Asymmetric Aminohydroxylation of Vinylfuran

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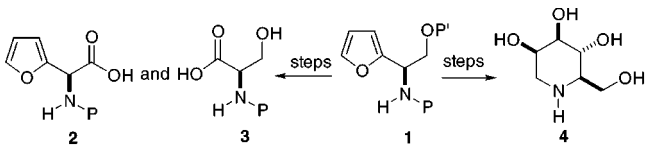
Introduction

The β-hydroxyfurfurylamine functionality is an important synthetic building block for various biologically important molecules.[1] Such amino alcohols can be envisioned as precursors to furan-containing amino acids **2** by oxidation of the alcohol functionality. Furthermore, oxidative cleavage of the furan ring can lead to derivatives of the amino acid serine **3** (Scheme 1).[2,3] By employing the aza-Achmatowicz reaction,[1] furan **1** can be converted into various piperidines, in particular, azasugar **4**.[4]

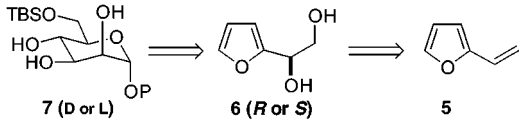
Because of our interest in studying unnatural azasugars, we are interested in an efficient asymmetric synthesis of both enantiomers of **1**. Previously, Ciufolini/Wong[5] and Zhou[6] have shown that furans similar to **1** can be produced via resolution strategies. A significant improvement of this work could be realized by the development of a catalytic enantioselective procedure capable of producing either enantiomer of **1**.[7] Drawing from our successful experience with the Sharpless asymmetric dihydroxylation of vinylfuran and subsequent conversion to D- and L-sugars (Scheme 2),[8] we envisioned the synthesis of **1** being readily achievable via a Sharpless asymmetric aminohydroxylation (AA) of vinylfuran, in a single transformation (Scheme 3).

Sharpless and co-workers first reported the oxyamination (aminohydroxylation) of olefins in 1975 and subsequently have extended the reaction into an efficient one-step catalytic enantioselective method.[9] We were particularly encouraged by the observation of the Sharpless group that the asymmetric aminohydroxylation of electron rich styrenes proceeds with excellent enantio- and regioselectivity, providing the primary alcohol as the major isomer.[10] We felt that the polarization of the vinyl group in **1** was approximated by *p*-benzyloxystyrene which gave high regioselection for the primary alcohol (88:12). The dihydroxylation results for vinylfuran[8] ameliorated our concerns regarding the susceptibility of the furan ring to oxidation.[11]

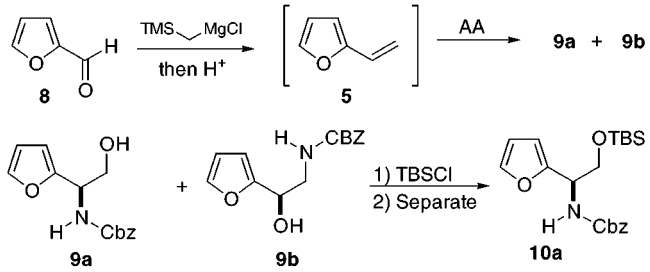
Scheme 1



Scheme 2



Scheme 3



Herein we report our application of the asymmetric aminohydroxylation to vinylfurans and a study of regiocontrol. Our ultimate goal is to extend this methodology to the synthesis of azasugars and aminosugars.[12]

Results and Discussion

Following literature procedures, our efforts to synthesize vinylfuran were met with only mediocre results.[13] Success has been achieved using the Peterson olefination reaction on furfural **8** to generate a solution of vinylfuran **5**, which can be used directly in the asymmetric dihydroxylation reaction (Scheme 2).[8] Our initial effort to extend this simple procedure to the aminohydroxylation reaction of vinylfuran, was unsuccessful using Chloramine-T as the nitrene source;[9a] however, simply switching to Sharpless's alternative procedure using benzylcarbamate gave higher yields of products via simple purification. The addition of a 2 M ether solution of vinylfuran to an aqueous *t*-BuOH solution of the sodium salt of *N*-chlorobenzylcarbamate, 1 mol % of OsO_4, and 1.2 mol % of $(DHQ)_2PHAL$ afforded a 42% yield of a 1:2 mixture of aminohydroylation adducts **9a** and **9b**, respectively (Scheme 3). Consistent with the results for styrenes,[10] the primary alcohol **9a** was obtained in high enantioexcess ($\geq$86% ee)[14] and the regioisomer **9b** was formed in a much lower 14% ee. The amino alcohols **9a** and **9b** were be separated by flash chromatography (SiO_2, 5−40% EtOAc/hexane gradient elution) and isolated in 14% and 28% yields, respectively. A significantly less tedious separation procedure was realized by selective protection of the primary

