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Catalytic asymmetric construction of spiro pyrrolidines with contiguous quaternary centers *via* 1,3-dipolar cycloaddition of azomethine ylides

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ABSTRACT

Bioactive 5-*aza*-spiro[2,4]heptanes with high functionality and up to three contiguous all-carbon quaternary stereogenic centers were synthesized by Cu(I)-catalyzed asymmetric *endo*-selective 1,3-dipolar cycloaddition of azomethine ylides with cyclopropylidene acetates. This synthesis system performs well for a broad scope of substrates. α-unsubstituted/α-substituted azomethine ylides and cyclopropylidene acetates are compatible 1,3-dipoles and dipolarophiles, which afford the spiro heterocycles with contiguous quaternary centers at 2-, 3- and 4-positions of the pyrrolidine ring in good yield (up to 97%) and high diastereoselectivity (95:5–>98:2 d.r) and excellent enantioselectivity (87%–98% ee).

1. Introduction

All-carbon quarternary centers in a variety of natural products and pharmacrutical drugs are increasingly difficult chemical synthesis. Over the past decades, chiral quaternary stereogenic centers have been constructed by several methods [1–7], but the construction of contiguous quaternary centers in a single enantioselective transformation is a daunting challenge in natural product synthesis [8]. Recently, a few methods for the construction of adjacent quaternary centers have been developed [9–11], such as Pd-catalyzed decarboxylation asymmetric allylic alkylation (Pd-DAAA) [12] or double decarboxylation allylation [13], Pd-catalyzed asymmteric [3+2] annulation of 5-vinyloxazolizinones with trisubstituted alkenes [14], sequential Michael reactions [15] and alkylation of 3-bromooxinodoles with 3-substituted indoles [16].

Nitrogen heterocyclic pyrrolidines are key structural motifs frequently present in biological compounds and building blocks that occupy a privileged position in organic synthesis [17,18]. Moreover, pyrrolidine derivatives have also been utilized as organocatalysts in recent years [19–21]. The general strategy for constructing five-membered heterocycles was the cycloaddition reaction of various 1,3-dipoles with electron-deficient alkenes or alkynes as the dipolarophiles [22–27]. Although

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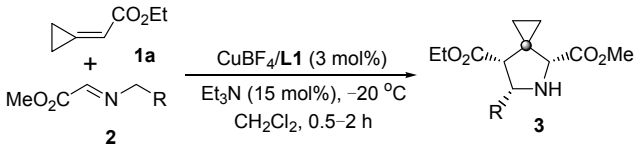
metal-stabilized azomethine ylides have been employed as readily available 1,3-dipole in the chiral-auxiliary-induced asymmetric 1,3-dipolar cycloaddition for the construction of enantiomerically enriched pyrrolidines [28–37], the first catalytic asymmetric variant of the 1,3-dipolar cycloaddition reaction of azomethine ylides was reported by Zhang's group [38] using a Ag(I)/xylyl-FAP complex and Jörgensen's group [39] using a Zn(II)/bisoxazoline complex only in 2002. Since then, enormous efforts have been made on the development of catalytic stereoselective 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient olefins to give a variety of highly functionalized pyrrolidines with multiple stereogenic centers [40–55]. The construction of quaternary, especially spiro quaternary, stereogenic centers has also been developed [56–61]. Most recently, the catalytic asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides with trisubstituted electron-deficient alkenes for the construction of spiro[oxindole-pyrrolidine]s were developed by Gong's group [62–64], Waldmann's group [65,66], Arai's group [67], Wang's group [68,69] and our group [70–74]. However, the synthesis of chiral sprio pyrrolidine heterocycles with vicinal quaternary stereogenic centers by 1,3-dipolar cycloaddition of azomethine ylides has been seldom reported.

Cyclopropane structures are common components in many natural products such as terpenoids and steroids exhibiting significant biological activity [75–77]. Methylenecyclopropanes (MCPs) have been well documented as important synthetic intermediates in organic synthetic chemistry in the past three decades [78,79], and MCPs were used as a three-carbon unit dipole in a variety of the transition metal-catalyzed ring-opening processes [80,81] due to the potent thermodynamic driving force rendered by the relief of the 3-membered ring strain. Examples on ring-untouched transformations employing MCP derivatives as dipolarophiles [82] have also been reported in 1,3-dipolar cycloaddition reactions, in which nitrones, nitrile oxides, azides, diazoalkanes, nitrile ylides and oximes were employed as the corresponding 1,3-dipoles.

