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Cu(II)/DM-Segphos catalyzed asymmetric 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes and azomethine ylides†

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Cu(OTf)₂/DM-Segphos catalyzed asymmetric 1,3-dipolar cycloaddition between benzoisothiazole-2,2-dioxide-3-ylidenes and azomethine ylides was studied. The spiropyrrolidinyl-benzoisothiazolines were obtained in high yields with up to >99 : 1 dr and 99% ee. The enantioselective cycloaddition could be explained by the coordination of the imino esters **2** and chiral ligand DM-Segphos to the metallic center. The *exo*-selective cycloaddition course was attributed to the steric repulsion between the dipolarophiles and the 3,5-dimethylphenylphosphine group of the ligand.

Benzosultams are an important privileged class of structures in drug discovery, and are attractive synthetic targets due to their biological activities and intermediates for constructing molecular complexity and diversity.¹ The catalytic asymmetric 1,3-dipolar cycloaddition reaction plays a crucial role in the enantioselective preparation of five-membered heterocycles.² More specifically, the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with activated olefins has become one of the most powerful methods for the construction of chiral spirocyclic pyrrolidines containing spiro quaternary stereogenic centers,³ which represent the key structural moiety widely present in a myriad of natural products and biologically active compounds.⁴ Since the pioneering work of Gong⁵ employing stoichiometric amounts of chiral organocatalyst, much attention has been paid to develop a catalytic asymmetric approach to synthesize spirocyclic pyrrolidines.⁶ Although various methods are developed for this transformation, most dipolarophiles applied in these reactions are 2-oxoindolin-3-ylidene,^{6a-e} α -methylene- γ -butyrolactone,^{6f,g} ethyl cyclopropylidene acetate,^{6h} 2-alkylidene-cycloketone,⁶ⁱ 5-alkylidene thia(oxa)zolidine-2,4-dione,^{6j} and 3-alkylidene-4-chromanone.^{6k}

In the past several years, our research has been focused on developing spiro benzoisothiazole dioxide derivatives, which have been known to exhibit a variety of biological activities.^{7,8} To the best of our knowledge, there have no reports on catalytic asymmetric 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidene as the dipolarophile. Herein, we reported the first example of Cu(II)/DM-Segphos catalyzed asymmetric 1,3-

dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidene derivatives with azomethine ylides to give spiropyrrolidinyl-benzoisothiazoline derivatives in high diastereo- and enantioselectivity.

Our investigations began with a set of experiments directed at the identification of an optimal chiral Lewis acid system for the cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidene **1a** with azomethine ylide precursor **2a** (Table 1). The initial reactions were performed with the combination of copper(II) trifluoromethanesulfonate and various chiral ligands as the chiral Lewis acid systems in dichloromethane at -15 °C. Under all reaction conditions, the *exo*-cycloadduct **3a** was obtained in excellent diastereoselectivities (>99 : 1). Reactions with PyBox ligand **L1**, **L2** led to the *exo*-cycloadduct **3a** in low yields with moderate enantioselectivities, while the use of bisoxazoline ligands **L3**, **L4** did not produce significant improvement (entry 1–4). Chiral ferrocene ligands **L5** and **L6** catalyzed the reaction efficiently to give *exo*-**3a** in good yields but also with moderate enantioselectivities (entry 5, 6). Chiral *P,P*-bidentate ligands **L7** and **L8** also could catalyse the reaction efficiently but with even lower enantioselectivities (entry 7, 8). Chiral *P,P*-axially ligands catalyzed the reaction efficiently with much better enantioselectivities (entry 9–12). Gratifyingly, we find that the bulky and electron-donating DM-Segphos ligand⁹ **L11** catalyzed the reaction efficiently with excellent enantioselectivity. The spiropyrrolidinyl-benzoisothiazoline **3a** was obtained in 95% yield and 96% ee (entry 11). The other Cu(I/II) salts, such as Cu(CH₃CN)₄ClO₄ or Cu(CH₃CN)₄BF₄ and Cu(OAc)₂, produced *exo*-**3a** in slightly lower yields and enantioselectivities in combination with ligand **L11** (entry 13–15).

