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# Communications

## Addition of Racemic Alkoxyallylstannanes to an Enantiomerically Pure 2-Methoxyoxazolidine: An Example of Combined Mutual Diastereoface Selection and Kinetic Resolution

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*Summary:* The $BF_3$·$Et_2O$-promoted addition of racemic $\alpha$- and $\gamma$-alkoxyallylstannanes **2** or **3** to the 2-methoxyoxazolidine **1** afforded adducts **4** and **5** in diastereomeric ratios up to 95:5 accompanied by enantioenriched $\gamma$-stannanes (***R***)-**3**. This behavior is consistent with a fast $\alpha$-to-$\gamma$ rearrangement of the alkoxystannanes followed by an enantiomer- as well as mutual diastereoface-discriminating condensation.

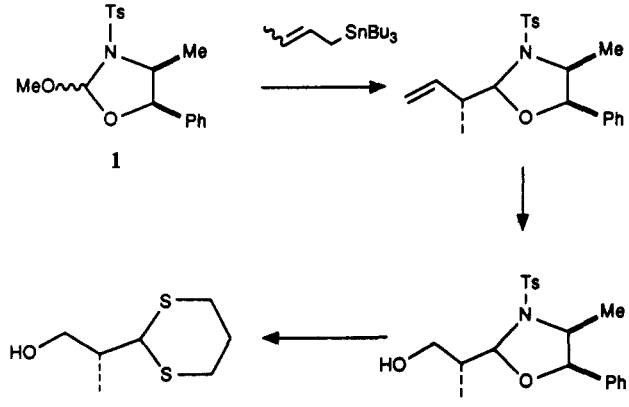
We recently reported our findings on the Lewis acid promoted crotylstannane addition to the enantiomerically pure (ep) oxazolidine **1** and the subsequent conversion of the resulting adducts into enantioenriched dithianols (Scheme I).[1]

In view of the ever increasing role played by heterosubstituted allylic stannanes[2] as nucleophilic reagents in carbon–carbon bond forming reactions with electrophiles, we turned our attention to the condensation of chiral alkoxyallylstannanes with **1**.

Aside from the different functionalization of the expected adducts with respect to those obtained in Scheme I, such a study raises two related and conceptually different stereochemical issues: enantiomer discrimination (kinetic resolution)[3] and diastereoface selection associated with each reactant.

The racemic $\alpha$-alkoxyallylstannanes **2a–c** employed in this study were prepared according to a literature procedure[4] by addition of tri-*n*-butylstannyllithium to crotonic aldehyde followed by treatment of the crude products with methoxymethyl-, (benzyloxy)methyl- or diphenyl-*tert*-butylsilyl chloride respectively.

**Scheme I**




These compounds were rearranged to the corresponding $\gamma$-stannanes **3a–c** by treatment with $BF_3$·$Et_2O$ in $CH_2Cl_2$, according to Marshall's procedure[5,6] (Scheme II).

(1) Pasquarello, A.; Poli, G.; Potenza, D.; Scolastico, C. *Tetrahedron: Asymmetry* **1990**, *1*, 429.

(2) (a) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987. (b) Poli, G.; Scolastico, C. *Chemtracts, Org. Chem.* **1991**, (July/August issue).

(3) (a) Morrison, D. J. In *Asymmetric Synthesis*; Morrison, D. J., Ed.; Academic Press: New York, 1983, Vol. 1, Chapter 1, p 6. (b) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1988; Vol. 18, p 249.

(4) Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1521.

(5) (a) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 7349. (b) Marshall, J. A.; Welmaker, G. S.; Gung, W. Y. *J. Am. Chem. Soc.* **1991**, *113*, 647.

