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Hydrozirconation of Unsaturated Fatty Acid Derivatives

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ABSTRACT

In the hydrozirconation reaction, developed by Schwartz and coworkers, bis(π-cyclopentadienyl)zirconium hydridochloride Cp$_2$Zr(H)Cl, is added to the double bond of an olefin. The organozirconium intermediate can be functionalized by reaction with a variety of electrophiles such as oxygen, halogens, acetyl chloride and carbon monoxide. Furthermore, the double bond can be reformed by treatment with a hydride acceptor such as triphenylmethyl tetrafluoroborate. When a short-chain internal olefin is hydrozirconated, the initially formed alkylzirconium intermediate is rapidly isomerized to a compound in which the zirconium moiety is bound to the sterically least hindered position, which most often is the terminal position. The isomerization occurs rapidly at room temperature in contrast to the corresponding organoboron or aluminum compounds, which slowly positionally rearrange only at elevated temperatures. Because of the facile isomerization of internal alkylzirconium compounds to the terminal ones, we investigated application of the reaction to unsaturated fatty acids such as oleic and erucic acids. However, reactions on long-chain alkenes (such as oleic acid) are frequently much slower than those conducted on shorter-chain alkenes, and attention must be given to optimizing the reaction conditions if good yields are to be obtained. It was also be necessary to find an easily removable protecting group for the carboxylic function, as Cp$_2$Zr(H)Cl reduces carboxylic acids to alcohols. We found that the 4,4-dimethyl-2oxazoline function is a suitable protecting. group, and therefore synthesized the oxazolines from oleic acid and erucic acid. Hydrozirconation of the 4,4-dimethyl-2-oxazoline of oleic acid followed by oxidation with t-butyl hydroperoxide and conversion to methyl esters, gave methyl 3-hydroxy and methyl 18-hydroxy stearate in 13% and 17% yield, respectively. The relatively low yield is due to competing hydrogenation, the mechanism of which is discussed. Recent results indicate that the carboxyl group can be protected as t-butyl esters in the hydrozirconation and that oleyl alcohol derivatives can also be used. To understand the isomerization pattern in hydrozirconation, the reaction with α,β- and β,γ-unsaturated fatty acid oxazolines is discussed. Possibilities of making the hydrozirconation reaction catalytic by binding of the hydrozirconation reagent to a solid support as well as the synthetic potential in combining hydrozirconation with the olefin metathesis reaction are briefly reviewed.

INTRODUCTION

In 1970, Wailes and Weigold prepared bis(π-cyclopentadienyl) zirconium hydridochloride, Cp$_2$Zr(H)Cl, by reaction of certain aluminum hydrides with cyclopentadienylzirconium dichloride (1) (Fig. 1). They also found that olefins reacted with Cp$_2$Zr(H)Cl to give alkylzirconium(IV) complexes, Cp$_2$Zr(R)Cl (2). This hydrozirconation reaction was extensively studied in the 1979s by J. Schwartz and coworkers, who mostly used short-chain olefins (3). The reaction is similar to hydroboration but, in contrast to hydroboration, a rapid isomerization to the terminal zirconium derivatives was observed at room temperature. Thus, all three isomeric octenes (Fig. 2) gave the same alkylzirconium derivative. Two other cases are shown in Figure 3. Note that 2-methyl-2-butene gives the 3-methylbutylzirconium derivative. It was found that the order of reactivity of olefins was α-olefins > cis-olefins $\approx$ trans-olefins > oxocyclic olefins > cyclic olefins. Branching at the double bond also decreased the reactivity and trisub-
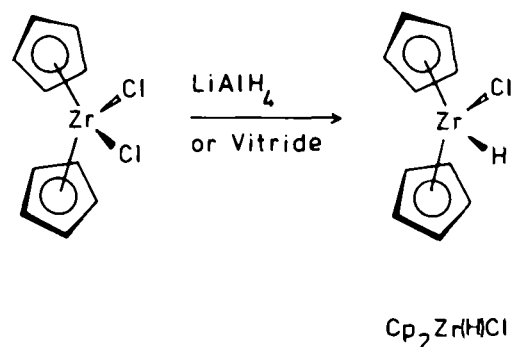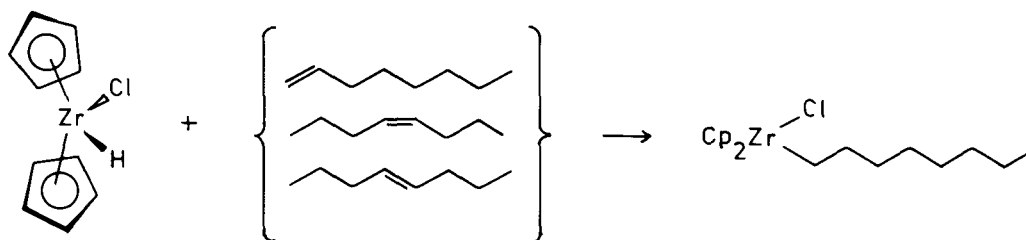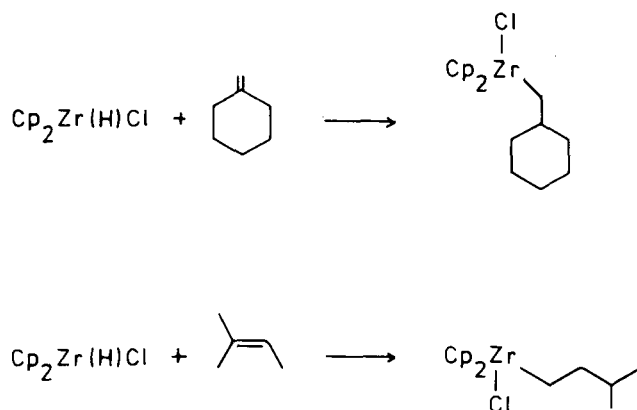

