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CHIRAL AMINAL TEMPLATES 3[1]. DIASTEREOSELECTIVITY OF ORGANOMETALLIC ATTACK ON ALDEHYDES BEARING A CHIRAL IMIDAZOLIDINE GROUP

A. Alexakis*, R. Sedrani, J.F. Normant and P. Mangeney

Laboratoire de Chimie des Organoéléments, CNRS URA 856
Université P et M Curie, 4 Place Jussieu, F-75252 Paris Cedex 05, France

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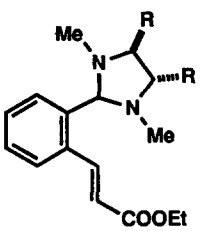
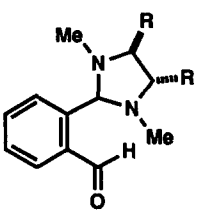
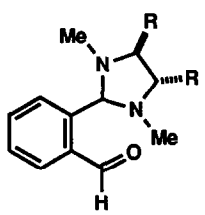
Abstract *Monoprotected phthalaldehydes 3 and 4, bearing a chiral imidazolidine auxiliary were reacted with various organometallic reagents Lithium organocuprates gave almost exclusively one diastereomer whereas an organomanganese reagent gave the opposite one Hydrolysis of the aminal moiety affords the enantiomerically pure lactols 7a-d. In both 3 and 4 the chiral imidazolidine auxiliary is very effective, but affords opposite results which are rationalized by chelation and/or steric factors*

In the course of our studies on chiral 1,2-diamines, having a C_2 axis of symmetry[2], we have recently described the use of chiral imidazolidines, as auxiliaries, in conjugate addition reactions[1] The results obtained on the model cinnamate system **1** and **2** were extended to other enones and enoates with equal success[3] The conjugate addition of an organometallic reagent to an enone and the direct attack of a carbonyl group do not obey to the same rules, their mechanisms are intrinsiqually different The aim of the work presented herein is to compare the stereochemical effects of a chiral imidazolidine in both these reactions using a similar model system The most closely related compound to cinnamates **1** and **2**, are aldehydes **3** and **4**[4] However, **1** and **2** are conformationally stable in the "exo" conformation, shown in the scheme, whereas aldehydes **3** and **4** are almost equally stable in both conformations A and B





A



B

1 R = Ph

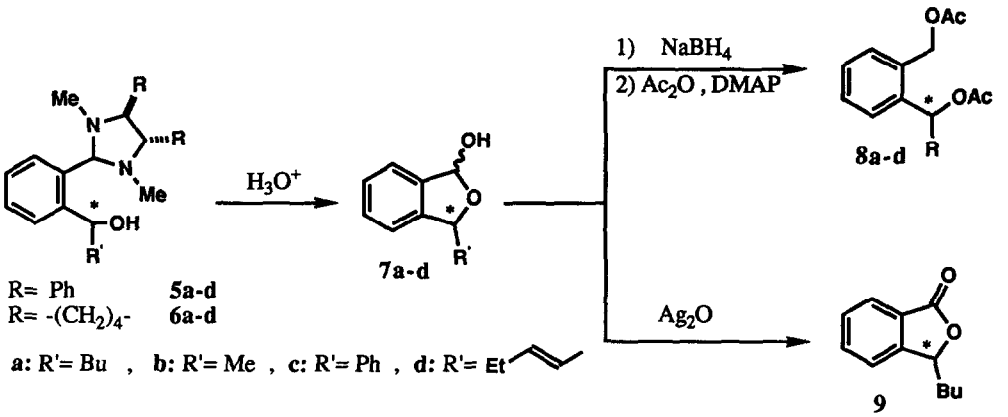
2 R,R = -$(CH_2)_4$-

3 R = Ph

4 R ,R = -$(CH_2)_4$-

Only conformation A is analogous to cinnamates **1** and **2**. As for our previous study[1], we used, as homochiral auxiliaries, two diamines 1,2-bis *N*-methylamino-1,2-diphenyl ethane for **3** and 1,2-bis *N*-methylamino cyclohexane for **4**

Aldehydes **3** and **4** were reacted with various organometallic reagents, among which the most significant are shown in the table The reaction products **5a-d** and **6a-d**, were submitted to acid hydrolysis to remove the chiral auxiliary, and to recover the diamine The obtained lactols **7a-d** were reduced and acetylated to the diacetates **8a-d** in order to determine the enantiomeric excess by ^{1}H NMR with the chiral shift reagent[5] (Eu(hfc)$_3$) Alternatively, the lactol **7a** was oxidized to the known lactone **9** [6] , the comparison of the optical rotation allowed, thus, the determination of the absolute configuration



