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Aromatic-Amide-Derived Nonbiaryl Atropisomer as Highly Efficient Ligand for Asymmetric Silver-Catalyzed [3 + 2] Cycloaddition

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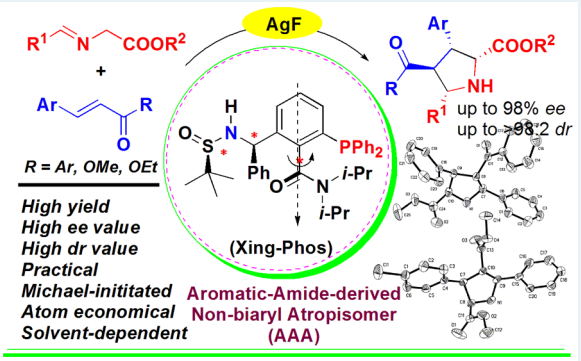
Supporting Information

ABSTRACT: In this work, we have successfully determined that the aromatic amide-derived nonbiaryl atropisomer/silver complex (silver-Xing-Phos) is an effective catalyst system for the solvent-dependent *exo*-selective cycloaddition of glycine aldimino esters with chalcones or less-reactive methyl cinnamates to give the corresponding chalcone- or cinnamate-derived pyrrolidines with multiple stereogenic centers in good yields and high diastereoselectivities as well as excellent enantioselectivities. Remarkably, it is the first example of highly enantioselective silver-catalyzed [3 + 2] cycloaddition of methyl cinnamates with glycine aldimino esters.



KEYWORDS: *asymmetric catalysis, pyrrolidines, silver, homogeneous catalysis, atropisomers, cycloaddition*

The functionalized pyrrolidine ring is an important core structure of numerous five-membered azaheterocyclic-unit-containing natural products and also considered to be a privileged scaffold in medicinal chemistry because its derivatives are valuable backbones for the discovery of new biologically active molecules or therapeutic agents.[1] As a result, the enantioselective construction of pyrrolidine rings has drawn considerable attention from synthetic chemists in recent years.[2] Among these, the asymmetric metal-catalyzed [3 + 2] cycloaddition was proved to be one of the most convergent and atom-economical protocols for the stereoselective synthesis of pyrrolidine derivatives.[3] Since the pioneering work of employing stoichiometric amounts of chiral metal complex reported by Grigg and Allway,[4] as well as the first catalytic asymmetric cycloaddition with aldimino esters reported by Zhang and co-workers,[5] much attention have been paid to the development of enantioselective [3 + 2] cycloaddition over the past decade, in which various activated olefins, such as malonates, maleimides, acrylates, nitroalkenes, and complicated alkenes bearing electron-withdrawing groups, have been utilized as dipolarophiles in such asymmetric [3 + 2] cycloaddition reactions.[6] However, both chalcones and alkyl cinnamates, which have been employed widely for the catalytic synthesis of chiral carbonyl compounds via conjugate addition reactions, have not yet been successfully applied as dipolarophiles in the catalytic asymmetric [3 + 2] cycloadditions with glycine imino esters. Only limited examples of cycloaddition reaction have been reported for the synthesis of functionalized pyrrolidines involving enones or alkyl cinnamates as the dipolarophiles so far.[7−11] Furthermore, the sole example of catalytic asymmetric [3 + 2] cycloaddition of alkyl cinnamate with aldimino ester was reported by Kobayashi et al. in 2008,[11] in which the moderate ee value of the desired product was achieved in the presence of calcium catalyst system (from $Ca(OiPr)_2$ and chiral bisoxazoline ligand). Interestingly, there is no report on the enantioselective synthesis of *exo*-adducts through silver-catalyzed cycloaddition of chalcones with aldimino esters so far. Thus, accordingly, the development of new methods for the enantioselective construction of chalcone- or cinnamate-derived pyrrolidines with high level of diastereo- and enantioselectivity is still in great demand.