FIG. 1. Preparation of Cp$_2$Zr(H)Cl.

FIG. 2. Reaction of $Cp_2Zr(H)Cl$ with 1-octene, cis-4-octene and trans-4-octene.

FIG. 3. Reaction of $Cp_2Zr(H)Cl$ with methylenecyclohexane and 2-methyl-2-butene.

stituted cyclic olefins such as 1-methyl cyclohexene and tetrasubstituted olefins did not react. Like hydroboration, hydrozirconation is a cis addition and isomerization is assumed to occur via rapid addition-elimination reactions.

The alkylzirconium compounds can be reacted with various electrophiles as shown in Figure 4. Thus, iodine and bromine give alkyl iodides and alkyl bromides in high yields; phenyliodoso dichloride gives the alkyl chloride. N-Bromosuccinimide and N-chlorosuccinimide can also be used for the preparation of alkyl bromides and alkyl chlorides. Acid hydrolysis gives the saturated hydrocarbon. Several methods have been developed for the oxidation of alkylzirconium derivatives to alcohols. The best yields (ca. 70%) are usually obtained using t-butyl hydroperoxide, but aqueous hydrogen peroxide, sodium hydroxide, meta-chloroperbenzoic acid and chromyl chloride have also been used.

The reaction with acetyl chloride leads to alkylmethyl ketones. Insertion of carbon monoxide occurs easily, and the resulting intermediates have been hydrolyzed to aldehydes, converted to carboxylic acids with N-bromosuccinimide and water or the corresponding esters with N-bromosuccinimide and alcohols.

Some other interesting synthetic possibilities of the alkylzirconium complexes are shown in Figure 5. Alkylzirconium(IV) complexes do not react at all with carbon dioxide, and only slowly with ethylene oxide, but the reaction is catalyzed by silver salts and ca. 70% yields of the alcohol with two more carbon atoms are obtained. It is also possible to generate the terminal olefin by hydride abstraction with triphenylcarbonium salts (3).

To increase the reactivity of the zirconium(IV) complexes towards carbon electrophiles, transmetalation using metallic electrophiles is of great importance. It has been
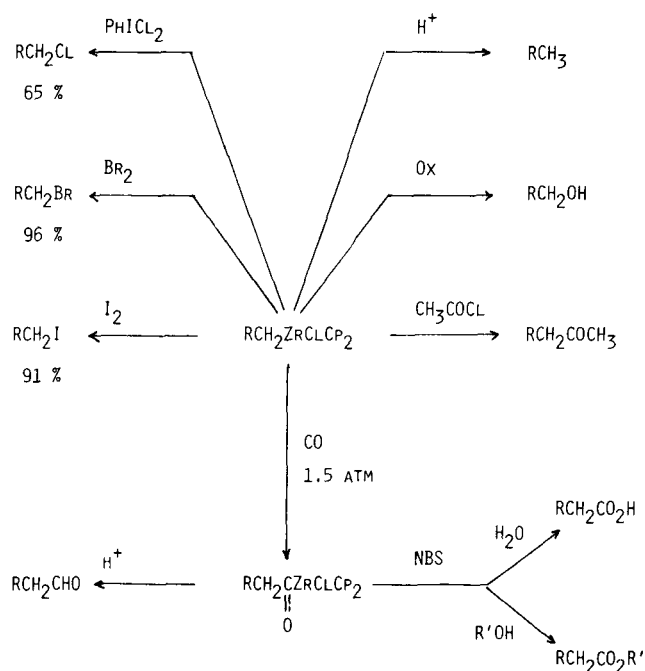

