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Published on Web 11/21/2008

# Three-Component Ag-Catalyzed Enantioselective Vinylogous Mannich and Aza-Diels−Alder Reactions with Alkyl-Substituted Aldehydes

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***Abstract:*** Efficient protocols for three-component catalytic enantioselective vinylogous Mannich (VM) reactions of alkyl-substituted aldimines (including those bearing heteroatom-containing substituents) and readily available siloxyfurans are presented. High efficiency and stereoselectivity is achieved through the use of *o*-thiomethyl-*p*-methoxyaniline-derived aldimines. Reactions, performed under an atmosphere of air and in undistilled THF, can be promoted in the presence of as little as 1 mol % of easily accessible amino acid−based chiral ligands and commercially available AgOAc. The desired products are obtained in 44 to 92% yield, and in up to >98:<2 diastereomer and >99:<1 enantiomer ratio (>98% ee). Removal of the N-activating group is performed through a one-vessel oxidation/hydrolysis operation, which proceeds via a stable aza-quinone (characterized by X-ray crystallography). Evidence is presented indicating that reactions with chiral nonracemic aldehydes are subject to catalyst control: both substrate enantiomers react to afford the desired product diastereomers in high stereoselectivity. Aryl- and alkynyl-substituted *o*-thiomethyl-*p*-methoxyaniline-derived aldimines undergo Ag-catalyzed enantioselective VM reactions more efficiently and with higher selectivity than the corresponding *o*-anisidyl substrates. Additionally, Ag-catalyzed aza-Diels−Alder reactions of the alkyl-substituted aldimines bearing the structurally modified N-aryl unit afford enantiomerically enriched (up to 95% ee) products in up to 88% yield.

## Introduction

Mannich reactions rank among the most versatile class of transformations in organic chemistry. Development of efficient and practical catalytic enantioselective variants of such reactions stands as a critical goal in chemical synthesis.[1,2] One set of Mannich-type processes involves additions of siloxyfurans to aldimines; as illustrated in Scheme 1, highly diastereo- and enantioselective versions of such processes generate small organic molecules that can be functionalized in a number of ways. We recently outlined an efficient and selective protocol for Ag-catalyzed[3,4] enantioselective vinylogous Mannich (VM) reactions of aryl-substituted aldimines.[5] The desired products can be obtained in excellent diastereo- (typically >99:<1 dr) and enantioselectivity (typically >95:<5 er) by transformations that often require as little as 1 mol % of a readily available phosphine ligand and commercially available Ag salt; transformations do not require distilled solvents or inert atmosphere conditions.[5] In an earlier investigation, also represented in Scheme 1, we utilized the above Ag-based chiral complexes to effect enantioselective aza-Diels−Alder reactions[6] with the Danishefsky diene.[7] Transformations in the above two classes of Ag-catalyzed reactions involve nonenolizable aryl-substituted aldimines. In the case of protocols disclosed by other laboratories, catalytic enantioselective VM and aza-Diels−Alder reactions with aldimines derived from alkyl-substituted aldehydes are either not included or are limited to two examples or less.[8−10] Enantioselective VM processes involving this limited set of substrates are effected with diminished efficiency and diastereoselectivity than those of the more common aryl-substituted aldimines.

Herein, we describe the development of a protocol for efficient three-component Ag-catalyzed enantioselective VM

(1) For a recent review of Mannich reactions involving aldimines, see: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112. For select recent reports of catalytic enantioselective Mannich reactions (not VM) involving aldimines, see: (b) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768–7769. (c) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777–8785. (d) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525–1529. (e) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600–3603. (f) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049. (g) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805. (h) Chen, Z.; Yakura, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 3239–3242.

(2) For an overview regarding applications of Mannich reactions to the preparation of biologically active molecules and target-oriented synthesis, see:(a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221–3242.

(3) For an overview of utility of chiral Ag-based phosphine complexes in enantioselective reactions, see: Yanagisawa, A.; Arai, T. *Chem. Commun.* **2008**, 1165–1172.

(4) For a review of Ag-catalyzed enantioselective reactions, see: Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148.

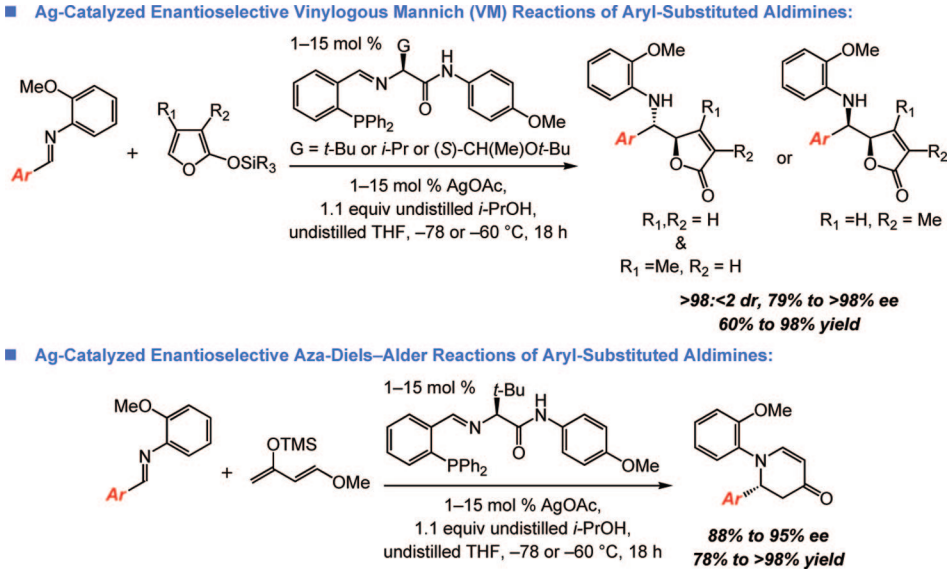
(5) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230–7233.

(6) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019.

(7) (a) Kerwin, J. F., Jr.; Danishefsky, S. J. *Tetrahedron Lett.* **1982**, *23*, 3739–3742. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23.

