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Asymmetric Construction of Spirocyclic Pyrrolidine-thia(oxa)zolidinediones via N,O-Ligand/Cu(I) Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with 5-Alkylidene Thia(oxa)zolidine-2,4-diones

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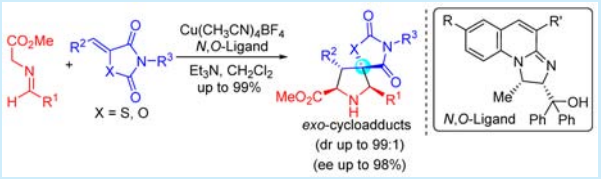
Supporting Information

ABSTRACT: A highly efficient asymmetric 1,3-dipolar cycloaddition of azomethine ylides to 5-alkylidene thia(oxa)zolidine-2,4-diones catalyzed by a chiral *N,O*-ligand/$Cu(CH_3CN)_4BF_4$ system is reported, affording structurally novel spirocyclic pyrrolidine-thia(oxa)zolidinediones with a spiro-heteroquaternary stereogenic center in good to excellent yields (up to 99%), with excellent levels of diastereo- and enantioselectivity (dr up to 99:1; ee up to 98%).



Chiral pyrrolidine has long been considered a "privileged scaffold" in many natural bioactive products and pharmaceuticals.[1] Spirocyclic pyrrolidine[2] is an important subset of pyrrolidine-based molecules, which represents an attractive synthetic target due to the biological activities and as the intermediates for generating further molecular complexities.[3] The significance of these spirocyclic pyrrolidine skeletons has led to a demand for efficient synthetic methods, particularly those producing enantiomerically pure spirocyclic pyrrolidines. In the past decade, catalytic asymmetric 1,3-dipolar cycloaddition[4,5] of azomethine ylides to a variety of electron-deficient alkene dipolarophiles has arguably been one of the most ideal and powerful synthetic strategies for the construction of a range of structurally novel and stereochemically enriched spirocyclic pyrrolidine derivatives.[6−11]

On the other hand, thiazolidinediones (TZDs)[12] have become a very interesting class of heterocyclic compounds since the introduction of various glitazones into clinical use for the treatment of type II diabetes mellitus.[13] The interest in TZDs has been heightened markedly, and chemical modifications of TZDs constantly result in compounds with a wide spectrum of biological and pharmacological activities.[14] Therefore, combining the two classes of key motifs (Pyrrolidine and TZD) through a unique spiro-quaternary stereogenic carbon would rebuild a structurally novel spirocyclic pyrrolidine-thiazolidinedione (Figure 1), which may provide some unprecedented benefits to medicinal chemistry, with the hope of finding valuable applications in drug discovery.

We have recently established a library of newly designed DHIPOH-based *N,O*-ligands with successful applications to catalytic asymmetric reactions.[15] Among them, the first highly diastereo- and enantioselective catalytic 1,3-dipolar cycloaddition of azomethine ylides to α-phthalimidoacrylates (Scheme 1, eq 1)[15e] and α-alkylidene succinimides (Scheme

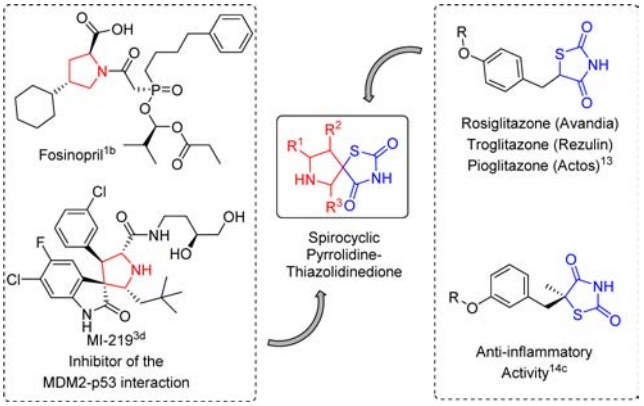
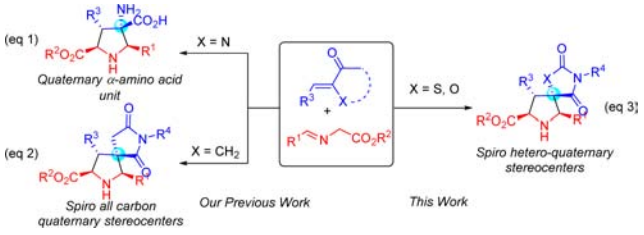


Figure 1. Key motif integration from biologically active molecules with chiral pyrrolidine and thiazolidinediones into a novel spirocyclic pyrrolidine-thiazolidinedione scaffold.

