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 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 Gong\(^5\) 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-oxindolin-3-ylidene,\(^6\)\(^a\)\(^e\)\(^\text{-}z\)-methylene-$\gamma$-butyrolactone,\(^6\)\(^c\) ethyl cyclopropylidene acetate,\(^6\)\(^b\) 2-alkylidene-cycloketone,\(^6\)\(^d\) 5-alkylidene thia(oxa)zolidine-2,4-dione,\(^6\)\(^n\) and 3-alkylidene-4-chromanone.\(^6\)\(^h\)

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.\(^7\)\(^a\) 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 spiro[2,5]pyrrolidinyl-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-ylidine 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 $-15^\circ$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 ligand\(^*\) L11 catalyzed the reaction efficiently with excellent enantioselectivity. The spiro[2,5]pyrrolidinyl-benzoisothiazoline 3a was obtained in high yield and 96% ee (entry 11). The other Cu(II) salts, such as Cu(CH$_3$CN)$_2$ClO$_4$ or Cu(CH$_3$CN)$_2$BF$_4$, 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
Table 1 The effects of ligands on the asymmetric 1,3-dipolar cycloaddition\(^a\)

| Entry | Ligand | Lewis acid | Yield\(^b\) (%) | \(\text{dr}^d\) | ee\(^c\) (%) |
|-------|--------|------------|----------------|----------------|------------|
| 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    | L13    | Cu(CH\(_2\)CN)\(_2\)ClO\(_4\) | 83          | >99/1          | 90         |
| 14    | L11    | Cu(CH\(_2\)CN)Br\(_2\)F\(_4\) | 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 mol), DBU (0.12 mol), CH\(_2\)Cl\(_2\) (0.4 mL), \(-15^\circ\text{C}\), 2 h. \(^b\) Isolated yield. \(^d\) Determined by chiral HPLC analysis. \(^c\) Reaction performed with a 5 mol% catalyst.

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

| Entry | Solvent | Base | Temp. \(^{\circ}\text{C}\) | Time (h) | Yield\(^b\) (%) | \(\text{dr}^d\) | ee\(^c\) (%) |
|-------|---------|------|--------------------------|---------|----------------|----------------|------------|
| 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  | 2                        | 95      | >99/1          | 99         |
| 11    | CH\(_2\)Cl\(_2\) | DBU  | 2                        | 73      | >99/1          | 97         |
| 12*   | CH\(_2\)Cl\(_2\) | DBU  | 25                       | 95      | >99/1          | 97         |
| 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 mol), base (0.12 mol), solvent (0.4 mL). \(^b\) Isolated yield. \(^d\) Determined by chiral HPLC analysis. \(^c\) 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 enantimERIC excess (99% ee, entry 10 vs. 1) was achieved when the temperature was decreased from \(-15^\circ\text{C}\) to \(-25^\circ\text{C}\). 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 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(n)/DM-Segphos catalyzed 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidene derivative 1a with a variety of azomethine 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-electron-donating substituent (3-Me) led to 3i in moderate to good yields. Electron-withdrawing substituents had no major effect on the reaction yields and enantioselectivities. Both substrates with electron-donating substituents (Me, OMe) and those with electron- withdrawing ones (F, Cl, Br, CF\(_3\)) gave the cycloadduct 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 \((R^{1}=tBu)\) 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.
(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 amine base, the attack of benzoisothiazole-2,2-dioxide-3-ylidene 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 sulfuryl 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-ylidene. The corresponding spiropyrroldinylbenzoisothiazoline 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.

**Notes and references**

1 (a) K. C. Majumdar and S. Mondal, Chem. Rev., 2011, 111, 7749; (b) T. Mezei, N. Mesterházy, T. Bakó, M. Porcs-Makkay, G. Simig and B. Volk, Org. Process Res. Dev., 2009,
For reviews, see: (a) K. V. Gothelf, in Cycloaddition Reactions in Organic Synthesis, ed. S. Kobayashi and K. A. Jørgensen, Wiley-VCH, Weinheim, Germany, 2002, p. 211; (b) K. V. Gothelf and K. A. Jørgensen, in Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, ed. A. Padwa and W. Pearson, Wiley & Sons, New York, 2002, ch. 12, p. 817; (c) K. V. Gothelf and K. A. Jørgensen, Chem. Rev., 1998, 98, 863; (d) S. Kanemasa, Synlett, 2002, 1371; (e) H. Pellissier, Tetrahedron, 2007, 63, 2887; (f) L. M. Stanley and M. P. Sibi, Chem. Rev., 2008, 108, 5366; (g) A. Bádoiu, Y. Brinkmann, F. Viton and E. P. Kündig, Pure Appl. Chem., 2008, 80, 1013; (h) W. M. Golebiowski and M. Guema, J. Heterocycl. Chem., 2008, 45, 1687; (i) S. Kanemasa, Heterocycles, 2010, 82, 87; (j) M. Kissane and A. R. Maguire, Chem. Soc. Rev., 2010, 39, 845; (k) C. Nájera, M. Santos and M. Yus, J. Braz. Chem. Soc., 2010, 21, 377; (l) Y. Xing and N.-X. Wang, Coord. Chem. Rev., 2012, 256, 938; (m) T. Hashimoto and K. Maruoka, Chem. Rev., 2015, 115, 5366.

