

## Ag-Catalyzed Diastereo- and Enantioselective Vinylogous Mannich Reactions of $\alpha$ -Ketoimine Esters. Development of a Method and Investigation of its Mechanism

Laura C. Wieland, Erika M. Vieira, Marc L. Snapper,\* and Amir H. Hoveyda\*

Department of Chemistry, Merkert Chemistry Center, Boston College,  
Chestnut Hill, Massachusetts 02467

Received August 7, 2008; E-mail: amir.hoveyda@bc.edu

**Abstract:** An efficient diastereo- and enantioselective Ag-catalyzed method for additions of a commercially available siloxyfuran to  $\alpha$ -ketoimine esters is disclosed. Catalytic transformations require an inexpensive metal salt (AgOAc) and an air stable chiral ligand that is prepared in three steps from commercially available materials in 42% overall yield. Aryl- as well as heterocyclic substituted ketoimines can be used effectively in the Ag-catalyzed process. Additionally, two examples regarding reactions of alkyl-substituted ketoimines are presented. An electronically modified *N*-aryl group is introduced that is responsible for high reaction efficiency (>98% conversion, 72–95% yields after purification) as well as diastereo- (up to >98:2 dr) and enantioselectivity (up to 97:3 er or 94% ee). The new *N*-aryl unit is crucial for conversion of the asymmetric vinylogous Mannich (AVM) products to the unprotected amines in high yields. Spectroscopic and X-ray data are among the physical evidence provided that shed light on the identity of the Ag-based chiral catalysts and some of the mechanistic subtleties of this class of enantioselective C–C bond forming processes.

### 1. Introduction

Catalytic enantioselective additions of C-based nucleophiles to ketoimines offer direct access to nonracemic *N*-substituted quaternary carbon stereogenic centers, components of several biologically active molecules.<sup>1</sup> Ketoimines, however, are relatively unreactive,<sup>2</sup> often exist as a mixture of *E* and *Z* isomers, and contain a sterically congested C=N bond that carries difficult-to-differentiate substituents.<sup>3</sup> There are only two reported studies of Mannich-type additions<sup>4</sup> to ketoimines. One case corresponds to additions of aldehyde-derived enols to geometrically constrained ketone-derived cyclic imines;<sup>5</sup> another disclosure outlines reactions of simple ketene acetals with ketoimines that are mostly generated from methyl-substituted ketones.<sup>6</sup> Herein, we disclose a method for catalytic asymmetric vinylogous Mannich (AVM) reactions of ketoimines; additions are performed in the presence of a chiral Ag complex, which

can be easily prepared and stored in air for an extended period of time. Transformations are highly site-, diastereo-, and enantioselective, require a commercially available siloxyfuran and readily accessible substrates, and furnish products that bear an  $\alpha$ -quaternary amino ester.<sup>1</sup> We have identified an electronically modified class of *N*-aryl ketoimines that readily undergo AVM, affording products that can be converted to the unprotected amines efficiently. Through the studies described below, we offer insight regarding the identity of this emerging class of Ag-based chiral catalysts for asymmetric Mannich reactions.<sup>7–9</sup>

- (1) For stereoselective synthesis of *N*-substituted quaternary carbon stereogenic centers and quaternary  $\alpha$ -amino acids, see: Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623.
- (2) For catalytic enantioselective additions of C-based nucleophiles to ketoimines, see: (CN additions) (a) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784–10785. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014. (c) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635. (d) Wang, J.; Hu, X.; Jiang, J.; Gou, S.; Huang, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 8468–8470. (e) Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, *349*, 759–764. (Alkylmetal additions) (f) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743–2745. (g) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530–5541. (Allylmetal additions) (h) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691.

- (3) For a review on catalytic asymmetric reactions of ketoimines and ketones, see: Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888.
- (4) For a recent review of Mannich reactions of aldimines, see: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112. (b) For select recent reports of catalytic asymmetric Mannich reactions (not AVM) involving aldimines, see: 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) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805. (f) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600–3603. (g) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049. (h) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805. (i) Chen, Z.; Yakura, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 3239–3242.
- (5) (a) Saaby, S.; Nakama, K.; Alstrup Lie, M.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 6145–6154. (b) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476–4478.
- (6) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500–501.
- (7) For Ag-catalyzed Mannich-type reactions to aldimines (not AVM) in the presence of **1**, see: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019. (b) Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 2711–2713.

**Table 1.** Examination of Ketoimines Bearing Different N-Aryl Groups<sup>a</sup>

entry	G	temp (°C)	conv (%) <sup>b</sup>	anti:syn <sup>b</sup>	er; ee (%) <sup>c</sup>
1		+4	68	<2>:98	63.5:36.5; 27
2		-15	45	<2>:98	67:33; 34
3		-30	20	<2>:98	64.5:35.5; 29
4		-78	<2	nd	nd
5		-78	>98	93:7	95.5:4.5; 91
6		-78	>98	80:20	89.5:10.5; 79
7		-78	43	8:92	77.5:22.5; 55

<sup>a</sup> Reactions performed under N<sub>2</sub> atmosphere. <sup>b</sup> Conversion levels and diastereomeric ratios were determined by analysis of 400 MHz <sup>1</sup>H NMR spectra of unpurified products. <sup>c</sup> Enantiomeric ratio (er) values were determined by HPLC analysis; see Supporting Information for details. nd = not determined.