Our initial investigation began with the catalytic asymmetric cycloaddition of chalcone **1a** and glycine aldimino ester **2a** in the presence of Xing-Phos[12] and AgF (Scheme 1 and Table S1 of Supporting Information (SI)). Although good yield (>95%) was obtained under the reaction conditions, disappointingly, the pyrrolidine adduct was obtained in poor diastereoselectivity (see Scheme 1, *exo/endo/endo'/exo'* = 52/39/9/0) and varied enantioselectivity for the three diastereoisomers (94% ee/64% ee/49% ee/-). This result supported the binuclear silver-Xing-Phos (CCDC 1042429)[12] exhibited poor activity and selectivity under the reaction conditions. The solvent effect on the

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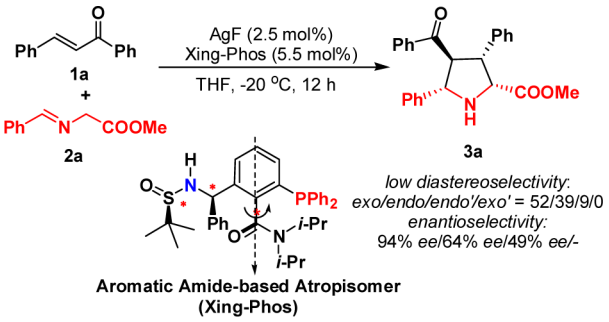
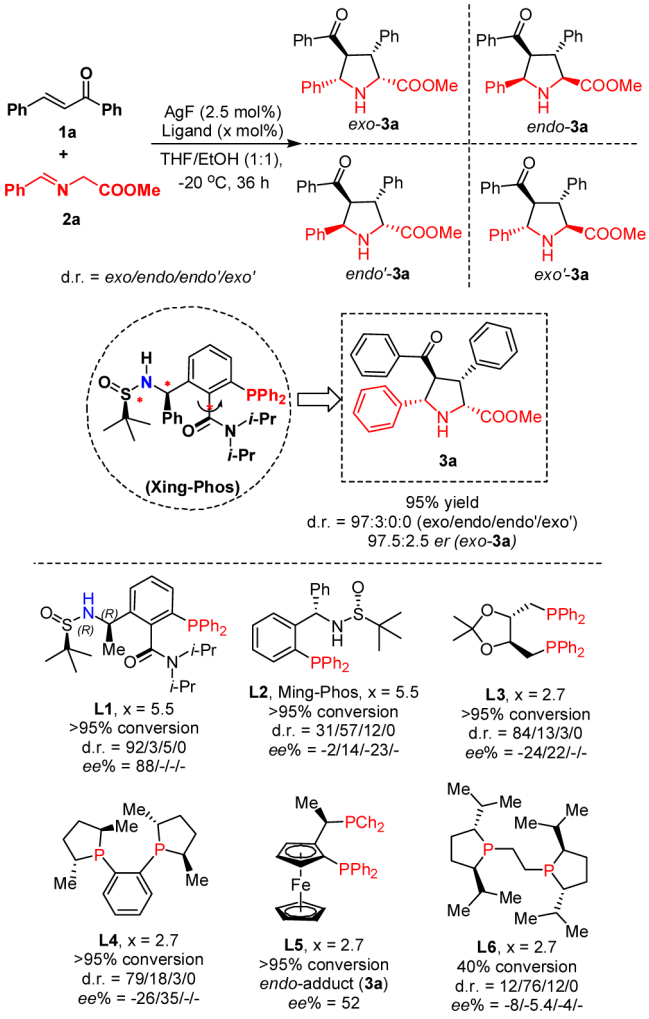
Scheme 1. Initial Result in the Asymmetric Silver-Catalyzed Cycloaddition of Chalcone 1a with Glycine Aldimino Ester 2a in the Presence of Aromatic Amide-Derived Non-Biaryl Atropisomer (Xing-Phos)



