Asymmetric Catalysis

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Aromatic Amide-Derived Non-Biaryl Atropisomers as Highly Efficient Ligands in Silver-Catalyzed Asymmetric Cycloaddition Reactions**

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Abstract: *The synthesis of a series of aromatic amide-derived non-biaryl atropisomers with a phosphine group and multiple stereogenic centers is reported. The novel phosphine ligands exhibit high diastereo- and enantioselectivities (up to >99:1 d.r., 95–99% ee) as well as yields in the silver-catalyzed asymmetric [3+2] cycloaddition of aldiminoesters with nitroalkenes, which provides a highly enantioselective strategy for the synthesis of optically pure nitro-substituted pyrrolidines. In addition, the experimental results with regard to the carbon stereogenic center as well as the amide stereochemistry confirmed the potential of hemilabile atropisomers as chiral ligand in catalytic asymmetric [3+2] cycloaddition reaction.*

There is an ever-growing interest in asymmetric synthesis and the conformational properties of atropisomers that result from the sterically hindered rotation of one single bond.[1] Interestingly, despite its biological importance in drug discovery and development,[2] few methods have emerged for the direct preparation and application of this compound class in asymmetric catalysis.[1,2] Especially for non-biaryl atropisomers, the thermal stereochemical stability of atropisomers that are sensitive to temperature or solvent would lead to axial rotation and possible racemization.[3] This feature actually causes a synthetic problem in the application of optically pure atropisomers including tertiary aromatic amide-derived non-biaryl atropisomers in organic synthesis. Meanwhile, to the best of our knowledge, the truly enantioselective synthesis of aromatic amide-derived non-biaryl atropisomers was only reported firstly at the end of the 1990s.[4] In this context, the groups of Clayden and Miller, gave much effort to the enantioselective synthesis of atropisomers and related stereochemistry.[5,6]

On the other hand, the design and synthesis of structurally novel and highly efficient phosphine ligands to meet the demand of certain catalytic asymmetric transformations remains a formidable challenge.[7] As described in previous reports, although there is a number of chiral phosphine ligands used for catalytic asymmetric transformation, the enantioselective synthesis and catalytic application of non-biaryl atropisomeric P,O-ligands with hemilabile aromatic amide is yet to be explored. The early syntheses and catalytic exploration of phosphine-containing non-biaryl atropisomers have paved the way for the catalytic application of phosphine-containing atropisomeric amides as chiral ligands in asymmetric synthesis.[8] Unfortunately, previous results on non-biaryl atropisomeric phosphine-promoted catalytic asymmetric reactions including asymmetric allylic alkylation (Pd-AAA reaction)[8a–d,g] and asymmetric Heck reaction (up to 55.2% *ee*) were not successful in terms of enantioselectivity. Notably, tertiary aromatic amide-derived phosphines were found to be highly efficient hemilabile P,O-ligands in palladium-catalyzed cross coupling reactions.[9] Thus inspired by previous work and on the basis of our preliminary work on the synthesis and catalytic application of tertiary aromatic amides,[10] we hypothesized that the dynamic steric hindrance of rotatable aromatic tertiary amides and the weak coordination between such a ligand with a metal center would be beneficial for obtaining high selectivity in various reactions because of the hemilability and nonrigidity of aromatic amide-derived phosphine ligands. Therefore, we set out to produce a new family of non-biaryl atropisomeric amides bearing a phosphine group and to apply them to the silver-catalyzed [3+2] cycloaddition of iminoesters with nitroalkenes.

