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An Experimental and Theoretical Study on Stereoselective Addition to 3-Formyl-Δ^2-isoxazolines. Part 1. 1,3-anti-Selectivity Induced by $BF_3 \cdot OEt_2$

Akio Kamimura,*[†] Akikazu Kakehi,[‡] and Kenzi Hori[†]

[†]Department of Chemistry, Faculty of Liberal Arts, Yamaguchi University, Yamaguchi 753, Japan

[‡]Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Nagano 380, Japan

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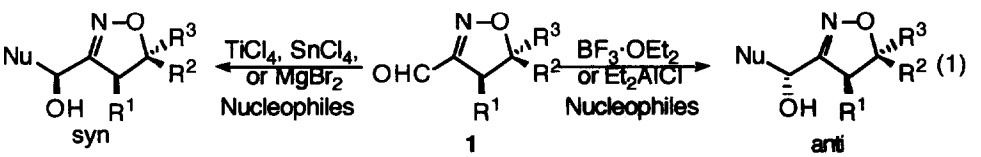
Summary: Experimental and theoretical investigations of the anti-selective nucleophilic addition induced by BF_3 to 3-formyl-Δ^2-isoxazolines are described. *Ab initio* molecular orbital (MO) calculations show that the 3-formyl-Δ^2-isoxazoline-BF_3 complex prefers s-trans conformation to s-cis conformation. Nucleophiles attack the stable s-trans conformer from the opposite side of C(4) substituent, giving anti-adducts selectively. The B-O bond lengths and the stabilization energies suggest that the features of the complex resemble those of aliphatic aldehyde-BF_3 complexes. Introduction of substituent to allyl tin improves the anti-selectivity from 87/13 to 98/2. These results suggest that the reaction proceeds via anti-periplanar transition state.

Δ^2-Isoxazolines have frequently been used for stereoselective formation of new carbon-carbon bonds.[1] We reported elsewhere that 3-formyl-Δ^2-isoxazolines **1** undergo stereoselective addition along with effective 1,3-inductions (eq 1).[2] The stereoselectivity of the reaction depends on the choice of Lewis acid. $TiCl_4$, $SnCl_4$, and $MgBr_2$ promote the reactions 1,3-syn-selectively, while BF_3 and Et_2AlCl promote 1,3-anti-selectively. Silyl enolates and allyl metal reagents are useful as nucleophiles. Alkenes are used for the carbonyl-ene reaction to **1** mediated by Lewis acid.[2d] Both of the syn- and anti-selectivity are observed only when the substituent is present at the C(4) position of the isoxazolines.



Nucleophiles: silyl enolate, Allyl silane, allyl stannane, etc.

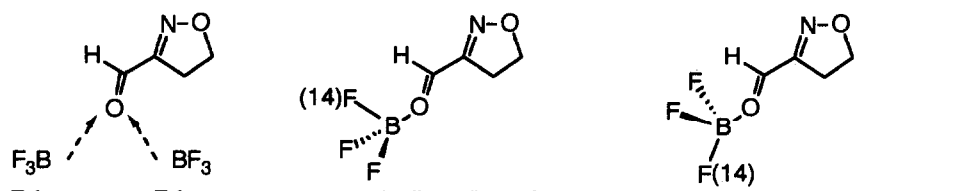
[†]Yamaguchi University [‡]Shinshu University

Characteristic of the Δ^2-isoxazoline ring are several features which bring about the high 1,3-anti-selectivity. For example, the C=N double bond participates in the N=C-C=O conjugate system in **1**, which feature fixes **1**, making s-trans or s-cis conformation of it. The relatively planar structure of the ring, revealed by X-ray analysis,[2a] firmly fixes the ring substituent. The C(4) substituent develops an effective steric bias around the reaction center. In our previous paper,[2a] we presumed that the nucleophiles attack the Lewis acid-**1** complex from the opposite side of the C(4) substituent. We inferred by analogy with the chelation and non-chelation process that the stereoselectivity of the reaction is determined by the favorable conformation of the complex.[3] The nature of Lewis acid-**1** complexes governs the stereoselectivity. We investigated the features of the complex to delve into the stereoselectivity. In this paper, we report in full detail the anti-selective addition promoted by BF_3. The geometrical and electronic features of BF_3-**1** complex (**A-D**) are discussed on the basis of *ab initio* molecular orbital (MO) calculations.[4] The theoretical results are applied to those of the experiments. We found that the anti-selectivity of the nucleophilic addition is improved up to 98:2 in the reaction to **1** where methallyl tin or crotyl tin is used in place of allyl tin. There have been many extensive studies on allylation reactions induced by BF_3.[5] The anti-periplanar and the syn-clinal approaches have been proposed by Yamamoto,[6,7] Denmark,[8] and Gung.[4,9] We compare our results both theoretical and experimental with those indicated in these works, and discuss the stereochemical approaches of tin reagents to BF_3-**1** complex.