## 2. Results and Discussion

**2.1. Development of Ag-Catalyzed AVM of  $\alpha$ -Ketoimine Esters.** **2.1.1. Enhancement of Reactivity through Electronic Alteration of the N-Activating Group.** We began by investigating the ability of **1**, a small-molecule ligand (molecular weight = 508.6 g/mol) used to promote Ag-catalyzed enolsilane additions to *o*-anisidyl aldimines,<sup>7,8</sup> to initiate the reaction of **2** with  $\alpha$ -ketoimine ester **3** (see Table 1).<sup>10</sup> Although high diastereoselectivity is observed (>98:2 *syn/anti*; entries 1–3, Table 1), reactions are inefficient (20–68% conv, 15 h) and enantioselectivity is low (<35% ee); at lower temperatures (–78 °C), the desired products are not formed (entry 4).

To enhance AVM efficiency, we chose to alter the *N*-aryl unit of the ketoimine by installing a nitro group *para* to the imine. Such a modification allows AVM of **2** with **4a** (entry 5, Table 1) to proceed to >98% conversion at –78 °C, affording *anti*-**7a** in 91% ee (95.5:4.5 er). The sense of diastereoselectivity is reversed (vs **3**), as the *anti* product isomer is now selectively generated (dr = 93:7). Pure *anti*-**7a** is obtained after purification

in 72% yield (entry 1, Table 2).<sup>11</sup> The finding in entry 6 (Table 1) indicates that the *o*-methoxy group is beneficial to diastereo- and enantioselectivity; it is the electron-withdrawing unit *para* to the *N*-aryl, however, that is largely responsible for the enhanced efficiency. The observation summarized in entry 7 of Table 1 suggests that the positive effect of the *o*-methoxy group is not simply due to steric effects. Reaction with a substrate that bears an *o*-methyl-substituted *N*-aryl group (**6**) proceeds to only 43% conversion and results in the formation of *anti*-**7a** in 55% ee (77.5:22.5 er); it should be noted, however, that such processes proceed with relatively high diastereoselectivity in favor of the *syn* product isomer (*anti/syn* = 8:92).

**2.1.2. Range of Aryl-Substituted  $\alpha$ -Ketoimine Esters.** As the data summarized in Table 2 indicates, aryl-substituted  $\alpha$ -ketoimine esters undergo AVM reactions to furnish *anti*-**7a–h** diastereoselectively (75:25–93:7 dr), in 81–92% ee (90.5:9.5 to 96:4 er) and 51–78% yield; minor diastereomers (*syn*-**8a–h**) are typically obtained in 40–60% ee. (Data involving NaHCO<sub>3</sub> quench are shown in the left column; reactions with acid quench, the results of which are illustrated in the right-hand columns, are discussed below).

As represented by the example in entry 9, ketoimines with an *o*-substituted aryl group are not transformed with high enantioselectivity (<40% ee); such processes are efficient (>98% conv), however, and occur diastereoselectively, although it is the *syn* isomer that is generated predominantly (*anti/syn* = <2>:98). The outcome of the transformation shown in entry 9 of Table 2 is not as a result of electronic effects imposed by the presence of the halide substituent; catalytic AVM reactions of the corresponding  $\alpha$ -ketoimine ester bearing an *o*-methylphenyl moiety exhibits the same selectivity and reactivity profile. It is worth noting that a similar diastereoselectivity preference is observed when the *N*-aryl unit of the ketoimine bears an *ortho* substituent (see entry 7, Table 1).

**2.1.3. Effect of Workup Conditions on AVM Efficiency as well as Diastereo- and Enantioselectivity.** We next wondered whether the lower diastereomeric ratios (data in left columns, Table 2) and moderate yields of *anti* isomers could be improved by a better understanding of the origin of the selectivity reversal in reactions of **3** versus **4a** (entries 1–3 and 5, Table 1). Such considerations led us to determine that when the reaction of **2** and **4a** (–78 °C) is quenched with aqueous NaHCO<sub>3</sub>, there is 71% conversion after only 30 min; *syn*-**8a**, however, is formed predominantly (20:80 *anti*-**7a**/*syn*-**8a** vs 93:7 after 15 h), and enantioselectivity for both isomers is low (<25% ee). After 6 h, there is >98% conversion and *anti*-**7a** is obtained in 90% ee as the major diastereomer of a 91:9 mixture.

A plausible interpretation of the above data is that the addition of aqueous NaHCO<sub>3</sub> (Table 2) might not result in complete quenching of the reaction at –78 °C (i.e., excess **2** is not completely proto-desilylated);<sup>12</sup> the *syn*-selective transformation might occur as the solution is allowed to warm up. When the reaction is quenched after extended periods of time (i.e., 10–15 h), *anti*-**7a** is generated predominantly, since most of the ketoimine has been consumed. Moreover, examination of the unpurified mixture pointed to the formation of a byproduct, derived from Michael addition of the unreacted enolsilane **2**

(8) For Ag-catalyzed AVM reactions to aldimines in the presence of ligand **1**, see: (a) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230–7233. (b) For related investigations, see: Uruguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805. (c) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319–2322. (d) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399–402.

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

(10) Ketoimine substrates exist predominantly as an *E* isomer (2.5–20:1 *E/Z*); there appears to be no correlation between diastereo- or enantioselectivity and such ratios. For example, **4b** (93% ee) is a 5:1 *E/Z* ratio, whereas **4h** (94% ee) is nearly exclusively *E* (95:5). Spectroscopic studies indicate that the ketoimine isomers can readily interconvert at 22 °C.

(11) The absolute stereochemistry of *anti* product diastereomers in Table 2 is based on an X-ray crystal structure analysis. See Supporting Information for details.

