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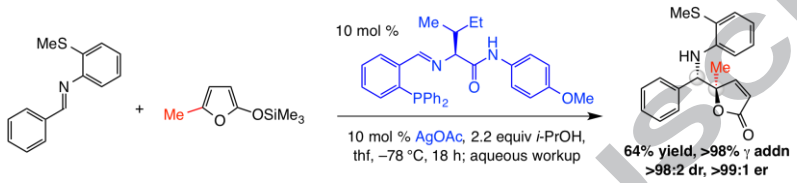

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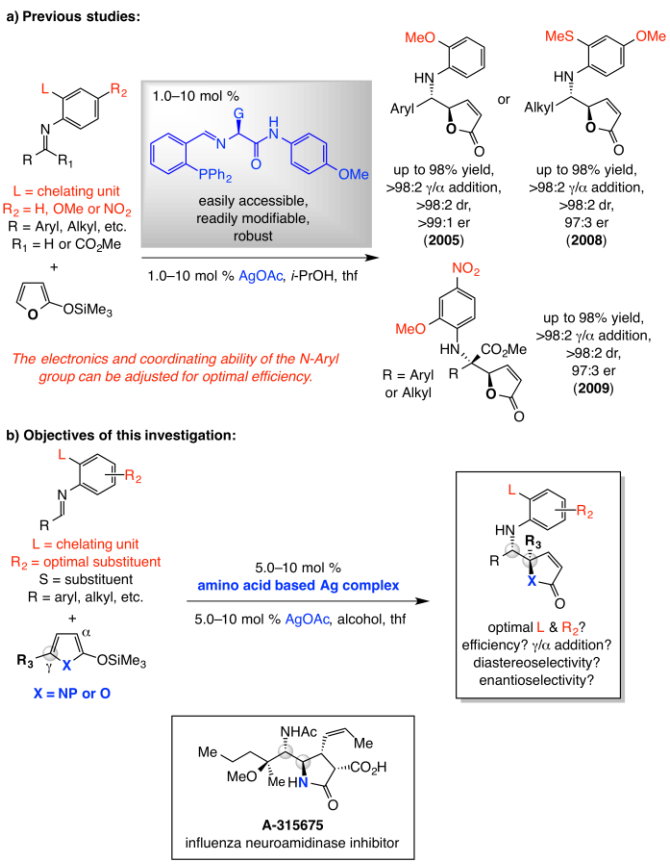
ABSTRACT

A readily accessible small-molecule phosphine, derived from commercially available starting materials such as an enantiomerically pure amino acid, serves as the precursor to a Ag-based chiral complex that can be prepared and used in situ to promote a variety of enantioselective vinylogous Mannich (EVM) reactions that involve siloxypyrroles as reaction partners. Transformations with unsubstituted nucleophilic components proceed efficiently and with exceptional site- (γ vs α-addition), diastereo- and enantioselectivity [up to 98% yield, generally >98:2 γ/α and diastereomeric ratio (dr) and up to 99:1 enantiomeric ratio (er)]. The first examples of efficient, diastereo- and enantioselective vinylogous Mannich additions with 5-methyl-substituted siloxyfuran, resulting in the formation of O-substituted quaternary carbon stereogenic centers are presented as well. Appreciable efficiency and diastereo- and enantioselectivity (up to >98:2 dr and >99:1 er) is accompanied by formation of α-addition products that can be oxidatively removed.