Results and Discussion

MO studies on 3-Formyl-Δ^2-isoxazoline 1a and its BF_3 Complex A-D.

Free **1a** is expected to take two conformers: s-trans and s-cis conformations in N=C-C=O conjugate system. We assumed several possible geometries for BF_3-**1a**.[10] BF_3 is coordinated to **1** in two possible ways as shown in Chart 1, since the carbonyl oxygen takes sp^2 hybridization. We call them E and Z form. The free rotation around the B-O bond yields two possible conformers: the one is the conformer with the dihedral angle for C(10)=O(11)-B(13)-F(14) is 0 °, which we call e (eclipsed); and the other the conformer with the angle 180 °, which we call s (staggered) (Chart 1).



E-form Z-form e (eclipsed) conformer s (staggered) conformer

Chart 1

Some of the initial geometries changed into different ones during optimization, after which we obtained E-e and Z-s structures for example, though we started with E-s and Z-e geometries. All optimized structures of **1a** and BF_3-**1a** (**A** - **D**) are depicted in Chart 2, with some of the geometrical parameters and the total energies summarized in Table 1 and Table 2.

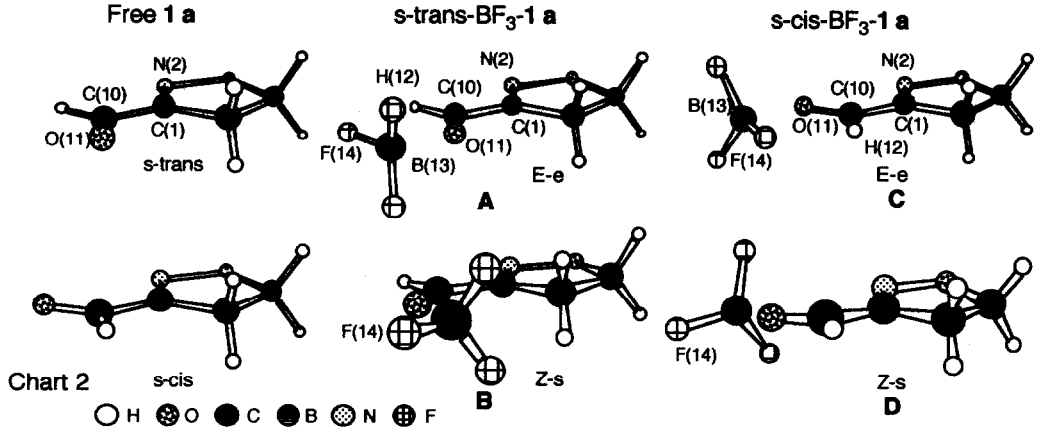


Table 1. Some geometrical parameters of the optimized structure. [a]

run	conformer[b]	B(14)-O(11)	B(13)-F(14)[c]		C(10)-(O11)-B(13)	N(2)=C(1)-C(10)=O(11)	F(14)-B(13)-O(11)=C(10)
1	*s-trans*-**1a**	–	–	–	–	180.0	–
2	*s-cis*-**1a**	–	–	–	–	0.3	–
	s-trans-BF_3-**1a**						
3	E-e (**A**)	1.656	1.380	(1.361)	123.1	180.2	0.1
4	Z-s (**B**)	1.645	1.354	(1.376)	133.7	180.0	180.0
	s-cis-BF_3-**1a**						
5	E-e (**C**)	1.662	1.383	(1.360)	122.5	0.0	-0.0
6	Z-s (**D**)	1.712	1.357	(1.360)	137.4	9.1	165.5

a) All optimized parameters were in Å and degree. b) Structures are illustrated in Chart 1. c) The values in parenthesis are averaged lengths of the other B-F bonds.

The dihedral angles of N=C-C=O were calculated to be 0.3 ° and 180.0 ° for s-cis **1a** and s-trans **1a**, respectively (Table 1, run 1 and 2); those of s-trans-BF_3-**1a** to be nearly 180 ° (Table 1, run 3 and 4). The s-trans conformations are always more stable than the s-cis conformations. For instance, the s-trans conformation of BF_3-**1a** (**A**) was more stable by 6.2 kcal/mol than s-cis **C** (Table 2, run 5). (We use hereafter the energies from MP2/6-31G*//RHF/3-21G calculations.)

