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THREE-MEMBERED RING FORMATION REACTION—III

MECHANISM OF THE REACTION OF α-HALOGENOACRYLIC ESTER WITH ORGANOZINC COMPOUNDS

T. TSURUTA and Y. KAWAKAMI

Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

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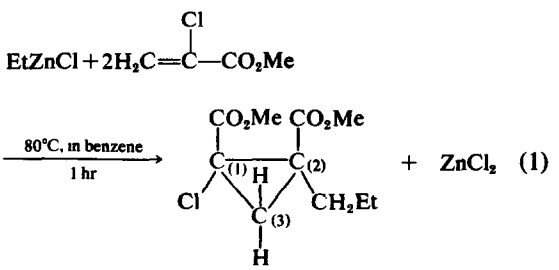
Abstract—The stereochemistry of ring formation in the reaction of α-halogenoacrylic ester with organozinc compounds was studied using β-deuterated α-halogenoacrylic ester. A quantitative study was made on the steric course of every step of the reactions involved in the synthesis of methyl β-deuterio-α-bromoacrylate-*cis*-d_1 starting from methyl propiolate. The mode of the C=C double bond opening of methyl β-deuterio-α-bromoacrylate-*cis*-d_1 to form dimethyl 1-bromo-2-propyl-*cis*-1,2-cyclopropanedicarboxylate-d_2 was confirmed to be *cis* and *trans* in a 50 to 50 ratio. Asymmetric syntheses for the cyclopropanedicarboxylic ester were possible, especially under the influence of chiral organozinc alkoxide system. A stepwise mechanism was postulated for the ring formation reaction.

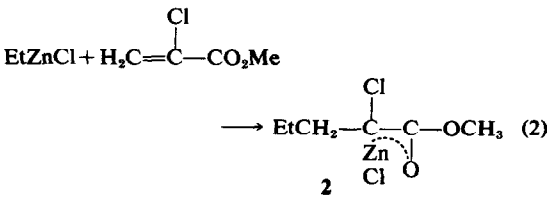
INTRODUCTION

In a previous paper[1] it was reported that methyl α-chloroacrylate undergoes a ring formation reaction with ethylzinc chloride to form dimethyl 1-chloro-2-propyl-*cis*-1,2-cyclopropanedicarboxylate (1):



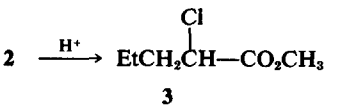
1 (yield 50%)

Referring to the general reaction scheme[2-8] of metal alkyls with α,β-unsaturated carbonyl compounds, the first step of the condensation should be a Michael type addition of the Et group of EtZnCl to methyl α-chloroacrylate:



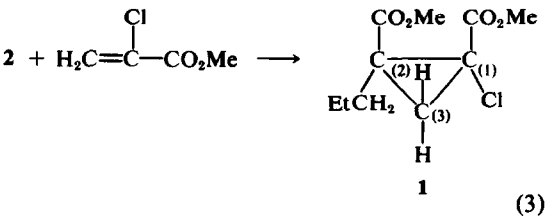
2

The conjugate addition product, 3, was detected among products of reaction (1).



3

The formation of the cyclopropanedicarboxylic ester, (1), can be regarded as the consequence of a reaction between 2 and methyl α-chloroacrylate as shown in Eq (3):



1 (3)

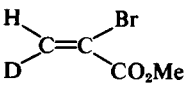
It was further revealed that an asymmetric synthesis was possible with respect to the chiral structure of carbon (1) and carbon (2) in 1.[9] Another study[10] revealed that 1 was also formed in lower yield by using dialkylzinc instead of RZnCl. Ethylcadmium chloride was also found active for the ring formation reaction, but the yield of 1 was only 7% under the same conditions. Other organometallic compounds examined, however, virtually failed to produce the cyclopropane derivatives as shown in Table 1.