(6) General procedure for the isomerization of $\alpha$-alkoxy stannanes **2a–c** to $\gamma$-alkoxy stannanes **3a–c**: to a stirred solution of **2a** or **2b** (0.288 mmol) in 2.88 mL of $CH_2Cl_2$, at −78 °C, was added 80 $\mu$L of $BF_3$·$Et_2O$ (0.648 mmol). After 5–10 min of stirring at this temperature the mixture was treated with phosphate buffer (pH = 7) and warmed to room temperature. The solution was extracted with $Et_2O$ and dried ($Na_2SO_4$), and the solvent was removed in vacuo to afford the crude $\gamma$-stannane. Flash chromatography (hexane–$Et_2O$ (95:5)) gave pure **3a** (68.5%) or **3b** (45.6%). Analogously, **3c** was obtained via $BF_3$·$Et_2O$-promoted rearrangement of **2c** at room temperature. Flash chromatography (hexane) gave **3c** (21%).

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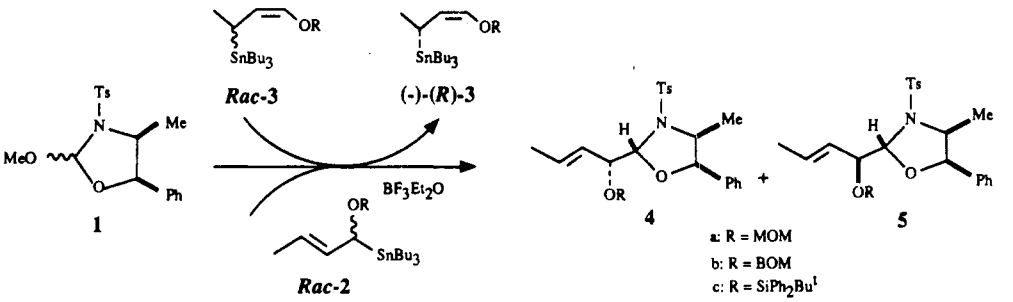
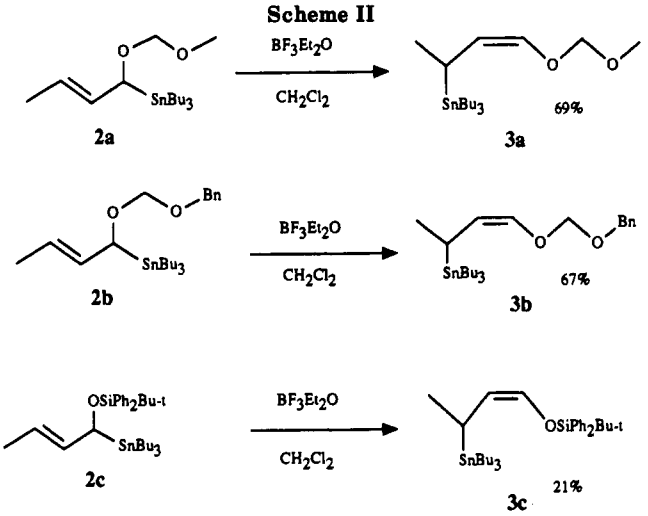
**Table I. $BF_3 \cdot Et_2O$ Promoted Addition of α- and γ-Alkoxyallylstannanes to Oxazolidine I**




| exp | oxazolidine | stannane | equiv. | 4:5 | Yield | $[\alpha]^{20}_D$ of recov 3 | $[\alpha]^{20}_D$ of 4 |
|---|---|---|---|---|---|---|---|
| 1 | 1 | α, OMOM, racemic | 2 | 87:13 | 85 | −62.8 (*c* 4.89, $CHCl_3$) | −55.3 (*c* 1.52, $CH_2Cl_2$) |
| 2 | 1 | γ, OMOM, racemic | 2 | 87:13 | 82 | | |
| 3 | 1 | α, OMOM, racemic | 1 | 87:13 | 41 | −55.2 (*c* 1.49, $CH_2Cl_2$) | |
| 4 | 1 | γ, OMOM, recovered | 2 | 87:13 | 10 | | |
| 5 | *Rac* 1 | γ, OMOM, recovered | 1 | 87:13 | 35 | | +23.1 (*c* 1.60, $CH_2Cl_2$) |
| 6 | 1 | α, OBOM, racemic | 2 | 95:5 | 93 | −90.6 (*c* 1.05, $CH_2Cl_2$) | −66.8 (*c* 1.79, $CH_2Cl_2$) |
| 7 | 1 | α, OBOM, racemic | 1 | 95:5 | 32 | −90.2 (*c* 1.66, $CH_2Cl_2$) | |
| 8 | 1 | γ, OBOM, racemic | 1 | 95:5 | 30 | | |
| 9 | *Rac* 1 | α, OBOM, racemic | 1 | 95:5 | 91 | | |
| 10 | 1 | α, $OSiBu^tPh_2$, racemic | 2 | 80:20 | 87 | | |