The E-forms of the complex are more stable than Z-forms. Conformer **A**, for example, was more stable by 1.0 kcal/mol than **B** (Table 1 run 3 vs. 4). The angle of C(10)-O(11)-B(13) for **A** was calculated to be 123.1 degrees (Table 1, run 3). This is very close to the sp^2 bond angle. X-ray crystallographic analysis for BF_3-methacrolein (CH_2=$C(CH_3)$CHO) complex showed that the angle was 123.8 degree.[11,12] On the other hand, the angle for **B** was calculated to be 133.7 ° (Table 1, run 4). This deviation from the sp^2 angle comes from the steric repulsion between BF_3 and the Δ^2-isoxazoline ring.

Table 2. Calculated total energy for **1a**-BF_3 complex.

run	conformer[a]	Total energy (relative energy)[b] RHF/3-21G		MP2/6-31G*//RHF/3-21G		Stabilization energy[c] RHF/3-21G	MP2/6-31G*//RHF/3-21G
1	s-*trans*-**1a**	-356.46332	(0.0)	-359.49422	(0.0)	–	–
2	s-*cis*-**1a**	-356.45320	(6.4)	-359.48477	(5.9)	–	–
	s-*trans*-BF_3-**1a**						
3	E-e(**A**)	-677.97128	(0.0)	-683.29074	(0.0)	27.5	11.3
4	Z-s(**B**)	-677.97031	(0.6)	-683.28911	(1.0)	26.9	10.2
	s-*cis*-BF_3-**1a**						
5	E-e(**C**)	-677.96077	(6.6)	-683.28081	(6.2)	27.3	11.0
6	Z-s(**D**)	-677.94913	(13.9)	-683.27180	(11.9)	20.0	5.3
7	BF_3	-321.46408		-323.77859		–	–

a) Structures are illustrated in Chart 1. b) Total energies are in Hartree. Relative energies are in kcal/mol. **1** and BF_3-**1** are compared separately. c) Stabilization energies, E_{Stab}, were calculated by the following way: $E_{stab} = E_{1a} + E_{BF3} - E_{comp}$, where E_{1a}, E_{BF3}, and E_{comp} are total energies of **1a**, BF_3, and the complex, respectively. The stabilization energies are in kcal/mol.

The B-O bond length of the most stable conformer **A**, being optimized, became 1.656 Å. This is longer by 0.030 Å than the calculated length for PhCHO-BF_3, and very close to that for CH_3CHO-BF_3.[13] This comparison indicates that the B-O bond of BF_3-**1a** is formed as tightly not as that of PhCHO-BF_3 but as that of CH_3CHO-BF_3. This tendency is also seen in the comparisons among the three in terms of stabilization energy. The energy by the B-O bond formation for **A** was estimated to be 11.3 kcal/mol (Table 2, run 3). This is smaller by 1.9 kcal/mol than the value for PhCHO-BF_3, and almost the same as that for CH_3CHO-BF_3.[14] Comparing of the B-O bond lengths and the stabilization energies means that some of the features of BF_3-**1a** resemble those of CH_3CHO-BF_3.

The E-forms **A** and **C** prefer the C(10)=O(11)-B(13)-F(14) eclipsed conformation (e conformers). The initial geometries corresponding to the staggered conformers changed into **A** and **C** during the optimization by turning round the B-O bond axis. The B(13)-F(14) bonds for **A** and **C** were longer by about 0.02 Å than the other B-F bonds (Table 1, run 3 and 5). This elongation of the bonds is explained by the interaction between the σ* orbital of the B-F bond and the lone pair orbital (n_{CO}) of the oxygen (Chart 3). The geometries of **A** and **C** maximize the overlapping between these orbitals. This effect is well known as the anomeric effect.[4,9,15] On the other hand, we do not anticipate the effect on the staggered conformers because of the decreases in the overlapping of the two orbitals.

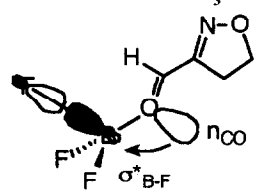


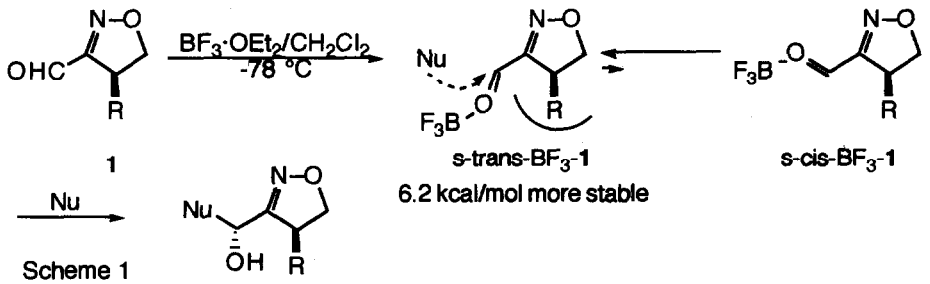
Chart 3

On the contrary, when the initial geometries of Z-e type were optimized, they turned into those of Z-s type, **B** and **D**. The eclipsed conformation in the Z-coordination of BF_3 is less stable than the staggered ones. F(14) in Z-e conformation was located very close to the Δ^2-isoxazoline ring. F(14) and the ring collaborate to cause a steric repulsions; the Z-s conformation somewhat relaxes the strain. The steric repulsion overrides

the stabilization owing to the anomeric effect in the Z-type structure.