In a previous communication, we developed a highly efficient Cu(I)/TF-BiphamPhos-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with ethyl cyclopropylidene acetates leading to the synthesis of spiro [cyclopropan-3,3'-pyrrolidine] with excellent *endo*-selectivity and enantioselectivity (Table 1) [71]. The spiro[cyclopropan-3,3'-pyrrolidine], that is, 5-*aza*-spiro[2,4]heptane, structure motif with a spiro carbon connecting two key units of cyclopropane and pyrrolidine plays an important role in the structure-activity relationship of many antibacterial agents. The unique 5-*aza*-spiro[2,4] heptane scaffold can remarkably enhance the carbapenems analogs, substituted oxazolidinones and quinolone antibiotics, especially against both *gram*-positive and *gram*-negative bacteria [83–89].

As part of our continuing efforts in this area, here we report a full account of the catalytic asymmetric synthesis of diversified 5-*aza*-spiro[2,4]heptanes with high functionalities and three stereogenic centers including up to three contiguous all-carbon quaternary centers by Cu(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of azomethine ylides derived from both α-unsubstituted and α-substituted α-amino acid with a variety of α-substituted cyclopropylidene acetates (Scheme 1).

Table 1
Asymmetric 1,3-dipolar cycloaddition of various glycinate-derived imino esters **2** with ethyl cyclopropylidene acetate **1a** for the synthesis of 5-*aza*-spiro[2,4]heptanes.



Entry	R (**2**)	**3**	Yield [a] (%)	*endo*:*exo* [b]	ee [b] (%)
1	*p*-Cl-C_6H_4 (**2a**)	**3aa**	90	>98:2	98
2	*o*-Cl-C_6H_4 (**2b**)	**3ab**	97	97:3	97
3	*p*-Br-C_6H_4 (**2c**)	**3ac**	87	95:5	98
4	*p*-F-C_6H_4 (**2d**)	**3ad**	85	97:3	97
5	Ph (**2e**)	**3ae**	81	95:5	95
6	*p*-Me-C_6H_4 (**2f**)	**3af**	78	96:4	97
7	*m*-Me-C_6H_4 (**2g**)	**3ag**	90	>98:2	98
8	*o*-Me-C_6H_4 (**2h**)	**3ah**	87	>98:2	96
9	*p*-MeO-C_6H_4 (**2i**)	**3ai**	78	>98:2	98
10	1-Naphthyl (**2j**)	**3aj**	82	>98:2	92
11	2-thienyl (**2k**)	**3ak**	89	>98:2	94
12[c]	cinnamyl (**2l**)	**3al**	76	>98:2	93

All reactions were carried out with 0.20 mmol of **1a** and 0.40 mmol of **2** in 2 mL of CH_2Cl_2. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$.
[a] Isolated yield.
[b] Enantiomeric excesses and diastereomeric ratio were determined by chiral HPLC analysis. Minor *exo*-isomer was not detected on the crude ^1H NMR.
[c] Reaction was carried out at 0 °C in 1 h.

