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Endo-Selective Construction of Spiro-[butyrolactone-pyrrolidine] via Ag(I)/CAAA-Amidphos-Catalyzed 1,3-Dipolar Cycloaddition between Azomethine Ylides and α-Methylene-γ-Butyrolactone

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Received: 8 December 2019; Accepted: 23 December 2019; Published: 25 December 2019

Abstract: Construction of spirocyclic pyrrolidines bearing a spiro quaternary stereocenter is an enormous challenge in synthetic organic chemistry. In this report, we introduce a Ag(I)/CAAA-amidphos-catalyzed enantioselective 1,3-dipolar cycloaddition between azomethine ylides and α-methylene-γ-butyrolactone as an effective strategy for the construction of excellent *endo*-selective spiro-[butyrolactone-pyrrolidine] derivatives. Meanwhile, the catalytic system was also successfully applied in the three-component one-pot reaction of azomethine ylides formed in situ under the action of *N*,*N*′-diisopropylcarbodiimide serving as a dehydrator. Under the optimal conditions, *endo*-pyrrolidine derivatives bearing a spiro quaternary stereocenter were obtained with high to excellent yields (up to 95% yield) and enantioselectivities (up to 93% ee).

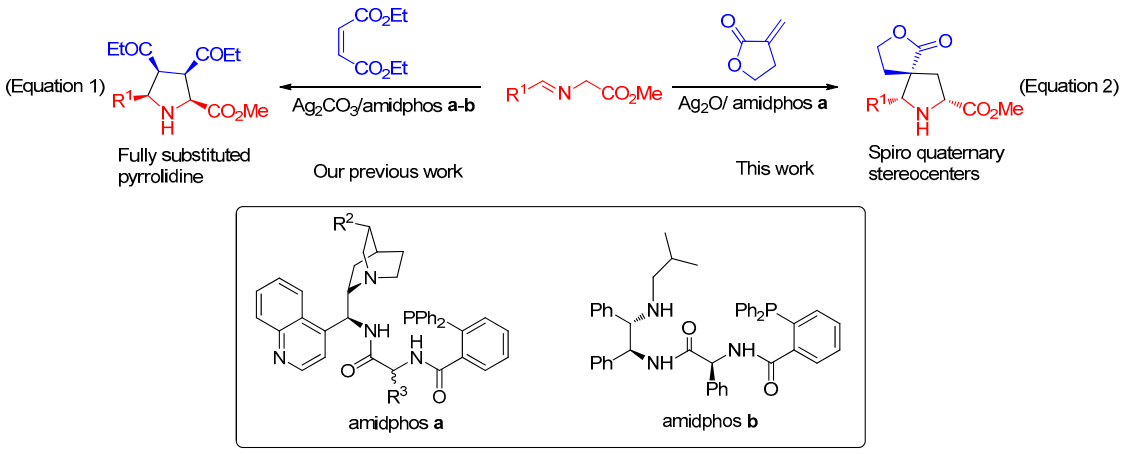
Keywords: *endo*-selective; 1,3-dipolar cycloaddition; CAAA-amidphos; azomethine ylides; spirocyclic pyrrolidines

1. Introduction

Highly substituted pyrrolidine motifs widely exist in natural alkaloids and bioactive molecules [1,2]. In particular, spirocyclic pyrrolidine compounds bearing a spiro quaternary stereocenter at the 4-position are especially useful [3,4]. In this context, various synthetic methods have been utilized for the chiral synthesis of spirocyclic pyrrolidine skeletons in recent years. Among most approaches, the 1,3-dipolar cycloaddition between azomethine ylides and electron-deficient alkenes is one of the most effective tools for building such skeletons with high to excellent *endo*/*exo*-diastereo- and enantioselectivities [5–8]. Since the first asymmetric version of synthesis of spirooxindole-pyrrolidine derivatives was realized by Gong et al., via chiral BINOL-derived phosphoric acids, to catalyze the 1,3-dipolar cycloaddition of azomethine ylides formed in situ with *N*-Ac 2-oxoindolin-3-ylidenes [9]. A relatively broad range of dipolarophiles (such as 2-oxoindolin-3-ylidenes [10–15], cyclopropylidene acetates [16], 2-alkylidenecycloketones [17,18], α-alkylidene succinimides [19], and 5-alkylidene thia(oxa)zolidine-2,4-diones [20]) have been applied in the azomethine ylides-involved 1,3-dipolar cycloaddition to construct structurally and stereochemically rich spirocyclic pyrrolidine derivatives in the past decade. In contrast, little attention has been paid to α-methylene-γ-butyrolactone as

