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Asymmetric Vinylogous Mannich Reaction of Silyloxy Furans with *N*-*tert*-Butanesulfinyl Ketimines

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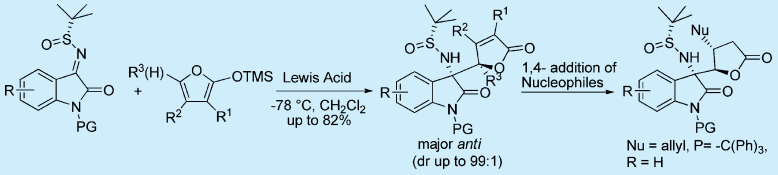
Supporting Information



ABSTRACT: A highly regio- and diastereoselective TMSOTf promoted vinylogous Mannich reaction for the synthesis of chiral quaternary 3-aminooxindole butenolides from 2-silyloxy furans and chiral ketimines is described. The method is found to be very efficient and also provides a facile access to sterically challenging 3-aminooxindole butenolides bearing two quaternary centers in continuation. Further, the versatility of the method is demonstrated by the 1,4-addition of nucleophiles on the sterically congested butenolide substructure.

Functionalized chiral oxindoles bearing a 3,3′-disubstituted carbon stereocenter are the common structural core in natural products and pharmaceuticals.[1] Such cores also offer valuable chiral building blocks for the enantioselective synthesis of biologically active compounds.[2] Especially, the oxindoles with the amino group at the 3-position are vital in drug discovery and considered important for the bioactivity of these molecules.[3] For instance, the amino-indoles are found in many promising molecules such as antimalarial drug candidate NITD609,[3a] a gastrin/CCK-B receptor antagonist AG-041R,[3b] in a CRTH2 antagonist,[3c] and in a molecule that inhibits the protein−protein interactions of a tumor suppressor (transcription factor p53) and its negative regulator (Hdm2) (Figure 1).[3d] In fact, it has been shown that the oral bioavailability of a CRTH2 antagonist improves because of the presence of a heteroatom at the C3 position.

In the past decade, various synthetic strategies for achieving these oxindole frameworks have been employed. The most commonly used methods for synthesizing 3-substituted-3-aminooxindoles are the alkylation of 3-aminooxindoles,[4] intermolecular arylation,[5] amination of 3-substituted oxindoles,[6] imine addition reaction, and Mannich reaction.[7] Although considerable effort has been made in developing such methodologies, achieving the structural complexity of a natural product has been a big challenge, due to the lack of adequate functional groups that can be incorporated in the 3-aminooxindoles cores. One way of achieving the complexity would be by using functionally rich nucleophiles such as 2-silyloxy furans.[8] We hypothesized that development of an enantioselective nucleophilic addition reaction of 2-silyloxy furans to isatin derived ketimines can offer a more practical and direct approach to obtain chiral 3-substituted 3-aminooxindoles with increased functionality in the core, thus, assisting in the synthesis of structurally complex natural products.

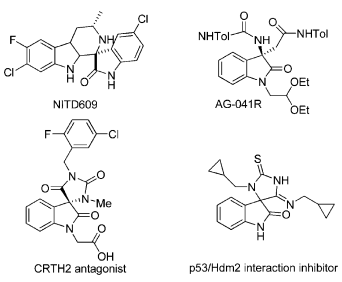


Figure 1. Some examples of biologically active quaternary 3-aminooxindoles.

The Mannich reaction of ketimines and trimethylsilyloxy furan remains less explored due to the steric challenges that the structure imposes. To date, there are only four reports for the vinylogous Mannich reaction of ketimines and silyloxyfurans.[9] A vinylogous Mannich reaction of 2-silyloxy furans and isoquinolines using acyl/sulfonyl chlorides as an activating agent was recently reported by Dodd's group.[9a] Later, the first asymmetric vinylogous Mannich reaction of 2-silyloxy furans to α-ketimine esters was realized by Snapper and Hoveyda.[9b] Recently, Deng and co-workers reported a AgOAc catalyzed diastereoselective vinylogous Mannich reaction of ketimines derived from isatin.[9c] Very recently, Nakamura reported the $Cu(OAc)_2$/cinchona alkaloid amide catalyzed asymmetric vinylogous Mannich reaction of ketimines and silyloxy furans.[9d] However, the enatioselective vinylogous Mannich reaction of isatin ketimines and 2-silyloxy furans for the synthesis of chiral quaternary 3-aminooxindoles is yet to be achieved.

