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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).

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1. Introduction

All-carbon quaternary centers in a variety of natural products and pharmaceuticals are increasingly difficult to synthesize. 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 asymmetric [3+2] annulation of 5-vinylloxazolizones with trisubstituted alkenes [14], sequential Michael reactions [15] and alkylation of 3-bromooxindoles 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 Jørgensen'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 spiro 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

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 (%)	<i>endo:exo</i> ^b	<i>ee</i> ^b (%)
1	<i>p</i> -Cl-C ₆ H ₄ (2a)	3aa	90	>98:2	98
2	<i>o</i> -Cl-C ₆ H ₄ (2b)	3ab	97	97:3	97
3	<i>p</i> -Br-C ₆ H ₄ (2c)	3ac	87	95:5	98
4	<i>p</i> -F-C ₆ H ₄ (2d)	3ad	85	97:3	97
5	Ph (2e)	3ae	81	95:5	95
6	<i>p</i> -Me-C ₆ H ₄ (2f)	3af	78	96:4	97
7	<i>m</i> -Me-C ₆ H ₄ (2g)	3ag	90	>98:2	98
8	<i>o</i> -Me-C ₆ H ₄ (2h)	3ah	87	>98:2	96
9	<i>p</i> -MeO-C ₆ H 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 CH₂Cl₂. CuBF₄ = Cu(CH₃CN)₄BF₄.

^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.

from both α -unsubstituted and α -substituted α -amino acid with a variety of α -substituted cyclopropylidene acetates (Scheme 1).

2. Experimental

General procedure for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with ethyl cyclopropylidene acetates catalyzed by Cu(CH₃CN)₄BF₄/(*S*)-TF-BiphamPhos complex. Under an argon atmosphere, (*S*)-TF-BiphamPhos (0.0072 mmol) and Cu(CH₃CN)₄BF₄ (2.0 mg, 0.006 mmol) were dissolved in 2 mL CH₂Cl₂ and stirred at room temperature for 1 h. Then, the imine substrate (0.4 mmol), Et₃N (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 ($\pm$)-alanine, ($\pm$)-leucine, ($\pm$)-2-aminobutyric acid and ($\pm$)-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**.

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 CH₂Cl₂, CuBF₄ = Cu(CH₃CN)₄BF₄.

^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 $\alpha,\alpha,\beta,\beta$ -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			3ba	80	95:5	96
2			3ca	72	>98:2	96
3			3da	70	96:4	95
4			3ea	66	>98:2	96
5			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 CH₂Cl₂, CuBF₄ = Cu(CH₃CN)₄BF₄.

^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(CH₃CN)₄BF₄/(*S*)-TF-BiphamPhos (**L1**) and 15 mol% Et₃N in CH₂Cl₂ 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(CH₃CN)₄BF₄ 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 ₃ CN) ₄ BF ₄	L1	55	82
2	AgOAc	L1	25	31
3	Cu(CH ₃ CN) ₄ BF ₄	L2	25	31
4	Cu(CH ₃ CN) ₄ BF ₄	L3	29	61
5	Cu(CH ₃ CN) ₄ BF ₄	L4	80	95

All reactions were carried out with 0.40 mmol of **5e** and 0.20 mmol of **1a** in 2 mL CH₂Cl₂.

^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.

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

Based on these results and previous DFT studies [90,91], a stepwise Michael/Mannich mechanism [92–95] can be pro-

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-dipolar 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 enantioselectivities (up to 98% ee).

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Graphical Abstract

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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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亚甲胺叶立德参与的不对称1,3-偶极环加成构建含连续季碳中心的螺四氢吡咯衍生物

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摘要: Cu(I)催化的亚甲胺叶立德和亚环丙基乙酸乙酯参与的不对称 $endo$ -1,3-偶极环加成反应, 高效构建了多官能化、含有多个连续季碳中心的5-氮杂-[2,4]庚烷化合物。此反应具有广泛的底物适用性, α -取代的和 α -非取代的亚甲胺叶立德和亚环丙基乙酸乙酯都能很好的参与反应, 并以很高的产率、优秀的非对映选择性(95:5 $\rightarrow$ 98:2 d.r)和对映选择性(87%–98% ee)生成相应的在2,3,4位上含有连续季碳中心的螺四氢吡咯化合物。

