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One-Pot Synthesis of Nitrogen Heterocycles Initiated by Regio- and Diastereoselective Carbon−Carbon Bond Formation of Bifunctional Carbonyl Compounds

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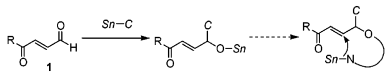
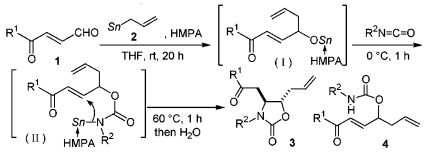
Tin−oxygen bonds can be easily generated by the addition of organotin nucleophiles to carbonyl compounds.[1] Although the allylation of carbonyl compounds by allylic tins is a well-known method for carbon−carbon bond formation,[2] the resulting tin alkoxides have been scarcely used for further transformation in which most tin−oxygen bonds are hydrolyzed to homoallylic alcohols. However, tin−oxygen and tin−nitrogen bonds bear high nucleophilicity. In some cases, their nucleophilicity is higher than that of the corresponding free alcohols and amines.[3] Herein, we report a one-pot synthesis of nitrogen heterocyclic compounds initiated by the allylation of the formyl group of bifunctional carbonyl compounds **1**. The generated tin−oxygen bonds worked as key intermediates to prepare various heterocyclic compounds accompanying chemo-, regio-, and diastereoselective carbon−carbon bond formation in the side chain moieties (Scheme 1).

Scheme 1



Allylic tri-*n*-butyltins bear low reactivities toward carbonyl groups. To achieve effective allylation, representative Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ have been used as activators of carbonyl substrates.[2] However, these conventional Lewis acids did not afford chemoselective allylation of the formyl groups of bifunctional substrates **1** because of their instability to acids. We fortunately found here that the allylic chlorodi-*n*-butyltin (**2b**) system[4] effectively reacted with the formyl group of substrate **1** without any strong Lewis acids. The allylation was highly chemoselective to the formyl group where the enone moiety of **1a** did not react at all. As shown in Table 1, after the allylation, the successive reaction with an isocyanate followed by heating afforded 4,5-*trans*-disubstituted-2-oxazolidinones **3a** and **3b** selectively (entries 3 and 4).[5] The chloro substituents on the tin center are essential because allyltri-*n*-butyltin (**2a**) was not reactive at all (entry 1). In addition, HMPA is essential to cause the cyclization to give **3** because only linear adduct **4** was obtained in the absence of HMPA (entry 2). The reaction course to **3** is explained as shown in the equation of Table 1. After the chemoselective allylation of the formyl group, the generated tin−oxygen bond of (I) reacts with an isocyanate spontaneously.[6] As a result, an adduct (II) is formed. The resulting tin−nitrogen bond successively adds to the enone moieties of **1** in a fashion of conjugate addition to give 2-oxazolidinones **3** in a one-pot procedure. HMPA plays an important role for the conjugate addition of the stannylcarbamate (II) where HMPA coordinates to the tin center to form pentacoordinate tin amide species, increasing their nucleophilicity.[7,8] The intramolecular conjugate addition did not take place at all in the absence of HMPA.

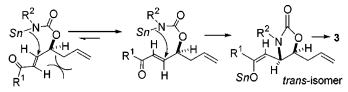
Table 1. One-Pot Synthesis of 2-Oxazolidinones[a]



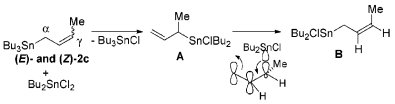
entry	R^1	R^2	*Sn* (**2**)	product and yield/%
1	*n*-C_8H_{17} (**1a**)	Ph	Bu_3Sn (**2a**)	no reaction
2			Bu_2ClSn (**2b**)	**4a** 99%[b]
3			**2b**	**3a** 81% (trans:cis = 91:9)
4	*p*-ClC_6H_4 (**1b**)	Ts	**2b**	**3b** 54% (trans:cis = 100:0)

[a] **1**, 1 mmol; **2**, 1 mmol; HMPA, 1 mmol; R^2NCO, 1 mmol; THF, 1 mL. [b] Without HMPA.

Scheme 2



Scheme 3



In the 2-oxazolidinones **3**, 4,5-*trans*-disubstituted isomers predominated. The *trans* selectivity is explained in terms of 1,3-allylic strain in the intramolecular addition (Scheme 2).

