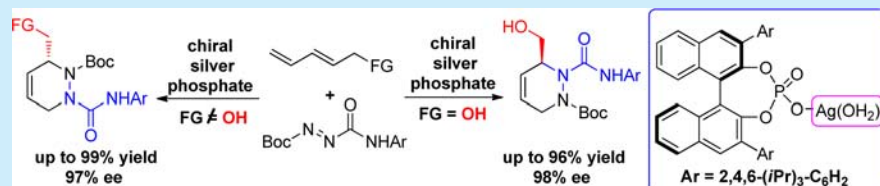


Asymmetric Hetero-Diels–Alder Reaction of Diazenes Catalyzed by Chiral Silver Phosphate: Water Participates in the Catalysis and Stereocontrol

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S Supporting Information



ABSTRACT: The chiral silver phosphate was confirmed to efficiently catalyze a highly regio- and enantioselective hetero-Diels–Alder reaction of diazenes to furnish piperazine derivatives in high yields and excellent ee values. DFT calculations revealed that the water molecule participates in the catalysis by coordination to silver phosphate and also found that the hydroxy group of 1-hydroxy-2,3-hexadiene not only formed a hydrogen bond with the oxygen of phosphate but also coordinated to the Ag(I) to simultaneously stabilize the transition states and control the regioselectivity.

The hetero-Diels–Alder (HDA) reaction undoubtedly stands as one of the most important transformations in organic synthesis and has long received worldwide interest driven by the requirement of efficient protocols to access six-membered heterocyclic structures, which have been found in numerous natural products and pharmaceutically relevant molecules.¹ In particular, the azo hetero-Diels–Alder reaction of diazene compounds with dienes directly builds up chiral piperazine structural motifs, which frequently appear in both natural products and bioactive compounds, as exemplified in Figure 1, leading to great demand for enantioselective variants.²

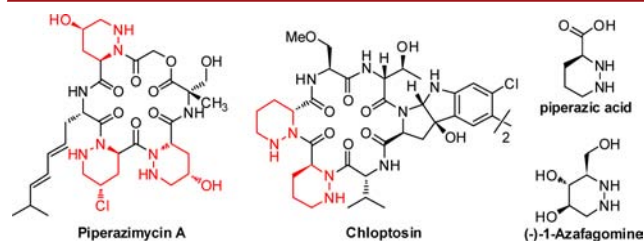
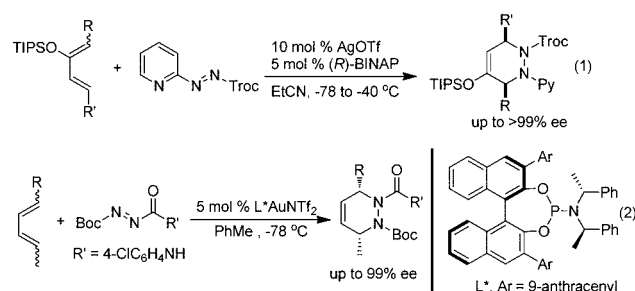


Figure 1. Natural products and bioactive compounds containing the piperazine core structure.

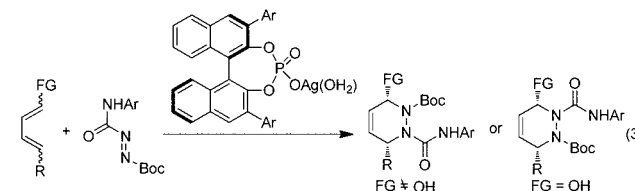
However, either the chiral auxiliary-induced strategy or the optical resolution has remained the practical choice to prepare optically pure piperazines in the synthesis of natural products.^{2d} The asymmetric catalytic version was initially attempted by Jørgensen, wherein the optimal chiral copper complex only gave 22% ee.³ In 2006, Yamamoto found that the cationic silver complex prepared from silver triflate and BINAP was able to

render the 2-azopyridine to undergo a highly enantioselective azo-HDA reaction with siloxydienes (eq 1).⁴ Very recently, we

previous reports on highly enantioselective HDA:
---stereoselectivity controlled by chiral ligands



this work



1. stereoselectivity is controlled by chiral anion

2. hydroxyl group in the diene controls the regioselection

established a chiral gold complex-catalyzed highly enantioselective hetero-Diels–Alder reaction of diazenes with a diverse spectrum of dienes (eq 2).⁵ Despite these successful examples,

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some important issues, particularly concerning substrate scope and regioselectivity, are still challenging and need to be solved. For example, although the gold-catalyzed HDA tolerates a wide scope of dienes, it was unable to give good results to some dienes functionalized in the form of allylic alcohol. Moreover, the asymmetric HDA reactions of 1-monosubstituted 1,3-dienes, which are quite synthetically useful in the natural product synthesis,^{2d} have been unexploited, yet. Therefore, the finding of new chiral catalyst systems capable of figuring out a solution to the formidable problems remains highly desirable and will be of great synthetic importance.

