Intramolecular reaction of γ-alkoxyallylstannane with hydrazone: stereoselective synthesis of β-aminotetrahydro-pyran and -furan

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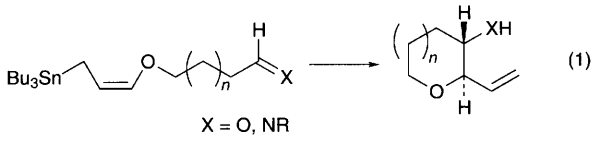
The Lewis acid mediated cyclization of γ-oxygen substituted allylic stannanes 1, 2 and 9, bearing a hydrazone group at the terminus of the carbon chain, afforded the corresponding *trans*-β-amino cyclic ethers 3a, 4a and 10, respectively, with very high diastereoselectivities in high chemical yields.

In recent years there has been an explosion of interest in the synthesis of cyclic ethers because they are a constitutional unit of marine natural polycyclic ethers.[1] Recently, we developed an efficient synthesis of medium sized cyclic ethers *via* the intramolecular reaction of γ-alkoxyallylstannane with aldehyde [eqn. (1), X = O].[2] The usefulness of this methodology has

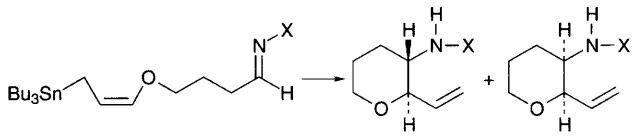


(1)

been demonstrated by the total synthesis of hemibrevetoxin B[3] and related polycyclic ethers.[1,4] To extend our methodology, we aimed at replacing the oxygen atom by a nitrogen atom as shown in eqn. (1) (X = NR), because the allylation of imines has been well studied as well as that of aldehydes,[5] and such a transformation would be an efficient synthesis of cyclic amine derivatives. Here we report the stereoselective synthesis of β-aminotetrahydro-pyran and -furan *via* the intramolecular reaction of γ-alkoxyallylstannane with hydrazone as an imine equivalent [eqn. (1), X = NR].

After several fruitless attempts, we found hydrazones are suitable as a carbon–nitrogen double bond functional group for the intramolecular reaction. The cyclization substrates **1** and **2**, γ-alkoxyallylstannanes having a hydrazone group at the terminus of the carbon chain, were easily prepared by the reaction of the corresponding aldehyde with hydrazines, and could be easily purified by silica gel column chromatography. The results of the cyclization of **1** and **2** are summarized in Table 1. In all the Lewis acid mediated reactions, *trans*-isomers **3a** and **4a** were obtained as the sole product in high to good yields (entries 2, 4–7 and 11–15). None of the *cis*-isomers **3b** and **4b** could be detected by ^{1}H NMR analysis of the crude product. Although the use of $TiCl_4$ caused decomposition of the substrate (entry 1), $TiCl_2(OPr^i)_2$ promoted the cyclization of the tosylhydrazone **1** at −78 °C to give **3a** in 94% yield (entry 2). No reaction took place with $Ti(OPr^i)_4$ even at room temperature, presumably due to its low Lewis acidity (entry 3). The use of Lewis acids, such as $ZrCl_4$, $AlCl_3$, $ZnCl_2$ and $BF_3{\cdot}OEt_2$, gave lower yields of the product (entries 4–7). Although the reaction proceeded quantitatively in the presence of protic acids such as CF_3SO_3H and CF_3CO_2H, the *trans*-selectivity decreased to *ca.* 7 : 3 (entries 8 and 9). These results suggested that the thermal cyclization of **1** would proceed *via* cyclic transition state to give *cis*-isomer **3b** with high stereoselectivity.[2b] However, unfortunately, only decomposition of **1** took place when it was refluxed in toluene (entry 10). Diphenylhydrazone **2** also cyclized in the presence of $TiCl_2(OPr^i)_2$ to give the *trans*-

Table 1 Cyclization of **1** and **2**[a]



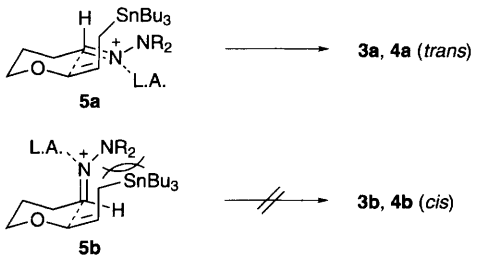
1 X = NHTs **3a** X = NHTs **3b** X = NHTs