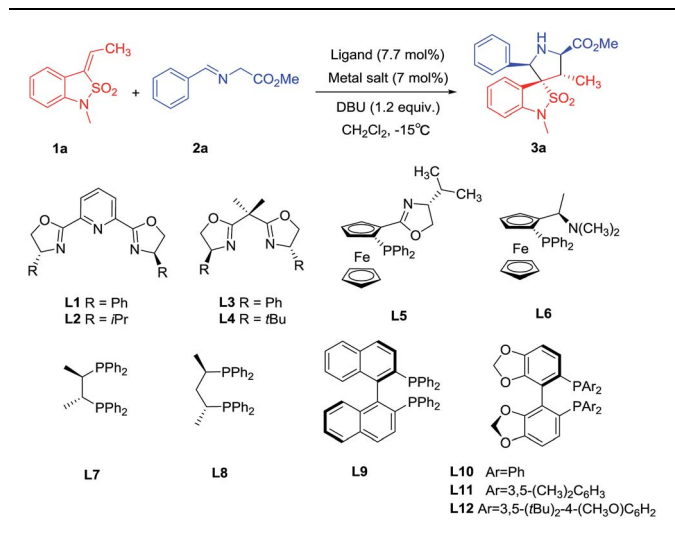
Having identified a promising chiral Lewis acid system for the asymmetric 1,3-dipolar cycloaddition, we examined the effects of bases, solvents, and temperature on the reaction yield, diastereoselectivity, and enantioselectivity (Table 2). The

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Table 1 The effects of ligands on the asymmetric 1,3-dipolar cycloaddition^a

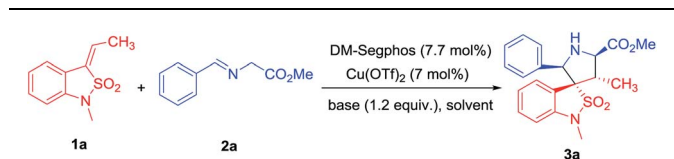


Entry	Ligand	Lewis acid	Yield ^b (%)	dr ^c	ee ^d (%)
1	L1	Cu(OTf) ₂	21	>99/1	55
2	L2	Cu(OTf) ₂	11	>99/1	56
3	L3	Cu(OTf) ₂	17	>99/1	40
4	L4	Cu(OTf) ₂	15	>99/1	60
5	L5	Cu(OTf) ₂	94	>99/1	53
6	L6	Cu(OTf) ₂	92	>99/1	54
7	L7	Cu(OTf) ₂	92	>99/1	35
8	L8	Cu(OTf) ₂	93	>99/1	25
9	L9	Cu(OTf) ₂	93	>99/1	66
10	L10	Cu(OTf) ₂	95	>99/1	70
11	L11	Cu(OTf) ₂	95	>99/1	96
12	L12	Cu(OTf) ₂	94	>99/1	58
13	L11	Cu(CH ₃ CN) ₄ ClO ₄	83	>99/1	90
14	L11	Cu(CH ₃ CN) ₄ BF ₄	89	>99/1	92
15	L11	Cu(OAc) ₂	92	>99/1	94

^a Reaction condition: dipolarophile **1a** (0.1 mmol), imino ester **2a** (0.12 mmol), ligand (0.0077 mmol), Lewis acid (0.007 mmol), DBU (0.12 mmol), CH₂Cl₂ (0.4 mL), -15 °C, 2 h. ^b Isolated yield. ^c Determined by HPLC analysis. ^d Determined by chiral HPLC analysis after purification.

reactions using triethylamine, DBU, DIPEA, and DABCO all afforded *exo*-**3a** with good diastereoselectivities and enantioselectivities (entry 1–4). High reaction yield was achieved when DBU was used, while the other bases gave low yields. Solvents have much effect on the reaction yields and enantioselectivities, but little on the diastereoselectivities. It was shown that dichloromethane is the best solvent of choice (entry 1 vs. 5–7). Investigation on the effect of temperature showed that the reaction yields could be slightly improved but the enantioselectivities were decreased when the reaction temperature was increased (entry 1, 8, 9). It was noted that higher enantiomeric excess (99% ee, entry 10 vs. 1) was achieved when the temperature was decreased from -15 °C to -25 °C. Even lower temperature caused adverse effect on both reactivity and enantioselectivity (entry 11). Optimization on the catalyst loading showed that both diastereoselectivity and enantioselectivity were reduced when lowering the catalytic loading from

Table 2 The effects of reaction conditions on the asymmetric 1,3-dipolar cycloaddition^a