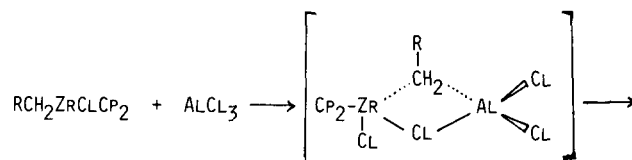FIG. 4. Reaction of alkylzirconium(IV) complexes with electrophiles.
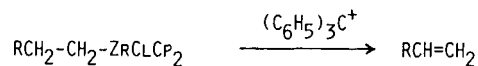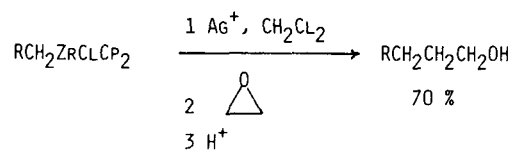

FIG. 5. Reaction of alkylzirconium(IV) complexes with ethylene oxide, triphenylcarbonium salts and aluminum trichloride.

shown that alkylzirconium complexes react with aluminum trichloride to give alkyl aluminum derivatives and Cp_2ZrCl_2 (4). Similar transfer of the organic group to more electropositive elements such as Hg(II), Cu(I), Pd(II), Ni(II) and Sn(IV) has been achieved. This is of great preparative importance and, as will be discussed later, also opens the possibility to make the hydrozirconation catalytic.

Certain functional groups shown in Table I react with $Cp_2Zr(H)Cl$. Thus, alcohols give zirconium(IV) alcoholates, whereas aldehydes, ketones, carboxylic acids and esters are reduced, and after hydrolysis, alcohols are obtained. Cyanides give aldehydes after hydrolysis. As protecting groups for alcohols, the trimethylsilyl group has been suggested. Aldehydes and ketones are protected as acetals and, for carboxylic acids, 4,4-dimethyl oxazolines have been suggested as protecting groups (3). It should be pointed out that almost all investigations have been carried out on short olefins and it has been reported in the literature that isomerization of the long-chain alkene 15-triacontene failed (5).

DISCUSSION

A few years ago, we became interested in applying this new chemistry to renewable resources such as oleic acid and erucic acid. It was necessary to protect the carboxylic acid

and we found that the 4,4-dimethyl oxazoline was useful for this purpose (3).

We found that hydrozirconation of the oxazolines of oleic and erucic acids was much slower than of a terminal unsaturated acid such as 10-hendecenoic acid oxazoline, and we undertook a detailed investigation of the influence of solvent hydrozirconation reagent and temperature to find optimum conditions for hydrozirconation (6). The reaction conditions and the product composition after hydrolysis are shown in Table II. The degree of saturation was determined by gas liquid chromatography (GLC) of the methyl esters obtained by reaction of the oxazolines with 95% methanolic sulfuric acid. Attempts to analyze the oxazolines directly were not satisfactory, as no good separation was achieved. The percentage of *cis-trans* isomers was determined by ^{13}C-nuclear magnetic resonance (NMR), either on the oxazolines or the methyl esters, utilizing the different chemical shifts of the allylic carbons of the *cis* and *trans* isomers. In a few cases the *trans* content was confirmed by infrared (IR) spectroscopy. It is clear from Table II that the solvent plays an important role in the hydrozirconation. In benzene and tetrahydrofuran (THF), saturation of the double bond was obtained which increased with increasing amounts of $Cp_2Zr(H)Cl$. In ether and hexane, no hydrogenation of the double bond was observed. In ether, not even *cis-trans* isomerization was observed. As the best results were obtained in benzene solution, hydrozirconations of the oleic and erucic acid derivatives were done under different conditions in this solvent (Table III). However, we subsequently found that toluene can be used as well. Reaction at 50 C for 20 hr with two equivalents of $Cp_2Zr(H)Cl$ was found to be most convenient, giving 86% methyl stearate. The reason for using two equivalents was the slow reaction. In addition, we have shown that $Cp_2Zr(H)Cl$ is not stable for longer periods at 50 C, and

TABLE I

Reactions of Cp_2ZrHCl with Certain Functional Groups

Starting material	Product
R—OH	R—O—$ZrCp_2Cl$
R—C—H ‖ O	R—CH_2OH
R—C—R' ‖ O	R—C—R' with H above and OH below (R—CH(OH)—R')
R—C—OH ‖ O	R—CH_2OH
R—C—OR' ‖ O	R—CH_2OH
R—C≡N	R—CHO

TABLE III

Effect of Temperature, Time and Molar Ratio on Hydrozirconation

Temperature (C)	Reaction time (hr)	$\dfrac{Cp_2Zr(H)Cl}{Substrate}$	Methyl stearate (%)[a]
RT	20	1.1	14
50	20	1.1	27
RT	240	1.2	32
50	20	1.2	35
50	20	2.0	86

[a]Calculated by GLC.

