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Asymmetric Nucleophilic Addition to β- and γ-Alkoxy Aldehydes using Carbohydrate as a Chiral Auxiliary

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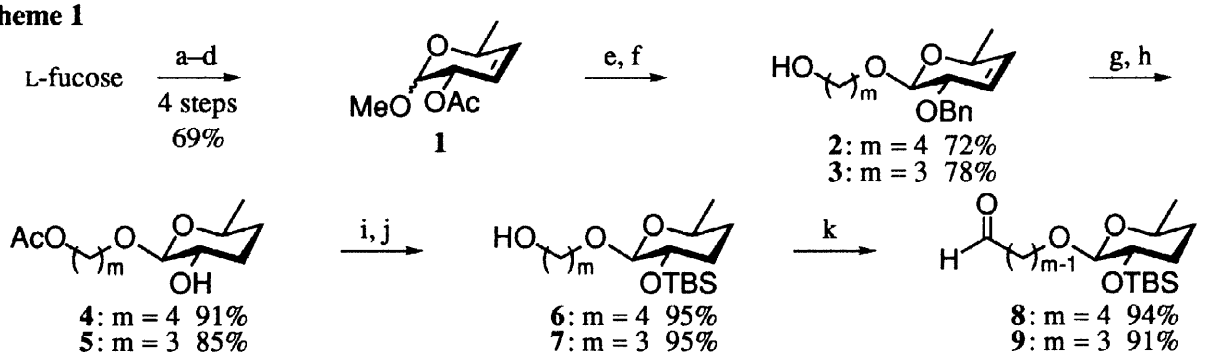
Abstract: The nucleophilic addition of Grignard reagents and allyltributyltin to chiral ω-tetrahydropyranyloxy propanal and butanal derived from L-fucose and D-arabinose gave the corresponding alcohols with high diastereoselectivity (up to 51% de by 1,6-asymmetric induction and 95% de by 1,5-asymmetric induction).

Nucleophilic addition to chirality modified aldehyde[1] is an important method for the synthesis of optically active secondary alcohol derivatives which are important chiral building blocks. Charette *et al.* have reported that the 2-benzyloxytetrahydropyranyl group is an efficient chiral auxiliary for the α-alkoxy aldehyde in the $MgBr_2$-mediated addition reactions of Grignard reagents and allyltributyltin.[2] However, Keck has pointed out that the $MgBr_2$-mediated allyltributyltin addition reaction is much less successful in producing the chelation-controlled product in the case of β-alkoxy aldehyde.[3] Charette has also reported that the addition of allyltributyltin to β-alkoxy aldehyde possessing the same chiral auxiliary under the optimized conditions resulted in low selectivity.[2a] Presumably because of such reasons, studies focusing on nucleophilic additions of allyltributyltin and Grignard reagents to β- and γ-alkoxy aldehyde using a chiral auxiliary are limited.

Herein we describe a nucleophilic addition to β- and γ-alkoxy aldehyde in which a remote chiral auxiliary provides high levels of asymmetric induction. The design of the chiral auxiliary was based on assumption of a complex involving $MgBr_2$ and oxygen atoms on the auxiliary. For this purpose, a carbohydrate derivative was chosen as the chiral auxiliary[4] due to its oxygenate nature.

Scheme 1



(a) MeOH, AcCl, reflux; (b) $CH(OMe)_3$, TsOH(cat.), CH_2Cl_2; (c) Ac_2O, Et_3N, CH_2Cl_2; (d) Ac_2O, reflux; (e) KO*t*-Bu then BnBr, THF; (f) 1,4-butanediol or 1,3-propanediol, H_2SO_4(cat.), ~90 ℃; (g) Ac_2O, Et_3N, CH_2Cl_2; (h) H_2, Pd/C, EtOH; (i) TBSCl, imid., DMF; (j) NaOMe (cat.), MeOH; (k) Swern Ox.