Entry	Solvent	Base	Temp. (°C)	Time (h)	Yield ^b (%)	dr ^c	ee ^d (%)
1	CH ₂ Cl ₂	DBU	-15	2	95	>99/1	96
2	CH ₂ Cl ₂	Et ₃ N	-15	2	49	>99/1	91
3	CH ₂ Cl ₂	DIPEA	-15	2	42	>99/1	94
4	CH ₂ Cl ₂	DBACO	-15	2	35	>99/1	94
5	Toluene	DBU	-15	2	80	>99/1	86
6	THF	DBU	-15	2	79	>99/1	56
7	CH ₃ CN	DBU	-15	2	89	99/1	45
8	CH ₂ Cl ₂	DBU	0	2	96	>99/1	93
9	CH ₂ Cl ₂	DBU	r.t.	2	96	>99/1	91
10	CH ₂ Cl ₂	DBU	-25	2	95	>99/1	99
11	CH ₂ Cl ₂	DBU	-40	2	73	>99/1	97
12 ^e	CH ₂ Cl ₂	DBU	-25	2	95	97/3	96
13	CH ₂ Cl ₂	DBU	-25	1.5	89	>99/1	99
14	CH ₂ Cl ₂	DBU	-25	2.5	95	>99/1	99

^a Reaction condition: dipolarophile **1a** (0.1 mmol), imino ester **2a** (0.12 mmol), DM-Segphos (0.0077 mmol), Cu(OTf)₂ (0.007 mmol), base (0.12 mmol), solvent (0.4 mL). ^b Isolated yield. ^c Determined by HPLC analysis. ^d Determined by chiral HPLC analysis after purification. ^e Reaction performed with a 5 mol% of catalyst.

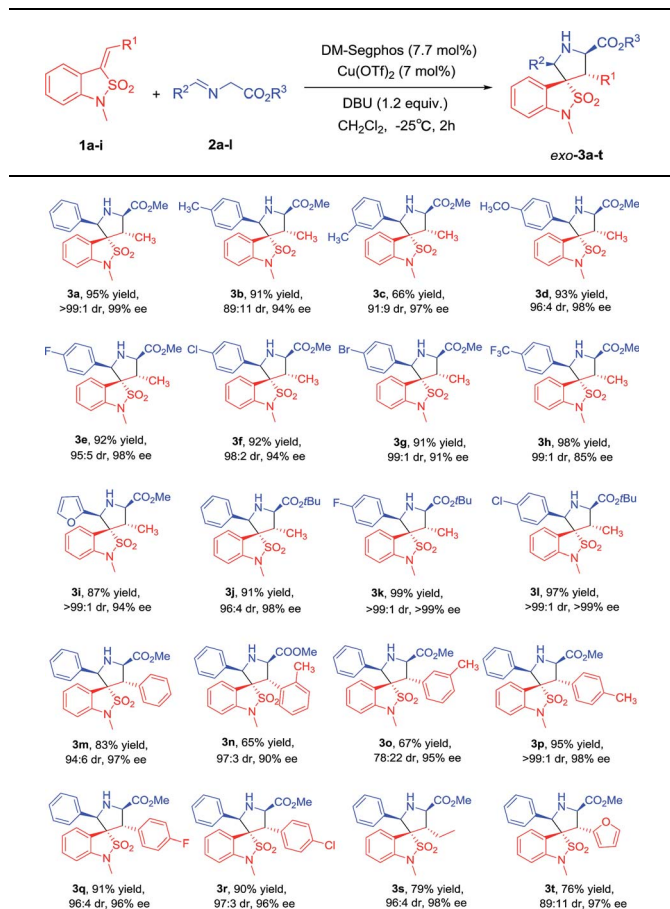
7 mol% to 5 mol% (entry 12). Examination of different reaction times disclosed that 2 h was the best choice (entry 13, 14).

Under the optimized conditions, we next studied the Cu(II)/DM-Segphos catalyzed 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidene derivative **1a** with a variety of azemothine ylides. As summarized in Table 3, a wide array of imino esters **2a–l** derived from aromatic aldehyde reacted smoothly with **1a** affording the desired *exo*-adducts **3a–l** in good diastereoselectivities and enantioselectivities. The yields of the cycloadducts were sensitive to the position of the substituent on the phenyl group. Substrate with a *para*-substituent (4-Me) gave higher yield than that with a *meta*-substituent (3-Me) (**3b** vs. **3c**). It appeared that the electronic property of the benzene ring had very limited effect on the reaction yields and enantioselectivities. Both substrates with electron-donating substituents (Me, OMe) and those with electron-withdrawing ones (F, Cl, Br, CF₃) gave the cycloadducts in high yields and enantioselectivities (**3b** and **3d** vs. **3e–h**). The imino ester **2i** derived from heteroaromatic aldehyde also gave **3i** in 87% yield and 94% ee. The imino ester **2j–l** with a much bulkier group (R³ = *t*Bu) led to *exo*-cycloadducts **3j–l** in good diastereoselectivity and enantioselectivity.