***Scheme 1.*** Previously Reported Ag-Catalyzed Enantioselective Vinylogous Mannich and Aza-Diels-Alder Reactions of Aryl-Substituted Aldimines




reactions of the more demanding alkyl-substituted aldimines, a class of substrates that cannot be readily isolated and purified and are typically prone to decomposition. Use of an N-aryl unit bearing an *o*-thiomethyl and a *p*-methoxy substituent is critical for efficient access to alkyl-substituted aldimines (vs *o*-anisidyl in Scheme 1), which are prepared and used *in situ* through diastereo- and enantioselective three-component processes (up to >98:<2 dr and >99:<1 er). We illustrate that alkyl-substituted aldimines can be used in Ag-catalyzed three-component enantioselective aza-Diels−Alder reactions as well.

## Results and Discussion

**I. Development of Ag-Catalyzed Enantioselective VM of Alkyl-Substituted Aldimines. a. Examination of various N-aryl groups.** We began by examining the reaction of the aldimine derived from cyclohexylcarboxaldehyde **3a** and aniline **1a** (Table 1), a substrate that bears the previously and commonly utilized *o*-anisidine N-aryl group, with the commercially available (unpurified) siloxyfuran **2**. Chiral ligand **4a**, formerly demonstrated to be effective in promoting Mannich-type processes,[5,6] was used. As the data in entry 1 of Table 1 indicate, with 5 mol % **4a** and AgOAc in THF at −78 °C, there is complete aldimine consumption and unsaturated γ-lactone **5** is obtained in 95:5 dr and 94:6 er (88% ee), but in only 44% yield. Examination of the 400 MHz $^1$H NMR spectrum of the unpurified mixture indicates the presence of a substantial amount of byproducts, pointing to the relative instability of the *in situ*-generated imine.

In search of a more robust substrate, we examined the reaction of the aldimine derived from **3a** and methyl-substituted anisidine **1b** (entry 2, Table 1). We surmised that the presence of a methyl group *ortho* to the C=N bond[11] might provide sufficient steric hindrance to discourage formation of the aminal (i.e., addition of aniline to aldimine), a byproduct detected in the reaction with *o*-anisidine **1a**. As illustrated in entry 2 of Table 1, treatment of the aldimine derived from **1b** to the above conditions results in <2% conversion. Based on the hypothesis that a more electrophilic imine might be induced to undergo efficient catalytic enantioselective VM, we turned to the electronically activated *p*-nitro-substituted aldimine derived from **1c** and **3a**; we have recently demonstrated that use of **1c** leads to efficient, diastereo- and enantioselective VM reactions of α-ketoimine esters.[12] As shown in entry 3 of Table 1, however, the process involving aniline **1c** and aldehyde **3a** results in <2% conversion to the desired VM product.

To determine whether the inefficiency in cases involving anilines **1b** and **1c** is due to ineffective aldimine generation, substrate decomposition and/or lack of substrate reactivity, we

(8) For disclosures regarding catalytic enantioselective VM reactions that include examples of alkyl-substituted aldimines, see: With *i*-Pr- and Cy-substituted aldimines: (a) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399–402. With two closely related *n*-alkyl-substituted aldimines: (b) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319–2322. Only aryl-substituted aldimines: (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805.

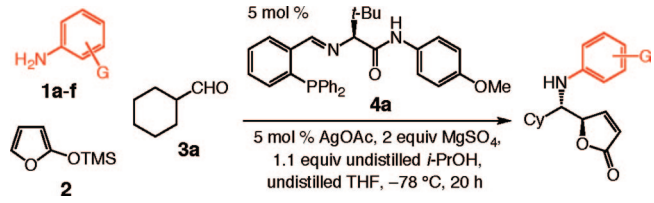
(9) For reports on catalytic enantioselective aza-Diels-Alder reactions that include examples with alkyl-substituted aldimines, see: With only Cy-substituted aldimines: (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979–981. With *i*-Pr- and Cy-substituted aldimines: (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796–4798. With 2-propyl-substituted aldimine: (c) Shang, D.; Xin, J.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. *J. Org. Chem.* **2008**, *73*, 630–637. For a related catalytic enantioselective aza-Diels-Alder protocol, see: (d) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877–4880.

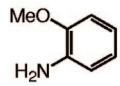
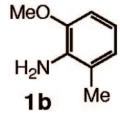
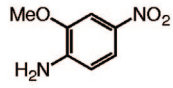
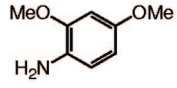
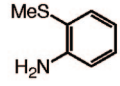
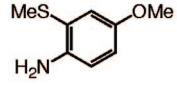
(10) For catalytic enantioselective Mannich-type reactions (not VM or aza-Diels-Alder) that include reactions of alkyl-substituted aldimines, see: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186. (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337. (c) González, A. S.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 2977–2980. (d) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624–9634. (e) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533–3536. (f) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985–3989. (g) Trost, B. M.; Jaratjaroonphong, J.; Reutrakaul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779. (h) Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603–606. (i) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem.−Eur. J.* **2007**, *13*, 8338–8351.

(11) For use of a related N-arylimine in Zr-catalyzed Mannich reactions with silylketene acetals, see: Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154.

(12) Wieland, L. C.; Vieira, E. V.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* in press.