So far, we have looked into the information obtained from the outcomes of our theoretical calculations. The information goes as follows: BF_3-**1a** prefers s-trans conformation **A** and **B**. The energy differences between **A** and **C** were estimated to be 6.2 kcal/mol. As shown in Scheme 1 we can explain the origin of 1,3-anti-induction. The s-trans conformer is dominant under the reaction conditions at -78 °C. To avoid the steric repulsion, the nucleophiles, then, attack the formyl carbon from the opposite side of the C(4) substituent.

The B-O bond lengths and the stabilization energies are close to those of CH_3CHO-BF_3 rather than PhCHO-BF_3.[4] BF_3-**1a** is likely to behave as other aliphatic aldehyde-BF_3 complexes do. This suggests that the reaction of allyl tin reagents mediated by BF_3 proceeds via anti-periplanar transition state (see the next section).[6,7,9]



Substituent Dependence of anti-Selectivity:

We examined on the anti-selectivity of the nucleophilic addition of substituted allyl tin catalyzed by BF_3 (eq 2). Table 3 summarizes the results.

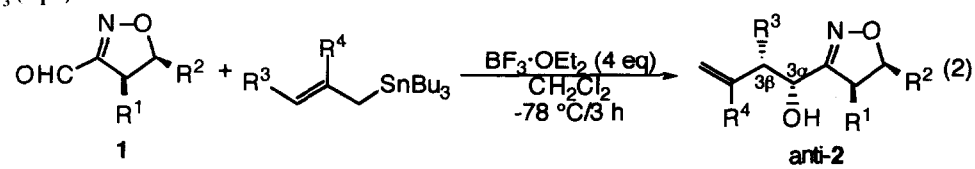


Table 3. BF_3 Catalyzed Nucleophilic Addition of Substituted Allyl Tributyltin to **1**

run	1	R^1	R^2	R^3	R^4	2; Yield (%)[a]	anti/syn[b]
1	**1b**	-$(CH_2)_3$-		H	H	**2a** 73	87/13[c]
2	**1b**	-$(CH_2)_3$-		H	Me	**2b** 75	98/2
3	**1b**	-$(CH_2)_3$-		Me	H	**2c** 75	98/2
4	**1c**	Me	Me	H	H	**2d** 85	82/18
5	**1c**	Me	Me	H	Me	**2e** 78	96/4
6	**1c**	Me	Me	Me	H	**2f** 78	96/4
7	**1d**	H	C_6H_{13}	H	Me	**2g** 81	50/50

a) Isolated yield. b) Determined by GLC analyses. c) See ref. 2a.

Treatment of **1b** with methallyl tributyl tin in the presence of $BF_3{\cdot}OEt_2$ (4 eq) resulted in the formation of the methallylated adduct **2b** in 75% yield (run 2).[16,17] ^1H NMR spectrum of **2b** showed that the adduct consists almost alone of a single isomer. Its GLC analysis revealed that the diastereomeric ratio was 98/2. The addition of (E)-crotyl group to **1b** also proceeded smoothly under the same condition. Although the addition of crotyl group produces a new stereogenic center at the C(3β) position, the adduct **2c** was obtained as almost one single isomer (run 3). The nucleophilic addition to **1c** gave similar results to **1b** (run 4-6). However, the anti-selectivity disappeared when C(4) unsubstituted **1d** was used for this addition.