TABLE II

Hydrozirconation of 4,5-Dihydro-4,4-dimethyl-2-(*cis*-8-heptadecenyl)Oxazole Followed by Hydrolysis

Solvent	Temperature (C)	Reaction time (hr)	$\dfrac{Cp_2Zr(H)Cl}{Substrate}$	Degree of saturation[a] (%)	*trans* Content in unsaturated fraction[b] (%)
Benzene	RT	20	1.1	14	60[c]
Benzene	50	20	3.0	83	100
Ether	RT	20	1.1	0	0
Ether	35	22	1.1	0	0
Hexane	50	20	3.0	<1	25
THF	RT	21	1.1	11	71
THF	50	21	2.0	29	63

[a]Calculated by GLC analysis of the methyl esters.
[b]Calculated by ^{13}C NMR.
[c]The ratio also determined by IR analysis of the methyl esters.

this is the reason why higher temperatures cannot be used in hydrozirconation.

We also found that the hydrozirconation was very much dependent on the quality of commercially available Cp_2Zr-(H)Cl. Other workers have come to the same conclusion and have suggested that it is best to generate the hydrozirconating agent by reduction of Cp_2ZrCl_2 with vitride, $NaAlH_2(OCH_2CH_2OCH_3)_2$, and use it directly without further purification. With this method they were also able to move double bonds in long-chain olefins over as many as 20 carbon-carbon bonds (7).

It is clear that through the hydrolysis reaction, information about the positional isomers of the zirconium complex is lost. However, the remaining unsaturated fraction provided evidence that, in addition to cis-trans isomerization, positional isomerization had occurred. A detailed investigation of the mass spectra indicated at least the formation of C-18 oxazolines with the double bond in the 8- and 7-positions.

To study the positional isomeric distribution and the synthetic usefulness of the reaction, we reacted the zirconium complexes with carbon monoxide. From 10-hendecenoic acid oxazoline we obtained a 49% yield of the ω-formylated oxazoline together with 28% of hydrogenated product and 19% of the starting material (Fig. 6). However, our attempts to apply the carbonylation to the long-chain oxazolines from oleic or erucic acids failed — most probably due to polymerization of the formylated products. We then turned to hydroxylation through the reaction with t-butylhydroperoxide which with 10-hendecenoic acid oxazoline gave a 31% yield of the ω-hydroxy derivative. As can be seen in Figure 7, this was also successful with the oxazolines from oleic acid and erucic acid. However, both the ω-hydroxy and the 3-hydroxy derivatives, separated by chromatography, were obtained. This is as far as we know the first observation that zirconium can migrate to a position other than the ω-position. The reason for this could be the stability of the 5-membered intermediate (Fig. 7), in which nitrogen donates electrons to zirconium to give an 18-electron configuration around the metal. However, the total yield of hydroxylated product is rather low and 20-30% of hydrogenated products, the oxazolines of the corresponding saturated acids, are formed. Although part of this could be due to unintentional hydrolysis of the intermediate zirconium complexes, the larger proportion

of it could hardly have been formed in this way. It seems, therefore, likely that when hydrozirconation is slow, competing hydrogenation can occur.

To investigate the hydrozirconation more closely and to find conditions under which the undesired hydrogenation is more or less completely suppressed, we studied the hydrozirconation of oxazolines of shorter α,β- and β,γ-unsaturated acids. In addition, information on the influence of the original position of the double bond on product distribution in the hydrozirconation could be obtained. The position of the carbon-zirconium bond was determined by reaction with DCl in D_2O (Fig. 8).

The α,β-unsaturated derivatives derived from 2-butenoic and 2-hexenoic acids with nonterminal double bonds gave somewhat unexpectedly the 2-deuterium derivative, indicating a 2-zirconium complex together with 9 and 16% of the saturated product containing no deuterium. The analogous α,β-unsaturated compounds with a terminal double bond, the acrylic and methacrylic acid derivatives, quite unexpectedly gave hydrogenation as the main reaction giving a 70% yield of nondeuterated saturated product and only 12-15% of deuterated isomers. It is thus clear that hydrogenation in certain structures can become the main reaction. In the β,γ-unsaturated derivatives, hydrozirconation also competes with hydrozirconation. Thus, the 3-butenoic acid derivative gave selectively the ω-substituted zirconium derivative, which on hydrolysis gave 70% of the 4-deuterobutanoic acid derivative together with 11% of undeuteriated product. The 3-hexenoic acid derivative gave a mixture of 32% of the 2-deutero-, 16% of the 3-deutero and 12% of nondeuterated product, indicating that in this system the isomerization to the terminal zirconium compound is slow.