Next, we applied crotyltin reagents in the initial carbon−carbon bond formation. Crotylmetalation of the carbonyl functionality incurs problems of regio- and diastereoselectivities. A chloro substituent on the tin center is easily introduced by the redistribution of crotyltri-*n*-butyltin (**2c**) with *n*-Bu_2SnCl_2 (Scheme 3).[9] The redistribution proceeds by the initial formation of chlorodi-*n*-butyl(1-methylallyl)tin **A** through the reaction at the terminal γ-carbon of **2c**, and the subsequent isomerization takes place to give (*Z*)-crotyldi-*n*-butylchlorotin **B**. It has been reported that (*Z*)-isomers **B** are formed irrespective of the starting (*E*/*Z*)-crotyltin **2c**.[10] Generated allylictins **A** and **B** both work as nucleophiles to aldehydes, and here we controlled the reaction species by the order of the addition of *n*-Bu_2SnCl_2, determining α/γ regioselectivity of the products.

Initially, crotyltri-*n*-butyltin **2c**, *n*-Bu_2SnCl_2, HMPA, and the enone **1** were heated in one portion at 60 °C for 3 h. The subsequent addition of RN═C═O at 0 °C followed by heating gave 4,5-*trans*-substituted 2-oxazolidones **5a**−**c** which include (*Z*)-crotyl and carbonylmethyl substituents on the rings (Scheme 4).

As shown in Scheme 5, it is considered that the (*Z*)-crotyl substituent in **5** is derived from the in situ generated chlorodi-*n*-butyl(1-methylallyl)tin **A** which adds to the formyl group of **1** at

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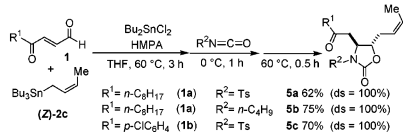
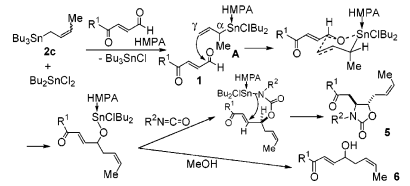
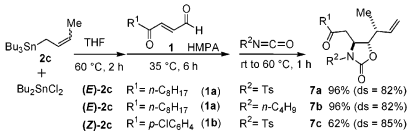
Scheme 4



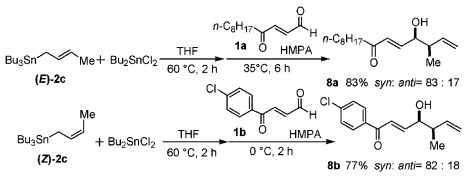
Scheme 5



Scheme 6



Scheme 7



the terminal γ-carbon. This regioselectivity is confirmed by quenching the mixture of the crotylation product of the carbonyl substrates, where (*Z*)-homocrotyl alcohols **6** were obtained.

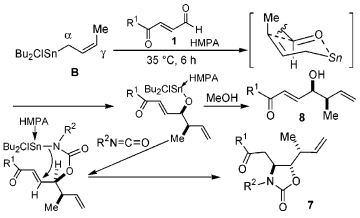
On the contrary, when crotyltri-*n*-butyltin **2c** and *n*-Bu_2SnCl_2 were preheated at 60 °C for 2 h, the subsequent reaction with **1** followed by the addition to an isocyanate afforded 4,5-*trans*-disubstituted-2-oxazolidones **7a**−**c** which include carbonylmethyl- and 1-methylallyl groups on the ring (Scheme 6).

The regioselectivity to introduce a 1-methylallyl group on the ring of **7** is derived from the initial reaction of the in situ generated (*Z*)-chlorocrotyldi-*n*-butyltin **B** through preferential isomerization from **A** by preheating at 60 °C for 2 h. In addition, it is noted that high diastereoselectivity in the side chain, 1-methylallyl substituent, was obtained.

The same diastereoisomers of **7** predominated irrespective of the *E*/*Z*-stereochemistry of **2c**. This diastereoselectivity is derived from the crotylation step. Thus, quenching the solution of crotylation of **1** gave the corresponding homoallylic alcohols **8** with high syn selectivities from both (*E*)- and (*Z*)-crotyltins **2c** (Scheme 7). As described in Scheme 3, (*Z*)-crotyltin **B** is formed by the redistribution of **2c** with *n*-Bu_2SnCl_2 irrespective of the *E*/*Z*-stereochemistry of **2c**, reacting with the formyl group of **1** at the terminal γ-carbon. As shown in Scheme 8, the crotylation of the (*Z*)-isomer **B** proceeds through a six-membered chairlike transition state, affording syn adducts predominantly.[11]

In summary, a one-pot synthesis of nitrogen heterocyclic compounds was initiated by chemoselective allylation of **1**. Regio- and diastereoselective carbon−carbon bond formation was established in the side chain of the rings.

Scheme 8



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Supporting Information Available: Experimental details and characterization data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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