Pure & Appl. Chem., Vol. 64, No. 12, pp. 1925–1931, 1992.
Printed in Great Britain.

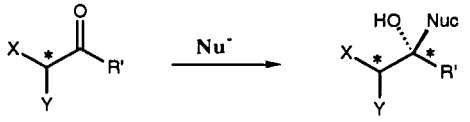
Design, synthesis, and applications of new oxygenated chiral auxiliaries

André B. Charette*, Christophe Mellon, Langis Rouillard and Éric Malenfant

Département de Chimie, Université de Montréal, Montréal, Canada H3C 3J7

Abstract. The magnesium bromide etherate-mediated addition of allyltributyltin to an α-alkoxyaldehyde bearing a protected 3-hydroxytetrahydropyranyl- moiety was shown to be highly diastereoselective. The sense and the level of induction depend on the nature of the protecting group at *C*-3. Esters and benzyl ether gave the opposite relative stereochemistry in comparison to silyl ethers. It was also found that the other enantiomer of an optically active 1,2-diol could be obtained using the same chiral auxiliary simply by changing the stereochemistry at the anomeric position. The exceptionally high level of 1,4-induction in these systems was attributed to the formation of a tridentate chelate involving one oxygen atom of the auxiliary and both oxygen atoms of the aglycone.

Since the pioneering work of Cram and later Still (ref. 1) showing that the stereochemistry in the addition of nucleophiles to chiral α-alkoxycarbonyl compounds (eq 1, X or Y = O) could be controlled by the α stereogenic center of a chelated species (ref. 2), very few studies have focused on using remote, removeable stereogenic centers to generate stereochemically well-defined chelates as controllers in these reactions. The chiral auxiliaries for this type of reaction have been relatively limited (ref. 3). Today I will describe our efforts to develop some conceptually new chiral auxiliaries for this general type of reaction that produces optically active secondary alcohols.



(1)

We anticipated that the use of a new chiral auxiliary (Figure 1) bearing two additional potential chelating sites would allow selective formation of a tridentate complex between the substrate and the Lewis acid and thus serve as an efficient chiral controller for these reactions.

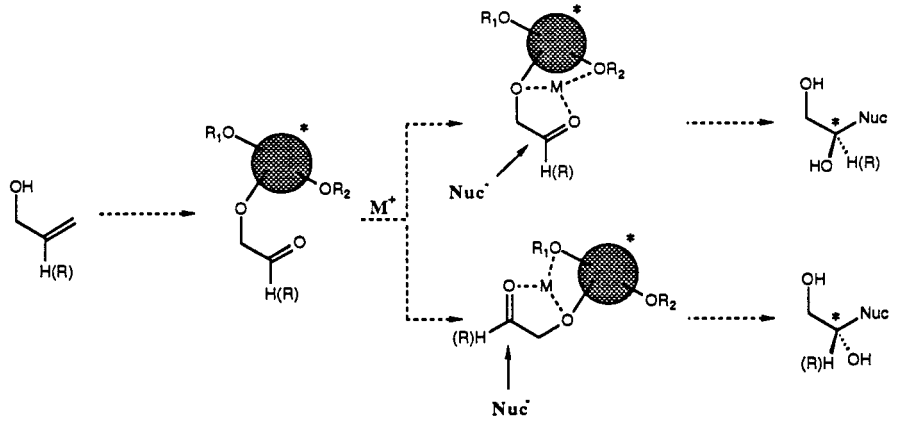


Figure 1

Depending on the nature of the two protecting groups (R_1 and R_2) (ref. 4) either tridentate complex will hopefully be formed preferentially and thus we anticipated that we could access either diastereomer of an alcohol upon nucleophilic addition. Two new potential auxiliaries (**1**, **2**) possessing these structural features are conceivable and are shown in Figure 2.