Although chiral metal phosphates have been applied to asymmetric transformations for more than two decades,⁶ they were reconsidered as promising chiral catalysts⁷ after the appearance of BINOL-based chiral phosphoric acid catalysis first introduced by Terada and Akiyama.⁸ As a result, a diverse spectrum of metal phosphates based on 3,3'-substituted BINOL turned to be excellent catalysts for various enantioselective reactions wherein the metal acts to activate substrates and chiral phosphate controls the stereoselection.⁷ Although silver complexes have been known as excellent Lewis acid catalysts for a diverse range of reactions,⁹ surprisingly, the silver rarely played a key role in the activation of the electrophiles by σ -coordination to lower the LUMO in its phosphate-catalyzed reactions.¹⁰ Herein, we will demonstrate that silver phosphates can work as excellent chiral Lewis acid catalysts enabling a highly enantioselective azo hetero-Diels–Alder reaction of diazenes with dienes (eq 3). More interestingly, we also found that the hydrogen-bonding element presented in the diene could switch the regioselection and residual water participates in the catalysis by hydrogen-bonding interaction.

Our initial investigation commenced with an azo-HDA reaction of commercially available 2,4-hexadiene (**1a**) with urea-based diazene dienophile **2** at $-40\text{ }^{\circ}\text{C}$ for the evaluation of different metal phosphates (Table 1). BINOL-derived chiral phosphoric acid showed considerable catalytic activity but with a poor enantioselectivity (entry 1), while its silver phosphate gave the desired adduct **4a** in 74% yield with 50% ee (entry 2). However, the corresponding magnesium,¹¹ calcium,¹² and gold phosphates^{7b,13} were able to catalyze the HDA reaction but with no stereoselection (entries 3–5). The introduction of the substituents at 3,3'-positions of BINOL skeleton led to considerable variation in the stereochemical outcomes, and we found that the use of silver phosphate **3j** allowed the reaction to proceed cleanly and gave the product with 97% ee (entries 6–10). The enantioselectivity dropped slightly to 94% ee when the reaction was conducted in toluene (entry 11). Notably, the diazene **2b**, derived from **2a** by methylation, showed no reactivity under the optimized reaction conditions (entry 12), implying that the proton of the nitrogen of **2a** also played a crucial role in the reaction, as reported previously.⁵ Interestingly, a control experiment to evaluate the influence of external ligand on the transformation found that the addition of PPh_3 was deleterious to both the catalytic activity and the stereoselectivity (entry 13).

Under the optimized reaction conditions, we next explored the generality of this asymmetric azo-HDA reaction (Scheme 1). Alkyl-monosubstituted terminal dienes **1b–f** could undergo the cycloaddition smoothly, leading to the desired chiral piperazines **4b–f** in high yields and with high levels of enantioselectivity ranging from 90% to 95% ee. Significantly, extremely high regioselectivity was observed in these cases with the exception of **4b**. Both 1,3- and 1,4-dialkyl-substituted

Table 1. Evaluation of Metal Salts and Optimization of Reaction Conditions^a

1a + **2** (10 mol %) $\xrightarrow[\text{solvent, } -40\text{ }^{\circ}\text{C}]{\text{3}}$ **4**