**Scheme II**




The $BF_3 \cdot Et_2O$-promoted condensation[7] between 2.0 equiv of racemic α-stannane **2a** and oxazolidine 1 gave adducts **4** and **5** as an 87:13 mixture (Table I, experiment 1) in 85% yield, accompanied by the rearranged γ-stannane **3a**. The isomeric constitution of the observed adducts indicated that the expected intermolecular α-to-γ rearrangement[5] of the tin reagent must have taken place prior to the condensation. The optical rotation of the recovered γ-stannanes, whose absolute configuration is known in the case of **3a**,[5] indicated that the condensation proceeded with substantial *S* enantiomer recognition. In order to confirm the above findings and to evaluate the diastereoselectivity as a function of the kinetic resolution,

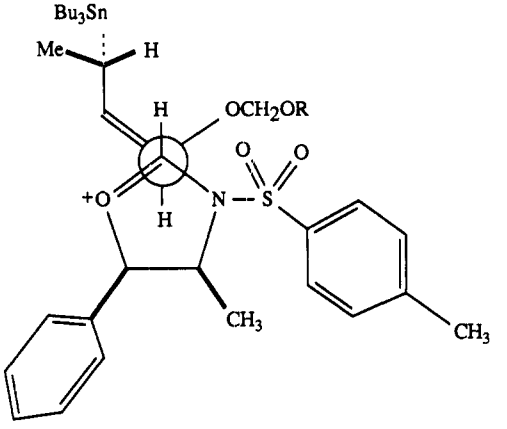


**Figure 1.**

we decided to perform additional experiments.

As expected, the direct use of excess racemic γ-stannane **3a** gave the same results (Table I, experiment 1 and 2). When equimolar amounts of oxazolidine 1 and α- or γ-stannane were used, the yield dropped drastically, but the **4:5** ratio remained unchanged (Table I, experiment 3; compare also experiments 6–8). Recycling of unreacted **3a**, recovered from experiment 3,[8] provided additional information. Thus, further treatment of this γ-stannane (39% ee)[8] with 1 gave only trace amounts of adducts (Table I, experiment 4), whereas reaction with excess (±)-**1** gave ***ent*-4** with an optical purity reflecting that of the starting stannane (Table I, experiment 5).

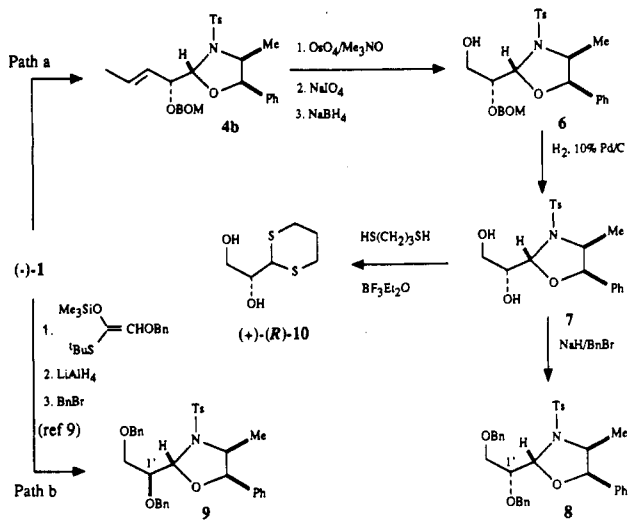
Interestingly, the diastereoselectivity of the condensation was found to be quite sensitive to the oxy substitution of the γ-stannane.[9] Thus, the diastereomeric ratio (dr) improved to 95:5 using the (benzyloxy)methyl (BOM)-protected α-stannane **2b** (Table I, experiment 6), whereas it decreased to an 80:20 ratio with the diphenyl-*tert*-butylsilyl-substituted α-stannane **2c** (Table I, experiment 10). When conditions of mutual kinetic resolution[10] were ap-

