methyl and electron-withdrawing trifluoromethyl substituents gave moderate selectivity (Table 1, entries 3 and 4). The highest enantioselectivity was observed for the 3,5-dimethoxyphenyl substituent, albeit at the expense of diastereoselectivity (Table 1, entry 5). Among the aryl substituents tested, the azlactone with an unsubstituted phenyl group was optimal in terms of the enantio- and diastereoselectivity (Table 1, entry 1).

Although *cis*-**3aa** was obtained with high diastereoselectivity (Table 1, entry 1), the enantioselectivity remained moderate despite thorough screening of the Ar substituent. Hence, we next optimized the reaction conditions by changing the solvent and reaction temperature (Table 2). Delightfully, the enantioselectivity could be slightly improved with acyclic ethers as solvents, which gave an increase in *cis* selectivity (Table 2, entries 3–5). Among the acyclic ethers tested, diethyl ether displayed the highest enantio- and diastereoselectivity (Table 2, entry 3). Further optimization of the reaction conditions by lowering the reaction temperature resulted in an increase in enantioselectivity (Table 2, entries 6 and 7). However, in the reaction conducted at −60 °C for 2 h, a considerable amount of the acyclic product **5** (the Michael addition product resulting from protonation of intermediate **A**, see Scheme 1) was detected by ^{1}H NMR spectroscopic analysis of the crude product (Table 2, entry 7).[10] Compound **5** was transformed to the desired cyclic product **3aa** by warming the reaction to room temperature, after the azlactone **1a** had been consumed completely

Table 1. Enantioselective and diastereoselective cycloaddition reaction of **1** with **2a** catalyzed by an axially chiral guanidine (*R*)-**4**.[a]



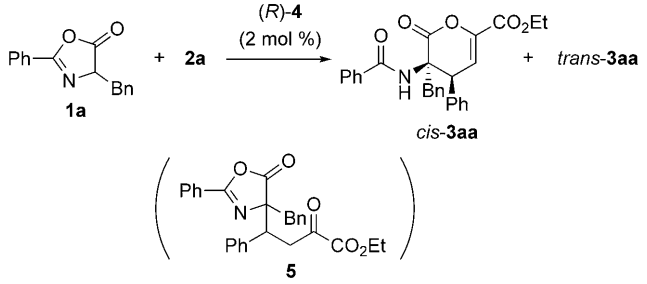
a: Ar = C_6H_5- **e**: Ar = 3,5-$(CH_3O)_2C_6H_3$-
b: Ar = 4-$CH_3OC_6H_4$- **f**: Ar = 3,5-$(CH_3)_2C_6H_3$-
c: Ar = 4-$CH_3C_6H_4$- **g**: Ar = 3,5-$(CF_3)_2C_6H_3$-
d: Ar = 4-$CF_3C_6H_4$- **h**: Ar = 3,4,5-$(CH_3O)_3C_6H_2$-



Entry	**1**	**3**	*t* [h]	Yield [%][b]	*cis*/*trans*[c]	*ee* [%][d]
1	**1a**	**3aa**	2	94	93:7	72
2	**1b**	**3ba**	6	95	93:7	6
3	**1c**	**3ca**	1.5	98	91:9	69
4	**1d**	**3da**	6	92	96:4	48
5	**1e**	**3ea**	4.5	93	80:20	73
6	**1f**	**3fa**	2	70	79:21	59
7	**1g**	**3ga**	4.5	95	95:5	62
8	**1h**	**3ha**	1.5	97	94:6	<1

[a] Unless otherwise noted, all reactions were carried out with (*R*)-**1** (0.002 mmol, 2 mol%), **1** (0.10 mmol), and **2a** (0.11 mmol, 1.1 equiv) in THF (0.5 mL) at room temperature. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral stationary phase HPLC analysis of the major *cis* isomer.

Table 2. Optimization of the cycloaddition reaction of **1a** with **2a**, catalyzed by (*R*)-**4**.[a]



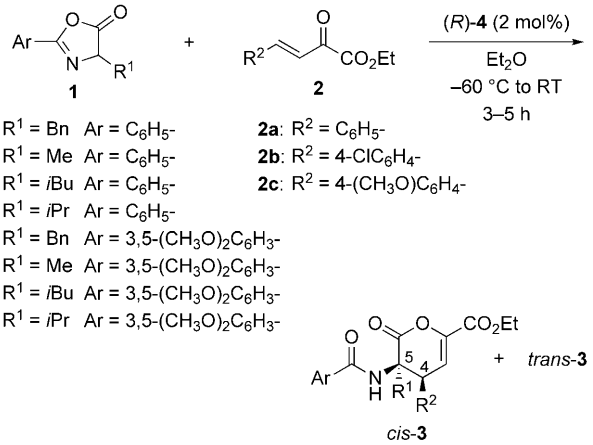
Entry	Solvent	*T*	Yield [%][b]	*cis*/*trans*[c]	*ee* [%][d]
1	THF	RT	94	93:7	72
2	DME[e]	RT	99	91:9	69
3	Et_2O	RT	97	97:3	80
4	*t*BuOMe	RT	90	95:5	79
5	CPME[f]	RT	97	96:4	79
6	Et_2O	−20 °C	92	96:4	88
7	Et_2O	−60 °C	86	95:5	90
8	Et_2O	−60 °C to RT[g]	99	99:1	91

