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Asymmetric Formal [3 + 2]-Cycloaddition of Azomethine Imines with Azlactones To Synthesize Bicyclic Pyrazolidinones

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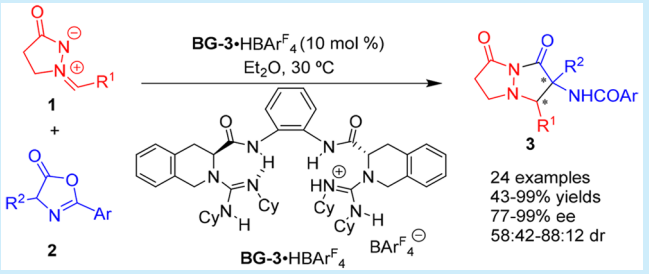
Supporting Information

ABSTRACT: An efficient enantioselective formal [3 + 2]-cycloaddition of azomethine imines with azlactones has been realized by using a chiral bifunctional bisguanidinium hemisalt as the catalyst. Optically active bicyclic pyrazolidinone compounds were generated under mild reaction conditions in high yields (up to 99%) with good dr (up to 88:12) and excellent ee values (up to 99%). This simple and efficient strategy provides a method to construct biologically important chiral tetrahydropyrazolo[1,2-*a*]pyrazole-1,7-dione derivatives bearing vicinal aza-quaternary and tertiary carbon centers.



Pyrazolidinones and their analogues represent a group of heterocyclic compounds which exhibit rich biological activities.[1] The *N,N*-bicyclic derivatives, especially tetrahydropyrazolo[1,2-*a*]pyrazolones, have attracted considerable attention due to the fact that compounds **A** were investigated as analogues of penicillin and cephalosporin antibiotics,[2] and compound **B** was developed as a potent drug for treatment of cognitive dysfunctions such as Alzheimer's disease[3] (Figure 1).

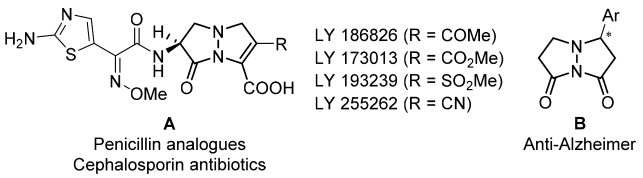


Figure 1. Selected examples of biologically active tetrahydropyrazolo-[1,2-*a*]pyrazolones.

Substituted tetrahydropyrazolo[1,2-*a*]pyrazolones are usually chiral compounds; therefore, the development of efficient approaches to construct such molecules in an enantioselective manner is highly desirable for pharmaceutical assay and other fields.

1,3-Dipolar cycloaddition of azomethine imines **1** with various dipolarophiles, including olefins,[4] alkynes,[5] isocyanides,[6] allenes,[7] ketenes,[8] ynolates,[9] azlactones,[10] and other types,[11] provides a straightforward route for the synthesis of pyrazolidinone-based bicyclic derivatives. However, there are a few examples related to the enantioselective synthesis of the *N,N*-fused bicyclic five-membered ring system. The Fu group utilized a chiral Cu(I) complex to accelerate the reaction of alkynes to generate 2,3-dihydropyrazolo[1,2-*a*]pyrazol-1-ones.[5a,b] Later, Brière and co-workers reported the asymmetric synthesis of tetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione via organocatalyzed Knoevenagel−aza-Michael cyclocondensation of Meldrum's acid.[8b] Very recently, Kerrigan's group demonstrated the formation of chiral tetrahydropyrazolo[1,2-*a*]-pyrazole-1,7-diones bearing 2,3-disubstituents from 1,3-dipolar cycloaddition of ketenes generated *in situ*.[8c] Using lithium ynolates as the dipolarophiles allowed access to similar structures but only in a diastereoselective fashion.[9a] Despite these reports, the core framework (Figure 1) bearing substituents at both C2 and C3 positions could be obtained from a spontaneous cyclization between azomethine imines with azlactones.[10a] This reaction occurred efficiently without a catalyst, but it would be difficult to achieve an enantioselective catalytic version. This is also one of the few applications of azlactones acting as dipolarophiles in [3 + 2]-cycloaddition,[12] rather than as masked azomethine ylides.[13,14] Encouraged by our studies on the asymmetric transformations of azlactones promoted by bifunctional guanidine catalysts,[15] we were interested in the challenging asymmetric synthesis of tetrahydropyrazolo[1,2-*a*]pyrazole-1,7-diones containing vicinal aza-quaternary and tertiary carbon centers. We report a chiral bisguanidinium hemisalt promoted diastereo- and enantioselective formal 1,3-dipolar cycloaddition of azlactones with azomethine imines. The reaction represents a unique approach for the enantioselective construction of 2,2-disubstituted derivatives of compound **B**.