Various carbohydrate derivatives were examined and, finally, it was found that the fucose derivative was an efficient chiral auxiliary for the $MgBr_2$-mediated nucleophilic addition to β- and γ-alkoxy aldehydes. The enantiomerically pure aldehydes possessing chiral auxiliary were readily prepared from L-fucose as shown in

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Scheme 1. γ-Alkoxy aldehyde **8** and β-alkoxy aldehyde **9** were allowed to react with a CH_2Cl_2 solution of Grignard reagents[2c] and allyltributyltin in the presence of $MgBr_2 \cdot OEt_2$. Table 1 shows the results of the addition reactions.[5] It should be noted that the addition of PhMgBr to **8** resulted in 51% de with *re*-facial selectivity by 1,6-asymmetric induction (Entry 1), while the addition to **9** resulted in 77% de with opposite (*si*-face) facial selectivity by 1,5-asymmetric induction (Entry 2).[6]

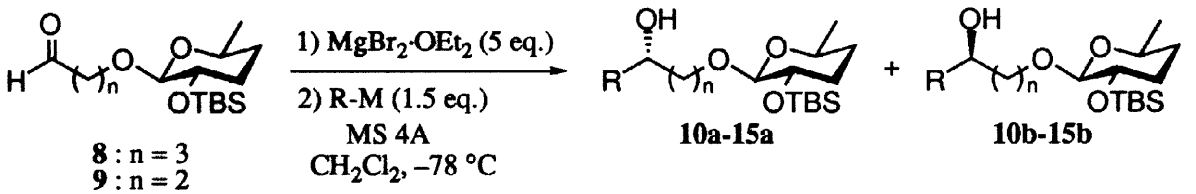


Table 1. The Nucleophilic Addtions to β- and γ-Alkoxy Aldehyde. [a]

Entry	n	R-M	Yield / %	a : b [b]	% de
1	3	PhMgBr	98 (**10**)	25 : 75	51
2	2	PhMgBr	97 (**11**)	89 : 11	77
3	2	*i*-PrMgBr	88 (**12**)	82 : 18	64
4	2	*n*-BuMgBr	97 (**13**)	90 : 10	80
5	2	MeMgI	90 (**14**)	78 : 22	55
6	2	CH_2=$CHCH_2MgBr$	74 (**15**)	64 : 36	28
7 [c]	2	CH_2=$CHCH_2SnBu_3$ (neat)	96 (**15**)	12 : 88	75

a General Procedure: To a CH_2Cl_2 solution of aldehyde (0.07 M), $MgBr_2 \cdot OEt_2$ (5 eq.)[7] was added in the presence of flame-dried molecular sieves 4A (1 g/1 mmol) at –78 °C and the resulted suspension was equilibrated for 45 min. The nucleophile (1.5 eq.) was added to the suspension and stirred for 3 h at –78 °C. After standard work up, the alcohol was isolated by silica gel flash chromatography. *b* The diastereoselectivity was determined by ^{1}H- and/or ^{19}F-NMR inspection of the corresponding Mosher ester. *c* Run at –78 °C (2 h) then warmed slowly to –30 °C.

The absolute configurations of **10** and **11** were determined by conversion to the known 1-phenyl-1,4-butanediol **16** and 1-phenyl-1,3-propanediol **17** and comparison of $[\alpha]_D$ with literature value[8] (Scheme 2).

Scheme 2

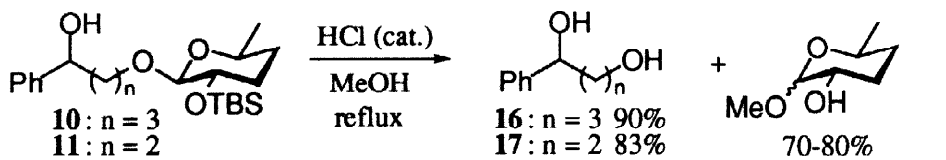
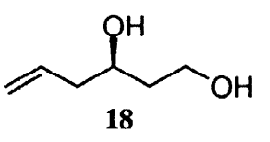


