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CHIRAL INDUCTION IN THE CYCLOCONDENSATION OF ALDEHYDES WITH SILOXYDIENES

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Summary: Eu(hfc)$_3$ catalyzes the title reaction with substantial asymmetric induction.

Traces of soluble lanthanide complexes such as Eu(fod)$_3$[1] catalyze the cyclocondensation of activated dienes with aldehydes. The process[2a] conforms to what has been described as the pericyclic model[2b] (i.e. suprafaciality in the diene component with high endo selectivity).[2c] The major advantage of lanthanide catalysis lies in the survival of otherwise labile systems of the type **2**, which bear exploitable functionality. It was also noted that Eu(hfc)$_3$[3] provides asymmetric induction in the cycloaddition reaction. In this Letter, we report on a systematic investigation of this exciting new finding.

We first encountered the Eu(hfc)$_3$ induced enantiomeric enrichment in the reaction of parent diene **1a** with benzaldehyde (CDCl$_3$,rt) using 1 mole % of the catalyst. Cleavage of **2a** with trifluoroacetic acid afforded **3**. The sense and extent of this induction was ascertained via optical[4a,b] and nmr[5] measurements on **4**, which was obtained from **3** by previously described protocols ((*i*) O$_3$/MeOH, (*ii*) H_2O_2;OH^-, (*iii*) CH_2N_2/Et_2O).[6] In all of the cases described in this work the 6R pyrone enantiomer was enriched.[7]

Some possibilities for improving upon the rather modest enantiomeric enrichment (18% e.e.) in the case of diene **1a** were pursued. It seemed likely that increasing the size of the alkoxy substituent at C$_1$ of the diene might increase the extent of induction. Dienes **1b** and **1c** were obtained by enol silylation (Et$_3$N-TMSOTf)[8] of the corresponding alkoxyenones. These enones are readily prepared by acid catalyzed (TsOH, ROH/ϕH) exchange with the commercially available trans-1-methoxy-1-buten-3-one. The effect of the C$_1$ alkoxy variation is seen from the data in figure 1.

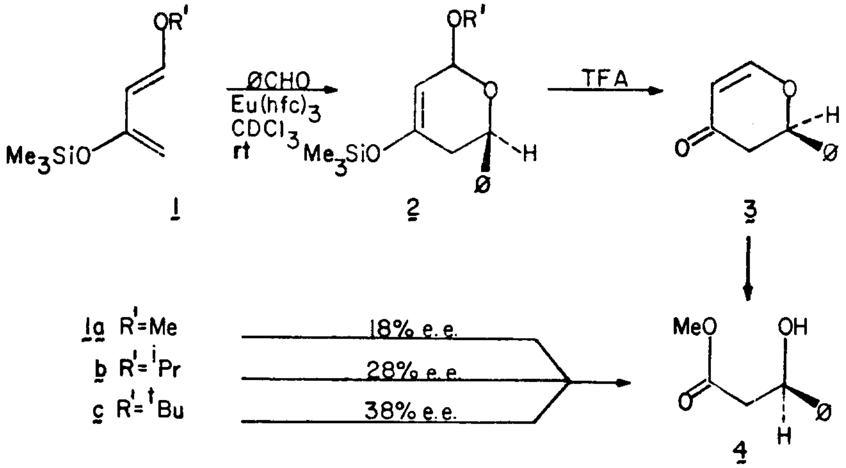

figure 1

The effects of methyl substitution at C_2, and of dimethyl substitution at C_2 and C_4, were probed with dienes 1d-g [9] under conditions identical to those used for 1a-c.

In the 1-methoxy series, the 2-methyl substituent appears to be of little consequence (compare 1a and 1d), but a significant effect arises with a 4-methyl group (compare 1a, 1d, and 1f). However, with R' = ^{t}Bu, the effects of additional substitution are attenuated (compare 1c, 1e and 1g).

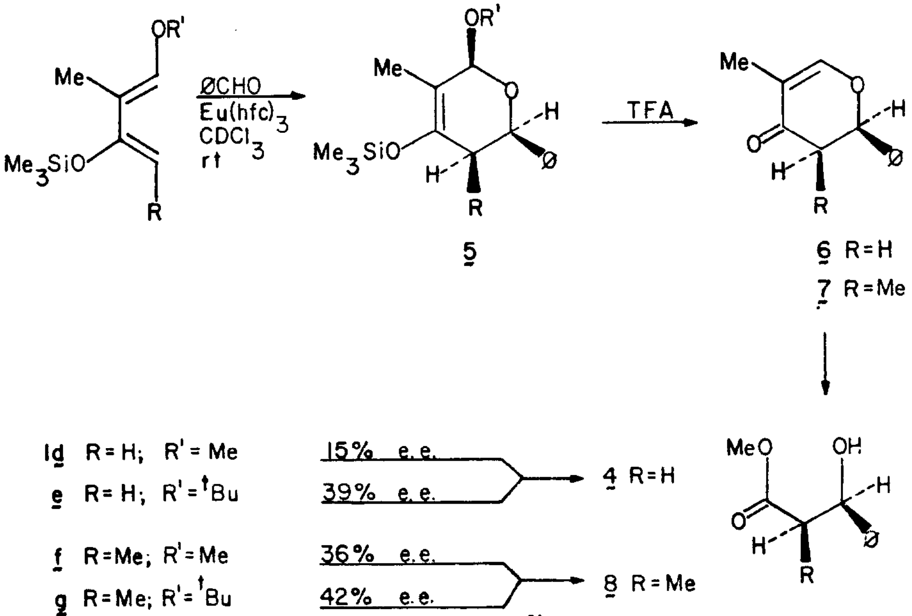

figure 2

The extent of induction in the reaction of the more oxygenated dienes 1h and 1i with benzaldehyde was also investigated. As before, the dienes were obtained by enol silylation (TMSOTf-Et$_3$N) of the corresponding 1,2-dioxygenated 1-buten-3-one compounds.[10] The conditions for the cycloaddition were the same as used with 1a-1g. The adducts, upon treatment with trifluoracetic acid, afforded dihydropyrones 9 and 10.[11] These were converted to hydroxyester 4 using the same oxidation protocol as described above. The data (fig. 3) indicate that the 2-acetoxy function exerts little effect on the extent of induction with the 1-^{t}OBu dienes (compare 1c and 1h). The difference between 1h and 1i is interesting, though the generality of this effect remains to be determined.