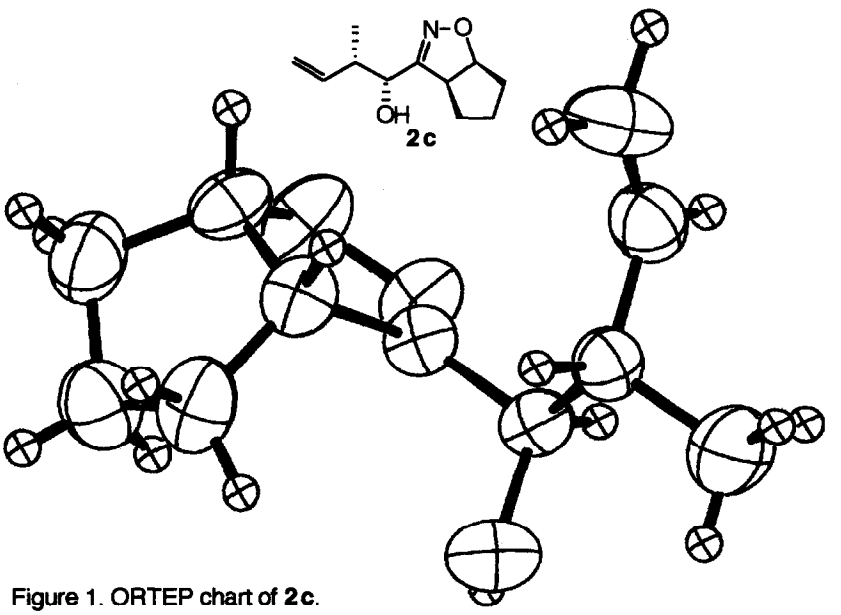


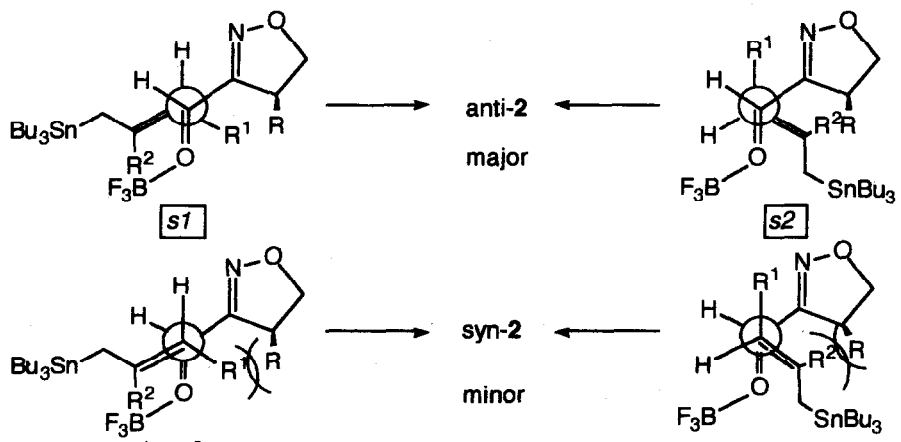
Figure 1. ORTEP chart of **2c**.

The configurations of methallyl and allyl adducts, **2b**, **2c**, and **2e**, were determined by comparing their GLC and NMR patterns with those of **2a**. For example, the peaks attributed to major-**2**s always appear after the peaks of minor-**2**s. GLC analysis of anti enriched **2a** also showed the same pattern. We were not able to determine the configurations of the (E)-crotyl adduct, **2c** and **2f**, by comparing their GLC and NMR spectra with those of our previous data. With the fortunate success in spontaneous crystalization of **2c**, we performed its X-ray analysis by using **2c** recrystallized from hexane-ether. Figure 1 shows the ORTEP drawing of **2c**.[18] Thus, the relative configuration of **2c** is unambiguously determined to be C(3α)-C(4) anti and C(3α)-C(3β) syn. The configuration of **2f** was determined by comparing **2f**'s NMR and GLC with those of **2c**.

The nucleophilic addition always proceeds with high 1,3-anti induction. It is remarkable that the selectivity improves up to 98:2 by using either methallyl tin or (E)-crotyl tin in place of allyl tin. The addition of (E)-crotyl tin, in particular, gave almost one single isomer of the compounds with four stereogenic centers. From the synthetic point of view, the present result provides a useful method for preparing carbon skeletons with several stereogenic centers. The introduction of crotyl group produces a new carbon-carbon bond between C(3α) and C(3β) syn-selectively. This is a result analogous to other examples of the addition of crotyl tin induced by BF_3.[5-9] Although Scheme 1 explains the 1,3-anti-selectivity well, another question

arises from our results: Why does the anti-selectivity dramatically improve when methallyl or (E)-crotyl tin is used? To answer the question, we will discuss the stereochemical approach of allyl tin to BF_3-**1** complex in the following section.

We considered four possible approaches of allyl tin to BF_3-**1** complex. Two of them are syn-clinal approaches, *s1*, and *s2*, depicted in Chart 4, and the rest of two anti-periplanar approaches, *a1* and *a2*, depicted in Chart 5. We use E-configurations of BF_3-**1** as representatives in both the charts and the discussion, when the following discussions are also applicable to Z-configurations. Allyl tin, methallyl tin, and (E)-crotyl tin are abbreviated as **A**, **M**, and **C**, respectively. The approaches of crotyl group drawn in Charts 4 and 5 give C(3α)-C(3β) syn-adducts.