The unique behavior of the organozinc compound as seen in Table 1 prompted us to study in more detail the stereochemistry of the ring formation reaction. A deuterated halogenoacrylate such as methyl β-deuterio-α-bromoacrylate-*cis*-d_1 (4)

Table 1. Cyclopropane dicarboxylate formation reaction by various organometallic compounds

Organometallic compound	Solvent	Reaction time, hr	Temp °C	Yield based on ½[MCA](%)
EtZnCl	Bz.	1	70	50·0
Et_2Zn	Bz.	1	70	25·2
BuZnCl	Bz.	1	70	48·2
EtCdCl	Bz.-THF	1	70	7 0
Et_2AlCl	Bz.	10	70	0
$EtAlCl_2$	Bz.	10	70	0
EtMgBr	Bz.-Et_2O	0·5	20	trace
Bu_2BCl	Bz.	10	70	0
BuLi	Bz.	0·5	20	trace

as the reactant could offer information on the mode of breaking of the C=C double bond of the halogenoester in the ring formation reaction (3).



4

Since no convincing method of stereospecific preparation of **4** had been established, it was essential to examine quantitatively the steric course of every step of reactions, (i), (ii), (iii) and (iv), starting from methyl propiolate to cyclopropanedicarboxylic ester *via* **4**: (i) Hydrogenation (by D_2) of methyl propiolate, (ii) Bromination of dideuterated acrylic ester, (iii) Elimination of DBr from methyl α,β-dibromopropionate, and (iv) Reaction of methyl α-bromoacrylate with organozinc compound.

RESULTS AND DISCUSSION

1. *Hydrogenation of methyl propiolate with* D_2. Methyl propiolate was hydrogenated by D_2 in the presence of Pd-$CaCO_3$[11] into methyl acrylate-α,β-d_2, (**5**). NMR measurement[12] revealed that **5** consisted of 80% *cis* and 20% *trans* isomers.

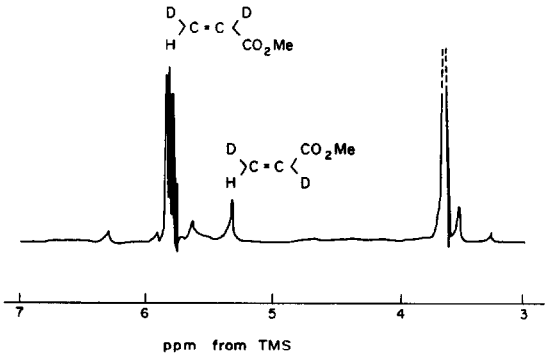
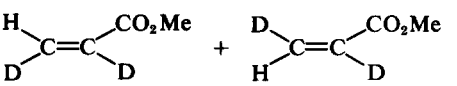
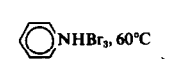


Fig 1. NMR spectrum of methyl acrylate-α,β-d_2.

2. *Bromination of methyl acrylate-*α,β-d_2. Methyl acrylate-α,β-d_2 was brominated with pyridinium tribromide[13] into methyl α,β-dibromopropionate-α,β-d_2,



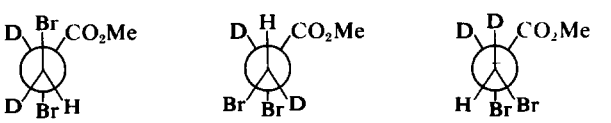
5 (*cis*), 80% + **5** (*trans*), 20%



$$\text{DCH(Br)–DC(Br)CO}_2\text{Me} \quad (4)$$

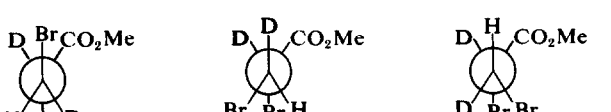
6

If we assume the *trans* addition mechanism starting from (**5**) (*cis*), favorable conformers of the dibromide formed should be drawn as $\mathbf{6}_A$ and $\mathbf{6}_B$ and their mirror images. The third conformer, $\mathbf{6}_C$, and its mirror image must be unstable owing to the steric interaction among the three bulky groups. The *cis* addition mechanism, on the other hand, should give favorable conformers $\mathbf{6}_D$, $\mathbf{6}_E$ and $\mathbf{6}_F$.