To further investigate the scope of the reaction, various benzoisothiazole-2,2-dioxide-3-ylidene derivatives **1b–i** were then examined under the optimal conditions. Regardless of the electronic properties, the electron-donating and electron-withdrawing substituents had no major effect on the reaction and led to *exo*-cycloadducts **3m–t** in moderate to good yields



Table 3 Substrate scope of Cu(OTf)₂/DM-Segphos catalyzed asymmetric 1,3-dipolar cycloaddition^a



^a General procedure: after a suspension of the DM-Segphos (0.0077 mmol) and Cu(OTf)₂ (0.007 mmol) in CH₂Cl₂ (0.2 mL) was stirred for 1 h at room temperature, a solution of the imino ester **2** (0.12 mmol) in CH₂Cl₂ (0.2 mL) was added. After being stirred at -25 °C for 10 min, DBU (0.12 mmol) and dipolarophile **1** (0.1 mmol) was added and the resulting solution was stirred at -25 °C for 2 h.

(65–95%), high diastereoselectivities (78 : 22 to >99 : 1 dr), and enantioselectivities (90% to 98% ee). The position of substituents on the benzyl ring had somewhat effect on the yields and enantiomeric excesses. Substrate with a *para*-substituent (4-Me, 95% yield, 98% ee) gave higher yield and enantioselectivity than that with an *ortho*- or *meta*-substituent (2-Me and 3-Me, 65–67% yield, 90–95% ee) (**3p** vs. **3n–o**). The substrates with alkyl and heteroaromatic substituents also gave the cycloadducts in good yields, high diastereoselectivities, and enantioselectivities (**3s** and **3t**). The absolute configuration of the product **3m** was determined by crystal structure analysis (Fig. 1). The absolute configurations of the other cycloadducts were determined by analogy.¹⁰

The stereochemical course of the reaction can be rationalized by means of the model proposed in Scheme 1.¹¹ Firstly, the complex **A** is generated by coordination of the imino esters **2** and the bidentate chiral ligand DM-Segphos to Cu(II) in a tetrahedral arrangement. After the abstraction of a proton by the

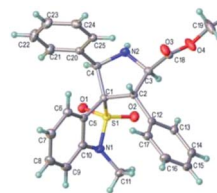
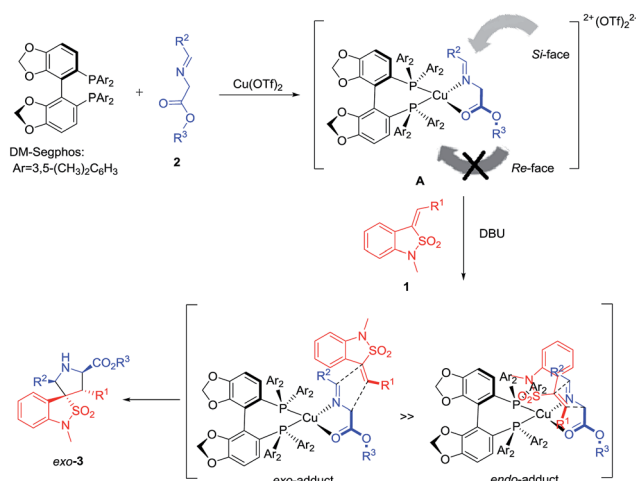


Fig. 1 X-ray crystallography of compound **3m**.



Scheme 1 Mechanistic proposal for the stereochemical course of the reaction.

amine base, the attack of benzoisothiazole-2,2-dioxide-3-ylidenes **1** is favored to the *Si*-face avoiding the steric interaction with two 3,5-dimethylphenyl groups of the ligand. Finally, the steric repulsion between the sulfonyl group of dipolarophile and the substituent of the ligand inhibits the *endo*-orientation leading to high *exo*-selectivity for the Cu(II)/DM-Segphos catalyzed cycloaddition.

Conclusions

In summary, we have developed a highly enantioselective Cu(II)/DM-Segphos catalytic system for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with benzoisothiazole-2,2-dioxide-3-ylidenes. The corresponding spiropyrrolidinyl-benzoisothiazoline derivatives were afforded in good yields with high diastereo- and enantioselectivities under mild reaction conditions. Further investigations on the evaluation of alternative azomethine ylides that carry electron withdrawing groups other than esters, and the substituent tolerance of the benzoisothiazol-2,2-dioxide on the benzene ring are underway and will be reported in due course.

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