The synthesis of optically pure aromatic amide-derived atropisomers **5** containing a phosphine group started with the aromatic tertiary amide **1** as shown in Scheme 1. Aldehyde **3** was available by lithiation of **1**, followed by reaction with PPh_2Cl to afford phosphine **2**. A lithiation and formylation of **2** gave aldehyde-substituted phosphine **3**. Condensation of aldehyde **3** with (R_S)-*tert*-butanesulfinamide[11] and subsequent 1,2-addition of Grignard reagent to *N*-*tert*-butanesulfinyl imine **4** resulted in the formation of a new carbon stereogenic center adjacent to the aromatic amide. Similar to previous work on the synthesis of isolable atropisomeric amides with secondary alcohol or amine moieties,[10a] we found that the air-stable *syn*-(R,R_S)-**5b** and *syn*-(S,R_S)-**5b**

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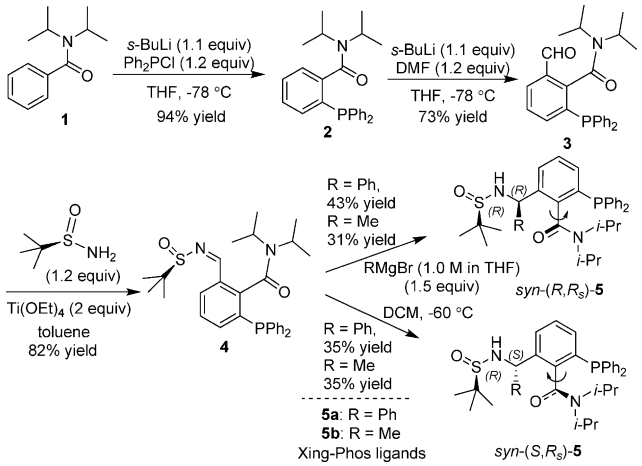
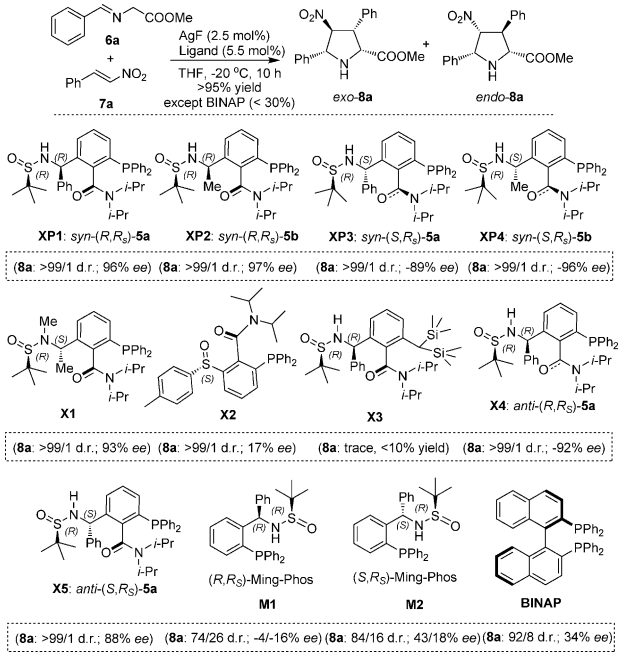


Scheme 1. Stereodivergent preparation of a new class of non-biaryl atropisomers with a phosphine group and multiple stereogenic centers.

could be obtained easily by flash column chromatography. The X-ray crystal structures of *syn*-(*R*,R_S)-**5b** and *syn*-(*S*,R_S)-**5b** confirmed the stereochemistry of the new carbon stereogenic center and the orientation of the amide group (Figure S11 of the Supporting Information, SI).

Although the *anti*-(*R*,R_S)-**5a** or *anti*-(*R*,R_S)-**5b** did not form during the 1,2-addition of Grignard reagent to Schiff base **4** (Scheme 1), we were able to successfully obtain two corresponding atropisomers *anti*-(*R*,R_S)-**5a** and *anti*-(*S*,R_S)-**5a** (Scheme 2, **X4** and **X5**) that have an amide stereochemistry different from *syn*-(*S*,R_S)-**5a** and *syn*-(*R*,R_S)-**5a**, respectively, by epimerization and subsequent purification by flash column chromatography. In this case, the thermally promoted Ar–$CONR_2$ rotation could lead to the formation of two isolable



Scheme 2. Various chiral P-ligands for the silver-catalyzed cycloaddition of **6a** and **7a**. Reaction results are showed in parentheses.

atropisomers with different polarity detected by TLC because of the adjacent conformationally constrained amide group.