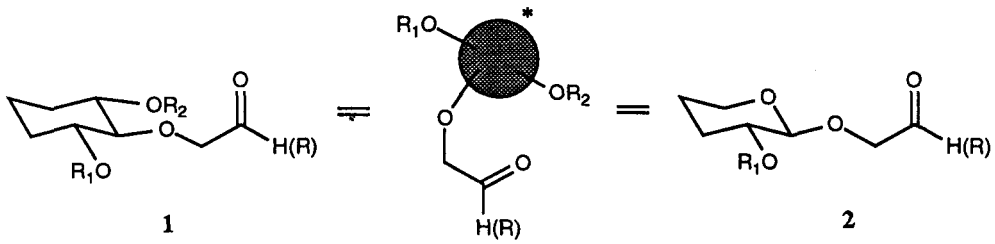
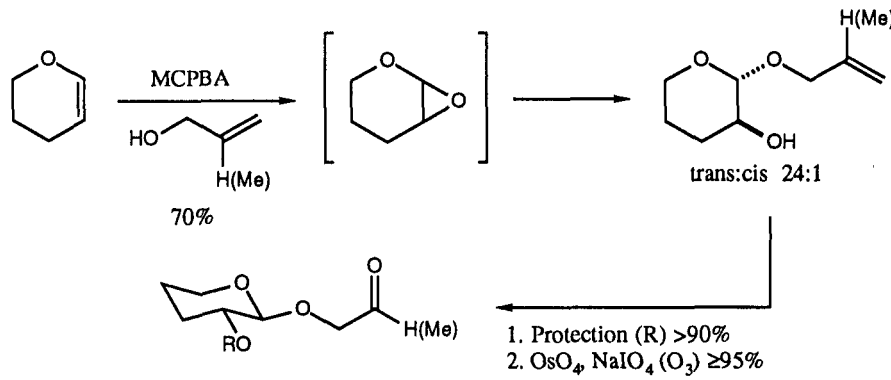


Figure 2

Although auxiliary **1** would be the ideal auxiliary since participation of a OR_1 or the OR_2 group should lead to two very similar complexes, auxiliary **2** was initially chosen for a number of reasons: 1. it was anticipated that the enantiomerically pure synthesis should be relatively easy; 2. the cleavage of the alcohol after the addition should be relatively straightforward; 3. the auxiliary should be readily recoverable after the cleavage of the aglycone moiety. Several questions however need to be answered regarding auxiliary **2**: 1. How will the nature of R_1O will influence the sense and the level of stereochemical induction if the group R_2O is an acetal and cannot be modified?; 2. What is the preferred conformation of this auxiliary in the absence vs in the presence of a metal ion?; 3. Is the rate of addition of the nucleophile to the carbonyl of the tridentate species will be faster than the rate of addition to the bidentate species? (ref. 5). In order to test the feasibility of this approach, initial studies were carried out on racemic material and focused on determining whether of not the nature of the protecting group R_1 had any effect on the sense and level of stereochemical induction when a nucleophile is added to the carbonyl. The racemic synthesis of **2** is illustrated in Scheme 1. Epoxidation of a solution of dihydropyran in the appropriate allylic alcohol with MCPBA produced the corresponding 2-hydroxytetrahydropyran derivative in 65-70% yield as a 24:1 chromatographically separable mixture of trans and cis isomers. The reaction proceeded equally well with allyl alcohol and 2-methyl-2-propen-1-ol. Subsequent protection with a number of different protecting groups followed by oxidative cleavage of the olefin produced the desired compounds for the initial study. The oxidative cleavage could be accomplished either with $OsO_4/NaIO_4$ or with O_3/DMS and a dye indicator. The resulting aldehydes were generally not very stable and were generally not purified prior to the addition reaction.