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(1) For an excellent review of the subject, see: Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105.
(2) Shono, T.; Matsumura, Y.; Tsubata, J. *Chem. Lett.* **1981**, 1121.
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(4) (a) Xi, N.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 6595. (b) Yang, C. F.; Xu, Y. M.; Liao, L. X.; Zhou, W.-S. *Tetrahedron Lett.* **1998**, *39*, 9227. (c) See ref 1.
(5) Drueckhammer, D. G.; Barbas, C. F., III; Nozaki, K.; Wong, C.-H.; Wood, C. Y.; Ciufolini, M. A. *J. Org. Chem.* **1988**, *53*, 1607.
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(8) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982.
(9) (a) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.
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(11) Dress, K. R.; Gossen, L. J.; Liu, H.; Jerina, D. M.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 7669.
(12) Haukaas, M. H.; O'Doherty, G. A. *Abstracts of Papers,* 216th National Meeting of the American Chemical Society, Boston, MA, Aug 23−27, 1998; American Chemical Society: Washington, D.C., 1998; ORGN 369.
(13) This in situ use of vinylfuran allows for much higher yields of diol **6**. Wittig technology provides vinylfuran in yields on the order of 10%. A previous approach to vinylfuran involves a four-step sequence from furfural that involves a stoichiometric Cu-mediated decarboxylation of 3-furylpropanoic acid, see: Schmidt, U.; Werner, J. *Synthesis* **1986**, 986.
(14) At a smaller scale, the level of enantioinduction has been as high as 94%, as determined by Mosher ester analysis.

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Table 1. Influence of Ligands on Regioselectivity for AA of Vinylfuran

ligand	**9a**:**9b**	yield, %	% ee (**9a**)
$(DHQ)_2PHAL$	1:2	42	86
$(DHQD)_2PHAL$	1:2.4	45	85
$(DHQD)_2AQN$	1:2.3	35	82
$(DHQD)_2PYR$	1:2	17	46

alcohol of **9a** using TBSCl to give **10a** (12% yield from **8**).[15] Considering the value of the enantioenriched product **10a** and ease of purification, the overall yield for the transformation is acceptable.

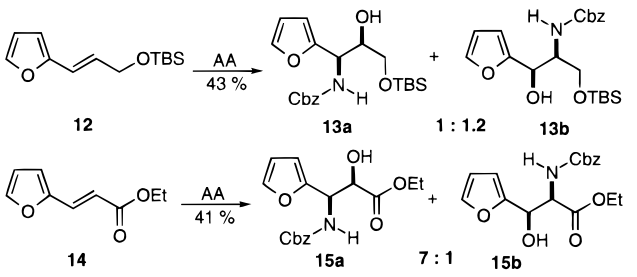
To investigate the origins of the poor regioselectivity for the primary alcohol **9a** in comparison to the *p*-benzyloxystyrene results (**9a** to **9b**, 1:2 vs 88:12), the reaction was repeated in other organic solvents (*n*-PrOH, CH_3CN). The solvent *t*-BuOH was found to consistently give the highest yields and enantioexcesses of **9a** (using the ligand $(DHQ)_2PHAL$), although the resulting changes were rather small (Table 1). Similarly, we varied the chiral alkaloid ligands and found that the AD-mix ligands ($(DHQ)_2PHAL$, $(DHQD)_2PHAL$) gave the best results (86 and 85% ee, respectively), with the resulting products displaying opposite signs of optical rotation. A potentially significant deviation of this procedure from the Sharpless procedure is the use of 1.2 equiv of benzylcarbamate versus 3.1 equiv. No change in regio- or enantiocontrol was observed using 3.1 equiv of nitrene source; however, a slightly lower yield was observed.[16]

To further explore the origins of poor regioselectivity, we chose to study two vinyl-substituted furans **12** and **14** (Scheme 4). The *tert*-butyldimethylsiloxymethyl-substituted furan **12** was chosen to probe for steric effects. We chose the electron deficient vinylfuran **14** for its increased polarization of the vinyl group. Treatment of TBS-protected vinylfuran **12** under the similar AA condition as above gave a 43% yield of a 1 to 1.2 mixture of **13a** to **13b** (61% yield at 70% conversion, 8 h reaction time).[17] Although the regioselectivity is still poor, this corresponds to an increase in selectivity for **13a** compared to **9a**. While substitution of a bulky *tert*-butyldimethylsiloxymethyl group on the vinylfuran increased the regioselectivity, it was at the cost of enantioselectivity. The enantioexcess of **13a** was 62% compared to 86% ee for **9a**.

