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Asymmetric Synthesis of β-Amino Cyclic Ethers *via* the Intramolecular Reaction of γ-Alkoxyallylstannane with Chiral Imine

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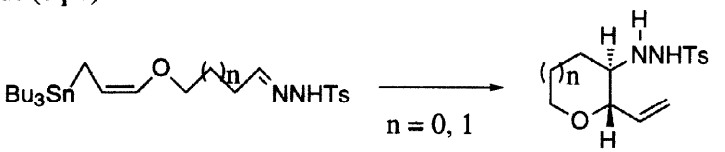
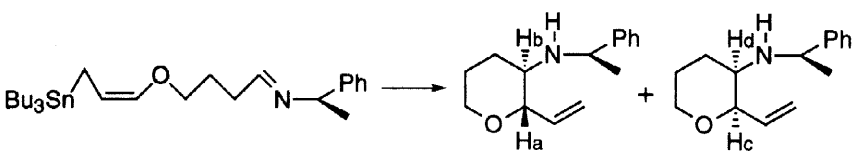
Abstract: The Lewis acid mediated cyclization of γ-oxygen substituted allylic stannane **1**, having a chiral imine group at the terminus of the carbon chain, afforded *trans* β-amino cyclic ether **2** with very high to good diastereoselectivities in high chemical yields.

The allylation of imines has been extensively studied as well as the allylation of aldehydes[1] and this transformation has become important for the efficient synthesis of acyclic and cyclic amine derivatives. Although the asymmetric *intermolecular* allylation of imines with allylstannanes has been investigated during last decade[2], to the best of our knowledge, the asymmetric *intramolecular* allylation of imines has not been reported so far. We previously reported the stereoselective synthesis of β-aminotetrahydro-pyran and -furan *via* the Lewis acid mediated intramolecular cyclization of γ-alkoxyallylstannanes, bearing a hydrazone group at the terminus of the carbon chain (eq 1).[3] We were interested in the asymmetric synthesis of β-amino cyclic ethers *via* the intramolecular reaction of γ-alkoxyallylstannanes with a C=N–R* group, in which R* is a chiral auxiliary. We report herein that $ZrCl_4$ or HCl mediated cyclization of γ-alkoxyallylstannane **1**, having (R)-(+)-1-phenylethylamine as a chiral auxiliary, affords *trans* β-amino cyclic ether **2** with very high *de* in very high chemical yields (eq 2).



(1)



(2)

1 **2** *trans* **3** *cis*

γ-Alkoxyallylstannane **1**[4] was easily prepared from the reaction of the corresponding aldehyde precursor, Z-4-(3-tributylstannyl-1-propenoxy)butanal, with (R)-(+)-1-phenylethylamine. The results of the cyclization of **1** are summarized in Table 1. The Lewis acid or protic acid mediated reactions gave *trans* isomer **2** as a major product in high to good yields. The use of $TiCl_2(O\text{-}iPr)_2$ in CH_2Cl_2 at -78 °C afforded a 77:23 mixture of *trans* **2** and *cis* **3** in 63% yield (entry 1). The stereochemistry of **2** and **3** was unambiguously determined to be *trans* and *cis*, respectively, by ^1H NMR analysis and NOE experiments; Ha and Hb of **2** appeared at δ 3.49 and 2.34, respectively, with coupling constant *J*ab 9.0 Hz. NOEs between Ha and Hb were not observed. On the other hand, Hc and Hd of **3** appeared at δ 3.97 and 2.63, respectively and NOEs between Hc and Hd were

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observed (7%). ^{1}H NMR Analysis of the product mixture revealed that the diastereomeric excess (*de*) of **2** and **3** was >95 and 36%, respectively. The use of $Yb(OTf)_3$ in CH_2Cl_2 at room temperature afforded an 84:16 mixture of **2** and **3** in 70% yield (entry 2). The *de* of **2** and **3** was >95 and 36%, respectively. Interestingly, the use of $ZrCl_4$ (entry 3) or aqueous HCl solution (36%) (entry 4) gave *trans* isomer **2** as a sole product in 97 or 98% yield, respectively. The *de* was also high ; 91% in entry 3 and 92% in entry 4. The use of Lewis acids such as $AlCl_3$, $EtAlCl_2$ and Et_2AlCl, gave **2** and **3** in the ratio of 84:16 in all cases (entries 8-10). Only decomposition of **1** took place when it was refluxed in toluene (entry11).