Amines are present in a great number of biologically significant molecules; reliable, efficient, diastereo- and enantioselective methods that furnish access to such valuable entities, particularly when promoted by easily accessible and robust chiral catalysts, are critical to future developments in chemistry.[1] As part of a program aimed at introducing robust and practical catalytic systems that can be used to prepare different types of amines in high enantiomeric purity,[2] we have developed a set of amino acid based chiral phosphine compounds that are simple to synthesize and promote enantioselective additions efficiently. Some members of this family of chiral ligands can be obtained by condensation of commercially available *o*-diphenylphosphono benzaldehyde and various amines that are derived from enantiomerically pure amino acids.[3] A notable set of transformations corresponds to Mannich-type additions[4] that are promoted by an in situ-generated phosphine–Ag complex[5] and entail the addition of a siloxyfuran to aldimines[6] or α-ketoimine esters[7] (Scheme 1a); such enantioselective vinylogous Mannich (EVM) processes[8] can be used to synthesize heterocyclic structures that contain a tertiary or a more sterically congested quaternary N-substituted stereogenic center and readily lend themselves to subsequent site- and/or stereoselective modifications. From the point of view of reaction development, the N-aryl moiety used in the above transformations offers a critical advantage: fine tuning of the chelating ability and/or electronic attributes of this unit can provide a significant boost to the observed efficiency levels. Thus, the more electron donating *p*-methoxyaryl group prolongs the lifetime of the more reactive alkyl-substituted imines (vs aryl variants); together with the stronger chelating ability of a sulfide group with a Ag metal, the moiety proved optimal for EVM with

Scheme 1. Enantioselective Mannich Reactions Promoted by Ag-Based Catalysts

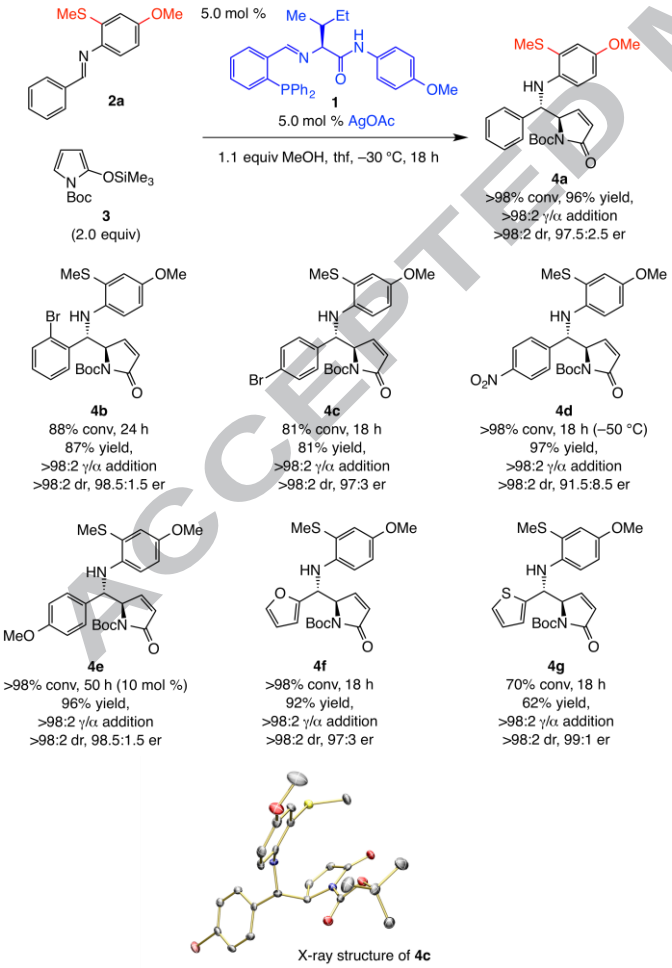


aliphatic aldimines (Scheme 1a). In a similar vein, the strongly electron withdrawing *p*-nitro unit proved necessary for additions to the comparatively less reactive ketoimines (despite the presence of an α-ester moiety) to proceed efficiently (Scheme 1a). Methods to convert the N-aryl unit to the corresponding unprotected amine have been developed as well.[6,7]

