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Vinylogous Mannich reactions. Catalytic, asymmetric additions of triisopropylsilyloxyfurans to aldimines

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Abstract

The vinylogous Mannich reaction of triisopropylsilyloxyfurans with aldimines in the presence of catalytic amounts of the Ti(O^{i}Pr)$_4$/(*S*)-BINOL complex gave substituted aminoalkyl butenolides in good yield and enantioselectivities (up to 54% ee). © 1999 Elsevier Science Ltd. All rights reserved.

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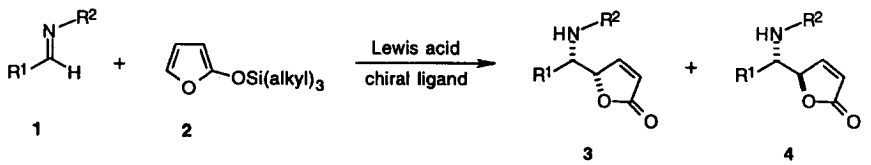
The vinylogous Mannich reaction of trialkylsilyloxyfurans[1] with either an iminium or acyl iminium salt is an important process that is being increasingly employed for the synthesis of alkaloids and other nitrogen-containing, biologically active compounds.[2–5] Because of the utility of this addition, we were intrigued by the prospect of developing an enantioselective variant in order to control the absolute stereochemistry at the newly formed, contiguous chiral centers (Scheme 1). Prior art suggested that the reaction of the furan **2** with the imine **1** should furnish the *threo*-adduct **3** as the major product together with smaller quantities of the *erythro*-adduct **4**,[1] so the key question was whether use of a chiral Lewis acid as catalyst would deliver **3** in optically pure form. Although there are several examples of catalytic, enantioselective additions of silyloxyfurans to aldehydes,[6–8] we are aware of no precedent for the corresponding additions to imines. We now report the first example of a catalytic, asymmetric vinylogous Mannich reaction of aldimines.



1 2 3 4

Scheme 1.

Several chiral Lewis acid complexes have been reported to catalyze the enantioselective addition of nucleophiles including metal enolates, enol silyl ethers and ketene silyl acetals to imines.[9] In exploratory

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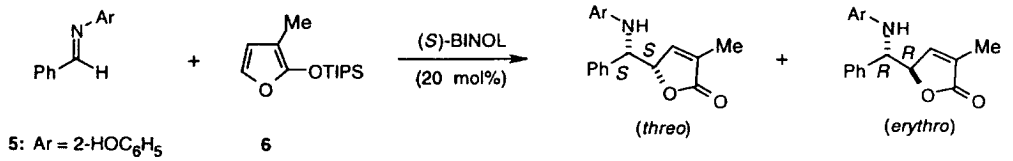
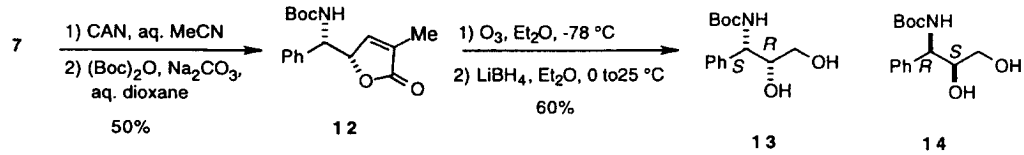
studies, we discovered, however, that when some of these Lewis acids were employed to catalyze the addition of 3-methyl-2-triisopropylsilyloxyfuran (**6**) to the aromatic aldimine **5**, the additions proceeded in high yields and diastereoselectivity, but the major *threo*-adduct **7** was produced in racemic form (Scheme 2).[10] For example, use of $Cu(OTf)_2$ and Evans' bisoxazoline ligand or a $CuClO_4$/(*R*)-BINAP complex afforded the adducts in good yield and 95:5 diastereomeric ratio.[11] After some experimentation, we discovered that the additions proceeded with modest (48%) enantioselectivity when the $Ti(O^iPr)_4$/(*S*)-BINOL complex was used as the Lewis acid. The relative stereochemistry of the major product was assigned by correlating the diagnostic chemical shifts of the vinyl Me signal (*threo*: 1.73 ppm, *erythro*: 1.69 ppm) in the ^1H NMR spectrum of isomer **7** with that of **10**, whose structure was established by an X-ray crystal structure. The diastereomeric ratio of the adducts was determined by integration of this signal. As expected, the coordinating hydroxyl group on the aromatic ring of the imine **5** played a critical role in enhancing the level of enantioselectivity in the addition reaction, presumably by enforcing a specific transition state organization via coordination with the Lewis acid.[9] Thus, although the vinylogous Mannich reactions of **6** with imines such as **9** that lack chelating functionality proceeded in good yields and with good diastereoselectivity, the adducts were obtained with little or no enantioselectivity (<5% ee). In preliminary experiments, we found that the aldimines prepared from aliphatic aldehydes and 2-aminophenol were unstable, and complex mixtures were obtained on their attempted reaction with **6**.



