Asymmetric Catalysis

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A Highly Efficient and Practical Method for Catalytic Asymmetric Vinylogous Mannich (AVM) Reactions**

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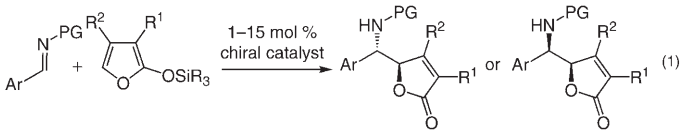
Stereoselective vinylogous Mannich reactions[1] are of significant utility in organic synthesis.[2] Through diastereoselective addition of vinylogous enol equivalents to enantiomerically enriched imines, α,β-unsaturated, δ-amino carbonyls have been synthesized and used as chiral building blocks. A catalytic asymmetric vinylogous Mannich (AVM) process would constitute a more efficient strategy, one that does not require pre-existing chirality.[3] As illustrated in Equation (1)



(1)

(PG = protecting group), a catalytic AVM involving a siloxyfuran can deliver synthetically versatile, enantiomerically enriched products that bear two stereogenic centers appended to a γ-butenolide.

In 1999, Martin and Lopez reported a method (Ti-catalyzed) for addition of siloxyfurans to 2-aminophenol-derived imines; reactions proceeded in 40–92% *de* but in only up to 54% *ee*.[4] Terada and co-workers have outlined an enantioselective (up to 97% *ee*) protocol for Brønsted acid catalyzed Friedel–Crafts reactions of *N*-Boc aldimines with 2-methoxyfuran. Enantiomerically enriched furan-2-ylamines may be oxidized to afford alkylamine-substituted γ-butenolides [Eq. (1)] by a two-step sequence that generates the carbinol stereogenic center with moderate diastereoselectivity (70% *de*).[5]

Herein we report the first highly diastereo- and enantioselective protocol for catalytic AVM reactions. Ag-catalyzed transformations[6] proceed in >98% *de*, in 79 to >98% *ee* and 60–98% isolated yield. The catalytic method is practical: transformations are carried out in air with undistilled solvent and undistilled additive, in the presence of 1–15 mol% commercially available AgOAc (not purified) and an easily accessible chiral phosphine (three steps, 50% yield). Siloxyfurans are commercially available and/or readily prepared (one step, 90% yield).

As the data summarized in entry 1 of Table 1 illustrate, in the presence of 1 mol% **1a**,[6b–d] 1 mol% AgOAc, 1.1 equivalents *i*PrOH, in undistilled THF and in air, reaction of aldimine **2a** and commercial siloxyfuran **3** affords γ-butenolide **4a** in >98% *de*, 95% *ee*,[7] and 82% yield. When **1b**, bearing a *t*Leu (vs. *i*Leu) unit (entry 2) or ligand **1c**, containing the less expensive Val (entry 3) is used, similar reactivity and selectivity is observed.[8] The efficient reaction with **3** is especially noteworthy and was somewhat surprising, since we had previously established that silylketene acetals do not participate (<2% conv.) in this class of catalytic Mannich reactions.[6d] It is likely that this change in reactivity, in spite of somewhat lower nucleophilicity of siloxyfurans (vs. ketene acetals)[9] is the result of reduced steric hinderance at the reacting carbon. As represented by catalytic AVM in entries 4–5 (Table 1), one of the chiral phosphines (**1a**, **1b**, or **1c**) can deliver slightly higher efficiency (90% vs. 85% conv.) and enantioselectivity (97% vs. 93% *ee*); others are shown in entries 12–13 and 15–16. Reactions proceed readily and with high enantioselectivity with electron-rich (entries 4–5 and 15–16) and electron-poor (entries 6–9 and 14) arylimines. Sterically demanding *ortho*-substituted aldimines, such as **2f** (entries 10–11), **2g** (entries 12–13), and **2h** (entry 14)

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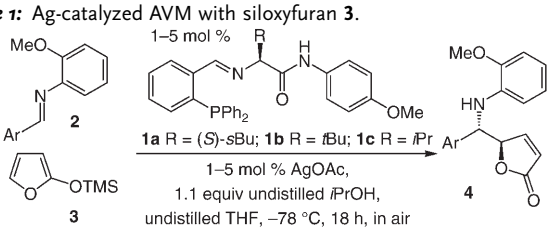
Table 1: Ag-catalyzed AVM with siloxyfuran **3**.