关键词: 不对称催化; 季碳中心; 1,3-偶极环加成; 亚甲胺叶立德; 亚环丙基乙酸乙酯; 5-氮杂-[2,4]庚烷

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1. 前言

天然产物以及药物分子中全碳季碳中心的存在, 增加了这些分子的合成难度. 在过去的几十年中, 报道了多种构建手性的全碳季碳中心的方法^[1–7]. 但是通过简单的一步不对称转化构建连续的全碳季碳中心仍然是“在天然产物合成领域一个艰巨的挑战”^[8]. 最近^[9–11], 有关连续季碳中心的构建方法主要有: Pd催化的去CO₂不对称烯丙基烷基化反应(Pd-DAAA)^[12,13], Pd催化的5-乙烯基噁唑啉酮与三取代烯酮的不对称[3+2]环加成反应^[14], 连续的Michael加成反应^[15]以及3-溴代氧化吡啶与3-取代吡啶的烷基化反应^[16]等.

氮杂环的四氢吡咯类化合物是许多天然产物、药物分子以及一些具有生理活性分子中重要的结构单元, 且作为重要的分子骨架在有机合成中占据重要的地位^[17,18]. 同时, 近几年手性的四氢吡咯衍生物还用作为有机小分子催化剂^[19–21]. 而构建五元杂环最有效的方法就是各种1,3-偶极子和缺电子的烯烃或炔烃的1,3-偶极环加成反应^[22–27]. 虽然在手性辅剂诱导的1,3-偶极环加成反应中, 金属稳定的亚甲胺叶立德是构建手性四氢吡咯的一个很好的1,3-偶极子^[28–37], 但是对于催化量的手性催化剂催化的亚甲胺叶立德与缺电子烯烃的不对称1,3-偶极环加成反应, 至2002年才由Zhang课题组^[38]和Jørgensen课题组^[39]分别用Ag(I)/xylyl-FAP和Zn(II)/bisoxazoline催化剂实现. 自此之后, 亚甲胺叶立德与缺电子烯烃之间催化不对称1,3-偶极环加成反应受到了广泛的关注, 并合成了一系列多官能化的手性四氢吡咯化合物^[40–55]. 对于季碳中心, 特别是螺环的季碳中心的构建也有报道^[56–61]. 最近, Gong课题组^[62–64], Waldmann课题组^[65,66], Arai等^[67], Wang课题组^[68,69]以及我们课题组^[70–74]均通过亚甲胺叶立德与三取代的缺电子烯烃的催化不对称1,3-偶极环加成反应, 来合成含有手性螺环季碳中心四氢吡咯化合物; 但是, 通过该反应

来构建含有连续季碳中心的手性四氢吡咯化合物, 到目前为止尚未见报道.

在许多的天然产物以及药物分子(如萜类化合物和甾类化合物)中, 环丙烷结构都表现出重要的生理活性^[75–77]. 在过去的几十年里, 亚甲基环丙烷(MCP)一直是有机合成中重要的中间体^[78,79], 在金属催化的反应中, MCP由于三元环的环张力而使得它们一般经过开环反应后作为碳三合成子参与反应^[80,81]. 同样地, 在不开环的情况下, MCP能作为亲偶极体与硝酮、腈氧化物、叠氮、重氮化合物、腈叶立德以及脲等发生1,3-偶极环加成反应以及Diels-Alder反应等^[82].

我们已经报道了Cu(I)/TF-Biphosphos催化的亚甲胺叶立德与亚环丙基乙酸乙酯的不对称1,3-偶极环加成反应, 高效地构建了螺[环丙烷-3,3'-四氢吡咯]类化合物, 且具有非常高的 $endo$ 选择性和对映选择性(表1)^[71]. 通过螺碳原子将这两个具有生理活性的部分连接在一起的螺[环丙烷-3,3'-四氢吡咯], 也就是5-氮杂-螺[2,4]庚烷在一些抗菌试剂中起着重要的作用. 现已证明, 5-氮杂-螺[2,4]庚烷结构能够显著提高碳青霉烯类似物, 取代的噁唑啉酮类以及喹诺酮类抗生素对革兰氏阳性和革兰氏阴性细菌的作用^[83–89].

为了深入研究此反应, 本文通过Cu(I)/TF-Biphosphos催化的各种 α 取代的及 α 未取代的亚胺酯和各种 α 取代的亚环丙基乙酸乙酯的不对称1,3-偶极环加成反应, 高效地构建含有高达三个连续季碳中心的多官能化的手性5-氮杂-螺[2,4]庚烷化合物(图式1).

