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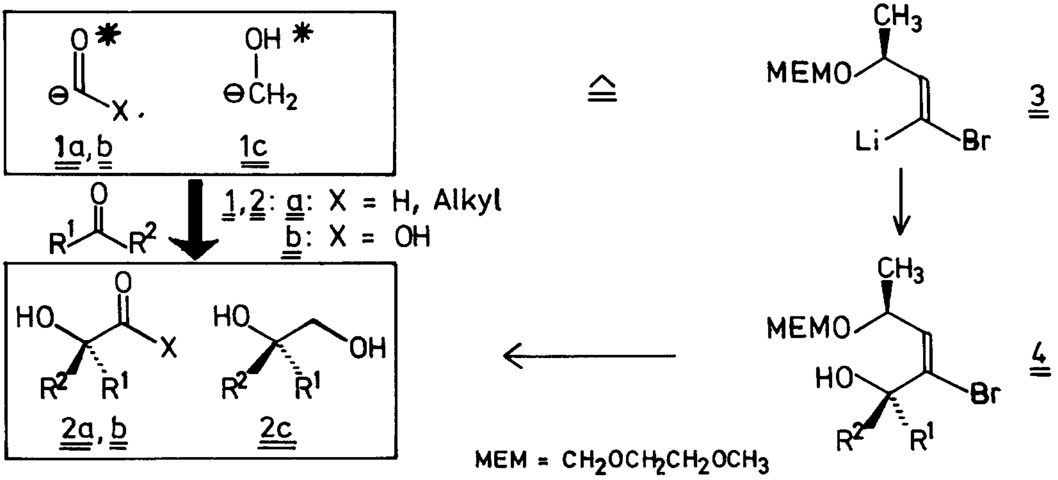
STEREOSELECTIVE ADDITION OF A NOVEL, ENANTIOMERICALLY PURE VINYLLITHIUM REAGENT TO PROCHIRAL CARBONYL COMPOUNDS

Hellmut Mahler and Manfred Braun*
Institut für Organische Chemie und Makromolekulare Chemie der Universität Düsseldorf
Universitätsstrasse 1, D-4000 Düsseldorf, FRG

Summary: The vinyllithium reagent (S)-3, generated from the alkene 6 by bromine/lithium exchange, reacts stereoselectively with prochiral carbonyl compounds. Debromination of the adducts 4/8 affords the (Z)-olefins 11/12, which can be cleaved by ozonolysis.

The addition of α-heterosubstituted carbanions ("d^1-reagents"[1]) to aldehydes or prochiral ketones has become an important stereogenic reaction for forming carbon-carbon bonds[2]. Enantiomerically pure acyloins 2a, α-hydroxy carboxylic acids 2b as well as vicinal diols 2c should be available by using chiral equivalents of aldehyde-, formic acid-, and methanol-d^1-synthons 1a-c. The nucleophilic reagents, developed so far for this purpose[3], are either plagued by tedious preparation[4a] and moderate diastereoselectivity[4b] or applicable to a special problem only[4c]. In this communication, we report on the generation of the enantiomerically pure vinyllithium reagent 3, its highly diastereoselective addition to prochiral carbonyl compounds, and on the oxidative cleavage of the double bond.



Lactic acid, a commercial product available in both enantiomeric forms, is chosen as chiral auxiliary material. Thus, (S)-ethyl lactate is protected as MEM-ether[5] and reduced to the aldehyde 5[6]. Chain extension with carbon tetrabromide[7] affords the alkene 6 as a colorless liquid in 67-75% overall yield (distilled product).

Considering the isomeric lithium reagents 3 and 7, it is evident, that only the (E)-reagent 3 could open a possibility for stereoselective addition, whereas the isomer 7 will have no chance to discriminate between the enantiotopic faces of the carbonyl group. Thus, the specific exchange of the (Z)-bromine atom in 6 versus lithium is the "conditio sine qua non". Fortunately, the desired isomer 3 is formed exclusively, when a slight excess of the dibromide 6 is used (n-butyllithium; diethyl ether; 30 min). Obviously, the thermodynamically favoured reagent 3 is generated by an exchange reaction between the lithiated species 7 and the dibromide 6[8,9]. The addition of the intermediate 3 to benzaldehyde was performed in several solvent systems. The diastereomeric adducts 4a and 8a, whose ratios are shown in table 1, differ significantly in their ^1H- and ^{13}C-NMR-spectra. Tetrahydrofuran (THF) or mixtures of THF and diethyl ether proved to be most suitable, resulting in diastereomer ratios higher than 98:2.