Herein, we illustrate that the same family of amino acid based chiral Ag complexes can be used to promote efficient and exceptionally selective EVM[8] reactions with different siloxypyrroles serving as the nucleophilic component and which afford two contiguous N-substituted tertiary carbon stereogenic centers (Scheme 1b).[9] These transformations deliver enantiomerically enriched 1,2-diamine compounds that can be functionalized in a variety of manners and cannot be accessed readily be alternative protocols.[6c] In addition to the aforementioned N-Ar group products contain an easily removable Boc-amide (Boc = *t*-butoxycarbonyl). The importance of the present type of EVM processes is underscored by a recent total synthesis of influenza neuroaminidase inhibitor A-315675 (Scheme 1b);[10] preparation of this biologically active compound and its analogues would likely be facilitated substantially due to the availability of the catalytic protocols that are outlined below. We also report on the first examples of diastereo- and enantioselective phosphine–Ag-catalyzed additions with 5-substituted siloxyfurans, leading to the formation of O-substituted quaternary carbon stereogenic centers that are adjacent to a tertiary N-substituted stereogenic center (Scheme 1b). Such products have been used in the preparation of biologically active alkaloids.[10]

Initial screening studies involving aldimines derived from benzaldehyde indicated that the optimal N-aryl unit for EVM with Boc-protected siloxypyrrole **3**[11] is that which was previously utilized for reactions involving alkyl-substituted aldimines and oxygenated heterocyclic nucleophiles (Scheme 1a). Thus, as illustrated in Scheme 2, reaction with aldimine **2a** in the presence of isoleucine-derived phosphine ligand **1**, resulted in the formation of **4a** in 96% yield, >98:2 γ/α and diastereomeric ratio (dr) and 97.5:2.5 enantiomeric ratio (er).[12] Additions to imines with a bromo-substituted aryl unit (cf. **4b**,**c**), an electron withdrawing (cf. **4d**) or an electron-donating unit (cf. **4e**,**f**) proceeded with similar degrees of efficiency and selectivity. With regard to the influence of the N-aryl moiety, process with the alternative substrate derivatives was somewhat less enantioselective. For example, the EVM involving the *p*-bromophenyl *o*-anisidylimine (cf. **4c**) gave the desired product with complete site- and diastereoselectivity but in 88.5:11.5 er (vs 97:3); the same process with the *o*-thioanisidylimine furnished the expected diamine and in 90:10 er (>98:2 γ/α and dr). Heterocyclic aldimines can be used as well, as indicated by the site-selective, diastereoselective and enantioselective formation of furyl- and thienyl-containing products **4f,g** (Scheme 2). The lower conversion in the reaction leading to **4g** might be attributed to competitive chelation of the Ag-based complex with the S atom of the thienyl group. The stereochemical identity of the products derived from this phase of our study was ascertained by X-ray crystallography (cf. structure for **4c** in Scheme 2).

Scheme 2. Additions of Siloxypyrrole **3** to Aryl-Substituted Aldimines[a]

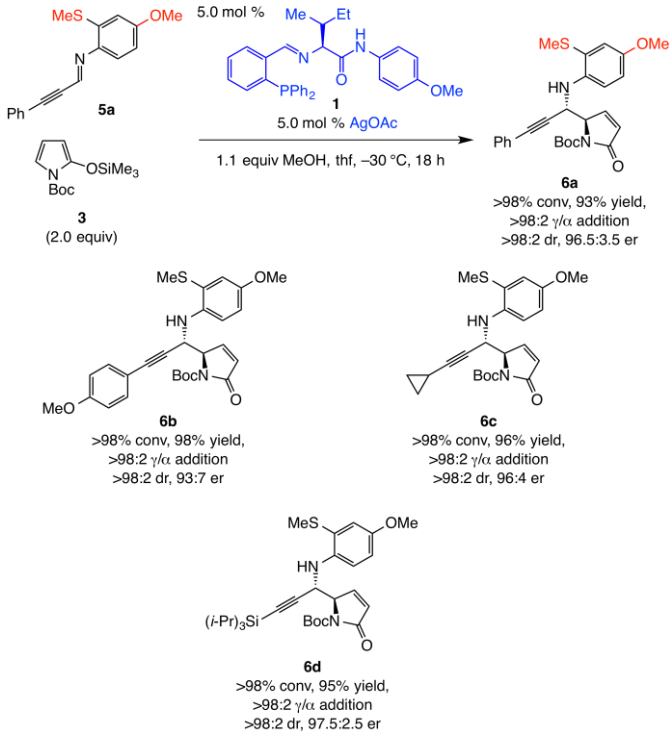


[a]See the Supporting Information for experimental and analytical details. Boc, *t*-butoxycarbonyl