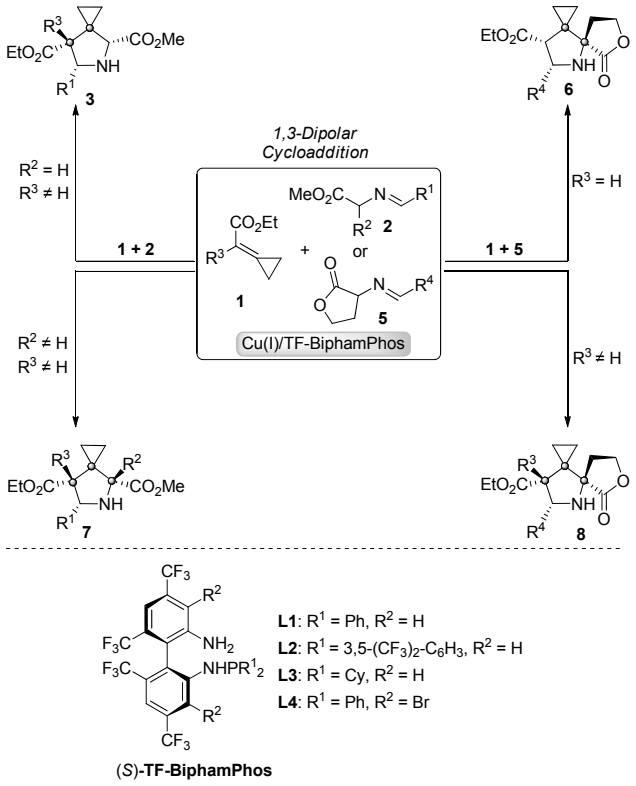
2. Experimental

General procedure for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with ethyl cyclopropylidene acetates catalyzed by $Cu(CHC_3CN)_4BF_4$/(*S*)-TF-BiphamPhos complex. Under an argon atmosphere, (*S*)-TF-BiphamPhos (0.0072 mmol) and $Cu(CHC_3CN)_4BF_4$ (2.0 mg, 0.006 mmol) were dissolved in 2 mL CH_2Cl_2 and stirred at room temperature for 1 h. Then, the imine substrate (0.4 mmol), Et_3N (0.03 mmol), and ethyl cyclopropylidene acetates (0.2 mmol) were added sequentially. Once the starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The product was purified by column chromatography to give the corresponding cycloaddition product, which was then directly analyzed by chiral HPLC to determine the enantiomeric excess.

3. Results and discussion

3.1. Cu(I)-catalyzed 1,3-dipolar cycloaddition of α-substituted azomethine ylides with ethyl cyclopropylidene acetates

Encouraged by the excellent results achieved with α-unsubstituted azomethine ylides derived from glycinate in our previous communication [71], we further investigated the possibility of employing α-substituted imino esters as the di-



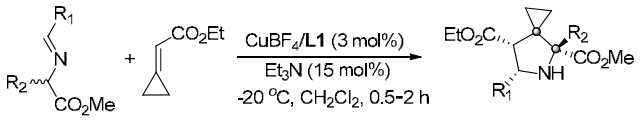
Scheme 1. Construction of spiro pyrrolidine heterocycles with contiguous quaternary centers *via* Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with cyclopropylidene acetates.

pole precursors. These are challenging substrates due to the unfavourable steric hindrance because two contiguous quaternary centers can be formed and the lower acidity of the corresponding methene CH group between the imine and ester. Hence, although the generated pyrrolidines containing a unique quaternary stereogenic center are of great importance and synthetic potential, α-substituted imino esters have been seldom employed in the asymmetric 1,3-dipolar cycloaddition compared with α-unsubstituted imino esters derived from glycinate. To our delight, under the optimal conditions in the previous communication, various imino esters derived from α-substituted amino acid, such as (±)-alanine, (±)-leucine, (±)-2-aminobutyric acid and (±)-phenylalanine were tolerated in this catalytic system, which provided the corresponding highly functionalized pyrrolidines containing a unique nitrogen-substituted quaternary stereogenic center adjacent to the spiro quaternary carbon center in exclusive diastereoselectivities and excellent enantioselectivities (Table 2).

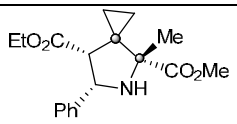
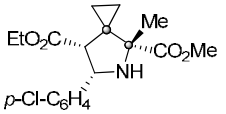
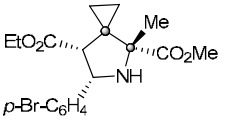
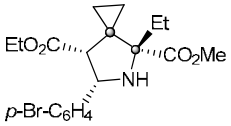
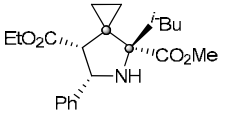
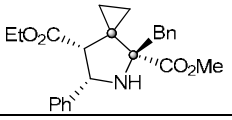
3.2. Cu(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with α-substituted ethyl 2-cyclopropylidene acetates

To better define the substrate scope with respect to the dipolarophiles, the more sterically hindered α-substituted ethyl 2-cyclopropylidene acetates were employed. Spiro[cyclopropan-3,3'-pyrrolidine] with two adjacent quaternary centers at

Table 2
Asymmetric 1,3-dipolar cycloaddition of α-substituted imino esters **2** with ethyl 2-cyclopropylidene acetate **1a**.