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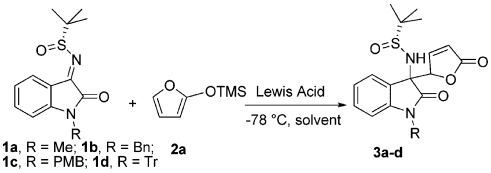
Herein, we report a trimethylsilyltriflate (TMSOTf) promoted synthesis of quaternary 3-substituted 3-amino-oxindoles by a very practical and highly diastereoselective vinylogous Mannich reaction of chiral *N*-*tert*-butanesulfinyl ketimines and various 2-trimethylsilyloxy furans. We have achieved the enantioselectivity *via* chiral *tert*-butyl sulfinamide and demonstrated how the vinylogous Mannich adduct can be converted into a rich structural backbone.

The chiral sulfinyl amine auxiliaries such as *p*-toluene-sulfinimines and *N*-*tert*-butanesulfinimines (NTBS) have shown great success in asymmetric induction.[10] We began our investigation by catalyst screening and reaction optimization using a series of N-protected isatin-derived *N*-*tert*-butanesulfinyl ketimines (**1a**–**d**), obtained under literature reported procedure,[11,7j] and reacted them with 2-trimethyl silyloxy furan (**2a**) under different conditions (Table 1). A number of Lewis acids, such as $In(OTf)_3$, $BF_3{\cdot}OEt_2$, and TMSOTf, were screened in the model vinylogous Mannich reaction at −78 °C for 2.5 h (Table 1, entries 2–4). In accordance with the previous reports on NTBS aldimine activations, it was found that the TMSOTf mediated[12] transformation yielded better conversion for the vinylogous Mannich adduct **3a** with modest selectivity (Table 1, entry 4). $In(OTf)_3$ and $BF_3{\cdot}OEt_2$ both gave poor yields. However, better selectivity was observed for $In(OTf)_3$ (Table 1, entries 2 and 3). In the absence of a catalyst, a trace amount of the vinylogous Mannich adduct **3a** was observed at −78 °C (Table 1, entry 1). Interestingly, isatin-ketimines bearing a bulkier N-protecting group such as *N*-trityl *via* TMSOTf activation in dichloromethane afforded excellent stereocontrol at −78 °C (Table 1, entry 7). This improved stereoselectivity due to a bulky group could be because bulky substituents on isatin-ketimines have been shown to promote the formation of a specific isomer (*trans*) over a mixture of isomers.[13] This specificity can lead to easy control of the stereochemistry. To further improve the yield and selectivity, we screened various Lewis acids and solvents for the reaction of *N*-tritylketimine with 2-trimethylsilyloxy furan. Interestingly, many metal triflates, including $Sc(OTf)_3$, $In(OTf)_3$, $Yb(OTf)_3$, and $BF_3{\cdot}OEt_2$, did not provide any further improvement in stereocontrol and reactivity (Table 1, entries 8–11). We next investigated the impact of solvents on the reaction. We were delighted to realize that dichloromethane produced the best yield and selectivity for the reaction compared to all other tried solvents (Table 1, entries 7, 12–14). The optimized conditions were then used to explore the generality of the reaction. *N*-Tritylisatin ketimines with various substituents on the aromatic ring of isatin were explored. All reactions reached completion at −78 °C in about 2.5 h. Generally moderate yields and good selectivities were obtained in the presence of a variety of substituents including electron-donating groups (**3d**–**3f**), withdrawing groups (**3i**–**3j**), and halogen substituents at various positions (**3g**, **3h**, and **3k**) (Table 2) on the aromatic ring of oxindole ketimine **1**. To our surprise, substitution at the 5- or 6-position of the aromatic ring of oxindole ketimines did not significantly impede stereocontrol of the reaction. Electron-donating groups at the 5-position of isatin ketimines showed a marginal loss in reactivity (Table 2, **3e** and **3f**).

We also investigated the reaction with various substituted 2-trimethylsilyloxy furans (**2b**–**2g**) (Table 3). Remarkably, TMSOTf afforded very high selectivity in all the cases. The selectivity for reactions of sterically hindered 5-substituted 2-trimethylsilyloxy furans (**2d**–**2g**), which generate chiral adducts bearing adjacent quaternary–quaternary centers, was very high (up to 99:1).