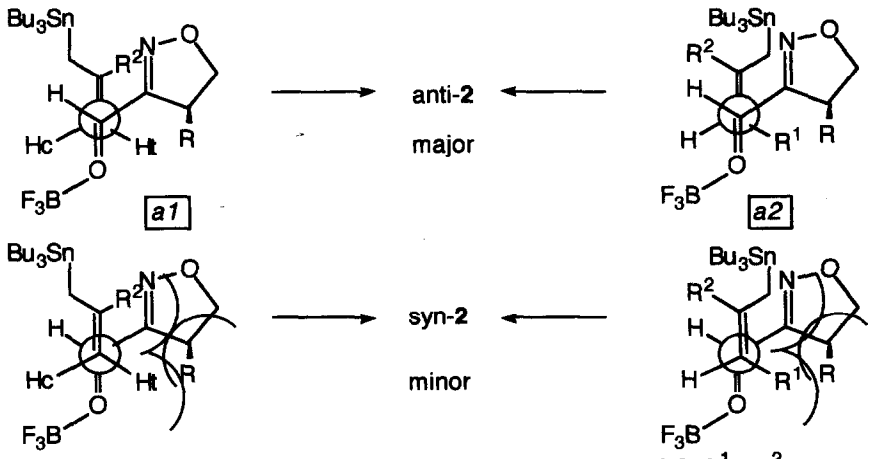


s1-**A**: $R^1 = R^2 = H$;
s1-**M**: $R^1 = H$, $R^2 = Me$;
s1-**C**: $R^1 = Me$, $R^2 = H$

s2-**A**: $R^1 = R^2 = H$;
s2-**M**: $R^1 = H$, $R^2 = Me$;
s2-**C**: $R^1 = Me$, $R^2 = H$

Chart 4

Since the Δ^2-isoxazoline ring including the formyl group has a planar structure, BF_3 does not influence the selectivity, with the boron atom placed within the plane. The C(4) substituent, R, alone acts as the steric bias to distinguish the formyl face. Therefore, the extent of anti-selectivity is determined by steric interaction between R and the approaching allyl group. In *s1* approach, *s1*-**A** shows an anti-selectivity similar to *s1*-**M**, because both approaches have the same steric interactions between R^1 = H and R. We can anticipate a higher anti-selectivity for *s1*-**C** approach than for *s1*-**A** and *s1*-**M** approaches owing to large steric repulsion between R and R^1 = Me. The order of the anti-selectivity via *s1* approach is (E)-crotyl tin > methallyl tin ≈ allyl tin. In *s2* approach, the repulsion between R and R^2 becomes the most important interaction for the selectivity. The largest interaction is observed in *s2*-**M** (R^2 = Me), setting the order of the anti-selectivity via *s2* approach as methallyl tin >> (E)-crotyl tin ≈ allyl tin. Our experimental results show the order is (E)-crotyl tin ≈ methallyl tin >> allyl tin. These *s1* and *s2* approaches are inconsistent with the observed results. Hence, the addition of allylic group to **1** does not go through the syn-clinal approaches to BF_3-**1**.



a1-**A**: R^2 = H;
a1-**M**: R^2 = Me;

a2-**A**: $R^1 = R^2$ = H;
a2-**M**: R^1 = H, R^2 = Me;
a2-**C**: R^1 = Me, R^2 = H

Chart 5

There are two possible pathways for the anti-periplanar approach, *a1* and *a2*. The steric interaction between either Ht and R in *a1*-**A** or R^1 (= H) and R in *a2*-**A** mainly provides a steric bias of the reaction in which to give anti-**2** selectively. With *a2*-**A** approach, we have to consider an additional steric repulsion between R and CH_2SnBu_3 group. This interaction enhances the steric bias to repress the formation of syn-**2**; thus the addition via *a2*-**A** proceeds more anti-selectively than the addition via *a1*-**A**. The reaction of allyl tin proceeds via both the approaches to give anti-**2** with the selectivity rate of anti/syn = 87/13. In the case of methallyl tin, the steric bias in *a2*-**M** is identical to that in *a2*-**A** approach. *a1*-**M** approach also develops steric bias to almost the same extent as *a2*-**M** due to the interaction between R and R^2 (= Me). Both approaches, *a1*-**M** and *a2*-**M**, provide the additional steric bias to prevent the formation of syn-**2**; thus we observe a higher anti-selectivity for methallylation than for allylation. Since the reaction of crotyl tin always forms C(3α)-C(3β) bond in syn configuration, *a2*-**C** is the only possible approach, and since the interaction between R and the CH_2SnBu_3 provides the same steric bias as observed in *a2*-**M**, the crotylation proceeds with a selectivity similar to the methallylation. Consequently, the order of anti-selectivity via the anti-periplanar approaches is: methallyl tin ≈ (E)-crotyl tin > allyl tin. This order is consistent with our experimental results. We, therefore, conclude that the anti-periplanar approach is the most appropriate reaction pathway. As discussed above, this is consistent with the expectations arising from our theoretical study in the former section.