2 **1a** **3**

Entry	Product	3	Yield[a] (%)	d.r[b]	ee[b] (%)
1		**3am**	89	>98:2	98
2		**3an**	87	>98:2	97
3		**3ao**	87	95:5	97
4		**3ap**	74	>98:2	97
5		**3aq**	81	>98:2	97
6		**3ar**	62	95:5	96

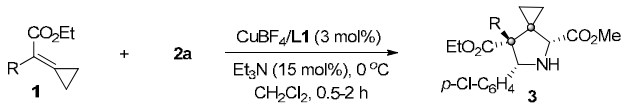
All reactions were carried out with 0.20 mmol of **1a** and 0.40 mmol of **2** in 2 mL of CH_2Cl_2, $CuBF_4$ = $Cu(CH_3CN)_4BF_4$.

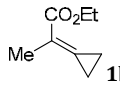
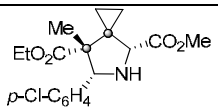
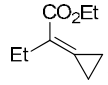
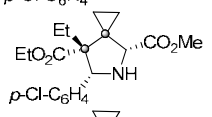
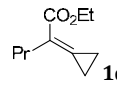
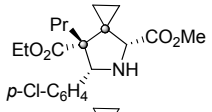
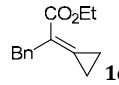
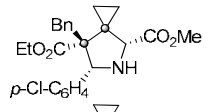
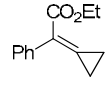
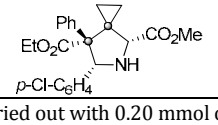
[a] Isolated yield.

[b] Enantiomeric excesses and diastereomeric ratios were determined by chiral HPLC analysis. Minor *exo*-isomer was not detected on the crude ^1H NMR.

the 3 and 7 positions of the spiro pyrrolidine rings were expected. Under the optimal reaction conditions, we successfully extended the dipolarophile scope to various α-substituted 2-cyclopropylidene acetates. As shown in Table 3, ethyl 2-cyclopropylidene acetates bearing alkyl substitutes such as methyl (**1b**, entry 1), ethyl (**1c**, entry 2), *n*-propyl (**1d**, entry 3), and benzyl (**1e**, entry 4), and aromatic ring substitutes such as phenyl (**1f**, entry 5) groups at the α position of the ester group were all proven compatible in this annulation process with azomethine ylide **2a**, smoothly affording the corresponding spiro cycloadducts exclusively in good yields and excellent diastereoselectivities and high enantioselectivities (up to >98:2 d.r, and 92%–96% ee). This is the first example of the α,α,β,β-tetrasubstituted electron-deficient alkenes used as the dipolarophiles in the catalytic asymmetric 1,3-dipolar cycloaddition. The absolute configuration of spiro pyrrolidine **3ca** was determined as (4*R*,6*R*,7*R*) by X-ray analysis of its corresponding *N*-tosylated derivative **4** (Fig. 1. CCDC 962660 (**4**) contains the supplementary crystallographic data for this paper).

Table 3
Asymmetric 1,3-dipolar cycloaddition of **2a** with various of α-substituted ethyl 2-cyclopropylidene acetates **1**.



Entry	1	Product	3	Yield [a] (%)	d.r [b]	ee [b] (%)
1	 **1b**		**3ba**	80	95:5	96
2	 **1c**		**3ca**	72	>98:2	96
3	 **1d**		**3da**	70	96:4	95
4	 **1e**		**3ea**	66	>98:2	96
5	 **1f**		**3fa**	64	>98:2	92

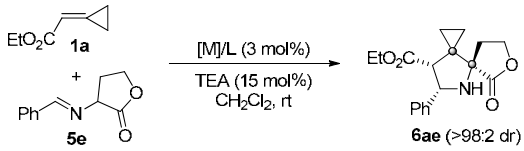
All reactions were carried out with 0.20 mmol of **1** and 0.40 mmol of **2a** in 2 mL of CH_2Cl_2, $CuBF_4$ = $Cu(CH_3CN)_4BF_4$.
[a] Isolated yield.
[b] Enantiomeric excesses and diastereomeric ratios were determined by chiral HPLC analysis. The minor *exo*-isomer was not detected in the crude ^1H NMR.