***Table 1.*** Examination of Various N-Aryl Groups in Three-Component Enantioselective VM Reaction Involving an Aliphatic Aldehyde[a]




| entry | N-aryl group | product | conv (%)[b] | yield (%)[c] | dr[b] | er; ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 |  **1a** | **5** | >98 | 44 | 95:5 | 94:6; 88 |
| 2 |  **1b** | – | <2 | – | – | – |
| 3 |  **1c** | – | <2 | – | – | – |
| 4 |  **1d** | **6** | >98 | 81 | 96:4 | 94:6; 88 |
| 5 |  **1e** | **7** | >98 | 58 | >98:<2 | 98.5:1.5; 97 |
| 6 |  **1f** | **8a** | ***>98*** | ***90*** | ***>98:<2*** | ***>99:<1; >98*** |

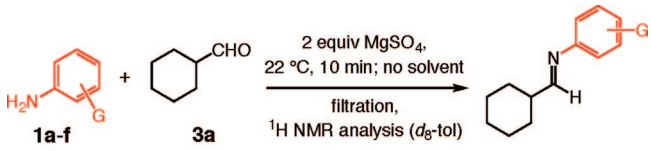
[a] Reactions performed under an atmosphere of air. [b] Conversions and diastereomer ratio (dr) values were determined by analysis of 400 MHz $^1$H NMR spectra of unpurified products (based on disappearance of **3a**). [c] Yields of isolated and purified products. [d] Enantiomer ratio (er) values were determined by HPLC analysis; see the Supporting Information for details.

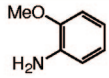
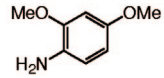
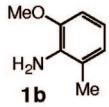
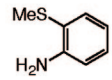
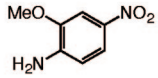
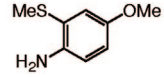
performed the studies summarized in Table 2. We thus find that, whereas imine formation is relatively efficient with *o*-anisidine **1a** and *o*-methyl-substituted **1b** (42 and 61% conv, respectively; entries 1–2), the mixture that contains aldehyde **3a** and aniline **1c** (entry 3) consists of unidentifiable side products (minimal aldimine detected). These observations imply that the electronically activated aldimine derived from **3a** and **1c** is unstable.

In light of the above findings, and based on the assumption that the corresponding electron rich aldimine is less electrophilic and thus less prone to decomposition, we prepared and examined the reaction of the aldimine derived from **3a** and 2,4-dimethoxyaniline **1d** (entry 4, Table 1). As illustrated in entry 4 of Table 1, >98% conversion is achieved and **6** is isolated in 81% yield, an outcome significantly superior to that obtained when **1a** is used (entry 1) but with equally high diastereo- (96:4 dr) and enantioselectivity (94:6 er, 88% ee). As the data in entry 4 of Table 2 indicate, with aniline **1d**, imine formation is more efficient than when **1a** or **1b** are used (83% conv vs 42% and 61% conv, respectively).

With a relatively effective catalytic enantioselective VM reaction in hand (entry 4, Table 1), we turned to determining whether product enantiopurity (96:4 dr, 88% ee in entries 1 and 4, Table 1) might be improved through further adjustment of the structure of the N-aryl group. Within this context, we chose to examine an N-aryl unit that bears a S-based metal-coordinating group. We reasoned that a more effective association of the "softer" chelating heteroatom with the late transition metal may lead to a more organized transition state structure and improved enantiodifferentiation. As illustrated in entry 5 of Table 1, when *o*-thiomethylaniline **1e** is used to prepare the aldimine derived from **3a**, the desired product (**7**) is isolated as a 98.5:1.5 mixture of enantiomers (97% ee), which is a higher degree of enantiopurity than observed with the corresponding *O*-substituted N-aryl group **1a** (entry 1, 94:6 er); the diastereoselectivity of the process is improved as well, with the product now obtained as a single diastereomer (>98:<2 dr). Since rendering the N-aryl group more electron rich leads to more efficient VM reactions in the case of methoxy-substituted N-aryl groups (i.e., entry 1 vs 4 in Tables 1–2), we prepared the aldimine derived from S-substituted aniline **1f**. As shown in entry 6 of Table 1, Ag-catalyzed enantioselective VM with the cyclohexyl-substituted aldimine derived from the *o*-thiomethyl-*p*-methoxyaniline (**1f**) proceeds to >98% conversion, affording **8a** in 90% yield after chromatography, >98:<2 diastereoselectivity and as a single enantiomer (>99:<1 er, >98% ee). The stereochemical identity of **8a** has been determined by X-ray

***Table 2.*** Examination of the Relative Facility of Aldimine Formation[a]




| entry | N-aryl group | conv (%)[b] | entry | N-aryl group | conv (%)[b] |
|---|---|---|---|---|---|
| 1 |  **1a** | 42 | 4 |  **1d** | 83 |
| 2 |  **1b** | 61 | 5 |  **1e** | 68 |
| 3 |  **1c** | <2[c] | 6 |  **1f** | 90 |

[a] Reactions run under an atmosphere of air. [b] Conversion determined by analysis of 400 MHz $^1$H NMR spectra of the unpurified reaction mixtures (based on disappearance of **3a**). [c] Complex mixture of products formed.

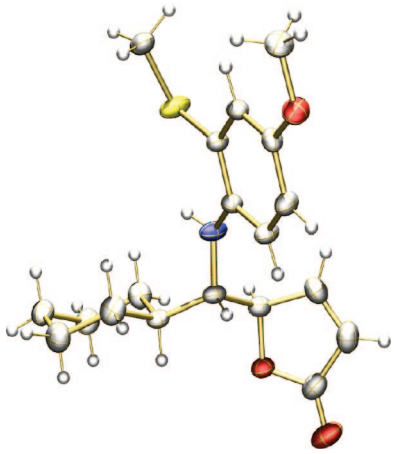
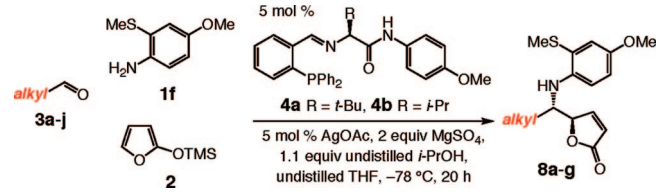


***Figure 1.*** X-ray structure of product **8a**.

structure analysis (Figure 1). As indicated by the data summarized in entries 5−6 of Table 2, similar to anilines **1a** and **1d** (entries 1 and 4, Table 2), aldimine formation is more efficient in the case of S-substituted aldimines that bear a more electron rich N-aryl unit (90% conv in 10 min).