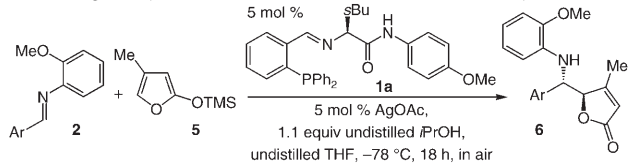
Entry	Ar		Ligand (mol%)	Conv. [%][a]	Yield [%][b]	*de* [%][b]	*ee* [%][c]
1	Ph	**a**	**1a** (1)	91	82	>98	95
2	Ph	**a**	**1b** (1)	94	82	>98	96
3	Ph	**a**	**1c** (1)	85	77	>98	92
4	*p*-MeOC$_6$H$_4$	**b**	**1a** (1)	85	76	>98	93
5	*p*-MeOC$_6$H$_4$	**b**	**1b** (1)	90	85	>98	97
6	*p*-NO$_2$C$_6$H$_4$	**c**	**1a** (1)	>98	98	>98	91
7	*p*-ClC$_6$H$_4$	**d**	**1a** (1)	94	89	>98	93
8	*p*-ClC$_6$H$_4$	**d**	**1c** (1)	98	86	>98	92
9	*m*-NO$_2$C$_6$H$_4$	**e**	**1a** (1)	94	75	>98	93
10	2-naphthyl	**f**	**1a** (1)	96	94	>98	98
11	2-naphthyl	**f**	**1b** (1)	>98	94	>98	>98
12	*o*-MeC$_6$H$_4$	**g**	**1a** (5)	86	73	>98	93
13	*o*-MeC$_6$H$_4$	**g**	**1b** (5)	73	65	>98	94
14	*o*-BrC$_6$H$_4$	**h**	**1a** (3)	89	60	>98	93
15	2-furyl	**i**	**1a** (1)	98	77	>98	84
16	2-furyl	**i**	**1b** (1)	98	78	>98	90

[a] Determined by analysis of 400-MHz ^{1}H NMR spectra. [b] Isolated yields of purified products. [c] Determined by chiral HPLC analysis; see the Supporting Information for details.

can be used; higher catalyst loadings, however, may be required (3–5 vs. 1 mol%). The presence of *i*PrOH as an additive is required for high conversions,[10] particularly with larger-scale processes where adventitious moisture is less available (H_2O is an effective additive[11]).

Reactions of 4-Me-substituted **5**, prepared from the commercially available lactone precursor (TMSOTf, Et_3N, 0°C; 90% yield; TMS = $SiMe_3$, OTf = OSO_2CF_3) have been examined. As the data in Table 2 indicate, with 5 mol% **1a** and AgOAc, **6a–b**, **6d**, **6h**, and **6j** are obtained in >98% *de*, 64–97% yield, and 83–90% *ee*.[12] Phosphine **1c**, bearing the less expensive Val moiety, can be used, but products are obtained in slightly lower selectivities (e.g., 93% conv., 90% yield, 84% *ee* for **6a** in entry 1). Higher catalyst loadings are

Table 2: Ag-catalyzed AVM reactions with substituted siloxyfuran **5**.



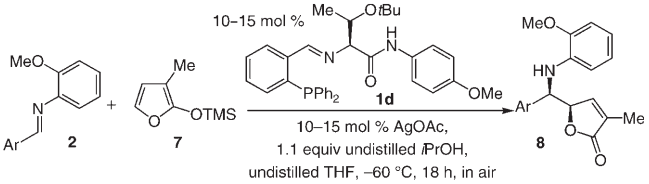
Entry	Ar		Conv. [%][a]	Yield [%][b]	*de* [%][a]	*ee* [%][c]
1	Ph	**a**	92	85	>98	87
2	*p*-MeOC$_6$H$_4$	**b**	80	70	>98	83
3	*p*-ClC$_6$H$_4$	**d**	>98	97	>98	90
4	*o*-BrC$_6$H$_4$	**h**	98	64	>98	89
5	*p*-BrC$_6$H$_4$	**j**	>98	90	>98	88

[a]–[c] See Table 1.

needed for synthetically useful conversions and yields (5 mol% vs. 1 mol% typically required for **3**).