2. 实验部分

Cu(CH₃CN)₄BF₄/(S)-TF-Biphosphos催化的亚甲胺叶立德与亚环丙基乙酸乙酯的不对称1,3-偶极环加成反应的一般步骤如下. N₂保护下, 在25 mL反应管中, 将(S)-TF-Biphosphos (0.0072 mmol) 与 Cu(CH₃CN)₄BF₄ (2.0 mg, 0.006 mmol)溶于2 mL二氯甲烷中, 并在室温下

搅拌1 h. 然后依次加入亚胺酯(0.40 mmol), 三乙胺(0.03 mmol)和亚环丙基乙酸乙酯 (0.20 mmol), 以TLC监测反应. 反应完成后, 硅藻土过滤, 将滤液旋干得粗产物, 通过¹H NMR来确定d.r.值, 柱层析纯化得到环加成产物, 产物的ee值由HPLC测定.

3. 结果与讨论

3.1. Cu(I)/TF-BipharmPhos催化的 α 取代的亚甲胺叶立德2与亚环丙基乙酸乙酯1a的[3+2]环加成反应

基于 α 未取代的亚胺酯与亚环丙基乙酸乙酯1a之间良好的反应结果^[71], 我们将 α 取代的亚胺酯作为1,3-偶极子前体参与反应. 反应时, α 取代的亚胺酯由于亚胺与羧酸酯之间的亚甲基的酸性减弱使得它们的反应活性降低, 导致它们作为偶极子参与反应的困难更大, 更具有挑战性. 尽管含有手性季碳中心的四氢吡咯化合物具有重要的作用, 但是 α 取代的亚胺酯参与催化不对称1,3-偶极环加成的例子并不多. 令人欣慰的是, 在此Cu(I)/TF-BipharmPhos (**L1**)催化的亚甲胺叶立德与亚环丙基乙酸乙酯1a的不对称1,3-偶极环加成反应中, α 取代的亚胺酯也能很好地参与反应, 如表2所示. 在最佳反应条件下, 由 α 取代的氨基酸, 如丙氨酸、2-氨基丁酸、亮氨酸、苯甘氨酸以及2-氨基苯丙酸衍生的 α 取代亚胺酯都能参与反应, 且能以很高的非对映选择性和对映选择性获得含有两个(其中一个为手性的季碳中心)的环加成产物.

3.2. 亚甲胺叶立德2a与 α 取代的亚环丙基乙酸乙酯1的[3+2]环加成反应

为了进一步拓展反应底物的适用范围, 我们尝试具有较大空间位阻的亲偶极体, 因此, 将 α 取代的亚环丙基乙酸乙酯作为亲偶极体用于Cu(I)/TF-BipharmPhos (**L1**)催化的亚甲胺叶立德参与的不对称1,3-偶极环加成反应中, 从而在螺[环丙烷-四氢吡咯]的3位和7位上构建两个连续的季碳中心. 如表3所示, 在最佳的反应条件下, 我们成功地将亲偶极体的范围拓展到 α 取代的亚环丙基乙酸乙酯. 亚环丙基乙酸乙酯的 α 位上有烷基取代基[如甲基(**1b**)、乙基(**1c**)、正丙基(**1d**)和苄基(**1e**)]以及芳基取代基[苯基(**1f**)]等在Cu(I)/TF-BipharmPhos (**L1**)的催化下, 都可以与亚胺酯(**2a**)发生不对称1,3-偶极环加成反应, 且目标产物的产率、非对映选择性和对映选择性都比较高(>98:2 d.r., 92%–96% ee). 这是第一例关于四取代的缺电子烯烃与亚甲胺叶立德的催化不对称1,3-偶极环加成反应. 通过单晶衍射测定**3ca**的对甲苯磺酰化产物**4**的绝对构型, 环加成产物的绝对构型确定为(4*R*,6*R*,7*R*).

3.3. Cu(I)/TF-BipharmPhos催化的高丝氨酸内酯衍生的环状亚胺5与亚环丙基乙酸乙酯1a的[3+2]环加成反应

为了继续深入拓展Cu(I)/TF-BipharmPhos催化的亚甲胺叶立德与亚环丙基乙酸乙酯的不对称1,3-偶极环加成构建螺[环丙烷-3,3'-四氢吡咯]反应底物的适用范围, 我们还将由高丝氨酸内酯衍生的环状亚胺作为偶极子, 以期在手性四氢吡咯环上的2位和3位上构建两个连续的季碳中心, 且获得同时含有环丙烷、四氢吡咯和丁内酯结构的三环化合物.