$\mathbf{6}_A$ *trans*-form | $\mathbf{6}_B$ *gauche*(−)-form | $\mathbf{6}_C$ *gauche*(+)-form

trans-addition products from (**5**) (*cis*)



$\mathbf{6}_D$ *trans*-form | $\mathbf{6}_E$ *gauche*(−)-form | $\mathbf{6}_F$ *gauche*(+)-form

cis-addition products from (**5**) (*cis*)

From the IR analysis of undeuterated **6** in various solvents, it was concluded that the *trans* conformer is more stable than the *gauche* conformer. As shown in Fig 2 that the absorbance (673 cm^{-1}; 660 cm^{-1}) and (635 cm^{-1}; 619 cm^{-1}) can be assigned to primary and secondary C-Br stretching modes of *trans* and *gauche* conformation, respectively, because the latter conformation should be more favorable in more polar solvents. Fig 2

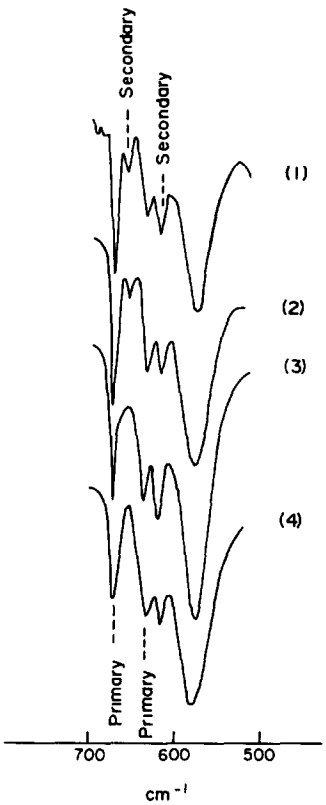


Fig 2. IR spectra of methyl α,β-dibromopropionate 5 mol % in (1) carbon disulfide (2) cyclohexane (3) neat (4) acetonitrile.

shows the undeuterated **6** to exist as the *trans* from in about 70% population in carbon disulfide or cyclohexane solution. Almost the same population of conformers should be established in the deuterated **6** in similar solvents.

The next step was to choose one of the two types of *trans* conformers (6_A, 6_D) by analysing the NMR data.

The NMR spectra of **6** and undeuterated **6** are shown in Fig 3.

The spectrum of undeuterated **6** has three quartets of AMX type ($J_{AM} = -14$ Hz, $J_{AX} = -5$ Hz, $J_{MX} = 14$ Hz, by 100 Mc). Comparing the spectra (1) and (2) the quartet located at 4·40 ppm is assigned to the methine proton (H_X). The values of the

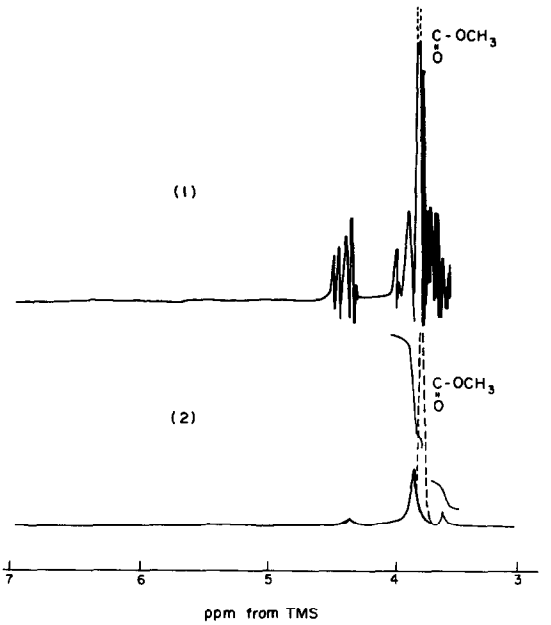
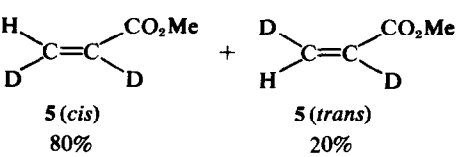
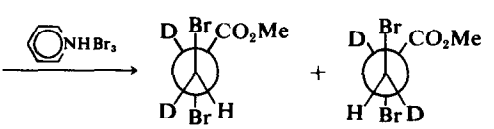


Fig 3. NMR spectra of methyl α,β-dibromopropionate (**6**) in CS_2 (1) undeuterated (**6**) deuterated (**6**).

coupling constants indicate that the M proton (3·85 ppm) and A proton (3·62 ppm) are located in *trans* and *gauche* positions, respectively, to the methine proton (H_X). Therefore, it was concluded from Fig 3, (2) that (**6**) consists of 80% of 6_A and 20% of 6_D. Thus the stereochemistry of reaction (4) becomes as follows:



