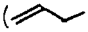
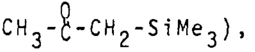
Tetrahedron Letters,Vol.25,No.29,pp 3083-3086,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

ASYMMETRIC CLEAVAGE OF CHIRAL ACETALS BY R_2CuLi,BF_3 REAGENTS

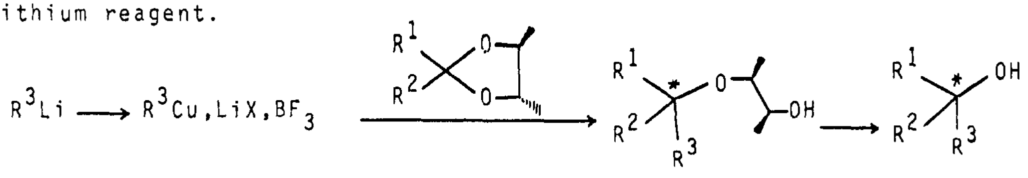
A. Ghribi, A. Alexakis*, J.F. Normant

Laboratoire de Chimie des Organo-Eléments
Tour 44, 4 place Jussieu 75230 PARIS Cédex 05 France

Summary - The title reagents cleave diastereoselectively the acetals derived from various aldehydes and chiral 2-3 butane diol (or higher homologs). This reaction affords an asymetric synthesis of secondary alcohols from an aldehyde and a trivial organolithium reagent.

Asymmetric nucleophilic attack on a carbonyl center is, in theory, an easy way to create a new chiral carbon. For example, the reduction of aryl or alkynyl prochiral ketones by complex chiral metal hydrides has found many applications in organic synthesis[1,2]. However, access to a chiral alcohol by carbon carbon bond formation from an aldehyde or a ketone and an organometallic reagent has met with scarce success[3]. The use of a chiral acetal (usually from the commercially available R,R-2,3-butanediol or R,R-2,-4-pentanediol) in place of the free carbonyl, permits a better diastereoselection. The elegant recent work by Johnson[4], and then Kishi[5] and Yamamoto[6], showed that silicon derivatives ($SiMe_3$, $R\text{-}C{\equiv}C\text{-}Si,Me_3$, $N{\equiv}C\text{-}Si,Me_3$, $CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}SiMe_3$), in the presence of a Lewis acid ($TiCl_4$ or $SnCl_4$) were able to react with such acetals with high asymmetric induction. The diastereomeric excess (d.e.) are usually high (80-96%) and the free alcohol may be easily liberated without loss of enantiomeric purity. Although this methodology has been described only with silyl derivatives, a wide range of synthetic applications may be envisioned.

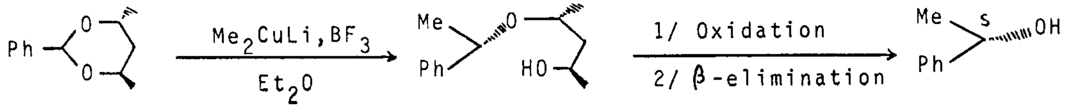
In the preceding note we described that RCu,BF_3 or R_2CuLi,BF_3 reagents are able to cleave acetals with concomitant carbon-carbon bond formation. If these reagents were also able to react with chiral acetals with high diastereoselection a new step in this methodology would be achieved, allowing the introduction of any organic group generated from an organolithium reagent.



We report in this preliminary note our first findings in this area.