(12) Use of 2 equiv of enolsilane is required for efficient AVM (to achieve >98% conv).

Table 2. Ag-Catalyzed AVM of Aryl-Substituted  $\alpha$ -Ketoimine Esters<sup>a</sup>

entry	Ar	substrate	NaHCO <sub>3</sub> workup (-78 °C → 22 °C)			HOAc workup (-78 °C → 22 °C)		
			7:8 <sup>b</sup>	yield 7 (%) <sup>c</sup>	7 er; ee (%) <sup>d</sup>	7:8 <sup>b</sup>	yield 7 (%) <sup>c</sup>	7 er; ee (%) <sup>d</sup>
1	C <sub>6</sub> H <sub>5</sub>	4a	93:7	72	95.5:4.5; 91	95:5	88	96:4; 92
2	<i>m</i> -OMeC <sub>6</sub> H <sub>4</sub>	4b	80:20	76	93:7; 86	95:5	95	96.5:3.5; 93
3	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	4c	75:25	51	90.5:9.5; 81	92:8	72	93.5:6.5; 87
4	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	4d	88:12	78	96:4; 92	95:5	80	96:4; 92
5	<i>p</i> -IC <sub>6</sub> H <sub>4</sub>	4e	86:14	62	95:5; 90	>98:<2	81	96.5:3.5; 93
6	<i>p</i> - <i>t</i> -BuC <sub>6</sub> H <sub>4</sub>	4f	75:25	68	93:7; 86	89:11	77	95:5; 90
7	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4g	89:11	67	95.5: 4.5; 91	95:5	87	97:3; 94
8	2-naphthyl	4h	93:7	68	95:5; 90	>98:<2	81	95.5:4.5; 91
9	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	4i	<2>98	87 <sup>e</sup>	66:34; 32 <sup>e</sup>	<2>98	87 <sup>e</sup>	66:34; 32 <sup>e</sup>

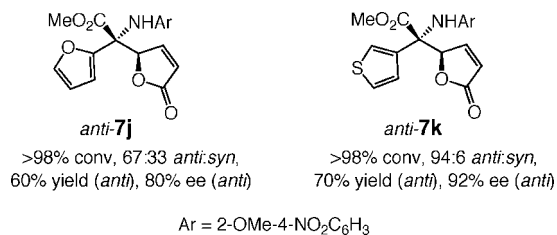
<sup>a</sup> Reactions performed under N<sub>2</sub> atmosphere; >98% conversion in all cases (substrate consumption based on internal standard). <sup>b</sup> Diastereomeric ratios were determined by analysis of 400 MHz <sup>1</sup>H NMR spectra of the unpurified reaction mixtures. <sup>c</sup> Yields are of the purified *anti*-7. <sup>d</sup> Enantiomer ratio (er) values were determined by HPLC analysis; see Supporting Information for details. <sup>e</sup> Data for *syn*-8i as the major isomer.

with unsaturated lactones *anti*-7 and *syn*-8 (<sup>1</sup>H NMR and mass spectroscopic analysis).<sup>13</sup>

The above observations suggested that a quenching procedure that more efficiently removes unreacted enolsilane at -78 °C could enhance diastereo- and enantioselection (i.e., minimal Mannich addition at elevated temperatures) as well as afford higher yields (i.e., minimal Michael addition). Indeed, as illustrated in entries 1–8 of Table 2 (right column), when reaction mixtures are treated with HOAc in MeOH (vs aq. NaHCO<sub>3</sub>), *anti*-7a–h are formed in 89:11 to >98:2 dr (vs 75:25–93:7 dr), 93.5:6.5–97:3 er (vs 90.5:9.5–96:4 er), and 72–95% yield (vs 51–78% yield). As the data in entry 9 indicate, the modification in quenching conditions exerts little or no effect on the AVM of *o*-substituted  $\alpha$ -ketoimine ester 4i.

It should be noted that ketoimine substrates are required for adventitious *syn*-selective AVM to occur at higher temperatures during workup. Control experiments (internal reference) illustrate that, after 15 h, >98% of the substrate is converted to AVM products. It is therefore likely that retro-Mannich reactions take place to a limited extent during the basic NaHCO<sub>3</sub> quench, generating the small amount of ketoimine.

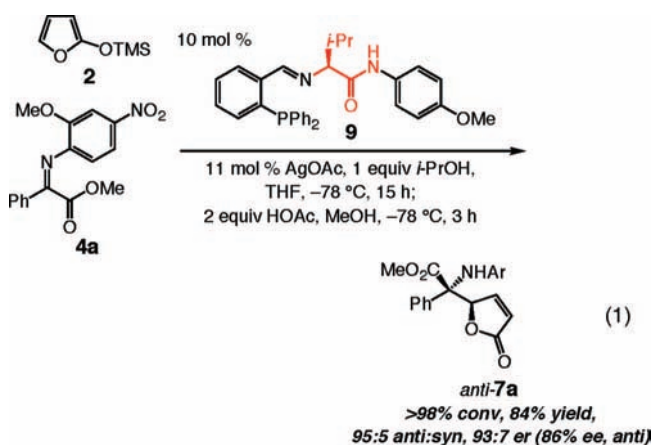
As illustrated by the enantioselective synthesis of amino esters 7j and 7k, respectively, transformations can be performed with heteroaromatic  $\alpha$ -ketoimine esters. The lower selectivities obtained for 7j versus 7k may be due to competitive chelation of the Lewis basic furyl oxygen (vs OMe of the *N*-aryl) with the Lewis acidic Ag-based complex.