Our initial investigations commenced with a model reaction between azomethine imine **1a** and azlactone **2a** in Et$_2$O at 25 °C for chiral guanidine catalyst optimization (Table 1). When chiral guanidine-amides **G-1** to **G-3** were used as the catalyst, the reaction performed smoothly and two diastereomers of the product **3aa** were generated almost equally without obvious

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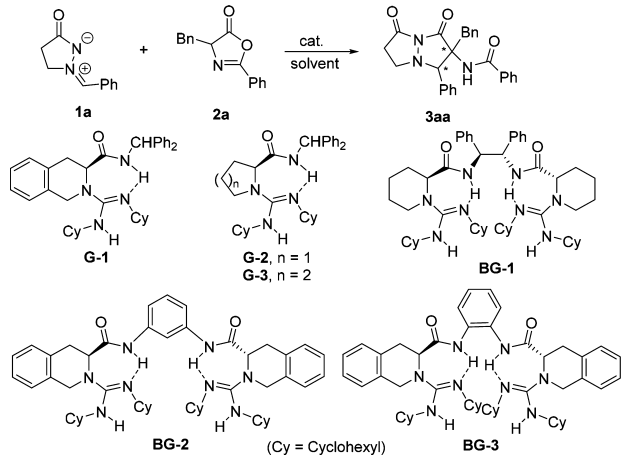
Table 1. Optimization of the Reaction Conditions[a]



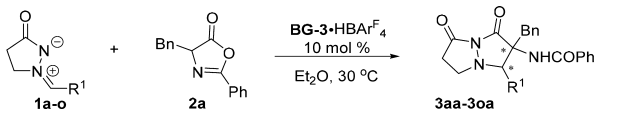
entry	cat.	solvent	yield (%)[b]	dr[c]	ee (%)[c]
1	**G-1**	Et_2O	33	47:53	5/3
2	**G-2**	Et_2O	26	53:47	0/3
3	**G-3**	Et_2O	18	45:55	0/17
4	**BG-1**	Et_2O	5	50:50	20/30
5	**BG-2**	Et_2O	42	50:50	19/14
6	**BG-3**	Et_2O	15	64:36	14/18
7	**BG-1**·$HBAr^F_4$	Et_2O	75	21:79	51/57
8	**BG-2**·$HBAr^F_4$	Et_2O	30	30:70	10/11
9	**BG-3**·$HBAr^F_4$	Et_2O	84	18:82	66/83
10	**BG-3**·$HBAr^F_4$	toluene	34	79:21	25/28
11	**BG-3**·$HBAr^F_4$	THF	27	68:32	18/69
12	**BG-3**·$HBAr^F_4$	CH_2Cl_2	35	71:29	30/59
13[d]	**BG-3**·$HBAr^F_4$	Et_2O	22	18:82	−/85
14[e]	**BG-3**·$HBAr^F_4$	Et_2O	96	17:83	−/90

[a]Unless otherwise noted, the reactions were carried out with guanidine (10 mol %), **1a** (0.05 mmol), and **2a** (1.0 equiv) in solvent (1.0 mL) at 25 °C. [b]Isolated yield. [c]Determined by HPLC analysis. [d]At 0 °C. [e]**1a** (0.10 mmol), and **2a** (1.2 equiv) in Et_2O (6.0 mL) at 30 °C. $HBAr^F_4$ = $HB[3,5\text{-}(CF_3)_2C_6H_3]_4$.