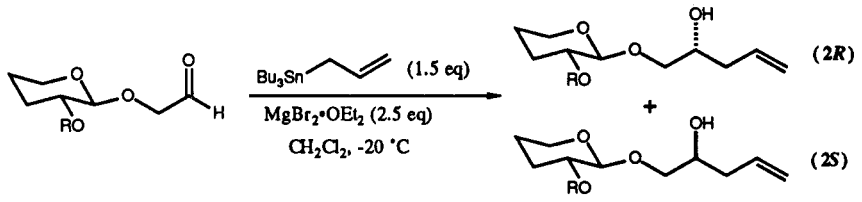
Scheme 1



Among the metals that are known to be efficient to produce chelation-controlled products in the addition of organometallics to α-alkoxycarbonyl compounds (magnesium, titanium, tin, zinc) (ref. 2), the most appealing for the initial studies was magnesium due to its relative ability to complex oxygen atoms, its tendency to adopt the tetrahedral geometry and its relatively small coordination sphere.

Therefore with the desired compounds in hand, the addition reaction of allyltributyltin mediated by $MgBr_2{\cdot}OEt_2$, reagents known to give very good selectivities with simple substituted α-alkoxy aldehydes (ref. 6) was chosen. Gratifyingly, the effect of the protecting group, located *6 atoms away from the reactive center*, turned out to be tremendous (Table 1). The diastereoselectivities observed when esters were used as protecting groups, were reasonably good reaching 92:8 when a pivalate was used. It would appear that the relative basicity of the carboxyl oxygen along with the steric hindrance

Table 1. Effect of the protecting group on the diastereoselection.

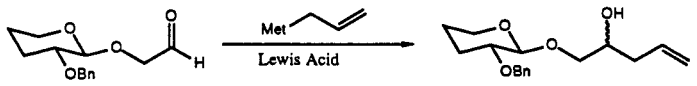


Protecting Group (R)	Diastereomeric ratio (2R:2S)
-Si*i*-Pr$_3$	12 : 88
-Si(*t*-Bu)Ph$_2$	15 : 85
-C(O)CH$_3$	86 : 14
-C(O)C(CH$_3$)$_3$	92 : 8
-C(O)Ph	87 : 13
-C(O)2-Np	86 : 14
-C(O)4-*t*-BuPh	86 : 14
-CH$_2$Ph	93.7 : 6.3
-H	89 : 11

of the ester group were the two predominating factors for high selectivity. A benzyl ether, however, turned out to be the best protecting group under these conditions producing a 93.7:6.3 ratio of diastereomeric alcohols. The sense of induction with esters and with the benzyl ether was the same. Interesting results were obtained when silyl ethers were used as protecting groups. In these cases, *reversal in the sense of induction was observed* and significant levels of induction were also obtained.

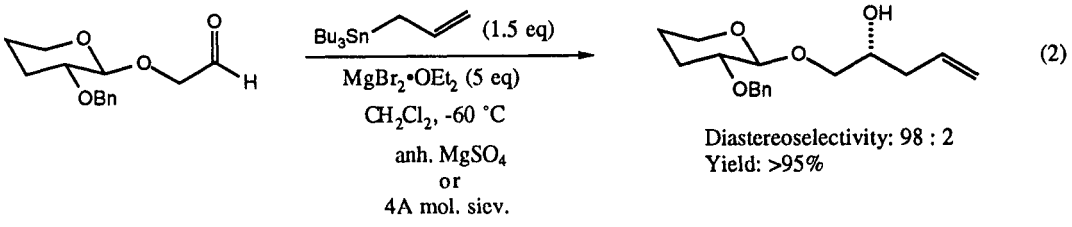
The nature of the metal with the optimal protecting group (benzyl ether) was then investigated (Table 2). As it turned out the reactions of $BF_3{\cdot}OEt_2$, titanium tetrachloride and zinc halide-promoted allyltributyltin addition were almost completely ineffective and gave almost no diastereoselection. The addition of the silane-derived reagent produced also disappointing results. Surprisingly, the addition of the Grignard reagent in the presence of magnesium bromide etherate in ether gave a 1:1 mixture of diastereomers. These results led us to believe that: 1. Mg^{2+} was essential in these reaction probably due to the geometrical requirements for the formation of a tridentate chelate between the metal and the chiral auxiliary; 2. the presence of etheral solvents was unsuitable in these reactions. The use of more sophisticated reagents such as CH_3TiCl_3 or other lanthanide-derived reagents are presently under investigation and will be reported in due course.