catalytic activity and the enantioselectivity of the silver catalyst system in this reaction are summarized in Table S1 (see SI). The enantio- and *exo/endo*-selectivity proved obviously dependent on the reaction medium. Most of solvents evaluated in this work, such as Et_2O, DCM, *tert*-butylmethyl ether, and toluene, gave promising enantioselectivities, but the diastereomeric ratios was quite poor. Notably, despite the relatively similar polarity of 1,4-dioxane in comparison to that of other ethers, the 1,4-dioxane significantly does impact the *exo/endo* ratio. This remarkably solvent-controlled diastereoselectivity stands in marked contrast to the tetrahydrofuran (*endo*-selective in dioxane versus *exo*-selective in THF). Gratifyingly, we found that alcoholic solvent gave high diastereoselectivity (up to 99:1 *exo/endo*) and good enantioselectivity (95.5:4.5 *e.r.* in EtOH) in this reaction. We suggested that the polar protic solvent with strong hydrogen-bonding-accepting properties might interrupt the formation of the weak intermolecular interaction between two AAA ligands, whereas nonprotic solvents have a stabilizing effect for dimeric silver-Xing-Phos complex. We have also found that the binuclear silver-Xing-Phos could be transferred into mononuclear silver complex with two Xing-Phos molecules with the aid of protic alcohol (see ESI-MS analysis of Figure S1), and thus, the noncovalent interaction came from solvent and Xing-Phos should not be neglected in the asymmetric cycloaddition reaction.

Encouraged by these results, we next investigated the combinational use of ethanol and THF for this reaction. To our delight, employing the ethanol/THF (1:1) as solvent, the cycloadduct **3a** was exclusively obtained in good yield (>95%) with excellent enantioselectivity (97.5:2.5 er) albeit sacrificed diastereoselectivity (96:4 *exo/endo*) in comparison to that in ethanol. The excellent result with high *exo/endo* ratio and enantioselectivity led us to test the possibly privileged role of Xing-Phos in this reaction through the controlled experiment with other phosphine ligands under the similar reaction conditions (−20 °C, 2.5 mol % AgF, 5.5 mol % ligand (Ag:L = 1:2.2), in EtOH/THF (1:1)). As expected, aromatic amide-derived ligand (**L1**), several representative ligands (**L2-L6**), such as Ming-Phos (**L2**)[13] and other commercial available P-ligands (**L3-L6**), shown in Scheme 2 provided varied diastereo- and enantioselectivities (2−88% ee for *exo*-**3a**), which indicated the stereoselectivity in this reaction is significantly dependent on the nature of the chiral ligand. These results clearly supported the powerful potential of Xing-Phos as both ligand and organic promoter in this enantioselective cycloaddition reaction.

Scheme 2. Ligand Survey for Silver-Catalyzed Cycloaddition of 1a and 2a



Having established the optimal reaction conditions with present silver-Xing-Phos, we explored various chalcones to examine the catalytic activation of Xing-Phos in the silver-catalyzed cycloaddition reactions. All the experimental results in this catalytic asymmetric [3 + 2] cycloaddition are summarized in Scheme 3. It can be seen that a wide range of aldimino esters bearing electron-rich, electron-neutral, or electron-deficient groups on the phenyl ring, reacted with chalcones to afford the corresponding *exo*-**3** in high yields (80−97%) and excellent enantioselectivities (88−96% ee) as well as good diastereoselectivities (up to >98/2 *exo/endo*). Noticeably, almost the same level of enantioselectivities and yields was observed regardless of the different substituent patterns on the aromatic ring, as well as the electron-withdrawing or electron-donating nature of the substituents. Thus, as shown in Scheme 3, all the desired products (23 examples) in this reaction were obtained in good results. Notably, the relative and absolute configuration of the cycloadduct **3a** was determined to be (2*R*,3*R*,4*S*,5*S*) by X-ray diffraction analysis (CCDC 1401264).

