Synthesis of oxazolidinones initiated by regio- and diastereo-controlled crotylation of α-dicarbonyl compounds†

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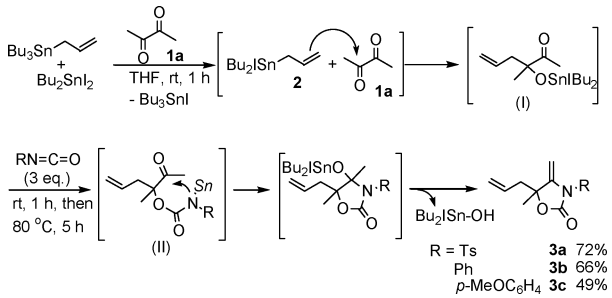
A one-pot synthesis of oxazolidinones was initiated *via* the allylation of α-dicarbonyl compounds, accompanying regio- and diastereo-controlled carbon–carbon bond formation on the side chains of the oxazolidinones.

Oxazolidinones[1] are important heterocyclic compounds that are useful as intermediates in organic synthesis and as biologically active compounds.[2] Allylation of the oxazolidinone ring is important not only for the introduction of a 3-C unit but also for the introduction of alkene functionality. As an example, oxazolidinones with an allylic group at the 5-position of the ring are used as an NK1-antagonist[3] or as a precursor for an HIV-1 protease inhibitor.[4] Although the allylation of carbonyl compounds by allyl tin reagents is a well-known method of carbon–carbon bond formation,[5] the resulting tin alkoxides are rarely used for further transformation; most frequently the tin–oxygen bonds are hydrolysed to homoallylic alcohols. However, Sn–O and Sn–N bonds bear high nucleophilicity. In some cases, their nucleophilicity is higher than that of the corresponding free alcohols and amines.[6] In the present study, we performed a one-pot synthesis of oxazolidinones initiated by the addition of allylic tin reagents to α-dicarbonyl compounds, **1**. The reactions involved both regio- and diastereocontrolled, carbon–carbon bond formation in the side chains of oxazolidinones.[7,8]

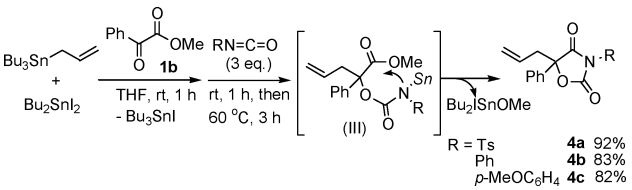
Scheme 1 shows the reaction using 2,3-butanedione (**1a**). After the allylation of **1a**, the resulting mixture reacted with an isocyanate, and subsequent heating afforded 5-methyl-5-allyl-4-methylene-2-oxazolidinones **3a–3c**.[9] As a reaction course, the allylation was promoted by allyliodobis-*n*-butyltin **2** generated *in situ* by the redistribution of allyltri-*n*-butyltin and Bu_2SnI_2.[10] Although allylic tri-*n*-butyltins bear low reactivities toward carbonyl groups, allylic iodobis-*n*-butyltin **2**[10] worked well with no addition of a Lewis acid.

Next, the generated tin–oxygen bond of I spontaneously reacted with an isocyanate.[11] The resulting tin–nitrogen bond of II successively added to the remaining carbonyl moiety and β-elimination of tin hydroxide afforded products **3** in a one-pot procedure.[12]



Scheme 1 Synthesis of oxazolidinones from allylation of **1a**.

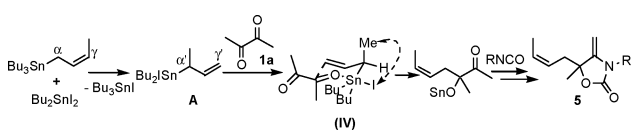
Using α-ketoester **1b** in place of diketone **1a** also afforded cyclization. Elimination of tin methoxide from III occurred to give 1,3-oxazolidine-2,4-dione **4a–c** (Scheme 2)



Scheme 2 Synthesis of heterocycles from the allylation of α-ketoester (**1b**).