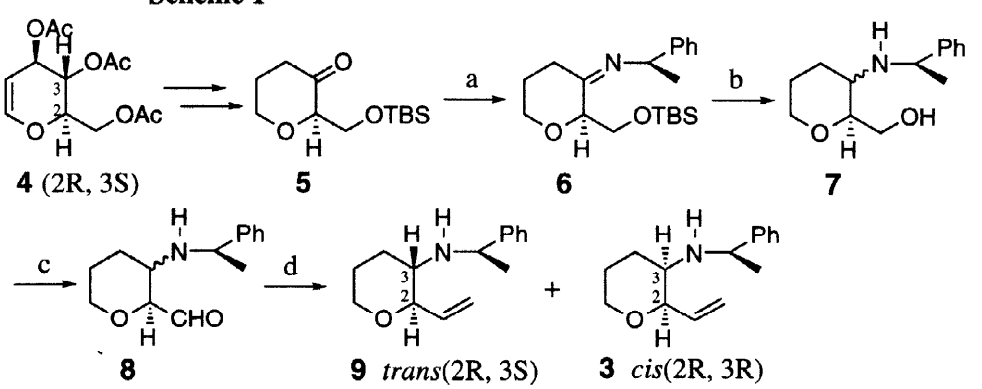
Table 1. Asymmetric synthesis of β–aminotetrahydropyran derivative[a]

entry	reagent	temp (°C)	time (min)	*trans* (de) : *cis* (de)[b]	yield (%)[c]
1	$TiCl_2(OiPr)_2$	-78	120	77(>95) : 23(36)	63
2	$Yb(OTf)_3$	rt	180	84(>95) : 16(36)	70
3	$ZrCl_4$	-78	180	100(91) : 0	97
4	aq. HCl	0	40	100(92) : 0	98
5	$BF_3{\cdot}OEt_2$	-78	60	90(81) : 10(>95)	88
6	CF_3CO_2H	0	10	87(63) : 13(>95)	97
7	$ZnCl_2$	0	120	91(68) : 9(88)	94
8	$AlCl_3$	-78	180	84(82) : 16(70)	87
9	$EtAlCl_2$	0	10	84(72) : 16(47)	89
10	Et_2AlCl	0	90	84(74) : 16(40)	94
11	_[d]	100	2280	decomposition	

[a]The reactions were carried out in CH_2Cl_2. In all cases, 2 equiv of reagents were used. [b]Diastereomeric exess(de) was analyzed by ^{1}H NMR analysis. [c]Isolated yield. [d]Toluene was used as a solvent.

To determine the absolute configuration[5] of **2** and **3**, we decided to synthesize authentic β-amino cyclic ethers (Scheme 1). Tri-O-acetyl-D glucal **4** was converted to **5** acoording to the reported procedure.[6] Treatment of **5** with (R)-(+)-1-phenylethylamine gave **6** in 98% yield. Reduction of **6** with DIBAH afforded a

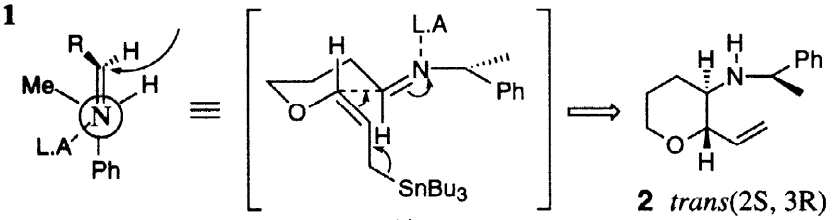
Scheme 1[a]



[a] Synthesis of compound **9** and **3**. Reagents and conditions: (a)1.0 equiv of (R)-(+)-1-phenylethylamine, Na_2SO_4, CH_2Cl_2, 25°C, 1h, 98%; (b)2.5 equiv of DIBAH 1.0M in CH_2Cl_2, Et_2O, 0°C, 1h, then washed with 1N HCl/1N NaOH, 69%; (c)1.5 equiv of oxalyl chloride, 2.0 equiv of DMSO, CH_2Cl_2, -78°C, 1h, then 4.0 equiv of Et_3N, 51%; (d)2.0 equiv of CH_3Ph_3PBr, 2.0 equiv of NaHMDS, THF, 0°C, 1h, 69%.

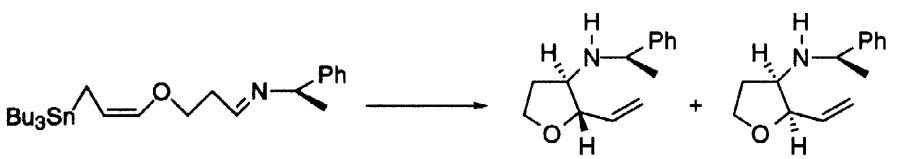
diastereomeric mixture of **7**[7] in 69% yield. Swern oxidation of **7** produced a diastereomeric mixture of the aldehyde **8** in 51% yield. The Wittig reaction of **8** with methyltriphenylphosphonium bromide gave a 1:3 mixture of *trans* isomer **9** and *cis* isomer **3** in 69% yield. The NMR spectra of the *cis* (2R, 3R) isomer obtained from **4** was completely identical with those of the *cis* isomer **3** obtained in entries 5 and 6 of Table 1. Therefore, the absolute stereochemistry of **3** was determined unambiguously to be (2R, 3R). The NMR spectra of the trans (2R, 3S) **9** was completely identical with those of a minor diastereomer of *trans* **2**, which was obtained in entries 6–10 of Table 1. Accordingly, the absolute configuration of **2** was determined unambiguously to be (2S, 3R). The intramolecular addition of the allylstannane unit to chiral imine would proceed through the transition state geometry **10** (Fig 1). At the stage for 6-membered ring formation in **10**, equatorial- equatorial orientation of C=C and C=N double bond would be more favorable, leading to predominant or exclusive formation of *trans* **2**. The asymmetric induction at the imine carbon (C-3 position of **2**) can be explained by the modified *Cram*[8,2a] model (**10′**) for imines. The allylic γ-carbon would attack the imine carbon from the direction shown by an arrow (**10′**), producing R chirality at the C-3 position of **2**.