Remarkably, to highlight the usability of aromatic amide-derived nonbiaryl atropisomer/silver complex (silver-Xing-Phos) in the catalytic asymmetric cycloaddition with challenging and less reactive alkenes, we explored the [3 + 2] cycloaddition of alkyl cinnamates and glycine aldimino esters for synthesis of 1,3-diester-containing pyrrolidines. In 2008,

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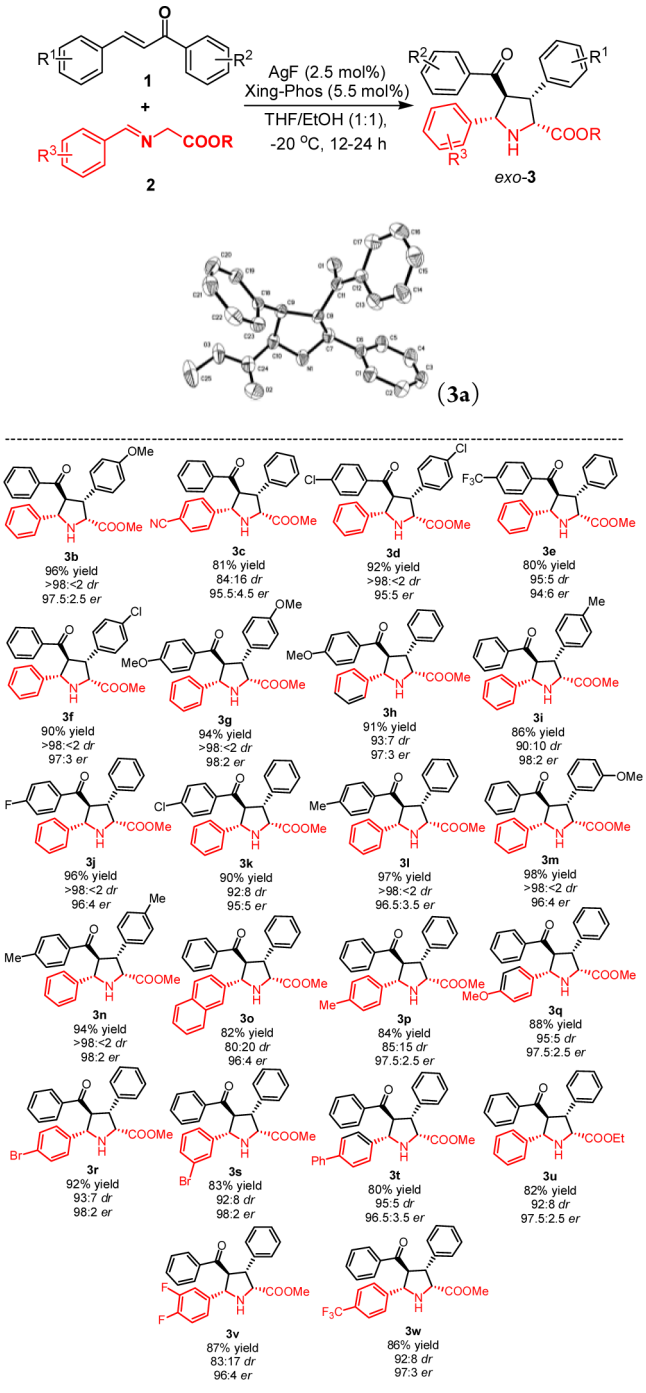
Scheme 3. Asymmetric Cycloaddition of Chalcones with Glycine Aldimino Esters Catalyzed by Xing-Phos-AgF system



Kobayashi and co-workers reported the first enantioselective and *endo*-selective cycloaddition of challenging ethyl cinnamate with glycine Schiff base; however, the enantioselectivity did not yet reach a sufficient level (91% yield and 61% ee).[11] This fact could be at least partly explained by the challenge or difficulty in controlling the stereoselectivity of cycloaddition due to the presence of two coordinately similar ester groups on two substrates, respectively. Herein, we describe the first silver-catalyzed synthesis of cinnamate-derived pyrrolidines with *exo*-selectivity through the catalytic asymmetric cycloaddition of less-reactive alkyl cinnamates with glycine aldimino esters.