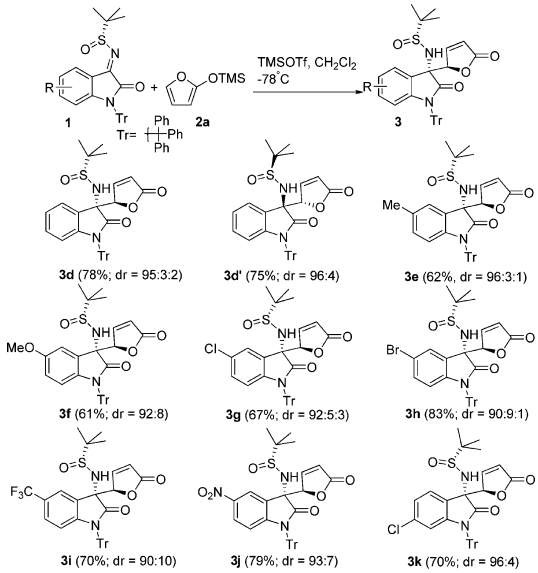
Table 1. Vinylogous Mannich Reactions of Isatin Ketimines 1 with 2-Trimethylsilyloxyfuran 2a[a]



entry	R_1	Lewis Acid	solvent	yield (%)[b]	ratio of stereoisomers[c]
1	Me	none	CH_2Cl_2	~5	–
2	Me	$In(OTf)_3$	CH_2Cl_2	24	73:12:8:7
3	Me	$BF_3{\cdot}OEt_2$	CH_2Cl_2	32	40:23:22:14
4	Me	TMSOTf	CH_2Cl_2	69	52:30:10:8
5	Bn	TMSOTf	CH_2Cl_2	72	61:19:11:8
6	PMB	TMSOTf	CH_2Cl_2	25	63:25:8:4
7	Tr	TMSOTf	CH_2Cl_2	78	95:3:2
8	Tr	$Sc(OTf)_3$	CH_2Cl_2	40	92:6:1:1
9	Tr	$In(OTf)_3$	CH_2Cl_2	35	86:5:5:4
10	Tr	$Yb(OTf)_3$	CH_2Cl_2	29	90:6:4
11	Tr	$BF_3{\cdot}Et_2O$	CH_2Cl_2	30	95:3:2
12	Tr	TMSOTf	toluene	72	94:5:1
13	Tr	TMSOTf	Et_2O	45	94:6
14	Tr	TMSOTf	THF	50	78:11:7:4

[a]Unless noted otherwise, reactions were performed under argon with 0.2 mmol of **1** and 0.3 mmol of **2a** in 1.0 mL of solvent with 0.2 mmol of catalyst. [b]Isolated combined yield based on **1**. [c]Ratios determined by ^{1}H NMR analysis of crude mixtures.

Table 2. Diastereoselective Vinylogous Mannich Reaction of Various Isatin Ketimines 1 and 2-Trimethylsilyloxy Furan 2a Using TMSOTf[a,b,c]



[a]Unless noted otherwise, reactions were performed under argon with 0.2 mmol of **1d**–**k** and 0.3 mmol of **2a** in 1.0 mL of solvent with 0.2 mmol of catalyst. [b]Isolated combined yield of inseparable stereoisomers of vinylogous Mannich adducts **3d**–**k**. [c]Ratios determined by ^{1}H NMR analysis of crude mixtures.

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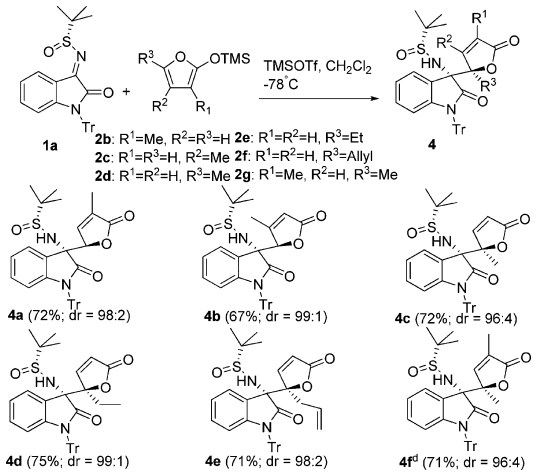
Table 3. Diastereoselective Vinylogous Mannich Reaction of Various Isatin Ketimine 1 with Substituted 2-Trimethylsilyloxy Furan 2a Using TMSOTf[a,b,c]