a key electron-deficient alkene in the asymmetric 1,3-dipolar cycloaddition to construct the highly substituted spirocyclic [butyrolactone-pyrrolidine] skeletons with multiple contiguous stereocenters, although such skeletons with the lactone moiety have important biological activities. To the best of our knowledge, apart from a few of limited racemic examples [21–23], only an asymmetric version has been reported by Wang et al. on the construction of *exo*-selective spiro-[butyrolactone-pyrrolidine] via Cu(I)/DTBM-BIPHEP-catalyzed α-methylene-γ-butyrolactone-involved process so far [24]. It is thus necessary to realize the preparation of such medicinally useful and synthetically challenging molecules with different stereochemical selectivities.

Recently, we have made a breakthrough by exploiting multifunctional Ag_2CO_3/amidphos catalytic system with different scaffolds of cinchona alkaloids, chiral 1,2-diphenylethylenediamines and α-amino acids to cooperatively catalyze the 1,3-dipolar cycloadditions between α-imino esters and diethyl maleate affording excellent *endo*-selective adducts with high enantioselectivities (Scheme 1, Equation (1)) [25–28]. (See Supplementary Materials). Encouraged by these findings, we envisaged that such a catalytic system may also be applied in the α-methylene-γ-butyrolactone-involved asymmetric 1,3-dipolar cycloaddition. Herein, we firstly described the Ag(I)/CAAA-amidphos-catalyzed 1,3-dipolar cycloaddition between α-imino esters and α-methylene-γ-butyrolactone as well as three-component one-pot reaction of α-imino esters formed in situ, affording excellent *endo*-selective spirocyclic [butyrolactone-pyrrolidine] with high levels of enantioselectivities (Scheme 1, Equation (2)).



Scheme 1. Azomethine ylides-involved the asymmetric 1,3-dipolar cycloadditions.