Scheme 1. Asymmetric Construction of Pyrrolidines Bearing Quaternary Stereocenters via 1,3-Dipolar Cycloaddition of Azomethine Ylides



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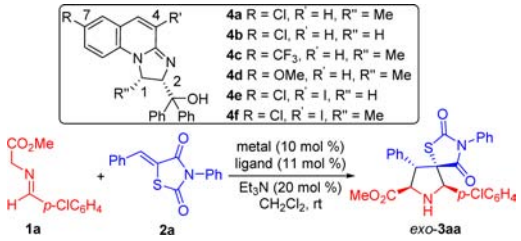
1, eq 2)[15f] were reported, providing the chiral pyrrolidines containing a quaternary α-amino acid unit and the spirocyclic pyrrolidine derivatives with all-carbon quaternary stereogenic centers with excellent diastereo- and enantioselectivity (dr up to 98:2; ee up to 97%), respectively.

Encouraged by these results, we wondered whether the thiazolidinedione (TZD) derived alkylidenes (Scheme 1, eq 3) could serve as α-heteroatom substituted dipolarophiles in 1,3-dipolar cycloaddition with azomethine ylides. To the best of our knowledge, it is the first example of a straightforward catalytic asymmetric method to construct structurally novel and potentially bioactive spirocyclic pyrrolidine-thiazolidinediones. Therefore, we would like to describe herein the preliminary result of the new application of the DHIPOH/Cu(I) catalytic system for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with 5-alkylidene thia(oxa)zolidine-2,4-diones.

To validate our hypothesis, a chiral *N*,*O*-ligand/Cu-$(CH_3CN)_4BF_4$ catalyst system previously reported by us for 1,3-dipolar cycloaddition of azomethine ylides to 2-methylene-*N*-phenyl succinimides was applied to this challenging, newly designed, 1,3-dipolar cycloaddition of azomethine ylides to 5-alkylidene thiazolidine-2,4-diones. Initially, (*Z*)-5-benzylidene-3-phenylthiazolidine-2,4-dione **2a** was chosen as the model dipolarophile to investigate the feasibility of 1,3-dipolar cycloaddition with *N*-(4-chlorobenzylidene)glycine methyl ester **1a** in the presence of chiral *N*,*O*-ligand **4a**/Cu-$(CH_3CN)_4BF_4$ as the catalyst and Et_3N as the base in CH_2Cl_2 at rt (Table 1, entry 1). Gratifyingly, the 1,3-dipolar cycloaddition proceeded smoothly affording spirocyclic pyrrolidine-thiazolidinediones *exo*-**3aa** in 95% yield with excellent enantioselectivity (ee = 93%). Encouraged by this promising result, different metal salts and chiral *N*,*O*-ligands were subsequently screened to establish optimal reaction conditions, and the representative results are summarized in Table 1. Both Cu(I) and Ag(I) salts afforded the desired cycloadducts with excellent diastereoselectivities (Table 1 entries 1−5). Among the tested metal salts, $Cu(CH_3CN)_4BF_4$ gave the best result in terms of the reaction yield and enantioselectivity (Table 1 entry 1). Further ligand survey revealed that the introduction of a methyl group on the imidazole ring of the ligands improved the yields and enantioselectivities (Table 1, entries 1, 6−10), which was consistent with our earlier findings.[15a,b,e,f] Both *N*,*O*-ligands **4c** bearing trifluoromethyl at the C7 position of the quinoline backbone and **4f** bearing iodine at the C4 position of the quinoline backbone gave excellent yields and enantioselectivities (Table 1, entries 7, 10). Screening of other bases and solvents did not show any better results (see the Supporting Information (SI), Table S1). In addition, lowering the reaction temperature to 0 °C led to a slight improvement in enantioselectivity (Table 1, entries 11−12). A decrease in the catalyst loading from 10 to 5 mol % in the presence of ligand **4c** did not cause any loss in the stereoselectivity and yield, affording *exo*-**3aa** in 95% yield, 97:3 dr, and 96% ee (Table 1, entry 13). The relative and absolute configuration of *exo*-**3aa** was assigned as (5*S*,6*R*,8*R*,9*S*) by its single crystal X-ray diffraction analysis (see the SI for details).