**b. Ag-Catalyzed Enantioselective VM with Alkyl-Substituted Aldimines.** Aniline **1f** can be used in three-component enantioselective VM reactions involving an assortment of alkyl-substituted aldehydes and commercially available siloxyfuran **2**; transformations are promoted in the presence of chiral amino acid−based phosphine ligands **4a** and **4b** and commercially available AgOAc (Table 3). Reactions proceed to >98% conversion and afford a single diastereomer (>98:<2) with *in situ*-generated aldimines that bear an α-branched (entries 1−4), a *β*-branched (entry 5), as well as an *n*-alkyl substituent (entries 7−8). Ag-catalyzed VM with *t*-Bu-substituted **3e** (entry 6, Table 3) requires 30 mol % loading and elevated temperature (−30 vs −78 °C), affording **8e** in 50% yield. In all cases involving the *t*-Leu-bearing phophine **4a** (entries 1 and 3−8, Table 3), products **8a**−**g** are obtained as a single enantiomer (>99:<1 er, >98% ee); only when the less expensive Val-containing **4b** is used (entry 2 of Table 3), is any of the minor enantiomer of **8a** detected by HPLC analysis (98.5:1.5 er, 97% ee).

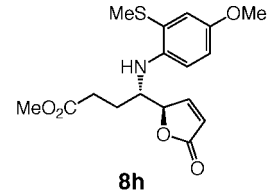
***Table 3.*** Ag-Catalyzed Three-Component Enantioselective VM Reactions of Alkyl-Substituted Aldimines with Siloxyfuran **2**[a]



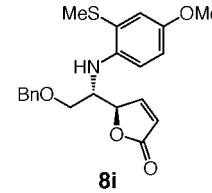

| entry | aldehyde | ligand | product | yield (%)[b] | dr[c] | er; ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | CyCHO | **4a** | **8a** | 90 | >98:<2 | >99:<1; >98 |
| 2 | CyCHO | **4b** | **8a** | 74 | >98:<2 | 98.5:1.5; 97 |
| 3 | *i*-PrCHO | **4a** | **8b** | 89 | >98:<2 | >99:<1; >98 |
| 4 |  | **4a** | **8c** | 88 | >98:<2 | >99:<1; >98 |
| 5 | *i*-BuCHO | **4a** | **8d** | 92 | >98:<2 | >99:<1; >98 |
| 6[e] | *t*-BuCHO | **4a** | **8e** | 50 | >98:<2 | >99:<1; >98 |
| 7 | $Ph(CH_2)_2CHO$ | **4a** | **8f** | 79 | >98:<2 | >99:<1; >98 |
| 8 | *n*-HexCHO | **4a** | **8g** | 75 | >98:<2 | >99:<1; >98 |

[a] Reactions performed under an atmosphere of air with 1.0 equiv of aldehyde and aniline in the presence of 2.0 equiv of siloxyfuran **2**; >98% conversion in all cases (based on disappearance of aldehyde), except for entry 6 (93% conv). [b] Yields of isolated purified products. [c] Diastereomer ratio (dr) values were determined by analysis of 400 MHz $^1$H NMR spectra of the unpurified reaction mixtures. [d] Enantiomer ratio (er) values were determined by HPLC analysis; see the Supporting Information for details. [e] Reaction performed with 30 mol % catalyst at −30 °C.

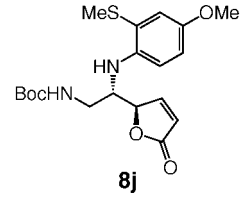
***Scheme 2.*** Products from Catalytic Enantioselective VM Reactions of Heteroatom-Bearing Aldimines[a]



**8h**
***>98% conv, 56% yield, >98:<2 dr, >99:<1 er (>98% ee)***



**8i**
***>98% conv, 51% yield, >98:<2 dr, >99:<1 er (>98% ee)***



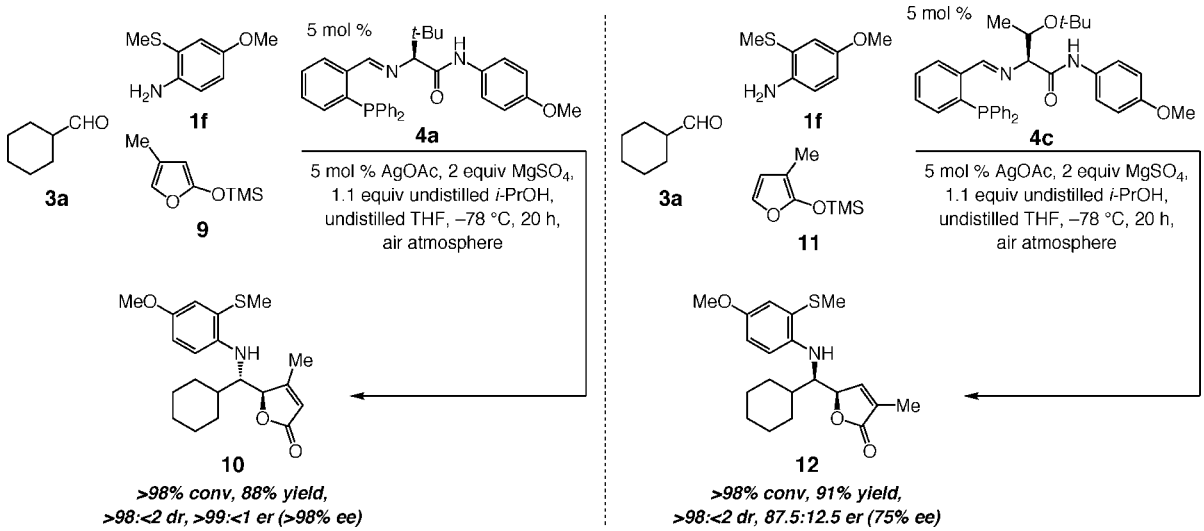
**8j**
***>98% conv, 44% yield, >98:<2 dr, >99:<1 er (>98% ee)***

[a] Reactions performed under identical conditions as shown in Table 3.