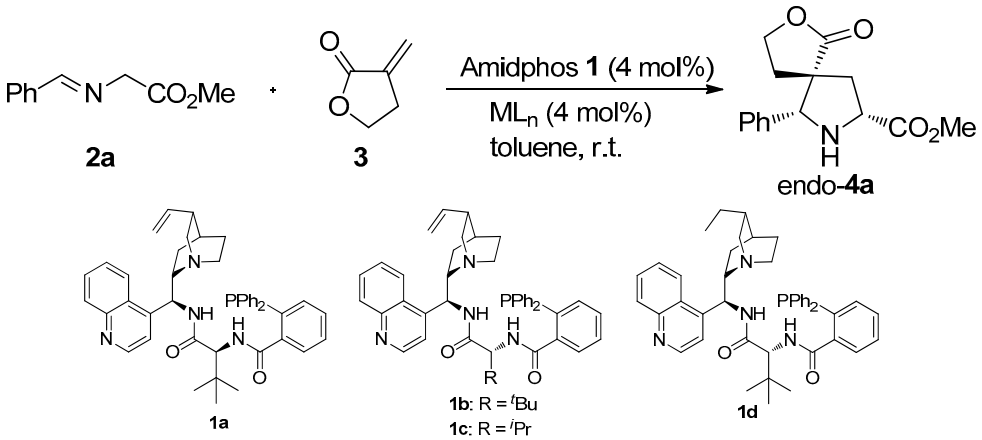
2. Results and Discussion

2.1. Optimization of the 1,3-Dipole Cycloaddition Reaction Conditions

We first investigated the 1,3-dipolar cycloaddition of α-imino ester **2a** and α-methylene-γ-butyrolactone **3** catalyzed cooperatively by silver(I) oxide and different CAAA-Amidphos **1a–d** (Table 1, entries 1–4). Through the screening of amidophosphanes, we found that the combination of Ag_2O and the amidphos **1d** gave relatively satisfactory reactivity and enantioselectivity (Table 1, entry 4). In order to achieve higher enantioselectivities in the process, different metal salts, such as Ag_2CO_3, AgF, AgOAc, AgOTf, and $Cu(OTf)_2$, were screening for the process (entries 5–9). Disappointingly, the yields and enantioselectivities of *endo*-**4a** adduct have not been greatly improved when compared with the catalytic system Ag_2O/**1d**. Next, when the reaction temperature was reduced to −20 °C, the enantioselectivity was increased to 92% ee, albeit with a slightly decreased yield and a prolonged reaction time (6 h, 90% yield, entry 10). Gratifyingly, when 20 mol% H_2O was added, the reaction rate was accelerated to 0.7 h with a slightly increased enantioselectivity (93% ee, entry 11). We speculated the water (H_2O) reacted with silver(I) oxide (Ag_2O) to produce the strong base silver(I) hydroxide (AgOH), which could promote deprotonation of the α-imino esters to generate the azomethine ylide and accelerate the reaction process. Therefore, the optimal conditions for the asymmetric 1,3-dipolar

cycloaddition of α-imino ester **2** and α-methylene-γ-butyrolactone **3** were established as 2 mol% Ag_2O/4 mol% **1d**/20 mol% H_2O in toluene at −20 °C.

Table 1. Optimization of the reaction conditions between α-imino ester **2a** and α-methylene-γ-butyrolactone **3** [a].