(7) General procedure for the $BF_3 \cdot Et_2O$-promoted condensation of alkoxyallylstannanes **2** and **3** with oxazolidine **1**: to a stirred solution of oxazolidine **1** (2.21 mmol) and the appropriate amount of **2** or **3** in 22.1 mL of $CH_2Cl_2$ at −78 °C was added $BF_3 \cdot Et_2O$ (9.93 mmol). After 1 h of stirring the mixture was treated with phosphate buffer (pH = 7) and warmed to room temperature. The solution was extracted with $Et_2O$ and dried ($Na_2SO_4$), and the solvent was removed in vacuo. Flash chromatography (hexane–$Et_2O$ (95:5) → 70:30)) gave unreacted (−)-**3a** or (−)-**3b** plus adducts **4a–c** and **5a–c** (see Table I). Yield of recovery of (−)-(**R**)-**3a,b** (with respect to the total amount of used racemic stannane): 21% for experiment 1, 26% for experiment 3, 22% for experiment 5, 30% for experiment 6. **4a**: mp 63–64 °C (hexane); $[\alpha]^{20}_D$ −55.3 (*c* 1.52, $CH_2Cl_2$). **4b**: mp 97–99 °C (MeOH); $[\alpha]^{20}_D$ −66.8 (*c* 1.79, $CH_2Cl_2$).

(8) The estimated optical purity of (−)-(***R***)-**3a** recovered from exp 3 of Table I is 39% (≥95% ee (+)-(***S***)-**3a**: $[\alpha]_D$ +135, $CHCl_3$, ref 5b).

(9) For a comparison of diastereoselectivity in additions of MOM- versus BOM-protected α-alkoxyallylstannanes to aldehydes, see: Marshall, J. A.; Gung, W. Y. *Tetrahedron* **1989**, *45*, 1043.

**Scheme III**




plied to **2b** (i.e., using **1** in racemic form), the resulting dr did not improve (Table I, experiment 9).[11] All these data are in line with a virtually complete recognition of the (+)-(*S*) antipodes of the γ-stannanes **3** from the racemic mixtures.[12]

Although it was not possible to obtain suitable crystals of the major diastereoisomers **4a** or **4b** for X-ray analysis, the stereochemistry of these adducts was indirectly inferred on the basis of the following information: (a) $^1$H NMR analysis unequivocally showed that in both **4** and **5** the transferred alkenyl moiety was *E* configured and trans disposed with respect to the preexisting oxazolidine substituents and (b) the reactive γ-stannane enantiomers are the *dextrorotatory S* antipodes.[5b] Since these condensations are known to take place via an anti $S_E$, pathway,[13] the stereochemistry of adducts **4** and **5** must be as indicated. The stereochemical analysis shows therefore that the diasteroface discrimination at the oxazolidine site, as well as the kinetic preference for the (*S*)-γ-stannanes, are virtually total.

These results support the open-staggered transition state depicted in Figure 1. The preferred attack involves a *Si*-face anti $S_{E'}$ addition of the (*S*)-γ-stannane to the *Re* face of the oxazolinium cation.[14] The α-H is expected to occupy the most crowded position over the ring, and the C=C bond of the stannane is oriented synclinal to the C–O bond of the oxazolidine ring, a disposition already met in the analogous crotylstannane addition.[1] In agreement with the model for electrophilic additions to chiral *Z* alkenes,[15] the γ-H in the reactive stannane conformation occupies the "*inside*" position, thereby generating an *E* double bond. On the other hand, the impossibility of the 3*R* enantiomers to fulfill all these geometrical requirements at one time nicely justifies the lack of reactivity of these antipodes.[16]

Further manipulation of the BOM-protected adduct was then addressed for correlative as well as auxiliary removal purposes (Scheme III). Osmylation of **4b** gave the corresponding diol which was directly transformed into the primary alcohol **6** via $NaIO_4$ treatment followed by reductive ($NaBH_4$) workup. Hydrogenolysis of the BOM protecting group gave the key diol **7**, whose dibenzyl derivative **8** was shown, as expected, to differ from the silyl ketene thioacetal (SKTA)-derived[17] C-1′ epimer **9**. On the other hand, auxiliary removal from **7**, via oxazolidine-to-dithiane ring exchange, afforded dithiandiol (+)-(*R*)-**10**,[18] which confirmed the previous stereochemical assignments.