Table 1. Catalyst Screening for the Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylide 1a to 5-Benzylidene-3-phenylthiazolidine-2,4-dione 2a[a]



entry	metal	ligand	yield (%)[b]	dr[c]	ee (%)[c]
1	$Cu(CH_3CN)_4BF_4$	**4a**	95	96:4	93
2	$Cu(CH_3CN)_4ClO_4$	**4a**	90	96:4	93
3	$Cu(CH_3CN)_4PF_6$	**4a**	73	96:4	92
4	AgOAc	**4a**	95	96:4	85
5	$AgBF_4$	**4a**	83	96:4	56
6	$Cu(CH_3CN)_4BF_4$	**4b**	50	96:4	68
7	$Cu(CH_3CN)_4BF_4$	**4c**	95	97:3	94
8	$Cu(CH_3CN)_4BF_4$	**4d**	47	97:3	87
9	$Cu(CH_3CN)_4BF_4$	**4e**	83	98:2	91
10	$Cu(CH_3CN)_4BF_4$	**4f**	92	98:2	93
11[d]	$Cu(CH_3CN)_4BF_4$	**4c**	95	97:3	96
12[d]	$Cu(CH_3CN)_4BF_4$	**4f**	92	98:2	96
13[d,e]	$Cu(CH_3CN)_4BF_4$	**4c**	95	97:3	96

[a]All reactions were carried out with 0.12 mmol of **1a** and 0.1 mmol of **2a** in 1 mL of CH_2Cl_2 at rt. [b]Isolated yield of two diastereomers. [c]The dr and ee were determined by chiral HPLC analysis; the ee referred to the major diastereomer. [d]Reaction conducted at 0 °C. [e]5 mol % catalyst was used.

The generality and substrate scope were then investigated under the optimal conditions [5 mol % of $Cu(CH_3CN)_4BF_4$, 5.5 mol % of chiral *N*,*O*-ligand **4c**, 20 mol % of Et_3N, CH_2Cl_2 as solvent at 0 °C]. A wide array of azomethine ylides **1** and 5-alkylidene thiazolidine-2,4-diones **2** were probed, as shown in Tables 2 and 3, respectively. A series of azomethine ylides **1** bearing electron-rich, electronically neutral, and electron-deficient groups on the aryl ring reacted with 5-alkylidene thiazolidine-2,4-dione **2a** smoothly affording the corresponding *exo*-cycloadducts **3aa**−**3ja** in good to excellent yields (80−99%), with high to excellent diastereo- and enantioselectivity (dr = 86:14−98:2; ee = 89−97%). It is noteworthy that the sterically hindered *ortho*-chloro substituted azomethine ylide **1c** and *ortho*-methyl substituted azomethine ylide **1g** afforded the *exo*-cycloadducts with obviously lower diastereo- and enantioselectivities (Table 2, entries 3 and 8). Utilizing *N*,*O*-ligand **4f** instead of **4c** led to the improvement of diastereo- and enantioselectivities (Table 2, entries 4 and 9). The 2-furyl substituted azomethine ylide **1k** worked well in this reaction, affording the desired *exo*-cycloadduct **3ka** in 88% yield, 98:2 dr, and 93% ee when *N*,*O*-ligand **4f** was used (Table 2, entry 14). Additionally, less reactive alkyl substituted azomethine ylide **1l** also proved to be suitable in this process, providing the corresponding spirocyclic pyrrolidine-thiazolidinedione **3la** with high diastereo- and enantioselectivity (dr = 90:10; ee = 89%) in the presence of 10 mol % catalyst at rt (Table 2, entry 16).

