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# Catalytic enantioselective allylation of aldehydes using β-amido functionalized allylstannanes with chiral In(OTf)$_3$/*i*-Pr-pybox complexes

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ABSTRACT

The enantioselective allylation of aldehydes using a variety of β-amido functionalized allyltributylstannanes proceeded smoothly with good to high yields and enantioselectivities in the presence of 10 mol % of a chiral catalytic complex prepared from In(OTf)$_3$ and 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine {(*S*)-*i*-Pr-pybox}, providing the corresponding chiral γ-hydroxy amides.

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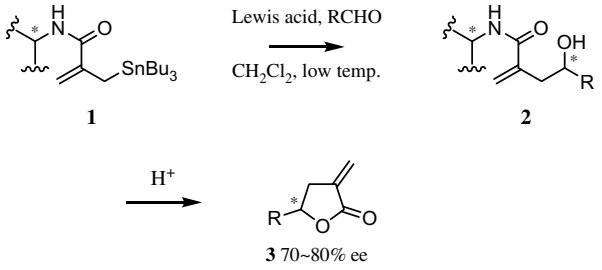
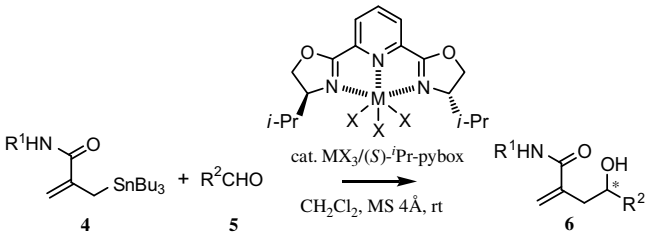
Asymmetric allylation of aldehydes using various allyl-metal reagents such as allylsilanes and allylstannanes is one of the most useful methods for chiral carbon–carbon bond formation.[1] Although a large number of methods have been developed, there are, to the best of our knowledge, few examples of reactions using allylstannanes with a β-amido function.[2] Pioneering studies developed by Tanaka et al.[2a,b] described Lewis acid mediated stoichiometrically diastereoselective allylation between aldehydes (RCHO) and optically active β-amido functionalized allyltributylstannanes **1**, furnishing the corresponding chiral γ-hydroxy amides **2**. These can be easily converted to α-methylene-γ-butyrolactones **3** possessing a wide range of potent biological activities (Scheme 1).[3]

Recently, chiral Lewis acid complexes composed of metal triflates M(OTf)$_3$ and 2,6-bis(oxazolin-2-yl)pyridine (pybox) were shown to be effective catalysts for the enantioselective allylation of carbonyl groups to afford the corresponding homoallylic alcohols in excellent enantiomeric excesses.[4] Herein, we report the first example of catalytic enantioselective allylation between β-amido functionalized allyltributylstannanes **4** and aldehydes **5** mediated by MX$_3$ and 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine {(*S*)-*i*-Pr-pybox} complexes (Scheme 2).

We attempted to determine the optimum reaction conditions for the enantioselective allylation of benzaldehyde **5a** using 2-methylene-*N*-phenyl-2-[(tributylstannyl)methyl]propan-amide




**Scheme 1.** Diastereoselective allylation of aldehydes with β-amido allyltributylstannanes **1** and the synthesis of α-methylene-γ-butyrolactones **3**.




**Scheme 2.** Enantioselective allylation of aldehydes **5** with β-amido allyltributylstannanes **4** catalyzed by MX$_3$/(*S*)-*i*-Pr-pybox complexes.

**4a**.[5] Among the various MX$_3$/(*S*)-*i*-Pr-pybox complexes examined, the reactions did not proceed under any conditions when InCl$_3$,

