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N-tert-Butanesulfinyl imine and aromatic tertiary amide derived non-biaryl atropisomers as chiral ligands for silver-catalyzed *endo*-selective [3+2] cycloaddition of azomethine ylides with maleimides

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ABSTRACT

Simple modifications of our novel ligand (Xing-Phos) were presented in this work, and a series of aromatic tertiary amide derived non-biaryl atropisomers were successfully synthesized in good yields. In addition, it was found that the multifunctional aromatic tertiary amide derived non-biaryl atropisomers exhibited an excellent *endo*-selectivity in the silver-catalyzed [3+2]-cycloaddition of azomethine ylides with *N*-aromatic maleimide. And especially, good to high levels of enantioselectivity (up to 98% *ee*) was obtained with a wide range of substrates in the presence of *syn*-(R, R_S)-**2a** (Xing-Phos). Furthermore, on the basis of the experimental data, it was demonstrated that a trace amount of water play an important role in the enhancement of enantioselectivity.

1. Introduction

During the past decades, intense research efforts have been devoted to develop highly effective silver-based catalyst systems with functional chiral ligands, including S-ligands and P-ligands.[1] Especially, the chiral silver complexes have been attracted much attention from organic chemists because of its privileged catalytic activity in many organic reactions, which provided versatile and powerful potential for the synthesis of synthetically useful and optically active molecules.[2] Despite numerous elegant methods have been established for the construction of the highly efficient silver-based catalyst system, the development of novel silver complex with new chiral ligands as an effective catalyst is highly desired in comparison to that of other transition metals, such as palladium, rhodium, etc. In addition, the crucial role of chiral ligand promoted the chemists to design functional ligands to control the catalytic activity of silver complex.[1–3] However, the synthesis of chiral ligands, including chiral phosphine ligands, with good catalytic activity is not an easy task and still be recognized as a great challenge in asymmetric catalysis. In this context, we became interested in the synthesis of chiral phosphine ligands with sulfinyl groups and its potential application as a controlled element in the catalytic asymmetric [3+2] cycloaddition of azomethine ylides with maleimides, for the preparation of functional pyrrolidines.

Functionalized pyrrolidines are key units in medicinal chemistry and also a type of highly valuable synthetic building blocks for nature products.[4] In addition, chiral proline derivatives, similarly to the basic structure of pyrrolidines, also proved to be useful organic catalysts in many catalytic asymmetric transformations.[5] The great synthetic potential of this five-membered ring heterocycles inspired the huge development of diastereoselective [3+2] cycloadditions of azomethine ylide with activated alkenes, which is an extremely powerful and atom-economical strategy for the enantioselective construction of pyrrolidine ring.[6] Since the pioneering work of Grigg[7] and Zhang,[8] much more efficient high diastereo- and enantioselective catalytic system have been reported with the efforts of Jørgensen,[9] Schreiber,[10] Zhou,[11] Carrerero,[12] Hou,[13] Wang,[14] Fukuzawa[15] and other groups.[16] Organocatalyzed 1,3-dipolar [3+2] cycloadditions also made progress in MacMillan[17] and other chemist's efforts.[18]

Very recently, we have reported the design and synthesis of a kind of novel multifunctional ligand, aromatic tertiary amide

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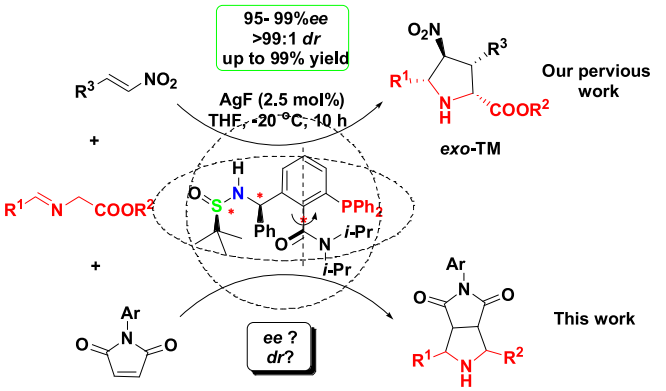
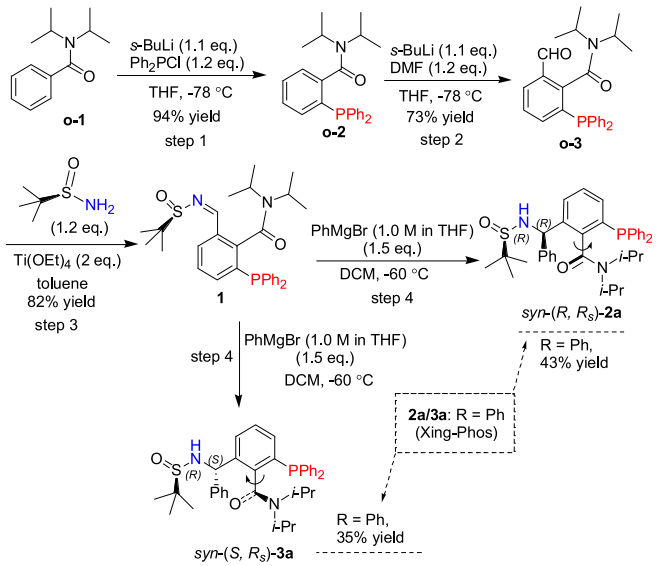
derived non-biaryl atropisomer as phosphine ligand (also called as Xing-Phos).[19] We have also found that the Xing-Phos was a highly efficient ligand in the Ag^{I}-catalyzed *exo*-selective [3+2] cycloaddition of azomethine ylides with *trans*-β-nitrostyrene (Scheme 1).[19a] Although this protocol has made great success in this field, the variety of aromatic amide-derived non-biaryl atropisomer derivatives still too limited and the application of aromatic amide-derived non-biaryl atropisomer with both phosphine and sulfinyl groups in silver-catalyzed [3+2] cycloaddition remained to be widened. It is necessary to synthesis versatile aromatic amide-derived non-biaryl atropisomer derivatives and figure out whether high diastereo- and enantioselectivity cloud be obtained when other dipolarophilic olefins used instead of *trans*-β-nitrostyrene. Interesting, previously reported silver-catalyzed [3+2] cycloadditions of azomethine ylide are almost *endo*-selective in most cases, especially with substituted maleimides.[11,16,20] Thus previous works inspired our curiosity about whether it is possible to get higher *endo*-selectivity and high *ee* value under suitable conditions in the presence of Xing-Phos and other aromatic tertiary amide derived non-biaryl atropisomers. We speculated that the geometrical configuration of olefins might change the mutual effect of [3+2] cycloaddition procedure in this Ag/Xing-Phos catalysis system, and accordingly, we considered that maleimide derivatives could be used as Z-alkene. Herein, we report the enantioselective synthesis of aromatic amide-derived non-biaryl atropisomer derivatives, the analogues of Xing-Phos, and investigate their application in silver-catalyzed cycloaddition of azomethine ylide with *N*-aromatic maleimide. This work reveals that the silver-catalyzed asymmetric [3+2] cycloaddition reaction of glycine imino esters with maleimide can proceed smoothly to give the corresponding pyrrolidine derivatives in good to excellent enantioselectivity in the presence of the Xing-Phos under mild conditions.



