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DIASTEREOSELECTIVE CONJUGATE ADDITION WITH ACETALS, OXAZOLIDINES AND IMIDAZOLIDINES AS CHIRAL AUXILIARIES

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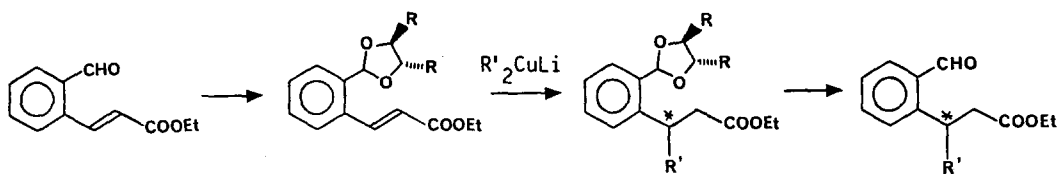
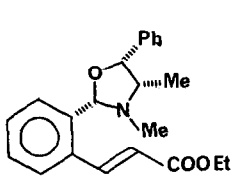
Abstract - *Organocopper reagents undergo highly diastereoselective conjugate addition on cinnamates bearing a chiral oxazolidine or imidazolidine ring.*

Chiral acetals with a C_2 axis of symmetry are very useful auxiliaries in asymmetric synthesis. We have already published their diastereoselective cleavage by RCu,BF_3 reagents[1]. We have, now, explored their influence on the diastereoselective conjugate addition of cuprates to α,β-ethylenic esters bearing this chiral moiety with the following model system :

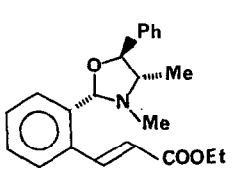


R = Me, Ph, $-CH_2OMe$

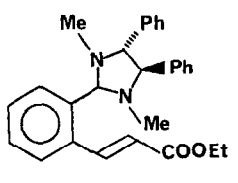
In this case, the chiral acetal group may act by its chelating ability or by its steric interaction. It turned out, however, that this reaction affords only low diastereomeric excesses (15-20%) with Me_2CuLi under a variety of conditions. We were, thus, led to study the replacement of one or two oxygen atoms of the acetal ring by a nitrogen atom, which would be a better σ donnor than oxygen or a more crowded steric center. Thus, the following structures have been examined, prepared respectively from (-)Ephedrine (for 1), (+) Pseudoephedrine (for 2), (R,R)(+) 1,2-bis N-methylamino-1,2-diphenyl ethane[2] (for 3) and (R,R)(-)1,2-bis N-methylamino cyclohexane[3] (for 4).