Figure 1



10' **10** **2** *trans*(2S, 3R)

We next examined the asymmetric synthesis of β-aminotetrahydrofuran derivatives. The results of the cyclization of **11** are summarized in Table 2. The use of $ZrCl_4$ produced *trans* isomer **12** as a sole product in 80% yield with 11% de (entry 1). Although the use of $ZnCl_2$ afforded **12** as a major product, the *de* was 0% (entry 2). When $Yb(OTf)_3$ was used at rt for 10 min, an 88:12 mixture of **12** and **13** was obtained in 90% yield (entry 3). The use of protic acid, such as HCl (entry 4) or TFA (entry 5), also afforded **12** as a major product. The *de* of **12** was lower than that of **2**. Perhaps, a shorter length of the carbon chain in **11** would make it difficult to take a transition state geometry which fits well to the *Cram* model (see **10′**).



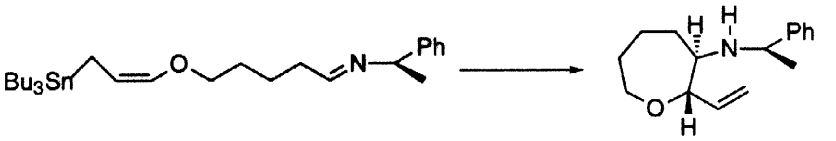
11 **12** *trans* **13** *cis*

Table 2. Asymmetric synthesis of β–aminotetrahydrofuran derivative[a]

entry	reagent	temp (°C)	time (min)	*trans* (de) : *cis* (de)[b]	yield (%)[c]
1	$ZrCl_4$	-78→0	120	100(11) : 0	80
2	$ZnCl_2$	0	60	85(0) : 15(45)	72
3	$Yb(OTf)_3$	rt	10	88(12) : 12(100)	90
4	aq.HCl	0	90	80(12) : 20(100)	89
5	CF_3CO_2H	-78→0	120	88(23) : 12(100)	71

[a]The reactions were carried out in CH_2Cl_2. In all cases, 2 equiv of reagents were used.
[b]Diastereomeric exess(de) was analyzed by ^1H NMR analysis. [c]Isolated yield.

It is noteworthy that cyclization to a 7-membered ether derivative proceeded very smoothly (eq 3). The use of 50 mol% $Yb(OTf)_3$ in CH_2Cl_2 at rt for 24 h afforded a >98:2 mixture of the *trans* and *cis* isomer in 62% yield.[9] ^1H NMR Analysis revealed that the *de* of the *trans* isomer was regrettably 0%.



(3)

In conclusion, the Lewis acid mediated cyclization of γ-oxygen substituted allylic stannane having a chiral imine group at the terminus of the carbon chain afforded the *trans* β-amino cyclic ethers predominantly or exclusively in high chemical yields with high diastereomeric exess (*de*).

References and notes

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4 γ-Alkoxyallylstannane **1** was used for further reaction immediately after the reaction of the aldehyde precursor with (R)-(+)-1-phenylethylamine, since it was decomposed very readily upon treatment with silica-gel column.

5 The specific rotations of compound **2**, **3** and **9** were $[\alpha]_D^{19}$ 2.04 (c=0.20, $CHCl_3$), $[\alpha]_D^{19}$ 77.05 (c=0.62, $CHCl_3$) and $[\alpha]_D^{18}$ 32.98 (c=0.20, $CHCl_3$) respectively. The specific rotation of the minor diastereomer of the *trans* product **2** was $[\alpha]_D^{18}$ 33.12 (c=0.20, $CHCl_3$).

6 Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.

7 The work-up procedure was following. After reduction with DIBAH, aqueous HCl solution(1N) and ether were added. The aqueous solution was separated, and aqueous NaOH solution(1N) and ether were added. The organic layer was separated, dried with anhydrous $MgSO_4$, and concentrated. During these processes, the TBS protecting group was removed and **7** was obtained in an almost pure form.

8 (a) Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031. (c) Wuts, P. G. M.; Jung, Y. W. *Tetrahedron Lett.* **1986**, *27*, 2079.

9 When $TiCl_2(O\text{-}iPr)_2$, $ZrCl_4$, or TFA was used as an activator, the substrate was decomposed.