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Protecting Group Controlled Diastereoselective Allylation of Asymmetrized *Bis* (hydroxymethyl)acetaldehydes (BHYMA*)

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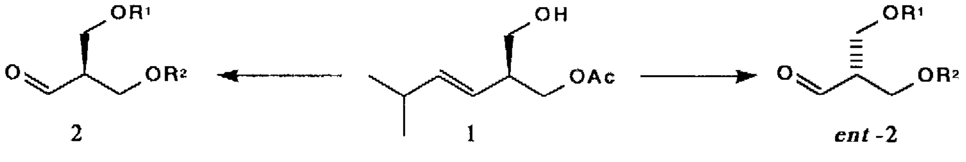
Abstract: $MgBr_2$ catalysed allylation of a series of diprotected asymmetrized *bis*(hydroxymethyl)acetaldehydes **2** with allyltributylstannane proceeds with good diastereoselectivity. The stereochemical results are in line with a cyclic chelated transition state, where only one of the two CH_2OR appendages, due to the different nature of protecting groups, is capable of coordinating the Lewis acid.

We have recently reported the chemoenzymatic preparation in excellent e.e. of monoacetate **1**, which had been in turn converted, in an enantiodivergent manner, into both enantiomers of a series of "asymmetrized *bis*(hydroxymethyl)acetaldehydes" (BHYMA*) **2**.[1] These aldehydes represent a new very promising class of chiral building blocks endowed with peculiar stereochemical properties connected to their latent C_{3v} symmetry.[2a] The development of efficient methodologies for the diastereoselective addition of C-nucleophiles to **2** is crucial for many potential synthetic applications. Since in **2** the two synthetically equivalent CH_2OR branches are distinguished only by R^1 and R^2, the achievement of this goal requires a "protecting group controlled asymmetric synthesis".

We have previously succeeded in obtaining excellent diastereoselectivities in the addition of simple dialkyl lithium cuprates to **2** (R^1= Me_2tBuSi, R^2= Bn-OCH_2) and have applied this methodology to the synthesis of a fragment of Tylonolide. [2] In this communication we now report the extension of this strategy to the addition of allyl-metal compounds to **2** to give homoallylic alcohols, whose great synthetic utility descends from their formal equivalence to aldols.[3] Also in this case our approach is based on placing on **2** two different protecting groups $R^1$and R^2, that can be classified as "chelating"[4] or "non-chelating".[4]

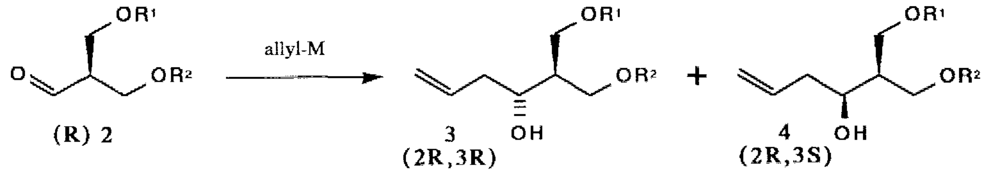
Thus we prepared a series of aldehydes **2a-e** where the "chelating group" is $PhCH_2OCH_2$ (BOM) or *p*-MeO-C_6H_4-CH_2OCH_2 (PMBOM)[5] and the "non-chelating group" is a silyl ether[6] like Me_2tBuSi, Ph_2tBuSi or $(i Pr)_3Si$,[7,8] and studied their reaction with several allyl-metal compounds (Scheme 1 and Table).

