Communications

# Metal-Mediated Diastereoselective Allylation Reaction of Chiral α,β-Epoxy Aldehyde. Part 1

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Received July 20, 2006

Key Words : Metal-mediated allylation, Laulimalide, Epoxy aldehydes

The allylmetal-aldehyde addition reaction has proven to be very useful for the synthesis many important complex organic molecules.[1] The stereochemistry and reactivity of this reaction usually depend critically on the metal used. Furthermore, stereoselective allylation can be performed using allylic organometallic reagents in the presence of chiral catalysts which coordinates the metal ions.

Compared with α-alkoxy aldehyde, the reaction of α,β-epoxy aldehyde with allylic metal has been used in a limited way.[2] Generally, the nucleophilic addition to α,β-epoxy aldehyde provides predominantly *anti*-product.[3]
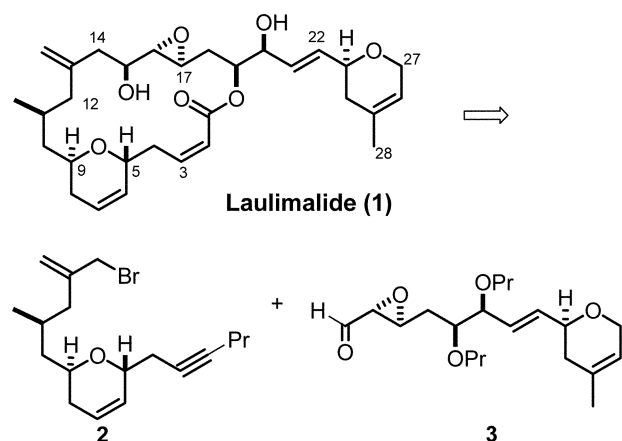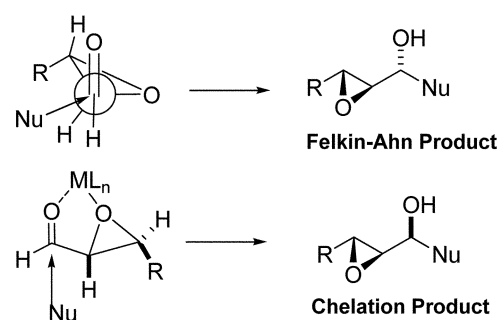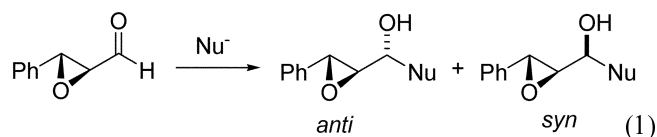
This stereoselectivity for Eq. (1) can be explained by the Felkin-Ahn and chelation models for *anti*- and *syn*-products, respectively.

In the course of our synthetic efforts toward the total synthesis of laulimalide (**1**) we required a strategy that enables stereoselective allylation resulting in *anti*-product for the coupling of two synthetic fragments **2** and **3**.

Metal-mediated allylation has advantages over utilization of allylmetal because of the synthetic convenience saving extra synthetic steps. Besides, in case of the indium-mediated allylation reaction, it does not require inert atmosphere or dry solvents.[4] With this fact in our minds, we decided to examine the indium-mediated allylation reaction between methallyl bromide and (2*R*,3*S*)-3-phenyloxirane-2-carbaldehyde as shown in Eq. (2).

(1)

Felkin-Ahn Product

Chelation Product

Laulimalide (1)

2   **3**

(2)
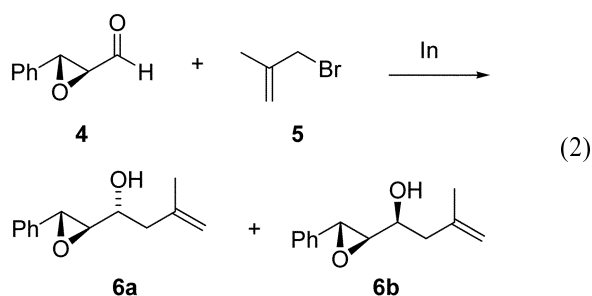
Comparing to Felkin-Ahn model, indium-mediated allylation precedes through the transition state of a chair conformation. For the chair conformational transition state,

A (stable)   *anti*-**6a** (major)

B   *syn*-**6b** (minor)
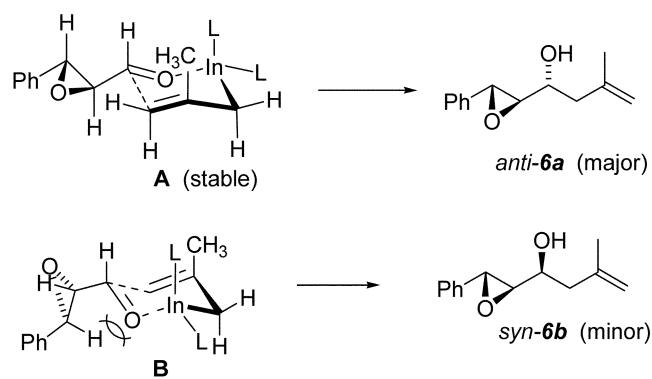
Table 1. Indium-Mediated Allylation of Aldehyde **4**