Guided by the above results and the application of silver-Xing-Phos, we began our optimization of reaction conditions by testing the effect of solvents and additives (see Table S2 of Supporting Information). As expected, the [3 + 2] cycloaddition of methyl cinnamate with glycine aldimino ester was quite sluggish under the optimization reaction conditions for chalcones, which further confirmed the less-reactive activity of alkyl cinnamates in this reaction. On the basis of the screening studies of the catalytic asymmetric cycloaddition of methyl cinnamate **4a** with glycine aldimino ester **2a** (Table S2), the major findings including: 1) The addition of inorganic base to promote the addition and cyclization reaction is necessary. It was found that potassium carbonate was a suitable base in this reaction; 2) Similarly to the catalytic asymmetric cycloaddition of chalcones with glycine aldimino esters, the silver-catalyzed [3 + 2] cycloaddition of methyl cinnamate **4a** with Xing-Phos as the ligand was sensitive to the solvent. Gratifyingly, under the optimized reaction conditions, none of the other diastereoisomers (*exo′* and *endo′*-**5a**) was detected, and the reaction reached completion in THF/MeOH (1:1) at −20 °C and delivered a high level of diastereoselectivity (*exo/endo* = 96/4) with excellent enantioselectivity (>90% *ee*).

Having observed that highly efficient silver-catalyzed synthesis of cinnamate-derived pyrrolidine can be achieved with highly stereoselective control in the presence of Xing-Phos, we decided to investigate the substrate scope of this process (Scheme 4). We were pleased to find that a wide array of methyl cinnamates containing methyl and chloride groups on aromatic rings as well as glycine aldimino esters derived from aromatic aldehydes bearing electron-deficient and electron-neutral substituents on the aryl rings reacted smoothly with glycine aldimino esters. Moreover, the enantioselectivities of the desired products were extremely high (90−98% ee). This result also supports the crucial role of Xing-Phos in this reaction because of the high level of enantio- and diastereoselectivity in this reaction. The absolute configuration of the product **5l** was determined to be (2*R*,3*R*,4*S*,5*S*) by using of X-ray crystallographic analysis of *exo*-**5l** (CCDC 1401265). In addition, superior effects on activity and stereoselectivity were confirmed in the mixed solvent (THF/MeOH = 1:1) illustrating the unique features of Xing-Phos, in particular the hemilability and nonrigidity of Xing-Phos as well as the conformational preferences-directed flexibility of Xing-Phos.[14]

Although the possibility of the concerted mechanism cannot be excluded in the base-free conditions, we suggested that the catalytic asymmetric [3 + 2] cycloaddition was initiated probably through the Michael addition on the basis of the experimental results (Schemes 1−5 and Tables S1−5 of SI). As shown in Figure 1, we proposed a plausible stepwise mechanism to account for this silver-catalyzed stereospecific formal [3 + 2] cycloaddition (Figure 1). Initially, coordination of glycine aldimino ester **2** to the chiral silver-Xing-Phos complex led to the formation of the key silver-bound azomethine ylide dipole (**IV**) that would attack the chalcone or methyl cinnamate via 1,4-conjugate addition. Notably, the reactive intermediate in the first step of conjugate addition reaction was monitored by ^{1}H NMR, in which we can find the acyclic adduct in the initiated stage of silver-catalyzed conjugate addition of glycine aldimino ester **2a** to methyl cinnamate **4a** in pure MeOH (Figure S2 and Table S5 of SI). It was also found that the Michael adduct **6** could be easily transferred into **7** and **3a** at room temperature in several minutes (see Scheme 5 and Table S5 of Supporting Information). However, the role of