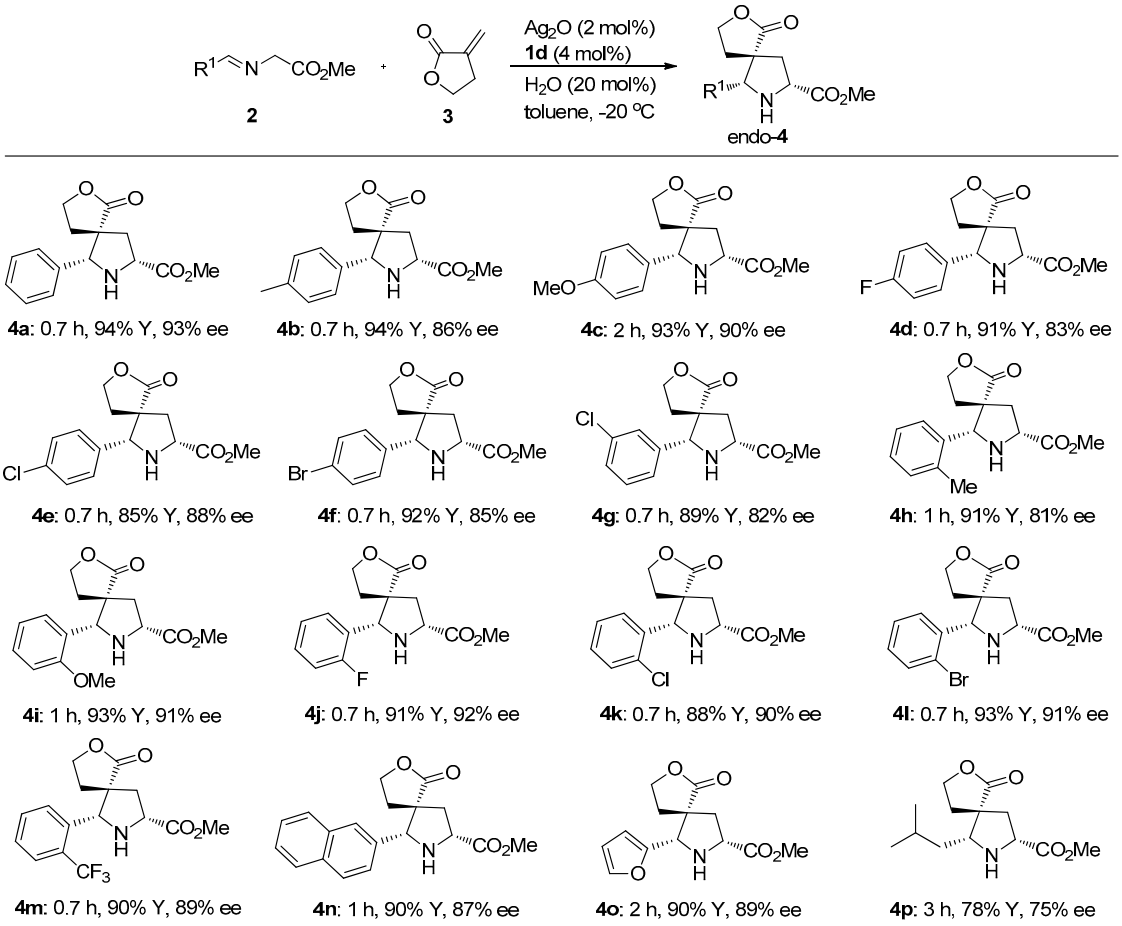


Entry	Precat.	ML_n	Temp. [°C]	Time [h]	Yield [%] [b]	Ee [%] [c]
1	**1a**	Ag_2O	rt	2.5	74	14
2	**1b**	Ag_2O	rt	2	92	84
3	**1c**	Ag_2O	rt	2	91	76
4	**1d**	Ag_2O	rt	2	93	87
5	**1d**	Ag_2CO_3	rt	2	78	84
6	**1d**	AgF	rt	2	80	45
7	**1d**	AgOAc	rt	18	61	4
8	**1d**	AgOTf	rt	24	trace	-
9	**1d**	$Cu(OTf)_2$	rt	24	trace	-
10	**1d**	Ag_2O	−20	6	90	92
11 [d]	**1d**	Ag_2O	−20	0.7	94	93

[a] Reaction conditions: Imino ester **2a** (0.30 mmol), α-methylene-γ-butyrolactone **3** (0.20 mmol), ML_n (4 mol%), amidphos **1** (4 mol%). [b] Isolated yield based on **2a**. [c] Determined by HPLC. [d] H_2O (20 mol%) was added.

