

ASYMMETRIC INDUCTION IN THE CYCLOADDITION REACTION OF DICHLOROKETENE WITH CHIRAL ENOL ETHERS. A VERSATILE APPROACH TO OPTICALLY ACTIVE CYCLOPENTENONE DERIVATIVES.

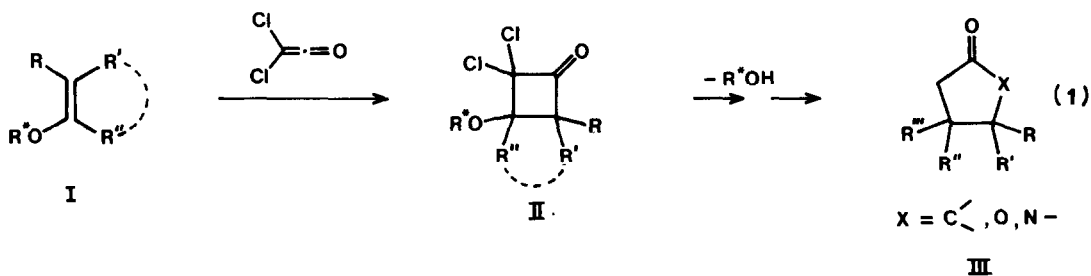
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Abstract: Significant asymmetric induction has been observed in the cycloaddition reaction of dichloroketene with chiral enol ethers. The resultant diastereomeric cyclobutanones have been converted to synthetically useful α -chlorocyclopentenones in optically active form.

The asymmetric Diels-Alder reaction using dienophiles bearing chiral control elements has been extensively studied by several groups and has found considerable application in synthesis.¹ Notwithstanding the importance of the ketene-olefin cycloaddition reaction,² there has been no parallel effort made to date to assess the possibility of obtaining synthetically useful diastereofacial differentiation in the reaction of ketenes with ketenophiles bearing chiral auxiliaries.³ In this communication we disclose our preliminary results in this area.

α,α -Dichlorocyclobutanones are highly versatile cycloadducts, easily affording, inter alia, regioselectively substituted cyclopentanones, γ -butyrolactones, and pyrrolidones,² and thus they are particularly attractive targets for asymmetric synthesis. We have successfully synthesized these intermediates (II, eq 1) through such a process using, in the present study, principally

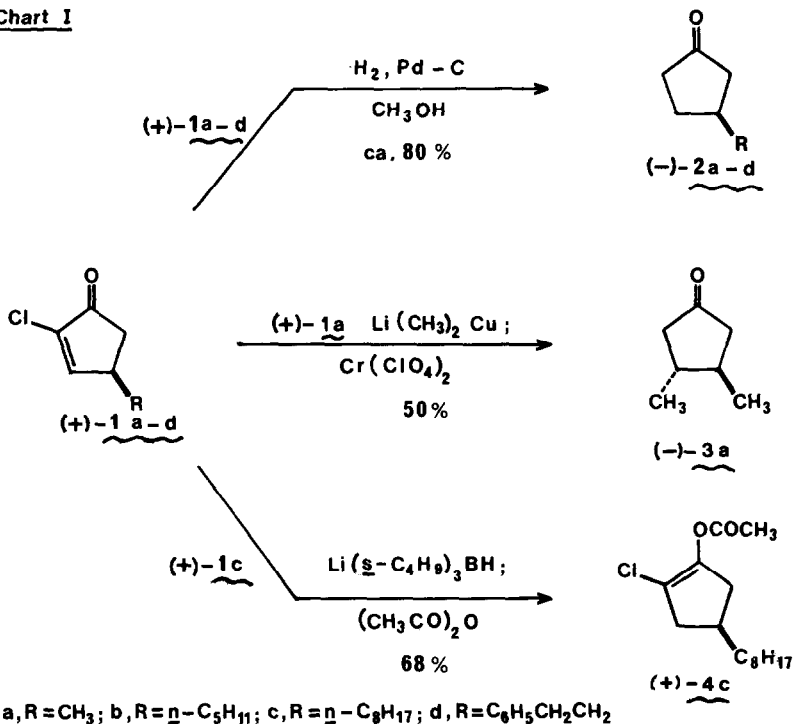


"common" chiral auxiliaries (R^*OH) that are available in both antipodal series and Z enol ethers (where $R'=R''=H$); to illustrate the potential of this approach, these intermediates have been converted to several optically active cyclopentenone derivatives.

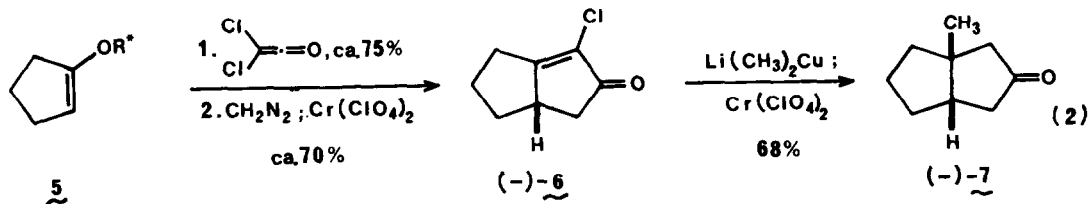
The enol ethers, exclusively Z, can easily be obtained by isomerization of the corresponding allyl ethers, with⁴ or without,⁵ concomitant alkylation. Dichloroketene⁶ (1.1-2.5 equiv CCl_3COCl , 4 equiv Zn-Cu, ether, 20°C) was found to add smoothly to these compounds to produce selectively, and in generally high crude yield, the diastereomeric α,α -dichlorocyclobutanones that are indicated in Table I.