5 (*cis*) 80% **5** (*trans*) 20%



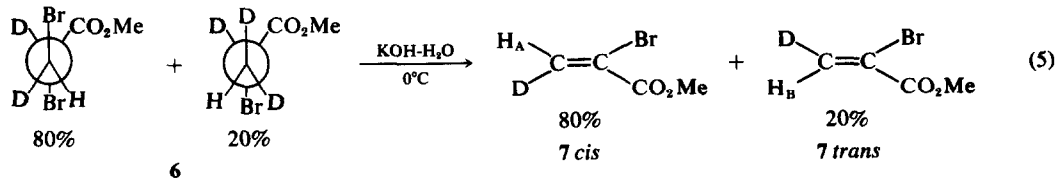
80% 20%

This indicates that pyridinium tribromide adds bromine to methyl acrylate in the exclusive manner of *trans* addition. The result affords a concrete example of reactions of pyridinium tribromide as a *trans*-addition reagent.[13b]

3. *Elimination of* DBr *from methyl α,β-dibromopropionate.* Methyl α,β-dibromopropionate-$α,β-d_2$ was transformed into **4** by potassium hydroxide (10 mol/l) at 0°.

The NMR spectrum of **7** is shown in Fig 4.

Considering the known relationship between substituent X and the chemical shift of the vinyl



proton located in the *cis* position to the X,[14] the signals at 6·8 ppm and 6·1 ppm are assigned to *cis* and *trans* proton to carbomethoxy group, respectively. Measured contact shifts by $Ni(AcAc)_2$[15] at H_A and H_B of **7** were −6·0 Hz and −8·0 Hz (0·5 mol/l **7**, 0·05 mol/l $Ni(AcAc)_2$, in $CDCl_3$), respectively, a fact which may support the above assignment.

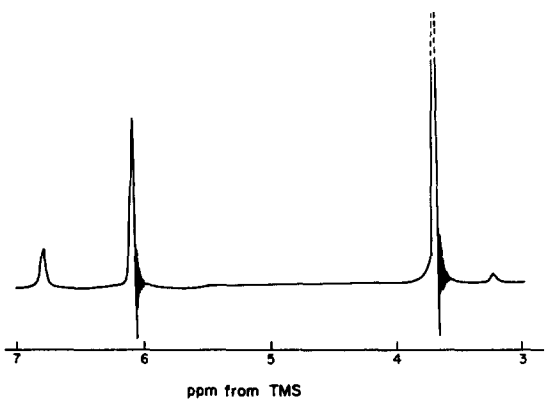


Fig 4. NMR spectrum of methyl β-deuterio-α-bromoacrylate.

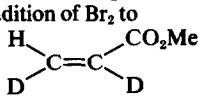
Since the ratio of **7** *cis* to **7** *trans* was calculated to be 80% to 20% from Fig 4, the elimination of DBr from **6** was concluded to proceed via the *trans* mechanism to give methyl β-deuterio-α-bromoacrylate-*cis*-d_1. When diethylaniline was used for the elimination reaction, the stereospecificity of the reaction was much lower.

The stereochemistry of reactions discussed above are summarized in Table 2.

4. *Reaction of methyl α-bromoacrylate with ethylzinc chloride.* The reaction of EtZnCl with **7** (consisting of 80% *cis* and 20% *trans* isomers) was carried out in benzene at 70° according to the procedure reported previously.[1] Dimethyl 1-bromo-2-propyl-*cis*-1,2-cyclopropanedicarboxylate-d_2 (**8**) was obtained in 80% yield (based on ½ (**7**)). The NMR spectra of **8** and undeuterated $\mathbf{8}_H$ are shown in Fig 5.

Two ester Me groups were assigned as reported elsewhere:[16] the lower field singlet, (3·62 ppm), was assignable to the carbomethoxy group linked to carbon (1), while the higher field singlet, (3·54 ppm), to the carbomethoxy group linked to carbon (2). Measured contact shifts at protons d and e of **8** were ~0 Hz and −8 Hz, respectively, (0·5 mol/l **8**), 0·05 mol/l $Ni(AcAc)_2$ in $CDCl_3$) in agreement with the assignment that the higher field signal (1·15 ppm) is one of the methylene protons located in the *trans* position (H_d) to the two carbomethoxy groups and the lower one (2·11 ppm) to the *cis* proton (H_e).