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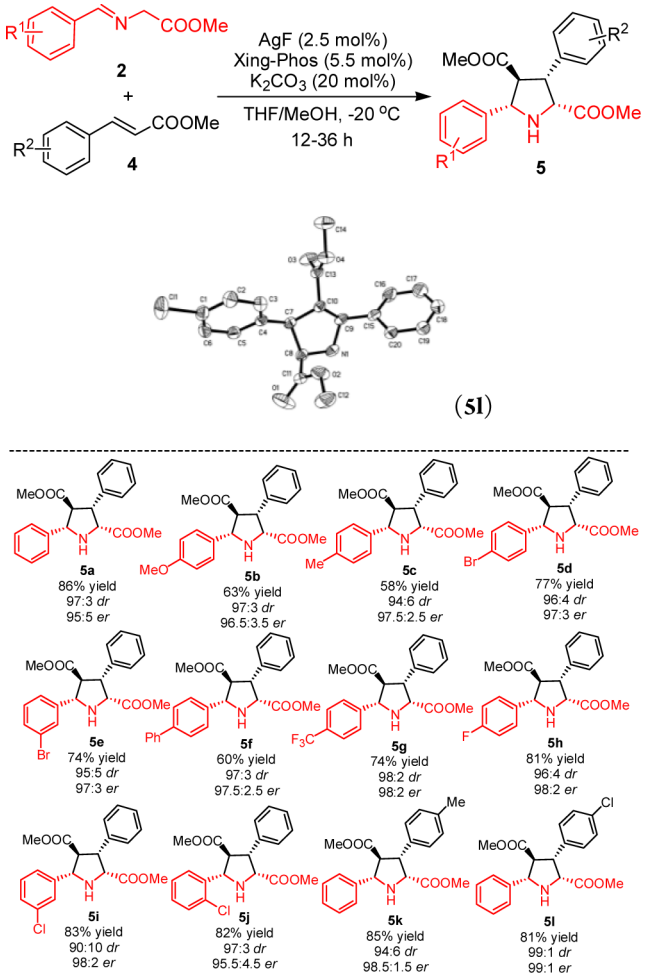
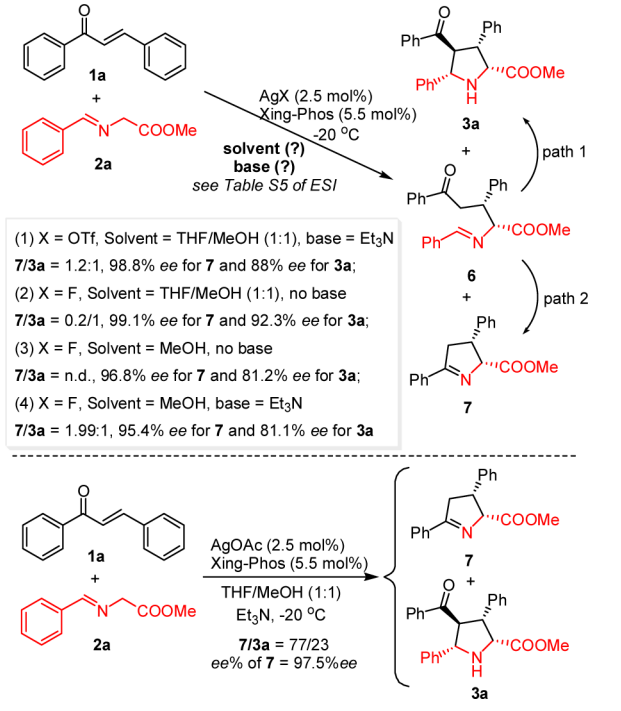
Scheme 4. Asymmetric Cycloaddition of Methyl Cinnamate with Glycine Aldimino Esters Catalyzed by Silver-Xing-Phos



Scheme 5. Determination of Possible Silver-Catalyzed Michael-Initiated Cycloaddition of 1a and 2a



