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Diastereocontrol in the Opening of *vic*-Acceptor-Donor Cyclopropanes. Application to the Synthesis of (*cis*) 1-EWG-2-Hydroxymethylcyclopropanes.

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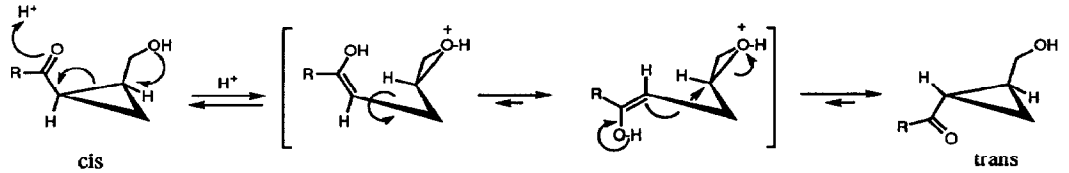
Abstract: Basic intramolecular ring opening reactions of vicinally substituted acceptor-donnor (*trans*)-cyclopropanes were studied. An application to the diastereoselective synthesis of (cis)-1-EWG-2-hydroxymethylcyclopropanes is presented.

Electrophilic cyclopropanes derivatives have been widely used as intermediates in organic synthesis[1]. The cyclopropane ring behaves in a manner analogous to that of an alkene substituted on one carbon atom by one or two electron-withdrawing groups. In contrast to double bonds, which are prone to Michael addition by virtue of one activating group, cyclopropanes require two such activating groups for homoconjugate addition in most cases[2,3].

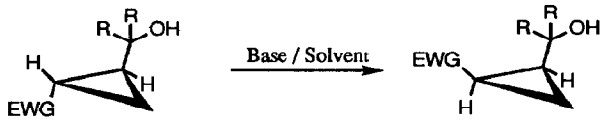
We have recently reported that vicinally substituted (*cis*)-acceptor-donor cyclopropanes isomerized, in few days, under acidic conditions (TFA/ $CDCl_3$), to afford the corresponding *trans* isomers *via* an intramolecular homo-Michael addition of an hydroxymethylene group[4] (scheme 1).



Scheme 1

Here we wish to report reversal diastereocontrol in the opening of substituted acceptor-donnor cyclopropanes by an alcoholate homo-Michael addition and its application to the synthesis of (*cis*)-cyclopropanes.

Many (*trans*) 1-EWG-2-hydroxymethylcyclopropanes were synthetized and treated in different basic conditions to allow access to the corresponding *cis* isomers. The results are summarized in table 1.



trans cis

Entry	EWG	R	Base[a]	Solvent	Reac. time[b]	cis/trans[c]	combined yields (%)[d]
1	PhCO	H	NaOMe	MeOD	inst.	>99/1	>95
2	PhCO	H	dimsylNa	DMSO	1hr	>99/1	>95
3	PhCO	H	NaH	THF	1hr	>99/1	>95
4	PhCO	H	$Mg(OMe)_2$	MeOD	72hr	>99/1	>95
5	PhCO	H	K_2CO_3	MeOD	1hr	>99/1	>95
6	PhCO	H	TEA	MeOD	72hr	20/80	>95
7	PhCO	H	BuLi	THF	1hr	>99/1	>95
8	PhCO	H	KCl	MeOD	72hr	<1/99	>95
9	PhCO	Me	NaOMe	MeOD	inst.	>99/1	>95
10	CH_3CO	H	NaOMe	MeOD	inst.	>99/1	>95
11	iPrCO	H	NaOMe	MeOD	inst.	>99/1	>95
12	tBuCO	H	NaOMe	MeOD	inst.	>99/1	>95
13	NO_2	H	NaOMe	MeOD	inst.	>99/1	>95

[a] 1 equivalent mole of base was used[5]
[b] inst.= instantaneous: The completion of the reactions was estimated by TLC.
[c] The *cis/ trans* product ratio were easily confirmed by examination of the relative intensities of the resonance for the two hydroxymethylene protons in the ^1H NMR of the crude mixture.
[d] Detemined by ^1H NMR.

Table 1.

The results obtained allow us to make the following comments.

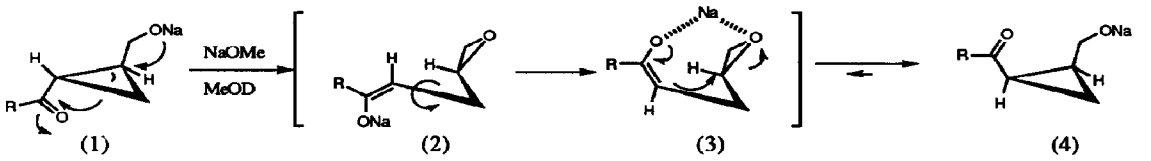
The rate of the isomerization process is closely related to the strength of the bases. When non basic anions are utilized, such as KCl, the process is forbidden (entry 8). When triethylamine was used the rate significantly decreased (entry 6). Surprisingly, the less basic potassium carbonate base allows the process (entry 5).

The kinetics of the reaction (instantaneous with MeONa in MeOD) (entries 1,9-12) indicates that this reaction was under kinetic control. In contrast, the acidic isomerization (TFA, $CDCl_3$) (2-5 days)[3] implies a thermodynamically controlled process.