Table 2. Effect of the metal in nucleophilic addition to the benzyl protected auxiliary.



Entry	Metal	Lewis Acid	Solvent (°C)	Diastereomeric ratio
1	SnBu$_3$	$BF_3{\cdot}OEt_2$	CH_2Cl_2 (-78)	1.4 : 1
2		$TiCl_4$ (1 eq)	CH_2Cl_2 (-78)	1 : 2
3		$TiCl_4$ (2 eq)	CH_2Cl_2 (-78)	1 : 2
4		$TiCl_4$ (1 eq, rev. adn)	CH_2Cl_2 (-78)	1 : 1
5		$MgBr_2{\cdot}OEt_2$	CH_2Cl_2 (-20)	15 : 1
6		$ZnBr_2$	CH_2Cl_2 (-30)	1 : 2.9
7		ZnI_2	CH_2Cl_2 (-30)	1 : 1.9
8	SiMe$_3$	$BF_3{\cdot}OEt_2$	CH_2Cl_2 (-78)	1.5 : 1
9	MgBr	$MgBr_2{\cdot}OEt_2$	Et_2O (-78)	1 : 1
10		$ZnBr_2$	Et_2O (-78)	1 : 1

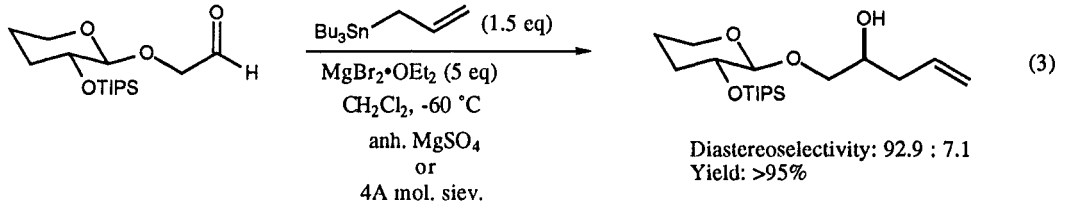
Having determined which was the best protecting group to use along with the optimal metal ion, the reaction conditions were optimized to improve the diastereoselectivity (eq 2).



(2)

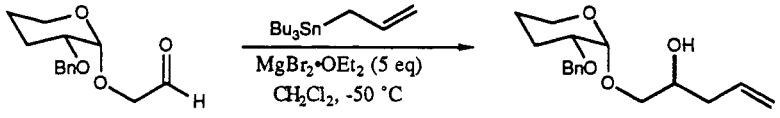
If the reaction was run with a larger excess of magnesium bromide etherate (5 equiv) and at lower temperature (-60 °C), diastereoselectivities in the range of 93:7 to 98:2 were observed. It was also noted that if the reaction was run in the presence of 5 equivalents of H_2O a 94:6 ratio was obtained. It turned out that excellent and reproducible diastereoselectivities were obtained if a drying agent ($MgSO_4$ or 4A mol. siev.) was added to the reaction mixture. The absolute stereochemistry of the newly created stereogenic center was established by cleaving the optically pure chiral auxiliary (*vide infra*) (allyl alcohol, H_2SO_4 (cat.), 100 °C) and comparing the pentenediol derivative to known material.[7] Under the cleaving conditions the precursor to the aldehyde, 2-allyloxy-3-benzyloxy-tetrahydropyran, could be regenerated in a 4:1 (trans:cis) ratio.

The optimized conditions were also applied to the triisopropylsilyl ether auxiliary and the diastereomeric ratio improved to *ca.* 93:7 (eq 3).