Table 1: Addition of 3 to Benzaldehyde in Different Solvents

Solvent	Temperature	4a : 8a
Isopentane	-115°C	63 : 37
Et_2O	-105°C	89 : 11
THF/Isopentane	-120°C	98 : 2
THF	-100°C	>98 : 2
THF/Et_2O	-105°C	>98 : 2

Under optimized conditions[10], the addition of the vinyllithium reagent 3 to aliphatic aldehydes and to acetophenone was performed. In these cases too, satisfactory diastereoselectivity is obtained (see table 2)[11]. The pure diastereomers 4a-d can be isolated by preparative thin-layer or column chromatography.

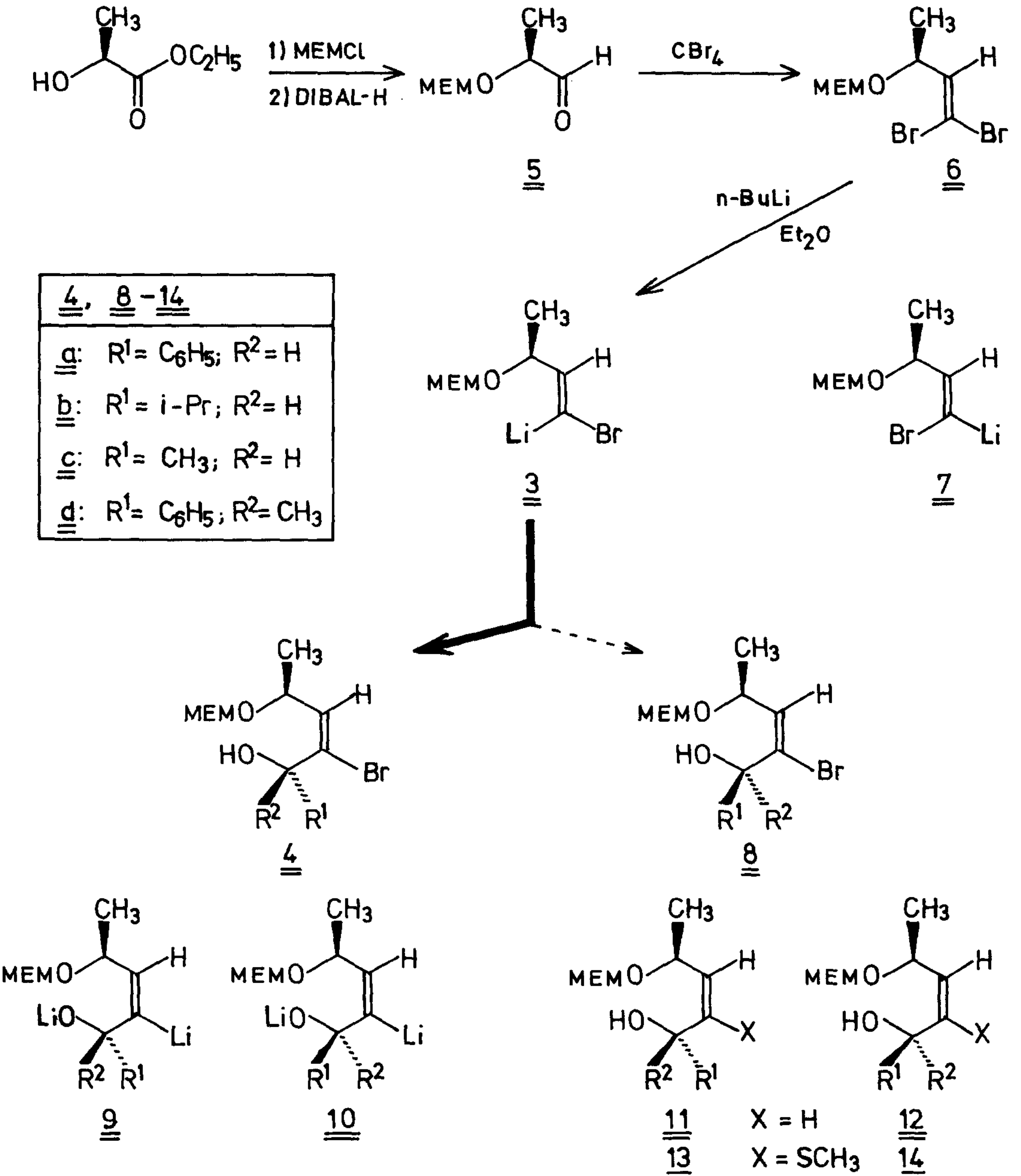
Table 2: Addition of 3 to Several Carbonyl Compounds in THF/Et_2O at -105°C

Carbonyl Compound	Diastereomers 4/8	Yield[a] 4+8	Ratio of Diastereomers 4 : 8
PhCHO	a: R^1=Ph, R^2=H	93%	>98 : 2
$(H_3C)_2CHCHO$	b: R^1=$CH(CH_3)_2$, R^2=H	82%	94 : 6
CH_3CHO	c: R^1=CH_3, R^2=H	84%	91 : 9
$PhCOCH_3$	d: R^1=Ph, R^2=CH_3	93%	>98 : 2

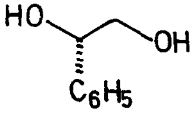
a) The crude products contain 3-5% of the dibromide 6.