Scheme 1. Additions of Siloxypyrrole 3 to Aryl-Substituted Aldimines[a]

The catalytic method can be extended to alkyne-substituted aldimines (Scheme 3). Here, too, the EVM products are obtained, under the same conditions as illustrated above, in 93–98% yield with exceptional site- and diastereoselectivity. It is not surprising that processes involving these less sterically demanding starting materials proceed to higher conversion (vs those involving the more sizeable arylimines in Scheme 2). The resident acetylene

Scheme 3. Additions of Siloxypyrrole **3** to Alkynyl-Substituted Aldimines[a]

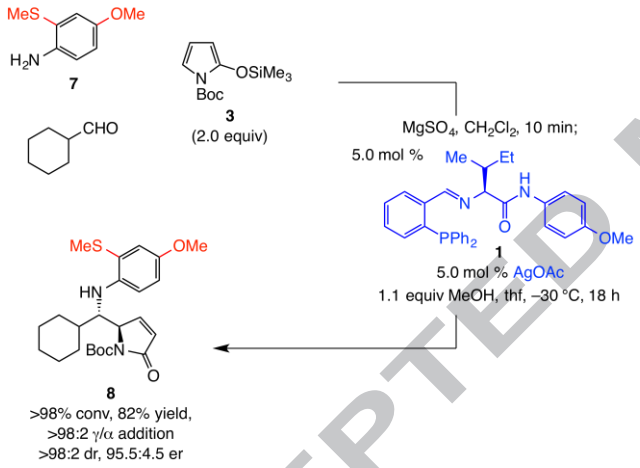


[a]See the Supporting Information for experimental and analytical details.

may carry an aryl (cf. **6a**,**b**), an alkyl (cf. **6c**) or a silyl substitutent (cf. **6d**). What is especially notable is that high er values persist (93:7–97.5:2.5 er) despite the lower degree of steric difference between the aldimine substituents (H and an alkyne vs H and an aryl group). The alkynyl-substituted diamine products may be converted to a variety of other useful derivatives, including those that would be formed from EVM with alkenylimines; this is an important point, since our attempts to identify conditions that would afford the latter set of products proved unsuccessful (led to complex mixtures of unidentified side products).

Synthesis of an alkyl-substituted EVM product, however, can be carried out with the same N-aryl moiety and chiral phosphine ligand **1** without any complications. Because aliphatic aldimines are comparatively unstable and subject to adventitious and debilitating enamine formation, it is best that such substrates are prepared by subjection of the aldehyde and the appropriate aniline in the presence of a common drying agent (e.g., $MgSO_4$, 10 min) and used in the same vessel, as illustrated in the multicomponent process depicted in Scheme 4.[6b] Cyclohexyl-substituted diamine **8** was thus obtained in 82% yield, without the formation of any detectable amounts of α-addition side product, in >98:2 dr and 95.5:4.5 er.[13]

Scheme 4. Multicomponent EVM Involving an Alkyl-Substituted Aldimine[a]