The α -chlorocyclopentenones are choice intermediates themselves, readily undergoing a variety of synthetically useful conversions. Thus, for example, the dextrorotatory enones $\underline{1a-d}$ are transformed in high yield to the corresponding (S)-(-)-cyclopentanones $\underline{2a-d}$ by catalytic hydrogenation (Chart I). In addition, cuprate reagents¹⁷ can be used to obtain trans-3,4-disubstituted cyclopentanones from these enones (e.g., (+)- $\underline{1a}$ \rightarrow (-)- $\underline{3a}$), and their treatment with lithium tri-sec-butylborohydride followed by acetic anhydride¹⁸ yields the corresponding chloro enol acetates (e.g., (+)- $\underline{1c}$ \rightarrow (+)- $\underline{4c}$). Of course, many other transformations of these enones are possible.

Chart I



Importantly, this approach can also be applied to cyclic enol ethers. The enol ether $\underline{5}$, derived from cyclopentanone dimethyl acetal and (-)-menthol (TsOH, toluene, Δ , 70%), affords the α -chloro enone (-)- $\underline{6}$ in 43% enantiomeric excess (eq 2); the use of (-)-8-phenylmenthol¹⁹ in this sequence also yields (-)- $\underline{6}$, but now in 67% optical purity. The chloro enone (-)- $\underline{6}$ can readily be transformed to (-)- $\underline{7}$ as shown.²⁰



In summary, this preliminary study has demonstrated for the first time that significant asymmetric induction can, in fact, be achieved in the [2+2]-cycloaddition reaction of dichloro ketene with chiral enol ethers. Refinement and extension of this methodology and its application in natural product synthesis are currently under investigation.

Acknowledgment. We thank Prof. A. Rassat and Dr. J.-L. Luche for their interest in this work and Dr. H. Felkin and Dr. J. d'Angelo for gifts of samples. This work was supported by the CNRS(LA332).

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- (9) The diastereomer ratios IIa:IIb could not be dependably measured by any of the usual direct techniques (^{13}C NMR, ^1H NMR, HPLC). The enantiomeric excesses of Ia-d are assumed to reflect the diastereoselectivities of the corresponding cycloadditions.
- (10) (a) $\text{R}=\text{CH}_3$: the diastereoselectivity was calculated on the basis of the optical rotation of the corresponding α -chloro enone Ia [pure (+)-Ia (by SiO_2 separation of diastereomers, entry 5): $[\alpha]_D^{20} +118^\circ$ c 1, acetone] and/or from the ^{13}C NMR spectrum of the diastereomeric acetals of Ia formed with (R,R)-(-)-2,3-butanediol;¹¹ the absolute configuration was determined by conversion (O_3 ; HCO_2H) of (+)-Ia to (R)-(+)-2-methylsuccinic acid,¹² and was confirmed through the transformation of (+)-Ia to the (S)-(-)-2,4-dinitrophenylhydrazone^{13a} and (R,R)-(-)-semicarbazone¹⁴ derivatives of (-)-2a and (-)-3a, respectively. (b) $\text{R}=\text{n-C}_5\text{H}_{11}$: the diastereoselectivity was determined from the optical rotation of (-)-2b^{13c} and from the ^{13}C NMR spectra of the diastereomeric acetals of (+)-1b and (-)-2b;¹¹ the absolute configuration^{13c} was confirmed by oxidation (O_3 ; HCO_2H) of (+)-1b to (R)-(+)-2-pentylsuccinic acid¹² and by circular dichroism of (-)-2b (negative Cotton effect¹⁵). (c) $\text{R}=\text{n-C}_8\text{H}_{17}$: the diastereoselectivity was found by ^{13}C NMR analysis of the diastereomeric acetals of (+)-1c and (-)-2c;¹¹ the absolute stereochemistry was determined by circular dichroism of (-)-2c (negative Cotton effect¹⁵). (d) $\text{R}=\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$: the diastereoselectivity was determined from the ^{13}C NMR spectra of the diastereomeric acetals of (+)-1d and (-)-2d;¹¹ the absolute stereochemistry was assigned by circular dichroism of (-)-2d (negative Cotton effect¹⁵).
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- (20) The enantiomeric excesses were determined from the ^{13}C NMR spectra of the diastereomeric acetals¹¹ of (-)-6 and (-)-7. The absolute stereochemistry has been assigned on the basis of the circular dichroism curve of (-)-7 (negative Cotton effect¹⁵).