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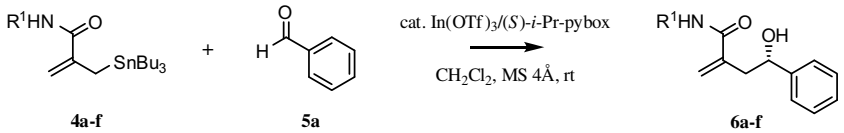
$La(OTf)_3$, $Sm(OTf)_3$, and $Yb(OTf)_3$ were used even in the presence of stoichiometric amounts of metal salts. Treatment of this reaction with $Sc(OTf)_3$, however, gave the desired γ-hydroxy amide **6a** but in low yield and enantiomeric excess (ee). In contrast to these findings, use of $In(OTf)_3$ had a significant effect on the rate and stereoselectivity, and an expected enhancement was observed in the use of only 30 mol % of this reagent, leading to **6a** in high yield with moderate enantioselectivity as shown in Table 1 (81%, 37% ee; entry 1). We next examined the catalytic amounts in order to study the reactivity of the $In(OTf)_3$/(*S*)-*i*-Pr-pybox complex (entries 1–3). Improved yield and ee were finally obtained in reaction employing 10 mol % of catalyst (96%, 63% ee, entry 3), although the use of 5 mol % of catalyst as well as the case of the addition of TMSCl (1.2 equiv)[4a] reversely decreased the enantiomeric excesses, respectively (entries 4 and 5). With these results in hand, further experiments have been performed on the catalytic allylation using several N-substituted β-amido allyltributylstannanes **4b–f** under the same reaction conditions. In the cases that N-aromatic reagents **4d–f** were employed, the beneficial stereoselective effect was found, providing the corresponding γ-hydroxy amides **6d–f** in satisfactory ees as well as good yields, respectively (entries 7–9). In particular, we were delighted to find that the reaction using *N*-(4-*tert*-butylphenyl) allyltributylstannane **4f** gave **6f** with the highest enantioselectivity (entry 9).

Encouraged by this success, we extended the scope of this methodology employing different aldehydes **5a–h** and the results from our survey are summarized in Table 2. The characteristic features of these reactions are as follows: (i) use of aliphatic aldehydes decreased the stereoselectivity as well as the reactivity (entries 1 and 2); (ii) little effect of the substituents on the aromatic aldehyde was observed (entries 3–5); (iii) the reaction with the large alkyl-substituent connected to the aromatic ring gave the highest enantioselectivity (79% ee, entry 8).

Although the obvious reason for these results is not clarified at present and the mechanistic research of the related reactions has not been appeared to date,[4] it should be considered that the steric hindrance between the alkyl-substituent on aromatic aldehydes employed and the isopropyl group of $In(OTf)_3$/(*S*)-*i*-Pr-pybox

**Table 1**
Enantioselective allylation of **5a** with allyltributylstannanes **4a–f** catalyzed by $In(OTf)_3$/(*S*)-*i*-Pr-pybox complex[a,b]

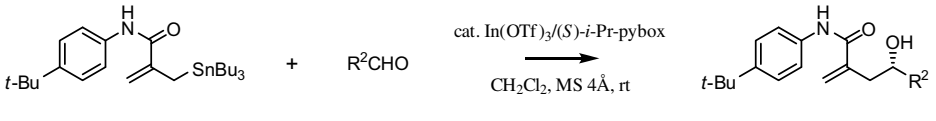



**4a-f** **5a** **6a-f**

| Entry | $R^1$ | $In(OTf)_3$ (mol %) | TMSCl (equiv) | Time (h) | Yield[c] (%) | ee[d] (%) | Configuration |
|---|---|---|---|---|---|---|---|
| 1 | Phenyl (**4a**) | 30 | — | 16 | 81 (**6a**) | 37 | *S*[e] |
| 2 | Phenyl (**4a**) | 20 | — | 4 | 72 (**6a**) | 51 | *S*[e] |
| 3 | Phenyl (**4a**) | 10 | — | 16 | 96 (**6a**) | 63 | *S*[e] |
| 4 | Phenyl (**4a**) | 10 | 1.2 | 21 | 85 (**6a**) | 32 | *S*[e] |
| 5 | Phenyl (**4a**) | 5 | — | 4 | 41 (**6a**) | 53 | *S*[e] |
| 6 | $C_2H_5$ (**4b**) | 10 | — | 24 | 78 (**6b**) | 31 | *S*[f] |
| 7 | *c*-$C_6H_{11}$ (**4c**) | 10 | — | 72 | 78 (**6c**) | 39 | *S*[f] |
| 8 | biphenyl-3-yl (**4d**) | 10 | — | 16 | 74 (**6d**) | 63 | *S*[f] |
| 9 | (3,5-Di-*tert*-butyl)phenyl (**4e**) | 10 | — | 16 | 81 (**6e**) | 70 | *S*[f] |
| 10 | (4-*tert*-Butyl)phenyl (**4f**) | 10 | — | 24 | 78 (**6f**) | 77 | *S*[f] |

[a] All reactions employed **4** (1.0 equiv) and **5a** (1.2 equiv) in the presence of activated MS 4 Å (120 mg) in $CH_2Cl_2$ (0.2 M).
[b] See experimental procedure in Ref. 6.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis using a Daicel Chiralpak IB column.
[e] See Ref. 7.
[f] Predicted absolute configuration on the basis of reaction mechanism and the sign of the specific rotations of **6**.