[a] Unless otherwise noted, all reactions were carried out by using (*R*)-**4** (0.002 mmol, 2 mol%), **1a** (0.10 mmol), and **2a** (0.11 mmol, 1.1 equiv) in the indicated solvent (0.5 mL) for 2 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral stationary-phase HPLC analysis of the major *cis* isomer. [e] 1,2-Dimethoxyethane. [f] Cyclopentyl methyl ether. [g] Carried out at −60 °C for 2 h, then warmed to room temperature and stirred for 1 h.

at −60 °C for 2 h. Under the optimal reaction conditions, the cycloaddition product *cis*-**3aa** was afforded exclusively in almost quantitative yield, and the enantiomeric excess (*ee*) increased to 91 % (Table 2, entry 8).

Next, the substrate scope of the cycloaddition reaction of β,γ-unsaturated α-ketoesters **2** with various azlactones **1** was investigated. As shown in Table 3, the cycloaddition reaction is well suited to β,γ-unsaturated α-ketoesters **2** that have either an electron-withdrawing or electron-donating substituent on the aromatic ring,[11] and afforded the corresponding products with similarly high enantio- and diastereoselectivity (Table 3, entries 1 and 2). Introduction of alternative alkyl substituents onto the benzyl group at the C4 atom on azlactone **1** resulted in a considerable decrease in enantioselectivity however the high *cis* selectivity was maintained (Table 3, entries 3–5). Because the azlactone **1e** (substituted with a 3,5-dimethoxyphenyl group at the C2-position) gave the highest enantioselectivity (Table 1, entry 5), we next investigated derivatives of **1e** (Ar = 3,5-$(MeO)_2C_6H_3$-) with a series of alkyl substituents (Table 3, entries 6–9). In fact, an enhancement of the enantioselectivity was observed albeit with a slight reduction in diastereoselectivity.

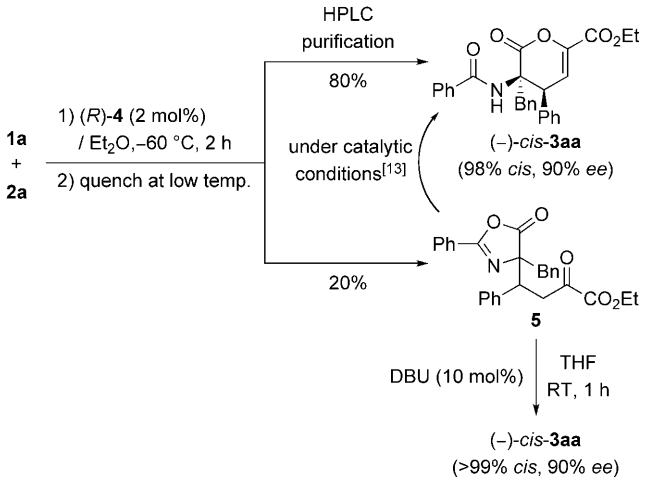
Table 3. The enantio- and diastereoselective cycloaddition reaction of a series of azlactones **1** with **2**, catalyzed by (*R*)-**4**.[a]



Entry	1	2	3	Yield [%][b]	*cis*/*trans*[c]	*ee* [%][d]
1	**1a**	**2b**	**3ab**[e]	99	98:2	89
2	**1a**	**2c**	**3ac**	84	94:6	88
3	**1i**	**2a**	**3ia**	93	91:9	78
4	**1j**	**2a**	**3ja**	97	87:13	80
5	**1k**	**2a**	**3ka**	74	>99:<1	66
6	**1e**	**2a**	**3ea**	80	94:6	81
7	**1l**	**2a**	**3la**	93	87:13	86
8	**1m**	**2a**	**3ma**	80	77:23	85
9	**1n**	**2a**	**3na**	81	93:7	87