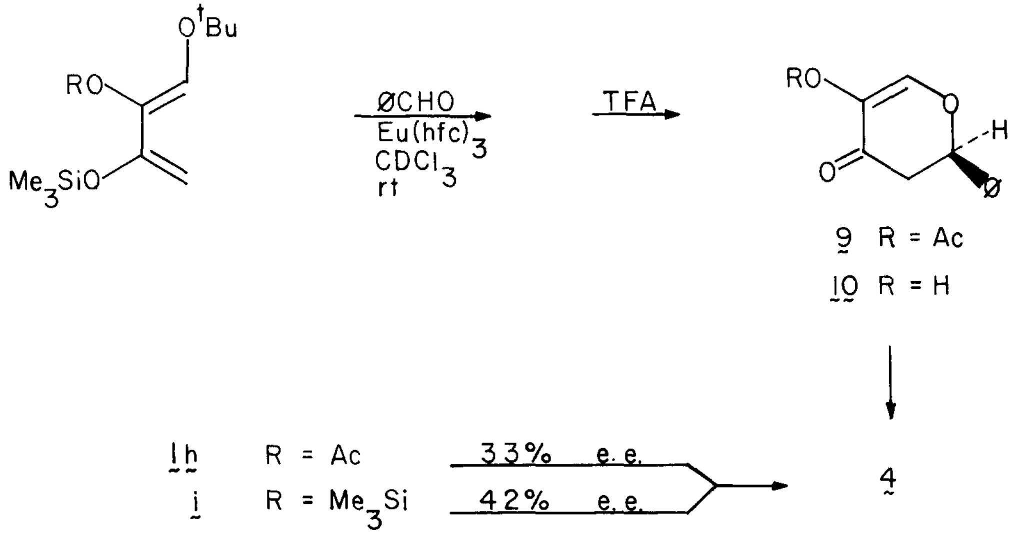

figure 3

With two of the dienes, we attempted to increase induction by modification of the experimental conditions. It was found that considerable improvement could be realized by conducting the reaction in the absence of solvent at reduced temperatures (see fig. 4). We also note there is essentially no change in e.e. by increasing the proportion of Eu(hfc)$_3$ to 10 mole %, though the reaction rate is sharply increased. Thus, while the causes of the induction are not presently understood, they seem to be rooted in the catalytic process rather than in a more general medium effect.

$$\mathbf{1e} \xrightarrow[\text{Eu(hfc)}_3\ (^-10°\text{C})]{\text{1.) ØCHO (neat)}} \mathbf{6} \longrightarrow \mathbf{4} \quad \text{(58\% e.e.)}$$

$$\text{2.) TFA}$$

$$\mathbf{g} \xrightarrow{\text{"}} \mathbf{7} \longrightarrow \mathbf{8} \quad \text{(55\% e.e.)}$$

figure 4

Experiments designed to enlarge upon and exploit these findings are in progress.

[1] Tris (6,6,7,7,8,8,8 - heptafluro, 2,2-dimethyl-3, 5-octanedionato) europium. This compound is commercially available from Aldrich.

[2a] M. Bednarski and S. Danishefsky, J. Amer. Chem. Soc., In Press.

[2b] E.R. Larson and S. Danishefsky, ibid **104**, 6458 (1982).

[2c] S. Danishefsky, E.R. Larson and D. Askin, ibid **104**, 6457 (1982).

[3] Tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato], europium (III). This compound is commercially available from Aldrich.

[4] The sense of the optical enrichment was determined by the sign of the optical rotation of the acid precursor of compound **4**. The absolute configation of this acid has been established by (a) S.G. Cohen and S.Y. Winstein, J. Amer. Chem. Soc., **86**, 725 (1964); and also reported by (b) D.A. Evans and T.R. Taber, Tetrahedron Lett., 4675 (1980).

[5] NMR shift studies (Eu(hfc)$_3$/CDCl$_3$) were carried out on the methyl ester **4**. Resolution of the "enantiomeric" methyl singlets of the ester was observed, with the predominant R enantiomer at higher field relative to its S counterpart.

[6] S. Danishefsky, N. Kato, D. Askin and J.F. Kerwin, Jr., J. Amer. Chem. Soc., **104**, 360 (1982).

[7] Induction in pyrone **7** was determined by rotation of **8**. D.A. Evans, J. Bartoli and T.L. Shih, J. Amer. Chem. Soc., **103**, 2127 (1981).

[8] G. Simchen, et. al., Synthesis, 1 (1982).

[9] S. Danishefsky, C.F. Yan, R.K. Singh, R.Gammill, P. McCurry, Jr., N. Fritsch and J. Clardy, J. Amer. Chem. Soc., **101**, 7001 (1979).

[10] S. Danishefsky and T.A. Craig, Tetrahedron, **37**, 4081 (1981).

[11] The first demonstration of the use of 1,2,3,-trioxygenated dienes in the cyclocondensation reaction (using zinc chloride and in the 1-methoxy series) was described by Dr. Todd Craig.

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