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Asymmetric conjugate addition reactions of allyl- and crotylstannanes

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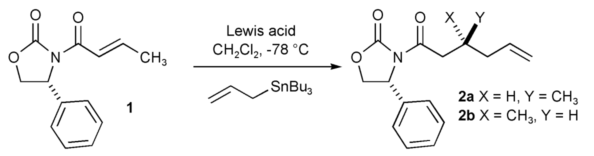
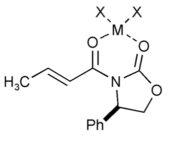
The conjugate addition reactions of allylic stannanes have been investigated utilizing nonracemic *N*-enoyl-4-phenyl-1,3-oxazolidinones with Lewis acid precomplexation.

The success of substituted 1,3-oxazolidinones as chiral auxiliaries in synthetic endeavors has been well-documented for their ability to effect stereoselective carbon–carbon bond forming reactions.[1] Coupled with the use of Lewis acids to enhance electrophilicity, developments of stereoselective 1,3-dipolar cycloaddition,[2] Diels–Alder,[3] ene,[4] and organocopper conjugate addition reactions[5] have been enabled by the use of nonracemic α,β-unsaturated *N*-enoyl-1,3-oxazolidinones. Our total syntheses of myxovirescin A$_1$,[6] sambutoxin,[7] *O*,*O*-dimethylfuniculosin,[8] amphidinolide J,[9] and laulimalide[10] have illustrated the use of Yamamoto organocopper reagents for asymmetric conjugate additions to advance enantiomerically enriched precursors toward these ends. More recently, we have established the use of nonracemic 4-phenyloxazolidinones as auxiliaries for organocopper conjugate additions leading to the stereocontrolled formation of *syn*- and *anti*-1,3- and 1,2-dimethyl arrays.[5f] One area that has received surprisingly little attention is the 1,4-conjugate addition of allylic stannanes. This communication describes the unprecedented diastereoselectivity of reactions for asymmetric conjugate addition in a series of allylic stannanes with Lewis acid precoordination of *N*-enoyl-4-phenyl-1,3-oxazolidinones.

Initial studies have examined the conjugate addition of allyltri-*n*-butylstannane to **1** using a number of Lewis acids. While reactions with aluminium-based Lewis acids resulted in moderate stereoselectivity (~3 : 1), excellent results have been obtained by the precomplexation of **1** with scandium(III) triflate, zirconium(IV) chloride or samarium(III) triflate. These cases proceeded in 80–85% yields with pronounced diastereoselection favoring formation of **2a** (dr 10 : 1; **2a** : **2b**).



By comparison, previous results in our laboratories which featured the asymmetric conjugate addition of Yamamoto allylcopper reagent to **1** yielded **2b** as the major isomer. Thus, the allylstannane addition demonstrated an interesting reversal of facial selectivity.[5c,f] Utilizing the oxazolidinone as a chiral auxiliary in conjunction with bidentate Lewis acids, the stereoselectivity of conjugate addition reactions is generally presumed to arise from preferential formation of the more stable bis-coordinated Lewis acid complex **3**.[11] Reactions occur to the α-face of the *syn-S-cis* enoyl conformation **3**, which is unencumbered by the C-4 phenyl substituent. Rotational isomerization to **4**, which would infer a reversal of facial selectivity, is destabilized by nonbonded interactions of the β-carbon and C-4 of the oxazolidinone. The utilization of monodentate Lewis acids has been shown to provide opposite diastereofacial selectivity through *anti-S-cis* **5**.[5h]



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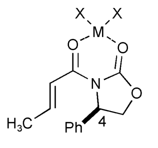

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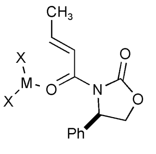

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Based upon the success of this model, Wu and coworkers recently described the titanium(IV) chloride-promoted reaction of allyltrimethylsilane with the 4(*S*)-enantiomer of **1**, which provided a reported 11 : 89 mixture of *ent*-**2a** : *ent*-**2b**.[12] Intrigued by the improbability that the change from allylsilane to allylstannane could be at the root of this reversal in selectivity, we chose to reexamine this reaction. Following the published procedure, our studies revealed that allyltrimethylsilane led to the predominant production of **2a** (dr 89 : 11; **2a** : **2b**). Thus, our findings reverse the stereochemical assignments of the previous report and converge with those of the allylstannane experiments.[13] Documentation of our results is readily apparent by comparison of ^{1}H NMR spectra of crude reaction products (Fig. 1) for the signals of the diagnostic α-methylene hydrogens of **2a** and **2b** [**2a**: δ_A 2.89 (J_{AX} = 6.44 Hz) and δ_B 2.83 (J_{BX} = 6.79 Hz); **2b**: δ_A 2.96 (J_{AX} = 5.20 Hz) and δ_B 2.72 (J_{BX} = 8.20 Hz)].