**2.1.4. Issues of Practicality and Removal of the *N*-Activating Group.** The Ag-catalyzed process is performed in the presence of an air stable chiral ligand that can be prepared, on

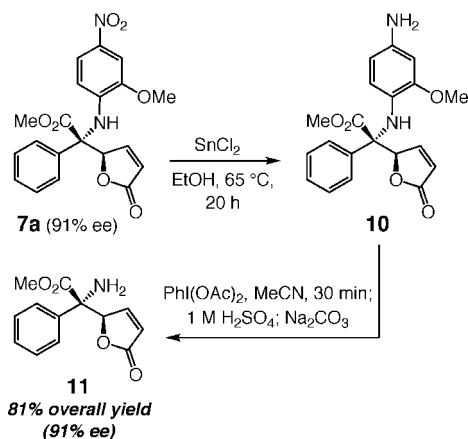
gram scale, in three simple steps and 42% overall yield from commercially available starting materials; the amino-acid-based phosphine ligand can be purified by a single crystallization. Moreover, the requisite AgOAc and siloxyfuran are commercially available.

Ag-catalyzed AVM reactions can be easily performed on significant amounts of  $\alpha$ -ketoimine esters. As an example, reaction with 2.0 g of 4a affords 2.24 g of purified *anti*-7a (88% yield) with high selectivity (96:4 er). Furthermore, although *t*-Leu-containing ligand 1 is optimal, the corresponding phosphine 9, bearing the less expensive valine moiety, promotes AVM efficiently and in lower—but useful—selectivity; the example in eq 1 is illustrative.



The *N*-aryl group can be removed by a two-step procedure that affords the desired amines in >80% yield; an example is presented in Scheme 1. Several points regarding deprotection of the *N*-aryl unit are worth noting: (a) Removal of the *o*-anisidyl group in a corresponding AVM product (e.g., 3, entry 1, Table 1) is substantially less efficient (<25% yield). That is, the sterically unencumbered amine of the *N*-aryl unit, generated from reduction of the NO<sub>2</sub> group, is likely to react more readily with PhI(OAc)<sub>2</sub> than the more sterically encumbered heteroatom

## Scheme 1. Removal of the N-Aryl Unit



of the quaternary carbon. (b) Attempts to unmask the amine through oxidative procedures involving DDQ (e.g., 1.5 equiv of oxidant, 20:1  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , 22  $^\circ\text{C}$ , 2 h) results in <2% conversion. (c) When ceric ammonium nitrate (CAN) is used, unprotected **11** can be obtained in one step but only in 45% yield.<sup>14</sup> (c) Subjection of **7a** to catalytic hydrogenation conditions (1 atm of  $\text{H}_2$ , 10% w/w Pd(C), EtOAc, 22  $^\circ\text{C}$ , 4 h) leads to isolation of the saturated lactone bearing the *p*-nitroaryl moiety in 79% yield along with 10% of the saturated aniline.

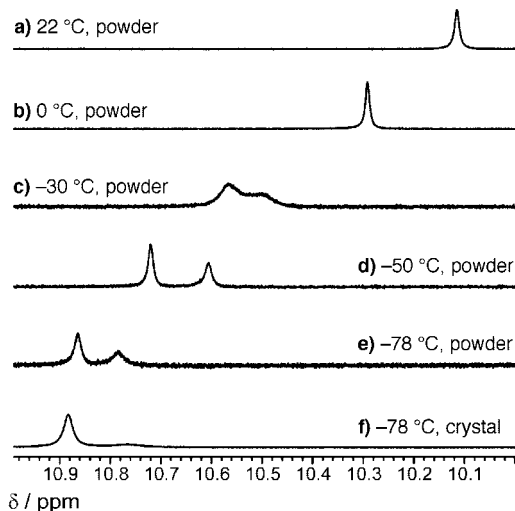
**2.2. Structures of Chiral Ag-Based Complexes and Related Mechanistic Issues. 2.2.1. Dependence of Selectivity on Temperature.** We verified the strong dependence of diastereoselectivity on reaction temperature through systematic investigations; the results of these studies are summarized in Table 3. Such findings have notable mechanistic implications. The reversal of selectivity (see entries 1 and 5, Table 3) implies a change in the energetics of the catalytic cycle; alterations in the structure of the chiral catalyst may also be responsible for different stereochemical outcomes. To gain additional insight, we explored the identity of the active chiral complex.

**2.2.2. Identity and Catalytic Activity of Ag-Based Chiral Complexes.** Treatment of **1** with AgOAc (1.0 equiv, 22  $^\circ\text{C}$ , THF) for 5 min followed by filtration (to remove uncomplexed AgOAc, as determined by IR analysis) and solvent removal results in isolation of an air stable white powder that can serve as an effective AVM catalyst. The transformations in entries 1–2 and 7 of Table 2 are initiated by 10 mol % (based on ligand **1**; –78  $^\circ\text{C}$ , 15 h) of a 1 year old sample of the powder, affording *anti*-**7a–b** and **7g** with nearly identical reactivity and selectivity. For example, in the presence of the aforementioned powder sample, **7g** is isolated in 95:5 dr, 97:3 er, and 89% yield. When a solution of the powder ( $d_8$ -THF) is allowed to cool to –78  $^\circ\text{C}$ , there is a notable change in the  $^1\text{H}$  NMR spectrum (see spectra a–e, Figure 1): while the signal for the amide proton shifts downfield from  $\delta$  10.09 ppm (spectrum a, Figure 1, 22  $^\circ\text{C}$ ), it splits into two peaks of approximately equal intensity at  $\delta$  10.87 and  $\delta$  10.78 ppm at –78  $^\circ\text{C}$  (spectrum e, Figure 1).<sup>15</sup> Signals recombine and return to their original chemical shifts