Scheme 2.

In order to determine the absolute configuration of the major enantiomer of **7**, it was converted into the amino diol **13** by a straightforward series of reactions (Scheme 3). The diol **13** had a specific rotation [α] of +9.8°, whereas the rotation of the known enantiomer **14** has a reported rotation of −19.2°.[12] The major enantiomer of **7** thus has the (*S,S*) configuration, and the optical purity based upon the rotation of **13** (e.g., 51%) compares favorably with the optical purity (48%) that was determined by HPLC.



Scheme 3.

Having identified a catalyst that delivered enantiomerically enriched products, it remained to optimize the conditions required to obtain higher enantiomeric excesses (ee). The results of these experiments are summarized in Table 1, and in the end many of our observations paralleled those of Keck in catalytic, enantioselective Mukaiyama reactions.[13] When the reaction was conducted in non-coordinating solvents such as CH_2Cl_2 or toluene, the reaction was slow, and the optimal solvent was Et_2O. The catalyst was prepared from (*S*)-BINOL and $Ti(O^iPr)_4$ in a 2:1 ratio.

Significantly, when (*S*)-BINOL was omitted from the reaction mixture, the addition proceeded in good yield but with poor diastereoselectivity (**17**:**18**=2:1). Hence, the chiral ligand affects not only enantioselectivity, but also the diastereoselectivity. The reaction failed when other sources of titanium(IV)

Table 1
Stereoselectivity of vinylogous Mannich reactions of **5** with **6**

Entry	Lewis acid (20 mol%)	Solvent	Temp (°C)	Yield (%)	7/8[c]	ee (%)[d]
1	$Ti(O^iPr)_4$	Et_2O	-78	80	91/09	48
2	$Ti(O^iPr)_2Cl_2$	THF	-78/-20	NR	-	-
3	$Ti(O^iPr)_4$	CH_2Cl_2	-20	NR	-	-
4	$TiCl_4$	Et_2O	-78/-20	NR	-	-
5	$Ti(O^iPr)_4$ [a]	Et_2O	-78	65	90/10	36
6	$Ti(O^iPr)_4$ [b]	Et_2O	-78	62	85/15	35
7	$Ti(O^iPr)_4$	Et_2O	-20	80	71/29	44

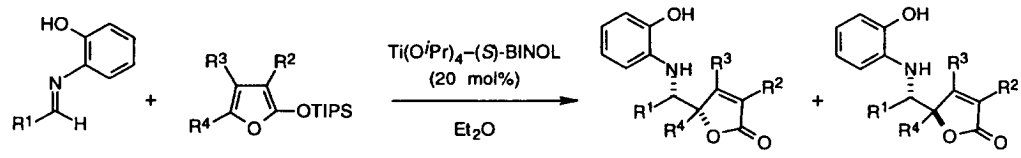
[a]50% mol catalyst. [b]in the presence of molecular sieves 4 Å. [c]*threo/erythro* ratio was determined by ^1H NMR of the crude reaction mixture. [d]ee was determined by chiral HPLC: DIACEL CHIRACEL OD; heptane/ethanol/diethylamine (90:10:0.1, v/v); flow rate, 1.0 mL/min; retention times, 13.4 min for (*R,R*)-**7** and 17.8 min for (*S,S*)-**7**.