To determine the origin of the second hydrogen atom, we did the hydrozirconation of 1-decene in hexadeuterated benzene and hydrolyzed the zirconium complex with hydrochloric acid (Fig. 9). No deuterated decane was obtained, showing that the second hydrogen is not extracted from the solvent. It is also clear that the second hydrogen does not come from the hydrido group of $Cp_2Zr(H)Cl$, since the hydrogenation of 2-methyl octene with $Cp_2Zr(D)Cl$, on hydrolysis with hydrochloric acid, gave only 2-deutero-2-methyloctane as reaction product. No dideutero derivative was formed. On hydrolysis with DCl/D_2O, 1,2-dideutero-2-methyloctane and 2-deutero-2-methyl-octane were obtained
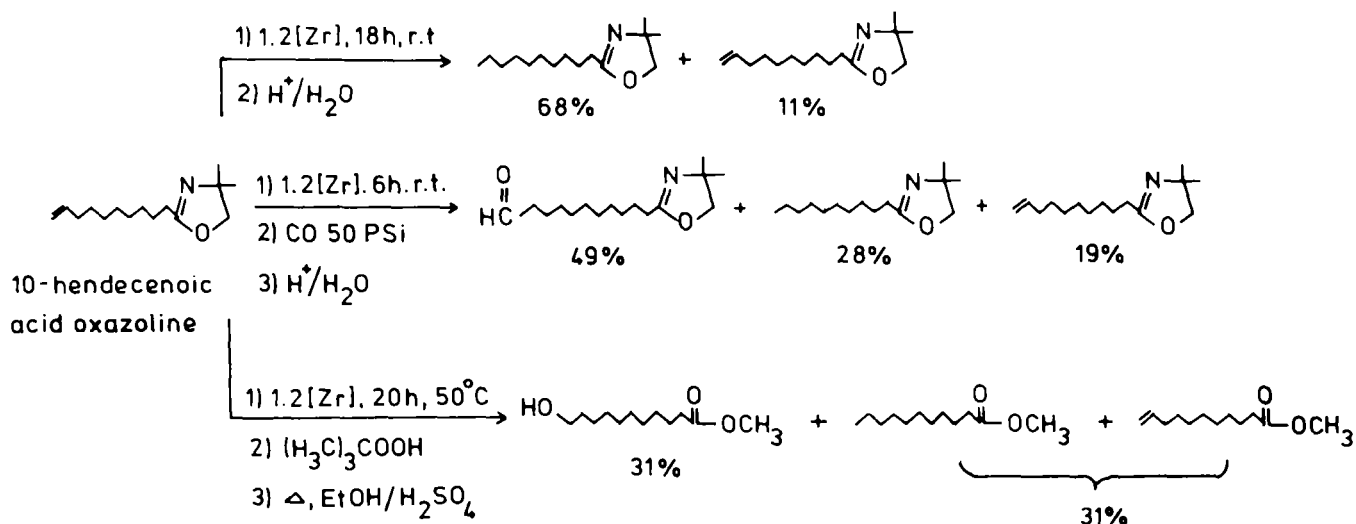

FIG. 6. Reactions of the alkylzirconium(IV) complex from 10-hendecenoic acid oxazoline.

