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DIASTEREOSELECTIVE CONJUGATE ADDITION TO CHIRAL α,β ETHYLENIC ACETALS

P. Mangeney, A. Alexakis, J.F. Normant
Laboratoire de Chimie des Organo-éléments, tour 44-45
Université Pierre et Marie Curie, 4 place Jussieu F-75252 PARIS Cédex 05

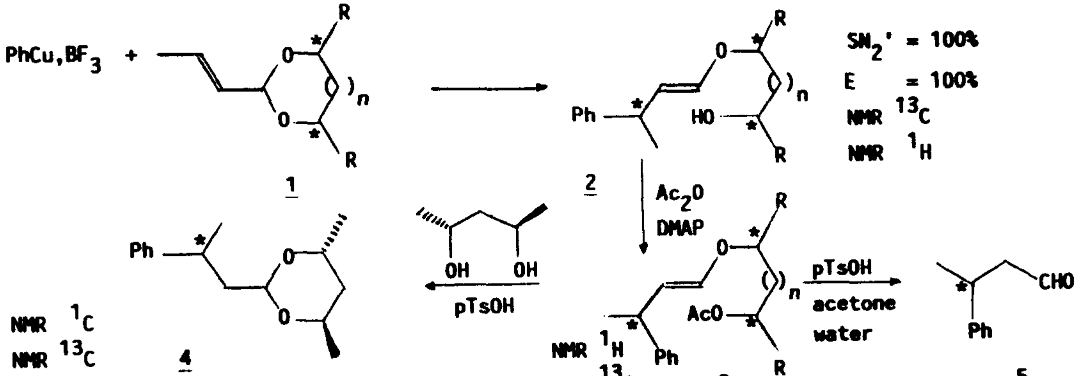
Summary -
The phenyl copper reagent associated with Lewis acid (BF_3) reacts regio (SN_2') and stereoselectively with chiral α,β ethylenic acetals.

The chiral acetals derived from chiral diols with a C_2 axis of symmetry have been recognized as very useful synthons in asymmetric synthesis (1).

In our laboratory, an asymmetric synthesis of secondary alcohols was described using the highly diastereoselective addition of RCu,BF_3 or R_2CuLi,BF_3 reagents on such chiral acetals (2).

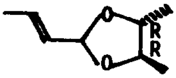
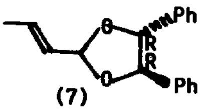
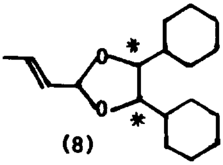
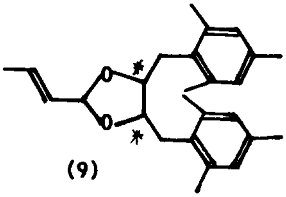
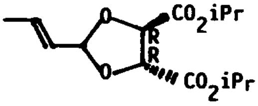
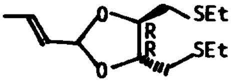
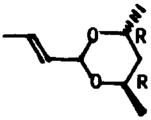
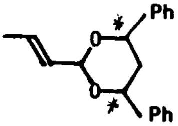
In a recent work, Yamamoto reported either 1,4 or 1,2 addition of organoaluminium reagents to chiral α,β unsaturated acetals with high asymmetric induction (3).

We wish here to describe the conjugate addition of the $PhCu,BF_3$ reagent on several acetals. This study was effected in order to determine the influence of the ring size (n) and the nature of the substituents (R) of the acetal ring (scheme 1).



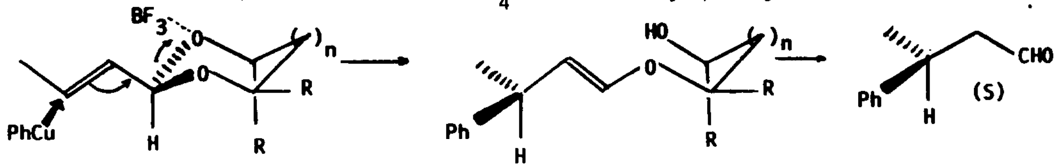
Scheme 1

Acetal 1 (4) was reacted with a two fold excess of $PhCuLiBr,BF_3$ reagent in Et_2O at -78°C. The reaction mixture was allowed to warm up until all of the starting material was consumed.The diastereoselectivity (d.e.) of the reaction was established by NMR ^1H or ^{13}C (250MHz) of the enol ether 2, of the acetate 3 and acetal 4 (obtained by transacetalisation with R-R 2,4-pentanediol) and also by G.C. analysis (5) of this acetal. All d.e. values were in complete agreement with each other. The enantiomeric excess (ee) was measured on aldehyde 5 (in Et_2O). The results of several experiments with a variety of substrates are summarized in the table.