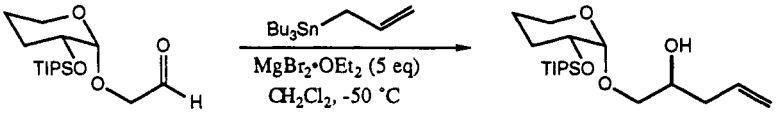


(3)

The effect of the acetal stereochemistry on the sense and level of induction in these reactions was next examined. The corresponding cis-benzyl ether auxiliary (eq 4) reacted under the same reaction conditions to produce the desired homoallylic alcohols in a 96:4 ratio. Gratifyingly, the stereochemistry of the newly created stereogenic center was opposite to that formed with the *trans*-isomer. The *cis*-TIPS ether auxiliary, however, produced a much lower ratio and no reversal in the sense of induction was observed.

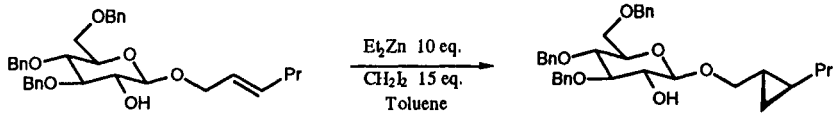


(4)

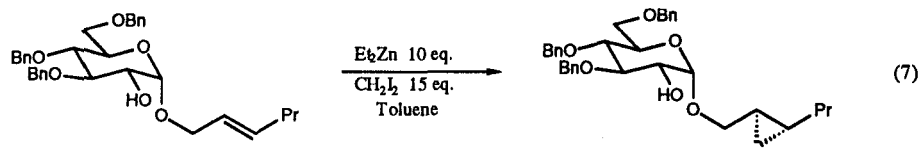


(5)

These observations concerning the relationship between the acetal (or anomeric) configuration and the stereochemistry of the newly formed stereogenic center are consistent with our previous reports regarding the development of a new chiral auxiliary in the cyclopropanation reaction (eq 6,7) (ref. 8)



(6)

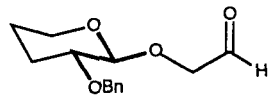


(7)

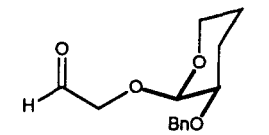
Diastereoselectivity: 23 : 1

These observations can be readily explained if we consider that the cis-isomer is actually a pseudo-mirror image of the trans-isomer if we consider only the key atoms that are presumably involved in the formation of the chelate of the cyclopropanation transition state (bold, Scheme 2).

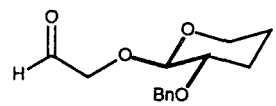
Scheme 2



1*S*, 2*R*-series



1*S*,2*S*-series



1*R*,2*S*-series

The following three chelates are consistent with the observed selectivities in the examples presented above (Figure 3). The C-2 oxygen atom of the trans-benzyl ether auxiliary should presumably participate in the formation of a type A chelate. One face of the aldehyde becomes therefore completely shielded by the phenyl group and nucleophilic attack occurs from the *Re* face. The chelating ability of the C-2 oxygen atom of the trans-TIPS ether auxiliary should be completely inhibited and chelate B is expected to be favored. The lower diastereomeric ratios obtained with this auxiliary may be explained by the fact that the *Re*-face of the aldehyde does not appear to be as efficiently shielded as in the case of chelate A. The formation of chelate C is expected to be formed preferentially with the cis-benzyl ether auxiliary.