As the three examples in Scheme 2 illustrate, the three-component Ag-catalyzed enantioselective VM process can be performed with heteroatom-containing aldimines, synthetically versatile imines scarcely examined in this context.[13] Products **8h**−**j** are obtained in moderate yields after purification (44−56%); these lower yields might be the result of adventitious intramolecular addition of the hydroxyl group of the intermediate

(13) To the best of our knowledge, there is only one reported example of a catalytic enantioselective Mannich reaction that involves a heteroatom-containing imine (benzyloxy acetaldehyde-derived imine); see ref 10b.

***Scheme 3.*** Ag-Catalyzed Enantioselective VM Reactions with Me-Substituted Siloxyfurans




hemiamanal to the proximal ester unit (in the case of **8h**) or the relative instability of highly electrophilic aldimines and their precursor aldehydes (with **8i** and **8j**). Nonetheless, reactions represented in Scheme 2 proceed with the same diastereo- and enantioselectivity as observed with unfunctionalized alkyl-substituted aldehydes (Table 3).

Ag-catalyzed enantioselective VM reactions can be performed with various substituted siloxyfurans. Transformations proceed with similar efficiency as observed with reactions of unsubstituted **2** and with exceptional diastereoselectivity (Scheme 3). The degree and sense of enantiodifferentiation, however, consistent to that previously observed with the related reactions with aryl-substituted aldimines,[5] depend on the identity of the Si-based nucleophile. Whereas reaction with 4-methyl-substituted siloxyfuran **9** results in the formation of *anti*-**10** in >99:<1 er, in the case of 3-methyl-substituted **11**, it is *syn*-**12** that is isolated as the exclusive diastereomer in 87.5:12.5 er (75% ee). Although **4a** promotes the reaction of **9** with aldimine prepared from **3a** and **1f** with high diastereo- and enantioselectivity (Scheme 3), the optimal chiral ligand required for VM of **11**, identified through screening studies, is one that bears a *t*-Bu-Thr moiety (vs *t*-Leu).[14] When **4a** is used to promote the reaction of the aldimine derived from **3a** and **1f** with **11**, *syn*-**12** is obtained in >99:<1 dr but only in 61:39 er (22% ee). Although the mechanistic rationale for the change in the identity of the chiral ligand is unclear, working models proposed previously[5] for reactions of aryl-substituted aldimines, which undergo Ag-catalyzed enantioselective VM with similar reactivity and selectivity trends, can be applied to the present cases.

**c. Catalyst vs Substrate Control in Ag-Catalyzed Enantioselective VM Reactions of Chiral Alkyl-Substituted Aldimines.** With an efficient protocol for catalytic enantioselective VM of alkyl-substituted aldimines, particularly those containing a heteroatom, in hand, we addressed the issue of catalyst versus substrate control in three-component transformations involving chiral aldehydes. Such considerations address the possibility of whether the catalytic enantioselective method can be used in a setting where the substrate is chiral and nonracemic. In cases where the stereogenic center is relatively remote from the C=N bond (i.e., at the $\beta$ or $\gamma$ carbons of the aldimine), it is likely that both substrate enantiomers react readily with the same chiral catalyst isomer to afford the two possible diastereomers with high selectivity. There are, however, it is in cases where the stereogenic center is proximal to the imine that the substrate enantiomers can exhibit substantially different reactivity and selectivity patterns, as the neighboring stereogenic center can have a significant influence on the transformation. That is, one substrate enantiomer might undergo reaction more readily and selectively than the other (substrate control); in such instances, the catalytic reaction can be utilized to carry out kinetic resolution.[15] Alternatively, both imine enantiomers might react readily, such that the stereochemical outcome of the reaction is dictated by the identity of the chiral catalyst (catalyst control), allowing access to either diastereomer selectively.

To address the above questions, the studies summarized in Table 4 were performed. As illustrated in entry 1, when enantiomerically enriched *S*-**13**[16] is used, **14** is obtained in 68% yield and with high diastereoselectivity (>98:<2 dr) as a single enantiomer (>99:<1 er, >98% ee). Precisely the same outcome is observed, as shown in entry 2 of Table 4, with enantiomerically enriched *R*-**13**: **15** is isolated in 75% yield as a single isomer. Use of *rac*-**13** leads to the formation of products **14** and **15** with no detectable contamination from any of the alternative stereoisomers. The above studies demonstrate that effective catalyst control is operative in Ag-catalyzed enantioselective VM reactions and efficient control of stereochemistry can be achieved by the appropriate choice of the chiral catalyst.

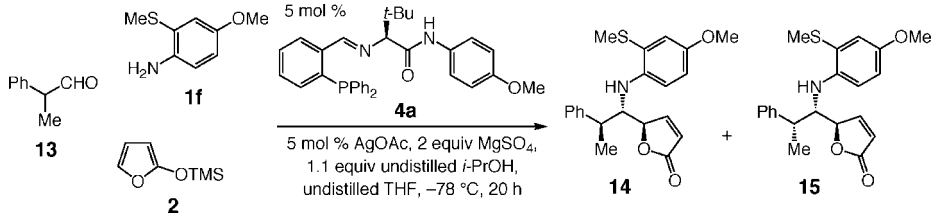
**d. Practicality of the Catalytic Protocol.** One of the hallmarks of Ag-catalyzed reactions is the simplicity of the procedures: reactions are performed in undistilled THF, with undistilled additive (*i*-PrOH) and in an atmosphere of air. Aniline **1f** is

(14) See the Supporting Information for details of ligand screening studies.

(15) For a case involving an enantioselective conjugate addition of an enantiomerically enriched enone with a stereogenic center $\alpha$ to the reacting site, where use of an amino acid-based chiral phosphine catalyst results in enhancement of selectivity, see: (a) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96–101. For an example where an enantioselective alkylation of an enantiomerically enriched allylic phosphate promoted by amino acid-based catalyst proceeds readily and selectively with only one of the substrate enantiomers, see: (b) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676–10681.

(16) See the Supporting Information for details regarding the preparation and enantiomeric purity of chiral non-racemic aldehydes used in this study. The selectivity values shown in Table 4 are corrected.

