

Metal-Mediated Diastereoselective Allylation Reaction of Chiral α,β -Epoxy Aldehyde. Part 2

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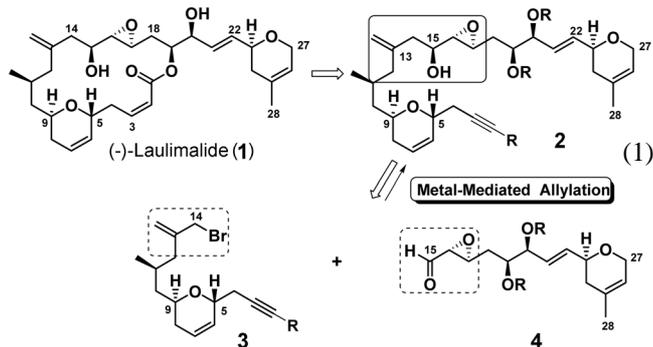
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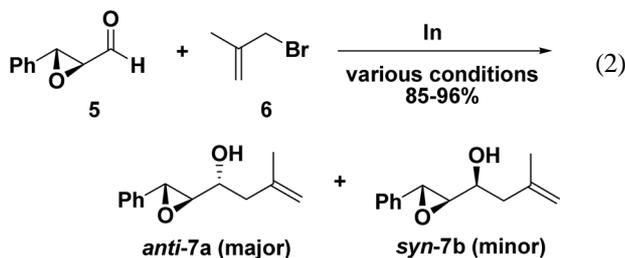
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Metal-mediated allylation of carbonyl compounds is an important carbon-carbon bond formation in organic chemistry for the preparation of homoallylic alcohols.¹ This methodology is useful for the construction of complex molecules and important building blocks for the synthesis of natural products. As part of our studies toward the total synthesis of laulimalide (**1**), an antimiotic macrolide isolated from marine sponges,² we became interested in the synthesis of a key intermediary, homoallylic alcohol **2** (Eq. 1). We envisaged that the homoallylic alcohol **2** could be obtained from the metal-mediated allylation of chiral epoxy aldehyde **4** and allyl bromide **3**.



In the previous communication,³ we reported indium-mediated allylation reaction with chiral epoxy aldehyde **5** in order to find the optimum reaction condition for the construction of C13-C15 homoallylic alcohol unit of laulimalide. Also, we examined the stereoselective effects of indium metal in the presence of Lewis acids and chiral ligands on allylation. We successfully demonstrated that the indium-mediated allylation reaction of (2*R*,3*S*)-3-phenyloxirane-2-carbaldehyde **5** proceeded smoothly with methyl allyl bromide **6** in water/solvent mixtures to give almost exclusively the homoallylic alcohol adducts **7** in moderate to good yields (Eq. 2).



In this communication, we would like to report the improved synthesis of homoallylic alcohols utilizing several metals such as zinc, magnesium, tin, and gallium.⁴ Among these, the use of zinc metal as a mediator under Barbier-type condition was first reported by Wolinsky in 1977.⁵ Compared to other metals, zinc offers a number of advantages, including its low toxicity, tolerance towards air and moisture, and a high reactivity in the absence of external activators and proton sources due to its low ionization potential. The use of zinc generally requires the application of saturated aqueous NH_4Cl as a proton source.

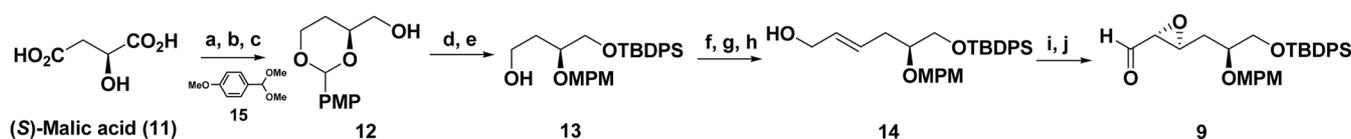
For model studies, we investigated the allylation of (2*R*,3*S*)-3-phenyloxirane-2-carbaldehyde **5** using several metals in order to establish its suitability for the preparation of homoallylic alcohol. The experimental results are summarized in Table 1.

It was discovered that the use of acidic condition in THF as co-solvent increased the stereoselectivity (entry 1, 2, 3). The best condition was obtained when the reaction was carried out in saturated aqueous NH_4Cl . The reaction was completed after 30 min affording the product in good yield (entry 4). We also screened chiral ligands under the optimized reaction condition. Chiral ligands (Pybox-*i*-Pr) **8** were found to be significantly less effective as chiral promoters (entry 5, 6). The reaction in the presence of other metals such as magnesium, tin, and gallium proceeded to afford the product in either no stereoselectivity or low yield (entry 7, 8, 9).

