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Remote Asymmetric Induction. New Mechanistic Insights Concerning the S_N' and S_N'' Substitution in Organocopper Chemistry

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Summary: The addition of the PhCu, BF_3·Et_2O reagent to chiral dienic acetals was studied. The regioselectivity of the reaction was found to be dependent on the nature of the starting acetal. More importantly, the stereochemistry of the S_N2'' reaction was found to be opposite to the one observed for the S_N2' reaction. Acidic hydrolysis of the resulting enol ethers afforded the corresponding chiral δ-substituted aldehydes.

Chiral acetals, prepared from 1,2-diols of C_2 symmetry, are widely used in asymmetric synthesis.[1] We have previously shown that α,β-ethylenic acetals **1** are regio- and diastereoselectively opened to the substituted enol ethers **2** by action of aryl- or vinylcopper reagents in the presence of BF_3 (Scheme 1). The corresponding β chiral aldehydes **3** were then obtained by acidic hydrolysis. The *E* stereochemistry of the enol ethers **2** and the absolute configuration of the new stereogenic center can be rationalized by an overall *anti* S_N2' process on the acetal **1** reacting in a transoid conformation. The leaving group is the BF_3 complexed oxygen next to the pseudoaxial group.[2] Such reaction involves the formation of an *anti* σ-allyl complex **A** which is in equilibrium with **B**, the regioselectivity of the S_N reaction being dependent on the relative kinetics of the reductive elimination of **A** and **B** versus the isomerization (Scheme 1).[3]

The application of the same reaction on dienic acetals could afford a convenient way to prepare aldehydes with a remote chiral center, provided a regioselective S_N2'' process is possible. Furthermore, owing to the interconversion of the Cu^{III} intermediates,[4] it was anticipated that the stereoelectronic chiral information may be transmitted along the dienic chain (Scheme 2).

In order to test this hypothesis, we have studied the addition of PhCu, BF_3·Et_2O on dienic acetals. Indeed, this reagent was shown to be regioselective with mo-

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(1) For a review, see: Alexakis, A.; Mangeney, P. *Tetrahedron Asymm.* **1990**, *1*, 477−511.

(2) The mechanism of organometallic mediated cleavage of chiral acetals in the presence of Lewis acid is still not well elucidated. A tight ion paired S_N1-like mechanism is generally proposed. In a recent paper, Sammakia has shown that the selectivity in the asymmetric cleavage of chiral acetals promoted by allylstannanes is not due to preferential complexation to one of the acetal oxygens but rather to a diastereoselective addition to an oxocarbenium ion. In our case, we still believe in an S_N2 substitution. Indeed, it is difficult to explain diastereocontrol at the δ position by a S_N1'' type reaction. For related papers, see: Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998−10999 and references therein.

(3) (a) Bäckvall, J. E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc* **1990**, *112*, 6615−6621. (b) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1990**, *55*, 2757−2761.

(4) For such interconversion a Cu^{III} π-allyl complex is generally postulated: (a) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1991**, *56*, 2563−2572. (b) Nakanishi, N.; Matsubara, S.; Utimoto, K.; Kozima, S.; Yamaguchi, R. *J. Org. Chem.* **1991**, *56*, 3278−3283.

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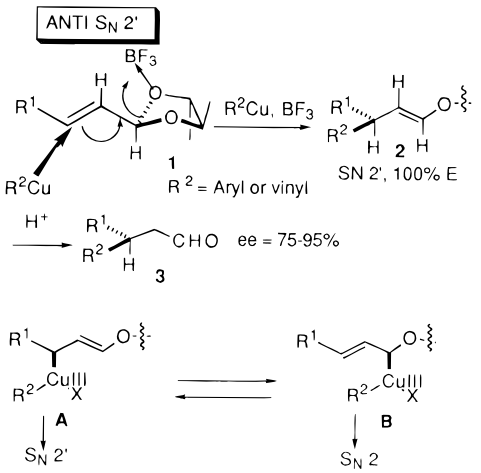
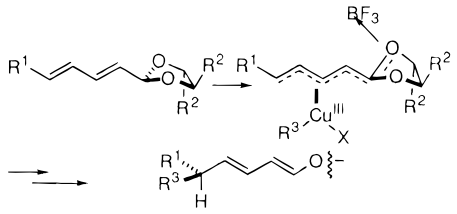
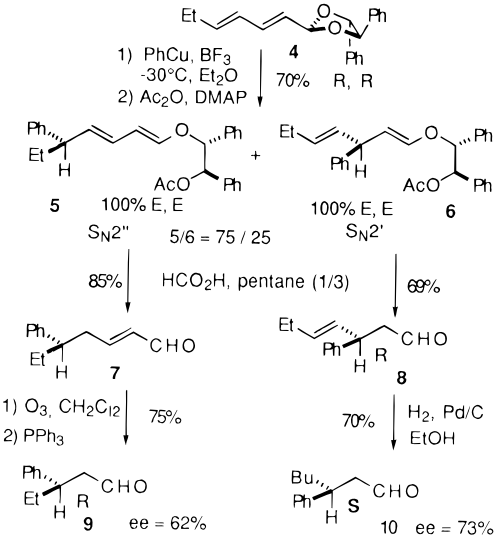
Scheme 1