2a, R = 4-ClC₆H₄NH
2b, R = 4-ClC₆H₄NMe

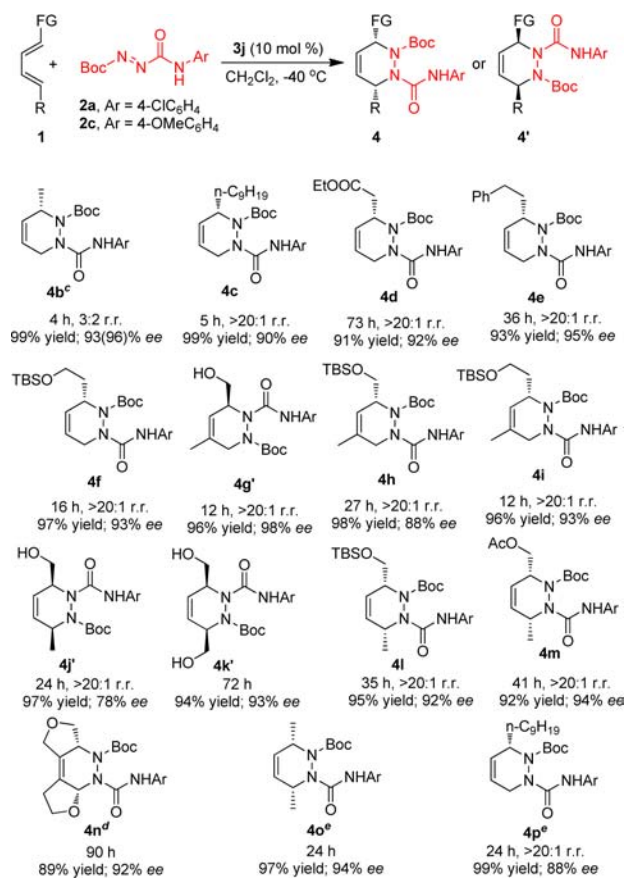
3a, R = H, X = H, n = 1
3b, R = H, X = Ag, n = 1
3c, R = H, X = Ca, n = 2
3d, R = H, X = Mg, n = 2
3e, R = H, X = AuPPh₃, n = 1
3f, R = phenyl, X = Ag, n = 1
3g, R = 2-naphthyl, X = Ag, n = 1
3h, R = 9-anthracenyl, X = Ag, n = 1
3i, R = SiPh₃, X = Ag, n = 1
3j, R = 2,4,6-(iPr)₃-C₆H₂, X = Ag, n = 1
3k, R = 2,4,6-(iPr)₃-C₆H₂, X = AgPPh₃, n = 1

entry	catalyst	2	time (h)	yield ^b (%)	ee ^c (%)
1	3a	2a	78	84	2
2	3b	2a	46	74	50
3	3c	2a	60	80	0
4	3d	2a	60	83	0
5 ^d	3e	2a	54	71	0
6	3f	2a	22	96	50
7	3g	2a	46	99	24
8	3h	2a	17	93	8
9	3i	2a	22	99	8
10	3j	2a	4	99	97
11 ^e	3j	2a	12	99	94
12	3j	2b	24	nr	
13 ^f	3k	2a	24	76	77

^aThe reaction of **1a** (0.3 mmol) and **2** (0.1 mmol) was carried out in dichloromethane at $-40\text{ }^{\circ}\text{C}$ in the presence of catalyst **3** (10 mol %) in the dark. ^bIsolated yield. ^cThe ee was determined by HPLC. ^dThe gold catalyst was prepared in situ from PPh_3AuMe and phosphoric acid **3a**. ^eIn toluene. ^fThe silver catalyst was prepared in situ from **3j** (10 mol %) and PPh_3 (12 mol %).

dienes, including those bearing functional groups, could also be successfully tolerated, providing the cycloadducts with excellent regioselectivity (see: **4g'–m**). Tetrasubstituted diene **1n** was seemingly much less reactive than other dienes but still participated in the HDA reaction at $-15\text{ }^{\circ}\text{C}$, giving the product in 89% yield and with 92% ee. More interestingly, 2,4-pentadienol derivatives and their protected analogues gave completely different regioisomers; that is, the presence or absence of the protecting group was able to switch the regioselection, as shown by comparison of **4g'** with **4h** and of **4j'** with **4l** and **4m**, respectively. This unusual regioselectivity might result from a hydrogen-bonding interaction between the 2,4-pentadienol and the chiral silver phosphate. Although 2,4-hexadiene-1,6-diol (**1k**) reacted slowly with diazene due to its lower solubility, it still provided satisfactory results (94% yield and 93% ee) by prolonging the reaction time to 3 days. Moreover, the variation of *N*-aryl substituent of the diazenes **2** was also allowed. For instance, the *N*-PMP urea diazenes underwent reaction to generate **4o** and **4p** in excellent yields and with high levels of enantioselectivity. The configuration of **4l** was determined by X-ray analysis of its single crystal with 99% ee (see the Supporting Information).¹⁴ Notably, the *N*-protecting groups could be readily removed (see the Supporting Information).

To better understand the catalytic model¹⁵ for this asymmetric hetero-Diels–Alder reaction, theoretical calcula-

Scheme 1. Substrate Scope^{a,b}

^aUnless indicated otherwise, reactions of **1** (0.15 mmol), **2a** (0.10 mmol), and **3j** (10 mol %) were carried out in dichloromethane (1 mL) in the dark at -40 °C. ^bIsolated yield. The ee was determined by HPLC analysis, and the ee of minor product **4b'** is presented in parentheses. The regiomer ratio was determined by ¹H NMR. ^c0.3 mmol of **1b** was used. ^dAt -15 °C, **2a** was recovered. ^e**2c** (0.10 mmol) was used.