The optically pure atropisomers **5a** and **5b** were found to be very stable in solid form. However, similarly to previous work reported by Clayden and co-workers,[12] it was also observed that the Ar–CO rotation led to partial racemization in THF solution at room temperature (Figure S1). The rate constant and thermodynamic ratio that is provided in the SI (Figures S1–S9) showed the conformational stability of atropisomeric amide *syn*-(*R*,R_S)-**5a** in solution. Notably, at lower temperature (−20 °C), the d.e. value of *syn*-(*R*,R_S)-**5a** was not decreased in solution, which gave the opportunity to apply these ligands in catalytic asymmetric synthesis.

Next, considering the synthetic importance of enantioselective and diastereoselective [3+2] cycloaddition of azomethine ylides and nitroalkenes, we investigated the catalytic performance of these two sets of atropisomers (**5a**,**b**), named Xing-Phos ligands (simplified as **XP1**–**4**), in this reaction (Scheme 2). The catalytic asymmetric [3+2] cycloaddition of iminoesters with activated alkenes is undoubtedly an important synthetic reaction because it is one of the most straightforward and atom-economical methods for the enantioselective construction of five-membered carbocycles as well as heterocycles, which are structurally divers motifs in biologically active molecules and natural products.[13] Interestingly, although the importance of chiral pyrrolidines highlights the need for the development of asymmetric [3+2] cycloaddition reactions,[14] the first example of catalytic asymmetric 1,3-dipolar cycloaddition of iminoesters and alkenes was not reported until 2002.[15] Due to the difficulty of generating single isomers out of four possible diastereoisomers (classified as *endo*, *exo*, *endo′*, and *exo′*) in the 1,3-dipolar cycloaddition of azomethine ylides and nitroalkenes, most of the ligands have been shown to be unsuccessful in achieving high enantioselectivity or diastereoselectivity.[16] Despite the success of several groups in the *endo*,*exo′*, or *exo*-selective cyclization reactions catalyzed by copper or nickel complexes,[17] the asymmetric silver-catalyzed [3+2] cycloaddition of aldiminoesters and nitroalkenes is in its infancy and the development of conceptually novel ligands showing high reactivity, diastereoselectivity, and enantioselectivity with regard to a broad variety of substrates still remains a great challenge.[18] To the best of our knowledge, there is no successful report on the asymmetric silver-catalyzed [3+2] cycloaddition of aldiminoesters with nitroalkenes with high diastereo- and enantioselectivities.[19] Herein, on the basis of the successful design and synthesis of a new class of tertiary amide-derived phosphine ligands with multiple stereogenic centers, we found that the novel hemilabile non-biaryl atropisomer could be efficiently used as chiral phosphine ligand for remarkably *exo*-selective silver-catalyzed [3+2] cycloaddition of aldiminoesters with nitroalkenes.