Conclusion

Our theoretical calculations show that BF_3-**1** complex favors the s-trans structure. The nucleophilic attack occurs from the opposite side of the C(4) substituent to avoid steric repulsion. The chemical features of BF_3-**1** are similar to those of aliphatic aldehyde-BF_3 complexes. The addition of methallyl or crotyl group by use of tin reagents undergoes a higher anti-selectivity than the addition of allyl group. The addition of

(E)-crotyl tin, in particular, gives diastereomerically pure Δ^2-isoxazolines with four stereogenic carbons. A discussion for stereochemical approach of tin reagents reveals that the anti-periplanar approach is the most appropriate for the transition structure of the reaction.

Method for Calculations

We performed MO calculations by using 3-21G basis set[19] in GAUSSIAN90 program[20] on Fujitsu S-4/2 (SPARC station) workstation. All geometrical parameters were fully optimized. Single point calculations with the optimized structures were performed with Moller-Plesset electron correlation (MP2/6-31G*//RHF/3-21G). These calculations are important to avoid basis set superposition errors for the estimation of the stabilization energies coming from BF_3-**1** complexes.

Experimental

General: ^{1}H NMR spectra were measured by Hitachi R-250H NMR spectrometer at 250 MHz. $CDCl_3$ was used as solvent with tetramethylsilane as an internal standard. Elemental analyses were performed by Advanced Instrumentation Center for Chemical Analysis, Ehime University. GLC analyses were performed Shimadzu GC-14 gas chromatography analyzer with SE30 capillary column (25 m). CH_2Cl_2 was dried over calcium hydride and distilled before use. THF was dried over benzophenone-ketyl and distilled before use. 3-formyl-Δ^2-isoxazolines **1**[2] and substituted allyl tributylstannane[21] were prepared by the previously reported method.

anti-Selective Addition of Substituted Allyl Tin to 3-formyl-Δ^2-isoxazolines: Addition of (E)-Crotyl Tin to 1b; General Procedure. To a solution of **1b** (65 mg, 0.47 mmol) and crotyl tributyltin (534 mg, 3 eq) in dry CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (230 μL, 4 eq) at -78 °C. The reaction mixture was then stirred for 2.5 h. When **1b** disappeared on tlc analysis, the solution was poured into dil HCl (50 mL) and the resulting solution was extracted by CH_2Cl_2 for 3 times. The organic layer was combined and washed with brine, then dried over anhydrous Na_2SO_4. After filtration and evaporation, the crude adduct was purified by flush column chromatograph (silica gel/hexane/ethyl acetate 20:1 then 3:1) to give **2c** (68 mg, 75%) as colorless oil, which then crystallized spontaneously. GLC alnalysis showed the diastereomeric ratio to be 98/2.

Physical data of **2** are listed below:

2b: colorless liquid. ^{1}H NMR ($CDCl_3$) δ 5.07 (dd, J = 4.3 Hz, 9.2 Hz, 1 H), 4.96 (s, 1 H), 4.87 (s, 1 H), 4.62 (dq, J = 3.8 Hz, 4.9 Hz, 1 H), 3.75 (t, J = 9.0 Hz, 1 H), 2.52 (d, J = 4.3 Hz, 1 H), 2.50 (d, J = 8.3 Hz, 1 H), 2.05-2.18 (m, 2 H), 2.01 - 2.04 (m, 1 H), 1.80 (s, 3 H), 1.65-1.76 (m, 2 H), 1.61-1.64 (m, 1 H), 1.43-1.58 (m, 1 H). IR (neat) ν 3200-3700, 1650, 1610, 1440, 1300, 1070, 890 cm^{-1}. Anal. calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.97; H, 8.73; N, 7.10.

2c: mp. 44 - 45 °C. ^{1}H NMR ($CDCl_3$) δ 5.80 (ddd, J = 7.6 Hz, 10.4 Hz, 17.6 Hz, 1 H), 5.13 (td, J = 1.5 Hz, 17.4 Hz, 1 H), 5.10 (td, J = 1.5 Hz, 10.4 Hz, 1 H), 5.03 (dd, J = 4.6 Hz, 9.2 Hz, 1 H), 4.35 (dd, J = 6.1 Hz, 6.7 Hz, 1 H), 3.65 (t, J = 7.3 Hz, 1 H), 2.65 (ttd, J = 1.1 Hz, 6.7 Hz, 7.6 Hz, 1 H), 2.01-2.17 (m, 2 H), 1.98

(d, J = 5.8 Hz, 1 H), 1.60-1.76 (m, 2 H), 1.42-1.52 (m, 2 H), 1.16 (d, J = 7.0 Hz). IR (neat) ν 3200-3700, 1640, 1600, 1460, 1300, 1030, 910 cm^{-1}. Anal. calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.55; H, 8.73; N, 7.08.