**Table 3.** Dependence of Ag-Catalyzed AVM Selectivity on Temperature<sup>a</sup>

entry	temp ( $^\circ\text{C}$ )	<b>7a/8a</b> <sup>b</sup>	yield (%) <sup>c</sup>	<b>7a</b> er; ee (%) <sup>d</sup>	<b>8a</b> er; ee (%) <sup>d</sup>
1	–78	93:7	88	95.5:4.5; 91	82.5:17.5; 65
2	–50	33:66	76	85:15; 70	85:15; 70
3	–30	14:86	58	58:42; 16	81:19; 62
4	–15	10:90	32	63:37; 26	79.5:20.5; 59
5	+4	8:92	41	<55:45; <10	77:23; 54

<sup>a</sup> Reactions performed under  $\text{N}_2$  atmosphere; all reactions were quenched at the specified temperature and kept at that temperature for 3 h before allowing to warm to 22  $^\circ\text{C}$ . All conversions = >98% (substrate consumption based on internal standard). <sup>b</sup> Diastereomeric ratios were determined by 400 MHz  $^1\text{H}$  NMR analyses of product mixtures prior to purification. <sup>c</sup> Yields are of purified products; with the exception of entry 1 (yield of only *anti*-**7a**); total yields of isomeric mixtures are shown. <sup>d</sup> Enantiomer ratio (er) values were determined by HPLC analysis; see Supporting Information for details.



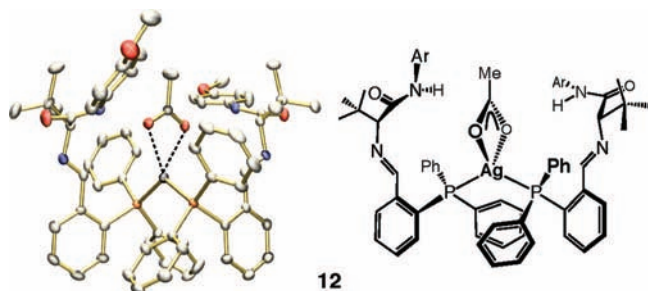
**Figure 1.**  $^1\text{H}$  NMR spectra (400 MHz,  $d_8$ -THF) of chiral Ag-based complexes of **1**.

when the sample is allowed to warm to 22  $^\circ\text{C}$ .<sup>15</sup> These data indicate that the powder consists of two complexes that rapidly interconvert at ambient temperature.

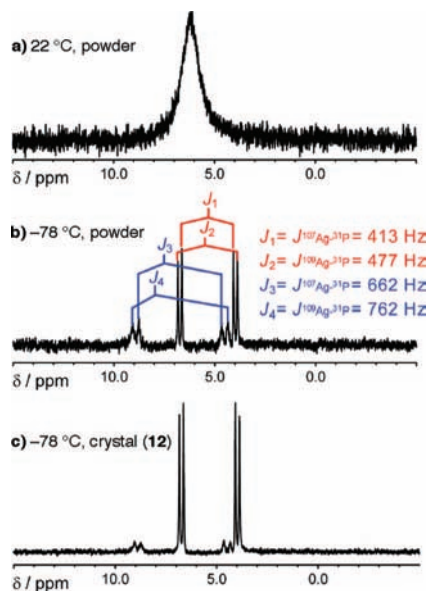
When petroleum ether is added to a THF solution of the powder, a crystalline solid is formed, which, as confirmed by X-ray analysis, is the 2:1 complex **12** (Figure 2). In contrast to the powder form, **12** is not an effective catalyst at –78  $^\circ\text{C}$  (10 mol %, 15 h: 48% conv) and delivers products with low selectivity (*anti*-**7a**/*syn*-**8a** = 33:67 dr; er<sub>*anti*</sub> = 74:26; er<sub>*syn*</sub> = 83:17).

At 22  $^\circ\text{C}$ , the chemical shifts of the signals in the  $^1\text{H}$  NMR spectrum of the crystalline form are identical to those observed for the powder.<sup>15</sup> Upon cooling, an identical downfield shift of the amide proton is observed; as shown in spectrum f in Figure 1, however, one of the singlets ( $\delta$  10.87 ppm at –78  $^\circ\text{C}$ ) now predominates (2:1 by peak integration; see below for more details). The above observations imply that the powder consists

- (13) Control experiments indicate that Michael addition is Ag-catalyzed but does not stereoselectively consume one product diastereomer. Thus, selective catalytic Michael reaction is likely not the cause of the difference in dr values observed with different quenching procedures.
- (14) Removal of the N-aryl group in **7a** in the presence of CAN was performed in the following manner: 3 equiv of CAN, 1:1 MeCN/ $\text{H}_2\text{O}$ , 0  $^\circ\text{C}$ , 10 min; 10 equiv of  $\text{H}_2\text{SO}_4$ , 0  $^\circ\text{C}$ , 10 min;  $\text{Na}_2\text{CO}_3$  (pH = 10), wash with  $\text{CH}_2\text{Cl}_2$ .
- (15) For further details, see Supporting Information.