**Table 2**
Enantioselective allylation of aldehydes **5a–h** with **4f**




**4f** **5a-h** **6f-m**

| Entry | $R^2CHO$ | Time (h) | Yield[a] (%) | ee[b] (%) | Configuration |
|---|---|---|---|---|---|
| 1 | Isovaleraldehyde (**5b**) | 20 | 45 (**6g**) | 48 | *R*[c] |
| 2 | Pivaldehyde (**5c**) | 20 | 45 (**6h**) | 58 | *R*[d] |
| 3 | 4-Nitrobenzaldehyde (**5d**) | 20 | 91 (**6i**) | 58 | *S*[d] |
| 4 | 4-Anisaldehyde (**5e**) | 20 | 92 (**6j**) | 59 | *S*[d] |
| 5 | 3-Chloroaldehyde (**5f**) | 20 | 90 (**6k**) | 61 | *S*[d] |
| 6 | 1-Naphthaldehyde (**5g**) | 14 | 89 (**6l**) | 74 | *S*[d] |
| 7 | Benzaldehyde (**5a**) | 16 | 78 (**6f**) | 77 | *S*[e] |
| 8 | 4-Isopropylbenzaldehyde (**5h**) | 20 | 94 (**6m**) | 79 | *S*[d] |

[a] Isolated yield.
[b] Determined by chiral HPLC analysis using a Daicel Chiralpak IA, IB, or IC column.
[c] See Ref. 8.
[d] Predicted absolute configuration on the basis of reaction mechanism and the sign of the specific rotations of **6**.
[e] See Ref. 7.

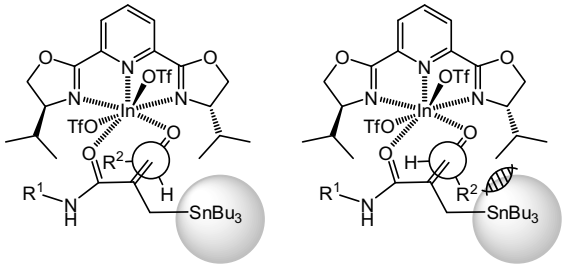



**Figure 1.** Plausible transition structure model.

complex plays an important role in this selectivity. Thus, we postulate that the observed high degree of stereoselectivity in these reactions may be attributed to the stronger chelating ability of indium ion which coordinates with the amide moiety of the organotin reagent and the oxygen atom of the aldehyde to organize cyclic transition states A and B (Fig. 1). Model A would be preferred over B in which the steric interaction between the stannyl group and the aryl group ($R^2$) of the aldehyde is minimized to occupy the remotest positions each other. In addition, the allyltributylstannane approaches the carbonyl *si*-face because the *re*-face is shielded by the isopropyl substituent on the oxazoline ring of the pybox ligand,[9] leading to the (*S*)-adduct predominantly.

Furthermore, allylated products thus obtained were easily converted to potentially useful α-methylene-γ-butyrolactones, respectively.[3]

In summary, we have demonstrated the first example of catalytic enantioselective allylation of various aldehydes using β-amido functionalized allyltributylstannanes with 10 mol % of In(OTf)$_3$/(*S*)-*i*-Pr-pybox complex, and found that the reactions between *N*-aryl allyltributylstannanes and aromatic aldehydes were effective to give high enantioselectivity.

This method possesses desirable advantages of being not only catalytic and enantioselective in the allylation, but able to give optically active α-methylene-γ-butyrolactones directly without employing chiral allylstannanes prepared through tedious elaboration.[2a,b] Further work on a more detailed mechanism and effort to expand the scope of synthetic applications are currently in progress and will be discussed elsewhere.