3.3. Cu(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of homoserine lactone derived cyclic azomethine ylides with ethyl 2-cyclopropylidene acetate

To further probe the applicability of this 1,3-dipolar cycloaddition reaction to construct the more complex spiro[cyclopropan-3,3'-pyrrolidine], we turned our attention to the cyclic azomethine ylides derived from homoserine lactones. A tricyclic spiro heterocycle bearing one cyclopropane, one pyrrolidine and one butylactone moiety would be expected along with two generated quaternary centers in this transformation. When the cyclic imino ester **5e** reacted with ethyl 2-cyclopropylidene acetate **1a** in the presence of 3 mol% of $Cu(CH_3CN)_4BF_4$/(*S*)-TF-BiphamPhos (**L1**) and 15 mol% Et_3N in CH_2Cl_2 at room temperature, the designed product was obtained with a moderate yield although only with 82% ee (Table 4, entry 1). Thus, the reaction conditions were re-optimized to improve the asymmetric induction efficiency. Having screened the reaction parameters including the metal source, chiral ligand and reaction temperature, it was elucidated that the best result in terms of both the yield and enantioselectivity was achieved when the reaction was catalyzed by the complex of $Cu(CH_3CN)_4BF_4$ and chiral **L4** at room temperature (Table 4, entry 5).

The substrate scope and limitation of the cyclic imino esters in this annulation was further extended under the re-optimized reaction condition. The results are listed in Table 5. In general,

Table 4
Optimization of the reaction conditions for cyclo imino esters **5**.



Entry	[M]	L	Yield [a] (%)	ee [b] (%)
1	$Cu(CH_3CN)_4BF_4$	**L1**	55	82
2	AgOAc	**L1**	25	31
3	$Cu(CH_3CN)_4BF_4$	**L2**	25	31
4	$Cu(CH_3CN)_4BF_4$	**L3**	29	61
5	$Cu(CH_3CN)_4BF_4$	**L4**	80	95

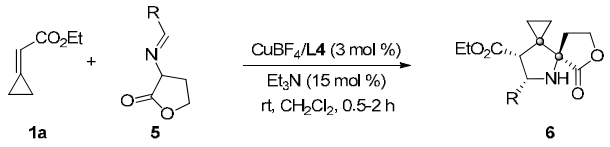
All reactions were carried out with 0.40 mmol of **5e** and 0.20 mmol of **1a** in 2 mL CH_2Cl_2.
[a] Isolated yield.
[b] Enantiomeric excesses and diastereomeric ratios were determined by chiral HPLC analysis. The minor *exo*-isomer was not detected on the crude ^1H NMR.

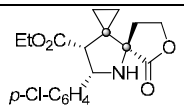
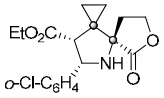
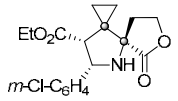
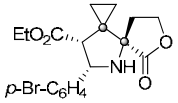
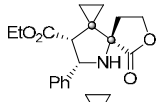
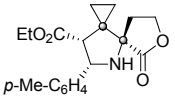
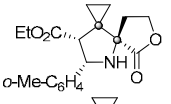
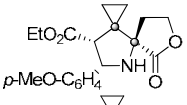
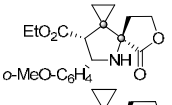
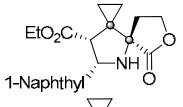
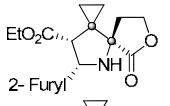
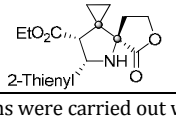
ethyl cyclopropylidene acetate **1a** reacted with various cyclic imino esters generated from aldehydes and homoserine lactone smoothly affording the desired adducts in high yields (40%–82%) with exclusive diastereoselectivities (>98:2 d.r) and excellent enantioselectivities (87%–96% ee). The 10-position of the spiro-pyrrolidines can be substituted with arenes containing electron-withdrawing (Table 5, entries 1–4), electron-neutral (Table 5, entry 5) and electron-donating groups (Table 5, entries 6–9) as well as heterocycles such as 2-furanyl (**6ak**) and 2-thienyl (**6al**). Cyclic imino esters derived from α-naphthylaldehyde also worked well in this reaction, and the desired spirocyclic **6aj** can be obtained in 70% yield and 90% ee (Table 5, entry 10). However, the less reactive aliphatic cyclic imino esters did not work in this cycloaddition reaction under the re-optimized reaction condition. The absolute configuration of the spiro-pyrrolidines **6ad** was established by X-ray diffraction analysis (Fig. 1. CCDC 962659 (**6ad**) contains the supplementary crystallographic data for this paper).