To examine the generality of our observations, a series of asymmetric conjugate addition reactions were undertaken with a variety of substituted allylic stannanes (Table 1). In general, good yields were obtained in all cases (entries 1–6). Reactions utilizing less hindered allylstannanes (entries 1, 2 and 5) proceeded more rapidly (12–16 h) with good selectivity. Zirconium(IV) chloride and scandium(III) triflate were preferable since reactions proceeded at a slightly faster rate than examples using samarium(III) triflate. As the steric demands of the stannane increased, the reaction rates decreased significantly (60–72 h), and diastereoselectivity was reduced (entries 3, 4 and 6). The mild reaction conditions were notably tolerant of primary and secondary silyl ethers (entries 3, 4 and 6). Furthermore, the exploration of alkyl substitution (R$_2$) led to reactions of *E* olefins in the starting stannanes (entries 5 and 6). These reactions proceeded with complete allylic transposition, and the generation of two vicinal stereogenic centers in a single reaction.[14]

A general procedure for the conjugate addition process is as follows: To a flame-dried round bottomed flask under an argon atmosphere containing oxazolidinone **1** (1 equiv.) in CH_2Cl_2

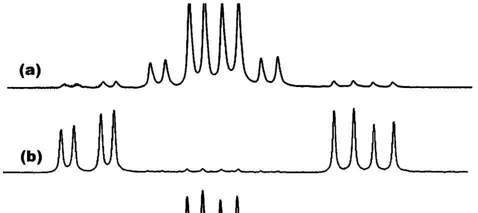

Fig. 1 Absorption patterns for diastereotopic C-2 methylene hydrogens from ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of product mixtures of **2a** and **2b** obtained from (a) allyltributylstannane, **1**, and Sc(OTf)$_3$, −78 → −20 °C; (b) Yamamoto allylcopper reagent and **1**, −78 → −20 °C; and (c) allyltrimethylsilane, **1**, and $TiCl_4$ at −78 °C.

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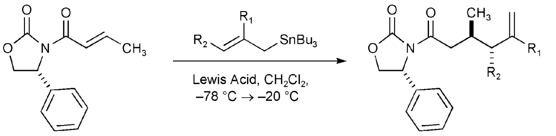
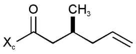
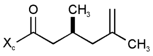
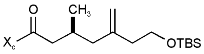
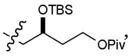
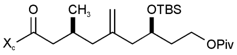
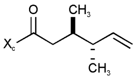
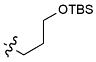
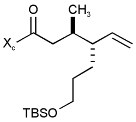
Table 1 Lewis acid promoted conjugate addition of allylic stannanes[a]



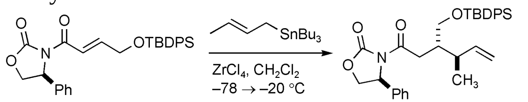
Entry	R_1, R_2	Lewis acid	Major product	Yield (%) (d.r.)
1a	H, H	A		85 (10 : 1)
1b	H, H	B		83 (10 : 1)
1c	H, H	C		80 (10 : 1)
2	CH_3, H	A		81 (7 : 1)
3	CH_2CH_2OTBS, H	A		81 (6 : 1)
4	, H	A		80 (4.5 : 1)[b]
5a	H, CH_3	A		85 (10 : 1)[14]
5b	H, CH_3	B		89 (10 : 1)
6	H, 	B		75 (5 : 1)[14]

[a] Reactions used 2 equiv. of allylstannane in CH_2Cl_2: A = Sc(OTf)$_3$, B = $ZrCl_4$, C = Sm(OTf)$_3$. Product ratios were determined by integration of the diastereotopic α-methylene signals in the crude ^{1}H NMR spectra. Yields represent the mixture of pure diastereomers following flash chromatography. X_c = 4(*R*)-phenyl-1,3-oxazolidinone. [b] 8 equiv. of stannane.