such as $TiCl_2(O^iPr)_2$ were used (entries 2 and 4). The optimal amount of catalyst was 20 mol%. When 50 mol% of catalyst was employed, the addition proceeded with good diastereoselectivity, but both the chemical yield and ee decreased (entry 5). The addition of molecular sieves, which appears to be critical to the success of some catalytic additions,[14] had a negative impact on these additions, decreasing both the yield and the enantioselectivity (entry 7). When the reaction was executed at higher temperatures such as −20°C, the diastereoselectivity decreased from 90:10 to 71:29 (entry 6). Having identified the basic elements required for effecting asymmetric, vinylogous Mannich reactions, experiments to probe the scope of the reaction were conducted using a series of triisopropylsilyloxy furans and aldimines; these results are summarized in Table 2.

The silyloxyfuran **16** (R^2=Me; R^3=R^4=H) reacted with aromatic aldimines under the optimized conditions to give adducts in typically good yields, diastereoselectivities and in ee up to 54% (Table 2). The products **17** and **18** were inseparable in every case, but the major product was always the *threo*-adduct **17** as determined by the diagnostic chemical shifts of the vinyl methyl groups on the butenolide. This resonance appeared downfield (1.79–1.73 ppm) in the *threo* isomer relative to the *erythro* isomer (1.69–1.63 ppm). Although the data are too limited to make compelling generalizations, the presence of an electron rich aromatic ring on the imine carbon appeared to lead to lower diastereoselectivities (entry 4), whereas an electron deficient ring seemed to exert little effect (entries 2, 3, and 6). There were no discernable trends in the observed enantioselectivities of the reactions. The substitution pattern on the furan ring influenced its reactivity. For example, the furan **16** (R^2=R^3=R^4=H) added to the imine **15** (R^1=Ph) only when the reaction was warmed to −20°C, whereas **16** (R^2=R^3=H; R^4=Me) did not react with **15** (R^1=Ph) at temperatures up to −20°C. At higher temperatures the reaction proceeded in low yield and was unselective.

In summary, we have succeeded in developing the first catalytic and asymmetric vinylogous Mannich reaction involving silyloxyfurans and aryl aldimines. Current efforts are directed toward improving the enantioselectivity of the procedure and applying it to the synthesis of natural products; these results will be reported in due course.

Table 2
Asymmetric addition of silyloxyfurans to aldimines[15]



15 16 17 18

Entry	R^1	R^2	R^3	R^4	Temp (°C)	Combined Yield (%)	**17/18**	ee (%) **17**	ee (%) **18**
1	Ph	Me	H	H	-78	80	91/09	48	23
2	4-ClC_6H_5	Me	H	H	-78	79	94/06	54	ND[a]
3	4-$NO_2C_6H_5$	Me	H	H	-78	79	94/06	30	ND[a]
4	4-$MeOC_6H_5$	Me	H	H	-78	63	71/29	36	15
5	1-Naphthyl	Me	H	H	-78	80	71/29	44	19
6	1-Pyridyl	Me	H	H	-78	55	96/04	33	ND[a]
7	Ph	H	H	H	-20	50	66/34	28	20
8	Ph	H	Me	H	-78	65	86/14	45	ND[a]
9	Ph	H	H	Me	-78/-20	NR	-	-	-

[a]ee not determined.

Acknowledgements

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15. General procedure: Neat Ti(O*i*-Pr)$_4$ (60 μL, 0.21 mmol) was added to a solution of (*S*)-BINOL (115 mg, 0.4 mmol) in anhydrous Et_2O (4 mL), and the resulting solution was stirred for 1 h at rt. After cooling the red-brown solution to −78°C, a solution of imine **15** (1.0 mmol) in Et_2O (4 mL) was added, followed by a solution of the silyloxyfuran (1.5 mmol) in Et_2O (4 mL). After 8 h at −78°C, the crude mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated, and the resulting residue was purified by flash chromatography eluting with hexanes:EtOAc (70:30) to yield the adduct. The (*S*)-BINOL can be recovered.