Scheme 1. Silver-catalyzed [3+2] cycloaddition of azomethine in the presence of Xing-Phos: *exo*-selectivity or *endo*-selectivity for the silver-catalyzed cycloaddition of maleimide?

2. Results and discussion

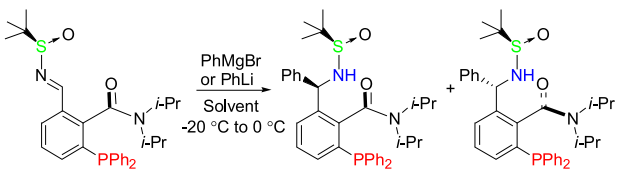
We initiated our studies by synthesizing a series of novel aromatic amide-derived non-atropisomer derivatives bearing both axial and sp^3 central chirality. We had prepared a special aromatic amide-derived non-biaryl atropisomer, also called as Xing-Phos, started with *N*,*N*-diisopropylbenzamide in four steps (Scheme 2).[19] All the first three steps were simple and classic transformations with high yield, while the fourth step was frustrating, in which 43% yield of *syn*-(*R*, R_S)-**2a** and 35% yield of *syn*-(*S*, R_S)-**3a** was achieved in this 1,2-addition reaction. Not only the stereocontrol of diastereoselectivity but also the epimerization should be cautious in this 1,2-addition reaction of Grignard reagents or organometallic reagents to aromatic amide-derived sulfinyl imine **1**. Actually, we observed that the addition of Grignard reagent to sulfinyl imino **1** almost was not occurred until the temperature rose to about −20 °C, and the epimerization was quenched when temperature was below 0 °C. If keep the reaction mixture at room temperature (20 °C), new isomers produced by epimerization of Ar−CO bond would grow as time goes on. Hence, we decreased the reaction temperature to −20 °C because of the possible epimerization at room temperature.



Scheme 2. Stereodivergent preparation of aromatic amide-derived non-biaryl atropisomers with both phosphine and sulfinyl groups.[19].

As shown in Table 1, the diastereoselectivities were varied under different reaction conditions, for example, the desired aromatic amide-derived non-biaryl atropisomer could be obtained in a diastereoisomer ratio of 67/33 when phenyl Grignard reagent as

Table 1
Optimization of the 1,2-addition of aromatic amide derivative **1** with phenyl metal reagents[a]



Entry	Solvent	Additive	PhMgBr or PhLi	**2**/**3**[b]
1	DCM	—	PhMgBr in THF (1.0M)	67/33
2	DCM	—	PhLi in THF (1.7M)	56/44
3	THF	—	PhLi in THF (1.7M)	69/31
4	Toluene	—	PhLi in THF (1.7M)	56/44
5	Toluene	—	PhLi in ether (1.5M)	54/46
6	Toluene	—	PhMgBr in THF (1.0M)	71/29
7	Toluene	Me_3Al	PhLi in THF (1.7M)	53/47
8	Toluene	HMPA	PhMgBr in THF (1.0M)	56/43
9	Toluene	TMEDA	PhMgBr in THF (1.0M)	49/51

[a] The reaction was carried out under N_2 atmosphere and solvents were dried before use in all cases.

[b] The ratio of *syn*-(*R*, R_S)-**2a**/*syn*-(*S*, R_S)-**3a** was determined by chiral HPLC with chiarlpark AD-H column (Hexane:*i*-PrOH=96:4, 1 mL/min).

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