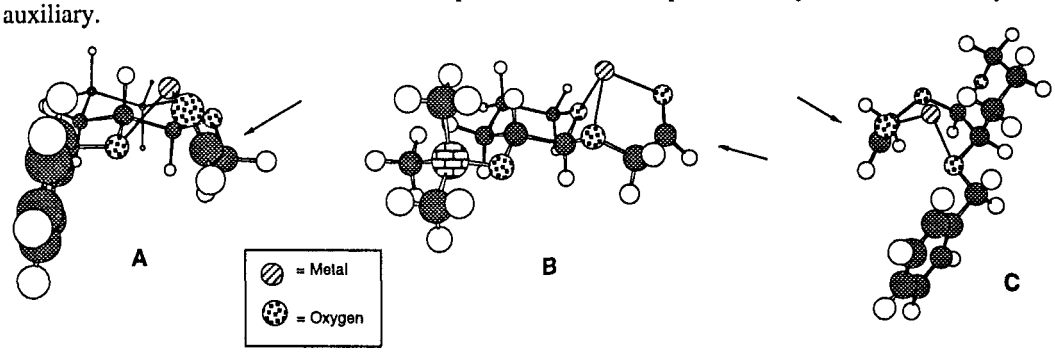
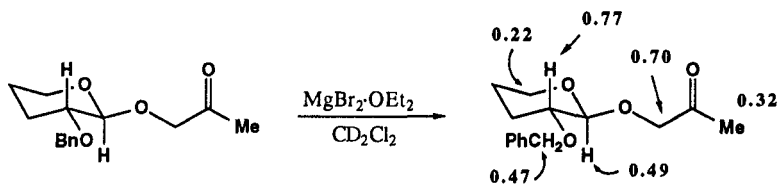


Figure 3

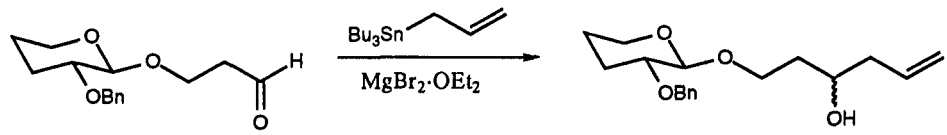
So far, we have been able to obtain only little evidence for the formation of these complexes. When the methyl ketone-derived auxiliary was treated with 1 equivalent of $MgBr_2 \cdot OEt_2$ in CD_2Cl_2 a very complex NMR showing several species was obtained. However, if the ketone was mixed with an excess of $MgBr_2 \cdot OEt_2$ (5 equiv) in the same solvent, the NMR spectrum of the upper layer solution was extremely clean. A first interesting observation is that the anomeric coupling constant went from 3.9 Hz for the free ketone to 7.7 Hz for the chelated species, suggesting that both substituents of the chair are near equatorial. Furthermore all the protons near the oxygen atoms that are thought to be involved in the chelate are strongly deshielded by the following values (ppm):



***J* = 3.9 Hz** ***J* = 7.7 Hz**

These values are consistent with those reported by Eliel for simple α-alkoxyketones (ref. 5). Unfortunately, a similar NMR study with the *trans*-TIPS ether has not been successful thus far.

It is interesting to point out that Keck has shown that the magnesium bromide-mediated allyltributyltin addition reaction has been much less successful in producing the chelation-controlled product in the case of β-alkoxy aldehydes. This was also observed with this auxiliary. Treatment of β-alkoxy aldehyde under the optimized conditions led to a 1.35:1 mixture of diastereomers:



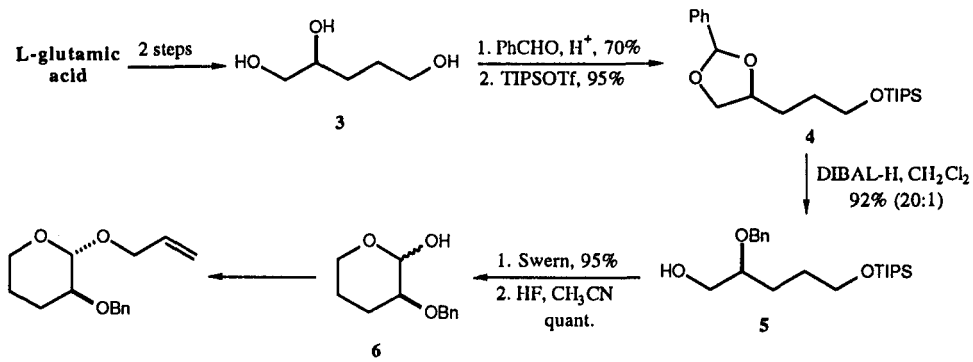
Ratio: 1.35 : 1

We are currently investigating the use of other metal ions that would be more suitable for these reactions.