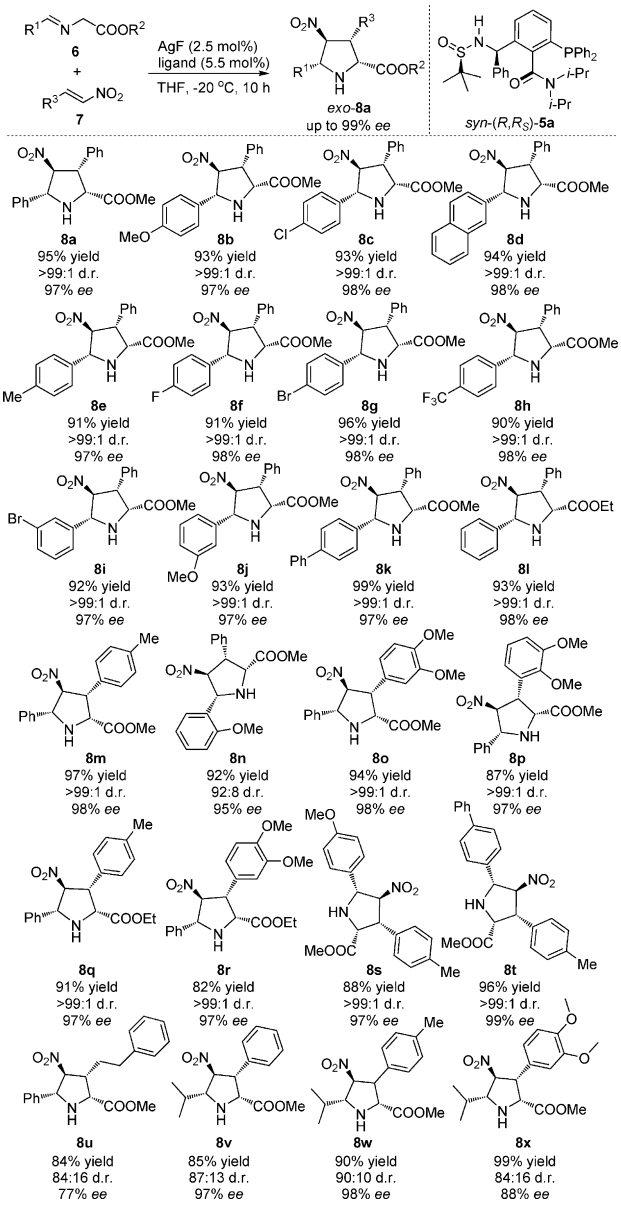
Initially, we focused our attention on the establishment of the optimal reaction conditions for the model cycloaddition of **6a** and **7a** by the combination of silver catalyst and ligand **XP1** (*syn*-(*R*,R_S)-**5a**). We found that the reaction proceeded well in various solvents and the diastereoselectivity varied largely from 34:66 (*endo*-selectivity) to > 99:1 (*exo*-selectiv-

ity) in the presence of *syn*-(R,R_S)-**5a** (Table S4). The experimental results represented in Scheme 2 show that the Xing-Phos ligands (**XP1**–**4**) are stable enough for asymmetric catalysis. Notably, no addition of ligand or use of triphenylphosphine (PPh_3) in this reaction led to the *endo*-selective cyclization of **6a** and **7a**. The aromatic amide-derived phosphine **2** with hemilabile P,O-centers reversed the selectivity to pyrrolidine **8a** with *exo*-selectivity (Scheme 2 and SI). The reaction temperature and the amounts of silver catalyst and phosphine ligand as well as the type of silver salt were also screened and the optimal conditions with regard to screening the catalyst system were: no additive, AgF (2.5 mol%), **XP1** (5.5 mol%) at −20°C (96% *ee*, >99:1 d.r.). Notably, the structure and stereochemistry of the product was confirmed by X-ray crystallographic analysis of a crystal of enantiomerically pure **8a** (Figure S12).

With the optimized reaction conditions for **XP1**, we continued to evaluate the enantiomeric induction of various Xing-Phos ligands as well as structurally similar phosphine ligands, such as Zhang's Ming-Phos (**M1** and **M2**)[20] and ligands **X1**–**5**, that were derived from the modification of Xing-Phos, in this cycloaddition reaction. All reactions with these ligands resulted in high yields (>95% conversion; except when noted otherwise). Several points are noteworthy as following: a) The importance of the new carbon stereogenic center (NH–C*–R) was confirmed by the experimental results. For example, when **XP3** was used as a ligand in this reaction, it was found that the desired product **8a** was obtained in −89% *ee*. Interestingly, the use of **XP4** instead of **XP2** as ligand led to the same high enantioselectivity but with reversed configuration (−96% *ee*). b) The catalytic activity of **X4** and **X5** further supported the crucial role of amide stereochemistry. The experimental data represented in Figure S10 showed that the orientation of the amide on this ligand is crucial for the highly enantioselective cycloaddition. Fortunately, it was possible to grow a single crystal of Ag–**XP1** with a triflate anion and it was subjected to X-ray diffraction analysis (Figure S13). The single-crystal structure of the Ag–**XP1** complex shows an unexpected binuclear silver structure in which two oxygen atoms on the S(=O)–NH and tertiary amide groups as well as the phosphine atom coordinate to a silver center. This supports that the chiral environment of the silver catalyst was affected by ligand epimerization, because the Ag–**XP1** complex not only relied on the atropisomeric amide but also depended on *tert*-butanesulfinamide and the carbon stereogenic center.