Next, 5-alkylidene thiazolidine-2,4-diones **2** were investigated under the optimized conditions to test the dipolarophile scope of this asymmetric 1,3-dipolar cycloaddition, and representative results are summarized in Table 3. 5-Benzylidene-thiazolidine-2,4-diones **2b**−**2d** bearing *para*- and *meta*-substituents on the *N*-phenyl ring reacted smoothly with azomethine ylide **1a** to afford the corresponding *exo*-cycloadducts **3ab**−**3ad** in excellent yields (90−98%), with excellent diastereo- and enantioselectivity (dr = 97:3−99:1; ee = 95−96%) (Table 3,

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Table 2. Substrate Scope of Azomethine Ylides 1[a]

entry	1	R^1	3	yield (%)[b]	dr[c]	ee (%)[c]
1	**1a**	*p*-ClC_6H_4	**3aa**	95	97:3	96 (>99[d])
2	**1b**	Ph	**3ba**	98	97:3	96
3	**1c**	*o*-ClC_6H_4	**3ca**	80	87:13	90
4[e]	**1c**	*o*-ClC_6H_4	**3ca**	90	99:1	92
5	**1d**	*m*-ClC_6H_4	**3da**	98	97:3	96
6	**1e**	*p*-BrC_6H_4	**3ea**	98	97:3	97
7	**1f**	*p*-$CF_3C_6H_4$	**3fa**	99	98:2	96
8	**1g**	*o*-MeC_6H_4	**3ga**	95	86:14	89
9[e]	**1g**	*o*-MeC_6H_4	**3ga**	93	98:2	91
10	**1h**	*p*-MeC_6H_4	**3ha**	98	97:3	96
11	**1i**	*p*-$MeOC_6H_4$	**3ia**	98	97:3	95
12	**1j**	2-naphthyl	**3ja**	99	97:3	96
13	**1k**	2-furyl	**3ka**	93	94:6	93
14[e]	**1k**	2-furyl	**3ka**	88	98:2	93
15[f]	**1l**	*i*Bu	**3la**	90	88:12	87
16[e,f]	**1l**	*i*Bu	**3la**	88	90:10	89

[a]All reactions were carried out with 0.24 mmol of **1** and 0.2 mmol of **2a** in 2 mL of CH_2Cl_2 at 0 °C. [b]Isolated yield of two diastereomers. [c]The dr and ee were determined by chiral HPLC analysis; the diastereomers can be separated by using column chromatography; the ee referred to the major diastereomer. [d]After recrystallization. [e]Ligand **4f** was used instead of **4c**. [f]10 mol % catalyst was used at room temperature.

Table 3. Substrate Scope of 5-Alkylidene Thiazolidine-2,4-diones 2[a]

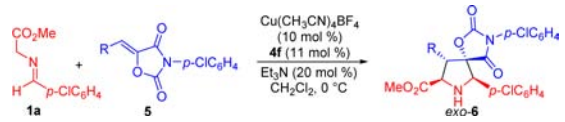
entry	2	R^2/R^3	3	yield (%)[b]	dr[c]	ee (%)[c]
1	**2b**	*p*-ClC_6H_4/Ph	**3ab**	98	97:3	95
2	**2c**	*m*-ClC_6H_4/Ph	**3ac**	95	98:2	96
3	**2d**	*p*-$MeOC_6H_4$/Ph	**3ad**	90	99:1	96
4	**2e**	2,6-di-MeC_6H_3/Ph	**3ae**	40	88:12	95
5	**2f**	Ph/*p*-BrC_6H_4	**3af**	98	98:2	98
6	**2g**	Ph/*m*-BrC_6H_4	**3ag**	99	97:3	94
7	**2h**	Ph/*o*-BrC_6H_4	**3ah**	98	98:2	95
8	**2i**	Ph/*p*-$NO_2C_6H_4$	**3ai**	99	97:3	97
9	**2j**	Ph/*p*-$MeOC_6H_4$	**3aj**	95	98:2	97
10	**2k**	Ph/*m*-$MeOC_6H_4$	**3ak**	98	98:2	96
11	**2l**	Ph/2-Fury	**3al**	93	96:4	94
12	**2m**	Ph/PhCH=CH	**3am**	85	96:4	94 (>99[d])
13	**2n**	Ph/CO_2Et	**3an**	85	80:20	89
14	**2o**	Ph/H	**3ao**	80	86:14	94
15	**2p**	Ph/*n*Pr	**3ap**	80	97:3	95
16	**2q**	Me/Ph	**3aq**	98	98:2	94

[a]All reactions were carried out with 0.24 mmol of **1** and 0.2 mmol of **2a** in 2 mL of CH_2Cl_2 at 0 °C. [b]Isolated yield of two diastereomers. [c]The dr and ee were determined by chiral HPLC analysis, the diastereomers can be separated by using column chromatography, the ee referred to the major diastereomer. [d]After recrystallization.