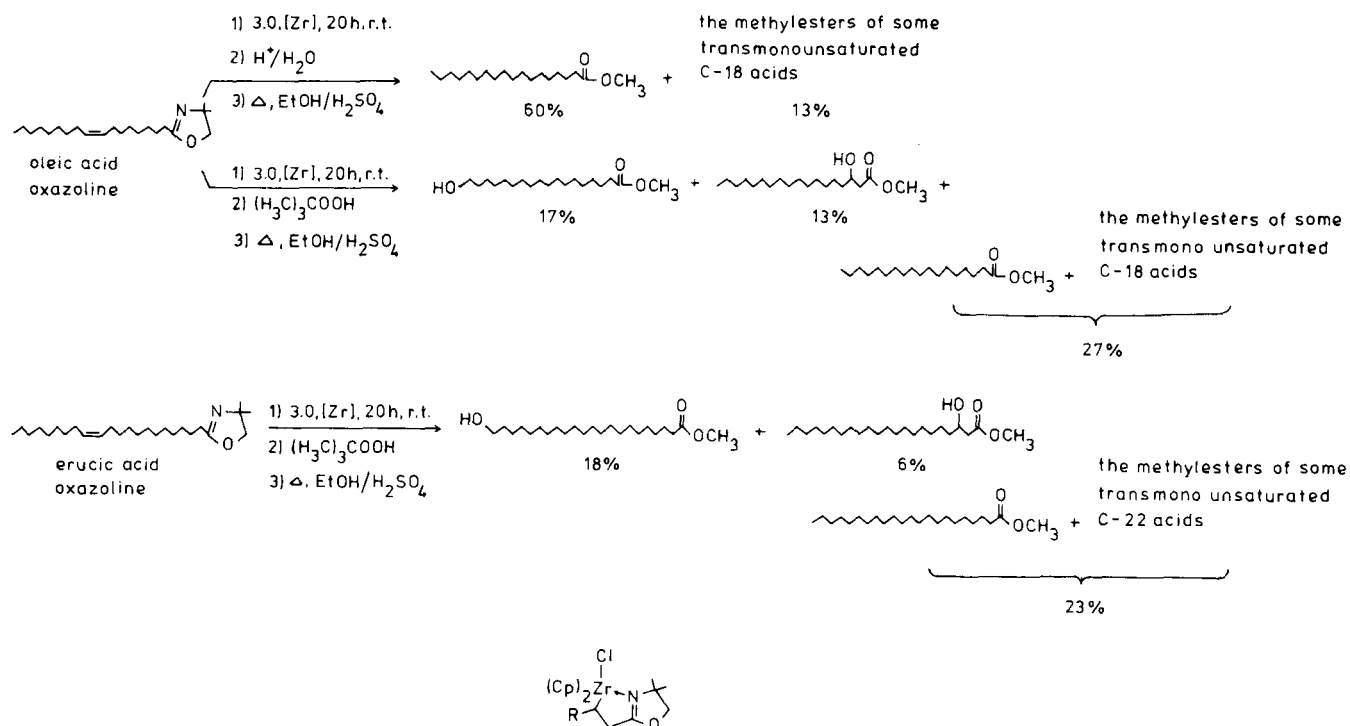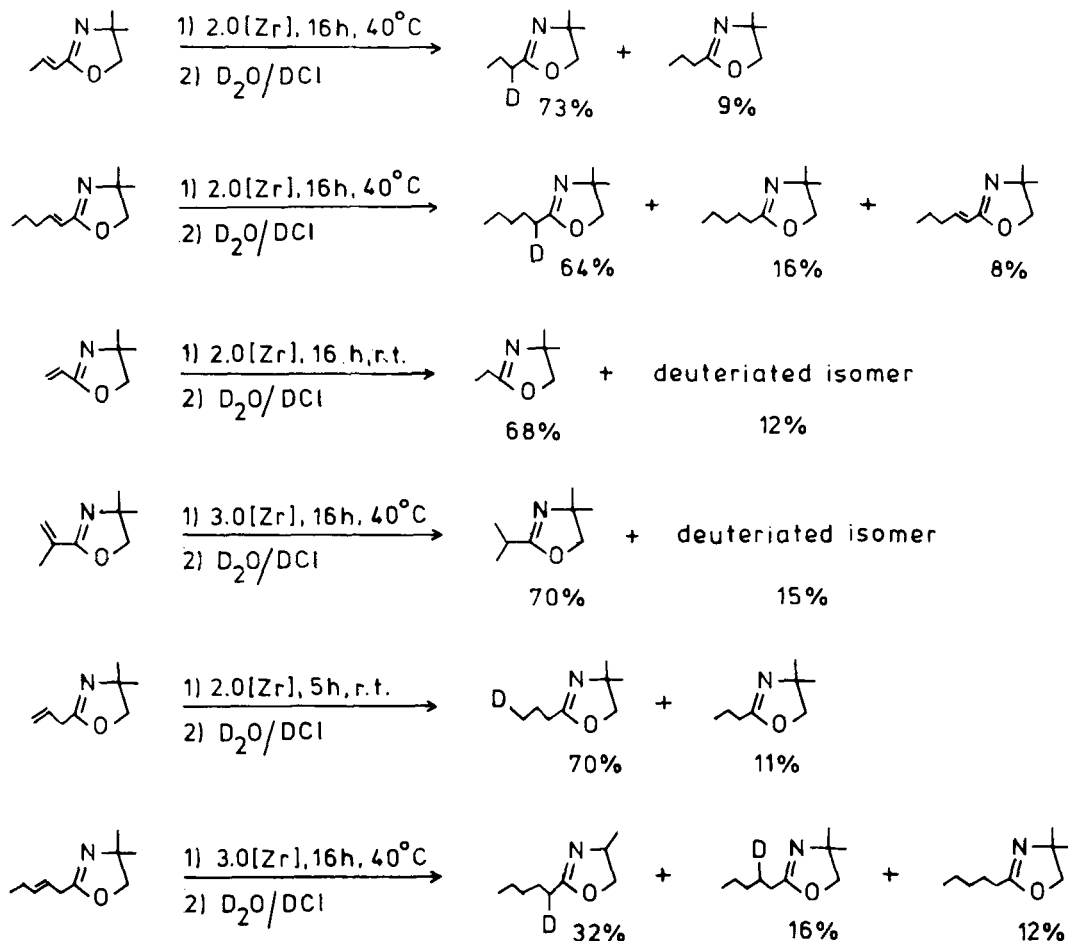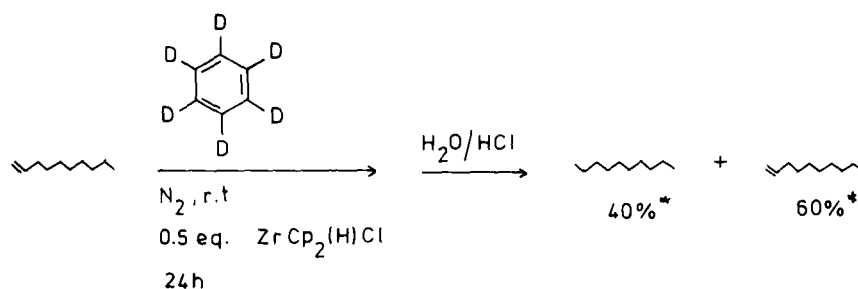J. ALVHÄLL, S. GRONOWITZ, A. HALLBERG AND R. SVENSON