Due to the promising results obtained so far with these new chiral auxiliaries two syntheses of enantiomerically pure material were developed.

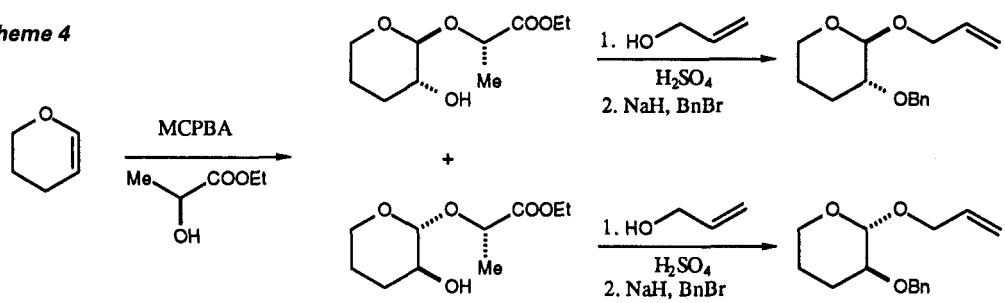
The first one starts with 2*S*-pentane-1,2,5-triol, which is readily available in 2 steps from L-glutamic acid (Scheme 3). Protection of the 1,2-diol as a benzylidene acetal followed by subsequent protection of the primary alcohol afforded silyl ether **4**. Reductive opening of the benzylidene acetal to introduce the 2-benzyloxy substituent proceed smoothly with DIBAL in CH_2Cl_2. Swern oxidation and final deprotection afforded lactol **6** in almost quantitative yield. The allylic side chain was introduced by heating lactol **6** in allyl alcohol containing a trace amount of concentrated sulfuric acid to afford the desired precursor in 4:1 ratio of *trans* and *cis* isomers.

Scheme 3



Alternatively both enantiomers of the benzyl auxiliary can be readily synthesized using Mash's methodology (Scheme 4) (ref. 9). Oxidation of dihydropyran in a mixture of ethyl lactate (10 equivalents) and benzene with MCPBA produced a chromatographically separable mixture of diastereomers. Both diastereomers were then treated with allyl alcohol at 100 °C in the presence of a catalytic amount of sulfuric acid to introduce the allylic side-chain at the anomeric position. Subsequent benzylation produced both enantiomerically pure chiral auxiliaries.

Scheme 4



In summary, we have shown that a remote protecting group can drastically influence the sense and level of the stereochemical induction in the $MgBr_2 \cdot OEt_2$-mediated tributylallyltin carbonyl addition reaction. New and efficient chiral auxiliaries can therefore be developed to provide access to both enantiomers of a secondary alcohol. The use of these enantiomerically pure chiral auxiliaries in this and other nucleophilic addition reactions as well as shorter syntheses of these auxiliaries are in progress and will be reported in due course.

Acknowledgements I would like to thank my co-workers on this project: Christophe Mellon, Langis Rouillard and Éric Malenfant. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, Bio-Méga Inc., F.C.A.R. (Québec). C.M and L.R. thank the FCAR (Québec) and the NSERC respectively for postgraduate fellowships.

REFERENCES AND NOTES

1. (a) W. C. Still and J. H. McDonald III *Tetrahedron Lett. 21*, 1031 (1980),. (b) W. C. Still and J. A. Schneider *Tetrahedron Lett. 21*, 1035 (1980). (c) D. J. Cram and K. R. Kopecky *J. Am. Chem. Soc. 81*, 2748 (1959).