Entry	Substrate	Reagent (equiv.)	*T*/°C	*t*/min	*trans* : *cis*	Yield (%)[b]
1	**1**	$TiCl_4$ (2.0)	−78	5	decomposition	
2		$TiCl_2(OPr^i)_2$ (2.0)	−78	5	>95 : 5	94
3		$Ti(OPr^i)_4$ (2.0)	room temp.	30	no reaction	
4		$ZrCl_4$ (2.0)	−78	180	>95 : 5	81
5		$AlCl_3$ (2.0)	−78	120	>95 : 5	68
6		$ZnCl_2$ (2.0)	−6	180	>95 : 5	71
7		$BF_3{\cdot}OEt_2$ (2.0)	−78	5	>95 : 5	61
8		CF_3SO_3H (2.0)	−78	30	71 : 29	98
9		CF_3CO_2H (2.0)	−78	90	70 : 30	97
10		—[c]	120	60	decomposition	
11	**2**	$TiCl_2(OPr^i)_2$ (2.0)	−78	5	>95 : 5	97
12		$Yb(OTf)_3$ (0.5)	room temp.	1080	>95 : 5	97
13		$Yb(OTf)_3$ (0.2)	room temp.	2880	>95 : 5	81(16)
14		$Yb(OTf)_3$ (0.2)	40	2400	>95 : 5	75(24)
15		$La(OTf)_3$ (0.2)	room temp.	2880	>95 : 5	71(29)

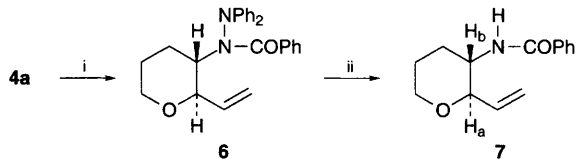
[a] The reactions were carried out with 0.1 mol dm^{-3} substrate in CH_2Cl_2. [b] Isolated yield; values in parentheses are recovery yields. [c] Toluene was used as a solvent.

isomer **4a** quantitatively (entry 11). The use of a catalytic amount of $Yb(OTf)_3$ (0.5 equiv.) promoted the cyclization to give **4a** with high stereoselectivity in high yield (entry 12).[6] The use of smaller amount of the lanthanide catalysts decreased the conversion yield (entries 13–15).

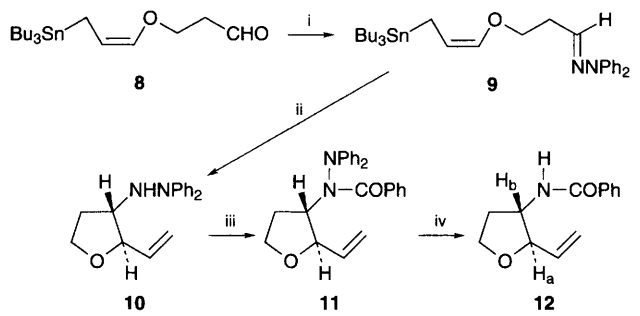
The *trans*-preference for the cyclization of **1** and **2** is consistant with the proposed acyclic transition state model (Scheme 1).[7] The reaction *via* **5a** is favoured in comparison with that *via* **5b**, because the steric repulsion between the tributylstannyl group and the bulky substituent (NR_2) on the nitrogen atom is alleviated in **5a**. In the presence of protic acids, the formation of the *cis*-isomer **3b** increased although it was still a minor product (entries 8 and 9). This may be due to intervention of a cyclic transition state as we previously proposed.[2b]



Scheme 1



Scheme 2 *Reagents and conditions*: i, BuLi, THF, −78 °C, then $(PhCO)_2O$, −78 °C to room temp., 83%; ii, SmI_2, HMPA, THF, room temp., 98%



Scheme 3 *Reagents and Conditions*: i, Ph_2NNH_2·HCl, Et_3N, CH_2Cl_2, room temp., 87%; ii, $TiCl_2(OPr^i)_2$, CH_2Cl_2, −78%, 82%; iii, BuLi, THF, −78 °C, then $(PhCO)_2O$, −78 °C to room temp., 82%; iv, SmI_2, HMPA, THF, room temp., 45%

To confirm the stereochemistry of the cyclization product and enhance synthetic utility of this reaction, product **4a** was converted to protected amine **7** by a known procedure (Scheme 2).[8] The treatment of **4a** with BuLi followed by reaction with benzoic anhydride afforded acylated hydrazine **6** in 83% yield. The N–N bond cleavage of **6** was performed using SmI_2 in the presence of HMPA to give the benzoyl amide **7** in 98% yield. The stereochemistry of **7** was unambiguously determined as *trans* by ^1H NMR analysis and NOE experiments; H_a and H_b appeared at δ 3.67 and 4.04, respectively, with coupling constant J_{ab} 8.4 Hz. No NOE was observed between H_a and H_b.

We next examined the stereoselective synthesis of β-aminotetrahydrofuran derivative (Scheme 3). Aldehyde **8** was treated with 1,1′-diphenylhydrazine hydrochloride and Et_3N to give hydrazone **9** in 87% yield. The cyclization of **9** mediated by $TiCl_2(OPr^i)_2$ afforded **10** as a sole product in 82% yield. Cyclic hydrazine **10** was converted to **12** *via* **11** by a similar procedure as shown in Scheme 2. The structural determination of **12** was performed by ^1H NMR analysis and NOE experiments; H_a and H_b appeared at δ 4.29 and 4.48, respectively, with coupling constant J_{ab} 4.1 Hz. Irradiation of H_a induced a remarkable enhancement (5.1%) of NH signal.

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