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Regio- and diastereoselective S_N2' or S_N2'' reactions on chiral acetals of cyclic aldehydes promoted by PhCu, BF_3

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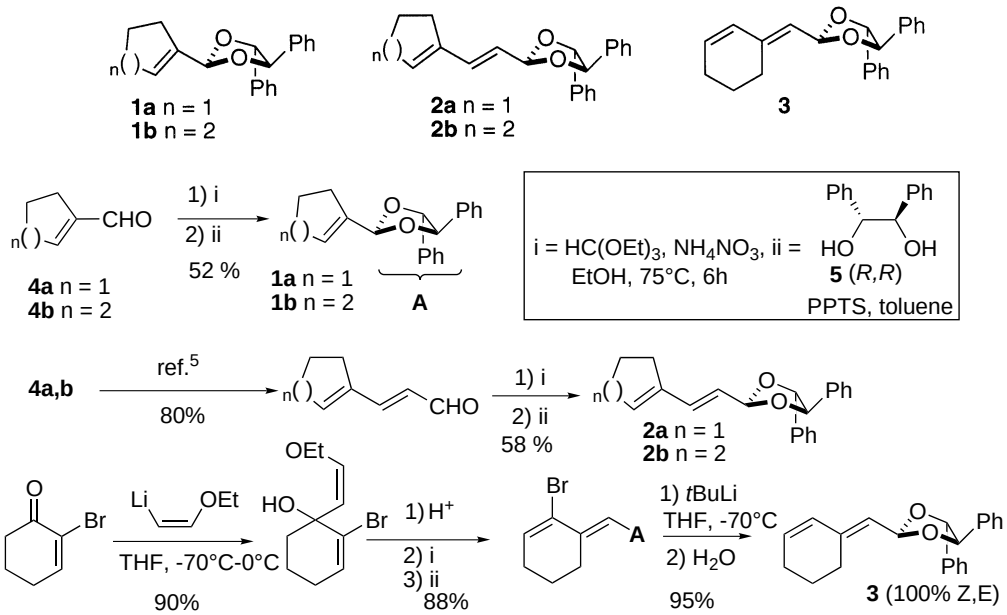
Abstract—The regio- and diastereoselectivity of the addition of PhCu, BF_3 reagent on chiral acetals derived from several mono or dienic aldehydes was studied. It was found that monoethylenic acetals react regio- and diastereoselectively via an overall *anti* S_N2' reaction. The regioselectivity observed with the dienic acetals seems to be strongly dependent on the nature of the acetal. In all cases the S_N2''reaction was the result of an *anti* process. © 2001 Elsevier Science Ltd. All rights reserved.

Acetals prepared from chiral non-racemic diols with C_2 symmetry have been intensively used in asymmetric synthesis.[1] We have already reported regio- and diastereoselective S_N2' and S_N2'' reactions on ethylenic or dienic acetals derived from acyclic aldehydes, promoted by vinyl or aryl organocopper reagents in the presence of BF_3.[2] In this communication, we wish to report the preliminary results obtained by using acetals **1a**–**1b**, **2a**–**2b** and **3** derived from cyclic aldehydes.

Acetals **1a**–**1b** were obtained, respectively, from 1-cyclohexene-1-carboxaldehyde **4a** or 1-cyclopentene-1-carboxaldehyde[3] **4b** and the (*R*,*R*)-diol **5**[4] (Scheme 1). From these aldehydes we have also prepared acetals **2a**–**2b** (Scheme 1) using the Bellassoued procedure,[5] acetalisation and then transacetalisation. The isomerically pure acetal **3** was prepared from 2-bromo-cyclohexene-2-one (Scheme 1).

$BF_3{\cdot}Et_2O$ was slowly added at −30°C to acetals **1a**–**1b**,



Scheme 1.