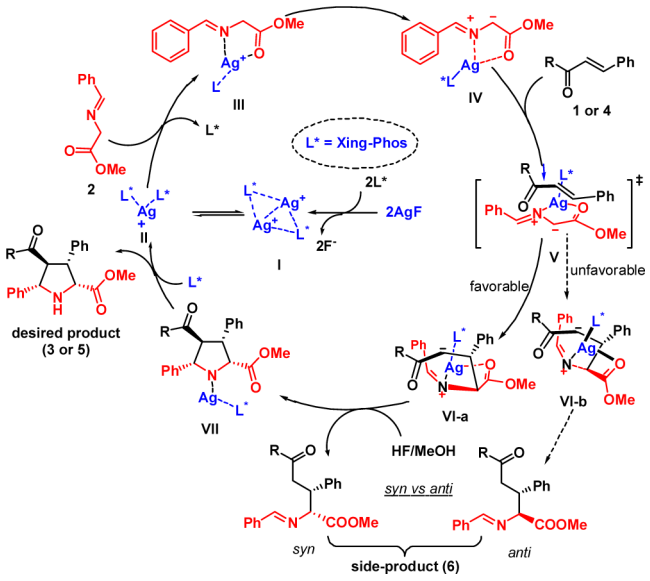


Figure 1. Proposed catalytic cycle of silver-catalyzed cycloaddition in the presence of Xing-Phos: a plausible stepwise Mechanism.

excess amount of Xing-Phos in the cycloaddition is unclear at present. It is possible that the Xing-Phos could activate the diastereoselective cycloaddition by solvent-controlled noncovalent interaction between ligand and substrate and in favor of regeneration of AgL_2 (L = Xing-Phos) complex in the last step. The major difference between chalcone and methyl cinnamate is only the degree of difficulty for the formation of silver-bound enolate intermediate in the initial step of conjugate addition as well as the reactivity of the enolate intermediate in the next cyclization step.

Notably, there are two possibilities for the addition of silver-bound azomethine ylide dipole (**IV**) to chalcone or methyl cinnamate. One scenario is that the intermediate **IV** nucleophilically attacks electrophilically activated chalcone or methyl cinnamate by favorable *syn*-fashion (path 1, Figure 2). The other possibility is that nucleophilic addition of the intermediate **IV** with different chirality to activated alkene occurred through the path 2, which led to the formation of *anti*-side product (**6**). However, it is a disfavored model because of the sandwich-type steric repulsion. Thus, it is possible that an *exo* approach of chalcone or methyl cinnamate controlled by the silver catalyst arose predominately from the steric repulsion and noncovalent interaction between the multifunctional Xing-Phos ligand and activated olefin substrate during the intramolecular cyclization of the silver-Xing-Phos-bounded enolate intermediate (Figure 1).

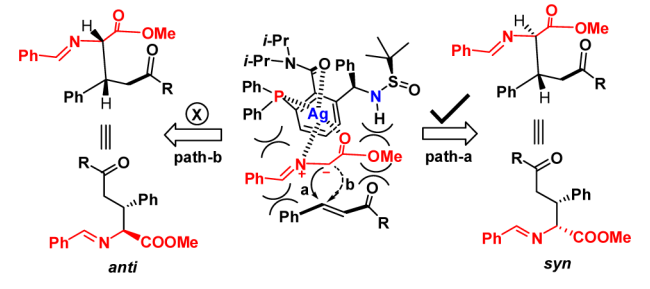


Figure 2. Models for possible states to rationalize the stereoselectivity of Michael addition of **2** to **1**/**4**.

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In summary, the novel silver-Xing-Phos is an effective catalyst system for the catalytic asymmetric cycloaddition of glycine aldimino esters with chalcones or less-reactive methyl cinnamates to give the corresponding chalcone- or cinnamate-derived pyrrolidines with multiple stereogenic centers in good yields and high diastereoselectivities (up to >98:2 dr) as well as excellent enantioselectivities (up to 99:1 er). Remarkably, we reported the first example of highly enantioselective and *exo*-selective silver-catalyzed [3 + 2] cycloaddition of methyl cinnamates or chalcones with glycine aldimino esters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01685.

Experimental details, additional reaction data, and NMR and HPLC spectra of products (PDF)
Crystallographic data file 1 (CIF)
Crystallographic data file 2 (CIF)

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Notes

The authors declare no competing financial interest.

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