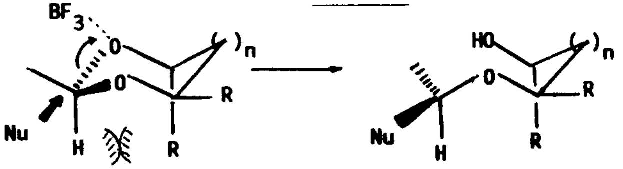
Entry	Acetal 1	Condition (a)	Yield % (b)	d.e. % (c)	Config. of 5	$[\alpha]^{25}_{D}$ (C) (Et_2O)	ee % (6)
1		-20	70	76	S	+29 (10)	73
2	 (7)	15	50	75	S	+29.6(25)	75
3 (d)	 (8)	15	60	73	-	-	-
4 (d)	 (9)	15	74	74	-	-	-
5		-10	67	35	S	+13,4(5)	34
6	 (10)	-20	70	29	S	+11,3(3)	29
7		-20	70	77	S	+29 (5)	73
8 (d)	 (11)	15	76	58	-	-	-

a/ temperature at the end of the reaction ; b/ isolated aldehyde or enol ether 2 (entry 3,4,8) ; c/ by NMR and G.C. ; d/ The reaction was performed on the racemic mixture ; yield of isolated enol ether 2 ; d.e. was measured by NMR.

Only SN_2' addition is observed and the stereochemistry of the enol ether 2 is always 100% E. In all cases where the substituent of the acetal ring do not bear any heteroatom (entry 1,2,7), the copper reagent approaches from the face of the double bond which is on the side of the equatorial substituent. The C-O bond which is the nearest of the axial substituent is cleaved, according to an overall anti SN_2' process (12) (Scheme 2).
The selectivity of the acetal cleavage was mainly attributed, by Johnson (13), to H-CH_3 diaxal interactions (Scheme 3) in the $TiCl_4$ mediated ring opening of saturated acetals.

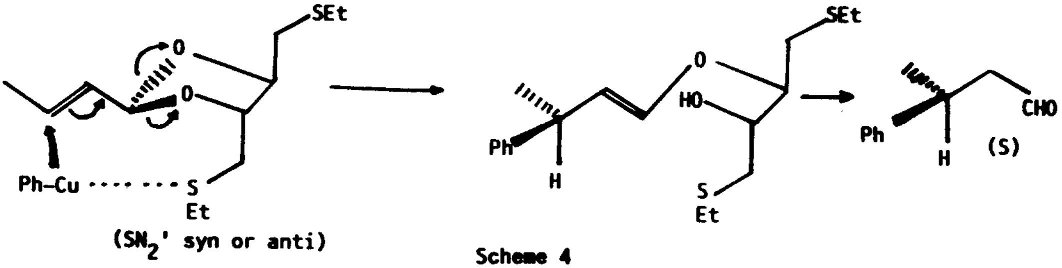


Scheme 2



Scheme 3

Variation of the steric hindrance of R (entry 1,2,3,4 and 7,8 on the other hand) does not affect dramaticaly the diastereoselectivity of the reaction neither does the size of the acetal ring (entry 1 and 7 or entry 2 and 8).
In cases where the substituent of the acetal ring bear an heteroatom (entry 5,6) we have used an auxiliary alcohol of reverse stereochemistry. The copper reagent approaches now from the face of the double bond which is on the side of the pseudo-axial substituent. The stereoselectivity of the addition is therefore the reverse. This result may be explained by a complexation of the copper reagent by the heteroatom. This effect interferes with the steric hindrance and this fact can account for the low d.e. observed (Scheme 4)



Scheme 4

In conclusion, it appears that $PhCu,BF_3$ is an efficient reagent for a clean SN_2' attack with a good diastereoselectivity. Alkylcopper reagents react differently and further studies will be reported in futur papers.

Acknoledgements -

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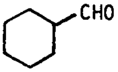
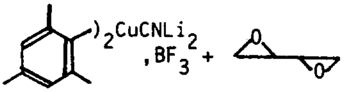
J. Org. Chem., 41, 260 (1976) Using 

(9) 

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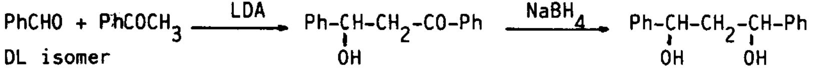
(11) 

$$PhCHO + PhCOCH_3 \xrightarrow{LDA} Ph\text{-}\underset{OH}{CH}\text{-}CH_2\text{-}CO\text{-}Ph \xrightarrow{NaBH_4} Ph\text{-}\underset{OH}{CH}\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}Ph$$

and isolation of DL isomer

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