Entry	Reaction Condition[*]	Product Ratio[a] (**6a:6b**)	Yield (%)
1	AcOH, THF, 5 min	71:29	96
2	THF, 2 h	67:33	91
3	AcOH, DMF, 5 min	69:31	93
4	LiI, AcOH, THF, 5 min	29:71	94
5	InCl₃, Pd(PPh₃)₄, THF, 2 h	75:25	94
6	Yb(OTf)₃, THF, 2 h	37:63	87
7	Sc(OTf)₃, THF, 2 h	49:51	85
8	(*R,R*)-**7**, THF, 2 h	52:48	92
9	(*S,S*)-**7**, THF, 2 h	37:63	91

[*]All the reactions were performed at room temperature with aldehyde : bromide : In = 1 : 1.5 : 1. [a]Determined by ¹H NMR.

the simple computational calculation on the level of PM3 was performed in order to explain the stereochemical outcome of the indium-mediated allylation of α,β-epoxy aldehyde.[4] Relative stabilization energy of transition conformation **A** to **B** was found to be 1.6 kcal/mol. The energy difference may come from steric and electronic effects such as Felkin-Ahn transition state. This calculation predicts *anti*-product **6a** is the major product in the reaction.

With this prediction we carried out the indium-mediated allylation under various reaction conditions as shown in Table 1.

Entry 1 employing the simple allylation under the acidic condition in THF provided the good result compared with entries 2 and 3. As for entry 4, the stereochemical outcome for major product is *syn*. The addition of Li ion resulted in chelation between epoxide and aldehyde oxygens and for that reason the chelation model worked for the *syn*-product. Pd(0) catalytic condition showed almost same result as entry 1. For entry 6 and 7, the addition of lanthanide Lewis acid did not give noticeable influence on the selectivity. Entry 6 shows that using of Yb(OTf)₃ gave insignificant preference toward *syn*-product. Also we looked at the role of chiral ligands for the stereochemical selectivity using chiral 2,6-*bis*(4-isopropyl-2-oxazolin-2-yl)pyridines(**7**, Pybox-*i*-Pr).[5] Entry 8 and 9 displays daunting observation for the stereoselectivity. In these cases, the influence of the stereochemistry of the substrates seems to prevail over the chiral ligands.

(*S,S*)-**7**   (*R,R*)-**7**
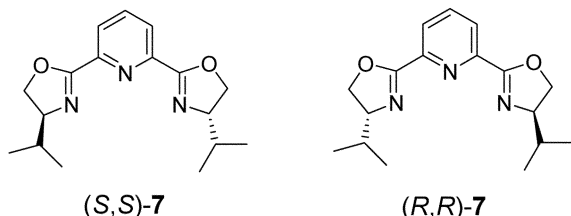
With these results in hand, we surveyed the further experiments with more realistic model for the total synthesis of laulimalide as shown below in Eq. (3) with chiral ligands.

The results are delineated in Table 2. As the previous experiments, the addition of the chiral ligands does very little effects on the stereochemical selectivity. This kind of ligands is not recommendable for our experiments.

$$(3)$$
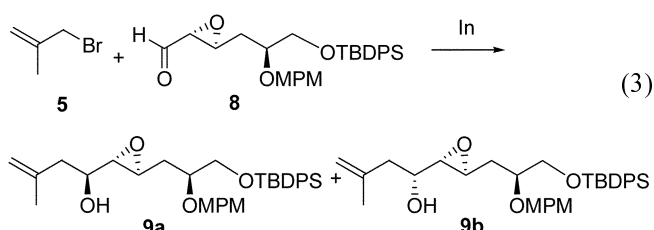
Table 2. Indium-Mediated Allylation of Aldehyde **8**

Entry	Reaction Condition[*]	Product Ratio[a] (**9a:9b**)	Yield (%)
1	AcOH, THF, 5 min	73:27	90
2	(*R,R*)-**7**, THF, 3 h	63:37	87
3	(*S,S*)-**7**, THF, 3 h	49:51	85

[*]All the reactions were performed at room temperature with aldehyde/bromide/In = 1 : 1.5 : 1. [a]Determined by ¹H NMR.

So far we have demonstrated the indium-mediated allylation reaction with chiral α,β-epoxy aldehyde under the various experimental conditions. We found that simple addition of acetic acid in THF is the simplest resolution for stereoselectivity of indium-mediated allylation for our systems and we need to work on with other metals for metal-mediated allylation. The on-going search for other metal-mediated allylation will be soon reported.

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