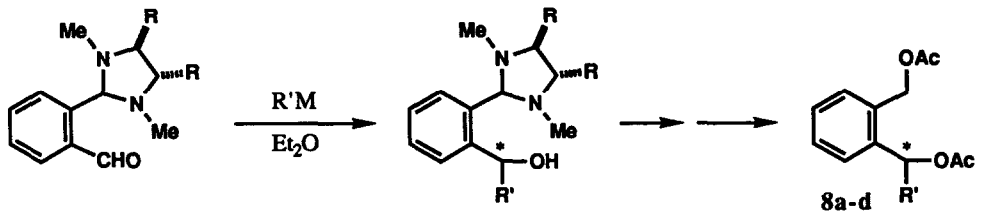
With aldehyde **3**, organolithium and Grignard reagents, in Et_2O, are moderately selective Remarkably, lithium dibutyl cuprate (entry 4), a reagent which is not especially used for carbonyl attack, affords only one detectable enantiomer[7] All three reagents led to the same major enantiomer In contrast, butyl manganese bromide[8] gave the opposite enantiomer almost exclusively (entry 3) !

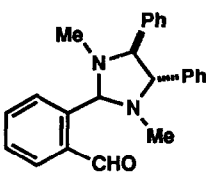
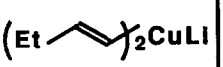
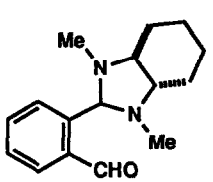
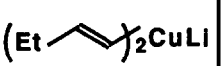
Other organocuprates gave variable results, Me_2CuLi (entry 5) being excellent, whereas Ph_2CuLi (entry 6) is almost non-diastereoselective Such a variability is not encountered with R_2CuLi and aldehyde **4**, having a different imidazolidine auxiliary All organic groups of R_2CuLi afforded an excellent diastereoselectivity in this case

The stereochemical results obtained herein are in complete contrast to those obtained with our previous cinnamate model[1] If our proposed explanations were correct (chelation control with cinnamate **1** and steric control on cinnamate **2**), that would mean that aldehydes **3** and **4** react in a different conformation than cinnamates **1** and **2** *viz* endo conformation **B** instead of exo conformation **A** Indeed, if we assume that the carbonyl attack occurs frontside[1] with a 109° angle (Burgi-Dunitz angle)[9], it is easy to understand that such a nucleophilic attack on conformer **A** is more sterically hindered than on conformer **B**[10]

It, thus, appears that in 1,2 carbonyl attack, as in our previous 1,4 conjugate addition, the chiral imidazolidine template acts as an efficient auxiliary in asymmetric reactions Moreover, as described in the next letter, chiral imidazolidines are equally effective when placed on the nucleophile instead of the electrophile In both cases, the diamine, through formation of an aminal, acts as a protecting group of an aldehydic carbonyl

TABLE

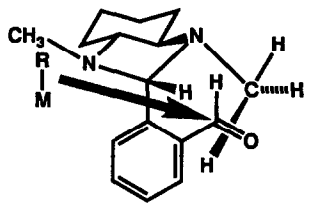


Starting aldehyde	Entry	Organometallic reagent R'M	Product	Overall chemical yield[a] %	Optical yield[b] %	Absolute configuration
 3	1	BuLi	8a	72	40	S
	2	BuMgCl	8a	67	68	S
	3	BuMnBr	8a	64	99	R
	4	Bu_2CuLi	8a	70	100	S
	5	Me_2CuLi	8b	71	100	S
	6	Ph_2CuLi	8c	72	9	S
	7		8d	73	44	S
 4	8	Me_2CuLi	8b	55	90	R
	9	Bu_2CuLi	8a	89	90	R
	10	Ph_2CuLi	8c	70	98	R
	11		8d	42	72	R

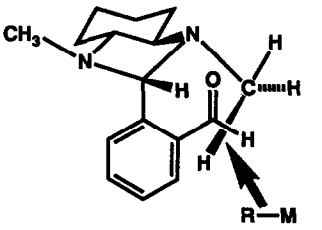
a) Yield of isolated diacetates 8a-d

b) Based on the value of the chiral diamine e e 88-100%

functionality The C_2 axis of symmetry of the starting diamine allows a great simplification of the elements of stereocontrol[11]



A



B

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   Part 2 Alexakis, A , Sedrani, R , Mangeney, P *Tetrahedron Lett* , **1990**, *31*, 0000
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4. Aldehydes **3** and **4** are prepared, in Et_2O, by stirring an equimolecular amount of *o*-phthalic dialdehyde and diamine, at room temperature, in the presence of molecular sieves 4 Å After 0 5-2h, the reaction is completed, the sieves are filtered off, and the solvent evaporated. **3** is obtained in 95% yield after column chromatography and **4** in 96% yield after Kugelrohr distillation
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7. There are few reports on the higher diastereoselection of organocopper reagents in aldehyde attack, as compared to other organometallic reagents See, among others
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   b) Burgi, H B *Ang Chem Int Ed Engl* , **1975**, *14*, 460
10. Davies, S G , Goodfellow,C L , *Synlett* , **1989**, 59
11. Whitesell, J K *Chem Rev* , **1989**, *89*, 1581