Asymmetric Allylation of Aromatic Aldehydes Using Chiral Allylic Tin Reagents

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Chiral allylating reagents, readily generated *in situ* from $2\lambda^2$-1,3,2-benzodioxastannole [$Sn^{II}(O_2C_6H_4)$], allyl halides, chiral dialkyl tartrates and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) smoothly react with aromatic aldehydes at -78 °C in the presence of a catalytic amount of copper salts to afford the corresponding homoallylic alcohols in high yields with high enantioselectivities.

A number of allylic metal reagents[1] have been developed for constructing homoallylic alcohols, which are often employed as key intermediates in natural products synthesis.[2] In 1980, it was reported[3] from our laboratory that tin(II) fluoride undergoes oxidative addition with allyl iodide to generate allylic tin(IV) which is highly reactive toward carbonyl compounds to form homoallylic alcohols in excellent yields even in the absence of Lewis acids.

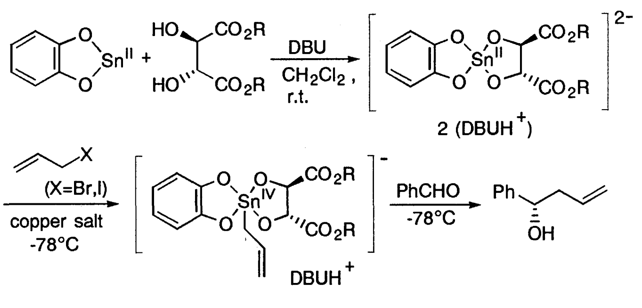
Allylic tin(IV) is known as one of convenient allylic metal reagents and several asymmetric allylation reactions have been successfully achieved by using allylic tin reagents in the presence of chiral Lewis acids[4] or by using stoichiometric amount of chiral allylic tin(IV) reagents.[5] In the latter reports by C. Trombini et al., enantioselective allylation reaction using several kinds of aldehydes was carried out with penta coordinated allylic tin(IV) complex containing diethyl tartrate ($H_2O_2R^*$) as a chiral auxiliary ligand[6] and Na [$CH_2=CHCH_2-Sn^{IV}(O_2R^*)_2$] was proposed as an active species. In case of the allylation of benzaldehyde at 0 °C, the corresponding homoallylic alcohol was obtained in up to 82% yield with up to 62% ee. Trials to improve the enantioselectivity at lower temperature did not succeeded since the present reaction proceeded very slowly below 0 °C and virtually stopped at -30 °C owing to the insolubility of this allylic tin(IV) complex.

As for the reducing ability of $Sn^{II}(OR)_2$ type compounds toward alkyl halides, $Sn^{II}(O_2C_6H_4)$ is known to produce no adduct with methyl iodide while oxidative addition with 1,2-dioxo compounds such as *o*-quinone proceed to afford $Sn^{IV}(O_2C_6H_4)(O_2Ar)$ type adducts.[7] On the other hand, tin(II) acetylacetonate undergoes oxidative addition with alkyl iodides on heating. The difference between these two tin(II) compounds may be attributed to the fact that $Sn^{II}(O_2C_6H_4)$ is highly associated by way of intermolecular tin-oxygen bridging while tin(II) acetylacetonate bearing carbonyl functions exists in benzene as its monomeric structure.[8]

Further, T. Imai et al., observed that the presence of a catalytic amount of cuprous salts enables efficient allylation of aldehydes with allyl halides and tin(II) chloride dihydrate at room temperature *via* the active tin-copper complex.[9]

Based on these observations, utilization of tin(II) compounds in asymmetric allylation reaction was studied. Then, it was found that $Sn^{II}(O_2C_6H_4)$, readily prepared from tin(II) chloride and catechol,[10] undergoes oxidative addition at -78 °C in freshly distilled CH_2Cl_2 with allyl halide (bromide or iodide) in the presence of chiral dialkyl tartrate, DBU and a catalytic amount of copper salt such as CuI (see *Scheme 1*). The resulting chiral allylating reagents readily react with aromatic aldehydes at the same temperature to afford the corresponding homoallylic alcohols in high yields with high enantioselectivities.

It is noted that the present allylation reaction proceeded very smoothly even at -78 °C in the coexistence of CuI when $Sn^{II}(O_2C_6H_4)$ was used. In the absence of CuI, the present reaction using allyl iodide proceeded with low reproducibility, and allyl bromide did not form the desired adduct.



Scheme 1.

Besides CuI, cupric salts($CuCl_2$, $CuSO_4$, etc.) were also found to be effective in addition to other cuprous salts (CuBr, CuCl, CuCN, etc.). Copper salts apparently have a key role in promoting the step of oxidative addition to allylhalide forming an active allylic tin reagent, though the detailed mechanism has not yet been made clear.