FIG. 7. Reactions of the alkylzirconium(IV) complexes from oleic and erucic acid oxazolines.

FIG. 8. Reactions of the alkylzirconium(IV) complexes from α,β- and β,γ-unsaturated acid oxazolines.

H_2O/HCl

N$_2$, r.t

0.5 eq. ZrCp$_2$(H)Cl

24h

40%*   +   60%*

*relative yields based on GLC

FIG. 9. Hydrozirconation of 1-decene in hexadeuteriated benzene and subsequent hydrolysis with H$_2$O.

1/4 LiALD$_4$ + Cp$_2$ZrCl$_2$ $\xrightarrow{\text{THF}}$ Cp$_2$Zr(D)Cl

+ Cp$_2$Zr(D)Cl

0.47 EQ

$\xrightarrow[\text{R.T. 20 H}]{C_6H_6}$

D$_2$O

H$_2$O

81 %*   19 %*

+ Cp$_2$Zr(H)Cl

0.47 EQ

$\xrightarrow[\text{R.T. 20 H}]{C_6H_6}$

D$_2$O

H$_2$O

81 %*   19 %*
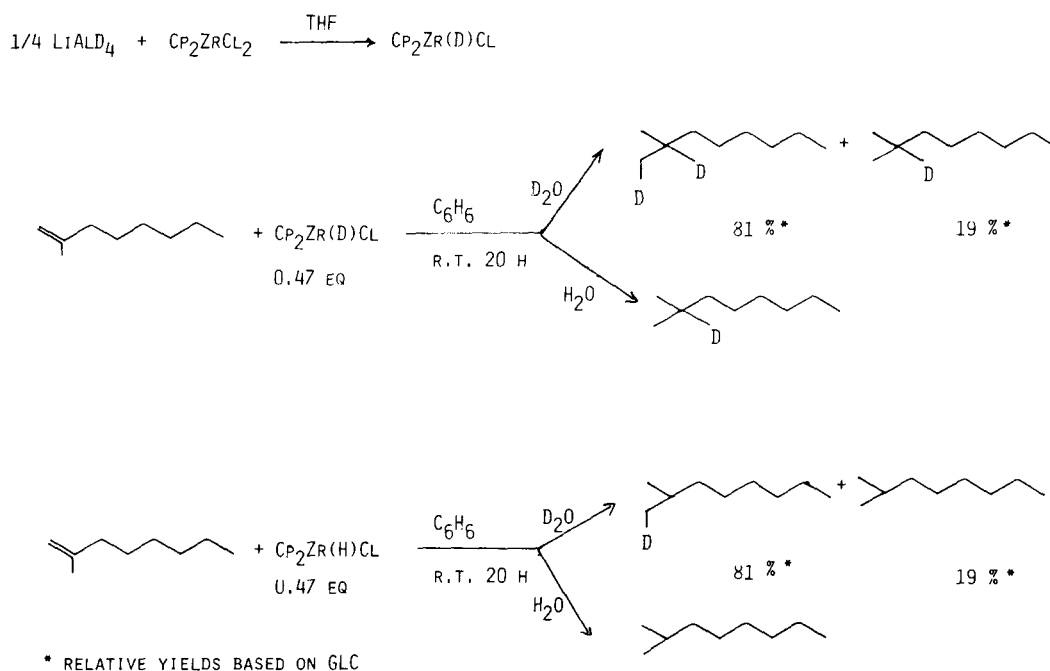
* RELATIVE YIELDS BASED ON GLC