2d: colorless liquid. ^1H NMR ($CDCl_3$) δ 5.85 (ddd, J = 6.7 Hz, 9.8 Hz, 17.1 Hz, 1 H), 5.21 (d, J = 17.7 Hz, 1 H), 5.91 (d, J = 10.4 Hz, 1 H), 4.47-4.61 (m, 2 H), 3.25 (quint, J = 7.3 Hz, 1 H), 2.59 (q, J = 6.7 Hz, 2 H), 1.86 (s, 1 H), 1.28 (d, J = 6.7 Hz, 3 H), 1.13 (d, J = 7.3 Hz, 3 H). IR (neat) ν 3200-3600, 1640, 1600, 1440, 1380, 1050, 920 cm^{-1}. Anal. calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.23. Found: C, 63.56; H, 9.00; N, 8.23.

2e: colorless liquid. ^1H NMR ($CDCl_3$) δ 4.95 (t, J = 1.5 Hz, 1 H), 4.85 (dd, J = 0.9 Hz, 1.8 Hz, 1 H), 4.63 (m, 6.7 Hz, 1 H), 4.57 (m, 6.4 Hz, 1 H), 3.26 (qd, J = 7.3 Hz, 8.6 Hz, 1 H), 2.59 (ddd, J = 0.6 Hz, 4.9 Hz, 14.7 Hz, 1 H), 2.47 (ddd, J = 0.9 Hz, 9.2 Hz, 14.0 Hz, 1 H), 1.99-2.02 (m, 1 H), 1.80 (s, 3 H), 1.32 (d, J = 6.7 Hz, 3 H), 1.14 (d, J = 7.3 Hz, 3 H). IR (neat) ν 3200-3700, 1650, 1600, 1440, 1380, 1060, 880 cm^{-1}. Anal. calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.48; H, 9.25; N, 7.61.

2f: colorless liquid. ^1H NMR ($CDCl_3$) δ 5.80 (ddd, J = 7.6 Hz, 10.4 Hz, 17.1 Hz, 1 H), 5.13 (td, J = 1.5 Hz, 17.4 Hz, 1 H), 5.10 (dd, J = 1.2 Hz, 10.4 Hz, 1 H), 4.53 (qd, J = 6.4 Hz, 8.9 Hz, 1 H), 4.38 (dd, J = 5.5 Hz, 6.4 Hz, 1 H), 3.13 (qd, J = 7.3 Hz, 8.5 Hz, 1 H), 2.65 (dq, J = 0.8 Hz, 7.3 Hz, 1 H), 1.95-2.00 (m, 1 H), 1.58-1.60 (m, 1 H), 1.30 (d, J = 6.4 Hz, 3 H), 1.16 (d, J = 6.7 Hz, 3 H), 1.13 (d, J = 7.3 Hz, 3 H). IR (neat) ν 3200-3700, 1640, 1600, 1450, 1380, 1030, 870 cm^{-1}. Anal. calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 64.85; H, 9.16; N, 7.47.

2g: colorless liquid. Two diastereomers (**2g-A** and **2g-B**, **2g-A** has larger Rf value on tlc) were separated by column chromatography (silica gel/hexane/ethyl acetate 3:1 v/v). **2g-A**: ^1H NMR ($CDCl_3$) δ 4.94 (m, 1 H), 4.85 (m, 1 H), 4.55-4.70 (m, 2 H), 3.05 (ddd, J = 0.6 Hz, 10.4 Hz, 17.1 Hz, 1 H), 2.70 (ddd, J = 0.6 Hz, 8.5 Hz, 16.8 Hz, 1 H), 2.43 (s, 1 H), 2.41 (s, 1 H), 2.11 (d, J = 3.4 Hz, 1 H), 1.74 (s, 3 H), 1.18-1.31 (m, 10 H), 0.82 (t, J = 6.7 Hz, 3 H). **2g-B**: ^1H NMR ($CDCl_3$) δ 4.93 (dd, J = 1.5 Hz, 3.3 Hz, 1 H), 4.85 (m, 1 H), 4.69 (dt, J = 3.1 Hz, 6.1 Hz, 1 H), 4.59 (m, 1 H), 3.12 (dd, J = 10.1 Hz, 17.1 Hz, 1 H), 2.63 (dd, J = 7.9 Hz, 17.1 Hz, 1 H), 2.42 (d, J = 7.0 Hz, 2 H), 2.14-2.18 (m, 1 H), 1.80 (s, 3 H), 1.21-1.38 (m, 10 H), 0.88 (t, J = 6.7 Hz, 3 H). IR (neat) ν 3200-3700, 1645, 1605, 1440, 1370, 1060, 890 cm^{-1}.

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