Scheme 2



Scheme 3

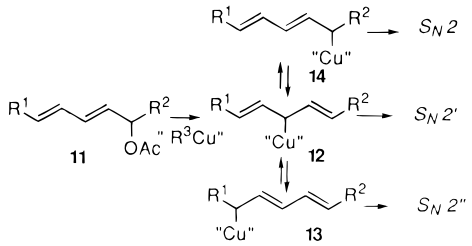


noethylenic acetals. Aditionally, in contrast to the arylcopper reagent, we have found that the use of an alkylcopper reagent resulted in a totally non regioselective reaction (S_N2 + S_N2' + S_N2'').

Acetal **4** is easily obtained from commercialy available (*E*,*E*)-hepta-2,4-dienal[5] and (1*R*,2*R*)-1,2-diphenylethane-1,2-diol.[6] The action of phenylcopper reagent (PhLi + CuBr, Me_2S) in the presence of BF_3 on this acetal in ether at −30 °C afforded, after standard acetylation, the enol ethers **5** and **6** with a good regioselectivity in favor of the S_N2'' product (**5**/**6** = 75/25; Scheme 3).[7]

After chromatographic separation, **5** and **6** (both 100% *E*,*E* configuration, as shown by ^{1}H NMR) were hydrolyzed into the corresponding aldehydes **7** and **8** (Scheme 3). **7** (resulting from S_N2'' reaction) was converted by ozonolyzis into **9**.[8] The absolute configuration and the enantiomeric purity of aldehydes **8** (resulting from S_N2' reaction) and **9** were established by known methods.[9] Furthermore, in order to confirm our results, **8** was hydrogenated into the known aldehyde **10**.[8] As shown in Scheme 3, starting from the (*R*,*R*) acetal **4**, the aldehydes **9** and **8** of *R* configuration were obtained. Therefore, the reaction occurs via overall *anti* S_N2' and *syn* S_N2'' processes. The result obtained for the S_N2'' reaction is worthy of comment with respect to the previously reported mechanism of organocopper-mediated S_N2'' reactions.[10] It has been postulated, in the case of dienic acetates **11**, that the first step of the reaction involves the formation of the σ-allyl complex **12.** This complex undergoes either a reductive elimination affording the S_N2' product or an isomerization to **13** and **14**, which are precursors of respectively the S_N2'' and S_N2 products (Scheme 4).

Scheme 4



The stereochemistry of this substitution has never previously been studied except in one special case where an *anti* S_N2'' reaction was postulated.[11] Nevertheless, the *anti* stereochemistry of the S_N2' reaction is well documented[12] and was observed for monoethylenic acetals.[1] Therefore, according to the fact that the isomerization of σ-allyl complexes occurs with retention of configuration, and if the dienic acetal reacts in a transoid conformation, we expected, in our case, to observe an *anti* S_N2'' reaction. The *E*,*E* stereochemistry of the obtained enol ethers **5** and **6** is in agreement with reaction of acetal **4** in the transoid conformation. Therefore the S_N2'' mechanism seems to be really *syn*. The reasons for such stereochemistry are still unclear.[13] As far as the regioselectivity is concerned, one hypothesis is possible. The first step of the addition of PhCu,

(5) The commercialy available hepta-2,4-dienal is not 100% *E*,*E*. Pure (*E*,*E*) acetal was obtained after chromatographic purification.

(6) Wang, Z. M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302−8303.

(7) Typical procedure for addition of phenylcopper, BF_3 reagent to acetals: To a solution of iodobenzene (0.450 mL, 4.03 mmol) in anhydrous ether (50 mL) at −80 °C under N_2 atmosphere was added *tert*-butyllithium (8.06 mmol). The resulting solution was stirred for 20 min at 0 °C and then cooled to −60 °C. The complex CuBr, Me_2S (822 mg, 4 mmol) was added in the solution and the temperature allowed to warm to 0 °C. To the resulting brown mixture, cooled to −30 °C, was added a solution of dienic acetal (2 mmol) in Et_2O (10 mL). A solution of BF_3, Et_2O (0.5 mL, 4 mmol) in ether (2 mL) was then added dropwise and the resulting mixture stirred for 30 min. The reaction was then quenched by addition of an aqueous solution of NH_4OH/NH_4Cl (1/1). The mixture was diluted with Et_2O and washed with an aqueous solution of NH_4OH/NH_4Cl (1/1) and then with water. The organic layer was dried (Na_2CO_3) and concentrated under vacuum to afford a yellow oil which was used without further purification.