enantioselection (Table 1, entries 1−3). In view of the fact that the structure and counterion of guanidine catalysts are critical for both the reactivity and enantioselectivity in our previous study,[15,16] we next examined the performance of several C_2-symmetric bisguanidine catalysts and the corresponding hemisalts. It was disappointing that when **BG-1**−**BG-3** were used, no satisfactory results were obtained in terms of yield and stereoselectivity (Table 1, entries 4−6). **BG-1**, which was useful for a formal [4 + 2]-cycloaddition of azlactones with chalcone,[15a] resulted in an extremely low yield (Table 1, entry 4). (*S*)-Tetrahydroisoquinoline-3-carboxylic acid derived bisguanidines **BG-2** and **BG-3** containing benzene-1,3-diamine and benzene-1,2-diamine linkage showed a difference in reactivity, resulting in 42% and 15% yields, respectively (Table 1, entry 6 vs 5). This indicates that the linkage changes the catalytic environment remarkably. Furthermore, the use of bisguanidinium hemisalts instead changed both the reactivity and stereoselectivity significantly, especially for the related salts of **BG-1** and **BG-3** (Table 1, entries 7−9). Catalyst **BG-3**·$HBAr^F_4$ led to a striking result, and product **3aa** could be isolated in 84% yield with good diastereo- and enantioselectivities (dr = 82:18 and ee = 83% for the major diastereomer) (Table 1, entry 9). Sterically hindered acid with stronger acidity afforded a higher yield and ee value (see Supporting Information). Screening of the solvents revealed that other reaction solvents including toluene, THF, and CH_2Cl_2 reduced the yield and enantioselectivity sharply, along with reverse diastereoselection (Table 1, entries 9−12). In addition, lower temperatures restrained the reaction activity (Table 1, entry 13). Increasing the ratio of azlactone **2a** to azomethine imine **1a** and reducing the reaction concentration delivered a slight improvement with a 96% yield, 82:18 dr, and 90% ee at 30 °C (Table 1, entry 14).

Substrate generality was investigated by changing the aryl group of azomethine imines (Table 2). These, with electron-

Table 2. Scope of Azomethine Imines 1 in Cycloaddition with Azlactone 2a[a]



entry	**1**, R^1	**3**, yield (%)[b]	dr[c]	ee (%)[c]
1	**1a**; C_6H_5	**3aa**, 96	84:16	90
2	**1b**; 2-FC_6H_4	**3ba**, 96	85:15	98
3	**1c**; 2-ClC_6H_4	**3ca**, 97	85:15	95
4	**1d**; 2-BrC_6H_4	**3da**, 99	79:21	97
5	**1e**; 2-MeC_6H_4	**3ea**, 96	70:30	95
6	**1f**; 2-$MeOC_6H_4$	**3fa**, 56	84:16	95
7	**1g**; 2-$O_2NC_6H_4$	**3ga**, 69	64:36	95
8	**1h**; 3-FC_6H_4	**3ha**, 76	79:21	81
9	**1i**; 3-$MeOC_6H_4$	**3ia**, 77	75:25	81
10	**1j**; 4-FC_6H_4	**3ja**, 76	85:15	81
11	**1k**; 4-$MeOC_6H_4$	**3ka**, 73	88:12	86
12	**1l**; 4-*i*PrC_6H_4	**3la**, 86	84:16	83
13	**1m**; 2-furyl	**3ma**, 94	81:19	84
14	**1n**; 2-thienyl	**3na**, 90	77:23	86
15	**1o**; 1-naphthyl	**3oa**, 89	81:19	87

[a]Unless otherwise noted, the reactions were carried out with **BG-3**·$HBAr^F_4$ (10 mol %), **1** (0.10 mmol), and **2** (1.2 equiv) in Et_2O (6.0 mL) at 30 °C for 10 h. [b]Isolated yield of the two diastereomers. [c]Determined by HPLC analysis.

rich and -deficient substituents on the aromatic ring, reacted smoothly with azlactone **2a**, generating the desired tetrahydropyrazolo[1,2-*a*]pyrazole-1,7-diones **3aa**−**3oa** in moderate to good yields (56−99%) with good to excellent enantioselectivities (ee = 81−98%) and good diastereoselectivities (Table 2, entries 1−12). Higher enantioselectivities were achieved with substituents at the *ortho*-position of the aryl group than at the *meta*- and *para*-positions (Table 2, entries 1−7 vs 8−12). Heteroaromatic and 1-naphthyl substituted azomethine imines were also tolerable in the current system. The products **3ma**−**3oa** were given in high yields (89−94%) with satisfactory stereoselectivity (ee = 84−87%, dr = 81:19−78:22) (Table 2, entries 13−15).