Next, we applied crotyltin reagents in the initial carbon–carbon bond formation. Crotylmetalation of the carbonyl functionality incurred regio- and diastereoselectivities. A halogen substituent on the tin center was easily introduced by the redistribution of crotyltri-*n*-butyltin with *n*-Bu_2SnI_2.[13] Initially, crotyltri-*n*-butyltin, *n*-Bu_2SnI_2, and **1a** were combined at rt for 4 h. The subsequent addition of RN=C=O at rt, followed by heating, gave 2-oxazolidinones **5a–d**‡, which included *Z*-crotyl substituents on the oxazolidinone rings (Table 1).

As shown in Scheme 3, it is assumed that the *Z*-crotyl substituents in **5** were derived from the *in situ*-generated iodobis-*n*-butyl(1-methylallyl)tin **A**, which was added to the carbonyl group of **1a** at the terminal γ′-carbon of **A**. This (*Z*)-preference of allylated products was derived from the steric congestion between



Scheme 3 Reaction route to **5**.

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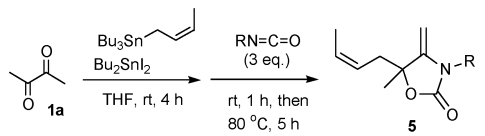
† Electronic supplementary information (ESI) available: Synthetic procedures and experimental data for the products. CCDC reference numbers 729634–729638. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000197j

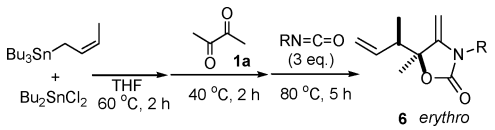
Table 1 Synthesis of **5**[a]



Entry[a]	R	Product	Yield (%)
1	Ts	**5a**	66
2	Ph	**5b**	69
3	*p*-$MeOC_6H_4$	**5c**	66
4	*p*-IC_6H_4	**5d**	40

[a] The reaction was carried out on **1a** 1 mmol, crotylSnBu$_3$ 1 mmol, Bu_2SnI_2 1 mmol, RN=C=O 3 mmol scale.

Table 2 Synthesis of **6**



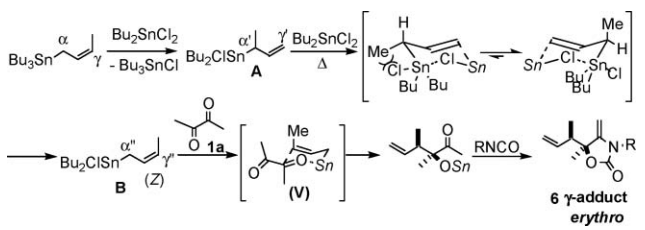
Entry[a]	R	Product	Yield (%)	dr
1	Ts	**6a**	72	73 : 27
2		**6a**	65	61 : 39[b]
3	Ph	**6b**	59	75 : 25
4	*p*-$MeOC_6H_4$	**6c**	55	74 : 26
5	*p*-IC_6H_4	**6d**	42	75 : 25

[a] The reaction was carried out on **1a** 1 mmol, crotylSnBu$_3$ 1 mmol, Bu_2SnCl_2 1 mmol, RN=C=O 3 mmol scale. [b] Bu_2SnI_2 was used instead of Bu_2SnCl_2.

the methyl substituent at C-1 of the allyl moiety and the iodine substituent on tin in the transition state (IV).[14]

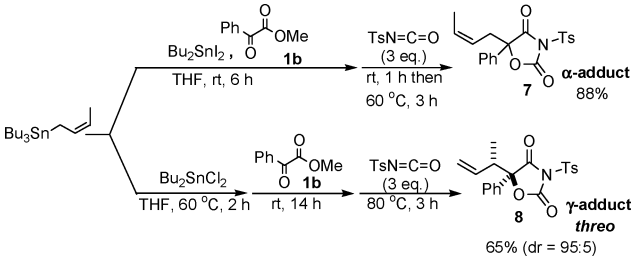
Alternatively, when crotyltri-*n*-butyltin and *n*-Bu_2SnHal_2 were preheated at 60 °C for 2 h, the subsequent reaction with **1a**, followed by addition to an isocyanate, afforded oxazolidinones **6a–d**, which included 1-methylallyl groups on the ring (Table 2). Namely, *erythro*-isomers were obtained as the major diastereomers. In this case, using *n*-Bu_2SnCl_2 afforded both a higher yield and a higher dr compared with the use of *n*-Bu_2SnI_2.