Reactivity of the resulting coordinated complex was dependent on the structure of a ligand; that is, similar reactive allylating reagent was not formed when vicinal dihydroxy compound with no carbonyl functions (1,2-cyclohexanediol and 2,3-butanediol for example) was employed, which was different from the case of using dialkyl tartrate mentioned above. Carbonyl function of the dialkyl tartrate is expected to dissociate polymeric $Sn^{II}(O_2C_6H_4)$ into its monomeric structure which leads to facile addition of the complex to allyl halides.

The dissociation of $Sn^{II}(O_2C_6H_4)$ also seemed to be assisted by DBU because the suspension of $Sn^{II}(O_2C_6H_4)$ in CH_2Cl_2 turned to a clear solution by adding DBU at room temperature.

The desired homoallylic alcohol was obtained in 96% yield with 85% ee when a mixture of $Sn^{II}(O_2C_6H_4)$ (2.0 eq), (+)-diisopropyl tartrate[(+)-DIPT] (5.0 eq), DBU (5.0 eq) and CuI (0.1 eq) in CH_2Cl_2 was stirred at room temperature and then allyl bromide (2.0 eq) and benzaldehyde (1.0 eq) were allowed to react with thus formed coordinated complex at -78 °C. Performing the reaction at higher temperature apparently diminished optical yield. The amounts of the reagents influenced yield and enantiomeric excess of the product; that is, the corresponding homoallylic alcohol was obtained in 70% yield with 49% ee, when 2.0 eq of (+)-DIPT and 4.0 eq of DBU were used in the above reaction.

An enantiomer of the above product was obtained in the same way by employing commercially available (-)-DIPT.

Concerning the structure of dialkyl tartrate, methyl ester (69% yield, 57% ee), ethyl ester (88% yield, 72% ee) and benzyl ester (90% yield, 73% ee) did not give better results than isopropyl ester (DIPT). Satisfactory results were obtained when *cyclo*-hexyl ester (97% yield, 87% ee) and *tert*-butyl ester (98% yield, 91% ee) were used.

After optimizing the reaction conditions, several aromatic aldehydes were allylated according to the present procedure employing (+)-di-*tert*-butyl tartrate.[11] All of the substrates examined afforded the corresponding homoallylic alcohols in high chemical and optical yields. Results obtained here are summarized in *Table 1*.

Table 1. Asymmetric allylation of aromatic aldehydes (ArCHO) [a] with a chiral allylic tin(IV) reagent [b]

entry	Ar	homoallylic alcohols yield / %[c]	ee / %[d]
1	Ph	98	91[e]
2	*p*-ClPh	99	89
3	*p*-CH_3Ph	96	92
4	*o*-CH_3Ph	99	94
5	1-naphthyl	97	91

[a] 0.2 mmol scale. [b] Prepared from $Sn^{II}(O_2C_6H_4)$ (0.4 mmol), allyl bromide (0.4 mmol), DBU (1.0 mmol), (+)-di-*tert*-butyl tartrate (1.0 mmol) and CuI (0.02 mmol). [c] Isolated yields. [d] Determined by HPLC. [e] (S) configuration.

Application of this new allylating reagent to aliphatic aldehydes afforded the corresponding homoallylic alcohols in high yield; however, enantioselectivities were not always high as shown in the case of aromatic aldehydes. For example cyclohexanecarboxyaldehyde was allylated with 82% ee (84% yield) while *n*-nonyl aldehyde gave the product with 60% ee (88% yield).

A typical experimental procedure (*Table 1*, entry 1) is as follows; to a suspension of $Sn^{II}(O_2C_6H_4)$ (0.4 mmol), (+)-di-*tert*-butyl tartrate (1.0 mmol), CuI (0.02 mmol) in CH_2Cl_2 (0.6 ml) was added DBU (1.0 mmol) in CH_2Cl_2 (0.6 ml) at room temperature under an argon atmosphere. The reaction mixture turned to a clear solution immediately and stirring was continued for 30 min. Then benzaldehyde (0.2 mmol) in CH_2Cl_2 (0.6 ml) and allyl bromide (0.4 mmol) in CH_2Cl_2 (0.6 ml) were successively introduced at -78 °C. After stirring for 20 h at this temperature, 1N HCl (15 ml) and hexane (5 ml) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with hexane-CH_2Cl_2 (2:1) mixture. The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica-gel TLC to afford the corresponding homoallylic alcohol in 98% yield. The enantiomeric purity of the product was determined to be 91% ee by HPLC analysis (Chiralcel OD, Daisel Chemical Industries, Ltd.). The absolute configuration was determined to be (S) by comparison of the optical rotation[12] with that reported in the literature.[13]

Thus, a simple and effective procedure for asymmetric allylation of aromatic aldehyde *via in situ* formed chiral allylic tin reagent has been successfully developed. Further studies on detailed mechanism of this asymmetric allylation and the scope of this reaction including aliphatic aldehydes are now in progress.

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