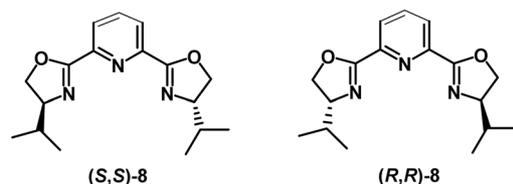
Table 1. Metal-Mediated Allylation of Aldehyde **5**

Entry	Reaction Condition ^a	Product Ratio ^b (7a : 7b)	Yield (%)
1	Zn, AcOH, THF, 5 min	63:37	86
2	Zn, AcOH, DMF, 5 min	60:40	88
3	Zn, DMF, 2 h	58:42	85
4	Zn, aq. NH_4Cl , 30 min	73:27	84
5	Zn, (<i>R,R</i>)- 8 , THF, 2 h	51:49	77
6	Zn, (<i>S,S</i>)- 8 , THF, 2 h	35:65	75
7	Mg, AcOH, THF, 5 min	53:47	65
8	Sn, AcOH, THF, 5 min	50:50	71
9	Ga, THF, 30 min ^c	42:58	63

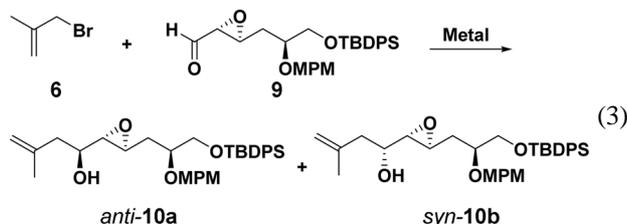
^aAll the reaction were performed at room temperature with aldehyde:bromide:M = 1:1.5:1. ^bDetermined by ¹H NMR. ^cPromoted by sonication.



Scheme 1. Reagents and conditions: a) MeOH, *p*-TsOH, Benzene, reflux, 24 h, 95%; b) LAH, THF, 0 °C, 3 h, 95%; c) **15**, *p*-TsOH, CH₂Cl₂, 0 °C, 1 h, 80%; d) TBDPSCl, Imidazole, CH₂Cl₂, rt, 98%; e) DIBAL-H, CH₂Cl₂, rt, 1 h, 89%; f) DMP, CH₂Cl₂, 0 °C; g) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, -78 °C, 1 h, 66% (over two steps); h) DIBAL-H, THF, -78 °C to rt, 1 h, 96%; i) L-(+)-DIPT, Ti(Oi-Pr)₄, TBHP, CH₂Cl₂, -20 °C, 12 h, 85%; j) DMP, CH₂Cl₂, rt, 1 h, 92%.



With these results in hand, we conducted more experiments in which the structure of the substrate **9** is closer to the C15-C20 fragment of laulimalide (Eq. 3).



The chiral epoxy aldehyde **9** was prepared in 10 steps from commercially available (*S*)-malic acid as a starting material (Scheme 1). First, (*S*)-malic acid was esterified by treatment with MeOH and *p*-TsOH in benzene. The resulting ester was reduced to the triol by LiAlH₄ and 1,3-diol moiety of the triol was protected as MPM acetal **12** using the 4-methoxybenzaldehyde dimethylacetal **15**. The protection of the primary hydroxy group in **12** with TBDPSCl and the subsequent partial reduction with DIBAL-H provided the another primary alcohol **13**, and the alcohol was subjected to Dess-Martin oxidation to furnish aldehyde. The Horner-Wadsworth-Edmmons (HWE) reaction in THF at 0 °C provided the α,β -unsaturated ester (*E/Z* = 95:5), which was reduced to allylic alcohol **14** by DIBAL-H. Epoxy alcohol, prepared *via* Sharpless asymmetric epoxidation, was converted to chiral epoxy aldehyde **9** through Dess-Martin oxidation in 92% isolated yield.

With the optimized reaction conditions, the reactions of methallyl bromide **6** with chiral epoxy aldehyde **9** were investigated. The results are summarized in Table 2.

In all cases, the reactions proceeded smoothly to afford the corresponding products in good yields. Unfortunately, like the previous experiment, use of metals other than indium does very little effects on the stereochemical selectivity. The two diastereomers of the mixture could be easily separated by flash column chromatography. Absolute configuration of the homoallylic alcohols **10** could be decided from ¹H-NMR spectral data of MTPA derivative.⁶ The major isomers in all cases were found to have *anti* configurations. The dominant

Table 2. Metal-Mediated Allylation of Aldehyde **9**

Entry	Reaction Condition ^a	Product Ratio ^b (10a : 10b)	Yield (%)
1	Zn, AcOH, THF, 5 min	68:32	88
2	Zn, AcOH, DMF, 5 min	66:34	84
3	Zn, aq. NH ₄ Cl, 30 min	74:26	86

^aAll the reaction were performed at room temperature with aldehyde:bromide:M = 1:1.5:1. ^bDetermined by ¹H NMR.

anti selectivity observed can be explained using the previously proposed mechanism.⁷

In summary, we have demonstrated a general method for the metal-promoted diastereoselective allylation of chiral epoxy aldehydes using methallyl bromide. The homoallylic alcohol products are obtained in moderate diastereomeric excesses and in excellent yields and purity. Our on-going synthetic effort toward the synthesis of laulimalide will be reported in the near future.

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