(8) Berlan, Y.; Besace, Y.; Pourcelot, G.; Cresson, P. *Tetrahedron* **1986**, *42*, 4757−4765.

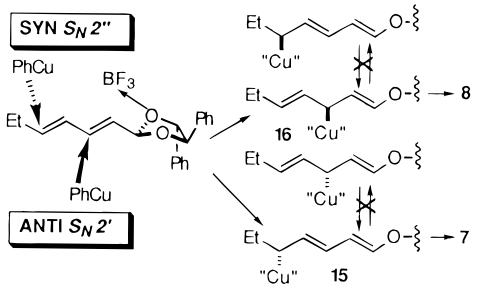
(9) (a) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2677−2680. (b) Cuvinot, D.; Mangeney, P.; Alexakis, A.; Normant, J. F. *J. Org. Chem.* **1989**, *54*, 2420−2425.

(10) Kang, S. K.; Cho, D. G.; Chung, J. U.; Kim, D. Y. *Tetrahedron Asymm.* **1994**, *5*, 21−22. See also ref 4.

(11) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1988**, *53*, 1140−1146.

(12) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

Scheme 5

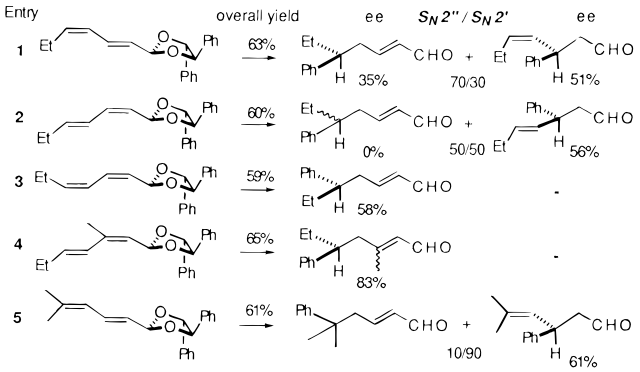


BF_3 to dienic acetals is the formation of two σ-allyl complexes **15** (*syn*) and **16** (*anti*). Each complex then undergoes reductive elimination before isomerization. Indeed if such isomerization occurred, this would produce the racemic aldehydes **7** and **8**, which is not observed here (Scheme 5).

The same reaction was applied to several dienic acetals: the other geometric isomers of **4** (entries 1−3, Scheme 6), a β-disubstituted acetal (entry 4) and a δ-disubstituted one (entry 5). The δ substituted products obtained were the *E*,*E* enol ethers, and the β substituted products obtained were the *E* enol ethers. All these compounds were then hydrolyzed into the corresponding aldehydes. The ee and absolute stereochemistry of each aldehyde were determined as above.[14]

As shown in Scheme 6, the regioslectivity strongly depends on the stereochemistry of the dienic system. It is interesting to observe that the *Z*,*Z* isomer reacts regioselectively to give solely the S_N2'' product (entry

Scheme 6



3). The regioslectivity is also affected by the substitution pattern of the dienic system. Substitution of the β position leads exclusively to the S_N2'' product (entry 4), and conversely, substitution of the δ position gave mainly the S_N2' product (entry 5); thus, it appeared that the reaction is favored at the less substituted center. In all the cases, except for entry 2, *syn* S_N2'' and *anti* S_N2'' reactions were observed.

At this time, it is difficult to explain all our results. The only rational hypothesis that we are able to postulate is the formation of the two σ-allyl complexes **15** (*syn*) and **16** (*anti*) without (or with a slow) equilibration between them. Importantly, we have found an inversion of stereochemistry between the S_N2'' (*syn* process) and S_N2' reactions (*anti* process) in organocopper chemistry. We are presently studying this reaction in order to understand the origin of the observed regio- and diastereoselectivities and, if possible, to increase them. Attempts to generalize the *syn* process of the S_N2'' substitution to other substrates are also underway.

Supporting Information Available: For **4**−**8**, text giving experimental procedures and ^{1}H NMR and ^{13}C NMR data (4 pages). Ordering information is given on any current masthead page.

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(13) The *anti* stereochemistry observed for the S_N2' reaction can be rationalized by a stereoelectronic effect: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063−3066. Orbital symmetry considerations would suggest a reversal of the stereoselectivity for direct S_N2'' and S_N2' processes: Nguyen Trong Anh. *J. Chem. Soc., Chem. Commun.* **1968**, 1089.

(14) For entry 4, the absolute stereochemistry was attributed from the optical rotation of the 4-phenylhexan-2-one obtained by ozonolyzis of the aldehyde ($[\alpha]_D^{25}$ −25 (*c* 2.5, EtOH)): Brienne, M. J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613−623. For entry 5, the absolute stereochemistry was attributed by ^{1}H NMR, as described in ref 6a, from the 3-phenyl-5-methylhexanal obtained by hydrogenation.