**Figure 2.** X-ray structure of Ag-based complex **12** (Ar = *p*-OMeC<sub>6</sub>H<sub>4</sub>).



**Figure 3.** <sup>31</sup>P NMR spectra (162 MHz, *d*<sub>8</sub>-THF) of the powder and crystal forms of the chiral Ag-based complexes of **1** at various temperatures.

of a mixture of **12** and another complex (NH at  $\delta$  10.78 ppm at  $-78$  °C), which likely promotes reactions more readily and with higher selectivity at  $-78$  °C. Thus, in the crystalline sample, the more catalytically active Ag-based complex is the minor constituent.<sup>16</sup>

The findings summarized below indicate that the active catalyst is likely the less sterically encumbered 1:1 ligand/Ag complex (component represented by the more upfield signal in spectra e–f, Figure 1):<sup>17</sup>

First, as illustrated in Figure 3 (spectrum b), analysis of the <sup>31</sup>P NMR of a sample of the powder form indicates two distinct sets of doublets, with coupling constants consistent with complexes bearing a P–Ag–P (2:1 complex;  $J_{P-Ag} = 413$  and 477 Hz)<sup>18</sup> and a P–Ag (1:1 complex;  $J_{P-Ag} = 622$  and 762 Hz) unit.<sup>19</sup> In agreement with the <sup>1</sup>H NMR data discussed above (spectrum e, Figure 1), the 1:1 and 2:1 complexes exist in a 2:1 ratio in the powder form,<sup>20</sup> as judged by the <sup>31</sup>P NMR spectrum b (Figure 3). Analysis of the <sup>31</sup>P NMR spectrum derived from **12** (spectrum c, Figure 3) indicates a 2:1 mixture with the 1:1 complex being the minor component,<sup>20</sup> a finding that is also consistent with <sup>1</sup>H NMR spectrum f in Figure 1.

(16) The lower selectivity in reactions with **12**, containing a small amount of the more active 1:1 complex, is consistent with the observations that, at low catalyst loadings, AgOAc and **1** deliver inferior results.

(17) The minor amount of the 1:1 complex in the solution derived from crystalline **12** is likely due to a small degree of phosphine dissociation. Accordingly, addition of excess **1** leads to complete disappearance of the 1:1 complex (NH at  $\delta$  10.78 ppm).

Second, peaks corresponding to the cationic 1:1 (calculated *m/z* for **1**•Ag<sup>+</sup>: 615.1331, found: 615.1327) and the cationic 2:1 complex (calculated *m/z* for **12**•Ag<sup>+</sup>: 1123.3610, found: 1123.3625) are detected in the high-resolution mass spectra of the powder as well as of the crystal.

Third, addition of excess AgOAc<sup>21</sup> to a THF solution of 2:1 complex **12** causes an increase in the amount of the catalytically more active system (<sup>1</sup>H NMR analysis);<sup>15</sup> nearly identical results are obtained from this sample as observed with the aforementioned powder.<sup>15</sup> Similarly, addition of excess **1** to a solution of the crystalline form (see spectrum f, Figure 1 and spectrum c, Figure 3) affords a sample that is >98% **12** (<2% 1:1 complex).

The availability of a sample of **12** uncontaminated by the 1:1 complex has allowed us to substantiate that the former is a relatively ineffective catalyst at  $-78$  °C (~25% conv, 15 h, 95:5 *syn/anti*, 76:24 *er* in favor of the *syn* diastereomer) and that, at  $-50$  °C, the 2:1 complex promotes a highly *syn*-selective AVM with improved efficiency (~70% conv, 15 h, 95:5 *syn/anti*, 71:29 *er*). These observations indicate that the turnover in diastereoselectivity as a function of temperature (see Tables 1 and 3) is due to higher activity of the *syn*-selective 2:1 complex (**12**) at higher temperatures as well as a change in the stereochemical preference in the reaction promoted by the 1:1 complex (e.g., due to a change in the identity of the stereochemistry-determining step). At  $-78$  °C, the 1:1 complex preferably catalyzes the formation of the *anti* diastereomer but favors more of the *syn* adduct at elevated temperatures.

**2.2.3. Transition State Working Models.** The above mechanistic considerations support the scenarios put forth previously for reactions of aldimines, involving a 1:1 Ag/ligand complex.<sup>8a</sup> A model (*endo* mode of approach **I**, *G* = H, Figure 4), wherein the substrate binds in a manner to minimize interaction with the bulky amino acid substituent (R in **I**) and ketoimine's sterically hindered aryl substituent is situated *trans* to the Si-based nucleophile, may be proposed. Another noteworthy feature is the Lewis base activation<sup>22</sup> of the siloxyfuran by the amide terminus. We have previously demonstrated the importance of the chiral phosphine's Lewis basic C-terminus to the facility of this class of transformations; for example, we have shown<sup>8a</sup> that replacement of the *p*-methoxyphenyl amide with a *p*-trifluoromethylphenyl amide results in significant diminution in AVM efficiency.

The *o*-methoxy group of the N-activating unit is required for the *anti*-diastereomer to be strongly favored as well as high enantioselectivity to be achieved (see entries 5–7, Table 1), since the bidentate mode of coordination enhances transition structure organization within the catalyst–substrate complex. Thus, in spite of unfavorable steric repulsion caused by the presence of the *o*-methoxy unit, it elevates catalytic activity (compare entries 5–7, Table 1).