While several known allyl-derivatives[9] failed to give acceptable diastereomeric ratios (entries 1-8) we obtained good results by the Lewis acid catalysed addition of allyltributylstannanes.[10] Although Keck[10a] has shown that condensation of allyl-stannanes with racemic 3-benzyloxy-2-methyl-propanal, which is similar to our



BHYMA* **2**, takes place with excellent relative asymmetric induction by employing $SnCl_4$ as the catalyst, in the present case, both with $SnCl_4$ or $TiCl_4$, we experienced extensive decomposition of the aldehydes, perhaps

Scheme 1



a: R^1= Me_2tBuSi; R^2= $PhCH_2OCH_2$
b: R^1= Ph_2tBuSi; R^2= $PhCH_2OCH_2$
c: R^1= Ph_2tBuSi; R^2= p-MeO-C_6H_4-CH_2OCH_2
d: R^1= $(iPr)_3Si$; R^2= p-MeO-C_6H_4-CH_2OCH_2
e: R^1= Me_2tBuSi; R^2= p-MeO-C_6H_4-CH_2OCH_2

Table: Allylation of aldehydes **2a-e**

Entry	Aldehyde	Allyl-M	Solvent	Temp.	Yield[a]	**3** : **4**[b]
1	**2e**	Allyl-MgBr	THF	-78°C	51%	51 : 49
2	**2e**	Allyl-MgBr, $ZnBr_2$[c]	Et_2O	-78°C	44%	50 : 50
3	**2a**	Allyl-Br, $CrCl_2$[c]	THF	-15°C → r.t.	53%	45 : 55
4	**2a**	Allyl-MgBr, Cp_2ZrCl_2[d]	Et_2O	-78°C	46%	63 : 37
5	**2a**	Allyl-MgBr, Cp_2TiCl_2[d]	Et_2O	-78°C	21%	70 : 30
6	**2a**	$(Allyl)_2CuCNLi_2$[e]	THF	-78°C	65%	55 : 45
7	**2a**	Allyl-$SiMe_3$, $MgBr_2$[f]	CH_2Cl_2	-55°C → 0°C	36%	72 : 28
8	**2e**	Allyl-$Sn(Ph)_3$, $MgBr_2$[f]	CH_2Cl_2	-25°C → 0°C	37%	75 : 25
9	**2e**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-25°C → 0°C	73%	84 : 16
10	**2e**	Allyl-$Sn(nBu)_3$, $ZnBr_2$[f]	CH_2Cl_2	-25°C → 0°C	65%	62 : 38
11	**2e**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-78°C → 0°C	70%	**86 : 14**
12	**2a**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-25°C → 0°C	90%	78 : 22
13	**2a**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	toluene	-25°C → 0°C	92%	76 : 24
14	**2a**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-55°C	70%[g]	**83 : 17**
15	**2b**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-78°C	55%[g]	91 : 9
16	**2b**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-78°C → 0°C	92%	**87 : 13**
17	**2c**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f]	CH_2Cl_2	-25°C → 0°C	91%	82 : 18
18	**2c**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f,h]	CH_2Cl_2	-78°C → -20°C	84%	**87 : 13**
19	**2d**	Allyl-$Sn(nBu)_3$, $MgBr_2$[f,h]	CH_2Cl_2	-78°C → -20°C	76%	**85 : 15**

[a] Isolated yields of **3** + **4** (2 steps including ozonolysis); yields of entries 1-8 are unoptimized. [b] Determined by ^1H n.m.r. of crude products in the presence of $Yb(FOD)_3$. [c] see ref. 9a. [d] Cp= cyclopentadienyl (see ref. 9b and 9c). [e] see ref. 9d. [f] 2 equiv. of Lewis acid were used; lowering the amount of catalyst to 1.5 equiv. resulted in slightly lower diastereoselection, while increasing it had no detectable effect. [g] Incomplete reaction: yields calculated on unrecovered **2** (isolated yields: 64% (entry 14) and 40% (entry 15). [h] Carried out in presence of powdered 4 Å molecular sieves.

because of protecting group lability.[10b] Moreover the few literature reports regarding use of these Lewis acids in various condensation with optically pure 3-alkoxy-2-methyl-propanals suggest the possibility of racemization.[11] Finally, in anticipation of extending this methodology to crotyl-derivatives, an unsatisfactory internal asymmetric induction was expected in the $SnCl_4$ catalysed crotylstannane condensations with **2**.[10a]