***Table 4.*** Ag-Catalyzed Three-Component Enantioselective VM Reactions of Chiral Alkyl-Substituted Aldimines with Siloxyfuran **2**[a]

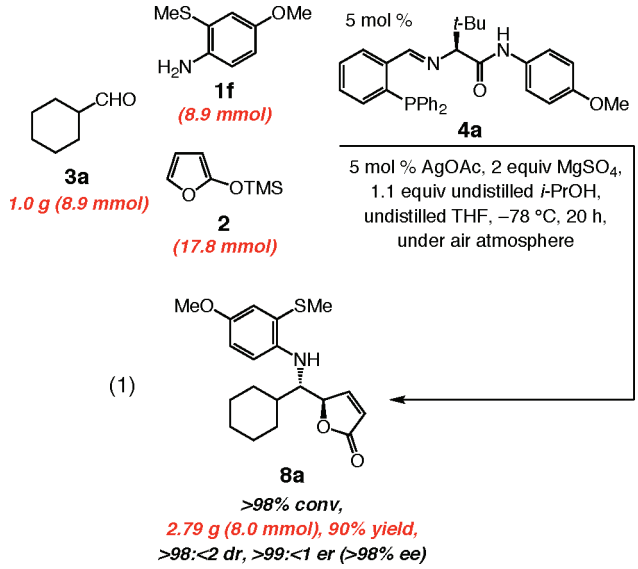



| entry | aldehyde | **14** yield (%)[b] | dr[c] | er; ee (%)[d] | **15** yield (%)[b] | dr[c] | er; ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | *S*-**13** | 68 | >98:<2 | >99:<1; >98 | – | – | – |
| 2 | *R*-**13** | – | – | – | 75 | >98:<2 | >99:<1; >98 |
| 3 | *rac*-**13** | 38 | >98:<2 | >99:<1; >98 | 42 | >98:<2 | 99:1; 98 |

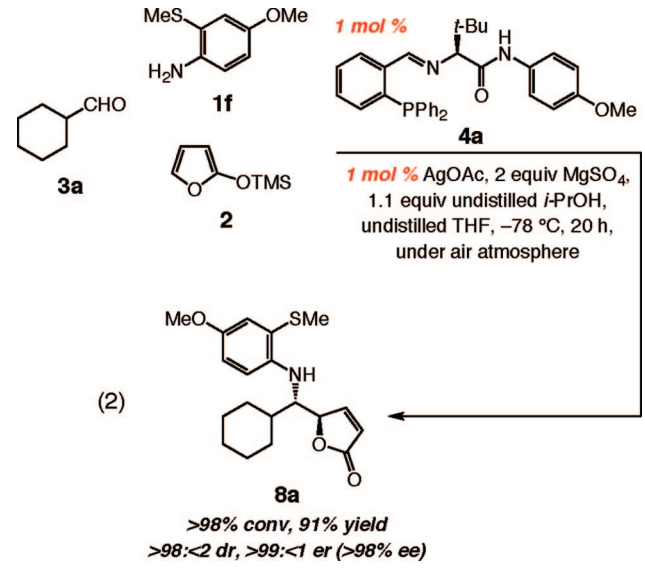
[a] Reactions performed in an atmosphere of air with 1.0 equiv of aldehyde and aniline and with 2.0 equiv of siloxyfuran **2**; >98% conversion in all cases (based on disappearance of aldehyde). [b] Yields of isolated purified products. [c] Diastereomeric ratios were determined by analysis of 400 MHz $^1$H NMR spectra of the unpurified reaction mixtures. [d] Enantiomer ratio (er) values were determined by HPLC analysis; see the Supporting Information for details.

prepared from easily accessible, as well as commercially available (Aldrich), 2-amino-6-methoxybenzothiazole through a simple basic hydrolysis/alkylation process, which proceeds in 67−82% yield.[17]

The enantioselective protocol is amenable to gram scale preparation of products. As illustrated in eq 1, such reactions proceed with nearly identical efficiency, as well as diastereo- and enantioselectivity, as illustrated previously.




Although the studies detailed above involve transformations promoted by 5 mol % catalyst loading,[18] the catalytic reactions proceed to >98% conversion in the presence of 1 mol % of the chiral ligand and AgOAc, affording the desired products with nearly identical efficiency and enantioselectivity.[19] The case depicted in eq 2 is illustrative.



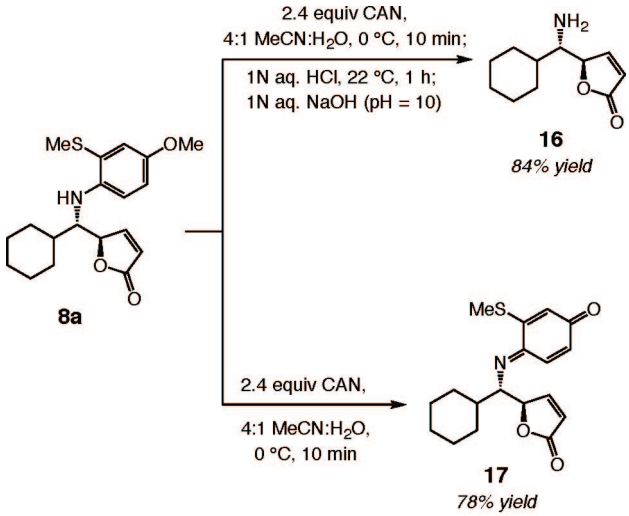

**e. Removal of the N-Activating Group; Characterization of the Corresponding Intermediate.** The S-containing N-activating group can be removed through a one-vessel operation that involves oxidation mediated by cerric ammonium nitrate

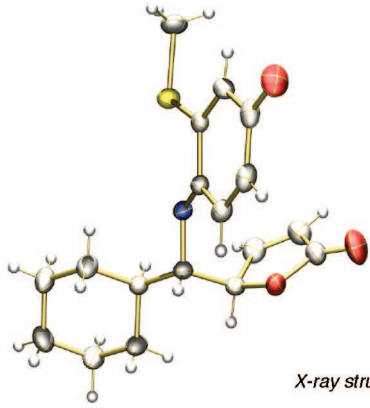
(17) McDonald, F. E.; Burova, S. A.; Huffmann, L. G., Jr. *Synthesis* **2000**, 970–974.