Table 2. Stereochemistry of reactions leading to methyl β-deuterio-α-bromoacrylate-*cis*-d_1 from methyl propiolate

Reaction	Stereochemistry	Selectivity
Addition of D_2 to $HC{\equiv}C{\cdot}CO_2Me$	*cis* addition	80%
Addition of Br_2 to 	*trans* addition	100%
Elimination of DBr from $DCH(Br)CDBr{\cdot}CO_2Me$ by KOH	*trans* elimination	100%
by Et_2N— 	*trans* elimination	65%

From the NMR spectrum of deuterated **8**, it was found that **8** contains 50:50 of *cis* and *trans* protons to the two carbomethoxy groups. Therefore, the manner of C=C double bond opening

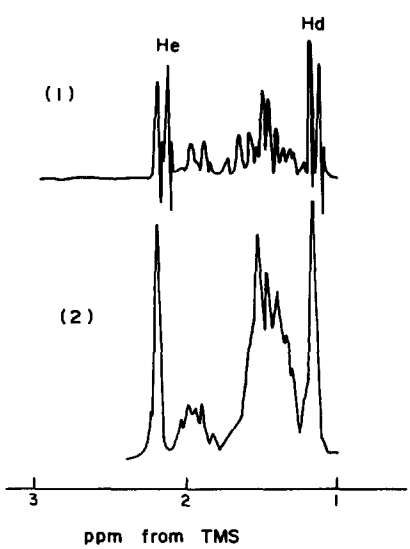
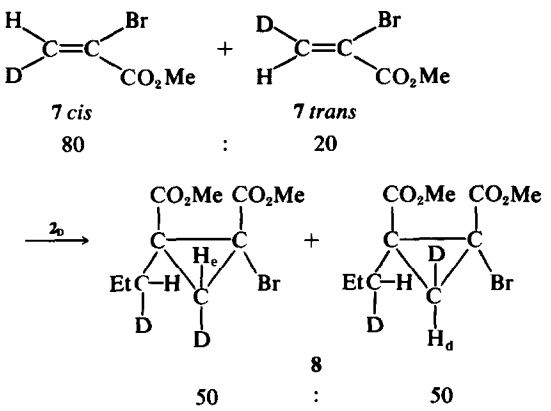
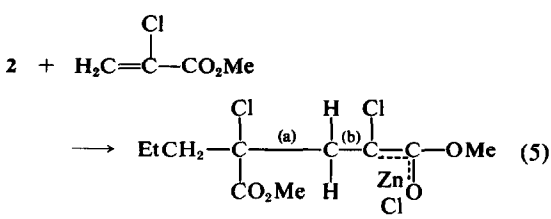


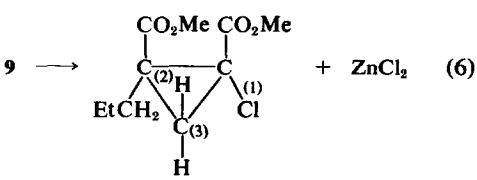
Fig 5. NMR spectra of dimethyl 1-bromo-2-propyl-*cis*-1,2-cyclopropanedicarboxylate (**8**), (1) undeuterated **8**, (2) deuterated **8**.

of reaction (3) has now been established to be 50:50 *cis* and *trans* opening as shown below:



5. A stepwise mechanism of the ring forming reaction. In the first communication,[1] we proposed a stepwise mechanism *via* an intermediate, **9**, for the ring formation reaction:





The observed mode of the double bond opening of reaction (3) can be explained in terms of the stepwise addition mechanism (reactions 5 and 6), in which rotations around bonds (a) and (b) in **9** are assumed to take place prior to the ring formation reaction, (6).

In response to the intensity of influence of chiral elements introduced to the reaction system, the ratio of *S* to *R* of the chiral centers produced carbon (1) and carbon (2) in **1** should be varied. The ratio of *R* to *S* at the two chiral centers must be strongly correlated with each other, because the relative position of the two ester groups in **1** was proved to be *cis*.

Results obtained from some asymmetric syntheses are shown in Table 3.