3.4. Cu(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of α-substituted azomethine ylides with α-substituted ethyl 2-cyclopropylidene acetate for the construction of spiro heterocycles with three adjacent quaternary centers

In addition, we tested the construction of spiro[cyclopropan-3,3'-pyrrolidine] bearing three adjacent quaternary centers, two of which are quaternary stereogenic centers, generated by 1,3-dipolar cycloaddition of the α-methyl substituted azomethine ylide **2n** or cyclic azomethine ylide **5e** with α-benzyl ethyl 2-cyclopropylidene acetate **1e** (Scheme 2). The reactions were carried out successfully in the Cu(I)-catalytic system employing chiral ligands **L1** and **L4**, respectively. The target products were obtained with excellent diastereoselectivities and enantioselectivities (96% ee for **7** and 93% ee for **8**) although with moderate yields. This construction of chiral pyrrolidines with contiguous three quaternary centers *via* the 1,3-dipolar cycloaddition reaction was developed for the first time.

Table 5
Asymmetric 1,3-dipolar cycloaddition of various cyclo imino esters **5** with cyclopropyl-ideneacetate **1a**.



Entry	Product	6	Yield[a] (%)	d.r[b]	ee[b] (%)
1		**6aa**	82	> 98:2	95
2		**6ab**	67	95:5	92
3		**6ac**	67	> 98:2	89
4		**6ad**	62	> 98:2	96
5		**6ae**	80	> 98:2	96
6		**6af**	61	> 98:2	93
7		**6ag**	61	> 98:2	96
8		**6ah**	71	> 98:2	93
9		**6ai**	40	> 98:2	91
10		**6aj**	70	> 98:2	90
11		**6ak**	80	> 98:2	90
12		**6al**	82	> 98:2	87

All reactions were carried out with 0.20 mmol of **1a** and 0.40 mmol of **5** in 2 mL of CH_2Cl_2. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$.
[a] Isolated yield.
[b] Enantiomeric excesses and diastereomeric ratios were determined by chiral HPLC analysis. The minor *exo*-isomer was not detected in the crude ^1H NMR.

3.5. Possible transition state in the Cu(I)/TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with cyclopropylidene acetate

Based on these results and previous DFT studies [90,91], a stepwise Michael/Mannich mechanism [92–95] can be proposed. The transition state model in Fig. 2 accounts for the observed *endo*-selectivity of the 1,3-dipolar cycloaddition of imino esters with ethyl 2-cyclopropylidene acetates in the presence of $Cu(CH_3CN)_4BF_4$/(*S*)-TF-BiphamPhos (**L1**). The *in-situ* formed azomethine ylide is coordinated to the metallic center and oriented as determined by the steric repulsion between the two phenyl group in the ylide and on the phosphorus atom of the chiral ligand. The dipolarophile ethyl 2-cyclopropylidene acetate **1** approaches the less-hindered face of the azomethine ylide, that is, the *Si* (C=N) face in this case, to avoid steric congestion, and hence form the *endo*-selective (4*R*,6*S*,7*R*)-5-*aza*-spiro[2,4]-heptane observed in the experimental results. The possible hydrogen bond interaction between the carbonyl group of the dipolarophile **1** and the NH_2 group of the chiral (*S*)-TF-BiphamPhos ligand (**L1**) would stabilize the transition state [96,97].

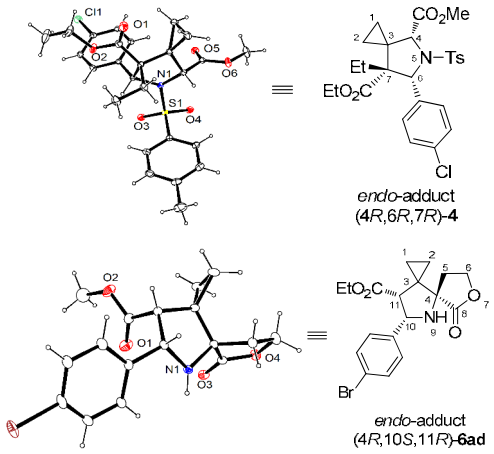
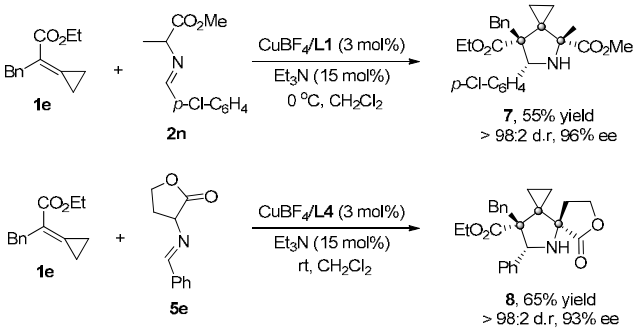