For examples, (a) M. M. M. Santos, Tetrahedron, 2014, 70, 9735; (b) Z. Zhang, X.-J. Chu, J.-J. Liu, Q. Ding, J. Zhang, D. Bartkovitz, N. Jiang, P. Karnach, S.-S. So, C. Tovar, Z. M. Filipovic, B. Higgins, K. Glenn, K. Packman, L. Vassilev and B. Graves, ACS Med. Chem. Lett., 2014, 5, 124; (c) A. I. Almansour, R. S. Kumar, F. Beevi, A. N. Shirazi, H. Osman, R. Ismail, T. S. Choon, B. Sullivan, K. McCaffrey, A. Nahlas, K. Parang and M. A. Ali, Molecules, 2014, 19, 10033; (d) S. Hati, S. Tripathy, P. K. Dutta, R. Agarwal, R. Srinivasan, A. Singh, S. Singh and S. Sen, Sci. Rep., 2016, 6, 32213; (e) A. P. Antonchick, C. Gerdin-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, Nat. Chem., 2010, 2, 735; (f) S. M. Rajesh, K. Hunady, I. Fujita, T. Okumura, A. Sakakibara and M. Kato, S. Kawai and S. Matsumoto, J. Med. Chem., 2000, 43, 2040; (g) Z. Brzozowski, F. Saczewski and N. Neamati, Bioorg. Med. Chem. Lett., 2006, 16, 5298; (h) Y. Misu and H. Togo, Organ. Biomol. Chem., 2003, 1, 1342; (i) J. G. Wells, M. Tao, K. A. Josef and R. Bihsow, J. Med. Chem., 2001, 44, 3488; (j) R. J. Cherney, R. Mo, D. T. Meyer, K. D. Hardman, R.-Q. Liu, M. B. Covington, M. Qian, Z. R. Wasserman, D. D. Christ, J. M. Tzasko, R. C. Newton and C. P. Decieco, J. Med. Chem., 2004, 47, 2981.

6 For catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides, see: (a) A. P. Antonchick, C. Gerdin-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, Nat. Chem., 2010, 2, 735; (b) T.-L. Liu, Z.-Y. Xue, H.-Y. Tao and C.-J. Wang, Org. Biomol. Chem., 2011, 9, 1980; (c) L. Wang, X.-M. Shi, W.-P. Dong, L.-P. Zhu and R. Wang, Chem. Commun., 2013, 49, 3458; (d) W. Dai, X.-L. Jiang, Q. Wu, F. Shi and S.-J. Tu, J. Org. Chem., 2015, 80, 5737; (e) J.-X. Zhang, H.-Y. Wang, Q.-W. Jin, C.-W. Zheng, G. Zhao and Y.-J. Shang, Org. Lett., 2016, 18, 4774; (f) Q.-H. Li, T.-L. Liu, L. Wei, X. Zhou, H.-Y. Tao and C.-J. Wang, Chem. Commun., 2013, 49, 9642; (g) J. Castulik, J. Marek and C. Mazal, Tetrahedron, 2001, 57, 8339; (h) T.-L. Liu, Z.-L. He, H.-Y. Tao, Y.-P. Cai and C.-J. Wang, Chem. Commun., 2011, 47, 2616; (i) T.-L. Liu, Z.-L. He, Q.-H. Li, H.-Y. Tao and C.-J. Wang, Adv. Synth. Catal., 2011, 353, 1713; (j) W.-L. Yang, F.-F. Tang, F.-S. He, C.-Y. Li, X. Yu and W.-P. Deng, Org. Lett., 2015, 17, 4822; (k) T.-L. Liu, Z.-L. He and C.-J. Wang, Chem. Commun., 2011, 47, 9600; (l) T.-L. Liu, Z.-L. He, H.-Y. Tao and C.-J. Wang, Chem.–Eur. J., 2012, 18, 8042; (m) K. Liu, H.-L. Teng, L. Yao, H.-Y. Tao and C.-J. Wang, Org. Lett., 2013, 15, 2250; (n) F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu and L.-Z. Gong, Chem.–Eur. J., 2012, 18, 6885; (o) X. Ma, Y. Zhu, Q. Sun, X. Li, J. Su, L. Zhao, Y. Zhao, S. Qiu, W. Yan, K. Wang and R. Wang, Chem. Commun., 2015, 51, 8799; (p) G. Zhu, B. Wang, X. Bao, H. Zhang, Q. Wei and J. Qu, Chem. Commun., 2015, 51, 15510.

7 (a) G. Cao, F. Long, Y. Zhao, Y. Wang, L. Huang and D. Teng, Tetrahedron, 2014, 70, 9359; (b) G. Cao, Y. Wang, T. Cui, L. Huang and D. Teng, RSC Adv., 2016, 6, 22519.

8 (a) S. Petry, K.-H. Baringhaus, N. Tennagels and G. Mueller, US 20,050,070, A1, 2005; (b) M. A. Collins, V. A. Mackner, J. E. Wrobel, J. P. Edwards, T. K. Jones, C. M. Tegley and L. Zhi, US 6,339,098, 2002; (c) H. Masako, M. Sachiko,
For the use of Segphos ligands in catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides, see: (a) R. Joseph, C. Murray and P. Garner, *Org. Lett.*, 2014, 16, 1550; (b) M. González-Esguevillas, J. Adrio and J. C. Carretero, *Chem. Commun.*, 2013, 49, 4649; (c) E. E. Maroto, S. Filippone, A. Martín-Domenech, M. Suarez and N. Martín, *J. Am. Chem. Soc.*, 2012, 134, 12936; (d) J. Hernández-Toribio, S. Padilla, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2012, 51, 8854; (e) M. González-Esguevillas, J. Adrio and J. C. Carretero, *Chem. Commun.*, 2012, 48, 2149; (f) Y. Yamashita, T. Imaizumi and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2011, 50, 4893; (g) A. López-Pérez, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2009, 48, 340; (h) Y. Oderaotoshi, W. Cheng, S. Fujitomi, Y. Kasano, S. Minakata and M. Komatsu, *Org. Lett.*, 2003, 5, 5043.

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M. Potowski, A. P. Antonchick and H. Waldmann, *Chem. Commun.*, 2013, 49, 7800.