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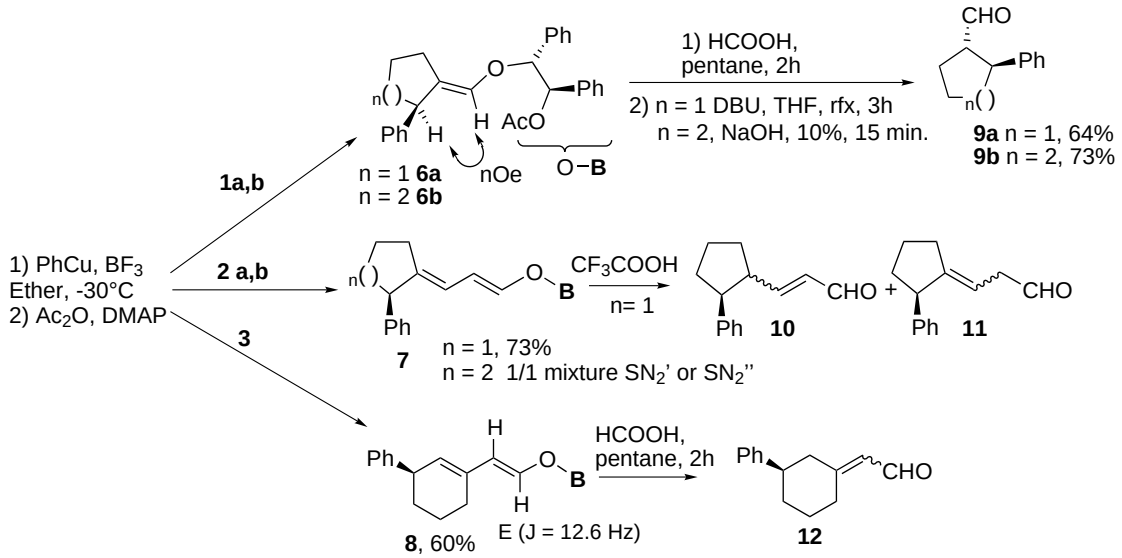
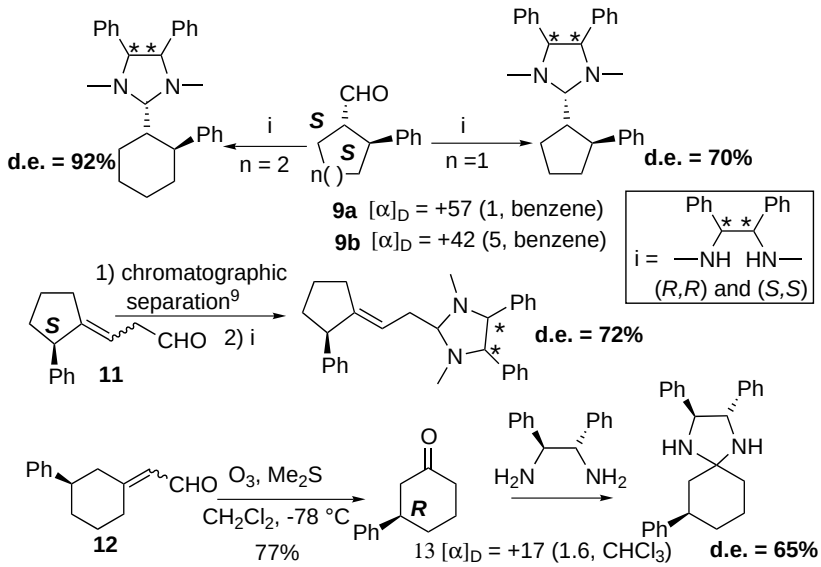
2a–**2b** or **3** in the presence of phenyl copper reagent (prepared in ether from iodobenzene, 2 equiv. *tert*-BuLi and then $CuBr{\cdot}SMe_2$) to give, after acetylation, the corresponding enols ethers resulting from S_N2' or S_N2'' reactions (Scheme 2). The monoethylenic acetals **1a** and **1b** yielded to the corresponding S_N2' enol ethers **6a** and **6b**. The (*E*)-stereochemistry of the double bond was determined by ^1H NMR (NOE experiments). The acetal **2a** yielded regioselectively to the dienic dienol **7** resulting from a S_N2'' reaction. The (*E*,*E*)-stereochemistry of the double bonds was determined by X-ray analysis[6] of the crystals (73% yield) obtained from the crude compound. The reaction with acetal **2b** was not regioselective and a 1:1 mixture of enol ethers resulting from S_N2' or S_N2'' reactions was obtained. With the acetal **3**, the reaction was again regioselective to give the enol ether **8** from S_N2'' reaction. The (*E*)-stereochemistry of the exocyclic double bound was determined by ^1H NMR (Scheme 2). All enol ethers were hydrolysed under acidic conditions (HCOOH, pentane) to give the corresponding aldehydes. Starting from **6a**–**6b**, a mixture of *cis*- and *trans*-2-phenylcyclohexane-(or cyclopentane-) carbaldehydes was obtained. Isomerisation according to Scheme 2 yielded *trans*-aldehydes **9a**–**9b**. The hydrolysis of **7a**–**7b** under the same conditions gave, in both cases, a complex mixture. Using trifluoroacetic acid on **7a**, a quantitative formation of a 1:1 mixture of *cis*- and *trans*-conjugated aldehydes **10** and non-conjugated aldehyde **11** was obtained. From **7b**, a complex mixture was again obtained. A mixture of (*E*)- and (*Z*)-aldehydes **12** was obtained from **8** by treatment with formic acid.

Absolute configurations of the aldehydes **9a**–**9b** were determined by comparison of specific rotation values with reported data (Scheme 3).[7] The absolute configura-



Scheme 2.

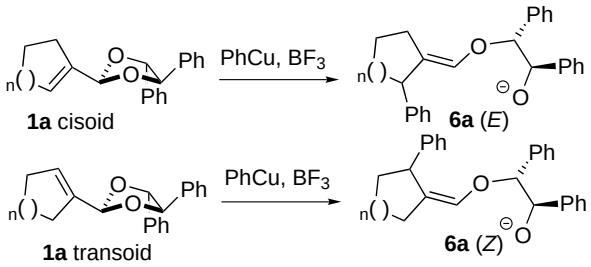


Scheme 3.

tion of the new stereogenic centre in **7a** was determined from X-ray crytallographic analysis (Fig. 1). The mixture of aldehydes **12** was transformed into the known 3-phenyl cyclohexanone[8] **13** by ozonolysis (Scheme 3). The diastereoisomeric excesses of these compounds were determined according to our previously reported procedures.[9] All values are shown on Scheme 3.