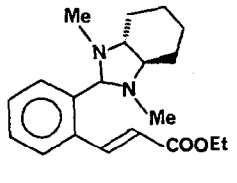
1



2

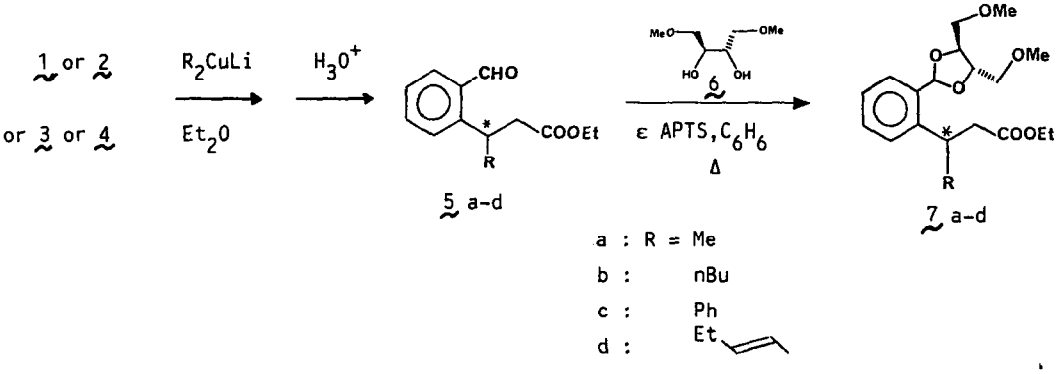


3



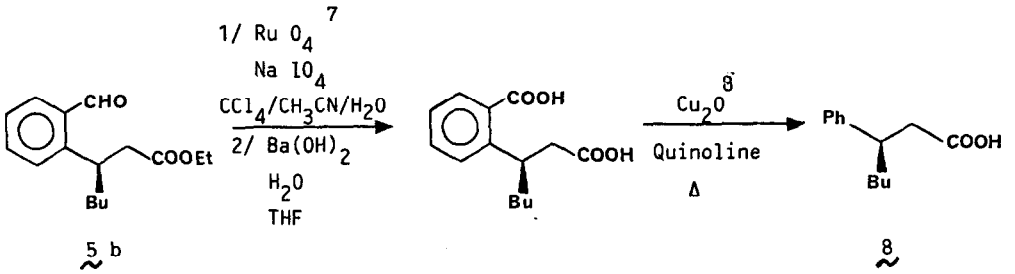
4

Conjugate addition of R_2CuLi, in Et_2O, takes place smoothly, around 0°C, and the crude adduct is hydrolyzed directly to the aldehydes 5a-5d[4]. The enantiomeric excess was determined by ^1H and ^{13}C NMR spectroscopy, after acetalisation with (S,S)1,4-dimethoxy-2,3 butanediol 6 :

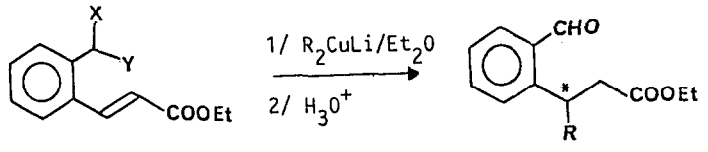


a : R = Me
b : nBu
c : Ph
d : Et

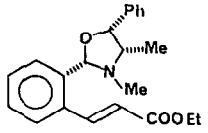
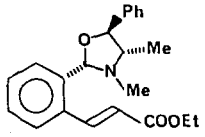
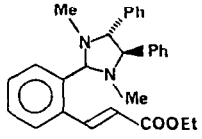
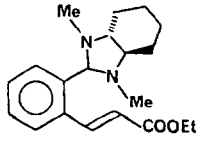
The absolute stereochemistry of the newly created stereogenic center was ascertained by comparison with a known compound 8[5] through the following sequence[6]:



The results of this study are shown in the table. It is clear that structure 4, derived from (R,R)(-)1,2-bis N-methylamino cyclohexane is the most efficient one for both asymmetric induction, and yields of conjugate addition. As compared to 4, compound 1 obtained from (-)Ephedrine as auxiliary, affords steadily the opposite enantiomer of 5 a-d. Therefore 1 was tested purposedly with all types of cuprate reagents in order to get both enantiomers of 5 a-d and thus to achieve a more accurate NMR determination of d.e. for compounds 7.