was added the anhydrous Lewis acid (1.5 equiv.) at −78 °C. The white suspension was stirred for 30 minutes at −78 °C, at which time neat allylstannane (2 equiv.) was slowly added dropwise. The heterogeneous reaction mixture, cooled by an acetone–dry ice bath, was then transferred into a −20 °C freezer, and allowed to warm slowly from −78 to −20 °C with continuous stirring. Reaction progress was monitored by TLC (12–72 h), after which time reactions were diluted with CH_2Cl_2 and quenched with aqueous $NaHCO_3$. Phases were separated, and the aqueous layer was extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Filtration through a small column of silica gel removed starting stannanes and tin-containing byproducts providing the conjugate addition products as white solids (entries 1 and 5) or clear oils (entries 2–4 and 6).

In the course of these studies, a general trend emerged from the ^{1}H NMR data as previously illustrated for addition products in Fig. 1. In consistent fashion, the pattern of proton signals for diastereotopic α-methylene (C-2) hydrogens of the products was an indication of the relative stereochemistry of the β-stereogenic center (C-3), and the chirality of the 4(*R*)-phenyloxazolidinone. In summation, the major products of Table 1, which possess an *anti*-relationship of the β-methyl substituent and the 4(*R*)-phenyl as drawn in the *S-cis*-enoyl depiction, demonstrate an AB pattern with a small chemical shift difference for H_A and H_B ($\delta_A - \delta_B < 0.1$ ppm). On the other hand, *syn*-stereochemistry leads to a significant chemical shift difference for the AB pattern ($\delta_A - \delta_B \sim 0.3$ ppm). In combination with a series of diastereomers from our previous asymmetric conjugate additions of organocopper species,[5c,f] this observation provides a useful technique for recognition of the relative stereochemistry of the β-methyl substitution (C-2) pattern of these products. Finally, the stereochemistry of the major product of entry 5a,b was unambiguously proven *via* a single crystal X-ray diffraction study.[15,16] As expected, the *anti*-1,2-dimethyl arrangement was obtained, presumably arising from an anticlinal open transition state.

The reactivity of *E*-crotyl-tri-*n*-butylstannane has facilitated efforts for the construction of compounds of greater complexity while generating two contiguous stereocenters. Reactions of *E*-crotylstannane with *N*-enoyl-1,3-oxazolidinones **6** and **8** led to excellent stereocontrol in the formation of **7** and **9**, respectively.



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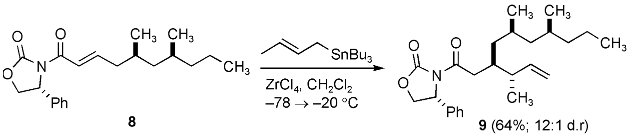
7 (75%; 9:1 d.r.)



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9 (64%; 12:1 d.r)

In conclusion, the Lewis acid precomplexation of $ZrCl_4$ or Sc(OTf)$_3$ with *N*-enoyl-4-phenyl-1,3-oxazolidinones has provided for asymmetric conjugate addition of allylstannanes. The observed diastereoselectivity is counter to predictions based on bis-chelated models, and will prove useful in the efficient construction of complex acyclic systems. Further investigations will examine the origins of stereocontrol of these reactions, and their utility for natural product synthesis.

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14 For entries 5 and 6 and reactions leading to **7** and **9**, only *anti* diastereomers were observed by ^{1}H NMR (400 MHz). For entry 5, HPLC analysis revealed a full diastereomer inventory of 10.5 : 1.0 : 0.3 : 0.01.

15 Crystal data: $C_{17}H_{21}NO_3$, M = 287.36, monoclinic, a = 21.75(2), b = 5.316(5), c = 12.868(13) Å, β = 91.12(4)°, V = 1487(2) Å^3, T = 137 K, space group *c*2, Z = 4, μ(Mo-Kα) = 0.88 mm^{-1}, 9184 reflections measured, 3511 unique (R_{int} = 0.347) which were used in all calculations. The final R_1 was 0.089 (observed data). CCDC reference number 214215. See http://www.rsc.org/suppdata/cc/b3/b305159e/ for crystallographic data in CIF or other electronic format.

16 The assignment of stereochemistry for the purified products of entries 1 and 2 were secured *via* the conversion to known optically active carboxylic acids.