[a]Unless noted otherwise, reactions were performed under argon with 0.2 mmol of **1a** and 0.3 mmol of **2b**−**g** in 1.0 mL of solvent with 0.2 mmol of catalyst. [b]Isolated combined yield of inseparable stereoisomers of vinylogous Mannich adduct based on **1a**. [c]Ratios determined by ^{1}H NMR analysis of crude mixtures. [d]The absolute configuration of Mannich adduct *anti*-**4f** was established by single crystal X-ray structure analysis (see SI).

The relative and absolute configuration of the Mannich adduct was determined by X-ray crystal structure analysis of **4f** bearing a trityl group at N_1 and a *tert*-butyl sulfinyl group at N_2 (Figure 2). The relative configuration of the major stereoisomer

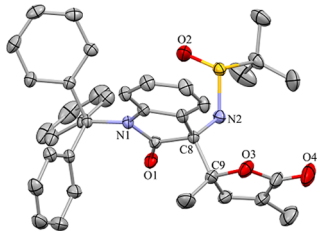


Figure 2. Single crystal X-ray structure of **4f** (hydrogen atoms are omitted for clarity).

of Mannich adduct **4f** was established to be *anti* (see Supporting Information (SI)). The observed *anti* stereochemical configuration in these vinylogous Mannich reactions can be due to an acyclic transition state model illustrated in Figure 3. Most likely, the 1 equiv of the Lewis acid, which is required for high yields, forms a monocoordinated transition state (TS) at the *N*-sulfinyl group.

Assuming that the possible conformation of the TS is *syn* periplanar and the bulky *tert*-butyl group is positioned at the *si*-

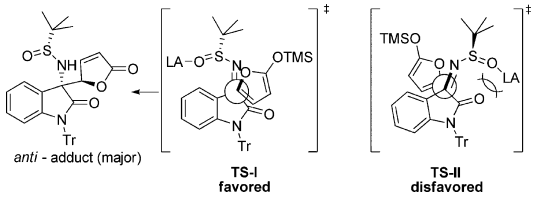
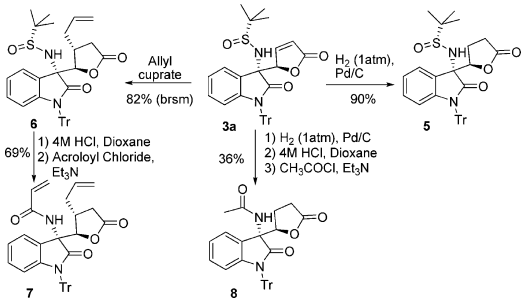


Figure 3. Plausible transition state for the stereochemical outcome.

face of ketimine molecule (as depicted in the favored TS1), the only favored attacking position for the silyloxy furan on the ketimine is *via* the sterically unblocked *re*-face. This results in the formation of the anti (*R*,*R*)-Mannich adduct.

To demonstrate the synthetic utility of the Mannich adduct **3a**, we subjected it to hydrogenation and 1,4-allylation (Scheme 1). Treatment of **3a** with H_2 (1 atm)/Pd−C reduced the *α*,*β*-

Scheme 1. Transformation of Mannich Adduct 3a



unsaturated lactone moiety and yielded the corresponding saturated compound **5**.[12d] Whereas, the 1,4 allylation with an allyl cuprate yielded lactone **6**.[14] The sulfinyl group deprotection of **6** followed by acryllylation of the tertiary amine of aminooxoindole produced compound **7**. Sequential treatment of **3a** with H_2 (1 atm)/Pd−C for hydrogenation, 4 M HCl for sulfinyl group deprotection, and CH_3COCl for protection of the tertiary amine gave compound **8**.

In summary, a highly practical asymmetric approach for the efficient preparation of chiral tetrasubstituted 3-aminooxindoles has been developed, based on a simple Lewis acid mediated diastereoselective vinylogous Mannich process. The method provides easy access to a wide range of highly enantiomerically enriched 3-butenolide substituted 3-aminooxindoles, which is the essential core structural motif in natural products and biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterizations of the compounds (^{1}H, ^{13}C NMR) including X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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