tions were performed by density functional theory (DFT) to explore the transition states of HDA between diene **1a** with diazene **2a** catalyzed by chiral silver phosphate **3j**.¹⁶ However, all of the TS structures located above failed to rationalize the stereochemistry observed experimentally (Figure S1, Supporting Information). Thus, we carefully reconsidered the reaction conditions. Previous studies suggested that trace amounts of residual water in the solvent have a considerable effect on the Lewis acid catalyzed reactions.¹⁷ While the reactions were conducted in the solvent without strict dehydration, it is quite possible that the water might participate in the asymmetric catalysis. Indeed, HRMS analysis identified that the silver phosphates form stable complexes with one molecule of water and even if the sample was prepared in anhydrous solvent, one molecule of water was incorporated in the complexes (Figure S2, Supporting Information). Thus, we considered introducing one water molecule as an achiral ligand to Ag(I) for the location of new reaction transition states. As anticipated, the most stable transition states were located (Figure 2). The **TS-W-1** indicated the *Re*-face of the σ -coordinated nitrogen of urea-bonded azo moiety was easier to access via the *S-cis* bond of the incoming diene to afford the major enantiomer, as experimentally observed. The corresponding TS of enantiomer of **4a** was located as **TS-W-2** in Figure 2. **TS-W-2** was predicted

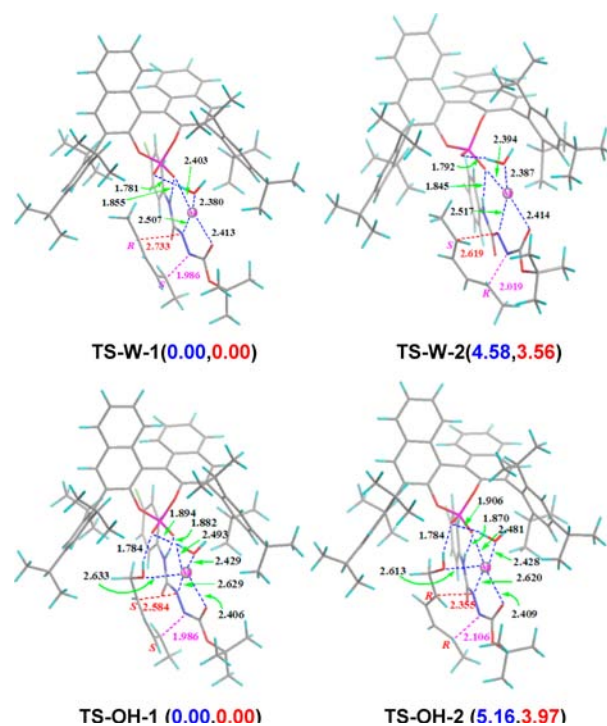


Figure 2. Fully optimized complex and TS structures at the level of B3LYP with basis set 6-31G* for C, H, O, N, P, Cl, and lan12dz for Ag atom. The relative energies are shown as blue for enthalpy and red for Gibbs free energy. The distances are shown in angstroms.

to be less stable than **TS-W-1** by about 4 kcal/mol, due to the origination of *S-cis* bond far away from the coordinated Ag(I) moiety. While 1-hydroxy-2,3-hexadiene was used as a substrate, the most stable transition state was located as **TS-OH-1**, giving the product **4j'**. The hydroxy group of 1-hydroxy-2,3-hexadiene not only formed a hydrogen bond with the oxygen of phosphate but also coordinated to the Ag(I), as shown in **TS-OH-1**, to simultaneously stabilize the TS and control the regioselectivity. Similarly, the located TS to generate the enantiomer of **4j'**, as shown in **TS-OH-2**, was predicted to be less stable than **TS-OH-1** by more than 4 kcal/mol. The theoretical computations clearly indicated that the H₂O participates in the catalysis and plays a crucial role in the control of stereochemistry.

In summary, we have demonstrated that chiral silver phosphates can be excellent catalysts for the enantioselective azo-HDA reaction of diazene derivatives, which shows a nice tolerance for a diverse spectrum of dienes to furnish piperazine derivatives in high yields and with excellent levels of regio- and enantioselectivities. The chiral phosphate was confirmed to efficiently control the regio- and stereoselectivities. More importantly, the presence or absence of the hydroxyl group in the dienes could switch the regioselection. DFT calculations revealed that the water molecule participates in the catalysis by formation of a complex with silver phosphate and also found that the hydroxy group of 1-hydroxy-2,3-hexadiene not only formed a hydrogen bond with the oxygen of phosphate but also coordinated to the Ag(I) to simultaneously stabilize the transition states and control the regioselectivity.

■ ASSOCIATED CONTENT

■ Supporting Information

Complete experimental procedures and characterization data for the prepared compounds and complete ref 16. This material is available free of charge via the Internet at <http://pubs.acs.org>

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Notes

The authors declare no competing financial interest.

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