The large steric regulation of Et_2Zn-*l*-menthol (1·0:1·2 mole ratio) system can be seen from Table 3. In the Et_2Zn-*l*-menthol (1·0:1·2) system, a small quantity of zinc di-*l*-menthoxide must form along with excess ethylzinc *l*-menthoxide. Furthermore, it is safe to consider that most of the dimenthoxide species are complexed with the monomenthoxide in one to six mole ratio according to previous work by Ishimori and Tsuruta,[17] and Bruce and Farren.[18]

The reactivity of zinc alkoxides toward α,β-unsaturated carbonyl compounds was previously confirmed to be much lower than that of the Et group of ethylzinc chloride or diethylzinc itself.[19] Therefore, the one to six complex should not participate in the ring formation reaction as a reactant but as a producer of a reaction field with strong chirality. Ethylzinc chloride as the reactant must be governed by this chiral environment.

On the other hand, an optically active ester of the halogenoacrylic acid would have only a small chiral effect in this reaction, because the chiral centers in the ester group are too distant site from the chiral centers to be produced.

Only a small optical rotation was observed

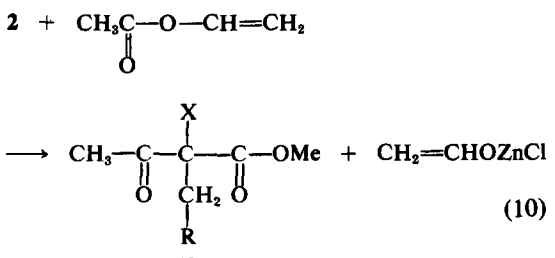
Table 3. Partial asymmetric synthesis of **1**[a]

No.	Additive molar ratio to EtZnCl	Reaction time (hr)	Yield (%)[b]	$[\alpha]_D^{20}$ (benzene)
1	Methyl menthyl ether 3·0	3·0	52·0	−0·06°
2	Ethylzinc *l*-menthoxide 1·0[c]	5·0	35·0	−0·70°
3	Et_2Zn-*l*-menthol (1·0:1·2) 1·0[c]	20·0	10·3	−30·7°
4	Et_2Zn-*l*-menthol (1·0:1·2)	10·0	49·8	−1·32°
5[d]	EtZnCl—CH_2=C(Cl)$CO_2\overset{*}{Am}$[f] (1·0:1·0)	50·0	20·0	−0·09°[e]
6[d]	EtZnCl—CH_2=C(Cl)$CO_2\overset{*}{Men}$[f] (1·0:1·0)	50·0	10·0	−3·7°[e]

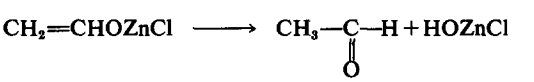
[a] 0°C in benzene.
[b] The yield was calculated based on (MCA)/2.
[c] The values indicate the molar ratio of Et_2Zn to EtZnCl.
[d] The reaction was carried out without additives.
[e] The product was converted into **1** by successive esterification after hydrolysis.
[f] $\overset{*}{Am}$ and $\overset{*}{Men}$ means *l*-AmOH and *l*-MenOH residue, respectively.

(Table 3, No. 6) in *l*-menthyl α-chloroacrylate as a starting reactant.

The validity of the stepwise addition mechanism can also be shown in reactions of methyl α-chloroacrylate with ethylzinc chloride in the presence of vinyl acetate, in which the formation of methyl α-propyl-α-chloroacetoacetate was confirmed. The reaction presumably takes place according to equations (10) and (11):



(10)



(11)

It is noticeable that most of alkyl esters of acetic acid did not undergo such a carbonyl addition type reaction with 2.

EXPERIMENTAL

Benzene was distilled over Na wire. Methyl α-chloroacrylate and methyl α-bromoacrylate were prepared according to the literature.[20] Commercial menthol was used without any purification. Commercial vinyl acetate was purified by distillation. Methyl propiolate was synthesized from propargyl alcohol.[21] Pyridinium tribromide was synthesized according to the literature.[13b] Commercial Et_2Zn and Et_2AlCl were distilled under reduced pressure. EtMgBr, n-BuLi,[22] di-n-BuZn,[23] Et_2Cd,[24] and Bu_2BCl[25] were prepared according to the literature. Ethylzinc menthoxide was prepared by adding equimolar Et_2Zn to the benzene soln of Et_2Zn to the benzene soln of menthol. The diethylzinc-*l*-menthol (1·0; 1·2) system was prepared by adding Et_2Zn to the soln of *l*-menthol and aged for 1 hr at 60°. The NMR spectra were recorded by 100 Mc high resolution NMR spectrometer, model JEOL JNM-4H-100.

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