在上文最佳反应条件 (3 mol%的Cu(CH₃CN)₄BF₄/TF-BipharmPhos (**L1**)为催化剂, 15 mol%的三乙胺为碱, DCM为溶剂, -20 °C)下, 由高丝氨酸内酯和苯甲醛合成的环状亚胺**5e**与亚环丙基乙酸乙酯**1a**发生[3+2]环加成反应, 以中等收率(78%)和82%的ee获得了目标产物. 因此, 我们需要重新优化反应条件, 结果如表4所示. 在室温时, 3 mol%的Cu(CH₃CN)₄BF₄/TF-BipharmPhos (**L4**)的催化下反应结果最好(**6ae**, 产率80%, ee值95%).

在重新确定的最佳反应条件下, 我们拓展了环状亚胺的适用范围(表5). 亚环丙基乙酸乙酯**1a**能够与各种取代的环状亚胺发生[3+2]环加成反应且目标产物的产率(40%–82%)、非对映选择性(>98:2的d.r.值)和对映选择性(87%–96%)都比较高. 螺四氢吡咯的10位上的取代基可以是芳基[如给电子基团(表5, 实验1–4, **6aa**–**6ad**)、电中性基团(表5, 实验5, **6ae**)和拉电子基团(表5, 实验6–9, **6af**–**6ai**)]以及杂环的芳基[如2-咪唑(**6ak**)和2-噻吩(**6al**)]. 1-萘醛衍生的亚胺酯也能反应并得到70%的收率以及90% ee. 但是烷基取代的环状亚胺在此反应中的活性太低, 没有获得相应的环加成产物. 螺环化合物的绝对构型为(4*R*,10*S*,11*R*).

3.4. 构建含有三个连续季碳中心的螺四氢吡咯化合物的催化不对称1,3-偶极环加成反应

最后, 我们尝试构建含有三个连续季碳中心, 其中两个是手性季碳中心的手性螺[环丙烷-3,3'-四氢吡咯]化合物. 在Cu(CH₃CN)₄BF₄/TF-BipharmPhos (**L1**或**L4**)的催化下, α 取代的亚胺酯**2n**和环状亚胺**5e**分别与 α 苄基取代亚环丙基乙酸乙酯**1e**发生[3+2]环加成反应(图式2), 可以获得相应的目标产物, 且反应的非对映选择性和对映选择性(ee值: **7**, 96%; **8**, 93%)都很高, 尽管产率中等. 这是首次通过催化不对称1,3-偶极环加成反应构建含有三个连续季碳中心的四氢吡咯衍生物.

3.5. 可能的反应过渡态

根据反应产物的绝对构型以及我们对金属

/TF-BiphamPhos催化体系在1,3-偶极环加成反应作用的理解和密度泛函(DFT)计算^[90,91],我们提出了Michael/Mannich的分步过程及其可能的过渡态模型^[92–95],如图2所示.由于亚胺酯的芳基与手性配体的磷原子上的芳基具有很大的空间位阻作用,使得新形成的亚甲胺叶立德与金属中心只能以图中所示的最佳方式配位,为了减少反应的阻力以及提高反应的选择性,随后亚环丙基乙酸乙酯作为亲偶极体只能进攻络合物中空间位阻比较小的一面,即C=N的*Si*面,从而获得*endo*构型的环加成产物.亲偶极体中的C=O与配体TF-BiphamPhos中的NH₂可能形成氢键,这样也能更好的稳定反应的过渡态^[96,97].

4. 结论

发现了一个高效、简单快捷的方法构建手性的*endo*构型的5-氮杂-螺[2,4]庚烷衍生物.即铜(I)催化的各种 α 取代的亚甲胺叶立德与 α 取代和无取代的亚环丙基乙酸乙酯的不对称1,3-偶极环加成反应.该方法为构建含有多达三个连续季碳中心的多取代5-氮杂-螺[2,4]庚烷提供了简单直接的方法,且可以高立体选择性的获得同时含有环丙烷、四氢吡咯和丁内酯结构的三环两螺原子结构的手性四氢吡咯化合物.

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