Moreover, the decreased rates observed in THF and DMSO (entries 2,3,7) suggest that alcohol proton abstraction was involved in the rate determining step.

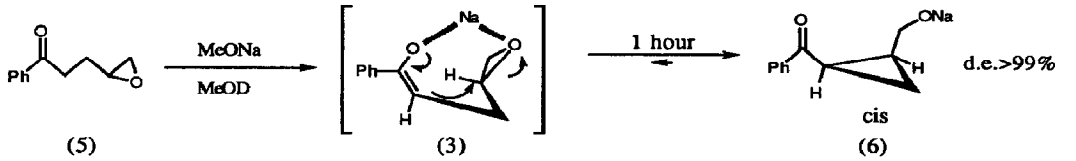
The methodology could be applied to cyclopropanes bearing as EWG different ketone functions (entries 9-12) as well as a nitro group (entry 13).

The inversion of configuration in deuterated methanol without H/D exchange and the correlation between the rate of inversion and the strength of the base suggest the mechanism presented in scheme 2.



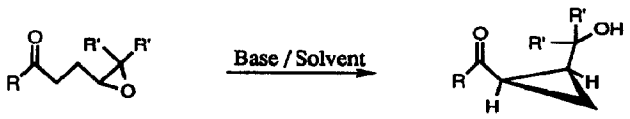
Scheme 2

The isomerization *via* an open ring mechanism should involve the formation of a chelated intermediate γ,δ-epoxyenolate (3). This mechanism was furthermore confirmed by the result obtained with the rearrangment of the corresponding γ,δ-epoxy ketone (5) with sodium methanolate in deuterated methanol. The (*cis*)-cyclopropane (6) was formed with complete diastereoselectivity and total retention of the α-keto hydrogen (scheme 3).



Scheme 3

This process which was kinetically controlled by homo-Michael addition and which furthermore involves the formation of a chelated intermediate epoxy enolate should be applied to the diastereocontrolled synthesis of (*cis*) 1-keto-2-hydroxymethylcyclopropanes. The results of the rearrangement of γ,δ-epoxy ketones in different basic conditions are presented in table 2[6].



Entry	R	R'	Base	Solvent	cis/ trans
1	Ph	H	MeONa	MeOH	>99/1
2	CH_3	H	MeONa	MeOH	>99/1
3	tBu	H	MeONa	MeOH	>99/1
4	Ph	Me	MeONa	MeOH	>99/1
5	Ph	H	BuLi	THF	>99/1
6	Ph	H	NaH	THF	>99/1
7	Ph	H	NaH	DMSO	>99/1

Table 2

As postulated, (*cis*)-cyclopropanes were formed under basic conditions with complete diastereocontrol. The overall yields are high (>80%), even in the dipolar DMSO solvent, where a loss of regiocontrol was observed (10% of O-alkylated products were recovered). The high stereocontrol of the reaction is a consequence of the alcoholate homo-Michael intramolecular addition, which should annihilate any racemization via an α-keto proton abstraction[7].

In summary, our study on the basic catalysed ring opening reaction of vicinally di-substituted acceptor-donnor cyclopropanes allows the diastereocontrolled synthesis of *cis* cyclopropanes from the corresponding *trans* isomers. The mechanism certainly involves the formation of an intermediate chelated γ,δ-epoxyenolate. An application of this study was found in the diastereoselective synthesis of (*cis*)1-keto-2-hydroxymethylcyclopropanes from γ,δ-epoxy ketones.

Acknowledgments: We thank Dorothée Deuring for reviewing this manuscript.

References and Notes.

(1) For a review in the acceptor-donor-substituted cyclopropanes chemistry see: Reiβig, H.U. *Topics in Current Chemistry* 1988, *144*, 73-135.
(2) Danishefsky, S. *Acc. Chem.Res.* 1979, *12*, 66-72.
(3) Some examples of cyclopropane ring opening bearing one EWG group are reported with very strong nucleophiles: Mioskowski, C.; Manna, S.; Falck, J.R. *Tetrahedron Lett.* 1993, *24*, 5521-5524.
(4) Dechoux, L.; Doris, E. *Tetrahedron Lett.* 1994, *35*, 2017-2020.
(5) Catalytic amount of bases (K_2CO_3 or NaH) were found to be as effective as quantitative amounts.
(6)The formation of cyclopropanes by intramolecular displacements is a well documented reaction: Majewski, M.; Snieckus, V.; *J.Org.Chem.* 1984, *49*, 2682-2687. Schauman, E.; Kirsching, A.; Narjes, F. *J.Org.Chem.* 1991, *56*, 717-723. Gaoni, Y. *Israel J.Chem.* 1971, *9*, 63-69. Recently we published a diastereoselective preparation of cyclopropanes using KOH/ DMSO as alkylation conditions: Dechoux, L.; Ebel, M.; Jung, L.; Stambach, J.F. *Tetrahedron Lett.* 1993, *34*, 7405-7408.
(7) Using until 10 eq. moles NaH or MeONa as base, no decrease of diastereoexcess was observed.

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