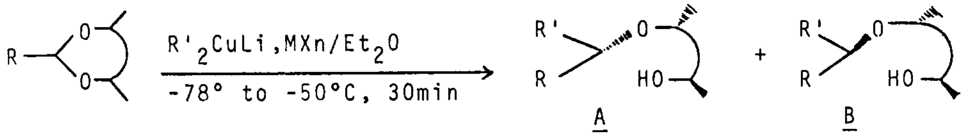
Benzaldehyde acetal derived from R,R-2,3-butanediol was reacted with a threefold excess of Me_2CuLi,BF_3 reagent, in Et_2O, at -78°C (see table, entry 1). After 10min at -78° and 20min at -50° all of the starting material was consumed and two products were obtained, A and B, in a 83.5/16.5 ratio after G.L.C. analysis (product A has the shortest retention time). In order to check if there was any kinetic preference for product A or B, the same experiment was performed, and aliquots were taken every 5min. G.L.C. analysis showed that products A and B were present in the same ratio from the begining up to the end of the reaction, indicating no kinetic diastereoselection. Changing the experimental procedure, by adding $BF_3.Et_2O$ to the mixture of Me_2CuLi and acetal at -70°, did not modify the above result. On the other hand, changing the nature of the organometallic reagent has some influence on the proportion of A and B. RCu,BF_3 (entry 2) was slighly more selective for A and $R_2CuLi,TiCl_4$ (entry 3) was clearly more selective, again for product A. Although in both cases, the yield was low, these results suggest that the observed selectivity depends more on the nature of the Lewis acid than on the type of the organocopper or organocuprate reagent.

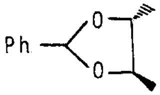
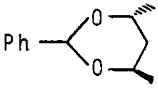
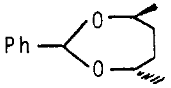
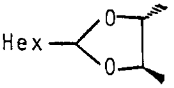
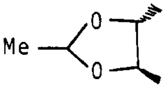
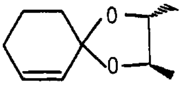
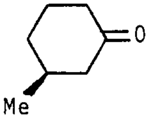
Johnson et al[4a] and Yamamoto et al[6] reported that their asymmetric reaction was greatly improved when six membered ring acetals were used instead of five membered ones. Indeed, when benzaldehyde acetal derived from R,R-2,4-pentanediol was reacted with Me_2CuLi,BF_3 (entry 4), the diastereomeric excess jumped to 91% in favor of product A (with the shortest retention time). A comparison was also made with the seven membered ring, the benzaldehyde acetal derived from S,S-2,5-hexanediol[7] (entry 5). Again, the product with the shortest retention time was the major one with a d.e. of 86%. These results confirm that the six membered ring acetals are the most efficient for such diastereoselective reactions. In fact they are advantageous for two other reasons : a/ both R,R and S,S enantiomers are easily available by asymetric hydrogenation of acetonyl acetone[8], and b/ removal of the chiral auxiliary is easily effected without racemisation. Indeed, the product obtained in entry 4 was flash chromatographied to afford pure isomer A, which was oxidized [9] (oxalyl chloride/DMSO in CH_2Cl_2) and subjected to β-elimination (THF/MeOH/7.5M KOH, +20°, overnight). Pure 1-phenyl-1-ethanol was obtained of S configuration (100% e.e.)[11].



$[\alpha]_D^{25}$:-59.45(c.6.17,pentane)

The configuration of this alcohol indicates that the Me_2CuLi,BF_3 reagent approaches from the Si-face of the masked carbonyl, a result which is in accordance to Johnson's findings[4] with $RSiMe_3/TiCl_4$. The same mechanism may

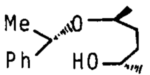
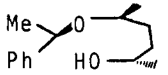


Entry	Acetal	Cuprate	Yield	Ratio A/B[a]	d.e. %
1		Me_2CuLi, BF_3	95%	83.5/16.5	67
2	"	$MeCu, BF_3$	50%[b]	86 /14	72
3	"	$Me_2CuLi, TiCl_4$	48%[b]	94 / 6	88
4		Me_2CuLi, BF_3	93%	95.5/ 4.5	91
5		"	92%	7 /93[c,d]	86
6		"	96%	100/ 0	100
7		Ph_2CuLi, BF_3	94%	100/ 0[c]	100
8	"	Hex_2CuLi, BF_3	89%	100/ 0[c]	100
9		Me_2CuLi, BF_3	71%		ee : 26[f]

a : Determined by capillary glass gas chromatography (OV 1,20m,H_2).Products A and B were base line separated. The indicated ratio is an average of three injections and the values given are ±0.5%.

