

STEREOCONVERGENT CROTYLSTANNANE ADDITION TO
NOR-EPHEDRINE-DERIVED 2-METHOXY OXAZOLIDINES.
A CLUE TOWARDS A SYNCLINAL TRANSITION STATE GEOMETRY

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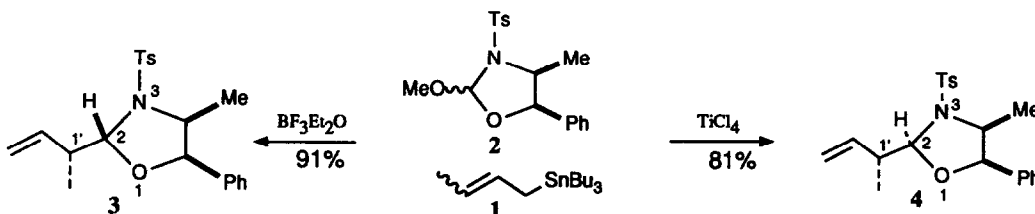
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ABSTRACT- The Lewis acid promoted addition of crotyl-*n*-tributylstannane to a nor-ephedrine-derived 2-methoxy-oxazolidine has been studied. This stereoconvergent reaction allows highly selective C-C bond formation and takes place with opposite stereochemistry with respect to the analogous silylketenethioacetal addition. This result suggests a preference for a synclinal transition state geometry.

The Lewis acid promoted addition of crotyl-stannanes to aldehydes and acetals is a useful and well known transformation.¹ This reaction takes place with clean allylic shift affording, in general, high *syn* selectivity regardless of the stannane double bond geometry. Oxygen atom activation by the Lewis acid is a crucial step and is believed to trigger either a fully synchronous process (S_N2), or the formation of a discrete oxocarbenium ion (S_N1), depending upon the reaction conditions.²

The analogous addition to orthoester-type electrophiles has only a few precedents,³ the mechanistic details are unknown and no asymmetric C-C bond formation studies using allylstannanes have been undertaken so far.

As part of a program directed toward the exploitation of nor-ephedrine-derived oxazolidines as chiral formyl cation equivalents,⁴ we now report the condensation between crotyltri-*n*-butyltin **1** and orthoamide **2**.



SCHEME 1

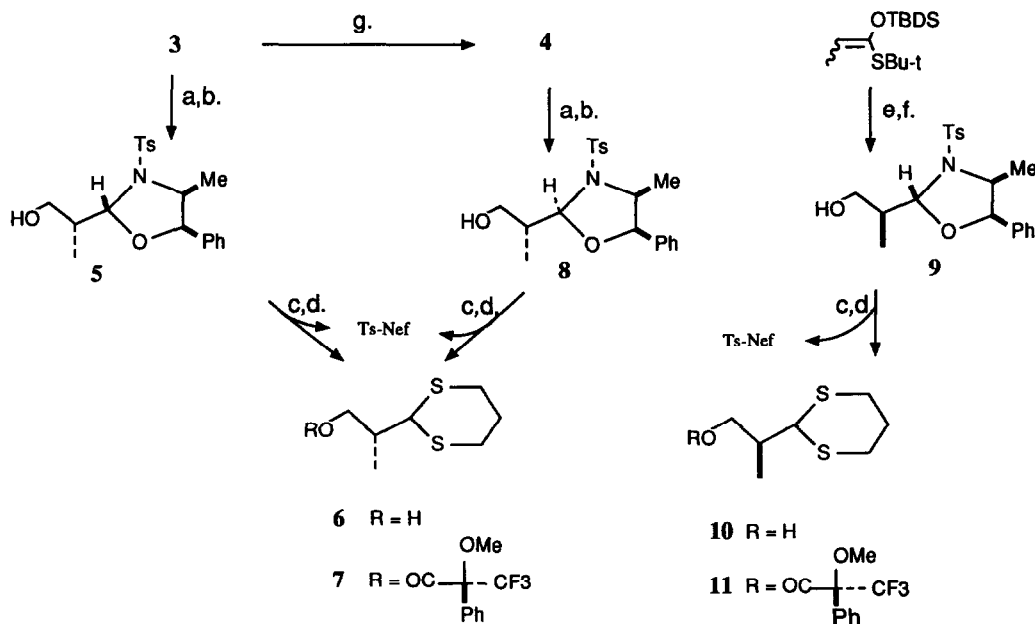
Addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C to a 2.5/1 mixture of **1** (85/15 E/Z) and **2** (50/50 epimeric at C-2), smoothly afforded adduct **3** as the only product⁵ (Scheme 1). This material proved to be stereohomogeneous as judged by ^1H - ^{13}C -NMR and 96% pure by capillary GC.

Further experiments showed that thermal conditions (160°C , neat, without Lewis acid) or catalytic amounts of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, did not allow the reaction to proceed. Since the selectivity of the reaction did not change using a half equivalent of the stannane, the stereoconvergent behaviour of **1** (besides that of **2**) is apparent.⁶

On the other hand, crotylstannane addition to **2** using TiCl_4 as the Lewis acid gave, stereospecifically, adduct **4** (Scheme 1).⁵

Treatment of **3** with $\text{OsO}_4/\text{Me}_3\text{NO}$,⁷ and subsequent NaIO_4 promoted diol cleavage, provided the expected aldehyde which was reduced *in situ* to the primary alcohol **5**. Auxiliary removal using 1,3-propanedithiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 ,⁸ released N-tosyl-nor-ephedrine (Ts-Nef) and dithiane **6** which was esterified to its (S)-Mosher derivative **7** (Scheme 2).