2.2. Study on Substrate Adaptability

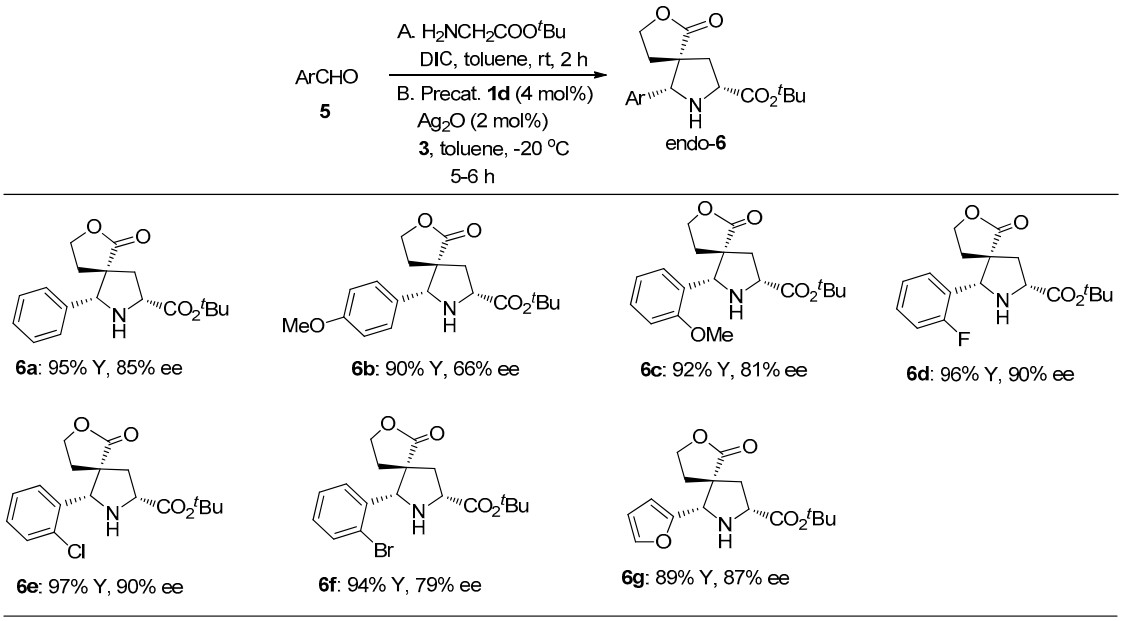
Under the optimal reaction conditions, the adaptability of substrates was explored. As shown in Scheme 2, α-imino esters **2a**–**n** from aromatic aldehydes with different electronic properties and steric hindrance reacted with α-methylene-γ-butyrolactone **3** to provide the exclusively *endo*-selective spirocyclic pyrrolidines **4a**–**n** with high to excellent yields (85%–94%) and enantioselectivities (81%–93% ee) in the presence of the catalytic Ag_2O/**1d**. Notably, the iminoesters derived from 2-substituted aromatic aldehydes afforded relatively high enantioselectivities except for the iminoester 2h. When R^1 was the heteroaromatic group, the *endo*-**4o** was also successfully obtained with 90% yield and 89% enantioselectivity in 2 h. Delightedly, the primary alkyl iminoester **2p** derived from 3-methylbutanal was also tolerated, affording the desired *endo*-**4p** adduct with moderate yield and enantioselectivity, albeit for requiring prolonged reaction time (4 h, 78% yield, 75% ee).



Scheme 2. Ag_2O/**1d**-catalyzed cycloaddition of various α-imino esters **2a**–**p** with **3** [a]. [a] Reaction conditions: Imino ester **2** (0.30 mmol), **3** (0.20 mmol), Ag_2O (2 mol%), precat. **1d** (4 mol%), isolated yield, and ee value determined by HPLC.

2.3. Study on the Construction of Spiro Pyrrolidines by the Three-Component One-Pot Method

We next transferred our attention to evaluate the three-component one-pot 1,3-dipolar cycloaddition of the in situ generated α-iminoesters from tert-butyl glycinate and different aromatic aldehydes under the action of *N*,*N*′-Diisopropylcarbodiimide (DIC) serving as a dehydrator with α-methylene-γ-butyrolactone **3** [29,30]. As shown in Scheme 3, arene-substituents with different electronic properties and steric hindrance were well tolerated and the desired *endo*-**6a**–**6f** were obtained in one-pot process with excellent yields (92%–97%) and moderate to high enantioselectivities (66%–90% ee). Notably, when Ar was 2-furyl group, the corresponding sipro *endo*-**6g** was also obtained with 89% yield and 87% enantioselectivity.



Scheme 3. Ag_2O/**1d**-catalyzed three-component reaction of α-imino esters generated in situ [a]. [a] Reaction conditions: Aldehyde **5** (0.30 mmol), tert-butyl glycinate (0.30 mmol), *N*,*N*′-Diisopropylcarbodiimide (DIC) (0.30 mmol), **3** (0.20 mmol), Ag_2O (2 mol%), precat. **1d** (4 mol%), isolated yield, ee value determined by HPLC.