Figure 1

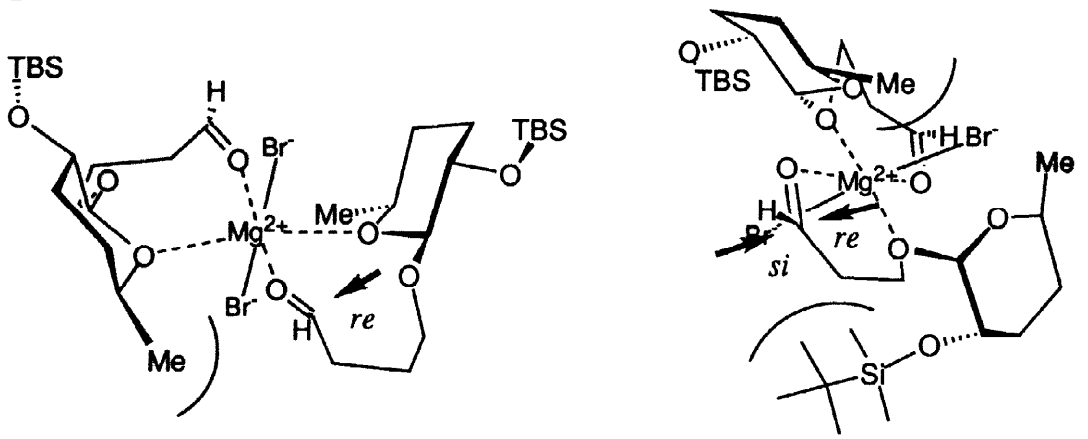


The alkyl Grignard reagents gave the corresponding optically active secondary alcohol with good selectivity (Entry 3-5). It is interesting to point out that Charette has shown that $MgBr_2$-mediated addition of allylmagnesium bromide to α-alkoxy ketone resulted in lower selectivity due to the breakup of the chelate by the reagent prior to reaction.[2c] This was also observed in our system (Entry 6). However, the desired homoallylic alcohol was produced with satisfactory selectivity (75% de) when allyltributyltin was used as a nucleophile (Entry 7). However, the facial selectivity of allylstannane (*re*-face) was reversed compared with Grignard reagents (*si*-face). The absolute configuration of this homoallylic alcohol was determined by conversion to 5-hexene-1,3-diol **18** and comparison of $[\alpha]_D$ with literature value[9] (Figure 1).

It is very difficult to explain these results by the formation of an usual intramolecular complex[2] (aldehyde-$MgBr_2$ 1:1 complex). In trying to understand the surprising facial selectivitiy of these nucleophilic additions, we hypothesized the formation of an aldehyde-$MgBr_2$ 2:1 complex as shown in Figure 2. The formation of the aldehyde-$MgBr_2$ 2:1 complex has been previously reported.[10] In the case of γ-alkoxy aldehyde **8**, the

observed diastereoselectivity could be explained by the addition of PhMgBr to the diastereoface opposite to the methyl group of the 2:1 complex **19**. In the case of β-alkoxy aldehyde **9**, it was considered that complexation involving the anomeric oxygen atom (**20**) which is capable of forming a six-membered ring is faster than complexation involving the ring oxygen atom like **19**. Therefore, the addition of Grignard reagents may preferentially proceed to *si*-face because of the steric effect of the methyl group shown in complex **20**.[11]

Figure 2

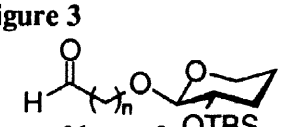


19
γ-Alkoxy Aldehyde

20
β-Alkoxy Aldehyde

According to our mechanistic hypothesis regarding the source of stereoselectivity in these addition reactions, absence of the methyl group should lower the diastereoselectivity. Indeed, addition of PhMgBr to the corresponding D-arabinose derivatives shown in Figure 3 yielded the corresponding alcohols with decreased diastereoselectivity (γ-alkoxy aldehyde **21**: 35% de *S*, β-alkoxy aldehyde **22**: 48% de *R*).[12]

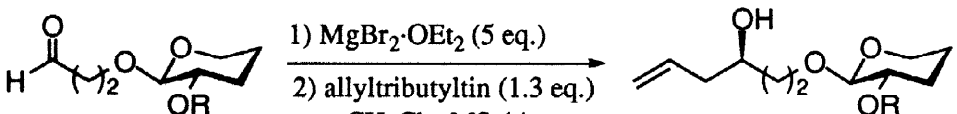
Figure 3



21: n = 3
22: n = 2

In the addition of allyltributyltin[13] to β-alkoxy aldehyde **9**, it could be interpreted that the *re*-facial selectivity was determined by steric repulsion between the bulky $SnBu_3$ group of the nucleophile and the TBS group located in the side of *si*-face rather than by the steric effect of the methyl group located in the side of *re*-face as shown in the 2:1 complex **20** (Figure 2). This interpretation would lead to the suggestion that absence of the methyl group should enhance the diastereoselectivity in the addition of allyltributyltin. Furthermore, we would also expect to see enhanced diastereoselectivity by exchanging the TBS group for the more bulky TIPS group.