(18) For accuracy in measuring small amounts of chiral ligand and Ag salt, transformations were performed in the presence of 5 mol % catalyst.

(19) Although the gram scale reaction shown in eq 1 was performed with 5 mol % catalyst, previous studies involving related Mannich-type processes indicate that lower catalyst loadings can be readily extended to larger scale transformations; for example, see ref 5.

***Scheme 4.*** Oxidative Removal of the N-Activating Group and Isolation of the Intermediate



*X-ray structure of 17*

(CAN) followed by hydrolytic workup. The example in Scheme 4, leading to formation of enantiomerically pure amine **16** in 84% yield is a case in point. An attribute of the new N-activating group is that, in contrast to the formerly reported *o*-anisidyl groups, the derived aza-quinone, oxidation product (**17**) that is hydrolyzed to obtain the unmasked amine (e.g., **16**), can be isolated and purified. As also shown in Scheme 4, subjection of **8a** with 2.4 equiv of CAN for 10 min at 0 °C results in the formation of **17** in 78% yield after silica gel chromatography. The identity of aza-quinone **17** has been ascertained by X-ray crystallography (Scheme 4). That the initial oxidation product, an electrophilic entity that can be functionalized in a variety of manners, can be easily isolated and purified,[20] suggests that derivatives previously inaccessible through the use of *o*-anisidyl imines are now within reach.

**II. Effectiveness of the S-Containing N-Aryl Group in Other Ag-Catalyzed Enantioselective Mannich-Type Reactions. a. Ag-Catalyzed Enantioselective Mannich Reactions with Aryl- and Alkynyl-Substituted Aldimines.** The efficiency and high degrees of enantiodifferentiation in catalytic enantioselective VM reactions described above are not limited to alkyl-substituted aldimines. As the examples in Table 5 demonstrate, the utility of the S-containing N-aryl group extends to related catalytic transformations with aryl- (entry 1, Table 5) and alkynyl-substituted (entry 3, Table 5) substrates. As comparison of transformations in entries 1 and 3 with those in entries 2 and 4 of Table 5 indicate, VM with *o*-thiomethyl-*p*-methoxyaniline-derived imines are more efficient (>98% vs 86% yield for phenyl-substituted and 89% vs 70% for alkynyl-substituted aldimines, respectively). Whereas reactions in all cases proceed with high diastereoselectivity, processes involving the S-containing N-aryl group are more selective (>99:<1 vs 98:2 er and >99:<1 er vs 96.5:3.5 er, respectively). The above observations underline the special utility of the new N-activating group in allowing for exceptionally efficient and selective enantioselective VM reactions with a range of substrates.[21]

**b. Ag-Catalyzed Enantioselective Aza-Diels–Alder Reactions of Alkyl-Substituted Aldimines and the Danishefsky Diene.** *o*-Thiomethyl-*p*-methoxy aniline **1f** can be used efficiently in enantioselective three-component aza-Diels–Alder reactions with a range of alkyl-substituted aldehydes; examples are illustrated in Table 6. As the transformations in entries 1–2 (Table 6) indicate, cycloadditions can be performed in the presence of Val-containing chiral ligand **4b** with similar efficiency and selectivity as observed with *t*-Leu-bearing **4a**.

Cycloadditions are effective with aldimines bearing an *n*-alkyl substituent (entry 3, Table 6), as well as those that carry heteroatom-containing functional groups (entries 4–5, Table 6); as observed with the related enantioselective VM reactions (see Scheme 2), however, catalytic aza-Diels–Alder processes with the latter class of substrates afford dihydropiperidines in lower yields.

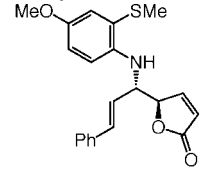
Two additional points regarding the observations in Table 6 merit mention: (1) Ag-catalyzed cycloaddition with *i*-Bu-substituted aldimine derived from *o*-methoxyaniline **1a** and aldehyde **3d** (under identical conditions as shown in Table 6) affords the desired dihydropiperidine in only 16% yield (98:2 er), since the reaction mixture contains unidentified byproducts. (2) Transformations performed at lower temperature are equally selective but significantly less efficient. As an example, the reaction shown in entry 1 of Table 6 results in only ~30% yield of **27d** under otherwise identical conditions (>98% consumption of aldimine; >99:<1 er).

## Conclusions

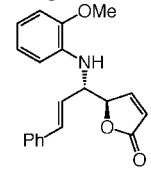
We present a reasonably general method for catalytic enantioselective vinylogous Mannich-type reactions that involve alkyl-substituted aldimines. The three-component Ag-catalyzed process is performed through a practical procedure (undistilled solvent, in an atmosphere of air) and proceeds efficiently (44%–92% yield) and with exceptional diastereo- (>98:<2 dr) and enantioselectivity (95:5 er to >99:<1 er).

(20) For a related oxidation process, see: Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190–1195.

(21) As illustrated by the examples below, enantioselective VM reactions with aldimines derived from α,β-unsaturated aldehydes proceed to >98% conversion and in high diastereo- and enantioselectivity but in low yields. Control experiments point to product instability.