b : After 3h at room temperature

c : Clean G.C. separation was obtained after conversion into the trimethyl silyl ether

d : In this case the products were A :  , B 

e : The intermediate enol ether was directly hydrolyzed into the ketone (oxalic acid/MeOH/H_2O)

f : $[\alpha]^{25}_{D}$: -3.8(c. 7.0, $CHCl_3$)

also be assumed with the five and seven membered ring acetals (entries 1 and 5) since in all cases the predominent product was the one with the shorter retention time. Confirmation of this assumption may be found in the example in entry 6. Heptanal acetal, derived from R,R-2,3-butanediol reacted to afford only one diastereo isomer. Oxidation (PPC) and treatment with excess

Na in Et_2O at +20° for 4 days[4a] afforded pure S-2-octanol $[\alpha]_D^{25}$:+9.06 (c.15, pentane) (100%) e.e.). Thus the same si-face approach is observed in the five membered ring system.

Acetaldehyde acetal derived from R,R-2,3-butanediol reacted under the usual conditions with Ph_2CuLi,BF_3 and Hex_2CuLi,BF_3 (entries 7 and 8) to afford, in both cases, a single diastereoisomer of opposite configuration, of course, to the ones obtained in entries 4 and 6. Thus, various R_2CuLi,BF_3 reagents may be used successfully in this reaction.

These overall transformations may finally be viewed as a successful enantioselective attack of an aldehyde by any available organolithium reagent.

The extension of this concept to formal conjugate addition was less promising. Reaction of cyclohexenone acetal derived from R,R-2,3-butanediol with Me_2CuLi,BF_3(entry 9) afforded an enol ether, which, after hydrolysis, gave, in 71%, 3-methyl cyclohexanone $[\alpha]_D^{25}$:-3.8°(c.7.0,$CHCl_3$) of S configuration (e.e.:26%). Again attack of the organometallic reagent occured from the si-face. Surprisingly the same reaction with the six membered ring acetal (entry 10) was not stereoselective at all.

A better choice of the chiral diol auxiliary may afford higher selectivities and work is in progress in the field.

Acknowledgements : We thank the CNRS (ERA 825) for financial support.

1. a/ J.P. Vigneron, V. Bloy : Tetrahedron Lett. 2683 (1979)
   b/ M.M. Midland, D.C. McDowell, R.L. Hatch, A. Tramontano : J. Am. Chem. Soc. 102 867 (1980)
   c/ M. Nishizawa, M. Yamada, R. Noyori : Tetrahedron Lett. 22 247 (1981)
2. a/ J.P. Vigneron, R. Méric, M. Dhaenens : Tetrahedron Lett. 21 2057(1980)
   b/ R. Noyori, I. Tomino, M. Nishizawa : J. Am. Chem. Soc. 101 5843(1979)
3. Reaction of RLi with benzaldehyde is a noteworthy exception :
   a/ J.P. Mazaleyrat, D.J. Cram : J. Am. Chem. Soc. 103 4585 (1981)
   b/ D. Seebach in "Modern Synthetic Methods", Ed. R. Scheffold, Salle - Sauërlander, Frankfurt, 1983
   c/ T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, K. Suzuki : J. Am. Chem. Soc. 101 1455 (1979)
4. a/ P.A. Bartlett, W.S. Johnson, J.D. Elliot : J.Am.Chem.Soc. 105 2088(1983)
   b/ W.S. Johnson, R. Elliott, J.D. Elliot : J.Am.Chem.Soc. 105 2904 (1983)
   c/ J.D. Elliott, V.M.F. Choi, W.S. Johnson : J.Org.Chem. 48 2294 (1983)
   d/ V.M.F. Choi, J.D. Elliott, W.S. Johnson : Tetrahedron Lett. 25 591(1984)
5. J.M. McNamara, Y.Kishi : J. Am. Chem. Soc. 104 7371 (1982)
6. A. Mori, J. Fujiwara, K. Maruoka, H. Yamamoto: Tetrahedron Lett. 24 4581(1983)
7. J.K. Lieser : Synthetic Comm. 13 765 (1983)
8. K. Ito, T. Harada, A. Tai : Bull. Soc. Chim. Jap. 53 3367 (1980)
9. A.J. Mancuso, D. Swern : Synthesis 168 (1981)

(Received in France 5 April 1984)