Catalytic AVM of 3-substituted siloxyfuran **7** (Table 3) proved more complicated, requiring identification of a new

Table 3: Ag-catalyzed AVM reactions with substituted siloxyfuran **7**.

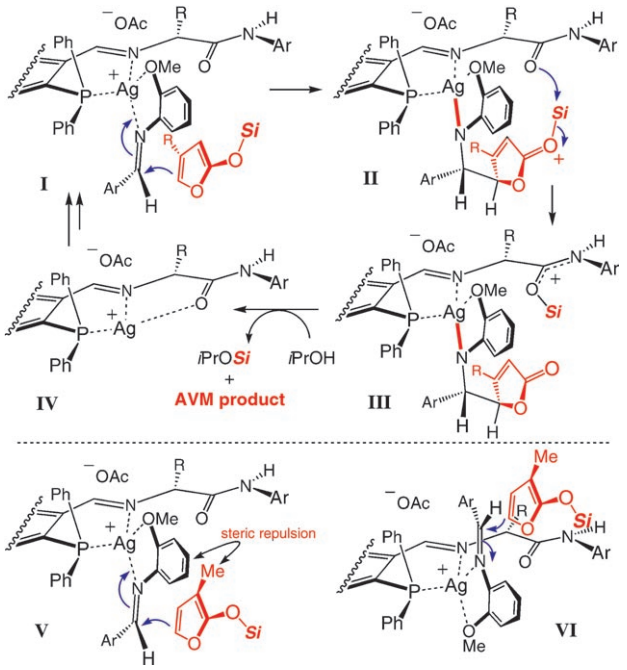


Entry	Ar		Mol%	Conv. [%][a]	Yield [%][b]	*de* [%][a]	*ee* [%][c]
1	Ph	**a**	10	88	70	>98	85
2	*p*-MeOC$_6$H$_4$	**b**	15	71	66	>98	88
3	*p*-ClC$_6$H$_4$	**d**	10	93	82	>98	83
4	*o*-BrC$_6$H$_4$	**h**	10	>98	65	>98	79

[a]–[c] See Table 1.

optimal chiral ligand. Catalytic AVM of **7** and **2a** with **1a** or **1b** (5 mol% loading, −78°C, 18 h) resulted in diastereoselective (>98% *de*) but inefficient transformations (25% and 34% conv., respectively); furthermore, enantioselectivity was disappointingly low (35% and 23% *ee*, respectively). Examination of alternative chiral ligands was thus performed, leading us to discover that **1d**, bearing a Thr(*t*Bu) residue, delivers the AVM product in 79% *ee* (48% conv.). Subsequent optimization led us to establish that at −60°C, **8a** is obtained in >98% *de*, 85% *ee*, and 70% yield. Ag-catalyzed AVM of **7** with electron-rich **2b** and electron-poor **2d** and **2h** gives **8b**, **8d**, and **8h** in 66–82% isolated yield and 79–88% *ee* (entries 2–4, Table 3). Two additional points merit mention: 1) Ligand **1d** is ineffective for reactions of **3** or **5**. For example, with 3 mol% **1d** (−78°C), formation of **6a** (entry 1, Table 2) proceeds to 91% conversion but in <5% *ee*. 2) In contrast to catalytic AVM of **3** (Table 1) and **5** (Table 2), with 3-substituted **7**, it is the *syn* diastereomer that is formed exclusively (Table 3). Determination of the absolute stereochemistry of **8**[13] indicates that the opposite aldimine enantioface undergoes addition.