The relatively lower asymmetric induction observed with substrates bearing an *o*-substituted aryl unit (e.g., entry 9, Table

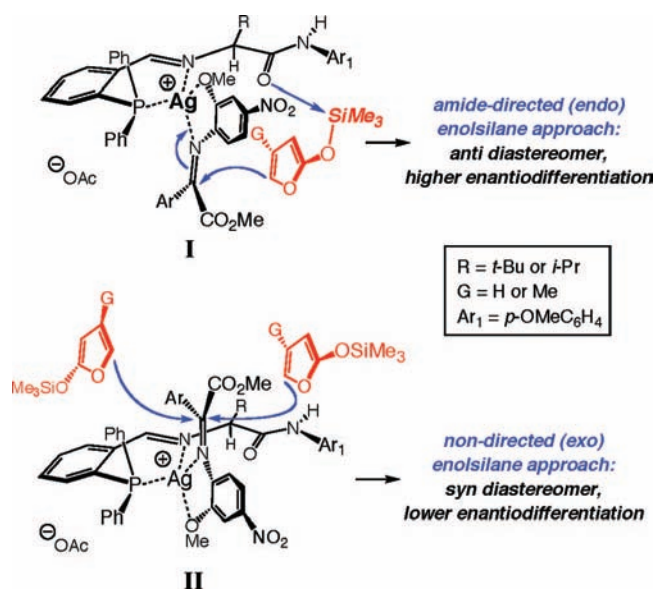
(18) For P–Ag–P coupling constants, see: (a) Ohkouchi, M.; Masui, D.; Yamaguchi, M.; Yamagishi, T. *J. Mol. Catal. A* **2001**, *170*, 1–15.

(19) For P–Ag coupling constants, see: (a) Goel, R. G.; Pilon, P. *Inorg. Chem.* **1978**, *17*, 2876–2879.

(20) The integration value obtained by analysis of the <sup>1</sup>H and <sup>31</sup>P NMR spectra must be corrected since one complex bears two amide protons and two P atoms, respectively.

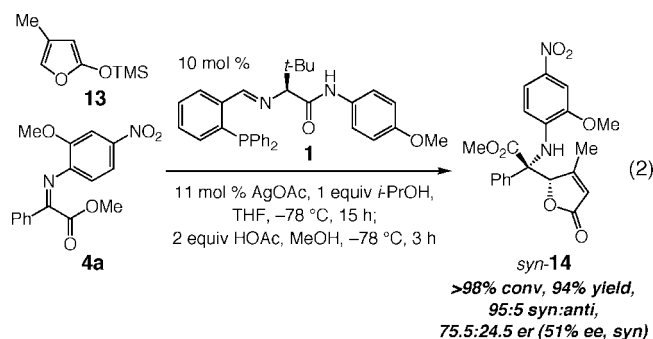
(21) The precise amount of excess AgOAc cannot be measured due to the salt's incomplete solubility in the reaction solvent.

(22) For a review regarding Lewis base activation of Lewis acids, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.



**Figure 4.** Proposed working models for Ag-catalyzed AVM reactions of aryl-substituted  $\alpha$ -ketoimine esters, including Lewis acid activation of the substrate and Lewis base activation of the enolsilane nucleophile.

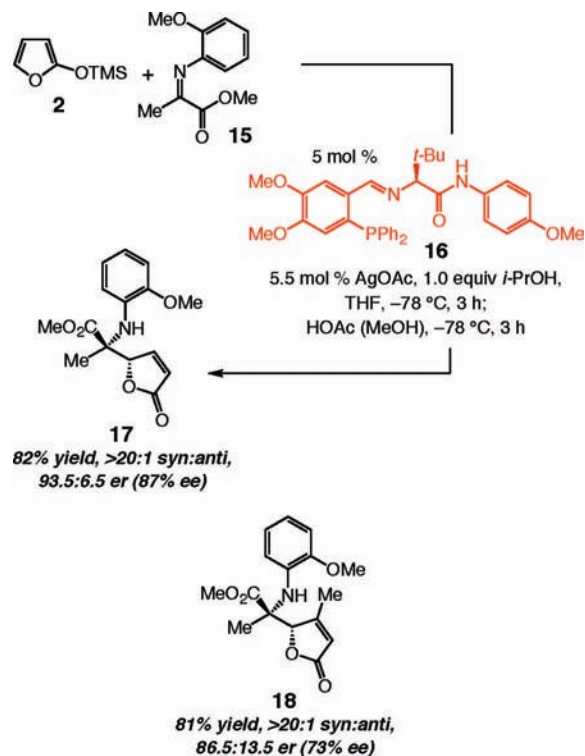
2) could be attributed to the steric interactions caused by such a structural modification, leading to a preference for AVM to proceed through the *exo* catalyst–substrate complex **II** (G = H, Figure 4). The suggested scenario accounts for the reversal of diastereoselectivity in such cases as well (preferential formation of *syn* isomers). The diminished enantioselectivity might be attributed to the geometric constraints associated with interaction of the Lewis basic amide terminus with the Si atom of the siloxyfuran. Enantiofacial control may thus be largely governed by the steric differentiation between the two modes of attack, as illustrated in **II** (Figure 4); while the phenylphosphine partially hinders approach from one face of the ketoimine in **II**, the sterically hindered *t*-Leu might block siloxyfuran from the opposite enantiotopic face of the C=N bond. Such a model implies that increasing the size of the Si-based nucleophile should have a deleterious effect on enantioselectivity, giving rise to preferable generation of the *syn* diastereomer. As shown by the example in eq 2, Ag-catalyzed AVM of  $\alpha$ -ketoimine ester **4a** (G = Me, Figure 4) with 4-methyl-substituted siloxyfuran **13** results in near exclusive formation of *syn*-**14** (95:5 *syn/anti*) in 75.5:24.5 er (51% ee).<sup>23</sup>



It is plausible that the difference in the stereochemical preferences of the two types of substrates discussed above lies

(23) The stereochemical identity of AVM product *syn*-**14** is based on <sup>1</sup>H NMR analysis (comparison with other related *syn* and *anti* diastereomers, the structures of which have been determined by X-ray analysis).