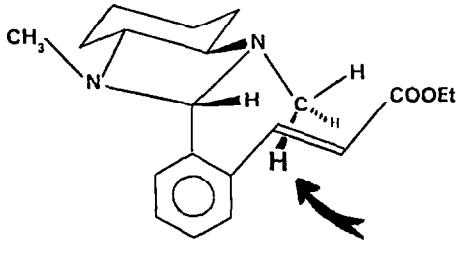


1, 2, 3, 4 — 5 a-d

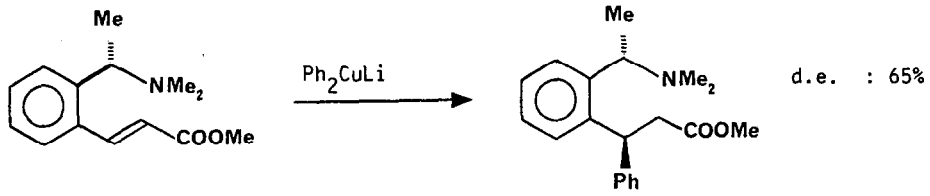
	Starting enoate		Me_2CuLi	Bu_2CuLi	Ph_2CuLi	$Et\!\!\rangle_2CuLi$
			5a	5b	5c	5d
1		Yield %	51	68	73	73
		e.e. %	**55**(R)	**62**(R)	**98**(S)[a]	**82**(S)[a]
2		Yield %	43	65		
		e.e. %	**93**(S)	**70**(S)		
3		Yield %	57			
		e.e. %	**78**(R)			
4		Yield	85	90	84	80
		e.e. %	**94**(S)	**95**(S)	**96**(R)[a]	**90**(R)[a]

a : This inversion of configuration is only due to the CIP selection rules and not to the steric course of the reaction.

The most striking aspects of these various chiral auxiliaries is that with the same absolute stereochemistry compounds 3 and 4 gave opposite enantiomers of 5a. Examination of molecular models shows that the bicyclic nature of 4 creates a rigid molecule where the steric hindrance is the predominant factor and can explain the absolute stereochemistry of the obtained product



On the other hand, in compound 3, the steric aspects are efficiently counterbalanced by the chelating ability of one of the two N atoms of the ring thus leading to the reverse stereochemistry of the adduct 5a. Such a chelation effect has already been demonstrated by C. Ullenius et al[9] in a very close system, having a built-in chiral center :



As for oxazolidines 1 and 2, they both differ only by the stereochemistry at C5 (oxazolidine numbering)[10]. If we assume, here again, a chelation control of the reaction, by the oxygen atom of the oxazolidine ring[11], it is easy to understand the reversal of stereochemistry for the corresponding adducts 5.

As compared to dioxolanes, imidazolidine rings, are quite interesting chiral auxiliaries. The starting chiral diamines are very easily obtained[2] and they are also very easily recovered. A major advantage stems from the presence of a C2 axis of symmetry which saves up a stereochemical control during the formation of the imidazolidine ring, as is the case with oxazolidines[9]. The use of imidazolidines as chiral auxiliaries is actively studied in our laboratory and further results will be soon reported.

Acknowledgements -

The authors thank Prof. C. Ullenius for stimulating discussions and the C.N.R.S. (U.A. 473) for financial support.

References -

1. For an overview see : A. Alexakis, P. Mangeney, A. Ghribi, I. Marek, R. Sedrani, C. Guir, J. Normant : Pure and Appl. Chem. 60 49 (1988)
2. P. Mangeney, F. Grojean, A. Alexakis, J. Normant : Tetrahedron Lett. 0000 (1988)
3. M. Fiorini, G.M. Giongo : J. Molec. Catalysis 5 303 (1979)
4. Reactions with 4 are hydrolyzed directly with HCl 1N. With 1, 2 and 3, the reaction is hydrolyzed with aqueous NH_4Cl/NH_4OH and the crude oxazolidines treated with acid silica gel according to : P. Mangeney, A. Alexakis, J. Normant : Tetrahedron 40 1803 (1984)
5. A.I. Meyers, C.E. Whitten, Heterocycles, 4, 1687 (1976)
6. The absolute configuration of the asymmetric carbon atom of compounds 5a, 5c and 5d is assumed to be as indicated in the table, by analogy with the corelation established for compound 5b.
7. P.H.J. Carlsen, T. Katsuki, V.S. Martin, K.B. Sharpless, J. Org. Chem., 46, 3936 (1981)
8. M. Nilsson, Acta. Chem. Scand., 20, 423 (1966)
9. C. Ullenius, B. Christenson : Pure and Appl. Chem. 60 57 (1988)
10. C. Agami, T. Rizk : Tetrahedron 41 537 (1985)
11. It is usually admitted that in 1,3 oxazolidines, the O atom is a better donating group than N. See for ex. : J. Ficini, H. Normant : Bull. Soc. Chim. France 1454 (1957)

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