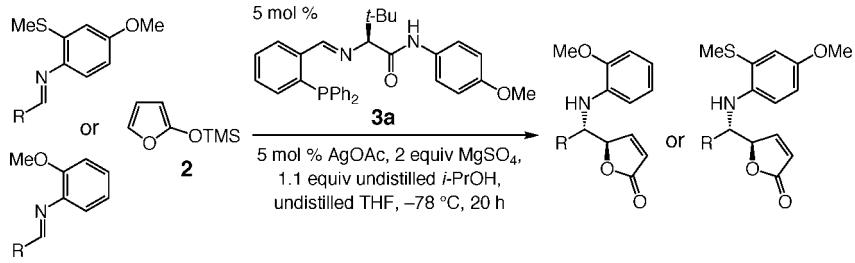


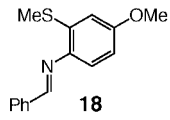
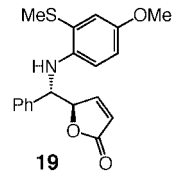
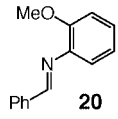
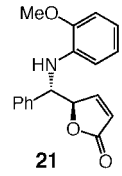
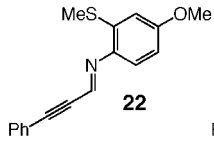
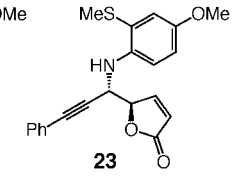
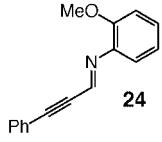
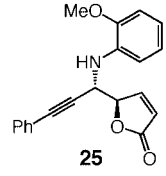

*>98% conv, 32% yield, >98:<2 dr, 97.5:2.5 er (95% ee)*




*>98% conv, 24% yield, >98:<2 dr, 96:4 er (92% ee)*

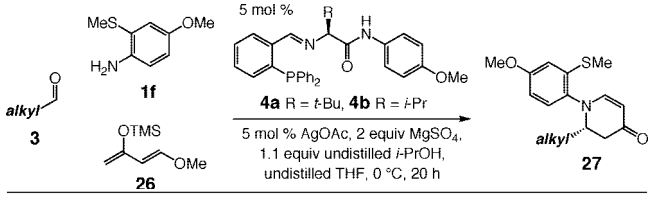
***Table 5.*** Ag-Catalyzed Enantioselective VM Reactions of Isolable Aldimines with Siloxyfuran **2**[a]




| entry | aldimine | product | yield (%)[b] | dr[c] | er; ee (%)[d] |
|---|---|---|---|---|---|
| 1 |  **18** |  **19** | >98 | >99:<1 | >99:<1; >98 |
| 2 |  **20** |  **21** | 86 | >99:<1 | 98:2; 96 |
| 3 |  **22** |  **23** | 89 | >99:<1 | >99:<1; >98 |
| 4 |  **24** |  **25** | 70 | >99:<1 | 97.5:2.5; 95 |

[a] Reactions performed under an atmosphere of air with 1.0 equiv of isolable imine in the presence of 2.0 equiv of siloxyfuran 2. [b] See Table 3. [c] See Table 3. [d] See Table 3.

***Table 6.*** Ag-Catalyzed Asymmetric Aza-Diels-Alder Reactions of Alkyl-Substituted Aldimines with Danishefsky Diene[a]




| entry | aldehyde | ligand | product | yield (%)[b] | er[c] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | *i*-BuCHO (**3d**) | **4a** | **27d** | 88 | 96:4 | 92 |
| 2 | *i*-BuCHO (**3d**) | **4b** | **27d** | 85 | 96:4 | 92 |
| 3 | $Ph(CH_2)_2CHO$ (**3f**) | **4a** | **27f** | 88 | 96.5:3.5 | 93 |
| 4 | $MeO_2C(CH_2)_2CHO$ (**3h**) | **4a** | **27h** | 53 | 95:5 | 90 |
| 5 | $BnOCH_2CHO$ (**3i**) | **4a** | **27i** | 66 | 97.5:2.5 | 95 |

[a] Reactions performed in an atmosphere of air with 1.0 equiv of aldehyde and aniline in the presence of 2.0 equiv of diene **26**; >98% conversion in all cases. [b] Yields of the isolated purified products. [c] Enantiomer ratio (er) values were determined by HPLC analysis; see the Supporting Information for details.

The present studies furnish an illustration of the utility of aniline-derived aldimines as effective substrates for catalytic enantioselective C−C bond forming reactions. Conversion of the enantiomerically enriched products obtained requires removal of N-aryl groups through oxidative protocols; such procedures can be more demanding than simple hydrolyses required for functionalization of products obtained from reactions of other classes of imine substrates (e.g., acid labile phosphinoylimines).[8b,10f,g] N-aryl-derived imines, however, offer an advantage: electronic tuning and modification of the coordinating heteroatom (in addition to N of the C=N bond) involved in bidentate chelation with the transition metal can be used to increase aldimine stability as well as elevate reaction efficiency and selectivity. We thus demonstrate that catalytic enantioselective VM and aza-Diels−Alder reactions of one of the more challenging sets of substrates, namely alkyl-substituted aldimines, can be performed with exceptional efficiency and enantioselectivity when substrates carry an N,S-based bidentate chelating structure (vs N,O) and an electron donating *p*-methoxy

unit. The availability of a S-based chelating group likely allows for a more effective association of the substrate with the Ag-based chiral catalyst and the presence of the electron donating *p*-methoxy unit gives rise to aldimines that are less prone to decomposition.

Design of new chiral amino acid−based ligands and catalysts[22] that promote efficient and selective additions to C═N bonds, development of other catalytic enantioselective processes involving aldimines and ketoimines derived from structurally optimized anilines and their application to synthesis of biologically active molecules are the focus of ongoing studies.

**Acknowledgment.** Financial support was provided by the NIH (GM-57212) and the Yamada Foundation (postdoctoral fellowship to H. M.). We thank L. C. Wieland (Boston College) and Dr. J. Kung (Boston College and Chungbuk National University, S. Korea) for many helpful discussions. Mass spectrometry facilities at Boston College are supported by the NSF (DBI-0619576).

**Supporting Information Available:** Experimental procedures and spectral data for substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA807243T

(22) For other related examples of catalytic enantioselective additions promoted by this class of amino acid-based chiral ligands, see: (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1668–1671. (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285. (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984–985. (d) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410. (e) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009–1012. (f) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273–3275. (g) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244–4247. (h) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779–1785. (i) Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 15453–15456. (j) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532–6533. (k) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530–5541. (l) Friel, D. K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 9942–9951.