From these results, we were able to determine the stereochemical outcome (*anti* or *syn*) of the substitution reactions. The (*Z*)- or (*E*)-stereochemistries of the double bonds of the enol ethers reflect the reactive conformation of the starting acetal.[1] For example, cisoid or transoid acetals **1a** are, respectively, precursors of (*E*)- or (*Z*)-enol ethers **6a** (Scheme 4).

According to stereochemistries observed for enols ethers **6a**–**6b**, **7** and **8**, conformations of starting acetals are those shown on Scheme 5. The stereodetermining step of the reactions is the selective complexation of BF_3 on the oxygene, which is near the pseudo axial phenyl group.[1] Therefore, according to all results reported in Schemes 2 and 3 (stereochemistries of double bonds and absolute configurations of stereogenic centres) it is clear that all substitution reactions (S_N2' or S_N2'') are *anti* (Scheme 4).



Scheme 4.

In conclusion, acetals derived from cyclohexene or cyclopentene carboxaldehydes react regio- and diastereoselectively with PhCu, BF_3 via an *anti* overall S_N2' process. Furthermore the e.e. (92%) obtained with the six-membered ring **1b** is good. The regioselectivity observed with the dienic acetals seems to be strongly dependent on the nature of the acetal. Indeed, the reaction is regioselective (S_N2'') with **2a** ($n=1$) and **3** but not with **2b** ($n=2$). Diastereoselectivities are similar to those generally obtained for such reactions, but the stereochemistry is opposite to the one observed with acetals derived from acyclic aldehydes.[2]

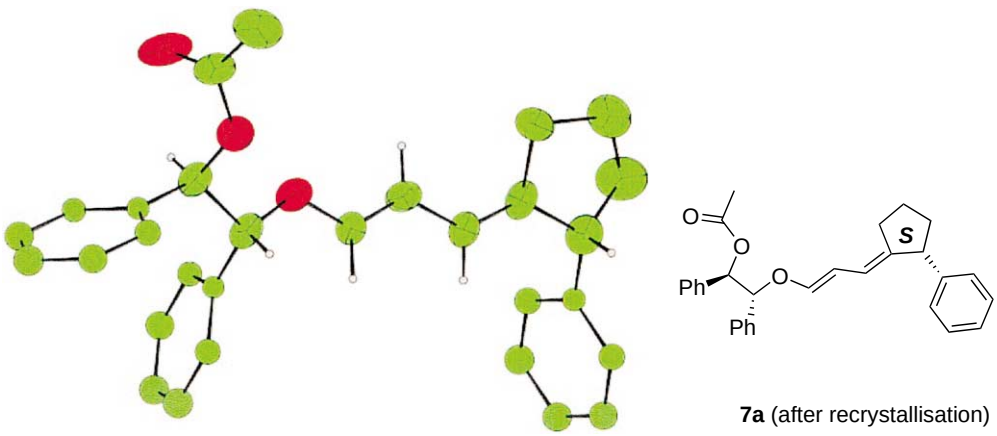
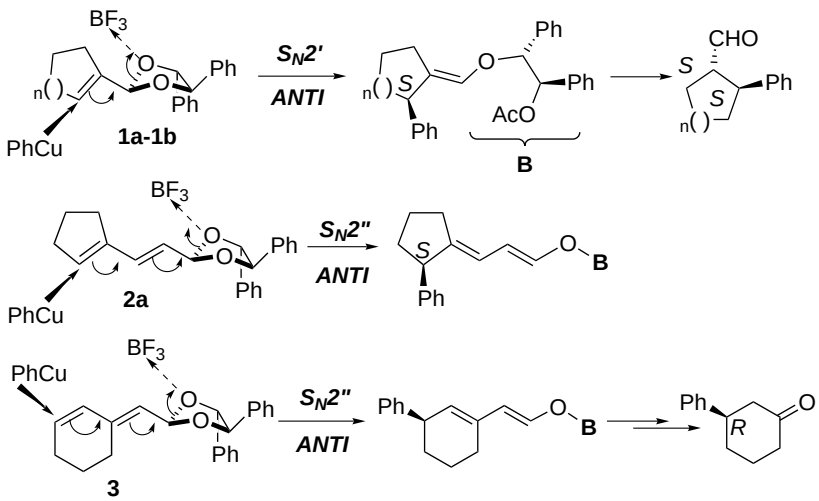


Figure 1.



Scheme 5.

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9. The treatment of **7** by CF_3COOH gave a mixture of aldehydes **10** and **11**. From this mixture it was possible, by chromatography, to obtain small amounts of pure (*Z*)- or (*E*)-**11** and to determine the enantiomeric excess. Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2677–2680; Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431–24310.