2. For an early review see: (a) M. T. Reetz *Ang. Chem. Int. Ed. Engl. 23*, 556 (1984). For X-Ray structural analyses of α-alkoxycarbonyl/metal chelates see: (b) M. T. Reetz, K. Harms and W. Reif *Tetrahedron Lett. 29*, 5881 (1988). (c) M. T. Reetz, M. Hüllmann and T. Seitz *Angew. Chem. Int. Ed. Engl. 26*, 477 (1987). For NMR and other mechanistic studies see: (d) X. Chen, E. R. Hortelano, E. L. Eliel and S. V. Frye, *J. Am. Chem. Soc. 114*, 1778 (1992) and references cited therein.

3. For chiral auxiliaries involving the temporary formation of an α-stereogenic center see: (a) J. E. Lynch and E. L. Eliel *J. Am. Chem. Soc. 106*, 2943-2948. (b) M. Asami and T. Mukaiyama *Chem. Lett.* 93-96 (1983). (c) Y. Ukaji, K. Yamamoto, M. Fukui and T. Fujisawa *Tetrahedron Lett. 32*, 2919-2922 (1991) and references cited therein. For chiral auxiliaries involving chiral glyoxylate: (d) J. K. Whitesell, A. Bhattacharya and K. Henke *J. Chem. Soc. Chem. Comm.* 988-989 (1982). (e) T. Akiyama, H. Nishimoto, K. Ishikawa and S. Ozaki *Chem. Lett.* 447-450 (1992). (f) Y. Tamai, T. Nakano and S. Miyano *Chem. Lett.* 807-808 (1992). (g) K. Soai and M. Ishizaki *J. Org. Chem. 51*, 3290-3295 (1986). (h) Y. Kawanami, I. Fujita, S. Ogawa and T. Katsuki *Chem. Lett.* 2063-2066 (1989). (i) Y. Kawanami and K. Katayama *Chem. Lett.* 1749-1752 (1990).

4. For the effect of protecting groups on chelation see: (a) S. Shambayati, J. F. Blake, S. G. Wierschke, W. L. Jorgensen and S. L. Schreiber, *J. Am. Chem. Soc. 112*, 697-703 (1990). (b) A. J. Stern and J. S. Swenton *J. Org. Chem. 54*, 2953-2958 (1989). (c) S. D. Kahn, G. E. Keck and W. J. Hehre *Tetrahedron Lett. 28*, 279-280 (1987). (d) G. E. Keck and S. Castellino *Tetrahedron Lett. 28*, 281-284 (1987). (e) S. V. Frye and E. L. Eliel, *Tetrahedron Lett. 27*, 3223-3226 (1986). (f) M. T. Reetz, M. Hüllmann *J. Chem. Soc. Chem. Comm. 21*, 1600-1602 (1986).

5. Eliel has shown that the bidentate chelated species reacts faster than a complexed species: X. Chen, E. R. Hortelano, E. L. Eliel, S. V. Frye *J. Am. Chem. Soc. 114*, 1778-1784 (1992).

6. G. E. Keck and E. P. Boden *Tetrahedron Lett. 25*, 265-268 (1984).

7. The relative stereochemistry of the newly created stereogenic center was established by using the aldehyde derived from optically pure (2*S*,3*R*)-2-allyloxy-3-benzyloxy-tetrahydro-2*H*-pyran, compound prepared from L-glutamic acid. The addition product was converted in 2 steps to known 2*R*-2-benzyloxy-4-pentcn-1-ol ($[\alpha]_D$ +32.9 (*c* 0.996, $CHCl_3$); litt: $[\alpha]_D$ +33.0 (*c* 2, $CHCl_3$), J. Mulzer, and A. Angermann *Tetrahedron Lett. 24*, 2843-2846 (1983)): 1. NaH, BnBr, DMF; 2. allyl alcohol, H_2SO_4 (cat.).

8. A. B. Charette, B. Côté, J.-F. Marcoux *J. Am. Chem. Soc. 113*, 8166-8167 (1991).

9. E. A. Mash, J. B. Arterburn, J. A. Fryling, S. H. Mitchell *J. Org. Chem. 56*, 1088-1093 (1991).