In summary, these results show the diastereoselective coupling between a racemic (*E*)-crotyloxyanion equivalent[2b] and an ep formyl cation equivalent[19] which takes advantage of the $BF_3$·$Et_2O$-promoted addition of γ-alkoxyallylstannanes to a norephedrine-derived 2-methoxyoxazolidine. This condensation shows a virtually total recognition of the (+)-(*S*) antipodes of the stannanes **3** from the racemic mixtures when ep **1** is used. Suitable protection of the α-hydroxy stannane precursor secures a very high mutual diastereoface differentiation of the components, allowing the formation of only two diastereomeric adducts, out of the eight possible,[20] in ratios up to 95:5. Subsequent functional group transformation allows easy access to dithianyl-protected D-glyceraldehyde, an interesting enantioenriched $C_3$ building block. This method nicely complements the one based on SKTA addition to **1**[17] (Scheme III, path b) and confirms the different stereochemical behavior between allylstannanes and silyl ketene acetals in these condensations. We are currently studying the transformation of adduct **4b** into 5-deoxypentoses and 6-deoxyhexoses of synthetic interest.

**Acknowledgment.** We would like to thank "Consiglio Nazionale delle Ricerche" (Progetto Chimica Fine II) and "Ministero dell'Universita' e della Ricerca Scientifica" for financial support of this research.

**Registry No.** 1, 136862-88-9; (±)-**2a**, 125058-31-3; (±)-**2b**, 133319-48-9; (±)-**2c**, 136862-91-4; (±)-**3a**, 136981-88-9; (*R*)-**3a**, 131352-17-5; (±)-**3b**, 136983-04-5; (*R*)-**3b**, 124664-85-3; (±)-**3c**, 136862-93-6; **4a**, 136862-89-0; *ent*-**4a**, 136981-85-6; **4b**, 136862-90-3; **4c**, 136862-92-5; **5a**, 136981-84-5; **5b**, 136981-86-7; **5c**, 136981-87-8; **6**, 136862-94-7; **7**, 136862-95-8; **8**, 133732-88-4; (*R*)-**10**, 86040-12-2.

(10) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, D. J., Ed.; Academic Press: New York, 1984; Vol. 3B, Chapter 2, p 165. (b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290.

(11) Mutual kinetic resolution conditions could not improve the amount of resolution since it is already at its maximum value. As a result, the intrinsic diastereofacial preference cannot be altered. This is consistent with a total lack of reactivity associated with the (*R*)-γ-stannanes.

(12) The reasons for only the partial enrichment of the recovered γ-stannane (*R*)-**3a** are presently under investigation.

(13) Marshall, J. A.; Wellmaker, G. S. *Tetrahedron Lett.* **1991**, *32*, 2101.

(14) The high preference of the cation deriving from **1** to react at the *Re* face is well precedented (see refs 1, 17, and 19).

(15) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, J. *Science* **1986**, *231*, 1108.

(16) From a mechanistic point of view, it is interesting to note that a high kinetic resolution unequivocally confirms that C–C bond formation, and not C–Sn breaking, is the rate limiting step. In the latter case, in fact, an achiral (*E*)-crotyloxyanion equivalent would be involved. See also: Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.

(17) Bernardi, A.; Piarulli, U.; Scolastico, C.; Villa, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 751.

(18) Redlich, H.; Schneider, B. *Liebigs Ann. Chem.* **1983**, 412.

(19) (a) Bernardi, A.; Cardani, S.; Carugo, O.; Colombo, L.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 2779. (b) Conde-Frieboes, K.; Hoppe, D. *Synlett* **1990**, 99.

(20) Two stereogenic centers plus a stereogenic double bond are generated in the condensation.