entries 1−3). When 5-benzylidene-thiazolidine-2,4-dione **2e** with an *ortho*-dimethyl substituent was used, the spirocyclic pyrrolidine-thiazolidinedione **3ae** was obtained in excellent enantioselectivity (ee = 95%), albeit only in moderate yield (40%) and diastereoselectivity (dr = 88:12), presumably due to the steric encumbrance (Table 3, entry 4). Various arylidene thiazolidine-2,4-diones **2** bearing electron-rich (Table 3, entries 9−10) and electron-deficient groups (Table 3, entries 5−8) on the phenyl ring in different substitution patterns proved to be viable substrates for this transformation, providing excellent yields (95−99%), with excellent diastereo- and enantioselectivities (dr = 97:3−98:2; ee = 94−98%). Notably, thiazolidine-2,4-diones with a 2-furyl substituent (Table 3, entry 11) and cinnamyl substituent (Table 3, entry 12) also worked well in this transformation affording the corresponding *exo*-cycloadducts with excellent diastereo- and enantioselectivities. Additionally, more reactive substrate **2n** and **2o** were also able to undergo the asymmetric 1,3-dipolar cycloaddition, providing the desired products in high yields and enantiomeric excesses, albeit only moderate diastereoselectivities were attained (Table 3, entries 13−14). Thiazolidine-2,4-diones with an aliphatic substituent of either R^2 or R^3 also worked well in this reaction (Table 3, entries 15−16).

In addition, an oxygen surrogate 5-alkylidene oxazolidine-2,4-dione **5a** was employed for this asymmetric catalysis under the optimal reaction conditions (Table 4). To our delight, the

Table 4. Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides 1a to 5-Alkylidene Oxazolidine-2,4-diones 5[a]



entry	5	R	6	yield (%)[b]	dr[c]	ee (%)[c]
1	**5a**	*p*-ClC_6H_4	**6aa**	90	98:2	97
2	**5b**	*p*-FC_6H_4	**6ab**	88	98:2	92
3	**5c**	2,4-di-ClC_6H_3	**6ac**	92	80:20	96

[a]All reactions were carried out with 0.24 mmol of **1a** and 0.2 mmol of **5** in 2 mL of CH_2Cl_2 at 0 °C. [b]Isolated yield of two diastereomers. [c]The dr and ee were determined by chiral HPLC analysis; the diastereomers can be separated by using column chromatography; the ee referred to the major diastereomer.

reaction proceeded smoothly to give the *exo*-spirocyclic pyrrolidine-oxazolidinedione **6aa** in 86% yield and 93% ee, however with only moderate diastereoselectivity (dr = 89:11). Furthermore, the chiral *N*,*O*-ligand **4f**/$Cu(CH_3CN)_4BF_4$ catalyst system was found to be more suitable for this transformation, affording the *exo*-spirocyclic pyrrolidine-oxazolidinedione **6aa** in excellent enantio- and diastereoselectivity (ee = 97%; dr = 98:2). Two other arylidene oxazolidine-2,4-diones **5b−c** bearing electron-deficient groups on the phenyl ring proved to be also suitable for this reaction, providing the desired products in high yields (88−92%) and enantiomeric excesses (92−97%), albeit only moderate diastereoselectivity (dr = 80:20) was obtained when 5-alkylidene oxazolidine-2,4-diones **5c** with *ortho*-chloro substitution was utilized.

In conclusion, we have developed a highly efficient chiral *N*,*O*-ligand/$Cu(CH_3CN)_4BF_4$ catalytic system for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with 5-alkylidene thia(oxa)zolidine-2,4-diones, affording *exo*-spirocy-

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clic pyrrolidine-thia(oxa)zolidinediones in good to excellent yields (up to 99%), with excellent levels of diastereo- and enantioselectivity (dr up to 99:1; ee up to 98%). Notably, it is the first example of the highly stereoselective construction of structurally novel spirocyclic pyrrolidine-thia(oxa)zolidinedione bearing spiro heteroquaternary stereocenters, which suggests a highly efficient synthetic protocol of potential importance to medicinal chemistry and diversity-oriented synthesis. Further investigations in the area of spirocyclic pyrrolidine synthesis and applications are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02387.

Experimental details, characterization of new compounds, NMR and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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