**Scheme 2.** Ag-Catalyzed AVM Reactions of Methyl-Substituted  $\alpha$ -Ketoimine Esters and Electronically Unactivated *N*-Aryl Groups



in the identity of the turnover-limiting (stereochemistry-determining) steps. With ketoimines carrying a *p*-nitroaryl group (e.g., **4a–h**, *anti* selective), substrate–catalyst association may be relatively slow, since the electrophile is a ketoimine of diminished Lewis basicity (more reluctant to associate with the chiral Lewis acidic Ag). Thus, once **I**, which may be kinetically favored, is generated, it might readily undergo AVM to afford the *anti* diastereomer in high enantioselectivity. In contrast, with substrates bearing an unactivated *N*-aryl moiety (e.g., **3** in Table 1 and **15** in Scheme 2), association with the Ag-based catalyst might be relatively facile and reversible, while the addition step is turnover-limiting. The above mechanistic scheme is consistent with the proposal that reactions involving sterically bulky imines or siloxyfurans proceed through complex **II**, allowing the nucleophile to have less obstructed access to the catalyst-bound ketoimine.

Initial studies regarding Ag-catalyzed reactions of alkyl-substituted ketoimines indicate that caution must be exercised in extending the mechanistic conclusions described above to other classes of related processes. As the preliminary data summarized in Scheme 2<sup>24</sup> regarding transformations of alkyl-substituted  $\alpha$ -ketoimine esters suggest, AVM reactions of varying types of electrophiles can be governed by different mechanistic regimes and energetic nuances. With the smaller methyl substituent in **15** (vs aryl groups in **4a–i**), the presence of an *N*-activating group bearing a *p*-nitro unit is no longer required; this is a critical difference that, as indicated by the data in Table 1, leads to the exclusive formation of the *syn*

(24) The chiral ligand related to **16** but lacking the two methoxy substituents at the *N*-terminus is only slightly less effective (>98% conv under identical conditions; 91.5:8.5 er, 83% ee, 66% yield for **16**).

isomer (>98: <2 *syn/anti* for **17**<sup>25</sup> and **18**).<sup>26</sup> Studies to develop efficient catalytic AVM of other alkyl-substituted imines and delineation of the aforementioned mechanistic differences are subjects of ongoing studies.

### 3. Conclusions

We have developed a Ag-catalyzed process for AVM of  $\alpha$ -ketoimine esters that involves a commercially available metal salt (AgOAc) and nucleophile (siloxyfuran **2**) and an easily prepared chiral ligand (amino acid-based phosphines **1** or **9**). The products, generated in high diastereo- and enantioselectivity, bear an *N*-substituted all-carbon quaternary stereogenic center as well as an unsaturated lactone moiety that is amenable to various functionalization procedures.<sup>8a</sup> These investigations highlight one of the important aspects of *N*-aryl units as general imine activating groups. The reactivity and, in certain instances, the stereoselectivity of the corresponding catalytic reactions can be controlled effectively by electronic modification of such moieties. The *p*-nitro unit introduced in ketimine substrates discussed above is not only crucial to obtaining high efficiency in addition to diastereo- and enantioselectivity, the resulting aniline (after reduction of the NO<sub>2</sub> unit) is critical to the facility with which the *N*-aryl group is removed (see the example in eq 2).

The studies detailed above demonstrate that the active chiral Ag complex in catalytic Mannich reactions of this particular

class of substrates is a 1:1 complex that exhibits different stereochemical preferences at different temperatures. We illustrate that, depending on the reaction conditions, a competing 2:1 complex can prove competitive and, in at least certain cases, cause diminution of stereoselectivity. The investigations described herein should therefore prove crucial to future explorations in catalyst design, as they suggest that structurally modified chiral ligands that are less prone to generate the less active 2:1 complexes might prove to be more effective catalysts in at least certain types of Ag-catalyzed asymmetric Mannich reactions.

Studies directed toward more efficient chiral catalysts for enantioselective Mannich reactions and design of other sterically and/or electronically modified *N*-aryl groups for reactions of aldimines and ketoimines are in progress. Future investigations will include development of catalytic AVM processes for a wider range of substrates and additional Ag-catalyzed asymmetric processes with ketoimines.

**Acknowledgment.** Financial support was provided by the NIH (GM-57212) and Novartis (fellowship to L.C.W.). We are grateful to Dr. H. Mandai (Boston College) for valuable discussions. We are indebted to Mr. S. J. Malcolmson (Boston College), Ms. K. Mandai (Boston College), Dr. B. Li (Boston College), Dr. P. Müller (MIT), and Dr. R. Staples (Harvard University) for their generous assistance in securing X-ray structures. We thank Mr. A. T. Colucci (Boston College) for experimental assistance. 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>.

JA8062315

- 
- (25) The relative and absolute stereochemistry of **17** has been established by X-ray crystal structure analysis. See Supporting Information for details.
- (26) Attempts to prepare and study Ag-catalyzed AVM reactions of the methyl-substituted ketoimine ester that bears a *p*-nitro-*o*-methoxyphenylimine led to complex mixtures of products, presumably as a result of enamine formation.