3. Materials and Methods

3.1. Materials

Unless noted otherwise, ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer (Bruker Biospin, Fällanden, Switzerland) in $CDCl_3$. $CDCl_3$ served as the internal standard (δ = 7.26) for ^1H NMR and (δ = 77.0) for ^{13}C NMR. Diastereomeric ratios were determined from crude ^1H NMR. Chiral HPLC was performed on a Agilent 1260 apparatus (Agilent Technologies, California, US) equipped with a spectrophotometric detector (monitoring at 205–230 nm) with Daicel chiral AS-H and AD-H columns (Daicel Chemical Industries Co., Ltd., Tokyo, Japan). All solvents are used after reevaporation. The α-methylene-γ-butyrolactone were purchased from Adamas-beta® Co., Ltd. (Shanghai, China). Other commercially available reagents were not further purified. All reactions were monitored by thin-layer chromatography (TLC) plates (Qingdao Marine Chemistry Company, Qingdao, China). Flash column chromatography was completed by using silica gel 200–300 (particle size 0.0040–0.0750 mm) (Qingdao Marine Chemistry Company, Qingdao, China). The absolute configuration of endo-**6e** was determined by X-ray diffraction analysis (Bruker AXS, Karlsruhe, Germany), and those of other products were deduced on the basis of these results.

3.2. General Synthesis Methods of **4a**–**4p**

To a solution of precat. **1d** (5.57 mg, 0.008 mmol) in toluene (1.4 mL) was added Ag_2O (0.92 mg, 0.004 mmol), followed by water dropwise (0.72 mg, 0.04 mmol) at room temperature under N_2 atmosphere. After the reaction mixture was stirred for 1 h, α-imino ester **2** (0.30 mmol) and α-methylene-γ-butyrolactone **3** (19.6 mg, 0.20 mmol) were successively added at −20 °C. The reaction was monitored by TLC plate, and the residue was purified by column chromatography on silica gel (gradient, ethyl acetate:petroleum ether, 20:80 to 30:70) to afford the spiro *endo*-**4** adducts.

3.3. General Synthesis Methods of **6a**–**6g** *via Three-Component "One-Pot"*

To a solution of tert-butyl glycine (39.3 mg, 0.30 mmol) in toluene (1.0 mL) was added the aldehyde **5** (0.30 mmol) and *N*,*N*′-diisopropylcarbodiimide (37.8 mg, 0.30 mmol), which was stirred for 2 h at room temperature. Then, a solution of precat. **1d** (5.57 mg, 0.008 mmol) and Ag_2O (0.92 mg, 0.004 mmol) in toluene (0.5 mL) stirred for 1 h, was mixed with the above solution, followed by α-methylene-γ-butyrolactone **3** dropwise (19.6 mg, 0.20 mmol) at −20 °C. The reaction was monitored by TLC plate, and the residue was purified by column chromatography on silica gel (gradient, ethyl acetate:petroleum ether, 20:80 to 30:70) to afford the spiro *endo*-**6** adducts.

4. Conclusions

In conclusion, we have developed the Ag(I)/CAAA-amidphos **1d**-catalyzed 1,3-dipolar cycloaddition between azomethine ylides and α-methylene-γ-butyrolactone, achieving excellent *endo*-selective Spiro-[butyrolactone-pyrrolidine] derivatives in moderate to excellent yields (75%–94%) and enantioselectivities (78%–93%) under mild conditions. Furthermore, the three-component one-pot reaction of α-imino esters formed in situ, and α-methylene-γ-butyrolactone was also successfully realized by the catalytic system under the action of DIC. Further investigations on mechanistic aspects and other applications are in progress.

Supplementary Materials: The following are available at http://www.mdpi.com/2073-4344/10/1/28/s1, experimental procedures and detailed characterization data of all new compounds.

Author Contributions: H.W. and Q.H. designed the experiments of the project; Y.Y., X.S., Y.W. and K.C. performed the experiments; Y.Y. drafted this manuscript; H.W. proofread the manuscript and supervised the studies. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by National Nature Science Foundation of China (Nos. 21202042, 51374103, 51674114) and the Hunan Provincial Natural Science Foundation of China (Nos. 2017JJ2067), and the Zhuzhou Municipal Science and Technology Program and Undergraduate Innovation Fund of Hunan Province.

Conflicts of Interest: The authors declare no conflict of interest.

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