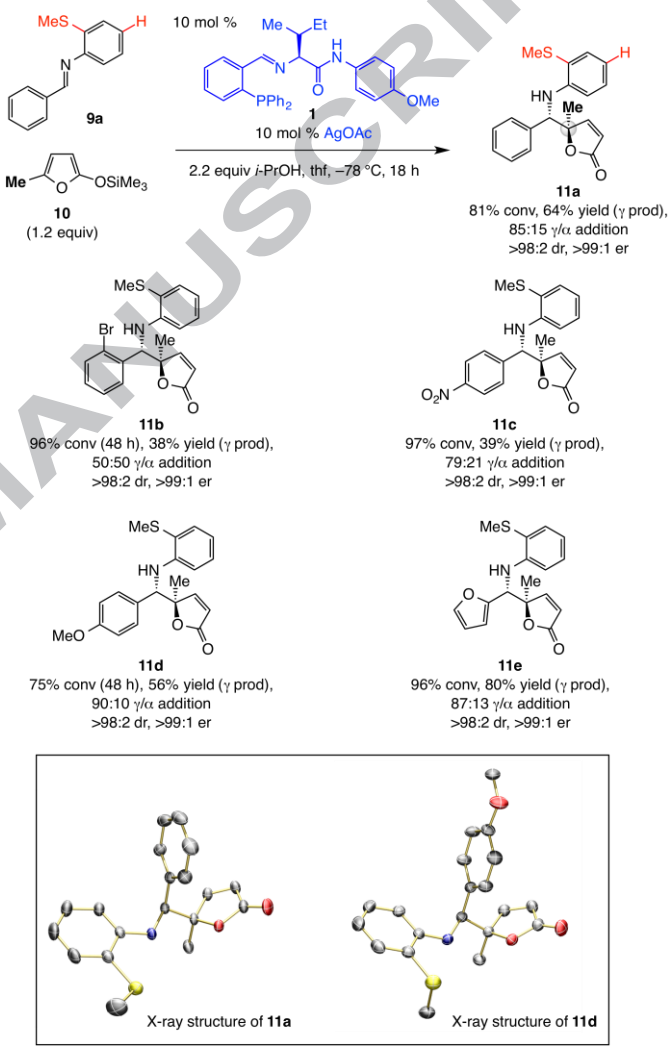


[a]See the Supporting Information for experimental and analytical details.

At this point, we turned our attention to the more challenging EVM reactions involving 5-methyl-substituted siloxyfuran **10**[14] that generate an O-substituted quaternary carbon stereogenic center within the heterocyclic moiety of the product (Scheme 5). This category of transformations has received scarce attention. As far as we are aware, there is only one disclosure that addresses related catalytic EVM processes with 5-methyl-substituted siloxyfurans to access such products [chiral aminoxide ligands and $Sc(OTf)_3$].[15] In another report it was stated that attempts to effect the same additions with chiral Ti-diolate complexes, did not lead to formation of any desired product.[6c]

Although chiral phosphine **1** again proved to be optimal, successful implementation of this set of transformations required that the aldimine be rendered more electrophilic through removal of the electron donating *p*-methoxy unit of the N-Ar substituent (cf. **9a**, Scheme 5); this modification likely arises from the higher energy barrier required for the addition of the fully substituted γ-carbon of the siloxyfuran **10**.[16] What's more, possibly for the same reason, higher catalyst loadings were needed to achieve appreciable conversion values (10 vs 5.0 mol % ligand and AgOAc). Another distinction is that in reactions with **10** larger amounts of α-addition products are observed, again probably since additions from this inherently less nucleophilic site are more competitive due to lower accessibility of the γ site. Nevertheless, the yield values shown in Scheme 5 correspond to pure γ-addition compounds, since entities derived from reactions of the alternative heterocyclic site readily undergo elimination to compounds that can be easily removed.[12] This class of EVM reactions is particularly enantioselective, regardless of the electronic attributes of the aryl-substituted aldimine used (i.e., **11a-e** obtained in >99:1 er). The X-ray structures obtained for **11a**,**d** serve to establish the relative and absolute stereochemical identity of the enantiomerically enriched products.

Scheme 5. Additions of Siloxypyrrole **10** to Aryl-Substituted Aldimines[a]