FIG. 10. Hydrozirconation of 2-methyl-1-1-octene with Cp$_2$Zr(D)Cl and Cp$_2$Zr(H)Cl and subsequent hydrolysis of the alkylzirconium(IV) complexes with H$_2$O and D$_2$O.

TABLE IV

Reaction between 1-Decene and Cp$_2$Zr(H)Cl with Subsequent Hydrolysis with D$_2$O

Reaction time (hr)	Eq. Cp$_2$Zr(H)Cl	A[a] (%)	B[a] (%)	C[a] (%)
3.3	1.2	10	70	20
20.0	1.2	10	60	30
1.5	0.69	61	35	3.5
21.0	0.53	60	29	10
3.5	1.2[b]	10.5	84.0	5.5
24	1.2[b]	10.9	58.1	30.5

[a]Relative yields based on GLC.
[b]Prepared in situ.

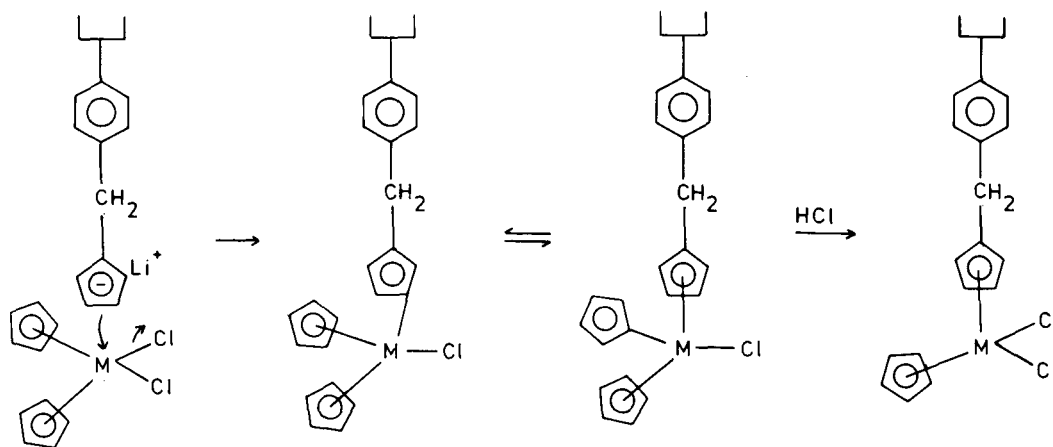J. ALVHÄLL, S. GRONOWITZ, A. HALLBERG AND R. SVENSON

FIG. 11. Proposed preparation of polymer-supported zirconium complexes.

in the ratio of 81:19, showing that competitive hydrogenation of the double bond is occurring (Fig. 10). We have also used $(C_5D_5)_2Zr(H)Cl$ in the hydrozirconation reaction to check whether the second hydrogen comes from the cyclopentadienyl group of $Cp_2Zr(H)Cl$ or from the intermediate alkylzirconium complex. Our results indicate that this is not the case, so that only the possibility of hydrogen abstraction from the alkyl chain remains. However, experiments with 1-decene, using different reaction times showed that the amount of nondeuterated decane increased with time, with no decrease in the amount of starting olefin when a deficit of $Cp_2Zr(H)Cl$ was used. The increase of nondeuterated decane with time was even more striking when a slight excess of $Cp_2Zr(H)Cl$ was used (Table IV).

It is thus evident that, to make the hydrozirconation reaction useful for the slowly reacting fatty acids of the oleic and erucic acid types, more active hydrozirconation reagents must be developed. Our main efforts are at present in this direction. We are also attempting to make the reac-

tion catalytic by attachment of the zirconium complex to a polymer support (8) as shown in Figure 11. Another future prospect would be to combine hydrozirconation-isomerization with the metathesis reaction. This is of course first possible when conditions for the isomerization of oleic and erucic acid derivatives to the terminal olefin have been established.

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