Fig. 1. The structures of (4*R*,6*R*,7*R*)-**4** and (4*R*,10*S*,11*R*)-**6ad**.



Scheme 2. 1,3-Dipolar cycloaddition of α-substituted azomethine ylides with α-substituted cyclopropylidene acetate **1e** for the construction of spiro pyrrolidines with three adjacent quaternary centers.

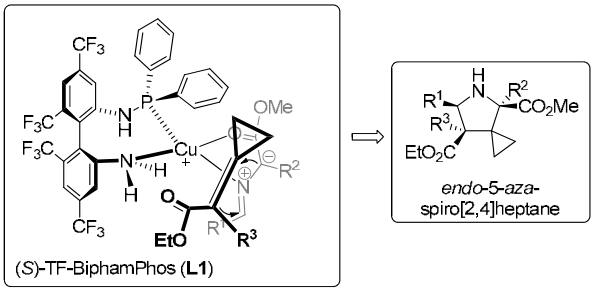


Fig. 2. Transition states leading to *endo*-5-*aza*-spiro[2,4]heptane.

4. Conclusions

We have developed a general methodology for the direct and facile synthesis of various enantiomerically enriched *endo*-5-aza-spiro[2,4]heptane derivatives by the highly efficient Cu(I)-catalyzed 1,3-dipoalr cycloaddition of a variety of α-unsubstituted and α-substituted azomethine ylides with various cyclopropylidene acetates. This reaction provides a convenient method to access highly substituted spiro[cyclopropan-3,3'-pyrrolidine] with up to three contiguous quaternary centers in high yields and excellent diastereoselectivities (up to >98:2 dr) and enantioselectivites (up to 98% ee).

Acknowledgments

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Graphical Abstract

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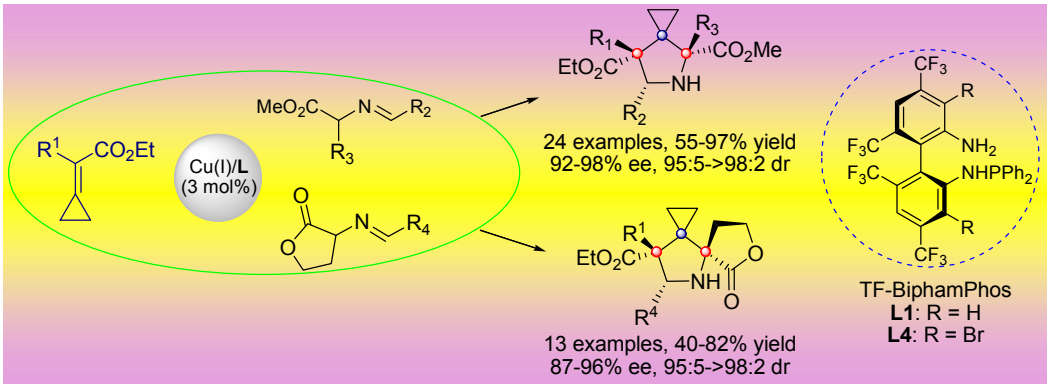
Catalytic asymmetric construction of spiro pyrrolidines with contiguous quaternary centers *via* 1,3-dipolar cycloaddition of azomethine ylides

Tanglin Liu, Qinghua Li, Zhaolin he, Jiawei Zhang, Chunjiang Wang*
Wuhan University; Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences



Bioactive 5-*aza*-spiro[2,4]heptanes with high functionality and up to three contiguous all-carbon quaternary centers were synthesized by Cu(I)-catalyzed asymmetric *endo*-selective 1,3-dipolar cycloaddition of azomethine ylides with cyclopropylidene acetates.

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