The TBS ether **22** and TIPS ether **23** were subjected to the addition of allyltributyltin under the same conditions (Table 2).



22 or **23**

24 or **25**

Table 2. The Nucleophilic Addtions of Allyltributyltin to β-Alkoxy Aldehyde 22 and 23

Entry	R	Yield / %	% de
1	TBS (**22**)	quant. (**24**)	90
2	TIPS (**23**)	99 (**25**)	95

In line with our predictions, the addition to TBS ether **22** quantitatively yielded homoallylic alcohol **24** with 90% de (Entry 1). On the other hand, the addition to TIPS ether **23** yielded **25**[14] with higher (95% de)

selectivity (Entry 2). Thus, the additions of allyltributyltin to **22** and **23** reinforce the validity of the aldehyde-$MgBr_2$ 2:1 complex proposed.

Although the diastereomers were formed in these reactions, isolation of the major product was accomplished easily by silica gel flash column chromatography because of the large differences in *Rf* value between the diastereomers in the case of nucleophilic additions to β-alkoxy aldehyde.

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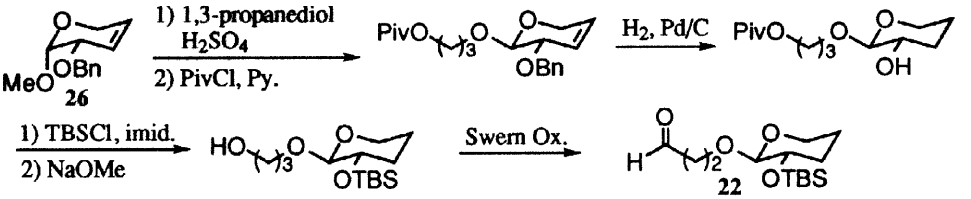
4. Review of carbohydrates as chiral auxiliaries: Kunz, H.; Rück, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336
5. Without MS 4A, addition reactions resulted in decreased yields.
6. In the addition of PhMgBr to δ-alkoxy aldehyde (n=4), the corresponding alcohol was obtained with 30% de by 1,7- asymmetric induction.
7. $MgBr_2 \cdot OEt_2$ dissolves slightly in dichloromethane. Hence, we thought that an excess amount of $MgBr_2 \cdot OEt_2$ is necessary to form the aldehyde-$MgBr_2$ complex. Actually, a decreased amount of $MgBr_2 \cdot OEt_2$ lowered the diastereoselectivity.
8. (a) 1-Phenyl-1,4-butanediol **16** $[\alpha]_D = -13.2°$ (*c* 0.7 MeOH), lit. (*S*)-**16** $[\alpha]_D = -27.2°$ (*c* 0.7 MeOH): Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1994**, *59*, 2676. (b) 1-Phenyl-1,3-propanediol **17** $[\alpha]_D = +56.7°$ (*c* 0.7 $CHCl_3$), lit. (*R*)-**17** $[\alpha]_D = +69.0°$ (*c* 1.5 $CHCl_3$): Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.
9. 5-Hexene-1,3-diol **18** (83% yield) $[\alpha]_D = -9.2°$ (*c* 0.4 $CHCl_3$), lit. (*S*)-**18** $[\alpha]_D = +10.0°$ (*c* 0.7 $CHCl_3$): Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S. *Chem. Lett.* **1989**, 2001.
10. Aldehyde-$MgBr_2$ or $SnCl_4$ 2:1 complex: Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. Other examples of aldehyde-Lewis acid 2:1 complexes: Aldehyde-$TiCl_4$ 2:1 complex: Kiyooka, S.; Nakano, M.; Shiota, F.; Fujiyama, R. *J. Org. Chem.* **1989**, *54*, 5409. Aldehyde-$SnCl_4$ 2:1 complex: Denmark S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984.
11. These aldehyde-$MgBr_2$ 2:1 complexes are thought to be in equilibrium with components. Therefore, the new aldehyde-$MgBr_2$ 2:1 complex may be reformed quickly after the addition to one of the aldehydes.
12. β-Alkoxy aldehyde **22** was prepared from methyl arabinoside **26**[2c].



13. Review of allylmetals : Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
14. The absolute configuration of TIPS ether **25** (95% de) was confirmed by the conversion to 5-hexene-1,3-diol **18** (91% yield). $[\alpha]_D = -14.0°$ (*c* 0.5 $CHCl_3$).