To highlight the importance of the phosphine center, an aromatic amide-derived atropisomer **X3** with a silicon-based bulky group was also prepared for the asymmetric [3+2] cycloaddition reaction. As expected, atropisomer **X3** shows no activity in this reaction. Notably, two structurally similar Ming-Phos ligands that were not atropisomers, were also examined, but unfortunately, low enantioselectivity (up to 43% *ee*) and poor diastereoselectivity (up to 84:16 *exo*/*endo*) was observed.

Having established the optimal reaction conditions for the [3+2] cycloaddition of aldiminoester **6a** with nitroalkene **7a**, we next studied the performance of AgF-*syn*-(R,R_S)-**5a** in the catalytic asymmetric [3+2] cycloaddition of iminoesters with



Scheme 3. Substrate scope of the synthesis of optically pure nitro-substituted pyrrolidines

nitroalkenes (**8a**–**8x**). As shown in Scheme 3, the scope of our new ligand was quite satisfying and excellent yields and *ee* values were obtained in most cases. First, the cycloaddition of iminoesters containing different groups on the amine moiety with nitroalkanes gave the corresponding products in excellent yields and high enantioselectivities (88–98% *ee*) and diastereoselectivities (>99:1 d.r. for **8a**–**8m**; **8n** is the only exception). Next, substituted nitroalkanes all reacted well with iminoesters to form the corresponding products in excellent diastereo- and enantioselectivity (up to 99% *ee* and >99:1 d.r.). Importantly, this catalytic asymmetric cycloaddition reaction could also be expanded to other types of substrates bearing alky groups (**8u**–**8x**).[21]

At last, it should be noted that 0.25 mol% of the Ag–**5a** catalyst system was sufficient for this reaction because of the

excellent diastereo- and enantioselectivity as well as excellent yield (Scheme S1).

In summary, we have developed a new type of optically pure aromatic amide-derived atropisomers with a phosphine group and multiple stereogenic centers, called Xing-Phos ligands, for catalytic asymmetric cycloaddition reactions. The silver-catalyzed asymmetric [3+2] cycloaddition of aldiminoesters with nitroalkenes, resulted in high diastereo- and enantioselectivities (up to > 99:1 d.r., 95–99% *ee*) as well as yields without any additives. This method provides a highly enantioselective strategy for the synthesis of optically pure nitro-substituted pyrrolidines with multiple stereogenic centers. Moreover, the effect of the carbon stereogenic center, the chiral S(=O)–NH group, and the amide stereochemistry on the enantioselectivity of Xing-Phos ligands was investigated in this work. This is a first example to clearly show the powerful potential of non-biaryl atropisomers (P,O-ligand) in asymmetric catalysis. Further studies, regarding the mechanism of silver-catalyzed cycloaddition and the catalytic performance of Xing-Phos ligands in other catalytic asymmetric reactions, are underway in our group and will be reported in the near future.

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Communications

Asymmetric Catalysis

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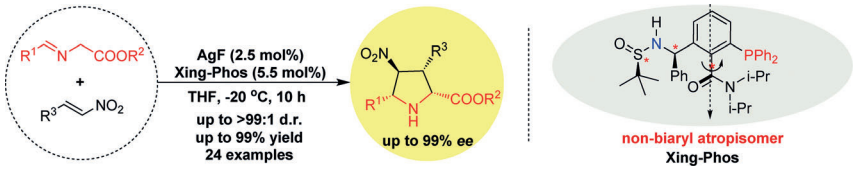
W.-S. Huang, L.-W. Xu* ——

Aromatic Amide-Derived Non-Biaryl Atropisomers as Highly Efficient Ligands in Silver-Catalyzed Asymmetric Cycloaddition Reactions



New chiral ligands: Optically pure aromatic amide-derived atropisomers were shown to be powerful phosphine ligands in the enantioselective silver-catalyzed [3+2] cycloaddition. This method provides a highly efficient strategy for the synthesis of optically pure nitro-substituted pyrrolidines with multiple stereogenic centers.