Next, the substrate scope was probed through azlactones with varied substituents at the C2 and C4 positions (Table 3). Azomethine imine **1b** was selected as the dipole. Azlactones **2b**−**2d** synthesized from alanine, 2-aminobutanoic acid, and leucine were tolerated under optimized reaction conditions, providing methyl, ethyl, or isobutyl substitution on to the core scaffold in moderate to good yields with good enantioselectivities (ee = 88−89%) (**3bb**−**3bd**). High enantioselectivity (ee = 99%) was achieved for one diastereomer with an indolylmethyl group albeit with a lower 45% yield and diastereoselectivity of

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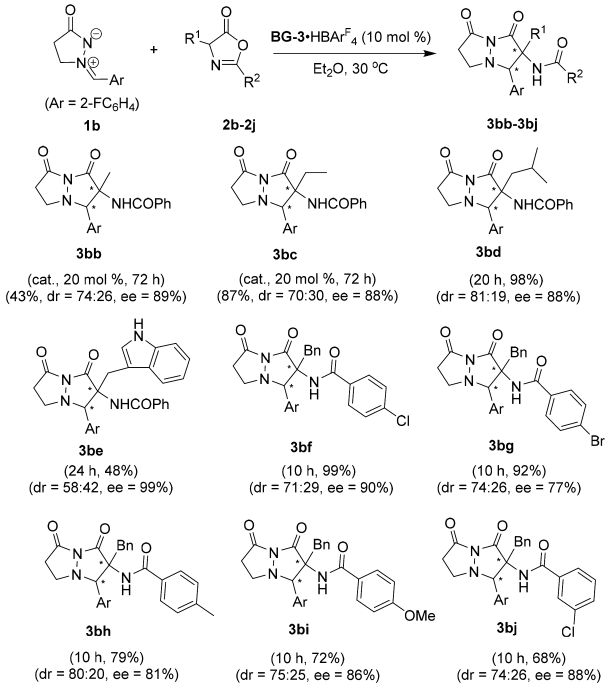
Table 3. Scope of Azlactones 2 in Cycloaddition with Azomethine Imines 1b[a]

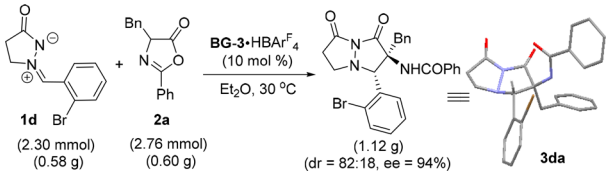


[a]Same as in Table 2.

3be. Further investigation suggested that the position and its electronic property of the substituent at the C2-aryl group of azlactones had a significant impact on yields and diastereo- and enantioselectivities. 4-Halo-substituted ones gave higher yields than the electron-donating substituted ones, and the corresponding cyclization products of **3bf**–**3bj** were afforded in good to excellent yields (68–99%) and stereoselectivities (ee = 77–90%, dr = 71:29–80:20).

To demonstrate the scalability and the practicality of this protocol, we conducted a gram-scale reaction with **1d** (2.30 mmol) and **2a** (2.76 mmol) in the presence of 10 mol % of **BG-3**·HBAr$^F_4$ in Et_2O at 30 °C (Scheme 1). Gratifyingly, the

Scheme 1. Scale-up Version of the Reaction and X-ray Crystal Structure of the Product 3da



reaction proceeded smoothly, and **3da** was isolated with high yield and excellent selectivity. The absolute configuration of the major enantiomer of the product **3da** was determined to be (2*S*, 3*S*) by X-ray crystallographic analysis.[17]

Mechanistically, the bisguanidinium hemisalt was proposed to work as a bifunctional catalyst for this cycloaddition reaction. One guanidine unit of the catalyst acts as a base to form the enolate intermediate from the azlactone. On the other hand, the guanidinium salt interacts with the N–C═O portion of the dipole to activate the azomethine imine via hydrogen bonding. The nucleophilic addition occurs preferably between the *Re*-face of azomethine imine and the *Si*-face of the azlactone intermediate. Subsequent lactonization leads to the formation of the 2-alkyl-2-amino-3-aryl substituted tetrahydropyrazolo-[1,2-*a*]pyrazo-le-1,7-dione product.

In conclusion, an organocatalyzed asymmetric formal [3 + 2]-cycloaddition of *N*,*N*-cyclic azomethine imines with azlactones has been developed. A new bisguanidinium hemisalt was selected as a bifunctional catalyst to promote the reaction in good to excellent yields and enantioselectivity. It provided easy access to tetrahydropyrazolo[1,2-*a*]pyrazole-1,7-dione derivatives with vicinal aza-quaternary and tertiary carbon centers that represent scaffolds with potential bioactivity. We anticipate that chiral guanidine and guanidinium may find utility in other reactions for the synthesis of biologically intriguing small molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02772.

Crystallographic data for **3da** (CIF)
Experimental details, analytic data (NMR, HPLC, ESI-HRMS, and X-ray) (PDF)

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Notes

The authors declare no competing financial interest.

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