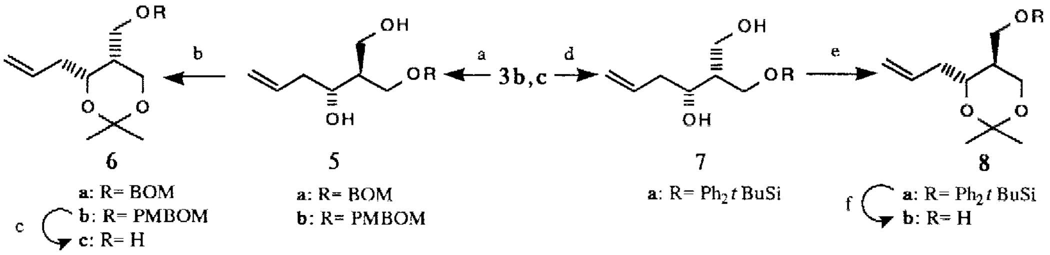
Thus, rather than attempting to find a way to avoid decomposition, for example by using alternative protecting groups, we concentrated on the use of $MgBr_2$, which, on the contrary, provided very clean reactions. As shown in the Table, good diastereoselectivities, accompanied by excellent yields (calculated on 2 steps including ozonolysis) were achieved (entries 11,14, 16, 18, and 19).[12] At -78°C induction resulted higher, but reactions were very sluggish (entry 15); so the best conditions involved addition of reagents at -78°C, followed by slow increase of temperature (during 20 h) to -20°C. The presence of powdered molecular sieves helps the reaction to go to completion. As expected, all the five aldehydes texted gave comparable results, although compounds bearing Ph_2*t*BuSi as the "non-chelating protecting group" afforded slightly better diastereomeric ratios and yields. CH_2Cl_2 turned out to be the best solvent. In every cases the two diastereoisomers could be separated by silica gel chromatography. It should be pointed out that the diastereoselections found in this work were higher than that observed by Keck for the reaction, under the same conditions, of 3-benzyloxy-2-methyl-propanal (70:30 ratio).[10a]

The relative configuration was unambigously established, in the case of **3b** and **3c**, through conversion into *cis* or *trans* *iso*-propylidene derivatives **6** and **8** (see Scheme 2), whose identity was ascertained through ^1H and ^{13}C n.m.r..[13] Homoallylic alcohols **3a**, **3d**, and **3e** were correlated to **3b** and **3c**, by clear t.l.c. and ^1H n.m.r. analogies. The preference for (2R,3R) diastereoisomers can be explained by assuming a cyclic chelated transition state[4] where $MgBr_2$ is coordinated by the carbonyl oxygen and by the CH_2OCH_2OR group. Attack then takes place from the less hindered C=O face.

The transformation of **3c** into **6c** and **8b**, which are epimers, demonstrates once again the peculiar stereochemical properties of asymmetrized *bis*(hydroxymethyl)acetaldehydes **2**.[2a] Although only one diastereoisomer can be directly obtained efficiently from chelation-controlled allylation, the latent C_s symmetry still present in the right hand of **3** allows the diastereodivergent preparation of both epimers of a given compound. Since, as stated before, also the (S) aldehydes **2a-e** are easily accessible,[7,8] all four stereoisomers of *iso*-propylidene derivatives **6c** and **8b** can be prepared (double stereodivergency).[14]

Application of homoallylic alcohols **3a-e** to the synthesis of biologically active compounds is in progress and will be reported in due course.

Scheme 2



6
a: R= BOM
b: R= PMBOM
c: R= H

5
a: R= BOM
b: R= PMBOM

7
a: R= Ph_2*t*BuSi

8
a: R= Ph_2*t*BuSi
b: R= H

a) *n*$Bu_4NF{\cdot}3H_2O$, THF, r.t., 2-3h, 79% from **3b**, 92% from **3c**; **b**) $MeOC(CH_3)=CH_2$, *p*TSA, CH_2Cl_2, 79% (**5a**) or 88% (**5b**); **c**) DDQ, CH_2Cl_2, pH 7 buffer, r.t. 62%; **d**) DDQ, CH_2Cl_2, pH 7 buffer, r.t. 80%; **e**) $MeOC(CH_3)=CH2$, *p*TSA, CH_2Cl_2, 88%; **f**) *n*$Bu_4NF{\cdot}3H_2O$, THF, r.t., 2-3h, 78%.