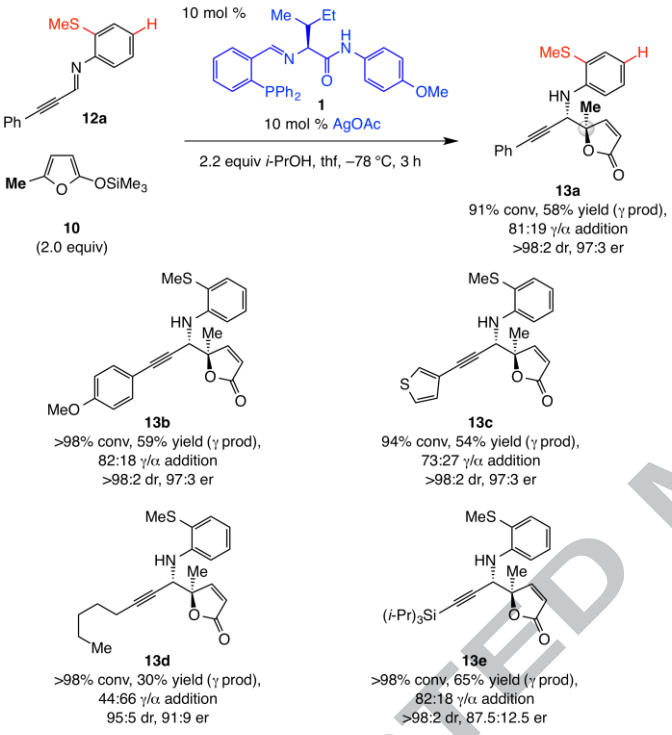
[a]See the Supporting Information for experimental and analytical details.

Catalytic EVM reactions performed in the presence of 5-methyl-substituted siloxyfuran **10** can be readily extended to alkynyl-substituted imines (Scheme 6). The same chiral ligand employed throughout this study (phosphine **1**) and the N-aryl group utilized in the related additions to arylimines can also be used in these instances. However, additions are more facile, probably because of the smaller size of the alkynyl vs aryl substituents of the electrophilic component. Similar to the transformations presented in Scheme 5, α-addition products are detected, but the desired isomers can be isolated in high purity (>98:2 γ/α).

In brief, the studies described in this report demonstrate that readily accessible amino acid based chiral phosphine **1** in conjunction with commercially available AgOAc can be used to promote a variety of EVM reactions that involve aryl-, alkyl, or

alkynyl imines. Products involving two different types of nucleophilic entities, which can be similarly synthesized in a straightforward manner, lead to the formation of relatively complex products that contain vicinal C–N or vicinal C–N and C–O bonds and are formed with high diastereo- and enantioselectivity. In cases where the nucleophilic component does not contain a methyl unit, exceptional γ selectivity is observed (>98:2 γ/α), whereas in reactions with 5-methyl-siloxyfuran, which generate an O-substituted quaternary carbon stereogenic center, site selectivity is lower. Nonetheless, pure γ-addition products can be easily obtained by simple purification procedures in the latter cases.

Scheme 6. Additions of Siloxyfuran **10** to Alkynyl-Substituted Aldimines[a]



[a]See the Supporting Information for experimental and analytical details.

Studies aimed at the development of additional catalysts and further methods for efficient and selective additions of different types of nucleophilic entities to various imine substrates are in progress and will be reported in due course.

Acknowledgments

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11. The siloxypyrrole can be prepared in four steps and ~50% overall yield. See the Supporting Information for details.
12. See the Supporting Information for all experimental and analytic details.
13. After completion of the present studies but prior to preparation of this manuscript, the present catalytic system was employed by Zanardi and co-workers to promote EVM reactions with siloxypyrrole **3**. These workers report that with alkyl-substituted aldimines, *o*-thiomethyl,*p*-methoxyphenylimines (cf. **2a**) are most suitable, whereas, in contrast to the present studies, *o*-anisidylimines are best for aryl imines. See: (a) Curti, C.; Battistini, L.; Ranieri, B.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 2248–2252. (b) Ranieri, B.; Curti, C.; Battistini, L.; Sartori, A.; Pinna, L.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 10291–10298.
14. 5-Methyl-siloxyfuran can be prepared in ~65% overall yield from readily accessible starting materials. See the Supporting Information for details.
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16. Usually, the optimal proton source in these phosphine–Ag-catalyzed reactions is *i*-PrOH (see ref 4a–b and ref 7). The reason for use of MeOH in the transformations depicted in Schemes 2–4 is that slightly higher er values for obtained (e.g., **4a** was obtained in 88:12 and 82:18 er with MeOH and *i*-PrOH, respectively with the unoptimal *o*-anisidylimine substrate).