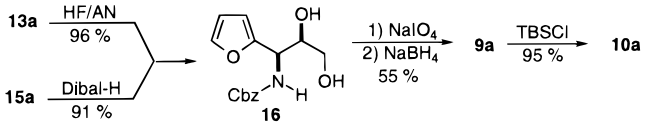
Good regioselectivity in the aminohydroxylation was ultimately achieved with the electron deficient vinylfuran **14**.[18] Vinylfuran **14** was subjected to similar AA conditions, affording a 41% yield of two regioisomers **15a** and **15b** in a 7:1 ratio (59% yield at 70% conversion, 3 h reaction time).[17] Fortunately, the increased regiocontrol was not at the cost of enantioselection; hence the furfurylamine isomer **15a** was produced in ≥86% ee (Scheme 4).

With the regioselectivity problem addressed, we turned our attention to determining the absolute configurations of **9a**, **13a**, and **15a**. Mosher ester analysis[19] of **15a** showed

Scheme 4



Scheme 5



that the $(DHQ)_2PHAL$ ligand gave the *R*,*R* isomer as drawn, which is consistent with the furan ring replacing the aromatic ring of syrene in the Sharpless mnemonic.[20] The absolute configuration of **13a** was correlated with **15a** by conversion to a common synthetic intermediate (Scheme 5). Silyl deprotection of **13a** produced the diol **16**; likewise, a Dibal-H reduction of **15a** also afforded diol **16**. Both reaction products **16** displayed positive values of optical rotation.

An alternative procedure for the formation of **10a** was achieved by a three-step, two-pot oxidation/reduction sequence from **16** (Scheme 5). The 1,2-diol **16** was treated with $NaIO_4$ to give an α-aminoaldehyde in situ, which was reduced with a slight excess of $NaBH_4$, affording **9a**. To complete the alternative synthesis of **10a**, alcohol **9a** was protected using TBSCl to give the protected amino alcohol **10a** in a 95% yield. By converting the amino alcohols **13a** and **15a** into **9a**, the absolute configuration induced by the AA on vinylfuran was also confirmed. The product **9a**, from this latter route (via **15a**), had the same sign and degree of optical rotation. Not surprisingly, these results show that the vinylfurans **5**, **12**, and **14** undergo the asymmetric aminohydroxylation to give products with absolute configurations predicted by the Sharpless mnemonic.

In conclusion, the versatile furan amino alcohol **10a** was synthesized via two equally serviceable routes in high enantioexcesses (≥86% ee) and in 12% and 16.5% yields, respectively. Both synthetic routes can be performed on a multigram scale. The first route has the advantage of forming **10a** in two steps; however, we feel the four-step route maybe more convenient for the large scale synthesis of **10a** (simpler purification). We are currently advancing these products toward the synthesis of azasugars, as well as investigating other nitrogen sources to increase the conversion of these reactions.[21]

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Supporting Information Available: Spectroscopic and analytical data for all new compounds as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) This procedure was carried out with a slight excess of TBSCl compared to the primary alcohol and typically afforded less that 1% of the silyl-protected secondary alcohol.

(16) This lower yield may be due to over-oxidation of the furan ring. We have observed that excess nitrene source or longer reaction times leads to furan oxidation.

(17) These reactions were run to 70% conversion because of our concerns of oxidation of the furan ring (ref 18) and to prevent a ligandless background reaction.

(18) In addition to various electron rich styrene derivatives, excellent regioselectivity is observed in the aminohydroxylation of α,*β*-unsaturated esters. For cinnamates, see: (a) Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649−651. (b) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507. (c) Also ref 9b. (d) For nonaromatic α,*β*-unsaturated esters, see: Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045−2048.

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(21) (a) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (b) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483. (c) Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 3667. (d) O′Brien, P.; Osborne, S. A.; Parker, D. D. *Tetrahedron Lett.* **1998**, *39*, 4099.