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4) With the term "chelating protecting group" we mean a group which increases (or at least does not decrease) the Lewis basicity of oxygen, thus allowing, when other conditions are met, the establishment of a cyclic chelated transition state; on the contrary, with "non-chelating protecting group" we denote a group which sensibly decreases (or completely suppresses) the ability of oxygen to coordinate a Lewis acid. For a review on "chelation control" in addition to chiral aldehydes or ketones see Reetz M.T., *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 556.

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6) The low tendency of silyl ethers to coordinate metal ions, both for electronic and steric reasons, is well known. See Chen X., Hortelano E.R., Eliel E.L., and Frye S.V., *J. Am. Chem. Soc.*, **1990**, *112*, 6130, and references therein; Shambayati S., Blake J.F., Wiersche S.G., Jorgensen, W.L., and Schreiber S.L., *J. Am. Chem. Soc.*, **1990**, *112*, 697, and references therein.

7) Although for the sake of brevity Scheme 1 shows only the (R) aldehydes **2a-e**, we have also prepared the enantiomeric (S) aldehydes **2a-d**.

8) Full experimental details on the preparation of **2a-e** are reported in ref. 1c. For (R) & (S) **2a** & **2b** see also ref. 2a & 1a. We anticipate here conditions and yields for the synthesis of the other aldehydes starting from **1**: (R) **2c**: i) Ph$_2$*t*BuSiCl, DMF, imidazole, r.t.; then KOH, MeOH, 83%; ii) PMBOM-Cl, EtN(*i*Pr)$_2$, CH_2Cl_2, 0°C → r.t., 82%; iii) O_3, Me_2S. (S) **2c**: i) PMBOM-Cl, EtN(*i*Pr)$_2$, CH_2Cl_2, 0°C → r.t.; then KOH, MeOH, 0°C, 79%; ii) Ph$_2$*t*BuSiCl, DMF, imidazole, r.t., 84%; iii) O_3, Me_2S; (R) **2d**: i) (*i*Pr)$_3$Si-OTf, 2,6-lutidine, CH_2Cl_2, 0°C; then KOH, MeOH, 83%; ii) PMBOM-Cl, EtN(*i*Pr)$_2$, CH_2Cl_2, 0°C → r.t., 92%; iii) O_3, Me_2S. (S) **2d**: i) PMBOM-Cl, EtN(*i*Pr)$_2$, CH_2Cl_2, 0°C → r.t.; then KOH, MeOH, 79%; ii) (*i*Pr)$_3$Si-Cl, DMF, imidazole, r.t., 89%; iii) O_3, Me_2S. (R) **2e**: i) Me$_2$*t*BuSiCl, DMF, imidazole, r.t.; then KOH, MeOH, 88%; ii) PMBOM-Cl, EtN(*i*Pr)$_2$, CH_2Cl_2, 0°C → r.t., 85%; iii) O_3, Me_2S.

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12) The enantiomeric purity of products was checked on compound **3c**, by synthesis of (S) and (R) Mosher's esters and ^{1}H n.m.r. analysis, which indicated an e.e. > 95%.

13) In particular compounds **6a** and **6b** showed $J_{4\text{-}5}$= 2.6 (**6a**) and 2.4 Hz. (**6b**) and $J_{5\text{-}6}$= 1.7 & 2.8 (**6a**) or 2.6 & 1.7 (**6b**) indicating clearly that H-5 is equatorial and H-4 most likely axial. On the other hand $J_{5\text{-}6}$= 5.0 & 10.5 Hz. in **8a** showed H-5 to be axial. A more detailed discussion of ^{1}H and ^{13}C n.m.r. of these *iso*-propylidene derivatives will be reported in a forthcoming full-paper.

14) For definition of "stereodivergency" see ref. 2a.

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