The regio- and diastereoselectivities were determined in the crotylation step, as shown in Scheme 4. (*Z*)-Crotyltin **B** was formed through (1-methylallyl)tin **A** irrespective of the *E*/*Z*-stereochemistry of the starting crotyltri-*n*-butyltin,[13b,c] and reacted with one of the carbonyl groups of **1a** at the terminal γ″-carbon of **B**. The crotylation proceeded through a six-membered chair-like transition state (V), predominantly affording *erythro*-γ-adducts **6**.[15]



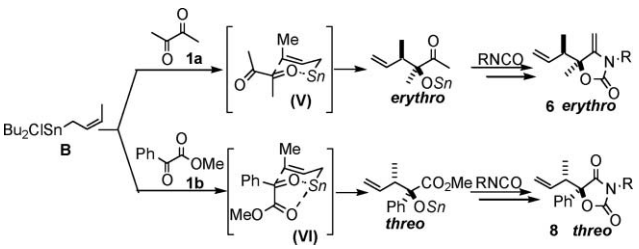
Scheme 4 Reaction route to **6**.

Thus, regio-controlled carbon–carbon bond formation was established in the side chain of the oxazolidinone rings. A similar change in regio-selectivity by the order of the addition of tin reagents also was found in the reaction using α-ketoester **1b** (Scheme 5). The reaction of crotyltri-*n*-butyltin, *n*-Bu_2SnHal_2, and α-ketoester **1b** in a single portion afforded α-adduct **7**, whereas the preheating of two tin reagents afforded γ-adduct **8**.



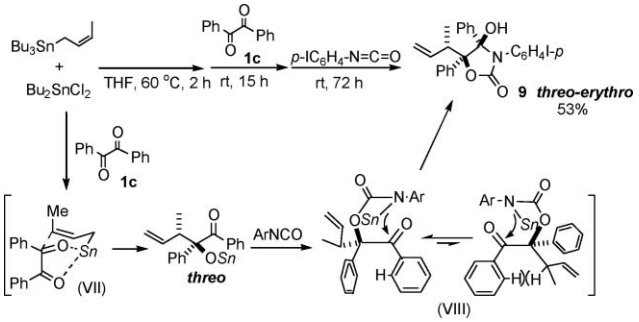
Scheme 5 Change of regio-selectivity using α-ketoester (**1b**).

In the formation of γ-adduct **8**, the *threo* isomer was obtained predominantly (95% ds), which is the reverse of the diastereo-selectivity in the formation of **6** (Table 2). The change of diastereo-selectivity between the two γ-adducts **6** and **8** can be explained in terms of chelate formation of the tin center with dicarbonyl substrate **1a** or **1b** (Scheme 6). In the *erythro*-forming reaction of **1a** with the *in situ*-generated (*Z*)-crotyltin **B**, an acetyl group occupied the equatorial position in a six-membered chair as in a transition state (V), whereas in the *threo*-forming reaction of **1b**, the reaction proceeded through a bicyclic chelation transition state (VI). Thus, the coordinating ability of carbonyl groups in dicarbonyl substrates **1** determined the diastereo-selectivity.



Scheme 6 Difference in diastereo-selectivity between **6** and **8**.

In the last stage, we performed the reaction using benzil (**1c**) under the conditions that form a γ-adduct (Scheme 7). As a result, a hydroxyl-substituted oxazolidinone ring **9** was obtained where no β-elimination of tin alkoxide had occurred, because



Scheme 7 Synthesis of **9**.

the substrate bore no β-hydrogen. Interestingly, high chelation control of the three contiguous stereogenic centers in product **9** was accomplished. Thus, the stereochemistry between the methylallyl side chain and the ring carbon was *threo*, and that between the two ring carbons was *erythro*. The reaction proceeded through a bicyclic chelation transition state (VII) to give *threo* γ-crotylation adduct. The *erythro* selectivity on the oxazolidinone ring could be explained in terms of steric repulsion between the allylic and benzoyl group in VIII.

In conclusion, a one-pot synthesis of nitrogen heterocyclic compounds was initiated by the allylation of dicarbonyls **1**. Regio- and diastereoselective carbon–carbon bond formation was established on the side chains of the rings.

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‡ The structures of **5d**, **6d** and **7–9** were confirmed by crystal structure determinations.

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