## Acknowledgments

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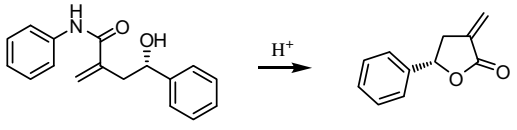
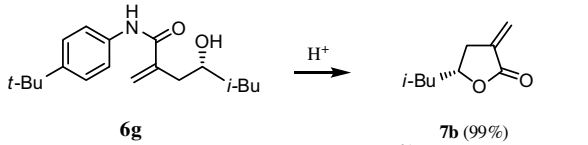
5. A general method for preparation of β-amido allylstannanes was reported in Ref. 2b.
6. *Representative procedure for the synthesis of* **6a** (Table 1, entry 3): Under argon atmosphere, to the suspension of In(OTf)$_3$ (14.3 mg, 0.0254 mmol) {predried at 120 °C for 1 h under reduced pressure (ca, 1.0 Torr)} and MS 4 Å (120 mg) {also predried at 180 °C for 3 h under reduced pressure (ca, 1.0 Torr)} in $CH_2Cl_2$ (0.8 mL) was added *i*-Pr-pybox (15.3 mg, 0.0508 mmol) at room temperature. After stirring for 0.5 h, a solution of benzaldehyde **5a** (32.0 mg, 0.305 mmol) in $CH_2Cl_2$ (0.2 mL) was added and stirred for 1 h. Then, 2-methylene-*N*-phenyl-2-[(tributylstannyl)methyl]propanamide **4a** (114 mg, 0.254 mmol) in $CH_2Cl_2$ (0.3 mL) was slowly added dropwise at the same temperature. After stirring for 16 h, the reaction was quenched with aq $Na_2CO_3$ (5 mL), then $CH_2Cl_2$ was removed in vacuo. The mixture was filtered with Celite and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (3:1 to 2:1 hexane/ethyl acetate) to give the allylated product **6a** (65.0 mg, 0.243 mmol, 96%, 63% ee) as a white solid: mp 99–100 °C; $[\alpha]_D^{17}$ −46.7 (*c* 1.00, $CHCl_3$); IR (KBr) 3279 (O–H), 2868 (N–H), 1614 cm$^{-1}$ (C=O); $^1$H NMR (300 MHz. $CDCl_3$): δ 8.51 (br, 1H, N*H*), 7.55–7.51 (m, 2H, Ar*H*), 7.37–7.22 (m, 7H, Ar*H*), 7.15–7.09 (m, 1H, Ar*H*), 5.84 (s, 1H, C=C*H*), 5.33 (s, 1H, C=C*H*), 4.90 (dt, *J* = 3.3, 8.1 Hz, 1H, PhC*H*), 4.28 (d, *J* = 2.9 Hz, 1H, O*H*), 2.78 (ddd, *J* = 0.84, 7.0, 14 Hz, 1H, C*H*$_2$), 2.67 (dd, *J* = 8.3, 14 Hz, 1H, C*H*$_2$); $^{13}$C NMR (75 MHz. $CDCl_3$): δ 172.4 (*C*=O), 144.5 (*C*=CH$_2$), 144.3 (C=*C*H$_2$), 140.1 (*C*H), 129.4 (*C*H), 128.2 (*C*H), 127.2 (*C*H), 127.1 (*C*H), 126.6 (*C*H), 125.7 (*C*H), 122.7 (*C*H), 74.1 (*C*H$_2$), 44.8 (*C*H); HRMS (ESI+) *m/z* calcd for $C_{17}H_{17}NO_2$+Na: 290.1157, found 290.1128.
7. The absolute configuration of the stereogenic center of **6a** was easily determined to be *S* after derivation to the corresponding α-methylene-γ-butyrolactone **7a** as shown below, see: Csuk, R.; Schröder, C.; Hutter, S.; Mohr, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1411.



**6a** **7a** (91%)
$[\alpha]_D^{31}$ +12.9 (*c* 1.00,$CHCl_3$)

8. The absolute configuration of the stereogenic center of **6g** was determined to be *R*[2a] after cyclization again to the corresponding lactone **7b** as shown below.



**6g** **7b** (99%)
$[\alpha]_D^{21}$ +26.1 (*c* 0.956, EtOH)

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