By another bromine/lithium exchange reaction, the crude mixture 4a/8a is transformed into the intermediates 9a/10a, which are protonated to give the (Z)-olefins 11a/12a in 90% yield. On the other hand, treatment of the vinyllithium reagents 9/10 with dimethyl disulfide affords the vinyl thioethers 13/14 (43-67%). Since the configuration of the isomers 13a-c has been proven[12], the major products in the addition of 3 have evidently the structures 4a-d[13]. The (S)-reagent 3 attacks the prochiral carbonyl group predominantly from the Re-side.

The cleavage of the double bond in the debrominated olefins 11/12 delivers the desired products 2a-c with oxygen functionality in 1,2 distance. For example, ozonolysis of the crude mixture 11a/12a and subsequent reduction ($NaBH_4$) afford the diol 15 in 95% optical purity[14] besides of



$\underline{\underline{4}}$, $\underline{\underline{8}}$ – $\underline{\underline{14}}$
$\underline{\underline{a}}$: $R^1 = C_6H_5$; $R^2 = H$
$\underline{\underline{b}}$: $R^1 = i\text{-Pr}$; $R^2 = H$
$\underline{\underline{c}}$: $R^1 = CH_3$; $R^2 = H$
$\underline{\underline{d}}$: $R^1 = C_6H_5$; $R^2 = CH_3$



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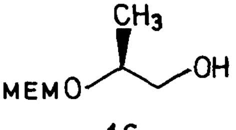

16

MEM = $CH_2OCH_2CH_2OCH_3$

of the chiral auxiliary reagent 16[15], which can be removed by distillation or by chromatography. The use of the (Z)-alkenes 11 as chiral building blocks will be investigated; the reaction of the vinyllithium reagent 9 with other electrophiles should enhance the versatility.

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8) When the dibromide 6 is treated with 1.1 equivalents n-butyllithium, the reagents 3 and 7 are formed in a ratio of 0.47:1. - Similar results were found in the bromine/lithium exchange reaction of dibromonorcarane: D. Seyferth, R. L. Lambert, Jr., J. Organomet. Chem. 55 (1973) C 53.

9) Carboxylation was found to be a reliable method for proving the structures of the carbenoids 3 and 7.

10) Typical procedure: To a mixture of 2.63g 6 (8.27 mmol) and 80ml Et_2O, which is stirred at -105°C under N_2, 4.9ml (7.84 mmol) of 1.6 M solution of n-butyllithium in hexane are added dropwise within 5 min. A colorless precipitate forms gradually, and stirring is continued for 30 min at the same temperature. A solution of 1.0ml benzaldehyde in 20ml THF, cooled to -100°C, is added. The reaction temperature is allowed to reach -70°C within 45 min. After addition of 10ml saturated aqueous NH_4Cl, the usual isolation affords 2.62g (92%) crude 4a/8a (98:2).

11) All new compounds gave correct C,H analyses. - Some characteristic physical and spectroscopic data:

6: $|\alpha|_D^{25}$ = -62.5° (c=1.35; 95% aq. EtOH). - b.p. 52-53°C/0.001Torr. - ^{1}H-NMR (300MHz; δ; $CDCl_3$): 1.28 (d, J=6.6Hz), 6.42 (d, J=8.0Hz). - ^{13}C-NMR: 19.72, 59.02, 67.04, 71.69, 72.84, 90.36, 93.52, 140.30.

4a: $|\alpha|_D^{20}$ = - 193.4° (c=2.2; 95% aq. EtOH). - b.p. 132-136°C/0.001Torr.- ^{1}H-NMR: 1.30 (d, J=6.6Hz), 5.66 (s), 6.03 (d, J=9Hz). - ^{13}C-NMR: 21.31, 58.93, 66.82, 69.19, 71.57, 73.45, 92.97, 126.22, 127.78, 128.24, 130.60, 136.25, 140.44.

12) For 13a: see lit. 4c); for 13b by transformation into (S)-3-hydroxy-2-methylheptanone-4 according to lit. 4c); for 13c by hydrogenation and deprotection to (S,S)-2,5-hexanediol.

13) The configuration of 4d was determined by transformation of 11d into (S)-2-phenyl-1,2-propanediol according to the procedure described for 11a.

14) 82% yield. - $|\alpha|_D^{20}$ = +39.3° (c=2; 95% aq. EtOH); $|\alpha|_D^{20}$ = -41.2° according to R. L. Elsenbaumer, H. S. Mosher, J. Org. Chem. 44 (1979) 600 for (R)-15.

15) 91% yield. - $|\alpha|_D^{25}$ = +11.6°; a sample prepared from (S)-ethyl lactate shows +11.7° (95%EtOH).

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