Preliminary mechanistic models are shown in Scheme 1. The Lewis acidic[14] chiral complex may associate with the aldimine substrate through bidentate chelation (cf. **I**, Scheme 1). In the activated complex, to minimize steric interactions, the substrate is bound *anti* to the bulky amino acid substituent (R). The catalyst-bound imine may react with the siloxyfuran by an *endo*-type addition (**I**)[15] to generate **II**.[16] Intramolecular desilylation by the Lewis basic amide terminus of the chiral ligand delivers **III**. Product release is facilitated by *i*PrOH by desilylation of the amide terminus and protonation of the N–Ag bond. Such a pathway should be unfavorable for siloxyfuran **7** because of steric repulsion in the catalyst-bound imine (**V**). Thus, in reactions involving **7**, the *exo*-type mode of addition **VI** may be favored, leading to **8** (Table 3). Additions of **7** may be more sluggish because of a transition structure that requires positioning of the imine's

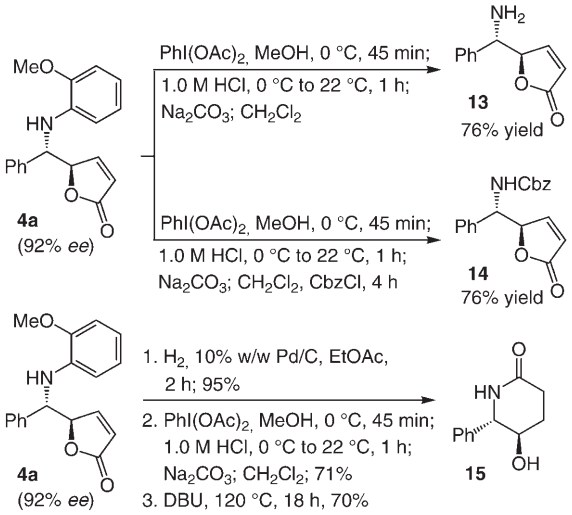


Scheme 1. Mechanistic models. ***Si*** = trimethylsilyl group.

aryl group and the siloxyfuran in the proximity of the amino acid substituent (R).[17] The origin of the dependence of specific catalyst classes for reactions of particular siloxyfurans (e.g., inefficiency of **1a** for AVMs of **7** or of **1d** for additions of **5**) is unclear.

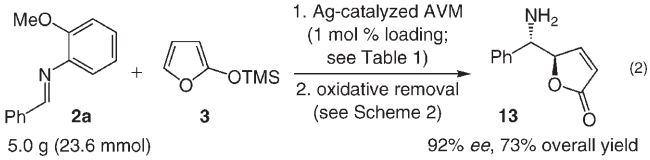
The above hypotheses suggest that C-terminal amide Lewis basicity is critical to reactivity and enantioselectivity of catalytic AVM reactions; this is supported by the data in Table 4. In contrast to the AVM of **2a** and **3** promoted by **1a** (>98% conv., 94% *ee*), the ligand bearing a *p*-trifluoromethylaniline amide (**9**; entry 2, Table 4) gives 55% conversion into **4a** in 85% *ee*. Ligand **10** (entry 3), with an *n*-butylamide terminus, is equally active (>98% conv.) but initiates a less enantioselective AVM (87% vs. 94% *ee* with **1a**). The less Lewis basic methyl ester of **11** (entry 4) is less effective (70% conv.) than **1a** and delivers nearly racemic **4a** (−13% *ee*). The amide moiety might prolong catalyst longevity by providing stabilization of cationic Ag complexes (e.g., **IV**). Moreover, amide termini can stabilize intermediates (e.g., **III**, Scheme 1), which contain a positively charged C terminus. The lower activity of electron-rich phosphine **12** (entry 5) points to the importance of a Lewis acidic phosphine·Ag complex.

Anisidyl groups are removed by a one-pot procedure with $PhI(OAc)_2$ (commercial, used directly).[18] Synthetically versatile derivatives, such as amine **13** and Cbz amide **14**, can be obtained in >98% *de* (Scheme 2). Conversion into enantiomerically enriched **15** (Scheme 2) illustrates one of several functionalization possibilities that the butenolide moiety offers.



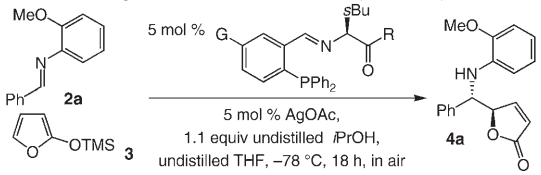
Scheme 2. Functionalizations of catalytic AVM products. Cbz = benzyloxycarbonyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

The present catalytic asymmetric protocol is exceptionally practical. As shown in Equation (2), Ag-catalyzed AVM and unmasking of the enantiomerically enriched amine can be carried out efficiently on a multigram scale with only 1 mol% catalyst loading.