When the same synthetic protocol was applied to **4**, dithiane **6** and its ester **7** were again obtained. Comparison of these compounds with the known isomers **10** and **11**, obtained through silylketenethioacetal (SKTA) addition to **2**⁹ and subsequent LAH reduction, revealed that **3** and **4** are epimeric at C-2 (see scheme 1 for numbering) and, more interestingly, that the crotylstannane additions took place with opposite stereochemistry with respect to the related SKTA addition.



SCHEME 2

a: OsO_4 0.1 mol.eq., Me_3NO 2 mol.eq., acetone/ H_2O 8/1 (95%); b: NaIO_4 1.5 mol.eq., dioxane/ H_2O 4/1, then NaBH_4 excess, (67%); c: $\text{HS}(\text{CH}_2)_3\text{SH}$ 10 mol.eq., $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 1 mol.eq., (62%) [**6**: $[\alpha]_D^{20}$ -4.8 (c=1, CHCl_3)] d: (S)-Mosher acid chloride, $\text{CCl}_4/\text{pyridine}$, (99%); e: **2** 0.5 mol.eq., $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 1 mol.eq., CH_2Cl_2 , -78°C , (90%); f: LiAlH_4 excess, THF, (93%); g: TiCl_4 2.5 mol.eq., CH_2Cl_2 , -50°C , (99%)

In line with our previous studies on the Lewis acid mediated oxazolidine formation¹⁰ we speculated that the stereochemical diversity between the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and the TiCl_4 promoted condensation might be due to an equilibration step following the C-C bond formation. As expected, addition of TiCl_4 at -50°C , quantitatively converted a CH_2Cl_2 solution of **3** into **4**, thereby confirming the above hypothesis.

We believe that the condensation of crotylstannane **1** with **2** shares the following peculiar features with the analogous SKTA addition⁴:

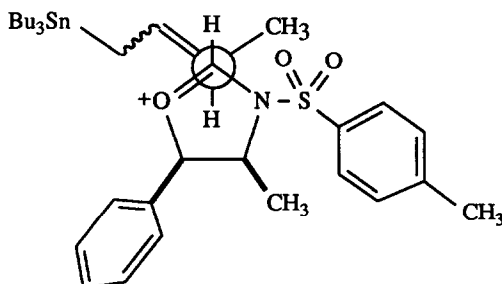
- the transient formation of a carbocationic intermediate¹¹, mainly stabilized by the oxygen atom¹².
- a virtually exclusive addition of the nucleophile on the *Re* face of the cationic system¹³.
- an open transition state where the less demanding group of the nucleophile occupies the inside position (see figure).

On the other hand, the reversal of stereochemistry observed between silylketene(thio)acetals and the crotyl-stannane, in the Lewis acid promoted addition to **2**, is striking and suggestive of different biases in their respective transition states.

Actually, whereas silylketene(thio)acetal additions to acetals are expected to favor an extended open transition state,¹⁴ convincing evidence for a preferred synclinal orientation of double bonds in the analogous addition of allylstannanes has recently been demonstrated for intramolecular reactions and postulated for acyclic cases.^{2b,15} We believe that the present example further confirms the general validity of the above mentioned synclinal preference and, accordingly, propose the transition state depicted in the figure as a working model.

The process described herein is of relevance for acyclic stereocontrol in natural product synthesis and marks the first successful combination of allylstannane chemistry with a chiral formyl cation equivalent.

Further preparative and spectroscopic studies are in progress.



References and Notes

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5. In a typical procedure the Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ 4.5 mol.eq. or TiCl_4 2.5 mol.eq.) was added at -78°C to a mixture of orthoamide **2** (1 mol.eq.) and crotyl tri-*n*-butylstannane (2.5 mol.eq.) in CH_2Cl_2 (12.5 ml per mmol of **2**). After 2h stirring ($-78 \rightarrow -50^\circ\text{C}$ in 1h) the mixture was quenched with phosphate buffer. Extractive work-up (Et_2O) and flash chromatography gave pure **3** (91% yield) or **4** (81% yield).
6. The reactive configuration of **1** is still a matter of speculation owing to the possible $\text{BF}_3 \cdot \text{Et}_2\text{O}$ promoted $\text{E}=\text{Z}$ crotylstannane isomerization: a) Naruta, I.; Nishigaichi, Y.; Maruyama, K.; *Tetrahedron*, **1989**,45,1067. b) Keck, G.E.; Abbott, D.E.; Boden, E.P.; Enholm, E.J.; *Tetrahedron Lett.* **1984**,25,3927. See also ref. 13.
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8. Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J.Org.Chem.*, **1986**,51,5041. Slow decomposition of Ts-Nef into the thioderivative $\text{HS}(\text{CH}_2)_3\text{SCH}(\text{Ph})\text{CH}(\text{Me})\text{NHTs}$ has been observed. Therefore, if recycling of Ts-Nef is desired, care should be taken in order to avoid too long reaction periods.
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12. The postulated cationic structure could be detected by NMR spectroscopy. These studies will be reported elsewhere.
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