[a] Unless otherwise noted, all reactions were carried out with (*R*)-**4** (2 mol %, 0.002 mmol), **1** (0.10 mmol), and **2** (0.11 mmol, 1.1 equiv) in Et_2O (0.5 mL) at −60 °C for 2–4 h, then warmed to room temperature and stirred for 1 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral stationary-phase HPLC analysis of the major *cis* isomer. [e] The absolute stereochemistry was unambiguously determined to be 4*S*,5*R* by X-ray crystallographic analysis.[12]

As proposed in Scheme 1, it is assumed that the reaction has three consecutive steps involving Michael addition, cyclization, and finally a ring-opening process. To confirm that Michael addition was the initial step, we attempted to isolate the acyclic product **5** by quenching the reaction at a low temperature, followed by purification using HPLC column chromatography (Scheme 2). The diastereo- and enantioselectivity of the isolated acyclic product **5** were determined to be greater than 99 % *cis* and 90 % *ee*. These results were obtained after transformation of **5** into **3aa** by cyclization/ring-opening reactions using an achiral base catalyst, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which was employed to avoid kinetic optical resolution of enantioenriched **5** by (*R*)-**4** during the transformation.[13] The resulting *cis* selectivity, *ee* value, and absolute configuration are consistent with those observed for the cycloaddition product obtained directly from the catalytic enantioselective reaction (98 % *cis*, 90 % *ee*).[14] Consequently, these results strongly suggest that **3** is formed via an enolate form of acyclic intermediate **5**, thus anionic intermediate **A**, and the initial Michael addition reaction can be regarded as the stereo-determining step. More importantly, it is likely that the present cycloaddition reaction is composed of three consecutive steps.[15]



Scheme 2. Mechanistic investigation of the cycloaddition reaction.

In conclusion, we have demonstrated the enantio- and diastereoselective cycloaddition reaction of azlactones with β,γ-unsaturated α-ketoesters catalyzed by an axially chiral guanidine base. The most plausible pathway of the cycloaddition reaction involves three consecutive transformations as evidenced by the isolation and characterization of the acyclic intermediate, formed from the initial Michael addition. The method provides an efficient and highly stereoselective access to optically active α-amino δ-lactones with a sugar framework. Further studies on the development of chiral guanidine-catalyzed stereoselective transformations with azlactones are underway in our laboratory.

Experimental Section

General procedure: Compound (*R*)-**4** (2.5 mg, 0.002 mmol) was added to a solution of 4-benzyl-2-phenyloxazol-5(4*H*)-one (**1a**; 25.1 mg, 0.10 mmol) and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**; 20.0 μL, 0.11 mmol) in Et_2O (0.5 mL) at −60 °C. The resulting mixture was stirred at −60 °C for 2 h, then warmed to room temperature and stirred for 1 h. The reaction was quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography (hexane/ethyl acetate 10:1 to 4:1) to afford the cycloaddition product **3aa** (99% yield, *cis*/*trans* = 99:1, 91% *ee* (*cis*)). The diastereomeric ratio and enantiomeric excess were determined by NMR spectroscopy of the crude product and HPLC analysis, respectively.

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Keywords: amino sugar · asymmetric catalysis · cycloaddition · guanidine · organocatalysis

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[10] During purification by silica gel column chromatography, acyclic product **5** was partially transformed into cyclic product **3aa**. The yield indicated in Table 2 entry 7 (86%) was calculated after purification of **3aa**. Indeed, the acyclic product **5** was detected in greater than 20% yield by ^1H NMR spectroscopy of the crude material.

[11] The reaction of β,γ-unsaturated α-ketoesters with a methyl substituent (instead of the aromatic counterpart) at the γ-position gave the product in moderate yield (56%) despite the fact that the starting reactant, methyl-substituted α-ketoester in THF, was consumed completely in 3 h at room temperature. A significant amount of by-products was formed in this reaction, although the desired product could be obtained with moderate stereoselectivity (64% *cis*, 54% *ee*).

[12] CCDC-787766 (**3ab**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] It was confirmed that the cyclization/ring-opening reactions of **5** took place under the catalytic conditions with chiral guanidine base **4** (see Table 2, entries 7 and 8). In addition, at the beginning of the reaction, acyclic intermediate **5** could be detected by TLC even at room temperature, but this intermediate had completely disappeared by the end of the reaction.

[14] It can be considered that kinetic optical resolution of enantioenriched acyclic product **5** by chiral guanidine catalyst **4** would occur during the following cyclization/ring-opening steps. However, it seems unlikely that these processes occur because of the nearly equal enantio- and diastereoselectivity observed in both cycloaddition product **3aa** and acyclic intermediate **5**.

[15] We cannot completely rule out the possibility that the reaction proceeds by a concerted process, that is, by an inverse-electron-demand hetero-Diels–Alder reaction, in parallel to the stepwise process that is proposed as the most dominant mechanism in this transformation. Also see reference [4].

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