Applications to reactions of enolizable aldimines[19] and mechanistic studies are in progress.

Table 4: Effect of ligand structure on efficiency of catalytic AVM.



Entry	G	R	Ligand	Conv. [%][a]	*de* [%][a]	*ee* [%][b]
1	H	N(H)-*p*-$MeOC_6H_4$	**1a**	>98	>98	94
2	H	N(H)-*p*-$CF_3C_6H_4$	**9**	55	>98	85
3	H	N(H)*n*Bu	**10**	>98	>98	87
4	H	OMe	**11**	70	>98	−13
5	OMe	N(H)-*p*-$MeOC_6H_4$	**12**	86	>98	82

[a] Determined by analysis of 400-MHz ^{1}H NMR spectra of unpurified products. [b] Determined by chiral HPLC analysis; see the Supporting Information for details.

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[1] For reviews on utility of stereoselective vinylogous Mannich reactions, see: a) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929 – 1972; b) S. F. Martin, *Acc. Chem. Res.* **2002**, *35*, 895 – 904.

[2] For example, see: a) S. F. Martin, S. Liras, *J. Am. Chem. Soc.* **1993**, *115*, 10450 – 10451; b) S. Liras, C. L. Lynch, A. M. Fryer, B. T. Vu, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 5918 – 5924; c) M. V. Spanedda, M. Ourévitch, B. Crousse, J.-P. Bégué, D. Bonnet-Delopn, *Tetrahedron Lett.* **2004**, *45*, 5023 – 5025.

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[7] For determination of relative and absolute stereochemical identity of AVM products from reactions of **3**, see the Supporting Information.

[8] See the Supporting Information for all data.

[9] For relative p nucleophilicity of various enol silanes, see: H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66 – 77.

[10] For a similar effect in Cr-catalyzed enantioselective aldol additions of siloxyfurans to aldehydes, see: S. Onitsuka, Y. Matsuoka, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 974 – 975.

[11] For example, when carried out on a 0.5-g (2.4-mmol) scale, AVM of **2a** and **3** proceeds to only 43% conversion (93% *ee*) in the absence of *i*PrOH (>98% conv., 82% yield, 91% *ee* with 1.1 equiv of the alcohol additive). Ag-catalyzed AVM to afford **4a** proceeds to 97% conversion (87% yield) in 92% *ee* with 1.1 equivalents H_2O (conditions in Table 1).

[12] Relative and absolute stereochemical identity of products derived from **5** was established through an X-ray crystal structure of **6j** (entry 5, Table 2). See the Supporting Information for details.

[13] For relative and absolute stereochemical identity of products derived from **7**, see the Supporting Information.

[14] Preliminary data indicate that the chiral Ag complex likely serves as a Lewis acid catalyst (vs. Ag enolate). For example, there is ca. 30% conversion in the presence of 20 mol% of Et_3N (synthesis of **4a** with 1 mol% **1a**, −78 °C).

[15] Preference for *endo*-type ("Diels–Alder"-type) transition states has been suggested for diastereoselective (non-asymmetric) vinylogous Mannich reactions; see: S. K. Burr, S. F. Martin, *Org. Lett.* **2000**, *2*, 3445 – 3447.

[16] The C=N bond of chiral ligands do not undergo addition likely because of steric hinderance provided by the amino acid substituent.

[17] Pre-association of the amide moiety with the siloxyfuran is also feasible; such an interaction would enhance enolsilane nucleophilicity and facilitate delivery; see: a) S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774 – 3789, and references therein; b) Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67 – 70.

[18] a) J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.* **2001**, *123*, 10409 – 10410; b) L. C. Akullian, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4376 – 4379; Angew. *Chem. Int. Ed.* **2003**, *42*, 4244 – 4247.

[19] Preliminary results show that the present procedure is applicable to AVM of aldimines derived from aliphatic aldehydes.

